

**Potential of Phytonutrients to act as
Mimetics for Caloric Restriction –
Identification of the Transcriptional and
Functional Overlap in *silico***

Dissertation

zur Erlangung des Doktorgrades
der Agrar- und Ernährungswissenschaftlichen Fakultät
der Christian-Albrechts-Universität zu Kiel

vorgelegt von

M.Sc. Stefanie Rieper

Kiel, 2016

Aus dem Institut für Humanernährung und Lebensmittelkunde
der Christian-Albrechts-Universität Kiel

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Summary

Caloric restriction (CR) is known for its beneficial effects on life- and healthspan (lifespan without the occurrence of age-related diseases) in several model organisms. Studies in rhesus monkeys and humans are still ongoing, but the first results are promising. Nonetheless, it is assumed to be very difficult for humans to reach long-term CR because food is always available and because CR has many side effects, such as hunger and sensitivity to cold. Therefore, it is of interest to identify CR mimetics which are able to enhance health- and lifespan without affecting calorie intake. Some promising pharmaceutical substances have been identified (e.g., rapamycin and metformin) but most of them also show side effects. Therefore it will be of interest to identify food derived compounds such as plant bioactives (phytonutrients) as potential CR mimetics.

The aim of this study is to develop a new approach that will allow identifying potential CR mimetics *in silico*. Therefore, the transcriptional and functional overlap between CR and putative plant derived CR mimetics is analysed by using data of previously published investigations from the databases ArrayExpress and Gene Expression Omnibus (GEO).

In the present thesis nine CR experiments are identified, four experiments investigating the impact of different phytonutrients supplementing a normal diet (e.g., resveratrol, phloridzin and quercetin) and one experiment investigating the influence of phytonutrients administered intraperitoneally (quercetin, genistein). The results of these experiments were summarised with the R package RankProd to identify genes that were consistently differently regulated by CR, resveratrol, phloridzin, quercetin and genistein. These gene lists were compared to identify the transcriptional and functional overlap between CR and the putative mimetics.

Our results show that resveratrol had the largest overlap in gene expression regulation, so it is assumed that resveratrol can mimic many functions of CR. However, our results were unable to show that resveratrol increases the expression of sirtuin 1 (Sirt1; typically mentioned as a mediator of CR effects) or influences insulin-like growth factor-1 (Igf1) signalling. However, our results indicate that quercetin administered into a diet could be a CR mimetic, although only a smaller overlap in gene expression compared to resveratrol could be identified. Quercetin increases the expression of Sirt1 and regulates the expression of several genes, which indicate that Igf1 signalling could be reduced, probably leading to increased activity of Foxo1 and enhanced defence against oxidative stress. Quercetin increases the lifespan of *C. elegans* and *Saccharomyces cerevisiae*, and it modulates PI3K/Akt activation, Foxo1 phosphorylation, mTOR signalling and oxidative stress defence, as has already been seen in previous investigations.

Therefore, it is concluded that quercetin could be a CR mimetic, as it and CR address similar mechanisms.

In conclusion, our results show that in *silico* analyses can be used to identify potential CR mimetics. This is in sense of ethical principles of animal welfare and avoids additional animal studies because already existing array data are used. Unfortunately, however, our results are limited to a few substances because no further data are available on ArrayExpress or GEO. Thus the results of our in *silico* analysis are limited to the availability and quality of existing data.

Zusammenfassung

Kalorienrestriktion (CR, engl.: caloric restriction) führt bei verschiedenen Modellorganismen zu einer gesteigerten Lebenserwartung und einer verlängerten Gesundheitsspanne (Lebensspanne ohne altersbedingte Erkrankungen). Erste Studienergebnisse aus Rhesusaffen und Menschen sind bereits vielversprechend. Allerdings ist davon auszugehen, dass eine langfristige Kalorienrestriktion für Menschen nur sehr schwer durchzuhalten ist, weil Lebensmittel so gut wie immer verfügbar sind und CR häufig mit Nebenwirkungen wie Hunger und frieren einhergeht. Deshalb ist es von Interesse Mimetika für CR zu identifizieren, die ebenfalls einen positiven Einfluss auf die Lebenserwartung und die Gesundheitsspanne haben, ohne dabei die Kalorienzufuhr zu beeinflussen. Bisher konnten potentiell wirksame pharmakologische Substanzen wie Rapamycin und Metformin identifiziert werden, deren Einnahme jedoch mit zum Teil schweren Nebenwirkungen verbunden ist. Deswegen ist die Suche nach potentiell wirksamen Substanzen aus Lebensmitteln wie etwa sekundären Pflanzenstoffen besonders interessant.

Ziel dieser Studie ist es, eine neue Methode zu entwickeln, mit der potentielle CR Mimetika *in silico* (d.h. computergestützt) identifiziert werden können. Hierfür wird die transkriptionelle und funktionelle Übereinstimmung zwischen CR und verschiedenen Substanzen analysiert. Dazu wird auf bereits publizierte Ergebnisse (Expressionsprofile) früherer Studien zurückgegriffen. Datenbanken wie ‚arrayexpress‘ und ‚Gene expression omnibus (GEO)‘ wurden genutzt um entsprechende Microarray-Experimente zu identifizieren, die den Einfluss von CR bzw. sekundären Pflanzenstoffen auf die Genexpression untersucht haben.

Von den als relevant für die Fragestellung eingestuften Studien untersuchten neun den Einfluss von CR, vier den Einfluss von sekundären Pflanzenstoffen, die mit der Diät zugeführt wurden (Resveratrol, Phloridzin und Quercetin), und eine den Einfluss von sekundären Pflanzenstoffen, die intraperitoneal verabreicht wurden (Quercetin und Genistein). Die Ergebnisse dieser Experimente wurden mit Hilfe des R Pakets ‚Rank-Prod‘ zusammengefasst, um Gene zu identifizieren, deren Expression konsistent über alle Behandlungen (CR und sekundäre Pflanzenstoffe) reguliert wurde. Die so erhalten Genlisten wurden miteinander verglichen, um die transkriptionelle und funktionelle Übereinstimmung herauszufinden.

Unsere Ergebnisse zeigten, dass Resveratrol die größte Übereinstimmung bezüglich der Genexpression zeigte, und damit als potentielles Mimetikum am ehesten in Frage käme. Allerdings konnte die in der Literatur beschriebene Induktion von Sirt1 (ein bekannter Vermittler einiger CR Wirkungen) oder die Modulation des Igf1 Signalweges

durch Resveratrol hier nicht gezeigt werden. Interessanterweise wurde für Quercetin gezeigt, dass trotz geringer numerischer Übereinstimmung in der Genexpression eine übereinstimmende Modulation wichtiger metabolischer Schlüsselsignalwege analog zu CR bestand. Quercetin steigerte die Expression von Sirt1 und modulierte mehrere Gene innerhalb des IGF1 Signalweges, was zu einer gesteigerten Foxo1 Aktivität und damit zu einer verstärkten Abwehr oxidativer Schäden führen kann. Es ist bereits bekannt, dass Quercetin einen positiven Effekt auf die Lebenserwartung von *C. elegans* und *Saccharomyces cerevisiae* und einen regulierenden Einfluss auf die PI3K/Akt Aktivierung, die Foxo1 Phosphorylierung, den mTOR Signalweg und die Abwehr von oxidativem Stress hat. Demnach wird Quercetin hier als ein potentielles CR Mimetikum herausgestellt da ähnliche molekulare Signalwege wie durch CR moduliert werden.

Zusammenfassend kann gesagt werden, dass der hier vorgestellte *in silico* Ansatz grundsätzlich geeignet ist, um potentielle CR Mimetika zumindest hypothetisch zu identifizieren. Dies ist im Sinne ethischer Grundregeln des Tierschutzes und vermeidet zusätzliche tierexperimentelle Studien, indem bereits vorhandene Array Daten verwendet werden. Allerdings ist die Aussagekraft der *in silico* Analyse beschränkt auf die in den Datenbanken (‘arrayexpress’ und ‘GEO’) frei verfügbaren Datensätze und abhängig von der Qualität der Daten.

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Abbreviations

AGEs	advanced glycosylation end-products
Akt	Protein kinase B
AMPK	adenosine monophosphate-activated protein kinase
CPDB	online tool ConsensusPathDB
CR	caloric restriction
Cry1	cryptochrome 1
DAVID	Database for Annotation, Visualization and Integrated Discovery
FDR	False discovery rate
Foxo	forkhead member of the class O
G6pc	glucose 6-phosphatase
GH	growth hormone
Ghr	growth hormone receptor
Gi	genistein administered intraperitoneal
Glut4	glucose transporter type 4
GO	Gene ontology
GSEA	gene set enrichment analysis
HIF-1 α	hypoxia inducible factor 1-alpha
Igf1	insulin-like growth factor-1
Igfals	insulin-like growth factor binding protein, acid labile subunit
Igfbp1	Insulin-like growth factor binding protein 1
Irs1	insulin receptor substrate 1
MEA	modular enrichment analysis
MNAM	N1-methylnicotinamide
mTOR	mechanistic target of rapamycin
NA	nicotinic acid
NAD	nicotinamide adenine dinucleotide
NAM	nicotinamide
NF- κ B	nuclear factor κ B
Nnmt	nicotinamide N-methyltransferase
Nrf1	nuclear respiratory factor 1
Nrf2	Nuclear factor erythroid 2-related factor 2
P	phloridzin
Pepck	phosphoenolpyruvate carboxykinase
Per1/2	period circadian clock 1/2
PGC-1 α	peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PI3K	phosphoinositide 3-kinase

PPAR	peroxisome proliferator activated receptor
Qd	quercetin administered per diet
Qi	quercetin administered intraperitoneal
R	resveratrol
ROS	reactive oxygen species
S6k	ribosomal protein 6 kinase
SAM	S-adenosylmethionine
SEA	singular enrichment analysis
Sirt	sirtuin
Srebp1c	sterol regulatory element binding protein 1c
TFAM	transcription factor A, mitochondrial
TF	transcription factor
TFBs	transcription factor binding sites
TGF beta	transforming growth factor beta
TNF- α	tumor necrosis factor alpha

1. Introduction

Life expectancy has been increasing for several decades. However, large differences nonetheless exist between individuals and between regions and countries (1). This leads to the question of which factors are responsible for the determination of lifespan. In addition to genetic disposition, lifestyle and nutrition seem to be important. In antiquity, Hippocrates had already recognised a relationship between high calorie intake and early death (2; 3). Since then, many more hints have become available that food amount and quality are associated with health, ageing and lifespan (3). The first studies to investigate the relationship between food or calorie restriction (CR) and ageing or lifespan occurred in the early 20th century. OSBORNE et al. (1917) showed that food restriction for four female rats increased lifespan, retarded reproduction and reduced growth rate (4; 5). Moreover, MCCAY et al. (1935) observed an increased lifespan in rats following a reduced calorie intake based on a diet containing 20% indigestible cellulose (2; 6). Currently, many more investigations are available indicating that CR increases the maximum and/or median lifespan in many model organisms, such as yeast, flies, worms, fish, mice and rats (2). CR refers to reducing calorie intake by 10–50% for animals fed ad libitum. These diets are often supplemented with micronutrients to prevent deficits and malnutrition (2).

However, it is important to not only increase lifespan but also enhance the occurrence of healthy ageing. Age-related diseases increase costs for health care systems and decrease the quality of life drastically (7; 8; 9). Interventions to increase both lifespan and healthy ageing have been the subject of research for several decades. CR seems to be effective in preventing physiological decline and age-related diseases such as cancer, cardiovascular diseases, neurodegenerative diseases (e.g., Alzheimer's disease) and insulin resistance (which is linked to diabetes mellitus) as well, leading to increased healthspan (lifespan without age-related diseases) (10; 11; 12; 13).

If CR is able to increase lifespan and improve health in model organisms, then it is important to investigate whether CR is beneficial in humans, too. Experiments with humans and rhesus monkeys are still ongoing. The available results for rhesus monkeys to date are inconsistent regarding lifespan but already indicate that CR improves health, cardiovascular factors and insulin sensitivity (2; 12; 14). The differences in lifespan expansion could be explained by differences in dietary composition and genetic background (14). The CALERIE (Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy) study in humans indicates that CR also shows health benefits but that bone mineral density is reduced (14). Nonetheless, further investigations are necessary to determine conclusively whether CR improves health- and increases lifespan in humans too. However, even if CR is effective, it will be very diffi-

cult for humans to achieve a lifelong restriction in calorie intake because CR shows some side effects (such as hunger and sensitivity to cold) and because food is available all the time for most people in Western countries. Therefore, identifying other interventions that can improve health and increase lifespan could be of interest. To determine these factors, it may be useful to examine the underlying mechanisms of beneficial CR effects.

1.1. Mechanisms of CR effects

To identify mechanisms that could be responsible for the lifespan-expanding effect of CR, it is important to know what happens during ageing and which risk factors promote the development of age-related diseases. Ageing is known to be associated with increased metabolic and oxidative stress, higher concentrations of reactive oxygen species (ROS), reduced antioxidant defence, enhanced lipid and DNA damage, reduced capability in DNA damage-repair mechanisms, mitochondrial dysfunction, chronic inflammation, nicotinamide adenine dinucleotide (NAD⁺) depletion, and higher rates of apoptosis (13; 15; 16). Interestingly, previous studies indicate that CR regulates many of these mechanisms, such as apoptosis, ROS production and defence systems (17). However, how CR influences these factors and which factors are necessary for improved health and increased lifespan are not clear. SINCLAIR (2005) reviewed the many hypotheses that exist regarding the potential mechanisms of CR (17). For example, endocrine changes based on reduced fat mass, reduced ROS availability or increased cell survival could be responsible for CR's longevity effect. However, some studies have refuted these hypotheses and most of the mentioned mechanisms alone have not been able to explain the multitudinous effects of CR, which have made it impossible until now to completely identify the underlying CR mechanisms (17). However, the most accepted theory to date is the hormesis hypothesis, which states that CR functions as a mild stressor that activates several defence mechanisms. This activation protects against the effects of factors that are involved in the ageing process or in the development of age-related diseases (17). Nonetheless, further studies are necessary to finally identify the CR mechanisms.

However, even if the CR effect is not completely understood, many pathways and key players have been identified that are most likely involved, including sirtuins, the mechanistic targets of rapamycin (mTOR) signalling, adenosine monophosphate-activated protein kinase (AMPK) signalling, forkhead members of the class O (Foxos), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), growth hormone (GH) / insulin-like growth factor-1 (Igf1) signalling, Ras-protein kinase A (PKA), glycolysis, autophagy and possibly fibroblast growth factor 21 (Fgf21) (2; 10; 12;

14; 15; 18; 19). Moreover, CR is known to influence the regulation of oxidative stress, suppress inflammation, have proangiogenic effects and increase DNA repair mechanisms and protein synthetic capacity (20; 21). Furthermore, CR may increase the serum concentration of glucocorticoids (e.g., cortisol), which results in the activation of anti-stress and anti-inflammatory pathways (22). In the following, it will be provided an overview of the potential mechanisms that have been identified. Figure 1 summarises these results.

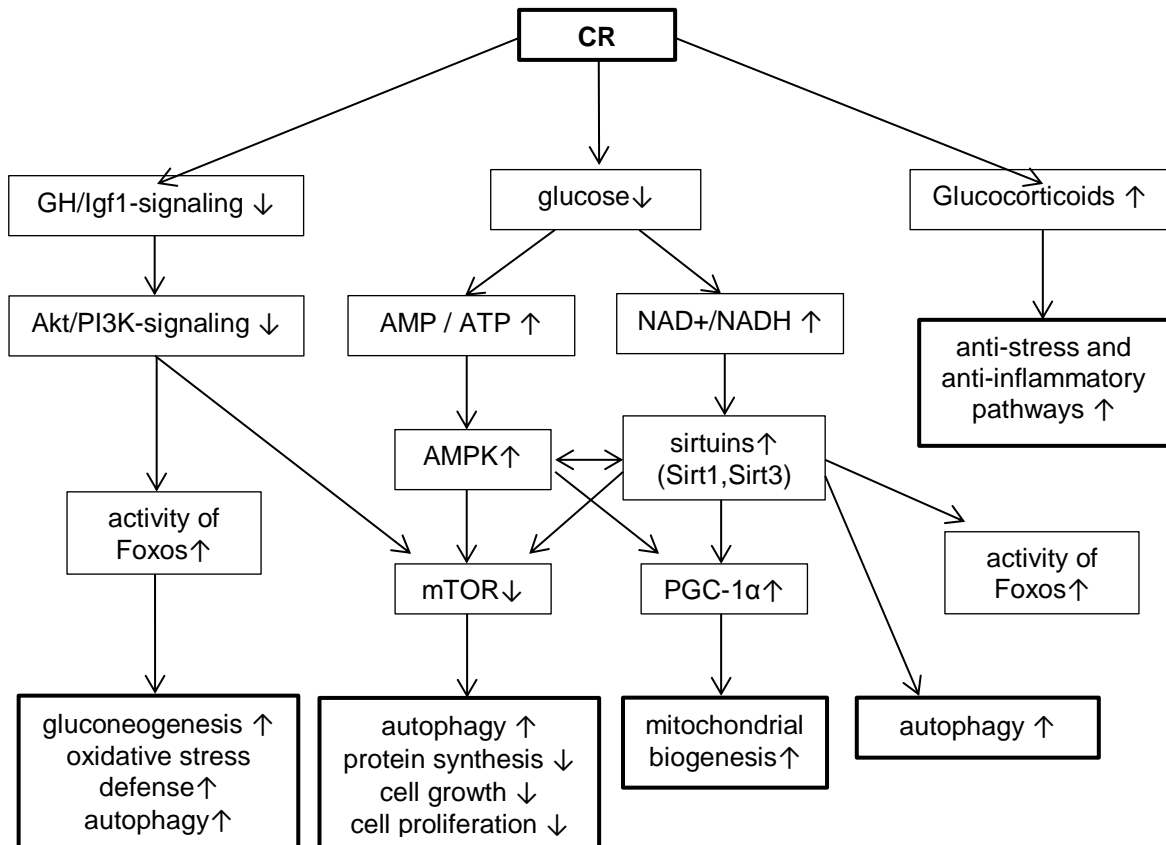


Figure 1: Metabolic changes and underlying molecular mechanisms upon caloric restriction

GH and Igf1 signalling; Foxo1

CR lowers the levels of growth hormone (GH), Igf1, plasma insulin and plasma glucose, which leads to reduced activity in GH/Igf1 signalling, improved glucose homeostasis and increased insulin sensitivity (20; 12). GH activity is associated with ageing, and reduced plasma levels of GH and Igf1 or reduced Igf1 signalling leads to an increased lifespan (21; 23). This is supported by BABAR et al. (1999), who showed that an inhibition of the phosphoinositide 3-kinase (PI3K) pathway is associated with longevity in *C. elegans* (24; 25). PI3K/Protein kinase B (Akt) signalling is a target of GH/Igf1 signalling, which leads, for example, to the activation of mTOR/ribosomal protein 6 kinase (S6k) signalling (12). Moreover, activation of PI3K/Akt signalling leads to

the inactivation of Foxo1 by phosphorylation (26). Foxos, especially Foxo1, are involved in oxidative stress responses, apoptosis, cell cycles, detoxification and immune homeostasis (27; 26). Foxo1 increases the expression of antioxidant genes such as superoxide dismutase (Sod), promotes the scavenging of ROS, and prevents damage to DNA and cells. Moreover, Foxos interacts with Sirt1, another important factor for the effects of CR (26). In particular, the increased oxidative defence mechanisms could be important for the lifespan-expanding effect of CR because ROS generated in mitochondria may promote ageing processes (15). That CR results in increased oxidative defence was already mentioned by MITCHELL et al. (2015) (28). Moreover, Igf1-dependent inhibition of daf-16 (an orthologue of Foxo) decreases lifespan in *C. elegans* and *D. melanogaster* (12; 29).

Thus, the CR-mediated inhibition of GH/Igf1 signalling is associated with increased autophagy, reduced plasma glucose, increased hepatic insulin sensitivity, increased resistance against oxidative stress, increased expression of antioxidant genes and reduced mTOR signalling (30; 12; 20). The effect on autophagy seems to be important for mediating CR's effects as well. CR is already associated with increased autophagy, whereas ageing is associated with a decline in this process (31; 32; 33; 22). Autophagy is necessary for eliminating damaged cell organelles and dysfunctional proteins and for mobilising energy reserves (22; 32). The first mentioned effects are important for cell health and function. MORSELLI et al. (2010) showed that Sirt1 is also necessary for the induction of autophagy by CR (32).

Sirtuins and NAD⁺ metabolism

As mentioned above, sirtuins (especially Sirt1) are important for mediating CR's effects in mammals, yeast and drosophila (34). Sirtuins are class III histone deacetylases that remove acetyl groups from lysine residues (34). These processes are dependent on NAD⁺ and are inhibited by nicotinamide (NAM), a side product of these reactions (34). NAD⁺ is derived de novo from L-tryptophan, nicotinic acid (NA) or NAM (35). NAD⁺ is important for energy production, DNA repair and genomic signalling (16). Sirtuins in general are involved in circadian rhythm, cell cycle regulation and other important metabolic processes (36).

There are seven sirtuins (Sirt1 – Sirt7), but Sirt1, Sirt3 and Sirt6 have been best studied in the context of CR (34; 37; 38). Studies indicate that Sirt1 overexpression induced by CR is responsible for the lifespan-expanding effect of CR, but some investigations also associate Sirt1 with ageing under certain circumstances (34). This indicates that the effects of sirtuins in mammals seem to depend on context, tissue and sirtuin type, so it is not possible to say that sirtuins are always involved in longevity (38).

CR may activate Sirt1 by increasing the NAD⁺ level and upregulating AMPK (38; 12). On the other hand, it is assumed that Sirt1 mediates its effects via AMPK (39). Sirt1 functions as a tumour suppressor protein, enhances mitochondrial biogenesis, increases the catabolism of triglycerides and cholesterol, promotes the repair of DNA damage, inhibits chronic inflammatory response, reduces apoptosis, downregulates hypoxia inducible factor 1-alpha (HIF-1 α) transcription factor, increases the expression of Sirt6 by forming a complex with Foxo3a and nuclear respiratory factor 1 (Nrf1), activates gluconeogenesis and fatty acid oxidation, inhibits glycolysis and is involved in regulating macroautophagy and mitophagy (38; 34). These functions can be explained by the many transcription factors targeted by Sirt1 that are involved in cell survival and metabolism. Best known are the tumour suppressor p53, Foxo, nuclear factor κ B (NF- κ B), HIF-1 α , nuclear factor erythroid 2-related factor 2 (Nrf2) and PGC-1 α (34).

For example, PGC-1 α is assumed to be important for the Sirt1-dependent regulation of glycolysis, gluconeogenesis and fatty acid oxidation (38). Moreover, PGC-1 α is involved in mitochondrial biogenesis by activating Nrf1, Nrf2 and transcription factor A, mitochondrial (TFAM). TFAM stimulates mitochondrial DNA replication and mitochondrial gene expression (34). The Sirt1-dependent effect on mitochondrial biogenesis seems to be important for mediating CR's effects (12). Mitochondrial activity depends on the ability to reduce DNA and oxidative damage, because the electron transport chain leads to enhanced production of ROS. That CR influences antioxidant defence mechanisms has already been mentioned above. An increase in mitochondrial biogenesis has already been seen for CR but some experiments have not been able to replicate this result (34; 40; 41).

The anti-inflammatory effect of Sirt1 is mediated by inhibiting tumour necrosis factor alpha (TNF- α) and NF- κ B, and the inhibition of lipogenesis and of the catabolism of triglycerides are mediated by the inhibiting of sterol regulatory element binding protein 1c's (Srebp1c's) actions as well as the activation of Foxo1 (38). The effect on apoptosis seems to be mediated via p53 and Ku70 protein (17).

Sirt3, Sirt4 and Sirt5 are located in the mitochondria and are involved in regulating ATP synthesis, the electron transport chain, mitochondrial biogenesis, apoptosis and ROS formation; stimulating the mitochondrial antioxidant defence system, gluconeogenesis and fatty acid oxidation; and inhibiting lipogenesis (38; 36; 37). Moreover, Sirt3 seems to be important for the phosphorylation of AMPK (36).

Sirt6 is involved in DNA repair mechanisms and is important for maintaining genomic stability. Moreover, Sirt6 acts as a tumour suppressor protein and induces apoptosis in cancer cells but not normal cells (42). Furthermore, Sirt6 has anti-inflammatory activity,

which is probably mediated by the inhibition of TNF- α (38). Sirt6 seems to inhibit Igf signalling as well by inhibiting c-Jun activity (43). Thus, Sirt6 could also be involved in the lifespan-expanding effect of CR. Sirt6 overexpression has been shown to increase the lifespans of male mice but not female mice (44). That CR increases Sirt6 levels has already been seen but some hints indicate that this is caused not by increased expression but through an enhanced stability of Sirt6 (38; 45).

AMPK and mTOR activity

As mentioned above, AMPK could be activated by Sirt1. However, CR also increases AMPK expression by influencing the AMP/ATP ratio, which results in deprived plasma glucose (12; 46). AMPK increases mitochondrial biogenesis, promotes insulin sensitivity and is involved in shifting energy production from glycolysis to, for example, fat oxidation (39; 46). Moreover, AMPK is able to activate PGC-1 α by phosphorylation independent of Sirt1 and to inhibit the mechanistic target of rapamycin (mTOR) signalling, which is seen for CR as well (33; 46; 34). Moreover, AMPK seems to promote the expression of small heterodimer protein (SHP) and decreases the expression of phosphoenolpyruvate carboxykinase (Pepck) and glucose 6-phosphatase (G6pc), which are involved in regulating gluconeogenesis and glycolysis (47). Moreover, AMPK is assumed to promote glucose transporter type 4 (Glut4) translocation to the plasma membrane, which increases the insulin-independent glucose uptake (48). AMPK activity is positively associated with lifespan (12; 49; 50; 51). However, CR in mammals is not associated with increased AMPK activity in any investigations, indicating that other regulatory factors (besides CR) are necessary (12).

mTOR is involved in regulating metabolism and cellular growth (33). Activated mTOR signalling inhibits autophagy and stimulates cell growth, cell proliferation and protein synthesis (12). The inhibition of mTOR by CR is associated with an increased lifespan in many organisms (e.g., mice), and dysregulation of this pathway is associated with age-related diseases like cancer and diabetes mellitus (52; 53). The CR-mediated inhibition of mTOR signalling may mediate its beneficial effects by modulating protein synthesis, autophagy and ribosomal biogenesis but the exact underlying mechanism is not clear. However, targeting mTOR complex 1 (mTORC1), S6k and eukaryotic translation initiation factor 4E-binding protein 1 (4E-bp1, a translational repressor) is necessary for these effects (33). Furthermore, Cai and Wei (2016) could demonstrate that RNA polymerase III-inhibiting protein Maf1 (Maf1) is involved in the lifespan-expanding effect of mTOR inhibition in yeast but not in *C. elegans* (52). Maf1 is a stress-responsive transcriptional factor that inhibits tRNA synthesis by binding to RNA polymerase III complex (52).

Glycolysis and gluconeogenesis

The previous explanations indicate that glucose metabolism is important for lifespan regulation. Investigations show that high glucose availability is associated with a decreased lifespan, whereas the inhibition of glycolysis by 2-deoxy-D-glucose, glucosamine or glycerol is associated with an increased lifespan in *C. elegans* (54; 55). Moreover, glycolysis in *C. elegans* is increased in aged organisms, whereas gluconeogenesis is decreased (56). Glycolysis could be involved in ageing processes by producing advanced glycosylation end-products (AGEs) and methylglyoxal (15). AGEs are associated with diabetes mellitus, brain ageing and Alzheimer's disease (15). Methylglyoxal is associated with ROS production, increased cellular peroxide concentration and enhanced oxidative damage (15). How CR influences glycolysis and gluconeogenesis is not fully understood, although it is known that AMPK, mTOR and Foxo1 are involved in this process (54; 56; 27). For example, Foxo increases the expression of gluconeogenic genes like G6pc and Pepck (57).

Detoxification system

As mentioned above, ageing is associated with increased damage of DNA and macromolecules. Therefore, ageing may lead to a reduction in detoxification capabilities (10). CR increases the expression of phase I and phase II enzymes, which could also be responsible for the age-preventing effects of CR (10). This is supported by the observation that the mRNA expression of these genes is decreased in the livers of aged mice (10). In contrast, long-lived Little mice (*Ghrhr^{lit/lit}*) showed upregulation in the genes of detoxification enzymes, and JIANG et al. (2013) showed that the expression of these genes is downregulated by GH/Igf1 signalling (58). This is another hint that the inhibition of GH/Igf1 signalling is important for the beneficial effects of CR.

Circadian clock

Furthermore, CR influences the expression of circadian clock genes. Period circadian clock 1 (*Per1*), *Per2* and cryptochrome 1 (*Cry1*) are upregulated in the hypothalamus under CR conditions (59). This is assumed to be important for lifespan, since *Per1* and *Per2* are tumour-suppressor genes (59). The reduction of the TNF- α signalling pathway triggered by CR may be responsible for the changes in clock genes' expression (59). Circadian clock disruption is associated with ageing, and CR is able to normalise and synchronise the circadian clock, which is probably responsible for the longevity effect (59).

1.2. Mimetics

The identification of these mechanisms could be useful to identify CR mimetics. This is necessary because it is very difficult for humans to reach lifelong CR. In addition to the

large availability of food which entices humans to eat, there are many side effects of CR. These are, for example a reduced satiety; higher sensitivity to cold; hypotension; reduced bone health; reduced libido; menstrual irregularities; infertility; reduced stamina and strength; slow wound healing; and psychological problems such as depression, emotional deadening and irritability (60; 25; 20; 47). Therefore, it is of interest to find substances which are able to mimic CR's effect on metabolism, stress response, healthy ageing and longevity without affecting calorie intake (47). Many substances have been analysed as potential CR mimetics, such as inhibitors of fat digestion (chitosan, orlistat and mannan-oligosaccharides), inhibitors of carbohydrate digestion (acarbose), inhibitors of glycolytic pathways (2-deoxy-d-glucose, glucosamine, 3-bromopyruvate, Iodoacetate and mannoheptulose), biguanides (phenformin, buformin, and metformin), polyamines (spermidine and thermospermine), thiazolidinediones, pegvisomant (which targets the GH receptor), sirtuin activators (resveratrol, nicotinamide and oxaloacetic acid), agmatine (a product of arginine decarboxylation), 17 β -estradiol, glycerol, ursolic acid and rapamycin (47; 54; 61; 62; 63). However, many of these substances have side effects such as digestive issues (indigestion, loose stools, excessive flatus and faecal incontinence), suppression of the immune system and toxicity in high dosages (47). Some of the potential CR mimetics are discussed in the following.

Glycerol

Glycerol increases lifespan, enhances mitochondrial activity, improves stress resistance and prevents the accumulation of protein aggregates (54). Moreover, glycerol decreases glycolysis and increases oxidative phosphorylation which indicates that glycerol could be a CR mimetic. However, in high dosages, glycerol shows toxic effects which are associated with a decreased lifespan. If further studies confirm that glycerol is a CR mimetic, determining the best dosage in humans will be quite important.

Glucosamine

Glucosamine is known to decrease glycolysis but to a much lesser extent than does 2-deoxy-d-glucose. Moreover, glucosamine administration increases lifespan in nematodes and mice (55). Furthermore, glucosamine is associated with a decrease in overall mortality in humans as well (64; 65). D-glucosamine is used in the treatment of osteoarthritis in humans and shows no side effects besides of occasional allergic reactions in contrast to 2-deoxy-d-glucose which is cardio-toxic and increases the occurrence of tumours (55; 12). WEIMER et al. (2014) could further show that glucosamine administration is associated with AMPK activation, which leads to increased mitochondrial biogenesis and enhanced mitochondrial respiration of fatty acids and amino acids. This is followed by an increase in ROS formation and in the expression of genes of the

stress defence system. Interestingly, in nematodes, ROS formation is an important requirement for the lifespan-expanding effect of glucosamine.

Rapamycin

Until now, only rapamycin, an inhibitor of the mTOR pathway, has seemed to be able to mimic CR's effects on longevity consistently in both genders (47; 53; 60; 66; 67). Rapamycin is known to inhibit mTOR, mTOR complex 1 and mTOR complex 2 (by chronic administration of rapamycin); this inhibition is associated with increased lifespan in yeast and mammals (25; 20; 18). Studies indicate that rapamycin is very effective in expanding lifespan but that it has many side effects. This means dysregulation of glucose and insulin homeostasis, cataracts and immunosuppression (18). Further investigation is necessary to determine the dose at which beneficial effects occur without side effects. Moreover, CR and rapamycin can prevent or reverse cardiac ageing (33). Rapamycin is normally used for immunosuppression and cancer treatment (18).

Metformin

Metformin is discussed as a potential CR mimetic as well. This biguanide is normally used in the treatment of type 2 diabetes (18; 68). Metformin decreases gluconeogenesis, increases fatty acid oxidation, enhances peripheral glucose uptake and suppresses glucose uptake in the gastrointestinal tract (47). How metformin mimics CR is not clear, but metformin is theorized to activate AMPK, which inhibits mTOR signalling (18; 20; 39). AMPK activation may be mediated by the metformin-induced inhibition of complex 1 of the respiratory chain, which leads to a decrease in ATP production and an increased AMP/ATP ratio (39; 69). On the other hand, metformin activates autophagy via Sirt1 independent of AMPK (69). Both CR and metformin increase mitophagy in *ob/ob* mice (69). This seems to be mediated by a reduction in endoplasmic reticulum stress markers and the expression of cytosolic p53.

To be a CR mimetic, metformin must also influence lifespan and the occurrence of age-related diseases. Metformin decreases all-cause mortality in diabetic and cardiovascular disease patients; enhances lifespan in worms and mice; and depresses the occurrence of cancer, cardiovascular disease and chronic kidney disease (47). However, no effect on longevity is seen in drosophila and rats, and the meta-analysis of BOUS-SAGEON et al. (2012) found that metformin had no beneficial effect on overall mortality (70; 47). These different results can be explained by the doses of metformin. For example, MARTIN-MONTALVO et al. (2013) showed that a high dosage (1% of diet) decreased survival and that a low dosage (0.1% of diet) led to increased lifespan and improved health (47; 68). Further studies are necessary to clarify whether metformin is

a CR mimetic and which minimum dosage is necessary to achieve the health-improving and lifespan-expanding effect.

Dietary plant bioactives such as resveratrol

Dietary plant bioactives may also be able to mimic CR's effect because various phytonutrients protect against age-related diseases (46; 71; 72). Dietary plant bioactives are components of fruits, vegetables, nuts, cereals and most foods which are made from herbal ingredients like juice, wine, coffee and chocolate (13). Some secondary plant bioactives are already mentioned in context of CR such as resveratrol (18; 73).

Resveratrol is present in mulberries, peanuts, grapes and red wine; it has been shown to extend lifespan in yeast, worms, flies, fish and mice (73; 74; 75; 76; 77; 78; 79; 46; 80). However, in mice, the results are contradictory because PEARSON et al. (2008) cannot find an effect on longevity among mice fed a normal diet – though several beneficial effects on health are seen (81). Other experiments show no effect on lifespan as well (82; 66; 73). However, resveratrol improves health in mammals, including a reduction in cardiovascular diseases, an improvement in bone health, a reduced cataract incidence and increased insulin sensitivity (78; 81; 46). The phenotypic and molecular effects of resveratrol seem to partially overlap with those seen in CR mice (78). Resveratrol is theorized to mediate its CR-mimicking effects via sirtuins by activating AMPK, but the exact underlying mechanism is still unclear (18; 11; 73). Moreover, resveratrol downregulates glycolysis and both IGF1 and mTOR signalling, and it upregulates Stat3 signalling, just as CR does (46). However, resveratrol and CR show different effects on cell-cycle regulation and apoptosis (46). Nonetheless, resveratrol induces gene expression changes similar to CR (73; 11).

These studies indicate that resveratrol is a potential CR mimetic. However, the differences in study design (e.g., in study size, dosage and application of resveratrol) could be responsible for the conflicting results. Therefore, further studies are necessary to investigate toxicity, dose, bioavailability and the underlying mechanism (18). Other phytonutrients such as epicatechin, epigallocatechin, quercetin, curcumin and Korean mistletoe extract have also been discussed in the context of longevity and beneficial health effects (13; 83; 84). However, it is not known yet if these substances are CR mimetics.

1.3. Identification of CR mimetics

To identify CR mimetics, *in vivo* experiments could be used to investigate lifespan and metabolic changes. Gene expression analysis could also be useful because gene expression influences proteomes and metabolomes. Moreover, many genes are associated with increased or decreased lifespan (as mentioned by the GenAge database, <http://genomics.senescence.info/genes/> (85)), and CR reverses many of the mRNA

changes triggered by ageing (10). Some of the genes which are influenced by CR (e.g., sirtuins) are already mentioned above. Other genes, such as Indy (an acronym for 'I am Not Dead, Yet', a homolog in mice: mIndy, Slc13A5), have been little studied but are promising. Downregulation of Indy promotes longevity in *Drosophila* and *C. elegans* via mechanisms similar to those in CR (e.g., increasing AMPK activity) (39; 86). Indy encodes for a transporter of citrate-cycle intermediates such as citrate, pyruvate and α -ketoglutarate (86). Although genetic regulation of metabolism is not completely understood, gene expression analysis could be very useful in identifying potential CR mimetics, and their impact on lifespan and health can be further investigated *in vivo*.

1.3.1. Methods for identification of relevant biological functions addressed by the differently expressed genes (enrichment tools)

Methods are available which allow investigating the expression changes of few genes in one experiment (e.g., real-time PCR). However, for this it is necessary to know which genes are influenced by CR and which ones are important for mediating the beneficial CR effects. It can be assumed that not all of the relevant genes have been identified. Thus, methods are necessary which allow for the genome-wide investigation of gene regulation to identify novel and important CR genes and to compare expression changes triggered by several interventions. High-throughput genomic, proteomic and bioinformatics scanning approaches (e.g., expression microarray, promoter microarray, proteomics, and ChIP-on-CHIPs) could be used for this (87). However, a problem with these methods is that they could provide lists of up to 1000 differently regulated genes, which would make it difficult to interpret the results. Many bioinformatics methods (e.g., Gene Ontology (GO) (88), Database for Annotation, Visualisation and Integrated Discovery (DAVID) (89), ConsensusPathDB (CPDB; <http://cpdb.molgen.mpg.de>) (92; 93), GSEA version 2.0.10 (<http://www.broadinstitute.org/gsea/downloads.jsp>) (90), BiNGO (<http://www.psb.ugent.be/cbd/papers/BiNGO/Home.html>) (91) and PANTHER (www.pantherdb.org/) (94)) have been developed to facilitate the identification of relevant and over-represented biological functions in the organism (87). Many more enrichment tools are available (reviewed by HUANG et al. (2009)), and the number may continuously increase in coming years (87).

Although these tools have made a major contribution to gene functional analysis, all tools are in the improving stage, and no method is the universal standard in analysis. Thus, it is very difficult for investigators to decide which tool is the most suitable for their analytic needs. Moreover, comparisons between the tools indicate that the provided results could be different. Therefore, users are advised to try different tools (87).

To decide which method is best, it is necessary to identify the aim of enrichment analysis. This requires identifying a group of genes which belong to a certain biological function and which are over-represented in a list of genes (87). Therefore, the interpretation of the results switched from a gene-oriented view to a relevant-gene group-based view. This will identify the most influenced biological functions of the differently regulated genes. For this analysis, three different classes of enrichment tools (which differ in their statistical methods) are available. These are singular enrichment analysis (SEA), gene set enrichment analysis (GSEA) and modular enrichment analysis (MEA) (87). They are explained in detail by HUANG et al. (2009). In SEA, a preselected list of genes (normally determined by p-value or fold change) is investigated. The results are sorted by enrichment p-value (determined by different statistical methods depending on if the genes are over-represented in the investigated gene pool or if there is a random hit). Therefore, SEA can be used to extract the major biological meaning for a list of differently expressed genes. However, one disadvantage of this method is that these tools can provide a large list of interesting biological functions which make it difficult to interpret the results and determine the function of interest. Moreover, it is possible that a biological function is mentioned several times under different terms. Finally, the results strongly depend on the quality of the preselected genes; it is possible that different statistical methods (e.g., a chi-squared test or Fischer test) might obtain a different list of interesting biological functions (87).

GSEA contains the idea of SEA, but the algorithm it uses to calculate enrichment p-value is different. Another modification is that all genes from the microarray experiment are included in the analysis, which means that genes with small expression change are considered. These genes are often ignored in SEA. This will allow an interpretation which is nearer to natural biological circumstances because small expression changes can result in large biological consequences. However, GSEA tools have some disadvantages, too. For example, a summarised biological value (e.g., fold change) for each of the investigated genes is necessary for analysis. This can be a problem when the biological study or the genomic platform is too complex. For example, an array could include several single-nucleoid polymorphisms (SNPs) of a gene with different expression changes and p-values. Another disadvantage is that it is not possible with GSEA to simultaneously investigate multiple factors in a study. Furthermore, the revealed biological functions with the highest p-value include the genes with the greatest expression change. As mentioned above, these genes cannot be assumed to be the most important ones (87).

MEA tools include SEA's basic enrichment calculations but consider the interrelationships of GO terms. This means that terms which address the same biological function

are summarised in one term. This could reveal the biological meaning of a gene list, which is closer to the true nature of the biology. However, a disadvantage of MEA is that terms or genes without strong relationships to other terms or genes could get lost (87).

The explanations above indicate that the choice of the enrichment tool can influence the results of an analysis. However, other factors influence the results of an investigation. One is the analyst. He or she determines the interesting biological functions based on his or her biological knowledge and excludes annotations with high p-values when they do not make sense based on the user's question. Another important fact that should be considered is that a high number of analysed annotations linearly increases the rate of false-positive results. To reduce this, performing multiple test corrections of enrichment p-values is recommended. Examples are Bonferroni, Benjamini-Hochberg, Holm and q-value (87). Moreover, the selection of the background has a big impact on the results because the list of interesting genes is compared with this background. Thus, it is a great benefit when a tool allows an individual background to be uploaded rather than only choosing from preselected ones. Furthermore, no tool provides all the biological aspects which can be obtained from different databases, but some tools (e.g., DAVID and CPDB) do include several of these databases. Examples are the GO (95) database, which provides information about biological processes, molecular functions and cellular components; the BIND (96) database, which provides information about protein-protein interactions; the KEGG (97) and REACTOME (98) databases, which provide information about pathways; the TRANSFAC (99) and JASPAR (100) databases, which give information about gene regulation (e.g., transcription factor binding sites (TFBs)); and the OMIM (101) database, which is used to obtain gene-disease associations. Other databases are not mentioned here (87).

Moreover, it is necessary that all genes are clearly mapped to a gene identifier. If this is not possible, the analysis is strongly impaired. Several identifiers could be available in the analyst's present gene list. Examples are the Affymetrix array identifiers (102), NCBI Entrez gene (103), UniProt (104) and PIR-NREF (105). The interconversion could be necessary when the enrichment tool does not support the present identifier. This conversion could be a great challenge because the ID which belongs to another ID is not always clear. Many tools should facilitate this interconversion (IDconverter (106), Synergizer [<http://lama.mshri.on.ca/synergizer/doc/>] (108) and DAVID ID converter (107)). However, it is possible that some of the IDs cannot be converted (87).

Another fact which influences the results is that not all of the gene interactions and physiological mechanisms have been revealed. This means that repeating the analysis

of a gene list a few years later can lead to completely different results based on the newly discovered interactions. However, gene expression analysis could be a useful tool to identify relevant biological functions in the organism.

1.3.2. Advantage of *in silico* analysis for identifying CR mimetics

Regarding the number of potential substances which can act as CR mimetics, their investigation could last decades because *in vivo* studies, which must be conducted for gene expression analysis, have a high duration (as they are highly dependent on the life expectancy of the analysed animal model), and only a few substances can be analysed at the same time in one experiment. To accelerate the process of identifying potential CR mimetics, an *in silico* analysis could be useful. This approach allows for the analysis of many substances at the same time and for the use of data from previously conducted experiments – regardless of whether they are examined in a CR context. FORTNEY et al. (2012) give an example by searching for potential CR mimetics in *in silico* (109).

Databases such as ArrayExpress (<http://www.ebi.ac.uk/ArrayExpress/>) and Gene Expression Omnibus (GEO; <http://www.ncbi.nlm.nih.gov/geo/>) can be used to identify relevant experiments (110; 111; 112). One challenge of *in silico* analysis is that the results of several experiments which investigate the influence of the same substance or intervention need to be summarised to get one biological value (e.g., fold change) for a gene. A requirement for this is that the genes are represented by the same identifier. Several statistical methods are available to obtain significantly expressed genes or fold changes. An example is the RankProd R package, which reveals fold changes and p-values for the genes over many experiments (113). The genes which are significantly expressed in the different interventions can be compared to identify an overlap in gene expression. Furthermore, they can be analysed using different enrichment tools to investigate if the substances address the same biological functions as CR.

1.4. Aim of the present analysis

Our work should provide a new approach which allows for faster identification of potential CR mimetics; these potential mimetics should subsequently be investigated *in vivo* to confirm their desired positive effect on ageing, health and lifespan. This analysis is limited to phytonutrients because they may show fewer side effects than pharmaceuticals. Moreover, there are hints that a diet rich in fruits, vegetables and whole grains (such as the Mediterranean diet) – in other words, a diet rich in phytochemicals – is associated with a healthier life (114; 115). Therefore, whether phytonutrients other than resveratrol can mimic CR is of great interest. To our knowledge no *in silico* analysis has investigated the role of dietary plant bioactives as CR mimetics. Therefore, it is our interest to

examine a potential transcriptional overlap between CR and different phytonutrients. In our analysis, an overlap refers to genes which are regulated in the same direction by both interventions (CR and the respective phytonutrient).

In the present thesis a few tools are tried, but it is decided at last to pre-process the raw data with different R packages, to unify the Entrez IDs (based on the annotation information mentioned for the different chips), to consistently identify up- and downregulated genes with the RankProd package and to carry out the enrichment analysis with CPDB. Supplementary information is obtained from NCBI: gene (116). The results could be used to identify new functions of CR and to compare the overlap in gene expression or function between CR and the respective dietary plant bioactive. This indicates whether a phytonutrient could be a mimetic for CR or if the dietary plant bioactive mimics at least one function.

2. Methods

To identify an overlapped gene expression between CR and a phytonutrient, only public data are used, and none of our own experiments are performed. Figure 2 summarises the methods used, which are then further explained in the following sections.

2.1. Public data collection

The databases ArrayExpress (<http://www.ebi.ac.uk/ArrayExpress/>) and GEO (<http://www.ncbi.nlm.nih.gov/geo/>) are used to find gene expression data for experiments which investigate the influence of dietary plant bioactives or CR in murine liver (112; 111; 110). The search items are 'hepatic' or 'liver' in combination with 'diet', 'food', 'dietary', 'caloric', 'calorie' and 'treatment'. The organism *Mus musculus* is used.

The descriptions of all mentioned studies are analysed to identify relevant experiments. The selection criteria are that the experiments must have a control and at least one intervention group and that the intervention and collection of RNA probes must be in the same generation. All experiments in which the plant bioactives are administered by food, intraperitoneally or intravenously are included, but the types of administration are analysed separately. Furthermore, the raw experiment data must be available. If they are not public, the authors are asking for this data.

2.2. Pre-processing of raw data and standardisation of array information

Before performing enrichment analysis, the raw data must be pre-processed (background correction, normalisation, etc.). In the selected experiments, different arrays are used for examining gene expression changes, so different pre-processing methods are necessary. For a better comparison between the arrays, all are quantile normalised with the corresponding Bioconductor packages in R. For Affymetrix arrays, the 'affy'

and 'oligo' packages are used (117; 118). 'Affy' contains the 'rma' function (robust multi-array average), which includes all pre-processing steps (119; 120; 121), such as background correction, quantile normalisation and summarisation. The 'oligo' package is specially designed for the Affymetrix Mouse Gene 1.0 ST array, so this is used instead of 'affy' for experiments using this array (118). The 'oligo' package contains the 'rma' function, too. The annotation information of the Affymetrix arrays is available in different R packages, which are provided by Bioconductor.

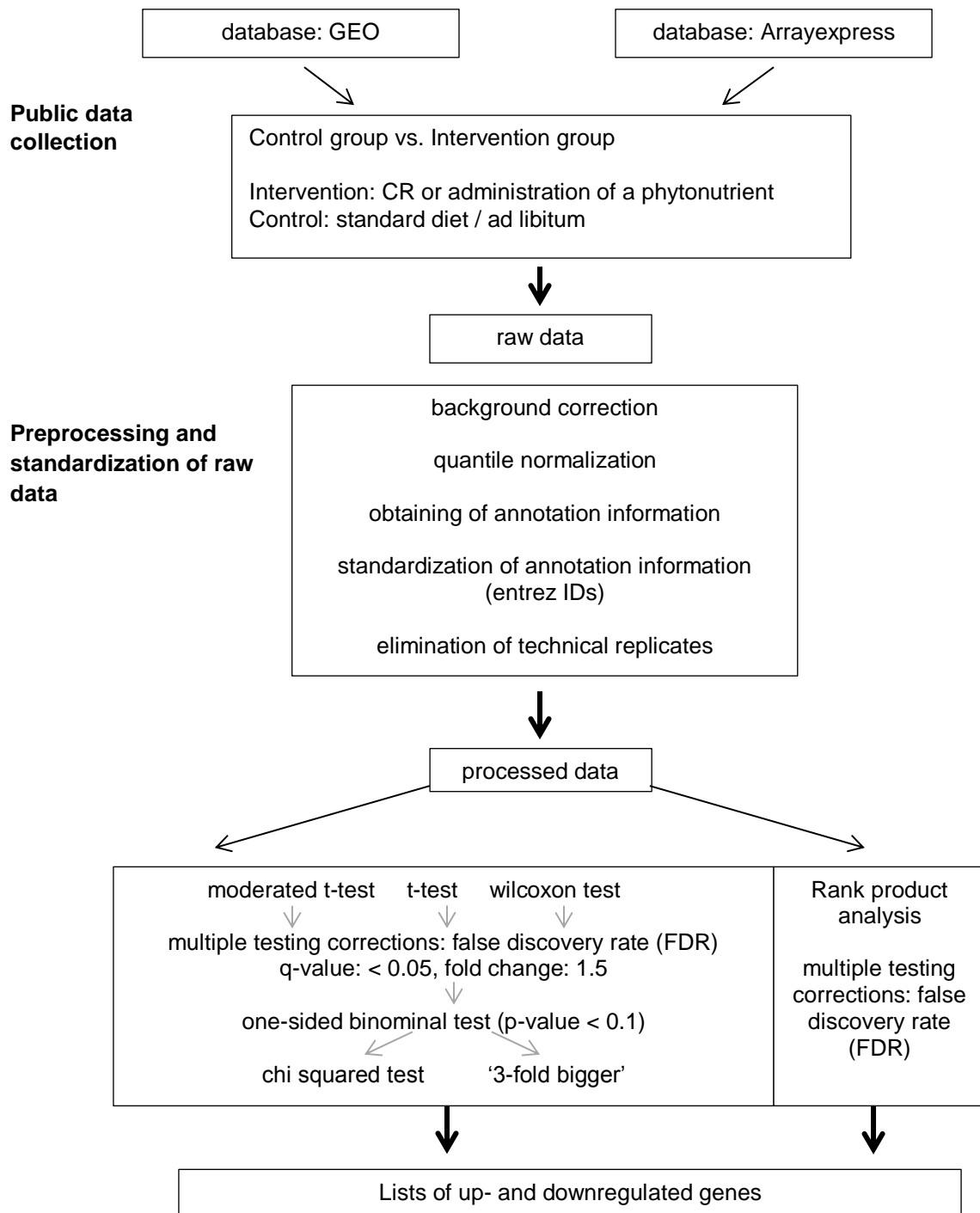


Figure 2: Data collection, preprocessing, standardization and analysis methods

Illumina's beadarrays does not work with 'affy' or 'oligo', so the 'lumi' package is used instead (122; 123; 124; 125). First, the data are background-corrected using the 'bgAdjust.affy' method. Then, the data are log₂-transformed and quantile normalised. The annotation information is downloaded directly from the Illumina website (<http://www.Illumina.com/>) (126). For the Agilent array the 'limma' package is used (127). Before quantile normalisation the data are background-corrected using the 'normexp' method (128; 129). The array annotation information is downloaded together with the raw data.

Before the pre-processed data can be analysed, more steps are necessary. First, all genes must be coded with the same ID system. The Entrez IDs are used because the gene names have changed often in the past. There are many synonyms, so the assignment is not always clear. In some cases, only an array's gene name is mentioned. To get the corresponding Entrez ID, the online tools Synergizer (108), NCBI:gene (116) and Ensembl mouse (http://www.ensembl.org/Mus_musculus/Info/Index) (130) are used. If no Entrez ID is revealed, the array ID is used instead. Finally, the technical replicates for one gene in one biological replicate are summarised by calculating the mean values with Excel.

2.3. Identification of significantly regulated genes observable over all data sets

To identify the genes which are up- and downregulated across all studies, four different methods are used: the t-test and moderated t-test of the limma R package and the Wilcoxon test and rank product analysis of the RankProd R package (113). The rank-product method ranks all genes by the expression levels of all experiments at the same time. Therefore, genes are identified which are probably up- or downregulated over all studies. A p-value is calculated, and, as a multiple-testing correction method, a false discovery rate (FDR, $q < 0.05$) is used.

The t-test is the standard method in gene expression analysis, so the t-test is calculated in Excel; FDR is used as a multiple-testing correction method (cut-off value = 0.05). The moderated t-test is calculated with the 'limma' R package. The moderated t-test differs from the normal t-test in that it moderates the standard errors across the genes using a simple Bayesian model (131). The p-value is also corrected using FDR (cut-off value = 0.05). One contribution of the t-test or moderated t-test is that the data are normally distributed. However, the box plots of the different experiments show that the data are skewed to the left; thus, the t-test should not be used. The Wilcoxon test seems to be the right method to analyse gene expression changes. The results are corrected using FDR as well (cut-off value = 0.05). All three methods are then combined with a fold change ≥ 1.5 .

While the rank product analysis works with all experiments at the same time, the t-test, moderated t-test and Wilcoxon test must be calculated separately for each intervention design. To get a list of up- and downregulated genes, further steps are necessary. First, a one-sided binominal-test is calculated to see if the change in gene regulation is real or random over all experiments ($p < 0.1$). The multiple-testing corrections are omitted because the data have been previously corrected often. Next, two further methods are used to see whether the levels of up- and downregulation differ significantly. The first is a chi-squared test, which is the standard test to identify the significant differences; however, this test does not work with a small number of experiments. Therefore, another method called '3-fold bigger' is also used. This means that if the number of studies which show the same regulation rate is 3-fold bigger than the number of studies which show the opposite regulation rate, the gene is mentioned in the list of regulated genes.

2.4. Functional Analysis

Afterwards, the functions of the significantly regulated genes are analysed to identify the potential mechanisms which are targeted by CR and the respective phytonutrient. First, the over-represented pathways are identified, then the most strongly regulated CR genes are investigated in terms of their function and their expression by the phytonutrients, and finally, the expression regulation of known longevity genes by CR and the phytonutrients is analysed.

2.4.1. Overrepresented pathways

For pathway analysis, the online tool ConsensusPathDB (CPDB, <http://cpdb.molgen.mpg.de/MCPDB>; MM9 release 11.10.2013) is used (92; 93). CPDB uses data from 16 different public resources (e.g., Reactome, KEGG or MouseCyc) and contains interactions curated from the literature. An over-representation analysis is done to identify pathways which are influenced by both CR and dietary plant bioactives. Inclusion criteria are $q < 0.05$ (multiple-testing p-value corrected with FDR) and at least 2 genes involved in the mentioned pathway.

At first, only the significantly regulated CR genes are analysed to identify unknown CR functions. Then, CR and the respective dietary plant bioactive are examined together. The investigated genes in the different interventions are dependent on the array used, so a gene's expression changes are not necessarily analysed by both the CR and the respective phytonutrient expressions. Therefore, only the genes which are investigated for all interventions are included in the gene pool (see Table 1). The rank product analysis is repeated for these reduced lists. To identify co-mentioned functions, two different approaches are applied (Table 1). First, all significantly regulated genes of CR and

the dietary plant bioactives are analysed separately, and the co-mentioned pathways are discovered (Table 1, separate analysis). Second, only the genes overlapping between CR and the respective dietary plant bioactive are analysed (Table 1, overlapped analysis). All pathway resources mentioned by CPDB are included (KEGG, Reactome, MouseCyc and Wikipathways).

Table 1: Overview of the approaches used in the functional analysis

gene pools (compare Figure 2)	I. all genes which are investigated by CR (bgCR) II. genes investigated by CR and R (bgR) III. genes investigated by CR and P (bgP) IV. genes investigated by CR and Qd (bgQd) V. genes investigated by CR and Qi (bgQi) VI. genes investigated by CR and Gi (bgGi)
identification of CR functions	significantly regulated genes by CR are calculated for each gene pool with rank product analysis. CR functions are identified with ConsensusPathDB a) Regulated CR genes with bgCR b) Regulated CR genes with bgR c) Regulated CR genes with bgP d) Regulated CR genes with bgQd e) Regulated CR genes with bgQi f) Regulated CR genes with bgGi g) Regulated genes which are identified in a-f, bgCR

Identification of pathways that are affected by both, the CR and the respective plant bioactive treatments

separate analysis	- all significantly regulated CR genes (gene pool: I-VI or gene pool: II-VI) - all significantly regulated R genes - all significantly regulated P genes - all significantly regulated Qd genes - all significantly regulated Qi genes - all significantly regulated Gi genes	→	overlapped pathways between CR and the respective phytonutrient are identified
overlapped analysis	- overlapped genes between CR and R; bgR - overlapped genes between CR and P, bgP - overlapped genes between CR and Q, bgQd - overlapped genes between CR and Qi, bgQi - overlapped genes between CR and Gi, bgGi		

CR= caloric restriction, R = Resveratrol, P = phloridzin, Qd=quercetin administered by diet, Qi = quercetin administered intraperitoneal, Gi= genistein administered intraperitoneal

2.4.2. Functions of the most strongly regulated CR genes identified by fold change or q-value

Next, to reduce the list of interesting CR pathways, the over-representation analysis is repeated for the CR genes with a fold change ≥ 1.5 . Moreover, PubMed reveals the functions of these genes, and Multiple Experiment Viewer (MeV 4.9.0, <https://sourceforge.net/projects/mev-tm4/files/mev-tm4/MeV%204.9.0/>) identifies and illustrates the overlap in gene expression between CR and the phytonutrients.

Next, the top 50 overlapped genes are identified by q-value for the different interventions. Genes or IDs with unknown functions are excluded. The functions of these genes are revealed using NCBI:gene.

2.4.3. Functions of the genes which are investigated for CR and all dietary phytonutrients

As mentioned above, not all genes are investigated for each phytonutrient. This impedes the identification of the best CR mimetic in our analysis. Therefore, it is decided to repeat the rank product analysis for the investigated genes using all dietary interventions. The phytonutrients administered intraperitoneally are excluded from this analysis.

Next, the overlap in gene expression is determined. Then, the Pearson correlation between the expression changes (mediated by CR) and the phytonutrients is calculated for all genes which are included in the respective CR pathways. The CR pathways are identified using CPDB. This means that all pathways for which at least one of the strongly regulated CR genes ($FC \geq 1.5$) is involved are included, independent of p- or q-value.

2.5. Investigation of genes with special regard for longevity

For a better assessment of whether a phytonutrient is able to mimic the lifespan-expanding effect of CR, it is analysed if the phytonutrients address the same longevity genes as CR. To identify genes associated with longevity, the GenAge database is used (<http://genomics.senescence.info/genes/>) (85). All longevity genes which are regulated by CR in our analysis are discovered. Afterwards, the resulting list is compared with the expression changes triggered by the phytonutrients. A high number of overlapped genes probably indicates a mimicking effect on longevity.

2.6. Analysis of transcription factor binding sites

Finally, it is analysed whether CR and the phytonutrients address the same TFBs. Several methods are investigated, but most are excluded because they are not suitable. The online tool oPOSSUM 3.0 (<http://opossum.cisreg.ca/oPOSSUM3/>) is selected because it is able to identify over-represented TFBs for a list of genes (132; 133). OPOSSUM uses the JASPAR database (100). First, using single site analysis, all significantly regulated CR genes are uploaded to determine TFBs which are over-represented either in the upregulated genes or in the downregulated genes. Afterwards, the genes overlapping between CR and the phytonutrients are uploaded, and the co-mentioned TFBs are identified. For mice, the results contain the JASPAR collections CORE and PBM. The results can be sorted by z-score or Fischer (F)-score. The z-score compares the rate of a TFB's occurrence in the list of target genes to the expected rate, which is estimated from the background gene list. The F-score (based on one-tailed Fisher exact probability) compares the proportion of co-expressed genes containing a particular TFB to the proportion of the background set that contains the site. For further explanation, see oPOSSUM help (<http://opossum.cisreg.ca/oPOSSUM3/help.html>). In our analysis, all TFBs with either z

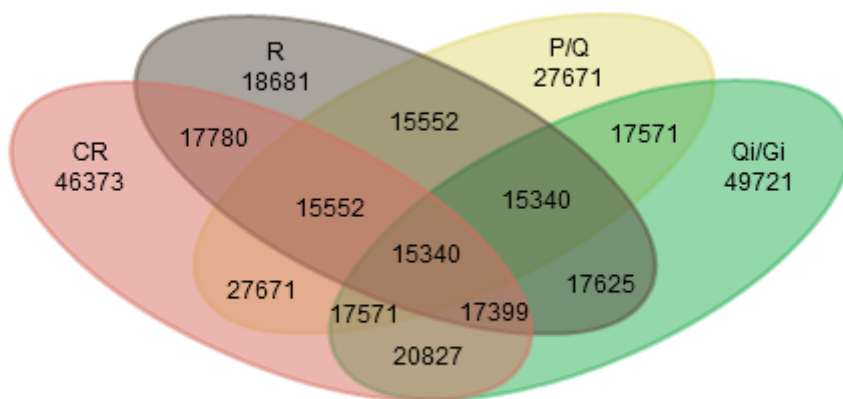
> 5 or $F > 5$ are included. The functions of the transcription factors (TF) belonging to the revealed TFBs are identified with the UniProt database (104).

3. Results

3.1. Public Data Collection

As of November 2014, a total of 717 experiments had been mentioned on ArrayExpress along with 174 datasets or 1679 series on GEO using the search items. After reviewing the experiment designs, nine CR and five dietary plant bioactives experiments are included in the analysis (Tables 2 and 3).

As seen in Tables 2 and 3, CR's effect and the phytonutrient treatments on gene expression are analysed with different microarrays. This means that many genes are not analysed by all treatments (Figure 3). For example, the effect of CR is analysed for 46373 Entrez IDs whereas the effect of R is analysed for 18681 Entrez IDs; 17780 IDs are analysed by both interventions. Due to the fact that the p-value and q-value calculations are based on the total number of genes in the gene pool, it is decided to perform the rank product analysis with limited gene pools (see Table 1).



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Figure 3: Venn diagram of the shared gene pool between CR and the dietary plant bioactives (CR = caloric restriction; R = resveratrol; P/Q = phloridzin/quercetin; Qi/Gi = quercetin/genistein administered intraperitoneal)

Figures 4 and 5 indicate that the number of regulated CR genes strongly depends on the used gene pool. Only 285 upregulated and 338 downregulated genes are identified with each gene pool. This is probably based on the large CR gene pool (bgCR) because over 50% of these genes are not analysed by the phytonutrients. Excluding bgCR, 812 upregulated genes and 1106 downregulated genes are identified within each gene pool.

Table 2: Overview of the characteristics of the analyzed caloric restriction studies

	Mouse strain	sex	start age	n	Standard diet	Intervention	duration	Array
CR1 (134)	C57BL6/J 129S1/SvImJ C3H/HeJ CBA/J DBA/2J B6C3F1/J	male	8 wk	n=8	AIN93M 10,2 % fat	25 % Caloric restriction C: 12,7 kcal/day (88.9 kcal/wk) CR: 9,44 kcal/day (66 kcal/wk) Strains (129S1/SvImJ and C57BL6/J), food intake was subsequently decreased to 7.34 kcal/day at 16 weeks of age	14 wks	Affymetrix Mouse Genome 430 2.0 Array
CR2 (135)	B6C57/J	male	27 wk	n=5	AIN-93G 16,4% Fat	Lifelong 40 % Caloric restriction Control: 13,3 kcal per day (93,1 kcal/wk)	to age: 1 year	Illumina MouseRef-8 v2.0 expression beadchip
CR3 (136)	C57Bl/6J	male	8 wk	C n=3 CR n=4	2916 global diet (Harlan) 12 % Fat	40 % Caloric restriction	2 wk	Illumina MouseRef-8 v2.0 expression beadchip
CR4 (137)	C57BL/6J	male	5 wks	n=3	D12450B, Re-search Diets 10% fat	adaption phase: 1 wk 30% calorie restriction	57 wks	Affymetrix Mouse Genome 430 2.0 Array
CR5 (138)	C57BL/6J	female	15-16 month	n=3	standard chow diet (5053 PicoLab Diet) 13,2 % Fat	ad libitum (106 kcal /wk) vs. Caloric Restriction (80 kcal /wk for 2 weeks, followed by 53 kcal/d for 2 weeks)	4 wk	Affymetrix Mouse Gene 1.0 ST Array [transcript (gene) version]
CR6 (139)	long-lived B6C3F1	male	CRL: 5 mo CRS: 20 mo	n=4	AIN-93M 10,2 % fat	C: 93 kcal/wk or 13,3 kcal/day ad libitum CRS: 77 kcal/wk of CR diet for 2 wk, followed by 52.2 kcal/wk of CR diet for 6 wk.) CRL: 52,2 kcal/wk or 7,5 kcal/d	CRS: 8 wk CRL: 25 mo	Affymetrix Murine Genome U74A Version 2 Array
CR7 (140)	normal mouse (+/+ or +/df)	female	2 mo	C n=7 CR n=8	LabDiet, PMI Feeds, Inc., St Louis, MO	1 wk 10 % CR, than 1 wk 20 % CR, for the remaining time 30 % CR	4 mo	Affymetrix Murine Genome U74A Version 2 Array
CR8 (141)	C57BL/6	male	16 wk	n=12 pooled to 4 groups	2018 Global Rodent diet, Harlan Teklad, U.K. 18% fat	Ad libitum vs. 30 % caloric Restriction	48 h	Affymetrix Mouse Genome 430 2.0 Array
CR9 (142)	C57BL6/J	male	2 mo	n=11	LabDiet 5LG6-JL 12,2% Fat	Ad libitum vs. 40% Caloric Restriction	6 mo	Illumina MouseRef-8 v2.0 expression beadchip

CR = caloric restriction, C = Control, wk = week

Table 3: Overview of the characteristics of the plant bioactive studies

	Mouse strain	sex	age at start	n	Standard diet	Intervention	duration	Array
Q1 (143)	C57BL/6	male	6-8 wk	n = 9 pooled in 3 groups	RM3 (E) 801710 Soya-free powdered diet from B.S & S; no further information	Quercetin was added separately to the semi-purified diets at a concentration of 6200 ppm (0.62 %; 6.2 g per kg)	adaption phase 2 wks, 4 h food with quercetin	Affymetrix Mouse Expression 430A Array
Q2 (144)	BALB/c	male	6 wk	n = 6	AIN-93G diet fat: 16,4 % (kcal/g)	approximately 7 mg/mouse diet containing 0 % (C), 0,1 %, 0,5 %, or 1,0 % quercetin, ad libitum	2 wk	Affymetrix Mouse Genome 430 2.0 Array
Q3 (145)	n.m.	male	n.m.	n = 2	_____	Quercetin: intraperitoneal (ip) injection in DMSO with 0 mg/kg (C), 500 mg/kg, 1500 mg/kg or 2000 mg/kg	24 h after administration	Agilent Mouse 60K Genotypic Designed Array
G (145)						Genistein: intraperitoneal (ip) injection in DMSO with 0 mg/kg (C), 500 mg/kg, 1500 mg/kg or 2000 mg/kg		
R (146)	C57BL/6NIA	male	11 mo	C18 n = 4 C27 n = 3 LR n = 5 HR n = 4	AIN-93G diet fat: 16,4 % (kcal/g)	low res (LR): 0.01% resveratrol high res (HR): 0.04% resveratrol	adaption phase 1 mo 7 (C18) or 16 mo	Illumina mouseRef-8 v1.1 expression beadchip
P (147)	BALB/c	male	6 wk	n = 6 p.g.	AIN-93G diet fat: 16,4 % (kcal/g)	diet containing 0 % (C), 0.1 %, 0.5 %, or 1.0 % phloridzin (purity > 97%)	2 wk	Affymetrix Mouse Genome 430 2.0 Array

Q=quercetin, G= genistein, R = Resveratrol, P = phloridzin, C = control, wk = week, n.m. = not mentioned, mo = month

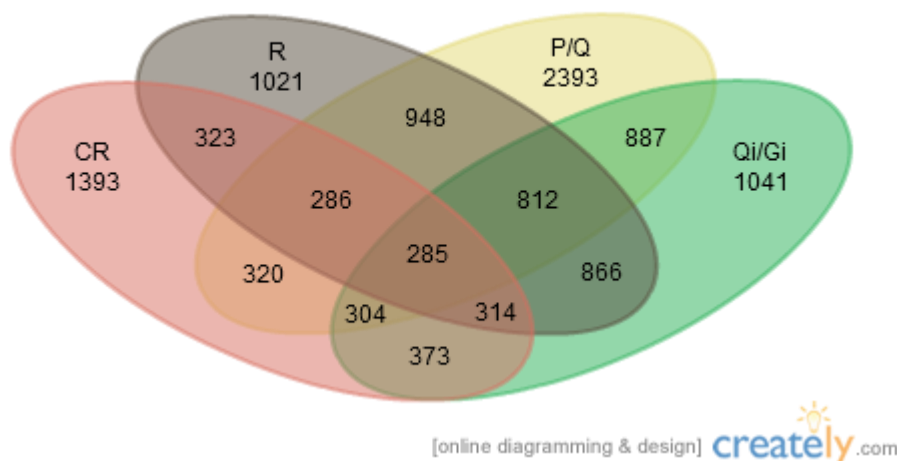


Figure 4: Venn diagram of the upregulated CR genes identified from rank product analysis with the different gene pools
 (CR = bgCR; R = bgR; P/Q = bgP and bgQd; Qi/Gi = bgQi and bgGi)

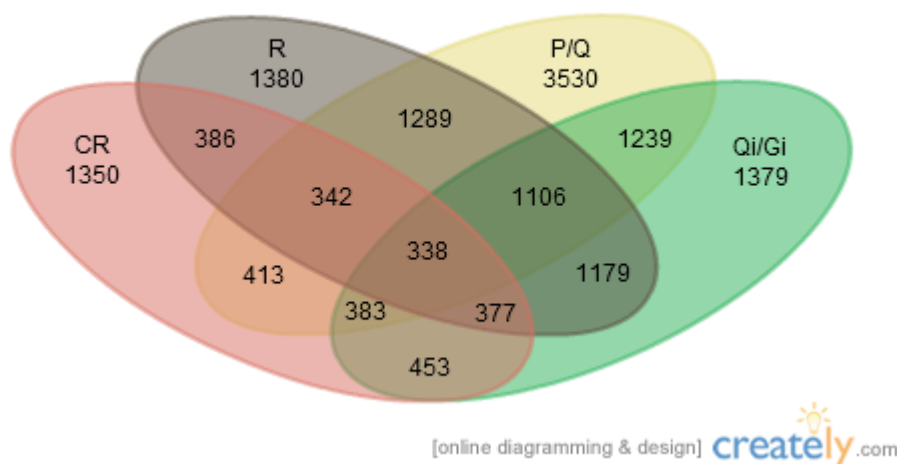


Figure 5: Venn diagram for the downregulated CR genes identified from rank product analysis with the different gene pools
 (CR = bgCR; R = bgR; P/Q = bgP and bgQd; Qi/Gi = bgQi and bgGi)

3.2. Comparison of analysis methods used to identify significantly regulated genes/Finding the appropriate p-value test

The number of differently expressed genes varies between the analysis methods used (Table 4; for detailed information, see Appendix A), whereby the rank product analysis shows a larger number than the t-test, the moderated t-test or the Wilcoxon test. The moderated t-test shows more regulated genes than the normal t-test. The Wilcoxon test shows a significant regulation in response to CR but not to the phytonutrient treatments. A combination of the three tests with a fold change ≥ 1.5 additionally reduces the number of regulated genes. No significant up- or downregulation was detected for the phytonutrient treatments when the chi-squared test was applied. This may be explained by the limited number of repetitions per phytonutrient (three to five single experiments, which is too small for the chi-squared test). Therefore, the chi-squared test

was replaced by the 3-fold bigger method, which modestly increased the number of significantly regulated genes.

Table 4: Number of genes that are regulated by caloric restriction or dietary plant bioactives (different analysis methods)

	chi-squared-test ¹	t-test	t-test + FC	moderated t-test	moderated t-test + FC	Wilcoxon test	Wilcoxon test + FC	rank prod	rank prod + FC
upregulated genes									
CR	yes	26	0	79	1	49	0	3503 ²	464 ²
	no	347	3	571	7	331	0		
R	yes	0	0	0	0	0	0	1304 ³	318 ³
	no	53	10	553	34	0	0		
Qd	yes	0	0	0	0	0	0	826 ³	29 ³
	no	0	0	0	0	0	0		
P	yes	0	0	0	0	0	0	1789 ³	13 ³
	no	277	0	901	0	0	0		
Gi	yes	0	0	0	0	0	0	559 ³	292 ³
	no	0	0	498	3	0	0		
Qi	yes	0	0	0	0	0	0	866 ³	564 ³
	no	0	0	2487	4	0	0		
downregulated genes									
CR	yes	54	0	81	0	64	0	4479 ²	608 ²
	no	460	1	577	2	366	1		
R	yes	0	0	0	0	0	0	1080 ³	228 ³
	no	48	2	530	7	0	0		
Qd	yes	0	0	0	0	0	0	899 ³	4 ³
	no	0	0	0	0	0	0		
P	yes	0	0	0	0	0	0	2922 ³	30 ³
	no	416	0	951	0	0	0		
Gi	yes	0	0	0	0	0	0	917 ³	872 ³
	no	0	0	440	11	0	0		
Qi	yes	0	0	0	0	0	0	1498 ³	1495 ³
	no	0	0	2451	13	0	0		

¹ no chi-squared test means that the '3-fold bigger' method is used; both methods are not used in rank prod analysis

² this number include all Entrez IDs which are significantly up- and downregulated by at least on approach based on the gene pools shown in Table 1

³ results are obtained from rank product analysis with the limited gene pools (Table 1)

FC = fold change, rank prod = rank product method, CR= caloric restriction, R = resveratrol, Qd=quercetin (diet), P = phloridzin, Qi = quercetin (intraperitoneal), Gi= genistein (intraperitoneal)

Based on these results, an overlap between the genes regulated by CR and dietary plant bioactives is calculated (Table 5, Table 6 and Figure 6; overlapped genes; see Appendix B). The results of the 3-fold bigger method are used. The percentage overlap calculation is based on the number of regulated CR genes, which is also investigated using the respective dietary plant bioactive.

Table 5: Total and percent¹ overlap in gene expression between caloric restriction and plant bioactives

	t-test	t-test + FC	moderated t-test	moderated t-test + FC	Wilcoxon test	Wilcoxon test + FC	rank prod ²	rank prod + FC
upregulated genes								
R	2 (0.9%)	0	33 (11%)	0	0	0	275 (29%)	12 (25%)
Qd	0	0	0	0	0	0	158 (7%)	2 (3%)
P	5 (1.1%)	0	15 (2.8%)	0	0	0	172 (8%)	1 (2%)
Gi	0	0	10 (3.0%)	0	0	0	75 (8%)	8 (13%)
Qi	0	0	14 (1.2%)	1 (33%)	0	0	71 (7%)	8 (13%)
downregulated genes								
R	12 (3.7%)	0	41 (11%)	0	0	0	315 (24%)	25 (25%)
Qd	0	0	0	0	0	0	274 (8%)	0 (0%)
P	28 (8.3%)	0	68 (13%)	0	0	0	1106 (34%)	3 (3%)
Gi	0	0	28 (6.8%)	0	0	0	168 (13%)	31 (25%)
Qi	0	0	88 (22%)	0	0	0	255 (19%)	38 (30%)

¹ % of the CR genes, based on number of regulated CR genes which are analyzed by the respective phytonutrient too

² the values of rank product method based on the results of limited gene pool (see Table1)

FC = fold change, rank prod = rank product method, CR= caloric restriction, R = resveratrol, Qd=quercetin (diet), P = phloridzin, Qi = quercetin (intraperitoneal), Gi= genistein (intraperitoneal)

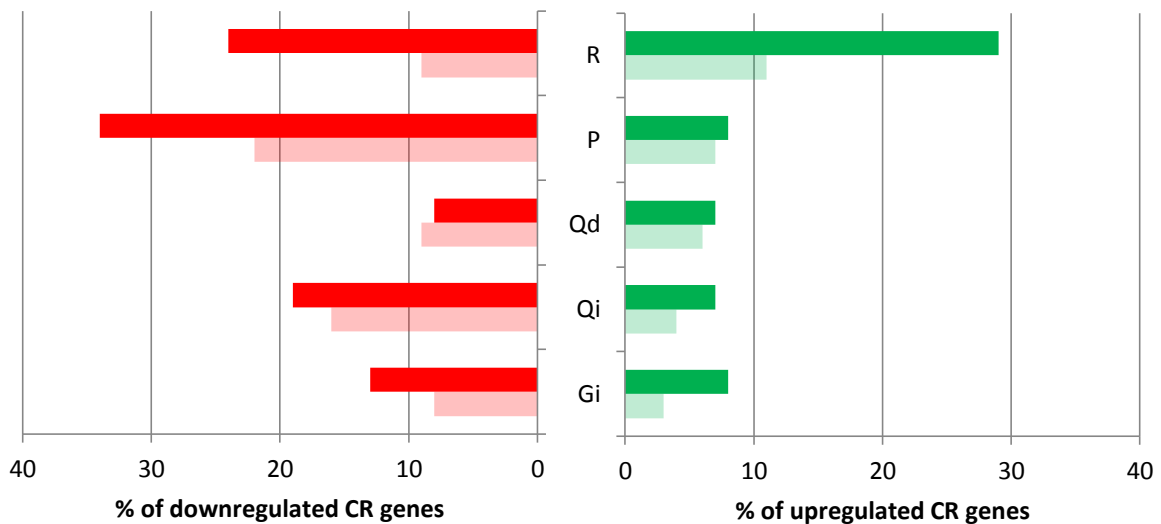


Figure 6: Overlap and opposite regulation of up- and downregulated CR genes in presence of plant bioactives

(Dark bars overlapped regulation, light bars opposite regulation)

Table 6: Total and percental¹ overlap in gene expression regulation between caloric restriction and plant bioactives based on the results of the rank product analysis

	total number of genes ¹	Number of genes regulated by CR	Number of genes regulated by phyto-nutrient	Number of overlapping genes ²
<i>upregulated genes</i>				
R	17780	941	1304	275 (29 %)
P	27671	2135	1789	172 (8 %)
Qd	27671	2135	826	158 (7 %)
Qi	20827	969	866	71 (7 %)
Gi	20827	969	559	75 (8 %)
<i>downregulated genes</i>				
R	17780	1328	1080	315 (24 %)
P	27671	3257	2922	1106 (34 %)
Qd	27671	3257	899	274 (8 %)
Qi	20827	1337	1498	255 (19 %)
Gi	20827	1337	917	168 (13 %)

¹ calculation of the percental overlap based on the number of regulated genes by CR

² only genes from the respective shared gene pool (investigated by both treatments)

² overlapping genes are regulated in the same direction by both treatments

CR= caloric restriction, R = resveratrol, Qd=quercetin (diet), P = phloridzin, Qi = quercetin (intra-peritoneal), Gi= genistein (intra-peritoneal)

In the t-test, only phloridzin (P) and resveratrol (R) show an overlap for up- and down-regulated genes, but the overlap disappears after use of the fold change. With the moderated t-test, an overlap is seen for all phytonutrients except for Q administered per diet (Qd), but this disappears again after using the fold change. No overlap is found with the Wilcoxon test, whereas more overlapped genes are identified with the rank product analysis. The biggest overlap is seen for R regarding the upregulated genes and for P and R regarding the downregulated genes. This result is consistent between the moderated t-test and the rank product analysis. After including the fold change, resveratrol is again the only phytonutrient which shows a large overlap regarding the up- and downregulated genes, whereas quercetin administered intraperitoneally (Qi) and genistein administered intraperitoneally (Gi) show a large overlap regarding the downregulated genes.

For a better determination of whether phytonutrients are able to mimic CR-induced gene expression, it is further analysed whether the phytonutrients also show opposite regulations compared to CR. The results presented in Figure 6 indicate as well that R is the phytonutrient which best mimics the influence of CR on gene expression. All other phytonutrients show a large opposite regulation.

3.3. Functional analysis

Next the results of functional analysis are shown. In this analysis only the genes identified by rank product analysis are included, because the t-test, the moderated t-test and

the Wilcoxon test reveal only a small number of overlapped genes. First, the regulated CR genes are examined to identify potential new functions of CR; then, the overlap between CR and the respective plant bioactives is identified.

3.3.1. Identification of over-represented pathways for the regulated CR genes with CPDB

To identify the functions of CR, all genes which are significantly regulated in at least one approach (see Table 1) are analysed with CPDB. In total, 3502 upregulated IDs and 4479 downregulated IDs are included (Appendix C) and 402 significantly affected pathways are mentioned by the up- and downregulated genes in over-representation analysis. Some of them are excluded because the cited functions are not important in murine liver (Appendix E). This leads to 353 pathways which are included in our analysis (Appendix D).

Cholesterol and steroid biosynthesis, bile acid metabolism

Many of the mentioned pathways indicate that CR influences cholesterol metabolism. Most of the involved genes are upregulated by CR, probably indicating that CR increases cholesterol biosynthesis. The epoxysqualene biosynthesis pathway (MouseCyc), trans trans-farnesyl diphosphate biosynthesis pathway (MouseCyc) and mevalonate pathway I (MouseCyc) are mentioned as well. Analysis of the pathways and regulated genes indicate that the steroid biosynthesis in general could be upregulated, whereas the steroid hormone synthesis (e.g., androgen, oestrogen) is mentioned by the downregulated genes.

While the cholesterol biosynthesis is probably increased, the peroxisome proliferator activated receptor (PPAR) signalling pathway (KEGG) indicates that the cholesterol metabolism is reduced. Moreover, CR increases the expression of transporters which excrete cholesterol in the bile canaliculus. In particular, the Abcg5:Abcg8-mediated export of cholesterol and phytosterols (both genes are overexpressed) is upregulated by CR. This complex transports the cytosolic sterols to the gut lumen or in the bile (148). Furthermore, the KEGG bile secretion pathway, which is mentioned by up- and downregulated genes, indicates that CR promotes the transport of cations, bile acid and water into bile canaliculus and upregulates carriers which are responsible for the back absorptions of bile acids. Carriers which transport bile acid into the circulating system are upregulated too. There are also hints that CR promotes LDL and HDL uptake in hepatocytes.

Detoxification

Moreover, the results indicate that CR is involved in the regulation of the metabolism of xenobiotics (e.g., drugs and arsen) and endogenous substances (e.g., fatty acids and

sterols) including phase I (functionalisation of compounds) and phase II reactions (conjugation). The phase I reactions make different xenobiotics more chemically reactive by exposing functional groups. The phase II reactions, especially the glutathione conjugation, cytosolic sulfonation of small molecules and glucuronidation, increase the excretory potential of different compounds. Genes of these pathways are up- and downregulated by CR.

Most regulated genes belong to the cytochrome P450 system, which is involved in phase I reactions. It is not clear which effect CR has on phase I reactions because the cytochrome P450 monooxygenases are mentioned by the up- and downregulated genes. It is interesting that most of the regulated Cyp 450 isoenzymes are of the Cyp2 family. Besides their effects in detoxification, they are also involved in eicosanoid metabolism in humans (149). Furthermore, the results indicate that CR influences the expression of glutathione S-transferases and UDP-glucuronosyltransferases which are involved in phase II reactions. Genes which are involved in cytosolic sulfonation of small molecules (3'-phosphoadenosine 5'-phosphosulfate synthase 2 (Papss2), sulfotransferase family 1E member 1 (Sult1e1), and sulfotransferase family 2A dehydroepiandrosterone (DHEA)-preferring member 3 (Sult2a3)) are upregulated as well. Moreover, CR seems to influence glutathione metabolism in general, including the γ -glutamyl cycle (MouseCyc).

Lipid metabolism

Furthermore, CR seems to regulate the metabolism of lipids and lipoproteins. Several pathways which are part of fatty acid biosynthesis are mentioned by the upregulated genes (e.g. 'triglyceride biosynthesis' (Reactome), 'biosynthesis of unsaturated fatty acids' (KEGG) and 'biosynthesis of a long-chain fatty-acyl-CoA' (KEGG)), but there are always genes that are downregulated, too. Moreover, it is possible that CR is involved in fatty-acid activation. The results of the PPAR signalling pathway (KEGG) indicate as well that CR probably promotes lipogenesis, whereas the beta-oxidation rate is reduced. A few genes of beta-oxidation are upregulated, but most genes are downregulated. Several pathways of beta-oxidation are mentioned for the downregulated genes in over-representation analysis.

Additionally, it is possible that CR has a limiting effect on ketogenesis and lipid transport ('Lipid digestion, mobilisation, and transport' – Reactome). Moreover, phospholipid metabolism (including glycerophospholipid biosynthesis and the Kennedy pathway) is shown by both forms of regulation, alpha-linolenic acid and linoleic acid metabolism are mentioned by the downregulated genes, and arachidonic acid metabolism is revealed by the upregulated genes. The last pathway indicates that CR influ-

ences the formation of lecithin, DHETs, HETEs and EETs and seems to regulate prostaglandin and leukotriene metabolism. HETEs can be produced from arachidonic acid and are involved in vasodilation/vasoconstriction and angiogenesis (150). Eicosanoids in general are involved in different biological processes including regulation of insulin sensitivity, stimulation of lipid metabolism, activation of PPAR α and PPAR γ , maintaining of blood pressure (vasodilation/vasoconstriction), anion and proton transport, and inflammation and thermoregulation.

Carbohydrate metabolism/glycolysis/gluconeogenesis/citric acid cycle/respiratory electron chain

Moreover, the pathway analysis indicates that CR is involved in the regulation of glucose metabolism (including glycolysis and gluconeogenesis). One of the upregulated genes is tuberous sclerosis 2 (Tsc2), which is known to interact with Sirt1 and is involved in the inhibition of mTOR signalling (151). Moreover, the results indicate that CR probably increases gluconeogenesis. Furthermore, pyruvate metabolism, the pentose phosphate pathway, the citric acid cycle and the electron transport chain are revealed in pathway analysis. CR upregulates the expression of several genes which are involved in the formation of the different complexes of the electron transport chain (complex I: NADH ubiquinone dehydrogenases like Ndufa5, Ndufa6, Ndufa8, Ndubf6, Ndubf10, Ndufc1, Ndufc2, Ndufs1, Ndufs2, Ndufs8, and Ndufv1; complex II: succinate dehydrogenases like Sdhb, Sdhc, and Sdhc; complex III: ubiquinol-cytochrome c reductases like Uqcrc1, Uqcr10, and Uqcrcs1, complex IV: cytochrome c oxidases like Cox5a, Cox7a1 and complex V: ATP synthases like Atp5a1, Atp5c1, Atp5f1, Atp5g1, Atp5l, Atp5o). Furthermore, the results indicate that CR upregulates Na⁺-independent, facilitative glucose transporters (GLUTs). These are Glut2 (Slc2a2), Glut4 (Slc2a4), Glut5 (Slc2a5) and Glut8 (Slc2a8).

Amino acid and protein metabolism

CR seems to be involved in the metabolism of different amino acids as well. For example, the tryptophan, phenylalanine, tyrosine, serine, glycine, threonine, arginine, glutamate, proline, cysteine, homocysteine, methionine, valine, leucine and isoleucine metabolisms have been discovered. The results indicate that phenylalanine and tyrosine catabolism could be increased by CR, whereas most genes of tyrosine metabolism in general are downregulated. Tyrosine is a substrate for different catecholamines. The 'catecholamine biosynthesis' pathway is shown by the downregulated genes as well. The 'valine, leucine and isoleucine degradation' pathway (KEGG) is mentioned for downregulated genes too. Moreover, CR regulates the expression of several genes which are involved in homocysteine metabolism.

The urea cycle seems to be influenced as well. This hypothesis is supported by the increase of carbamoyl-phosphate synthetase 1 (Cps1) expression, which is a key enzyme of the urea cycle (152). Of particular interest is that the NAD⁺ biosynthesis from tryptophan is mentioned for the upregulated genes, as are nicotinate and nicotinamide metabolism. These regulations could be important for the Sirt1 activity which is regulated by NAD⁺ and NAM (see above). Besides, CR seems to be involved in the apoptotic cleavage of cellular proteins and in ubiquitin mediated proteolysis.

Signalling pathways

Moreover, the pathway analysis indicates that CR regulates several signalling pathways, including growth hormone receptor signalling, insulin signalling, PPAR signalling, leptin receptor signalling, Jak/STAT signalling, 'androgen receptor signalling pathway' (Wikipathways), 'epidermal growth factor receptor (EGFR1) signalling' (Wikipathways), TNF- α and NF- κ B signalling and the transforming growth factor (TGF) beta receptor signalling. Several of these pathways indicate that CR is involved in the regulation of insulin sensitivity and insulin resistance, which has already been mentioned as important for beneficial CR effects (see above). The influence on growth hormone and insulin signalling is an interesting observation as well.

Immune system and inflammation

CR seems to influence inflammation processes and immune function too. Most of these pathways are mentioned by the downregulated genes. These are the 'antigen processing and presentation' (MHC I and II) (KEGG), 'type II interferon signalling (IFNG)' (Wikipathways), toll like receptor cascade (especially TLR3 and TLR4), complement cascade, coagulation and interleukin signalling (5, 6, 7 and 9). The pathway 'macrophage markers' (Wikipathways) is mentioned on over-representation analysis too.

Translation regulation/Regulation of gene expression

Moreover, the pathway analysis indicates that CR is involved in gene expression regulation. In particular, genes that are involved in translation (including elongation, initiation and termination) are upregulated. For example, 3'-UTR mediated translation, cap-dependent translation initiation and activation of gene expression by Srebp are mentioned. Furthermore, CR upregulates genes that code for cytoplasmic ribosomal proteins (large (60S) and small (40S) subunits). They are important for translation too. Moreover, the results indicate that CR is involved in the processing of mRNA (including mRNA transport, splicing and the regulation of mRNA stability by binding of proteins) and post-translational protein modification. Transcription processes are mentioned by the downregulated genes too.

Transporter

Several transporters are regulated by CR. For example, the expression of ABC (ATP-binding cassette) transporters, which are important for the ATP-dependent transport of different compounds against the concentration gradient, is influenced (153). Furthermore, CR seems to be involved in the binding and uptake of ligands by scavenger receptors and the membrane trafficking. This function is important for vesicle-mediated transport, which itself is mentioned by the downregulated genes in over-representation analysis. One of the upregulated receptors is secreted acidic cysteine rich glycoprotein (Sparc). Sparc is involved in liver cell proliferation, migration and extracellular matrix remodelling. The expression of Sparc is increased in fibrotic livers (154). Furthermore, Sparc interacts with AMPK and could be involved in the regulation of Glut4 expression or in regulation of glucose metabolism via AMPK activation (155). Therefore, Sparc upregulation could probably be involved in mediating beneficial CR effects. Moreover, the results indicate that CR is involved in the regulation of metal ion SLC transporters. In particular, transporters that are involved in the zinc influx into cells are downregulated by CR.

Other pathways

Moreover, there are indications that CR is involved in vitamin metabolism. In particular, 'Biotin transport and metabolism' (upregulation) and retinol metabolism (up- and downregulation) are mentioned. In addition, CR upregulates genes which are involved in the circadian clock (Per1, Per2, Cry1 and Cry2). Pathways belonging to circadian regulation are mentioned by the up- and downregulated genes. The cell cycle itself seems to be influenced by CR as well (upregulation; 'G1 to S cell cycle control' – Wikipathways). Moreover, CR seems to downregulate genes of the meiotic recombination. Additionally, the results indicate that CR could be involved in purine and pyrimidine metabolism. For example, the pyrimidine salvage reactions are mentioned in over-representation analysis for upregulated genes.

Heme biosynthesis seems to be influenced as well because the pathways 'heme biosynthesis' (MouseCyc, Wikipathways, Reactome), 'porphyrin and chlorophyll metabolism' (KEGG), 'metabolism of porphyrins' (Reactome) and 'tetrapyrrole biosynthesis II' (MouseCyc) are shown by the downregulated genes. Porphyrins are a special form of tetrapyrroles which can react with metals such as iron to generate different haemoproteins (haemoglobin, cytochromes). Furthermore, the results indicate that CR is involved in phagocytosis. The Wikipathway 'oxidative stress' is also mentioned for the up- and downregulated genes. Moreover, the results indicate that CR is involved in propionate and butanoate metabolism. Whereas the propionate metabolism is mentioned for both up- and downregulated genes, the butanoate metabolism is primarily mentioned for the

downregulated genes of CR. Finally, CR seems to influence methylation processes, (deoxy)ribose phosphate degradation, selenium metabolism and formaldehyde oxidation.

3.3.2. Determining the overlap between CR and the dietary plant bioactives regarding the over-represented pathways

Knowing whether a phytonutrient is a CR mimetic is necessary to determine overlapped functions/pathways besides the transcriptional overlap. Two different approaches are used for this purpose. First, all up- and downregulated genes of the different interventions are investigated independently from each other in over-representation analysis, and co-mentioned pathways are identified (separate analysis). Because this approach does not determine whether CR and the dietary plant bioactive regulate the same genes and mechanisms in the pathway, only the overlapped genes between CR and the respective phytonutrient are analysed in the second approach (overlapped analysis).

3.3.2.1. Separate analysis

For the separate analysis, different methods can be used to identify over-represented pathways by CR. For example, it is feasible to investigate all identified Entrez IDs by the different limited gene pools against the background bgCR (see Table 1, a), which leads to 122 significantly upregulated and 97 significantly downregulated pathways. Moreover, it is possible to take all results of the limited gene pools by themselves and combine them into a list of regulated pathways (see Table 1, a-f). This leads to 211 significantly upregulated and 155 significantly downregulated pathways. Both approaches are used to identify overlapped pathways between CR and the dietary plant bioactives. To identify the over-represented pathways for the phytonutrients, the limited gene pools (bgR, bgP, bgQd, bgQi and bgGi – dependent on the phytonutrient) are used.

Table 7 shows the number of over-represented pathways revealed by the different phytonutrients and the total and percentage overlap between CR and the dietary plant bioactives. The overlap analysis indicates that R is the best mimetic for the upregulated pathways (17% or 11%), and Qi (40% or 33%) and P (28% or 28%) are the best mimetics for downregulated pathways. This coincides with the outcomes of the gene expression analysis. The observation that Qd shows no or only a small overlap with CR is based on the fact that no or only a few over-represented pathways are identified.

Combining the results of all three plant bioactives which are administered per diet shows that no benefit is seen regarding the upregulated genes compared to R alone. For the downregulated genes, a small benefit is seen compared to P alone, which is

caused by the R pathways, whereas Qd results in no further benefit. After including the plant bioactives which are administered intraperitoneally, two further overlapped pathways could be identified regarding the upregulated genes, whereas 18 or 23 further pathways were mimicked by Qi and Gi regarding the downregulated genes. Table 8 shows all overlapped pathways, which are identified in a separate analyses.

The results indicate that the investigated plant bioactives, especially R, are able to mimic the upregulating influence of CR on the biological oxidation (phase I and phase II reactions), the steroid and cholesterol biosynthesis, the fatty acid degradation, the pyruvate metabolism, the pentose and glucuronate interconversions and the binding and uptake of ligands by scavenger receptors. On the other hand, the downregulating effect of CR on the lipid and lipoprotein metabolism (beta oxidation, arachidonic acid metabolism), biological oxidation (phase 1 reactions), steroid and steroid hormone biosynthesis, bile secretion, meiotic recombination, retinol metabolism, protein processing in endoplasmic reticulum, amino acid metabolism (valine, leucine, Isoleucine, tryptophan, cysteine, homocysteine, glycine, serine and threonine), gene expression (including RNA transport, processing and splicing), complement cascade and circadian rhythm seems to be mimicked by phytonutrients as well.

Table 7: Total and percental overlap between the pathways affected by caloric restriction and plant bioactives in separate analyses

	R	P	Q	Qi	Gi	phyto-nutrients per diet*	all phy-tonutrients
upregulated genes							
number of regulated pathways by the phytonutrients	99	1	0	3	5		
Overlap with CR 122 pathways (total and percental overlap)	21 (17%)	1 (1%)	0 (0%)	3 (3%)	1 (1%)	21 (17%)	23 (19%)
Overlap with CR 211 pathways (summarizing all approaches (total and percental overlap)	23 (11%)	1 (1%)	0 (0%)	3 (1%)	1 (1%)	23 (12%)	25 (12%)
downregulated genes							
number of regulated pathways by the phytonutrients	19	83	5	144	38		
Overlap with CR 97 pathways (total and percental overlap)	10 (10%)	27 (28%)	4 (4%)	39 (40%)	22 (23%)	31 (32%)	49 (51%)
Overlap with CR 155 pathways (summarizing all approaches (total and percental overlap)	10 (7%)	43 (28%)	5 (3%)	51 (33%)	27 (17%)	47 (30%)	70 (45%)

* Pathways of the experiments with intraperitoneal administration are not considered

Table 8: Overlapping pathways between CR and plant bioactives identified in separate analysis

overlapped upregulated pathways	overlapped downregulated pathways
Metabolism – Reactome ¹	Metabolism – Reactome ^{1,2,4,5}
Biological oxidations – Reactome ^{1,4,5}	Meiotic Recombination – Reactome ¹
Cholesterol Biosynthesis – Wikipathways ^{1,2}	Tryptophan metabolism – Wikipathways ^{1,2}
Cholesterol biosynthesis – Reactome ¹	Metabolism of lipids and lipoproteins – Reactome ^{1,4,5}
Metabolism of lipids and lipoproteins – Reactome ¹	Sulfur amino acid metabolism – Reactome ^{1,4}
Drug metabolism - cytochrome P450 - Mus musculus (mouse) – KEGG ¹	Steroid hormone biosynthesis - Mus musculus (mouse) – KEGG ^{1,2,4}
Pyruvate metabolism - Mus musculus (mouse) – KEGG ¹	Drug metabolism - other enzymes - Mus musculus (mouse) – KEGG ^{1,2,4,5}
Phase 1 - Functionalization of compounds – Reactome ¹	Protein processing in endoplasmic reticulum - Mus musculus (mouse) – KEGG ^{1,2,4,5}
Cytochrome P450 - arranged by substrate type – Reactome ¹	Fatty acid, triacylglycerol, and ketone body metabolism – Reactome ^{1,2}
cholesterol biosynthesis III (via desmosterol) – MouseCyc ¹	Systemic lupus erythematosus - Mus musculus (mouse) – KEGG ^{1,4}
Metapathway biotransformation – Wikipathways ¹	Xenobiotics – Reactome ^{2,3,4,5}
superpathway of cholesterol biosynthesis – MouseCyc ¹	nicotine degradation III – MouseCyc ^{2,4,5}
Terpenoid backbone biosynthesis - Mus musculus (mouse) – KEGG ¹	Valine, leucine and isoleucine degradation - Mus musculus (mouse) – KEGG ^{2,4,5}
cholesterol biosynthesis II (via 24,25-dihydrolanosterol) – MouseCyc ¹	Retinol metabolism - Mus musculus (mouse) – KEGG ^{2,3,4,5}
Pentose and glucuronate interconversions - Mus musculus (mouse) – KEGG ¹	Exercise-induced Circadian Regulation – Wikipathways ^{2,4}
Phase II conjugation – Reactome ¹	mRNA processing – Wikipathways ²
Steroid biosynthesis - Mus musculus (mouse) – KEGG ¹	nicotine degradation II – MouseCyc ^{2,4,5}
mevalonate pathway I – MouseCyc ¹	Gene Expression – Reactome ^{2,4}
cholesterol biosynthesis I – MouseCyc ¹	bupropion degradation – MouseCyc ^{2,4,5}
Fatty acid degradation - Mus musculus (mouse) – KEGG ¹	Butanoate metabolism - Mus musculus (mouse) – KEGG ^{2,4}
Propanoate metabolism - Mus musculus (mouse) – KEGG ¹	Diurnally Regulated Genes with Circadian Orthologs – Wikipathways ^{2,4}
Diurnally Regulated Genes with Circadian Orthologs – Wikipathways ¹	Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET) – Reactome ²
Binding and Uptake of Ligands by Scavenger Receptors – Reactome ¹	Drug metabolism - cytochrome P450 - Mus musculus (mouse) – KEGG ^{2,4,5}
Chemical carcinogenesis - Mus musculus (mouse) – KEGG ⁴	Processing of Capped Intron-Containing Pre-mRNA – Reactome ^{2,4}
Leptin Insulin Overlap – Wikipathways ⁴	mRNA Processing – Reactome ^{2,4}
	mRNA Splicing – Reactome ^{2,4}
	Spliceosome - Mus musculus (mouse) – KEGG ²
	mRNA Splicing - Major Pathway – Reactome ^{2,4}
	Cytochrome P450 - arranged by substrate type – Reactome ^{2,3,4,5}
	Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE) – Reactome ^{2,5}
	Chemical carcinogenesis - Mus musculus (mouse) – KEGG ^{2,4,5}
	Metabolism of xenobiotics by cytochrome P450 - Mus musculus (mouse) – KEGG ^{2,4,5}
	mRNA 3,-end processing – Reactome ²
	Post-Elongation Processing of Intron-Containing pre-mRNA – Reactome ²
	fatty acid β -oxidation I – MouseCyc ²

Tab 8/b: Overlapped pathways between CR and the plant bioactives identified in separate analysis

overlapped upregulated pathways	overlapped downregulated pathways
	Phase 1 - Functionalization of compounds – Reactome ^{2,3,4,5}
	RNA transport - Mus musculus (mouse) – KEGG ²
	Tryptophan metabolism - Mus musculus– KEGG ²
	2-methylbutyrate biosynthesis – MouseCyc ²
	Fatty acid degradation - Mus musculus – KEGG ^{2,4,5}
	Toll-Like Receptors Cascades – Reactome ²
	Mitochondrial Fatty Acid Beta-Oxidation – Reactome ²
	Biological oxidations – Reactome ^{2,3,4,5}
	Fatty Acid Beta Oxidation – Wikipathways ²
	Propanoate metabolism - Mus musculus – KEGG ^{2,4}
	Bile secretion - Mus musculus (mouse) – KEGG ²
	fatty acid β -oxidation IV (unsaturated, even number) – MouseCyc ²
	Complement cascade – Reactome ^{4,5}
	Regulation of Complement cascade – Reactome ^{4,5}
	Complement and coagulation cascades - Mus musculus (mouse) – KEGG ^{4,5}
	Bile acid and bile salt metabolism – Reactome ⁴
	Synthesis of bile acids and bile salts – Reactome ⁴
	Complement Activation, Classical Pathway - Wikipathways ^{4,5}
	Synthesis of bile acids and bile salts via 7 α -hydroxycholesterol – Reactome ⁴
	Lipoprotein metabolism – Reactome ^{4,5}
	Retinoid metabolism and transport – Reactome ⁴
	Beta-oxidation of pristanoyl-CoA – Reactome ⁴
	Primary bile acid biosynthesis - Mus musculus (mouse) – KEGG ⁴
	Lipid digestion, mobilization, and transport – Reactome ^{4,5}
	Synthesis of bile acids and bile salts via 24-hydroxycholesterol – Reactome ⁴
	Porphyrin and chlorophyll metabolism - Mus musculus (mouse) – KEGG ⁴
	Initial triggering of complement – Reactome ^{4,5}
	Peroxisomal lipid metabolism – Reactome ⁴
	Prion diseases - Mus musculus (mouse) – KEGG ^{4,5}
	Degradation of cysteine and homocysteine – Reactome ⁵
	Steroid Biosynthesis – Wikipathways ⁴
	Statin Pathway – Wikipathways ⁴
	superpathway of cholesterol biosynthesis – MouseCyc ⁴
	Synthesis of bile acids and bile salts via 27-hydroxycholesterol – Reactome ⁴
	Glycine, serine and threonine metabolism - Mus musculus (mouse) – KEGG ⁵

¹ overlap between caloric restriction (CR) and resveratrol, ² overlap between CR and phloridzin, ³ overlap between CR and quercetin administered per diet, ⁴ overlap between CR and quercetin administered intraperitoneal, ⁵ overlap between CR and genistein administered intraperitoneal

3.3.2.2. Overlapped analysis

As mentioned above, the separate analysis does not answer the question of whether the phytonutrients address the same genes as CR in the pathways. Different gene expression changes can result in different effects in the pathway. Therefore, only the overlapped genes between CR and the respective dietary plant bioactives are next analysed with ConsensusPathDB. The overlapping genes of CR and the respective plant bioactive and the identified pathways ($q < 0.05$) are presented in Appendix F to O.

Resveratrol

A total of 275 upregulated genes and 315 downregulated genes are regulated by both CR and R. The upregulated genes are over-represented in 44 pathways, whereas the downregulated genes are over-represented in 17 pathways. They are summarised in Table 9. The results indicate that R could be able to mimic many CR functions, such as steroid and cholesterol metabolism, biological oxidation, the circadian clock, PPAR signalling, and nicotinate and nicotinamide metabolism. As mentioned above, some of them could be important for the beneficial effects of CR, including the detoxification system, the circadian clock and the nicotinamide metabolism. Table 10 shows the overlapped genes between CR and R for the pathways identified in separate and overlapped analysis. Interesting is that both interventions upregulate the expression of *Cry2*, *Per1*, *Per2* and *Per3*, indicating an influence on circadian regulation.

Moreover, nicotinamide N-methyltransferase (*Nnmt*) is upregulated by CR and R. SCHMEISSER et al. (2013) indicate that *Nnmt* expression is important for the Sirt1-mediated effect on lifespan in *C. elegans* and that *Nnmt* can prolong lifespan independent of Sirt1 (35). Moreover, the production of ROS by aldehyde oxidases (*Aox*) is necessary for the lifespan-expanding effect of *Nnmt* in *C. elegans*. Our analysis indicates that CR and R downregulate the expression of *Aox1* and *Aox3* in murine liver. However, *Nnmt* may be able to increase ROS production independent of *Aox*, because many stress defence genes like *Gstm5*, *Gstm7* and *Gsto1* are upregulated in our analysis. Figure 7 gives an overview of the mechanisms affected by *Nnmt*.

Nnmt methylates NAM using S-adenosylmethionine (SAM), which leads to the formation of N1-methylnicotinamide (MNAM). NAM is known to possibly prevent the lifespan-expanding effects of CR by increasing the level of NADH, which is known to be an inhibitor of Sir2 (Sirt1) in yeast (156). MNAM, on the other hand, is known for its antithrombotic and anti-inflammatory effects and for mediating Foxo- or Nrf2-dependent increased expression of genes which are involved in detoxification and stress response

(35; 157). Thus, Nnmt could be involved in the Sirt1- and Foxo1-dependent increase of lifespan in mice.

Table 9: Summarized results of pathway analysis of the overlapping genes of CR and resveratrol

upregulated pathways	downregulated pathways
Cholesterol Biosynthesis, mevalonate pathway, Terpenoid backbone biosynthesis, steroid biosynthesis Metabolism of lipids and lipoproteins - Reactome	Steroid hormone biosynthesis - Mus musculus (mouse) - KEGG Metabolism of lipids and lipoproteins; Fatty acid, triacylglycerol, and ketone body metabolism; Retinol metabolism
Retinol metabolism	Retinol metabolism
Biological oxidations – Reactome, phase I (cytochrome P40s) and phase II reactions (Glucuronidation, Glutathione conjugation)	Biological oxidations
Pentose and glucuronate interconversions	Protein processing in endoplasmic reticulum
PPAR signaling pathway	glycerol-3-phosphate shuttle / Glycolysis
Metapathway biotransformation	Sulfur amino acid metabolism; L-cysteine degradation
Circadian clock	Drug metabolism
Glutathione metabolism	Taurine and hypotaurine metabolism
Trafficking of dietary sterols, bile secretion	Meiotic Recombination
Porphyrin and chlorophyll metabolism	glutathione biosynthesis
Pyruvate metabolism	
Starch and sucrose metabolism	
salvage pathways of pyrimidine ribonucleotides	
Nicotinate and nicotinamide metabolism	

Table 10: Genes that are regulated by caloric restriction and resveratrol in selected pathways

Pathway	upregulated genes	downregulated genes
biological oxidation	Acss2, Cyp2b9, Cyp2b13, Cyp3a13, Cyp4a10, Cyp4a14, Cyp7a1, Cyp17a1, Cyp51, Fmo3, Gstm5, Gstm7, Gsto1, Gstt2, Nnmt, Papss2, Sult1a1, Sult1c2, Ugp2, Ugt1a2	Aldh1a1, Cyp2d9, Cyp2f2, Cyp4a12a, Cyp4a12b, Cyp7b1, Glc, Gclm, Slc35d1, Sult2a8, Ugt2b1, Ugt2b34, Ugt2b35
Circadian regulation	Bhlhe40, Cebpb, Cry2, Gfra1, Gstm5, Idi1, Nr1d1, Per1, Per2, Per3, Prkab1, Stbd1, Ugp2	G0s2, Ppp1r3c, Tab2
PPAR signaling pathway	Acox1, Angptl4, Cyp4a10, Cyp4a14, Cyp7a1, Fabp5, Pck1, Ppara	Acaa1b, Cpt2, Cyp4a12a, Cyp4a12b, Rxra
Nicotinate and nicotinamide metabolism	Enpp1, Nadsyn1, Nmrk1, Nnmt	Aox1, Aox3
steroid and cholesterol biosynthesis	Cyp17a1, Cyp51, Dhcr24, Dhcr7, Fdps, Hmgcr, Hmgcs1, Idi1, Lss, Mvk, Nsdhl, Pmvk, Sqle	Hsd3b2, Hsd3b5, Lipa
bile secretion; Trafficking of dietary sterols	Abcc4; Abcg5, Abcg8, Atp1b1, Cyp7a1, Hmgcr, Slco1a4	Abcb4, Aqp8, Baat, Slc22a7, Rxra

That Nnmt is upregulated by CR has already been observed by ESTEP et al. (2009) (156). Whereas previous studies indicate that a high Nnmt expression leads to unwanted effects in adipocytes and is associated with obesity, diabetes, cancer and neu-

rodenerative diseases, HONG et al. (2015) show that the effects of Nnmt in liver are wanted (158; 159; 160). These effects seem to be mediated by Nnmt-dependent stabilising of Sirt1 (159). Moreover, in vitro analyses indicate that Nnmt increases the expression of Sirt1, Sirt2 and Sirt3 in human neuroblastoma cells and that Sirt3 is a key mediator for enhancing the Nnmt-dependent increase in complex I activity and ATP synthesis (161). Furthermore, there are indications that Nnmt is involved in the regulation of gluconeogenesis and lipogenesis (160; 159).

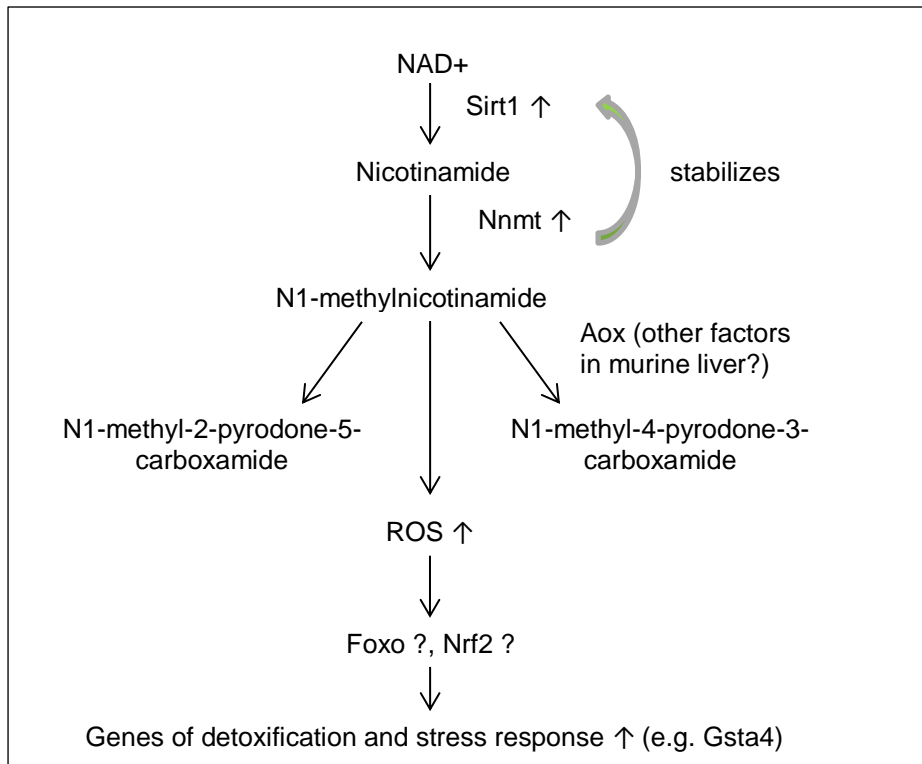


Figure 7: Overview of the potential mechanism mediated by Nnmt

Moreover, R also upregulates the complex Abcg5:Abcg8, which indicates a mimicking effect on cholesterol efflux via bile acid. The upregulation of 24-dehydrocholesterol reductase (Dhcr24) seems to be important as well. Besides its effects in cholesterol biosynthesis, Dhcr24 can directly scavenge ROS, protecting cells from oxidative stress-induced apoptosis (162). Another interesting overlap is the upregulation of PPAR α . It is known that PPAR α is activated during fasting, which stimulates fatty acid oxidation, ketogenesis and gluconeogenesis through transactivation of target genes (57). Moreover, PPAR α is involved in bile acid synthesis and in modulating inflammatory responses.

Phloridzin

There were 158 upregulated and 1106 downregulated genes that overlapped between P and CR. The 19 pathways over-represented by upregulated genes and the 46 pathways over-represented by downregulated genes are summarised in Table 11. They

indicate that phloridzin could be able to mimic some effects of CR on cholesterol metabolism, circadian clock, biological oxidation and PPAR signalling as well, but the genes mentioned Table 12 indicate that P operates somewhat differently from R. Moreover, it is possible that phloridzin mimics some effects of CR on amino acid metabolism, the complement cascade, mRNA processing and fatty acid β -oxidation. It is particularly interesting that P mimics the downregulating effect of CR on insulin receptor substrate 1 (Irs1) and growth hormone receptor (Ghr). This indicates that P could be able to inhibit GH/Igf1 signalling as well. Moreover, Nnmt expression is also increased by P.

Table 11: Summarized results of pathway analysis of the overlapping genes of CR and phloridzin

upregulated pathways	downregulated pathways
Cholesterol Biosynthesis; Terpenoid backbone biosynthesis	mRNA processing; Regulation of mRNA Stability by Proteins that Bind AU-rich Elements
salvage pathways of pyrimidine ribonucleotides	nicotine degradation
Circadian Clock	Toll-Like Receptors Cascades
Metabolism of lipids and lipoproteins; Fatty Acid Biosynthesis	Valine, leucine and isoleucine degradation - Mus musculus (mouse)
Phenylalanine, tyrosine and tryptophan biosynthesis - Mus musculus (mouse)	Protein processing in endoplasmic reticulum - Mus musculus (mouse)
Regulation of mRNA Stability by Proteins that Bind AU-rich Elements	Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET) - Reactome
(deoxy)ribose phosphate degradation	Drug metabolism
	Retinol metabolism - Mus musculus (mouse)
	bupropion degradation
	Butanoate metabolism - Mus musculus (mouse)
	Circadian Clock
	Biological oxidation – Phase I (Cytochrome P 450s)
	Porphyrin metabolism
	Type II interferon signaling (IFNG)
	2-methylbutyrate biosynthesis
	fatty acid β -oxidation; Fatty acid degradation
	PPAR signaling pathway
	Complement Activation, Classical Pathway – Wikipathways

Quercetin (diet)

There are 158 upregulated and 274 downregulated overlapped genes between CR and Qd. The upregulated genes are over-represented in nine pathways, whereas the downregulated genes are over-represented in one pathway (summarised in Table 13). These pathways indicate that Qd could be able to mimic the effect of CR on biological oxidation and the circadian clock. The expression of Nnmt is increased for Qd as well (Table 14). Moreover, the downregulation of choline kinase alpha (Chka) indicates that Qd could be able to inhibit Akt signalling (163; 164). Therefore, it is possible that Qd

inhibits mTOR signalling and increases the activity of Foxos even if relevant gene expression changes are not shown in Table 14.

Table 12: Genes that are regulated by caloric restriction and phloridzin in selected pathways

Pathway	upregulated genes	downregulated genes
Growth hormone receptor signaling	Cish, Socs2	Adam17, Ghr, Irs1, Stat5a
circadian clock	Idi1, Per1, Tubb4a	Azin1, Clock, Dnaja1, G0s2, Klf9, Nr1d1, Ppp1r3c, Psm4, Stbd1, Tab2
Bile secretion		Abcb4, Abcc2, Abcc3, Abcg2, Aqp4, Aqp9, Ephx1, Ldlr, Slc22a1, Slc22a7, Slco1a1, Slco1b2
Cholesterol biosynthesis	Dhcr7, Fdps, Idi1, Nsdhl, Pmvk, Sqle	Acat1, Nudt12, Sc5d
PPAR signaling pathway	Cyp4a14, Fabp5, Scd1	Acaa1b, Acadm, Acox2, Cd36, Cpt1a, Ehhadh, Fabp2, Fabp7, Gyk, Ppara, Sorbs1
biological oxidation	Acss2, Cyp2c39, Cyp4a14, Nnmt	Adh4, Cyp2a12, Cyp2c37, Cyp2c50, Cyp2c54, Cyp2d12, Cyp2d40, Cyp2j5, Cyp2j6, Cyp3a13, Cyp3a25, Gclc, Gclm, Sult1c2, Tpm1, Ephx1, Ugt2b34, Ugt2b35

Table 13: Summarized results of pathway analysis of the overlapping genes of CR and dietary quercetin

upregulated pathways	downregulated pathways
Biological oxidations – Phase I (cytochrome P450s)	Destabilization of mRNA by AUF1 (hnRNP D0)
Macrophage markers	
Circadian Clock	
Retinol metabolism	
Hypertrophy Model	

Quercetin (administered intraperitoneally)

The overlapped analysis included 71 upregulated and 255 downregulated genes overlapping between Qi and CR. Sixty over-represented pathways could be identified for the upregulated genes, whereas 93 could be identified for the downregulated genes (summarised in Table 16). These pathways indicate that Qi could be able to mimic some effects on biological oxidation, lipid metabolism, growth hormone and insulin signalling, bile metabolism, glucose metabolism, PPAR signalling and the circadian clock. The genes, presented in Table 15, indicate that Qi seems to influence GH/Igf1 signalling as well because Ghr is downregulated by Qi too.

Table 14: Genes that are regulated by caloric restriction and dietary quercetin in selected pathways

Pathway	upregulated genes	downregulated genes
Kennedy pathway		Chka, Sgpl1
Circadian clock	Cebpb, Per1	G0s2, Nr1d1, Ppp1r3c
biological oxidation	Cyp2b10, Cyp4a14, Nnmt, Sult1e1	Cyp2d12, Cyp2d40, Slc26a1, Sult1c2

Table 15: Genes that are regulated by caloric restriction and quercetin administered intraperitoneally in selected age-related pathways

pathway	upregulated genes	downregulated genes
Methylation	Inmt, Nnmt	
Growth hormone receptor signaling	Cish, Irs2, Socs2	Ghr, Socs3, Stat5a
Adipocytokine signaling pathway, insulin signaling pathway, Leptin Insulin Overlap	Irs2, Pklr, Lepr, Slc2a4, Socs2	Cd36, Hras, Ppp1ca, Ppp1cb, Rheb, Socs3, Stat5a
Regulation of Insulin-like Growth Factor (IGF) Transport and Uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	Igfbp1	Igfals

Moreover, CR and Qi increases the expression of insulin-like growth factor binding protein 1 (Igfbp1) and decreases the expression of insulin-like growth factor binding protein, acid labile subunit (Igfals). Then Igfbp1 binds Igf1, which results in decreased Igf1 activity (165). It is already seen that Igfbp1 expression is increased in humans after CR and in rats with a protein- and calorie-restricted diet (166; 167; 168; 169; 170). GAN et al. (2005) could further show that Sirt1 increases Igfbp1 expression by Foxo-dependent and -independent mechanisms (171). In addition, Igfbp1 mediates Igf1-dependent and independent effects on glucose metabolism, postnatal growth, and cell regeneration and survival (172), while Igfals is important for Igf1 stability (173). Thus, decreased expression of Igfals leads to reduced Igf1 levels without affecting Igf1 expression. XU and SONNTAG (1996) have already shown that CR decreases plasma Igf1 level compared to ad libitum fed mice (21). Furthermore, Qi increases the expression of Nnmt. This indicates that Qi could be able to mimic the effects of CR on NAM and NAD⁺ metabolism.

Genistein (administered intraperitoneally)

The analysis showed that 71 upregulated and 255 downregulated genes overlapped between Gi and CR. The upregulated genes were over-represented in 39 pathways, whereas the downregulated genes were over-represented in 57 pathways (summarised in Table 17). These pathways indicate that Gi could be able to mimic some effects of CR on biological oxidation, lipid and glucose metabolism, GH signalling, PPAR signalling, immune system and bile metabolism.

3.3.3. Analysis of the top genes up- and downregulated by CR identified with fold change (> 1.5)

As seen above, many pathways are revealed by over-representation analysis. To investigate the overlap between CR and the more purposeful phytonutrients, only the CR IDs with a fold change > 1.5 and a known gene symbol are analysed next. This leads to 81 upregulated genes and 148 downregulated genes (Appendix P). Already known

genes which are important for mediating CR effects (like sirtuins and Foxos) are not included in this list.

Table 16: Summarized results of pathway analysis of the overlapping genes of CR and quercetin administered intraperitoneally

upregulated pathways	downregulated pathways
Biological oxidations – Phase I (Cytochrome P450s) and phase II reactions (glutathione-mediated detoxification; Cytosolic sulfonation of small molecules)	Biological oxidations – Phase I (Cytochrome P450s)
Retinol metabolism	Retinol metabolism
Metabolism of lipids and lipoproteins; arachidonic acid metabolism, biosynthesis of unsaturated fatty acids; alpha-linolenic (omega3) and linoleic (omega6) acid metabolism; Fatty acid degradation; Fatty Acyl-CoA Biosynthesis; Fatty acid elongation; Triglyceride Biosynthesis	arachidonic acid metabolism; Synthesis of Prostaglandins (PG) and Thromboxanes (TX); Fatty acid degradation (Beta-oxidation; omega-oxidation); Peroxisomal lipid metabolism; sphingosine and sphingosine-1-phosphate metabolism; Lipoprotein metabolism; Fat digestion and absorption; Chylomicron-mediated lipid transport; Linoleic acid metabolism
Growth hormone receptor signaling	Growth hormone receptor signaling
Metabolism of carbohydrates; Hexose / Glucose transport; Glycolysis and Gluconeogenesis, especially glycolysis	Bile acid and bile salt metabolism; Synthesis and recycling of bile acids and bile salts, Bile salt and organic anion SLC transporters
Estrogen metabolism; biosynthesis of estrogens	Steroid hormone biosynthesis, Steroid biosynthesis
PPAR signaling pathway	PPAR signaling pathway
Adipocytokine signaling pathway	Peroxisome
Insulin signaling pathway; Regulation of Insulin-like Growth Factor (IGF) Transport and Uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	Immune System, especially innate immune system; Cytokine Signaling; Interleukin-6 signaling; Complement and coagulation cascades; Interferon Signaling; Antigen processing and presentation
Metapathway biotransformation	heme biosynthesis, porphyrin metabolism
Methylation - Wikipathways	bupropion degradation - MouseCyc
Signaling by Leptin	Synthesis and degradation of ketone bodies
Glutathione metabolism	mevalonate pathway; Terpenoid backbone biosynthesis
Steroid hormone biosynthesis	Protein processing in endoplasmic reticulum
Selenium - Wikipathways	Androgen biosynthesis
Prolactin signaling pathway	Phagosome
bupropion degradation	Tryptophan metabolism
EPO Receptor Signaling	Proteasome
	Statin Pathway
	Circadian Clock
	One carbon metabolism and related pathways
	Valine, leucine and isoleucine degradation

Nonetheless, CR does upregulate Sirt1, Ppargc1a (codes for PGC-1 α), Foxo1 and Foxo3, but with a smaller fold change. Qd is the only phytonutrient which shows an

upregulation for Sirt1 too. This is really surprising because previous experiments have indicated that resveratrol is a Sirt1 activator (80; 174). Probably these missing upregulations could be explained by study design or mouse strain. P shows a significant downregulation in Sirt1 expression. The expression of Foxo1, Foxo3 and Ppargc1a is not influenced by phytonutrients.

Table 17: Summarized results of pathway analysis of the overlapping genes of CR and genistein administered intraperitoneally

upregulated pathways	downregulated pathways
Biological oxidations – Phase I (Cytochrome P450s) and phase II reactions (Cytosolic sulfonation of small molecules; glutathione-mediated detoxification)	Biological oxidations – Phase I (Cytochrome P450s)
Retinol metabolism	Retinol metabolism
Metabolism of lipids and lipoproteins; Fatty acid, triacylglycerol, and ketone body metabolism; Arachidonic acid metabolism; Fatty acid elongation; Biosynthesis of unsaturated fatty acids; Triglyceride Biosynthesis; Fatty Acyl-CoA Biosynthesis; acyl-CoA hydrolysis	Metabolism of lipids and lipoproteins, arachidonic acid metabolism; Fatty acid degradation; Beta-oxidation; Synthesis and degradation of ketone bodies; Lipoprotein metabolism; Lipid digestion, mobilization, and transport
Growth hormone receptor signaling	Complement and Coagulation Cascades
Phenylalanine, tyrosine and tryptophan biosynthesis; Phenylalanine metabolism	Bile acid and bile salt metabolism, Primary bile acid biosynthesis; bile secretion; Bile salt and organic anion SLC transporters
Glycolysis and Gluconeogenesis, especially gluconeogenesis	Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds
bupropion degradation	heme biosynthesis; Porphyrin metabolism
Estrogen metabolism; biosynthesis of estrogens	cholesterol biosynthesis; Terpenoid backbone biosynthesis
Metapathway biotransformation	Destabilization of mRNA by AUF1 (hnRNP D0)
Leptin Insulin Overlap	Protein processing in endoplasmic reticulum
Prolactin signaling pathway	Abacavir transport and metabolism
EPO Receptor Signaling	SLC-mediated transmembrane transport;
Cysteine and methionine metabolism	Organic cation/anion/zwitterion transport
IL-3 Signaling Pathway	Interferon signaling
	PPAR signaling pathway
	Peroxisome
	Proteasome

For the genes with FC > 1.5, over-representation analysis with CPDB is repeated (Appendix Q). Table 18 summarises the results of this analysis. Moreover, it is analysed whether these genes are already mentioned in the context of CR, ageing, lifespan or longevity. Nnmt and Igfbp1 are strongly upregulated by CR in our analysis. As mentioned above, Igfbp1 is important for Igf1 activity, and Nnmt increases the stability of Sirt1 and is necessary for Sirt1-dependent longevity in *C. elegans*. Figure 8 shows the

expression changes of the genes which are strongly regulated by CR and which are already mentioned in the context of CR or of known CR mechanisms.

More genes indicate that CR is involved in the regulation of Igf1 signalling and insulin sensitivity. For example, CR increases the expression of Glut4 (also known as Slc2a4). Glut4 is associated with increased insulin sensitivity and increased glucose uptake (158; 17). For this, Glut4 must translocate to the cell membrane. This is mediated either by Akt or by AMPK (48). That CR increases Glut4 expression has already been seen in muscle (11). The upregulation of FK506 binding protein 5 (Fkbp5) could be important for the CR effects too because it is seen in tumour cells that Fkbp5 inhibits the activity of Akt by phosphorylation (175). Thus, the function of Fkbp5 in murine liver and its role in Igf1 signalling must be further investigated. The downregulation of phosphatidylcholine transfer protein (Pctp) could be interesting as well because genetic ablation or chemical inhibition of Pctp is associated with increased insulin sensitivity by promoting Irs2 activity (176). The expression of Irs2 is increased by CR in our analysis, but the fold change is smaller than 1.5. Interferon gamma induced GTPase (Igtg) is downregulated by CR in our analysis. There are indications that Igtg expression is necessary for PI3K/Akt signalling, which suggests that the reduced PI3K/Akt signalling mentioned in relation to CR is probably at least partially mediated by Igtg (177).

Table 18: Summarized results of pathway analysis of the top regulated genes of caloric restriction

upregulated pathways	downregulated pathways
Biological oxidations (Phase 1, Phase 2)	Biological oxidations (Phase 1)
Fatty acid and triglyceride biosynthesis, arachidonic acid metabolism, beta oxidation	Metabolism of lipids and lipoproteins, arachidonic acid metabolism, fatty acid degradation
Retinol metabolism	Retinol metabolism
Amino acid synthesis and interconversion (transamination), Amino acid transport across the plasma membrane, Alanine, aspartate and glutamate metabolism, Amino acid and oligopeptide SLC transporters,	Metabolism of amino acids and derivatives, tyrosine metabolism, sulfur amino acid metabolism, Glycine, serine and threonine metabolism
Glucose metabolism, Pyruvate metabolism, Glycolysis and Gluconeogenesis	Steroid hormone and steroid biosynthesis, androgen biosynthesis, glycoprotein hormones, Peptide hormone biosynthesis
Glutathione metabolism	Meiotic Recombination
pentose phosphate pathway	Immune system, complement and coagulation cascades, Interferon Signaling
Insulin signaling pathway	catecholamine biosynthesis
Cholesterol biosynthesis	Bile acid and bile salt metabolism, Synthesis of bile acids and bile salts
Biotin transport and metabolism	NFkB activation
	PPAR signaling pathway
	Binding and Uptake of Ligands by Scavenger Receptors



Figure 8: Heat map showing the fold change of selected genes regulated by caloric restriction and plant bioactives

Flavin containing monooxygenase 3 (Fmo3) is the most strongly upregulated gene in our analysis. A strong upregulation is also seen before by FU and KLAASSEN (2014) and in the meta-analysis from SWINDELL (2009) (10; 178). Moreover, Fmo3 expression and activity changes during ageing indicating that CR could be able to prevent these changes (179; 180). Fmos are part of phase I reactions in biological oxidation, catalyse the oxidation of endobiotics and xenobiotics and are involved in the regulation of glucose and lipid homeostasis (181; 10; 57). As mentioned above, the upregulation of genes of the xenobiotic metabolism could be important for the retardation of ageing, and studies show that Fmo3 expression, in particular, is regulated by insulin and GH/Igf1 signalling (182; 58). Moreover, Fmo3 is necessary for Foxo1 expression, which is known to be important for CR effects as well (183). These explanations indicate that Fmo3 could be important for mediating beneficial CR effects. The expression of Fmo3 is upregulated by all phytonutrients, but the strongest upregulation is seen for R, Qi and Gi.

Other upregulation genes involved in biological oxidation include for example glutathione S-transferase alpha 4 (Gsta4), glutathione S-transferase mu 3 (Gstm3), Sult1e1 and Sult2a3. That CR upregulates several genes of phase II reactions, including Gsta4, Gstm3 and Sult1e1, has already been observed (10; 184). It is proposed that besides its effects in biological oxidation, Sult1e1 could be involved in the regulation of GH/Igf1 signalling. LI et al. (2009) have shown that Sult1e1 inhibits GH-stimulated STAT5b phosphorylation and Igf1 synthesis in transfected HepG2 cells (185). Gsta4 and Gstm3 expressions are associated with reduced cellular oxidative damage, which is important for beneficial CR effects (10; 186). It is seen in *C. elegans* that increased expression of Gsta4 is associated with stress resistance and lifespan (187). The fact that CR reduces oxidative damage is confirmed by the downregulation vanin 1 (Vnn1). Vnn1 is a marker for oxidative stress (188). Alcohol dehydrogenase 4 (class II), pi polypeptide (Adh4) is linked to lifespan and oxidative stress as well. Lifespan is increased in Adh4 knockout worms, possibly mediated by increased ROS production (189). This supports the hormesis theory of ageing, which says that CR causes an increased lifespan by promoting mild stress. To our knowledge, no study is available that has investigated the impact of Adh4 on lifespan in mice. Therefore, it should be analysed whether Adh4 is involved in the lifespan-expanding effect of CR in mice too. Nox4 (NADPH oxidase 4) is another gene that is downregulated by CR in our analysis. It is known that high levels of NADPH oxidases are associated with increased oxidative stress and damage (190). Stress-resistant mouse strains show an increased lifespan, which indicates that the downregulation of Nox4 by CR could be involved in the lifespan-expanding effect of CR as well.

Furthermore, CR downregulates the expression of several major urinary proteins (Mup3, Mup4, Mup5, Mup6, Mup10, Mup20, Mup21). It is already mentioned that dietary restriction decreases Mup expression in adipose tissue and liver (191; 192; 193; 28; 194). Mups are markers of reproductive performance. Higher reproduction is associated with increased protein synthesis and enhanced oxidative damage. Therefore, reduced reproduction, which is indicated by reduced Mups, can result in an increased lifespan (28). Moreover, Mups are involved in glucose, lipid and energy metabolism, so mTOR may be involved in the regulation of Mup expression (195; 196; 197; 194). ZHOU et al. (2009) have shown that Mup1 overexpression decreases the expression of gluconeogenic and lipogenic genes (196). Therefore, it is possible that CR increases gluconeogenesis at least partly by inhibiting the expression of Mups. It is known that Mup expression is increased by growth hormone, testosterone and thyroid hormone, whereas glucocorticoids inhibit expression, all factors which are influenced by CR as well (198; 194).

The downregulation of growth differentiation factor 15 (Gdf15) could be involved in mediating CR effects as well. It is known that Gdf15 increases with ageing and is a predictor of all-cause mortality and cardiovascular diseases (199). Moreover, a high Gdf15 level functions as a biomarker for mitochondrial disorders (200). The expression of Gdf15 is increased in stress conditions (199). To our knowledge, the influence of CR on Gdf15 expression has not been investigated before but could be an important factor in CR-mediated longevity. Gdf15 expression is strongly downregulated by all phytonutrients except Gi.

Foxa3, which is downregulated by CR in our analysis, could be another interesting gene. Whereas PANOWSKI et al. (2007) have shown that PHA-4 (an orthologue of Foxa1, 2, 3) is involved in the lifespan-expanding effect of dietary restriction in *C. elegans* but is not necessary, MA et al. (2014) have shown that Foxa3 KO mice show an increased lifespan and insulin sensitivity (201; 202). Moreover, Foxa3 is a negative regulator of PGC1 α , which is known to be increased under the CR condition (202). The role of Foxa3 on murine lifespan and the mechanisms that are targeted by Foxa3 should be further analysed.

Regarding the up- and downregulated genes of CR, some genes that are predominant in females, such as Fmo3, Nnmt, Cyp2b9, Cyp2b10, Cyp2b13 and Cyp4a10, are up-regulated, whereas genes that are predominant in males, such as hydroxy-delta-5-steroid dehydrogenase 3 beta- and steroid delta-isomerase 5 (Hsd3b5), Cyp4a12a, Cyp4a12b, Cyp7b1, UDP glucuronosyltransferase 2 family polypeptide B1 (Ugt2b1) and solute carrier organic anion transporter family member 1a1 (Slco1a1), are down-regulated (203; 179; 204; 205). Interestingly, the expression of most genes is testosterone dependent, indicating a reduction of testosterone level by CR in murine liver (203). It has already been shown that CR feminises gene expression (10).

Other genes could be interesting as well, but the connection to CR mechanisms is not really clear. For example, the upregulation of the regulator of G-protein signalling 16 (Rgs16) could be involved in the inhibition of mTOR signalling (206), the downregulation of Slco1a1 could promote the accumulation of bile acids in the serum (207), the upregulation of eukaryotic translation initiation factor 4E binding protein 3 (Eif4ebp3) could be involved in regulation of protein synthesis (208), the upregulation of neuregulin 4 (Nrg4) could mediate the downregulated effect on lipogenesis (209) and the upregulation of protein phosphatase 1 regulatory subunit 3G (Ppp1r3g) could be important for the CR effects on glucose metabolism (210; 211). Nonetheless, the other genes mentioned in Appendix P could be important for mediating CR effects as well.

3.3.4. Overlap between the top 50 regulated genes identified by q-value

To specify the functions which are mimicked by the phytonutrients, the top 50 up- and downregulated genes (sorted by q-value) of each intervention are compared, and the overlapped genes are identified. The functions of these genes are recognised with CPDB and NCBI:gene (Table 19 and 20). R shows the largest number of overlapped genes (seven upregulated genes and 11 downregulated genes) followed by Gi (six upregulated genes and four downregulated genes) and Qd (four upregulated genes and four downregulated genes). This indicates furthermore that R is the best mimetic for CR.

Interestingly, Igfbp1 and Nnmt are included in this list too. A new observation is that Igfbp1 is one of the top genes regulated by Qd but not by Qi. Previous analyses have not indicated that Qd could be a CR mimetic except of the upregulation of Sirt1. The strong upregulation of Igfbp1 could refute this assumption. Figure 8 illustrates the regulation of Igfbp1 and the mechanisms influenced by Igfbp1. The expression of Igfbp1 seems to be dependent on Sirt1 through Foxo and mitogen-activated protein kinase (MAPK) activation (172). Whereas Sirt1 is upregulated by Qd and CR in our analysis, the expression of Foxo1 is only increased by CR. However, CR and Qd reduce Irs1 expression, which probably indicates that PI3K/Akt signalling is reduced. This inhibition could lead to increased Foxo1 activity without affecting gene expression. In contrast, FARDINI et al. (2014) have shown that Foxo1 inhibits PI3K/Akt signalling itself by upregulating Igfbp1 (212). Foxa1, which is upregulated by CR and Qd, is also known to increase igfbp1 activity (213; 214).

Another indication that Qd could be involved in the inhibition of Igf1 signalling is the reduced expression of Igfals. As mentioned above, Igfals, together with Igfbp3, is important for Igf1 stability and increases the half-life of Igf1 from a few minutes up to 15 hours (173). The expression of Igfbp3 is downregulated by CR as well but is not influenced by Qd. Besides, Igfbp1 could be involved in the inhibition of mTOR signalling by reducing PI3K/Akt signalling (215).

Metallothionein 1 (Mt1) and lipin 1 (Lpin1), two genes upregulated by CR and Qd, could further indicate that Qd is a CR mimetic. It has already been shown that CR increases the expression of Mt1 in liver and that overexpression in murine heart is associated with increased lifespan (220; 221; 178). Mt1 is involved in the inhibition of oxidative stress damage and in scavenging of ROS (220; 222). As mentioned above, this is supposed to be important for mediating beneficial CR effects. Another Mt1 mechanism that could be involved in CR effects is that Mt1 lowers zinc bioavailability (220; 223). This could explain the reduced immune response observed by CR, which is important for

successful ageing. The results of SWINDELL et al. (2010) indicate that Mt1 expression is increased by inhibition of GH/Igf1 signalling in murine kidney (224).

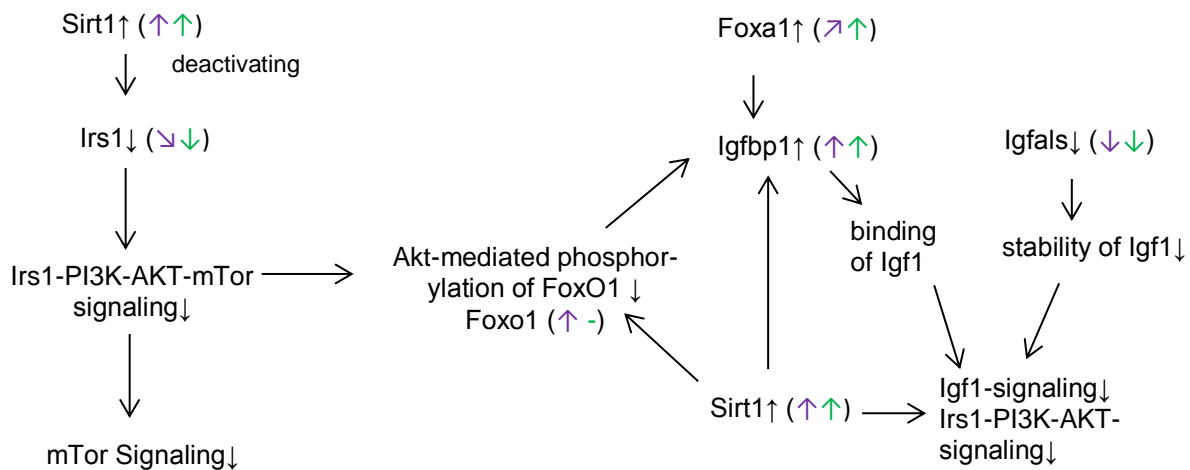


Figure 9: Interaction of the overlapped genes between caloric restriction and quercetin (administered per diet)

(Purple arrow: CR effect, green arrow: Qd effect, ↑: upregulation, ↓: downregulation, ↗: tendency in upregulation, ↘: tendency in downregulation, - no influence on gene expression)

Lpin1 is less investigated in the context of CR and lifespan, but knockdown of Lpin1 decreases PGC-1 α (225; 226). Moreover, FINCK et al. (2005) have mentioned that Lpin1 is a coactivator for PPAR α and PGC-1 α and is involved in the enhanced fatty acid beta oxidation in murine liver (227). Based on the fact that Sirt1 is important for PGC-1 α , it is possible that Lpin1 is involved in Sirt1-dependent CR effects. This is supported by the observation that ethanol-induced Sirt1 inhibition affects transcription regulation by Lpin1 in alcoholic fatty liver disease (228; 229). Moreover, troxerutin, a derivate of the bioflavonoid rutin, improves hepatic lipid homeostasis by increasing NAD $^{+}$ level and Sirt1 activity and reduces Lpin1 signalling (230). It is assumed that Sirt1 activates AMPK, inhibiting the mammalian target of rapamycin complex 1 (mTORC1) signalling and modified Lpin1 signalling. The influence of CR on the interaction of Lpin1 and Sirt1 in healthy liver should be further investigated.

Table 19: Pathways and biological functions of the overlapping genes between the top 50 upregulated genes of caloric restriction and the plant bioactives

upregulated genes					
	R	P	Qd	Qi	Gi function / pathways
Mt1	X		X		<u>pathways</u> : oxidative stress, mineral absorption; <u>GO function</u> : copper and zinc ion binding; <u>GO process</u> : cellular zinc ion homeostasis, cellular response to zinc ion and chromate, detoxification of copper ion, negative regulation of neuron apoptotic process, nitric oxide mediated signal transduction
Cyp2b9	X				<u>pathways</u> : biological oxidation (phase I), retinol metabolism; <u>GO function</u> : arachidonic acid epoxygenase activity, aromatase activity, heme, oxygen or iron ion binding, steroid hydroxylase activity; <u>GO process</u> : epoxygenase P450 pathway, exogenous drug catabolic process, oxidation-reduction process, xenobiotic metabolic process
Cyp2a5	X			X	<u>pathways</u> : biological oxidation (phase I), retinol metabolism; <u>GO function</u> : arachidonic acid epoxygenase activity, coumarin 7-hydroxylase activity, enzyme, heme or oxygen binding, steroid hydroxylase activity; <u>GO process</u> : cellular response to cadmium ion, coumarin metabolic process, epoxygenase P450 pathway, exogenous drug catabolic process, heme metabolic process, oxidation-reduction process, xenobiotic metabolic process
Nsdhl	X				<u>pathways</u> : steroid / cholesterol biosynthesis; <u>GO function</u> : 3-beta-hydroxy-delta5-steroid dehydrogenase activity, sterol-4-alpha-carboxylate 3-dehydrogenase (decarboxylating) activity; <u>GO process</u> : lipid metabolic process, oxidation-reduction process, smoothened signaling pathway
Nipal1	X				<u>GO function</u> : magnesium ion transmembrane transporter activity
Usp2	X	X			<u>pathway</u> : TNF-alpha NF-kB signaling pathway; <u>GO function</u> : cysteine-type endopeptidase activity, ubiquitin-specific protease activity, metal ion binding; <u>GO process</u> : positive regulation of mitotic cell cycle, circadian behavior, circadian regulation of gene expression, negative regulation of transcription from RNA polymerase II promoter, proteasome-mediated ubiquitin-dependent protein catabolic process, protein deubiquitination, protein stabilization, regulation of proteasomal protein catabolic process
Rgs16	X				<u>pathways</u> : EGFR1 signaling, calcium regulation in the cardiac cell; <u>GO function</u> : GTPase activator activity; <u>GO process</u> : termination of G-protein coupled receptor signaling pathway, positive regulation of GTPase activity
Nnmt		X			<u>pathways</u> : biological oxidation (phase II) / methylation, nicotinate and nicotinamide metabolism; <u>GO function</u> : nicotinamide N-methyltransferase activity
Dhcr7		X			<u>pathways</u> : activation of gene expression by SREBF (SREBP) / regulation of cholesterol biosynthesis by SREBP (SREBF); <u>GO function</u> : 7-dehydrocholesterol reductase activity; <u>GO process</u> : blood vessel development, cell differentiation, oxidation-reduction process, regulation of cell proliferation
Lpin1			X		<u>pathways</u> : glycerophospholipid metabolism, triglyceride biosynthesis, cell cycle (M Phase); <u>GO function</u> : RNA polymerase II transcription factor binding, transcription coactivator activity, histone deacetylase binding, phosphatidate phosphatase activity, peroxisome proliferator activated receptor binding; <u>GO process</u> : actin cytoskeleton reorganization, cellular response to insulin stimulus, fatty acid catabolic process, mitochondrial fission, negative and positive regulation of transcription from RNA polymerase II promoter, positive regulation of histone deacetylation, protein dephosphorylation, ruffle organization
Nrg4		X			<u>pathways</u> : innate and adaptive immune system, cytokine signaling (interleukin signaling), involved in signal transduction, MAPK family signaling cascades
Igfbp1			X		<u>pathways</u> : regulation of Insulin-like Growth Factor (IGF) transport and uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs), metabolism of proteins; <u>GO function</u> : insulin-like growth factor I and II binding; <u>GO process</u> : regulation of cell growth, regulation of insulin-like growth factor receptor signaling
Fmo3			X	X	<u>pathway</u> : phase I of biological oxidation / detoxification; <u>GO function</u> : NADP binding, amino acid binding, flavin adenine dinucleotide binding, N,N-dimethylaniline monooxygenase activity, trimethylamine monooxygenase activity
Sult2a3			X	X	<u>pathways</u> : biological oxidation (phase II), bile secretion; <u>GO function</u> : sulfotransferase activity, 3'-phosphoadenosine 5'-phosphosulfate binding, drug binding
Cyp17a1				X	<u>pathways</u> : biological oxidation (phase I), steroid and Steroid hormone biosynthesis, metabolism of lipids and lipoproteins; <u>GO function</u> : 17-alpha-hydroxyprogesterone aldolase activity, heme or iron binding, steroid 17-alpha-monooxygenase activity; <u>GO process</u> : glucocorticoid biosynthetic process, positive regulation of steroid hormone biosynthetic process, oxidation-reduction process, progesterone metabolic process
Cyp2b13				X	<u>pathways</u> : arachidonic acid metabolism, biological oxidation (phase I), retinol metabolism, steroid hormone biosynthesis; <u>GO functions</u> : arachidonic acid epoxygenase activity, heme binding, oxidoreductase activity, steroid hydroxylase activity, oxygen binding
Mfsd2a				X	<u>GO functions</u> : phospholipid transporter activity, symporter activity; <u>GO process</u> : fatty acid / phospholipid transport, lipid transport across blood brain barrier
Slc22a7				X	<u>pathways</u> : SLC-mediated transmembrane transport / transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds

Table 20: Pathways and biological functions of the overlapping genes between the top 50 downregulated genes of caloric restriction and the plant bioactives

downregulated genes	R	P	Qd	Qi	Gi	function / pathways
Elovl3	X				X	<u>pathways</u> : fatty acid biosynthesis/elongation, triglyceride biosynthesis, fatty acyl-CoA biosynthesis, linoleic acid (LA) and alpha-linolenic acid (ALA)metabolism; <u>GO function</u> : transferase activity
Hsd3b5	X			X	X	<u>pathways</u> : metabolism of vitamin D, steroids and steroid hormones (e.g. androgen), glucocorticoid and mineralcorticoid metabolism; <u>GO function</u> : oxidoreductase activity, acting on the CH-OH group of donors, NAD or NADP as acceptor, steroid dehydrogenase activity, aldo-keto reductase (NADP) activity, NAD binding
Pdilt	X					<u>GO function</u> : protein disulfide isomerase activity, protein binding, peptidyl-proline 4-dioxygenase activity; <u>GO process</u> : spermatid development, cell migration, cell differentiation, cell redox homeostasis, multicellular organismal development, protein folding
G0s2	X	X	X			<u>pathways</u> : circadian regulation; <u>GO process</u> : positive regulation of extrinsic apoptotic signaling pathway
Wfdc2	X					<u>GeneRIFs</u> : affecting high density lipoprotein levels (216); <u>GO function</u> : aspartic-type endopeptidase inhibitor activity, cysteine-type endopeptidase inhibitor activity, serine-type endopeptidase inhibitor activity; <u>GO process</u> : negative regulation of peptidase activity
Cyp4a12a	X				X	<u>pathways</u> : phase I of biological oxidation / detoxification, arachidonic acid metabolism / synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE), retinol metabolism, PPAR signaling pathway, fatty acid degradation, inflammatory mediator regulation of TRP channels; <u>GO function</u> : iron ion binding, heme binding, aromatase activity, alkane 1-monooxygenase activity
Ddc	X					<u>pathways</u> : catecholamine biosynthesis; serotonin and melatonin biosynthesis; tyrosine, tryptophan, histidine and phenylalanine metabolism / biogenic amine synthesis; dopaminergic synapse/ dopaminergic neurogenesis; <u>GO function</u> : L-dopa decarboxylase activity, amino acid binding, enzyme binding, protein domain specific binding, pyridoxal phosphate binding; <u>GO process</u> : cellular amino acid metabolic process, dopamine biosynthetic process, response to toxic substance, serotonin biosynthetic process, synaptic vesicle amine transport
Alas2	X					<u>pathways</u> : metabolism of porphyrins / heme biosynthesis; glycine, serine and threonine metabolism; <u>GO function</u> : 5-aminolevulinat synthase activity, coenzyme binding, glycine binding, pyridoxal phosphate binding; <u>GO process</u> : heme biosynthetic process, hemoglobin biosynthetic process, cellular iron ion homeostasis, response to hypoxia, erythrocyte differentiation, cellular iron ion homeostasis
Hsph1	X					<u>pathways</u> : protein processing in endoplasmic reticulum, vesicle-mediated transport (binding and uptake of ligands by scavenger receptors), cellular response to stress; <u>GO process</u> : chaperone mediated protein folding requiring cofactor, negative regulation of intrinsic apoptotic signaling pathway in response to hydrogen peroxide, negative regulation of establishment of protein localization to mitochondrion, negative regulation of p38MAPK cascade, positive regulation of MHC class I biosynthetic process, positive regulation of NK T cell activation, positive regulation of protein tyrosine kinase activity, positive regulation of transcription from RNA polymerase II promoter, regulation of microtubule cytoskeleton organization
Car3	X	X				<u>pathways</u> : reversible hydration of carbon dioxide, nitrogen metabolism; <u>GO function</u> : metal ion binding (zinc, nickel), carbonate dehydratase activity, phosphatase activity; <u>GO process</u> : response to oxidative stress
Creld2	X					<u>GeneRIFs</u> : Probably a mediator in regulating the onset and progression of endoplasmic reticulum stress-associated diseases (217); <u>GO function</u> : calcium ion binding
Obp2a		X	X			<u>GeneRIFs</u> : Decreases lipid levels in liver → inhibits lipogenesis, stimulates beta-oxidation (218); enhances insulin signaling, suppress hepatic glucose production (219)
Hspa1b		X	X			<u>pathways</u> : metabolism of RNA / spliceosome / regulation of mRNA stability, MAPK signaling pathway, endocytosis, protein processing in endoplasmic reticulum, estrogen signaling pathway, antigen processing and presentation, cellular response to stress/ heat stress; <u>GO Process</u> : negative regulation of apoptotic process, negative regulation of cysteine-type endopeptidase activity involved in apoptotic process, response to heat
Csad		X				<u>pathways</u> : degradation of cysteine and homocysteine, sulfur amino acid metabolism, taurine and hypotaurine metabolism, mRNA processing; <u>GO function</u> : sulfinoalanine decarboxylase activity, pyridoxal phosphate binding; <u>GO process</u> : L-cysteine catabolic process to taurine
Ifit1					X	<u>pathways</u> : interferon signaling, antiviral mechanism by IFN-stimulated genes, cytokine signaling in immune system; <u>GO Process</u> : cellular response to interferon-alpha and -beta; innate immune response; defense response to virus

R = Resveratrol, P = phloridzin, Qd=quercetin diet, Qi = quercetin intraperitoneal, Gi = genistein intraperitoneal

The downregulation of G0s2 by CR, R, Qd and Qi could be interesting as well. NIELSEN et al. (2011) have shown that fasting decreases G0s2 expression in human adipose tissue, and AHN et al. 2013 have shown that short-term fasting decreases G0s2 expression in porcine adipose tissue, whereas 8-day CR does not influence G0s2 expression (231; 232). Nonetheless, this indicates that G0s2 expression depends on nutritional status. G0s2 codes for an inhibitor of adipose triglyceride lipase (ATGL), indicating that downregulation of G0s2 promotes lipolysis. Moreover, it is known that G0s2 is involved in the regulation of the cell cycle (231). ZHANG et al. (2016) have shown that G0s2 expression is inhibited by Foxo1 in liver and that this regulation is important for Foxo1's dependent effect on glucose and lipid metabolism (233). This probably indicates that G0s2 is involved in mediating CR effects and that phytonutrients are able to mimic this effect.

3.3.5. Calculation of Pearson correlation for gene expression between CR and phytonutrients in over-represented pathways for a better comparison between phytonutrients and their mimicking effect

Although there are several indications that R, Qd and Qi could be CR mimetics, it is difficult to say which is the best phytonutrient for mimicking CR effects because not every Entrez ID has been investigated in relation to every phytonutrient. For a better comparison, only the Entrez IDs which are investigated by all diet interventions are included in the rank product analysis (Qi and Gi are excluded). This leads to 15552 investigated Entrez IDs (compare Figure 2). Furthermore, it would be interesting if synergistic effects indicated that a diet rich in different phytonutrients would show a better mimicking effect than ingestion of one phytonutrient alone. For this, the results are combined whereby opposite regulations by the different phytonutrients lead to an exclusion of the gene. The mean values of the fold changes are calculated for the heat map.

Table 21: Number of regulated genes based on the q-value or the q-value in combination with a fold change (FC) > 1.5

	CR	R	P	Q	RP	RQ	PQ	RPQ
<i>number of upregulated genes based on ...</i>								
q value	1365	1185	1151	603	1973	1553	1453	2192
q-value & FC	38	304	6	23	304	315	26	316
<i>number of downregulated genes based on ...</i>								
q-value	1833	998	1793	548	2316	1347	1988	2462
q-value & FC	80	216	13	2	225	214	14	223
CR = caloric restriction, R = resveratrol, P = phloridzin, Q = quercetin, RP / RQ / PQ / RPQ = combined results of the different interventions, FC = fold change								

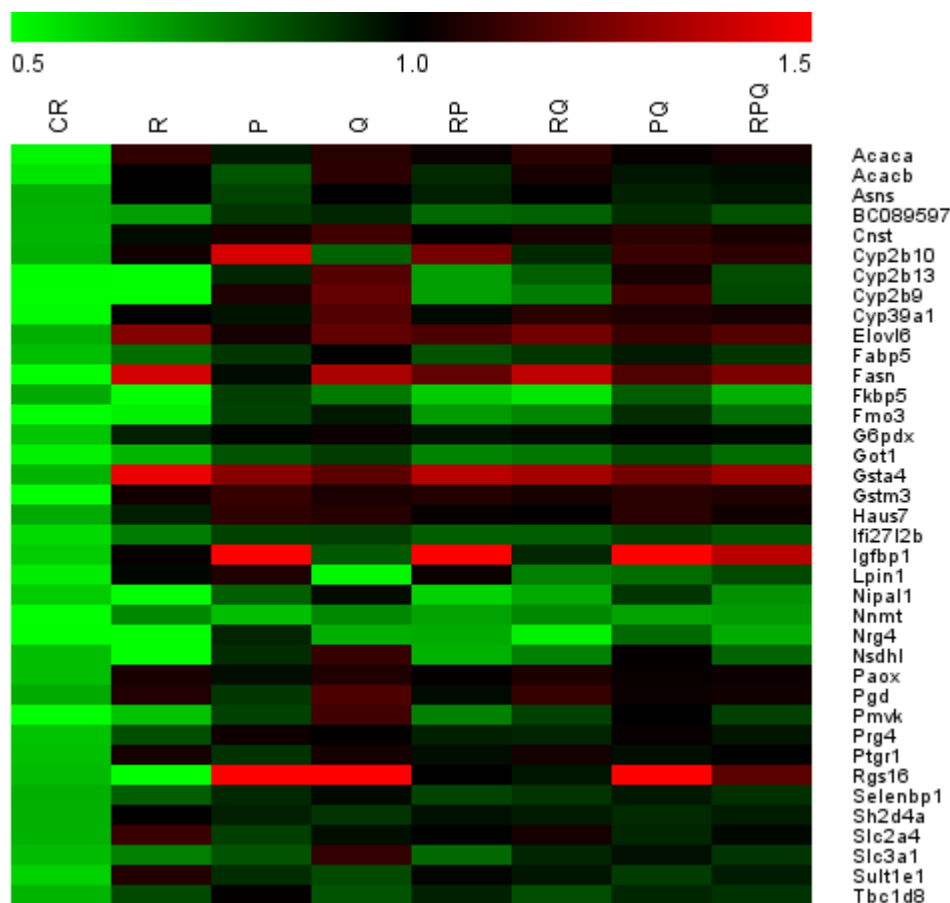


Figure 10: Heat map showing the fold changes of all upregulated CR genes with a fold change > 1.5 in presence of the different plant bioactives (individual and synergistic analysis)

Table 21 shows the number of regulated genes either based on the q-value or on the q-value combined with a fold change > 1.5. Figure 12 shows the percentage overlap based on the results from Table 21. These results show that when only the q-value is respected, R and P show a similar overlap, although P shows a bigger overlap for downregulated genes. Combining the results of R and P indicates that both phytonutrients together have a greater effect in mimicking CR. Further inclusion of Qd shows only a very small benefit regarding the upregulated genes. After including the fold change, only R was able to mimic the gene expression of CR. Combining the results of R with P or P and Qd shows only a small benefit, whereby a combination with Qd shows a deterioration in the overlap.

On further analysis, only the CR genes with a fold change > 1.5 are included. The heat maps presented in Figures 10 and 11 show the gene expression regulation for these genes by CR and the phytonutrients including synergistic effects. A small fold change indicates an upregulation in gene expression. Next it was analysed whether a phytonutrient can mimic the gene expression over all 15552 genes. Therefore, the Pearson correlation was calculated (Table 22A). All phytonutrients show a significant weak positive correlation with CR. Although the correlation between CR and Qd is weak, the result is significant probably because of the large number of genes.



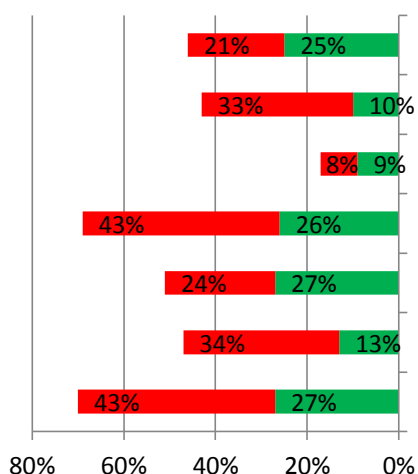
Figure 11: Heat map showing the fold changes of all downregulated CR genes with a fold change > 1.5 in presence of the different plant bioactives (individual and synergistic analysis)

Table 22: A.) Pearson correlation between CR and the plant bioactives (including synergistic analysis) based on all 15552 IDs; B.) Number of pathways with a high Pearson correlation between caloric restriction (CR) and the plant bioactives (total: 358 CR pathways)

(R = based on the fold changes of resveratrol, P = based on the fold changes of phloridzin, Q = based on the fold changes of quercetin, RP = based on the mean values of the fold changes of resveratrol and phloridzin, RQ = based on the mean values of the fold changes of resveratrol and quercetin, PQ = based on the mean values of the fold changes of phloridzin and quercetin, RPQ = based on the mean values of the fold changes of resveratrol, phloridzin and quercetin)

A.)	Pearson correlation	p-value	B.)	Pearson correlation					
				≥ 0.5	≥ 0.6	≥ 0.7	≥ 0.8	≥ 0.9	≥ 0.95
R	0.26	< 0.0001	R	106	82	58	40	23	17
P	0.20	< 0.0001	P	53	37	26	16	6	2
Q	0.02	<0.05	Q	45	34	26	16	4	1
RP	0.31	< 0.0001	RP	121	93	75	45	24	18
RQ	0.24	< 0.0001	RQ	104	90	63	36	22	17
PQ	0.17	< 0.0001	PQ	56	41	32	18	8	4
RPQ	0.29	< 0.0001	RPQ	120	99	77	39	25	19

Overlap based on the q-value



Overlap based on the q-value & fold change

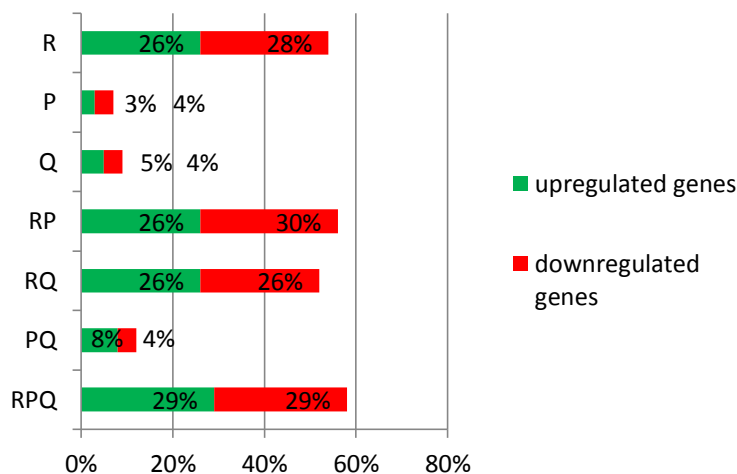


Figure 12: Overlap between CR and plant bioactives including synergistic effects

(Calculation based on the regulated genes identified by limited gene pool (15552 IDs); significant regulated genes identified with the q-value or the q-value in combination with a fold change > 1.5)

For a better determination of which pathways are mimicked by the phytonutrients, a Pearson calculation is repeated for all pathways that include at least one CR gene with a fold change > 1.5. Small pathways that consist of one or two genes are excluded. This leads to 358 relevant pathways (Appendix L). Table 22B shows the number of pathways with a correlation of 0.5 to 0.95 for the respective intervention. R seems to be able to mimic the gene expression of the most pathways. Furthermore, a combination with P, Qd or both is able to increase the number of mimicked pathways. Table 23 shows all pathways with a Pearson correlation $r > 0.9$.

Nnmt and Igfbp1 are genes which seem to be of interest in our analysis. The pathways 'Regulation of Insulin-like Growth Factor (IGF) Transport and Uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)' (Reactome) and 'Nicotinate and nicotina-

mid metabolism – *Mus musculus* (mouse)’ (KEGG) include these genes, so the heat maps of these pathways are presented in Figures 13 and 14. As expected, Qd is the only dietary phytonutrient that shows a positive correlation regarding the Igfbp1 pathway; the other phytonutrients show a negative correlation (see Appendix L). The results for the pathway ‘Nicotinate and nicotinamide metabolism – *Mus musculus* (mouse)’ (KEGG) indicate that P and all combinations with P (RP, PQ, RPQ) show a high correlation with CR expression.

Table 23: Pathways with a high Pearson correlation (≥ 0.9) in gene expression between caloric restriction (CR) and the plant bioactives

pathway	R	P	Q	RP	RQ	PQ	RPQ
Glycoprotein hormones - Reactome	0,86	0,89	0,91	0,89	0,89	0,94	0,91
Peptide hormone biosynthesis - Reactome	0,87	0,84	0,87	0,89	0,90	0,90	0,91
Steroid Biosynthesis - Wikipathways	0,98	0,25	0,50	0,99	0,98	0,44	0,98
Androgen biosynthesis - Reactome	0,97	0,31	0,52	0,97	0,97	0,46	0,97
Metabolism of steroid hormones and vitamin D - Reactome	0,97	0,35	0,37	0,97	0,97	0,42	0,96
Steroid hormones - Reactome	0,97	0,35	0,37	0,97	0,97	0,42	0,96
FMO oxidizes nucleophiles - Reactome	0,93	0,79	0,91	0,99	0,98	0,85	1,00
L-cysteine degradation I - MouseCyc	1,00	0,95	0,51	1,00	0,98	1,00	1,00
Serotonin and melatonin biosynthesis - Reactome	1,00	-0,38	-0,38	0,98	1,00	-0,39	0,97
Catecholamine biosynthesis - Reactome	0,99	-0,50	-0,69	0,99	0,98	-0,76	0,99
serotonin and melatonin biosynthesis - MouseCyc	1,00	-0,38	-0,38	0,98	1,00	-0,39	0,97
biosynthesis of serotonin and melatonin - MouseCyc	1,00	-0,38	-0,38	0,98	1,00	-0,39	0,97
4-hydroxyproline degradation I - MouseCyc	0,90	0,96	0,99	0,95	0,94	0,98	0,96
Organic anion transport - Reactome	0,95	0,97	0,77	0,99	0,96	0,96	0,99
tetrapyrrole biosynthesis II - MouseCyc	0,98	0,65	0,32	0,99	0,96	0,57	0,97
phenylalanine degradation III - MouseCyc	0,90	-0,26	0,84	0,65	0,93	0,26	0,75
Methionine salvage pathway - Reactome	0,98	0,78	0,78	0,93	0,97	0,94	0,97
Mineralocorticoid biosynthesis - Reactome	1,00	0,32	0,48	1,00	1,00	0,44	1,00
Glucocorticoid biosynthesis - Reactome	1,00	0,30	0,49	1,00	1,00	0,44	1,00
ADP signalling through P2Y purinoceptor 1 - Reactome	0,51	0,52	0,90	0,58	0,69	0,72	0,68
Highly calcium permeable nicotinic acetylcholine receptors - Reactome	0,70	0,94	0,80	0,90	0,77	0,96	0,91
Taurine and hypotaurine metabolism - Mus musculus (mouse) - KEGG	0,95	0,92	-0,71	0,98	0,92	0,84	0,99
Ovarian steroidogenesis - Mus musculus (mouse) - KEGG	0,96	0,21	0,40	0,96	0,96	0,33	0,96
Nicotine Activity on Dopaminergic Neurons - Wikipathways	0,93	-0,22	0,18	0,92	0,95	-0,15	0,94
Glucuronidation - Wikipathways	0,90	0,15	0,06	0,89	0,90	0,14	0,86
Reversible Hydration of Carbon Dioxide - Reactome	0,91	0,18	0,85	0,90	0,92	0,76	0,92
Glucocorticoid & Mineralcorticoid Metabolism - Wikipathways	1,00	0,34	0,53	1,00	1,00	0,48	1,00
Highly calcium permeable postsynaptic nicotinic acetylcholine receptors - Reactome	0,64	0,93	0,74	0,89	0,74	0,93	0,90
Biogenic Amine Synthesis - Wikipathways	0,90	-0,09	-0,10	0,91	0,87	-0,11	0,86
Dopaminergic Neurogenesis - Wikipathways	0,90	0,01	-0,15	0,91	0,84	-0,11	0,86

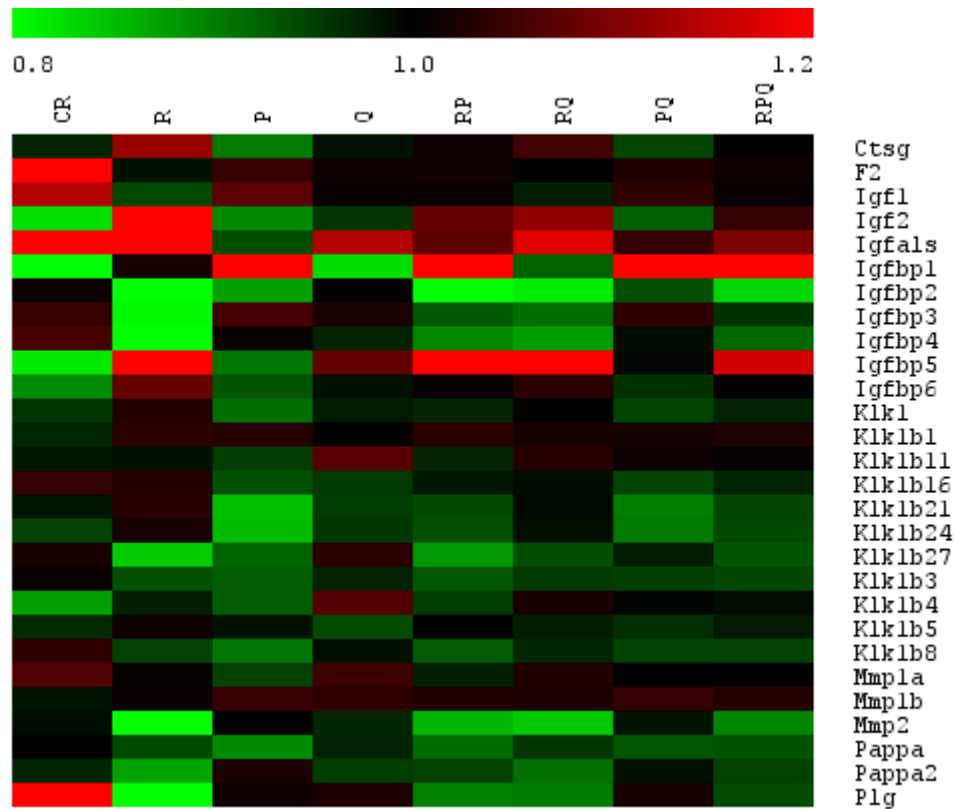


Figure 13: Heat map of genes of the pathway 'Regulation of Insulin-like Growth Factor (IGF) Transport and Uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)' (Reactome)

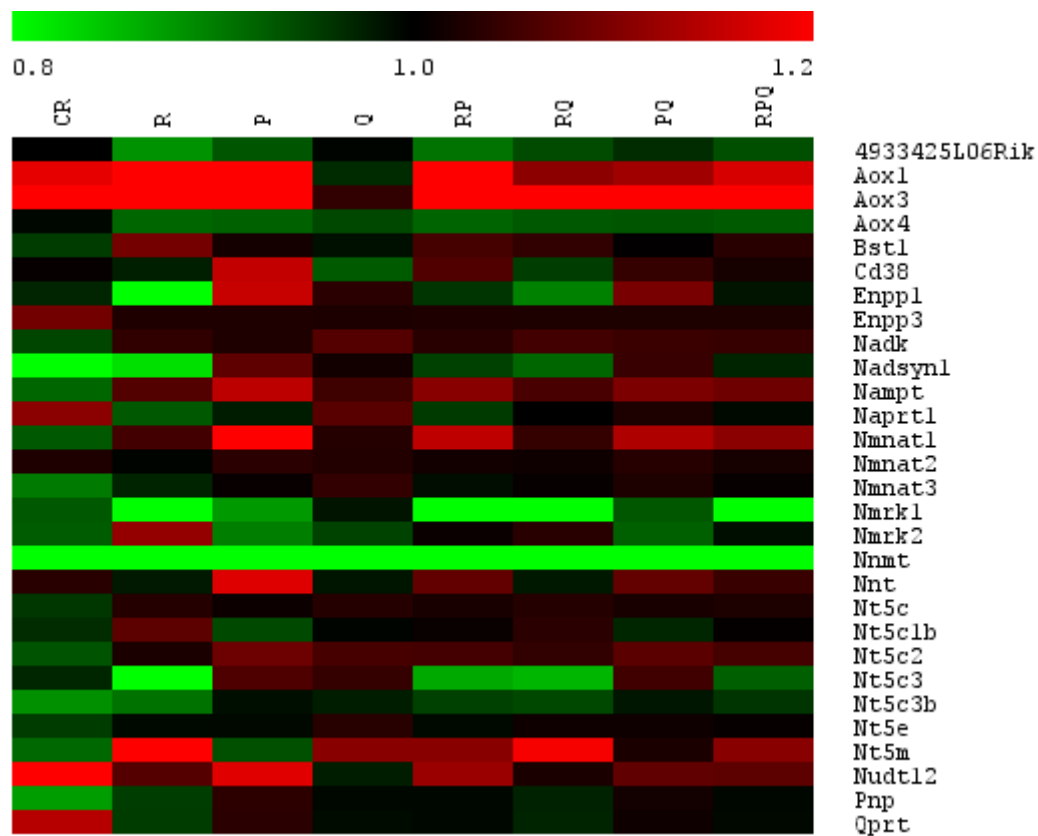


Figure 14: Heat map of genes of the pathway 'Nicotinate and nicotinamide metabolism - Mus musculus (mouse)' (KEGG)

3.4. Analysis of longevity genes in mouse

As already mentioned, CR is known for a lifespan-expanding effect (106). Therefore, it is of interest whether phytonutrients are able to extend the lifespan as well. In *Mus musculus*, 112 genes are mentioned in context with longevity; 34 of them have anti-longevity effects, 75 have pro-longevity effects and 3 have not been classified (234). Genes in each category are up- and downregulated by the different intervention groups (Table 24). Therefore, it is impossible to say whether CR or a phytonutrient has an impact on longevity because it is difficult to say which gene has the biggest impact. According to GenAge, Ghr is mentioned as the gene with the largest impact on lifespan in mice (235). The knockout of Ghr increases lifespan by up to 40-50%. The results show that CR, P and Qi downregulate the expression of Ghr (Table 25). R, Qd and Gi do not influence gene expression.

Table 24: Influence of caloric restriction and plant bioactives on longevity genes

<u>anti-longevity genes (n = 34)</u>	CR	R	P	Q	Qi	Gi
upregulation	3	1	1	2	3	2
downregulation	5	2	4	2	3	2
<u>pro-longevity genes (n = 75)</u>	CR	R	P	Q	Qi	Gi
upregulation	8	8	5	5	5	3
downregulation	17	5	13	3	6	2

Table 25: CR longevity genes which are influenced by at least one of the plant bioactive

<i>downregulated anti-longevity genes by CR</i>				R	P	Q	Qi	Gi
12575	Cdkn1a	cyclin-dependent kinase inhibitor 1A (P21)		↓		↑		
66143	Eef1e1	eukaryotic translation elongation factor 1 epsilon 1						
14600	Ghr	growth hormone receptor			↓		↓	
625249	Gpx4	glutathione peroxidase 4		----	↑			
20416	Shc1	src homology 2 domain-containing transforming protein C1						↓
<i>upregulated pro-longevity genes by CR</i>								
12189	Brca1	breast cancer 1						
218294	Cdc14b	CDC14 cell division cycle 14B				↓	↓	
14824	Grn	granulin		↑				
17685	Msh2	mutS homolog 2 (E. coli)						
114774	Pawr	PRKC, apoptosis, WT1, regulator			↑			
18534	Pck1	phosphoenolpyruvate carboxykinase 1, cytosolic		↑				
22590	Xpa	xeroderma pigmentosum, complementation group A		↑				
22596	Xrcc5	X-ray repair complementing defective repair in Chinese hamster cells 5						

Next it is analysed whether the phytonutrients regulate the same genes as CR (Table 25). R could be the only phytonutrient which mimics the effect of CR on longevity because four genes are regulated in the same direction as CR and no gene is regulated in the opposite direction. Qd regulates only two of these genes, but both are regulated

in the opposite direction as compared to CR. P regulates two genes in the same direction as CR, but the other two show opposite regulation. However, it is nonetheless possible that phytonutrients have a life-extending effect without affecting the same genes as CR.

3.5. Transcription factor binding sites (TFBs)

To further clarify whether the phytonutrients are mimetics of CR, it was investigated whether they address the same transcription factor binding sites (TFBs) as CR. To identify TFBs which are important for CR, all significantly regulated CR genes which are investigated by at least one phytonutrient were uploaded in oPOSSUM separated by up- and downregulated genes. Not all downregulated genes could be analysed because oPOSSUM limits the number of potential genes to 2000. Therefore, only the top 2000 downregulated genes sorted by fold change were investigated.

All TFBs with $z > 5$ or $F > 5$ were included in the analysis. This resulted in 121 TFBs which are addressed by the upregulated CR genes and 94 TFBs which are addressed by downregulated CR genes (Appendix U and V). To determine whether the phytonutrients address the same TFBs as CR, next the overlapped genes between CR and the phytonutrients separated by up- and downregulated genes were analysed with oPOSSUM. All TFBs with $z > 5$ or $F > 5$ were included too. Table 26 shows the absolute and percentage overlaps between the TFBs mentioned by the CR genes and the TFBs revealed by the overlapped genes between CR and the respective phytonutrient. All phytonutrients address TFBs which are mentioned by CR. Regarding the upregulated genes, Qd shows the largest overlap followed by P and R. Regarding the downregulated genes P, Qd and Qi show a high overlap with CR. This confirmed that Qd could be a CR mimetic. Tables 27 and 28 show the top TFBs addressed by CR. For this, the top 10 TFBs sorted by z-score and the top 10 TFBs sorted by F-score are summarised. Table 29 shows the functions of the transcription factors (TF) which typically address the top TFBs mentioned by CR. The functions are revealed with the UniProt database. Functions and biological processes which are not important in murine liver cases are not mentioned but instead are presented in Appendix W.

Table 26: Total and percental overlap in transcription factor binding sites (TFBs) putatively affected by CR and the plant bioactives

	total (and percental) overlap				
	R	P	Qd	Qi	Gi
121 TFBs addressed by upregulated CR genes	67 (55%)	73 (60%)	78 (64%)	53 (44%)	61 (50%)
94 TFBs addressed by downregulated CR genes	17 (18%)	64 (68%)	61 (65%)	67 (71%)	13 (14%)

TFBs = transcription factor binding sites, CR = caloric restriction; R = resveratrol, P = phloridzin, Qd = quercetin (diet), Qi = quercetin (intraperitoneal), Gi = genistein (intraperitoneal)

Table 27: Top transcription factor binding sites (TFBs) putatively affected by upregulated genes of caloric restriction identified with the z- or F-score and the overlap with the plant bioactives

JASPAR ID	Transcription factor	UniProt ID	R	P	Qd	Qi	Gi
MA0006.1	Ahr - Aryl hydrocarbon receptor, Arnt - Aryl hydrocarbon receptor nuclear translocator	P30561 P53762					
MA0141.1	Esrrb - Steroid hormone receptor ERR2	Q61539					
MA0099.2	Fos - Proto-oncogene c-Fos, Jun - Transcription factor AP-1	P01101 P05627					
MA0158.1	Hoxa5 - Homeobox protein Hox-A5	P09021					
PB0142.1	Jdp2 - Jun dimerization protein 2	P97875					
MA0039.2	Klf4 - Krueppel-like factor 4	Q60793					
PB0039.1	Klf7 - Krueppel-like factor 7	Q99JB0					
MA0059.1	Max - Protein max, Myc - Myc proto-oncogene protein	P28574 P01108					
MA0104.2	Mycn - N-myc proto-oncogene protein	P03966					
MA0056.1	Mzf1 - Myeloid zinc finger 1	A1L358					
MA0057.1	Mzf1 - Myeloid zinc finger 1	A1L358					
MA0060.1	Nfya - Nuclear transcription factor Y subunit alpha	P23708					
MA0065.2	Pparg - Peroxisome proliferator-activated receptor gamma, Rxra - Retinoic acid receptor RXR-alpha	P37238 P28700					
MA0079.2	Sp1 - Transcription factor Sp1	O89090					
MA0081.1	Spib - Transcription factor Spi-B	O35906					
MA0095.1	Yy1 - Transcriptional repressor protein YY1	Q00899					
MA0103.1	Zeb1 - Zinc finger E-box-binding homeobox 1	Q64318					
MA0146.1	Zfx - Zinc finger X-chromosomal protein	P17012					
MA0130.1	Znf354c - Zinc finger protein 354C	Q571J5					

R = resveratrol, P = phloridzin, Qd = quercetin (diet), Qi = quercetin (intraperitoneal), Gi = genistein (intrap.)

Table 28: Top transcription factor binding sites (TFBs) putatively affected by downregulated genes of caloric restriction identified with the z- or F-score and the overlap with the plant bioactives

JASPAR ID	Transcription factor	UniProt ID	R	P	Qd	Qi	Gi
PB0002.1	Arid5a - AT-rich interactive domain-containing protein 5A	Q3U108					
MA0102.2	Cebpa - CCAAT/enhancer-binding protein alpha	P53566					
MA0099.2	Fos - Proto-oncogene c-Fos, Jun - Transcription factor AP-1	P01101 P05627					
MA0041.1	Foxd3 - Forkhead box protein D3	Q61060					
PB0016.1	Foxj1 - Forkhead box protein J1	Q61660					
PB0017.1	Foxj3 - Forkhead box protein J3	Q8BUR3					
PB0123.1	Foxl1 - Forkhead box protein L1	Q64731					
MA0046.1	Hnf1a - Hepatocyte nuclear factor 1-alpha	P22361					
MA0158.1	Hoxa5 - Homeobox protein Hox-A5	P09021					
MA0056.1	Mzf1 - Myeloid zinc finger 1	A1L358					
MA0060.1	Nfya - Nuclear transcription factor Y subunit alpha	P23708					
MA0063.1	Nkx2-5 - Homeobox protein Nkx-2.5	P42582					
MA0122.1	Nkx3-2 - Homeobox protein Nkx-3.2	P97503					
MA0081.1	Spib - Transcription factor Spi-B	O35906					
MA0084.1	Sry - Sex-determining region Y protein	Q05738					
PB0080.1	Tbp - TATA-box-binding protein	P29037					
MA0103.1	Zeb1 - Zinc finger E-box-binding homeobox 1	Q64318					
PB0093.1	Zfp105 - Putative uncharacterized protein	Q3UHV1					
MA0130.1	Znf354c - Zinc finger protein 354C	Q571J5					

R = resveratrol, P = phloridzin, Qd = quercetin (diet), Qi = quercetin (intraperitoneal), Gi = genistein (intrap.)

Table 29: Overview on the transcription factors and their biological function

TF	function / biological process
Ahr	activates the expression of multiple phase I and II enzyme genes / xenobiotic metabolic process / response to stress / toxic substance / xenobiotic stimulus, circadian regulation of gene expression, regulation of cell cycle / morphogenesis / size, cellular response to cAMP, common bile duct and liver development, regulation of gene expression and transcription
Arid5a	regulation of histone acetylation, regulation of transcription
Arnt	cell differentiation, regulation of hormone biosynthetic process, regulation of protein sumoylation, regulation of transcription (for example in response to oxidative stress), response to hypoxia and toxic substance,
Cepba	regulates gluconeogenesis and lipogenesis by interacting with Foxo1 and Srebf1, liver development, cholesterol metabolic process, cytokine-mediated signaling pathway, mitochondrion organization, regulation of cell cycle /maturation / proliferation, regulation of transcription, Notch signaling pathway, urea cycle
Esrrb	regulation of transcription
Fos	ageing, signal transduction (e.g. SMAD protein signaling), cell proliferation and differentiation, regulation of transcription, transforming growth factor (TGF) beta receptor signaling pathway
Foxd3	regulation of transcription
Foxj1	activation of GTPase activity, cell differentiation, regulation of NF-kappaB transcription factor activity, regulation of transcription
Foxj3	cell differentiation, regulation of transcription
Foxl1	cell differentiation, regulation of transcription, Wnt signaling pathway
Hnf1a	transport of bile acid, bile salt, cholesterol (reverse) and fatty acids, bile acid, fatty acid and cholesterol biosynthetic process, glucose homeostasis, response to glucose and oxidative stress, liver development, regulation of transcription / histone acetylation, regulation of hormone secretion (e.g. insulin), Wnt and SMAD signaling pathway
Hoxa5	cell migration, regulation of apoptotic process, positive regulation of receptor biosynthetic process, regulation of transcription
Jdp2	regulation of transcription, positive regulation of histone deacetylation
Jun	ageing, circadian rhythm, liver development, regulation of apoptotic process, regulation of protein autophosphorylation, regulation of transcription (e.g. in response to endoplasmic reticulum stress), regulation of cell cycle / differentiation / proliferation, regulation of ERK1 and ERK2 cascade, regulation of GTPase activity, release of cytochrome c from mitochondria, SMAD protein signal transduction, TGF beta receptor signaling pathway
Klf4	Wnt signaling pathway, cellular response to growth factor stimulus, regulation of cell migration /differentiation / proliferation, regulation of apoptotic process, regulation of ERK1 and ERK2 cascade, negative regulation of NF-kappaB transcription factor activity, negative regulation of phosphatidylinositol 3-kinase signaling, negative regulation of protein kinase B signaling, negative regulation of response to cytokine stimulus, regulation of transcription, positive regulation of cellular protein metabolic process, positive regulation of nitric oxide biosynthetic process, positive regulation of telomerase activity
Klf7	regulation of transcription
Max	regulation of transcription
Myc	Wnt signaling pathway, regulation of apoptotic process, cell cycle arrest, cellular response to DNA damage stimulus /drugs / interferon-alpha, chromatin remodeling / chromosome organization / regulation of DNA biosynthetic process and telomere maintenance, MAPK cascade, regulation of gene expression and transcription, regulation of cell proliferation, protein processing
Mycn	regulation of ROS metabolic process, positive regulation of cell death and proliferation, regulation of transcription
Mzf1	regulation of transcription
Nfya	regulation of transcription, regulation of circadian clock genes

Table 29/b: Overview on the transcription factors and their biological function

Nkx2-5	Wnt signaling pathway, cell differentiation /proliferation, apoptosis, regulation of gene expression and transcription, positive regulation of sodium ion transport
Nkx3-2	negative regulation of apoptotic process, regulation of transcription
Pparg	regulates beta-oxidation, regulation of apoptosis, signal transduction regulation of cell maturation / proliferation, cellular response to insulin stimulus, response to dietary excess, diet induced thermogenesis, glucose homeostasis, inflammatory response, lipoprotein and long-chain fatty acid transport, low-density lipoprotein particle receptor biosynthetic process, negative regulation of cholesterol storage, negative regulation of interferon-gamma-mediated signaling pathway, negative regulation of peptide hormone secretion, regulation of transcription, peroxisome proliferator activated receptor signaling pathway, regulation of circadian rhythm,
Rxra	ageing, cellular response to insulin stimulus, inflammatory response, liver development, regulation of cell proliferation, regulation of gene expression, transcription and translation, peroxisome proliferator activated receptor signaling pathway, regulation of apoptosis, retinoic acid receptor signaling pathway
Sp1	involved in cell growth, apoptosis, differentiation and immune responses , liver development, regulation of transcription, circadian rhythm
Spib	regulation of transcription
Sry	cell differentiation, regulation of gene expression and transcription
Tbp	regulation of transcription
Yy1	cell differentiation, cellular response to DNA damage stimulus, cellular response to interleukin-1, chromosome organization, regulation of gene expression and transcription
Zeb1	cellular response to amino acid stimulus, regulation of cell proliferation, regulation of transcription, regulation of TGF beta receptor signaling pathway
Zfp105	regulation of transcription
Zfx	regulation of transcription
Znf354c	regulation of transcription

TF = transcription factor

4. Discussion

This paper introduces a new approach to identify potential mimetics of CR. The advantages of this method are fast calculation, low cost and the ability to analyse several experiments together, which limits the occurrence of random results; in addition, no protracted in vivo or in vitro experiments are necessary. Furthermore, this method limits the risk of wasting time and research funds because it reduces the probability that an experiment does not show the desired result. Therefore, it allows for more purposeful work. The only condition of this approach is that gene expression data must be available. Databases like GEO and ArrayExpress are useful to find these data. All previous experiments can be included because no control group with a CR diet is necessary. The results of all available CR experiments can be summarised to get a control. For this, it is necessary to unify the different experiments. This could be a source of error because experimental design varies in the studies (e.g., in the number of animals and replicates, age, gender, genetic strain, degree of CR, concentration of phytonutrients, contribution of the standard diet and duration of the intervention). Furthermore, different microarrays are used, which can influence the results because each gene is not ana-

lysed on each array and because the different arrays (e.g., Affymetrix and Illumina) need different R packages for pre-processing and identifying the gene expression changes. It is tried to compensate for this by pre-processing the raw data using the quantile normalisation implemented in each R package. Another difficulty is that the genes are named differently on the microarray chips. It is tried to compensate for this by using the Entrez IDs, but errors in naming could not be ruled out. Moreover, each annotation update on a chip can change the results. Nonetheless, the mentioned approach is useful in getting a first indication about both the CR function and the overlap between CR and phytonutrients; this must be confirmed by further investigation.

To identify the best method for detecting significant expression changes, several methods are compared – the t-test, the moderated t-test, the Wilcoxon test and the rank product analysis in R. The t-test is the standard method of calculating expression changes, but the experiments' box plots show that the data are not normally distributed, so the Wilcoxon test should be used instead. However, our results indicate that the Wilcoxon test does not work with a small number of replicates. Consequently, no up- and downregulated genes other than CR can be identified with the Wilcoxon test. After combining the Wilcoxon test with the fold change, no genes were identified for CR. Therefore, the Wilcoxon test was useless in our analysis. The t-test and the moderated t-test show a larger number of regulated genes. However, one disadvantage of these methods is that each experiment was analysed by itself; the results had to be combined afterward with a one-sided binominal test and a chi-squared test. The chi-squared test also does not work with a small number of experiments. For example, if all three experiments show a significant upregulation, the chi-squared test leads to a non-significant result. Therefore, the '3-fold bigger' method was used instead. A few expression changes were identified, but after combining the t-test with a fold change, the number of regulated genes declined drastically. Moreover, one disadvantage of the t-test and moderated t-test is that they only reveal genes whose expressions have obviously changed. If the expression change is very low or the p-value is a little too large, the gene is not further mentioned. This can drastically influence the results of the overlapped analyses. This could be very important because the gene with the largest expression change does not always cause the effect in vivo. The rank product analysis avoids the disadvantages of the previous methods because the data for all experiments can be uploaded at the same time, and the expression changes of each experiment are ranked by size. Afterward, the positions of each gene in the rankings are multiplied, which leads to a general ranking over all the experiments. Therefore, this method includes the tendencies of expression changes and shows which genes are consistently up- or downregulated over all experiments – even if no significant p-value can be iden-

tified with a t-test. Thus, the rank product analysis seems to be the most useful method. The gene lists obtained for CR and the phytonutrients can be used to identify an overlap in gene expression or in function. Many tools are available for enrichment analysis, but it is decided to use CPDB because it includes the pathways of many known databases, such as KEGG, Reactome and MouseCyc. Nonetheless, other tools could provide other results.

As mentioned above, R is known as a potential CR mimetic (236). Our results indicate as well that R shows the largest overlap in gene expression and that therefore many CR functions could be mimicked. However, our results show too that each of the investigated phytonutrients regulates some genes in the same direction and that overlapped pathways could be identified in enrichment analysis. Further studies are necessary to see if this overlap is sufficient to mimic CR *in vivo*.

For a better assumption it could be useful to investigate the expression changes of genes which are known to be important for the beneficial effects of CR. Sirt1 is the most popular gene. In contrast to the results of past investigations, R shows no upregulation in our analysis, whereas Sirt1 expression is increased by Qd. Thus, the upregulation of Sirt1 indicates that Qd could be a CR mimetic even if only a small number of overlapped genes are identified.

The presumption that Qd is a CR mimetic is supported by the upregulation of Igfbp1 and the downregulation of Irs1 and Igfals. This indicates that Qd inhibits Igf1 signalling, which is associated with many beneficial CR effects (see above). The fact that CR downregulates Irs1 was shown by MA et al. (2014) in murine hippocampus too (237). In contrast, GESING et al. (2014) have shown that CR increases Irs1 expression in long-lived Ames dwarf (*df/df*) mice (238). The results of WANG et al. (2013) indicate that the effect of CR on Irs1 phosphorylation in skeletal muscle of humans is strongly dependent on the composition of the diet (fat content, carbohydrate content) (239). Moreover, the ability of CR to regulate phosphorylation of Irs1 is dependent on AMPK and mTOR signalling (240). To our knowledge, nothing is known about the influence of quercetin on the expression of these genes in murine liver, but quercetin ameliorates insulin resistance by beneficial regulation of Irs1 function in human umbilical vein endothelial cells (241). Furthermore, quercetin reduces Irs1 concentration in human keloid fibroblasts and in AT6.3 cells of rats (prostate adenocarcinoma cell line) (242; 243). This is associated with an inhibited Igf1-induced proliferation.

It is assumed that Qd and CR upregulate the expression of Igfbp1 by increasing the expression and/or activity of Foxo1 and Foxa1. PANOWSKI et al. (2007) have seen that the lifespan-expanding effect of CR in *C. elegans* is mediated by Pha-4 (ortholo-

gous to Foxa1, Foxa2 and Foxa3) (201). The authors suspect that the role of Pha-4 in longevity is specific for CR and that Pha-4 overexpression can increase the lifespan in daf-16(Foxo)-null mutant strains. Our results indicate that Qd probably addresses the same mechanism. Whether Foxa1 is important for lifespan extension in mice as well should be further analysed.

As mentioned above, Foxo1 is associated with oxidative stress. KIM et al. (2008) have shown that PI3K/Akt activation and Foxo1 phosphorylation increase with ageing, which leads to enhanced oxidative stress (244). Several previous investigations indicate that quercetin acts as an antioxidant and prevents oxidative stress (245; 246). Moreover, quercetin modulates PI3K/Akt activation, Foxo1 phosphorylation and mTOR signalling (247; 248; 249). This indicates that quercetin reduces oxidative stress by similar mechanisms to CR.

Whether Qd is also able to affect growth hormone signalling is not really clear. However, Qi decreases Ghr expression. This probably indicates that higher dosages of Q could be more effective in influencing the GH-Igf1 axis. As mentioned above, Ghr is discussed as the gene with the biggest impact on longevity (250). In summary, our results indicate that Qd could mimic CR effects by inhibiting GH/Igf1 signalling, increasing the activity of Foxo1 and increasing the expression of Sirt1 and Nnmt. Regarding its effect on longevity, it is found that quercetin increases lifespan in *C. elegans* and *Saccharomyces cerevisiae* (251; 252). To our knowledge, no experiments have analysed the effect of Q in mice. Whether quercetin is a CR mimetic should be further analysed in vivo.

Regarding the analysis of longevity genes, it is probable that each phytonutrient extends the lifespan because it is difficult to say how these genes interact and which gene triggers for the anti- or pro-longevity effect. P downregulates the expression of Ghr, which indicates that P probably increases longevity even though Sirt1 expression is decreased. P expands the lifespan of *Saccharomyces cerevisiae* dose-dependently (253). In contrast to our results, superoxide dismutases (Sod1 and Sod2) and Sirt1 seem to be involved in this effect. Whereas the expression of Sod1 and Sod2 is not influenced by P in our analysis, the expression of Sod3 is decreased. It is possible that these differences are attributable to the P dosage. This should be further investigated. Thus, it is impossible to say whether P increases lifespan in mice too.

For R, a lifespan-expanding effect is seen only in mice that are fed a high-calorie diet, not in mice that are fed a standard diet (46; 81). G is shown to promote lifespan in *C. elegans*, whereas in *D. melanogaster* there is an inverse correlation between G concentration and maximal lifespan (254; 255). In humans it is discussed too whether G

could promote longevity via its antioxidant effects and by activating the NF kappa B pathways (256; 257). In summary, our results indicate that all phytonutrients could be able to increase lifespan but via mechanisms other than CR.

Our results further indicate that CR addresses many more pathways than growth hormone and Igf1 signalling. Some of them are already mentioned in the context of CR (e.g., ABC transporters (258; 259; 260), cholesterol efflux (259; 261), bile metabolism (262; 261), the cholesterol metabolism (195), HDL and LDL uptake into hepatocytes via scavenger receptor class B, member 1 (Scarb1) and low-density lipoprotein receptor (Ldlr) (263; 264), the androgen metabolism and androgen receptor signalling (265; 266; 267), PPAR signalling pathway (268; 269; 270; 271; 272; 40), AMPK signalling (240), biological oxidation (10; 273; 274; 275; 276), the circadian rhythm (277; 278; 279), apoptosis (156; 280; 281), expression of ribosomal subunits (282), phagosome/autophagy/mitophagy mechanisms (283; 284; 285; 286; 32), processing of mRNA (including splicing) (178), gene expression/translation regulation (287), lipid metabolism (288; 274; 289; 290; 19; 291; 292), carbohydrate/pyruvate metabolism (293; 269; 294; 295), the citric acid cycle (296; 297), the electron transport chain (293; 296), the pentose phosphate pathway (298; 299; 300; 301), the biotin metabolism (302; 303; 304), the regulation of immune system/inflammation/oxidative stress (305; 306; 307; 308; 309; 310), Interleukin-6 signalling (311; 312), epidermal growth factor receptor (EGFR1) signalling (313; 314), amino acid metabolism, protein synthesis/processing/turnover, and ubiquitin-dependent protein degradation (315; 293; 294; 316; 295; 317; 318; 319)). However, others have not been revealed in the context of CR before, such as the influence on oestrogen metabolism, retinol metabolism, the urea cycle, glutathione metabolism including the γ -glutamyl cycle, starch and sucrose metabolism, vesicle-mediated transport, selenium metabolism, heme biosynthesis/metabolism of porphyrins, interferon signalling, toll-like receptor signalling, complement and coagulation cascade, and the expression of metal ion SLC transporters (especially of zinc transporters). It is necessary to confirm whether CR influences these pathways in vivo as well because they could lead to a better understanding of the mechanisms of CR. For example, it is known that all-trans-retinoic acid (atRA) is involved in bile acid homeostasis (320). Therefore, it is possible that the influence of CR on retinol metabolism is involved in the regulation of cholesterol and bile acid. The influence in zinc SLC transporters is very interesting too. It is known that zinc is involved in immune function, apoptosis and insulin resistance (321; 322; 323; 324). Furthermore, some sirtuins are zinc-dependent (325). CABREIRO et al. (2008) have shown that ageing is associated with zinc deficiency, which leads to higher oxidative stress (326). All of these functions have already been discussed in the context of CR as well

(see above). This leads to the hypothesis that the influence of CR on zinc transporters or zinc metabolism could be involved in the beneficial effects of CR. This hypothesis is supported by the upregulation of Mt1 by CR, which is important for cellular zinc ion homeostasis. Unfortunately, no phytonutrient is able to mimic the effect on SLC transporters, but R and Qd upregulate the expression of Mt1 too. Whether zinc is important for beneficial CR effects should be further analysed.

Nonetheless, all phytonutrients are partly able to mimic the effect of CR, although Qd and R seem to be the most useful. For a better determination of which phytonutrient is the best mimetic, it is necessary to understand in detail how CR affects the lifespan and health. Limiting the analysis on these pathways and the genes included in them will be more effective for identifying mimetics.

5. Conclusion

This work shows a new approach to identify CR mimetics *in silico*. The results show that all phytonutrients could be partly able to mimic CR but that R shows the largest overlap in gene expression. Nonetheless, it is hypothesised that Qd could be a CR mimetic as well, although only a small number of overlapping genes and pathways could be identified. However, Qd was shown to upregulate the expression of Sirt1 and Nnmt and probably to inhibit Igf1 and mTOR signalling and increase Foxo1 activity. For a better assessment of whether a phytonutrient could be a CR mimetic, it is necessary to understand all mechanisms that are important for the beneficial health effects of CR. *In silico* analysis could also be useful for finding them. For example, our analysis indicates that zinc ion homeostasis could be a new mechanism that explains many CR functions. R and Qd upregulate the expression of Mt1 as well, which indicates again that both are potential CR mimetics. It is impossible to say whether other phytonutrients are more effective than R or Qd to mimic CR because only datasets from a few phytonutrients are available. Therefore, it should be a goal to motivate scientists to upload their data to make *in silico* analyses more useful. Furthermore, it is important that datasets of different plant-based diets with varying concentrations of phytonutrients are available because it is impossible to say how the phytonutrients interact *in vivo*.

To carry out *in silico* analysis and make it easier to find CR mimetics, a database similar to a connectivity map could be useful; this could summarise the influences of different substances (e.g., phytonutrients, vitamins and drugs) on the expression of one gene in different organisms. This could be handy to answer questions such as ‘which substances upregulate Sirt1 in murine liver?’ or ‘which substance is available to regulate a group of genes in the same direction like CR?’. The mentioned substances could further be analysed *in vitro* and *in vivo*, which would allow identifying more purposefully

potential CR mimetics. To develop this database, it would be necessary for all authors to upload their results, for example on ArrayExpress or GEO or directly to the newly developed database. Therefore, further effort should be expended to motivate scientists to upload their data and to establish an organisation that summarises the results and develop this database. Furthermore, it is important to find or develop a tool for enrichment analysis which could be used as gold standard. This would facilitate comparison of the results of different studies.

Despite all the difficulties which limited the results of our analysis, the mentioned approach gives a first insight to the overlapped functions between CR and the phytonutrients and could be useful to find potential CR mimetics.

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Appendix

A: Number of regulated genes by the different interventions dependent on the used test

	upregulation				downregulation			
	in at least one exper.	binom. test	chi squared test	3-fold	in at least one exper.	binom. test	chi squared test	3-fold
CR								
ttest	15185	403	26	347	6649	508	54	460
ttestfc	34	3	0	3	62	1	0	1
modttest	16712	690	79	571	7128	742	81	577
modt-testfc	40	8	1	7	90	2	0	2
Wilcoxon	15017	428	49	331	6278	423	41	369
wilcox-onfc	30	3	0	3	58	0	0	0
R								
ttest	267	53	0	53	478	48	0	48
ttestfc	39	10	0	10	3	2	0	2
modttest	1415	561	0	553	1808	531	0	530
modt-testfc	150	34	0	34	12	7	0	7
Wilcoxon	0	0	0	0	0	0	0	0
wilcox-onfc	0	0	0	0	0	0	0	0
Q								
ttest	0	0	0	0	0	0	0	0
ttestfc	0	0	0	0	0	0	0	0
modttest	10	0	0	0	15	0	0	0
modt-testfc	0	0	0	0	0	0	0	0
Wilcoxon	0	0	0	0	0	0	0	0
wilcox-onfc	0	0	0	0	0	0	0	0
P								
ttest	1977	277	0	277	2050	417	0	416
ttestfc	0	0	0	0	0	0	0	0
modttest	4383	902	0	901	3890	952	0	951
modt-testfc	1	0	0	0	0	0	0	0
Wilcoxon	0	0	0	0	0	0	0	0
wilcox-onfc	0	0	0	0	0	0	0	0
Gi								
ttest	0	0	0	0	0	0	0	0
ttestfc	0	0	0	0	0	0	0	0
modttest	1879	503	0	498	1634	452	0	440
modt-testfc	19	3	0	3	15	11	0	11
Wilcoxon	0	0	0	0	0	0	0	0
wilcox-onfc	0	0	0	0	0	0	0	0
Qi								
ttest	0	0	0	0	0	0	0	0
ttestfc	0	0	0	0	0	0	0	0
modttest	4866	2504	0	2487	4688	2460	0	2451
modt-testfc	37	4	0	4	19	13	0	13
Wilcoxon	0	0	0	0	0	0	0	0
wilcox-onfc	0	0	0	0	0	0	0	0

B: Overlapping genes between C and the plant bioactives identified by the different analysis methods

	upregulation	downregulation
CR and resveratrol		
t-test	Gpx7, Rras	Acbd4, Ankrd46, Clock, Clpx, Cyp2d10, Fam98a, Gpd2, Hdhd3, Hspa5, Hsph1, Sec14l2, Stip1
moderated t-test	1810046K07Rik, 2610002J02Rik, Acpp, Aldoc, Cyp17a1, Cyp51, Dclk3, Fam167b, Fam3c, Flot1, Fmo4, Got1, Gpx7, H2-DMA, Hcls1, Ifi27l2b, Il18, Il1b, Lacc1, Mmd2, Mvk, Mycl, Ngef, Nipal1, Nrg4, Nsdhl, Orm1, Per1, Pla1a, Slc38a3, Tmem50a, Tox, Usp2	4931406C07Rik, Alas2, Alg12, Alg2, Atf5, Bbx, Bhmt, Clock, Creld2, Ddc, Ddx6, Dnase2a, Fgf21, G0s2, Gmppb, Gpd1, Gphn, Hsd3b2, Hspa4, Hspa5, Lipa, Lonp2, Lrrc59, March8, Mlec, Nat8, Nsmf, Pdiit, Pds5a, Pknox1, Ppp1r12a, S100a10, Sdr9c7, Sox6os, Srprb, Tex2, Tmcc1, Tmed9, Tsc22d1, Tubb4b, Wfdc2
rank product method	0610007P14Rik, 1110012L19Rik, 1110034G24Rik, 1810046K07Rik, 2610002J02Rik, 2610002M06Rik, 4933422H20Rik, 4933426M11Rik, 8430419L09Rik, Abcc4, Abcg5, Abcg8, Acot3, Acox1, Acpp, Acss2, Acvr2b, Adprm, Adrb2, Aim1, Akr1b3, Akr1b7, Alas1, Alb, Aldh1b1, Aldoc, Angptl4, Anxa5, Apbb3, Aqp11, Arhgap18, Arhgap21, Arrdc4, As3mt, Asah1, Atp10d, Atp1b1, Avpi1, Baiap2l1, BC089597, Bhlhe40, Casp3, Cbx7, Crmn4l, Cd55, Cd63, Cd9, Cdkn2c, Cebp, Cela2a, Chac1, Chp1, Chrna4, Cib3, Cirbp, Cish, Cnn3, Col4a2, Commd10, Coq10b, Cpsf4, Crp, Crip1, Cry2, Crym, Ctgf, Cux2, Cyp17a1, Cyp2b13, Cyp2b9, Cyp2g1, Cyp4a10, Cyp4a14, Cyp51, Dbp, Dclk3, Dhcr7, Egr1, Eif4ebp3, Emp2, Enpp1, Ephb4, Eppk1, Etnk2, Fabp5, Fam134b, Fam167b, Fam180a, Fam76b, Fbxo21, Fbxo31, Fdps, Fkbp5, Flcn, Flot1, Fmo3, Fmo4, Gal3st1, Gfra1, Gja4, Glrx, Gnat1, Gne, Gng10, Got1, Gpcpd1, Gpihbp1, Gpx6, Gpx7, Grn, Gstm5, Gstm7, Gsto1, Gstt2, Gtdc1, Gusb, Gypc, H2-K1, Hjrp, Hmgcr, Hmgcs1, Hmox1, Hnrnpa1, Hook2, Id1, Idh1, Idh3g, Idi1, Ier3, Ifi27l2b, Il15, Il15ra, Il17rb, Il18, Il6ra, Izumo4, Kctd12, Klfl1, Lacc1, Ldb1, Lgals4, Lpin2, Lss, Lyve1, Manea, Map3k6, Mapre2, Mast3, Med30, Mertk, Mfsd2a, Mknk2, Mmadhc, Mt1, Mthfd1l, Mvk, Myadm, Mycl, N4bp2l1, Naa38, Nadsyn1, Ngef, Nhp2l1, Nipal1, Nlrc5, Nme4, Nmrk1, Nnmt, Npc2, Nrg4, Nsdhl, Nudt2, Orm1, Orm2, Pafah1b3, Pank3, Papss2, Pck1, Pcolce, Pcsk4, Pcsk9, Pdk1, Pdzk1ip1, Per1, Per2, Per3, Pim3, Pitpnc1, Pla1a, Pmvk, Pnpla2, Pold4, Por, Ppargc1b, Ppl, Ppp3cc, Pptc7, Prdx2, Prdx3, Prg4, Pros1, Prss8, Psmb10, Pstpip2, Rapgef5, Rbp1, Rdh11, Rdh9, Rgs16, Ripk4, Rnase4, Rnaseh2b, Rnf145, Rpa3, Rpp38, Rras, S100a6, Sbk1, Sc4mol, Sds, Selenbp1, Setd4, Sgk1, Sh3d21, Slc15a4, Slc19a1, Slc20a1, Slc22a26, Slc38a3, Slc3a1, Slc46a3, Slc5a6, Slc7a2, Slc8b1, Slco1a4, Slpi, Smoc2, Snai2, Socs2, Sorbs3, Spata13, Spata2l, Spg21, Sqle, St3gal5, Stap2, Stard8, Sult1d1, Sun2, Tapbp, Tat, Tef, Timm8a1, Timp3, Tk1, Tm4sf4, Tmc7, Tmem41a, Tmem9,	0610009B22Rik, 1300002K09Rik, 1600002H07Rik, 2810007J24Rik, 4931406C07Rik, A1cf, Aatk, Abcb4, Acaa1b, Acbd4, Acsf2, Adap2, Adck5, Adipor2, Adra1b, Aes, Agpat2, Agpat3, Akr1c14, Alas2, Aldh1a1, Alg12, Als2, Ankrd46, Aox1, Aox3, Ap3s1, Apba3, Apoa4, Aqp8, Arhgef19, Arrdc3, Asb2, Atf5, Atg7, Atrip, Avpr1a, B3gat3, Baat, Bace1, Bag3, BC004004, Bcl3, Bcl6, Bhmt, Btaf1, C1galt1c1, Cacybp, Car3, Cda, Cdo1, Cela1, Ces1e, Ces1f, Ces2a, Ces3a, Cfd, Chordc1, Cidea, Cidec, Cldn1, Clpx, Cmtrm6, Cnpy3, Col27a1, Cox19, Cpt2, Creld2, Crygn, Csad, Cyp2d13, Cyp2d9, Cyp2f2, Cyp4a12a, Cyp4a12b, Cyp4v3, Cyp7b1, Dcaf11, Dcaf15, Dcakd, Ddc, Ddx3x, Dexi, Dnajb1, Dnajb11, Dnajb2, Dnase2a, Dpp9, Dtx3l, Dtx4, Eif4b, Eif4g1, Elovl3, Eme2, Ephx2, Eps8l2, Ept1, Ergic1, Exoc3, Extl1, Fam13b, Fam198a, Fam20a, Fam83h, Fam98b, Fgf21, Fitm1, Fkbp4, Fpgs, Ftsj3, Fzd7, G0s2, Galnt2, Gck, Gclc, Gclm, Gdf15, Gfer, Gfod2, Ggact, Gldc, Glo1, Gmppb, Gpd1, Gpd2, Gtf2f2, Hdhd3, Hectd1, Hipk2, Hist1h3d, Hist1h4j, Hist2h2aa1, Hist2h2ac, Hnf4aos, Hsd17b12, Hsd3b2, Hsd3b5, Hspa4, Hspa5, Hspb8, Hsph1, Hyou1, Id2, Id3, Ide, Il6st, Inhbc, Inhbe, Insc, Insig2, Kank2, Kctd15, Kpna1, Kpnb1, Kti12, L3mbtl2, Lag3, Lgals1, Lipa, Lman2l, Lonp2, Lpgat1, Lrrc59, Mad2l2, Mapk15, March8, Mettl1, Mlec, Mixipl, Mpst, Mtrm4, Mtnr1a, Mup2, Mup3, Mup4, Nat6, Nat8, Necab1, Nedd4l, Nek6, Nfatc3, Nfic, Nfil3, Nop58, Nox4, Nploc4, Npr2, Nrep, Nsmf, Nudt8, Obp2a, Odf3b, Olig1, Onecut2, Osgin1, Ovca2, Pbid2, Pdiit, Pelo, Pex11a, Pigyl, Pkdcc, Pknox1, Pla2g6, Plin2, Plin5, Pllp, Pnkd, Pnkp, Polb, Polr1e, Polr2i, Ppan, Ppp1r3b, Ppp1r3c, Ppp2r3a, Pprc1, Psen2, Psmc2, Psmd12, Psmd14, Ptma, Rab1, Rdx, Retsat, Rhbd1l, Rhbg, Rpl7l1, Rrp12, Rsad2, Rtn4rl1, S100a10, Scar5, Sdr9c7, Sec14l2, Sec23b, Sec24d, Sepw1, Serpina12, Serpina4-ps1, Sgk2, Sgms2, Sgpl1, Sgpp1, Slc13a2, Slc16a2, Slc17a4, Slc1a4, Slc22a7, Slc25a25, Slc25a30, Slc35d1, Slc39a7, Slc45a3, Smagp, Smarca4, Sox6os, Spg20, Spon2, Spryd7, Spsb3, Spsb4, Srd5a1, Srp68, Srr, St3gal1, St5,

Tmem97, Tox, Trib3, Tubb5, Uaca, Ugp2, Ugt1a2, Ulk1, Unc5b, Usp2, Vcam1, Vim, Wsb1, Zbtb48, Zfp275, Zfp36, Zfp933, Zkscan17

Stat2, Stip1, Stk16, Stt3b, Sucnr1, Swsap1, Syvn1, Tars, Tbl1x, Tesk1, Tex2, Tjp3, Tlr5, Tmcc1, Tmed9, Tmie, Tnnt1, Tnnt3, Tpgs1, Trappc13, Trim39, Trmt10a, Trp53inp2, Tsacc, Tsc22d1, Tspan33, Tssc4, Tstd2, Ttc7b, Tuba1c, Tubb4b, Tysnd1, Ugt2b1, Ugt2b34, Ugt2b35, Uso1, Vcp, Vps37b, Wdte1, Wfdc2, Wrap73, Xylb, Zbtb20, Zfand2a, Zfp322a, Zfp3611, Zfp809, Zswim1

CR and phloridzin

t-test	Alb, Chrna4, Nipal1, Tbc1d30, Tox	1415788_at, 1415789_a_at, 1417907_at, 1418520_at, 1423309_at, 1429272_a_at, 1450007_at, Acad11, Acp2, Aldh3a2, Amd1, Apol7a, Arf2, Ces1e, Chrna2, Decr1, Eaf1, Eif2b3, Entpd5, Fabp2, Gdf15, Gid8, Glo1, Hsd3b5, Ldha, Sdr42e1, Tmem33, Vcp
moderated t-test	1415895_at, 1415896_x_at, 1440212_at, 1441539_at, 1444973_at, 1449787_at, BC089597, Chrna4, Ggt6, Igsf8, Lrrc24, Nipal1, Slpi, Tbc1d30, Tox	1418520_at, 1420867_at, 1420868_s_at, 1423263_at, 1423308_at, 1423309_at, 1424185_a_at, 32842_s_at, 1439463_x_at, 1440325_at, 1443505_at, 1810058I24Rik, 4833417J20Rik, 4930506M07Rik, 4931406C07Rik, Abcb4, Acad11, Akr1c20, Alad, Aldh1a1, Aldh3a2, Amd1, Apol7a, Aptx, Aqp4, Arf2, Arpp19, Bcap29, Ccdc162, Cd1d1, Ces1e, Chrna2, Chuk, Cpsf2, Csad, Decr1, Dhx29, Dleu2, Dpys, Dsp, Eif2b3, Fabp2, Gdf15, Hsd3b2, Hsdl2, Ikbkg, Inhbc, Mal2, Mki67ip, Nadk2, Ndufaf1, Nras, Nsf1c, Pbl2, Pde12, Pex11a, Pik3c3, Pla2g12a, Pus7, Sco1, Sdr42e1, Sdr9c7, Slc16a7, Slc25a33, Smurf2, Tmem123, Tsc22d1, Ugt3a1
rank product method	1416021_a_at, 1418536_at, 1420570_x_at, 1428014_at, 1429466_s_at, 1430172_a_at, 1433107_at, 1434362_at, 1438009_at, 1438959_x_at, 1440016_at, 1440304_at, 1440587_at, 1441415_at, 1441539_at, 1442182_at, 1442725_at, 1443166_at, 1443377_at, 1443393_at, 1443719_x_at, 1444909_at, 1445001_at, 1445062_at, 1445492_at, 1445534_at, 1445612_at, 1445676_at, 1445728_at, 1446567_at, 1446614_at, 1449745_at, 1451626_x_at, 1452590_a_at, 1455930_at, 1456032_x_at, 1456973_at, 1457652_x_at, 1458382_a_at, 1458829_at, 1459557_at, 1459695_at, 1460132_at, 1500011K16Rik, 1810008I18Rik, 4930455C13Rik, 6030422H21Rik, Acacb, Acot3, Acss2, AFFX-18SRNAMur/X00686_3_at, Alas1, Ap1g2, Ap2a1, Arid5b, Asns, Atn1, BC094435, Bdkrb1, Ccl8, Ccne1, Crn4l, Cdk1, Cirbp, Cish, Coq10b, Crybb3, Ctrl, Cyp2c39, Cyp2g1, Cyp4a14, D530037H12Rik, D7Ert59e, Dbp, Defb1, Dhcr7, Egfl8, Erbb3, Fabp5, Fads1, Fbxl15, Fdps, Foxa1, Frat2, Gal3st1, Gale, Gapdhs, Ggt6, Gm129, Gm19313, Gnat1, Got1, Gpcpd1, Gpx3, Grem2, Guca1a, H2afz, Hhex, Hspb1, Id1, Idi1, Ifi2712b, Igsf8, Il15, Isyn1, Lce3b, Lefty1, Lrrc24, Mettl20, Mt1, Myc, Nab2, Nipal1, Nlrc5, Nme4, Nmrk1, Nnmt, Nsdhl, Orm1, Orm2, Orm3, Pawr, Pcsk4, Pcsk9, Pdzk1ip1, Per1, Per3, Pfkfb1, Pgd, Plekhj1, Plxbn1, Pmvk, Pnpla5, Por, Prss8, Rhob, Rnd2, Rps13, Rundc3b, Sbk1,	0610012H03Rik, 1110004F10Rik, 1415788_at, 1415789_a_at, 1415790_at, 1416336_s_at, 1416461_at, 1416706_at, 1416811_s_at, 1416946_a_at, 1416947_s_at, 1417057_a_at, 1417714_x_at, 1417907_at, 1418274_at, 1418520_at, 1419443_at, 1420136_a_at, 1420867_at, 1420868_s_at, 1421534_at, 1422414_a_at, 1422660_at, 1422993_s_at, 1422997_s_at, 1423262_a_at, 1423263_at, 1423308_at, 1423309_at, 1423397_at, 1424300_at, 1424752_x_at, 1425665_a_at, 1426266_s_at, 1426394_at, 1426395_s_at, 1426419_at, 1427660_x_at, 1427932_s_at, 1428658_at, 1429040_at, 1429169_at, 1429252_at, 1429272_a_at, 1429468_at, 1429554_at, 1429712_at, 1429784_at, 1431158_at, 1433592_at, 1433622_at, 1434054_at, 1434161_at, 1434328_at, 1434568_at, 1434861_at, 1435137_s_at, 1435384_at, 1435574_at, 1435792_at, 1436247_at, 1436338_at, 1436933_at, 1436944_x_at, 1437026_at, 1437354_at, 1437547_s_at, 1438221_at, 1438398_at, 1438415_s_at, 1438596_at, 1438714_at, 1438786_a_at, 1439290_at, 1439305_at, 1439426_x_at, 1439463_x_at, 1439616_at, 1439831_at, 1440038_at, 1440219_at, 1440264_at, 1440284_at, 1440325_at, 1440373_at, 1440388_at, 1440490_at, 1440533_at, 1440551_at, 1440841_at, 1440896_at, 1441052_at, 1441108_at, 1441141_at, 1441328_at, 1441498_at, 1441505_at, 1441547_at, 1441765_at,

Scd1, Sdf2l1, Serpinh1, Sertad1, Slc23a2, 1442049_at, 1442097_at, 1442109_at,
Slc3a1, Spli, Smad9, Socs2, Speer3, 1442331_at, 1442407_at, 1442509_at,
Sprr1a, Sqle, Tbc1d30, Tcf19, Thrsp, Tifa, 1442916_at, 1443056_at, 1443196_at,
Tmc5, Tmem159, Tmem71, Trib3, Ttc39a, 1443505_at, 1443533_at, 1443872_at,
Tubb2a, Tubb4a, Unc5b, Usp2, Vpreb3, 1444333_at, 1444506_at, 1444531_at,
Wbp2nl, Wfdc15b, Wnt5b, Zfp579, Zfp647, 1444735_at, 1444869_at, 1445379_at,
Zkscan17 1445966_at, 1446167_at, 1446504_at,
1446850_at, 1447064_at, 1447227_at,
1447502_at, 1447527_at, 1447977_x_at,
1448037_at, 1448232_x_at, 1448235_s_at,
1448462_at, 1448548_at, 1448854_s_at,
1449009_at, 1449480_at, 1449556_at,
1449855_s_at, 1449910_at, 1449972_s_at,
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1452463_x_at, 1452935_at, 1453078_at,
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1457263_at, 1457991_at, 1458324_x_at,
1458637_x_at, 1458943_at, 1459238_at,
1459360_at, 1459434_at, 1460052_at,
1600002H07Rik, 1600012H06Rik,
1700066M21Rik, 1810011O10Rik,
1810058I24Rik, 2010309G21Rik,
2010315B03Rik, 2410004B18Rik,
2610002M06Rik, 2610034B18Rik,
2700089E24Rik, 2900009J20Rik,
2900026A02Rik, 4632427E13Rik,
4833417J20Rik, 4930459C07Rik,
4930506M07Rik, 4931406C07Rik,
4933411K20Rik, 4933438K21Rik,
5033411D12Rik, 6030451C04Rik,
6330564D18Rik, 9130016M20Rik,
9130221J18Rik, 9130409I23Rik,
9230114K14Rik, 9430016H08Rik,
A130040M12Rik, A1cf, A230050P20Rik,
A430035B10Rik, A930035D04Rik,
AA408650, AA987161, Aadat, Aasdhppt,
Abat, Abca1, Abcb4, Abcc2, Abcc3, Abcc9,
Abce1, Abcg2, Abi3bp, Ablim3, Acaa1b,
Acad11, Acad9, Acadm, Acat1, Acot1,
Acot12, Acox2, Acsm3, Acsm5, Acy3, Ad-
am17, Adap2, Adh4, Adra1b, Adss, Aggf1,
Agl, Ahcyl1, AI314180, AI428301, AI464131,
Aif1, Ak3, Akap1, Akr1c14, Akr1c20, Akr1d1,
Alad, Alas2, Aldh3a2, Aldh5a1, Alg13,
Alkbh7, Amd1, Amdhd1, Amy1, Anapc2,
Anapc4, Angptl3, Anks4b, Anp32a, Anp32b,
Aox1, Aox3, Apobec1, Apol7a, Aptx, Aqp4,
Aqp9, Arel1, Arf2, Arl1, Arl5a, Arl6ip1, Arl8b,
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Atp11c, Atp6v1a, Atp7a, Atp8b1, AU041133,
Avpr1a, AW209491, AW987390, Azin1,
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BC003331, BC018507, Bcap29, Bcl3, Bcl6,
Bdh1, Bet1, Bpgm, C1galt1, C1galt1c1,
C1qb, C1s, C330007P06Rik, C4bp, C6,
C730027H18Rik, C730036E19Rik, C8a,
C8b, Caap1, Cab39, Cacybp, Caln1, Cand1,
Canx, Cap1, Capn2, Capn7, Caprin1,
Capza2, Car3, Car8, Casp8, Ccdc104,
Ccdc115, Ccdc117, Ccdc126, Ccdc162,
Ccdc59, Ccdc90b, Ccne2, Ccnf, Ccpg1,
Ccs, Cd1d1, Cd24a, Cd2ap, Cd300lb, Cd36,
Cd48, Cd68, Cd74, Cd86, Cdc123, Cdh2,
Cela1, Cenpb, Ces1e, Ces1g, Ces2a,

Cetn3, Cfdp1, Chac2, Chdh, Chka, Chkb, Chmp2b, Chn2, Chordc1, Chpt1, Chrna2, Chtop, Chuk, Cideb, Cited2, Cks1b, Clcn2, Cldn1, Cldn2, Clec14a, Clec4f, Clock, Clpx, Cltc, Cmas, Cml2, Cml5, Cmtm4, Cnot7, Col27a1, Commd6, Copb1, Cops2, Cox15, Cox18, Cp, Cpeb4, Cpsf2, Cpt1a, Crip2, Crnk1, Csad, Csde1, Cse1, Csf1r, Csgal-nact2, Ctcf, Ctla2b, Ctnnb1, Ctnnb1, Ctss, Cul2, Cul3, Cul4a, Cul4b, Cxcl10, Cxcl9, Cybb, Cyp2a12, Cyp2c37, Cyp2c50, Cyp2c54, Cyp2d12, Cyp2d13, Cyp2d40, Cyp2j5, Cyp2j6, Cyp3a13, Cyp3a25, Cyp4v3, D10Ert4709e, D1Ert448e, D5Ert4505e, D5Ert4798e, D830012124Rik, D930016D06Rik, Daam1, Dancr, Dars, Dcaf11, Dcakd, Dct, Ddx10, Ddx3y, Ddx52, Ddx60, Decr1, Dennd4c, Derl2, Dhra4, Dhx29, Dhx36, Dis3l, Dkc1, Dleu2, Dnaja1, Dnajb1, Dnajb4, Dnajb9, Dnajc14, Dnajc5, Dnase2a, Dnttip2, Dpm1, Dpys, Dr1, Dsg2, Dsp, Dtx4, Dync1i2, E130311K13Rik, Eaf1, Ear11, Eci2, Eea1, Efemp1, Efhd2, Efna1, Efr3a, Egln3, Ehhadh, Eif1a, Eif1b, Eif2ak2, Eif2b3, Eif2s3x, Eif3m, Eif4a2, Eif4g1, Eif5, Eif5b, Eil2, Elovl3, Emr4, Enpp2, Enpp5, Epc2, Epha2, Ephx1, Eps8l2, Ergic2, Esf1, Etfhd, Eva1a, Exoc3, F9, Fabp2, Fabp7, Fahd1, Fam107b, Fam126b, Fam149a, Fam149b, Fam151b, Fam20a, Fam210a, Fam214a, Fam35a, Fam98a, Farsb, Fastkd5, Fbxo11, Fbxo30, Fcer1g, Fcho2, Fcna, Fez2, Fgf21, Fgfr1op, Fgfr1op2, Ficd, Fitm1, Fkbp3, Foxn2, Fpgt, Fpr2, Ftsj3, Fus, Fzd8, G0s2, G3bp1, G6pc, Gabarapl1, Gabpa, Gadd45a, Galnt1, Galnt2, Gas5, Gatac, Gbp2, Gbp2b, Gbp3, Gbp6, Gbp8, Gck, Gclc, Gclm, Gdf15, Gemin2, Ggcy, Ghr, Gimap9, Gjb1, Glcc, Glo1, Glt28d2, Gm17586, Gm19696, Gm19966, Gm20300, Gm20319, Gm2701, Gm4354, Gm6484, Gmfb, Gna12, Gna14, Gpatch11, Gpbp1, Gphn, Gpr155, Gpr97, Grpel2, Gspt1, Gtf2f2, Gtf2h1, Gtf2h2, Gtpbp10, Gtpbp4, Guk1, Gyk, H2-Aa, H2-Ab1, H2-Eb1, H2-T24, Hadha, Hccs, Hdac2, Hdhd3, Herc6, Hes1, Hexim1, Hif1a, Hmgb3, Hnf4a, Hnrnpa3, Hnrnpu, Hsd17b12, Hsd17b2, Hsd3b2, Hsd3b3, Hsdl2, Hsp90aa1, Hsp90ab1, Hsp90b1, Hspa13, Hspa1b, Hspb6, Hspb8, Hsph1, Ide, Ifi202b, Ifih1, Ifit1, Ifit2, Ifit20, Igsf5, Iigp1, Ik, Ikbke, Ikbkg, Immt, Inhbc, Inhbe, Inpp5a, Insig2, Ints12, Ints2, Ints4, Irak2, Irf6, Irgm1, Irs1, Itfg1, Itga8, Jak1, Jmjd8, Jtb, Jun, Kat8, Kcnk5, Kctd15, Kdm1b, Kif5b, Klf10, Klf9, Klkb1, Kpna1, Kpna2, Kpna3, Kpnb1, Krr1, Lactb, Lamb3, Lamp2, Larp1, Larp7, Lars, Lcp1, Ldhd, Ldlr, Leprotl1, Lgals3bp, Lgals8, Lgals9, Lhpp, Lig4, Lima1, Lin7c, Lipg, Lonp2, Lpar6, Lrif1, Lrp5, Lrrc59, Lrrc8d, Lsm2, Ltb, Ltv1, Luc7l3, Lum, Ly86, Lyz2, Mad2l2, Mafb, Magix, Magt1, Mal2, Mamdc2, Map2k4, Mapk1, Mapk1ip11, March8, Mars, Mbd2, Med19, Meiob, Metap2, Mettl3, Mia2, Mir22hg, Mis12, Mki67ip, Mlf2, Mlxipl, Mmd, Mme, Mmgt1, Mmp19, Mn1, Mob4, Mocs2, Moxd1, Mpdz, Mpzl2, Mrpl50, Mrs2, Msh6,

Mtap, Mtif2, Mtm1, Mtmr9, Mtpn, Mtrf11, Mtus1, Mup10, Mx2, Naa15, Naa16, Naa50, Nadk2, Nae1, Nap111, Nbn, Ncbp2, Ncl, Ndn12, Ndufaf1, Ndufaf3, Neat1, Necab1, Nek4, Nek6, Nelfcd, Nenf, Nfe2l2, Nfil3, Nhp2, Nicn1, Nipa2, Nit2, Nln, Nlrp12, Nlrx1, Nmi, Nol8, Nolc1, Nop9, Nox4, Npr2, Nr1d1, Nr3c1, Nr5a2, Nras, Nrbf2, Nsfl1c, Nt5dc1, Nuak2, Nudcd2, Nudt12, Nup35, Nxt2, Oas2, Obp2a, Omd, Oplah, Osbpl8, Pabpc1, Paip2, Papola, Pard6b, Parn, Parp9, Parva, Pbd1, Pbd2, Pbrm1, Pcbd2, Pcbp4, Pcdh1, Pcgf6, Pcsk6, Pde12, Pdilt, Pdlim5, Pdzk1, Pelo, Pex11a, Pex13, Pex26, Pfdn1, Pgap1, Pgap2, Pgg1b, Pgm3, Phf17, Phkb, Phldb2, Picalm, Pigr, Pik3r1, Pim1, Pitpna, Pitpnb, Pja2, Pkp4, Pla2g12a, Pla2g15, Plekha1, Plekha2, Plin5, Plrg1, Plscr2, Pnn, Pno1, Pnpla7, Pnrc2, Polb, Ppap2b, Ppara, Ppcs, Ppp1r11, Ppp1r3b, Ppp1r3c, Ppp2ca, Ppp2r1b, Ppp2r5e, Ppp3ca, Ppp4r1, Ppp4r2, Ppp6c, Pprc1, Prkd3, Prkrir, Prorsd1, Prr16, Psap, Psma4, Psmc5, Psmc6, Psm1, Psm12, Psm14, Ptp4a2, Ptpn12, Pum1, Pus7, Qpct, Rab10, Rab11a, Rab18, Rab24, Rab30, Rab6a, Rab7, Rad17, Rad21, Ranbp1, Ranbp6, Rap1b, Rars, Rbbp9, Rbm8a, Rbmx1, Rchy1, Rdh16, Rdx, Rell1, Retsat, Rfwd2, Rgs5, Rhou, Rnf121, Rnf125, Rnf138, Rnf152, Rnf186, Rnf43, Rnf5, Rnf6, Rnft1, Rpp14, Rpp40, Rps4l, Rrp12, Rrp36, Rrp8, Rsad2, Rtfdc1, Rtn4r1, Rtp3, S1pr1, Saa4, Sc5d, Scaf11, Scnm1, Sco1, Scoc, Sdr42e1, Sdr9c7, Sec16b, Sec62, Sec63, Senp7, Serinc1, Serpina12, Serpina3a, Serpina3k, Serpina4-ps1, Serpina9, Sfr1, Sgk2, Sgms2, Sgpl1, Sgpp1, Siae, Slc15a3, Slc16a12, Slc16a13, Slc16a7, Slc17a2, Slc17a3, Slc22a1, Slc22a5, Slc22a7, Slc25a13, Slc25a16, Slc25a25, Slc25a33, Slc30a10, Slc33a1, Slc35a1, Slc35a3, Slc35b4, Slc39a8, Slc41a2, Slc45a3, Slco1a1, Slco1b2, Smad6, Smarca2, Smek2, Smg7, Smim8, Smn1, Smurf2, Smyd2, Snap23, Snhg12, Snhg6, Sntb1, Snx24, Snx5, Sorbs1, Sos2, Sp3, Spast, Spg20, Spop, Srd5a1, Srp68, Srr, Srsf1, Srsf10, Srsf3, Srsf7, Ssb, Stag1, Stap1, Stard13, Stat2, Stat5a, Stbd1, Stip1, Stk16, Strn3, Stx4a, Stxbp6, Sub1, Sucnr1, Sult1c2, Sumf1, Suox, Syncrip, Tab2, Taf1a, Tardbp, Tars, Tbc1, Tblk1, Tblk1x, Tcaim, Tcea1, Tceb1, Tcerg1, Tefm, Tenc1, Tenm3, Tfec, Thap11, Thrap3, Timd4, Tipin, Tk2, Tm9sf3, Tmbim1, Tmcc1, Tmem123, Tmem184b, Tmem230, Tnfaip8l1, Tnp03, Top2b, Tpm1, Tpp2, Trappc10, Trem14, Triap1, Trim39, Trmt10a, Trmt6, Trp53inp2, Tsc22d1, Ttc27, Ttc30b, Ttc32, Tvp23b, Twsg1, Txndc9, Tyw5, Uba3, Uba5, Ube2d1, Ube2e3, Ube2g2, Ube2l6, Ube2v2, Ubxn2a, Ubxn4, Ufd1l, Ufl1, Ugt2b34, Ugt2b35, Ugt3a1, Ulk2, Uso1, Usp18, Usp33, Utp6, Vcl, Vma21, Vprbp, Vps35, Vps41, Vwa8, Wbscr16, Wdr43, Wdr77, Wnt2, Xrn2, Xylb, Yap1, Ythdc2, Ythdf2, Ythdf3, Zbtb20, Zcchc10, Zcchc6, Zfand1,

Zfand2a, Zfp110, Zfp141, Zfp146, Zfp260, Zfp263, Zfp326, Zfp361l, Zfp386, Zfp445, Zfp51, Zfp58, Zfp617, Zfp62, Zfp825, Zfp866, Zfp932, Zfp935, Zfp946, Zfp955b, Znhit6, Znrdr1, Zranb2, Zscan29, Zswim7, Zwint

CR and quercetin diet

rank	1425222_x_at, 1427820_at, 1430172_a_at,	1418188_a_at, 1418189_s_at, 1420310_at,
product	1437867_at, 1439816_at, 1440587_at,	1424853_s_at, 1425918_at, 1426327_s_at,
method	1440815_x_at, 1442025_a_at, 1442026_at,	1434280_at, 1435267_at, 1436389_at,
	1442420_at, 1443322_at, 1445591_at,	1437162_at, 1437600_at, 1437821_at,
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	4933426M11Rik, 5330406M23Rik,	1440314_at, 1440790_x_at, 1440841_at,
	9130221J18Rik, Adora1, AAFX-	1441413_at, 1441498_at, 1442049_at,
	18SRNAMur/X00686_3_at, AI195470,	1442109_at, 1442470_at, 1443003_at,
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	Ccrn4l, Cd14, Cd163, Cebpbb, Cers6, Chac1,	1444001_at, 1444326_at, 1445267_at,
	Cib3, Cish, Col6a1, Coq10b, Ctgf, Cyp2b10,	1445402_at, 1446850_at, 1447227_at,
	Cyp4a14, D030063E12, D1Ertd622e,	1447329_at, 1451477_at, 1452433_at,
	Dusp14, Egr1, Epas1, Epcam, Errfi1,	1455961_at, 1456159_at, 1456386_at,
	Fam134b, Fbxl12, Fbxo31, Fkbp5, Fn1,	1456851_at, 1456960_at, 1457020_at,
	Foxa1, Frat2, Fst, Gadd45g, Gfpt2, Gja4,	1457367_at, 1457988_at, 1457991_at,
	Gm129, Gm15698, Gnat1, Got1, Gpcpd1,	1458134_at, 1458205_at, 1458637_x_at,
	Gps2, Grem2, Hhex, Hspb1, Id1, Ier3,	1458832_at, 1459008_at, 1459061_at,
	Iffi27l2b, Igfbp1, Il1r1, Il1rn, Il6ra, Ivns1abp,	1459238_at, 1459948_at, 1700023H06Rik,
	Kctd12, Klf2, Lonrf1, Lpin1, Lyve1, Map3k5,	2310007O11Rik, 2310067E19Rik,
	Mast3, Mettl20, Mfsd2a, Mfsd7c, Mgp,	2610507B11Rik, 2900064B18Rik,
	Mknk2, Mlxip, Mt1, Myadm, Myc, Nab2,	3110005L24Rik, 4633401B06Rik,
	Nlrc5, Nnmt, Nop56, Nrg4, Orm2, Orm3,	4930459C07Rik, 4930480G23Rik,
	Osmr, P2ry2, Pcgf1, Pcsk4, Per1, Plin4,	5730414N17Rik, 9030622O22Rik,
	Plk3, Por, Ppip5k2, Ppl, Rab20, Rasgef1b,	A930004J17Rik, Adck3, Adh6-ps1, Adipor2,
	Rhbdf1, Ripk4, Sds, Serpinh1, Sertad1,	Agpat2, AI464131, Anks4b, Apob, Aqp4,
	Sgk1, Sirt1, Slc25a22, Slc25a32, Slc25a51,	Aqp8, Arrdc3, Arsg, B230114P17Rik, Bag3,
	Slc43a1, Slc7a2, Slc8b1, Sorbs3, Sprr1a,	Bbs5, BC038331, Bcl6, C430003N24Rik,
	Sqle, Srsf5, St3gal5, Sult1e1, Susd2, Tacc2,	C730029A08Rik, Car3, Ccdc117, Ccdc58,
	Tagln, Tbc1d8, Tcp1l12, Thrsp, Tk1, Tns1,	Cd300lb, Cda, Cflar, Chka, Chordc1,
	Tpm4, Trib3, Trim47, Ttc39a, Tubb2a, Tuft1,	Chrna2, Cited2, Cks1b, Cldn1, Cldn3, Ctcf,
	Usp2, Vcam1, Vim, Vsig10, Wsb1, Zbtb16,	Cyp2d12, Cyp2d13, Cyp2d40, Cyr61,
	Zfand4, Zfp275	D5Wsu152e, Daam1, Ddx6, Decr2, Dhdh,
		Dhx36, Dhx58, Dnajb1, Dnajb14, Dnajb4,
		Dnajb9, Dusp6, E130110O22Rik, Ear11,
		Efna1, Epha2, Evi5, Fahd1, Fam214a,
		Fam26f, Fam89a, Fermt2, Fgf21, Ficd,
		Fpgs, G0s2, G6pc, Gadd45a, Gck, Gdap10,
		Gdf15, Ggact, Gm11772, Gm19696,
		Gm2788, Gm4354, Gm6484, Gna14, Gpr97,
		Gprin3, H2-T24, Hacl1, Hectd1, Hes1,
		Hexim1, Hist1h1c, Hist1h4i, Hps5, Hsd3b3,
		Hspa13, Hspa1b, Hyou1, Ift20, Igfals, Inhbe,
		Insig1, Irs1, Jun, Kcnk5, Keap1, Klf10, Lipg,
		Lmo2, Lnx2, LOC75771, Lppos, Lrn3, Lrp5,
		Luc7l3, Lysmd3, Magix, Mis12, Mme, Mn1,
		Mpst, Mup10, Nbeal1, Nfatc3, Nfib, Nfil3,
		Nr1d1, Nrep, Obp2a, Omd, Osbpl8, Osgin1,
		Paqr9, Parp16, Pblid1, Pcdh1, Pde6d, Pdpr,
		Pglyrp1, Phf17, Plcxd2, Plekhf1, Plscr2,
		Ppara, Ppp1r3b, Ppp1r3c, Prkd3, Prlr,
		Prox1, Pter, Pum1, Rab30, Rbm25, Rfc1,
		Rfesd, Rgs5, Rnf125, Rnf152, Rnf186,
		Rnf43, Rps4l, Rrp36, Rtp3, S1pr1, Sc5d,
		Secisbp2l, Serpina9, Sgpl1, Skiv2l, Slc1a4,
		Slc25a30, Slc26a1, Slc30a10, Slc40a1,
		Slc45a3, Smarca4, Smyd4, Srd5a1, Stap1,

Stard13, Sucnr1, Sult1c2, Taf1a, Tbccl, Tbl1x, Tenm3, Thap11, Thrb, Timd2, Tjp3, Tmcc1, Tmem98, Tmie, Trim2, Trim39, Tsc22d1, Ttc30b, Ube2d1, Ulk2, Unc119, Vnn1, Wbscr16, Wnk1, Wrap73, Zbed6, Zbtb11os1, Zfp322a, Zfp361l, Zfp551, Zfp62

CR and quercetin administered intraperitoneal

moderated Arg1, Cyp2b13, Etnppl, Fmo3, Fst, Gstt3, Hamp2, Sh2d4a, Slc22a27, Tat
t-test

rank 1600016N20Rik, 8430408G22Rik, Acly,
product Acot7, Arl4d, Atp10d, Ccdc57, Cdc42bpg,
method Cish, Cpeb2, Crym, Cux2, Cyp17a1, Cyp2b13, Cyp2c39, Cyp4a10, Cyp4a14, Cyp4a31, Dak, Ddb1, Elovl6, Eno1, Erdr1, Fads1, Fads2, Fmo3, Fnip2, Foxa1, Gadd45g, Gm5215, Gnat2, Gng11, Gpihbp1, Gsta4, Gstm2, Hlx, Igfbp1, Inmt, Irs2, Lce1i, Lepr, LOC100044177, LOC100046136, Lor, Lrrc24, Lss, Myh14, Nnmt, Nrg4, Pklr, Pnpla5, Ppp1r3g, Rnf39, Rpl32, Sdsl, Sh2d4a, Slc22a26, Slc22a27, Slc2a4, Smoc2, Snord15a, Snord22, Snord35a, Snord82, Snord87, Socs2, Spen, Sult1e1, Sult2a3, Tacc2, Tbc1d19

Adh4, Alad, C9, Crot, Cyp4a12a, Dio1, Hsd3b5, Hsd3b7, Hspa5, Ifi47, Ifit1, Igtp, Irgm2, Isg15, Ldha, Manf, Mbl1, Mgst1, Nat8, Ndufaf1, Pter, Rarres1, Serpina11, Slc16a7, Tbrg1, Tm9sf3, Ttpa, Ugt2b35

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CR and genistein administered intraperitoneal

moderated Acly, Cyp17a1, Eno1, Gsta4, Gstm2, Hamp2, Hlx, Igfbp1, Lrrc24, Lss, Nipal3, Nnmt, Ppp1r3g, Slc2a4
t-test

4931406C07Rik, Acaa1b, Acsl1, Adh4, Ak2, Alad, Aldh3a2, BC025446, Bcap29, C9, Ces1d, Cfh, Crot, Cryz, Csad, Csrp3,

		Cyp2j5, Cyp4a12a, Cyp7b1, Dio1, Dnaja1, Dsp, Eif2ak2, Ephx2, Etfhdh, Fgf21, G0s2, Gbp3, Gdf15, Hnf4aos, Hrsp12, Hsd17b4, Hsd3b5, Hsd3b7, Hspa5, Hspa8, Ifi35, Ifi47, Ifit1, Igtp, Inca1, Irgm2, Isg15, Lcn2, Ldha, Lin7a, Lipa, Lonp2, Lpgat1, Mal2, Manf, March8, Mbl1, Mgst1, Mien1, Mmd, Nadk2, Ndufaf1, Ostc, Pafah1b1, Papola, Paqr7, Phf17, Psm5, Pter, Rarres1, Rtp4, S100a10, Sdc1, Sdr42e1, Serbp1, Serpina11, Serpinb1a, Sh3bgrl2, Skp1a, Slc16a1, Slc16a7, Slc25a33 Supt16, Tbrg1, Tm9sf3, Tmem56, Tsc22d1, Ttpa, Ugt2b35, Ugt2b5, Ugt3a1, Usp18
moderated t-test, fold change > 1.5	Fmo3	
rank product method	1600016N20Rik, Acly, Acot3, Agpat9, Arg1, Atp10d, Casp3, Ccdc57, Cdc42bpg, Cish, Clmn, Cpeb2, Crym, Cux2, Cyp17a1, Cyp2b13, Cyp2b9, Cyp2c39, Cyp4a14, Cyp4a31, Dbp, Dntt, E130012A19Rik, Eif4ebp3, Elovl6, Eno1, Erdr1, Etnppl, Fbxo31, Fmo3, Fnip2, Fst, Fzd4, Gadd45g, Gm129, Gm5215, Gnat2, Gng11, Got1, Gpcpd1, Gstt3, Id1, Igfbp1, Inmt, Irs2, LOC100046136, Lss, Map3k5, Mfsd2a, Nrg4, Pdk4, Pdxp, Plin4, Ptgs, Rarb, Rpl32, Sdsl, Sh2d4a, Slc16a5, Slc22a26, Slc22a27, Slc37a4, Slc43a1, Snora21, Snord22, Snord82, Socs2, Sptssa, Sult1e1, Sult2a3, Tacc2, Tamm41, Tat, Tbc1d19, Unc93a	3010026O09Rik, Acat2, Adh4, Adprhl2, Aes, Akirin1, Alad, Alas2, Amacr, Amy1, Ankrd46, Anp32b, Aox1, Ap3s1, Apon, Avpr1a, Bag3, Bbox1, Bcl6, Bhmt2, C1galt1c1, C1qa, C1s, C4b, C4bp, C9, Cacybp, Ccdc86, Cdf5, Cdh2, Ces1d, Ces2a, Ces3a, Cfd, Chac2, Clpx, Cml5, Cmtr1, Colec10, Cris1, Crot, Csrp3, Ctss, Cxcl9, Cyp2c29, Cyp2d40, Cyp4a12a, Cyp4a12b, Cyr61, Dcakd, Dhrs3, Dio1, Dnaic1, Dnaja1, Dnajb1, Dnajb2, Ech1, Ei24, Elovl3, Ephx1, Fez2, Foxa3, G0s2, Gfod2, Glcd, Glyt, Gm5150, Gm6484, Gstm4, Guk1, Hmgb3, Hmgcs2, Hsd3b5, Hsd3b7, Hspa13, Hspa5, Hsph1, Ifi27l2a, Ifi35, Ifi47, Ifit1, Igfals, Igtp, Il6st, Inca1, Irgm2, Isg15, Keg1, Lamtor5, Lbp, Lcat, Lcn2, Ldha, Leap2, Lipa, Lrnf3, Lum, Ly6d, Ly6e, Mad2l2, Magoh, Manf, Mbl1, Med21, Mmp15, Mocos, Mpst, Mup20, Mup21, Mup6, Nat8, Ndufaf1, Oasl1, Ocel1, Paqr7, Pcnp, Pex26, Plcx2, Pnpla7, Polb, Ppp1r3b, Psmc2, Psmc1, Psmc6, Pter, Rarres1, Reep6, Rhbg, Rraga, Sdc1, Sec14l2, Serpina11, Serpina3n, Serpina7, Serping1, Sgk2, Sgpp1, Slc13a3, Slc16a7, Slc1a4, Slc22a1, Slc22a7, Slc25a45, Slc6a13, Slco1b2, Snap47, Spon2, St3gal3, Stbd1, Sucnr1, Syap1, Tbrg1, Timd4, Tjp3, Tmem254a, Tmie, Tomm20, Trex1, Tsc22d1, Ttpa, Tyrobp, Ube2e1, Ube2l6, Ugt2b35, Ugt3a1, Usp18, Wdct1, Zbtb20

C: All significantly regulated genes by caloric restriction which are identified in at least one approach sorted by alphabet

Upregulated CR genes (gene symbols known)

0610007P14Rik, 1110001J03Rik, 1110007C09Rik, 1110012L19Rik, 1110020A21Rik, 1110034G24Rik, 1190002N15Rik, 130004C03, 1500011K16Rik, 1500032P08Rik, 1700001J11Rik, 1700018L02Rik, 1700024P16Rik, 1700040L02Rik, 1810008I18Rik, 1810010H24Rik, 1810032O08Rik, 1810046K07Rik, 1810053B23Rik, 1810062G17Rik, 2010012O05Rik, 2010107E04Rik, 2210013O21Rik, 2310007J06Rik, 2310034O05Rik, 2310047D07Rik, 2310061I04Rik, 2510039O18Rik, 2610002J02Rik, 2610002M06Rik, 2900009J06Rik, 2900040J22Rik, 3000002C10Rik, 3010003L21Rik, 3110043O21Rik, 3110045C21Rik, 4631423B10Rik, 4732419C18Rik, 4833420G17Rik, 4921506L19Rik, 4921517O11Rik, 4930452B06Rik,

Upregulated CR genes (gene symbols known)

Eno1, Eno3, Enpep, Enpp1, Entpd2, Epas1, Epb4.1, Epb4114aos, Epcam, Epg5, Epha8, Ephb4, Epn1, Epor, Eppk1, Eps15, Erbb3, Erdr1, Errfi1, Esam, Esrra, Esyt2, Ethel1, Etnk2, Etnpl, Evx2, F7, Fabbp5, Fads1, Fads2, Fah, Fam103a1, Fam110c, Fam117a, Fam120a, Fam126a, Fam134b, Fam13a, Fam167b, Fam177a, Fam179a, Fam180a, Fam193b, Fam213a, Fam3c, Fam46a, Fam53b, Fam58b, Fam60a, Fam63b, Fam76b, Fam98c, Fars2, Fasn, Fastkd1, Fastkd3, Fat1, Fbxl12, Fbxl15, Fbxl4, Fbxl6, Fbxo18, Fbxo21, Fbxo31, Fbxo33, Fbxo47, Fbxo9, Fcgr2b, Fchsd2, Fdft1, Fdps, Fdxr, Fech, Fes, Fgd6, Fh1, Fhit, Fhl1, Fkbp14, Fkbp5, Flcn, Flot1, Flt4, Fmn1, Fmo2, Fmo3, Fmo4, Fmo5, Fn1, Fnip2, Foxa1, Foxo1, Foxo3, Frat2, Frmd4b, Fscn1, Fst, Fuom, Furin, Fzd4, Fzd5, G6pdx, Gab1, Gadd45g, Gal3st1, Gale, Galt, Gapdh, Gapdhs, Gareem, Gba, Gbe1, Gca, Gdap2, Gemin6, Gfm1, Gfpt2, Gfra1, Ggt6, Ggt7, Gimap4, Gja4, Gkap1, Glb1, Glrx, Glis2, Glud1, Gm10029, Gm10052, Gm10144, Gm10845, Gm11827, Gm12657, Gm12866, Gm13194, Gm13375, Gm14325, Gm14403, Gm14420, Gm15408, Gm15453, Gm15666, Gm15698, Gm15754, Gm15772, Gm15800, Gm16381, Gm16519, Gm19313, Gm19648, Gm19929, Gm21541, Gm2889, Gm3579, Gm3715, Gm4825, Gm4910, Gm5039, Gm5131, Gm5177, Gm5215, Gm5321, Gm5560, Gm5591, Gm5600, Gm5643, Gm5779, Gm5905, Gm6981, Gm7634, Gm826, Gm8580, Gm9202, Gm9222, Gm9391, Gm9405, Gm9731, Gm9798, Gml, Gmnn, Gnat1, Gnat2, Gne, Gng10, Gng11, Gng3, Gnlda1, Gnptab, Gns, Golim4, Got1, Gpam, Gpcpd1, Gpd1l, Gpi1, Gpihbp1, Gpn3, Gpr108, Gpr157, Gpr182, Gps2, Gpx3, Gpx6, Gpx7, Grem2, Grina, Grm8, Grn, Grsf1, Gspt2, Gsta2, Gsta4, Gstk1, Gstm1, Gstm2, Gstm3, Gstm5, Gstm6, Gstm7, Gsto1, Gstt2, Gstt3, Gtdc1, Gtf2a2, Gtf3c3, Gtpbp2, Guca1a, Gucd1, Gucy1b3, Gucy2c, Gusb, Gyg, Gypc, Gys2, H2afv, H2afz, H2-M10.5, Hal, Hao2, Hapln1, Hapln4, Hat1, Haus7, Hax1, Hbs1l, Hcls1, Hdac5, Hdac7, Hdhd2, Herpud1, Herpud2, Hexb, Hey1, Hgd, Hhex, Hic2, Hint1, Hist1h4c, Hjurp, Hlx, Hmgcr, Hmgcs1, Hmgn2, Hmgn5, Hmox1, Hnrnpa1, Hnrnpa1, Hnrnpa2b1, Hnrnpdl, Hnrnph1, Hnrnpl, Hnrnpll, Hnrnpm, Hook2, Hoxa5, Hoxc6, Hpcal1, Hsbp11l, Hsf4, Hspa2, Hspa9, Hspb1, lah1, lars2, lcam1, Id1, Idh1, Idh2, Idh3b, Idh3g, Idi1, Ier3, Ifi27l2b, Ifi30, Ifitm1, Ifna2, Ifna7, Ifngr1, Ifnz, Ifrd1, Ift27, Ift43, Igf2, Igfbp1, Igfbp5, Igsf23, Igsf8, Il10rb, Il11, Il15, Il15ra, Il17ra, Il17rb, Il18, Il1f9, Il1r1, Il1rn, Il33, Il34, Il6ra, Imp3, Impa2, Inmt, Inpp4a, Inpp5j, Ins2, Ip6k2, Ipmk, Ireb2, Irs2, Irx3, Isca1, Isyna1, Itga1, Itga6, Itgb1bp1, Itgb2, Itih5, Itpka, Itpr1, Ivd, Ivns1abp, Izumo4, Jup, Kansl3, Kat2b, Kcnn2, Kcnq1, Kcns1, Kctd12, Kdelc1, Kdm3a, Kdm6b, Kdr, Khdc3, Khk, Khnyn, Kif4, Kin, Klc4, Klf1, Klf13, Klf15, Klf2, Klf6, Klhdc2, Klhl21, Klhl24, Klhl3, Klk15, Klk1b4, Klrg2, Krcc1, Krt23, Krtcap2, L2hgdh, Lacc1, Lactb2, Lamc1, Lancl1, Lap3, Las1l, Lbr, Lce1i, Lce3b, Lce3c, Lclat1, Ldb1, Ldhd, Lect1, Lect2, Lefty1, Leng8, Lepr, Lgals4, Lgalsl, Lgm, Lhfp, Lig1, Lims2, Lipo1, Ligl1, Ligl2, Lmf2, Lmnd2, Lmo1, Lmo4, Lmo7, Lmod1, Lmod2, LOC100044087, LOC100044177, LOC100044756, LOC100044862, LOC100045522, LOC100045617, LOC100045887, LOC100046044, LOC100046080, LOC100046136, LOC100046406, LOC100046918, LOC100047012, LOC100047167, LOC100047261, LOC100047353, LOC100047579, LOC100047619, LOC100047794, LOC100047856, LOC100048187, LOC100048445, LOC100048480, LOC100048613, LOC100048622, LOC654842, LOC677528, LOC74457, Lonp1, Lonrf1, Lonrf3, Lor, Lpcat3, Lpin1, Lpin2, Lpin3, Lrit3, Lrp1, Lrp3, Lrrc16a, Lrrc24, Lrrc28, Lrrc45, Lrrn3, Lsm10, Lsm4, Lsm8, Lsr, Lss, Ltbp4, Lyl1, Lyve1, Mad2l1, Maf1, Mak16, Man2a1, Manea, Maa, Map1lc3b, Map2k6, Map3k15, Map3k4, Map3k5, Map3k6, Mapk12, Mapk1ip1, Mapre2, Marco, Marf1, Mast3, Mat2b, Mbd6, Mcam, Mccc1, Mcl1, Mcoln1, Mcts1, Mdh2, Me1, Med10, Med12, Med20, Med23, Med25, Med30, Med31, Med4, Mef2d, Mertk, Mettl17, Mettl20, Mettl7a1, Mettl7a2, Mff, Mfge8, Mfsd12, Mfsd2a, Mfsd7c, Mgam, Mgp, Mgst3, Micall1, Mid1ip1, Miip, Mknk2, Mkrn2os, Mix, Mixip, Mmadhc, Mmp7, Mms19, Morc3, Mpp1, Mpv17l, Mpv17l2, Mr1, Mrgprb13, Mrpl20, Mrpl23, Mrpl40, Mrpl48, Mrpl53, Mrps17, Mrps27, Mrps28, Mrps35, Mrps36, Msh2, Msh5, Msn, Mst1, Mt1, Mtch2, Mthfd1, Mthfd1l, Mtmr11, Mtmr14, Mtmr7, Mtss1, Mtx2, Mug-ps1, Mum1, Mvd, Mvk, Myadm, Myc, Mycl, Myh10,

Upregulated CR genes (gene symbols known)

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Upregulated CR genes (gene symbols known)

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Upregulated CR genes (only array IDs known)

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Upregulated CR genes (only array IDs known)

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Downregulated CR genes (gene symbols known)

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Downregulated CR genes (gene symbols known)

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Downregulated CR genes (gene symbols known)

Cybb, Cyp2a12, Cyp2a22, Cyp2c29, Cyp2c37, Cyp2c50, Cyp2c54, Cyp2c70, Cyp2d10, Cyp2d12, Cyp2d13, Cyp2d26, Cyp2d37-ps, Cyp2d40, Cyp2d9, Cyp2f2, Cyp2j5, Cyp2j6, Cyp2u1, Cyp3a13, Cyp3a25, Cyp46a1, Cyp4a12a, Cyp4a12b, Cyp4v3, Cyp7a1, Cyp7b1, Cyp8b1, Cyr61, D10ErtD709e, D130020L05Rik, D17Wsu92e, D1ErtD448e, D2ErtD612e, D430033H22Rik, D4ErtD76e, D5ErtD505e, D5ErtD579e, D5ErtD798e, D5Wsu152e, D630024D03Rik, D630039A03Rik, D830012I24Rik, D830014E11Rik, D930001B02, D930016D06Rik, D930017J03Rik, D9ErtD306e, Daam1, Dag1, Daglb, Dancr, Dapk2, Dars, Daxx, Dbnl, Dbr1, Dcaf10, Dcaf11, Dcaf15, Dcaf5, Dcaf8, Dcakd, Dct, Dcun1d1, Dcun1d4, Dcxr, Ddah1, Ddc, Ddx10, Ddx17, Ddx28, Ddx3x, Ddx3y, Ddx42, Ddx52, Ddx6, Ddx60, Decr1, Decr2, Def8, Dennd4c, Depdc7, Derl1, Derl2, Derl3, Dexi, Dhhdh, Dhhs13, Dhhs3, Dhhs4, Dhhs7b, Dhx15, Dhx29, Dhx30, Dhx36, Dhx58, Diablo, Diap2, Dio1, Dip2c, Dis3l, Dkc1, Dkk4, Dleu2, Dmbt1, Dmgdh, Dnaic1, Dnaja1, Dnajb1, Dnajb11, Dnajb14, Dnajb2, Dnajb4, Dnajb9, Dnajc1, Dnajc14, Dnajc2, Dnajc3, Dnajc30, Dnajc5, Dnase1, Dnase2a, Dnase2b, Dnlz, Dnph1, Dnttip2, Dok2, Dolk, Dpagt1, Dpm1, Dpp7, Dpp9, Dpt, Dpy19l1, Dpy19l4, Dpys, Dr1, Dram2, Drg2, Dsg2, Dsp, Dtx3l, Dtx4, Dus2, Dusp23, Dusp3, Dusp6, Dut, Dync1i2, Dynlrb1, E130110O22Rik, E130311K13Rik, E2f1, E2f8, E430010N07Rik, Eaf1, Ears2, Ebag9, Ech1, Eci1, Eci2, Edem3, Ednrb, Eea1, Eef1b2, Eef1e1, Efemp1, Efhd2, Efna1, Efr3a, Egfr, EglN1, EglN3, Ehd1, Ehhadh, Ei24, Eif1a, Eif1ax, Eif1b, Eif2ak2, Eif2b3, Eif2b4, Eif2b5, Eif2s2, Eif2s3x, Eif3e, Eif3k, Eif3m, Eif4a2, Eif4b, Eif4e, Eif4ebp2, Eif4g1, Eif5, Eif5b, Ell2, Elmod2, Elovl3, Elovl5, Eme2, Eml3, Endod1, Enpp2, Enpp3, Enpp4, Enpp5, Entpd5, Eny2, Epc2, Epha2, Ephx1, Ephx2, Epm2aip1, Eps8l2, Ept1, Ercc6, Ergic1, Ergic2, Erich1, Ermp1, Ero1lb, Esco1, Esd, Esf1, Esp2, Etfhd, Etnk1, Eva1a, Evi2a, Evi5, Exoc2, Exoc3, Exoc4, Exoc5, Extl1, F8, F9, Fabp2, Fabp7, Fads6, Faf2, Fahd1, Faim, Fam102a, Fam107b, Fam118b, Fam126b, Fam129b, Fam131c, Fam136a, Fam13b, Fam149a, Fam149b, Fam151b, Fam168a, Fam174a, Fam198a, Fam19a5, Fam206a, Fam208b, Fam20a, Fam210a, Fam210b, Fam213b, Fam214a, Fam219b, Fam220a, Fam228b, Fam25c, Fam26f, Fam32a, Fam35a, Fam46d, Fam47e, Fam63a, Fam73b, Fam83f, Fam83h, Fam89a, Fam96a, Fam98a, Fam98b, Farsb, Fas, Fastkd5, Fbxo11, Fbxo30, Fbxw11, Fbxw4, Fcfer1g, Fcgr1, Fcgr4, Fcgrt, Fcho2, Fchsd1, Fcmr, Fcna, Fen1, Fermt2, Fetub, Fez2, Fgf1, Fgf21, Fgfr1op, Fgfr1op2, Fgl1, Ficd, Fitm1, Fkbp3, Fkbp4, Fkbp8, Fkbp9, Fmn2, Fmr1nb, Fn3krp, Fnbp1l, Fnndc3a, Fnndc3b, Fnip1, Fntb, Folr2, Foxa2, Foxa3, Foxn2, Foxp1, Foxq1, Fpgs, Fpgt, Fpr2, Fsd1l, Ftsj2, Ftsj3, Fubp1, Fubp3, Fuca1, Fus, Fxn, Fyco1, Fzd7, Fzd8, G0s2, G3bp1, G3bp2, G630090E17Rik, G6pc, Gaa, Gabarapl1, Gabpa, Gabpb1, Gadd45a, Galk1, Galnt1, Galnt2, Gas2, Gas5, Gas6, Gatad2a, Gatac, Gbf1, Gbp10, Gbp2, Gbp2b, Gbp3, Gbp6, Gbp7, Gbp8, Gcat, Gcgr, Gck, Gclc, Gclm, Gcsh, Gdap10, Gdf15, Gemin2, Gfer, Gfm2, Gfod2, Ggact, Ggct, Ggcx, Ggh, Ggnbp2, Ghr, Gid8, Gigyf2, Gimap9, Gjb1, Gjb2, Gldc, Glo1, Glt28d2, Gltpd2, Glyat, Glyctk, Gm10104, Gm10804, Gm11437, Gm11772, Gm11837, Gm12250, Gm12474, Gm13212, Gm15417, Gm16551, Gm17586, Gm19331, Gm19696, Gm19966, Gm20300, Gm20319, Gm2568, Gm26853, Gm2701, Gm2788, Gm4285, Gm4354, Gm4794, Gm4951, Gm4956, Gm5150, Gm5486, Gm5590, Gm561, Gm5617, Gm5802, Gm5817, Gm6484, Gm6658, Gm6682, Gm7241, Gm8979, Gm8995, Gm9706, Gmfb, Gmppb, Gmps, Gna11, Gna12, Gna14, Gnai1, Gngt2, Gnprnat1, Gnrh1, Golga4, Golga7, Golph3, Gorasp1, Gorasp2, Gosr2, Gp49a, Gpatch11, Gpbp1, Gpbp1l1, Gpc1, Gpc4, Gpd1, Gpd2, Gphn, Gpn2, Gpr137, Gpr146, Gpr155, Gpr52, Gprin3, Gps1, Gpx4, Grhpr, Grpel2, Gse1, Gsn, Gspt1, Gss, Gsta3, Gstm4, Gstp2, Gt(ROSA)26Sor, Gtf2f1, Gtf2f2, Gtf2h1, Gtf2h2, Gtf2i, Gtf2ird1, Gtf3c4, Gtf3c5, Gtpbp1, Gtpbp10, Gtpbp4, Guk1, Gyk, H19, H1f0, H2-Aa, H2-Ab1, H2afx, H2-DMA, H2-DMb1, H2-Eb1, H2-M2, H2-Oa, H2-Q1, H2-Q4, H2-T24, H6pd, Hacd1, Hacd3, Hacl1, Hadha, Hadhb, Hao1, Hars, Haus8, Hba-a1, Hbb-b2, Hc, Hccs, Hcfc1r1, Hdac1, Hdac11, Hdac2, Hdhd3, Heca, Hectd1, Helz2, Herc6, Hes1, Hes6, Hexim1, Hfe, Hgf, Hgfac, Hgs, Hhip, Hiatl1, Hif1a, Hint2, Hipk2, Hist1h1c, Hist1h2ad, Hist1h2ae, Hist1h2af, Hist1h2ah,

Downregulated CR genes (gene symbols known)

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Downregulated CR genes (gene symbols known)

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Downregulated CR genes (gene symbols known)

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Downregulated CR genes (only array IDs known)

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96489_at, 96522_at, 96536_at, 96547_at, 96550_at, 96555_at, 96653_at, 96959_at, 96964_at, 96967_at, 96970_at, 97135_at, 97173_f_at, 97176_at, 97205_at, 97287_at, 97288_at, 97448_at, 97462_at, 97464_at, 97479_at, 97523_i_at, 97524_f_at, 97541_f_at, 97566_f_at, 97567_f_at, 97575_f_at, 97578_at, 97666_r_at, 97702_at, 97706_at, 97708_at, 98065_at, 98096_f_at, 98438_f_at, 98446_s_at, 98472_at, 98516_at, 98600_at, 98761_i_at, 99143_at, 99144_s_at, 99681_at, 99702_at, 99821_at, 99866_at, 99872_s_at, AFFX-18SRNAMur/X00686_5_at, AFFX-18SRNAMur/X00686_M_at, AFFX-BioB-3_at, AFFX-BioB-5_at, AFFX-BioB-M_at, AFFX-BioC-3_at, AFFX-BioC-5_at, AFFX-BioDn-3_at, AFFX-BioDn-5_at, AFFX-CreX-3_at, AFFX-CreX-5_at, AFFX-DapX-3_at, AFFX-DapX-M_at, AFFX-r2-Bs-dap-3_at, AFFX-r2-Bs-dap-5_at, AFFX-r2-Bs-dap-M_at, AFFX-r2-Ec-bioB-3_at, AFFX-r2-Ec-bioB-5_at, AFFX-r2-Ec-bioB-M_at, AFFX-r2-Ec-bioC-3_at, AFFX-r2-Ec-bioC-5_at, AFFX-r2-Ec-bioD-3_at, AFFX-r2-Ec-bioD-5_at, AFFX-YEL002c/WBP1_at

D: Pathways mentioned by CR in overrepresentation analysis and the number of overlapping genes with plant bioactives

Pathways	regulation	genes up-regulated by CR	Overlap					genes down-regulated by CR	Overlap				
			R	P	Q	Qi	Qi		R	P	Q	Qi	Qi
(deoxy)ribose phosphate degradation - MouseCyc	↑	4 of 10	1 of 4	2 of 4	1 of 4	1 of 4	1 of 4	2 of 10	1 of 2	1 of 2	1 of 2	0 of 2	0 of 2
2-amino-3-carboxymuconate semialdehyde degradation to glutaryl-CoA - MouseCyc	↑	2 of 2	0 of 2	0 of 1	0 of 1	0 of 2	0 of 2	0 of 2					
2-methylbutyrate biosynthesis - MouseCyc	↓	1 of 5	0 of 1	0 of 1	0 of 1	1 of 1	1 of 1	4 of 5	0 of 4	3 of 3	0 of 3	1 of 4	1 of 4
3, -UTR-mediated translational regulation - Reactome	↑	24 of 100	0 of 12	1 of 10	0 of 10	2 of 23	1 of 23	15 of 100	2 of 14	4 of 13	0 of 13	1 of 15	0 of 15
4-hydroxyproline degradation I - MouseCyc	↑	2 of 4	1 of 2	1 of 2	1 of 2	1 of 2	1 of 2	0 of 4					
ABC transporters - Mus musculus (mouse) - KEGG	↑	14 of 46	5 of 14	0 of 14	0 of 14	0 of 14	0 of 14	11 of 46	3 of 11	6 of 11	0 of 11	1 of 11	0 of 11
ABCA transporters in lipid homeostasis - Reactome	↑	6 of 13	4 of 6	0 of 6	0 of 6	0 of 6	0 of 6	3 of 13	1 of 3	0 of 3	0 of 3	0 of 3	0 of 3
ABC-family proteins mediated transport - Reactome	↑	12 of 31	5 of 12	0 of 12	0 of 12	0 of 12	0 of 12	6 of 31	1 of 6	3 of 6	0 of 6	0 of 6	0 of 6
acetyl-CoA biosynthesis (from pyruvate) - MouseCyc	↑	3 of 5	0 of 3	0 of 3	0 of 3	0 of 3	0 of 3	0 of 5					
Activated TLR4 signalling - Reactome	↓	13 of 94	4 of 12	2 of 11	2 of 11	1 of 12	0 of 12	28 of 94	2 of 26	16 of 28	4 of 28	1 of 28	0 of 28
Activation of Gene Expression by SREBP (SREBF) - Reactome	↑	3 of 7	0 of 3	0 of 3	0 of 3	1 of 3	1 of 3	0 of 7					
acyl-CoA hydrolysis - MouseCyc	↓	4 of 11	1 of 4	1 of 4	0 of 4	1 of 4	2 of 4	5 of 11	0 of 5	1 of 5	1 of 5	0 of 5	0 of 5
Adaptive Immune System - Reactome	↓	56 of 441	15 of 52	4 of 52	6 of 52	3 of 55	2 of 55	98 of 441	15 of 93	33 of 93	3 of 93	13 of 97	8 of 97
adenosine nucleotides de novo biosynthesis - MouseCyc	↑	8 of 22	1 of 7	1 of 7	0 of 7	0 of 8	0 of 8	2 of 22	0 of 2	2 of 2	0 of 2	0 of 2	0 of 2
Adipocytokine signaling pathway - Mus musculus (mouse) - KEGG	↑	18 of 71	4 of 16	1 of 18	1 of 18	4 of 18	2 of 18	16 of 71	3 of 15	7 of 16	4 of 16	2 of 16	0 of 16
aerobic respiration -- electron donor II - MouseCyc	↑	24 of 80	0 of 22	0 of 22	0 of 22	1 of 24	0 of 24	6 of 80	1 of 5	3 of 5	0 of 5	1 of 5	1 of 5
Alanine and aspartate metabolism - Wikipathways	↑	4 of 12	1 of 4	1 of 4	1 of 4	1 of 4	1 of 4	4 of 12	0 of 4	3 of 4	0 of 4	1 of 4	1 of 4

Alanine, aspartate and glutamate metabolism - Mus musculus (mouse) - KEGG	↑	14 of 33	1 of 11	3 of 14	3 of 14	0 of 14	1 of 14	8 of 33	1 of 8	5 of 8	0 of 8	1 of 8	1 of 8
alpha-linolenic (omega3) and linoleic (omega6) acid metabolism - Reactome	↑↓	4 of 12	1 of 4	1 of 4	0 of 4	2 of 4	0 of 4	8 of 12	2 of 8	1 of 8	0 of 8	2 of 8	1 of 8
alpha-linolenic acid (ALA) metabolism - Reactome	↑↓	4 of 12	1 of 4	1 of 4	0 of 4	2 of 4	0 of 4	8 of 12	2 of 8	1 of 8	0 of 8	2 of 8	1 of 8
Amino Acid metabolism - Wikipathways	↑	4 of 6	0 of 4	0 of 4	0 of 4	0 of 4	0 of 4	0 of 6					
Amino acid synthesis and interconversion (transamination) - Reactome	↑	8 of 17	1 of 8	2 of 8	1 of 8	0 of 8	1 of 8	1 of 17	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1
Amino sugar and nucleotide sugar metabolism - Mus musculus (mouse) - KEGG	↑	14 of 48	3 of 14	1 of 14	2 of 14	0 of 14	0 of 14	12 of 48	5 of 12	4 of 12	2 of 12	2 of 12	0 of 12
Androgen biosynthesis - Reactome	↓	1 of 13	1 of 1	0 of 1	0 of 1	1 of 1	1 of 1	4 of 13	3 of 4	3 of 4	2 of 4	2 of 4	1 of 4
Androgen Receptor Signaling Pathway - Wikipathways	↓	15 of 109	4 of 12	2 of 13	0 of 13	1 of 13	1 of 13	37 of 109	6 of 35	13 of 37	2 of 37	6 of 37	4 of 37
Antigen processing and presentation - Mus musculus (mouse) - KEGG	↓	13 of 76	5 of 10	1 of 11	2 of 11	0 of 12	0 of 12	26 of 76	3 of 22	11 of 23	3 of 23	6 of 25	4 of 25
Antigen processing: Ubiquitination & Proteasome degradation - Reactome	↓	12 of 128	3 of 11	0 of 10	2 of 10	1 of 11	0 of 11	34 of 128	8 of 31	14 of 34	1 of 34	3 of 34	2 of 34
Antigen processing-Cross presentation - Reactome	↓	6 of 33	2 of 5	0 of 5	0 of 5	0 of 6	0 of 6	13 of 33	0 of 11	3 of 10	0 of 10	4 of 12	3 of 12
Antiviral mechanism by IFN-stimulated genes - Reactome	↓	2 of 25	1 of 2	0 of 2	0 of 2	0 of 2	0 of 2	9 of 25	1 of 8	5 of 8	0 of 8	4 of 9	4 of 9
Apoptotic cleavage of cellular proteins - Reactome	↑	9 of 34	3 of 8	0 of 8	1 of 8	1 of 9	1 of 9	9 of 34	1 of 9	3 of 9	1 of 9	2 of 9	0 of 9
Arachidonic acid metabolism - Mus musculus (mouse) - KEGG	↑↓	25 of 71	7 of 23	4 of 22	3 of 22	5 of 25	6 of 25	19 of 71	4 of 17	7 of 18	1 of 18	6 of 19	5 of 19
Arachidonic acid metabolism - Reactome	↑↓	19 of 71	2 of 17	2 of 16	1 of 16	4 of 18	4 of 18	19 of 71	4 of 16	8 of 18	1 of 18	7 of 19	4 of 19
Arginine and proline metabolism - Mus musculus (mouse) - KEGG	↑	16 of 55	3 of 13	1 of 16	1 of 16	0 of 16	2 of 16	9 of 55	0 of 9	2 of 9	0 of 9	0 of 9	0 of 9
arginine biosynthesis IV - MouseCyc	↑	4 of 5	0 of 4	0 of 4	0 of 4	0 of 4	0 of 4	0 of 5					
arginine degradation I (arginase pathway) - MouseCyc	↑	3 of 4	0 of 3	0 of 3	0 of 3	0 of 3	1 of 3	0 of 4					
arsenate detoxification I (glutaredoxin) - MouseCyc	↑	5 of 6	2 of 5	0 of 5	0 of 5	0 of 5	0 of 5	1 of 6	1 of 1	0 of 1	0 of 1	0 of 1	0 of 1
Ascorbate and aldarate metabolism - Mus musculus (mouse) - KEGG	↑	6 of 22	3 of 3	0 of 3	1 of 3	0 of 3	0 of 3	8 of 22	3 of 8	3 of 8	1 of 8	3 of 8	2 of 8

beta-Alanine metabolism - Mus musculus (mouse) - KEGG	↓	3 of 30	1 of 3	0 of 3	0 of 3	1 of 3	1 of 3	8 of 30	0 of 7	6 of 8	0 of 8	1 of 8	1 of 8
Beta-oxidation of pristanoyl-CoA - Reactome	↓	0 of 8						7 of 8	0 of 7	1 of 7	0 of 7	4 of 7	2 of 7
Beta-oxidation of very long chain fatty acids - Reactome	↓	1 of 7	1 of 1	0 of 1	0 of 1	0 of 1	0 of 1	6 of 7	2 of 6	1 of 6	0 of 6	1 of 6	0 of 6
Bile acid and bile salt metabolism - Reactome	↓	9 of 36	3 of 9	1 of 9	1 of 9	0 of 9	0 of 9	19 of 36	3 of 19	7 of 19	1 of 19	8 of 19	4 of 19
bile acid biosynthesis, neutral pathway - MouseCyc	↓	2 of 6	1 of 2	1 of 2	1 of 2	0 of 2	0 of 2	4 of 6	1 of 4	0 of 4	1 of 4	0 of 4	0 of 4
Bile secretion - Mus musculus (mouse) - KEGG	↑↓	24 of 71	7 of 23	2 of 23	1 of 23	2 of 24	1 of 24	19 of 71	5 of 19	12 of 19	3 of 19	5 of 19	5 of 19
Binding and Uptake of Ligands by Scavenger Receptors - Reactome	↑	11 of 35	4 of 11	1 of 11	2 of 11	0 of 11	0 of 11	11 of 35	2 of 11	2 of 11	1 of 11	1 of 11	0 of 11
Biological oxidations - Reactome	↑↓	62 of 158	22 of 54	5 of 51	9 of 51	12 of 59	11 of 59	50 of 158	10 of 44	16 of 47	7 of 47	22 of 49	15 of 49
Biosynthesis of the N-glycan precursor (dolichol lipid-linked oligosaccharide, LLO) and transfer to a nascent protein - Reactome	↓	2 of 29	0 of 2	0 of 2	1 of 2	0 of 2	0 of 2	11 of 29	4 of 11	2 of 11	0 of 11	0 of 11	1 of 11
Biosynthesis of unsaturated fatty acids - Mus musculus (mouse) -KEGG	↑↓	10 of 25	2 of 10	3 of 10	0 of 10	4 of 10	3 of 10	12 of 25	1 of 4	3 of 4	0 of 4	0 of 4	0 of 4
Biotin transport and metabolism - Reactome	↑	5 of 10	1 of 5	1 of 5	0 of 5	0 of 5	0 of 5	2 of 10	1 of 2	1 of 2	0 of 2	0 of 2	0 of 2
biotin-carboxyl carrier protein assembly - MouseCyc	↑	2 of 3	0 of 2	1 of 2	0 of 2	2 of 2	2 of 2	0 of 3					
bupropion degradation - MouseCyc	↑↓	14 of 36	3 of 11	1 of 12	3 of 12	2 of 14	3 of 14	16 of 36	2 of 14	9 of 16	1 of 16	10 of 16	8 of 16
Butanoate metabolism - Mus musculus (mouse) - KEGG	↓	7 of 29	1 of 7	0 of 7	0 of 7	1 of 7	1 of 7	11 of 29	0 of 11	9 of 10	0 of 10	4 of 11	4 of 11
Caffeine metabolism - Mus musculus (mouse)	↑	5 of 8	1 of 5	0 of 4	0 of 4	1 of 5	1 of 5	1 of 8	0 of 1	1 of 1	0 of 1	0 of 1	0 of 1
Cap-dependent Translation Initiation - Reactome	↑	26 of 108	0 of 14	1 of 12	0 of 12	2 of 15	1 of 25	20 of 108	2 of 19	7 of 18	0 of 18	1 of 20	0 of 20
Caspase-mediated cleavage of cytoskeletal proteins - Reactome	↑	7 of 12	3 of 7	0 of 7	1 of 7	0 of 7	1 of 7	4 of 12	0 of 4	1 of 4	0 of 4	0 of 4	0 of 4
catecholamine biosynthesis - MouseCyc	↓	0 of 6						2 of 6	1 of 2	1 of 2	0 of 2	0 of 2	0 of 2
CDT1 association with the CDC6:ORC:origin complex - Reactome	↑	6 of 14	2 of 4	0 of 4	0 of 4	0 of 5	0 of 5	2 of 14	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2
Chemical carcinogenesis - Mus musculus (mouse)	↑↓	39 of 87	11 of 33	1 of 30	3 of 30	7 of 35	7 of 35	20 of 87	3 of 18	11 of 19	2 of 19	12 of 19	11 of 19

Cholesterol biosynthesis - Reactome	↑	19 of 22	14 of 19	6 of 19	2 of 19	1 of 19	1 of 19	6 of 22	1 of 6	2 of 6	1 of 6	3 of 6	1 of 6
Cholesterol biosynthesis - Wikipathways	↑	15 of 15	12 of 15	6 of 15	2 of 15	1 of 15	1 of 15	5 of 15	1 of 5	2 of 5	1 of 5	3 of 5	1 of 5
cholesterol biosynthesis I - MouseCyc	↑	11 of 12	8 of 11	3 of 11	1 of 11	1 of 11	1 of 11	4 of 12	0 of 4	1 of 4	1 of 4	3 of 4	0 of 4
cholesterol biosynthesis II (via 24,25-dihydrolanosterol) - MouseCyc	↑	8 of 8	5 of 8	2 of 8	1 of 8	1 of 8	1 of 8	3 of 8	0 of 3	1 of 3	1 of 3	3 of 3	0 of 3
cholesterol biosynthesis III (via desmosterol) - MouseCyc	↑	10 of 11	7 of 10	3 of 10	1 of 10	1 of 10	1 of 10	4 of 11	0 of 4	1 of 4	1 of 4	3 of 4	0 of 4
Circadian Clock - Reactome	↑	6 of 13	3 of 6	1 of 6	2 of 6	0 of 6	0 of 6	2 of 13	1 of 2	2 of 2	1 of 2	0 of 2	0 of 2
Circadian clock tutorial Cgrove - Wikipathways	↑	4 of 6	3 of 4	1 of 4	2 of 4	0 of 4	0 of 4	2 of 6	1 of 2	2 of 2	1 of 2	0 of 2	0 of 2
Circadian rhythm - Mus musculus (mouse) - KEGG	↑	11 of 30	7 of 11	2 of 11	2 of 11	0 of 11	0 of 11	6 of 30	1 of 5	3 of 6	2 of 6	0 of 6	0 of 6
Citrate cycle (TCA cycle) - Mus musculus (mouse) - KEGG	↑	18 of 32	4 of 18	0 of 18	0 of 18	1 of 18	1 of 18	1 of 32	0 of 1	1 of 1	0 of 1	0 of 1	0 of 1
Citric acid cycle (TCA cycle) - Reactome	↑	12 of 20	2 of 12	0 of 12	0 of 12	0 of 12	0 of 12	0 of 12					
citrulline biosynthesis - MouseCyc	↑	4 of 9	0 of 4	0 of 4	0 of 4	0 of 4	1 of 4	0 of 9					
citrulline-nitric oxide cycle - MouseCyc	↑	2 of 7	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2	0 of 7					
Class I MHC mediated antigen processing & presentation - Reactome	↓	22 of 173	6 of 20	0 of 19	2 of 19	1 of 21	0 of 21	51 of 173	9 of 46	18 of 48	1 of 48	7 of 50	5 of 50
Classical antibody-mediated complement activation - Reactome	↓	0 of 8						5 of 8	0 of 5	2 of 5	0 of 5	3 of 5	2 of 5
Clathrin derived vesicle budding - Reactome	↓	6 of 60	2 of 6	1 of 6	0 of 6	0 of 6	0 of 6	19 of 60	2 of 16	7 of 19	1 of 19	3 of 19	1 of 19
Cleavage of Growing Transcript in the Termination Region - Reactome	↓	4 of 43	0 of 6	0 of 6	1 of 6	0 of 6	0 of 6	16 of 43	1 of 16	7 of 15	0 of 15	3 of 16	2 of 16
colanic acid building blocks biosynthesis - MouseCyc	↑↓	6 of 14	1 of 6	1 of 6	1 of 6	0 of 6	0 of 6	5 of 14	2 of 5	0 of 5	1 of 5	1 of 5	0 of 5
Complement Activation, Classical Pathway - Wikipathways	↓	2 of 17	1 of 2	0 of 2	0 of 2	0 of 2	0 of 2	11 of 17	0 of 10	5 of 11	0 of 11	7 of 11	4 of 11
Complement and coagulation cascades - Mus musculus (mouse) - KEGG	↓	12 of 77	6 of 11	1 of 11	0 of 11	0 of 12	0 of 12	24 of 77	1 of 23	8 of 22	0 of 22	12 of 24	8 of 24
Complement and Coagulation Cascades - Wikipathways	↓	10 of 61	5 of 10	1 of 10	0 of 10	0 of 10	0 of 10	20 of 61	1 of 19	6 of 20	0 of 20	10 of 20	8 of 20

Complement cascade - Reactome	↓	4 of 36	3 of 4	0 of 4	0 of 4	0 of 4	0 of 4	17 of 36	1 of 16	5 of 16	0 of 16	9 of 17	5 of 17
Cysteine and methionine metabolism - Mus musculus (mouse) - KEGG	↑	9 of 35	3 of 9	2 of 9	3 of 9	0 of 9	2 of 9	11 of 35	4 of 11	3 of 11	1 of 11	1 of 11	2 of 11
cysteine biosynthesis II - MouseCyc	↑	2 of 2	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2					
cysteine biosynthesis/homocysteine degradation - MouseCyc	↑	2 of 2	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2					
Cysteine formation from homocysteine - Reactome	↑	2 of 2	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2					
Cytochrome P450 - arranged by substrate type - Reactome	↑↓	31 of 78	9 of 24	3 of 23	6 of 23	7 of 30	7 of 30	27 of 78	5 of 22	11 of 25	5 of 25	13 of 27	10 of 27
Cytochrome P450 - Wikipathways	↑	12 of 40	4 of 11	2 of 12	3 of 12	1 of 12	1 of 12	10 of 40	4 of 10	1 of 10	2 of 10	3 of 10	1 of 10
Cytokine Signaling in Immune system - Reactome	↓	20 of 190	8 of 19	4 of 20	5 of 20	3 of 20	3 of 20	50 of 190	7 of 48	22 of 49	3 of 49	12 of 50	8 of 50
Cytoplasmic Ribosomal Proteins - Wikipathways	↑	21 of 78	0 of 9	1 of 9	0 of 9	0 of 21	0 of 21	5 of 78	0 of 0	0 of 3	0 of 3	1 of 5	0 of 5
Cytosolic sensors of pathogen-associated DNA - Reactome	↓	9 of 55	3 of 7	1 of 7	1 of 7	1 of 8	0 of 8	17 of 55	1 of 17	8 of 16	1 of 16	3 of 17	3 of 17
Cytosolic sulfonation of small molecules - reactome	↑	7 of 16	3 of 6	0 of 6	1 of 6	2 of 7	2 of 7	5 of 16	1 of 1	1 of 5	2 of 5	0 of 5	0 of 5
Cytosolic tRNA aminoacylation - Reactome	↓	0 of 23						10 of 23	1 of 1	6 of 10	0 of 10	1 of 10	1 of 10
Deadenylation of mRNA - Reactome	↓	3 of 21	0 of 3	0 of 3	0 of 3	1 of 3	0 of 3	10 of 21	3 of 3	5 of 10	0 of 10	0 of 10	0 of 10
Deadenylation-dependent mRNA decay - Reactome	↓	5 of 45	0 of 5	0 of 5	0 of 5	1 of 5	0 of 5	15 of 45	3 of 13	7 of 15	1 of 15	0 of 15	0 of 15
Degradation of cysteine and homocysteine - Reactome	↓	3 of 8	0 of 3	0 of 3	0 of 3	0 of 3	0 of 3	5 of 8	3 of 3	2 of 5	0 of 5	2 of 5	1 of 5
Destabilization of mRNA by AUF1 (hnRNP D0) - Reactome	↓	3 of 7	0 of 3	2 of 3	2 of 3	0 of 2	0 of 2	7 of 7	2 of 2	4 of 4	3 of 7	0 of 6	2 of 6
Diurnally Regulated Genes with Circadian Orthologs - Wikipathways	↑↓	21 of 48	9 of 18	3 of 21	5 of 21	1 of 21	1 of 21	18 of 48	4 of 17	11 of 18	4 of 18	7 of 18	3 of 18
Drug metabolism - cytochrome P450 - Mus musculus (mouse) - KEGG	↑↓	39 of 88	12 of 35	1 of 32	3 of 32	7 of 36	7 of 36	25 of 88	6 of 23	12 of 24	2 of 24	14 of 24	13 of 24
Drug metabolism - other enzymes - Mus musculus (mouse) - KEGG	↑↓	16 of 51	7 of 14	2 of 12	3 of 12	2 of 13	2 of 13	19 of 51	6 of 18	11 of 19	2 of 19	6 of 19	6 of 19
EGFR1 Signaling Pathway - Wikipathways	↓	25 of 175	5 of 25	2 of 25	5 of 25	0 of 25	0 of 25	45 of 175	6 of 45	14 of 45	4 of 45	7 of 45	3 of 45

Electron Transport Chain - Wikipathways	↑	28 of 93	0 of 23	0 of 26	0 of 26	1 of 28	0 of 28	4 of 93	0 of 2	3 of 3	0 of 3	0 of 3	0 of 3
Endogenous sterols - Reactome	↑↓	4 of 14	3 of 4	1 of 4	1 of 4	1 of 4	1 of 4	4 of 14	1 of 4	0 of 4	1 of 4	1 of 4	0 of 4
epoxysqualene biosynthesis - Mousecyc	↑	2 of 2	1 of 2	1 of 2	1 of 2	0 of 2	0 of 2	1 of 2	0 of 1	0 of 1	0 of 1	1 of 1	0 of 1
Estrogen metabolism - Wikipathways	↑	8 of 11	3 of 8	0 of 5	1 of 5	2 of 6	2 of 6	1 of 11	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1
Eukaryotic Translation Elongation - Reactome	↑	23 of 82	0 of 11	1 of 10	0 of 10	3 of 22	1 of 22	6 of 82	0 of 5	0 of 4	0 of 4	2 of 6	0 of 6
Eukaryotic Translation Initiation - Reactome	↑	26 of 108	0 of 14	1 of 12	0 of 12	2 of 25	1 of 25	20 of 108	2 of 19	7 of 18	0 of 18	1 of 20	0 of 20
Eukaryotic Translation Termination - Reactome	↑	23 of 79	0 of 11	1 of 10	0 of 10	2 of 22	1 of 22	5 of 79	0 of 4	0 of 3	0 of 3	1 of 5	0 of 5
Exercise-induced Circadian Regulation - Wikipathways	↑↓	22 of 49	9 of 19	4 of 22	5 of 22	1 of 22	1 of 11	20 of 49	4 of 18	12 of 19	5 of 19	7 of 19	3 of 17
Facilitative Na ⁺ -independent glucose transporters - reactome	↑	4 of 11	1 of 4	0 of 4	0 of 4	1 of 4	0 of 4	0 of 11					
Fat digestion and absorption - Mus musculus (mouse)	↓	5 of 40	3 of 5	0 of 5	0 of 5	0 of 5	0 of 5	12 of 40	2 of 12	5 of 11	2 of 11	4 of 12	1 of 12
fatty acid activation - MouseCyc	↑	3 of 6	0 of 3	0 of 3	0 of 3	0 of 3	0 of 3	0 of 6					
Fatty Acid Beta Oxidation - Wikipathways	↑↓	7 of 34	2 of 7	1 of 7	0 of 7	0 of 7	0 of 7	16 of 34	2 of 16	8 of 16	1 of 16	3 of 16	2 of 16
Fatty acid biosynthesis - Mus musculus (mouse) - KEGG	↑	3 of 6	0 of 3	1 of 3	0 of 3	0 of 3	0 of 3	1 of 6	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1
Fatty Acid Biosynthesis - Wikipathways	↑	11 of 22	1 of 10	3 of 11	0 of 11	1 of 11	1 of 11	5 of 22	0 of 5	2 of 5	1 of 5	2 of 5	2 of 5
Fatty acid degradation - Mus musculus (mouse) - KEGG	↑↓	11 of 45	4 of 10	1 of 10	1 of 10	4 of 11	3 of 11	20 of 45	4 of 18	9 of 18	0 of 18	5 of 20	5 of 20
Fatty acid elongation - Mus musculus (mouse) - KEGG	↑↓	7 of 24	1 of 7	1 of 7	0 of 7	2 of 7	3 of 7	10 of 24	2 of 10	4 of 10	1 of 10	3 of 10	2 of 10
fatty acid β-oxidation I - MouseCyc	↓	5 of 27	0 of 5	0 of 5	0 of 5	1 of 5	1 of 5	12 of 27	0 of 12	7 of 12	0 of 12	3 of 12	1 of 12
fatty acid β-oxidation III (unsaturated, odd number) - MouseCyc	↓	2 of 3	0 of 2	0 of 2	0 of 2	1 of 2	1 of 2	3 of 3	0 of 3	2 of 3	0 of 3	0 of 3	0 of 3
fatty acid β-oxidation IV (unsaturated, even number) - MouseCyc	↓	2 of 8	0 of 2	0 of 2	0 of 2	1 of 2	1 of 2	7 of 8	0 of 7	4 of 7	1 of 7	1 of 7	1 of 7
Fatty acid, triacylglycerol, and ketone body metabolism - Reactome	↑↓	23 of 85	2 of 20	1 of 23	1 of 23	2 of 23	3 of 23	30 of 85	9 of 26	11 of 30	3 of 30	5 of 30	3 of 30

Fatty acids - Reactome	↑↓	6 of 16	2 of 4	1 of 5	1 of 5	3 of 6	2 of 6	6 of 16	2 of 5	2 of 5	0 of 5	3 of 6	2 of 6
Fatty Acyl-CoA Biosynthesis - Reactome	↑	9 of 17	0 of 8	0 of 9	0 of 9	2 of 9	2 of 9	4 of 17	2 of 4	2 of 4	0 of 4	2 of 4	1 of 4
formaldehyde oxidation I - MouseCyc	↑	2 of 5	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2	1 of 5	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1
Formation of a pool of free 40S subunits - Reactome	↑	24 of 89	0 of 12	1 of 10	0 of 10	2 of 23	1 of 23	8 of 89	0 of 7	0 of 6	0 of 6	1 of 8	0 of 8
Formation of ATP by chemiosmotic coupling - Reactome	↑	6 of 13	0 of 4	0 of 6	0 of 6	0 of 6	0 of 6	0 of 13					
Formation of the Editosome - Reactome	↓	0 of 2						2 of 2	1 of 2	2 of 2	0 of 2	0 of 2	0 of 2
Fructose and mannose metabolism - Mus musculus (mouse) - KEGG	↑	12 of 39	3 of 12	1 of 12	0 of 12	0 of 12	0 of 12	5 of 39	1 of 5	1 of 5	0 of 5	1 of 5	1 of 5
G1 to S cell cycle control - Wikipathways	↑	16 of 61	4 of 16	3 of 16	1 of 16	0 of 16	0 of 16	10 of 61	1 of 10	2 of 10	1 of 10	0 of 10	0 of 10
Galactose metabolism - Mus musculus (mouse) - KEGG	↑	10 of 32	3 of 10	1 of 10	1 of 10	1 of 10	1 of 10	5 of 32	3 of 5	2 of 5	3 of 5	1 of 5	1 of 5
Gamma-carboxylation, transport, and amino-terminal cleavage of proteins - Reactome	↑	4 of 10	1 of 4	0 of 4	0 of 4	0 of 4	0 of 4	4 of 10	0 of 4	2 of 4	0 of 4	1 of 4	1 of 4
GDP-mannose biosynthesis I - MouseCyc	↓	1 of 6	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1	2 of 6	1 of 2	0 of 2	0 of 2	0 of 2	0 of 2
Gene Expression - Reactome	↓	107 of 646	8 of 83	3 of 87	3 of 87	4 of 104	3 of 104	167 of 646	24 of 148	59 of 158	9 of 158	13 of 163	6 of 163
Gluconeogenesis - Reactome	↑	18 of 33	3 of 16	3 of 18	1 of 18	1 of 18	2 of 18	4 of 33	0 of 4	2 of 4	0 of 4	1 of 4	0 of 4
gluconeogenesis I - MouseCyc	↑	12 of 24	1 of 12	1 of 12	0 of 12	1 of 12	1 of 12	0 of 24					
Glucose metabolism - Reactome	↑	27 of 67	5 of 24	3 of 26	1 of 26	2 of 27	2 of 27	10 of 27	1 of 10	7 of 10	1 of 10	1 of 10	0 of 10
Glucuronidation - Reactome	↑	4 of 5	3 of 4	0 of 2	1 of 2	0 of 2	0 of 2	2 of 5	1 of 2	0 of 2	0 of 2	1 of 2	0 of 2
glutathione biosynthesis - MouseCyc	↓	0 of 3						3 of 3	2 of 3	2 of 3	0 of 3	2 of 3	1 of 3
Glutathione conjugation - Reactome	↑	11 of 26	4 of 11	0 of 11	0 of 11	1 of 11	1 of 11	8 of 26	2 of 7	2 of 7	0 of 7	4 of 7	3 of 7
Glutathione metabolism - Mus musculus (mouse) - KEGG	↑	27 of 54	8 of 26	3 of 26	0 of 26	3 of 27	2 of 27	14 of 54	2 of 11	3 of 13	0 of 13	5 of 13	3 of 13
Glutathione metabolism - Wikipathways	↑	7 of 19	4 of 7	1 of 6	0 of 6	2 of 7	1 of 7	7 of 19	2 of 6	3 of 7	0 of 7	3 of 7	1 of 7

Glutathione synthesis and recycling - Reactome	↓	0 of 6						4 of 6	2 of 4	2 of 4	0 of 4	2 of 4	1 of 4
glutathione-mediated detoxification - MouseCyc	↑	15 of 26	4 of 14	0 of 14	0 of 14	3 of 15	2 of 15	6 of 26	0 of 4	0 of 5	0 of 5	3 of 5	2 of 5
glycerol degradation IV - MouseCyc	↓	0 of 3						3 of 6	2 of 3	1 of 3	0 of 3	0 of 3	0 of 3
Glycerolipid metabolism - Mus musculus (mouse) - KEGG	↑	15 of 55	6 of 14	0 of 15	1 of 15	1 of 15	1 of 15	11 of 55	3 of 10	5 of 11	3 of 11	2 of 11	2 of 11
Glycerophospholipid biosynthesis - Reactome	↑↓	20 of 85	6 of 18	1 of 20	2 of 20	0 of 20	2 of 20	25 of 85	7 of 24	6 of 24	2 of 24	5 of 25	2 of 25
Glycerophospholipid metabolism - Mus musculus (mouse) - KEGG	↓	18 of 90	6 of 16	0 of 18	1 of 18	0 of 18	1 of 18	27 of 90	8 of 26	7 of 26	2 of 26	6 of 27	4 of 27
Glycine, serine and threonine metabolism - Mus musculus (mouse) - KEGG	↑↓	15 of 38	4 of 13	1 of 15	2 of 15	0 of 15	0 of 15	11 of 38	5 of 11	6 of 10	1 of 10	2 of 11	3 of 11
glycogen biosynthesis II (from UDP-D-Glucose) - MouseCyc	↑	4 of 5	1 of 3	0 of 4	0 of 4	0 of 4	0 of 4	0 of 5					
Glycogen synthesis - Reactome	↑	4 of 9	1 of 3	0 of 4	0 of 4	0 of 4	0 of 4	1 of 9	1 of 1	1 of 1	1 of 1	0 of 1	0 of 1
Glycolysis - Reactome	↑	14 of 30	2 of 12	2 of 14	0 of 14	2 of 14	1 of 14	3 of 30	0 of 3	2 of 3	0 of 3	0 of 3	0 of 3
Glycolysis / Gluconeogenesis - Mus musculus (mouse) - KEGG	↑	23 of 64	5 of 21	2 of 23	1 of 23	3 of 23	2 of 23	7 of 64	2 of 6	5 of 7	2 of 7	2 of 7	2 of 7
Glycolysis and Gluconeogenesis - Wikipathways	↑	26 of 49	5 of 24	2 of 26	2 of 26	4 of 26	3 of 26	5 of 49	2 of 5	3 of 5	2 of 5	2 of 5	1 of 5
glycolysis I - MouseCyc	↑	14 of 26	2 of 12	1 of 14	0 of 14	2 of 14	1 of 14	0 of 26					
glycolysis III - MouseCyc	↑	14 of 25	2 of 12	1 of 14	0 of 14	2 of 14	1 of 14	1 of 25	1 of 1	1 of 1	1 of 1	0 of 1	0 of 1
glycolysis V (Pyrococcus) - MouseCyc	↑	9 of 17	2 of 9	0 of 9	0 of 9	2 of 9	1 of 9	0 of 17					
Growth hormone receptor signaling - Reactome	↑↓	3 of 15	2 of 2	2 of 3	2 of 3	3 of 3	3 of 3	9 of 15	3 of 9	5 of 9	2 of 9	3 of 9	0 of 9
GTP hydrolysis and joining of the 60S ribosomal subunit - Reactome	↑	24 of 101	0 of 12	1 of 10	0 of 10	2 of 23	1 of 23	16 of 101	2 of 15	5 of 14	0 of 14	1 of 16	0 of 16
Heme biosynthesis - Reactome	↓	3 of 11	1 of 3	1 of 3	1 of 3	0 of 3	0 of 3	6 of 11	1 of 6	4 of 6	1 of 6	2 of 6	2 of 6
Heme Biosynthesis - Wikipathways	↓	3 of 9	1 of 3	1 of 3	1 of 3	0 of 3	0 of 3	5 of 9	1 of 5	3 of 5	1 of 5	2 of 5	2 of 5
heme biosynthesis II - MouseCyc	↓	3 of 9	1 of 3	1 of 3	1 of 3	0 of 3	0 of 3	5 of 9	1 of 5	3 of 5	1 of 5	2 of 5	2 of 5

IL-5 Signaling Pathway - Wikipathways	↓	7 of 67	2 of 6	0 of 7	0 of 7	0 of 7	0 of 7	21 of 67	1 of 21	9 of 21	2 of 21	4 of 21	2 of 21
IL-6 signaling Pathway - Wikipathways	↓	15 of 98	6 of 15	2 of 15	4 of 15	0 of 15	1 of 15	31 of 98	6 of 31	12 of 31	3 of 31	6 of 31	3 of 31
IL-9 Signaling Pathway - Wikipathways	↓	2 of 24	0 of 2	0 of 2	0 of 2	1 of 2	1 of 2	11 of 24	2 of 11	5 of 11	1 of 11	2 of 11	1 of 11
Immune System - Reactome	↓	94 of 863	30 of 87	9 of 89	13 of 89	8 of 92	5 of 92	202 of 863	27 of 191	77 of 192	12 of 192	42 of 199	27 of 199
Initial triggering of complement - Reactome	↓	2 of 17	1 of 2	0 of 2	0 of 2	0 of 2	0 of 2	8 of 17	1 of 7	2 of 8	0 of 8	5 of 8	4 of 8
Innate Immune System - Reactome	↓	52 of 462	13 of 47	5 of 48	4 of 48	5 of 50	3 of 50	104 of 462	10 of 99	43 of 100	8 of 8	25 of 102	15 of 102
Insulin signaling pathway - Mus musculus (mouse) - KEGG	↑	29 of 142	5 of 27	2 of 28	3 of 28	5 of 29	4 of 29	27 of 142	7 of 25	11 of 27	6 of 27	5 of 27	4 of 27
Interferon Signaling - Reactome	↓	5 of 61	2 of 5	0 of 5	0 of 5	0 of 5	0 of 5	16 of 61	2 of 15	7 of 15	0 of 15	7 of 16	6 of 16
Interleukin-7 signaling - Reactome	↓	0 of 9						6 of 9	0 of 6	2 of 6	0 of 6	0 of 6	0 of 6
ISG15 antiviral mechanism - Reactome	↓	2 of 25	1 of 2	0 of 2	0 of 2	0 of 2	0 of 2	9 of 25	1 of 8	5 of 8	0 of 8	4 of 9	4 of 9
Kennedy pathway - Wikipathways	↓	4 of 14	2 of 4	0 of 4	0 of 4	0 of 4	0 of 4	9 of 14	2 of 9	4 of 9	2 of 9	2 of 9	0 of 9
ketogenesis - MouseCyc	↓	2 of 8	1 of 2	0 of 2	0 of 2	0 of 2	0 of 2	5 of 8	0 of 5	3 of 4	0 of 4	2 of 5	2 of 5
Ketone body metabolism - Reactome	↓	0 of 5						3 of 5	0 of 3	2 of 3	0 of 3	1 of 3	1 of 3
L13a-mediated translational silencing of Ceruloplasmin expression - Reactome	↑	24 of 100	0 of 12	1 of 10	0 of 10	2 of 23	1 of 23	15 of 100	2 of 14	4 of 13	0 of 13	1 of 15	0 of 15
Leptin Insulin Overlap - Wikipathways	↑	4 of 18	1 of 4	1 of 4	1 of 4	3 of 4	2 of 4	4 of 18	1 of 4	1 of 4	2 of 4	1 of 4	0 of 4
Leukocyte transendothelial migration - Mus musculus (mouse) - KEGG	↓	15 of 121	6 of 14	0 of 15	1 of 15	0 of 15	0 of 15	32 of 121	1 of 31	8 of 32	3 of 32	6 of 32	1 of 32
Linoleic acid (LA) metabolism - Reactome	↑	3 of 6	0 of 3	1 of 3	0 of 3	2 of 3	0 of 3	3 of 6	1 of 3	0 of 3	0 of 3	1 of 3	0 of 3
Linoleic acid metabolism - Mus musculus (mouse) - KEGG	↑	13 of 48	1 of 12	1 of 12	1 of 12	1 of 13	1 of 13	14 of 48	1 of 13	9 of 14	1 of 14	6 of 14	5 of 14
Lipid digestion, mobilization, and transport - Reactome	↓	7 of 44	4 of 7	0 of 7	0 of 7	0 of 7	0 of 7	16 of 44	1 of 16	3 of 16	2 of 16	7 of 16	4 of 16
Lipoprotein metabolism - Reactome	↓	4 of 28	2 of 4	0 of 4	0 of 4	0 of 4	0 of 4	11 of 28	1 of 11	3 of 11	2 of 11	5 of 11	3 of 11

L-serine degradation - MouseCyc	↑	2 of 2	1 of 2	0 of 2	1 of 2	1 of 2	1 of 2	0 of 2					
Macrophage markers - Wikipathways	↓	4 of 10	3 of 4	0 of 4	3 of 4	0 of 4	0 of 4	6 of 10	1 of 6	4 of 6	0 of 6	1 of 6	0 of 6
Meiotic Recombination - Reactome	↓	3 of 52	0 of 2	1 of 2	0 of 2	0 of 2	0 of 2	17 of 52	6 of 10	0 of 2	0 of 2	1 of 13	1 of 13
Membrane Trafficking - Reactome	↓	20 of 146	4 of 18	1 of 17	0 of 17	0 of 19	0 of 19	41 of 146	4 of 36	11 of 41	1 of 41	5 of 41	3 of 41
Metabolism - Reactome	↑↓	369 of 1346	86 of 342	27 of 352	24 of 352	27 of 366	27 of 366	304 of 1346	66 of 282	107 of 298	31 of 298	86 of 302	53 of 302
Metabolism of amino acids and derivatives	↑	50 of 142	5 of 46	2 of 49	2 of 49	1 of 50	4 of 50	30 of 142	8 of 29	12 of 40	1 of 40	6 of 40	4 of 40
Metabolism of carbohydrates - Reactome	↑	62 of 243	10 of 59	5 of 59	3 of 59	4 of 62	3 of 62	42 of 243	8 of 41	14 of 41	6 of 41	8 of 42	7 of 42
Metabolism of lipids and lipoproteins - Reactome	↑↓	114 of 483	38 of 107	13 of 111	7 of 111	10 of 113	10 of 113	135 of 483	31 of 124	47 of 133	13 of 133	39 of 135	21 of 135
Metabolism of mRNA - Reactome	↑	33 of 158	1 of 17	3 of 20	2 of 20	3 of 31	1 of 31	34 of 158	6 of 28	13 of 32	5 of 32	2 of 33	3 of 33
Metabolism of nucleotides - Reactome	↑	21 of 80	5 of 20	3 of 21	2 of 21	1 of 21	1 of 21	20 of 80	4 of 20	5 of 20	1 of 20	4 of 20	2 of 20
Metabolism of porphyrins - Reactome	↓	5 of 15	3 of 5	1 of 5	1 of 5	0 of 5	0 of 5	6 of 15	1 of 6	4 of 6	1 of 6	2 of 6	2 of 6
Metabolism of proteins - Reactome	↑	81 of 458	10 of 63	4 of 65	4 of 65	5 of 80	2 of 80	97 of 458	19 of 91	30 of 94	4 of 94	15 of 97	7 of 97
Metabolism of vitamins and cofactors	↑	21 of 73	5 of 21	2 of 21	1 of 21	0 of 21	0 of 21	18 of 73	4 of 14	8 of 16	1 of 16	6 of 16	4 of 16
Metabolism of water-soluble vitamins and cofactors - Reactome	↑	21 of 73	5 of 21	2 of 21	1 of 21	0 of 21	0 of 21	18 of 73	4 of 14	8 of 16	1 of 16	6 of 16	4 of 16
Metabolism of xenobiotics by cytochrome P450 - Mus musculus (mouse) - KEGG	↑↓	36 of 88	10 of 31	1 of 28	3 of 28	7 of 33	7 of 33	25 of 88	5 of 23	11 of 24	3 of 24	14 of 24	13 of 24
Metal ion SLC transporters - Reactome	↓	2 of 25	0 of 2	1 of 2	0 of 2	0 of 2	0 of 2	11 of 25	1 of 11	3 of 11	1 of 11	0 of 11	1 of 11
Metapathway biotransformation - Wikipathways	↑	39 of 137	17 of 36	4 of 35	4 of 35	7 of 36	5 of 36	29 of 137	7 of 27	7 of 29	3 of 29	8 of 29	6 of 29
Methylation - Wikipathways	↑	4 of 9	1 of 4	1 of 4	1 of 4	2 of 4	1 of 4	3 of 9	0 of 3	1 of 3	0 of 3	0 of 3	0 of 3
mevalonate pathway I - MouseCyc	↑↓	6 of 11	5 of 6	2 of 6	1 of 6	0 of 6	0 of 6	6 of 11	1 of 6	3 of 5	0 of 5	2 of 6	3 of 6
Mitochondrial Fatty Acid Beta-Oxidation - Reactome	↓	2 of 15	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2	5 of 15	0 of 5	3 of 5	0 of 5	1 of 5	1 of 5

mitochondrial fatty acid beta-oxidation of unsaturated fatty acids - Reactome	↓	0 of 3						3 of 3	0 of 3	2 of 3	0 of 3	0 of 3	0 of 3
Mitochondrial LC-Fatty Acid Beta-Oxidation - Wikipathways	↓	4 of 16	0 of 4	0 of 4	0 of 4	1 of 4	1 of 4	9 of 16	1 of 9	4 of 9	0 of 9	0 of 9	0 of 9
Mitochondrial Protein Import - Reactome	↑	13 of 43	2 of 13	0 of 13	0 of 13	0 of 13	0 of 13	9 of 43	1 of 9	4 of 9	0 of 9	4 of 9	1 of 9
mRNA 3,-end processing - Reactome	↓	4 of 34	0 of 4	0 of 4	1 of 4	0 of 4	0 of 4	15 of 34	1 of 15	7 of 14	0 of 14	2 of 15	2 of 15
mRNA Editing - Reactome	↓	1 of 4	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1	3 of 4	1 of 3	2 of 3	0 of 3	0 of 3	0 of 3
mRNA Editing: C to U Conversion - Reactome	↓	0 of 2						2 of 2	1 of 2	2 of 2	0 of 2	0 of 2	0 of 2
mRNA Processing - Reactome	↓	25 of 157	3 of 22	0 of 23	1 of 23	0 of 25	0 of 25	51 of 157	5 of 50	19 of 49	0 of 49	6 of 50	2 of 50
mRNA processing - Wikipathways	↓	71 of 447	8 of 61	3 of 66	2 of 66	3 of 71	0 of 71	112 of 447	8 of 108	50 of 110	5 of 150	14 of 112	2 of 112
mRNA Splicing - Major Pathway - Reactome	↓	19 of 107	3 of 16	0 of 17	1 of 17	0 of 19	0 of 19	38 of 107	4 of 37	13 of 36	0 of 36	5 of 37	2 of 37
mRNA Splicing - Minor Pathway - Reactome	↓	7 of 42	2 of 5	0 of 7	0 of 5	0 of 7	0 of 7	15 of 42	3 of 14	5 of 14	0 of 14	2 of 14	1 of 14
mRNA Splicing - Reactome	↓	19 of 107	3 of 16	0 of 17	1 of 17	0 of 19	0 of 19	38 of 107	4 of 37	13 of 36	0 of 36	5 of 37	2 of 37
mRNA surveillance pathway - Mus musculus (mouse) - KEGG	↓	10 of 92	1 of 11	0 of 10	0 of 10	0 of 10	0 of 10	28 of 92	3 of 27	13 of 27	0 of 27	3 of 28	2 of 28
MyD88-independent cascade - Reactome	↓	12 of 88	4 of 11	2 of 10	2 of 10	1 of 11	0 of 11	28 of 88	2 of 26	16 of 28	4 of 28	1 of 28	0 of 28
NAD biosynthesis II (from tryptophan) - MouseCyc	↑	5 of 10	1 of 10	0 of 5	0 of 5	1 of 5	1 of 5	1 of 10	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1
Nicotinate and nicotinamide metabolism - Mus musculus (mouse) - Kegg	↑	10 of 31	4 of 10	2 of 10	1 of 10	1 of 10	0 of 10	5 of 31	2 of 5	4 of 5	0 of 5	1 of 5	2 of 5
nicotine degradation II - MouseCyc	↑↓	20 of 50	6 of 17	1 of 17	3 of 17	4 of 19	5 of 19	23 of 50	5 of 20	12 of 23	1 of 23	13 of 23	11 of 23
nicotine degradation III - MouseCyc	↑↓	15 of 43	4 of 12	1 of 12	3 of 12	2 of 14	3 of 14	22 of 43	5 of 19	12 of 22	1 of 22	13 of 22	11 of 22
Nonsense Mediated Decay Enhanced by the Exon Junction Complex - Reactome	↑	24 of 94	0 of 11	1 of 11	0 of 11	2 of 23	1 of 23	13 of 94	2 of 12	4 of 11	0 of 11	2 of 13	1 of 13
Nonsense Mediated Decay Independent of the Exon Junction Complex - Reactome	↑	23 of 84	0 of 11	1 of 10	0 of 10	2 of 22	1 of 22	10 of 84	2 of 9	3 of 8	0 of 8	1 of 10	0 of 10
Nonsense-Mediated Decay - Reactome	↑	24 of 94	0 of 11	1 of 11	0 of 11	2 of 23	1 of 23	13 of 94	2 of 12	4 of 11	0 of 11	2 of 13	1 of 13

Nuclear Receptor transcription pathway - Reactome	↓	9 of 49	2 of 9	0 of 9	0 of 9	0 of 9	1 of 9	17 of 49	2 of 14	7 of 17	3 of 17	0 of 17	0 of 17
Nuclear Receptors - Wikipathways	↓	7 of 38	1 of 7	0 of 7	0 of 7	0 of 7	1 of 7	14 of 38	2 of 13	5 of 14	2 of 14	0 of 14	0 of 14
Nuclear receptors in lipid metabolism and toxicity	↑↓	13 of 30	5 of 12	1 of 13	3 of 13	0 of 13	1 of 13	13 of 30	1 of 12	6 of 13	3 of 13	1 of 13	0 of 13
oleate biosynthesis II (animals) - Mousecyc	↑	3 of 7	0 of 3	2 of 3	0 of 3	2 of 3	0 of 3	2 of 7	0 of 2	0 of 2	1 of 2	2 of 2	2 of 2
One carbon metabolism and related pathways - Wikipathways	↓	10 of 49	4 of 10	1 of 10	0 of 10	0 of 10	0 of 10	20 of 49	7 of 18	8 of 20	1 of 20	6 of 20	2 of 20
Oxidative phosphorylation - Mus musculus (mouse) - KEGG	↑	39 of 124	0 of 33	0 of 36	0 of 36	1 of 39	0 of 39	7 of 124	1 of 6	3 of 6	0 of 6	1 of 6	0 of 6
Oxidative phosphorylation - Wikipathways	↑	18 of 52	1 of 14	0 of 17	0 of 17	1 of 18	0 of 18	1 of 52	0 of 0	0 of 0	0 of 0	0 of 0	0 of 0
Oxidative Stress - Wikipathways	↑↓	9 of 27	5 of 9	2 of 9	1 of 9	0 of 9	0 of 9	11 of 27	3 of 11	3 of 11	2 of 11	4 of 11	2 of 11
Pentose and glucuronate interconversions - Mus musculus (mouse) - KEGG	↑	11 of 29	7 of 10	0 of 7	1 of 7	0 of 8	0 of 8	10 of 29	4 of 9	4 of 10	2 of 10	3 of 10	2 of 10
pentose phosphate pathway - MouseCyc	↑	6 of 11	0 of 5	1 of 5	0 of 5	0 of 6	0 of 6	1 of 11	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1
Pentose phosphate pathway - Mus musculus (mouse) - KEGG	↑	13 of 30	1 of 13	1 of 12	0 of 12	0 of 13	0 of 13	1 of 30	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1
Pentose Phosphate Pathway - Wikipathways	↑	6 of 7	0 of 5	1 of 5	0 of 5	0 of 6	0 of 6	0 of 7					
Pentose phosphate pathway (hexose monophosphate shunt) - Reactome	↑	6 of 8	0 of 5	1 of 5	0 of 5	0 of 6	0 of 6	0 of 8					
pentose phosphate pathway (non-oxidative branch) - MouseCyc	↑	4 of 6	0 of 3	0 of 3	0 of 3	0 of 4	0 of 4	0 of 6					
pentose phosphate pathway (oxidative branch) - MouselCyc	↑	2 of 5	0 of 2	1 of 2	0 of 2	0 of 2	0 of 2	1 of 5	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1
Peptide chain elongation - Reactome	↑	23 of 79	1 of 11	1 of 10	0 of 10	3 of 22	1 of 22	5 of 79	0 of 4	0 of 3	0 of 3	1 of 5	0 of 5
Peroxisomal lipid metabolism - Reactome	↓	2 of 22	2 of 2	0 of 2	0 of 2	0 of 2	0 of 2	21 of 22	2 of 12	2 of 12	1 of 12	4 of 12	2 of 12
Peroxisome - Mus musculus (mouse) - KEGG	↑↓	21 of 80	7 of 19	1 of 21	0 of 21	1 of 21	1 of 21	32 of 80	7 of 32	9 of 32	2 of 32	7 of 32	4 of 32
Phagosome - Mus musculus (mouse)	↑	37 of 169	9 of 32	2 of 34	2 of 34	0 of 37	0 of 37	39 of 169	2 of 37	14 of 35	1 of 35	11 of 39	4 of 39
Phase 1 - Functionalization of compounds - Reactome	↑↓	37 of 96	11 of 30	4 of 29	6 of 29	8 of 36	8 of 36	31 of 96	6 of 26	12 of 29	5 of 25	16 of 31	11 of 31

Phase II conjugation - Reactome	↑	26 of 63	11 of 25	1 of 23	3 of 23	4 of 24	3 of 24	19 of 63	4 of 18	4 of 18	2 of 18	6 of 18	4 of 18
Phenylalanine and tyrosine catabolism - Reactome	↑	5 of 9	1 of 4	0 of 4	0 of 4	0 of 4	1 of 4	0 of 9					
Phenylalanine, tyrosine and tryptophan biosynthesis - Mus musculus (mouse) - KEGG	↑	4 of 7	2 of 4	2 of 4	2 of 4	0 of 4	2 of 4	1 of 7	0 of 1	0 of 1	0 of 1	0 of 1	0 of 1
phosphatidylcholine biosynthesis I - MouseCyc	↓	0 of 6						5 of 6	1 of 5	3 of 5	1 of 5	1 of 5	0 of 5
phosphatidylethanolamine biosynthesis II - MouseCyc	↓	3 of 8	1 of 2	0 of 3	0 of 3	0 of 3	0 of 3	5 of 8	2 of 4	2 of 5	1 of 5	1 of 5	0 of 5
Phospholipid metabolism - Reactome	↑	27 of 131	6 of 24	1 of 27	2 of 27	0 of 27	2 of 27	30 of 131	8 of 29	7 of 29	2 of 29	5 of 30	2 of 30
Platelet degranulation - Reactome	↑	24 of 85	12 of 22	1 of 21	1 of 21	1 of 24	0 of 24	20 of 85	2 of 19	5 of 19	0 of 19	7 of 20	5 of 20
Porphyrin and chlorophyll metabolism - Mus musculus (mouse) - KEGG	↓	9 of 37	6 of 8	1 of 6	1 of 6	0 of 6	0 of 6	14 of 37	5 of 14	8 of 14	2 of 14	4 of 14	4 of 14
Post-Elongation Processing of Intron-Containing pre-mRNA - Reactome	↓	4 of 34	0 of 2	0 of 4	1 of 4	0 of 4	0 of 4	15 of 34	1 of 15	7 of 14	0 of 14	2 of 15	2 of 15
Post-Elongation Processing of the Transcript - Reactome	↓	4 of 43	0 of 6	0 of 6	1 of 6	0 of 6	0 of 6	16 of 43	1 of 16	7 of 15	0 of 15	3 of 16	2 of 16
Post-translational protein modification - Reactome	↓	16 of 164	3 of 14	0 of 15	1 of 15	0 of 16	0 of 16	41 of 164	9 of 39	11 of 41	0 of 41	5 of 41	5 of 41
PPAR signaling pathway - Mus musculus (mouse) - KEGG	↑↓	20 of 78	8 of 17	4 of 19	3 of 19	6 of 19	4 of 19	32 of 78	5 of 30	13 of 31	4 of 31	7 of 32	5 of 32
PPAR signaling pathway - Wikipathways	↑↓	20 of 78	8 of 17	4 of 19	3 of 19	6 of 19	4 of 19	32 of 78	5 of 30	13 of 31	4 of 31	7 of 32	5 of 32
Primary bile acid biosynthesis - Mus musculus (mouse) - KEGG	↓	2 of 16	1 of 2	1 of 2	1 of 2	0 of 2	0 of 2	12 of 16	2 of 12	2 of 12	1 of 12	5 of 12	2 of 12
Processing of Capped Intron-Containing Pre-mRNA - Reactome	↓	22 of 138	3 of 19	0 of 20	1 of 20	0 of 22	0 of 22	45 of 138	4 of 44	15 of 43	0 of 43	6 of 44	2 of 44
Proline catabolism - Reactome	↑	2 of 2	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2					
Propanoate metabolism - Mus musculus (mouse) - KEGG	↑↓	9 of 31	3 of 9	2 of 9	0 of 9	1 of 9	1 of 9	9 of 31	0 of 8	6 of 8	0 of 8	3 of 9	3 of 9
Proteasome - Mus musculus (mouse) - KEGG	↓	3 of 44	1 of 3	0 of 3	0 of 3	0 of 3	0 of 3	17 of 44	3 of 16	6 of 17	0 of 17	5 of 17	5 of 17
Proteasome Degradation - Wikipathways	↓	9 of 57	2 of 9	1 of 9	0 of 9	0 of 8	0 of 8	19 of 57	3 of 18	6 of 19	1 of 19	5 of 19	5 of 19
Protein processing in endoplasmic reticulum - Mus musculus (mouse) - KEGG	↓	20 of 165	0 of 16	1 of 19	2 of 19	0 of 19	1 of 19	67 of 165	17 of 63	24 of 67	6 of 67	14 of 66	10 of 66

purine and pyrimidine metabolism - MouseCyc	↑	9 of 25	3 of 9	2 of 8	1 of 8	0 of 9	0 of 9	8 of 25	1 of 8	5 of 8	1 of 8	1 of 8	1 of 8
Purine metabolism - Mus musculus (mouse) - KEGG	↑	39 of 170	9 of 37	1 of 38	0 of 38	2 of 39	0 of 39	21 of 170	6 of 20	5 of 20	1 of 20	1 of 20	2 of 20
Purine metabolism - Wikipathways	↑	37 of 165	9 of 35	1 of 36	0 of 36	2 of 37	0 of 37	20 of 165	5 of 19	5 of 19	1 of 19	1 of 19	2 of 19
Pyrimidine salvage reactions - Reactome	↑	5 of 9	2 of 5	2 of 5	2 of 5	1 of 50	1 of 5	3 of 9	1 of 3	1 of 3	1 of 3	0 of 3	0 of 3
Pyruvate metabolism - Mus musculus (mouse) - KEGG	↑	16 of 42	6 of 15	2 of 16	0 of 16	1 of 16	0 of 16	10 of 42	1 of 10	6 of 10	0 of 10	2 of 11	2 of 11
Pyruvate metabolism - Reactome	↑	7 of 20	1 of 7	0 of 7	1 of 7	0 of 7	1 of 7	6 of 20	1 of 6	1 of 6	2 of 6	4 of 6	1 of 6
Pyruvate metabolism and Citric Acid (TCA) cycle - Reactome	↑	20 of 42	3 of 20	0 of 20	1 of 20	0 of 20	1 of 20	6 of 42	1 of 6	1 of 6	2 of 6	4 of 6	1 of 6
Regulation of Complement cascade - Reactome	↓	3 of 23	2 of 3	0 of 3	0 of 3	0 of 3	0 of 3	11 of 23	0 of 10	3 of 10	0 of 10	6 of 11	2 of 11
Regulation of pyruvate dehydrogenase (PDH) complex - Reactome	↑	6 of 12	1 of 6	0 of 6	1 of 6	0 of 6	1 of 6	2 of 12	1 of 2	1 of 2	2 of 2	0 of 2	0 of 2
Removal of aminoterminal propeptides from gamma-carboxylated proteins - Reactome	↑	4 of 9	1 of 4	0 of 4	0 of 4	0 of 4	0 of 4	3 of 9	0 of 3	1 of 3	0 of 3	1 of 3	0 of 3
Respiratory electron transport - Reactome	↑	23 of 68	0 of 21	0 of 21	0 of 21	1 of 23	0 of 23	2 of 68	0 of 1	1 of 1	0 of 1	1 of 1	0 of 1
Respiratory electron transport, ATP synthesis by chemiosmotic coupling, and heat production by uncoupling proteins - Reactome	↑	29 of 84	0 of 25	0 of 27	0 of 27	1 of 29	0 of 29	2 of 84	0 of 1	1 of 1	0 of 1	1 of 1	0 of 1
Response to elevated platelet cytosolic Ca2+	↑	24 of 90	12 of 22	1 of 21	1 of 21	1 of 24	0 of 24	21 of 90	2 of 20	6 of 20	0 of 20	7 of 21	5 of 21
Retinoid metabolism and transport - Reactome	↓	9 of 46	3 of 9	0 of 9	0 of 9	0 of 9	0 of 9	13 of 46	4 of 13	5 of 13	3 of 13	6 of 13	3 of 13
Retinol metabolism - Mus musculus (mouse) - KEGG	↑↓	29 of 77	9 of 25	2 of 22	5 of 22	6 of 26	6 of 26	31 of 77	9 of 29	16 of 29	4 of 29	15 of 31	12 of 31
RIG-I/MDA5 mediated induction of IFN-alpha/beta pathways - Reactome	↓	7 of 45	3 of 6	1 of 7	1 of 7	1 of 7	0 of 7	16 of 45	1 of 16	8 of 16	1 of 16	3 of 16	2 of 16
RNA Polymerase I Promoter Opening - Reactome	↓	1 of 21	0 of 0	0 of 0	0 of 0	0 of 0	0 of 0	6 of 21	1 of 1	1 of 1	0 of 1	0 of 4	0 of 4
RNA Polymerase II Transcription - Reactome	↓	14 of 101	1 of 12	0 of 13	1 of 13	0 of 14	0 of 14	30 of 101	5 of 28	13 of 28	0 of 28	3 of 29	2 of 29
RNA Polymerase II Transcription Termination - Reactome	↓	4 of 43	0 of 6	0 of 6	1 of 6	0 of 6	0 of 6	16 of 43	1 of 16	7 of 15	0 of 15	3 of 16	2 of 16
RNA transport - Mus musculus (mouse) - KEGG	↓	12 of 161	1 of 11	0 of 7	0 of 7	0 of 12	0 of 12	46 of 161	4 of 45	20 of 45	0 of 45	4 of 46	1 of 46

salvage pathways of pyrimidine ribonucleotides - MouseCyc	↑	7 of 15	3 of 7	4 of 7	1 of 7	1 of 7	1 of 7	3 of 15	1 of 3	1 of 3	1 of 3	0 of 3	0 of 3
Scavenging by Class B Receptors - Reactome	↓	2 of 6	1 of 2	1 of 2	1 of 2	0 of 2	0 of 2	4 of 6	0 of 4	1 of 4	1 of 4	1 of 4	0 of 4
Selenium - Wikipathways	↑	8 of 22	2 of 8	2 of 8	0 of 8	2 of 8	1 of 8	3 of 22	0 of 2	0 of 3	0 of 3	1 of 3	0 of 3
Selenium metabolism-Selenoproteins - Wikipathways	↓	8 of 47	3 of 7	1 of 7	0 of 7	0 of 8	0 of 8	18 of 47	4 of 16	4 of 17	3 of 17	3 of 18	3 of 18
Senescence and Autophagy - Wikipathways	↓	15 of 98	4 of 15	1 of 15	3 of 15	2 of 15	0 of 15	30 of 98	3 of 29	6 of 30	1 of 30	5 of 30	2 of 30
Serine biosynthesis - Reactome	↑	3 of 3	0 of 3	0 of 3	0 of 3	0 of 3	0 of 3	0 of 3					
Signaling by Interleukins - Reactome	↓	11 of 104	4 of 11	2 of 11	3 of 11	0 of 11	0 of 11	32 of 104	3 of 31	12 of 32	0 of 32	5 of 32	0 of 32
Spliceosome - Mus musculus (mouse) - KEGG	↓	20 of 129	3 of 14	1 of 17	2 of 17	0 of 19	0 of 19	43 of 129	3 of 38	16 of 42	3 of 42	4 of 42	3 of 42
SREBF and miR33 in cholesterol and lipid homeostasis - Wikipathways	↑	7 of 13	3 of 7	0 of 7	1 of 7	0 of 7	0 of 7	6 of 13	0 of 5	4 of 5	1 of 5	0 of 5	0 of 5
SRP-dependent cotranslational protein targeting to membrane - Reactome	↑	28 of 103	0 of 13	1 of 14	0 of 14	2 of 27	1 of 27	10 of 103	2 of 8	1 of 8	0 of 8	2 of 10	0 of 10
Starch and sucrose metabolism - Mus musculus (mouse) - KEGG	↑	15 of 46	5 of 13	0 of 11	2 of 11	1 of 12	1 of 12	13 of 46	5 of 13	6 of 13	3 of 13	5 of 13	5 of 13
Statin Pathway - Wikipathways	↓	5 of 19	2 of 5	1 of 5	1 of 5	0 of 5	0 of 5	9 of 19	1 of 9	3 of 9	2 of 9	3 of 9	2 of 9
Steroid biosynthesis - Mus musculus (mouse) - KEGG	↑	11 of 17	7 of 11	2 of 11	0 of 11	1 of 11	1 of 11	4 of 17	1 of 4	1 of 4	1 of 4	2 of 4	1 of 4
Steroid Biosynthesis - Wikipathways	↓	2 of 13	2 of 2	0 of 2	0 of 2	1 of 2	1 of 2	5 of 13	2 of 5	3 of 5	1 of 5	3 of 5	1 of 5
Steroid hormone biosynthesis - Mus musculus (mouse) - KEGG	↑↓	14 of 52	7 of 12	1 of 11	3 of 11	3 of 11	2 of 11	17 of 52	9 of 16	9 of 17	3 of 17	8 of 17	5 of 17
sucrose degradation V (mammalian) - MouseCyc	↑	4 of 7	1 of 4	0 of 4	0 of 4	0 of 4	0 of 4	0 of 7					
Sulfide oxidation to sulfate - Reactome	↓	2 of 5	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2	3 of 5	1 of 3	1 of 3	0 of 3	1 of 3	1 of 3
Sulfur amino acid metabolism - Reactome	↓	7 of 25	1 of 7	1 of 7	1 of 7	0 of 7	1 of 7	10 of 25	6 of 10	5 of 10	0 of 10	3 of 10	1 of 10
superpathway of acetyl-CoA biosynthesis - MouseCyc	↑	4 of 6	0 of 4	0 of 4	0 of 4	1 of 4	1 of 4	0 of 6					
superpathway of cholesterol biosynthesis - Mousecyc	↑↓	18 of 25	14 of 18	6 of 18	2 of 18	1 of 18	1 of 18	10 of 25	1 of 10	4 of 9	1 of 9	5 of 10	3 of 10

superpathway of citrulline metabolism - MouseCyc	↑	7 of 17	0 of 5	0 of 7	0 of 7	0 of 7	1 of 7	0 of 17						
Synthesis and degradation of ketone bodies - Mus musculus (mouse)	↓	2 of 10	1 of 2	0 of 2	0 of 2	0 of 2	0 of 2	5 of 10	0 of 5	3 of 4	0 of 4	2 of 5	2 of 5	
Synthesis and Degradation of Ketone Bodies - Wikipathways	↓	0 of 5						3 of 5	0 of 3	2 of 3	0 of 3	1 of 3	1 of 3	
Synthesis and interconversion of nucleotide di- and triphosphates - Reactome	↑	7 of 18	2 of 7	1 of 7	0 of 7	0 of 7	0 of 7	4 of 18	1 of 4	1 of 4	0 of 4	2 of 4	1 of 4	
Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE) - Reactome	↑↓	10 of 24	2 of 8	2 of 7	1 of 7	4 of 9	3 of 9	10 of 24	2 of 8	4 of 9	1 of 9	4 of 10	4 of 10	
Synthesis of bile acids and bile salts - Reactome	↓	6 of 27	1 of 6	1 of 6	1 of 6	0 of 6	0 of 6	15 of 27	3 of 15	4 of 15	1 of 15	6 of 15	2 of 15	
Synthesis of bile acids and bile salts via 24-hydroxycholesterol - Reactome	↓	4 of 18	0 of 4	0 of 4	0 of 4	0 of 4	0 of 4	8 of 18	1 of 8	3 of 8	0 of 8	3 of 8	2 of 8	
Synthesis of bile acids and bile salts via 27-hydroxycholesterol - Reactome	↓	3 of 14	0 of 3	0 of 3	0 of 3	0 of 3	0 of 3	6 of 14	2 of 6	3 of 6	0 of 6	3 of 6	1 of 6	
Synthesis of bile acids and bile salts via 7alpha-hydroxycholesterol - Reactome	↓	5 of 23	1 of 5	1 of 5	1 of 5	0 of 5	0 of 5	13 of 23	2 of 13	4 of 13	1 of 13	5 of 13	2 of 13	
Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET) - Reactome	↑↓	7 of 21	0 of 6	1 of 5	0 of 5	1 of 6	1 of 6	8 of 21	1 of 8	6 of 8	1 of 8	3 of 8	2 of 8	
Synthesis of GDP-mannose - Reactome	↓	0 of 5						2 of 5	1 of 2	0 of 2	0 of 2	0 of 2	0 of 2	
Synthesis of Ketone Bodies - Reactome	↓	0 of 4						3 of 4	0 of 3	2 of 3	0 of 3	1 of 3	1 of 3	
Synthesis of PC - Reactome	↑	5 of 18	1 of 5	0 of 5	1 of 5	0 of 5	0 of 5	6 of 18	1 of 6	3 of 5	1 of 5	1 of 6	0 of 6	
Synthesis of PE - Reactome	↑↓	5 of 12	2 of 5	0 of 5	1 of 5	0 of 5	0 of 5	7 of 12	2 of 6	2 of 6	1 of 6	1 of 7	0 of 7	
Synthesis of substrates in N-glycan biosynthesis - Reactome	↓	2 of 17	0 of 2	0 of 2	1 of 2	0 of 2	0 of 2	7 of 17	2 of 7	2 of 7	0 of 7	0 of 7	1 of 7	
Synthesis of very long-chain fatty acyl-CoAs - Reactome	↑	5 of 13	0 of 4	0 of 5	0 of 5	1 of 5	1 of 5	4 of 13	2 of 4	2 of 4	0 of 4	2 of 4	1 of 4	
Targeted protein degradation - MouseCyc	↓	3 of 59	1 of 3	0 of 3	0 of 3	0 of 3	0 of 3	23 of 59	3 of 21	8 of 23	0 of 23	6 of 23	5 of 23	
TCA cycle - MouseCyc	↑	9 of 13	1 of 9	0 of 9	0 of 9	0 of 9	0 of 9	0 of 9						
TCA Cycle - Wikipathways	↑	18 of 31	3 of 18	0 of 18	1 of 18	0 of 18	1 of 18	2 of 31	1 of 2	2 of 2	1 of 2	0 of 2	0 of 2	
TCA cycle variation III (eukaryotic) - MouseCyc	↑	10 of 16	2 of 10	0 of 10	0 of 10	0 of 10	0 of 10	0 of 16						

Terminal pathway of complement - Reactome	↓	0 of 7						6 of 7	0 of 6	3 of 6	0 of 6	3 of 6	1 of 6
Terpenoid backbone biosynthesis - Mus musculus (mouse) - KEGG	↑	8 of 21	6 of 7	3 of 8	1 of 8	0 of 8	0 of 8	6 of 21	1 of 6	2 of 5	0 of 5	2 of 6	3 of 6
tetrapyrrole biosynthesis II - MouseCyc	↓	1 of 5	1 of 1	1 of 1	1 of 1	0 of 1	0 of 1	4 of 5	1 of 4	3 of 4	1 of 4	2 of 4	2 of 4
TGF-beta Receptor Signaling Pathway - Wikipathways	↓	19 of 150	3 of 18	4 of 19	1 of 19	0 of 19	0 of 19	42 of 150	4 of 39	15 of 42	5 of 42	3 of 42	1 of 42
The citric acid (TCA) cycle and respiratory electron transport - Reactome	↑	46 of 122	3 of 42	0 of 44	1 of 44	1 of 46	1 of 46	8 of 122	1 of 7	2 of 7	2 of 7	5 of 7	1 of 7
TNF-alpha NF-kB Signaling Pathway - Wikipathways	↓	24 of 181	7 of 21	4 of 23	3 of 23	0 of 24	1 of 24	51 of 181	11 of 47	18 of 51	3 of 51	4 of 51	5 of 51
Toll Like Receptor 3 (TLR3) Cascade - Reactome	↓	12 of 88	4 of 11	2 of 10	2 of 10	1 of 11	0 of 11	28 of 88	2 of 26	16 of 28	4 of 28	1 of 28	0 of 28
Toll Like Receptor 4 (TLR4) Cascade - Reactome	↓	4 of 14	2 of 13	2 of 13	2 of 14	1 of 14		32 of 105	2 of 30	17 of 32	4 of 32	3 of 32	1 of 32
Toll Like Receptor signaling - Wikipathways	↓	4 of 12	1 of 4	0 of 4	0 of 4	1 of 4	2 of 4	12 of 33	2 of 12	8 of 12	0 of 12	1 of 12	0 of 12
Toll-like receptor signaling pathway - Wikipathways	↓	12 of 96	4 of 12	0 of 12	2 of 12	2 of 12	1 of 12	27 of 96	3 of 27	14 of 27	2 of 27	5 of 27	3 of 27
Toll-Like Receptors Cascades - Reactome	↓	18 of 125	5 of 17	2 of 16	2 of 16	2 of 17	1 of 17	38 of 125	3 of 36	22 of 38	5 of 38	6 of 38	3 of 38
Trafficking of dietary sterols - Reactome	↑	2 of 2	2 of 2	0 of 2	0 of 2	0 of 2	0 of 2	0 of 2					
trans, trans-farnesyl diphosphate biosynthesis - MouseCyc	↑	2 of 5	2 of 2	2 of 2	1 of 2	0 of 2	0 of 2	1 of 5	0 of 1	1 of 1	0 of 1	0 of 1	0 of 1
Transcription - Reactome	↓	19 of 173	1 of 17	0 of 17	1 of 17	0 of 18	1 of 18	48 of 173	9 of 43	16 of 41	1 of 41	5 of 45	3 of 45
trans-Golgi Network Vesicle Budding - Reactome	↓	6 of 60	2 of 6	1 of 6	0 of 6	0 of 6	0 of 6	19 of 60	2 of 16	7 of 19	1 of 19	3 of 19	1 of 19
Translation - Reactome	↑	34 of 141	1 of 19	1 of 19	0 of 19	3 of 33	1 of 33	26 of 141	4 of 24	8 of 24	0 of 24	3 of 26	0 of 26
Translation Factors - Wikipathways	↓	8 of 49	2 of 5	0 of 5	0 of 5	1 of 8	1 of 8	17 of 49	2 of 17	8 of 17	0 of 17	3 of 17	0 of 17
Transport of Mature mRNA derived from an Intron-Containing Transcript - Reactome	↓	5 of 51	0 of 5	0 of 5	1 of 5	0 of 5	0 of 5	18 of 51	1 of 18	6 of 17	0 of 17	2 of 18	2 of 18
Transport of Mature Transcript to Cytoplasm - Reactome	↓	5 of 51	0 of 5	0 of 5	1 of 5	0 of 5	0 of 5	19 of 55	1 of 19	7 of 18	0 of 18	2 of 19	2 of 19
Triacylglyceride Synthesis - Wikipathways	↓	4 of 23	2 of 4	0 of 4	0 of 4	0 of 4	0 of 4	9 of 23	3 of 9	3 of 9	2 of 9	2 of 9	1 of 9

TRIF-mediated TLR3/TLR4 signaling - Reactome	↓	12 of 88	4 of 11	2 of 10	2 of 10	1 of 11	0 of 11	28 of 88	2 of 26	16 of 28	4 of 28	1 of 28	0 of 28
Triglyceride Biosynthesis - Reactome	↑	17 of 36	1 of 14	0 of 17	1 of 17	2 of 17	3 of 17	9 of 36	5 of 9	3 of 9	1 of 9	3 of 9	1 of 9
Tryptophan metabolism - Mus musculus (mouse) - KEGG	↓	12 of 44	1 of 12	1 of 11	1 of 11	3 of 12	3 of 12	12 of 44	3 of 11	7 of 11	0 of 11	3 of 12	3 of 12
Tryptophan metabolism - Wikipathways	↓	9 of 43	1 of 9	0 of 8	0 of 8	2 of 9	2 of 9	15 of 43	5 of 14	7 of 15	1 of 15	4 of 15	3 of 15
Type II interferon signaling (IFNG) - Wikipathways	↓	4 of 33	4 of 4	0 of 4	0 of 4	0 of 4	0 of 4	17 of 33	2 of 16	8 of 16	0 of 16	6 of 17	3 of 17
tyrosine degradation I - MouseCyc	↑	3 of 7	1 of 3	0 of 3	0 of 3	0 of 3	1 of 3	1 of 7	0 of 1	1 of 1	1 of 1	0 of 1	0 of 1
Tyrosine metabolism - Mus musculus (mouse) - KEGG	↓	6 of 42	2 of 6	2 of 6	2 of 6	0 of 6	2 of 6	8 of 42	3 of 8	5 of 8	1 of 8	2 of 8	2 of 8
Ubiquinone and other terpenoid-quinone biosynthesis - Mus musculus (mouse) - KEGG	↑	4 of 10	1 of 4	0 of 4	0 of 4	0 of 4	1 of 4	2 of 10	0 of 2	1 of 2	0 of 2	0 of 2	1 of 2
Ubiquitin mediated proteolysis - Mus musculus (mouse) - KEGG	↓	9 of 136	0 of 9	0 of 9	0 of 9	1 of 9	0 of 9	44 of 136	5 of 42	15 of 43	2 of 43	9 of 44	4 of 44
urea cycle - MouseCyc	↑	4 of 6	0 of 4	0 of 4	0 of 4	0 of 4	1 of 4	0 of 6					
Urea cycle - Reactome	↑	5 of 9	0 of 5	0 of 5	0 of 5	0 of 5	1 of 5	0 of 9					
Urea cycle and metabolism of amino groups - Wikipathways	↑	8 of 20	0 of 8	0 of 8	0 of 8	0 of 8	1 of 8	3 of 20	0 of 3	0 of 3	0 of 3	0 of 3	0 of 3
Valine, leucine and isoleucine degradation - Mus musculus (mouse) - KEGG	↓	11 of 51	3 of 11	1 of 11	1 of 11	1 of 11	1 of 11	17 of 51	3 of 16	11 of 16	0 of 16	5 of 17	5 of 17
Xenobiotics - Reactome	↑↓	18 of 37	4 of 13	1 of 11	3 of 11	3 of 17	4 of 17	15 of 37	2 of 12	9 of 14	3 of 14	9 of 15	8 of 15
Zinc influx into cells by the SLC39 gene family - Reactome	↓	1 of 10	0 of 1	1 of 1	0 of 1	0 of 1	0 of 1	6 of 10	1 of 6	1 of 6	0 of 6	0 of 6	1 of 6
γ-glutamyl cycle - MouseCyc	↓	2 of 10	0 of 2	1 of 2	0 of 2	0 of 2	0 of 2	6 of 10	2 of 6	3 of 6	0 of 6	2 of 6	1 of 6

E: Pathways which are excluded from CR analysis

upregulated pathways	downregulated pathways
Smooth Muscle Contraction - Reactome	Pathways in cancer - Mus musculus (mouse)
Disease - Reactome	Chagas disease (American trypanosomiasis) - Mus musculus (mouse)
Legionellosis - Mus musculus (mouse)	XPodNet - protein-protein interactions in the podocyte expanded by STRING - Wikipathways
Collecting duct acid secretion - Mus musculus (mouse)	PluriNetWork - Wikipathways
Defects in vitamin and cofactor metabolism	Toxoplasmosis - Mus musculus (mouse)
Defective AMN causes hereditary megaloblastic anemia 1	Osteoclast differentiation - Mus musculus (mouse)
Defective BTM causes biotinidase deficiency	Hepatitis B - Mus musculus (mouse)
Defective CD320 causes methylmalonic aciduria	Leishmaniasis - Mus musculus (mouse)
Defective CUBN causes hereditary megaloblastic anemia 1	Hepatitis C - Mus musculus (mouse)
Defective GIF causes intrinsic factor deficiency	Epstein-Barr virus infection - Mus musculus (mouse)
Defective HLCS causes multiple carboxylase deficiency	Influenza A - Mus musculus (mouse)
Defective LMBRD1 causes methylmalonic aciduria and homocystinuria type cblF	Viral carcinogenesis - Mus musculus (mouse)
Defective MMAA causes methylmalonic aciduria type cblA	Prion diseases - Mus musculus (mouse)
Defective MMAB causes methylmalonic aciduria type cblB	Adipogenesis - Wikipathways
Defective MMACHC causes methylmalonic aciduria and homocystinuria type cblC	Staphylococcus aureus infection - Mus musculus (mouse)
Defective MMADHC causes methylmalonic aciduria and homocystinuria type cblD	Herpes simplex infection - Mus musculus (mouse)
Defective MTR causes methylmalonic aciduria and homocystinuria type cblG	Systemic lupus erythematosus - Mus musculus (mouse)
Defective MTRR causes methylmalonic aciduria and homocystinuria type cblE	Amoebiasis - Mus musculus (mouse)
Defective MUT causes methylmalonic aciduria mut type	Amyloids - Reactome
Defective TCN2 causes hereditary megaloblastic anemia	Alcoholism - Mus musculus (mouse)
Defects in biotin (B7) metabolism	
Defects in cobalamin (B12) metabolism	
Alzheimer,s disease - Mus musculus (mouse)	
Huntington,s disease - Mus musculus (mouse)	
Parkinson,s disease - Mus musculus (mouse)	
Non-alcoholic fatty liver disease (NAFLD) - Mus musculus (mouse)	
Proximal tubule bicarbonate reclamation - Mus musculus (mouse)	
Type II diabetes mellitus - Mus musculus (mouse)	

F: Pathways mentioned in overrepresentation analysis for overlapping genes between CR and resveratrol

upregulated pathways	downregulated pathways
cholesterol biosynthesis II (via 24,25-dihydrolanosterol) - MouseCyc	Steroid hormone biosynthesis - Mus musculus (mouse) - KEGG
Pentose and glucuronate interconversions - Mus musculus (mouse) - KEGG	Metabolism of lipids and lipoproteins - Reactome
salvage pathways of pyrimidine ribonucleotides - MouseCyc	Retinol metabolism - Mus musculus (mouse) - KEGG
Metabolism - Reactome	Metabolism - Reactome
Biological oxidations - Reactome	Biological oxidations - Reactome
Diurnally Regulated Genes with Circadian Orthologs - Wikipathways	Protein processing in endoplasmic reticulum - Mus musculus (mouse) - KEGG
Chemical carcinogenesis - Mus musculus (mouse) - KEGG	Fatty acid, triacylglycerol, and ketone body metabolism - Reactome
Cholesterol biosynthesis - Reactome	glycerol-3-phosphate shuttle - MouseCyc
Cholesterol Biosynthesis - Wikipathways	L-cysteine degradation VI - MouseCyc
Metabolism of xenobiotics by cytochrome P450 - Mus musculus (mouse) - KEGG	One carbon metabolism and related pathways - Wikipathways
Cytochrome P450 - arranged by substrate type - Reactome	Drug metabolism - other enzymes - Mus musculus (mouse) - KEGG
Steroid biosynthesis - Mus musculus (mouse) - KEGG	Triglyceride Biosynthesis - Reactome
Porphyrin and chlorophyll metabolism - Mus musculus - KEGG	Taurine and hypotaurine metabolism - Mus musculus (mouse) - KEGG
mevalonate pathway I - MouseCyc	Sulfur amino acid metabolism - Reactome
Terpenoid backbone biosynthesis - Mus musculus - KEGG	nicotine degradation III - MouseCyc
cholesterol biosynthesis III (via desmosterol) - MouseCyc	Meiotic Recombination - Reactome
Phase II conjugation - Reactome	glutathione biosynthesis - MouseCyc
Exercise-induced Circadian Regulation - Wikipathways	
Phase 1 - Functionalization of compounds - Reactome	
cholesterol biosynthesis I - MouseCyc	
Metabolism of lipids and lipoproteins - Reactome	
Glutathione metabolism - Mus musculus (mouse) - KEGG	
superpathway of cholesterol biosynthesis - MouseCyc	
Glucuronidation - Reactome	
Circadian clock tutorial CGrove - Wikipathways	
Retinol metabolism - Mus musculus (mouse) - KEGG	
Circadian rhythm - Mus musculus (mouse) - KEGG	
Metapathway biotransformation - Wikipathways	
Trafficking of dietary sterols - Reactome	
Drug metabolism - cytochrome P450 - mouse - KEGG	
glutathione-mediated detoxification - MouseCyc	
Pyruvate metabolism - Mus musculus (mouse) - KEGG	
Glutathione conjugation - Reactome	
Starch and sucrose metabolism - Mus musculus - KEGG	
nicotine degradation II - MouseCyc	
Circadian Clock - Reactome	
Bile secretion - Mus musculus (mouse) - KEGG	
Glycerolipid metabolism - Mus musculus (mouse) - KEGG	
Drug metabolism - other enzymes - mouse - KEGG	
Nicotinate and nicotinamide metabolism - mouse - KEGG	
trans, trans-farnesyl diphosphate biosynthesis - MouseCyc	
PPAR signaling pathway - Wikipathways	
PPAR signaling pathway - Mus musculus (mouse) - KEGG	

G: Overlapping genes between CR and resveratrol assigned to the overrepresented pathways mentioned in separate and overlapped analysis

Pathway	upregulated genes	downregulated genes
Tryptophan metabolism	Dhcr24	Aldh1a1, Aox1, Cyp2f2, Cyp7b1, Ddc
Sulfur amino acid metabolism	Got1	Bhmt, Cdo1, Csad, Ethe1, Gclc, Gclm
One carbon metabolism and related pathways	Etnk2, Gpx3, Gpx6, Gpx7	Baat, Bhmt, Cdo1, Chka, Csad, Gclc, Gclm
Protein processing in endoplasmic reticulum		Derl3, Dnajb1, Dnajb2, Dnajb11, Ero1lb, Hspa5, Hsph1, Hyou1, Lman2, Nploc4, Pdia6, Sec23b, Sec24d, Stt3b, Syvn1, Vcp, Wfs1
Circadian regulation	Bhlhe40, Cebpb, Cry2, Gfra1, Gstm5, Idi1, Nr1d1, Per1, Per2, Per3, Prkab1, Stbd1, Ugp2	G0s2, Ppp1r3c, Tab2
biological oxidation	Acss2, Cyp2b9, Cyp2b13, Cyp3a13, Cyp4a10, Cyp4a14, Cyp7a1, Cyp17a1, Cyp51, Fmo3, Gstm5, Gstm7, Gsto1, Gstt2, Nnmt, Papss2, Sult1a1, Sult1c2, Ugp2, Ugt1a2	Aldh1a1, Cyp2d9, Cyp2f2, Cyp4a12a, Cyp4a12b, Cyp7b1, Gclc, Gclm, Slc35d1, Sult2a8, Ugt2b1, Ugt2b34, Ugt2b35
Glutathione metabolism	Gpx3, Gpx6, Gpx7, Gstm5, Gstm7, Gsto1, Gstt2, Idh1	
retinol metabolism	Cyp2b9, Cyp2b13, Cyp3a13, Cyp4a10, Cyp4a14, Rdh11, Ugt1a2	Aldh1a1, Aox1, Aox3, Cyp4a12a, Cyp4a12b, Retsat, Ugt2b1, Ugt2b34, Ugt2b35
Meiotic Recombination		H2afx, Hist1h3d, Hist2h2aa1, Hist2h2ac
PPAR signaling pathway	Acox1, Angptl4, Cyp4a10, Cyp4a14, Cyp7a1, Fabp5, Pck1, Ppara	Acaa1b, Cpt2, Cyp4a12a, Cyp4a12b, Rxra
Binding and uptake of ligands by scavenger receptors	Alb, Col4a2, Marco, Saa2	Hba-a1, Scara5
Porphyrin and chlorophyll metabolism	Alas1, Blvra, Gusb, Hmox1, Ugt1a2	Alas2, Ears2, Ugt2b1, Ugt2b34, Ugt2b35
salvage pathways of pyrimidine ribonucleotides	Nme4, Nmrk1	Cda
Nicotinate and nicotinamide metabolism	Enpp1, Nadsyn1, Nmrk1, Nnmt	Aox1, Aox3
Metapathway biotransformation	Akr1b3, Cyp7a1, Cyp17a1, Cyp51, Fmo3, Fmo4, Gal3st1, Gpx3, Gstm5, Gstm7, Gsto1, Gstt2, Nnmt, Sult1a1, Sult1c2, Ugt1a2	Baat, Cyp2f2, Cyp4v3, Cyp7b1, Ephx2, Nat6, Nat8
glycerol-3-phosphate shuttle		Gpd1, Gpd2
Taurine / hypotaurine metab.		Baat, Cdo1, Csad
Pentose and glucuronate interconversions	Akr1b3, Akr1b7, Aldh1b1, Gusb, Ugp2, Ugt1a2	Ugt2b1, Ugt2b34, Ugt2b35, Xylb
Starch and sucrose metabolism	Enpp1, Gusb, Ugp2, Ugt1a2	G6pc, Gck, Ugt2b1, Ugt2b34, Ugt2b35
Pyruvat metabolism	Acss2, Akr1b3, Akr1b7, Aldh1b1, Pck1, Pkm	Glo1
Propanoate metabolism	Acss2, Aldh1b1, Suclg2	
lipid metabolism , Fatty acid degradation, Triglyceride Biosynthesis, Glycerolipid metabolism	Abcg1, Abcg5, Abcg8, Acox1, Alb, Akr1b3, Akr1b7, Aldh1b1, Asah1, Cyp4a10, Cyp4a14, Cyp7a1, Etnk2, Gal3st1, Gpcpd1, Idh1, Lpin2, Pld3, Pnpla2, Ppap2a, Ppara, Ptdss2, Scap, Slco1a4, Ugcg	Abcd1, Acaa1b, Agpat2, Agpat3, Akr1c14, Apoa4, Baat, Chka, Cpt2, Cyp4a12a, Cyp4a12b, Cyp7b1, Elovl3, Ephx2, Ept1, Glyctk, Gpd1, Gpd2, Hsd17b12, Kpnb1, Lpgat1, Mtmr4m, Pla2g6, Rxra, Sgms2, Sgpl1, Sgpp1, Srd5a1, Tbl1x
steroid and cholesterol biosynthesis, Terpenoid backbone biosynthesis, mevalonate pathway, trans, trans-farnesyl diphosphate biosynthesis	Cyp17a1, Cyp51, Dhcr24, Dhcr7, Fdps, Hmgcr, Hmgcs1, Idi1, Lss, Mvk, Nsdhl, Pmvk, Sqle	Hsd3b2, Hsd3b5, Lipa
steroid hormone biosynthesis	Cyp3a13, Cyp17a1, Cyp7a1, Srd5a2, Ugt1a2	Cyp7b1, Hsd3b2, Hsd3b5, Hsd17b12, Srd5a1, Ugt2b1, Ugt2b34, Ugt2b35
bile secretion; Trafficking of dietary sterols	Abcc4; Abcg5, Abcg8, Atp1b1, Cyp7a1, Hmgcr, Slco1a4	Abcb4, Aqp8, Baat, Slc22a7, Rxra

H: Pathways mentioned in overrepresentation analysis for overlapping genes between CR and phloridzin

upregulated pathways	downregulated pathways
superpathway of cholesterol biosynthesis - MouseCyc	Retinol metabolism - Mus musculus (mouse) – KEGG
Cholesterol biosynthesis - Reactome	nicotine degradation III - MouseCyc
Cholesterol Biosynthesis - Wikipathways	Toll-Like Receptors Cascades - Reactome
cholesterol biosynthesis I - MouseCyc	nicotine degradation II - MouseCyc
cholesterol biosynthesis III (via desmosterol) - MouseCyc	Butanoate metabolism - Mus musculus (mouse) – KEGG
Exercise-induced Circadian Regulation - Wikipathways	Exercise-induced Circadian Regulation – Wikipathways
Metabolism - Reactome	Xenobiotics – Reactome
salvage pathways of pyrimidine ribonucleotides - MouseCyc	Drug metabolism - other enzymes - Mus musculus (mouse) – KEGG
Metabolism of lipids and lipoproteins - Reactome	TRIF-mediated TLR3/TLR4 signaling - Reactome
Pyrimidine salvage reactions - Reactome	MyD88-independent cascade - Reactome
Terpenoid backbone biosynthesis - Mus musculus (mouse) - KEGG	Toll Like Receptor 3 (TLR3) Cascade - Reactome
Fatty Acid Biosynthesis - Wikipathways	mRNA processing – Wikipathways
oleate biosynthesis II (animals) - MouseCyc	bupropion degradation - MouseCyc
Biosynthesis of unsaturated fatty acids - Mus musculus (mouse) - KEGG	Diurnally Regulated Genes with Circadian Orthologs – Wikipathways
Phenylalanine, tyrosine and tryptophan biosynthesis - Mus musculus (mouse) - KEGG	Destabilization of mRNA by AUF1 (hnRNP D0) – Reactome
Destabilization of mRNA by AUF1 (hnRNP D0) - Reactome	MAP kinase activation in TLR cascade – Reactome
cholesterol biosynthesis II (via 24,25-dihydrolanosterol) - MouseCyc	Toll Like Receptor 4 (TLR4) Cascade - Reactome
trans, trans-farnesyl diphosphate biosynthesis - MouseCyc	Valine, leucine and isoleucine degradation - Mus musculus (mouse) – KEGG
(deoxy)ribose phosphate degradation - MouseCyc	Protein processing in endoplasmic reticulum - Mus musculus (mouse) – KEGG
	Activated TLR4 signalling - Reactome
	Toll Like Receptor 9 (TLR9) Cascade - Reactome
	Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET) - Reactome
	Porphyrin and chlorophyll metabolism - Mus musculus (mouse) – KEGG
	TRAF6 Mediated Induction of proinflammatory cytokines – Reactome
	Toll Like Receptor TLR6:TLR2 Cascade – Reactome
	Toll Like Receptor 2 (TLR2) Cascade - Reactome
	Type II interferon signaling (IFNG) - Wikipathways
	2-methylbutyrate biosynthesis - MouseCyc
	MyD88 dependent cascade initiated on endosome – Reactome

Toll Like Receptor 7/8 (TLR7/8) Cascade – Reactome
 fatty acid β -oxidation IV (unsaturated, even number) – MouseCyc
 Toll Like Receptor signaling - Wikipathways
 PPAR signaling pathway - Wikipathways
 PPAR signaling pathway - Mus musculus (mouse) – KEGG
 Fatty Acid Beta Oxidation - Wikipathways
 fatty acid β -oxidation I - MouseCyc
 MyD88 cascade initiated on plasma membrane – Reactome
 Toll Like Receptor 10 (TLR10) Cascade – Reactome
 Toll Like Receptor 5 (TLR5) Cascade - Reactome
 MyD88:Mal cascade initiated on plasma membrane – Reactome
 Toll Like Receptor TLR1:TLR2 Cascade – Reactome
 Fatty acid degradation - Mus musculus (mouse) – KEGG
 Complement Activation, Classical Pathway – Wikipathways
 Regulation of mRNA Stability by Proteins that Bind AU-rich Elements - Reactome

I: Overlapping genes between CR and phloridzin assigned to the overrepresented pathways mentioned in separate and overlapped analysis

Pathway	upregulated genes	downregulated genes
IL-6 signaling	Erb3, Hsp1	Hsp90aa1, Jak1, Jun, Map2k4, Mapk1, Pik3r1, Ppp2ca, Ppp2r1b, Ppp2r5e, Stat5a
Growth hormone receptor signaling	Cish, Socs2	Adam17, Ghr, Irs1, Stat5a
Androgen Receptor Signaling	Ccne1, Cdk1	Atf2, Casp8, Ctnnb1, Ghr, Gtf2f2, Gtf2h1, Jun, Mapk1, Nr3c1, Rchy1
RNA transport		Eif1a, Eif1b, Eif2b3, Eif2s3x, Eif4a2, Eif4g1, Eif5, Eif5b, Gemin2, Kpnb1, Ncbp2, Nup35, Nxt2, Pabpc1, Pnn, Rbm8a, Rpp14, Rpp40, Smn1
Butanoate metabolism		Abat, Acat1, Acsm3, Acsm5, Aldh5a1, Bdh1, Ehhadh, Hadha
mRNA processing & regulation of mRNA stability	Cirbp, Hsp1, Rps13, Ttc39a	A1cf, Abcb4, Akap1, Anp32a, Apobec1, Cpeb4, Cpsf2, Csad, Csde1, Eif2ak2, Eif4a2, Eif4g1, Ergic2, Fus, G3bp1, Gatac, Ggcx, Gtf2f2, Gtf2h1, Gtf2h2, Hnrnpa3, Hnrnpu, Hspa1b, Lsm2, Ltv1, Mettl3, Mki67ip, Ncbp2, Ncl, Nol8, Nop9, Npm1, Nup35, Oasl2, Pabpc1, Papola, Parn, Pcbp4, Pum1, Rad21, Rbm8a, Rbmx1, Rpp14, Rps4l, Smn1, Spop, Srp68, Srsf1, Srsf10, Srsf3, Srsf7, Ssb, Syncrip, Tardbp, Vprbp, Xrn2, Zfp3611
lipid metabolism and lipoprotein metabolism, Fatty acid biosynthesis; Fatty	Acacb, Acot3, Acss2, Dhcr7, Fads1, Fdps, Gal3st1, Gpcpd1, Idi1, Nsdhl, Pmvk, Scd1, Sqle	9130409I23Rik, Abca1, Abcc3, Acaa1b, Acad11, Acadm, Acat1, Acot1, Acox2, Akr1c14, Akr1c20, Akr1d1, Bdh1, Chkb,

acid, triacylglycerol, and ketone body metabolism; beta-oxidation		Cpt1a, Decr1, Eci2, Ehhadh, Elovl3, Gyk, Hadha, Hsd3b2, Hsd3b3, Hsd17b12, Kpnb1, Ldlr, Pik3r1, Pitpnb, Pla2g12a, Ppap2b, Ppara, Psap, Sc5d, Sgms2, Sgpp1, Slco1a1, Slco1b2, Srd5a1, Sumf1, Tbl1x
arachidonic acid metabolism	Cyp2c39, Cyp4a14	Cyp2c37, Cyp2c50, Cyp2c54, Cyp2j5, Cyp2j6
propanoate metabolism	Acacb, Acss2	Abat, Acadm, Acat1, Aldh3a2, Ehhadh, Hadha
Phenylalanine, tyrosine/tryptophan biosynthesis	Got1	
Tryptophan metabolism, Valine, leucine and isoleucine degradation		Aadat, Abat, Acaa1b, Acadm, Acat1, Aldh3a2, Aox1, Aox3, Cyp2j6, Ehhadh, Hadha
Protein processing in endoplasmic reticulum		Atf6, Atf6b, Canx, Capn2, Derl2, Dnaja1, Dnajb1, Dnajc5, Eif2ak2, Hsp90aa1, Hsp90ab1, Hsp90b1, Hspa1b, Hsph1, Nfe2l2, Nsf1c, Rnf5, Sec62, Sec63, Ube2d1, Ube2e3, Ube2g2, Ufd1l
circadian clock	Idi1, Per1, Tubb4a	Azin1, Clock, Dnaja1, G0s2, Klf9, Nr1d1, Ppp1r3c, Psm4, Stbd1, Tab2
Bile secretion		Abcb4, Abcc2, Abcc3, Abcg2, Aqp4, Aqp9, Ephx1, Ldlr, Slc22a1, Slc22a7, Slco1a1, Slco1b2
retinol metabolism	Cyp2c39, Cyp4a14	Adh4, Aox1, Aox3, Cyp2a12, Cyp2c37, Cyp2c50, Cyp2c54, Cyp3a13, Cyp3a25, Dhrr4, Rdh16, Retsat, Ugt2b34, Ugt2b35
glutathione metabolism and γ-glutamyl cycle	Ggt6	Gclc, Gclm, Oplah
Cholesterol biosynthesis	Dhcr7, Fdps, Idi1, Nsdhl, Pmvk, Sqle	Acat1, Nudt12, Sc5d
Steroid hormone biosynthesis		Akr1d1, Cyp3a13, Cyp3a25, Hsd17b12, Hsd17b2, Hsd3b2, Srd5a1, Ugt2b34, Ugt2b35
PPAR signaling pathway	Cyp4a14, Fabp5, Scd1	Acaa1b, Acadm, Acox2, Cd36, Cpt1a, Ehhadh, Fabp2, Fabp7, Gyk, Ppara, Sorbs1
Porphyryn and chlorophyll metabolism	Alas1	Acaa1b, Acot1, Decr1, Hadha, Hsd17b12
Kennedy pathway		Chka, Chkb, Chpt1, Sgpl1
biological oxidation	Acss2, Cyp2c39, Cyp4a14, Nnmt	Adh4, Cyp2a12, Cyp2c37, Cyp2c50, Cyp2c54, Cyp2d12, Cyp2d40, Cyp2j5, Cyp2j6, Cyp3a13, Cyp3a25, Gclc, Gclm, Sult1c2, Tpm1, Ephx1, Ugt2b34, Ugt2b35
Toll like receptor cascade	Cdk1	Atf2, Casp8, Cd36, Chuk, Ctss, Dhx36, Eea1, Eif2ak2, Hsp90b1, Ikbke, Ikbkg, Irak2, Jun, Ly86, Map2k4, Mapk1, Ppp2ca, Ppp2r1b, Tab2, Tbk1, Ube2d1
Type II interferon signaling (IFNG)		Cxcl10, Cxcl9, Cybb, Eif2ak2, Gbp2b, Ifit2, Jak1, Stat2
Pyrimidine salvage reactions		Tk2
Complement Activation		C1qb, C1s, C6, C8a, C8b
Class I MHC mediated antigen processing & presentation		Anapc2, Anapc4, Asb13, Canx, Cd36, Ctss, Cul2, Cul3, Cybb, Pja2, Rchy1, Rnf138, Rnf6, Smurf2, Tceb1, Uba3, Uba5, Vprbp
(deoxy)ribose phosphate degradation		Apobec1
2-methylbutyrate biosynthesis		Acat1, Ehhadh

J: Pathways mentioned in overrepresentation analysis for overlapping genes between CR and dietary quercetin

upregulated pathways	downregulated pathways
Cytochrome P450 - arranged by substrate type - Reactome	Destabilization of mRNA by AUF1 (hnRNP D0) – Reactome
Biological oxidations - Reactome	
Macrophage markers - Wikipathways	
Diurnally Regulated Genes with Circadian Orthologs - Wikipathways	
Exercise-induced Circadian Regulation - Wikipathways	
Phase 1 - Functionalization of compounds - Reactome	
Retinol metabolism - Mus musculus - KEGG	
Hypertrophy Model - Wikipathways	

K: Overlapped genes between CR and dietary quercetin assigned to the overrepresented pathways mentioned in separate and overlapped analysis

Pathway	upregulated genes	downregulated genes
Kennedy pathway		Chka, Sgp11
Destabilization of mRNA by AUF1	Hspb1	Hspa1b
Circadian clock	Cebpb, Per1	G0s2, Nr1d1, Ppp1r3c
biological oxidation	Cyp2b10, Cyp4a14, Nnmt, Sult1e1	Cyp2d12, Cyp2d40, Slc26a1, Sult1c2
retinol metabolism	Cyp2b10, Cyp4a14	
Macrophage markers	Cd14, Cd163	

L: Pathways mentioned in overrepresentation analysis for overlapping genes between CR and quercetin administered intraperitoneally

upregulated pathways	downregulated pathways
Biological oxidations - Reactome	Biological oxidations - Reactome
Metabolism - Reactome	Metabolism - Reactome
Phase 1 - Functionalization of compounds - Reactome	Phase 1 - Functionalization of compounds – Reactome
Cytochrome P450 - arranged by substrate type - Reactome	Cytochrome P450 - arranged by substrate type – Reactome
Chemical carcinogenesis - Mus musculus (mouse) - KEGG	Chemical carcinogenesis - Mus musculus (mouse) - KEGG
Drug metabolism - cytochrome P450 - Mus musculus (mouse) - KEGG	Drug metabolism - cytochrome P450 - Mus musculus (mouse) - KEGG
Metabolism of xenobiotics by cytochrome P450 - Mus musculus (mouse) - KEGG	Metabolism of xenobiotics by cytochrome P450 - Mus musculus (mouse) - KEGG
Retinol metabolism - Mus musculus (mouse) - KEGG	Retinol metabolism - Mus musculus (mouse) – KEGG
Metabolism of lipids and lipoproteins - Reactome	Metabolism of lipids and lipoproteins - Reactome
Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE) - Reactome	Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE) - Reactome
Biosynthesis of unsaturated fatty acids - Mus musculus (mouse) - KEGG	Complement and coagulation cascades - Mus musculus (mouse) - KEGG
Growth hormone receptor signaling - Reactome	Growth hormone receptor signaling - Reactome
Fatty acids - Reactome	Fatty acids - Reactome

Metapathway biotransformation - Wikipathways	Complement Activation, Classical Pathway - Wikipathways
Arachidonic acid metabolism - Mus musculus (mouse) - KEGG	Arachidonic acid metabolism - Mus musculus (mouse) - KEGG
nicotine degradation II - MouseCyc	nicotine degradation II - MouseCyc
Leptin Insulin Overlap - Wikipathways	Bile acid and bile salt metabolism - Reactome
nicotine degradation III - MouseCyc	nicotine degradation III - MouseCyc
Glycolysis and Gluconeogenesis - Wikipathways	Synthesis of bile acids and bile salts - Reactome
glutathione-mediated detoxification - MouseCyc	Primary bile acid biosynthesis - Mus musculus (mouse) - KEGG
Phase II conjugation - Reactome	Beta-oxidation of pristanoyl-CoA - Reactome
Arachidonic acid metabolism - Reactome	Complement cascade - Reactome
Linoleic acid (LA) metabolism - Reactome	Arachidonic acid metabolism - Reactome
Adipocytokine signaling pathway - Mus musculus (mouse) - KEGG	Synthesis of bile acids and bile salts via 7alpha-hydroxycholesterol - Reactome
PPAR signaling pathway - Mus musculus (mouse) - KEGG	PPAR signaling pathway - Mus musculus (mouse) - KEGG
PPAR signaling pathway - Wikipathways	PPAR signaling pathway - Wikipathways
Insulin signaling pathway - Mus musculus (mouse) - KEGG	Complement and Coagulation Cascades - Wikipathways
oleate biosynthesis II (animals) - MouseCyc	Terminal pathway of complement - Reactome
Xenobiotics - Reactome	Xenobiotics - Reactome
Fatty acid degradation - Mus musculus (mouse) - KEGG	Type II interferon signaling (IFNG) - Wikipathways
alpha-linolenic (omega3) and linoleic (omega6) acid metabolism - Reactome	Fatty acid degradation - Mus musculus (mouse) - KEGG
Signaling by Leptin - Reactome	Retinol metabolism - Wikipathways
Estrogen metabolism - Wikipathways	Peroxisomal lipid metabolism - Reactome
biosynthesis of estrogens - MouseCyc	Interferon Signaling - Reactome
alpha-linolenic acid (ALA) metabolism - Reactome	Regulation of Complement cascade - Reactome
Methylation - Wikipathways	ISG15 antiviral mechanism - Reactome
Glutathione metabolism - Mus musculus (mouse) - KEGG	Antiviral mechanism by IFN-stimulated genes - Reactome
Cytosolic sulfonation of small molecules - Reactome	Steroid hormone biosynthesis - Mus musculus (mouse) - KEGG
glycolysis V (Pyrococcus) - MouseCyc	Steroid Biosynthesis - Wikipathways
Steroid hormone biosynthesis - Mus musculus (mouse) - KEGG	Synthesis of bile acids and bile salts via 27-hydroxycholesterol - Reactome
Fatty Acyl-CoA Biosynthesis - Reactome	Peroxisome - Mus musculus (mouse) - KEGG
bupropion degradation - MouseCyc	Immune System - Reactome
Glutathione metabolism - Wikipathways	Initial triggering of complement - Reactome
Selenium - Wikipathways	tetrapyrrole biosynthesis II - MouseCyc
glycolysis III - MouseCyc	bupropion degradation - MouseCyc
Glycolysis / Gluconeogenesis - Mus musculus (mouse) - KEGG	Synthesis of bile acids and bile salts via 24-hydroxycholesterol - Reactome
Prolactin signaling pathway - Mus musculus (mouse) - KEGG	Synthesis of epoxy (EET) and dihydroxyeicosatrienoic acids (DHET) - Reactome
Fatty acid elongation - Mus musculus (mouse) - KEGG	Classical antibody-mediated complement activation - Reactome
glycolysis I - MouseCyc	Fatty Acid Omega Oxidation - Wikipathways
Drug metabolism - other enzymes - Mus musculus (mouse) - KEGG	Bile secretion - Mus musculus (mouse) - KEGG
Glycolysis - Reactome	ketogenesis - MouseCyc

Regulation of Insulin-like Growth Factor (IGF) Transport and Uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) - Reactome	Antigen processing and presentation - Mus musculus (mouse) - KEGG
Triglyceride Biosynthesis - Reactome	Ethanol oxidation - Reactome
Glucose transport - Reactome	Synthesis and degradation of ketone bodies - Mus musculus (mouse) - KEGG
Hexose transport - Reactome	Heme Biosynthesis - Wikipathways
EPO Receptor Signaling - Wikipathways	heme biosynthesis II - MouseCyc
Metabolism of carbohydrates - Reactome	sphingosine and sphingosine-1-phosphate metabolism - MouseCyc
	Cytokine Signaling in Immune system - Reactome
	Lipoprotein metabolism - Reactome
	Interleukin-6 signaling - Reactome
	Creation of C4 and C2 activators - Reactome
	mevalonate pathway I - MouseCyc
	Heme biosynthesis - Reactome
	Innate Immune System - Reactome
	Porphyrin and chlorophyll metabolism - Mus musculus (mouse) - KEGG
	Recycling of bile acids and salts - Reactome
	Transport of organic anions - Reactome
	Bile salt and organic anion SLC transporters - Reactome
	Protein processing in endoplasmic reticulum - Mus musculus (mouse) - KEGG
	Androgen biosynthesis - Reactome
	Phagosome - Mus musculus (mouse) - KEGG
	Metabolism of porphyrins - Reactome
	MHC class II antigen presentation - Reactome
	Fat digestion and absorption - Mus musculus (mouse) - KEGG
	Tryptophan metabolism - Wikipathways
	Chylomicron-mediated lipid transport - Reactome
	Lipid digestion, mobilization, and transport - Reactome
	Proteasome - Mus musculus (mouse) - KEGG
	Statin Pathway - Wikipathways
	Retinoid metabolism and transport - Reactome
	Linoleic acid metabolism - Mus musculus (mouse) - KEGG
	Exercise-induced Circadian Regulation - Wikipathways
	Diurnally Regulated Genes with Circadian Orthologs - Wikipathways
	One carbon metabolism and related pathways - Wikipathways
	Terpenoid backbone biosynthesis - Mus musculus (mouse) - KEGG
	Synthesis of Prostaglandins (PG) and Thromboxanes (TX) - Reactome
	Valine, leucine and isoleucine degradation - Mus musculus (mouse) - KEGG

M: Overlapping genes between CR and quercetin administered intraperitoneally assigned to the overrepresented pathways mentioned in separate and overlapped analysis

pathway	upregulated genes	downregulated genes
Tryptophan metabolism	Inmt, Tdo2	Aadat, Aldh1a1, Aox1, Cyp7b1
Valine, leucine and isoleucine degradation	Ehhadh	Abat, Acat2, Aox1, Hadhb, Hmgcs2
One carbon metabolism and related pathways		Bhmt2, Chkb, Csad, Gclc, Gsr, Gss
Protein processing in endoplasmic reticulum		Bag1, Derl1, Derl3, Dnaja1, Dnajb2, Edem3, Eif2ak2, Hspa5, Nfe2l2, Pdia4, Sec23b, Stt3b, Ube2e1, Ube2e3
Circadian Regulation	Tob1	Cebpb, Dnaja1, G0s2, Pasma4, Qk, Stbd1, Sumo3
Bile acid and bile salt metabolism; Synthesis of bile acids and bile salts from cholesterol, recycling of bile acids and salts	Adcy6, Sult2a3	Acox2, Akr1c14, Amacr, Aqp8, Cyp7b1, Ephx1, Hsd17b4, Hsd3b7, Slc22a7, Slco1a1, Slco1b2
Bile salt and organic anion SLC transporters		Slc13a3, Slc16a1, Slc16a7
biological oxidation	Cyp17a1, Cyp2b13, Cyp2c39, Cyp4a10, Cyp4a14, Cyp4a31, Fmo3, Gsta4, Gstm2, Nnmt, Sult1e1, Sult2a3	Adh4, Aldh1a1, Aldh1a7, Cyp2a12, Cyp2c29, Cyp2c50, Cyp2c70, Cyp2d10, Cyp2d12, Cyp2d40, Cyp2d9, Cyp2j5, Cyp3a13, Cyp3a25, Cyp4a12a, Cyp4a12b, Cyp7b1, Ephx1, Gclc, Ggh, Glyat, Gss, Gstm4, Mgst1, Ugdh, Ugt2b35, Ugt2b37
Steroid hormone biosynthesis, androgen and estrogen biosynthesis	Cyp17a1, Sts, Sult1e1	Cyp3a13, Cyp3a25, Cyp7b1, Hsd17b2, Hsd3b5, Srd5a1, Ugt2b35, Ugt2b37
Steroid biosynthesis	Cyp17a1, Lss	Hsd17b2, Hsd17b4, Hsd3b5, Sc4mol, Sc5d
Retinol / Retinoid metabolism and transport	Cyp2b13, Cyp2c39, Cyp4a10, Cyp4a14, Cyp4a31	Adh4, Akr1c14, Aldh1a1, Aldh1a7, Aox1, Cd36, Cyp2a12, Cyp2c29, Cyp2c50, Cyp2c70, Cyp3a13, Cyp3a25, Cyp4a12a, Cyp4a12b, Dhrr3, Gpc4, Sdc1, Sdc2, Sdc4, Ugt2b35, Ugt2b37
PPAR signaling pathway	Cyp4a10, Cyp4a14, Cyp4a31, Ehhadh, Fads2, Slc27a1	Acox2, Cd36, Cyp4a12a, Cyp4a12b, Hmgcs2, Scd1
Porphyryn / chlorophyll metab.		Alad, Ugt2b35, Ugt2b37
Type II interferon signaling (IFNG)		Cxcl10, Cxcl9, Eif2ak2, Ifngr2, Isg15, Socs3
Metabolism of lipids and lipoproteins; biosynthesis of fatty acids, fatty acyl-CoA biosynthesis; Linoleic acid (LA) and ALA metabolism, Fatty acid elongation, beta or omega oxidation, Lipoprotein metabolism, Fat digestion, absorption, mobilization, and transport, ketogenesis, statin pathway, sphingosine and sphingosine-1-phosphate metabolism, arachidonic acid metabolism	Acly, Acot7, Cyp17a1, Cyp2b13, Cyp2c39, Cyp4a10, Cyp4a14, Cyp4a31, Elovl6, Fads1, Fads2, Lss	Abca1, Acat2, Acox2, Adh4, Agpat2, Akr1c14, Aldh1a1, Amacr, Bmp1, Cd36, Cdipt, Chkb, Crot, Cyb5, Cyp2c29, Cyp2c50, Cyp2c70, Cyp2j5, Cyp3a13, Cyp3a25, Cyp4a12a, Cyp4a12b, Cyp7b1, Elovl3, Elovl5, Hadhb, Hmgcs2, Hpgd, Hsd17b4, Hsd3b5, Hsd3b7, Lcat, Lpgat1, Ppp1ca, Ppp1cb, Psap, Ran, Sc4mol, Sc5d, Sdc1, Sgpl1, Sgpp1, Slco1a1, Slco1b2, Sqle, Srd5a1
Metabolism of carbohydrates, Glycolysis and Gluconeogenesis	Eno1, Pklr, Slc2a4	Adh4, Amy1, B3gat3, Csgalnact2, Gpc4, Ldha, Mpc1, Sdc1, Sdc2, Sdc4, Slc25a13
Glucose/ Hexose transport	Slc2a4	
Glutathione metabolism	Gsta4, Gstm2	Gclc, Gsr, Gss, Gstm4, Mgst1

Methylation	Inmt, Nnmt	
Interferon Signaling		Ifit1, Ifngr2, Isg15, Socs3, Ube2e1, Ube2l6, Usp18
Immune System, Complement and coagulation cascades, Innate immune system, Creation of C4 and C2 activators	Adcy6, Cish, Irf7, Irs2, Nrg4, Rnf4, Socs2, Tirap	Actg1, Atg5, B2m, C1qa, C1s, C2, C4b, C4bp, C8a, C8b, C9, Capza2, Cd36, Cd74, Cdh1, Cfh, Crp, Ctnnb1, Ctss, Cyba, Dhx36, Egfr, F8, Ghr, H2-Aa, Hras, Ifit1, Ifngr2, Il6st, Isg15, Lbp, Ly86, Map2k4, Mbl1, Rap1a, Rnf135, Serping1, Socs3, Stat5a, Trex1, Tyrobp, Uba3, Ube2a, Ube2e1, Ube2l6, Usp18
Peroxisome, Peroxisomal lipid metabolism	Ehhadh	Acox2, Amacr, Crot, Ech1, Hsd17b4, Pex13, Pex26
Heme Biosynthesis		Alad
Selenium	Fads1, Fads2	Gsr
Phagosome		Actg1, Atp6v1h, Cd36, Clec7a, Ctss, Cyba, Dync1i2, H2-Aa, H2-Ab1, Mbl1, Sec22b
Proteasome		Psm4, Psm8, Psmc2, Psm1, Psm6
Growth hormone receptor signaling	Cish, Irs2, Socs2	Ghr, Socs3, Stat5a
Adipocytokine signaling pathway, insulin signaling pathway, Leptin Insulin Overlap	Irs2, Pklr, Lepr, Slc2a4, Socs2	Cd36, Hras, Ppp1ca, Ppp1cb, Rheb, Socs3, Stat5a
Regulation of Insulin-like Growth Factor (IGF) Transport and Uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs)	Igfbp1	Igfals
Transport of organic anions		Slco1a1, Slco1b2
Interleukin-6 signaling		Il6st, Socs3
Ethanol oxidation		Adh4, Aldh1a1, Aldh1a7

N: Pathways mentioned in overrepresentation analysis for overlapping genes between CR and genistein administered intraperitoneally

upregulated pathways	downregulated pathways
Biological oxidations - Reactome	Biological oxidations - Reactome
Metabolism - Reactome	Metabolism - Reactome
Phase 1 - Functionalization of compounds - Reactome	Phase 1 - Functionalization of compounds - Reactome
Cytochrome P450 - arranged by substrate type - Reactome	Cytochrome P450 - arranged by substrate type - Reactome
Chemical carcinogenesis - Mus musculus (mouse) - KEGG	Chemical carcinogenesis - Mus musculus (mouse) - KEGG
Drug metabolism - cytochrome P450 - Mus musculus (mouse) - KEGG	Drug metabolism - cytochrome P450 - Mus musculus (mouse) - KEGG
Metabolism of xenobiotics by cytochrome P450 - Mus musculus (mouse) - KEGG	Metabolism of xenobiotics by cytochrome P450 - Mus musculus (mouse) - KEGG
Retinol metabolism - Mus musculus (mouse) - KEGG	Retinol metabolism - Mus musculus (mouse) - KEGG
nicotine degradation II - MouseCyc	nicotine degradation II - MouseCyc
Arachidonic acid metabolism - Mus musculus (mouse) - KEGG	Complement and Coagulation Cascades - Wikipathways
Growth hormone receptor signaling - Reactome	Complement and coagulation cascades - Mus musculus (mouse) - KEGG
Xenobiotics - Reactome	Initial triggering of complement - Reactome
Metabolism of lipids and lipoproteins - Reactome	Metabolism of lipids and lipoproteins - Reactome

Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE) - Reactome	Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE) - Reactome
Biosynthesis of unsaturated fatty acids - Mus musculus (mouse) - KEGG	Complement Activation, Classical Pathway - Wikipathways
Fatty acid elongation - Mus musculus - KEGG	Complement cascade - Reactome
Arachidonic acid metabolism - Reactome	ISG15 antiviral mechanism - Reactome
Metapathway biotransformation - Wikipathways	Antiviral mechanism by IFN-stimulated genes - Reactome
Estrogen metabolism - Wikipathways	mevalonate pathway I - MouseCyc
bupropion degradation - MouseCyc	Interferon Signaling - Reactome
Triglyceride Biosynthesis - Reactome	nicotine degradation III - MouseCyc
Phenylalanine, tyrosine and tryptophan biosynthesis - Mus musculus (mouse) - KEGG	Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds - Reactome
nicotine degradation III - MouseCyc	tetrapyrrole biosynthesis II - MouseCyc
Phenylalanine metabolism - Mus musculus (mouse) - KEGG	Terpenoid backbone biosynthesis - Mus musculus (mouse) - KEGG
biosynthesis of estrogens - MouseCyc	Fatty acids - Reactome
Glycolysis and Gluconeogenesis - Wikipathways	Fatty acid degradation - Mus musculus (mouse) - KEGG
Cytosolic sulfonation of small molecules - Reactome	Destabilization of mRNA by AUF1 (hnRNP D0) - Reactome
Prolactin signaling pathway - Mus musculus (mouse) - KEGG	Classical antibody-mediated complement activation - Reactome
Fatty acid, triacylglycerol, and ketone body metabolism - Reactome	superpathway of cholesterol biosynthesis - MouseCyc
Phase II conjugation - Reactome	Metabolism of porphyrins - Reactome
Leptin Insulin Overlap - Wikipathways	ketogenesis - MouseCyc
acyl-CoA hydrolysis - MouseCyc	Beta-oxidation of pristanoyl-CoA - Reactome
Fatty acids - Reactome	Lipoprotein metabolism - Reactome
glutathione-mediated detoxification - MouseCyc	Synthesis and degradation of ketone bodies - Mus musculus (mouse) - KEGG
EPO Receptor Signaling - Wikipathways	Heme Biosynthesis - Wikipathways
Fatty Acyl-CoA Biosynthesis - Reactome	heme biosynthesis II - MouseCyc
Gluconeogenesis - Reactome	Abacavir transport and metabolism - Reactome
Cysteine and methionine metabolism - Mus musculus (mouse) - KEGG	Porphyrin and chlorophyll metabolism - Mus musculus (mouse) - KEGG
IL-3 Signaling Pathway - Wikipathways	Creation of C4 and C2 activators - Reactome
	Heme biosynthesis - Reactome
	SLC-mediated transmembrane transport - Reactome
	Organic cation/anion/zwitterion transport - Reactome
	Bile salt and organic anion SLC transporters - Reactome
	Bile acid and bile salt metabolism - Reactome
	Bile secretion - Mus musculus (mouse) - KEGG
	Retinol metabolism - Wikipathways
	PPAR signaling pathway - Mus musculus (mouse) - KEGG
	PPAR signaling pathway - Wikipathways
	Protein processing in endoplasmic reticulum - Mus musculus (mouse) - KEGG
	Peroxisome - Mus musculus (mouse) - KEGG
	Lipid digestion, mobilization, and transport - Reactome
	Proteasome - Mus musculus (mouse) - KEGG
	Primary bile acid biosynthesis - mouse - KEGG

O: Overlapping genes between CR and genistein administered intraperitoneally assigned to the overrepresented pathways mentioned in separate and overlapped analysis

Pathway	upregulation	downregulation
Growth hormone receptor signaling, Leptin Insulin Overlap	Cish, Irs2, Socs2	
biological oxidation	Cyp17a1, Cyp2b13, Cyp2b9, Cyp2c39, Cyp4a14, Cyp4a31, Fmo3, Gstt3, Sult1e1, Sult2a3	Adh4, Cyp2c29, Cyp2c55, Cyp2c70, Cyp2d10, Cyp2d12, Cyp2d40, Cyp2d9, Cyp3a13, Cyp3a25, Cyp4a12a, Cyp4a12b, Ephx1, Glyat, Gss, Gstm4, Mgst1, Ugt2b35, Ugt2b37
Protein processing in endoplasmic reticulum	Map3k5	Derl1, Dnaja1, Dnajb1, Dnajb2, Hspa5, Hsph1, Nfe2l2, Stt3b, Ube2e1
Bile secretion	Sult2a3	Ephx1, Slc10a2, Slc22a1, Slc22a7, Slco1b2
Retinol metabolism	Cyp2b13, Cyp2b9, Cyp2c39, Cyp4a14, Cyp4a31	Adh4, Aox1, Cyp2c29, Cyp2c55, Cyp2c70, Cyp3a13, Cyp3a25, Cyp4a12a, Cyp4a12b, Dhrs3, Ugt2b35, Ugt2b37
Cholesterol biosynthesis	Lss	Acat2, Hmgcs2
Metabolism of lipids and lipoproteins, Fatty acid, triacylglycerol, and ketone body metabolism, biosynthesis of fatty acids, beta oxidation, ketogenesis, Lipid digestion, mobilization, and transport, acyl-CoA hydrolysis, sphingosine and sphingosine-1-phosphate metabolism	Acly, Acot3, Agpat9, Cyp17a1, Cyp2c39, Cyp4a14, Cyp4a31, Elovl6, Gpcpd1, Lss, Ptgds	Acat2, Amacr, Crls1, Crot, Cyp2c29, Cyp2c55, Cyp4a12a, Cyp4a12b, Elovl3, Hadhb, Hmgcs2, Hsd3b5, Hsd3b7, Lcat, Ppp1ca, Psap, Sdc1, Sgpp1, Slc10a2, Slco1b2
Proteasome		Psmb8, Psmc2, Psmd1, Psmd4, Psmd6
Estrogen metabolism	Cyp17a1, Sult1e1	
Bile acid and bile salt metabolism; Primary bile acid biosynthesis		Amacr, Hsd3b7, Slc10a2, Slco1b2
Complement and coagulation cascades		C1qa, C1s, C4b, C4bp, C9, Cfd, Mbl1, Serping1
Interferon Signaling		Ifit1, Ifngr2, Isg15, Ube2e1, Ube2l6, Usp18
Peroxisome	Ehhadh	Amacr, Crot, Ech1, Pex26
Heme Biosynthesis		Alad, Alas2
Cysteine and methionine metabolism	Got1, Tat	Ldha, Mpst
Phenylalanine metabolism	Got1, Tat	Glyat
Retinol metabolism	Rarb	Adh4, Dhrs3
IL-3 Signaling Pathway	Cish, Id1, Socs2	Shc1
Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds, SLC-mediated transmembrane transport	Slc27a1, Slc43a1	Rhbg, Slc13a3, Slc16a7, Slc1a4, Slc22a1, Slc22a7, Slc39a4, Slc6a13, Slco1b2

P: All significantly regulated genes by caloric restriction with a fold change > 1.5 and the regulation of these genes by the different phytonutrients
(grey bars indicate that the gene is significantly co-regulated by the phytonutrient (q < 0.05))

Upregulated genes

Entrez ID	gene symbol	FC CR	FC R	FC P	FC Qd	FC Qi	FC Gi
100503969	1810008I18Rik	0,54	NA	0,8441*	1,19	NA	NA
109163	3010003L21Rik	0,65	1,09	NA	NA	NA	NA
107476	Acaca	0,52	1,10	0,95	1,08	0,74	0,87
100705	Acacb	0,55	1,01	0,8314*	1,09	1,01	1,06
266645	Acmsd	0,67	0,99	NA	NA	1,04	1,05
101494	Al132709	0,34	NA	1,03	1,04	NA	NA
27053	Asns	0,65	1,01	0,8699*	1,00	0,88	0,96
216454	BC089597	0,65	0,689*	0,89	0,93	0,76	0,93
100038725	Cep85l	0,65	NA	NA	NA	NA	NA
56398	Chp1	0,57	0,6905*	NA	NA	1,60	1,21
226744	Cnst	0,64	0,98	1,05	1,13	0,83	0,82
74161	Ctcflos	0,61	NA	0,91	0,94	NA	NA
13088	Cyp2b10	0,65	1,04	1,42	0,8061*	1,27	1,25
13089	Cyp2b13	0,50	0,4516*	0,93	1,17	0,7212*	0,349*
243881	Cyp2b23	0,32	NA	NA	NA	1,11	1,14
13094	Cyp2b9	0,37	0,3154*	1,06	1,20	0,79	0,7088*
56050	Cyp39a1	0,51	1,00	0,96	1,16	1,66	1,36
13117	Cyp4a10	0,63	0,5301*	NA	NA	0,682*	0,93
320187	E230001N04Rik	0,61	0,90	NA	NA	NA	NA
20918	Eif1	0,65	1,06	NA	NA	1,16	1,11
108112	Eif4ebp3	0,21	0,5482*	NA	NA	0,94	0,621*
170439	Elovl6	0,66	1,26	1,04	1,19	0,7564*	0,6802*
16592	Fabp5	0,63	0,7866*	0,8948*	1,00	4,25	1,90
73385	Fam177a	0,44	NA	NA	NA	0,98	1,01
208164	Fam180a	0,65	0,734*	NA	NA	1,13	1,20
14104	Fasn	0,46	1,42	0,98	1,34	1,22	1,18
14229	Fkbp5	0,67	0,3323*	0,88	0,7626*	1,01	1,16
14262	Fmo3	0,20	0,5247*	0,87	0,95	0,1682*	0,2886*
14381	G6pdx	0,61	0,94	0,99	1,03	1,27	1,34
654467	Gm10052	0,62	NA	NA	NA	1,55	1,17
667250	Gm12657	0,61	NA	NA	NA	NA	NA
433520	Gm14403	0,66	NA	NA	NA	0,86	0,93
100043257	Gm15453	0,21	NA	NA	NA	1,10	0,96
65956	Gm21541	0,65	NA	NA	NA	1,33	1,76
100041932	Gm3579	0,35	NA	NA	NA	NA	NA
333331	Gm5131	0,60	NA	NA	NA	0,72	0,85
629557	Gm6981	0,65	NA	NA	NA	1,13	1,04
14718	Got1	0,53	0,6449*	0,8357*	0,8839*	2,18	0,6836*
14860	Gsta4	0,65	1,46	1,27	1,18	0,7017*	0,85
14864	Gstm3	0,40	1,04	1,11	1,05	1,35	1,66
232493	Gys2	0,65	NA	1,08	1,08	1,18	1,06
73738	Haus7	0,67	0,94	1,09	1,07	1,32	1,25

217845	Ifi2712b	0,57	0,7565*	0,8721*	0,8796*	1,29	1,03
16006	Igfbp1	0,60	1,02	2,24	0,8266*	0,4983*	0,6048*
100044087	LOC100044087	0,57	NA	NA	NA	NA	NA
100045887	LOC100045887	0,57	NA	NA	NA	NA	NA
100046044	LOC100046044	0,53	NA	NA	NA	NA	NA
100046080	LOC100046080	0,59	NA	NA	NA	NA	NA
100047619	LOC100047619	0,65	NA	NA	NA	0,87	0,92
100047794	LOC100047794	0,66	NA	NA	NA	NA	NA
100048187	LOC100048187	0,60	NA	NA	NA	NA	NA
100048445	LOC100048445	0,66	NA	NA	NA	0,94	1,05
100048622	LOC100048622	0,61	NA	NA	NA	NA	NA
14245	Lpin1	0,54	0,99	1,06	0,5138*	1,14	1,10
70701	Nipal1	0,60	0,3599*	0,8128*	0,98	0,87	1,12
18113	Nnmt	0,41	0,7332*	0,6272*	0,7328*	0,5037*	0,69
83961	Nrg4	0,50	0,3985*	0,93	0,6556*	0,6885*	0,7205*
18194	Nsdhl	0,63	0,3863*	0,9121*	1,11	1,18	1,12
212503	Paox	0,62	1,05	0,97	1,06	1,10	1,03
110208	Pgd	0,66	1,07	0,8929*	1,15	1,20	1,14
628705	Phf11c	0,35	NA	NA	NA	0,89	0,98
68603	Pmvk	0,50	0,6176*	0,8738*	1,13	1,40	1,12
76487	Ppp1r3g	0,43	NA	1,03	1,07	0,5905*	0,87
320717	Pptc7	0,66	0,7002*	NA	NA	1,07	0,93
96875	Prg4	0,62	0,8444*	1,03	1,01	3,50	2,15
67103	Ptgr1	0,62	1,04	0,90	1,05	1,12	0,92
19734	Rgs16	0,63	0,3785*	1,62	1,54	0,93	1,24
68193	Rpl24	0,61	NA	NA	NA	1,34	1,31
20341	Selenbp1	0,65	0,8142*	0,92	0,98	1,08	1,07
72281	Sh2d4a	0,65	1,00	0,94	0,90	0,6742*	0,5954*
171405	Slc22a27	0,48	NA	1,02	1,05	0,6701*	0,4399*
236293	Slc22a29	0,60	0,99	NA	NA	1,07	0,99
20528	Slc2a4	0,65	1,12	0,88	0,97	0,6296*	0,79
20532	Slc3a1	0,63	0,7509*	0,8365*	1,10	2,03	0,97
72401	Slc43a1	0,58	NA	1,05	0,8808*	0,82	0,5474*
100216536	Snord1c	0,64	NA	NA	NA	NA	NA
27211	Snord35a	0,63	NA	NA	NA	0,5887*	0,72
100217454	Snord37	0,65	NA	NA	NA	NA	NA
20860	Sult1e1	0,59	1,07	0,91	0,8534*	0,6242*	0,6738*
629203	Sult2a3	0,50	NA	NA	NA	0,2972*	0,4026*
54610	Tbc1d8	0,65	0,86	1,01	0,8357*	1,02	1,03

Downregulated genes

Entrez ID	gene symbol	FC CR	FC R	FC P	FC Qd	FC Qi	FC Gi
74988	4930480G23Rik	1,81	NA	1,09	1,1384*	NA	NA
78934	4930581F22Rik	1,53	NA	0,99	0,92	NA	NA
70524	5730414N17Rik	1,73	NA	1,07	1,2184*	NA	NA
619326	9130409I23Rik	1,62	NA	1,2095*	0,97	0,97	1,06

230161	Acnat1	2,32	NA	NA	NA	0,72	0,88
26876	Adh4	1,63	1,21	1,1113*	1,16	2,9548*	2,0389*
11656	Alas2	1,63	2,2155*	1,1262*	1,02	1,02	1,5495*
71724	Aox3	1,75	1,4157*	1,4434*	1,04	1,59	1,50
71898	Apol9b	3,36	0,86	NA	NA	0,75	1,12
28194	Apon	1,55	1,06	1,08	1,02	1,20	1,5479*
74008	Arsg	1,77	1,09	1,135*	1,0948*	1,6881*	1,35
12116	Bhmt	1,57	1,5703*	1,04	0,95	0,90	1,07
320926	C730029A08Rik	2,04	NA	1,00	1,4113*	NA	NA
100038579	C730037M02Rik	1,58	NA	NA	NA	NA	NA
230558	C8a	1,76	1,18	1,1542*	0,91	1,9244*	1,52
110382	C8b	1,55	0,97	1,1587*	0,96	1,7269*	1,26
12279	C9	1,85	1,05	1,12	1,01	2,1596*	2,7851*
12350	Car3	1,71	1,654*	1,0056*	1,2897*	0,95	0,97
110794	Cebpe	2,04	NA	NA	NA	0,66	0,82
13897	Ces1e	1,57	1,4903*	1,2295*	1,00	0,75	0,91
382053	Ces3a	1,66	1,1807*	NA	NA	1,6871*	1,5197*
11537	Cfd	1,57	2,0347*	0,92	0,90	1,26	1,4692*
110902	Chrna2	1,83	1,13	1,1781*	1,0565*	0,98	1,17
93673	Cml2	1,82	0,85	1,2088*	0,94	1,15	1,13
246277	Csad	1,79	1,5578*	1,3108*	0,89	2,0712*	1,35
114564	Csprs	1,93	0,65	NA	NA	1,02	1,08
13009	Csrp3	1,89	0,46	1,00	1,03	2,0498*	1,6468*
627860	Cyp2d37-ps	2,17	NA	NA	NA	NA	NA
71519	Cyp2u1	1,54	NA	1,06	1,11	0,99	1,16
277753	Cyp4a12a	3,26	2,4161*	1,10	0,95	1,7058*	2,4006*
13118	Cyp4a12b	2,28	2,7108*	NA	NA	2,1124*	2,827*
13123	Cyp7b1	1,72	1,4917*	1,05	0,99	2,7255*	1,34
13124	Cyp8b1	1,62	0,77	0,93	0,95	0,74	0,89
320751	D830014E11Rik	1,92	1,14	NA	NA	1,40	1,08
13195	Ddc	1,65	2,2572*	0,89	0,98	1,55	1,41
13370	Dio1	2,14	0,87	0,99	0,97	2,7381*	2,2137*
13423	Dnase2a	1,81	1,9103*	1,0827*	0,75	1,22	1,14
12686	Elovl3	2,03	8,3276*	1,0935*	0,86	2,3594*	3,686*
245050	Fam198a	1,61	1,2857*	NA	NA	1,13	1,36
234199	Fgl1	1,51	0,59	0,66	0,82	1,24	1,21
68680	Fitm1	1,90	1,6911*	1,0739*	1,05	1,15	1,08
15377	Foxa3	1,67	0,65	0,95	0,77	1,21	1,4945*
14373	G0s2	1,63	2,3226*	1,1144*	1,4318*	4,0458*	1,7323*
100041085	G630090E17Rik	1,91	NA	NA	NA	NA	NA
626578	Gbp10	2,10	NA	NA	NA	NA	NA
100702	Gbp6	1,82	1,02	1,295*	0,98	1,09	0,97
23886	Gdf15	1,54	1,8197*	2,1827*	1,3954*	2,7155*	0,43
14619	Gjb2	1,60	0,86	0,98	0,99	1,42	1,41
216871	Gltpd2	2,21	1,11	NA	NA	1,23	1,06
100038514	Gm11837	2,40	NA	NA	NA	0,86	0,80
631323	Gm12250	1,75	NA	NA	NA	0,96	0,86
100040465	Gm2788	2,40	NA	0,91	1,2223*	NA	NA
215895	Gm4794	2,14	NA	NA	NA	0,86	0,65
240327	Gm4951	1,63	NA	NA	NA	1,23	1,39

241041	Gm4956	2,59	NA	NA	NA	0,97	1,13
626534	Gm6682	1,66	NA	NA	NA	1,10	0,91
668108	Gm8979	3,14	NA	NA	NA	NA	NA
668139	Gm8995	2,15	0,99	NA	NA	1,17	1,24
14675	Gna14	1,61	1,15	1,1426*	1,1567*	0,74	0,84
72748	Hdhd3	1,71	1,6199*	1,1382*	1,04	1,40	1,17
319165	Hist1h2ad	1,89	NA	NA	NA	NA	NA
319166	Hist1h2ae	1,54	1,23	NA	NA	1,38	1,22
319173	Hist1h2af	1,69	0,94	NA	NA	0,96	0,86
319168	Hist1h2ah	1,81	0,94	NA	NA	1,12	0,93
319169	Hist1h2ak	1,58	NA	NA	NA	0,82	0,75
319170	Hist1h2an	1,73	0,90	NA	NA	0,85	0,77
319171	Hist1h2ap	1,55	NA	NA	NA	NA	NA
15486	Hsd17b2	1,50	1,10	1,1485*	0,99	3,0345*	1,41
15496	Hsd3b5	3,81	5,0466*	1,08	1,14	3,8766*	3,4387*
15505	Hsph1	1,55	2,1185*	1,143*	1,00	0,96	1,531*
15957	Ifit1	2,14	1,01	1,2065*	0,98	2,9278*	3,0535*
15959	Ifit3	1,69	0,87	1,10	1,03	0,97	1,51
667370	Ifit3b	2,08	0,68	NA	NA	0,95	1,16
16145	Igtp	1,69	0,85	1,00	0,95	1,7593*	1,5083*
60440	Igtp1	1,54	0,96	1,1325*	1,01	1,25	1,06
16325	Inhbc	1,96	1,8439*	1,1772*	1,16	1,58	1,44
16326	Inhbe	2,05	1,4144*	1,0898*	1,1534*	1,19	1,12
54396	Irgm2	1,68	0,88	1,00	0,88	2,408*	1,4883*
100038882	Isg15	1,94	NA	NA	NA	2,4079*	3,2528*
64697	Keg1	1,75	1,16	1,03	1,12	3,0228*	2,0137*
100040592	LOC100040592	2,52	NA	NA	NA	NA	NA
100044576	LOC100044576	1,55	NA	NA	NA	1,18	1,07
100047173	LOC100047173	2,06	NA	NA	NA	0,52	0,58
100047200	LOC100047200	1,62	NA	NA	NA	NA	NA
100047427	LOC100047427	2,14	NA	NA	NA	NA	NA
100047651	LOC100047651	1,93	NA	NA	NA	NA	NA
100047674	LOC100047674	1,90	NA	NA	NA	NA	NA
100047707	LOC100047707	1,58	NA	NA	NA	NA	NA
641240	LOC641240	1,90	0,41	NA	NA	NA	NA
17194	Mbl1	1,81	1,20	1,00	1,03	1,9748*	2,049*
59012	Moxd1	1,62	0,91	1,2851*	0,97	0,69	0,82
17837	Mug2	1,67	1,02	NA	NA	1,16	0,88
100039008	Mup10	1,51	NA	1,0621*	1,147*	NA	NA
17841	Mup2	2,50	2,1592*	NA	NA	1,46	1,03
381530	Mup20	4,57	NA	NA	NA	4,5176*	3,4253*
381531	Mup21	3,32	NA	NA	NA	2,4537*	2,0524*
17842	Mup3	1,59	1,314*	0,99	0,85	1,11	1,02
17844	Mup5	1,62	0,97	0,82	0,96	1,38	1,43
620807	Mup6	2,78	NA	NA	NA	2,7742*	1,6157*
68396	Nat8	1,67	1,446*	0,99	0,93	1,65	2,1476*
50490	Nox4	1,61	1,0491*	1,3627*	0,99	1,27	1,34
231655	Oasl1	1,52	1,01	0,87	1,04	1,16	1,5838*
227627	Obp2a	1,96	1,3868*	1,6838*	1,1688*	1,00	1,10
259026	Olfir378	1,59	1,07	NA	NA	1,10	1,34

258590	Olf702	1,57	1,04	NA	NA	0,70	0,85
225631	Onecut2	1,59	1,3412*	1,07	1,11	0,96	0,89
75552	Paqr9	2,24	1,21	0,99	1,2768*	0,88	1,03
18559	Pctp	1,55	0,72	0,93	0,92	0,97	1,05
71830	Pdilt	1,62	2,5484*	1,3829*	1,05	1,15	1,05
75985	Rab30	1,59	1,04	1,177*	1,2221*	1,34	0,89
19369	Raet1d	3,43	NA	NA	NA	NA	NA
109222	Rarres1	1,86	0,88	1,03	1,04	2,2351*	1,6241*
58185	Rsad2	1,56	1,0615*	1,144*	0,97	0,87	0,96
20208	Saa1	2,43	0,45	0,55	0,53	0,95	0,99
20209	Saa2	1,79	0,44	0,28	0,44	0,99	1,07
20211	Saa4	1,74	0,91	1,5963*	0,87	1,7338*	1,30
74032	Sdr42e1	1,57	0,91	1,1449*	0,99	1,6722*	1,19
70061	Sdr9c7	1,80	1,5587*	1,3952*	1,05	1,23	1,13
20342	Selenbp2	2,16	NA	NA	NA	1,08	1,05
68054	Serpina12	2,14	1,2818*	1,1342*	1,04	0,87	0,91
20704	Serpina1e	2,49	0,95	NA	NA	0,82	1,02
238393	Serpina3f	2,69	0,69	NA	NA	0,99	1,01
321018	Serpina4-ps1	3,53	7,8202*	1,3025*	0,70	NA	NA
241877	Slc10a5	1,94	NA	NA	NA	0,89	0,75
319848	Slc17a4	2,49	1,6482*	NA	NA	1,15	1,27
108114	Slc22a7	1,78	1,3457*	1,1246*	1,05	1,7508*	2,0526*
226781	Slc30a10	1,61	NA	1,1206*	1,2085*	1,54	1,31
28248	Slco1a1	2,30	1,13	1,1611*	1,04	2,1771*	1,49
68469	Sox6os	1,78	1,4263*	0,94	1,01	1,12	1,09
78925	Srd5a1	1,66	2,855*	1,1092*	1,1425*	2,1705*	1,20
76971	Sult2a8	1,99	1,34*	1,08	1,01	1,12	1,04
96935	Susd4	1,59	0,93	0,95	1,02	0,55	0,68
21786	Tff3	1,55	0,13	0,87	0,90	0,49	0,28
66039	Tmem254a	2,13	1,04	NA	NA	2,7768*	2,2451*
21807	Tsc22d1	1,52	1,4446*	1,2676*	1,2241*	2,0054*	1,5902*
50500	Ttpa	1,53	0,87	1,03	0,95	4,5041*	2,2968*
71773	Ugt2b1	1,66	1,6716*	1,05	1,00	1,44	1,32
243085	Ugt2b35	1,62	1,2066*	1,1428*	1,02	1,9637*	1,7566*
105887	Ugt3a1	2,13	NA	1,1838*	0,98	2,011*	1,5946*
223337	Ugt3a2	1,53	0,95	1,10	0,97	1,39	1,25
24110	Usp18	1,60	0,72	1,126*	0,92	2,1211*	2,3037*
378472	Vaultrc5	3,99	NA	NA	NA	0,33	0,54
433070	Vmn2r96	1,55	NA	NA	NA	0,93	0,97
327956	Vmo1	1,84	NA	NA	NA	1,29	1,24
22361	Vnn1	2,13	1,02	0,93	1,0863*	0,96	0,88
67701	Wfdc2	1,62	2,2296*	0,95	1,07	0,86	1,36
381246	Xkr9	1,88	NA	NA	NA	1,06	1,01
668923	Zfp442	1,80	NA	NA	NA	1,13	1,05

Q: Overrepresented pathways identified by the regulated CR genes with fold change >1.5

upregulated pathways	downregulated pathways
Phase 1 - Functionalization of compounds - Reactome	Systemic lupus erythematosus - Mus musculus (mouse) - KEGG
Biological oxidations - Reactome	Meiotic Recombination - Reactome
Metabolism - Reactome	nicotine degradation III - MouseCyc
Xenobiotics - Reactome	nicotine degradation II - MouseCyc
Drug metabolism - cytochrome P450 - Mus musculus (mouse) - KEGG	Steroid hormone biosynthesis - Mus musculus (mouse) - KEGG
Metabolism of lipids and lipoproteins - Reactome	Terminal pathway of complement - Reactome
Cytochrome P450 - arranged by substrate type - Reactome	Complement and coagulation cascades - Mus musculus (mouse) - KEGG
Fatty acid biosynthesis - Mus musculus (mouse) - KEGG	Retinol metabolism - Mus musculus (mouse) - KEGG
Triglyceride Biosynthesis - Reactome	Alcoholism - Mus musculus (mouse) - KEGG
Chemical carcinogenesis - Mus musculus (mouse) - KEGG	Phase 1 - Functionalization of compounds - Reactome
Retinol metabolism - Mus musculus - KEGG	Biological oxidations - Reactome
Fatty acid, triacylglycerol, and ketone body metabolism - Reactome	Complement cascade - Reactome
Metabolism of xenobiotics by cytochrome P450 - Mus musculus (mouse) - KEGG	Cytochrome P450 - arranged by substrate type - Reactome
Arachidonic acid metabolism - Mus musculus (mouse) - KEGG	Complement Activation, Classical Pathway - Wikipathways
Fatty Acyl-CoA Biosynthesis - Reactome	Regulation of Complement cascade - Reactome
Glutathione metabolism - Mus musculus (mouse) - KEGG	Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE) - Reactome
biotin-carboxyl carrier protein assembly - MouseCyc	Scavenging by Class B Receptors - Reactome
Fatty Acid Biosynthesis - Wikipathways	catecholamine biosynthesis - MouseCyc
Phase II conjugation - Reactome	Metabolism - Reactome
pentose phosphate pathway - MouseCyc	Metabolism of lipids and lipoproteins - Reactome
Metapathway biotransformation - Wikipathways	Glycoprotein hormones - Reactome
Insulin signaling pathway - Mus musculus - KEGG	Prion diseases - Mus musculus (mouse) - KEGG
Pentose Phosphate Pathway - Wikipathways	Bile acid and bile salt metabolism - Reactome
Pentose phosphate pathway (hexose monophosphate shunt) - Reactome	Porphyrin and chlorophyll metabolism - Mus musculus (mouse) - KEGG
nicotine degradation II - MouseCyc	Cytochrome P450 - Wikipathways
Biotin transport and metabolism - Reactome	Peptide hormone biosynthesis - Reactome
pentose phosphate pathway (oxidative branch) - MouseCyc	Drug metabolism - cytochrome P450 - Mus musculus (mouse) - KEGG
Import of palmitoyl-CoA into the mitochondrial matrix - Reactome	Tyrosine metabolism - Mus musculus (mouse) - KEGG
Metabolism of water-soluble vitamins and cofactors - Reactome	Formyl peptide receptors bind formyl peptides and many other ligands - Reactome
Defective TCN2 causes hereditary megaloblastic anemia - Reactome	Fatty acid degradation - Mus musculus (mouse) - KEGG
Cytosolic sulfonation of small molecules - Reactome	Steroid Biosynthesis - Wikipathways
Amino acid synthesis and interconversion (transamination) - Reactome	Advanced glycosylation endproduct receptor signaling - Reactome
Metabolism of amino acids and derivatives - Reactome	DEX/H-box helicases activate type I IFN and inflammatory cytokines production - Reactome
Metabolism of carbohydrates - Reactome	Androgen biosynthesis - Reactome
Metabolism of polyamines - Reactome	Endogenous sterols - Reactome
Defective LMBRD1 causes methylmalonic aciduria and homocystinuria type cblF - Reactome	Synthesis of bile acids and bile salts via 27-hydroxycholesterol - Reactome
Cholesterol Biosynthesis - Wikipathways	Amine-derived hormones - Reactome

Defective AMN causes hereditary megaloblastic anemia 1 - Reactome	Drug metabolism - other enzymes - Mus musculus (mouse) - KEGG
Defective CUBN causes hereditary megaloblastic anemia 1 - Reactome	Primary bile acid biosynthesis - Mus musculus (mouse) - KEGG
Metabolism of vitamins and cofactors - Reactome	Fatty acids - Reactome
Defective GIF causes intrinsic factor deficiency - Reactome	Complement and Coagulation Cascades - Wikipathways
Defects in cobalamin (B12) metabolism - Reactome	Interferon Signaling - Reactome
Defective MMADHC causes methylmalonic aciduria and homocystinuria type cblD - Reactome	PPAR signaling pathway - Mus musculus (mouse) - KEGG
Defective MTRR causes methylmalonic aciduria and homocystinuria type cblE - Reactome	Metabolism of steroid hormones and vitamin D - Reactome
Defective MTR causes methylmalonic aciduria and homocystinuria type cblG - Reactome	Ascorbate and aldarate metabolism - Mus musculus (mouse) - KEGG
Defective MMAB causes methylmalonic aciduria type cblB - Reactome	Metabolism of xenobiotics by cytochrome P450 - Mus musculus (mouse) - KEGG
Defective MMAA causes methylmalonic aciduria type cblA - Reactome	Arachidonic acid metabolism - Mus musculus (mouse) - KEGG
Defective MUT causes methylmalonic aciduria mut type - Reactome	Binding and Uptake of Ligands by Scavenger Receptors - Reactome
Defective CD320 causes methylmalonic aciduria - Reactome	ISG15 antiviral mechanism - Reactome
Defective MMACHC causes methylmalonic aciduria and homocystinuria type cblC - Reactome	Antiviral mechanism by IFN-stimulated genes - Reactome
Defective HLCS causes multiple carboxylase deficiency - Reactome	Metapathway biotransformation - Wikipathways
Defective BTD causes biotinidase deficiency - Reactome	TAK1 activates NFkB by phosphorylation and activation of IKKs complex - Reactome
Defects in biotin (Btn) metabolism - Reactome	Synthesis of bile acids and bile salts - Reactome
Defects in vitamin and cofactor metabolism - Reactome	Metabolism of amino acids and derivatives - Reactome
Cholesterol biosynthesis - Reactome	Amoebiasis - Mus musculus (mouse) - KEGG
superpathway of cholesterol biosynthesis - MouseCyc	PPAR signaling pathway - Wikipathways
glutathione-mediated detoxification - MouseCyc	RIP-mediated NFkB activation via ZBP1 - Reactome
Pentose phosphate pathway - Mus musculus (mouse) - KEGG	Steroid hormones - Reactome
Propanoate metabolism - Mus musculus (mouse) - KEGG	Pentose and glucuronate interconversions - Mus musculus (mouse) - KEGG
Amino acid transport across the plasma membrane - Reactome	ZBP1(DAI) mediated induction of type I IFNs - Reactome
Alanine, aspartate and glutamate metabolism - Mus musculus (mouse) - KEGG	Chemical carcinogenesis - Mus musculus (mouse) - KEGG
bupropion degradation - MouseCyc	TRAF6 mediated NF-kB activation - Reactome
Pyruvate metabolism - Mus musculus (mouse)	Arachidonic acid metabolism - Reactome
nicotine degradation III - MouseCyc	Sulfur amino acid metabolism - Reactome
Glycolysis and Gluconeogenesis - Wikipathways	Peptide hormone metabolism - Reactome
Translation Factors - Wikipathways	bupropion degradation - MouseCyc
Amino acid and oligopeptide SLC transporters - Reactome	Glycine, serine and threonine metabolism - Mus musculus (mouse) - KEGG
Glucose metabolism - Reactome	
Adipocytokine signaling pathway - Mus musculus (mouse) - KEGG	
Arachidonic acid metabolism - Reactome	

R: Overlap between the upregulated CR genes (q-value < 0.05) based on the entrez IDs which are investigated by all dietary interventions (15552 IDs)
 (black squares indicate that the gene is regulated by the phytonutrient as well)

	R	P	Q	RP	RQ	PQ	RPQ		R	P	Q	RP	RQ	PQ	RPQ
58520	0610007P14Rik	■		■	■	■	■	26408	Map3k5		■	■	■		■
66117	1110001J03Rik							53608	Map3k6	■		■	■	■	■
68480	1110007C09Rik							29857	Mapk12						
68618	1110012L19Rik	■		■	■	■	■	69546	Mapk1ip1						
68531	1110020A21Rik			■	■	■	■	212307	Mapre2	■		■	■	■	■
73747	1110034G24Rik	■		■	■	■	■	223989	Marf1						
68861	1190002N15Rik							546071	Mast3	■	■		■		
67885	1500011K16Rik		■	■	■	■	■	108645	Mat2b						
73287	1700040L02Rik							110962	Mbd6						
69066	1810010H24Rik							17195	Mbl2	■		■	■	■	■
66293	1810032O08Rik							84004	Mcam	■		■	■	■	■
69809	1810046K07Rik	■		■	■	■	■	72039	Mccc1						
72056	1810055G02Rik	■	■	■	■	■	■	17210	Mcl1						
72282	1810062G17Rik			■	■	■	■	94178	Mcoln1						
66439	2010012O05Rik							17448	Mdh2						
70257	2010107E04Rik							28077	Med10						
381792	2310040G24Rik							59024	Med12						
69657	2310047D07Rik							75613	Med25						
69662	2310061I04Rik							69790	Med30						
73667	2410004P03Rik		■	■	■	■	■	67381	Med4						
77034	2510039Q18Rik							17289	Mertk	■			■		
67513	2610002J02Rik	■		■	■	■	■	70152	Mettl7a1						
77014	2700079J08Rik							73822	Mfsd12						
73205	3110043O21Rik		■	■	■	■	■	76574	Mfsd2a						
109292	4631423B10Rik							232714	Mgam			■	■	■	■
67392	4833420G17Rik							17313	Mgp		■	■	■	■	■
74430	4930452B06Rik							66447	Mgst3	■	■	■	■	■	■
75255	4930562F07Rik							27008	Micall1						
78817	4930588G05Rik							68041	Mid1ip1						
319582	6430573F11Rik							28010	Miip			■	■	■	■
213393	8430408G22Rik							17347	Mknk2	■	■		■		
74525	8430419L09Rik	■		■	■	■	■	70291	Mkrn2os						
319977	A530079E22Rik							21428	Mlx						
433752	AA415398							208104	Mlxip			■	■	■	■
78894	Aacs		■		■	■	■	109129	Mmadhc	■	■	■	■	■	■
67758	Aadac							75104	Mmd2	■	■	■	■	■	■
239435	Aard							17393	Mmp7						
30956	Aass		■	■	■	■	■	72199	Mms19						
27410	Abca3							93734	Mpv17l						
217258	Abca8a							234384	Mpv17l2	■		■	■	■	■
27413	Abcb11							15064	Mr1						
18671	Abcb1a							17533	Mrc1	■			■		
239273	Abcc4	■						18100	Mrpl40						
27421	Abcc6							52443	Mrpl48						
11307	Abcg1	■		■	■	■	■	66230	Mrps28						
27409	Abcg5							232536	Mrps35						
67470	Abcg8	■		■	■	■	■	66128	Mrps36				■		
76491	Abhd14b							17698	Msn	■			■		

99382	Abtb2				15235	Mst1	
107476	Acaca				17748	Mt1	
100705	Acacb	■	■	■	56428	Mtch2	
11363	Acadl				270685	Mthfd1l	■
140500	Acap3				194126	Mtmr11	■
104112	Acly				97287	Mtmr14	
66834	Acot13				54384	Mtmr7	
70025	Acot7				211401	Mtss1	
11430	Acox1	■	■	■	17855	Mvk	■
66659	Acp6				50918	Myadm	■
56318	Acpp	■	■	■	16918	Mycl	■
74205	Acs13				71960	Myh14	
50790	Acs14				98932	Myl9	
60525	Acss2	■	■	■	17909	Myo10	
67019	Actr6				17922	Myo7b	
11481	Acvr2b	■	■	■	17929	Myom1	
11501	Adam8				100637	N4bp2l1	■
108153	Adamts7				56292	Naa10	■
11515	Adcy9				67877	Naa20	
11539	Adora1	■	■	■	78304	Naa38	
66358	Adprm	■	■	■	17937	Nab2	■
11555	Adrb2	■	■	■	78914	Nadsyn1	
11556	Adrb3				27419	Naglu	
11565	Adssl1				17948	Naip2	
280662	Afm				17965	Nbl1	
55979	Agpat1	■	■	■	17966	Nbr1	
102247	Agpat6				78658	Ncapd3	
231510	Agpat9				320024	Nceh1	
11611	Agxt				56406	Ncoa6	
244886	Al118078	■	■	■	83431	Ndel1	
26926	Aifm1				29812	Ndr3	
11630	Aim1	■	■	■	17423	Ndst2	
11637	Ak2				68202	Ndufa5	
11639	Ak4				67130	Ndufa6	
83397	Akap12		■	■	68375	Ndufa8	
56399	Akap8				68493	Ndufaf4	
54194	Akap8l				69487	Ndufaf5	
11677	Akr1b3	■	■	■	76947	Ndufaf6	
11997	Akr1b7	■	■	■	66377	Ndufc1	
105349	Akr1c18				227197	Ndufs1	
432720	Akr1c19				226646	Ndufs2	
11657	Alb	■	■	■	17995	Ndufv1	
72535	Aldh1b1	■	■	■	23954	Nek3	
107747	Aldh1l1				27632	Nelfe	
212647	Aldh4a1				56349	Net1	
11674	Aldoa				18035	Nfkb1a	
11676	Aldoc	■	■	■	74164	Nfx1	
233065	Alkbh6				53972	Ngef	■
11687	Alox15	■	■	■	66866	Nhlrc2	■
105827	Amigo2	■	■	■	233280	Nipa1	■
56332	Amotl2				70701	Nipal1	■
57875	Angptl4	■	■	■	71966	Nkiras2	■

245886	Ankrd27					434341	Nlrc5		
224650	Anks1					18102	Nme1		
11747	Anxa5	■		■		56520	Nme4	■	■
11766	Ap1g2		■	■	■	66454	Nmnat1		
56369	Apip					225994	Nmrk1	■	■
55938	Apom	■		■	■	18113	Nnmt	■	■
68316	Apoo					18145	Npc1		
11821	Aprt	■		■	■	67963	Npc2	■	■
66333	Aqp11					18104	Nqo1		
11844	Arf5					18105	Nqo2		
11846	Arg1					23957	Nr0b2		
73910	Arhgap18	■		■	■	353187	Nr1d2		
71435	Arhgap21	■		■	■	18171	Nr1i2		
192662	Arhgdia					15370	Nr4a1		
230972	Arhgef16					223649	Nrbp2		
622434	Arhgef26		■	■	■	83961	Nrg4	■	■
54324	Arhgef5					68404	Nrn1		
93760	Arid1a					18194	Nsdhl	■	■
71371	Arid5b		■	■	■	68501	Nsmce2		
218639	Arl15					66617	Ntmt1		
56350	Arl3					75686	Nudt16		
80981	Arl4d					110959	Nudt19		
56297	Arl6					66401	Nudt2	■	■
67211	Armc10	■		■		68323	Nudt22		
215705	Arrdc1					71207	Nudt4		
70807	Arrdc2					56312	Nupr1		
66412	Arrdc4	■		■	■	53319	Nxf1		
57344	As3mt					18242	Oat		
11886	Asah1	■		■	■	18260	Ocln		
66929	Asf1b					18293	Ogdh		
109900	Asl					108155	Ogt		
27053	Asns		■	■	■	244198	Olfml1		
66514	Asrgl1					18405	Orm1	■	■
11898	Ass1		■	■	■	18406	Orm2	■	■
108888	Atad3a					18407	Orm3	■	■
1E+08	Atg14					12659	Ovgp1		
73683	Atg16l2					18441	P2ry1		
245860	Atg9a		■	■	■	140795	P2ry14	■	■
13498	Atn1		■	■	■	18442	P2ry2	■	■
231287	Atp10d	■	■	■	■	18476	Pafah1b3	■	■
170759	Atp13a1					100163	Pafah2		
74772	Atp13a2					18478	Pah		
11931	Atp1b1	■		■	■	67054	Paics		
11950	Atp5f1					103135	Pan2		
11951	Atp5g1					212503	Paox		
66349	Atp5sl					101744	Pap1		
70495	Atp6ap2	■		■	■	23972	Papss2	■	■
11972	Atp6v0d1					11546	Parp2		
76252	Atp6v0e2					110821	Pcca		
66335	Atp6v1c1					69837	Pcgf1	■	■
73834	Atp6v1d					76073	Pcgf5		
100317	AU040320					234069	Pcid2	■	■

69534	Avpi1		18534	Pck1	
106064	AW549877		245867	Pcmttd2	
503692	Aym1		104401	Pcnx13	
232987	B9d2		18542	Pcolce	
213539	Bag2		18551	Pcsk4	
66898	Baiap2l1		100102	Pcsk9	
225884	BC021614		68671	Pcyt2	
234878	BC021891		110855	Pde6c	
236848	BC023829		18585	Pde9a	
212547	BC027231		18597	Pdha1	
193286	BC049762		68263	Pdhb	
216454	BC089597		228026	Pdk1	
12036	Bcat2		18604	Pdk2	
12040	Bckdhd		14726	Pdpm	
63857	Bco1		67182	Pdzk1ip1	
69772	Bdh2		67245	Peli1	
70237	Bhlhb9		18618	Pemt	
20893	Bhlhe40		18626	Per1	
171543	Bmf		18627	Per2	
73230	Bmper		18628	Per3	
12176	Bnip3		18634	Pex7	
72399	Brap		18639	Pfkfb1	
12189	Brca1		18642	Pfkm	
55950	Bri3		18643	Pfn1	
69550	Bst2		110208	Pgd	
12226	Btg1		18655	Pgk1	
12227	Btg2		74016	Phf19	
227541	Camk1d		236539	Phgdh	
69697	Camsap3		75454	Phpt1	
232560	Caprin2		56176	Pigp	
12349	Car2		72084	Pigx	
239319	Card6		74769	Pik3cb	
12367	Casp3		223775	Pim3	
12368	Casp6		68943	Pink1	
12369	Casp7		19193	Pipox	
106757	Catsperd		71795	Pitpnc1	
12408	Cbr1		18770	Pklr	
12411	Cbs		85031	Pla1a	
52609	Cbx7		225845	Pla2g16	
231214	Cc2d2a		74055	Plce1	
229905	Ccbl2		18810	Plec	
71276	Ccdc57		217682	Plekhd1	
381175	Ccdc68		68354	Plekhd1os	
56221	Ccl24		101497	Plekhg2	
20301	Ccl27a		76509	Plet1	
20307	Ccl8		66905	Plin3	
12443	Ccnd1		102502	Pls1	
17151	Ccndbp1		22038	Plscr1	
12447	Ccne1		235611	Plxnb1	
12452	Ccng2		67784	Plxnd1	
12454	Ccnk		73078	Pmpcb	
56036	Ccnl2		68603	Pmvk	

101565	Ccp110		18950	Pnp	
12475	Cd14	■	66853	Pnpla2	■
93671	Cd163		116939	Pnpla3	■
69142	Cd209f		75772	Pnpla5	■
13136	Cd55	■	242608	Podn	
12516	Cd7		27205	Podxl	
12527	Cd9	■	69745	Pold4	■
673094	Cd99		18973	Pole	
218294	Cdc14b		50776	Polg2	
12531	Cdc25b		67710	Polr2g	
240505	Cdc42bpg		245841	Polr2h	■
104252	Cdc42ep2		74414	Polr3c	
58804	Cdc42ep5		107939	Pom121	■
109332	Cdcp1		18984	Por	■
66626	Cdip1		50706	Postn	
12534	Cdk1	■	74776	Ppa2	
18557	Cdk18		19012	Ppap2a	■
66971	Cdk5rap1		19017	Ppargc1a	
264064	Cdk8		170826	Ppargc1b	■
12577	Cdkn1c		231327	Ppat	
12580	Cdkn2c	■	19035	Ppib	
67177	Cdt1	■	19038	Ppic	
26365	Ceacam1		105675	Ppif	
12608	Cebpb	■	227399	Ppip5k2	■
13706	Cela2a	■	19041	Ppl	■
12614	Celsr1		26930	Ppnr	
12615	Cenpa	■	17872	Ppp1r15a	
83815	Cenpq		19057	Ppp3cc	■
99100	Cep152		54637	Praf2	
241447	Cers6	■	21672	Prdx2	■
72361	Ces2g		11757	Prdx3	■
26370	Cetn2		77619	Prelid2	
75472	Cfap126		96875	Prg4	■
14894	Cfap20		19089	Prkcsh	
12631	Cfl1	■	19125	Prodh	
69065	Chac1	■	19126	Prom1	
72170	Chchd4		19128	Pros1	■
66433	Chchd7		114863	Prosc	■
12648	Chd1		192159	Prpf8	
68058	Chd1l		19139	Prps1	
244059	Chd2		67763	Prpsap1	
320790	Chd7		75210	Prr3	
74277	Chic2		330657	Prss53	■
68038	Chid1	■	76560	Prss8	■
68953	Chmp2a		107272	Psat1	
11438	Chrna4	■	19171	Psmb10	■
234421	Cib3	■	26445	Psmb2	
71722	Cic		67151	Psmd9	
12696	Cirbp	■	19188	Psme2	
68379	Ciz1		100678	Psph	
12747	Clk1		19201	Pstpip2	
12750	Clk4		19215	Ptgds	

94040	Clmn		19216	Ptger1	
69634	Clybl		67103	Ptgr1	
76469	Cmya5	■	545622	Ptpn3	
71994	Cnn3	■	110095	Pygl	
69171	Cnppd1		110391	Qdpr	
226744	Cnst		60507	Qtrt1	
26920	Cntrl		19329	Rab17	■
67892	Coa6		19332	Rab20	■
319876	Cobll1		19335	Rab23	■
12825	Col3a1	■	19339	Rab3a	■
12827	Col4a2	■	69834	Rab43	
12833	Col6a1	■	19341	Rab4a	
12834	Col6a2		56382	Rab9	
17846	Commd1		70314	Rabep2	
69456	Commd10	■	19352	Rabggtb	
66199	Commd4		19355	Rad1	
59042	Cope		241694	Ralgapa2	
66423	Coprs	■	19730	Ralgds	
67876	Coq10b	■	54409	Ramp2	
217707	Coq6		74334	Ranbp10	
12850	Coq7		223332	Ranbp3l	
12865	Cox7a1		56705	Ranbp9	
70574	Cpm		57785	Rangrf	
234577	Cpne2		56508	Rapgef4	
54188	Cpsf4	■	217944	Rapgef5	■
12946	Cr1l	■	218772	Rarb	■
12909	Crcp	■	19414	Rasa3	■
12925	Crip1	■	320292	Rasgef1b	■
56693	Crtap	■	19395	Rasgrp2	■
12952	Cry1		192678	Rassf3	
12953	Cry2	■	54354	Rassf5	■
12962	Crybb3	■	73246	Rassf6	
68631	Cryl1		56275	Rbm14	
12971	Crym	■	229700	Rbm15	
104318	Csnk1d		381626	Rbm33	
70425	Csnk1g3		71684	Rbm43	
13007	Csrp1	■	19659	Rbp1	■
13008	Csrp2		71330	Rcbtb1	■
14219	Ctgf	■	17252	Rdh11	■
107869	Cth		105014	Rdh14	
13034	Ctse		19682	Rdh5	
13038	Ctsk		103142	Rdh9	■
13039	Ctsl		53614	Reck	
13041	Ctsw		72549	Reep4	
13048	Cux2	■	68703	Rere	
72017	Cyb5r1		232441	Rerg	
109754	Cyb5r3		19733	Rgn	
66445	Cyc1		19734	Rgs16	■
13074	Cyp17a1	■	19736	Rgs4	
77951	Cyp20a1		69159	Rheb1	
13088	Cyp2b10	■	69288	Rhobtb1	
13089	Cyp2b13	■	11854	Rhod	

13094	Cyp2b9			52428	Rhpn2		
13097	Cyp2c38			72388	Ripk4		
13098	Cyp2c39			68477	Rmnd5a		
226143	Cyp2c44			58809	Rnase4		
56448	Cyp2d22			67153	Rnaseh2b		
13108	Cyp2g1			223881	Rnd1		
74519	Cyp2j9			11858	Rnd2		
244209	Cyp2r1			74315	Rnf145		
56050	Cyp39a1			75234	Rnf19b		
13112	Cyp3a11			105239	Rnf44		
13113	Cyp3a13			252967	Ropn1l		
64385	Cyp4f14			19885	Rorc		
13121	Cyp51			68240	Rpa3		
225995	D030056L22Rik			71919	Rpap3		
210108	D130043K22Rik			19892	Rpe65		
52392	D1Ert622e			19895	Rpia		
65111	Dap3			67115	Rpl14		
69635	Dapk1			68028	Rpl22l1		
70248	Dazap1			20103	Rps5		
13171	Dbt			20130	Rras		
66686	Dcbld1			20133	Rrm1		
245038	Dclk3			20135	Rrm2		
13191	Dctn1			27981	Rsrp1		
66422	Dctpp1			20166	Rtkn		
13194	Ddb1			242819	Rundc3b		
107986	Ddb2			20196	S100a13		
72108	Ddhd2			20200	S100a6		
13200	Ddost			224903	Safb		
13202	Ddt			224902	Safb2		
13214	Defb1			58198	Sall1		
74754	Dhcr24			68653	Samm50		
13360	Dhcr7			269003	Sap130		
66375	Dhrs7			104175	Sbk1		
69192	Dhx16			107767	Scamp1		
71723	Dhx34			20778	Scarb1		
330938	Dixdc1			20249	Scd1		
235339	Dlat			20266	Scn1b		
53310	Dlg3			74617	Scpep1		
13388	Dll1			64136	Sdf2l1		
235380	Dmxi2			68002	Sdhaf4		
23950	Dnajb6			67680	Sdhd		
30045	Dnajc12			66925	Sdhd		
235567	Dnajc13			231691	Sds		
71972	Dnmbp			257635	Sdsl		
21673	Dntt			74136	Sec14l1		
319899	Dock6			20334	Sec23a		
208266	Dot1l			99683	Sec24b		
93838	Dqx1			69162	Sec31a		
13506	Dsc2			66212	Sec61b		
56405	Dusp14			20341	Selenbp1		
235661	Dync1li1			80795	Selk		
110350	Dync2h1			223776	Selo		

213575	Dync2li1		20351	Sema4a	
56455	Dynll1		26456	Sema4g	
103551	E130012A19Rik		93684	Sep15	
106389	Eaf2		20362	Sept8	
13595	Ebp		12401	Serpina6	■
52665	Echdc1		140742	Sesn1	■
52430	Echdc2		75747	Sesn3	
68545	Ecscr		208043	Setd1b	
192193	Edem1		224440	Setd4	■
13614	Edn1		20390	Sftpd	
13631	Eef2k		14057	Sfxn1	
81701	Egfl8	■	20393	Sgk1	■
77683	Ehmt1	■	16923	Sh2b3	
58521	Eid1		27387	Sh2d3c	
13685	Eif4ebp1		72281	Sh2d4a	
54326	Elov12		57028	Sh3bp1	
170439	Elov16		66938	Sh3d21	■
59308	Emcn	■	58234	Shank3	
72205	Eml2	■	20437	Siah1a	
13731	Emp2	■	20439	Siah2	
13803	Enc1		17691	Sik1	
13808	Eno3		57738	Slc15a2	
13809	Enpep		100561	Slc15a4	■
18605	Enpp1	■	72472	Slc16a10	■
12496	Entpd2		217316	Slc16a5	
13819	Epas1	■	76306	Slc18b1	
269587	Epb4.1		20509	Slc19a1	■
17075	Epcam	■	116914	Slc19a2	
1E+08	Epg5		20515	Slc20a1	■
13842	Epha8	■	70840	Slc22a16	■
13846	Ephb4	■	18400	Slc22a18	
223650	Eppk1	■	236149	Slc22a26	■
13867	Erbp3	■	20522	Slc23a1	
170942	Erdr1		54338	Slc23a2	■
74155	Errfi1	■	13358	Slc25a1	■
69524	Esam	■	67863	Slc25a11	
26379	Esrra		78830	Slc25a12	
214253	Etnk2	■	20523	Slc25a14	
71760	Etnppl		18408	Slc25a15	
14058	F10		68267	Slc25a22	■
14068	F7		214663	Slc25a29	
16592	Fabp5	■	69906	Slc25a32	■
76267	Fads1	■	104910	Slc25a47	
56473	Fads2		230125	Slc25a51	■
104943	Fam110c		26457	Slc27a1	
215512	Fam117a		63959	Slc29a1	
218236	Fam120a		20526	Slc2a2	■
84652	Fam126a		20528	Slc2a4	■
66270	Fam134b	■	56485	Slc2a5	
58909	Fam13a	■	56017	Slc2a8	■
230766	Fam167b	■	22782	Slc30a1	■
320159	Fam179a	■	108652	Slc35b3	

212483	Fam193b		70484	Slc35d2	
218850	Fam208a		14385	Slc37a4	
27999	Fam3c	■	67760	Slc38a2	
77938	Fam53b		76257	Slc38a3	■
56306	Fam60a		69354	Slc38a4	■
235461	Fam63b		72027	Slc39a4	■
72826	Fam76b	■	20532	Slc3a1	■
69955	Fars2		213603	Slc44a3	
14104	Fasn	■	71706	Slc46a3	■
320720	Fastkd1		330962	Slc51b	
69577	Fastkd3		330064	Slc5a6	■
217335	Fbf1	■	14411	Slc6a12	■
269514	Fbxl4		102857	Slc6a8	■
50755	Fbxo18		11988	Slc7a2	■
231670	Fbxo21	■	224022	Slc7a4	
76454	Fbxo31	■	170756	Slc8b1	■
70611	Fbxo33		28250	Slco1a4	
71538	Fbxo9		20568	Slpi	■
215384	Fcgbp		55994	Smad9	■
14130	Fcgr2b	■	69780	Smap2	
207278	Fchsd2		67155	Smarca2	
14137	Fdft1		226026	Smc5	
110196	Fdps	■	69029	Smdt1	
14149	Fdxr		64074	Smoc2	■
14151	Fech		29856	Smtn	
14159	Fes	■	20613	Snai1	
13998	Fgd6		20583	Snai2	■
14194	Fh1		319317	Snhg11	
14198	Fhit		20623	Snrk	
231997	Fkbp14	■	78372	Snrnp25	
14229	Fkbp5	■	20637	Snrnp70	
216805	Flcn	■	68981	Snrpa1	
14251	Flot1	■	20646	Snrpn	■
14257	Flt4		268534	Sntg2	
14260	Fmn1		55988	Snx12	
55990	Fmo2	■	244962	Snx14	■
14262	Fmo3	■	67804	Snx2	■
226564	Fmo4	■	223920	Soat2	
14263	Fmo5		216233	Socs2	■
15375	Foxa1	■	20657	Sod3	
56458	Foxo1		20410	Sorbs3	■
212398	Frat2	■	20671	Sox17	
232288	Frmd4b	■	20672	Sox18	■
14313	Fst	■	20692	Sparc	
14317	Ftcd	■	13602	Sparcl1	
69064	Fuom	■	219140	Spata13	■
18550	Furin	■	78779	Spata2l	■
14366	Fzd4		67629	Spc24	
14367	Fzd5		66442	Spc25	
14381	G6pdx		71026	Speer3	■
14388	Gab1		74288	Spem1	■
53897	Gal3st1	■	56381	Spn	

14430	Galt		27965	Spg21	
14433	Gapdh		20750	Spp1	
14447	Gapdhs	■	114715	Spred1	
14453	Gas2	■	20753	Sprr1a	
14466	Gba	■	20743	Sptbn2	
74185	Gbe1		104725	Sptssa	
227960	Gca		59010	Sqrdl	
14528	Gch1	■	225372	Sra1	
231103	Gckr		78586	Srbd1	
28030	Gfm1		94224	Srd5a2	
14584	Gfpt2	■	20787	Srebf1	
14585	Gfra1	■	20384	Srsf5	
71522	Ggt6	■	237860	Ssh2	
207182	Ggt7		16651	Sspn	
107526	Gimap4		20454	St3gal5	
14612	Gja4	■	54613	St3gal6	
56278	Gkap1	■	225742	St8sia5	
12091	Glb1		192187	Stab1	
93692	Glrx	■	20843	Stag2	
14661	Glud1		106766	Stap2	
269700	Gm15800		170459	Stard4	
57441	Gmn		170460	Stard5	
14685	Gnat1	■	99138	Stard7	
14686	Gnat2		236920	Stard8	
50798	Gne	■	72043	Sulf2	
14700	Gng10	■	20887	Sult1a1	
66066	Gng11		53315	Sult1d1	
26384	Gnpda1	■	20860	Sult1e1	
14718	Got1	■	22218	Sumo1	
14732	Gpam		223697	Sun2	
74182	Gpcpd1	■	217684	Susd6	
14751	Gpi1		232811	Suv420h2	
68453	Gpihbp1	■	64051	Sv2a	
68080	Gpn3		214804	Syde2	
78308	Gpr108		20979	Syt1	
11536	Gpr182		269589	Syt1l	
75512	Gpx6	■	57752	Tacc2	
67305	Gpx7	■	68776	Taf11	
14786	Grb7		21345	Tagln	
23893	Grem2	■	21351	Taldo1	
66168	Grina		27883	Tango2	
14824	Grn	■	21356	Tapbp	
231413	Grsf1		71807	Tars2	
14853	Gspt2		234724	Tat	
14858	Gsta2		66687	Tbc1d15	
14860	Gsta4		67249	Tbc1d19	
14862	Gstm1		224617	Tbc1d24	
14863	Gstm2		54610	Tbc1d8	
14864	Gstm3		237336	Tbpl1	
14866	Gstm5	■	232748	Tcaf2	
14867	Gstm6		66684	Tceal8	
68312	Gstm7		106795	Tcf19	

14873	Gsto1				21452	Tcn2			
14870	Gstp1				216198	Tcp11l2			
14872	Gstt2				66061	Tctex1d2			
103140	Gstt3				104884	Tdp1			
227835	Gtdc1				56196	Tdp2			
235459	Gtf2a2				21682	Tec			
56055	Gtpbp2				106529	Tecr			
14913	Guca1a				21685	Tef			
54195	Gucy1b3				71840	Tekt4			
110006	Gusb				211586	Tfdp2			
27357	Gyg				76355	Tgds			
71683	Gypc				21813	Tgfb2			
77605	H2afv				21815	Tgif1			
15007	H2-Q10				21816	Tgm1			
107766	Hao				21835	Thrsp			
84506	Hamp				21843	Tial1			
66438	Hamp2				30059	Timm10			
56185	Hao2				21854	Timm17a			
330790	Hapln4				30058	Timm8a1			
73738	Haus7				30056	Timm9			
56422	Hbs1l				21859	Timp3			
15163	Hcls1				21872	Tjp1			
76987	Hdhd2				21877	Tk1			
380629	Heca				225913	Tkfc			
64209	Herpud1				21881	Tkt			
80517	Herpud2				68385	Tlcd1			
15212	Hexb				21909	Tlx2			
15233	Hgd				229302	Tm4sf4			
58180	Hic2				107770	Tm6sf2			
15254	Hint1				74424	Tmc5			
15284	Hlx				209760	Tmc7			
15357	Hmgcr				56334	Tmed2			
50887	Hmgn5				71900	Tmem106b			
15368	Hmox1				216821	Tmem11			
140483	Hnmt				66271	Tmem126a			
15382	Hnrnpa1				56030	Tmem131			
53379	Hnrnpa2b1				66154	Tmem14c			
50926	Hnrnpdl				233806	Tmem159			
59013	Hnrnph1				66279	Tmem218			
170833	Hook2				71687	Tmem25			
15402	Hoxa5				69038	Tmem258			
53602	Hpcal1				66664	Tmem41a			
192232	Hps4				216395	Tmem5			
94175	Hrg				71817	Tmem50a			
27400	Hsd17b6				212090	Tmem60			
15490	Hsd17b7				96957	Tmem62			
26386	Hsf4				213068	Tmem71			
15512	Hspa2				66241	Tmem9			
15526	Hspa9				69071	Tmem97			
26559	Hunk				278279	Tmtc2			
67732	Iah1				66958	Tmx2			
15894	Icam1				18383	Tnfrsf11b			

15926	ldh1		21937	Tnfrsf1a	
269951	ldh2		228140	Tnks1bp1	
15929	ldh3g		21924	Tnnc1	
319554	ldi1		21961	Tns1	
209176	ldo2		209039	Tns2	
15937	ler3		81877	Tnxb	
52668	lfi27		22057	Tob1	
217845	lfi27l2b		71943	Tom1l1	
65972	lfi30		252838	Tox	
68713	lfitm1		233979	Tpcn2	
15965	lfna2		21987	Tpd52l1	
15979	lfngr1		326618	Tpm4	
319146	lfnz		72948	Tppp	
15982	lfrd1		67095	Trak1	
76411	lft43		59005	Trappc2l	
16002	lgf2		228775	Trib3	
16006	lgfbp1		94091	Trim11	
16011	lgfbp5		217333	Trim47	
70080	lgsf23		432613	Trim80	
140559	lgsf8		106628	Trip10	
16156	ll11		209456	Trp53bp2	
16168	ll15		100683	Trrap	
16169	ll15ra		22084	Tsc2	
16172	ll17ra		14605	Tsc22d3	
50905	ll17rb		72480	Tspyl4	
16173	ll18		77032	Tstd3	
16177	ll1r1		74569	Ttc17	
16181	ll1rn		67009	Ttc23	
77125	ll33		239570	Ttc38	
76527	ll34		230603	Ttc39a	
14204	ll4i1		22142	Tuba1a	
102462	lmp3		53857	Tuba8	
21743	lnmt		22154	Tubb5	
170835	lnpp5j		80286	Tusc3	
231070	linsig1		56551	Txn2	
64602	lreb2		70561	Txndc16	
16373	lrx3		72565	Uaca	
71780	lsyna1		98766	Ubac1	
209378	ltih5		22190	Ubc	
16438	ltpr1		22214	Ube2h	
56357	lvd		117146	Ube3b	
117198	lvns1abp		63958	Ube4b	
70337	lyd		224826	Ubr2	
71564	lzumo4		69116	Ubr4	
16480	Jup		56207	Uchl5	
18519	Kat2b		192169	Ufsp2	
140492	Kcnn2		22234	Ugcg	
239217	Kctd12		216558	Ugp2	
72050	Kdelc1		22241	Ulk1	
216850	Kdm6b		107449	Unc5b	
16542	Kdr		22262	Uox	
66991	Khdc3		22271	Upp1	

16548	Khk		76654	Upp2	■
219094	Khynyn		66152	Uqcr10	■
16588	Kin		66576	Uqcrh	■
74764	Klc4		22275	Urod	■
16596	Klf1	■	66477	Usmg5	■
50794	Klf13	■	53376	Usp2	■
66277	Klf15	■	235323	Usp28	■
16598	Klf2	■	78610	Uvrag	■
75785	Klhl24		234729	Vac14	■
18048	Klk1b4		22318	Vamp2	■
74253	Klrg2	■	22319	Vamp3	■
94179	Krt23	■	229658	Vangl1	■
210808	Lacc1	■	22323	Vasp	■
14768	Lancl1		22327	Vbp1	■
76130	Las1l		22329	Vcam1	■
76585	Lce1i	■	22334	Vdac2	■
66344	Lce3b	■	22339	Vegfa	■
94060	Lce3c		22340	Vegfb	■
16825	Ldb1	■	22352	Vim	■
16832	Ldhb		69568	Vkorc111	■
16835	Ldlr		22359	Vldlr	■
16840	Lect1		81013	Vmn1r65	■
16841	Lect2		22364	Vpreb3	■
13590	Lefty1	■	68505	Vps51	■
232798	Leng8	■	101568	Vrk3	■
16847	Lepr		71768	Vwce	■
16855	Lgals4	■	22371	Vwf	■
19141	Lgmn	■	22378	Wbp2	■
108927	Lhfp		74716	Wbp2nl	■
225341	Lims2	■	76773	Wdyhv1	■
381236	Lipo1	■	22390	Wee1	■
16897	Llg1		68221	Wfdc15a	■
72000	Lmntd2		192201	Wfdc15b	■
16911	Lmo4		78889	Wsb1	■
93677	Lmod2		22436	Xdh	■
74142	Lonp1		22590	Xpa	■
74365	Lonrf3	■	22596	Xrcc5	■
16939	Lor		68876	Xrcc6bp1	■
14792	Lpcat3		66090	Ypel3	■
14245	Lpin1	■	71970	Zbed5	■
64898	Lpin2	■	235320	Zbtb16	■
64899	Lpin3		100090	Zbtb48	■
239037	Lrit1		142682	Zcchc14	■
16971	Lrp1		67492	Zfand4	■
228357	Lrp4	■	80892	Zfhx4	■
72416	Lrpprc		22654	Zfp13	■
68732	Lrrc16a		27081	Zfp275	■
378937	Lrrc24	■	57247	Zfp276	■
67867	Lrrc28	■	22693	Zfp30	■
217366	Lrrc45	■	22695	Zfp36	■
16981	Lrrn3		68910	Zfp467	■
50783	Lsm4		68490	Zfp579	■

76522	Lsm8							269023	Zfp608				
16987	Lss							234725	Zfp612				
108075	Ltbp4							239546	Zfp647				
17095	Lyl1							319601	Zfp653				
56150	Mad2l1							319530	Zfp750				
67920	Mak16							387609	Zhx2				
17158	Man2a1							268417	Zkscan17				
242362	Manea							215693	Zmat1				
67443	Map1lc3b							114602	Zmynd10				
26399	Map2k6							22687	Zpr1				
26407	Map3k4												

S: Overlap between the downregulated CR genes (q-value < 0.05) based on the entrez IDs which are investigated by all dietary interventions (15552 IDs) (black squares indicate that the gene is regulated by the phytonutrient as well)

		R	P	Q	RP	RQ	PQ	RPQ		R	P	Q	RP	RQ	PQ	RPQ
66050	0610009B22Rik								16956	Lpl						
68347	0610011F06Rik								79235	Lrat						
66206	1110059E24Rik								233067	Lrfn3						
66202	1110059G10Rik								76905	Lrg1						
72016	1600002H07Rik								321000	Lrif1						
67912	1600012H06Rik								237253	Lrp11						
73467	1700066M21Rik								223665	Lrrc24						
69773	1810026J23Rik								237387	Lrrc3						
69861	2010003K11Rik								320184	Lrrc58						
72357	2210016L21Rik								98238	Lrrc59						
66374	2310011J03Rik								231549	Lrrc8d						
66952	2310030G06Rik								268490	Lsm12						
76455	2310067E19Rik								16988	Lst1						
66421	2410004B18Rik								17000	Ltbr						
66520	2610001J05Rik								353258	Ltv1						
67064	2610002M06Rik								110454	Ly6a						
112422	2610305D13Rik								17068	Ly6d						
330173	2610524H06Rik								17069	Ly6e						
67246	2810474O19Rik								17084	Ly86						
243219	2900026A02Rik								108755	Lyrm2						
68067	3010026O09Rik								380840	Lyrm4						
66598	3110001I22Rik								80289	Lysmd3						
73212	3110082I17Rik								17105	Lyz2						
218734	3830406C13Rik								93730	Lztf1						
70984	4931406C07Rik								23937	Mab21l2						
1E+08	9130023H24Rik								71890	Mad2l2						
75758	9130401M01Rik								17149	Magoh						
68115	9430016H08Rik								67075	Magt1						
69865	A1cf								105853	Mal2						
319277	A230046K03Rik								71738	Mamdc2						
320700	A930033H14Rik								17160	Man2b2						
23923	Aadat								74840	Manf						
66129	Aaed1								66734	Map1lc3a						
234734	Aars								270058	Map1s						

67618	Aasdhppt		26403	Map3k11	
56321	Aatf		245877	Map7d1	
11302	Aatk		332110	Mapk15	
268860	Abat		218975	Mapk1ip1l	
11303	Abca1		17165	Mapkapk5	
11305	Abca2		71779	March8	
18670	Abcb4		17167	Marco	
12780	Abcc2		232087	Mat2a	
76408	Abcc3		17184	Matr3	
11666	Abcd1		17192	Mbd3	
24015	Abce1		17194	Mbl1	
27406	Abcf3		193813	Mcfd2	
26357	Abcg2		66405	Mcts2	
57742	Abhd1		16543	Mdfic	
226016	Abhd17b		108098	Med21	
54608	Abhd2		230316	Megf9	
106861	Abhd3		104362	Meig1	
66082	Abhd6		75178	Meiob	
11308	Abi1		17299	Mettl1	
319713	Ablim3		72096	Mettl10	
113868	Acaa1a		74319	Mettl23	
235674	Acaa1b		75422	Mettl5	
102632	Acad11		69572	Mfsd3	
229211	Acad9		23945	Mgll	
11364	Acadm		17314	Mgmt	
110446	Acat1		338320	Mia2	
67131	Acbd4		338366	Mia3	
74159	Acbd5		218613	Mier3	
209186	Acnat2		69674	Mif4gd	
171210	Acot2		109154	Mlec	
171282	Acot4		58805	Mlxipl	
170789	Acot8		67468	Mmd	
93732	Acox2		17380	Mme	
11433	Acp5		236792	Mmgt1	
264895	Acsf2		17388	Mmp15	
14081	Acsl1		58223	Mmp19	
20216	Acsm3		19070	Mob4	
272428	Acsm5		17434	Mocs2	
11461	Actb		68393	Mogat1	
11465	Actg1		72825	Mon1a	
11472	Actn2		56397	Morf4l2	
71670	Acy3		68929	Mospd3	
11488	Adam11		59012	Moxd1	
11491	Adam17		55951	Mpc1	
58860	Adamdec1		67973	Mphosph10	
216991	Adap2		66308	Mplkip	
56417	Adar		56524	Mpp6	
268822	Adck5		246221	Mpst	
52614	Adgre4		17527	Mpv17	
54672	Adgrg3		14012	Mpzl2	
110789	Adgrv1		77037	Mrap	
26876	Adh4		107732	Mrp110	

11450	Adipoq		94066	Mrpl36	
68465	Adipor2		28028	Mrpl50	
100206	Adprh2		64655	Mrps22	
11548	Adra1b		27361	Msrb1	
56436	Adrm1		66902	Mtap	
11566	Adss		74238	Mterf2	
109254	Adtrp		76784	Mtif2	
68048	Aen		76366	Mtif3	
14797	Aes		17772	Mtm1	
71562	Afmid		170749	Mtmr4	
66549	Aggf1		210376	Mtmr9	
77559	Agl		17773	Mtnr1a	
319660	Agmo		108853	Mtrf1l	
67512	Agpat2		17836	Mug1	
28169	Agpat3		17842	Mup3	
74340	Ahcyl2		17843	Mup4	
11622	Ahr		17844	Mup5	
217737	Ahsa1		66175	Mustn1	
268390	Ahsa2		17858	Mx2	
230249	Al314180		28106	Mydgf	
233168	Al987944		17901	Myl1	
11629	Aif1		17906	Myl2	
72168	Aifm3		17919	Myo5b	
231872	Aimp2		381695	N4bp2l2	
100986	Akap9		68043	N6amt2	
68050	Akirin1		74838	Naa15	
105387	Akr1c14		66897	Naa16	
116852	Akr1c20		72117	Naa50	
208665	Akr1d1		74763	Naa60	
67605	Akt1s1		67991	Nacc2	
17025	Alad		68646	Nadk2	
11656	Alas2		234664	Nae1	
11658	Alcam		53605	Nap1l1	
11668	Aldh1a1		56441	Nat6	
214579	Aldh5a1		68396	Nat8	
56752	Aldh9a1		66176	Nat9	
207958	Alg11		269198	Nbeal1	
223774	Alg12		27354	Nbn	
67574	Alg13		52589	Ncald	
56737	Alg2		433702	Ncbp1	
231642	Alkbh2		68092	Ncbp2	
268420	Alkbh5		17972	Ncf4	
11647	Alpl		230822	Ncmap	
74018	Als2		228869	Ncoa5	
17117	Amacr		20185	Ncor1	
11702	Amd1		66647	Ndnl2	
71761	Amdhd1		69702	Ndufaf1	
11722	Amy1		69352	Necab1	
11727	Ang		83814	Nedd4l	
30924	Angptl3		23955	Nek4	
68420	Ankrd13a		59126	Nek6	
71452	Ankrd40		57314	Nelfcd	

68839	Ankrd46		66208	Nenf	
56503	Ankrd49		18021	Nfatc3	
99696	Ankrd50		18023	Nfe2l1	
72074	Anks4b		18024	Nfe2l2	
11737	Anp32a		18029	Nfic	
67628	Anp32b		18030	Nfil3	
66471	Anp32e		18032	Nfix	
16790	Anpep		105193	Nhlrc1	
11761	Aox1		66257	Nicn1	
71724	Aox3		67949	Nifk	
11772	Ap2a2		18081	Ninj1	
11777	Ap3s1		93790	Nipa2	
57267	Apba3		66536	Nipsnap3b	
11808	Apoa4		69721	Nkiras1	
238055	Apob		75805	Nln	
11810	Apobec1		101613	Nlrp6	
75761	Apol7a		270151	Nlrx1	
28194	Apon		64685	Nmi	
66408	Aptx		70769	Nolc1	
11829	Aqp4		55989	Nop58	
64008	Aqp9		50490	Nox4	
11835	Ar		217365	Nploc4	
68497	Arel1		230103	Npr2	
11841	Arf2		13864	Nr2f6	
228998	Arfgap1		26424	Nr5a2	
11855	Arhgap5		192292	Nrbp1	
213649	Arhgef19		18186	Nrp1	
11861	Arl4a		18193	Nsd1	
75423	Arl5a		386649	Nsfl1c	
54208	Arl6ip1		56876	Nsmf	
11865	Arntl		319638	Nt5dc1	
59046	Arpp19		70021	Nt5dc2	
11883	Arsa		74137	Nuak2	
74008	Arsg		26426	Nubp2	
142688	Asb13		52653	Nudcd2	
65256	Asb2		17766	Nudt1	
77987	Ascc3		67993	Nudt12	
58170	Asic5		66911	Nudt16l1	
70396	Asnsd1		213484	Nudt18	
11484	Aspa		67528	Nudt7	
320817	Atad2b		66387	Nudt8	
107503	Atf5		68564	Nufip2	
226641	Atf6		71805	Nup93	
12915	Atf6b		78252	Nxpe2	
11793	Atg5		237082	Nxt2	
74244	Atg7		231655	Oasl1	
212974	Athl1		227627	Obp2a	
71093	Atoh8		77090	Ocel1	
320940	Atp11c		70113	Odf3b	
11937	Atp2a1		72075	Ogfr	
11964	Atp6v1a		18295	Ogn	
11981	Atp9a		50914	Olig1	

230649	Atpaf1		27047	Omd	
235610	Atrip	■	15379	Onecut1	
20239	Atxn2		225631	Onecut2	■
54140	Avpr1a	■	403187	Opa3	■
54375	Azin1	■	75475	Oplah	■
26877	B3galt1		26428	Orc4	
72727	B3gat3	■	227102	Ormdl1	
101148	B630005N14Rik	■	71720	Osbp3	
12012	Baat	■	79196	Osbp5	
23821	Bace1		237542	Osbp8	■
12013	Bach1		71839	Osgin1	■
12017	Bag1		72201	Otud6b	
29810	Bag3	■	18813	Pa2g4	
224727	Bag6	■	18458	Pabpc1	■
12018	Bak1		18472	Pafah1b1	
170442	Bbox1	■	67869	Paip2	■
72569	Bbs5	■	72333	Palld	■
80748	BC004004	■	214627	Papd5	
227707	BC005624		18789	Papola	■
667597	BC023105	■	231474	Paqr3	
223631	BC025446		71904	Paqr7	
12033	Bcap29	■	75552	Paqr9	■
12927	Bcar1		58220	Pard6b	■
12041	Bckdk	■	26430	Parg	
12051	Bcl3	■	243771	Parp12	
71911	Bdh1	■	235587	Parp3	
12116	Bhmt	■	80285	Parp9	■
64918	Bhmt2		67683	Pbdc1	
12122	Bid		67307	Pbld2	■
53619	Bicap	■	68371	Pbld2	■
12151	Bmi1	■	66923	Pbrm1	■
12153	Bmp1		23983	Pcbp1	
12159	Bmp4		59092	Pcbp4	■
12162	Bmp7		75599	Pcdh1	■
12183	Bpgm	■	18553	Pcsk6	■
14312	Brd2	■	18559	Pctp	
76809	Bri3bp		18563	Pcx	
12215	Bsg		13026	Pcyt1a	
107182	Btaf1	■	18567	Pdcd2	
68815	Btbd10	■	67466	Pdcl	
26363	Btd	■	211948	Pde12	■
53414	Bysl		18582	Pde6d	■
57316	C1d		14827	Pdia3	
94192	C1galt1	■	12304	Pdia4	
59048	C1galt1c1	■	71853	Pdia6	■
12259	C1qa		71830	Pdilt	■
12260	C1qb	■	56376	Pdlim5	■
12262	C1qc		319518	Pdpr	■
50908	C1s1	■	59020	Pdzk1	■
77644	C330007P06Rik	■	105083	Pelo	■
12269	C4bp		64058	Perp	
12274	C6		64934	Pes1	

230558	C8a		18631	Pex11a	
110382	C8b		72129	Pex13	
69379	C8g		19298	Pex19	
12279	C9		74043	Pex26	
67770	Caap1		67199	Pfdn1	
12283	Cab39		18645	Pfn2	
12301	Cacybp		72542	Pgam5	
69719	Cad		241062	Pgap1	
54725	Cadm1		233575	Pgap2	
260299	Cadm4		57757	Pglyrp2	
109624	Cald1		109785	Pgm3	
140904	Caln1		66522	Pgpep1	
12317	Calr		239510	Phf20l1	
12330	Canx		78246	Phf23	
12333	Capn1		102093	Phkb	
12334	Capn2		21664	Phlda1	
12339	Capn7		208177	Phldb2	
53872	Caprin1		233489	Picalm	
12340	Capza1		98496	Pid1	
12343	Capza2		327942	Pigl	
12350	Car3		78928	Pigt	
12319	Car8		66268	Pigyl	
213819	Casd1		18708	Pik3r1	
12370	Casp8		18710	Pik3r3	
26885	Casp8ap2		170741	Pilrb1	
12389	Cav1		18712	Pim1	
104836	Cbll1		72400	Pinx1	
212139	Cc2d1a		56305	Pitpnb	
75565	Ccdc101		106522	Pkdcc	
69668	Ccdc115		18771	Pknox1	
104479	Ccdc117		227937	Pkp4	
108811	Ccdc122		66350	Pla2g12a	
57895	Ccdc126		69836	Pla2g12b	
67119	Ccdc159		192654	Pla2g15	
52713	Ccdc59		53357	Pla2g6	
108673	Ccdc86		18786	Plaa	
66365	Ccdc90b		104759	Pld4	
20304	Ccl5		27276	Plekhb1	
20305	Ccl6		72287	Plekhf1	
216527	Ccm2		11520	Plin2	
12450	Ccng1		66968	Plin5	
12453	Ccni		67801	Plip	
12455	Ccnt1		53317	Plrg1	
12460	Ccs		18830	Pltp	
12479	Cd1d1		18845	Plxna2	
246278	Cd207		29858	Pmm1	
12484	Cd24a		56695	Pnkd	
60533	Cd274		59047	Pnkp	
12488	Cd2ap		18949	Pnn	
217305	Cd300ld		66249	Pno1	
66205	Cd302		241274	Pnpla7	
12491	Cd36		103711	Pnpo	

70333 Cd3eap		18970 Polb	
12506 Cd48	■	66979 Pole4	■
23833 Cd52		64424 Polr1e	■
12508 Cd53		69920 Polr2i	■
11801 Cd5l		235036 Ppan	■
12514 Cd68	■	67916 Ppap2b	■
16149 Cd74	■	19016 Pparg	■
12520 Cd81		66496 Ppdpf	
12522 Cd83		223828 Pphln1	
12524 Cd86		67905 Ppm1m	
98828 Cdc123	■	19046 Ppp1cb	■
216150 Cdc34	■	76497 Ppp1r11	■
12558 Cdh2	■	17931 Ppp1r12a	
72040 Cdhr5		68458 Ppp1r14a	
52858 Cdipt		244416 Ppp1r3b	■
12575 Cdkn1a	■	53412 Ppp1r3c	■
12583 Cdo1	■	243725 Ppp1r9a	
12606 Cebpa		19052 Ppp2ca	
109901 Cela1	■	235542 Ppp2r3a	■
12616 Cenpb	■	226849 Ppp2r5a	
73139 Cenpv		26931 Ppp2r5c	
99712 Cept1		26932 Ppp2r5e	■
104158 Ces1d		70351 Ppp4r1	■
13897 Ces1e	■	232314 Ppp4r2	■
234564 Ces1f	■	67857 Ppp6c	
12623 Ces1g	■	226169 Pprc1	■
102022 Ces2a	■	110593 Prdm2	
216618 Cfac36	■	11758 Prdx6	
11537 Cfd	■	116847 Prelp	■
23837 Cfdp1	■	213760 Prepl	■
12628 Cfh		18747 Prkaca	
50702 Cfhr1		75292 Prkd3	■
12633 Cflar	■	72981 Prkrir	■
18636 Cfp		19116 Prlr	■
68567 Cgref1	■	15469 Prmt1	■
68044 Chac2	■	67939 Prorsd1	■
107932 Chd4		56194 Prpf40a	
109151 Chd9	■	66151 Prr13	
218865 Chdh	■	19152 Prtn3	
12660 Chka	■	19156 Psap	■
234852 Chmp1a	■	19165 Psen2	■
75608 Chmp4b	■	26442 Psma5	
69993 Chn2	■	16913 Psmb8	
66917 Chordc1	■	16912 Psmb9	
100910 Chpf2		19181 Psmc2	■
212862 Chpt1	■	23996 Psmc4	
110902 Chrna2	■	67089 Psmc6	■
66511 Chtop	■	66997 Psmd12	■
12683 Cidea	■	59029 Psmd14	■
12684 Cideb	■	19185 Psmd4	
14311 Cidec	■	66413 Psmd6	
54124 Cks1b	■	19192 Psme3	

12737	Cldn1		66645	Pspc1	
56173	Cldn14		19211	Pten	
12738	Cldn2		19212	Pter	
12739	Cldn3		19244	Ptp4a2	
224250	Cldnd1		15170	Ptpn6	
93694	Clec2d		19264	Ptprc	
94071	Clec2h		19268	Ptprf	
51811	Clec4f		80912	Pum1	
56644	Clec7a		19290	Pura	
12753	Clock		19291	Purb	
270166	Clpx		78697	Pus7	
232370	Clstn3		58998	Pvrl3	
67300	Cltc		59038	Pxmp4	
12764	Cmas		76563	Qrs1	
69574	Cmb1		104009	Qsox1	
74440	Cmip		71750	R3hdm2	
93673	Cml2		19324	Rab1	
69049	Cml5		19325	Rab10	
22169	Cmpk2		53869	Rab11a	
97487	Cmtm4		19330	Rab18	
67213	Cmtm6		216344	Rab21	
74157	Cmtr1		226422	Rab29	
72029	Cnpy3		75985	Rab30	
52469	Coa3		19338	Rab33b	
69893	Coa7		271457	Rab5a	
97484	Cog8		19346	Rab6a	
12812	Coil		67657	Rab13	
12819	Col15a1		19359	Rad23b	
373864	Col27a1		19363	Rad51b	
12826	Col4a1		19386	Ranbp2	
239447	Colec10		240614	Ranbp6	
12238	Commd3		19387	Rangap1	
99311	Commd7		109905	Rap1a	
12846	Comt		215449	Rap1b	
70349	Copb1		109222	Rarres1	
12848	Cops2		218397	Rasa1	
56358	Copz2		19646	Rbbp4	
230027	Coq3		26450	Rbbp9	
53419	Corin		74111	Rbm19	
226139	Cox15		67039	Rbm25	
68033	Cox19		170791	Rbm39	
333182	Cox6b2		241490	Rbm45	
12869	Cox8b		67010	Rbm7	
76703	Cpb1		60365	Rbm8a	
93721	Cpn1		19656	Rbmx1	
71756	Cpn2		54720	Rcan1	
12892	Cpox		68098	Rchy1	
51786	Cpsf2		217864	Rcor1	
12894	Cpt1a		19683	Rdh16	
12896	Cpt2		19684	Rdx	
12908	Crat		28193	Reep3	
58799	Crbn		70335	Reep6	

208677	Creb3l3		19692	Reg1	
233490	Crebzf		100532	Rell1	
433375	Creg1		67442	Retsat	
76737	Creld2		54391	Rfk	
68337	Crip2		242406	Rgp1	
66586	Crls1		50780	Rgs3	
66877	Crnl1		214951	Rhbdl1	
74114	Crot		58176	Rhbg	
12944	Crp		19744	Rheb	
214301	Crygn		69581	Rhou	
12972	Cryz		217835	Rin3	
246277	Csad		93726	Rnase2a	
229663	Csde1		29864	Rnf11	
110750	Cse1l		75212	Rnf121	
78752	Csgalnact2		71956	Rnf135	
211660	Cspp1		56515	Rnf138	
13009	Csrp3		66825	Rnf186	
13010	Cst3		268749	Rnf31	
83410	Cstf2t		207742	Rnf43	
13016	Ctbp1		19823	Rnf7	
13018	Ctcf		76892	Rnft1	
67181	Ctdnep1		215615	Rnpep	
67655	Ctdp1		19877	Rock1	
227292	Ctdsp1		66049	Rogdi	
66642	Ctnnb1		19934	Rpl22	
51797	Ctps		66229	Rpl7l1	
13040	Ctss		67053	Rpp14	
64138	Ctsz		208366	Rpp40	
71745	Cul2		68441	Rraga	
26554	Cul3		66922	Rras2	
75717	Cul5		81910	Rrbp1	
244672	Cwf19l2		107094	Rrp12	
14825	Cxcl1		224823	Rrp36	
15945	Cxcl10		101867	Rrp8	
55985	Cxcl13		59014	Rrs1	
13056	Cyb561		58185	Rsad2	
66427	Cyb5b		170728	Rtn4ip1	
230582	Cyb5rl		237847	Rtn4rl1	
13058	Cybb		235636	Rtp3	
13095	Cyp2c29		67775	Rtp4	
13096	Cyp2c37		216724	Rufy1	
107141	Cyp2c50		192174	Rwdd4a	
404195	Cyp2c54		20194	S100a10	
68444	Cyp2d13		20201	S100a8	
13105	Cyp2d9		20202	S100a9	
13107	Cyp2f2		13609	S1pr1	
13109	Cyp2j5		94226	S1pr5	
13110	Cyp2j6		20208	Saa1	
13116	Cyp46a1		20209	Saa2	
277753	Cyp4a12a		20210	Saa3	
102294	Cyp4v3		20211	Saa4	
13123	Cyp7b1		209086	Samd9l	

13124	Cyp8b1		72193	Scaf11	
16007	Cyr61	■	24044	Scamp2	
242484	D630039A03Rik	■	56807	Scamp5	
208846	Daam1	■	71145	Scara5	■
13143	Dapk2	■	56367	Scoc	■
13163	Daxx	■	240880	Scyl3	
83703	Dbr1	■	20969	Sdc1	
242418	Dcaf10	■	20971	Sdc4	■
28199	Dcaf11	■	68332	Sdhaf1	■
212123	Dcaf15	■	74032	Sdr42e1	■
98193	Dcaf8	■	70061	Sdr9c7	■
68087	Dcakd	■	67815	Sec14l2	■
13179	Dcn	■	20333	Sec22b	■
13190	Dct	■	27054	Sec23b	■
114893	Dcun1d1	■	69608	Sec24d	■
100737	Dcun1d4	■	69276	Sec62	■
13195	Ddc	■	140740	Sec63	■
77591	Ddx10	■	75420	Secisbp2	■
67040	Ddx17	■	70354	Secisbp2l	■
56200	Ddx21	■	114679	Selm	
71986	Ddx28	■	20345	Selplg	
13205	Ddx3x	■	320213	Senp5	
26900	Ddx3y	■	109079	Sephs1	
78394	Ddx52	■	235072	Sept7	
13209	Ddx6	■	53860	Sept9	
234311	Ddx60	■	20364	Sepw1	■
67460	Decr1	■	66870	Serbp1	■
26378	Decr2	■	56442	Serinc1	■
23854	Def8	■	230779	Serinc2	
329877	Dennd4c	■	218442	Serinc5	
70377	Derl3	■	217847	Serpina10	
58239	Dexi	■	380780	Serpina11	
71755	Dhdh	■	68054	Serpina12	■
70451	Dhrs13	■	74069	Serpina3a	■
20148	Dhrs3	■	20716	Serpina3n	
28200	Dhrs4	■	321018	Serpina4-ps1	■
216820	Dhrs7b	■	71907	Serpina9	■
13204	Dhx15	■	66222	Serpinb1a	
218629	Dhx29	■	20708	Serpinb6b	
72162	Dhx36	■	18787	Serpine1	
80861	Dhx58	■	12258	Serping1	
13370	Dio1	■	81898	Sf3b1	
72662	Dis3	■	66055	Sf3b6	
234130	Dkk4	■	67788	Sfr1	■
74129	Dmgdh	■	27219	Sgk2	■
68922	Dnaic1	■	74442	Sgms2	■
15502	Dnaja1	■	20397	Sgpl1	■
81489	Dnajb1	■	81535	Sgpp1	■
67838	Dnajb11	■	56726	Sh3bgrl	■
70604	Dnajb14	■	212531	Sh3bgrl2	■
56812	Dnajb2	■	24055	Sh3bp2	■
67035	Dnajb4	■	56392	Shoc2	■

74330	Dnajc14		71653	Shtn1	
22791	Dnajc2		22619	Siae	
1E+08	Dnajc3		18391	Sigmar1	
66114	Dnajc30		21402	Skp1a	
13002	Dnajc5		20494	Slc10a2	
13419	Dnase1		214601	Slc10a3	
13423	Dnase2a		18173	Slc11a1	
52838	Dnlz		20496	Slc12a2	
381101	Dnph1		20499	Slc12a7	
99480	Dnttip2		20500	Slc13a2	
227697	Dolk		114644	Slc13a3	
83768	Dpp7		240638	Slc16a12	
224897	Dpp9		69309	Slc16a13	
56429	Dpt		20502	Slc16a2	
244745	Dpy1911		104681	Slc16a6	
64705	Dpys		20503	Slc16a7	
13486	Dr1		20504	Slc17a1	
67171	Dram2		218103	Slc17a2	
13495	Drg2		105355	Slc17a3	
13511	Dsg2		55963	Slc1a4	
109620	Dsp		20516	Slc20a2	
209200	Dtx3l		20517	Slc22a1	
207521	Dtx4		319800	Slc22a30	
67603	Dusp6		20520	Slc22a5	
110074	Dut		108114	Slc22a7	
67068	Dynlrb1		27376	Slc25a10	
13555	E2f1		73132	Slc25a16	
108961	E2f8		57279	Slc25a20	
74427	Eaf1		66972	Slc25a23	
67417	Ears2		67554	Slc25a30	
55960	Ebag9		70556	Slc25a33	
51798	Ech1		107375	Slc25a45	
13177	Eci1		231583	Slc26a1	
23986	Eci2		26458	Slc27a2	
66967	Edem3		26569	Slc27a4	
216238	Eea1		69048	Slc30a5	
66143	Eef1e1		109108	Slc30a9	
216616	Efemp1		11416	Slc33a1	
27984	Efhd2		110172	Slc35b1	
76740	Efr3a		242585	Slc35d1	
112405	Egln1		215436	Slc35e3	
112407	Egln3		30791	Slc39a1	
13663	Ei24		213053	Slc39a14	
13664	Eif1a		214922	Slc39a2	
68969	Eif1b		14977	Slc39a7	
19106	Eif2ak2		67547	Slc39a8	
108067	Eif2b3		53945	Slc40a1	
13667	Eif2b4		338365	Slc41a2	
26905	Eif2s3x		54403	Slc4a4	
16341	Eif3e		218756	Slc4a7	
73830	Eif3k		14412	Slc6a13	
98221	Eif3m		28248	Slco1a1	

13682	Eif4a2		28253	Slco1b2	
75705	Eif4b		380773	Slirp	
13684	Eif4e		66390	Slmo2	
208643	Eif4g1		207818	Smagp	
217869	Eif5		20586	Smarca4	
226982	Eif5b		54380	Smarcal1	
244548	Elmod2		20588	Smarcc1	
12686	Elov13		68094	Smarcc2	
68801	Elov15		70099	Smc4	
193838	Eme2		170748	Smco4	
71946	Endod1		104570	Smek2	
209558	Enpp3		226517	Smg7	
224794	Enpp4		68552	Smim14	
83965	Enpp5		66487	Smim4	
12499	Entpd5		20595	Smn1	
223527	Eny2		319757	Smo	
227867	Epc2		66313	Smurf2	
13836	Epha2		319822	Smyd4	
13849	Ephx1		20619	Snap23	
13850	Ephx2		67826	Snap47	
77781	Epm2aip1		66618	Snrnp27	
13854	Epn1		76167	Snrnp35	
98845	Eps8l2		20643	Snrpe	
28042	Ept1		20649	Sntb1	
67458	Ergic1		266781	Snx17	
67456	Ergic2		102607	Snx19	
226090	Ermp1		69226	Snx24	
66580	Esf1		12702	Socs3	
77411	Esrp2		68469	Sox6os	
66841	Etfdh		20683	Sp1	
232146	Eva1a		20687	Sp3	
14020	Evi5		64406	Sp5	
66482	Exoc2		50850	Spast	
211446	Exoc3		66624	Spcs2	
20336	Exoc4		229285	Spg20	
14071	F9		20729	Spin1	
14079	Fabp2		100689	Spon2	
12140	Fabp7		20747	Spop	
68636	Fahd1		76857	Spopl	
23873	Faim		66674	Spryd7	
98952	Fam102a		79043	Spsb3	
66540	Fam107b		211949	Spsb4	
213056	Fam126b		18412	Sqstm1	
227737	Fam129b		78925	Srd5a1	
225358	Fam13b		19073	Srgn	
212326	Fam149a		20810	Srm	
105428	Fam149b		217337	Srp68	
73942	Fam151b		20818	Srprb	
319604	Fam168a		27364	Srr	
106014	Fam19a5		110809	Srsf1	
105203	Fam208b		14105	Srsf10	
208659	Fam20a		20382	Srsf2	

67017	Fam210b		20383	Srsf3	
235493	Fam214a		225027	Srsf7	
78323	Fam219b		76650	Srxn1	
67238	Fam220a		20823	Ssb	
69134	Fam25c		72475	Ssbp3	
215900	Fam26f		20442	St3gal1	
67922	Fam32a		20441	St3gal3	
75698	Fam35a		20443	St3gal4	
108958	Fam73b		20440	St6gal1	
213956	Fam83f		50935	St6galnac6	
105732	Fam83h		56792	Stap1	
69627	Fam89a		56018	Stard10	
68250	Fam96a		20846	Stat1	
72722	Fam98a		20847	Stat2	
68215	Fam98b		20850	Stat5a	
14102	Fas		20852	Stat6	
380601	Fastkd5		20867	Stip1	
246256	Fcgr4		20872	Stk16	
14132	Fcgrt		56274	Stk3	
218503	Fcho2		58231	Stk4	
14133	Fcna		13830	Stom	
218952	Fermt2		74152	Stra6l	
225020	Fez2		94186	Strn3	
14164	Fgf1		68292	Stt3b	
56636	Fgf21		20909	Stx4a	
75296	Fgfr1op		20024	Sub1	
234199	Fgl1		84112	Sucnr1	
231630	Ficd		192136	Sugct	
68680	Fitm1		76971	Sult2a8	
14228	Fkbp4		57429	Sult5a1	
54418	Fmn2		20610	Sumo3	
207854	Fmr1nb		211389	Suox	
214459	Fnbp1l		114741	Supt16	
319448	Fndc3a		96935	Susd4	
72007	Fndc3b		66962	Swsap1	
14276	Folr2		67043	Syap1	
15376	Foxa2		71846	Syce2	
15377	Foxa3		20962	Sycp3	
14236	Foxn2		56403	Syncrip	
14287	Fpgs		217030	Synrg	
75540	Fpgt		74126	Syvn1	
14289	Fpr2		213491	Szrd1	
56095	Ftsj3		231151	Tada2b	
51886	Fubp1		21339	Taf1a	
320267	Fubp3		21354	Tap1	
233908	Fus		230908	Tardbp	
14297	Fxn		110960	Tars	
17281	Fyco1		52440	Tax1bp1	
14369	Fzd7		56480	Tbk1	
14370	Fzd8		21372	Tbl1x	
14373	G0s2		21376	Tbrg1	
27041	G3bp1		21393	Tcap	

23881	G3bp2		21399	Tcea1	
57436	Gabarapl1	■	67923	Tceb1	
13197	Gadd45a		23965	Tenm3	■
17873	Gadd45b	■	21754	Tesk1	■
14635	Galk1		66654	Tex12	
14423	Galnt1	■	21763	Tex2	■
108148	Galnt2	■	75623	Tex30	
14455	Gas5	■	21780	Tfam	
14456	Gas6		21786	Tff3	
234366	Gatad2a		50765	Tfr2	
14469	Gbp2	■	22042	Tfrc	
14468	Gbp2b	■	21812	Tgfbr1	
55932	Gbp3		21817	Tgm2	
100702	Gbp6	■	74088	Them7	■
229900	Gbp7		331401	Thoc2	
14527	Gcgr	■	21832	Thpo	
14629	Gclc	■	21838	Thy1	
14630	Gclm	■	21846	Tie1	■
68133	Gcsh		68140	Tigd2	
14544	Gda		276891	Timd4	■
1E+08	Gdap10	■	76916	Timmdc1	
23886	Gdf15	■	66131	Tipin	■
66603	Gemin2	■	27375	Tjp3	■
11692	Gfer	■	21885	Tle1	
70575	Gfod2	■	21886	Tle2	
223267	Ggact	■	114606	Tle6	■
110175	Ggct		384059	Tlr12	
14600	Ghr	■	53791	Tlr5	■
76425	Gid8		73166	Tm7sf2	
317758	Gimap9	■	68059	Tm9sf2	
215751	Ginm1		107358	Tm9sf3	■
14618	Gjb1	■	69660	Tmbim1	
14619	Gjb2		330401	Tmcc1	■
104174	Gldc	■	68944	Tmco1	
109801	Glo1	■	67511	Tmed9	■
107146	Glyat		76547	Tmem101	■
235582	Glyctk	■	215210	Tmem120a	
63985	Gmfb	■	71929	Tmem123	
331026	Gmppb	■	230678	Tmem125	
229363	Gmps		66990	Tmem134	
14673	Gna12	■	232086	Tmem150a	■
14675	Gna14	■	66074	Tmem167	
14677	Gnai1		66058	Tmem176a	
30877	Gnl3	■	66343	Tmem177	
54342	Gnpnat1	■	75146	Tmem180	
54214	Golga4		231832	Tmem184a	
57437	Golga7		67226	Tmem19	
66629	Golph3		70612	Tmem230	■
73274	Gppbp1	■	652925	Tmem243	
14733	Gpc1		69981	Tmem30a	
14735	Gpc4	■	238257	Tmem30b	
14555	Gpd1	■	67878	Tmem33	

14571	Gpd2		66079	Tmem42	
268566	Gphn		99887	Tmem56	
107173	Gpr137		100201	Tmem64	
80290	Gpr146		67893	Tmem86a	
76238	Grhpr		103743	Tmem98	
227753	Gsn		20776	Tmie	
14852	Gspt1		19241	Tmsb4x	
14782	Gsr		72736	Tmx1	
14854	Gss		21928	Tnfaip2	
14859	Gsta3		66443	Tnfaip8l1	
14865	Gstm4		21925	Tnnc2	
98053	Gtf2f1		21955	Tnnt1	
68705	Gtf2f2		21957	Tnnt3	
14884	Gtf2h1		67952	Tomm20	
23894	Gtf2h2		28185	Tomm70a	
70239	Gtf3c5		72960	Top1mt	
207704	Gtpbp10		240832	Tor1aip2	
69237	Gtpbp4		30933	Tor2a	
14923	Guk1		110012	Tpgs1	
14933	Gyk		22004	Tpm2	
14958	H1f0		22019	Tpp2	
14960	H2-Aa		67808	Tprgl	
14961	H2-Ab1		22031	Traf3	
15270	H2afx		66975	Trappc13	
14969	H2-Eb1		58866	Treh	
15042	H2-T24		224840	Trem14	
30963	Hacd1		319236	Trim12c	
70757	Hacd2		80890	Trim2	
56794	Hacl1		20821	Trim21	
97212	Hadha		20128	Trim30a	
231086	Hadhb		209387	Trim30d	
15130	Hbb-b2		69807	Trim32	
353502	Hcfc1r1		79263	Trim39	
433759	Hdac1		108943	Trmt10a	
232232	Hdac11		66926	Trmt6	
72748	Hdhd3		328162	Trmt61a	
207304	Hectd1		60599	Trp53inp1	
67138	Herc6		68728	Trp53inp2	
15205	Hes1		58800	Trpm7	
55927	Hes6		22368	Trpv2	
192231	Hexim1		227682	Trub2	
15234	Hgf		76927	Tsacc	
54426	Hgfac		21807	Tsc22d1	
68917	Hint2		232670	Tspan33	
15258	Hipk2		22110	Tspyl1	
15259	Hipk3		69499	Tsr2	
50708	Hist1h1c		56844	Tssc4	
319158	Hist1h4i		234875	Ttc13	
319190	Hist2h2be		75516	Ttc32	
110521	Hivep1		72747	Ttc39c	
217082	Hlf		104718	Ttc7b	
15354	Hmgb3		75425	Tti1	

15360	Hmgcs2		50500	Ttpa	
21410	Hnf1b		117160	Ttyh2	
15378	Hnf4a	■	227613	Tubb4b	■
68314	Hnf4aos	■	67510	Tvp23b	■
229279	Hnrnpa3	■	65960	Twsg1	
15384	Hnrnpab		52700	Txndc17	
15381	Hnrnpc		105245	Txndc5	
11991	Hnrnpd		234723	Txnl4b	■
98758	Hnrnpf		22177	Tyropb	
56258	Hnrnpb2		71767	Tysnd1	■
15387	Hnrnpk		68736	Tyw5	■
74326	Hnrnpr		22200	Uba3	■
51810	Hnrnpu	■	66663	Uba5	■
74318	Hopx		24108	Ubd	
15439	Hp		22209	Ube2a	
15446	Hpgd		56550	Ube2d2a	
15460	Hr		66105	Ube2d3	
15108	Hsd17b10	■	22194	Ube2e1	
56348	Hsd17b12	■	218793	Ube2e2	
243168	Hsd17b13		67921	Ube2f	
15486	Hsd17b2		67128	Ube2g1	
15488	Hsd17b4		22213	Ube2g2	■
15493	Hsd3b2	■	56791	Ube2i6	■
15494	Hsd3b3	■	109161	Ube2q2	
15496	Hsd3b5	■	70620	Ube2v2	
101502	Hsd3b7		22215	Ube3a	
72552	Hsdl1		27643	Ubl4	
72479	Hsdl2	■	69459	Ubl7	
15519	Hsp90aa1	■	79560	Ublcp1	
15516	Hsp90ab1	■	225896	Ubxn1	
22027	Hsp90b1		217379	Ubxn2a	■
110920	Hspa13	■	67812	Ubxn4	■
15525	Hspa4	■	22245	Uck1	
14828	Hspa5	■	22230	Ufd1l	■
80888	Hspb8	■	67490	Ufl1	■
15505	Hsph1	■	71773	Ugt2b1	■
12282	Hyou1	■	100727	Ugt2b34	■
216792	Iba57	■	243085	Ugt2b35	■
15902	Id2	■	22238	Ugt2b5	
15903	Id3		223337	Ugt3a2	
15925	Ide	■	29869	Ulk2	■
15936	Ier2		22248	Unc119	■
26388	Ifi202b	■	19704	Upf1	
76933	Ifi27l2a		22276	Uros	
70110	Ifi35		56041	Uso1	■
99899	Ifi44		230484	Usp1	
15953	Ifi47		59025	Usp14	
71586	Ifih1		24110	Usp18	■
15957	Ifit1	■	170822	Usp33	■
15958	Ifit2	■	22284	Usp9x	
15959	Ifit3		231915	Uspl1	
15980	Ifngr2		217109	Utp18	

55978	lft20		216987	Utp6	
67286	lft22		22330	Vcl	
16005	lgfals	■	269523	Vcp	■
16009	lgfbp3		22361	Vnn1	
207683	lgsf11		26464	Vnn3	
16145	lgtp		52348	Vps37a	
60440	ligp1		330192	Vps37b	■
56489	lkbke	■	218035	Vps41	■
16151	lkbkg	■	21427	Vps72	■
67143	lkzf5		53612	Vti1b	
16164	ll13ra1		219189	Vwa8	■
16195	ll6st	■	225131	Wac	
66541	lmpmp1l		94254	Wbscr16	■
242291	lmpad1		216156	Wdr18	
103844	lnca1		70465	Wdr77	■
16325	lnhbc	■	230796	Wdtdc1	■
16326	lnhbe	■	192200	Wfdc12	
233752	lncs	■	67701	Wfdc2	■
72999	lncsig2	■	66107	Wfdc21	
70422	lnts2	■	232341	Wnk1	■
230673	lpo13	■	22413	Wnt2	■
75751	lpo4		59002	Wrap73	■
320727	lpo8		78903	Wrnip1	
74239	lqce		60532	Wtap	
16179	lrak1		22433	Xbp1	
108960	lrak2	■	11798	Xiap	
27056	lrf5	■	321003	Xpnpep3	
54139	lrf6	■	73192	Xpot	
16391	lrf9	■	74335	Xrcc3	
15944	lrgm1	■	102448	Xylb	■
54396	lrgm2		217119	Xylt2	
57444	lsg20		67008	Yae1d1	
26968	lslr		67057	Yaf2	
67441	lsoc2b	■	56449	Ybx3	
71927	ltfg1	■	67180	Yipf5	
106581	ltfg3	■	77929	Yipf6	
241226	ltga8	■	56418	Ykt6	
217837	ltpk1		27377	Yme11l	
269424	jade1	■	240255	Ythdc2	■
67767	jagn1		213541	Ythdf2	■
16453	jak3		229096	Ythdf3	■
16069	jchain		22627	Ywhae	
66124	jbsd2		22628	Ywhag	
16476	jun	■	58203	Zbp1	
16477	junb		66391	Zbtb11os1	■
16478	jund		30928	Zbtb18	
235041	kank2	■	56490	Zbtb20	■
14534	kat2a		81630	Zbtb22	
67773	kat8	■	56805	Zbtb33	
72425	katnbl1	■	226470	Zbtb41	
16529	kcnk5	■	237256	Zc3h12d	
84036	kcnk1	■	76014	Zc3h18	

233107	Kctd15		78781	Zc3hav1	
218214	Kdm1b		227449	Zcchc2	
70750	Kdsr		214290	Zcchc6	
50868	Keap1		66361	Zfand1	
64697	Keg1		100494	Zfand2a	
16573	Kif5b		11906	Zfhx3	
21847	Klf10		22640	Zfp1	
16601	Klf9		65020	Zfp110	
242721	Klhdc7a		72465	Zfp131	
77113	Klhl2		26465	Zfp146	
242521	Klh9		22661	Zfp148	
16646	Kpna1		26466	Zfp260	
16648	Kpna3		74120	Zfp263	
16649	Kpna4		30046	Zfp292	
16211	Kpnb1		218100	Zfp322a	
16691	Krt8		54367	Zfp326	
100087	Kti12		230761	Zfp362	
214669	L3mbtl2		12192	Zfp361l	
16763	Lad1		22701	Zfp41	
16768	Lag3		235682	Zfp445	
16774	Lama3		224691	Zfp472	
16780	Lamb3		22709	Zfp51	
16784	Lamp2		72672	Zfp518a	
68576	Lamtor5		240068	Zfp563	
217980	Larp4b		170938	Zfp617	
16796	Lasp1		22720	Zfp62	
16803	Lbp		72611	Zfp655	
16816	Lcat		319475	Zfp672	
212391	Lcor		1E+08	Zfp729b	
18826	Lcp1		233056	Zfp790	
16828	Ldha		240064	Zfp799	
52815	Ldhd		235047	Zfp809	
259301	Leap2		235956	Zfp825	
68192	Leprotl1		69504	Zfp932	
16854	Lgals3		71508	Zfp935	
19039	Lgals3bp		74149	Zfp946	
56048	Lgals8		22763	Zfr	
76429	Lhpp		218441	Zfyve16	
16880	Lifr		72739	Zkscan3	
319583	Lig4		22401	Zmat3	
108030	Lin7a		228880	Zmynd8	
22343	Lin7c		98999	Znfx1	
16889	Lipa		70103	Znhit1	
15450	Lipc		29805	Znhit2	
16891	Lipg		229937	Znhit6	
56722	Litaf		387524	Znrf2	
214895	Lman2l		99334	Zscan29	
232685	Lncpint		71971	Zswim1	
66887	Lonp2		69747	Zswim7	
16949	Loxl1		52696	Zwint	
226856	Lpgat1				

T: Pearson correlation values between CR and the plant bioactives (including synergistic analysis) for all pathways which include at least on CR gene with a fold change > 1.5

Pathway	set size (genes in bg)	CR genes	R	P	Q	RP	RQ	PQ	RPQ
4-hydroxyproline degradation I - MouseCyc	4(4)	1 (25.0%)	0,90	0,96	0,99	0,95	0,94	0,98	0,96
Acetylcholine Binding And Downstream Events - Reactome	14(14)	1 (7.1%)	0,55	0,87	0,53	0,82	0,67	0,87	0,85
Activated TLR4 signalling - Reactome	95(83)	2 (2.4%)	-0,39	-0,52	-0,57	-0,54	-0,52	-0,63	-0,60
Activation of Gene Expression by SREBP (SREBF) - Reactome	7(7)	1 (14.3%)	-0,30	-0,17	-0,74	-0,27	-0,62	-0,63	-0,53
Activation of Nicotinic Acetylcholine Receptors - Reactome	14(14)	1 (7.1%)	0,55	0,87	0,53	0,82	0,67	0,87	0,85
acyl-ACP thioesterase pathway - MouseCyc	1(1)	1 (100%)	-	-	-	-	-	-	-
Adaptive Immune System - Reactome	457 (399)	1 (0.3%)	0,02	0,14	0,14	0,08	0,06	0,18	0,11
Adipocytokine signaling pathway - Mus musculus (mouse) - KEGG	71(66)	2 (3.0%)	0,08	0,32	0,00	0,20	0,07	0,22	0,17
Adipogenesis - Wikipathways	133 (125)	3 (2.4%)	0,14	0,10	0,07	0,17	0,15	0,11	0,17
ADP signalling through P2Y purinoceptor 1 - Reactome	9(9)	1 (11.1%)	0,51	0,52	0,90	0,58	0,69	0,72	0,68
Advanced glycosylation endproduct receptor signaling - Reactome	13(12)	2 (16.7%)	-0,64	-0,78	-0,88	-0,79	-0,79	-0,85	-0,83
Alanine and aspartate metabolism - Wikipathways	12(12)	1 (8.3%)	0,49	0,60	0,29	0,78	0,46	0,66	0,73
Alanine, aspartate and glutamate metabolism - Mus musculus (mouse) - KEGG	35(29)	2 (6.9%)	0,26	0,46	0,37	0,43	0,31	0,53	0,45
Alcoholism - Mus musculus (mouse) - KEGG	202 (105)	1 (1.0%)	0,34	0,16	0,08	0,41	0,35	0,17	0,41
Alternative complement activation - Reactome	3(2)	1 (50.0%)	1,00	-1,00	-1,00	1,00	1,00	-1,00	1,00
Amine Oxidase reactions - Reactome	4(4)	1 (25.0%)	-1,00	0,70	0,34	0,19	-0,54	0,72	0,35
Amine-derived hormones - Reactome	14(14)	2 (14.3%)	0,33	0,02	-0,35	0,35	0,30	-0,09	0,32
Amino acid and oligopeptide SLC transporters - Reactome	50(46)	1 (2.2%)	0,38	0,28	0,16	0,51	0,38	0,37	0,50
Amino acid synthesis and interconversion (transamination) - Reactome	17(15)	2 (13.3%)	0,38	0,58	0,35	0,49	0,41	0,66	0,51
Amino acid transport across the plasma membrane - Reactome	32(30)	1 (3.3%)	0,46	0,35	0,03	0,60	0,40	0,35	0,54
Amoebiasis - Mus musculus (mouse) - KEGG	120 (108)	4 (3.7%)	0,16	0,35	0,19	0,33	0,20	0,38	0,35
Amphetamine addiction - Mus musculus (mouse) - KEGG	68(63)	1 (1.6%)	0,66	0,07	0,10	0,68	0,67	0,11	0,68
Androgen biosynthesis - Reactome	15(11)	2 (18.2%)	0,97	0,31	0,52	0,97	0,97	0,46	0,97
Antiviral mechanism by IFN-stimulated genes - Reactome	25(21)	1 (4.8%)	-0,04	0,33	-0,16	0,12	-0,08	0,20	0,08
Arachidonic acid metabolism - Mus musculus (mouse) - KEGG	98(78)	4 (5.1%)	0,69	0,17	-0,17	0,67	0,63	0,06	0,61
Arachidonic acid metabolism - Reactome	76(57)	2 (3.5%)	0,61	0,30	-0,19	0,63	0,55	0,14	0,57
Arginine and proline metabolism - Mus musculus (mouse) - KEGG	57(48)	1 (2.1%)	0,04	0,40	0,20	0,18	0,08	0,41	0,21
Ascorbate and aldarate metabolism - Mus musculus (mouse) - KEGG	27(14)	2 (14.3%)	0,75	0,44	0,09	0,80	0,69	0,34	0,71
asparagine biosynthesis I - MouseCyc	2(2)	1 (50.0%)	-1,00	1,00	1,00	1,00	-1,00	1,00	1,00
Bile acid and bile salt metabolism - Reactome	36(36)	4 (11.1%)	0,18	0,22	-0,18	0,23	0,11	0,08	0,17
bile acid biosynthesis, neutral pathway - MouseCyc	6(6)	1 (16.7%)	-0,35	-0,28	-0,82	-0,34	-0,49	-0,61	-0,45
Bile secretion - Mus musculus (mouse) - KEGG	72(68)	2 (2.9%)	0,25	0,22	0,03	0,31	0,23	0,17	0,28
Binding and Uptake of Ligands by Scavenger Receptors - Reactome	39(31)	2 (6.5%)	-0,46	-0,69	-0,65	-0,66	-0,61	-0,72	-0,69

Biogenic Amine Synthesis - Wikipathways	15(14)	1 (7.1%)	0,90	-0,09	-0,10	0,91	0,87	-0,11	0,86
Biological oxidations - Reactome	168 (128)	14 (10.9%)	0,54	0,21	-0,01	0,54	0,51	0,15	0,51
biosynthesis of estrogens - MouseCyc	12(11)	2 (18.2%)	0,35	0,80	0,50	0,53	0,47	0,80	0,61
biosynthesis of serotonin and melatonin - MouseCyc	5(4)	1 (25.0%)	1,00	-0,38	-0,38	0,98	1,00	-0,39	0,97
Biosynthesis of unsaturated fatty acids - Mus musculus (mouse) - KEGG	25(24)	1 (4.2%)	0,37	0,53	-0,41	0,49	0,18	0,15	0,37
Biotin transport and metabolism - Reactome	10(10)	2 (20.0%)	0,04	0,49	-0,60	0,18	-0,02	0,35	0,12
biotin-carboxyl carrier protein assembly - MouseCyc	3(3)	2 (66.7%)	-1,00	0,76	-0,99	-0,94	-1,00	0,46	-0,96
bupropion degradation - MouseCyc	38(29)	3 (10.3%)	0,81	-0,01	-0,24	0,75	0,78	-0,15	0,74
Calcium Regulation in the Cardiac Cell - Wikipathways	150 (135)	2 (1.5%)	0,21	-0,18	-0,23	0,09	0,10	-0,22	0,00
Calcium signaling pathway - Mus musculus (mouse) - KEGG	183 (165)	1 (0.6%)	0,06	0,20	0,19	0,14	0,10	0,26	0,17
catecholamine biosynthesis - MouseCyc	6(6)	2 (33.3%)	0,56	0,53	-0,81	0,78	0,52	0,41	0,75
Catecholamine biosynthesis - Reactome	4(4)	1 (25.0%)	0,99	-0,50	-0,69	0,99	0,98	-0,76	0,99
Cell cycle - Wikipathways	88(79)	1 (1.3%)	0,17	0,23	0,15	0,24	0,23	0,26	0,28
Chagas disease (American trypanosomiasis) - Mus musculus (mouse) - KEGG	104 (100)	1 (1.0%)	-0,02	0,28	0,15	0,12	0,04	0,30	0,15
Chemical carcinogenesis - Mus musculus (mouse)	95(70)	8 (11.4%)	0,36	0,09	-0,22	0,33	0,27	-0,04	0,26
Cholesterol biosynthesis - Reactome	22(22)	2 (9.1%)	0,40	0,44	0,00	0,49	0,38	0,33	0,46
Cholesterol Biosynthesis - Wikipathways	15(15)	2 (13.3%)	0,24	0,53	0,14	0,40	0,26	0,43	0,39
cholesterol biosynthesis I - MouseCyc	12(12)	1 (8.3%)	0,39	0,46	0,22	0,47	0,41	0,40	0,46
cholesterol biosynthesis III (via desmosterol) - MouseCyc	11(11)	1 (9.1%)	0,38	0,49	0,24	0,47	0,40	0,43	0,47
Class A/1 (Rhodopsin-like receptors) - Reactome	290 (234)	2 (0.9%)	-0,34	-0,25	-0,48	-0,39	-0,45	-0,42	-0,47
Clathrin derived vesicle budding - Reactome	61(52)	1 (1.9%)	0,62	0,15	-0,43	0,69	0,50	-0,09	0,56
Cocaine addiction - Mus musculus (mouse) - KEGG	50(46)	1 (2.2%)	0,68	0,14	0,04	0,73	0,67	0,12	0,72
Complement Activation, Classical Pathway - Wikipathway	17(13)	3 (23.1%)	0,54	0,34	-0,26	0,57	0,48	0,22	0,52
Complement and coagulation cascades - Mus musculus (mouse) - KEGG	77(65)	5 (7.7%)	0,27	0,25	0,02	0,38	0,26	0,22	0,36
Complement and Coagulation Cascades - Wikipathways	61(57)	3 (5.3%)	0,27	0,21	0,11	0,37	0,28	0,22	0,37
Complement cascade - Reactome	40(28)	4 (14.3%)	0,41	0,29	-0,13	0,52	0,38	0,16	0,49
Constitutive PI3K/AKT Signaling in Cancer - Reactome	81(77)	1 (1.3%)	0,23	0,28	0,31	0,32	0,33	0,37	0,40
Cysteine and methionine metabolism - Mus musculus (mouse) - KEGG	38(33)	2 (6.1%)	0,54	0,14	-0,01	0,58	0,48	0,12	0,53
Cytochrome P450 - arranged by substrate type - Reactome	84(55)	7 (12.7%)	0,64	0,07	-0,30	0,57	0,55	-0,10	0,49
Cytochrome P450 - Wikipathways	41(35)	3 (8.6%)	0,29	0,08	-0,25	0,25	0,21	-0,05	0,19
Cytokine Signaling in Immune system - Reactome	193 (168)	2 (1.2%)	0,00	0,27	0,01	0,13	0,00	0,19	0,11
Cytokine-cytokine receptor interaction - Mus musculus (mouse) - KEGG	266 (216)	2 (0.9%)	0,30	0,31	0,24	0,40	0,33	0,35	0,41
Cytosolic sensors of pathogen-associated DNA - Reactome	58(45)	2 (4.4%)	-0,64	-0,68	-0,77	-0,74	-0,76	-0,77	-0,78
Cytosolic sulfonation of small molecules - Reactome	18(14)	2 (14.3%)	0,34	0,41	0,44	0,61	0,49	0,54	0,73
DAP12 interactions - Reactome	158 (144)	1 (0.7%)	0,16	0,25	0,22	0,24	0,21	0,30	0,28
DAP12 signaling - Reactome	147 (138)	1 (0.7%)	0,16	0,25	0,23	0,24	0,22	0,30	0,28

Defective AMN causes hereditary megaloblastic anemia 1 - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective BTD causes biotinidase deficiency - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective CD320 causes methylmalonic aciduria - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective CUBN causes hereditary megaloblastic anemia 1 - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective GIF causes intrinsic factor deficiency - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective HLCS causes multiple carboxylase deficiency - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective LMBRD1 causes methylmalonic aciduria and homocystinuria type cblF - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective MMAA causes methylmalonic aciduria type cblA - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective MMAB causes methylmalonic aciduria type cblB - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective MMACHC causes methylmalonic aciduria and homocystinuria type cblC - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective MMADHC causes methylmalonic aciduria and homocystinuria type cblD - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective MTR causes methylmalonic aciduria and homocystinuria type cblG - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective MTRR causes methylmalonic aciduria and homocystinuria type cblE - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective MUT causes methylmalonic aciduria mut type - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defective TCN2 causes hereditary megaloblastic anemia - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defects in biotin (B7n) metabolism - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defects in cobalamin (B12) metabolism - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Defects in vitamin and cofactor metabolism - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Degradation of cysteine and homocysteine - Reactome	8(8)	1 (12.5%)	0,66	0,81	-0,47	0,76	0,58	0,89	0,74
DEx/H-box helicases activate type I IFN and inflammatory cytokines production - Reactome	13(12)	2 (16.7%)	-0,82	-0,81	-0,87	-0,86	-0,88	-0,84	-0,87
Disease - Reactome	608 (554)	4 (0.7%)	0,14	0,23	0,03	0,23	0,14	0,19	0,21
Diurnally Regulated Genes with Circadian Orthologs - Wikipathways	48(42)	1 (2.4%)	0,39	0,33	0,29	0,44	0,40	0,42	0,45
Dopaminergic synapse - Mus musculus (mouse) - KEGG	135 (120)	1 (0.8%)	0,27	0,18	0,15	0,32	0,28	0,21	0,32
Dopaminergic Neurogenesis - Wikipathways	30(30)	1 (3.3%)	0,90	0,01	-0,15	0,91	0,84	-0,11	0,86
Downstream signal transduction - Reactome	142 (134)	1 (0.7%)	0,17	0,26	0,24	0,26	0,23	0,31	0,30
Downstream Signaling Events Of B Cell Receptor (BCR) - Reactome	108 (104)	1 (1.0%)	0,21	0,24	0,28	0,29	0,30	0,32	0,35
Downstream signaling of activated FGFR - Reactome	130 (122)	1 (0.8%)	0,23	0,26	0,28	0,31	0,29	0,33	0,35
Drug metabolism - cytochrome P450 - Mus musculus (mouse) - KEGG	97(70)	10 (14.3%)	0,46	0,25	-0,17	0,48	0,40	0,12	0,43
Drug metabolism - other enzymes - Mus musculus (mouse) - KEGG	61(39)	3 (7.7%)	0,45	0,33	-0,17	0,53	0,35	0,15	0,42
EGFR1 Signaling Pathway - Wikipathways	176 (169)	1 (0.6%)	0,04	-0,17	-0,22	-0,07	-0,06	-0,23	-0,13
Endogenous sterols - Reactome	14(13)	3 (23.1%)	0,14	-0,14	-0,60	0,08	0,01	-0,41	-0,02
ErbB signaling pathway - Mus musculus (mouse) - KEGG	87(82)	1 (1.2%)	0,31	0,25	0,32	0,38	0,42	0,38	0,47
ErbB signaling pathway - Wikipathways	46(44)	1 (2.3%)	0,47	0,32	0,44	0,54	0,64	0,50	0,67

Estrogen metabolism - Wikipathways	14(8)	1 (12.5%)	0,42	0,71	0,84	0,60	0,64	0,89	0,74
Estrogen signaling pathway - Mus musculus (mouse) - KEGG	99(86)	1 (1.2%)	0,35	0,17	0,23	0,38	0,37	0,25	0,39
ethanol degradation II (cytosol) - MouseCyc	11(10)	1 (10.0%)	0,66	0,68	0,69	0,72	0,75	0,84	0,78
Ethanol oxidation - Reactome	10(9)	1 (11.1%)	0,81	0,76	0,37	0,83	0,87	0,78	0,88
Exercise-induced Circadian Regulation - Wikipathways	49(42)	2 (4.8%)	0,31	0,32	0,27	0,37	0,33	0,39	0,39
Facilitative Na+-independent glucose transporters - Reactome	11(10)	1 (10.0%)	-0,27	0,68	0,58	0,05	-0,15	0,77	0,21
Fatty acid biosynthesis - Mus musculus (mouse) - KEGG	6(6)	3 (50.0%)	-0,46	0,54	-0,76	-0,13	-0,62	-0,37	-0,43
Fatty Acid Biosynthesis - Wikipathways	22(21)	3 (14.3%)	-0,39	0,53	-0,37	0,03	-0,45	0,19	-0,17
fatty acid biosynthesis initiation II - MouseCyc	2(2)	1 (50.0%)	-1,00	1,00	-1,00	-1,00	-1,00	-1,00	-1,00
fatty acid biosynthesis initiation III - MouseCyc	2(2)	1 (50.0%)	-1,00	1,00	-1,00	-1,00	-1,00	-1,00	-1,00
Fatty acid degradation - Mus musculus (mouse) - KEGG	48(37)	2 (5.4%)	0,81	0,11	0,06	0,75	0,79	0,12	0,73
Fatty acid elongation - Mus musculus (mouse) - KEGG	24(24)	2 (8.3%)	0,78	0,38	-0,58	0,80	0,77	-0,06	0,78
Fatty Acid Omega Oxidation - Wikipathways	7(7)	1 (14.3%)	0,55	0,24	0,71	0,50	0,67	0,58	0,61
Fatty acid, triacylglycerol, and ketone body metabolism - Reactome	85(77)	6 (7.8%)	0,53	0,41	-0,10	0,57	0,52	0,21	0,56
Fatty acids - Reactome	18(9)	1 (11.1%)	0,90	0,15	-0,17	0,84	0,85	0,02	0,79
Fatty Acyl-CoA Biosynthesis - Reactome	17(16)	4 (25.0%)	0,77	0,38	-0,71	0,78	0,74	-0,36	0,75
Fc epsilon receptor (FCER1) signaling - Reactome	155 (141)	1 (0.7%)	0,22	0,26	0,31	0,31	0,32	0,36	0,37
FMO oxidizes nucleophiles - Reactome	3(3)	1 (33.3%)	0,93	0,79	0,91	0,99	0,98	0,85	1,00
formaldehyde oxidation I - MouseCyc	5(5)	1 (20.0%)	0,23	-0,51	-0,53	-0,03	-0,01	-0,88	-0,25
Formyl peptide receptors bind formyl peptides and many other ligands - Reactome	13(11)	2 (18.2%)	-0,58	-0,77	-0,84	-0,80	-0,78	-0,81	-0,83
G alpha (i) signalling events - Reactome	222 (156)	2 (1.3%)	-0,37	-0,36	-0,54	-0,46	-0,49	-0,50	-0,53
G alpha (q) signalling events - Reactome	167 (141)	3 (2.1%)	-0,33	-0,37	-0,48	-0,44	-0,44	-0,47	-0,49
G Protein Signaling Pathways - Wikipathways	91(84)	1 (1.2%)	0,17	0,24	0,46	0,27	0,30	0,40	0,37
GAB1 signalosome - Reactome	90(86)	1 (1.2%)	0,24	0,30	0,34	0,34	0,34	0,39	0,41
Gap junction assembly - Reactome	3(3)	1 (33.3%)	0,00	-0,87	0,86	-0,25	0,13	-0,54	-0,13
Gap junction trafficking - Reactome	10(10)	1 (10.0%)	-0,06	-0,23	0,08	-0,16	-0,05	-0,20	-0,14
Gap junction trafficking and regulation - Reactome	12(12)	1 (8.3%)	-0,04	-0,18	0,21	-0,12	0,00	-0,09	-0,08
Gastrin-CREB signalling pathway via PKC and MAPK - Reactome	188 (162)	3 (1.9%)	-0,29	-0,34	-0,46	-0,40	-0,40	-0,45	-0,45
Glucocorticoid & Mineralcorticoid Metabolism - Wikipathways	13(11)	1 (9.1%)	1,00	0,34	0,53	1,00	1,00	0,48	1,00
Glucocorticoid biosynthesis - Reactome	13(8)	1 (12.5%)	1,00	0,30	0,49	1,00	1,00	0,44	1,00
Gluconeogenesis - Reactome	35(30)	1 (3.3%)	0,19	0,42	0,12	0,33	0,20	0,37	0,33
Glucose metabolism - Reactome	69(60)	1 (1.7%)	0,26	0,48	0,08	0,42	0,26	0,41	0,39
Glucose transport - Reactome	40(37)	1 (2.7%)	0,24	0,40	0,18	0,31	0,26	0,37	0,32
Glucuronidation - Wikipathways	16(10)	1 (10.0%)	0,90	0,15	0,06	0,89	0,90	0,14	0,86
Glutathione and one carbon metabolism - Wikipathways	31(28)	2 (7.1%)	0,51	0,37	0,01	0,58	0,50	0,30	0,56
Glutathione conjugation - Reactome	26(25)	1 (4.0%)	0,37	0,11	0,13	0,35	0,37	0,14	0,35

Glutathione metabolism - Mus musculus (mouse) - KEGG	55(48)	4 (8.3%)	0,19	0,05	-0,09	0,18	0,16	0,00	0,15
Glutathione metabolism - Wikipathways	19(17)	1 (5.9%)	0,59	0,38	0,50	0,60	0,61	0,53	0,62
glutathione-mediated detoxification - MouseCyc	27(22)	2 (9.1%)	-0,11	-0,43	-0,29	-0,22	-0,15	-0,44	-0,25
Glycerolipid metabolism - Mus musculus (mouse) - KEGG	56(48)	1 (2.1%)	0,18	0,31	0,43	0,28	0,31	0,50	0,39
Glycerophospholipid biosynthesis - Reactome	86(79)	1 (1.3%)	0,15	0,29	0,40	0,21	0,23	0,46	0,28
Glycerophospholipid metabolism - Mus musculus (mouse) - KEGG	91(81)	1 (1.2%)	0,12	0,25	0,31	0,18	0,18	0,38	0,23
glycine betaine degradation - MouseCyc	8(8)	1 (12.5%)	0,79	-0,29	0,16	0,75	0,81	-0,06	0,75
Glycine, serine and threonine metabolism - Mus musculus (mouse) - KEGG	39(33)	2 (6.1%)	0,53	0,27	0,18	0,60	0,55	0,32	0,61
Glycolysis / Gluconeogenesis - Mus musculus (mouse) - KEGG	66(60)	1 (1.7%)	0,21	0,33	0,14	0,29	0,22	0,31	0,29
Glycolysis and Gluconeogenesis - Wikipathways	50(47)	2 (4.3%)	0,24	0,30	0,05	0,29	0,22	0,24	0,27
Glycoprotein hormones - Reactome	9(8)	2 (25.0%)	0,86	0,89	0,91	0,89	0,89	0,94	0,91
GPCR downstream signaling - Reactome	1065 (420)	3 (0.7%)	-0,22	-0,13	-0,31	-0,24	-0,30	-0,25	-0,30
GPCR ligand binding - Reactome	403 (306)	2 (0.7%)	-0,27	-0,21	-0,42	-0,33	-0,38	-0,36	-0,40
GRB2 events in ERBB2 signaling - Reactome	21(21)	1 (4.8%)	0,68	0,43	0,75	0,76	0,74	0,77	0,80
Heme biosynthesis - Reactome	11(11)	1 (9.1%)	0,79	0,42	0,07	0,81	0,75	0,35	0,77
Heme Biosynthesis - Wikipathways	9(9)	1 (11.1%)	0,88	0,47	0,09	0,87	0,84	0,36	0,83
heme biosynthesis II - MouseCyc	9(9)	1 (11.1%)	0,88	0,47	0,09	0,87	0,84	0,36	0,83
Hemostasis - Reactome	412 (364)	2 (0.5%)	0,08	0,21	0,08	0,18	0,10	0,21	0,19
Hepatitis C - Mus musculus (mouse) - KEGG	136 (120)	1 (0.8%)	-0,07	0,32	0,00	0,08	-0,07	0,22	0,07
Herpes simplex infection - Mus musculus (mouse) - KEGG	212 (164)	1 (0.6%)	-0,10	0,28	-0,07	0,01	-0,10	0,19	0,00
Hexose transport - Reactome	42(39)	1 (2.6%)	0,25	0,41	0,20	0,32	0,27	0,39	0,33
Highly calcium permeable nicotinic acetylcholine receptors - Reactome	9(9)	1 (11.1%)	0,70	0,94	0,80	0,90	0,77	0,96	0,91
Highly calcium permeable postsynaptic nicotinic acetylcholine receptors - Reactome	11(11)	1 (9.1%)	0,64	0,93	0,74	0,89	0,74	0,93	0,90
Histidine metabolism - Mus musculus (mouse) - KEGG	29(27)	1 (3.7%)	0,75	0,02	-0,01	0,76	0,74	0,01	0,73
Immune System - Reactome	894 (750)	9 (1.2%)	-0,02	0,06	-0,14	0,01	-0,06	-0,03	-0,03
Import of palmitoyl-CoA into the mitochondrial matrix - Reactome	9(7)	2 (28.6%)	0,21	0,87	-0,69	0,60	-0,13	0,46	0,30
Influenza A - Mus musculus (mouse) - KEGG	172 (146)	1 (0.7%)	-0,14	0,31	-0,05	0,01	-0,13	0,20	0,00
Initial triggering of complement - Reactome	21(12)	1 (8.3%)	0,60	0,00	-0,32	0,65	0,54	-0,23	0,61
Innate Immune System - Reactome	481 (399)	7 (1.8%)	-0,03	-0,05	-0,26	-0,05	-0,12	-0,17	-0,12
Insulin Signaling - Wikipathways	157 (150)	1 (0.7%)	0,24	0,20	-0,04	0,30	0,19	0,12	0,24
Insulin signaling pathway - Mus musculus (mouse) - KEGG	143 (125)	4 (3.2%)	0,19	0,36	-0,24	0,27	0,10	0,15	0,20
Integration of energy metabolism - Reactome	90(79)	1 (1.3%)	0,07	0,22	0,22	0,16	0,12	0,26	0,19
Interconversion of polyamines - Reactome	3(3)	1 (33.3%)	-0,83	0,72	0,45	-0,85	-0,83	0,76	-0,84
Interferon alpha/beta signaling - Reactome	28(20)	1 (5.0%)	-0,48	0,36	-0,18	-0,21	-0,41	0,14	-0,21
Interferon Signaling - Reactome	61(49)	2 (4.1%)	-0,10	0,30	-0,14	0,04	-0,13	0,13	0,00
ISG15 antiviral mechanism - Reactome	25(21)	1 (4.8%)	-0,04	0,33	-0,16	0,12	-0,08	0,20	0,08

L-cysteine degradation I - MouseCyc	3(3)	1 (33.3%)	1,00	0,95	0,51	1,00	0,98	1,00	1,00
L-cysteine degradation VI - MouseCyc	2(2)	1 (50.0%)	1,00	1,00	-1,00	1,00	1,00	1,00	1,00
Leptin and adiponectin - Wikipathways	10(10)	1 (10.0%)	0,17	0,50	-0,21	0,34	0,05	0,20	0,19
Lysosome - Mus musculus (mouse) - KEGG	124 (117)	2 (1.7%)	0,35	0,12	-0,25	0,40	0,29	-0,02	0,34
Lysosome Vesicle Biogenesis - Reactome	23(21)	1 (4.8%)	0,83	0,19	-0,75	0,83	0,75	-0,28	0,77
Maturity onset diabetes of the young - Mus musculus (mouse) - KEGG	26(24)	1 (4.2%)	-0,12	0,29	-0,41	0,03	-0,26	-0,08	-0,11
Membrane Trafficking - Reactome	148(129)	2 (1.6%)	0,39	0,08	-0,29	0,41	0,28	-0,09	0,30
Metabolism - Reactome	1386 (1211)	38 (3.1%)	0,43	0,21	0,03	0,46	0,42	0,18	0,45
Metabolism of amino acids and derivatives - Reactome	143 (130)	7 (5.4%)	0,29	0,18	-0,03	0,34	0,27	0,15	0,32
Metabolism of carbohydrates - Reactome	242 (214)	4 (1.9%)	0,10	0,28	-0,07	0,21	0,06	0,18	0,16
Metabolism of lipids and lipoproteins - Reactome	491 (437)	16 (3.7%)	0,51	0,26	-0,03	0,53	0,49	0,17	0,52
Metabolism of polyamines - Reactome	16(12)	2 (16.7%)	0,33	0,66	0,34	0,58	0,38	0,75	0,61
Metabolism of porphyrins - Reactome	16(14)	1 (7.1%)	0,81	0,42	0,08	0,83	0,77	0,36	0,79
Metabolism of proteins - Reactome	521 (380)	3 (0.8%)	0,17	0,12	0,23	0,20	0,22	0,20	0,24
Metabolism of steroid hormones and vitamin D - Reactome	30(25)	2 (8.0%)	0,97	0,35	0,37	0,97	0,97	0,42	0,96
Metabolism of vitamins and cofactors - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Metabolism of water-soluble vitamins and cofactors - Reactome	73(68)	3 (4.4%)	0,06	0,32	-0,24	0,19	-0,03	0,13	0,11
Metabolism of xenobiotics by cytochrome P450 - Mus musculus (mouse)	96(71)	8 (11.3%)	0,40	0,09	-0,24	0,37	0,32	-0,05	0,30
Metapathway biotransformation - Wikipathways	142 (116)	8 (6.9%)	0,29	0,29	-0,05	0,33	0,26	0,20	0,31
methionine salvage II (mammalia) - MouseCyc	3(2)	1 (50.0%)	1,00	1,00	-1,00	1,00	1,00	1,00	1,00
Methionine salvage pathway - Reactome	6(6)	1 (16.7%)	0,98	0,78	0,78	0,93	0,97	0,94	0,97
Methylation - Reactome	10(9)	1 (11.1%)	0,59	0,71	0,81	0,73	0,75	0,78	0,78
Methylation - Wikipathways	9(9)	1 (11.1%)	0,75	0,70	0,67	0,77	0,76	0,72	0,77
mevalonate pathway I - MouseCyc	11(10)	1 (10.0%)	0,72	0,74	-0,45	0,86	0,64	0,54	0,80
Mineralocorticoid biosynthesis - Reactome	12(7)	1 (14.3%)	1,00	0,32	0,48	1,00	1,00	0,44	1,00
mRNA processing - Wikipathways	465 (395)	1 (0.3%)	0,13	0,21	-0,07	0,22	0,09	0,14	0,18
MyD88 cascade initiated on plasma membrane - Reactome	69(61)	2 (3.3%)	-0,48	-0,61	-0,63	-0,62	-0,60	-0,69	-0,67
MyD88 dependent cascade initiated on endosome - Reactome	75(67)	2 (3.0%)	-0,47	-0,59	-0,62	-0,61	-0,60	-0,68	-0,66
MyD88:Mal cascade initiated on plasma membrane - Reactome	69(61)	2 (3.3%)	-0,48	-0,61	-0,63	-0,62	-0,60	-0,69	-0,67
MyD88-independent cascade - Reactome	89(79)	2 (2.5%)	-0,40	-0,52	-0,58	-0,55	-0,53	-0,63	-0,60
Myometrial Relaxation and Contraction Pathways - Wikipathways	157 (147)	2 (1.4%)	0,10	-0,38	-0,05	-0,12	0,07	-0,33	-0,12
Neuroactive ligand-receptor interaction - Mus musculus (mouse) - KEGG	282 (239)	1 (0.4%)	0,06	0,41	0,10	0,27	0,09	0,36	0,27
Neuronal System - Reactome	254 (220)	1 (0.5%)	0,12	0,25	0,18	0,23	0,17	0,28	0,26
Neurotransmitter Receptor Binding And Downstream Transmission In The Postsynaptic Cell - Reactome	133 (116)	1 (0.9%)	0,12	0,22	0,20	0,21	0,17	0,26	0,25
NGF signalling via TRKA from the plasma membrane - Reactome	184 (171)	1 (0.6%)	0,20	0,26	0,30	0,29	0,28	0,35	0,35
Nicotinate and nicotinamide metabolism -	32(29)	2	0,56	0,74	0,42	0,74	0,61	0,74	0,75

Mus musculus (mouse) - KEGG		(6.9%)							
Nicotine Activity on Dopaminergic Neurons - Wikipathways	10(10)	1 (10.0%)	0,93	-0,22	0,18	0,92	0,95	-0,15	0,94
nicotine degradation II - MouseCyc	56(40)	7 (17.5%)	0,79	0,13	-0,22	0,76	0,77	0,00	0,75
nicotine degradation III - MouseCyc	48(34)	6 (17.6%)	0,79	0,00	-0,25	0,74	0,76	-0,14	0,72
Nitrogen metabolism - Mus musculus (mouse) - KEGG	17(15)	1 (6.7%)	0,57	0,15	0,82	0,58	0,68	0,68	0,68
Nuclear receptors in lipid metabolism and toxicity - Wikipathways	30(28)	2 (7.1%)	-0,03	-0,20	0,04	-0,10	-0,02	-0,16	-0,09
Nuclear signaling by ERBB4 - Reactome	55(46)	1 (2.2%)	0,67	0,21	0,66	0,61	0,73	0,52	0,68
Oligomerization of connexins into connexons - Reactome	3(3)	1 (33.3%)	0,00	-0,87	0,86	-0,25	0,13	-0,54	-0,13
One Carbon Metabolism - Wikipathways	29(26)	1 (3.8%)	0,42	0,15	-0,13	0,46	0,39	0,04	0,43
One carbon metabolism and related pathways - Wikipathways	49(46)	2 (4.3%)	0,36	0,52	-0,18	0,45	0,31	0,35	0,40
Organic anion transport - Reactome	4(4)	1 (25.0%)	0,95	0,97	0,77	0,99	0,96	0,96	0,99
Organic cation/anion/zwitterion transport - Reactome	12(12)	1 (8.3%)	0,79	0,38	0,61	0,84	0,82	0,54	0,85
Ovarian steroidogenesis - Mus musculus (mouse) - KEGG	58(50)	2 (4.0%)	0,96	0,21	0,40	0,96	0,96	0,33	0,96
palmitate biosynthesis I (animals) - MouseCyc	1(1)	1 (100.0%)	-	-	-	-	-	-	-
Pantothenate and CoA biosynthesis - Mus musculus (mouse) - KEGG	16(16)	1 (6.2%)	0,15	-0,05	0,20	0,10	0,24	0,06	0,18
Pentose and glucuronate interconversions - Mus musculus (mouse) - KEGG	34(20)	2 (10.0%)	0,79	0,27	-0,12	0,77	0,74	0,11	0,68
pentose phosphate pathway - MouseCyc	11(10)	2 (20.0%)	0,08	-0,12	-0,65	0,02	-0,24	-0,62	-0,27
Pentose phosphate pathway - Mus musculus (mouse) - KEGG	30(28)	2 (7.1%)	0,02	0,25	-0,36	0,15	-0,11	-0,01	0,01
Pentose Phosphate Pathway - Wikipathways	7(6)	2 (33.3%)	0,66	-0,03	-0,18	0,57	0,58	-0,13	0,52
Pentose phosphate pathway (hexose monophosphate shunt) - Reactome	8(7)	2 (28.6%)	0,45	-0,21	-0,44	0,29	0,28	-0,42	0,16
pentose phosphate pathway (oxidative branch) - MouseCyc	5(5)	2 (40.0%)	0,46	-0,30	-0,62	0,61	0,02	-0,92	-0,18
Peptide hormone biosynthesis - Reactome	11(10)	2 (20.0%)	0,87	0,84	0,87	0,89	0,90	0,90	0,91
Peptide hormone metabolism - Reactome	36(32)	2 (6.2%)	0,64	0,47	0,61	0,71	0,69	0,57	0,73
Peptide ligand-binding receptors - Reactome	188 (145)	2 (1.4%)	-0,44	-0,37	-0,62	-0,52	-0,57	-0,55	-0,60
Peroxisome - Mus musculus (mouse) - KEGG	81(76)	2 (2.6%)	0,36	0,27	-0,26	0,44	0,30	0,08	0,39
Phagosome - Mus musculus (mouse) - KEGG	180 (137)	1 (0.7%)	-0,11	0,20	0,03	-0,02	-0,10	0,19	-0,01
Phase 1 - Functionalization of compounds	102(72)	10 (13.9%)	0,63	0,17	-0,21	0,58	0,55	0,02	0,52
Phase II conjugation - Reactome	67(57)	4 (7.0%)	0,36	0,34	0,40	0,45	0,45	0,44	0,50
phenylalanine degradation III - MouseCyc	6(5)	1 (20.0%)	0,90	-0,26	0,84	0,65	0,93	0,26	0,75
Phenylalanine metabolism - Mus musculus (mouse) - KEGG	24(19)	2 (10.5%)	0,73	0,01	0,28	0,75	0,76	0,13	0,76
Phenylalanine, tyrosine and tryptophan biosynthesis - Mus musculus (mouse) - KEGG	9(7)	1 (14.3%)	0,85	-0,14	0,41	0,42	0,79	-0,01	0,44
Phospholipid metabolism - Reactome	132 (120)	1 (0.8%)	0,12	0,25	0,30	0,19	0,18	0,35	0,24
PI-3K cascade - Reactome	86(82)	1 (1.2%)	0,24	0,30	0,33	0,34	0,34	0,39	0,41
PI3K events in ERBB2 signaling - Reactome	86(82)	1 (1.2%)	0,24	0,30	0,33	0,34	0,34	0,39	0,41
PI3K events in ERBB4 signaling - Reactome	86(82)	1 (1.2%)	0,24	0,30	0,33	0,34	0,34	0,39	0,41

PI3K/AKT activation - Reactome	89(85)	1 (1.2%)	0,24	0,30	0,33	0,34	0,34	0,39	0,41
PI3K/AKT Signaling in Cancer - Reactome	86(82)	1 (1.2%)	0,24	0,30	0,33	0,34	0,34	0,39	0,41
PIP3 activates AKT signaling - Reactome	86(82)	1 (1.2%)	0,24	0,30	0,33	0,34	0,34	0,39	0,41
Platelet activation, signaling and aggregation - Reactome	190 (166)	2 (1.2%)	0,18	0,14	0,13	0,24	0,21	0,17	0,26
Platelet degranulation - Reactome	86(70)	1 (1.4%)	0,28	0,09	-0,08	0,32	0,26	0,04	0,29
PodNet- protein-protein interactions in the podocyte - Wikipathways	315 (295)	1 (0.3%)	0,18	0,13	0,12	0,22	0,20	0,16	0,23
Polyamines are oxidized to amines, aldehydes and H2O2 by PAOs - Reactome	2(2)	1 (50.0%)	-1,00	1,00	1,00	-1,00	-1,00	1,00	-1,00
Porphyrin and chlorophyll metabolism - Mus musculus (mouse) - KEGG	43(27)	3 (11.1%)	0,75	0,27	-0,08	0,77	0,69	0,15	0,69
Postsynaptic nicotinic acetylcholine receptors - Reactome	14(14)	1 (7.1%)	0,55	0,87	0,53	0,82	0,67	0,87	0,85
PPAR signaling pathway - Mus musculus (mouse) - KEGG	81(67)	3 (4.5%)	0,43	0,15	-0,15	0,44	0,37	0,04	0,39
PPAR signaling pathway - Wikipathways	81(67)	3 (4.5%)	0,43	0,15	-0,15	0,44	0,37	0,04	0,39
Presynaptic nicotinic acetylcholine receptors - Reactome	12(12)	1 (8.3%)	0,61	0,88	0,55	0,84	0,70	0,89	0,86
Primary bile acid biosynthesis - Mus musculus (mouse) - KEGG	16(16)	3 (18.8%)	0,06	-0,03	-0,63	0,03	-0,08	-0,32	-0,07
Prion diseases - Mus musculus (mouse) - KEGG	35(32)	3 (9.4%)	0,25	0,44	-0,20	0,39	0,22	0,31	0,35
Propanoate metabolism - Mus musculus (mouse) - KEGG	31(28)	2 (7.1%)	-0,10	0,68	-0,48	0,39	-0,24	0,50	0,27
Protein digestion and absorption - Mus musculus (mouse) - KEGG	88(76)	1 (1.3%)	0,15	0,47	0,21	0,39	0,21	0,46	0,42
Protein processing in endoplasmic reticulum - Mus musculus (mouse) - KEGG	169 (156)	1 (0.6%)	0,25	0,11	-0,21	0,29	0,17	-0,02	0,21
Pyruvate metabolism - Mus musculus (mouse) - KEGG	42(39)	2 (5.1%)	0,15	0,51	-0,27	0,34	0,05	0,29	0,25
Recycling of bile acids and salts - Reactome	12(12)	1 (8.3%)	0,37	0,43	0,01	0,48	0,34	0,23	0,42
Regulation of Cholesterol Biosynthesis by SREBP (SREBF) - Reactome	12(11)	1 (9.1%)	0,04	0,07	-0,74	0,05	-0,27	-0,55	-0,21
Regulation of Complement cascade - Reactome	24(18)	3 (16.7%)	0,46	0,42	-0,05	0,57	0,42	0,28	0,52
Regulation of IFNA signaling - Reactome	27(19)	1 (5.3%)	-0,47	0,37	-0,22	-0,19	-0,41	0,12	-0,21
Regulation of Insulin Secretion - Reactome	69(60)	1 (1.7%)	0,02	0,21	0,36	0,10	0,10	0,32	0,17
Regulation of Insulin Secretion by Acetylcholine - Reactome	10(10)	1 (10.0%)	0,19	0,29	0,80	0,27	0,36	0,51	0,38
Regulation of Insulin Secretion by Fatty Acids Bound to GPR40 (FFAR1) - Reactome	8(7)	1 (14.3%)	0,46	0,44	0,86	0,50	0,73	0,64	0,63
Regulation of Insulin Secretion by Free Fatty Acids - Reactome	8(7)	1 (14.3%)	0,46	0,44	0,86	0,50	0,73	0,64	0,63
Regulation of Insulin-like Growth Factor (IGF) Transport and Uptake by Insulin-like Growth Factor Binding Proteins (IGFBPs) - Reactome	31(28)	1 (3.6%)	-0,22	-0,43	0,57	-0,49	-0,03	-0,33	-0,40
Regulation of thyroid hormone activity - Reactome	2(2)	1 (50.0%)	-1,00	1,00	-1,00	-1,00	-1,00	1,00	-1,00
Response to elevated platelet cytosolic Ca2+ - Reactome	92(75)	1 (1.3%)	0,27	0,11	-0,07	0,32	0,26	0,07	0,30
Retinol metabolism - Mus musculus (mouse) - KEGG	87(56)	8 (14.3%)	0,81	0,21	-0,21	0,76	0,75	0,07	0,70
Retinol metabolism - Wikipathways	39(38)	1 (2.6%)	0,41	0,37	0,16	0,54	0,43	0,35	0,53
Reversible Hydration of Carbon Dioxide - Reactome	12(11)	1 (9.1%)	0,91	0,18	0,85	0,90	0,92	0,76	0,92
RIG-I/MDA5 mediated induction of IFN-alpha/beta pathways - Reactome	45(40)	2 (5.0%)	-0,61	-0,69	-0,80	-0,74	-0,76	-0,78	-0,79
RIP-mediated NFkB activation via ZBP1 - Reactome	21(20)	2 (10.0%)	-0,73	-0,76	-0,84	-0,79	-0,82	-0,82	-0,83
Role of LAT2/NTAL/LAB on calcium mobilization - Reactome	96(87)	1 (1.1%)	0,23	0,31	0,34	0,34	0,33	0,40	0,41

Scavenging by Class B Receptors - Reactome	6(6)	2 (33.3%)	-0,82	-0,78	-0,73	-0,81	-0,78	-0,77	-0,79
Selenium metabolism-Selenoproteins - Wikipathways	47(41)	2 (4.9%)	0,16	0,09	0,01	0,17	0,14	0,07	0,16
Serotonergic synapse - Mus musculus (mouse) - KEGG	130(116)	1 (0.9%)	0,44	0,01	-0,11	0,36	0,40	-0,03	0,31
serotonin and melatonin biosynthesis - MouseCyc	5(4)	1 (25.0%)	1,00	-0,38	-0,38	0,98	1,00	-0,39	0,97
Serotonin and melatonin biosynthesis - Reactome	4(4)	1 (25.0%)	1,00	-0,38	-0,38	0,98	1,00	-0,39	0,97
SHC1 events in ERBB2 signaling - Reactome	24(24)	1 (4.2%)	0,66	0,48	0,65	0,75	0,69	0,76	0,78
SHC1 events in ERBB4 signaling - Reactome	19(19)	1 (5.3%)	0,68	0,46	0,77	0,76	0,73	0,80	0,79
SIDS Susceptibility Pathways - Wikipathways	61(57)	1 (1.8%)	0,74	0,05	0,18	0,73	0,76	0,13	0,72
Signal amplification - Reactome	16(14)	1 (7.1%)	0,50	0,36	0,64	0,50	0,66	0,62	0,63
Signal Transduction - Reactome	1870 (1160)	4 (0.3%)	-0,01	0,04	-0,12	0,01	-0,05	-0,03	-0,03
Signaling by EGFR - Reactome	161 (150)	1 (0.7%)	0,23	0,26	0,23	0,31	0,28	0,31	0,34
Signaling by EGFR in Cancer - Reactome	163 (152)	1 (0.7%)	0,21	0,25	0,21	0,30	0,26	0,29	0,32
Signaling by ERBB2 - Reactome	144 (133)	1 (0.8%)	0,20	0,24	0,20	0,27	0,24	0,27	0,30
Signaling by ERBB4 - Reactome	154 (137)	1 (0.7%)	0,25	0,23	0,25	0,32	0,31	0,30	0,36
Signaling by FGFR - Reactome	144 (132)	1 (0.8%)	0,21	0,27	0,20	0,30	0,26	0,30	0,32
Signaling by FGFR in disease - Reactome	155 (143)	1 (0.7%)	0,15	0,30	0,16	0,26	0,19	0,30	0,28
Signaling by GPCR - Reactome	1162 (502)	3 (0.6%)	-0,18	-0,08	-0,28	-0,19	-0,25	-0,20	-0,24
Signaling by PDGF - Reactome	160 (152)	1 (0.7%)	0,14	0,27	0,26	0,23	0,21	0,33	0,28
Signaling by SCF-KIT - Reactome	125 (120)	1 (0.8%)	0,14	0,31	0,25	0,25	0,21	0,35	0,30
Signaling by the B Cell Receptor (BCR) - Reactome	134 (125)	1 (0.8%)	0,18	0,15	0,27	0,22	0,26	0,25	0,29
Signalling by NGF - Reactome	275 (254)	1 (0.4%)	0,20	0,27	0,21	0,29	0,25	0,31	0,32
SLC-mediated transmembrane transport - Reactome	249 (229)	4 (1.7%)	0,28	0,27	0,17	0,36	0,30	0,29	0,36
sphingosine and sphingosine-1-phosphate metabolism - MouseCyc	9(9)	1 (11.1%)	0,46	0,66	0,10	0,59	0,43	0,50	0,54
Spinal Cord Injury - Wikipathways	103(95)	1 (1.1%)	0,10	0,26	0,14	0,24	0,13	0,28	0,24
Staphylococcus aureus infection - Mus musculus (mouse) - KEGG	52(44)	2 (4.5%)	0,19	0,07	-0,03	0,22	0,17	0,04	0,21
Starch and sucrose metabolism - Mus musculus (mouse) - KEGG	54(36)	2 (5.6%)	0,43	0,13	-0,08	0,39	0,36	0,06	0,33
Steroid biosynthesis - Mus musculus (mouse) - KEGG	17(17)	1 (5.9%)	0,54	0,22	-0,11	0,57	0,52	0,12	0,55
Steroid Biosynthesis - Wikipathways	13(11)	2 (18.2%)	0,98	0,25	0,50	0,99	0,98	0,44	0,98
Steroid hormone biosynthesis - Mus musculus (mouse) - KEGG	58(40)	7 (17.5%)	0,86	0,17	0,32	0,86	0,86	0,28	0,85
Steroid hormones - Reactome	30(25)	2 (8.0%)	0,97	0,35	0,37	0,97	0,97	0,42	0,96
Sterols are 12-hydroxylated by CYP8B1 - Reactome	1(1)	1 (100.0%)	-	-	-	-	-	-	-
Sulfur amino acid metabolism - Reactome	25(24)	3 (12.5%)	0,71	0,60	-0,09	0,75	0,65	0,47	0,71
superpathway of cholesterol biosynthesis - MouseCyc	25(24)	2 (8.3%)	0,57	0,61	-0,13	0,66	0,53	0,47	0,63
superpathway of methionine degradation - MouseCyc	19(18)	2 (11.1%)	0,49	0,21	0,01	0,53	0,48	0,17	0,51
Synthesis of (16-20)-hydroxyeicosatetraenoic acids (HETE) - Reactome	26(16)	1 (6.2%)	0,84	0,22	-0,28	0,80	0,77	0,01	0,73

Synthesis of bile acids and bile salts - Reactome	27(27)	3 (11.1%)	0,07	0,11	-0,47	0,09	-0,04	-0,10	0,01
Synthesis of bile acids and bile salts via 24-hydroxycholesterol - Reactome	18(18)	2 (11.1%)	-0,09	0,27	-0,54	0,10	-0,28	0,01	-0,06
Synthesis of bile acids and bile salts via 27-hydroxycholesterol - Reactome	14(14)	2 (14.3%)	0,36	0,16	-0,07	0,38	0,34	0,14	0,37
Synthesis of bile acids and bile salts via 7alpha-hydroxycholesterol - Reactome	23(23)	1 (4.3%)	-0,15	0,00	-0,24	-0,12	-0,18	-0,08	-0,14
Synthesis of Leukotrienes (LT) and Eoxins (EX) - Reactome	16(13)	1 (7.7%)	0,08	0,70	0,18	0,26	0,11	0,58	0,27
Synthesis of Lipoxins (LX) - Reactome	6(5)	1 (20.0%)	-0,18	0,56	0,25	-0,13	-0,13	0,63	-0,07
Synthesis of PC - Reactome	18(16)	1 (6.2%)	0,06	0,06	0,71	0,07	0,22	0,58	0,22
Synthesis of PE - Reactome	12(10)	1 (10.0%)	0,27	0,07	0,75	0,28	0,41	0,70	0,41
Synthesis of very long-chain fatty acyl-CoAs - Reactome	13(12)	2 (16.7%)	0,88	0,22	-0,67	0,88	0,87	-0,28	0,87
Systemic lupus erythematosus - Mus musculus (mouse) - KEGG	147(56)	3 (5.4%)	-0,14	0,53	-0,22	0,04	-0,16	0,40	0,00
TAK1 activates NFkB by phosphorylation and activation of IKKs complex - Reactome	26(23)	2 (8.7%)	-0,63	-0,72	-0,88	-0,72	-0,78	-0,81	-0,79
Taurine and hypotaurine metabolism - Mus musculus (mouse) - KEGG	10(9)	1 (11.1%)	0,95	0,92	-0,71	0,98	0,92	0,84	0,99
Terminal pathway of complement - Reactome	7(6)	3 (50.0%)	0,16	0,44	-0,41	0,46	0,01	0,27	0,40
Terpenoid backbone biosynthesis - Mus musculus (mouse) - KEGG	22(18)	1 (5.6%)	0,71	0,64	-0,36	0,83	0,66	0,43	0,78
tetrapyrrole biosynthesis II - MouseCyc	5(5)	1 (20.0%)	0,98	0,65	0,32	0,99	0,96	0,57	0,97
TGF-beta signaling pathway - Mus musculus (mouse) - KEGG	82(75)	2 (2.7%)	0,59	0,25	0,37	0,65	0,66	0,34	0,67
Thrombin signalling through proteinase activated receptors (PARs) - Reactome	17(17)	1 (5.9%)	0,22	0,33	0,66	0,40	0,38	0,53	0,51
Thromboxane signalling through TP receptor - Reactome	8(8)	1 (12.5%)	0,69	0,50	0,78	0,66	0,80	0,68	0,74
thyroid hormone metabolism I (via deiodination) - MouseCyc	3(2)	1 (50.0%)	-1,00	1,00	-1,00	-1,00	-1,00	1,00	-1,00
Thyroxine biosynthesis - Reactome	7(7)	1 (14.3%)	-0,70	0,19	-0,29	-0,37	-0,88	0,06	-0,44
TNF-alpha NF-kB Signaling Pathway - Wikipathways	184 (169)	1 (0.6%)	0,30	0,34	0,00	0,41	0,28	0,27	0,38
Toll Like Receptor 10 (TLR10) Cascade - Reactome	69(61)	2 (3.3%)	-0,48	-0,61	-0,63	-0,62	-0,60	-0,69	-0,67
Toll Like Receptor 2 (TLR2) Cascade - Reactome	73(65)	2 (3.1%)	-0,41	-0,59	-0,60	-0,58	-0,54	-0,67	-0,63
Toll Like Receptor 3 (TLR3) Cascade - Reactome	89(79)	2 (2.5%)	-0,40	-0,52	-0,58	-0,55	-0,53	-0,63	-0,60
Toll Like Receptor 4 (TLR4) Cascade - Reactome	106(94)	2 (2.1%)	-0,39	-0,48	-0,56	-0,54	-0,52	-0,61	-0,60
Toll Like Receptor 5 (TLR5) Cascade - Reactome	69(61)	2 (3.3%)	-0,48	-0,61	-0,63	-0,62	-0,60	-0,69	-0,67
Toll Like Receptor 7/8 (TLR7/8) Cascade - Reactome	75(67)	2 (3.0%)	-0,47	-0,59	-0,62	-0,61	-0,60	-0,68	-0,66
Toll Like Receptor 9 (TLR9) Cascade - Reactome	79(71)	2 (2.8%)	-0,46	-0,58	-0,62	-0,60	-0,59	-0,67	-0,65
Toll Like Receptor TLR1:TLR2 Cascade - Reactome	69(61)	2 (3.3%)	-0,48	-0,61	-0,63	-0,62	-0,60	-0,69	-0,67
Toll Like Receptor TLR6:TLR2 Cascade - Reactome	73(65)	2 (3.1%)	-0,41	-0,59	-0,60	-0,58	-0,54	-0,67	-0,63
Toll-Like Receptors Cascades - Reactome	126 (114)	2 (1.8%)	-0,32	-0,44	-0,54	-0,48	-0,45	-0,58	-0,55
Toxoplasmosis - Mus musculus (mouse) - KEGG	113 (105)	1 (1.0%)	-0,13	0,32	-0,11	0,04	-0,15	0,22	0,01
TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation - Reactome	73(65)	2 (3.1%)	-0,46	-0,60	-0,63	-0,61	-0,60	-0,69	-0,66
TRAF6 Mediated Induction of proinflammatory cytokines - Reactome	63(57)	2 (3.5%)	-0,50	-0,61	-0,64	-0,63	-0,62	-0,69	-0,68
TRAF6 mediated NF-kB activation - Reactome	24(22)	2 (9.1%)	-0,76	-0,74	-0,85	-0,81	-0,85	-0,81	-0,84
trans-Golgi Network Vesicle Budding - Reactome	61(52)	1	0,62	0,15	-0,43	0,69	0,50	-0,09	0,56

tome		(1.9%)							
Transmembrane transport of small molecules - Reactome	499 (443)	4 (0.9%)	0,21	0,29	0,13	0,31	0,23	0,28	0,32
Transmission across Chemical Synapses - Reactome	178 (158)	1 (0.6%)	0,14	0,29	0,21	0,26	0,19	0,32	0,29
Transport of connexins along the secretory pathway - Reactome	3(3)	1 (33.3%)	0,00	-0,87	0,86	-0,25	0,13	-0,54	-0,13
Transport of connexons to the plasma membrane - Reactome	2(2)	1 (50.0%)	1,00	-1,00	1,00	-1,00	1,00	-1,00	-1,00
Transport of glucose and other sugars, bile salts and organic acids, metal ions and amine compounds - Reactome	95(91)	2 (2.2%)	0,26	0,25	0,24	0,37	0,33	0,31	0,41
Transport of inorganic cations/anions and amino acids/oligopeptides - Reactome	93(85)	1 (1.2%)	0,35	0,23	0,24	0,46	0,38	0,35	0,48
Transport of organic anions - Reactome	12(11)	1 (9.1%)	0,46	0,52	-0,03	0,64	0,46	0,36	0,60
Transport of vitamins, nucleosides, and related molecules - Reactome	33(28)	1 (3.6%)	0,32	0,38	0,02	0,42	0,32	0,28	0,40
TRIF-mediated TLR3/TLR4 signaling - Reactome	89(79)	2 (2.5%)	-0,40	-0,52	-0,58	-0,55	-0,53	-0,63	-0,60
Triglyceride Biosynthesis - Reactome	36(33)	5 (15.2%)	0,70	0,30	-0,14	0,71	0,69	0,04	0,70
Tryptophan metabolism - Mus musculus (mouse) - KEGG	47(39)	2 (5.1%)	0,60	0,35	-0,01	0,67	0,57	0,29	0,64
Tryptophan metabolism - Wikipathways	44(41)	2 (4.9%)	0,66	0,06	0,07	0,65	0,66	0,08	0,65
Type II diabetes mellitus - Mus musculus (mouse) - KEGG	50(48)	1 (2.1%)	0,05	0,24	-0,16	0,14	-0,02	0,08	0,07
Tyrosine metabolism - Mus musculus (mouse) - KEGG	44(39)	4 (10.3%)	0,63	0,44	0,33	0,75	0,67	0,48	0,76
Valine, leucine and isoleucine degradation - Mus musculus (mouse) - KEGG	53(47)	1 (2.1%)	0,39	0,34	0,16	0,45	0,40	0,35	0,45
Vascular smooth muscle contraction - Mus musculus (mouse) - KEGG	128 (110)	1 (0.9%)	0,65	0,20	-0,04	0,65	0,62	0,14	0,60
Vitamin B5 (pantothenate) metabolism - Reactome	9(9)	1 (11.1%)	-0,29	0,57	-0,86	-0,10	-0,49	-0,39	-0,33
Vitamin B6 metabolism - Mus musculus (mouse) - KEGG	10(8)	1 (12.5%)	0,57	0,88	0,40	0,76	0,61	0,90	0,78
Xenobiotics - Reactome	41(25)	3 (12.0%)	0,61	0,01	-0,40	0,55	0,51	-0,30	0,48
XPodNet - protein-protein interactions in the podocyte expanded by STRING - Wikipathways	831(779)	1 (0.1%)	0,16	0,17	0,15	0,22	0,18	0,21	0,24
ZBP1(DAI) mediated induction of type I IFNs - Reactome	31(28)	2 (7.1%)	-0,65	-0,72	-0,83	-0,75	-0,78	-0,81	-0,80

U: Transcription factor binding sites (TFBs) with a z-score > 5 or a Fischer-score > 5 addressed by the upregulated CR genes and the overlap with the phytonutrients

(TF = transcription factor, R = resveratrol, P = phloridzin, Qd= quercetin (diet), Qi = quercetin (intraperitoneal), Gi = genistein (intraperitoneal))

JASPAR ID	TF	R	P	Qd	Qi	Gi
MA0099.2	AP1					
MA0007.1	Ar	■		■		
MA0151.1	ARID3A					
MA0004.1	Arnt	■	■	■	■	■
MA0006.1	Arnt::Ahr	■	■	■	■	■
PB0003.1	Ascl2_1		■	■	■	■
PB0004.1	Atf1_1	■	■	■	■	■
PB0007.1	Bhlhb2_1	■	■	■	■	■
MA0102.2	CEBPA					
MA0018.2	CREB1	■	■	■	■	■
MA0139.1	CTCF		■	■	■	■
MA0019.1	Ddit3::Cebpa					
MA0024.1	E2F1			■	■	■
PB0008.1	E2F2_1	■	■	■	■	■

PB0009.1	E2F3_1	
MA0154.1	EBF1	
PB0010.1	Egr1_1	
PB0114.1	Egr1_2	
PB0011.1	Ehf_1	
PB0012.1	Elf3_1	
MA0136.1	ELF5	
MA0028.1	ELK1	
MA0076.1	ELK4	
PB0014.1	Esrra_1	
PB0118.1	Esrra_2	
MA0141.1	Esrrb	
MA0156.1	FEV	
MA0148.1	FOXA1	
MA0041.1	Foxd3	
MA0157.1	FOXO3	
MA0035.2	Gata1	
PB0024.1	Gcm1_1	
MA0038.1	Gfi	
PB0027.1	Gmeb1_1	
MA0092.1	Hand1::Tcf2a	
PB0029.1	Hic1_1	
PB0133.1	Hic1_2	
MA0259.1	HIF1A::ARNT	
MA0043.1	HLF	
MA0114.1	HNF4A	
PB0030.1	Hnf4a_1	
MA0158.1	HOXA5	
MA0155.1	INSM1	
MA0050.1	IRF1	
PB0139.1	Irf5_2	
PB0038.1	Jundm2_1	
PB0142.1	Jundm2_2	
MA0039.2	Klf4	
PB0039.1	Klf7_1	
MA0058.1	MAX	
PB0043.1	Max_1	
MA0100.1	Myb	
PB0150.1	Mybl1_2	
MA0147.1	Myc	
MA0059.1	MYC::MAX	
MA0104.2	Mycn	
PB0047.1	Myf6_1	
MA0056.1	MZF1_1-4	
MA0057.1	MZF1_5-13	
MA0152.1	NFATC2	
MA0061.1	NF-kappaB	
MA0105.1	NFKB1	
MA0060.1	NFYA	
MA0063.1	Nkx2-5	
MA0122.1	Nkx3-2	
MA0125.1	Nobox	
MA0115.1	NR1H2::RXRA	
PB0049.1	Nr2f2_1	
PB0153.1	Nr2f2_2	

MA0113.1	NR3C1		
MA0160.1	NR4A2	[REDACTED]	
MA0068.1	Pax4		
MA0132.1	Pdx1		
PB0156.1	Plagl1_2	[REDACTED]	[REDACTED]
MA0066.1	PPARG		
MA0065.2	PPARG::RXRA	[REDACTED]	[REDACTED]
MA0075.1	Prrx2		
PB0053.1	Rara_1		
PB0157.1	Rara_2	[REDACTED]	[REDACTED]
MA0101.1	REL	[REDACTED]	[REDACTED]
MA0107.1	RELA	[REDACTED]	[REDACTED]
PB0158.1	Rfx3_2	[REDACTED]	[REDACTED]
PB0160.1	Rfxdc2_2	[REDACTED]	[REDACTED]
MA0071.1	RORA_1		
MA0073.1	RREB1	[REDACTED]	[REDACTED]
MA0002.2	RUNX1	[REDACTED]	[REDACTED]
MA0074.1	RXRA::VDR	[REDACTED]	[REDACTED]
PB0057.1	Rxra_1	[REDACTED]	[REDACTED]
PB0058.1	Sfpi1_1	[REDACTED]	[REDACTED]
PB0060.1	Smad3_1	[REDACTED]	[REDACTED]
PB0164.1	Smad3_2	[REDACTED]	[REDACTED]
MA0078.1	Sox17		
MA0079.2	SP1	[REDACTED]	[REDACTED]
PB0076.1	Sp4_1	[REDACTED]	[REDACTED]
PB0180.1	Sp4_2	[REDACTED]	[REDACTED]
PB0077.1	Spdef_1	[REDACTED]	[REDACTED]
MA0080.2	SPI1		
MA0081.1	SPIB	[REDACTED]	[REDACTED]
MA0111.1	Spz1	[REDACTED]	[REDACTED]
MA0083.1	SRF	[REDACTED]	[REDACTED]
MA0084.1	SRY		
MA0144.1	Stat3	[REDACTED]	[REDACTED]
PB0085.1	Tcfap2a_1	[REDACTED]	[REDACTED]
PB0086.1	Tcfap2b_1	[REDACTED]	[REDACTED]
PB0190.1	Tcfap2b_2	[REDACTED]	[REDACTED]
PB0088.1	Tcfap2e_1	[REDACTED]	[REDACTED]
MA0145.1	Tcfcp2l1	[REDACTED]	[REDACTED]
MA0093.1	USF1	[REDACTED]	[REDACTED]
MA0095.1	YY1	[REDACTED]	[REDACTED]
MA0103.1	ZEB1	[REDACTED]	[REDACTED]
PB0095.1	Zfp161_1	[REDACTED]	[REDACTED]
PB0200.1	Zfp187_2	[REDACTED]	[REDACTED]
PB0097.1	Zfp281_1	[REDACTED]	[REDACTED]
PB0098.1	Zfp410_1	[REDACTED]	[REDACTED]
MA0116.1	Zfp423	[REDACTED]	[REDACTED]
PB0100.1	Zfp740_1	[REDACTED]	[REDACTED]
MA0146.1	Zfx		
PB0205.1	Zic1_2	[REDACTED]	[REDACTED]
PB0206.1	Zic2_2	[REDACTED]	[REDACTED]
PB0207.1	Zic3_2	[REDACTED]	[REDACTED]
MA0130.1	ZNF354C	[REDACTED]	[REDACTED]

V: Transcription factor binding sites (TFBs) with a z-score > 5 or a Fischer-score > 5 addressed by the downregulated CR genes and the overlap with the phytonutrients

(TF = transcription factor, R = resveratrol, P = phloridzin, Qd= quercetin (diet), Qi = quercetin (intraperitoneal), Gi = genistein (intraperitoneal))

JASPAR ID	TF	R	P	Qd	Qi	Gi
MA0099.2	AP1					
MA0151.1	ARID3A					
PB0002.1	Arid5a_1					
MA0006.1	Arnt::Ahr					
PB0004.1	Atf1_1					
PB0007.1	Bhlhb2_1					
MA0102.2	CEBPA					
PB0113.1	E2F3_2					
PB0012.1	Elf3_1					
MA0136.1	ELF5					
PB0014.1	Esrra_1					
MA0148.1	FOXA1					
MA0047.2	Foxa2					
PB0015.1	Foxa2_1					
MA0031.1	FOXD1					
MA0041.1	Foxd3					
MA0042.1	FOX11					
PB0016.1	Foxj1_1					
PB0017.1	Foxj3_1					
PB0121.1	Foxj3_2					
PB0018.1	Foxk1_1					
PB0122.1	Foxk1_2					
PB0019.1	Foxl1_1					
PB0123.1	Foxl1_2					
MA0157.1	FOXO3					
MA0040.1	Foxq1					
MA0062.2	GABPA					
PB0020.1	Gabpa_1					
PB0021.1	Gata3_1					
PB0022.1	Gata5_1					
PB0028.1	Hbp1_1					
MA0043.1	HLF					
MA0046.1	HNF1A					
MA0153.1	HNF1B					
MA0114.1	HNF4A					
PB0134.1	Hnf4a_2					
PB0135.1	Hoxa3_2					
MA0158.1	HOXA5					
PB0032.1	IRC900814_1					
MA0050.1	IRF1					
MA0051.1	IRF2					
PB0035.1	Irf5_1					
PB0037.1	Isgf3g_1					
PB0143.1	Klf7_2					
MA0135.1	Lhx3					
PB0145.1	Mafb_2					
PB0043.1	Max_1					
PB0147.1	Max_2					
MA0052.1	MEF2A					
MA0056.1	MZF1_1-4					
MA0152.1	NFATC2					

MA0150.1	NFE2L2				
MA0060.1	NFYA				
MA0063.1	Nkx2-5				
MA0124.1	NKX3-1				
MA0122.1	Nkx3-2				
MA0125.1	Nobox				
MA0017.1	NR2F1				
MA0160.1	NR4A2				
PB0050.1	Osr1_1				
MA0069.1	Pax6				
MA0132.1	Pdx1				
MA0075.1	Prrx2				
PB0158.1	Rfx3_2				
PB0160.1	Rfxdc2_2				
MA0072.1	RORA_2				
PB0163.1	Six6_2				
PB0061.1	Sox11_1				
PB0165.1	Sox11_2				
PB0062.1	Sox12_1				
PB0166.1	Sox12_2				
PB0063.1	Sox13_1				
PB0064.1	Sox14_1				
PB0066.1	Sox17_1				
PB0067.1	Sox18_1				
PB0069.1	Sox21_1				
PB0070.1	Sox30_1				
PB0071.1	Sox4_1				
MA0087.1	Sox5				
PB0073.1	Sox7_1				
PB0074.1	Sox8_1				
MA0080.2	SPI1				
MA0081.1	SPIB				
MA0084.1	SRY				
PB0079.1	Sry_1				
MA0108.2	TBP				
PB0080.1	Tbp_1				
MA0095.1	YY1				
MA0103.1	ZEB1				
PB0093.1	Zfp105_1				
PB0095.1	Zfp161_1				
PB0199.1	Zfp161_2				
PB0096.1	Zfp187_1				
MA0130.1	ZNF354C				

W: All mentioned functions / biological processes revealed by UniProt database for the transcription factors (TF), which address the top TFs of caloric restriction

TF	Function	biological process
Ahr	Ligand-activated transcriptional activator. Binds to the XRE promoter region of genes it activates. Activates the expression of multiple phase I and II xenobiotic chemical metabolizing enzyme genes (such as the CYP1A1 gene). Mediates biochemical and toxic effects of halogenated aromatic hydrocarbons. Involved in	B cell differentiation; B (B-1) cell homeostasis; blood circulation; blood vessel development / morphogenesis / remodeling, camera-type eye development, cardiac left ventricle morphogenesis, cell cycle, cell morphogenesis, cellular response to cAMP, circadian regulation of gene expression, circumferential growth involved in left ventricle morphogenesis, common bile duct development, embryonic hemo-

	<p>cell-cycle regulation. Likely to play an important role in the development and maturation of many tissues. Regulates the circadian clock by inhibiting the basal and circadian expression of the core circadian component PER1. Inhibits PER1 by repressing the CLOCK-ARNTL/BMAL1 heterodimer mediated transcriptional activation of PER1.</p>	<p>poiesis, gland development, glomerulus morphogenesis, immune system process, intracellular receptor signaling pathway, kidney morphogenesis, liver development, lymphocyte homeostasis, negative regulation of necrotic cell death, negative regulation of systemic arterial blood pressure, negative regulation of transcription from RNA polymerase II promoter, negative regulation of vasoconstriction, patterning of blood vessels, positive regulation of cell size, positive regulation of growth rate, positive regulation of RNA polymerase II transcriptional preinitiation complex assembly, post-embryonic hemopoiesis, prostate gland development, regulation of B cell proliferation, regulation of blood pressure, regulation of blood vessel size, regulation of gene expression, regulation of heart growth, regulation of transcription, DNA-templated, reproductive structure development, response to stress, response to toxic substance, response to xenobiotic stimulus, smooth muscle tissue development, spleen development, T cell homeostasis, venous blood vessel development, xenobiotic metabolic process</p>
Arid5a	<p>DNA-binding protein that may regulate transcription and act as a repressor by binding to AT-rich stretches in the promoter region of target genes</p>	<p>chondrocyte differentiation, positive regulation of histone acetylation, positive regulation of transcription from RNA polymerase II promoter, transcription, DNA-templated</p>
Arnt	<p>Required for activity of the Ah (dioxin) receptor. This protein is required for the ligand-binding subunit to translocate from the cytosol to the nucleus after ligand binding. The complex then initiates transcription of genes involved in the activation of PAH procarcinogens. The heterodimer with HIF1A or EPAS1/HIF2A functions as a transcriptional regulator of the adaptive response to hypoxia</p>	<p>cell differentiation, embryonic placenta development, intracellular receptor signaling pathway, positive regulation of hormone biosynthetic process, positive regulation of protein sumoylation, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, positive regulation of vascular endothelial growth factor production, regulation of transcription from RNA polymerase II promoter in response to oxidative stress, response to hypoxia, response to toxic substance, transcription, DNA-templated</p>
Cebpa	<p>Transcription factor that coordinates proliferation arrest and the differentiation of myeloid progenitors, adipocytes, hepatocytes, and cells of the lung and the placenta; Binds directly to the consensus DNA sequence 5'-T[TG]NNGNAA[TG]-3' acting as an activator on distinct target genes. During early embryogenesis, plays essential and redundant functions with CEBPB. Essential for the transition from common myeloid progenitors (CMP) to granulocyte/monocyte progenitors (GMP). Critical for the proper development of the liver and the lung. Necessary for terminal adipocyte differentiation, is required for postnatal maintenance of systemic energy homeostasis and lipid storage. To regulate these different processes at the proper moment and tissue, interplays with other transcription factors and modulators. Downregulates the expression of genes that maintain cells in an undifferentiated and proliferative state through E2F1 repression, which is critical for its ability to induce adipocyte and granulocyte terminal differentiation. Reciprocally E2F1 blocks adipocyte differentiation by binding to specific promoters and repressing CEBPA binding to its target gene promoters. Proliferation arrest also depends on a func-</p>	<p>brown fat cell differentiation; cell maturation, cellular response to lithium ion, cellular response to organic cyclic compound, cholesterol metabolic process, cytokine-mediated signaling pathway, embryonic placenta development, fat cell differentiation, glucose homeostasis, granulocyte differentiation, inner ear development, lipid homeostasis, liver development, lung development, macrophage differentiation, mitochondrion organization, myeloid cell differentiation, negative regulation of cell cycle, negative regulation of cell proliferation, negative regulation of transcription, DNA-templated, negative regulation of transcription from RNA polymerase II promoter, Notch signaling pathway, positive regulation of fat cell differentiation, positive regulation of osteoblast differentiation, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase III promoter, positive regulation of transcription from RNA polymerase II promoter, regulation of cell proliferation, regulation of transcription, DNA-templated, regulation of transcription from RNA polymerase II promoter, transcription, DNA-templated, transcription from RNA polymerase II promoter, transcription from RNA polymerase I promoter, urea cycle, white fat cell differentiation</p>

	<p>tional binding to SWI/SNF complex. In liver, regulates gluconeogenesis and lipogenesis through different mechanisms. To regulate gluconeogenesis, functionally cooperates with FOXO1 binding to IRE-controlled promoters and regulating the expression of target genes such as PCK1 or G6PC. To modulate lipogenesis, interacts and transcriptionally synergizes with SREBF1 in promoter activation of specific lipogenic target genes such as ACAS2. In adipose tissue, seems to act as FOXO1 coactivator accessing to ADIPOQ promoter through FOXO1 binding sites</p>	
Esrrb	<p>Nuclear receptor, may regulate ESR1 transcriptional activity. Induces the expression of PERM1 in the skeletal muscle</p>	<p>embryonic placenta development, in utero embryonic development, positive regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-templated, stem cell population maintenance, trophoblastic cell proliferation / morphogenesis</p>
Fos	<p>Nuclear phosphoprotein which forms a tight but non-covalently linked complex with the JUN/AP-1 transcription factor. On TGF-beta activation, forms a multimeric SMAD3/SMAD4/JUN/FOS complex, at the AP1/SMAD-binding site to regulate TGF-beta-mediated signaling. Has a critical function in regulating the development of cells destined to form and maintain the skeleton. It is thought to have an important role in signal transduction, cell proliferation and differentiation. In growing cells, activates phospholipid synthesis, possibly by activating CDS1 and PI4K2A. This activity requires Tyr-dephosphorylation and association with the endoplasmic reticulum.</p>	<p>ageing, cellular response to calcium ion, cellular response to extracellular stimulus, cellular response to hormone stimulus, cellular response to reactive oxygen species, conditioned taste aversion, female pregnancy, nervous system development, positive regulation of osteoclast differentiation, positive regulation of pri-miRNA transcription from RNA polymerase II promoter, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, response to cAMP, response to cold, response to corticosterone, response to cytokine, response to drug, response to gravity, response to immobilization stress, response to light stimulus, response to lipopolysaccharide, response to muscle stretch, response to progesterone, response to toxic substance, skeletal muscle cell differentiation, sleep, SMAD protein signal transduction, transforming growth factor beta receptor signaling pathway</p>
Foxd3	<p>Binds to the consensus sequence 5'-A[AT]T[AG]TTTTGTTT-3' and acts as a transcriptional repressor. Also acts as a transcriptional activator. Promotes development of neural crest cells from neural tube progenitors. Restricts neural progenitor cells to the neural crest lineage while suppressing interneuron differentiation. Required for maintenance of pluripotent cells in the pre-implantation and peri-implantation stages of embryogenesis</p>	<p>embryonic placenta development, in utero embryonic development, negative regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter, transcription, DNA-templated, trophoblastic cell differentiation</p>
Foxj1	<p>Transcription factor required for motile ciliogenesis</p>	<p>actin cytoskeleton organization, activation of GTPase activity, brain development, cell differentiation, central tolerance induction, cilium assembly, cilium morphogenesis, determination of left/right symmetry, epithelium development, establishment of apical/basal cell polarity, glomerular parietal epithelial cell development, heart development, humoral immune response, left/right pattern formation, leukocyte migration, metanephric part of ureteric bud development, negative regulation of B cell activation, negative regulation of germinal center formation, negative regulation of humoral immune response mediated by circulating immunoglobulin, negative regulation of interleukin-6 biosynthetic process, negative regulation of NF-kappaB transcription factor activity, negative regulation of T cell differentia-</p>

		tion in thymus, negative regulation of T cell proliferation, negative regulation of transcription from RNA polymerase II promoter, positive regulation of central B cell tolerance induction, positive regulation of lung ciliated cell differentiation, positive regulation of transcription from RNA polymerase II promoter, regulation of epithelial cell differentiation, transcription from RNA polymerase II promoter
Foxj3	Transcriptional activator of MEF2C involved in the regulation of adult muscle fiber type identity and skeletal muscle regeneration	anatomical structure morphogenesis; cell differentiation; regulation of transcription from RNA polymerase II promoter; transcription, DNA-templated
Foxl1	Transcription factor required for proper proliferation and differentiation in the gastrointestinal epithelium. Target gene of the hedgehog (Hh) signaling pathway via GLI2 AND GLI3 transcription factors.	cell differentiation, heart development, Peyer's patch morphogenesis, proteoglycan biosynthetic process, regulation of transcription, DNA-templated, regulation of transcription from RNA polymerase II promoter, regulation of Wnt signaling pathway, transcription, DNA-templated, visceral mesoderm-endoderm interaction involved in midgut development
Hnf1a	Transcriptional activator that regulates the tissue specific expression of multiple genes, especially in pancreatic islet cells and in liver. Required for the expression of several liver specific genes. Binds to the inverted palindrome 5'-GTTAATNATTAAC-3'.	bile acid and bile salt transport; bile acid biosynthetic process, blastocyst development, bone resorption, cholesterol metabolic process, chromatin remodeling, embryonic limb morphogenesis, endocrine pancreas development, fatty acid biosynthetic process, fatty acid transport, glucose homeostasis, glucose import, heme biosynthetic process, histone acetylation, insulin secretion, liver development, negative regulation of transcription from RNA polymerase II promoter, paraxial mesoderm formation, placenta development, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription initiation from RNA polymerase II promoter, protein localization, regulation of hormone secretion, regulation of insulin secretion, regulation of transcription, DNA-templated, regulation of transcription from RNA polymerase II promoter, regulation of Wnt signaling pathway, renal glucose absorption, reproductive structure development, response to glucose, response to oxidative stress, reverse cholesterol transport, SMAD protein signal transduction
Hoxa5	Sequence-specific transcription factor which is part of a developmental regulatory system that provides cells with specific positional identities on the anterior-posterior axis. Also binds to its own promoter. Binds specifically to the motif 5'-CYYNATTA[TG]Y-3'	anterior/posterior pattern specification; bronchiole development, cartilage morphogenesis, cell-cell signaling involved in mammary gland development, cell migration, embryonic skeletal system development, embryonic skeletal system morphogenesis, epithelial tube branching involved in lung morphogenesis, intestinal epithelial cell maturation, lobar bronchus epithelium development, lung alveolus development, lung-associated mesenchyme development, lung development, lung goblet cell differentiation, mammary gland alveolus development, mammary gland epithelial cell differentiation, mesenchymal-epithelial cell signaling, morphogenesis of an epithelium, multicellular organism growth, negative regulation of angiogenesis, negative regulation of erythrocyte differentiation, pattern specification process, positive regulation of apoptotic process, positive regulation of myeloid cell differentiation, positive regulation of receptor biosynthetic process, positive regulation of transcription from RNA polymerase II promoter, regulation of mammary gland epithelial cell proliferation, respiratory gaseous exchange, respiratory system process, skeletal system development, thyroid gland development, trachea

		cartilage morphogenesis, trachea morphogenesis, transcription from RNA polymerase II promoter
Jdp2	Component of the AP-1 transcription factor that represses transactivation mediated by the Jun family of proteins. Involved in a variety of transcriptional responses associated with AP-1, such as UV-induced apoptosis, cell differentiation, tumorigenesis and antitumorigenesis. Can also function as a repressor by recruiting histone deacetylase 3/HDAC3 to the promoter region of JUN. May control transcription via direct regulation of the modification of histones and the assembly of chromatin	negative regulation of fat cell differentiation, negative regulation of transcription from RNA polymerase II promoter, positive regulation of histone deacetylation, transcription, DNA-templated
Jun	Transcription factor that recognizes and binds to the enhancer heptamer motif 5'-TGA[CG]TCA-3'. Promotes activity of NR5A1 when phosphorylated by HIPK3 leading to increased steroidogenic gene expression upon cAMP signaling pathway stimulation. Involved in activated KRAS-mediated transcriptional activation of USP28 in colorectal cancer (CRC) cells. Binds to the USP28 promoter in colorectal cancer (CRC) cells	ageing, angiogenesis, axon regeneration, cellular process, cellular response to calcium ion, cellular response to hormone stimulus, cellular response to potassium ion starvation, circadian rhythm, eyelid development in camera-type eye, leading edge cell differentiation, learning, liver development, membrane depolarization, microglial cell activation, monocyte differentiation, negative regulation by host of viral transcription, negative regulation of apoptotic process, negative regulation of cell proliferation, negative regulation of DNA binding, negative regulation of neuron apoptotic process, negative regulation of protein autophosphorylation, negative regulation of transcription, DNA-templated, negative regulation of transcription from RNA polymerase II promoter, negative regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress, outflow tract morphogenesis, positive regulation by host of viral transcription, positive regulation of cell differentiation, positive regulation of DNA replication, positive regulation of DNA-templated transcription, initiation, positive regulation of endothelial cell proliferation, positive regulation of epithelial cell migration, positive regulation of ERK1 and ERK2 cascade, positive regulation of fibroblast proliferation, positive regulation of GTPase activity, positive regulation of monocyte differentiation, positive regulation of neuron apoptotic process, positive regulation of pri-miRNA transcription from RNA polymerase II promoter, positive regulation of smooth muscle cell proliferation, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, regulation of cell cycle, regulation of transcription, DNA-templated, release of cytochrome c from mitochondria, response to cAMP, response to cytokine, response to drug, response to hydrogen peroxide, response to lipopolysaccharide, response to muscle stretch, response to radiation, SMAD protein import into nucleus, SMAD protein signal transduction, transforming growth factor beta receptor signaling pathway
Klf4	Transcription factor; can act both as activator and as repressor. Binds the 5'-CACCC-3' core sequence. Binds to the promoter region of its own gene and can activate its own transcription. Regulates the expression of key transcription factors during embryonic development. Plays an important role in maintaining embryonic stem cells, and in preventing their differentiation. Required for establishing the barrier function of the skin and for postnatal	canonical Wnt signaling pathway, cell differentiation, cellular response to cycloheximide, cellular response to growth factor stimulus, cellular response to hydrogen peroxide, cellular response to laminar fluid shear stress, cellular response to peptide, cellular response to retinoic acid, epidermal cell differentiation, epidermis morphogenesis, fat cell differentiation, negative regulation of cell migration, negative regulation of cell migration involved in sprouting angiogenesis, negative regulation of cell proliferation, negative regulation of chemokine (C-X-C motif)

	maturation and maintenance of the ocular surface. Involved in the differentiation of epithelial cells and may also function in skeletal and kidney development. Contributes to the down-regulation of p53/TP53 transcription	ligand 2 production, negative regulation of cysteine-type endopeptidase activity involved in apoptotic process, negative regulation of ERK1 and ERK2 cascade, negative regulation of heterotypic cell-cell adhesion, negative regulation of interleukin-8 biosynthetic process, negative regulation of muscle hyperplasia, negative regulation of NF-kappaB transcription factor activity, negative regulation of phosphatidylinositol 3-kinase signaling, negative regulation of protein kinase B signaling, negative regulation of response to cytokine stimulus, negative regulation of sequence-specific DNA binding transcription factor activity, negative regulation of smooth muscle cell proliferation, negative regulation of transcription, DNA-templated, negative regulation of transcription from RNA polymerase II promoter, positive regulation of cellular protein metabolic process, positive regulation of hemoglobin biosynthetic process, positive regulation of nitric oxide biosynthetic process, positive regulation of protein metabolic process, positive regulation of telomerase activity, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription regulatory region DNA binding, post-embryonic camera-type eye development, post-embryonic hemopoiesis, regulation of axon regeneration, regulation of cell differentiation, regulation of cell proliferation, regulation of transcription from RNA polymerase II promoter, response to organic substance, response to retinoic acid, stem cell population maintenance, transcription, DNA-templated, transcription from RNA polymerase II promoter
Klf7	Transcriptional activator. Binds specifically to an Ikaros core binding element that is crucial for in vivo NTRK1/TrkA enhancer function	axon guidance, axonogenesis, dendrite morphogenesis, positive regulation of transcription, DNA-templated, transcription, DNA-templated
Max	Transcription regulator. Forms a sequence-specific DNA-binding protein complex with MYC or MAD which recognizes the core sequence 5'-CAC[GA]TG-3'. The MYC:MAX complex is a transcriptional activator, whereas the MAD:MAX complex is a repressor. CpG methylation of the recognition site greatly inhibits DNA binding, suggesting that DNA methylation may regulate the MYC:MAX complex in vivo. May repress transcription via the recruitment of a chromatin remodeling complex containing H3 'Lys-9' histone methyltransferase activity	regulation of transcription, DNA-templated, transcription, DNA-templated
Myc	Transcription factor that binds DNA in a non-specific manner, yet also specifically recognizes the core sequence 5'-CAC[GA]TG-3'. Activates the transcription of growth-related genes	activation of cysteine-type endopeptidase activity involved in apoptotic process, B cell apoptotic process, branching involved in ureteric bud morphogenesis, canonical Wnt signaling pathway, canonical Wnt signaling pathway involved in negative regulation of apoptotic process, canonical Wnt signaling pathway involved in positive regulation of apoptotic process, cell cycle arrest, cellular iron ion homeostasis, cellular response to DNA damage stimulus, cellular response to drug, cellular response to interferon-alpha, chromatin remodeling, chromosome organization, detection of mechanical stimulus involved in sensory perception of sound, intrinsic apoptotic signaling pathway in response to DNA damage, MAPK cascade, middle ear morphogenesis, negative regulation of cell division, negative

		regulation of fibroblast proliferation, negative regulation of monocyte differentiation, negative regulation of protein binding, negative regulation of transcription from RNA polymerase II promoter, pigmentation, positive regulation of apoptotic signaling pathway, positive regulation of B cell apoptotic process, positive regulation of catalytic activity, positive regulation of cell proliferation, positive regulation of cysteine-type endopeptidase activity involved in apoptotic process, positive regulation of DNA biosynthetic process, positive regulation of epithelial cell proliferation, positive regulation of fibroblast proliferation, positive regulation of mesenchymal cell proliferation, positive regulation of metanephric cap mesenchymal cell proliferation, positive regulation of response to DNA damage stimulus, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, protein processing, regulation of apoptotic process, regulation of gene expression, regulation of telomere maintenance, regulation of transcription, DNA-templated, response to alkaloid, response to gamma radiation, response to radiation, skeletal muscle cell differentiation, skeletal system morphogenesis, transcription from RNA polymerase II promoter, Wnt signaling pathway
Mycn		branching morphogenesis of an epithelial tube, cartilage condensation, embryonic digit morphogenesis, embryonic skeletal system morphogenesis, lung development, negative regulation of astrocyte differentiation, negative regulation of reactive oxygen species metabolic process, positive regulation of cell death, positive regulation of cell proliferation, positive regulation of mesenchymal cell proliferation, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, regulation of auditory receptor cell differentiation
Mzf1		negative regulation of transcription from RNA polymerase II promoter; positive regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-templated, transcription from RNA polymerase II promoter
Nfya	Component of the sequence-specific heterotrimeric transcription factor (NF-Y) which specifically recognizes a 5'-CCAAT-3' box motif found in the promoters of its target genes. NF-Y can function as both an activator and a repressor, depending on its interacting cofactors. NF-YA positively regulates the transcription of the core clock component ARNTL/BMAL1.	positive regulation of stem cell proliferation, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, regulation of stem cell population maintenance, regulation of transcription, DNA-templated, rhythmic process, transcription from RNA polymerase II promoter
Nkx2-5	Implicated in commitment to and/or differentiation of the myocardial lineage. Acts as a transcriptional activator of ANF in cooperation with GATA4. It is transcriptionally controlled by PBX1 and acts as a transcriptional repressor of CDKN2B. Together with PBX1, it is required for spleen development through a mechanism that involves CDKN2B repression.	adult heart development, apoptotic process involved in heart morphogenesis, atrial cardiac muscle cell development, atrial septum morphogenesis, atrioventricular node cell development, atrioventricular node cell fate commitment, atrioventricular node development, BMP signaling pathway, bundle of His development, canonical Wnt signaling pathway, cardiac conduction system development, cardiac muscle cell differentiation, cardiac muscle cell proliferation, cardiac muscle contraction, cardiac muscle tissue development, cardiac muscle tissue morphogenesis, cardiac ventricle formation, cardiac ventricle morphogenesis, cardiovascular system development, cell differentiation, embryonic heart tube

		development, embryonic heart tube left/right pattern formation, endoderm development, heart contraction, heart development, heart looping, heart morphogenesis, heart trabecula formation, hemopoiesis, negative regulation of apoptotic process, negative regulation of canonical Wnt signaling pathway, negative regulation of cardiac muscle cell apoptotic process, negative regulation of myotube differentiation, negative regulation of transcription from RNA polymerase II promoter, outflow tract morphogenesis, outflow tract septum morphogenesis, pharyngeal system development, positive regulation of cardioblast differentiation, positive regulation of cell proliferation, positive regulation of gene expression, positive regulation of heart contraction, positive regulation of neuron differentiation, positive regulation of sodium ion transport, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription initiation from RNA polymerase II promoter, positive regulation of transcription via serum response element binding, proepicardium development, pulmonary myocardium development, Purkinje myocyte differentiation, regulation of cardiac conduction, regulation of cardiac muscle cell proliferation, regulation of cardiac muscle contraction, regulation of transcription from RNA polymerase II promoter, right ventricular cardiac muscle tissue morphogenesis, sarcomere organization, septum secundum development, spleen development, thyroid gland development, tongue development, transcription from RNA polymerase II promoter, vasculogenesis, ventricular cardiac muscle cell development, ventricular cardiac myofibril assembly, ventricular septum morphogenesis, ventricular trabecula myocardium morphogenesis
Nkx3-2	Transcriptional repressor that acts as a negative regulator of chondrocyte maturation. PLays a role in distal stomach development; required for proper antral-pyloric morphogenesis and development of antral-type epithelium. In concert with GSC, defines the structural components of the middle ear; required for tympanic ring and gonium development and in the regulation of the width of the malleus	animal organ development, determination of left/right symmetry, digestive system development, embryonic skeletal system development, intestinal epithelial cell development, middle ear morphogenesis, negative regulation of apoptotic process, negative regulation of chondrocyte differentiation, negative regulation of transcription from RNA polymerase II promoter, organ formation, pancreas development, skeletal system development, skeletal system morphogenesis, spleen development, transcription, DNA-templated
Pparg	Nuclear receptor that binds peroxisome proliferators such as hypolipidemic drugs and fatty acids. Once activated by a ligand, the nuclear receptor binds to DNA specific PPAR response elements (PPRE) and modulates the transcription of its target genes, such as acyl-CoA oxidase. It therefore controls the peroxisomal beta-oxidation pathway of fatty acids. Key regulator of adipocyte differentiation and glucose homeostasis. ARF6 acts as a key regulator of the tissue-specific adipocyte P2 (aP2) enhancer. Acts as a critical regulator of gut homeostasis by suppressing NF-kappa-B-mediated proinflammatory responses. Plays a role in the regulation of cardiovascular circadian rhythms by regulating the transcription of ARNTL/BMAL1 in the blood vessels	activation of cysteine-type endopeptidase activity involved in apoptotic process, brown fat cell differentiation, cell fate commitment, cell maturation, cellular response to insulin stimulus, cellular response to lithium ion, cellular response to organic cyclic compound, diet induced thermogenesis, epithelial cell differentiation, fat cell differentiation, glucose homeostasis, inflammatory response, lipoprotein transport, long-chain fatty acid transport, low-density lipoprotein particle receptor biosynthetic process, monocyte differentiation, negative regulation of cell proliferation, negative regulation of cellular response to insulin stimulus, negative regulation of cholesterol storage, negative regulation of cytokine production, negative regulation of interferon-gamma-mediated signaling pathway, negative regulation of macrophage derived foam cell differentiation, negative regulation of peptide hormone secretion, negative regulation of receptor biosynthetic process, negative regulation of sequestering of triglyceride, negative

		regulation of smooth muscle cell proliferation, negative regulation of transcription, DNA-templated, negative regulation of transcription from RNA polymerase II promoter, peroxisome proliferator activated receptor signaling pathway, placenta development, positive regulation of fat cell differentiation, positive regulation of sequence-specific DNA binding transcription factor activity, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, regulation of blood pressure, regulation of circadian rhythm, regulation of fat cell differentiation, regulation of gene expression, regulation of transcription, DNA-templated, regulation of transcription involved in cell fate commitment, response to dietary excess, response to food, response to light stimulus, response to lipid, response to low-density lipoprotein particle, response to retinoic acid, rhythmic process, signal transduction, transcription from RNA polymerase II promoter, white fat cell differentiation
Rxra	Receptor for retinoic acid. Retinoic acid receptors bind as heterodimers to their target response elements in response to their ligands, all-trans or 9-cis retinoic acid, and regulate gene expression in various biological processes. The RAR/RXR heterodimers bind to the retinoic acid response elements (RARE) composed of tandem 5'-AGGTCA-3' sites known as DR1-DR5. The high affinity ligand for RXRs is 9-cis retinoic acid. RXRA serves as a common heterodimeric partner for a number of nuclear receptors. The RXR/RAR heterodimers bind to the retinoic acid response elements (RARE) composed of tandem 5'-AGGTCA-3' sites known as DR1-DR5. In the absence of ligand, the RXR-RAR heterodimers associate with a multiprotein complex containing transcription corepressors that induce histone acetylation, chromatin condensation and transcriptional suppression. On ligand binding, the corepressors dissociate from the receptors and associate with the coactivators leading to transcriptional activation. The RXRA/PPARA heterodimer is required for PPARA transcriptional activity on fatty acid oxidation genes such as ACOX1 and the P450 system genes.	ageing, angiogenesis involved in coronary vascular morphogenesis, axon regeneration, camera-type eye development, cardiac muscle cell differentiation, cardiac muscle cell proliferation, cellular response to insulin stimulus, embryo implantation, heart development, heart morphogenesis, inflammatory response, in utero embryonic development, liver development, maternal placenta development, mesenchyme development, midgut development, modulation by virus of host morphology or physiology, negative regulation of cell proliferation, negative regulation of gene expression, negative regulation of transcription from RNA polymerase II promoter, peroxisome proliferator activated receptor signaling pathway, placenta development, positive regulation of apoptotic process, positive regulation of transcription, DNA-templated, positive regulation of transcription from RNA polymerase II promoter, positive regulation of transcription from RNA polymerase II promoter involved in cellular response to chemical stimulus, positive regulation of translational initiation by iron, protein homotetramerization, regulation of branching involved in prostate gland morphogenesis, regulation of myelination, regulation of transcription, DNA-templated, regulation of transcription from RNA polymerase II promoter, response to ethanol, response to glucocorticoid, response to retinoic acid, response to selenium ion, response to vitamin A, response to vitamin D, retinoic acid receptor signaling pathway, secretory columnar luminal epithelial cell differentiation involved in prostate glandular acinus development, transcription, DNA-templated, ventricular cardiac muscle cell differentiation, ventricular cardiac muscle tissue morphogenesis, visceral serous pericardium development
Sp1	Transcription factor that can activate or repress transcription in response to physiological and pathological stimuli. Binds with high affinity to GC-rich motifs and regulates the expression of a large number of genes involved in a variety of processes such as cell growth, apoptosis, differentiation and immune responses. Highly regulated by post-translational modifications (phosphorylations, sumoylation, proteolytic cleavage, glycosylation and acetylation). Binds also the PDGFR-	definitive hemopoiesis, embryonic camera-type eye morphogenesis, embryonic placenta development, embryonic process involved in female pregnancy, embryonic skeletal system development, enucleate erythrocyte differentiation, in utero embryonic development, liver development, lung development, megakaryocyte differentiation, mRNA transcription from RNA polymerase II promoter, ossification, positive regulation by host of viral transcription, positive regulation of hydrogen sulfide biosynthetic process, positive regulation of transcription, DNA-templated, positive regulation of transcription from

	alpha G-box promoter. May have a role in modulating the cellular response to DNA damage. Implicated in chromatin remodeling. Plays a role in the recruitment of SMARCA4/BRG1 on the c-FOS promoter. Plays an essential role in the regulation of FE65 gene expression (By similarity). Positively regulates the transcription of the core clock component ARNTL/BMAL1.	RNA polymerase II promoter, regulation of transcription, DNA-templated, rhythmic process, trophectodermal cell differentiation
Spib	Sequence specific transcriptional activator which binds to the PU-box, a purine-rich DNA sequence (5'-GAGGAA-3') that can act as a lymphoid-specific enhancer. Promotes development of plasmacytoid dendritic cells (pDCs), also known as type 2 DC precursors (pre-DC2) or natural interferon (IFN)-producing cells. These cells have the capacity to produce large amounts of interferon and block viral replication. Required for B-cell receptor (BCR) signaling, which is necessary for normal B-cell development and antigenic stimulation.	macrophage differentiation, regulation of transcription, DNA-templated, regulation of transcription from RNA polymerase II promoter, transcription, DNA-templated
Sry	Transcriptional regulator that controls a genetic switch in male development. It is necessary and sufficient for initiating male sex determination by directing the development of supporting cell precursors (pre-Sertoli cells) as Sertoli rather than granulosa cells. In male adult brain involved in the maintenance of motor functions of dopaminergic neurons (By similarity). Involved in different aspects of gene regulation including promoter activation or repression. SRY HMG box recognizes DNA by partial intercalation in the minor groove. Promotes DNA bending. Also involved in pre-mRNA splicing (By similarity). Binds to the DNA consensus sequence 5'-[AT]AACAA[AT]-3'.	cell differentiation, male gonad development, male sex determination, negative regulation of gene expression, negative regulation of transcription from RNA polymerase II promoter, positive regulation of male gonad development, positive regulation of transcription, DNA-templated, sex determination, transcription, DNA-templated
Tbp	General transcription factor that functions at the core of the DNA-binding multiprotein factor TFIID. Binding of TFIID to the TATA box is the initial transcriptional step of the pre-initiation complex (PIC), playing a role in the activation of eukaryotic genes transcribed by RNA polymerase II. Component of the transcription factor SL1/TIF-IB complex, which is involved in the assembly of the PIC (preinitiation complex) during RNA polymerase I-dependent transcription. The rate of PIC formation probably is primarily dependent on the rate of association of SL1 with the rDNA promoter. SL1 is involved in stabilization of nucleolar transcription factor 1/UBTF on rDNA	DNA-templated transcription, initiation, positive regulation of transcription, DNA-templated, spermatogenesis, transcription from RNA polymerase III promoter, transcription from RNA polymerase II promoter
Yy1	Multifunctional transcription factor that exhibits positive and negative control on a large number of cellular and viral genes by binding to sites overlapping the transcription start site. Binds to the consensus sequence 5'-CCGCCATNTT-3'; some genes have been shown to contain a longer binding motif allowing enhanced binding; the initial CG dinucleotide can be	anterior/posterior pattern specification, camera-type eye morphogenesis, cell differentiation, cellular response to DNA damage stimulus, cellular response to interleukin-1, cellular response to UV, chromosome organization, double-strand break repair via homologous recombination, negative regulation of gene expression, negative regulation of transcription from RNA polymerase II promoter, positive regulation of gene expression, positive

	<p> methylated greatly reducing the binding affinity. The effect on transcription regulation is depending upon the context in which it binds and diverse mechanisms of action include direct activation or repression, indirect activation or repression via cofactor recruitment, or activation or repression by disruption of binding sites or conformational DNA changes. Its activity is regulated by transcription factors and cytoplasmic proteins that have been shown to abrogate or completely inhibit YY1-mediated activation or repression. Binds to the upstream conserved region (UCR) (5'-CGCCATTTT-3') of Moloney murine leukemia virus (MuLV). Acts synergistically with the SMAD1 and SMAD4 in bone morphogenetic protein (BMP)-mediated cardiac-specific gene expression. Binds to SMAD binding elements (SBEs) (5'-GTCT/AGAC-3') within BMP response element (BMPRE) of cardiac activating regions. Proposed to recruit the PRC2/EED-EZH2 complex to target genes that are transcriptional repressed. Involved in DNA repair. In vitro, binds to DNA recombination intermediate structures (Holliday junctions). Involved in spermatogenesis and may play a role in meiotic DNA double-strand break repair. Proposed core component of the chromatin remodeling INO80 complex which is involved in transcriptional regulation, DNA replication and probably DNA repair; proposed to target the INO80 complex to YY1-responsive elements. </p>	<p> regulation of transcription from RNA polymerase II promoter, regulation of transcription, DNA-templated, response to prostaglandin F, response to UV-C, RNA localization, spermatogenesis, transcription, DNA-templated </p>
Zeb1	<p> Acts as a transcriptional repressor. Binds to E-box sequences in the immunoglobulin heavy chain enhancer as well as in the regulatory regions of many other tissue-specific genes. Represses E-cadherin promoter and induces an epithelial-mesenchymal transition (EMT) by recruiting SMARCA4/BRG1. Represses BCL6 transcription in the presence of the corepressor CTBP1 (By similarity). Positively regulates neuronal differentiation. Represses RCOR1 transcription activation during neurogenesis. Represses transcription by binding to the E box (5'-CANNTG-3'). Promotes tumorigenicity by repressing stemness-inhibiting microRNAs. </p>	<p> animal organ development, cartilage development, cellular response to amino acid stimulus, central nervous system development, cochlea morphogenesis, embryonic camera-type eye morphogenesis, embryonic morphogenesis, embryonic skeletal system morphogenesis, negative regulation of cell proliferation, negative regulation of epithelial cell differentiation, negative regulation of transcription, DNA-templated, negative regulation of transcription from RNA polymerase II promoter, pattern specification process, positive regulation of neuron differentiation, positive regulation of transcription from RNA polymerase II promoter, regulation of mesenchymal cell proliferation, regulation of smooth muscle cell differentiation, regulation of T cell differentiation in thymus, regulation of transforming growth factor beta receptor signaling pathway, semicircular canal morphogenesis, transcription, DNA-templated </p>
Zfp105		<p> regulation of transcription, DNA-templated </p>
Zfx		<p> fertilization, germ cell development, homeostasis of number of cells, multicellular organism growth, oocyte development, ovarian follicle development, parental behavior, post-embryonic development, regulation of transcription, DNA-templated, spermatogenesis, transcription, DNA-templated </p>
Znf354c	<p> May function as a transcription repressor. Suppresses osteogenic effects of RUNX2. Binds to 5'-CCACA-3' core sequence. May be involved in osteoblastic differentiation </p>	<p> regulation of transcription, DNA-templated, transcription, DNA-templated </p>

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