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Type-2-diabetes: Regulation of AMPK pathway using Natural and Synthetic Activators:A Systematic Review

Venkataramanaiah Poli[1] . Yenukolu Aparna[2] . Srinivasulu Reddy Motireddy[3*]

[1] Department of Zoology, Research Scholar, Sri Venkateswara University, Tirupati-517502, India.

[2] Department of Zoology, Research Scholar, Sri Venkateswara University, Tirupati-517502, India.

[3] Department of Zoology, Faculty of Natural Sciences (Professor), Sri Venkateswara University, Tirupati-517502, India

*** Correspondence:** Srinivasulu Reddy Motireddy, Department of Zoology, Faculty of Natural Sciences (Professor), Sri Venkateswara University, Tirupati-517502, India.Email- profmsrsvu@gmail.com

ABSTRACT

Diabetes is a metabolic disorder that affects the production and use of insulin in the body. 5'-adenosine monophosphate activated protein kinase (AMPK) and subunits play an important role in co-ordinating metabolic pathways and regulating the effects of Type-2-diabetes. AMPK is a key enzymatic Protein involved in linkiing the energy sensing to the metabolic manipulation and is ubiquitously expressed in various tissues of the living system such as kidney, heart, liver, brain and skeletal muscles. We systematically searched PubMed and Google to generate narrative reviews on this topic. A systematic literature search was conducted from various electronic databases on topics evaluating Type-2-diabetes and the resulting regulation of the AMPK pathway by natural and synthetic activators. This review depicts that the AMPK pathway is activated in various organs and shows its effect by altering hepatic glucose production, glucose production, cholesterol levels and protein synthesis. AMPK activation occurs with natural or synthetic compounds; have an effect on reducing the effects of diabetes. This review summarizes the fact that natural and synthetic compounds play an important role in ameliorating the effects of diabetes through direct or indirect activation. In addition to beneficial effects, synthetic compounds have many side effects. In this review, we focus on the toxic nature of synthetic drugs and compare their effects with plant extracts to determine their glucose-lowering effects, action and safety.

Keywords: Natural Compounds, Synthetic Compounds, AMPK pathway, Type-2-diabetes, Protein Synthesis

INTRODUCTION

Diabetes mellitus is a serious metabolic disorder characterized by hyperglycemia resulting in improper metabolism of carbohydrate, protein and lipids. Diabetes is a tremendously increasing Worldwide due to different factors like sedentary lifestyle, aging, stress, obesity, diet, ethnicity, physical inactivity and

inflammation, environmental and genetic factors. Progression in Type-2-diabetes leads to a developmental of diabetes-associated complications like oxidative stress, obesity, cardiovascular diseases, stroke, retinal blindness, kidney failure, hypertension, dyslipidemia, vision loss, polycystic ovary syndrome, neuropathy, atherosclerosis, peripheral gangrene, lower limb amputation, autonomic nervous system dysfunction, some types of cancers and may also leads to coma and death due to development of ketoacidosis [1].

Type-2-diabetes is a disorder caused by over nutrition that affects 5-10% of the world population [2]. The International Diabetes Federation (IDF), a show that the Type-2-diabetes is prevalent in 415 million people in 2015 that would be predicted to increase to 642 million people by 2040 [3]. The insulin secreted from β-cells of the pancreas lowers blood glucose levels and promotes glucose uptake into the skeletal muscle, adipose tissue and thereby inhibiting glucose production in the liver under normal conditions. Hence, it regulates glucose, fat and protein metabolism in the body. In the diabetic condition, the abnormal metabolism of carbohydrate, protein and lipids promotes insulin resistance in different tissues like the muscle, liver and fat tissue.

Low sensitivity to the levels of insulin results in the development of insulin resistance in Type-2-diabetes, a condition with high levels of blood sugar. Hence, Type-2-diabetes is accompanied with increased insulin resistance that is caused due to improper utilization of insulin. The pancreas β-cell destruction develops insulin-dependent diabetes. Hence the insulin resistance and pancreas β-cell dysfunction have resulted in Type-2 Diabetes. The relationship between the insulin resistance and pancreas β-cell dysfunction remains highly complex [4]. Increased Insulin resistance caused the decreased function of pancreas β-cell [5]. During hyperglycemia, an elevation in blood glucose levels occurs due to defect in the insulin secretion leads to Type-2 Diabetes. Under the hyperglycemic condition, insulinemia is results due to excess secretion of insulin from the pancreas, it developed insulin resistance. The insulin-mediated glucose uptake is impaired because of insulin resistance and increases blood glucose levels, leading to diabetes. Increased insulin resistance during diabetes results in decreased insulin sensitivity in the skeletal muscle, adipose tissue and liver. Hence, these cells fail to respond to the insulin levels and do not metabolize the glucose efficiently. Decrease in insulin secretion is due to decline in beta cell function that causes progression of diabetes [6].

The liver is the main site of gluconeogenesis that promotes hepatic glucose output. Excessive hepatic glucose production denotes the prevalence of Type-2-diabetes that increases the release of glucose in the blood [7]. An increased expression of gluconeogenesis subsequently leads to hyperglycemia. Hence, activation of AMPK in the liver, suppresses the ATP utilising gluconeogenesis pathway and may suppress hepatic glucose production. The improper regulation of glucose homeostasis by gluconeogenesis

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in kidneys may result in Diabetes mellitus. Diabetic complications are also enhanced due to over production of ROS and impaired antioxidant mechanism increases the oxidative stress in diabetes, mainly due to hyperglycaemia. Increased free radicals such as superoxide and hydrogen peroxide weakens the antioxidant enzyme activity, thus damages biomolecules, increases lipid peroxidation, and enhances insulin resistance in diabetes [8]. Pancreas β-cell injury also resulted due to the formation of advanced glycation end products formed via cross linking of proteins and impaired insulin production and action. Hence oxidative stress resulted in the pancreas β-cell death.

AMPK stands for "adenosine 5′ monophosphate-activated protein kinase." It is an enzyme present in all living beings that plays an important role in energy balance. It helps determine the body's balance between energy consumption and production. The body balances production of AMP by sensing its current AMP to adenosine triphosphate (ATP) ratio. ATP molecules are those that act as a source of fuel within cells. (1) Energy starts as ATP within cells and eventually breaks down into AMP. Based on your current levels of AMP and ATP, energy production and usage can be altered. This takes place via changes in your appetite, body temperature, desire for physical activity (your energy expenditure), hormone production and other processes. Where is AMPK found? It is stored throughout tissues in the body, especially those in the brain (including the hypothalamus), liver, fat cells and skeletal muscles. Adenosine 5′ monophosphate-activated protein kinase is influenced by a number of factors, including genetics, age, diet, sleep patterns, stress levels and exercise habits. 5-Adenosine monophosphate (AMP)-activated protein kinase (AMPK), a highly conserved and adaptive enzyme complex, is a sensor of the cellular energy status that regulates cellular metabolism and energy homeostasis. Mammalian AMPK senses the energy status by monitoring cellular AMP, ADP, and ATP levels. A reduction of cellular ATP content and a corresponding increase in AMP levels (high AMP/ATP ratio) results in an activation of AMPK, which restores the energy balance by inhibiting anabolic processes that consume ATP and promoting catabolic processes that generate ATP [9].

AMP-activated protein kinase (AMPK) is a phylogenetically conserved fuel-sensing enzyme that is present in both primitive unicellular organisms and mammals. It is activated by stresses that increase the cellular concentration of AMP relative to ATP due to either limited ATP production (e.g. glucose deprivation or hypoxia) or increased energy expenditure (e.g. muscle contraction). When this occurs, AMPK sets in motion processes that potentially both increase ATP generation, such as fatty-acid oxidation and glucose transport, and decreases others that consume ATP, but are not acutely required for survival, such as lipid and protein synthesis and cell growth and proliferation. In addition, it may specifically stimulate glycolysis in cardiac muscle. Recent evidence suggests that AMPK may have a much wider range of actions. For instance, it is involved in the regulation of such diverse events as

mitochondrial biogenesis, angiogenesis, cell polarity and the control of food intake and whole-body energy expenditure at the level of the hypothalamus. In addition, AMPK activation in peripheral tissues seems to counteract many of the cellular abnormalities observed in animal models of the metabolic syndrome including insulin resistance, inflammation and ectopic lipid deposition. Conversely, its dysregulation (defined as decreased activity or impaired activation) may contribute to these abnormalities [10].

A target pathway to control diabetes is the 5'-adenosine monophosphate-activated protein kinase (AMPK) signalling pathway. AMPK is a heterotrimeric protein with α, β, and γ subunits. In several studies, AMPK activation enhanced glucose uptake into cells and inhibited intracellular glucose production. Impairment of AMPK activity is present in diabetes, according to some studies. In diabetes, the pancreas does not produce a sufficient quantities of insulin, or the insulin cannot be utilized by the body. Heart, eyes, blood vessels, nerves, and many other structures of the body are damaged by elevated blood glucose levels in diabetic patients. Millions of people are currently reported to live with diabetes worldwide. According to the latest WHO report, diabetes accounted for about 1.6 million deaths since 2015. The frequency has been intensifying the most in the middle and low income grouped countries. Throughout the world, Type 2 diabetes mellitus (T-2-DM) is a rapidly developing human health issue [11]. Some standard drugs used for the treatment of T2DM are metformin, dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas, peroxisome proliferator-activated receptor-γ (PPARγ) agonists, α-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) analogues, and insulin. Hypoglycemia, weight gain, and lactic acidosis are some of the adverse effects associated with these drugs; often, these agents produce insufficient effects and lack toleration in patients [12]. As such, there is a need to develop novel strategies for the management of diabetes. One such target that can be utilized to fight diabetes is the 5′ adenosine monophosphate-activated protein kinase (AMPK) pathway [13].

As its name suggests, AMPK has a key role in maintaining the balance between anabolic and catabolic programs for cellular homeostasis in response to metabolic stress [14]. Given the functional attributes of AMPK in glucose/lipid homeostasis, body weight, food intake, insulin signalling and mitochondrial biogenesis, AMPK are considered to be a major therapeutic target for the treatment of metabolic diseases including Type 2 diabetes and obesity. Another important aspect of AMPK biology is the role of AMPK in autophagy, a lysosome-dependent catabolic program that maintains cellular homeostasis [15]. A number of studies have demonstrated that AMPK has important roles in autophagy regulation by directly phosphorylating two autophagy initiating regulators: a protein kinase complex ULK1 (Unc-51- like autophagy-activating kinase) [16] and a lipid kinase complex PI3KC3/VPS34 (phosphatidylinositol 3-kinase, catalytic subunit type 3; also known as VPS34). A number of reports have

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demonstrated the metabolic significance of autophagy in glycogenolysis (glycophagy) and lipolysis (lipophagy) and even in regulating adipose mass as well as differentiation *in vivo*. In this regard, elucidating the molecular connection between AMPK and autophagy will provide a novel avenue to expand the functional network of AMPK in cellular homeostasis, including metabolism. Given these functional attributes, much effort has been made to develop robust AMPK assays and to identify AMPK modulators to provide therapies for a variety of human diseases [17]. In this review, we present a comprehensive summary of both indirect and direct AMPK activators and their modes of action in relation to the structure of AMPK and discuss the implications of AMPK as a therapeutic target.

Given the positive effects of AMPK activators on glucose uptake, fatty acid oxidation, mitochondrial biogenesis and insulin sensitivity in preclinical models, more specific AMPK agonists targeting both the β1 and importantly the β2 isoform, which is highly expressed in skeletal muscle and important for stimulating glucose uptake, have recently been developed These pan-AMPK activators, 991, PF739, MK-8722 and O304, all enhance skeletal muscle glucose uptake and lower blood glucose in a variety of models including obese mice, dogs and non-human primates. Although speculative, this reduction in blood glucose independent of insulin might be anticipated to allow pancreas β-cells to recover, potentially alleviating or reversing Type-2-diabetes. Despite these positive effects, mice and non-human primates treated with MK-8722 also developed cardiac hypertrophy with glycogen accumulation, but without cardiac dysfunction26. This led to the speculation that the cardiac adaptations with MK-8722 may be similar to those observed with chronic endurance exercise. Given the known effects of AMPK activators to improve exercise capacity and spontaneous activity, it is interesting to speculate that perhaps this may have been a contributing factor to the cardiac hypertrophy observed with AMPK activation. Importantly, a recent phase IIa trial with O304 in individuals with Type-2-diabetes treated with metformin has also shown glucose-lowering effects, however, without cardiac hypertrophy. However, hypertrophy is also observed with chronic genetic and pharmacological activation of AMPK, effects that, in contrast to Wolff–Parkinson–White syndrome, have been associated with increased stroke volume and subsequent reductions in heart rate, suggesting that activation of cardiac AMPK may be potentially beneficial in people with heart failure. However, the pathways controlling cardiac hypertrophy are complex, and under some conditions, the activation of AMPK has been shown to be protective against cardiac hypertrophy. Activating cardiac AMPK may also help protect against cardiac reperfusion injury by enhancing glucose uptake and suppressing ER stress. Future studies investigating the effects of direct pharmacological AMPK activators in the context of heart failure and cardiac reperfusion injury are required [18].

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Consistent with this idea, mice lacking skeletal muscle AMPK have defects in mitophagy that lead to large dysfunctional mitochondria and sarcopenia. Interestingly, skeletal muscle AMPK is also important for controlling the ageing of skin, effects that are mediated through the transcriptional control of interleukin-15, which is an important cytokine regulating mitochondrial biogenesis. Activation of AMPK may also be beneficial for ageing owing to its suppressive effects on multiple inflammatory pathways which may involve the control of mitochondrial content. Indeed, metformin increases AMPK and mitochondrial function in multiple tissues, effects that are associated with reductions in oxidative damage, chronic low-grade inflammation and improved health span and lifespan in mice. The AMPK activator quercetin when used in combination with dasatinib has also been shown to exert anti-ageing effects of delaying the senescent cell accumulation or reducing the senescent cell burden in numerous tissues of rodents. Whether these beneficial effects are replicated in humans and/or are observed with the new generation of direct AMPK activators that do not inhibit mitochondrial function remains to be determined [18]. However, a side effect of this is that many of these compounds would also be AMPK activators and hence may have medicinal uses. It controls several metabolic pathways that are directly relevant to diabetes and other metabolic diseases. It also coordinates metabolic pathways and maintains balance between nutrient supplies based on energy demand. The AMPK is present in different organs such as the liver, heart, brain, lung, kidney and skeletal muscle [19].

AMPK is a highly conserved serine/threonine kinase that exists in almost all eukaryotes. Thr-172 phosphorylation involves the three protein kinases- liver kinase B1 (LKB1), Calcium-/Calmodulin-Dependent Kinase Kinase 2 (CaMKKβ) and TAK1 (TGFβ-activated Kinase 1) [20]. AMPK activation occurs by LKB1 dependent Thr-172 phosphorylation within an activation loop in the α-subunit and by sensing changes in AMP: ATP ratio by binding of AMP to the γ subunit [21]. Ca2+/calmodulin-dependent kinase kinases (CaMKKs), mediated phosphorylation and activated AMPK through increased intracellular calcium levels especially CaMKKβ. This mechanism is independent of the changes in adenine nucleotides. The upstream kinase, CaMKK2 activation is dependent on an increase in intracellular calcium levels [22]. A third kinase, TAK1 (transforming growth factor β activated kinase-1), is a MAPKKK family member (MAP3K7), that phosphorylates and promotes AMPK activation, remain yet require to be elucidated. But it is reported to directly phosphorylate AMPK in yeast. TAK1 phosphorylates and activates lysosomal AMPK is reported [23].

Phytoconstituents in the plant are alkaloids, flavonoids, tannins, phenols, saponins, carbohydrates, vitamins and minerals and several other aromatic compounds [24]. These compounds have been proven for various pharmacological activities, such as antioxidant, antimicrobial, antidiabetic, anti-cancer and so

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on. That is the result why until now scientists continue to investigate biological activities of this plant to production modern medicine and traditional medicine.

The database collected the information on natural products from textual-numeric. About 105,000 organism names, 195,000 pharmacological results and 190,000 identified compounds were collected. In addition, it provided a strategy to prophetically identify the classification source of the most promising specific biological activities. Compared with initial time-consuming laboratory experiments, network pharmacology approaches for well known pathways with various natural products will be more efficient for antidiabetic drug discovery. Based on combining the network, chemical, pharmacological, biomedical and computational results, we can achieve multi-components and multi-targets therapy for DM [25]. In order to find the potential inhibitors from traditional Chinese medicine (TCM) for the T-2-DM-related targets, developed an integrated approach that combined molecular docking and pharmacophore mapping, and they established the compound target interaction network. A total of 2,479 non-duplicated compounds from these 32 Chinese herbs of 52 classical TCM formulas were found from two databases. The Bayesian classifiers with satisfactory discrimination capabilities for 15 targets were employed to screen the 2,479 compounds. The results showed that molecular docking or pharmacophore mapping could give satisfactory predictions for most targets. It was proved that some herbal ingredients could directly interact with T-2-DM related targets, while some ingredients relieved T-2-DM via antioxidant effects or other supplementary pharmacological effects [26].

That is, they played important roles in the biological network, as well as the critical ingredients in Tangminling Pills were predicted and some of them had been reported in literatures. In addition, several compounds, *including Rheidin A, Sennoside C, Rheidin C, procyanidin C1, and Dihydrobaicalin* were of importance as the antidiabetic candidate due to its pharmacological effects [27]. One of the fundamental requirements of all cells is to balance ATP consumption and ATP generation. AMPK is a highly conserved sensor of intracellular adenosine nucleotide levels that is activated when even modest decreases in ATP production result in relative increases in AMP or ADP. In response, AMPK promotes catabolic pathways to generate more ATP, and inhibits anabolic pathways. Genetic analysis of AMPK orthologs in *Arabidopsis, Saccharomyces cerevisiae, Dictyostelium, C. Elegance, Drosophila*, and even the moss Physcomitrella patens have revealed a conserved function of AMPK as a metabolic sensor, allowing for adaptive changes in growth, differentiation and metabolism under conditions of low energy. In higher eukaryotes like mammals, AMPK plays a general role in coordinating growth and metabolism, and specialized roles in metabolic control in dedicated tissues such as the liver, muscle and fat. In mammals, there are two genes encoding the AMPK α catalytic subunit (α1 and α2), two β genes (β1 and β2) and three γ subunit genes (γ1, γ2 and γ3). The expression of some of these isoforms is tissue

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restricted, and functional distinctions are reported for the two catalytic α subunits, particularly of AMP- and LKB1-responsiveness and nuclear localization of AMPKα2 compared to the α1. However, the α1 subunit has been shown to localize to the nucleus under some conditions, and the myristoylation of the (β isoforms has been shown to be required for proper activation of AMPK and its localization to membranes. Additional control via regulation of the localization of AMPK or LKB1 remains a critical unexplored area for future research [28].

Our molecular understanding of the regulation and function of AMPK has significantly been advanced by the elucidation of the crystal structures of a variety of AMPK holoenzymes [29]. Although the reports differ in certain details, together they provide a detailed view of the architecture of the AMPK complex. The structure of the AMPK trimeric complex consists of three major segments or ‘‘modules’’: the catalytic module, the CBM, and the nucleotide-binding module (also called ‘‘regulatory fragment’’). The activation loop of the a subunit resides at the interface between the catalytic and nucleotide-binding modules, in close proximity to the C terminus of the b subunit and the CBS repeats of the g subunit. This structural arrangement ensures that phosphorylation and dephosphorylation of Thr172 is sensitive to conformational rearrangements induced by nucleotide binding. The catalytic domain exhibits a typical eukaryotic serine/threonine KD structure with a small N-lobe and a large C-lobe. The CBM directly contacts the N-lobe of the KD, and the interface between these two modules, forms a discrete pocket that was identified as the binding site for many direct AMPK-activating compounds. It is speculated that natural metabolites might bind this site to regulate AMPK; however, no such metabolite has been yet identified. The nucleotide-binding module is made up mostly by the g subunit, which forms a flattened disk with the CBS repeats symmetrically arranged around the disk, one in each quadrant.

AMPK can be activated by compounds that inhibit ATP synthesis as depletion of ATP always causes an increase in AMP and ADP. In cells that are primarily used glycolysis to generate ATP, AMPK is activated by inhibitors of glycolysis such as 2-deoxyglucose. A much larger class of activators is those that inhibit mitochondrial ATP synthesis by inhibiting the respiratory chain, such as metformin, phenformin, antimycin A, oligomycin, and resveratrol [30]. These agents increase cellular AMP: ATP and ADP: ATP ratios. It is, however, obvious that compounds that inhibit mitochondrial function, inhibit oxygen uptake, while those that inhibit glycolysis reduce lactate output and cause extracellular acidification [31]. Due to this, it is expected that different indirect agents, that act mostly by increasing the concentration of AMP, may lack specificity and trigger different unwanted side effects. For example, it has been shown that inhibition of the respiratory chain induced by metformin and phenformin develops life-threatening cases of lactic acidosis that results in phenformin being withdrawn from clinical use [32]. Orally administered metformin is effectively absorbed from the gastrointestinal tract to the portal vein. As

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a first-pass route, the liver is exposed to a high concentration of the drug, which causes gastrointestinal side effects (diarrhea, nausea, abdominal discomfort, anorexia), limiting its use in many patients [31].

Indirect AMPK activation can be caused by the intracellular accumulation of calcium or AMP. Because AMPK activity is regulated by phosphorylation and dephosphorylation events, the relationships between calcium and upstream kinases or phosphatases play a crucial role. For example, in muscle cells, the increase in cytosolic calcium affects AMPK activation and further influences GLUT-4 gene expression, a skeletal muscle-specific glucose transporter that mediates both insulin and contraction-stimulated glucose transport [33]. Because of indirect AMPK activation side effects, particular attention has been focused on compounds that activate AMPK directly. It is assumed that direct activation of AMPK does not change the AMP: ATP ratio or alter oxygen uptake and does not inhibit mitochondrial function. Direct AMPK activating compounds can be distinguished into two groups: AMP mimetic, which mimic AMP and activate AMPK similarly to physiological ligands, or non-nucleoside activators that bind AMPK at some other sites.

Mechanistically, these crystallographic studies reveal the molecular details of how adenine nucleotides and small-molecule activators activate AMPK. In the case of nucleotides, the crystal structures show that when AMP is bound to site 3, the g subunit forms stable interactions with a few amino acids within the a-linker's a-RIM1 anda-RIM2, which interact with the unoccupied site 2 and the AMP molecule bound at site 3, respectively [34]. The binding of the a-RIM motifs to the g subunit restricts the flexibility of the a-linker, resulting in tighter association of the catalytic and nucleotide binding modules, which physically protects Thr172 from dephosphorylation. Interestingly, the same effect is proposed to occur when ADP binds site 3, raising the possibility that in some contexts ADP might be the relevant AMPK-activating signal [35].

Plants and other natural sources have been useful in discovering drugs for treating patients with diabetes mellitus. Examples include the α-glucosidase inhibitor acarbose, and galegine, which contributed to the discovery and development of the biguanides. There are many traditionally used herbal medicines that lower blood glucose in experimental models, and, currently, there is considerable interest in exploring these plant extracts for compounds that might also be useful in the clinic or that might have novel effects, such as stimulation of β-cell proliferation. Often, neither their mechanism nor their active components have been defined, so it is possible that novel mechanisms of action and novel compounds will be discovered. In addition, there has been very little use of large collections of natural products in random screening campaigns against accepting therapeutic targets: there is great potential to find new chemical scaffolds for drugs with improved properties. This paper will provide an overview of recent

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activities relating to the use of natural products from plants as a source of compounds that might be beneficial in treating patients with diabetes [36].

Natural compounds and synthetic compounds are, in many respects, complementary as avenues for new drug substances from natural products often possess complex structural features not easily accessible by total synthesis. In this brief overview, some selected examples will be provided from the categories of natural, semisynthetic, and synthetic drugs in relation to the central theme of this review article (Fig. 1). The effects of AMPK activation are pleiotropic in key metabolically relevant tissues, equivalent to liver, skeletal muscle, adipose, and hypothalamus. During this review, we are going to focus the discussion on the useful effects of AMPK activation in liver and muscle on modulation of hypoglycaemic agent sensitivity and energy homeostasis. We are going to explore key problems and challenges that require to be self-addressed within the pursuit of AMPK activators for the treatment of diabetes, obesity, and connected metabolic diseases.

METHODS

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The PRISMA statement is designed to improve the quality of meta-analyses.

Literature search

This review consists of a systematic review study about the Type-2-diabetes: Regulation of AMPK pathway using Natural and Synthetic Activators. The ISI Web of Science, PubMed, Science Direct, and Google Scholar were included in the search. The search was conducted using the descriptors: "Type-2-diabetes" and "AMPK pathway" and "Natural and Synthetic compounds". Studies were restricted to those published from 2016 to 2021, in English language. The references of all retrieved articles and Review publications were also reviewed to identify other articles that may be missed using the above search terms. After the literature search, we screened the titles and abstracts of the extracted studies and further examined the full text of the included articles to confirm eligibility for inclusion in this review. Editorials, meeting abstracts, and studies with incorrect, incomplete, or unavailable data were excluded. Collectively, this literature search formed the basis of this integrative narrative review.

Study selection

The selection was based on the following criteria: (1) The Regulation of AMPK pathway, and (2) the using Natural and Synthetic compounds. Selected compounds were further discussed with respect to other bioactivities of Type-2-diabetes and toxicity profiles.

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Statistical Analysis

The primary outcomes were the Type-2-diabetes: Regulation of AMPK pathway using Natural and Synthetic compounds, in addition to reviewing their safety and Medicinal Plant compounds (Natural and Synthetic) based on data available in previous studies. All quantitative results are expressed as mean ± standard deviation. Statistically significant differences were obtained using Student's t-test or one-way analysis of variance. $P<0.05$ was considered to indicate statistical significance.

RESULTS AND DISCUSSION

The present study reveals, for the first time to our knowledge, the protective roles of the AMPK pathway in the Type-2-diabetes. Although numerous studies have explored the effects of natural bioactive compounds for their Type-2-diabetes properties, a frequently encountered limitation is the study of the broad Type-2-diabetes effects of an AMPK pathway the key active compounds. In this review, we focus our attention on a Regulation of AMPK pathway using Natural and Synthetic compounds in Type-2-diabetes.

In this review, we have summarized reports about Type-2-diabetes: AMPK path regulation using natural and synthetic compounds. Constituents of medicinal plants that have the potential to be relevant to the prevention of diabetes through AMPK activation.

Role of AMPK pathway in Type-2-diabetes

The AMPK exists as heterotrimer composed of a catalytic α subunit (α1 and α2) and a regulatory β (β1 and β2) and γ subunits (γ1,γ2 and γ3) with a molecular weight of 63, 38 and 35 kDa respectively. In AMPK activation β subunits have a prominent role. These are encoded by 7 different genes (α1, α2, β1, β2,γ1,γ2 and γ3) of the three subunits have been identified in mammals that produce 12 different heterotrimeric combinations to cater different tissue-specific functions [22]. α1 is predominantly in the liver, kidney, lung and adipose tissue, and α2 is predominant in the brain, heart, liver and skeletal muscle. AMPKα2 plays a prominent role in inhibiting gluconeogenesis and maintains normal blood glucose levels. AMPKα2 deletion in mice showed an enhancement in hepatic lipogenesis, increased plasma triglyceride levels and hepatic glucose production, whereas overexpression of AMPKα2 in hepatocytes lowered plasma triglyceride levels and raised plasma ketone bodies, a surrogate marker for hepatic β-oxidation. Thus AMPKα2 makes a balance between the hepatic lipogenesis and β-oxidation. AMPKα2 is essential for the whole-body insulin action and normal functioning of the β-cell where its absence reduces insulin-stimulated whole-body glucose utilization and skeletal muscle glycogen synthesis. The regulatory subunits β1 and γ1 complexes are predominant in rodent liver. β2 and γ3 are predominant in the skeletal muscle, whereas γ1 and γ2 subunits have a broad tissue distribution (Fig. 2 & 3).

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Thus LKB1 and AMPK plays a role in suppressing gluconeogenic and lipogenic pathways in the acute regulation of energy balance in the liver (Table.1).

Current therapeutic approaches for treating Type-2-diabetes (Natural and Synthetic compounds) and their mechanism in the AMPK Pathway Available Treatments – uses and problems Direct and Indirect Mechanisms

Natural Compounds

Though there are many synthetic drugs available for the treatment of diabetes mellitus, they have many side effects beyond their uses. The antidiabetic medications that includes *Sulphonylureas, Meglinitides, Thiazolidinediones, Bigunaides, Alpha-glucosidase inhibitors, Glucagon-like peptide 1 agonists, Sodium glucose transporter-2 inhibitor (SGLT-2), Dipeptidyl peptidase-IV inhibitors and Dopamine-2 agonists* etc. These therapeutic drugs failed to reach the expected targets and may produce different complications like liver injury, gastrointestinal problems, diarrhea, dizziness, mental disorders, weight gain, cardiovascular problems, and skin diseases. Sulphonylureas and meglinitides are the insulin secretagogues that promote the release of insulin from the pancreas and thus help in reducing blood sugars. Sulphonylureas are the second line glucose-lowering drugs used to treat diabetes. It causes side effects like weight gain, hypoglycemia, nausea, vomiting, diarrhea, constipation, dermatologic side effects, erythroderma, cholestatic hepatitis, jaundice [37]. It includes the first-generation agents, Tolbutamide, Acetohexamide, Tolazamide, Chlorpropamide and they are no longer used. Side effects of first-generation agents include headache, abdominal discomfort and nausea (Fig. 4). Many of those natural products are secondary metabolites of plants, and a few of them seem to be created to defend plants against infection by pathogens or grazing by phytophagous animals. Production of mitochondrial poisons could also be impacting an efficient a good} deterrent, however (observing the apothegm of physician that “the dose makes the poison”) at lower doses these compounds might solely cause gentle inhibition of mitochondria however still have the helpful effect of activating AMPK.

The majority are products of plants used in herbal remedies, particularly in traditional Asian medicine. The mechanism by which most of them activate AMPK is unknown, and a puzzling feature is why so many natural plant products should all be AMPK activators. One clue is that among the small number of these activators where the mechanism has been established, most are inhibitors of mitochondrial ATP synthesis, either by inhibiting Complex I of the respiratory chain, or by inhibiting the ATP synthase (Complex V). Most of the natural plant products that activate AMPK appear to be secondary metabolites, i.e., they are not required for plant growth, development or reproduction, and a reasonable working hypothesis is that many of them are molecules produced by plants to deter infection by pathogens, or grazing by insect or other herbivorous animals, to whom these molecules are toxic. In

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support of this idea, resveratrol is known to be produced by grapes in response to fungal infection, while *Galega officinalis*, the source of galegine from which metformin and phenformin were derived, is classified as a noxious weed in the USA because it is poisonous to herbivorous animals (reflected in one of the common names for *Galega officinalis*, Goat's Rue). It is also interesting to note that the barbiturate drug, phenobarbital, activates AMPK in an AMP-dependent manner by inhibiting the respiratory chain. In hepatocytes, AMPK activation is required for phenobarbital to induce expression of genes (e.g., CYP2B6) encoding enzymes of the cytochrome P450 (CYP) family, via the constitutively active/androstane receptor, constitutive active/androstane receptor (CAR). Some classes of CYP enzymes (especially the CYP1/CYP2/CYP3 families) catalyse the initial steps in the metabolism of drugs and other hydrophobic xenobiotics, making them more soluble for excretion. Plant products that are defensive agents inhibiting mitochondrial ATP synthesis would activate AMPK, and induction of CYP enzymes by AMPK might then be a good general way for the animal to mount a response to deal with potential poisoning by these xenobiotics.

The second-generation drugs *Glibenclamide, Glipizide, Glyburide, Glimepiride and Gliclazide* have a prominent role in enhancing pancreas function, but have side effects, including weight gain, Hyperinsulinemia, Non-fatal cardiovascular problems. Glibenclamide and glimepiride promotes the insulin secretion but cannot prevent the β-cell atrophy and also promotes weight gain and cardiovascular problems. Chlorpropamide and glipizide, are rarely reported in photosensitivity and hyponatraemia. Meglinitides are the nonsulphonyl urea secretagogue that includes Repaglinide and nateglinide used for treating diabetes efficiently by lowering the postprandial blood glucose level. They promote insulin secretion from the β-cells of the pancreas and lower the blood glucose levels. But they have some side effects like upper respiratory tract infection, sinusitis, constipation, arthralgia, headache and vomiting. The first drug in this class, Repaglinide caused hypoglycemia. Mild gastrointestinal problems, Hypoglycemia and weight gain are promoted due to usage of nateglinide, the second drug in this class. (Table. 2)

Synthetic Compounds

Thiazolidinediones (Rosiglitazone, Pioglitazone and Troglitazone) and biguanides (metformin, phenformin and buformin) are insulin action enhancers that played a beneficial role in diabetes. *Thiazolidinediones* are the insulin sensitive drugs that significantly reduced the insulin resistance by decreasing fasting and postprandial hyperglycemia and hence improved insulin sensitivity. They decreased the plasma cholesterol and increased the HDL cholesterol levels. They resulted in weight gain and other side effects like gastrointestinal problems, mild anaemia, renal toxicity, liver toxicity, edema, bone fractures, dizziness, decreases in the haemoglobin content, heart failures and bladder cancer. The

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TZD's that include *rosiglitazone, pioglitazone* caused cardiovascular risks like myocardial infarction, anaemia, edema, dizziness, Bladder cancer, increased fluid retention, weight gain and increased peripheral fractures [38]. *Troglitazone* that was effective in controlling glycemia resulted in hepatocellular injury. *Rosiglitazone* caused weight gain and heart failure.

Biguanides caused loss of appetite, nausea, diarrhoea and abdominal cramps. Metformin is the first line glucose-lowering drug, known to ameliorate hyperglycemia by inhibition of hepatic glucose output [39]. Metformin and phenformin caused kidney toxicity. Metformin is the only currently available oral biguanide for treating diabetes, but it resulted in the development of Diarrhoea, nausea, mild anorexia, intrahepatic cholestasis, abdominal discomfort, abdominal bloating, flatulence, gastrointestinal problems, vomiting and renal impairment. In some rare cases, it resulted in the lactic acidosis. The usage of phenformin and buformin is avoided due to the risk of lactic acidosis and cardiac mortality.

Based on Incretin system, there are two classes of drugs, Glucagon-like peptide 1 agonists (GLP1) and Dipeptidyl peptidase-IV inhibitors (DPP-IV). Beyond the maintenance of blood sugar homeostasis, increase of insulin secretion, glycemic control, weight loss, suppression of glucagon release and reduction of liver fat content incretin based drugs have gastrointestinal problems like vomiting, indigestion, diarrhea and nausea. In addition to the side effects these drugs are expensive [40]. Glucagon-like peptide 1 agonists (GLP1), Liraglutide, Exenatide and Albiglutide resulted in Pancreatitis, nausea and vomiting. Exenatide resulted in acute pancreatitis. Liraglutide resulted in nausea, vomiting, and diarrhea. The Dipeptidyl peptidase-IV inhibitors (DPP-IV), promoted the release of insulin from the pancreas and includes Sitagliptin, saxagliptin, Vildagliptine, Linagliptine and Alogliptine. They resulted in Hypoglycemia, Headache, Pancreatitis, allergic reactions and Heart disease. In addition to this Vildagliptin caused gastrointestinal problems. Among DPP-IV inhibitors, urinary tract infections and nasopharyngitis were observed more when treated with sitagliptin and vildagliptin.

Acute pancreatitis was resulted in diabetic patients receiving sitagliptin. Sitagliptin and saxagliptin caused nasopharyngitis and respiratory tract infections. Glucose absorption inhibitors include Alpha-glucosidase inhibitors and Sodium glucose transporter-2 inhibitor (SGLT-2) that decrease hyperglycemia and reduce glucose production in the intestine. Alpha-glucosidase inhibitors (disaccharide inhibitors) include the compounds like Acarbose, voglibos and miglitol. Acarbose caused side effects such as abdominal distension, stomach rumble and diarrhoea, while miglitol resulted in abdominal bloating, diarrhoea and flatulence when taken at higher doses. Voglibos, the first alpha-glucosidase inhibitor that delays the digestion and absorption of disaccharides, maltose and sucrose. It is known to cause hepatitis flatulence, diarrhea, abdominal discomfort and severe cholestasis.

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Sodium glucose transporter-2 inhibitor (SGLT-2), are known to shows its action mainly in the Kidneys and performs glucose homeostasis. It includes canagliflozin (Invokana, Janssen), Dapagliflozin, Jardiance, Empagliflozin, sergliflozin. SGLT2 inhibitors are not used for treating type-1-diabetes and diabetic ketoacidosis. They do not depend on the function of beta cells of the pancreas. Dapagliflozin, Jardiance, Empagliflozin resulted in Hyponatremia, Hypotension, ketoacidosis and Bone fracture. Different male and female genital mycotic infections, increased urination, and urinary tract infections are caused due to canagliflozin, dapagliflozin, and empagliflozin, the currently approved SGLT2 inhibitors in India [41]. Invokana caused complications such as hypoglycaemia and genital infections in females. Dapagliflozin enhanced insulin sensitivity and improved glucose tolerance.

Dopamine-2 aganist, Bromocriptine (Cycloset), resulted in fatigue, nausea, vomiting, dizziness, diarrhea, constipation and headache. Diabetic management without any side effects is a present challenge. Hence a study was done on phytocompounds to prevent such side effects. Management of diabetes is essential to reduce blood glucose levels and to ameliorate the insulin resistance. Many plant species are used for the treatment and prevention of diabetes worldwide. Hence World Health Organization (WHO) approved the use of plant products as drugs for different diseases, including diabetes mellitus. Studies were executed on plant extracts, to know their efficacy, their glucose-lowering effects, these mechanisms of action and safety. Hence, activation of the AMPK pathway by using natural compounds is discussed.

AMPK is activated in two ways, either by indirect or direct mechanisms. AMPK activation by indirect mechanism involves, Mitochondria that are essential for the ATP production and performs oxidation of carbohydrate, fatty acids and amino acids. Depletion in ATP levels causes increase in AMP and ADP, and AMPK gets activated by any compound that inhibits ATP synthesis. Hence AMPK activation is dependent on changes in the cellular adenosine nucleotides (AMP, ADP or ATP). The mitochondrial enzyme consists of complex-1 (NADH dehydrogenase), Complex-II (succinate dehydrogenase), Complex-III (cytochrome bc1), Complex-IV (cytochrome c oxidase) and complex-v (F_1-F_0 ATPase/ATP synthase). F_1-F_0 ATPase is present in the inner membrane of mitochondria that acts as the powerhouse of the cell by synthesizing ATP. Hence AMPK activation by indirect mechanism occurs by increasing cellular AMP and ADP levels, by inhibiting mitochondrial ATP synthesis. The increased AMP binds to the γ-subunit of AMPK and activates it by inhibiting Thr172 dephosphorylation by upstream protein phosphatases [42]. AMPK gets activated by both natural and synthetic products, and the mechanisms by which they activate the AMPK pathway are discussed.

AMPK activators inhibit mitochondrial ATP synthesis through the electron transport chain, increase cellular AMP and binds to γ-subunit of AMPK by indirect activators. They promote the AMPK activation indirectly by inhibiting the electron transport chain subunits. Indirect AMPK activation occurs

by inhibiting mitochondrial respiratory chain ATP synthesis, thus increasing the AMP: ATP ratio and ADP: ATP ratios in the cell and thus activate AMPK indirectly. Thiazolidinediones, Arctigenin, Metformin, Phenformin, Berberine and rotenone inhibits the complex-I of the respiratory chain.

Thiazolidinediones (TZDs) are a class of insulin sensitive drugs and includes rosiglitazone, pioglitazone and troglitazone. These drugs inhibit the complex-I of the respiratory chain and activate AMPK in skeletal muscle, liver and adipose tissue. They are known to decrease the fatty acid content in adipocytes. Metformin and Phenformin are the bigunaides that upregulates AMPK pathway by increasing fatty acid oxidation and down-regulates hepatic glucose production and stimulates glucose uptake. It activates AMPK indirectly by inhibiting complex-I of the respiratory chain, resulting in a fall in cellular ATP concentration and increase AMP: ATP ratio. Increased expression of mTORC1 signalling by different stresses is controlled by Metformin and Phenformin thus reducing protein synthesis [43].

Both *biguanides* and *TZDs* are inhibitors of complex 1 of the respiratory chain, causes inhibition of ATP synthesis and consequent increase in AMP indicating that they might activate AMPK and exert some of their antidiabetic effects. Arctigenin decreased serum cholesterol levels, lowered blood glucose levels, increased fatty acid oxidation diabetic mice [44]. Thus, it acts as a potential therapeutic agent in the prevention and treatment of Type-2-diabetes and insulin resistance. The natural product berberine works in a similar manner to metformin, that reduces body weight and improves glucose tolerance in db/db mice, regulates glucose metabolism while reducing body weight and plasma triacylglycerols, and improving insulin sensitivity, in rats fed a high-fat diet. It is used in treating diabetic nephropathy. Stimulation of glycolysis promoted glucose metabolism, thus caused mitochondrial inhibition independent of AMPK activation. Haemoglobin A1c levels were decreased after treatment with barber for 3 months [45].

Rotenone activated AMPK and enhanced glycolysis thus reduced hepatic glucose output, hence ameliorated hyperglycaemia. The enhancement in glycolysis reduced/inhibited gluconeogenesis causing reduction in cellular NAD^+/NADH (nicotinamide adenine dinucleotide (NAD^+) /reduced form of nicotinamide-adenine dinucleotide (NADH) ratio and inhibited complex I of the respiratory chain. It effectively reduced fasting blood glucose and improved the impaired glucose tolerance and insulin sensitivity in diabetic mice [43]. Antimycin In a similar way Antimycin A inhibited the complex III of the respiratory chain. Resveratrol, Oligomycin, Quercetin, Genistein, Epigallocatechin gallate, Curcumin, Picetannol, Apoptolidins A/C inhibits the electron transport chain by inhibiting F_1-F_0 ATPase activity present in mitochondria [46].

Resveratrol inhibited the excess of ATP production and the activated AMPK pathway by inhibiting ATP synthase activity in rat brain and liver. Picetannol, the hydroxylated analog of resveratrol

is found in Passiflora edulis seeds, grapes and rhubarb. Picetannol shows the activity similar to resveratrol but its content is low in plants when compared to resveratrol. AMPK activation lowered blood glucose levels in diabetic mice on treatment with picetannol and improved glucose intolerance [47].

Oligomycin, and Resveratrol works by inhibiting complex V, the mitochondrial F1 ATP synthase. Inhibition of the respiratory chain by this products inhibited ATP production and increasing the AMP and ADP ratios. The increase in AMP caused it to bind to the γ-subunit of AMPK results in allosteric activation and ameliorates the diabetic effects [48]. Quercetin, AMPK activation promoted glucose uptake in L6 myotubes by increasing the cellular AMP: ATP ratio [49]. An intake of quercetin decreases the risk of Type-2 diabetes. AMPK activation by Quercetin downregulated the oxidative damage and enhanced the glucose uptake and GLUT4 translocation [50]. Genistein, an isoflavonoid present in soybean is known to activate AMPK thereby promoting fatty acid oxidation and improving insulin sensitivity in rats and C2C12 myotubes.

The Epigallocatechin gallate Epigallocatechin-3-gallate (EGCG) activated AMPK pathway and improved metabolic disease. In rodents, it has a prominent role in ameliorating Type-1-diabetes and the treatment of Type-2-diabetes. AMPK activation by EGCG is mediated by the Ca2+/calmodulin-dependent protein kinase kinase (CaMKK) pathway and by inhibiting mitochondrial F1F0 –ATPase / ATP synthase activity [51]. The Comic mediated AMPK reduced hepatic gluconeogenesis. In L6 muscle cells EGCG promotes glucose uptake. Curcumin activated AMPK and suppressed the expression of hepatic gluconeogenic enzymes (glucose-6-phosphatase and phosphoenolpyruvate carboxykinase). Curcumin downregulated the expression of SREBP1c and ACC1 that decreased fatty acid synthesis [52]. GLUT4 expression is increased that promotes glucose uptake in rat L6 myotubes and translocates to the plasma membrane. (Table. 3)

Direct and Indirect Mechanisms

The direct activation of AMPK requires Thr172 phosphorylation of the α-subunit by one of its three upstream kinases: the tumor-suppressor LKB1 (Liver kinase B1), CaMKKβ (Calcium-dependent calcium/calmodulin-dependent protein kinase kinase β) and TAK1 (Transforming growth factor-β activated protein kinase-1). LKB1 and CaMKKβ are known to phosphorylate the Thr-172 of α-subunit.

Metformin in additionally inhibits the Complex-1 of respiratory chain by reducing ATP levels, and increasing AMP levels, It also stimulates phosphorylation of AMPK α-subunit at Thr-172 and increases the activity of the upstream kinase at low concentrations of metformin [53]. This increase in AMPK activity was dependent on LKB1 activity that lowered blood glucose levels by treatment with metformin. The Hepatic glucose production is reduced, thus suppressing expression of gluconeogenic genes (PEPCK and G6Pase), reduction of liver lipogenesis and improved insulin resistance and

hyperglycemia [54]. Thymoquinone, isolated from Nigella sativa have antioxidant properties to can scavenge against free radicals and reduce oxidative stress, and hence improves insulin secretion.

AMPK activation inhibits gluconeogenesis in muscle and liver due to hypoglycemic effects of thymoquinone. Thymoquinone phosphorylates and activates AMPK and Sirtuin-1 by an upstream activator, LKB1 by de-acetylation and activation of LKB1 [55].

Ursolic acid has an essential role in lowering blood glucose concentrations and improves insulin resistance and diabetes. It increases glucose uptake and liver glycogen synthesis. It showed decreases in the body weight, glucose intolerance and β-oxidation by AMPK activation [56]. Ampkinone promotes LKB1-dependent AMPK activation by phosphorylating AMPK at Thr-172 and improved glucose tolerance, increases glucose cellular uptake and insulin sensitivity. Besides LKB1, CaMKK also activates AMPK upon treatment with ampkinone. AMPK activation alters the expression of HMG-CoA reduces and acetyl-CoA carboxylase and decreases the levels of cholesterol and free fatty acids in the serum.

Adiponectin binds to α-subunit phosphorylation at Thr172 at increased concentrations of Ca^{2+} and activates CaMKK that is essential for 5′-AMP-activated protein kinase (AMPK) activation. It inhibits expression of PEPCK and G-6-P and suppresses gluconeogenesis, increases mitochondria biogenesis [57].

Monascin, Ankaflavin, Monascin and ankaflavin are the metabolites of fungus caused phosphorylation of α-subunit and proved to ameliorate the Type-2-diabetes by regulation of lipid disorder, inhibited fatty acid synthesis and SREBP-1c expression [58]. In addition, it also suppressed gluconeogenesis and promoted mitochondrial β-oxidation. Compound 13 a pro drug of C2 stimulated AMPK pathway which inhibited hepatic lipogenesis and stimulated fatty acid oxidation by preventing the α1 complex and reversed the metabolic defects [59].

CONCLUSIONS & FINAL SUGGESTIONS FOR FUTURE RESEARCH WORK

As a result, in our review, the regulation of the AMPK pathway by natural and synthetic compounds in Type-2-diabetes, AMPK activation through indirect mechanisms involves mitochondria, which are important for the production of ATP and oxidative carbohydrates, fatty acids and amino acids. Natural and synthetic compounds play an important role in ameliorating the effects of diabetes through direct or indirect activation. The natural products have a vast structural diversity and various bioactivities, which can provide the opportunities to find different lead compounds, different targets for DM. This review describes some classes of direct and indirect activators of AMPK. Further studies are required to understand the molecular interactions of these compounds and structural requirements for their specificity to the various subunits of AMPK or its upstream effectors. Such ongoing efforts may provide a novel class of drugs to treat diabetes and related metabolic abnormalities in the future.

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AUTHOR CONTRIBUTIONS

P.V.R; Reviewed the manuscript, **Y.A;** was a major contributor in editing and revising, **M.S.R;** conceptualized and reviewed the draft, Supervised data collection, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing-original draft, Writing-review and editing. Both authors critically edited the text and reviewed the published version of the review manuscript.

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The authors have declared that they have no conflicts of interest in this work. We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

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Table 1 Impact of AMPK pathway in Type-2-diabetes importance

AMPK subunit	Function Affected	References
Lack of AMPK	Reduced mitochondrial biogenesis	[60]
Knock out of AMPK	Capability of salicylate to increase fat utilization and lower plasma fatty acids were lost	[61]
Deletion of AMPK-α	Lowers blood glucose levels by Metformin	[62]
Deletion of AMPK-α1	Low intensity contraction stimulated glucose uptake in skeletal muscle was decreased	[63]
Deletion of AMPK-α2	1. Decreased plasma triglycerides and increased plasma ketone bodies	1. [64]
	2. Caused mild hyperglycemia and enhanced gluconeogenesis and in liver adiponectin loses its capacity to regulate hepatic glucose production	2. [65]
	3. Hepatic Insulin Resistance is no longer alleviated by dietary n-3 poly unsaturated fatty acid	3. [66]
Deletion of AMPK- α1 & α2	1.Lack of efficacy in AICAR-mediated control of blood glucose levels	1.[67]
	2. Stimulation of AMPK activity and phosphorylation of its known down-stream targets is abolished in primary mouse hepatocytes treated with A-769662	2. [68]
	3. In liver AICAR inhibits hepatic glucose phosphorylation hence ATP depletion occurs	3. [69]
	4. Did not affect ChREBP subcellular translocation into the nucleus under high carbohydrate diet feeding and retention in the cytosol under PUFA conditions	4. [70]
	5. 6-gingerol stimulated glucose uptake and protein expression was diminished in L6 myotubes	5. [63]
	6. Created insulin deficiency by changes in the morphology of the β-cell of pancreas	6. [71]
Knock out of α2	1. Reverses the protective effects and exacerbates the degree of fibrosis	1. [72]
	2. Blocked 6-gingerol induced glucose uptake and AS160 phosphorylation	2. [73]

	3. Glycogen synthase activity was blocked in mouse skeletal muscle treated with AICAR	3. [67]
	4. Developed hyperglycemia and impaired glucose intolerance as a result of increased hepatic glucose production & increased PEPCK and G6Pase activity, suggesting an elevated gluconeogenesis level associated with AMPK function loss	4. [45]
	5 Increased body weight and increased lipid storage in adipose tissue	5. [74]
Knockdown of the AMPK γ1	Abolishes the AMPK activating and lipid-lowering effects of cordycepin	[75]
Mutations in γ1	Abolishes allosteric activation by AMP	[76]
Mutations in γ2	1. Enhanced glycogen storage in cardiomyocytes, cardiac hypertrophy and electrophysiological abnormalities	1. [77]
Mutations in γ3	Chronic alterations in AMPK activity also have significant effects on skeletal muscle glycogen metabolism	[78]
Knock out of LKB1	1.Metformin is not efficacious in lowering blood glucose levels	1. [79]
	2. Diabetic mice did not respond to metformin and reduced the phosphorylation AMPK at Thr^{172} rendering AMPK insensitive to stimuli which normally activate it and fasting blood glucose levels were highly increased and hypoglycemic effects of metformin were lost.	2. [80]
	Exhibited fasting hyperglycemia and glucose intolerance and are unresponsive to metformin treatment, which inhibits gluconeogenesis by activating AMPK .	
	3. Complete inhibition of the phenformin induced activation of AMPK-α2	3. [81]
Deletion of LKB1	1. Reduced the phosphorylation AMPK leading to decreased glucose clearance and increased expression of G6Pase, PEPCK enzymes involved in regulating hepatic lipid metabolism and TORC2 expression	1. [82]
	2. Significant decrease in AMPK-α2 activity, but a significant	2. [83]

	increase in AMP:ATP and ADP:ATP levels, in response to high intensity, tetanic contractions, suggesting that LKB1 is the pre-dominant AMPK-α2 kinase in muscle in response to cellular energy stress.	
	3. Lack of hepatic LKB1 abolished AMPK activity and resulted in increased blood glucose levels	3. [81]
	4. Abolishes AMPK activation and leads to nuclear accumulation of TORC2, which in turn increases gluconeogenesis, AMPK phosphorylation atThr172 is decreased in liver rendering AMPK insensitive and complete loss of AMPK activity in the liver of adult mice	4. [80]
Transplanted bone marrow from AMPK β1-deficient mice	No AMPK activity in macrophages and mice had higher serum levels of inflammatory cytokines and increased systemic and Hepatic Insulin Resistance	[84]
Knock out of AMPK-β1	Inactivation of ACC1 and ACC2 that causes a rapid switch from fat synthesis to fat synthesis to fat oxidation is not occurring when injected with Salicylate or A-769662	[61]

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Table 2 Natural compounds treating Type-2-diabetes and that have been reported to mechanism in AMPK pathway

Compound Name	Obtained From	Mechanism	Target site	Molecular action	References
Salicylate	Salix alba (Willow bark)	Direct	Uncouples mitochondrial respiration & also causes allosteric change by binding to β1-subunit	Improves insulin sensitivity and decreased fasting glucose in obese mice and humans	[61]
Metformin	Galega officinalis	Direct & Indirect	Inhibits respiratory chain at complex 1 and increases cellular AMP & ADP	Decreased Hepatic glucose production, G-6-Pase & ACC2 activity, lipogenic enzymes, SREBP-1 expression is suppressed, Fattyacid oxidation is induced and stimulates glucose uptake	[85]
Phenformin	Galega officinalis	Indirect	Inhibits respiratory chain at complex 1	Reduces Hepatic glucose production & enhance Peripheral insulin sensitivity	[86]
Quercetin	Many plant units including fruits, vegetables, grains like pepper, coriander, fennel, radish, dill, berries, onions, apples and wine	Indirect	Inhibits mitochondrial F_1F_0 –ATPase / ATP synthase	Increase in cytosolic calcium levels on L6 myotubes, upregulated the gene expression of CaMKK and caused two fold increase in AMP to ATP and ADP to ATP ratio. Enhanced glucose uptake in L6 myotubes	[49]
Curcumin	Curcuma longa	Indirect	Inhibits mitochondrial F_1F_0 –ATPase / ATP synthase	Suppress G6Pase activity, PEPCK activity and hepatic gluconeogenic gene expression	[87]

Betulinic acid	Betula plant, From many plants	Indirect	Causes mitochondrial dysfunction and leads to increase in ATP production	Inhibits gluconeogenesis in liver, gene expression levels of PGC-1α, Inhibited PEPCK and G6Paseand caused suppression of hepatic glucose production	[88]
Ursolic acid	Mirabilis jalapa, other plants, fruits and herbs	Indirect	LKB1/AMPK Signaling	increased liver glycogen synthesis, increased pancreatic β-cell function increased fatty acid oxidation and decreased fatty acid synthesis in hepatocytes.	[89]
Rutin	Buck wheat, leaves and petioles of Rheum species and asparagus, passion flower, apple, and tea	Direct	Increased the Phosphorylated levels of AMPK	Enhanced IRS2 level in pancreas Decreased plasma glucose, glycosylated hemoglobin, plasma TBARS and increased insulin levels	[90]
Genistein	Soy beans	Indirect	Inhibits mitochondrial F_1F_0 –ATPase / ATP synthase	improved hyperglycemia, glucose tolerance, and blood insulin level in obese diabetic mice, decreased β-cells loss , reduced insulin sensitivity	[91]
Thymoquinone	Nigella sativa	Indirect	Increasing the Phosphorylated levels of AMPK via LKB1 signalling	Reduce oxidative stress, improves insulin secretion, Inhibits gluconeogenesis in liver and muscle	[55]
Rotenone	Roots of several members of Fabaceae	Indirect	Inhibits transfer of electrons from mitochondrial complex 1 to ubiquinone	Fasting blood glucose levels were reduced Improved impaired glucose tolerance Increase in AMPK and ACC phosphorylation Induced glycolysis	[43]

Resveratrol	Red grapes, grapes, berries, peanuts, blueberries, itadori tea, hops and pistachios	Indirect	Inhibits mitochondrial F_1F_0 –ATPase / ATP synthase	Plasma glucose, Insulin levels decreased Restore the function of β-cells fatty acid oxidation increased inhibition of acetyl-CoA-carboxylase (ACC), reduced levels of malonyl-CoA promote glucose uptake and mitochondrial biogenesis in muscle	[92]
Capsaicinoids	Hot peppers	Indirect	-----	Induce fatty acid oxidation and decrease body fat accumulation	[93]
Ginsenoside Rb1	Panax ginseng	Indirect	------	Glucose uptake, Hepatic triglyceride & Hepatic cholesterol increased Hepatic glucose production & Lipogenesis decreased Decreased hepatic fat accumulation Enhanced fatty acid oxidation via increase in CPT1 activity	[94]
Genistein	Soybeans and its derived products	Indirect	Inhibits mitochondrial F_1F_0 –ATPase / ATP synthase	Ameliorates glycaemia and improves glucose tolerance fatty acid oxidation increased Stimulates the insulin-dependent signalling pathway in hepatocytes	[95]
Epigallocatechin gallate	Camellia sinensis, Green tea	Indirect	Inhibits mitochondrial F_1F_0 –ATPase / ATP synthase	1. Enhance insulin signaling pathway by phosphorylation of IRS-1 (Insulin Receptor Substrate-1) 2. Reduces ROS and downregulates production of iNOS (inducible Nitric Oxide Synthase) to protect pancreatic islet β-cells	1. [96] 2. [97,98]
Berberine	*Phellodendron chinense*, Coptis chinensis & Hydrastic Canadensis	Indirect	Inhibits respiratory chain at complex 1	reduces whole-body adiposity and improves glucose tolerance, insulin sensitivity and lowered total and LDL cholesterol levels	[99]
6-gingerol	Zingiber officinale	Indirect	Ca2+/CaMKK-AMPK	Facilitated glucose uptake by triggering GLUT4 via phosphorylation of TBC1D1 and upregulated expression of	[63]

				PGC-1α	
Cryptotanshinone	Dried roots of Salvia miltiorrhiza	-------	ROS dependent AMPK activation	Increased insulin-stimulated glucose uptake in muscle tissue and adipose tissue	[100]
Arctigenin	Arctium lappa	Indirect	Inhibit mitochondrial respiratory chain at complex I	Reduced fasting blood glucose levels and decreased cholesterol levels Altered glucose and lipid metabolism in skeletal muscle and liver, inhibited gluconeogenesis	[44]
Hydroxytyrosol	Oleo Europea leaves	------	-------	Increase fattyacid oxidation and improves insulin sensitivity in 3T3-L1 adipocytes	[101]
Baicalein	Roots of Scuttellaria baicalensis and fruits of *Oroxylum indicum* (L.)	Direct	α Thr-172 phosphorylation	Lipid lowering effect on activation of AMPK-α2 in hepatocytes Increase insulin sensitivity in livers of diet-induced obese mice by blocking of AMPK-mediated MAPKs pathway Ameliorated insulin resistance and hyperglycemia through activation of AMPK signaling pathways in liver Activation of fatty acid oxidation, insulin signaling pathways	[102]
Sanguinarine	Sanguinaria canadensis	Direct	Interacts with AMPK in cleft between β & γ subunits similar to AMP	Reduced lipid accumulation	[103]
Picetannol (Resveratrol derivative)	Passiflora edulis	Indirect	Inhibits the rotary mechanism of F_1 ATP synthase	Reduced blood glucose levels	[47]
Scirpusin B (Dimer of Picetannol)	Passiflora edulis	------	-------	Reduced blood glucose levels through inhibition of alpha amylase	[104]
Theaflavin	Black tea (68.4% tea polyphenol	Indirect	Inhibit ATPase activity of	Inhibites ROS and prevented obesity through phosphorylation of AMPK	[105]

	s)		mitochondria	and promoting browning of white adipose tissue	
Hispidulin	Flowers of Millingtonia hortensis, S*aussurea involucrate*	Indirect	-------	Increased the antioxidant activity of SOD, Catalase and Glutathione (hepato protective activity)	[106]
Rooibos	Aspalathus linearis	---------	--------	promotes glucose uptake, mitochondrial activity, GLUT4 expression and ATP production reduced serum cholesterol, triglyceride, and free fatty acids	[107]
Naringenin	grapefruits, oranges and tomatoes	--------	---------	Improved blood glucose levels, increases glucose tolerance, Suppressed plasma glucose levels increases glucose tolerance, insulin sensitivity and decreased plasma glucose levels, enhanced antioxidant activity and improved hepatic function markers increase in glucose uptake in L6 myotubes	[108]

Table 3 Synthetic compounds treating Type-2-diabetes and that have been reported to mechanism in AMPK pathway

Compound Name	Obtained From	Mechanism	Target site	Molecular action	References	Obtained From
Thiazolidinediones	Insulin sensitizing drugs	Indirect	Inhibits respiratory chain at complex 1	1. Glucose uptake & Fatty acid oxidation increased Hepatic glucose production reduced	1. [109]	
Rosiglitazone	Insulin sensitizing drugs	Indirect	Inhibits respiratory chain at complex 1	Reduced serum levels of matrix metallo-proteinase-9 and C-reactive protein	[110]	
PT 1	Furanothiazolidine derivative	Direct	Increased phosphorylation of AMPK without changes in ATP:ADP & shows interaction with α-AMPK subunit	1. Lipid content, insulin resistance decreased & improved glucose tolerance 2. Increases the glucose uptake in hyperglycemic conditions in L6 myotubes	1. [111] 2. [112]	

α-Lipoic acid	spinach, broccoli, tomato	Direct	Increase in phosphorylation of AMPK α-subunit at Thr-172 by LKB1 or CaMKK	Improved insulin sensitivity and enhanced glucose uptake and utilisation AMPK activation and α-LA are associated with suppression of hepatic glucose output.	[113]
Phenobarbital	Barbiturate drug	Indirect	Inhibit mitochondrial respiratory chain	---------	[114]
A-769662 (Thienopyridone)	Synthetic activator	Direct	Activates AMPK-β1 subunit	1. Oxidation of fats increased in normal rats & Lowered body weight, plasma glucose, triglycerides and liver triglycerides in obese mice 2. Inhibits fatty acid synthesis in liver, Decreased PEPCK, G6Pase activity	1. [115] 2. [116]
AICAR	Synthetic drug	Direct	Phosphorylates to ZMP which is an analog of AMP that binds to AMPK-γ subunit	1. Improves glucose homeostasis, insulin sensitivity, and reduces lipid profile (triglycerides and free fatty acids), hepatic glucose output 2. Down regulated expression of PEPCK and G6Pase	1. [117] 2. [118]
WS070117	Synthetic adenosine derivative	Indirect	--------	Lipid lowering effects invivo. Reduced serum levels of triglycerides, low density lipoproteins, total cholesterol and hepatic cholesterol and triglycerides reduced dramatically Inhibits the expression of 3-hydroxy-3-methyl-glutaryl-CoA reductase	[119]
Ampkinone	Constructed by diversity oriented synthesis	Indirect		Occurs via LKB1 mediated mechanism Glucose uptake in C2C12 & L6 myotubes and significantly reduced blood glucose levels in obese mice. Improved glucose tolerance and insulin sensitivity with reduction in adiposity and body weight without affecting food consumption	[68]

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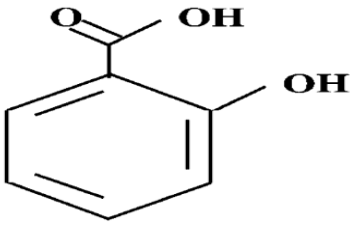
Natural Compounds



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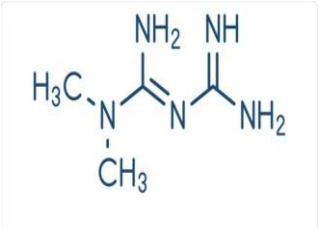

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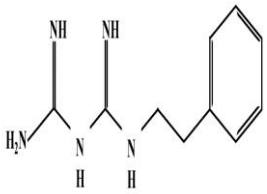

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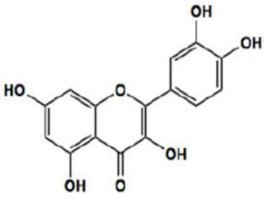

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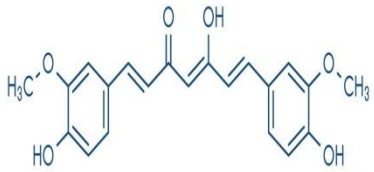

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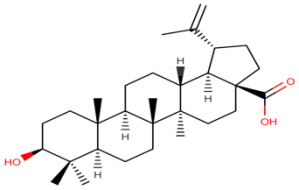

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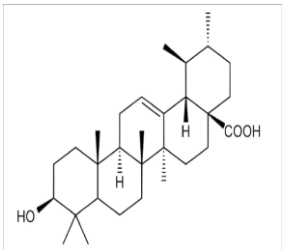

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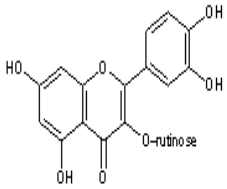
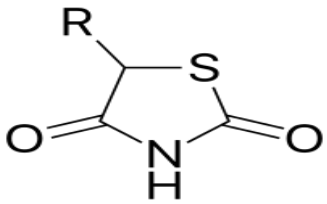


Rutin

Synthetic Compounds



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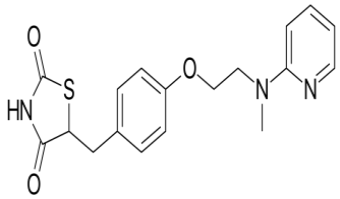

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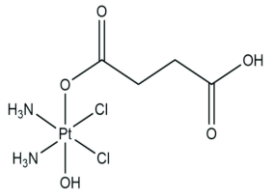
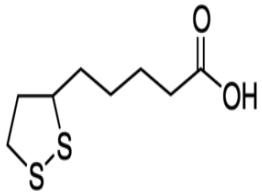
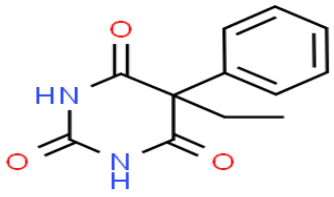


PT 1



α-Lipoic acid



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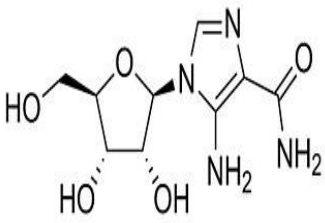

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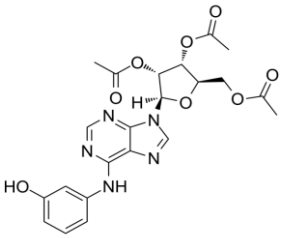

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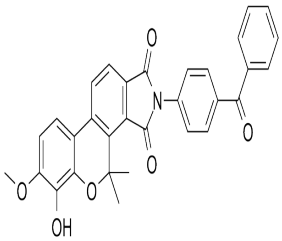

Ampkinone

Figure 1: Natural and Synthetic Compounds chemical structures

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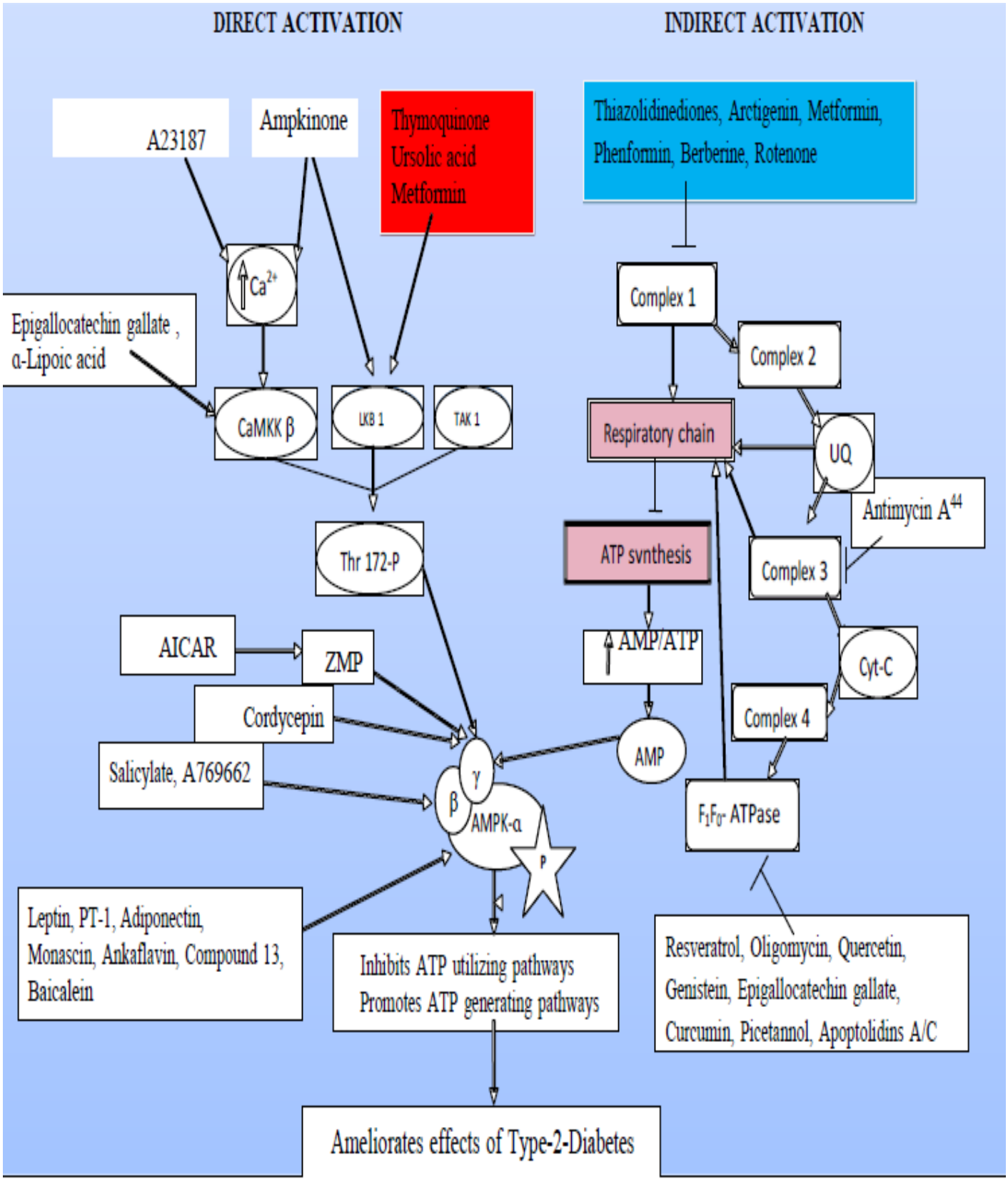

Figure 2: Impact of AMPK pathway in Type-2 Diabetes

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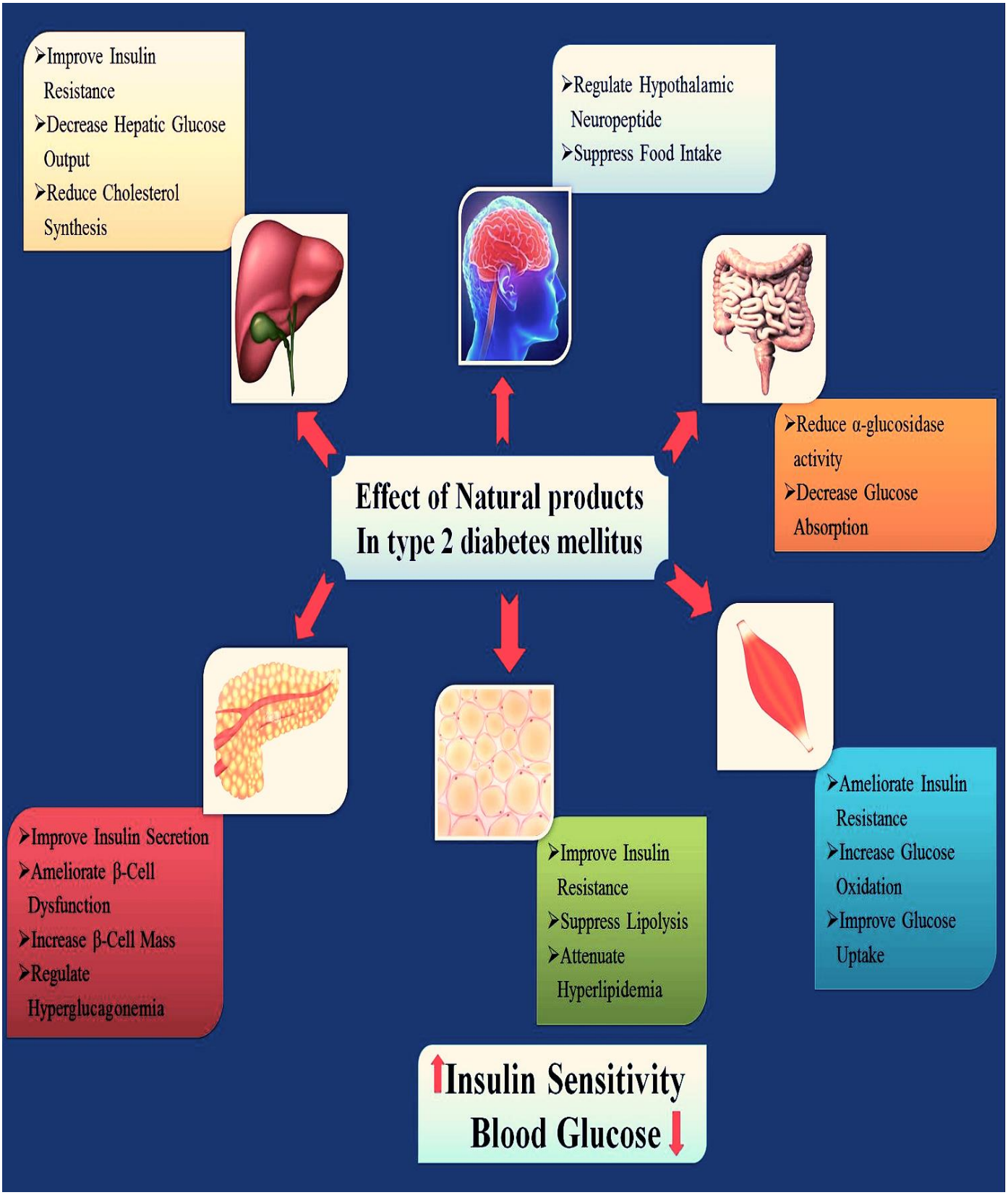

Figure 3: Natural products in Type-2-diabetes mellitus

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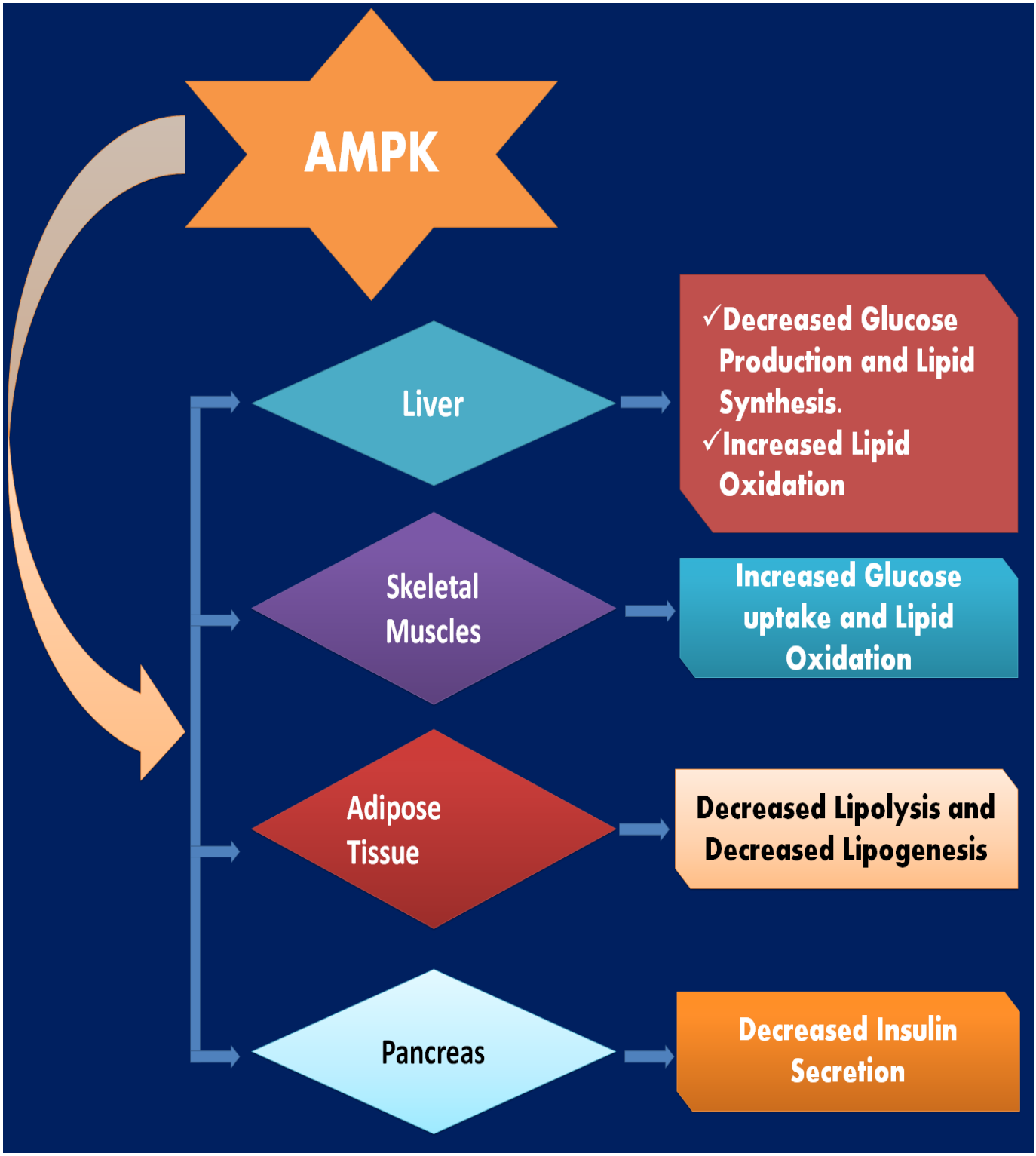

Figure 4: The effect of AMPK on various tissues and organs including liver, skeletal muscles, adipose,
and pancreas in the management of factors associated with glucose homeostasis.

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Graphical Abstract