Review

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Review

Therapeutic Properties of Polyphenols Affect AMPK Molecular Pathway in Hyperlipidemia

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Abstract: Hyperlipidemia is the fat particles excess in the serum. Hyperlipidemia increases the mortality rate that occurs with other metabolic disorders. Hyperlipidemia is classified into familial and acquired subgroups. Moreover, Hyperlipidemia etiology is based on environmental or genetic factors. For instance, abnormal HMG-CoA regulation down-regulates ubiquitin ligase and targets variable oxidative stress-related condition proteins. There has been proven reactive oxygen species (ROS) overshoot happens during hyperlipidemia occurrence. OS, directly and indirectly, regulates molecular cascades within the cell and leads to gene expression alteration. At this molecular juncture, AMPK is affected by ROS. AMPK is a serine-threonine kinase and a critical energy balance. Low energy conditions result in AMPK activation due to the down-regulation of protein and lipid synthesis. Furthermore, ER stress and activated unfolded protein proteasomal response and autophagy are AMPK mediated. Polyphenols are widespread dietary plant-based compounds that regulate gene expression and signal conduction. Through the hyperlipidemic state, FFAs releasing indirectly connect to AMPK/NF-κB pathway then polyphenols target them. AMPK, during this FFA exposure, down-regulates de novo lipid molecules generation. Likewise, if AMPK/mTOR pathway failure is prolonged, the hyperlipidemic state may be explicit, activated by natural herbal mediators, e.g., polyphenols. Polyphenols activate the AMPK signaling pathway and influence lipid metabolism. Polyphenol-mediated AMPK activation results in lipogenesis inhibition and lipophagy. Cholesterol efflux mediated polyphenols lipid-lowering effects, accessing LXR pathway. All these clues persist on direct or indirect AMPK-related polyphenolic anti-hyperlipidemic effects.

Keywords: AMPK; polyphenols; dyslipidemia; Nrf2

Introduction

Hyperlipidemia, also called hyperlipoproteinemia, is the excess fat particles in the serum [1–5]. This prevalent disorder is the leading cause of atherosclerosis [5–7] and metabolic syndrome [8,9]. Lipids, derived from exogenous resources or hepato-intestinal synthesized, are transported in the blood via many kinds of lipoproteins, including chylomicrons, low-density lipoproteins (LDL), and high-density lipoproteins (HDL) [2,9–11]. Lipid concentration overshoot, hyperlipidemia, raises the mortality rate when accompanied by other metabolic diseases [8,9]. It is also the most prevalent risk factor for atherosclerotic-based cardiovascular diseases [12–19]. Although many hyperlipidemia therapeutic compounds have been enhanced in past decades, it is still a significant health complication [20].

Since hyperlipidemia is associated with high morbidity and mortality, its control has become an essential scientific issue. In this article, according to past studies, we intend to review the role of a group of natural substances with medicinal properties in treating hyperlipidemia. In this article, we try to review the information available in the literature about a practical molecular pathway in the pathogenesis of dyslipidemia.

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Molecular Pathogenesis of Hyperlipidemia

Hyperlipidemia is asserted in two significant types: familial or primary and acquired or secondary [1], based on environmental or genetic factors [21]. The most important clinical feature of hyperlipidemia is LDL level elevation [21–23] and apolipoprotein B (ApoB) [24,25]. So, LDL reduction is a common approach in hyperlipidemia which mainly occur by hepatic 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors [26–30], which reduce the hepatic endogenous synthesis of cholesterol and decrease the LDL receptors expression [4,31–34] and increases baroreflex sensitivity [35]. It was also demonstrated that HMG-CoA reductase inhibitors have anti-oxidative effects [36] and anti-platelet aggregation effects [37].

HMG-CoA reductase, in combination with lecithin-cholesterol acyl transferase (LCAT), cholesterol 7α-hydroxylase (CYP7A1), and acyl CoA: cholesterol acetyltransferase (ACAT) plays a crucial role in lipids metabolisms [28,38–41]. Although HMG-CoA in hyperlipidemia incidence enrolls as the core enzyme, two other hepatic enzymes, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), also gather with this disorder [42–44].

Abnormal HMG-CoA regulation down-regulates a ubiquitin ligase called neural precursor cell expressed down-regulated 4 (NEDD4) and other less critical ubiquitin proteasome cascade proteins, including BIRC3, USP6, and UBE2D1 [45,46] developmentally. These pathway targets are variable, but oxidative stress (OS) -related condition proteins are mainly targeted by this cascade [47,48].

OS is a well-known mechanism of cellular change. Research indicates that an essential molecular system, reactive oxygen species (ROS), overshoots during hyperlipidemia [49–54]. The head enzymes of ROS-induced OS are NADPH oxidase, xanthine oxidase, superoxidase dismutase (SOD), and glutathione peroxidase (GSH-Px), which lead to more lipid peroxidation [49,55–60].

Some theoretical relation between ROS-induced mitochondrial dysfunction and mechanistic target of rapamycin complex 1 (mTORC1) pathway-related hyperlipidemic states had been determined [61–63], in which lipid homeostasis deregulated [64]. Also, an immune biomarker for hyperlipidemia, neopterin, is recognized as an OS-mediated molecule [65].

In addition to this mechanism, endoplasmic reticulum (ER) stress is another cellular stress condition combined with ubiquitin-proteasome-based lipid dysfunction disorders [66,67]. ER stress induces NEDD4 expression via E3 ubiquitin ligase [49,68], tightly in combination with HRD1 or SYVN1 [69]. Furthermore, NADPH oxidase, OS-related enzyme, Mdm2-p53 pathway, and glutamate receptor subunit 1 (GluA1) are related to ER stress-induced NEDD4 expression [70–75] and HMG-CoA reductase down-regulation [68]. NEDD4 indirectly down-regulates phosphatidyl inositol 3-kinase (PI3K) [76] but especially targets phosphatase and tensin homologue (PTEN) [45] and is activated via LDL receptors [77].

PTEN, a phosphatase, down-regulates the PI3K/AKT-mTORC1 pathway [78,79]. This pathway plays a role in cell proliferation, metabolism, and migration [80,81]. PI3K/AKT-mTOR pathway, which regulates apoproteins secretion [82], is also directly induced through the Mdm2-p53 pathway [70,71,75]. PI3K, as the AKT activator, in combination with mTORC1, is engaged with a Cullin-RING finger E3 ligases, CRC7 [76], which on by own regulated through neddylation, NEDD8 attachment [83]. However, neddylation is a critical mechanism in PI3K/AKT-mTOR direct regulation, and it may down-regulate this pathway indirectly via glycogen synthase kinase 3 (GSK3) [84–86]. The activation of GSK-3 also may lead to more nuclear factor kappa B (NF-κB) phosphorylation [87,88] involving PI3K/AKT signaling pathway [89–91].

Many studies firmly confirmed the NF-κB pathway role in obesity and OS-mediated disorders such as hyperlipidemia [92–94], in which Maf A [95] and apoprotein synthesis regulate [82].

This cascade prescribed not only the role of NF-κB induced cellular stress but also the combination of the Nrf2 signaling pathway with this disorder [93,96,97]. Phosphorylation, as the main component of this pathway [98], affects 26S proteasomal degeneration and NF-κB translocation [99]. NF-κB then binds to a specific genome region which promotes OS head enzymes via an anti-oxidant response element (ARE) [100,101]. Signal transducer and activator of transcription (STAT) can inactivate NF-κB [102] and enhance Nrf2-ARE mediated phase II detoxifying enzymes [103], e.g., heme oxygenase 1 (HO-1) [104].

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Nrf2 ubiquitination and degeneration based on cullin3/Rbx 1 complex link this molecule to Kelch-like ECH-associated protein 1 (Kap1) [90,105]; then, sirt1/Nrf2 pathway inhibition, activates P38/mitogen-activated protein kinase (MAPK) pathway accelerates the hepatic changes in hyperlipidemia [106].

Thus, the P38/MAPK signaling pathway is composed via the microRNA1- myosin light chain kinase (MLCK) pathway and LDL oxidation [107]. In addition, some other microRNAs, including microRNA144, emerged during hyperlipidemic states through the liver x receptor (LXR) signaling pathway [108].

LXR signaling cascade is also combined with peroxisome proliferation-activated receptors (PPARs) [109], which are responsible for lipid metabolism regulation [51,110]. Although PPARs overshooting may lead to liver damage [111], proper regulation has anti-inflammatory and lipid regulatory effects [112]. Also, the LXR/PPARs pathway is directly controlled by a cluster of differentiation 36 (CD36) [113].

CD36 expression on monocytes and platelet surface increased during free fatty acid (FFA) elevation [110,114,115]. CD36/CD36 receptor interaction up-regulates platelet activity during hyperlipidemia [115]. In monocyte differentiation, when CD36 appears on the cell surface, the NF-κB transcription factor activates. This pathway is inhibited when sirt1 is expressed in the cell [116]. CD36/sirt1 pathway affects fatty acid metabolism [117]. Moreover, sirt1 indirectly phosphorylates AMP-activated protein kinase (AMPK) [118]. This promotion of AMPK then leads to PPARγ co-activator 1α deacetylation, which up-regulates PPARα expression in the nucleus and interacts with CD36.

Further, AMPK activation conducts mTOR inhibition [119], which regulates Nrf2 [106]. Decreased AMPK levels and increased SREBP1 induce hyperlipidemic conditions [120,121]. Moreover, AMPK activation inhibits de novo lipogenesis [122], which increases the 5-lipoxygenase substrate [123].

So, AMPK phosphorylation increases the fluidity of the FFA oxidation pathway [124].

AMPK

AMPK, a serine-threonine kinase and a vital energy balance regulator in mammalian eukaryotic cell roles first identified in 1973 [125–128]. AMPK is rule outs as a heterodimeric substance with α catalytic, γ regulatory, and β scaffolding subunits [125,129,130].

Low energy conditions induced, with a high AMP/ATP ratio, AMPK activation increases adenosine triphosphate (ATP) de novo production [131–133] due to protein and lipid synthesis down-regulation [134]. It was also identified in such metabolic stresses that protein kinase A activation overshoots [135]. So, AMPK phosphorylation on threonine 172 regulates fatty acid oxidative pathways [136]; through acetyl CoA carboxylase [137], glycolysis [138], and ER stress [139]. The protease phosphate pathway also induces ROS, where AMPK inhibits and, as a result, ACC-related lipogenesis may be affected [140]. Threonine 172 phosphorylation linkage with liver kinase B1 (LKB1), also named serine/threonine kinase II (STK II), is well-identified; however, this effect exegesis is still unclear [125,141–143].

In 2003, LKB1 was recognized as the significant AMPK activator kinase [144,145], which phosphorylates downstream molecules by itself [146,147], mentioned further. It is also a target of metformin, an anti-diabetic drug [148]. LKB1 regulates AMPK activation in almost all tissues [149,150], such as the atrium [151] and in the liver, which leads to hepatic fibrosis [150]. In addition, two other AMPK upstream kinases were recognized; calmodulin-dependent protein kinase β (Cankkβ), which is based on Ca^{2+} homeostasis, and TGF β activated kinase 1 (TAK1) (Figure 1) [143,152–154].

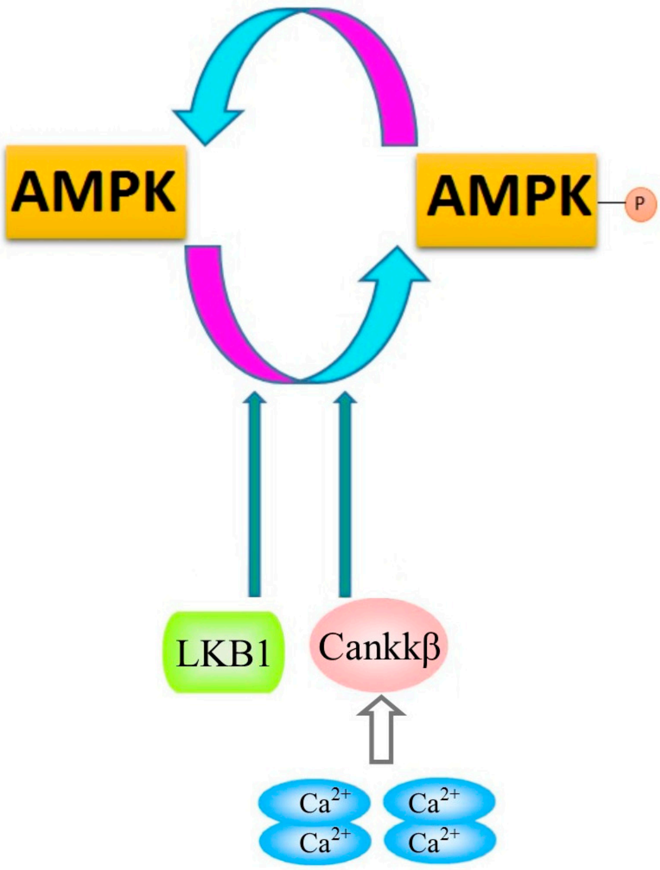

Figure 1. LKB1 regulates AMPK activation in almost all tissues, such as the atrium and liver, leading to hepatic fibrosis. In addition, calmodulin-dependent protein kinase β (Cankkβ), which is based on Ca2+ homeostasis, modulates AMPK phosphorylation.

An extracellular signal-regulated kinase (ERK) leads to LKB1 phosphorylation on serine 248, which interrupts the AMPK/LKB1 cascade [155] and p53/AMPK pathway [152]. Moreover, the adiponectin-mediated apoptotic cascade is AMPK/ERK pathway-dependent [156], and ERK inhibits via AMPK-derived ATP binding cassette transporter A1 (ABCA1) overexpression [157]. Furthermore, the LKB1/AMPK pathway affected during metabolic stress can regulate autophagy and apoptosis [158] and enhance adipogenesis [159] at the lysosome surface [160]. Also, LKB1 promoters E-box may affect by DEC1, and LKB1 activity level is reduced, which is related to circadian rhythm. This occurrence leads to AMPK activity depression [142]. Notch1 also results in specific tissues, such as the heart [161], or specific cell lines, e.g., T cells [162,163].

AMPK-induced lipid metabolism regulation is also supervised by PPARs and SREBP, which are impressed in adipogenesis in adipocytes [164,165]. SREBP1 is associated with triglyceride production, whereas SREBP2 is linked to cholesterol synthesis [166], which regulates LDL receptor genes [167]. PPARγ activation caused weight gain and some other side effects [168]. PPAR reduction, at the gene level, is associated with advanced glycosylation end products (AGEs) [169] and plays a critical role in hepatic stellate cell inactivation, which is combined with hepatic fibrosis [170].

The β oxidation and cholesterol synthesis primary regulator genes, PPAR [171,172], indirectly, through AMPK, is combined with mitochondrial biogenesis [173]. PPARγ co-activator 1α (PGC1α) during the mitochondrial biogenesis up-regulates the expression of nuclear respiratory factor (NRF), a transcription factor [174], resulting in energy imbalance and thereby AMPK pathway activation [175,176], related to NF-κB [177]. In addition to all these pathways, AMPK suppresses PPARγ to inhibit the differentiation of pre-adipocytes [178]; and the PGC1α level rising is assumed to promote hypo-methylation [179]. Adaption to mitochondrial dysfunction is not related to PGC1α and sirt1;

however, it is AMPK phosphorylation-related [175]. PGC1α phosphorylation and PGC1α and PGC1α deacetylation through sirt1 regulate mitochondrial biogenetic activity [180–182] and anti-inflammatory features [183].

Novel researches indicate sirt1 mitochondrial anti-oxidant features [184,185]; however, it may reduce the up-regulation of SREBP1 if over-expressed [186]. SREBP1 regulates PCSK9, LDL receptor, and angiopoietin-like 4, controlling cholesterolemia [187–191]. This NAD$^+$-dependent relation with the sirt1/AMPK pathway regulates the lipid metabolism network [192,193].

Although NFR and PPARs induced sirt1 activation firmly depend on some promoting proteins, for instance, MFN1/2 [194]; moreover, the α subunit of AMPK activity is sirt3 mediated [195], and PGC1α mediated Pdk4 up-regulation in lipid metabolism involves AMPK/sirt1/PGC1α pathway in combination with forkhead box O3 (FoxO3) (Figure 2) [196].

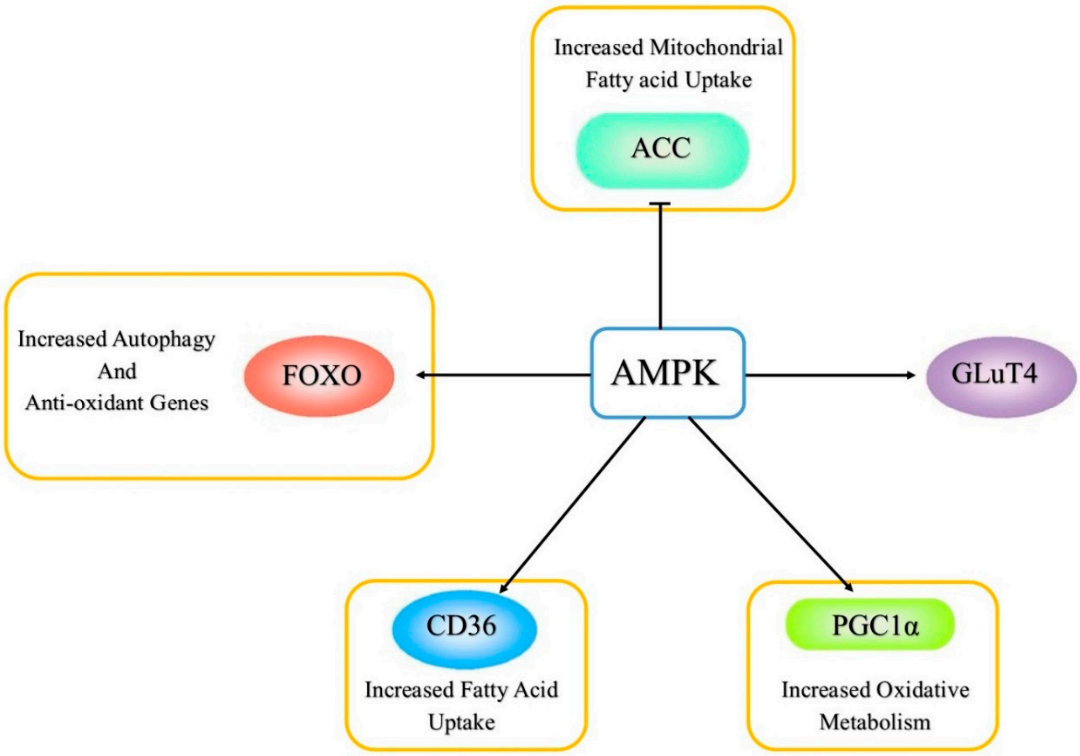

Figure 2. Activated AMPK upgrade glucose uptake via glucose transporter 4 (GLuT4) during mTOR-related PI3K/AKT pathway activating. In addition to all these pathways, AMPK suppresses PPARγ to inhibit the differentiation of pre-adipocytes; and the PGC1α level rising is assumed to promote hypo-methylation. PGC1α phosphorylation and PGC1α and PGC1α deacetylation through sirt1 regulate mitochondrial biogenetic activity and anti-inflammatory features. PGC1α mediated Pdk4 up-regulation in lipid metabolism involves AMPK/sirt1/PGC1α pathway in combination with forkhead box O3 (FoxO3). Moreover, CD36/CD36 receptor interaction up-regulates platelet activity during hyperlipidemia. CD36/sirt1 pathway affects fatty acid metabolism. However, sirt1 indirectly phosphorylates AMPK. This promotion of AMPK then leads to PPARγ co-activator 1α deacetylation, which up-regulates PPARα expression in the nucleus and interacts with CD36. Also, the protease phosphate pathway induces ROS, where AMPK inhibits, and ACC-related lipogenesis may be affected. Besides, AMPK induced ACC activation contact with the NF-κB pathway. However, NF-κB inhibition enhances monocyte cholesterol efflux.

Sirt1 level reduction indicates increased energy prevention related tightly to the mTOR pathway [197,198] and AMPK/glucagon-like peptide 1 (GLP1) [199,200]. This sirt1 level reduction down-regulates the NF-κB p65 subunit acetylation and phosphorylation, thereby, nuclear translocation [201,202]. So, sirt1 and NF-κB pathways show antagonistic features [203]. NF-κB activated when IκB-α degradation and ubiquitination occur, which is a result of IκB-α phosphorylation. Then NF-κB acts as an intra-nuclear transcription factor [204], which increases Bcl-2 after AMPK activation [205]. Besides, AMPK induced ACC activation contact with the NF-κB pathway [206]. However, NF-κB inhibition enhances monocyte cholesterol efflux [207].

Multiple cytokines, such as IL1β, TNFα also regulates NF-κB activation directly [208,209] and indirectly lead to pro-inflammatory molecules activation, e.g., COX2 [210]. AMPK activation is also related to TNFα-regulated NF-κB nuclear translocation [211]. Likewise, AMPK activation inhibits the mTOR signaling pathway [210], which leads to UNC51-like kinase 1 (ULK1) activation via dephosphorylation at serine 757; however, AMPK directly enhances ULK1 activation [211–213].

AMPK activation leads to tuberous sclerosis complex 2 (TSC2) threonine 1227 and serine 1345 phosphorylation [159,160] and then mTORC1 inactivation and lipogenesis suppression, an antagonistic effect [212,214–217]. In addition, rapamycin, the mTOR inhibitor, down-regulates mTORC2, and PPARγ, leading to the inhibition of adipocyte differentiation [218]. All this pathway may be a result of ROS [219]. The mTORC2 subunits, which regulate glucocorticoid inducible kinase1/2, SAPK-interacting protein (SIN1), and rapamycin-insensitive companion of mTOR (RAPTOR), and its substrates, such as AKT and autophagy-related proteins, are also undergrowth factors regulation [220–222]. However, protein phosphatase 3A activation and AMPK inhibition affect this regulatory pathway [223].

Nevertheless, mTORC1 regulates via amino acids linked to the lysosome and is needed for AMPK activation [224]. Activated AMPK upgrade glucose uptake via glucose transporter 4 (GLuT4) during mTOR-related PI3K/AKT pathway activating [225–228], which persists on OS [129] and regulates by IGF-1 [221], and down-regulates glycolysis (Warburg effect) [229]. If this activation becomes chronic, PGC1α-dependent angiotensin II reduction decreases endothelial dysfunction [230,231]; and lipid homeostatic unremarkable un-enrollment [232]. However, mitochondrial AMPK activation and mTOR/AKT inhibition may not remain long, especially in hepatocytes [233–235]. This AMPK activation and mTOR inhibition indirectly link Nrf2 to this pathway as an upstream regulatory molecule [236].

Moreover, PI3K inhibits VLDL production, based on insulin effects [234], and augments apoprotein A1 in adipocytes [237]. So, AMPK related PI3K/mTOR/ULK1signaling pathway causes insulin resistance [238], which targets vascular sorting protein 34 (Vps34) and Vps15/PI3K/ULK1 pathway too [239], by which mitochondrial endothelial NO synthase (eNOS) is regulated (240–244], broadcasts cytotoxicity effects [245] and as a small GTPases family member stimulates angiogenesis on partnership with MAPK/ERK pathway [246]. With all this, hepatocyte activation could be inhibited explicitly via an AMPK-specific inhibitor; however, PI3K/AKT inhibitors do not act like that [247–249]. However, AKT and AMPK are tightly linked [250,251], and sticking out on microRNA 41 inhibition in FFA-related inflammatory states [252], regularize Ca^{2+} homeostasis [253], microtubule transportation system organizing [252], amplifying insulin sensitivity through protein kinase B in some unique cell lines [254,255], and rolling as anti-oxidative conditions in cooperation with Nrf2 [256,257], and NF-κB [258].

The AKT/PI3K pathway activation by PDGF up-regulates S phase kinase-associated protein 2 (SKP2) [259], and leads to LKB1/AMPK activation [260], which by its own regulates PTEN, inhibits mTOR/S6 kinase 1 [261,262] and enhance ULK1 phosphorylated form [263], which is associated predominantly with autophagy cascade, and may directly activate by AMPK [264], within hepatocytes in addition to mTORC1 induction [265]. ULK1, which is needed for the autophagosome constitution, has two closely near phosphorylation sites modified by AMPK and mTOR, which interact with the lysosomal autophagic regulator, transcription factor EB (TFEB) [266].

Moreover, ER stress and activated unfolded protein proteasomal response and autophagy are AMPK mediated [267–269]. ER stress is the initial OS condition key [270–272]. Some studies importune on ER stress-dependent JNK-mediated hyperglycemic induced apoptosis, which is related to AMPK also [272]. Moreover, apoptosis is induced via activated AMPK/JNK stimulation in some types of cells [273]. JNK and NF-κB are two necessary inflammatory molecular signals [274]. It should be noticed here that although JNK/NF-κB molecular cascade provides the initial part of autophagy, AMPK phosphorylates TSC2 and inhibit mTORC1 and perform an impressive impact on autophagy [261]. Figure 3 shows a brief review of AMPK cascades.

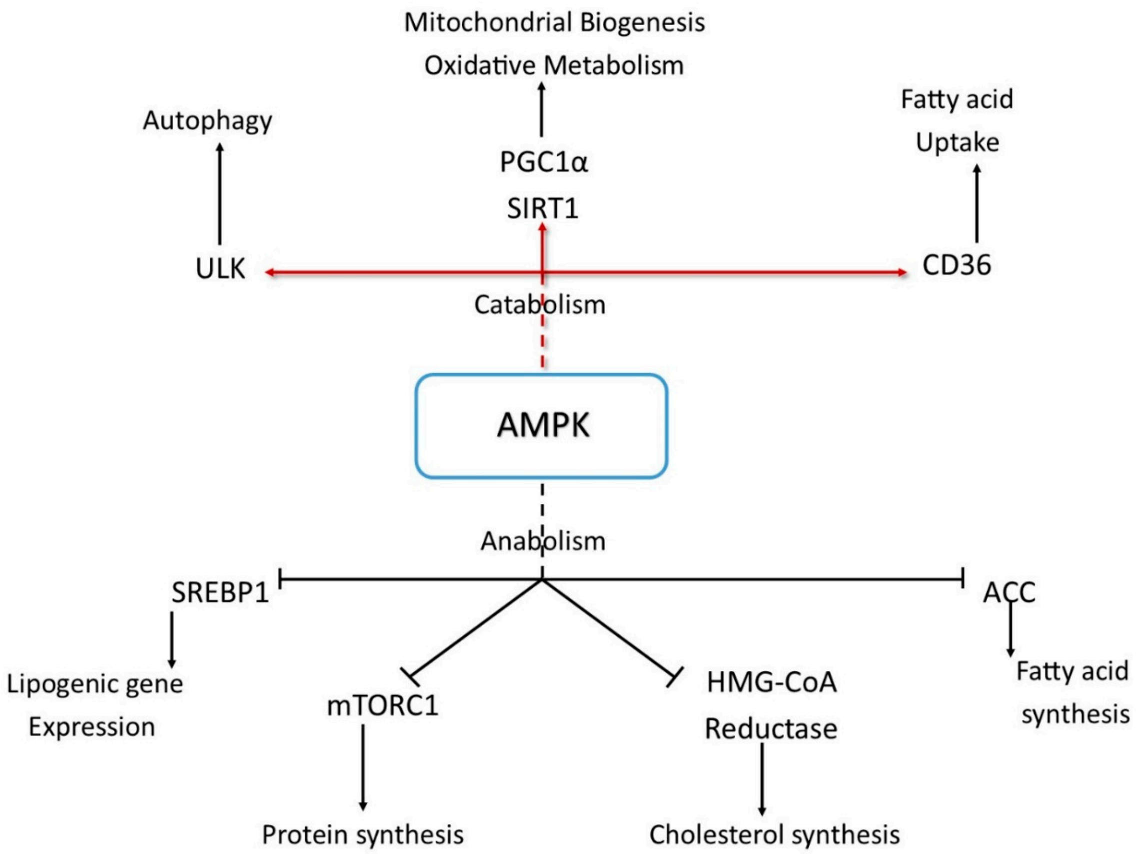

Figure 3. a brief review of AMPK cascades and effects.

Role of AMPK in Hyperlipidemia

AMPK, as the primary molecule in energy versus nutrient supply homeostasis, acts incorrectly during chronic disorders occurrence [275,276], such as obesity [277], and regulates some cellular conditions, e.g., oxidative stress [278].

Activated AMPK inhibited fatty acid synthesis via HMG-CoA reductase inactivation [279] and up-regulated PI3K pathway, leading to glucose over-uptake through insulin stimulation [280].

AMPK activation by intracellular Ca^{2+} level changes [281] and ER stress inhibits NADPH oxidase-induced OS and approves PPARs expression regulation [120,282], and governs GSK 3β [283]. However, fatty acid changes may reduce PPAR and improve SREBP1 in hepatocytes [124] during lipogenesis [284]. AMPK directly acts as the SREBP2 phosphorylase and, via this mechanism, blocks HMG-CoA reductase expression and activity [285,286] and up-regulates GLuT4 transcription [277]. In this protein synthesis, the mTOR system is the crucial point under the AMPK regulatory mechanism [287]. Otherwise, SREBP inhibits through activated AMPK. SREBP is a significant factor in fatty acid synthesis [288]. Also, de novo cholesterol production is controlled by AMPK/SREBP pathway [289].

PI3K/AMPK pathway uses ARE-mediated gene regulation and cooperates with the Nrf2 molecular system [278]. Here it should be noticed that PI3K/AKT-mTORC2/S6K is negatively regulated by PTEN [80,81], which is induced via Mdm2 [70,75]. However, Nrf2/ARE regulation of the PI3K/AKT pathway is more prior [93]. PI3K pathway affects eNOS, which is indirectly enhanced through AMPK. AMPK also down-regulates lipogenesis and cholesterol synthesis [229,240]; Through PPAR [51] and HMG-CoA reductase [285], expressed previously.

Although AMPK phosphorylation through AKT is essential, diacylglycerol, induced during hyperlipidemia, blocks AMPK activity via protein kinase C [276]. Moreover, AMPK promotes GLuT4 activity on the adipocyte cell membrane, reducing lipid agglomeration [277].

Alongside all these pathways, AMPK inhibits adipogenesis through growth factor independence 1 (Gif1)/Runt-related transcription factor 2 (Runx2)/PPARγ related pathway. In this case, AMPK up-regulates osteopontin (OPN) when adipogenesis tees off and decreases PPAR; however, Gif1 pickle on OPN promoter reduces AMPK effects [290]. Nonetheless, PPAR regulation via AMPK plays a pivotal role in lipid metabolism in which SREBP1 enlisted a therapeutic target for the lipid-based disorder [291].

AMPK and Polyphenols

Polyphenols are formed a widespread phytochemical unnecessary dietary nucleophilic group of plant-based compounds [292–294]. Too many polyphenols are classified into sub-classes such as phenolic acids, flavonoids, and tannins [294,295]. Nowadays, 8000 backbone molecules and 25000 polyphenols are determined [295,296]. Polyphenols' pharmacological activities, including gene regulation and signal conduction, have been widely explained during past decades [292,293].

As a diet-based gathering, polyphenols, health-beneficial nutrients [297], have medicinal and therapeutic effects in some diseases [298,299], as they relieve non-desired cellular conditions, including OS [300], in cooperation with Nrf2/, ARE signaling pathway [297]. While it involves PGC1α [301], it is followed by high glucose disclosing [302] in the presence of Quercetin, a polyphenol that up-regulates Nrf2 [303]. It also had been investigated that, Nrf2 indirectly related to sirt1 through FoxO3 [304]. On the other hand, Nrf2-linked pathways break out via polyphenol-induced situations, such as PI3K/AKT pathway [305].

The current pathway is occupied in insulin signaling [306] and GSK3β inhibition [307] and is affected during some polyphenols impression cascades, such as curcumin anti-apoptotic effect [308] and mitogenic stress concerning JNK signals inhibition [305,309]. The PI3K/AKT pathway inactivates YSC1, which is inhibited by AMPK/LKB1 on the other side [310]. Also, TSC1 indirectly regulates the mTORC1 pathway (Figure 4) [311]. mTOR suppresses the FoxO pathway, which may also be inactivated during ROS-induced PTEN and sirt1 inhibition [312,313]. Not only ROS medicated indirect mTOR effect, but also energy stress leads to mTOR activation; with the co-molecule diversity, the AMPK [314,315], which together are polyphenols proven targets in some disorders [316,317], such as breast cancer [318], and IBD [319].

AMPK/mTOR pathway affects Ca^{2+} concentration, whether it affects PI3K/AKT pathway [320], linked to NF-κB and MAPK/P38 pathway [321], and TGFβ activated kinase 1 [322], changing autophagic states [323,324], OS [325], and mitochondrial dysfunction [326,327]. Likewise, mTOR natural polyphenol-induced inhibition may start an autophagic cascade. Some polyphenols such as resveratrol blurt this non-ideal result [328], despite the fact they relieve inflammatory conditions influencing AMPK/sirt1/Nrf2 pathway [329,330], PGC1α molecular signals [331], and TSC2 [332], protecting cells during UV exposure [332], and induce AMPK within the heart [334].

Other polyphenols, e.g., Epigallocatechin 3 Gallate (EGCG), Glabridin, and Quercetin, impress the AMPK/Ca^{2+} pathway, so decrease hepatic gluconeogenesis [335–337]. It also may impel cells to express GLuT4 [338–340]. Furthermore, naringenin, another polyphenol, enhance muscular and neuronal glucose uptake through PI3K/AMPK/Ca^{2+} pathway [341–343].

In addition, Quercetin improves eNOS synthesis through the AMPK-mediated pathway [344,345]. As well as, both resveratrol and EGCG activate PGC1α/sirt1/AMPK pathway to ameliorate severe mitochondrial disturbances [346], and AMPK-related berberine, polyphenolic compound effects reduce mitochondrial OS upheaval so that lipid-based disorders may be adjusted through that [347].

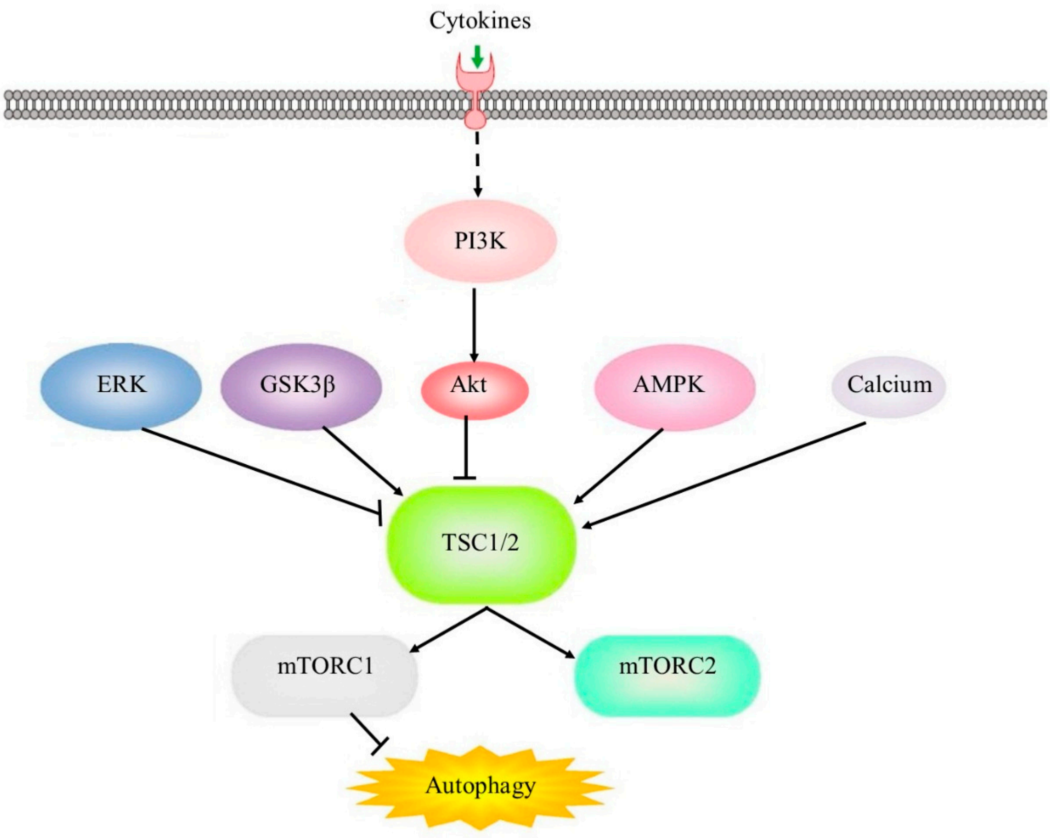

Figure 4. The AKT/PI3K pathway activation by PDGF up-regulates S phase kinase-associated protein 2 (SKP2) and leads to TSC activation. LKB1/AMPK also activates TSC. AMPK phosphorylates TSC2 and inhibits mTORC1, and performs an impressive impact on autophagy.

Targeting AMPK by Polyphenols: A Novel Therapeutic Strategy for Hyperlipidemia

Nowadays, routine statins are already used to reduce hyperlipidemic states [348], including LDL overshot level [21,22], as the primary approach in hyperlipidemia progression [23].

As we discussed previously, HMG-CoA may be a target for therapeutic agents during hyperlipidemia management [36,45], which is tightly linked to NEDD4, PTEN, and PI3K/AKT pathway [45,79]. Moreover, PI3K is related to mTOR and AMPK [78,82].

AMPK, a cellular energy balance modifier [125], regulates some cellular conditions as a checkpoint, including AMP/ATP ratio imbalance [349]. During hyperlipidemic situations, FFAs released into the circulation, PPARs act here, and adipocyte inferred peroxisome, indirectly connecting to AMPK/NF-κB pathway [350,351], and polyphenols target them [352]. AMPK, during this FFA exposure, down-regulates novel lipid molecules generation [122,353] and interlocks mTOR, Nrf2, GLuT4, and PI3K to this mechanism [209,228,252,354,355], and GSK3β to mitochondrial dysfunction [356], a momentous event when hyperlipidemia engender [61,63]. Moreover, if the AMPK/mTOR pathway malfunction is prolonged, the hyperlipidemic conditions may be explicit [313], which are activated by natural herbal mediators, polyphenols [357,358], and dietary anti-oxidant [359].

Polyphenols target AMPK, activate the AMPK signaling pathway, and influence lipid metabolism [360] and ROS-mediated energy stress [361,362]. Indeed, polyphenolic AMPK activation results in lipogenesis inhibition and lipophagy [363] through SREBP1/PPAR/AMPK pathway [364], JAK2 [365,366], sirt1 [367]. In addition, polyphenols in mid-white adipose tissue prevent lipotoxicity [368]. In addition, cholesterol efflux mediated polyphenols lipid-lowering effects, consulting LXR pathway [369]. LXR cumulates hepatic lipids and reacts to cholesterol at the extreme upper level through SREBP1 [370].

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All these pathways accede to AMPK eventually [186], which may directly or indirectly inhibit via polyphenolic compounds [371]. AMPK also inhibits SREBP1, which reduces hepatic lipogenesis [372], and triglyceride [332], regulating PI3K/AKT pathway [373], induces sirt1, which progresses PGC1α deacetylation and regulates mitochondrial biogenesis [374]. All these clues persist on direct or indirect AMPK-mediated polyphenolic anti-hyperlipidemic effects [375], resulting in a new hyperlipidemia therapeutic approach.

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References

1. Hill, Marcus F., and Bruno Bordoni. Hyperlipidemia. In *StatPearls [Internet]*; StatPearls Publishing: 2022.
2. Ezeh, Kosisochukwu J., and Obiora Ezeudemba. "Hyperlipidemia: A Review of the Novel Methods for the Management of Lipids." Cureus **2021**, *13*.
3. Shi L, Wang J, Wang Y, Feng Y. MDG-1, an Ophiopogon polysaccharide, alleviates hyperlipidemia in mice based on metabolic profile of bile acids. Carbohydrate Polymers. 2016 Oct 5;150:74-81.
4. Li S, Jin S, Song C, Chen C, Zhang Y, Xiang Y, Xu Y, Feng Y, Wan Q, Jiang H. The metabolic change of serum lysophosphatidylcholines involved in the lipid lowering effect of triterpenes from Alismatis rhizoma on high-fat diet induced hyperlipidemia mice. Journal of Ethnopharmacology. 2016 Jan 11;177:10-8.
5. Haiqiang Y, Zengliang Z, Ji W, Yu C, Libing Z, Xiaoke L, Zheng Y, Zisong W, Ranran S, Xuanxuan X, Changming L. Efficacy and safety of Yinchenwuling powder for hyperlipidemia: a systematic review and Meta-analysis. Journal of Traditional Chinese Medicine. 2016 Apr 30;36(2):135-43.
6. Singh U, Kumar S, Dhakal S. Future prospect of garlic usage in clinical practice of hyperlipidemia: A review. International Journal of Herbal Medicine. 2015;3(2 Part A):38-43.
7. Suica VI, Uyy E, Boteanu RM, Ivan L, Antohe F. Comparative proteomic analysis of membrane microdomains isolated from two hyperlipidemic animal models. Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics. 2016 Sep 30;1864(9):1061-71.
8. Deguchi Y, Miyazaki K. Anti-hyperglycemic and anti-hyperlipidemic effects of guava leaf extract. Nutrition & metabolism. 2010 Feb 2;7(1):1.
9. Bahmani M, Mirhoseini M, Shirzad H, Sedighi M, Shahinfard N, Rafieian-Kopaei M. A review on promising natural agents effective on hyperlipidemia. Journal of evidence-based complementary & alternative medicine. 2015 Jul 1;20(3):228-38.
10. Rouhi-Boroujeni H, Rouhi-Boroujeni H, Gharipour M, Mohammadizadeh F, Ahmadi S, Rafieian-kopaei M. Systematic review on safety and drug interaction of herbal therapy in hyperlipidemia: a guide for internist. Acta Bio Medica Atenei Parmensis. 2015 Sep 14;86(2):130-6.
11. Almeda-Valdes P, Cuevas-Ramos D, Mehta R, Muñoz-Hernandez L, Cruz-Bautista I, Perez-Mendez O, Tusie-Luna MT, Gomez-Perez FJ, Pajukanta P, Matikainen N, Taskinen MR. Factors associated with postprandial lipemia and apolipoprotein AV levels in individuals with familial combined hyperlipidemia. BMC endocrine disorders. 2014 Nov 25;14(1):1.
12. Liu Y, Wu J, Shi Q, Guo H, Ying H, Xu N. Primary genetic investigation of a hyperlipidemia model: molecular characteristics and variants of the apolipoprotein E gene in Mongolian gerbil. BioMed research international. 2014 Jun 1;2014.
13. Yin Y, Li X, Sha X, Xi H, Li YF, Shao Y, Mai J, Virtue A, Lopez-Pastrana J, Meng S, Tilley DG. Early hyperlipidemia promotes endothelial activation via a caspase-1-sirtuin 1 pathway. Arteriosclerosis, thrombosis, and vascular biology. 2015 Apr 1;35(4):804-16.
14. Yang ZW, Ouyang KH, Zhao J, Chen H, Xiong L, Wang WJ. Structural characterization and hypolipidemic effect of Cyclocarya paliurus polysaccharide in rat. International Journal of Biological Macromolecules. 2016 Oct 31;91:1073-80.

15. Cruz-Bautista I, Mehta R, Cabiedes J, García-Ulloa C, Guillen-Pineda LE, Almeda-Valdés P, Cuevas-Ramos D, Aguilar-Salinas CA. Determinants of VLDL composition and apo B-containing particles in familial combined hyperlipidemia. Clinica Chimica Acta. 2015 Jan 1;438:160-5.
16. Ibrahim AY, Hendawy SF, Elsayed AA, Omer EA. Evaluation of hypolipidemic Marrubium vulgare effect in Triton WR-1339-induced hyperlipidemia in mice. Asian Pacific journal of tropical medicine. 2016 May 31;9(5):453-9.
17. Hsu JH, Chien IC, Lin CH. Increased risk of hyperlipidemia in patients with bipolar disorder: a population-based study. General hospital psychiatry. 2015 Aug 31;37(4):294-8.
18. Correia-Costa A, Correia-Costa L, Afonso AC, Schaefer F, Guerra A, Moura C, Mota C, Barros H, Areias JC, Azevedo A. Determinants of carotid-femoral pulse wave velocity in prepubertal children. International journal of cardiology. 2016 Sep 1;218:37-42.
19. Safford MM, Gamboa CM, Durant RW, Brown TM, Glasser SP, Shikany JM, Zweifler RM, Howard G, Muntner P. Race–Sex Differences in the Management of Hyperlipidemia: The REasons for Geographic And Racial Differences in Stroke Study. American journal of preventive medicine. 2015 May 31;48(5):520-7.
20. Saravanan S, Pari L. Role of thymol on hyperglycemia and hyperlipidemia in high fat diet-induced type 2 diabetic C57BL/6J mice. European journal of pharmacology. 2015 Aug 15;761:279-87.
21. Chu SM, Shih WT, Yang YH, Chen PC, Chu YH. Use of traditional Chinese medicine in patients with hyperlipidemia: A population-based study in Taiwan. Journal of ethnopharmacology. 2015 Jun 20;168:129-35.
22. Han JM, Lee JS, Kim HG, Seol IC, Im HJ, Cho JH, Son CG. Synergistic effects of Artemisia iwayomogi and Curcuma longa radix on high-fat diet-induced hyperlipidemia in a mouse model. Journal of ethnopharmacology. 2015 Sep 15;173:217-24.
23. Minicocci I, Prisco C, Montali A, Di Costanzo A, Ceci F, Pigna G, Arca M. Contribution of mutations in low density lipoprotein receptor (LDLR) and lipoprotein lipase (LPL) genes to familial combined hyperlipidemia (FCHL): A reappraisal by using a resequencing approach. Atherosclerosis. 2015 Oct 31;242(2):618-24.
24. Di Taranto MD, Staiano A, D'Agostino MN, D'Angelo A, Bloise E, Morgante A, Marotta G, Gentile M, Rubba P, Fortunato G. Association of USF1 and APOA5 polymorphisms with familial combined hyperlipidemia in an Italian population. Molecular and cellular probes. 2015 Feb 28;29(1):19-24.
25. Niimi M, Yang D, Kitajima S, Ning B, Wang C, Li S, Liu E, Zhang J, Chen YE, Fan J. ApoE knockout rabbits: A novel model for the study of human hyperlipidemia. Atherosclerosis. 2016 Feb 29;245:187-93.
26. Thomas T, Ginsberg H. Development of apolipoprotein B antisense molecules as a therapy for hyperlipidemia. Current atherosclerosis reports. 2010 Jan 1;12(1):58-65.
27. Borahay MA, Fang X, Baillargeon JG, Kilic GS, Boehning DF, Kuo YF. Statin use and uterine fibroid risk in hyperlipidemia patients: a nested case-control study. American Journal of Obstetrics and Gynecology. 2016 Jun 28.
28. Variya BC, Bakrania AK, Patel SS. Emblica officinalis (Amla): A review for its phytochemistry, ethnomedicinal uses and medicinal potentials with respect to molecular mechanisms. Pharmacological Research. 2016 Sep 30;111:180-200.
29. Lim JH, Jung ES, Choi EK, Jeong DY, Jo SW, Jin JH, Lee JM, Park BH, Chae SW. Supplementation with Aspergillus oryzae-fermented kochujang lowers serum cholesterol in subjects with hyperlipidemia. Clinical Nutrition. 2015 Jun 30;34(3):383-7.
30. Wat E, Ng CF, Koon CM, Wong EC, Tomlinson B, San Lau CB. The protective effect of Herba Cistanches on statin-induced myotoxicity in vitro. Journal of Ethnopharmacology. 2016 Jun 7.
31. Bhaskaragoud G, Rajath S, Mahendra VP, Kumar GS, Krishna AG, Kumar GS. Hypolipidemic mechanism of oryzanol components-ferulic acid and phytosterols. Biochemical and biophysical research communications. 2016 Jul 22;476(2):82-9.
32. Dražić T, Molčanov K, Sachdev V, Malnar M, Hećimović S, Patankar JV, Obrowsky S, Levak-Frank S, Habuš I, Kratky D. Novel amino-β-lactam derivatives as potent cholesterol absorption inhibitors. European journal of medicinal chemistry. 2014 Nov 24;87:722-34.
33. Campolongo G, Riccioni CV, Raparelli V, Spoletini I, Marazzi G, Vitale C, Volterrani M. The combination of nutraceutical and simvastatin enhances the effect of simvastatin alone in normalising lipid profile without side effects in patients with ischemic heart disease. IJC Metabolic & Endocrine. 2016 Jun 30;11:3-6.
34. Yu HH, Chen PC, Yang YH, Wang LC, Lee JH, Lin YT, Chiang BL. Statin reduces mortality and morbidity in systemic lupus erythematosus patients with hyperlipidemia: A nationwide population-based cohort study. Atherosclerosis. 2015 Nov 30;243(1):11-8.
35. Reimann M, Rüdiger H, Weiss N, Ziemssen T. Acute hyperlipidemia but not hyperhomocysteinemia impairs reflex regulation of the cardiovascular system. Atherosclerosis Supplements. 2015 May 31;18:8-15.
36. Iqbal D, Khan MS, Khan MS, Ahmad S, Hussain MS, Ali M. Bioactivity guided fractionation and hypolipidemic property of a novel HMG-CoA reductase inhibitor from Ficus virens Ait. Lipids in health and disease. 2015 Mar 4;14(1):1.

37. Tabatabaei-Malazy O, Larijani B, Abdollahi M. Targeting metabolic disorders by natural products. Journal of Diabetes & Metabolic Disorders. 2015 Jul 8;14(1):1.
38. Wang M, Gao M, Liao J, Qi Y, Du X, Wang Y, Li L, Liu G, Yang H. Adipose tissue deficiency results in severe hyperlipidemia and atherosclerosis in the low-density lipoprotein receptor knockout mice. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2016 May 31;1861(5):410-8.
39. huan Liu Y, sheng Wu J, yuan Wang Z, huan Yu C, zhong Ying H, ying Xu N. Characteristic, polymorphism and expression distribution of LCAT gene in a Mongolian gerbil model for hyperlipidemia. Experimental and molecular pathology. 2014 Oct 31;97(2):266-72.
40. Jiang C, Wang Q, Wei Y, Yao N, Wu Z, Ma Y, Lin Z, Zhao M, Che C, Yao X, Zhang J. Cholesterol-lowering effects and potential mechanisms of different polar extracts from Cyclocarya paliurus leave in hyperlipidemic mice. Journal of ethnopharmacology. 2015 Dec 24;176:17-26.
41. He K, Hu Y, Ma H, Zou Z, Xiao Y, Yang Y, Feng M, Li X, Ye X. Rhizoma Coptidis alkaloids alleviate hyperlipidemia in B6 mice by modulating gut microbiota and bile acid pathways. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2016 Jun 7.
42. Umar A, Iskandar G, Aikemu A, Yiming W, Zhou W, Berké B, Begaud B, Moore N. Effects of Cydonia oblonga Miller leaf and fruit flavonoids on blood lipids and anti-oxydant potential in hyperlipidemia rats. Journal of ethnopharmacology. 2015 Jul 1;169:239-43.
43. Parikh NH, Parikh PK, Kothari C. Indigenous plant medicines for health care: treatment of Diabetes mellitus and hyperlipidemia. Chinese journal of natural medicines. 2014 May 31;12(5):335-44.
44. Qi SZ, Li N, Tuo ZD, Li JL, Xing SS, Li BB, Zhang L, Lee HS, Chen JG, Cui L. Effects of Morus root bark extract and active constituents on blood lipids in hyperlipidemia rats. Journal of ethnopharmacology. 2016 Mar 2;180:54-9.
45. Screen M, Jonson PH, Raheem O, Palmio J, Laaksonen R, Lehtimäki T, Sirito M, Krahe R, Hackman P, Udd B. Abnormal splicing of NEDD4 in myotonic dystrophy type 2: possible link to statin adverse reactions. The American journal of pathology. 2014 Aug 31;184(8):2322-32.
46. Moshourab R, Palada V, Grunwald S, Grieben U, Lewin GR, Spuler S. A Molecular Signature of Myalgia in Myotonic Dystrophy 2. EBioMedicine. 2016 May 31;7:205-11.
47. Zou X, Gao J, Zheng Y, Wang X, Chen C, Cao K, Xu J, Li Y, Lu W, Liu J, Feng Z. Zeaxanthin induces Nrf2-mediated phase II enzymes in protection of cell death. Cell death & disease. 2014 May 1;5(5):e1218.
48. Sakurai T, Isogaya K, Sakai S, Morikawa M, Morishita Y, Ehata S, Miyazono K, Koinuma D. RNA-binding motif protein 47 inhibits Nrf2 activity to suppress tumor growth in lung adenocarcinoma. Oncogene. 2016 Feb 29.
49. Yang RL, Shi YH, Hao G, Li W, Le GW. Increasing oxidative stress with progressive hyperlipidemia in human: relation between malondialdehyde and atherogenic index. Journal of clinical biochemistry and nutrition. 2008;43(3):154-8.
50. Fernandes DC, Alves AM, Castro GS, Junior AA, Naves MM. Effects of baru almond and brazil nut against hyperlipidemia and oxidative stress in vivo. Journal of Food Research. 2015 Aug 1;4(4):38.
51. Zhao Y, Peng L, Lu W, Wang Y, Huang X, Gong C, He L, Hong J, Wu S, Jin X. Effect of Eclipta prostrata on lipid metabolism in hyperlipidemic animals. Experimental gerontology. 2015 Feb 28;62:37-44.
52. Wat E, Ng CF, Wong EC, Koon CM, Lau CP, Cheung DW, Fung KP, San Lau CB, Leung PC. The hepatoprotective effect of the combination use of Fructus Schisandrae with statin–A preclinical evaluation. Journal of ethnopharmacology. 2016 Feb 3;178:104-14.
53. Wang Z, Fan J, Wang J, Li Y, Xiao L, Duan D, Wang Q. Protective effect of lycopene on high-fat diet-induced cognitive impairment in rats. Neuroscience letters. 2016 May 10.
54. Shin HS, Han JM, Kim HG, Choi MK, Son CG, Yoo HR, Jo HK, Seol IC. Anti-atherosclerosis and hyperlipidemia effects of herbal mixture, Artemisia iwayomogi Kitamura and Curcuma longa Linne, in apolipoprotein E-deficient mice. Journal of ethnopharmacology. 2014 Apr 11;153(1):142-50.
55. Ahmad S, Beg ZH. Evaluation of therapeutic effect of omega-6 linoleic acid and thymoquinone enriched extracts from Nigella sativa oil in the mitigation of lipidemic oxidative stress in rats. Nutrition. 2016 Jun 30;32(6):649-55.
56. Drummond GR, Sobey CG. Endothelial NADPH oxidases: which NOX to target in vascular disease?. Trends in Endocrinology & Metabolism. 2014 Sep 30;25(9):452-63.
57. Sarega N, Imam MU, Ooi DJ, Chan KW, Md Esa N, Zawawi N, Ismail M. Phenolic Rich Extract from Clinacanthus nutans Attenuates Hyperlipidemia-Associated Oxidative Stress in Rats. Oxidative medicine and cellular longevity. 2016 Jan 10;2016.
58. Tang Y, Zhong Z. Obtusifolin treatment improves hyperlipidemia and hyperglycemia: possible mechanism involving oxidative stress. Cell biochemistry and biophysics. 2014 Dec 1;70(3):1751-7.
59. Wahby MM, Yacout G, Kandeel K, Awad D. LPS-induced oxidative inflammation and hyperlipidemia in male rats: The protective role of Origanum majorana extract. Beni-Suef University Journal of Basic and Applied Sciences. 2015 Dec 31;4(4):291-8.

60. Chan PT, Matanjun P, Yasir SM, Tan TS. Oxidative stress biomarkers in organs of hyperlipidaemic and normal rats fed tropical red seaweed, Gracilaria changii. Journal of Applied Phycology. 2016 Apr 1;28(2):1371-8.
61. Singh AK, Pandey SK, Saha G, Gattupalli NK. Pyrroloquinoline quinone (PQQ) producing Escherichia coli Nissle 1917 (EcN) alleviates age associated oxidative stress and hyperlipidemia, and improves mitochondrial function in ageing rats. Experimental gerontology. 2015 Jun 30;66:1-9.
62. Nicolson GL, Ash ME. Lipid replacement therapy: a natural medicine approach to replacing damaged lipids in cellular membranes and organelles and restoring function. Biochimica et Biophysica Acta (BBA)-Biomembranes. 2014 Jun 30;1838(6):1657-79.
63. Fuhrmann A, Lopes PC, Sereno J, Pedro J, Espinoza DO, Pereira MJ, Reis F, Eriksson JW, Carvalho E. Molecular mechanisms underlying the effects of cyclosporin A and sirolimus on glucose and lipid metabolism in liver, skeletal muscle and adipose tissue in an in vivo rat model. Biochemical pharmacology. 2014 Mar 15;88(2):216-28.
64. Lee BC, Lee J. Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2014 Mar 31;1842(3):446-62.
65. Chuang SC, Boeing H, Vollset SE, Midttun Ø, Ueland PM, Bueno-de-Mesquita B, Lajous M, Fagherazzi G, Boutron-Ruault MC, Kaaks R, Küehn T. Cellular immune activity biomarker neopterin is associated hyperlipidemia: results from a large population-based study. Immunity & Ageing. 2016 Feb 25;13(1):1.
66. Sato H, Taketomi Y, Murakami M. Metabolic regulation by secreted phospholipase A 2. Inflammation and Regeneration. 2016 May 21;36(1):1.
67. Stevenson J, Huang EY, Olzmann JA. Endoplasmic Reticulum-Associated Degradation and Lipid Homeostasis. Annual Review of Nutrition. 2016(0).
68. Brambilla Pisoni G, Molinari M. Five Questions (with their Answers) on ER-Associated Degradation. Traffic. 2016 Feb 1.
69. Kaneko M, Iwase I, Yamasaki Y, Takai T, Wu Y, Kanemoto S, Matsuhisa K, Asada R, Okuma Y, Watanabe T, Imaizumi K. Genome-wide identification and gene expression profiling of ubiquitin ligases for endoplasmic reticulum protein degradation. Scientific Reports. 2016;6.
70. Jewett KA, Christian CA, Bacos JT, Lee KY, Zhu J, Tsai NP. Feedback modulation of neural network synchrony and seizure susceptibility by Mdm2-p53-Nedd4-2 signaling. Molecular brain. 2016 Mar 22;9(1):1.
71. Jewett KA, Zhu J, Tsai NP. The tumor suppressor p53 guides GluA1 homeostasis through Nedd4-2 during chronic elevation of neuronal activity. Journal of Neurochemistry. 2015 Oct 1;135(2):226-33.
72. Maeda T, Tanabe-Fujimura C, Fujita Y, Abe C, Nanakida Y, Zou K, Liu J, Liu S, Nakajima T, Komano H. NAD (P) H quinone oxidoreductase 1 inhibits the proteasomal degradation of homocysteine-induced endoplasmic reticulum protein. Biochemical and biophysical research communications. 2016 May 13;473(4):1276-80.
73. Spratt DE, Walden H, Shaw GS. RBR E3 ubiquitin ligases: new structures, new insights, new questions. Biochemical Journal. 2014 Mar 15;458(3):421-37.
74. Liu WQ, Zhang YZ, Wu Y, Zhang JJ, Li TB, Jiang T, Xiong XM, Luo XJ, Ma QL, Peng J. Myeloperoxidase-derived hypochlorous acid promotes ox-LDL-induced senescence of endothelial cells through a mechanism involving β-catenin signaling in hyperlipidemia. Biochemical and biophysical research communications. 2015 Nov 27;467(4):859-65.
75. Xu C, Fan CD, Wang X. Regulation of Mdm2 protein stability and the p53 response by NEDD4-1 E3 ligase. Oncogene. 2015 Jan 15;34(3):281-9.
76. Yang XD, Xiang DX, Yang YY. Role of E3 ubiquitin ligases in insulin resistance. Diabetes, Obesity and Metabolism. 2016 May 1.
77. Noyes NC, Hampton B, Migliorini M, Strickland DK. Regulation of Itch and Nedd4 E3 Ligase Activity and Degradation by LRAD3. Biochemistry. 2016 Feb 17;55(8):1204-13.
78. McCabe N, Kennedy RD, Prise KM. The role of PTEN as a cancer biomarker. Oncoscience. 2016;3(2):54.
79. Chen Y, van de Vijver MJ, Hibshoosh H, Parsons R, Saal LH. PTEN and NEDD4 in Human Breast Carcinoma. Pathology & Oncology Research. 2016 Jan 1;22(1):41-7.
80. Zhu G, Baker SJ. Detecting PTEN and PI3K Signaling in Brain. PTEN: Methods and Protocols. 2016:53-62.
81. Bai D, Zhang Y, Shen M, Sun Y, Xia Q, Zhang Y, Liu X, Wang H, Yuan L. Hyperglycemia and hyperlipidemia blunts the Insulin-Inpp5f negative feedback loop in the diabetic heart. Scientific reports. 2016;6.
82. Sundaram M, Yao Z. Recent progress in understanding protein and lipid factors affecting hepatic VLDL assembly and secretion. Nutrition & metabolism. 2010 Apr 27;7(1):1.
83. Cui D, Xiong X, Zhao Y. Cullin-RING ligases in regulation of autophagy. Cell Division. 2016 Jun 10;11(1):1.
84. Liu X, Yao Z. Chronic over-nutrition and dysregulation of GSK3 in diseases. Nutrition & Metabolism. 2016 Aug 4;13(1):49.

85. Koo J, Yue P, Gal AA, Khuri FR, Sun SY. Maintaining glycogen synthase kinase-3 activity is critical for mTOR kinase inhibitors to inhibit cancer cell growth. Cancer research. 2014 May 1;74(9):2555-68.
86. Zhao Y, Morgan MA, Sun Y. Targeting neddylation pathways to inactivate cullin-RING ligases for anticancer therapy. Antioxidants & redox signaling. 2014 Dec 10;21(17):2383-400.
87. Zhai K, Tang Y, Zhang Y, Li F, Wang Y, Cao Z, Yu J, Kou J, Yu B. NMMHC IIA inhibition impedes tissue factor expression and venous thrombosis via Akt/GSK3-NF-B signalling pathways in the endothelium. Thrombosis and Haemostasis. 2015;114(2015):114.
88. Bali A, Jaggi AS. Investigations on GSK-3β/NF-kB signaling in stress and stress adaptive behavior in electric foot shock subjected mice. Behavioural brain research. 2016 Apr 1;302:1-0.
89. Mathur A, Rizvi F, Kakkar P. PHLPP2 down regulation influences nuclear Nrf2 stability via Akt-1/Gsk3β/Fyn kinase axis in acetaminophen induced oxidative renal toxicity: Protection accorded by morin. Food and Chemical Toxicology. 2016 Mar 31;89:19-31.
90. Cuadrado A. Structural and functional characterization of Nrf2 degradation by glycogen synthase kinase 3/β-TrCP. Free Radical Biology and Medicine. 2015 Nov 30;88:147-57.
91. Jiang R, Wei L, Zhu M, Wu J, Wang L. Aspirin Inhibits LPS-Induced Expression of PI3K/Akt, ERK, NF-κB, CX3CL1, and MMPs in Human Bronchial Epithelial Cells. Inflammation. 2016 Apr 1;39(2):643-50.
92. Li W, Fang Q, Zhong P, Chen L, Wang L, Zhang Y, Wang J, Li X, Wang Y, Wang J, Liang G. EGFR Inhibition Blocks Palmitic Acid-induced inflammation in cardiomyocytes and Prevents Hyperlipidemia-induced Cardiac Injury in Mice. Scientific reports. 2016 Apr 18;6:24580.
93. Fang Q, Zou C, Zhong P, Lin F, Li W, Wang L, Zhang Y, Zheng C, Wang Y, Li X, Liang G. EGFR mediates hyperlipidemia-induced renal injury via regulating inflammation and oxidative stress: the detrimental role and mechanism of EGFR activation. Oncotarget. 2016 Mar.
94. Zhou X, Zhang W, Liu X, Zhang W, Li Y. Interrelationship between diabetes and periodontitis: Role of hyperlipidemia. Archives of oral biology. 2015 Apr 30;60(4):667-74.
95. Vinayagam R, Xu B. Antidiabetic properties of dietary flavonoids: a cellular mechanism review. Nutrition & metabolism. 2015 Dec 23;12(1):1.
96. Yao J, Zhao L, Zhao Q, Zhao Y, Sun Y, Zhang Y, Miao H, You QD, Hu R, Guo QL. NF-κB and Nrf2 signaling pathways contribute to wogonin-mediated inhibition of inflammation-associated colorectal carcinogenesis. Cell death & disease. 2014 Jun;5(6):e1283.
97. Choi GH, Jung YS, Shin HC. The Effects of Haedoksamul-tang on Oxidative Stress and Hyperlipidemia in LPS-induced ICR Mouse. Journal of Korean Medicine. 2016 Mar 31;37(1):77-89.
98. Song L, Wörmann S, Ai J, Neuhöfer P, Lesina M, Diakopoulos KN, Ruess D, Treiber M, Witt H, Bassermann F, Halangk W. BCL3 Reduces the Sterile Inflammatory Response in Pancreatic and Biliary Tissues. Gastroenterology. 2016 Feb 29;150(2):499-512.
99. Arlt A, Schäfer H, Kalthoff H. The 'N-factors' in pancreatic cancer: functional relevance of NF-kB, NFAT and Nrf2 in pancreatic cancer.2012
100. Park SY, Kim YH, Park G. Cucurbitacins attenuate microglial activation and protect from neuroinflammatory injury through Nrf2/ARE activation and STAT/NF-κB inhibition. Neuroscience letters. 2015 Nov 16;609:129-36.
101. de Oliveira MR, Ferreira GC, Schuck PF, Dal Bosco SM. Role for the PI3K/Akt/Nrf2 signaling pathway in the protective effects of carnosic acid against methylglyoxal-induced neurotoxicity in SH-SY5Y neuroblastoma cells. Chemico-biological interactions. 2015 Dec 5;242:396-406.
102. Liu CM, Ma JQ, Xie WR, Liu SS, Feng ZJ, Zheng GH, Wang AM. Quercetin protects mouse liver against nickel-induced DNA methylation and inflammation associated with the Nrf2/HO-1 and p38/STAT1/NF-κB pathway. Food and Chemical Toxicology. 2015 Aug 31;82:19-26.
103. Yang PM, Wu ZZ, Zhang YQ, Wung BS. Lycopene inhibits ICAM-1 expression and NF-κB activation by Nrf2-regulated cell redox state in human retinal pigment epithelial cells. Life sciences. 2016 Jun 15;155:94-101.
104. Khan A, Jamwal S, Bijjem KR, Prakash A, Kumar P. Neuroprotective effect of hemeoxygenase-1/glycogen synthase kinase-3β modulators in 3-nitropropionic acid-induced neurotoxicity in rats. Neuroscience. 2015 Feb 26;287:66-77.
105. Wang P, Peng X, Wei ZF, Wei FY, Wang W, Ma WD, Yao LP, Fu YJ, Zu YG. Geraniin exerts cytoprotective effect against cellular oxidative stress by upregulation of Nrf2-mediated antioxidant enzyme expression via PI3K/AKT and ERK1/2 pathway. Biochimica et Biophysica Acta (BBA)-General Subjects. 2015 Sep 30;1850(9):1751-61.
106. Gu L, Tao X, Xu Y, Han X, Qi Y, Xu L, Yin L, Peng J. Dioscin alleviates BDL-and DMN-induced hepatic fibrosis via Sirt1/Nrf2-mediated inhibition of p38 MAPK pathway. Toxicology and applied pharmacology. 2016 Feb 1;292:19-29.
107. Zhu HQ, Wang F, Dong LY, Zhou Q, Wang Y. MicroRNA1 modulates oxLDL-induced hyperlipidemia by down-regulating MLCK and ERK/p38 MAPK pathway. Life sciences. 2014 Jun 27;107(1):21-6.

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108. Neppl RL, Wang DZ. The myriad essential roles of microRNAs in cardiovascular homeostasis and disease. Genes & Diseases. 2014 Sep 30;1(1):18-39.
109. Palermo FA, Cocci P, Mozzicafreddo M, Arukwe A, Angeletti M, Aretusi G, Mosconi G. Tri-m-cresyl phosphate and PPAR/LXR interactions in seabream hepatocytes: revealed by computational modeling (docking) and transcriptional regulation of signaling pathways. Toxicology Research. 2016;5(2):471-81.
110. Wang YP, Wat E, Koon CM, Wong CW, Cheung DW, Leung PC, Zhao QS, Fung KP, San Lau CB. The beneficial potential of polyphenol-enriched fraction from Erigerontis Herba on metabolic syndrome. Journal of ethnopharmacology. 2016 Jul 1;187:94-103.
111. Bak EJ, Kim J, Choi YH, Kim JH, Lee DE, Woo GH, Cha JH, Yoo YJ. Wogonin ameliorates hyperglycemia and dyslipidemia via PPARα activation in db/db mice. Clinical Nutrition. 2014 Feb 28;33(1):156-63.
112. Gou SH, Huang HF, Chen XY, Liu J, He M, Ma YY, Zhao XN, Zhang Y, Ni JM. Lipid-lowering, hepatoprotective, and atheroprotective effects of the mixture Hong-Qu and gypenosides in hyperlipidemia with NAFLD rats. Journal of the Chinese Medical Association. 2016 Mar 31;79(3):111-21.
113. Sahini N, Borlak J. Recent insights into the molecular pathophysiology of lipid droplet formation in hepatocytes. Progress in lipid research. 2014 Apr 30;54:86-112.
114. Krauzová E, Kračmerová J, Rossmeislová L, Mališová L, Tencerová M, Koc M, Štich V, Šiklová M. Acute hyperlipidemia initiates proinflammatory and proatherogenic changes in circulation and adipose tissue in obese women. Atherosclerosis. 2016 Jul 31;250:151-7.
115. Podrez EA, Byzova TV, Febbraio M, Salomon RG, Ma Y, Valiyaveettil M, Poliakov E, Sun M, Finton PJ, Curtis BR, Chen J. Platelet CD36 links hyperlipidemia, oxidant stress and a prothrombotic phenotype. Nature medicine. 2007 Sep 1;13(9):1086-95.
116. Park SY, Lee SW, Kim HY, Lee SY, Lee WS, Hong KW, Kim CD. SIRT1 inhibits differentiation of monocytes to macrophages: amelioration of synovial inflammation in rheumatoid arthritis. Journal of Molecular Medicine. 2016 Mar 9:1-1.
117. Chen YP, Tsai CW, Shen CY, Day CH, Yeh YL, Chen RJ, Ho TJ, Padma VV, Kuo WW, Huang CY. Palmitic acid interferes with energy metabolism balance by adversely switching the SIRT1-CD36-fatty acid pathway to the PKC< zeta>-GLUT4-glucose pathway in cardiomyoblasts. The Journal of nutritional biochemistry. 2016 May 31;31:137-49.
118. Fu L, Bruckbauer A, Li F, Cao Q, Cui X, Wu R, Shi H, Zemel MB, Xue B. Interaction between metformin and leucine in reducing hyperlipidemia and hepatic lipid accumulation in diet-induced obese mice. Metabolism. 2015 Nov 30;64(11):1426-34.
119. Jia Y, Wang H, Wang Q, Ding H, Wu H, Pan H. Silencing Nrf2 impairs glioma cell proliferation via AMPK-activated mTOR inhibition. Biochemical and biophysical research communications. 2016 Jan 15;469(3):665-71.
120. Lu J, Huang G, Hu S, Wang Z, Guan S. 1, 3-Dichloro-2-propanol induced hyperlipidemia in C57BL/6J mice via AMPK signaling pathway. Food and Chemical Toxicology. 2014 Feb 28;64:403-9.
121. Liu X, Hao JJ, Zhang LJ, Zhao X, He XX, Li MM, Zhao XL, Wu JD, Qiu PJ, Yu GL. Activated AMPK explains hypolipidemic effects of sulfated low molecular weight guluronate on HepG2 cells. European journal of medicinal chemistry. 2014 Oct 6;85:304-10.
122. Gugliucci A. Fructose surges damage hepatic adenosyl-monophosphate-dependent kinase and lead to increased lipogenesis and hepatic insulin resistance. Medical Hypotheses. 2016 Aug 31;93:87-92.
123. Zhao L, Moos MP, Gräbner R, Pédrono F, Fan J, Kaiser B, John N, Schmidt S, Spanbroek R, Lötzer K, Huang L. The 5-lipoxygenase pathway promotes pathogenesis of hyperlipidemia-dependent aortic aneurysm. Nature medicine. 2004 Sep 1;10(9):966-73.
124. Dahlhoff C, Worsch S, Sailer M, Hummel BA, Fiamoncini J, Uebel K, Obeid R, Scherling C, Geisel J, Bader BL, Daniel H. Methyl-donor supplementation in obese mice prevents the progression of NAFLD, activates AMPK and decreases acyl-carnitine levels. Molecular metabolism. 2014 Aug 31;3(5):565-80.
125. Hardie DG, Schaffer BE, Brunet A. AMPK: an energy-sensing pathway with multiple inputs and outputs. Trends in cell biology. 2016 Mar 31;26(3):190-201.
126. Heinegård, D. and G. Tiderström (1973). "Determination of serum creatinine by a direct colorimetric method." Clinica chimica acta 43(3): 305-310.
127. Wang Y, Buyse J, Song Z, Decuypere E, Everaert N. AMPK is involved in the differential neonatal performance of chicks hatching at different time. General and comparative endocrinology. 2016 Mar 1;228:53-9.
128. Daskalopoulos EP, Dufeys C, Bertrand L, Beauloye C, Horman S. AMPK in cardiac fibrosis and repair: Actions beyond metabolic regulation. Journal of molecular and cellular cardiology. 2016 Feb 29;91:188-200.
129. Duan P, Hu C, Quan C, Yu T, Zhou W, Yuan M, Shi Y, Yang K. 4-Nonylphenol induces apoptosis, autophagy and necrosis in Sertoli cells: Involvement of ROS-mediated AMPK/AKT-mTOR and JNK pathways. Toxicology. 2016 Feb 3;341:28-40.

130. Moon S, Han D, Kim Y, Jin J, Ho WK, Kim Y. Interactome analysis of AMP-activated protein kinase (AMPK)-[agr] 1 and-[bgr] 1 in INS-1 pancreatic beta-cells by affinity purification-mass spectrometry. Scientific reports. 2014 Mar 14;4.
131. Jang S, Kim H, Jeong J, Lee SK, Kim EW, Park M, Kim CH, Lee JE, Namkoong K, Kim E. Blunted response of hippocampal AMPK associated with reduced neurogenesis in older versus younger mice. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2016 Nov 3;71:57-65.
132. Alenazi FS, Ibrahim BA, Al-Hamami H, Shakiya M, Briski KP. Role of estradiol in intrinsic hindbrain AMPK regulation of hypothalamic AMPK, metabolic neuropeptide, and norepinephrine activity and food intake in the female rat. Neuroscience. 2016 Feb 9;314:35-46.
133. Zaha VG, Qi D, Su KN, Palmeri M, Lee HY, Hu X, Wu X, Shulman GI, Rabinovitch PS, Russell RR, Young LH. AMPK is critical for mitochondrial function during reperfusion after myocardial ischemia. Journal of molecular and cellular cardiology. 2016 Feb 29;91:104-13.
134. Salminen A, Kaarniranta K, Kauppinen A. Age-related changes in AMPK activation: role for AMPK phosphatases and inhibitory phosphorylation by upstream signaling pathways. Ageing research reviews. 2016 Jul 31;28:15-26.
135. Xu S, Kang UG. Region-specific activation of the AMPK system by cocaine: The role of D1 and D2 receptors. Pharmacology Biochemistry and Behavior. 2016 Aug 31;146:28-34.
136. Kim DM, Leem YH. Chronic stress-induced memory deficits are reversed by regular exercise via AMPK-mediated BDNF induction. Neuroscience. 2016 Jun 2;324:271-85.
137. Hu X, Liu L, Song Z, Sheikhahmadi A, Wang Y, Buyse J. Effects of feed deprivation on the AMPK signaling pathway in skeletal muscle of broiler chickens. Comparative Biochemistry and Physiology Part B: Biochemistry and Molecular Biology. 2016 Jan 31;191:146-54.
138. Shrestha PK, Briski KP. Hindbrain lactate regulates preoptic gonadotropin-releasing hormone (GnRH) neuron GnRH-I protein but not AMPK responses to hypoglycemia in the steroid-primed ovariectomized female rat. Neuroscience. 2015 Jul 9;298:467-74.
139. Bairwa SC, Parajuli N, Dyck JR. The role of AMPK in cardiomyocyte health and survival. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2016 Jul 10.
140. Lin R, Elf S, Shan C, Kang HB, Ji Q, Zhou L, Hitosugi T, Zhang L, Zhang S, Seo JH, Xie J. 6-Phosphogluconate dehydrogenase links oxidative PPP, lipogenesis and tumour growth by inhibiting LKB1-AMPK signalling. Nature cell biology. 2015 Oct 19.
141. Liu X, Niu Y, Yuan H, Huang J, Fu L. AMPK binds to Sestrins and mediates the effect of exercise to increase insulin-sensitivity through autophagy. Metabolism. 2015 Jun 30;64(6):658-65.
142. Sato F, Muragaki Y. DEC1 negatively regulates AMPK activity via LKB1. Cancer Research. 2016 Jul 15;76(14 Supplement):2026-.
143. Dasgupta B, Chhipa RR. Evolving Lessons on the Complex Role of AMPK in Normal Physiology and Cancer. Trends in pharmacological sciences. 2016 Mar 31;37(3):192-206.
144. Cheng X, Kim JY, Ghafoory S, Duvaci T, Rafiee R, Theobald J, Alborzinia H, Holenya P, Fredebohm J, Merz KH, Mehrabi A. Methylisoindigo preferentially kills cancer stem cells by interfering cell metabolism via inhibition of LKB1 and activation of AMPK in PDACs. Molecular oncology. 2016 Feb 4.
145. Hardie DG, Alessi DR. LKB1 and AMPK and the cancer-metabolism link-ten years after. BMC biology. 2013 Apr 15;11(1):1.
146. Liu X, Xiao ZD, Han L, Zhang J, Lee SW, Wang W, Lee H, Zhuang L, Chen J, Lin HK, Wang J. LncRNA NBR2 engages a metabolic checkpoint by regulating AMPK under energy stress. Nature cell biology. 2016 Mar 21.
147. Lee JH, Jeong JK, Park SY. Sulforaphane-induced autophagy flux prevents prion protein-mediated neurotoxicity through AMPK pathway. Neuroscience. 2014 Oct 10;278:31-9.
148. Bandow K, Kusuyama J, Kakimoto K, Ohnishi T, Matsuguchi T. AMP-activated protein kinase (AMPK) activity negatively regulates chondrogenic differentiation. Bone. 2015 May 31;74:125-33.
149. Li X, Wang L, Zhou XE, Ke J, de Waal PW, Gu X, Tan ME, Wang D, Wu D, Xu HE, Melcher K. Structural basis of AMPK regulation by adenine nucleotides and glycogen. Cell research. 2015 Jan 1;25(1):50-66.
150. Bai T, Yang Y, Wu YL, Jiang S, Lee JJ, Lian LH, Nan JX. Thymoquinone alleviates thioacetamide-induced hepatic fibrosis and inflammation by activating LKB1–AMPK signaling pathway in mice. International immunopharmacology. 2014 Apr 30;19(2):351-7.
151. Kim GE, Young LH. AMPK and the atrial response to metabolic inhibition. Journal of the American College of Cardiology. 2015 Jul 7;66(1):59-61.
152. Faubert B, Vincent EE, Poffenberger MC, Jones RG. The AMP-activated protein kinase (AMPK) and cancer: many faces of a metabolic regulator. Cancer letters. 2015 Jan 28;356(2):165-70.
153. Zhao C, Zhang Q, Yu T, Sun S, Wang W, Liu G. Hypoxia promotes drug resistance in osteosarcoma cells via activating AMP-activated protein kinase (AMPK) signaling. Journal of bone oncology. 2016 Mar 31;5(1):22-9.

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154. García-Prieto CF, Gil-Ortega M, Aránguez I, Ortiz-Besoain M, Somoza B, Fernández-Alfonso MS. Vascular AMPK as an attractive target in the treatment of vascular complications of obesity. Vascular pharmacology. 2015 Jun 30;67:10-20.
155. Kawashima I, Mitsumori T, Nozaki Y, Yamamoto T, Shobu-Sueki Y, Nakajima K, Kirito K. Negative regulation of the LKB1/AMPK pathway by ERK in human acute myeloid leukemia cells. Experimental hematology. 2015 Jul 31;43(7):524-33.
156. Zhang L, Wen K, Han X, Liu R, Qu Q. Adiponectin mediates antiproliferative and apoptotic responses in endometrial carcinoma by the AdipoRs/AMPK pathway. Gynecologic oncology. 2015 May 31;137(2):311-20.
157. Kemmerer M, Wittig I, Richter F, Brüne B, Namgaladze D. AMPK activates LXRα and ABCA1 expression in human macrophages. The International Journal of Biochemistry & Cell Biology. 2016 Sep 30;78:1-9.
158. Lee KY, Kim JR, Choi HC. Genistein-induced LKB1–AMPK activation inhibits senescence of VSMC through autophagy induction. Vascular pharmacology. 2016 Jun 30;81:75-82.
159. Han J, Liang H, Tian D, Du J, Wang Q, Xi P, Wang H, Li Y. mTOR remains unchanged in diet-resistant (DR) rats despite impaired LKB1/AMPK cascade in adipose tissue. Biochemical and biophysical research communications. 2016 May 25.
160. Hardie DG. AMPK—sensing energy while talking to other signaling pathways. Cell metabolism. 2014 Dec 2;20(6):939-52.
161. Yang H, Sun W, Quan N, Wang L, Chu D, Cates C, Liu Q, Zheng Y, Li J. Cardioprotective actions of Notch1 against myocardial infarction via LKB1-dependent AMPK signaling pathway. Biochemical pharmacology. 2016 May 15;108:47-57.
162. Finley J. Oocyte activation and latent HIV-1 reactivation: AMPK as a common mechanism of action linking the beginnings of life and the potential eradication of HIV-1. Medical Hypotheses. 2016 Aug 31;93:34-47.
163. Gekas C, D'Altri T, Aligué R, González J, Espinosa L, Bigas A. β-Catenin is required for T-cell leukemia initiation and MYC transcription downstream of Notch1. Leukemia. 2016 Apr 29.
164. Zhang L, Huang Y, Liu F, Zhang F, Ding W. Vanadium (IV)-chlorodipicolinate inhibits 3T3-L1 preadipocyte adipogenesis by activating LKB1/AMPK signaling pathway. Journal of Inorganic Biochemistry. 2016 Jun 5.
165. Cheng KT, Wang YS, Chou HC, Chang CC, Lee CK, Juan SH. Kinsenoside-mediated lipolysis through an AMPK-dependent pathway in C3H10T1/2 adipocytes: Roles of AMPK and PPARα in the lipolytic effect of kinsenoside. Phytomedicine. 2015 Jun 1;22(6):641-7.
166. Park J, Yeom M, Hahm DH. Fucoidan improves serum lipid levels and atherosclerosis through hepatic SREBP-2-mediated regulation. Journal of pharmacological sciences. 2016 Mar 22.
167. Dong B, Singh AB, Fung C, Kan K, Liu J. CETP inhibitors downregulate hepatic LDL receptor and PCSK9 expression in vitro and in vivo through a SREBP2 dependent mechanism. Atherosclerosis. 2014 Aug 31;235(2):449-62.
168. Thakkar CS, Kate AS, Desai DC, Ghosh AR, Kulkarni-Almeida AA. NFAT-133 increases glucose uptake in L6 myotubes by activating AMPK pathway. European journal of pharmacology. 2015 Dec 15;769:117-26.
169. Chung MM, Chen YL, Pei D, Cheng YC, Sun B, Nicol CJ, Yen CH, Chen HM, Liang YJ, Chiang MC. The neuroprotective role of metformin in advanced glycation end product treated human neural stem cells is AMPK-dependent. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2015 May 31;1852(5):720-31.
170. Zhai X, Qiao H, Guan W, Li Z, Cheng Y, Jia X, Zhou Y. Curcumin regulates peroxisome proliferator-activated receptor-γ coactivator-1α expression by AMPK pathway in hepatic stellate cells in vitro. European journal of pharmacology. 2015 Jan 5;746:56-62.
171. Crescenti A, del Bas JM, Arola-Arnal A, Oms-Oliu G, Arola L, Caimari A. Grape seed procyanidins administered at physiological doses to rats during pregnancy and lactation promote lipid oxidation and up-regulate AMPK in the muscle of male offspring in adulthood. The Journal of nutritional biochemistry. 2015 Sep 30;26(9):912-20.
172. Zhang M, Wang C, Wang C, Zhao H, Zhao C, Chen Y, Wang Y, McClain C, Feng W. Enhanced AMPK phosphorylation contributes to the beneficial effects of Lactobacillus rhamnosus GG supernatant on chronic-alcohol-induced fatty liver disease. The Journal of nutritional biochemistry. 2015 Apr 30;26(4):337-44.
173. Alcocer-Gómez E, Garrido-Maraver J, Bullón P, Marín-Aguilar F, Cotán D, Carrión AM, Alvarez-Suarez JM, Giampieri F, Sánchez-Alcazar JA, Battino M, Cordero MD. Metformin and caloric restriction induce an AMPK-dependent restoration of mitochondrial dysfunction in fibroblasts from Fibromyalgia patients. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2015 Jul 31;1852(7):1257-67.
174. Wu SB, Wu YT, Wu TP, Wei YH. Role of AMPK-mediated adaptive responses in human cells with mitochondrial dysfunction to oxidative stress. Biochimica et Biophysica Acta (BBA)-General Subjects. 2014 Apr 30;1840(4):1331-44.

175. Distelmaier F, Valsecchi F, Liemburg-Apers DC, Lebiedzinska M, Rodenburg RJ, Heil S, Keijer J, Fransen J, Imamura H, Danhauser K, Seibt A. Mitochondrial dysfunction in primary human fibroblasts triggers an adaptive cell survival program that requires AMPK-α. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2015 Mar 31;1852(3):529-40.
176. Zhao B, Qiang L, Joseph J, Kalyanaraman B, Viollet B, He YY. Mitochondrial dysfunction activates the AMPK signaling and autophagy to promote cell survival. Genes & Diseases. 2016 Mar 31;3(1):82-7.
177. Ming W, Lu G, Xin S, Huanyu L, Yinghao J, Xiaoying L, Chengming X, Banjun R, Li W, Zifan L. Mitochondria related peptide MOTS-c suppresses ovariectomy-induced bone loss via AMPK activation. Biochemical and biophysical research communications. 2016 May 26.
178. Gao D, Zhang YL, Yang FQ, Li F, Zhang QH, Xia ZN. The flower of Edgeworthia gardneri (wall.) Meisn. suppresses adipogenesis through modulation of the AMPK pathway in 3T3-L1 adipocytes. Journal of Ethnopharmacology. 2016 Sep 15;191:379-86.
179. King-Himmelreich TS, Schramm S, Wolters MC, Schmetzer J, Möser CV, Knothe C, Resch E, Peil J, Geisslinger G, Niederberger E. The impact of endurance exercise on global and AMPK gene-specific DNA methylation. Biochemical and biophysical research communications. 2016 May 27;474(2):284-90.
180. Ducommun S, Deak M, Sumpton D, Ford RJ, Galindo AN, Kussmann M, Viollet B, Steinberg GR, Foretz M, Dayon L, Morrice NA. Motif affinity and mass spectrometry proteomic approach for the discovery of cellular AMPK targets: identification of mitochondrial fission factor as a new AMPK substrate. Cellular signalling. 2015 May 31;27(5):978-88.
181. Dixit D, Ahmad F, Ghildiyal R, Joshi SD, Sen E. CK2 inhibition induced PDK4-AMPK axis regulates metabolic adaptation and survival responses in glioma. Experimental cell research. 2016 May 15;344(1):132-42.
182. Kim TT, Dyck JR. Is AMPK the savior of the failing heart?. Trends in Endocrinology & Metabolism. 2015 Jan 31;26(1):40-8.
183. Lim R, Barker G, Lappas M. Activation of AMPK in human fetal membranes alleviates infection-induced expression of pro-inflammatory and pro-labour mediators. Placenta. 2015 Apr 30;36(4):454-62.
184. Wan D, Zhou Y, Wang K, Hou Y, Hou R, Ye X. Resveratrol provides neuroprotection by inhibiting phosphodiesterases and regulating the cAMP/AMPK/SIRT1 pathway after stroke in rats. Brain research bulletin. 2016 Mar 31;121:255-62.
185. Duan WJ, Li YF, Liu FL, Deng J, Wu YP, Yuan WL, Tsoi B, Chen JL, Wang Q, Cai SH, Kurihara H. A SIRT3/AMPK/autophagy network orchestrates the protective effects of trans-resveratrol in stressed peritoneal macrophages and RAW 264.7 macrophages. Free Radical Biology and Medicine. 2016 Jun 30;95:230-42.
186. Bai T, Yang Y, Yao YL, Sun P, Lian LH, Wu YL, Nan JX. Betulin alleviated ethanol-induced alcoholic liver injury via SIRT1/AMPK signaling pathway. Pharmacological research. 2016 Mar 31;105:1-2.
187. Liu S, Vaziri ND. Role of PCSK9 and IDOL in the pathogenesis of acquired LDL receptor deficiency and hypercholesterolemia in nephrotic syndrome. Nephrology Dialysis Transplantation. 2014 Mar 1;29(3):538-43.
188. Huang J, Li L, Lian J, Schauer S, Vesely PW, Kratky D, Hoefler G, Lehner R. Tumor-Induced Hyperlipidemia Contributes to Tumor Growth. Cell reports. 2016 Apr 12;15(2):336-48.
189. Ananthakrishnan S, Kaysen GA. Treatment of Hyperlipidemia Changes With Level of Kidney Function—Rationale. Advances in Chronic Kidney Disease. 2016 Jul 31;23(4):247-54.
190. Yadav K, Sharma M, Ferdinand KC. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitiors: Present Perspectives and Future Horizons. Nutrition, Metabolism and Cardiovascular Diseases. 2016 May 30.
191. Béliard S, Millier A, Carreau V, Carrié A, Moulin P, Fredenrich A, Farnier M, Luc G, Rosenbaum D, Toumi M, Bruckert E. The very high cardiovascular risk in heterozygous familial hypercholesterolemia: Analysis of 734 French patients. Journal of Clinical Lipidology. 2016 Jun 27.
192. Leyton L, Hott M, Acuna F, Caroca J, Nuñez M, Martin C, Zambrano A, Concha MI, Otth C. Nutraceutical activators of AMPK/Sirt1 axis inhibit viral production and protect neurons from neurodegenerative events triggered during HSV-1 infection. Virus research. 2015 Jul 2;205:63-72.
193. Banerjee J, Bruckbauer A, Zemel MB. Activation of the AMPK/Sirt1 pathway by a leucine–metformin combination increases insulin sensitivity in skeletal muscle, and stimulates glucose and lipid metabolism and increases life span in Caenorhabditis elegans. Metabolism. 2016 Jul 9.
194. Dose J, Huebbe P, Nebel A, Rimbach G. APOE genotype and stress response-a mini review. Lipids in Health and Disease. 2016 Jul 25;15(1):121.
195. Huh JE, Shin JH, Jang ES, Park SJ, Park DR, Ko R, Seo DH, Kim HS, Lee SH, Choi Y, Kim HS. Sirtuin 3 (SIRT3) maintains bone homeostasis by regulating AMPK-PGC-1β axis in mice. Scientific reports. 2016;6.
196. Sun Y, Hong J, Chen M, Ke Y, Zhao S, Liu W, Ma Q, Shi J, Zou Y, Ning T, Zhang Z. Ablation of Lgr4 enhances energy adaptation in skeletal muscle via activation of Ampk/Sirt1/Pgc1α pathway. Biochemical and biophysical research communications. 2015 Aug 21;464(2):396-400.

197. Talero E, Alcaide A, Ávila-Román J, García-Mauriño S, Vendramini-Costa D, Motilva V. Expression patterns of sirtuin 1-AMPK-autophagy pathway in chronic colitis and inflammation-associated colon neoplasia in IL-10-deficient mice. International immunopharmacology. 2016 Jun 30;35:248-56.
198. Genzer Y, Dadon M, Burg C, Chapnik N, Froy O. Ketogenic diet delays the phase of circadian rhythms and does not affect AMP-activated protein kinase (AMPK) in mouse liver. Molecular and Cellular Endocrinology. 2015 Dec 5;417:124-30.
199. Zhou Y, He X, Chen Y, Huang Y, Wu L, He J. Exendin-4 attenuates cardiac hypertrophy via AMPK/mTOR signaling pathway activation. Biochemical and biophysical research communications. 2015 Dec 11;468(1):394-9.
200. He Q, Sha S, Sun L, Zhang J, Dong M. GLP-1 analogue improves hepatic lipid accumulation by inducing autophagy via AMPK/mTOR pathway. Biochemical and biophysical research communications. 2016 May 18.
201. Kong X, Guan J, Li J, Wei J, Wang R. P66Shc-SIRT1 Regulation of Oxidative Stress Protects Against Cardio-cerebral Vascular Disease. Molecular Neurobiology. 2016:1-9.
202. Jung YS, Park JH, Kim H, Kim SY, Hwang JY, Hong KW, Bae SS, Choi BT, Lee SW, Shin HK. Probucol inhibits LPS-induced microglia activation and ameliorates brain ischemic injury in normal and hyperlipidemic mice. Acta Pharmacologica Sinica. 2016 Jun 27.
203. Gui Y, Li A, Chen F, Zhou H, Tang Y, Chen L, Chen S, Duan S. Involvement of AMPK/SIRT1 pathway in anti-allodynic effect of troxerutin in CCI-induced neuropathic pain. European journal of pharmacology. 2015 Dec 15;769:234-41.
204. Wu XB, Liu Y, Wang GH, Xu X, Cai Y, Wang HY, Li YQ, Meng HF, Dai F, Jin JD. Mesenchymal stem cells promote colorectal cancer progression through AMPK/mTOR-mediated NF-κB activation. Scientific reports. 2016;6.
205. Lee H, Oh ET, Choi BH, Park MT, Lee JK, Lee JS, Park HJ. NQO1-induced activation of AMPK contributes to cancer cell death by oxygen-glucose deprivation. Scientific reports. 2015 Jan 14;5.
206. Choi KM, Lee YS, Kim W, Kim SJ, Shin KO, Yu JY, Lee MK, Lee YM, Hong JT, Yun YP, Yoo HS. Sulforaphane attenuates obesity by inhibiting adipogenesis and activating the AMPK pathway in obese mice. The Journal of nutritional biochemistry. 2014 Feb 28;25(2):201-7.
207. Ehsan M, Singh KK, Lovren F, Pan Y, Quan A, Mantella LE, Sandhu P, Teoh H, Al-Omran M, Verma S. Adiponectin limits monocytic microparticle-induced endothelial activation by modulation of the AMPK, Akt and NFκB signaling pathways. Atherosclerosis. 2016 Feb 29;245:1-1.
208. Russo E, Andreozzi F, Iuliano R, Dattilo V, Procopio T, Fiume G, Mimmi S, Perrotti N, Citraro R, Sesti G, Constanti A. Early molecular and behavioral response to lipopolysaccharide in the WAG/Rij rat model of absence epilepsy and depressive-like behavior, involves interplay between AMPK, AKT/mTOR pathways and neuroinflammatory cytokine release. Brain, behavior, and immunity. 2014 Nov 30;42:157-68.
209. Mattaveewong T, Wongkrasant P, Chanchai S, Pichyangkura R, Chatsudthipong V, Muanprasat C. Chitosan oligosaccharide suppresses tumor progression in a mouse model of colitis-associated colorectal cancer through AMPK activation and suppression of NF-κB and mTOR signaling. Carbohydrate polymers. 2016 Jul 10;145:30-6.
210. Li W, Qiu X, Jiang H, Zhi Y, Fu J, Liu J. Ulinastatin inhibits the inflammation of LPS-induced acute lung injury in mice via regulation of AMPK/NF-κB pathway. International immunopharmacology. 2015 Dec 31;29(2):560-7.
211. Pan H, Zhong XP, Lee S. Sustained activation of mTORC1 in macrophages increases AMPKα-dependent autophagy to maintain cellular homeostasis. BMC biochemistry. 2016 Jul 7;17(1):14.
212. Liu J, Wu J, Sun A, Sun Y, Yu X, Liu N, Dong S, Yang F, Zhang L, Zhong X, Xu C. Hydrogen sulfide decreases high glucose/palmitate-induced autophagy in endothelial cells by the Nrf2-ROS-AMPK signaling pathway. Cell & bioscience. 2016 May 23;6(1):1.
213. Yao F, Zhang M, Chen L. 5'-Monophosphate-activated protein kinase (AMPK) improves autophagic activity in diabetes and diabetic complications. Acta Pharmaceutica Sinica B. 2016 Jan 31;6(1):20-5.
214. Zhan JK, Wang YJ, Wang Y, Tang ZY, Tan P, Huang W, Liu YS. Adiponectin attenuates the osteoblastic differentiation of vascular smooth muscle cells through the AMPK/mTOR pathway. Experimental cell research. 2014 May 1;323(2):352-8.
215. Bond P. Regulation of mTORC1 by growth factors, energy status, amino acids and mechanical stimuli at a glance. Journal of the International Society of Sports Nutrition. 2016 Mar 1;13(1):1.
216. Zhao Y, Donohoe D, Huang EC, Whelan J. Zyflamend, a polyherbal mixture, inhibits lipogenesis and mTORC1 signalling via activation of AMPK. Journal of Functional Foods. 2015 Oct 31;18:147-58.
217. Campos T, Ziehe J, Fuentes-Villalobos F, Riquelme O, Peña D, Troncoso R, Lavandero S, Morin V, Pincheira R, Castro AF. Rapamycin requires AMPK activity and p27 expression for promoting autophagy-dependent Tsc2-null cell survival. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2016 Jun 30;1863(6):1200-7.

218. Kim M, Cho HJ, Jeong YJ, Chung IK, Magae J, Chang YC. 4-O-methylascochlorin suppresses differentiation of 3T3-L1 preadipocytes by inhibiting PPARγ expression through regulation of AMPK/mTOR signaling pathways. Archives of biochemistry and biophysics. 2015 Oct 1;583:79-86.
219. Li GH, Lin XL, Zhang H, Li S, He XL, Zhang K, Peng J, Tang YL, Zeng JF, Zhao Y, Ma XF. Ox-Lp (a) transiently induces HUVEC autophagy via an ROS-dependent PAPR-1-LKB1–AMPK–mTOR pathway. Atherosclerosis. 2015 Nov 30;243(1):223-35.
220. Kleinert M, Parker BL, Chaudhuri R, Fazakerley DJ, Serup A, Thomas KC, Krycer JR, Sylow L, Fritzen AM, Hoffman NJ, Jeppesen J. mTORC2 and AMPK differentially regulate muscle triglyceride content via Perilipin 3. Molecular Metabolism. 2016 Aug 31;5(8):646-55.
221. Zhou H, Shang C, Wang M, Shen T, Kong L, Yu C, Ye Z, Luo Y, Liu L, Li Y, Huang S. Ciclopirox olamine inhibits mTORC1 signaling by activation of AMPK. Biochemical Pharmacology. 2016 Jul 7.
222. Hong SH, Kang M, Lee KS, Yu K. High fat diet-induced TGF-β/Gbb signaling provokes insulin resistance through the tribbles expression. Scientific Reports. 2016;6.
223. Kwon B, Querfurth HW. Palmitate activates mTOR/p70S6K through AMPK inhibition and hypophosphorylation of raptor in skeletal muscle cells: Reversal by oleate is similar to metformin. Biochimie. 2015 Nov 30;118:141-50.
224. Ha J, Guan KL, Kim J. AMPK and autophagy in glucose/glycogen metabolism. Molecular aspects of medicine. 2015 Dec 31;46:46-62.
225. Zhu KN, Jiang CH, Tian YS, Xiao N, Wu ZF, Ma YL, Lin Z, Fang SZ, Shang XL, Liu K, Zhang J. Two triterpeniods from Cyclocarya paliurus (Batal) Iljinsk (Juglandaceae) promote glucose uptake in 3T3-L1 adipocytes: The relationship to AMPK activation. Phytomedicine. 2015 Aug 15;22(9):837-46.
226. Andreozzi F, Raciti GA, Nigro C, Mannino GC, Procopio T, Davalli AM, Beguinot F, Sesti G, Miele C, Folli F. The GLP-1 receptor agonists exenatide and liraglutide activate Glucose transport by an AMPK-dependent mechanism. Journal of Translational Medicine. 2016 Jul 30;14(1):229.
227. Wu YL, Zhang YJ, Yao YL, Li ZM, Han X, Lian LH, Zhao YQ, Nan JX. Cucurbitacin E ameliorates hepatic fibrosis in vivo and in vitro through activation of AMPK and blocking mTOR-dependent signaling pathway. Toxicology Letters. 2016 Sep 6;258:147-58.
228. Jiang B, Le L, Pan H, Hu K, Xu L, Xiao P. Dihydromyricetin ameliorates the oxidative stress response induced by methylglyoxal via the AMPK/GLUT4 signaling pathway in PC12 cells. Brain research bulletin. 2014 Oct 31;109:117-26.
229. Schuster S, Penke M, Gorski T, Gebhardt R, Weiss TS, Kiess W, Garten A. FK866-induced NAMPT inhibition activates AMPK and downregulates mTOR signaling in hepatocarcinoma cells. Biochemical and biophysical research communications. 2015 Mar 6;458(2):334-40.
230. Osman I, Segar L. Pioglitazone, a PPARγ agonist, attenuates PDGF-induced vascular smooth muscle cell proliferation through AMPK-dependent and AMPK-independent inhibition of mTOR/p70S6K and ERK signaling. Biochemical pharmacology. 2016 Feb 1;101:54-70.
231. Li C, Reif MM, Craige SM, Kant S, Keaney JF. Endothelial AMPK activation induces mitochondrial biogenesis and stress adaptation via eNOS-dependent mTORC1 signaling. Nitric Oxide. 2016 Jun 1;55:45-53.
232. Walter C, Clemens LE, Müller AJ, Fallier-Becker P, Proikas-Cezanne T, Riess O, Metzger S, Nguyen HP. Activation of AMPK-induced autophagy ameliorates Huntington disease pathology in vitro. Neuropharmacology. 2016 Sep 30;108:24-38.
233. Zhao P, Dou Y, Chen L, Li L, Wei Z, Yu J, Wu X, Dai Y, Xia Y. SC-III3, a novel scopoletin derivative, induces autophagy of human hepatoma HepG2 cells through AMPK/mTOR signaling pathway by acting on mitochondria. Fitoterapia. 2015 Jul 31;104:31-40.
234. Gorgani-Firuzjaee S, Meshkani R. SH2 domain-containing inositol 5-phosphatase (SHIP2) inhibition ameliorates high glucose-induced de-novo lipogenesis and VLDL production through regulating AMPK/mTOR/SREBP1 pathway and ROS production in HepG2 cells. Free Radical Biology and Medicine. 2015 Dec 31;89:679-89.
235. Xu Y, Liu C, Chen S, Ye Y, Guo M, Ren Q, Liu L, Zhang H, Xu C, Zhou Q, Huang S. Activation of AMPK and inactivation of Akt result in suppression of mTOR-mediated S6K1 and 4E-BP1 pathways leading to neuronal cell death in in vitro models of Parkinson's disease. Cellular signalling. 2014 Aug 31;26(8):1680-9.
236. Kim TW, Kim YJ, Kim HT, Park SR, Lee MY, Park YD, Lee CH, Jung JY. NQO1 deficiency leads enhanced autophagy in cisplatin-induced acute kidney injury through the AMPK/TSC2/mTOR signaling pathway. Antioxidants & redox signaling. 2016 May 20;24(15):867-83.
237. Wang S, Peng DQ, Yi Y. The unsolved mystery of apoA-I recycling in adipocyte. Lipids in health and disease. 2016 Feb 24;15(1):1.
238. Shi L, Zhang T, Liang X, Hu Q, Huang J, Zhou Y, Chen M, Zhang Q, Zhu J, Mi M. Dihydromyricetin improves skeletal muscle insulin resistance by inducing autophagy via the AMPK signaling pathway. Molecular and cellular endocrinology. 2015 Jul 5;409:92-102.

239. Fan XY, Tian C, Wang H, Xu Y, Ren K, Zhang BY, Gao C, Shi Q, Meng G, Zhang LB, Zhao YJ. Activation of the AMPK-ULK1 pathway plays an important role in autophagy during prion infection. Scientific reports. 2015;5.
240. Tian F, Zheng XY, Li J, Zhang SM, Feng N, Guo HT, Jia M, Wang YM, Fan R, Pei JM. κ-Opioid Receptor Stimulation Improves Endothelial Function via Akt-stimulated NO Production in Hyperlipidemic Rats. Scientific reports. 2016;6.
241. Garcia-Prieto CF, Pulido-Olmo H, Ruiz-Hurtado G, Gil-Ortega M, Aranguez I, Rubio MA, Ruiz-Gayo M, Somoza B, Fernandez-Alfonso MS. Mild caloric restriction reduces blood pressure and activates endothelial AMPK-PI3K-Akt-eNOS pathway in obese Zucker rats. Vascular pharmacology. 2015 Mar 31;65:3-12.
242. Xing SS, Yang XY, Zheng T, Li WJ, Wu D, Chi JY, Bian F, Bai XL, Wu GJ, Zhang YZ, Zhang CT. Salidroside improves endothelial function and alleviates atherosclerosis by activating a mitochondria-related AMPK/PI3K/Akt/eNOS pathway. Vascular pharmacology. 2015 Sep 30;72:141-52.
243. Yu JW, Deng YP, Han X, Ren GF, Cai J, Jiang GJ. Metformin improves the angiogenic functions of endothelial progenitor cells via activating AMPK/eNOS pathway in diabetic mice. Cardiovascular Diabetology. 2016 Jun 18;15(1):88.
244. Zhang X, Xiao J, Li R, Qin X, Wang F, Mao Y, Liang W, Sheng X, Guo M, Song Y, Ji X. Metformin alleviates vascular calcification induced by vitamin D3 plus nicotine in rats via the AMPK pathway. Vascular pharmacology. 2016 Jun 30;81:83-90.
245. Shingu T, Holmes L, Henry V, Wang Q, Latha K, Gururaj AE, Gibson LA, Doucette T, Lang FF, Rao G, Yuan L. Suppression of RAF/MEK or PI3K synergizes cytotoxicity of receptor tyrosine kinase inhibitors in glioma tumor-initiating cells. Journal of translational medicine. 2016 Feb 9;14(1):1.
246. Wang L, Chen Q, Li G, Ke D. Ghrelin ameliorates impaired angiogenesis of ischemic myocardium through GHSR1a-mediated AMPK/eNOS signal pathway in diabetic rats. Peptides. 2015 Nov 30;73:77-87.
247. Lee SY, Lai FY, Shi LS, Chou YC, Yen IC, Chang TC. Rhodiola crenulata extract suppresses hepatic gluconeogenesis via activation of the AMPK pathway. Phytomedicine. 2015 Apr 15;22(4):477-86.
248. Lee J, Kim S. Upregulation of heme oxygenase-1 expression by dehydrodiconiferyl alcohol (DHCA) through the AMPK–Nrf2 dependent pathway. Toxicology and applied pharmacology. 2014 Nov 15;281(1):87-100.
249. Valentine RJ, Coughlan KA, Ruderman NB, Saha AK. Insulin inhibits AMPK activity and phosphorylates AMPK Ser 485/491 through Akt in hepatocytes, myotubes and incubated rat skeletal muscle. Archives of biochemistry and biophysics. 2014 Nov 15;562:62-9.
250. Roblet C, Doyen A, Amiot J, Pilon G, Marette A, Bazinet L. Enhancement of glucose uptake in muscular cell by soybean charged peptides isolated by electrodialysis with ultrafiltration membranes (EDUF): Activation of the AMPK pathway. Food chemistry. 2014 Mar 15;147:124-30.
251. Rawat AK, Korthikunta V, Gautam S, Pal S, Tadigoppula N, Tamrakar AK, Srivastava AK. 4-Hydroxyisoleucine improves insulin resistance by promoting mitochondrial biogenesis and act through AMPK and Akt dependent pathway. Fitoterapia. 2014 Dec 31;99:307-17.
252. Lu J, Cao Y, Cheng K, Xu B, Wang T, Yang Q, Yang Q, Feng X, Xia Q. Berberine regulates neurite outgrowth through AMPK-dependent pathways by lowering energy status. Experimental cell research. 2015 Jun 10;334(2):194-206.
253. Zheng Q, Zhao K, Han X, Huff AF, Cui Q, Babcock SA, Yu S, Zhang Y. Inhibition of AMPK accentuates prolonged caloric restriction-induced change in cardiac contractile function through disruption of compensatory autophagy. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2015 Feb 28;1852(2):332-42.
254. Lee H, Li H, Jeong JH, Noh M, Ryu JH. Kazinol B from Broussonetia kazinoki improves insulin sensitivity via Akt and AMPK activation in 3T3-L1 adipocytes. Fitoterapia. 2016 Jul 31;112:90-6.
255. Rogacka D, Piwkowska A, Audzeyenka I, Angielski S, Jankowski M. Involvement of the AMPK–PTEN pathway in insulin resistance induced by high glucose in cultured rat podocytes. The international journal of biochemistry & cell biology. 2014 Jun 30;51:120-30.
256. Kurutas EB. The importance of antioxidants which play the role in cellular response against oxidative/nitrosative stress: current state. Nutrition Journal. 2016 Jul 25;15(1):71.
257. Zimmermann K, Baldinger J, Mayerhofer B, Atanasov AG, Dirsch VM, Heiss EH. Activated AMPK boosts the Nrf2/HO-1 signaling axis—A role for the unfolded protein response. Free Radical Biology and Medicine. 2015 Nov 30;88:417-26.
258. Ibrahim BA, Alenazi FS, Briski KP. Energy status determines hindbrain signal transduction pathway transcriptional reactivity to AMPK in the estradiol-treated ovariectomized female rat. Neuroscience. 2015 Jan 22;284:888-99.
259. Song Y, Wu Y, Su X, Zhu Y, Liu L, Pan Y, Zhu B, Yang L, Gao L, Li M. Activation of AMPK inhibits PDGF-induced pulmonary arterial smooth muscle cells proliferation and its potential mechanisms. Pharmacological research. 2016 May 31;107:117-24.

260. Yang J, Leng J, Li JJ, Tang JF, Li Y, Liu BL, Wen XD. Corosolic acid inhibits adipose tissue inflammation and ameliorates insulin resistance via AMPK activation in high-fat fed mice. Phytomedicine. 2016 Feb 15;23(2):181-90.
261. Covarrubias AJ, Aksoylar HI, Horng T. Control of macrophage metabolism and activation by mTOR and Akt signaling. InSeminars in immunology 2015 Aug 31 (Vol. 27, No. 4, pp. 286-296). Academic Press.
262. Tao R, Gong J, Luo X, Zang M, Guo W, Wen R, Luo Z. AMPK exerts dual regulatory effects on the PI3K pathway. Journal of molecular signaling. 2010 Feb 18;5(1):1.
263. Tian W, Li W, Chen Y, Yan Z, Huang X, Zhuang H, Zhong W, Chen Y, Wu W, Lin C, Chen H. Phosphorylation of ULK1 by AMPK regulates translocation of ULK1 to mitochondria and mitophagy. FEBS letters. 2015 Jul 8;589(15):1847-54.
264. Schmitz KJ, Ademi C, Bertram S, Schmid KW, Baba HA. Prognostic relevance of autophagy-related markers LC3, p62/sequestosome 1, Beclin-1 and ULK1 in colorectal cancer patients with respect to KRAS mutational status. World Journal of Surgical Oncology. 2016 Jul 22;14(1):189.
265. Fritzen AM, Frøsig C, Jeppesen J, Jensen TE, Lundsgaard AM, Serup AK, Schjerling P, Proud CG, Richter EA, Kiens B. Role of AMPK in regulation of LC3 lipidation as a marker of autophagy in skeletal muscle. Cellular signalling. 2016 Jun 30;28(6):663-74.
266. Burkewitz K, Zhang Y, Mair WB. AMPK at the nexus of energetics and aging. Cell metabolism. 2014 Jul 1;20(1):10-25.
267. Kwak HJ, Choi HE, Jang J, Park SK, Bae YA, Cheon HG. Bortezomib attenuates palmitic acid-induced ER stress, inflammation and insulin resistance in myotubes via AMPK dependent mechanism. Cellular signalling. 2016 Aug 31;28(8):788-97.
268. Li W, Fu J, Zhang S, Zhao J, Xie N, Cai G. The proteasome inhibitor bortezomib induces testicular toxicity by upregulation of oxidative stress, AMP-activated protein kinase (AMPK) activation and deregulation of germ cell development in adult murine testis. Toxicology and applied pharmacology. 2015 Jun 1;285(2):98-109.
269. Li Y, Li J, Li S, Li Y, Wang X, Liu B, Fu Q, Ma S. Curcumin attenuates glutamate neurotoxicity in the hippocampus by suppression of ER stress-associated TXNIP/NLRP3 inflammasome activation in a manner dependent on AMPK. Toxicology and applied pharmacology. 2015 Jul 1;286(1):53-63.
270. Song J, Li J, Hou F, Wang X, Liu B. Mangiferin inhibits endoplasmic reticulum stress-associated thioredoxin-interacting protein/NLRP3 inflammasome activation with regulation of AMPK in endothelial cells. Metabolism. 2015 Mar 31;64(3):428-37.
271. Li J, Wang Y, Wang Y, Wen X, Ma XN, Chen W, Huang F, Kou J, Qi LW, Liu B, Liu K. Pharmacological activation of AMPK prevents Drp1-mediated mitochondrial fission and alleviates endoplasmic reticulum stress-associated endothelial dysfunction. Journal of molecular and cellular cardiology. 2015 Sep 30;86:62-74.
272. Yang TY, Yen CC, Lee KI, Su CC, Yang CY, Wu CC, Hsieh SS, Ueng KC, Huang CF. Molybdenum induces pancreatic β-cell dysfunction and apoptosis via interdependent of JNK and AMPK activation-regulated mitochondria-dependent and ER stress-triggered pathways. Toxicology and applied pharmacology. 2016 Mar 1;294:54-64.
273. Guan FY, Gu J, Li W, Zhang M, Ji Y, Li J, Chen L, Hatch GM. Compound K protects pancreatic islet cells against apoptosis through inhibition of the AMPK/JNK pathway in type 2 diabetic mice and in MIN6 β-cells. Life sciences. 2014 Jun 27;107(1):42-9.
274. Li N, Zhao Y, Yue Y, Chen L, Yao Z, Niu W. Liraglutide ameliorates palmitate-induced endothelial dysfunction through activating AMPK and reversing leptin resistance. Biochemical and Biophysical Research Communications. 2016 Sep 9;478(1):46-52.
275. Kim J, Yang G, Kim Y, Kim J, Ha J. AMPK activators: mechanisms of action and physiological activities. Experimental & molecular medicine. 2016 Apr 1;48(4):e224.
276. Jeon SM. Regulation and function of AMPK in physiology and diseases. Experimental & Molecular Medicine. 2016 Jul 1;48(7):e245.
277. Ma C, Li G, He Y, Xu B, Mi X, Wang H, Wang Z. Pronuciferine and nuciferine inhibit lipogenesis in 3T3-L1 adipocytes by activating the AMPK signaling pathway. Life sciences. 2015 Sep 1;136:120-5.
278. Park JS, Lee YY, Kim J, Seo H, Kim HS. β-Lapachone increases phase II antioxidant enzyme expression via NQO1-AMPK/PI3K-Nrf2/ARE signaling in rat primary astrocytes. Free Radical Biology and Medicine. 2016 Aug 31;97:168-78.
279. Xie W, Wang L, Dai Q, Yu H, He X, Xiong J, Sheng H, Zhang D, Xin R, Qi Y, Hu F. Activation of AMPK restricts coxsackievirus B3 replication by inhibiting lipid accumulation. Journal of molecular and cellular cardiology. 2015 Aug 31;85:155-67.
280. Han Y, Jung HW, Park YK. Effects of icariin on insulin resistance via the activation of AMPK pathway in C2C12 mouse muscle cells. European journal of pharmacology. 2015 Jul 5;758:60-3.

281. Young GH, Lin JT, Cheng YF, Huang CF, Chao CY, Nong JY, Chen PK, Chen HM. Identification of adenine modulating AMPK activation in NIH/3T3 cells by proteomic approach. Journal of proteomics. 2015 Apr 29;120:204-14.
282. Choy KW, Mustafa MR, Lau YS, Liu J, Murugan D, Lau CW, Wang L, Zhao L, Huang Y. Paeonol protects against endoplasmic reticulum stress-induced endothelial dysfunction via AMPK/PPARδ signaling pathway. Biochemical Pharmacology. 2016 Sep 15;116:51-62.
283. Ko HL, Jung EH, Jung DH, Kim JK, Ku SK, Kim YW, Kim SC, Zhao R, Lee CW, Cho IJ. Paeonia japonica root extract protects hepatocytes against oxidative stress through inhibition of AMPK-mediated GSK3β. Journal of Functional Foods. 2016 Jan 31;20:303-16.
284. Hwang EY, Yu MH, Jung YS, Lee SP, Shon JH, Lee SO. Defatted safflower seed extract inhibits adipogenesis in 3T3-L1 preadipocytes and improves lipid profiles in C57BL/6J ob/ob mice fed a high-fat diet. Nutrition Research. 2016 Sep 30;36(9):995-1003.
285. Lee JH, Lee SY, Kim B, Seo WD, Jia Y, Wu C, Jun HJ, Lee SJ. Barley sprout extract containing policosanols and polyphenols regulate AMPK, SREBP2 and ACAT2 activity and cholesterol and glucose metabolism in vitro and in vivo. Food Research International. 2015 Jun 30;72:174-83.
286. Mangels N, Awwad K, Wettenmann A, Dos Santos LR, Frömel T, Fleming I. The soluble epoxide hydrolase determines cholesterol homeostasis by regulating AMPK and SREBP activity. Prostaglandins & other lipid mediators. 2016 May 11.
287. Seo K, Ki SH, Shin SM. Sestrin2–AMPK activation protects mitochondrial function against glucose deprivation-induced cytotoxicity. Cellular signalling. 2015 Jul 31;27(7):1533-43.
288. Lee HI, Yun KW, Seo KI, Kim MJ, Lee MK. Scopoletin prevents alcohol-induced hepatic lipid accumulation by modulating the AMPK–SREBP pathway in diet-induced obese mice. Metabolism. 2014 Apr 30;63(4):593-601.
289. Tang H, Yu R, Liu S, Huwatibieke B, Li Z, Zhang W. Irisin Inhibits Hepatic Cholesterol Synthesis via AMPK-SREBP2 Signaling. EBioMedicine. 2016 Apr 30;6:139-48.
290. Wang YG, Qu XH, Yang Y, Han XG, Wang L, Qiao H, Fan QM, Tang TT, Dai KR. AMPK promotes osteogenesis and inhibits adipogenesis through AMPK-Gfi1-OPN axis. Cellular Signalling. 2016 Sep 30;28(9):1270-82.
291. Yin J, Luo Y, Deng H, Qin S, Tang W, Zeng L, Zhou B. Hugan Qingzhi medication ameliorates hepatic steatosis by activating AMPK and PPARα pathways in L02 cells and HepG2 cells. Journal of ethnopharmacology. 2014 May 28;154(1):229-39.
292. Lewandowska U, Fichna J, Gorlach S. Enhancement of anticancer potential of polyphenols by covalent modifications. Biochemical pharmacology. 2016 Jun 1;109:1-3.
293. Fratantonio D, Speciale A, Ferrari D, Cristani M, Saija A, Cimino F. Palmitate-induced endothelial dysfunction is attenuated by cyanidin-3-O-glucoside through modulation of Nrf2/Bach1 and NF-κB pathways. Toxicology letters. 2015 Dec 15;239(3):152-60.
294. Du G, Sun L, Zhao R, Du L, Song J, Zhang L, He G, Zhang Y, Zhang J. Polyphenols: Potential source of drugs for the treatment of ischaemic heart disease. Pharmacology & therapeutics. 2016 Jun 30;162:23-34.
295. Bhullar KS, Rupasinghe HV. Antioxidant and cytoprotective properties of partridgeberry polyphenols. Food chemistry. 2015 Feb 1;168:595-605.
296. Sirota R, Gibson D, Kohen R. The role of the catecholic and the electrophilic moieties of caffeic acid in Nrf2/Keap1 pathway activation in ovarian carcinoma cell lines. Redox biology. 2015 Apr 30;4:48-59.
297. Huang Y, Li W, Su ZY, Kong AN. The complexity of the Nrf2 pathway: beyond the antioxidant response. The Journal of nutritional biochemistry. 2015 Dec 31;26(12):1401-13.
298. Sun Z, Park SY, Hwang E, Park B, Seo SA, Cho JG, Zhang M, Yi TH. Dietary Foeniculum vulgare Mill extract attenuated UVB irradiation-induced skin photoaging by activating of Nrf2 and inhibiting MAPK pathways. Phytomedicine. 2016 Nov 15;23(12):1273-84.
299. Erlank H, Elmann A, Kohen R, Kanner J. Polyphenols activate Nrf2 in astrocytes via H 2 O 2, semiquinones, and quinones. Free Radical Biology and Medicine. 2011 Dec 15;51(12):2319-27.
300. Bayele HK, Debnam ES, Srai KS. Nrf2 transcriptional derepression from Keap1 by dietary polyphenols. Biochemical and biophysical research communications. 2016 Jan 15;469(3):521-8.
301. Mason SA, Morrison D, McConell GK, Wadley GD. Muscle redox signalling pathways in exercise. Role of antioxidants. Free Radical Biology and Medicine. 2016 Feb 18.
302. Liu J, Tang Y, Feng Z, Hou C, Wang H, Yan J, Liu J, Shen W, Zang W, Liu J, Long J. Acetylated FoxO1 mediates high-glucose induced autophagy in H9c2 cardiomyoblasts: Regulation by a polyphenol-(−)-epigallocatechin-3-gallate. Metabolism. 2014 Oct 31;63(10):1314-23.
303. Yarla NS, Bishayee A, Sethi G, Reddanna P, Kalle AM, Dhananjaya BL, Dowluru KS, Chintala R, Duddukuri GR. Targeting arachidonic acid pathway by natural products for cancer prevention and therapy. InSeminars in cancer biology 2016 Feb 4. Academic Press.

304. Das SK, Wang W, Zhabyeyev P, Basu R, McLean B, Fan D, Parajuli N, DesAulniers J, Patel VB, Hajjar RJ, Dyck JR. Iron-overload injury and cardiomyopathy in acquired and genetic models is attenuated by resveratrol therapy. Scientific reports. 2015;5.
305. Bak MJ, Truong VL, Ko SY, Nguyen XN, Jun M, Hong SG, Lee JW, Jeong WS. Induction of Nrf2/ARE-mediated cytoprotective genes by red ginseng oil through ASK1–MKK4/7–JNK and p38 MAPK signaling pathways in HepG2 cells. Journal of Ginseng Research. 2016 Jul 16.
306. Cordero-Herrera I, Martín MÁ, Goya L, Ramos S. CoCoA flavonoids attenuate high glucose-induced insulin signalling blockade and modulate glucose uptake and production in human HepG2 cells. Food and Chemical Toxicology. 2014 Feb 28;64:10-9.
307. Rios JA, Cisternas P, Arrese M, Barja S, Inestrosa NC. Is Alzheimer's disease related to metabolic syndrome? A Wnt signaling conundrum. Progress in neurobiology. 2014 Oct 31;121:125-46.
308. Mohankumar K, Pajaniradje S, Sridharan S, Singh VK, Ronsard L, Banerjea AC, Benson CS, Coumar MS, Rajagopalan R. Mechanism of apoptotic induction in human breast cancer cell, MCF-7, by an analog of curcumin in comparison with curcumin–an in vitro and in silico approach. Chemico-biological interactions. 2014 Mar 5;210:51-63.
309. Tsuneyoshi T, Kanamori Y, Matsutomo T, Morihara N. Dehydrodiconiferyl alcohol suppresses monocyte adhesion to endothelial cells by attenuation of JNK signaling pathway. Biochemical and biophysical research communications. 2015 Sep 25;465(3):408-13.
310. Lin CJ, Chen TL, Tseng YY, Wu GJ, Hsieh MH, Lin YW, Chen RM. Honokiol induces autophagic cell death in malignant glioma through reactive oxygen species-mediated regulation of the p53/PI3K/Akt/mTOR signaling pathway. Toxicology and applied pharmacology. 2016 Aug 1;304:59-69.
311. Cho CH. Frontier of epilepsy research-mTOR signaling pathway. Experimental & molecular medicine. 2011 May 31;43(5):231-74.
312. Pazoki-Toroudi H, Amani H, Ajami M, Nabavi SF, Braidy N, Kasi PD, Nabavi SM. Targeting mTOR signaling by polyphenols: A new therapeutic target for ageing. Ageing Research Reviews. 2016 Jul 21.
313. Cerella C, Gaigneaux A, Dicato M, Diederich M. Antagonistic role of natural compounds in mTOR-mediated metabolic reprogramming. Cancer letters. 2015 Jan 28;356(2):251-62.
314. Poulose SM, Fisher DR, Bielinski DF, Gomes SM, Rimando AM, Schauss AG, Shukitt-Hale B. Restoration of stressor-induced calcium dysregulation and autophagy inhibition by polyphenol-rich açaí (Euterpe spp.) fruit pulp extracts in rodent brain cells in vitro. Nutrition. 2014 Aug 31;30(7):853-62.
315. He LQ, Lu JH, Yue ZY. Autophagy in ageing and ageing-associated diseases. Acta Pharmacologica Sinica. 2013 May 1;34(5):605-11.
316. Daveri E, Maellaro E, Valacchi G, Ietta F, Muscettola M, Maioli E. Inhibitions of mTORC1 and 4EBP-1 are key events orchestrated by Rottlerin in SK-Mel-28 cell killing. Cancer Letters. 2016 Sep 28;380(1):106-13.
317. Kodali M, Parihar VK, Hattiangady B, Mishra V, Shuai B, Shetty AK. Resveratrol prevents age-related memory and mood dysfunction with increased hippocampal neurogenesis and microvasculature, and reduced glial activation. Scientific reports. 2015 Jan 28;5.
318. Law BY, Chan WK, Xu SW, Wang JR, Bai LP, Liu L, Wong VK. Natural small-molecule enhancers of autophagy induce autophagic cell death in apoptosis-defective cells. Scientific reports. 2014 Jul 1;4.
319. Wang K, Jin X, Chen Y, Song Z, Jiang X, Hu F, Conlon MA, Topping DL. Polyphenol-Rich Propolis Extracts Strengthen Intestinal Barrier Function by Activating AMPK and ERK Signaling. Nutrients. 2016 May 7;8(5):272.
320. Fan XX, Yao XJ, Xu SW, Wong VK, He JX, Ding J, Xue WW, Mujtaba T, Michelangeli F, Huang M, Huang J. (Z) 3, 4, 5, 4′-trans-tetramethoxystilbene, a new analogue of resveratrol, inhibits gefitinb-resistant non-small cell lung cancer via selectively elevating intracellular calcium level. Scientific reports. 2015;5.
321. Hytti M, Piippo N, Korhonen E, Honkakoski P, Kaarniranta K, Kauppinen A. Fisetin and luteolin protect human retinal pigment epithelial cells from oxidative stress-induced cell death and regulate inflammation. Scientific reports. 2015;5.
322. Moussa A, Li J. AMPK in myocardial infarction and diabetes: the yin/yang effect. Acta Pharmaceutica Sinica B. 2012 Aug 31;2(4):368-78.
323. Bastianetto S, Ménard C, Quirion R. Neuroprotective action of resveratrol. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2015 Jun 30;1852(6):1195-201.
324. Pasinetti GM, Wang J, Ho L, Zhao W, Dubner L. Roles of resveratrol and other grape-derived polyphenols in Alzheimer's disease prevention and treatment. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2015 Jun 30;1852(6):1202-8.
325. Zheng A, Li H, Xu J, Cao K, Li H, Pu W, Yang Z, Peng Y, Long J, Liu J, Feng Z. Hydroxytyrosol improves mitochondrial function and reduces oxidative stress in the brain of db/db mice: role of AMP-activated protein kinase activation. British Journal of Nutrition. 2015 Jun 14;113(11):1667-76.
326. Dong GZ, Lee JH, Ki SH, Yang JH, Cho IJ, Kang SH, Zhao RJ, Kim SC, Kim YW. AMPK activation by isorhamnetin protects hepatocytes against oxidative stress and mitochondrial dysfunction. European journal of pharmacology. 2014 Oct 5;740:634-40.

327. de Oliveira MR, Nabavi SF, Manayi A, Daglia M, Hajheydari Z, Nabavi SM. Resveratrol and the mitochondria: from triggering the intrinsic apoptotic pathway to inducing mitochondrial biogenesis, a mechanistic view. Biochimica et Biophysica Acta (BBA)-General Subjects. 2016 Apr 30;1860(4):727-45.
328. Park D, Jeong H, Lee MN, Koh A, Kwon O, Yang YR, Noh J, Suh PG, Park H, Ryu SH. Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition. Scientific reports. 2016;6.
329. Wang LM, Wang YJ, Cui M, Luo WJ, Wang XJ, Barber PA, Chen ZY. A dietary polyphenol resveratrol acts to provide neuroprotection in recurrent stroke models by regulating AMPK and SIRT1 signaling, thereby reducing energy requirements during ischemia. European Journal of Neuroscience. 2016 Apr 1;43(7):990-.
330. Kessoku T, Imajo K, Honda Y, Kato T, Ogawa Y, Tomeno W, Kato S, Mawatari H, Fujita K, Yoneda M, Nagashima Y. Resveratrol ameliorates fibrosis and inflammation in a mouse model of nonalcoholic steatohepatitis. Scientific reports. 2016;6.
331. Chung HJ, Sharma SP, Kim HJ, Baek SH, Hong ST. The resveratrol-enriched rice DJ526 boosts motor coordination and physical strength. Scientific reports. 2016;6.
332. Soetikno V, Sari FR, Sukumaran V, Lakshmanan AP, Harima M, Suzuki K, Kawachi H, Watanabe K. Curcumin decreases renal triglyceride accumulation through AMPK–SREBP signaling pathway in streptozotocin-induced type 1 diabetic rats. The Journal of nutritional biochemistry. 2013 May 31;24(5):796-802.
333. Chen X, Li M, Li L, Xu S, Huang D, Ju M, Huang J, Chen K, Gu H. Trehalose, sucrose and raffinose are novel activators of autophagy in human keratinocytes through an mTOR-independent pathway. Scientific Reports. 2016;6.
334. Song P, Zou MH. Regulation of NAD (P) H oxidases by AMPK in cardiovascular systems. Free Radical Biology and Medicine. 2012 May 1;52(9):1607-19.
335. Collins QF, Liu HY, Pi J, Liu Z, Quon MJ, Cao W. Epigallocatechin-3-gallate (EGCG), a green tea polyphenol, suppresses hepatic gluconeogenesis through 5′-AMP-activated protein kinase. Journal of Biological Chemistry. 2007 Oct 12;282(41):30143-9.
336. Trung TN, Hien TT, Dao TT, Yim N, Ngoc TM, Oh WK, Bae K. Selected compounds derived from Moutan Cortex stimulated glucose uptake and glycogen synthesis via AMPK activation in human HepG2 cells. Journal of ethnopharmacology. 2010 Sep 15;131(2):417-24.
337. Sawada K, Yamashita Y, Zhang T, Nakagawa K, Ashida H. Glabridin induces glucose uptake via the AMP-activated protein kinase pathway in muscle cells. Molecular and cellular endocrinology. 2014 Aug 5;393(1):99-108.
338. Dechandt CR, Siqueira JT, Souza DL, Araujo LC, Silva VC, Sousa Junior PT, Andrade CM, Kawashita NH, Baviera AM. Combretum lanceolatum flowers extract shows antidiabetic activity through activation of AMPK by quercetin. Revista Brasileira de Farmacognosia. 2013 Apr;23(2):291-300.
339. Eguchi T, Kumagai C, Fujihara T, Takemasa T, Ozawa T, Numata O. Black tea high-molecular-weight polyphenol stimulates exercise training-induced improvement of endurance capacity in mouse via the link between AMPK and GLUT4. PloS one. 2013 Jul 26;8(7):e69480.
340. Qiu J, Maekawa K, Kitamura Y, Miyata Y, Tanaka K, Tanaka T, Soga M, Tsuda T, Matsui T. Stimulation of glucose uptake by theasinensins through the AMP-activated protein kinase pathway in rat skeletal muscle cells. Biochemical pharmacology. 2014 Jan 15;87(2):344-51.
341. Zygmunt K, Faubert B, MacNeil J, Tsiani E. Naringenin, a citrus flavonoid, increases muscle cell glucose uptake via AMPK. Biochemical and biophysical research communications. 2010 Jul 23;398(2):178-83.
342. Hong NY, Cui ZG, Kang HK, Lee DH, Lee YK, Park DB. p-Synephrine stimulates glucose consumption via AMPK in L6 skeletal muscle cells. Biochemical and biophysical research communications. 2012 Feb 24;418(4):720-4.
343. Shah AK, Gupta A, Dey CS. AICAR induced AMPK activation potentiates neuronal insulin signaling and glucose uptake. Archives of biochemistry and biophysics. 2011 May 15;509(2):142-6.
344. Kane MO, SENE M, Anselm E, Dal S, Schini-Kerth VB, Augier C. Role of AMP-activated Protein Kinase in NO-and EDHF-mediated Endothelium-dependent Relaxations to Red Wine Polyphenols. Indian J Physiol Pharmacol. 2015;59(4):369-79.
345. Shen Y, Croft KD, Hodgson JM, Kyle R, Lee IL, Wang Y, Stocker R, Ward NC. Quercetin and its metabolites improve vessel function by inducing eNOS activity via phosphorylation of AMPK. Biochemical pharmacology. 2012 Oct 15;84(8):1036-44.
346. Valenti D, de Bari L, de Rasmo D, Signorile A, Henrion-Caude A, Contestabile A, Vacca RA. The polyphenols resveratrol and epigallocatechin-3-gallate restore the severe impairment of mitochondria in hippocampal progenitor cells from a Down syndrome mouse model. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2016 Jun 30;1862(6):1093-104.
347. Qiang X, Xu L, Zhang M, Zhang P, Wang Y, Wang Y, Zhao Z, Chen H, Liu X, Zhang Y. Demethyleneberberine attenuates non-alcoholic fatty liver disease with activation of AMPK and inhibition of oxidative stress. Biochemical and biophysical research communications. 2016 Apr 15;472(4):603-9.

348. de Barros Alencar AC, dos Santos TS, Neves RH, Torres EJ, Nogueira-Neto JF, Machado-Silva JR. Simvastatin and artesunate impact the structural organization of adult Schistosoma mansoni in hypercholesterolemic mice. Experimental parasitology. 2016 May 24.
349. Zhang FJ, Zhang HS, Liu Y, Huang YH. Curcumin inhibits Ec109 cell growth via an AMPK-mediated metabolic switch. Life sciences. 2015 Aug 1;134:49-55.
350. Herranz-López M, Barrajón-Catalán E, Segura-Carretero A, Menéndez JA, Joven J, Micol V. Lemon verbena (Lippia citriodora) polyphenols alleviate obesity-related disturbances in hypertrophic adipocytes through AMPK-dependent mechanisms. Phytomedicine. 2015 Jun 1;22(6):605-14.
351. Collins B, Hoffman J, Martinez K, Grace M, Lila MA, Cockrell C, Nadimpalli A, Chang E, Chuang CC, Zhong W, Mackert J. A polyphenol-rich fraction obtained from table grapes decreases adiposity, insulin resistance and markers of inflammation and impacts gut microbiota in high-fat-fed mice. The Journal of nutritional biochemistry. 2016 May 31;31:150-65.
352. Bansode RR, Randolph P, Ahmedna M, Hurley S, Hanner T, Baxter SA, Johnston TA, Su M, Holmes BM, Yu J, Williams LL. Bioavailability of polyphenols from peanut skin extract associated with plasma lipid lowering function. Food chemistry. 2014 Apr 1;148:24-9.
353. Ong KW, Hsu A, Tan BK. Anti-diabetic and anti-lipidemic effects of chlorogenic acid are mediated by ampk activation. Biochemical pharmacology. 2013 May 1;85(9):1341-51.
354. Fogarty S, Hardie DG. Development of protein kinase activators: AMPK as a target in metabolic disorders and cancer. Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics. 2010 Mar 31;1804(3):581-91.
355. Ko HJ, Lo CY, Wang BJ, Chiou RY, Lin SM. Theaflavin-3, 3′-digallate, a black tea polyphenol, stimulates lipolysis associated with the induction of mitochondrial uncoupling proteins and AMPK–FoxO3A–MnSOD pathway in 3T3-L1 adipocytes. Journal of Functional Foods. 2015 Aug 31;17:271-82.
356. Scola G, Laliberte VL, Kim HK, Pinguelo A, Salvador M, Young LT, Andreazza AC. Vitis labrusca extract effects on cellular dynamics and redox modulations in a SH-SY5Y neuronal cell model: a similar role to lithium. Neurochemistry international. 2014 Dec 31;79:12-9.
357. Price TJ, Dussor G. AMPK: An emerging target for modification of injury-induced pain plasticity. Neuroscience letters. 2013 Dec 17;557:9-18.
358. Finley J. Reactivation of latently infected HIV-1 viral reservoirs and correction of aberrant alternative splicing in the LMNA gene via AMPK activation: Common mechanism of action linking HIV-1 latency and Hutchinson–Gilford progeria syndrome. Medical hypotheses. 2015 Sep 30;85(3):320-32.
359. Vasamsetti SB, Karnewar S, Gopoju R, Gollavilli PN, Narra SR, Kumar JM, Kotamraju S. Resveratrol attenuates monocyte-to-macrophage differentiation and associated inflammation via modulation of intracellular GSH homeostasis: Relevance in atherosclerosis. Free Radical Biology and Medicine. 2016 Jul 31;96:392-405.
360. Mukai Y, Sun Y, Sato S. Azuki bean polyphenols intake during lactation upregulate AMPK in male rat offspring exposed to fetal malnutrition. Nutrition. 2013 Jan 31;29(1):291-7.
361. Papadimitriou A, Peixoto EB, Silva KC, de Faria JM, de Faria JB. Increase in AMPK brought about by coCoA is renoprotective in experimental diabetes mellitus by reducing NOX4/TGFβ-1 signaling. The Journal of nutritional biochemistry. 2014 Jul 31;25(7):773-84.
362. Couturier K, Hininger I, Poulet L, Anderson RA, Roussel AM, Canini F, Batandier C. Cinnamon intake alleviates the combined effects of dietary-induced insulin resistance and acute stress on brain mitochondria. The Journal of nutritional biochemistry. 2016 Feb 29;28:183-90.
363. Parafati M, Lascala A, Morittu VM, Trimboli F, Rizzuto A, Brunelli E, Coscarelli F, Costa N, Britti D, Ehrlich J, Isidoro C. Bergamot polyphenol fraction prevents nonalcoholic fatty liver disease via stimulation of lipophagy in cafeteria diet-induced rat model of metabolic syndrome. The Journal of nutritional biochemistry. 2015 Sep 30;26(9):938-48.
364. Ko SC, Lee M, Lee JH, Lee SH, Lim Y, Jeon YJ. Dieckol, a phlorotannin isolated from a brown seaweed, Ecklonia cava, inhibits adipogenesis through AMP-activated protein kinase (AMPK) activation in 3T3-L1 preadipocytes. Environmental toxicology and pharmacology. 2013 Nov 30;36(3):1253-60.
365. Palacios-González B, Zarain-Herzberg A, Flores-Galicia I, Noriega LG, Alemán-Escondrillas G, Zariñan T, Ulloa-Aguirre A, Torres N, Tovar AR. Genistein stimulates fatty acid oxidation in a leptin receptor-independent manner through the JAK2-mediated phosphorylation and activation of AMPK in skeletal muscle. Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids. 2014 Jan 31;1841(1):132-40.
366. Wu SJ, Huang GY, Ng LT. γ-Tocotrienol induced cell cycle arrest and apoptosis via activating the Bax-mediated mitochondrial and AMPK signaling pathways in 3T3-L1 adipocytes. Food and chemical toxicology. 2013 Sep 30;59:501-13.
367. Heebøll S, Thomsen KL, Clouston A, Sundelin EI, Radko Y, Christensen LP, Ramezani-Moghadam M, Kreutzfeldt M, Pedersen SB, Jessen N, Hebbard L. Effect of resveratrol on experimental non-alcoholic steatohepatitis. Pharmacological Research. 2015 Jun 30;95:34-41.

 doi:10.20944/preprints202301.0528.v1

368. van Schothorst EM, Bunschoten A, Hoevenaars FP, van der Stelt I, Janovska P, Venema D, Kopecky J, Hollman PC, Keijer J. Direct comparison of health effects by dietary polyphenols at equimolar doses in wildtype moderate high-fat fed C57BL/6JOlaHsd mice. Food Research International. 2014 Nov 30;65:95-102.
369. Zhao W, Li J, He X, Lv O, Cheng Y, Liu R. In vitro steatosis hepatic cell model to compare the lipid-lowering effects of pomegranate peel polyphenols with several other plant polyphenols as well as its related cholesterol efflux mechanisms. Toxicology Reports. 2014 Dec 31;1:945-54.
370. Li M, Meng X, Xu J, Huang X, Li H, Li G, Wang S, Man Y, Tang W, Li J. GPR40 agonist ameliorates liver X receptor-induced lipid accumulation in liver by activating AMPK pathway. Scientific reports. 2016;6.
371. Ding C, Zhao Y, Shi X, Zhang N, Zu G, Li Z, Zhou J, Gao D, Lv L, Tian X, Yao J. New insights into salvianolic acid A action: Regulation of the TXNIP/NLRP3 and TXNIP/ChREBP pathways ameliorates HFD-induced NAFLD in rats. Scientific Reports. 2016;6.
372. Wu CH, Ou TT, Chang CH, Chang XZ, Yang MY, Wang CJ. The polyphenol extract from Sechium edule shoots inhibits lipogenesis and stimulates lipolysis via activation of AMPK signals in HepG2 cells. Journal of agricultural and food chemistry. 2014 Jan 9;62(3):750-9.
373. Park CE, Kim M, Lee JH, Min B, Bae H, Choe W, Kim S, Ha J. Resveratrol stimulates glucose transport in C2C12 myotubes by activating AMP-activated protein kinase. Experimental and Molecular Medicine. 2007 Apr 30;39(2):222.
374. Hamidie RD, Yamada T, Ishizawa R, Saito Y, Masuda K. Curcumin treatment enhances the effect of exercise on mitochondrial biogenesis in skeletal muscle by increasing cAMP levels. Metabolism. 2015 Oct 31;64(10):1334-47.
375. Beltrán-Debón R, Rull A, Rodríguez-Sanabria F, Iswaldi I, Herranz-López M, Aragonès G, Camps J, Alonso-Villaverde C, Menéndez JA, Micol V, Segura-Carretero A. Continuous administration of polyphenols from aqueous rooibos (Aspalathus linearis) extract ameliorates dietary-induced metabolic disturbances in hyperlipidemic mice. Phytomedicine. 2011 Mar 15;18(5):414-24.