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AMPK signaling in diabetes mellitus, insulin resistance and diabetic complications: A pre-clinical and clinical investigation

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ABSTRACT

Diabetes mellitus (DM) is considered as a main challenge in both developing and developed countries, as lifestyle has changed and its management seems to be vital. Type I and type II diabetes are the main kinds and they result in hyperglycemia in patients and related complications. The gene expression alteration can lead to development of DM and related complications. The AMP-activated protein kinase (AMPK) is an energy sensor with aberrant expression in various diseases including cancer, cardiovascular diseases and DM. The present review focuses on understanding AMPK role in DM. Inducing AMPK signaling promotes glucose in DM that is of importance for ameliorating hyperglycemia. Further investigation reveals the role of AMPK signaling in enhancing insulin sensitivity for treatment of diabetic patients. Furthermore, AMPK upregulation inhibits stress and cell death in β cells that is of importance for preventing type I diabetes development. The clinical studies on diabetic patients have shown the role of AMPK signaling in improving diabetic complications such as brain disorders. Furthermore, AMPK can improve neuropathy, nephropathy, liver diseases and reproductive alterations occurring during DM. For exerting such protective impacts, AMPK signaling interacts with other molecular pathways such as PGC-

Abbreviations: DM, diabetes mellitus; TID, type I diabetes, TIID, type II diabetes; GM, gestational diabetes mellitus; Hsp90, heat shock protein-90; AMPK, AMP-activated protein kinase; AID, autoinhibition domain; α-CTD, C-terminus domain; CBD, glycogen-binding domain; CaMKK, calcium/calmodulin-dependent protein kinase kinase; TAK1, transforming growth factor-β-activated kinase 1; LKB1, liver kinase B1; mTOR, mammalian target of rapamycin; NAFLD, non-alcoholic fatty liver disease; Aβ, amyloid-beta; NF-κB, nuclear factor-kappaB; GLUT4, glucose transporet 4; IRS1, IR substrate 1; Akt, protein kinase-B; IR, insulin receptor; ACC, acetyl-CoA carboxylase; SIRT1, sirtuin 1; ROS, reactive oxygen species; JTXK, Jiang Tang Ke; DIF-1, differentiation-inducing factor-1; SGs, sesquiterpene glycosides; DEL-1, developmental endothelial locus-1; HO-1, heme oxygenase-1; MOTS-c, mitochondrial-derived peptide; METRNL, meteorin-like protein; AS-IV, astragaloside-IV; LPs, lipopolysaccharide; mTORC1, mTOR complex 1; GSIS, glucose-stimulated insulin secretion; ER, endoplasmic reticulum; CAPE, caffeic acid phenethyl ester; CHS, chikusetsu saponin Iva; I/R, ischemic/reperfusion; MDA, malondialdehyde; nmFGF1, non-mitogenic fibroblast growth factor 1; EETs, epoxyeicosatrinoic acids; SHE, soluble epoxide hydrolase; MH, 4-)-methylhonokiol; TSF, tangshen formula; SOL, Sonchus oleraceus Linn; OEA, oleoylethanolamide; AR, aldose reductase.

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1α, PI3K/Akt, NOX4 and NF-κB among others. Therefore, providing therapeutics based on AMPK targeting can be beneficial for amelioration of DM.

1. Introduction

One of the common diseases in modern world is diabetes mellitus (DM) resulting from a variety of factors including environmental and genetic alterations [1]. This chronic metabolic disease appears to have an increasing trend in coming years, as lifestyle has changed a lot in modern world. Currently, DM is considered as a life-threatening disease and it has various complications such as retinopathy, nephropathy, neuropathy and infertility as well as cardiovascular diseases that should be addressed in DM treatment [2–7]. Overall, DM is categorized into two types including type I diabetes (T1D) and type II diabetes (TIID). There are significant differences between TID and TIID. In TID, β cells of pancreas are destructed and it is considered as an autoimmune disease, leading to insulin secretion interference. However, the insulin levels are high in TIID and cells are resistance to insulin [8,9]. Another kind of DM is gestational diabetes (GM). The other rare kinds of DM include monogenic diabetes and cystic fibrosis-related diabetes (DFRD) [10]. Among various kinds of DM, TIID is the most common one and comprises up to 90% of all DM cases [11–13]. Based on epidemiological studies, DM will affect up to 629 million individuals in 2045, while it affected 425 million people in 2017 [10]. Therefore, managing and treatment of DM should be in priority to improve life quality and prevent development of its complications as well as destructive impacts on major organs of body.

Increasing evidence reveals role of molecular pathways in DM development and its emerging complications. Studies have attempted to identify signaling networks and their therapeutic targeting in DM therapy [14–18]. Inflammation seems to be a predisposing factor for DM development. The microRNA (miRNA)− 29 is able to stimulate inflammation in diabetes, leading to metabolic alterations in DM [19]. As cardiovascular diseases and hypertension commonly occur in DM, molecular pathways have provided a new insight in their treatment. The down-regulation of VE-PTP enhances eNOS phosphorylation to diminish blood pressure and prevent endothelial dysfunction [20]. Besides, heat shock protein-90 (Hsp90) participates in platelet hyperactivity in DM [21]. The Pdia4 can induce β-cell dysfunction and induces cell death that are in favor of DM development [22]. Interestingly, cross-talk among molecular pathways determines responses in DM. For instance, Hedgehog signaling is involved in diabetes-mediated complications and inflammation, while its interaction with Wnt signaling significantly enhances insulin sensitivity in DM [23]. The down-regulation of Wnt-10α, β-catenin and TGF-β by vitamin D improves peripheral neuropathy in DM [24]. Furthermore, STAT3 upregulation induces lung injury in DM [25]. The overexpression of lncRNA MEG8 occurs in DM and stimulates kidney damage [26].

Based on previous statements, molecular pathways mainly involve in DM development and its vital to therapeutically target them. The present review article focuses on the role of AMP-activated protein kinase (AMPK) in DM. For this purpose, we provide an overview of AMPK signaling and its function in disease development. Then, AMPK signaling in insulin resistance, β-cell function and development of diabetes complications are described. Finally, we emphasize on molecular pathways related to AMPK signaling, its therapeutic targeting and evidence based on pre-clinical and clinical studies.

2. AMPK and disease development

2.1. AMPK structure

AMPK is considered a cellular energy sensor and has three unique subunits including α, β and γ [27]. The regulation of AMPK signaling is vital for modulating homeostasis in cells. AMPKα has two subunits as α1 and α2; AMPKβ has also two subunits including β1 and β2l; AMPKγ has three subunits including γ1, γ2 and γ3 [27,28]. AMPK expression is tissue specific and various kinds of factors, for instance stress, can affect AMPK expression. *PRKA1/2*, *PRKAB1/2* and *PRKAG1/2/3* are genes capable of encoding AMPK. As AMPK has various subunits, it is a heterotrimeric complex. Each subunit has various parts that are of importance to be revealed. The α subunit has three well-known parts including a kinase domain at N-terminus end, an autoinhibition domain (AID) and a C-terminus domain (α-CTD). The AID is responsible for inducing kinase inactivation in absence of AMP. The α-CTD has serine residues and phosphorylation of serine 485/491 inhibits AMPK activity. The β subunit comprises of glycogen-binding domain (CBD) and an α and γ subunit interaction domain (β-CTD). The capacity of AMPK in binding to AMP, ADP and ATP results from β-synthase (CBS) domains (CBS1–4).

2.2. AMPK signaling

The activation of AMPK signaling occurs in stressful conditions, when energy is low. The α subunit has a catalytic activity and its phosphorylation at threonine 172 (T172) induces AMPK signaling activation. The calcium/calmodulin-dependent protein kinase kinase (CaMKK) β, transforming growth factor-β-activated kinase 1 (TAK1), and liver kinase B1 (LKB1) are considered as upstream mediators of AMPK signaling and induces T172 phosphorylation in AMPK signaling stimulation [29]. Metabolic stress is capable of triggering AMPK signaling via enhancing AMP levels and reducing ATP levels. The process of AMPK signaling seems to be interesting, as enhanced levels of AMP and ADP in metabolic stress result in AMPK activation by binding to γ subunit and inducing T172 phosphorylation [30]. Noteworthy, AMPK can be activated independent of AMP levels, so that calcium and its accumulation in cells can induce T172 phosphorylation, leading to AMPK upregulation dependent on CaMKKβ. There are endogenous inhibitors of AMPK signaling, and protein phosphatases such as PP2A, PP2Cα, and Ppm1E are able to inhibit AMPK via T172 dephosphorylation [31]. Fig. 1 demonstrates the AMPK signaling activation.

2.3. AMPK signaling in diseases

AMPK signaling is a druggable and potential therapeutic target in disease therapy. The inhibition of apoptosis appears to be promising in inflammatory bowel disease treatment. Dapagliflozin stimulates AMPK phosphorylation to reduce mammalian target of rapamycin (mTOR), leading to autophagy induction and reducing apoptotic cell death [32]. The autophagy induction by AMPK is also of interest in non-alcoholic fatty liver disease (NAFLD) therapy. Kynurenic acid stimulates autophagy via AMPK upregulation to alleviate NAFLD [33]. AMPK upregulation in NAFLD prevents apoptosis via caspase-6 down-regulation [34]. Noteworthy, AMPK function goes beyond regulating cell death. AMPK signaling activation by spermidine prevents inflammation via stimulating anti-inflammatory function of macrophages [35]. The involvement of AMPK signaling in suppressing inflammation is highlighted by a recent experiment, showing that amyloid beta (Aβ) induces inflammation via NLRP3 upregulation. The lychee seed polyphenol administration induces AMPK/autophagy axis to ameliorate inflammation [36]. The process for autophagy activation and preventing NLRP3 inflammasome is based on AMPK upregulation, mTOR down-regulation and subsequent induction of ULK1 [37]. Furthermore, AMPK signaling activation prevents generation of inflammatory factors that is of interest in reducing inflammation [38].

The development of osteoarthritis mainly depends on AMPK

deactivation. In fact, CCAL1 enhances nuclear factor-kappaB (NF-κB) expression to inhibit AMPK signaling and aggravate osteoarthritis [39]. Each experiment provides a unique pathway that shows potential role of AMPK in disease therapy. The activation of AMPK signaling by ginseng appears to be promising in disease therapy. AMPK overexpression prevents lipogenesis and p38 phosphorylation to inhibit MAPK signaling, leading to hepatic inflammation prevention in liver diseases [40]. Mitochondrial biogenesis significantly enhances by AMPK that is of importance for Parkinson's disease therapy [41]. Cervical cancer treatment is based on AMPK signaling. The metformin induces AMPK signaling to promote p53 levels, resulting in cell death in cervical tumor [42]. However, AMPK function in cancer is not certain. Another experiment reveals the role of AMPK overexpression in cervical lesion and lymph node metastasis [43]. AMPK upregulation prevents glucose uptake and induces cycle arrest in breast tumor cells [44].

The AMPK signaling demonstrates close association with inflammation in various diseases. The NF-κB is one of the most well-known downstream targets of AMPK signaling in inflammation process. Simvastatin exerts its anti-inflammatory activity via inducing AMPK signaling, subsequent upregulation of MAPK and inducing a significant decrease in NF-κB expression [45]. Hesperetin also exerts its anti-inflammatory activity via AMPK regulation. By stimulating AMPK/CREB axis, hesperetin induces SIRT1 expression that prevents acetylation of RelA/p65 in suppressing NF-κB signaling and alleviating inflammation [46]. One of the factors responsible for asthma pathogenesis is airway inflammation. Pterostilbene administration diminishes oxidative stress and inflammation in airway to alleviate asthma. For decreasing oxidative stress, pterostilbene induces Nrf2/HO-1 axis, while this therapeutic agent stimulates AMPK/SIRT1 axis to ameliorate inflammation in airway for asthma treatment [47].

An experiment has evaluated association between AMPK signaling and levels of pro-inflammatory cytokines including IL-6 and TNF-α. Based on the findings, metformin induces AMPK signaling to promote SIRT1 expression and then, significant decrease occurs in levels of IL-6 and TNF-α in serum [48]. The IL-1β is another cytokine responsible for inflammation and its levels increase by NLRP3 inflammasome. Urolithin A diminishes inflammation and protects pancreatic β cells via inducing AMPK signaling to reduce NLRP3/IL-1β levels [49]. It is worth mentioning that AMPK signaling has also antioxidant activities that can be of interest for treatment of disorders related to oxidative damage. Emodin administration prevents cell death and oxidative damage in liver cells via inducing AMPK signaling and subsequent phosphorylation of YAP [50].

It has been reported that high-fat diet significantly reduces levels of AMPKα1 in adipocytes to mediate non-alcoholic fatty liver disease development [51]. This is maybe due to function of AMPK in reducing lipid accumulation in liver [52]. Another experiment has exploited salvianolic acid A to stimulate AMPK signaling and upregulate SIRT1 expression as downstream target in protecting hepatocytes against lipotoxicity and preventing fatty liver development [53]. Noteworthy, by increasing SIRT1 expression, AMPK signaling is involved in decreasing Tau phosphorylation and improving memory impairment [54], as Tau hyperphosphorylation can result in development of neurological disorders [55]. Furthermore, in respect to role of AMPK signaling in autophagy induction, its upregulation can pave the way for degrading amyloid-beta and alleviation of neurological disorders [56]. Hence, AMPK signaling functions essentially in various diseases and its targeting seems to be ideal in disease alleviation [43,44,57–63].

3. AMPK signaling and diabetes

3.1. AMPK, glucose uptake and metabolism

One of the challenges in DM treatment is high glucose levels in blood. Therefore, strategies that can reduce glucose levels in blood, ameliorate DM. The aim of current section is to show how AMPK signaling can modulate glucose uptake and metabolism that are of importance in DM treatment. Muscle cells develop insulin resistance and they cannot absorb glucose in DM. The rosemary extract has been shown to participate in enhancing glucose uptake by muscle cells, although these cells have insulin resistance. The mechanism by which rosemary extract enhances glucose uptake by muscle cells is through inducing AMPK phosphorylation. Then, AMPK enhances levels of glucose transporter 4 (GLUT4) to stimulate glucose uptake by muscle cells [64]. Based on this experiment, novel therapeutic strategies can focus on targeting AMPK signaling to promote glucose uptake that partially can alleviate DM and its complications. Another experiment also provides a similar mechanism by asprosin. This protective agent is able to induce AMPK signaling

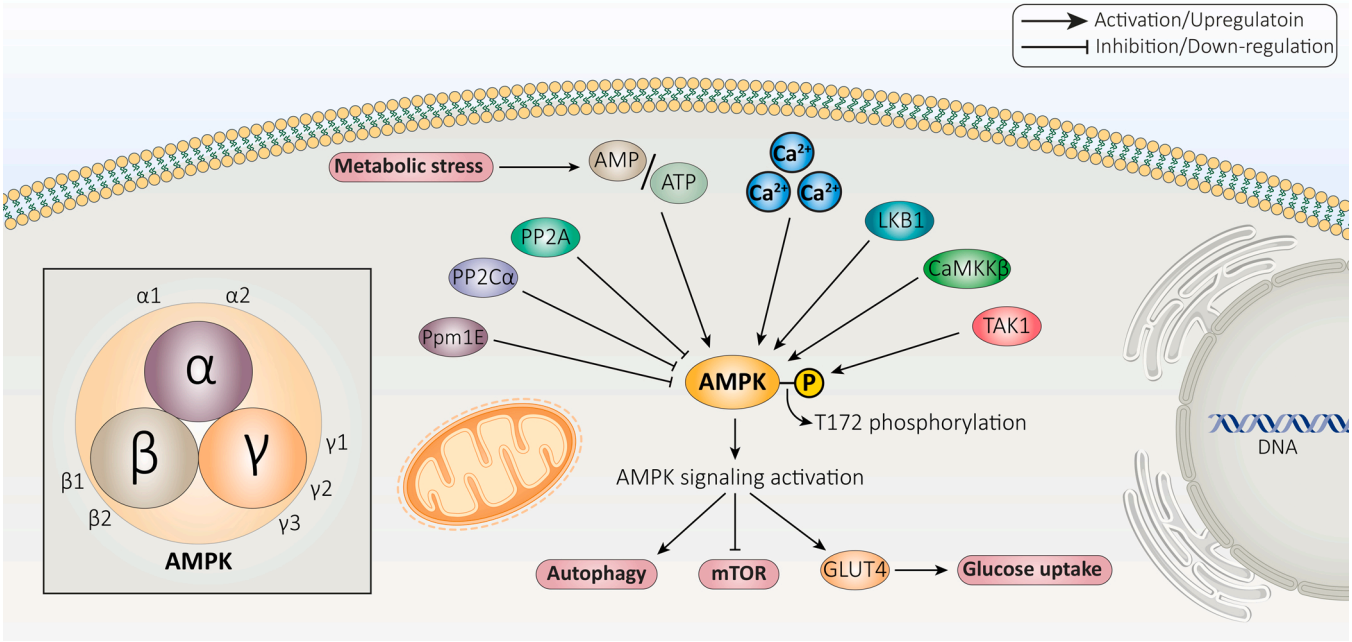

Fig. 1. AMPK signaling activation in cells.

and its phosphorylation in elevating GLUT4 expression, resulting in a significant increase in glucose uptake by muscle cells. Therefore, asprosin may demonstrate therapeutic impacts in TIID [65]. As muscle cells require high amount of energy, inducing glucose uptake by these cells can give promising results in DM therapy. A recent experiment has focused on targeting AMPK signaling in L6 myotubes. Based on the findings of this experiment, promalabaricone B can exert protective impacts during DM via AMPK signaling activation, GLUT4 upregulation and enhancing glucose uptake [66]. These experiments obviously highlight the fact that GLUT4 is a well-known target of AMPK signaling and targeting AMPK/GLUT4 axis can involve in DM treatment via regulating glucose uptake. In addition to GLUT4, GLUT1 is also affected by AMPK signaling in regulating glucose uptake [67]. The GLUT1 is considered as a promising target in DM therapy. The GLUT1 down-regulation alleviates diabetic retinopathy [68]. It has been reported that GLUT1 expression level increases at mRNA and protein levels isonymphaeol B and 3′-geranyl naringenin. For this purpose, isonymphaeol B and 3′-geranyl naringenin induces AMPK signaling to enhance GLUT1 levels in elevating glucose uptake and may be considered as new antidiabetic agents in near future [67]. Therefore, AMPK signaling and glucose transporters located on cell membrane are potential targets for promoting glucose uptake and improving DM [69].

In addition to muscle cells, AMPK signaling can affect glucose transporters in other cell types. In an experiment, C57BL/6 mice were used as animal model and they were fed with normal diet and high-fat diet. The administration of Ganoderma lucidum extract improves conditions in obese mice and diminishes weight gain in liver and fat tissues. This plant-derived natural compound is able to enhance glucose metabolism, decreases lipid accumulation and diminishes adipocyte size. All of these protective impacts are mediated by AMPK signaling as a potential upstream mediator. Based on the results, Ganoderma lucidum extract induces AMPK signaling phosphorylation to enhance expression level of GLUT1, GLUT4, protein kinase-B (Akt), IR substrate 1 (IRS1), insulin receptor (IR) and acetyl-CoA carboxylase (ACC) [70].

Overall, islets, liver and muscle are the main organs responsible for glucose homeostasis in body [71]. The role of muscle cells, targeting AMPK signaling and effect on glucose uptake were discussed previously. Glucose generated by liver and low consumption of glucose by muscles and adipose tissues can participate in hyperglycemia. These factors can jointly lead to occurrence of DM [72]. Up to 90% of glucose produced in the body, is generated in hepatic tissue [73]. Importantly, glucose metabolism dysregulation in liver occurs in TIID [74]. A recent experiment has shown how AMPK signaling and its downstream targets can involve in regulating glucose metabolism. The nano-MitoPBN reduces levels of reactive oxygen species (ROS) to induce AMPK signaling, resulting in PGC-1α upregulation and subsequent mitochondrial biogenesis. Noteworthy, AMPK signaling also induces sirtuin 1 (SIRT1) expression to enhance PGC-1α expression. Then, an increase occurs in metabolism of glucose and its serum levels significantly diminish [75]. The Jiang Tang Ke (JTXK) granules are shown to use a similar pathway in muscle cells. In this way, JTXK induces AMPK signaling to enhance expression level of SIRT1 and PGC-1α as its downstream targets. This axis induces mitochondrial respiration that consumes glucose and also elevates glucose uptake (GLUT4 upregulation) in muscle cells to reduce serum glucose levels, promising results in DM treatment [76].

Most of the experiments have focused on using protective agents in targeting AMPK signaling and promoting glucose metabolism. The differentiation-inducing factor-1 (DIF-1) is an alkylphenone capable of enhancing glucose uptake and metabolism in treatment of DM. By inducing AMPK signaling and its phosphorylation, DIF-1 significantly elevates glucose uptake and metabolism in 3T3-L1 cells to ameliorate DM [77]. This strategy is also beneficial in HepG2 cells. Based on a recent experiment, HepG2 resistant to insulin, do not show glucose uptake and metabolism. The administration of sesquiterpene glycosides (SGs) stimulates AMPK signaling to enhance glucose metabolism and uptake in insulin-resistant HepG2 cells [78]. AMPK signaling can even regulate translocation of GLUT4 as a glucose transporter in cells. It has been reported that AMPK is able to induce phosphorylation of Serine 168 residue of TBC1D17 to enhance Rab5 expression. Then, Rab5 mediates translocation of GLUT4 on myoblasts and skeletal muscles to enhance glucose uptake and reduce serum glucose levels [79] that are of importance in DM treatment. Fig. 2 is a schematic representation of AMPK signaling in glucose uptake and metabolism.

3.2. AMPK and insulin resistance/sensitivity

The insulin resistance is a major complication in DM and is considered as decreased response of peripheral tissues to insulin [80]. The insulin resistance participates in development of TIID [81]. The photobiomodulation is a new therapeutic strategy for DM. The photobiomodulation diminishes hepatic lipogenesis and stimulates insulin sensitivity. The photobiomodulation at 635 nm and 8 J/cm^2 enhances CaMKKβ expression to induce AMPK signaling, resulting in insulin sensitivity [82]. Exercise is beneficial in insulin sensitivity and for this purpose, exercise enhances developmental endothelial locus-1 (DEL-1) expression in skeletal muscle. The DEL-1 overexpression induces AMPK signaling to promote heme oxygenase-1 (HO-1) levels to ameliorate inflammation and mediate insulin sensitivity [83]. Rats with DM demonstrate lipid accumulation and insulin resistance. The ligustilide administration enhances AMPK phosphorylation to mediate insulin sensitivity in rats with DM [84]. Therefore, AMPK signaling activation can be considered as a protective mechanism in DM treatment [85]. Besides, oleuropein stimulates AMPK signaling to reduce insulin, glucose and glycogen levels in gestational diabetes [86]. Therefore, as oleuropein reduces serum levels of insulin, further experiments can focus on role of this agent in mediating insulin sensitivity.

Chrysin is another protective agent that shows therapeutic impacts in diabetes and tumor, and is capable of modulating various molecular pathways [87]. Chrysin administration suppresses insulin resistance and improves oxidative stress and inflammation as well as liver injury. To exert aforementioned protective impacts, chrysin induces AMPK signaling to prevent insulin resistance in HepG2 cells via enhancing IRS-1 overexpression and subsequent induction of Akt [88]. In order to potentially reverse insulin resistance, a combination of exercise and mitochondrial-derived peptide (MOTS-c) is utilized. The MOTS-c is capable of targeting folate cycle in AMPK stimulation. The serum levels of MOTS-c significantly diminish in high fat-diet mice. The PGC-1α down-regulation reduces MOTS-c expression. Furthermore, treadmill training is beneficial in enhancing PGC-1α and MOTS-c levels. A combination of MOTS-c and exercise exerts synergistic impact and enhances PGC-1α expression via AMPK phosphorylation [89]. The application of protective agents targeting AMPK signaling can improve diabetes. The meteorin-like protein (METRNL) is suggested to exert therapeutic impacts in DM. For instance, METRNL reverses insulin resistance and decreases glucose tolerance and weight gain. For these purposes, METRNL enhances AMPK expression. AMPK knock-down abrogates potential of METRNL in suppressing insulin resistance [90].

Each experiment provides a unique pathway in which AMPK signaling follows to reverse insulin resistance and exert its protective impacts in DM. For instance, AMPK signaling reduces NF-κB expression to prevent inflammation [91]. Furthermore, AMPK regulates PI3K/Akt axis to affect inflammation and reduces apoptosis in kidney to prevent nephropathy in TIID [92]. Therefore, understanding such interactions can provide new insight in reversing insulin resistance in DM. A newly published experiment has provided a new axis for anti-diabetic activity of astragaloside IV (AS-IV). The AS-IV administration is associated with AMPK phosphorylation that subsequently reduces mTOR expression to induce autophagy, leading to insulin resistance improvement and preventing liver injury in TIID (ameliorating inflammation and oxidative stress) [93]. The catalpol also affects AMPK signaling in reversing insulin resistance in TIID. The catalpol administration enhances AMPK expression to reduce NOX4 and oxidative stress. The NOX4

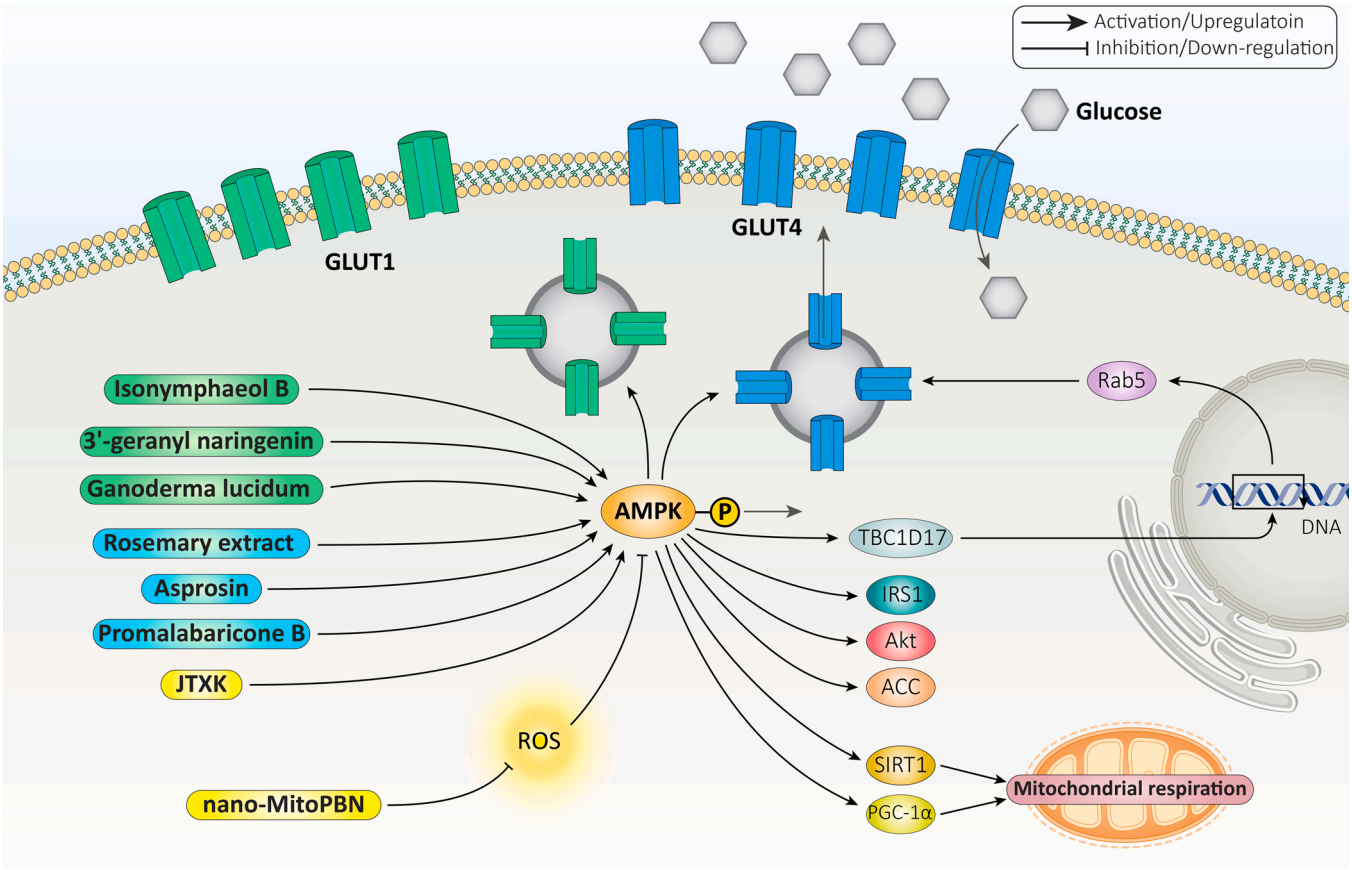

Fig. 2. The involvement of AMPK signaling in regulating glucose uptake and metabolism.

down-regulation leads to stimulation of PI3K/Akt axis that inhibits insulin resistance [94].

One of the important aspects of insulin resistance is the participation of inflammation. It has been reported that lipopolysaccharide (LPS) can induce inflammation in adipocytes via enhancing TNF-α and MCP-1 levels to induce insulin resistance. The administration of β-aminosobutyric acid induces AMPK signaling that prevents lipogenesis and suppresses NF-κB signaling to reduce inflammation, leading to insulin resistance improvement [95]. The potential of LPS in inflammation and mediating insulin resistance can be complicated. The LPS is able to induce M1 polarization of macrophages to enhance levels of pro-inflammatory factors, leading to insulin resistance. Restoring

Table 1
The involvement of AMPK signaling in insulin sensitivity.

Protective agent	In vitro/In vivo	Cell line/Animal model	Study design	Signaling networks	Remarks	Refs
Berberine	In vivo	Mice	50, 100 and 200 mg/kg	LKB1/AMPK/PGC-1α	Upregulation of LKB1 by berberine to induce AMPK signaling Enhancing PGC-1α expression to reverse insulin resistance	[109]
–	In vitro	Neuro-2a cells	–	AMPK/AS160	Silencing tankyrase enhances glucose uptake and mediates insulin sensitivity via inducing AMPK signaling	[110]
Geniposide	In vitro	3T3-L1 cells	10 μM	AMPK/TXNIP	Geniposide induces AMPK phosphorylation to mediate TXNIP degradation and significantly enhances insulin sensitivity	[111]
POCU1b	In vivo	Wistar rat	HFD containing 0.1% or 1.0% POCU1b	–	AMPK signaling activation by POCU1b enhances insulin sensitivity	[112]
–	In vivo	Mice	–	–	Transthyretin inhibits AMPK signaling to mediate insulin resistance and decreases potential of exercise in diabetes treatment	[113]
–	In vitro	HUVECs	–	miRNA-3138/KSR2/AMPK/GLUT4	miRNA-3138 induces insulin resistance via down-regulation of KSR2 to prevent AMPK signaling activation, leading to GLUT4 inhibition	[114]
Patchouli alcohol	In vitro	C2C12 and HepG2 cells	0–30 μg/mL	AMPK/SIRT1	Overexpression of SIRT1 by AMPK signaling Decreasing inflammation to prevent insulin resistance	[115]
Metformin	In vitroIn vivo	Cardiomyocytes Mice	5, 10 and 20 μM 250 mg/kg	AMPK/Akt/GLUT4	Metformin enhances Akt phosphorylation via inducing AMPK signaling to promote GLUT4 expression, leading to glucose uptake and insulin sensitivity	[116]
Spexin	In vivo	Rat	50 μg/kg/day	–	Spexin induces AMPK signaling to partially reduce inflammation and reverse dyslipidemia and insulin resistance	[117]
A,β-amyrin	In vivo	Mouse model of NAFLD	10 mg/kg	AMPK/mTORC1/SREBP1	AMPK signaling induction reduces mTORC1 and SREBP1 levels to prevent insulin resistance and can be considered as a therapeutic agent in DM treatment	[118]

FNDC5 expression stimulates AMPK signaling to prevent M1 polarization of macrophages by LPS, resulting in inflammation resolution and subsequent insulin resistance reversion [96].

Crocin is another agent capable of regulating insulin sensitivity in TIID. The crocin administration enhances AMPK expression to suppress CDK5/PARPγ axis, elevating insulin sensitivity [97]. The naringenin prevents insulin resistance, enhances glucose uptake and alleviates inflammation and oxidative stress via AMPK signaling activation [98]. Overall, studies demonstrate that insulin resistance in DM significantly enhances serum levels of glucose and to improve this condition, AMPK signaling activation is recommended (Table 1) [99–108]. Fig. 3 shows involvement of AMPK signaling in insulin sensitivity.

3.3. AMPK and β-cell function

Another implication of AMPK signaling can be investigated in regulating β cell function and apoptosis. For instance, AMPK signaling activation prevents apoptosis in β cells and improves its function in decreasing lipid accumulation [119]. As β cell dysfunction occurs in DM, this section is allocated to understanding AMPK signaling role in β cell function. Notably, the switch from mTOR signaling to AMPK is vital for pancreatic β cells to obtain their function and mature. Furthermore, AMPK signaling induction during weaning is necessary for adult β cell phenotype and for this purpose, AMPK suppresses mTOR complex 1 (mTORC1) signaling. The mTOR signaling inhibition prevents maturation of β cells and provides an abnormal phenotype. Furthermore, switch from mTOR to AMPK signaling appears to be essential for metabolic profile of β cells and AMPK is capable of inducing mitochondrial biogenesis in β cells. Based on this experiment, DM development results from AMPK down-regulation and mTORC1 induction. Furthermore, as β cells have ability of glucose-stimulated insulin secretion (GSIS), their abnormal function results in DM. Furthermore, AMPK down-regulation leads to mitochondrial degeneration and paves the way for DM development [120]. Hence, AMPK signaling is the first step for maturation and proper function of β cells. The protective agents can be beneficial in affecting AMPK signaling, so that O304 as a PAN-AMPK activator diminishes β cell stress and enhances rest of β cells that are of importance in treatment of TIID [121].

Understanding AMPK and mTORC1 switch seems to have clinical translation. β cell function and its mature phenotype result from mTORC1 switch to AMPK. Therefore, factors involved in AMPK to mTORC1 switch may result in de-differentiation of β cells and pave the way for TIID development. An experiment has shown how milk consumption can induce development of TIID via affecting mTORC1 and AMPK signaling pathways. Based on this experiment, milk contains exosomal miRNAs that regulate mTORC1-AMPK switch. The milk has high levels of exosomal miRNA-148a that suppresses AMPK signaling and enhance mTORC1 levels to induce de-differentiation of β cells, mediate endoplasmic reticulum (ER) stress and prevent capacity of β cells in insulin secretion. Notably, bacterial fermentation, boiling or ultra-heat treatment are able to suppress and degrade exosomal miRNAs in milk and prevent development of TIID [122]. In respect to role of miRNAs in different biological mechanisms [123–126], more investigations are required regarding their role in modulating AMPK signaling and DM treatment.

Caffeic acid and its derivative caffeic acid phenethyl ester (CAPE) have received much attention in recent years due to their great pharmacological activities including antidiabetic, antioxidant, anti-inflammatory and more importantly, anti-cancer [127]. An experiment has evaluated the role of CAPE-pNO$_2$ as a new derivative of CAPE in treatment of DM. The CAPE-pNO2 administration in obese and diabetic mice improves DM and prevents insulin resistance. Furthermore,

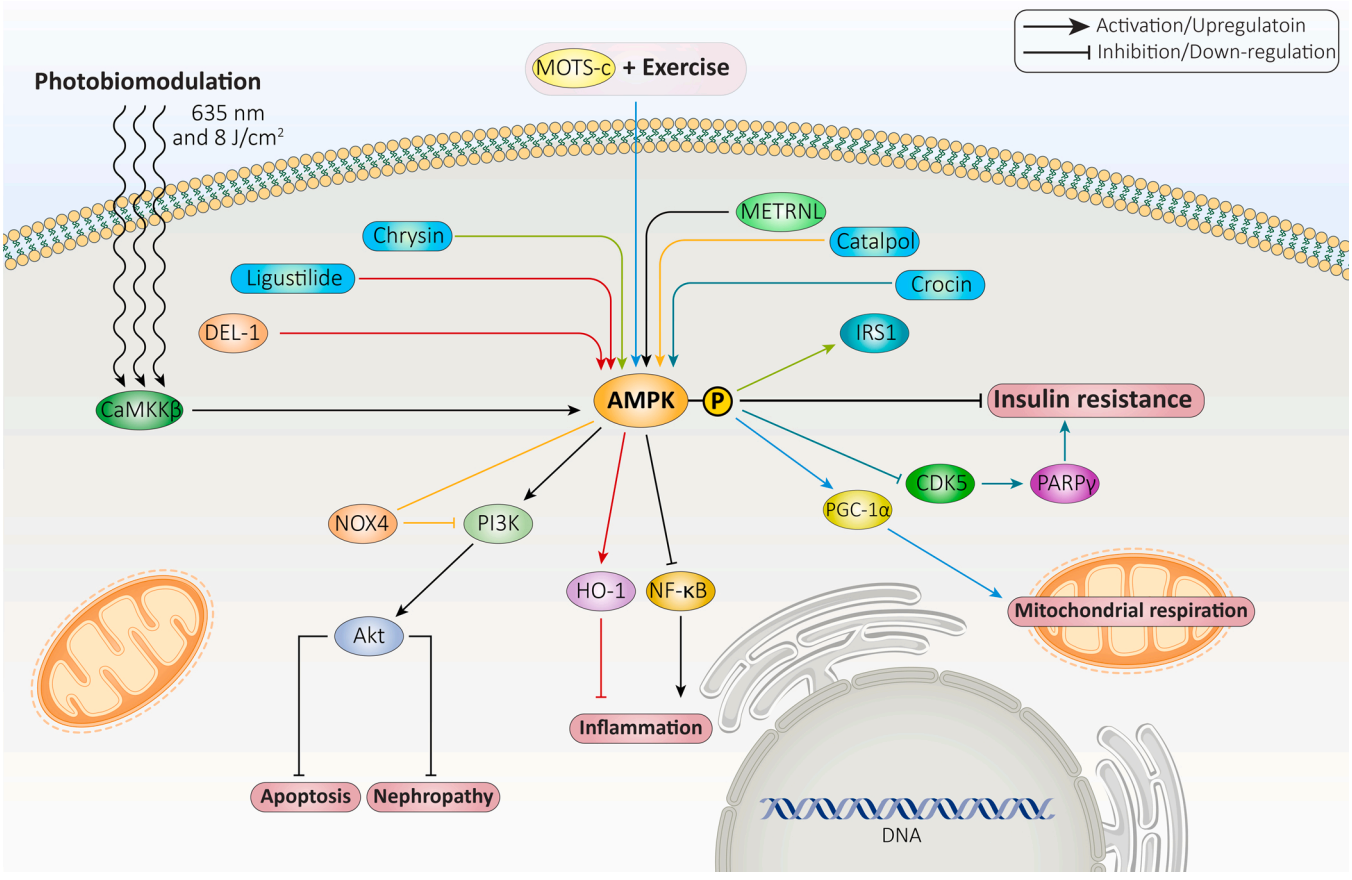

Fig. 3. AMPK and its association with insulin sensitivity.

CAPE-pNO2 is able to enhance viability of β cells and also, islet mass. Mechanistically, CAPE-pNO2 induces AMPK signaling to elevate GLUT4 expression. Then, a significant decrease occurs in GSK-3β expression to promote PARPα levels, leading to an increase in survival of β cells [128].

One of the underlying mechanisms responsible for β cell death is oxidative stress. The ROS overgeneration leads to oxidative damage in pancreatic β cells. The salidroside administration is associated with a significant decrease in ROS generation, oxidative stress alleviation, improving mitochondrial membrane potential, NOX2 down-regulation and JNK/caspase-3 axis inhibition that all together, can promote survival of β cells. Now, this question comes into mind that what is the function of AMPK signaling in these processes? Notably, oxidative stress in DM induces FOXO1 expression to mediate nuclear translation of PDX1 and stimulates β cell dysfunction. The salidroside administration triggers AMPK signaling to suppress FOXO1/PDX1 axis, improving β cell function and survival [129]. Due to the role of AMPK in improving antioxidant defense system, it is a potential therapeutic target in DM treatment. The morin administration is advantageous in protecting β cells against apoptosis via decreasing ROS generation, reducing PARP expression, enhancing NADPH levels and preventing cell death. For this purpose, morin induces AMPK signaling to mediate nuclear translocation of FOXO3. The inhibition of AMPK/FOXO3 axis abrogates protective impacts of morin. Therefore, AMPK signaling activation seems to be essential for protective impacts of morin on β cells and preventing DM development [130]. The best way for treatment of TIID is to maintain proper function of β cells and their capacity in secreting insulin. The irisin administration induces AMPK signaling to improve β cell function and prevent apoptosis as well as to preserve their ability in insulin secretion that are of interest in TIID treatment [131].

Kaempferol is another protective agent that has potential in enhancing β cell [132]. Kaempferol demonstrate protective and anti-cancer activities via regulating ER stress [133]. Kaempferol administration induces AMPK signaling to reduce mTOR expression, resulting in lipophagy. With this pathway, kaempferol prevents ER stress and improves β cell function via preventing cell death [132]. Previously, we mentioned that AMPK can induce SIRT1 expression in regulating glucose uptake and metabolism. Noteworthy, SIRT1 has been shown to participate in modulating AMPK expression. The SIRT1 induces AMPK signaling to enhance fatty acid oxidation, leading to neurogenin 3 overexpression, β cell restoration and endocrine progenitor differentiation [134].

Cholesterol accumulation can induce damages in β cells. Therefore, preventing internalization and entrance of cholesterol can be beneficial in preventing β cell damage and DM development. AMPK overexpression by GLP-1 reduces PARP-1 expression, while it enhances ABCA1 expression in an LXR-dependent manner. ABCA1 is a transporter and provides cholesterol efflux to significantly diminish its levels, leading to a decrease in β cell damage [135]. AMPK is well-known due to its capacity in stimulating autophagy. Autophagy modulators have received much attention in treatment of DM [8]. ROS overgeneration enhances AMPK expression to induce autophagy. Then, autophagy functions as pro-survival mechanism and protects β cells against cell death [136]. High glucose levels in diabetes are also responsible for β cell dysfunction. Pioglitazone induces AMPK signaling to enhance glutathione levels via TRAP1-GLS1 upregulation. Furthermore, activated AMPK signaling prevents mTORC1 signaling. These molecular pathways lead to inhibition of ER and mitochondrial stresses to prevent apoptosis in β cells [137]. Therefore, studies are in line with the fact that AMPK signaling activation is of interest for protecting β cells, preventing their dysfunction and inhibiting DM development (Table 2) [138–145]. Fig. 4 provides an overview of AMPK signaling in β cell function.

4. AMPK and diabetic complications

4.1. Neuropathy

The most common complication of DM is diabetic neuropathy [154–156]. The development of diabetic neuropathy has been observed in 60–70% of patients [157]. The emergence of diabetic neuropathy can occur in any stage of life, but its incidence rate and severity increase by age and longer duration of DM. It has been reported that diabetic neuropathy is high in patients having DM for at least 25 years. There are various factors responsible for diabetic neuropathy development including metabolic alterations, autoimmune factors, neurovascular factors, lifestyle and nerve injury among others that lead to nerve damage [158–161]. The diabetic neuropathy is divided into three major kinds including peripheral neuropathy, autonomic neuropathy and proximal neuropathy. In the peripheral neuropathy, nerves are affected in which sensation, movement, gland and organ functions are impaired. In the autonomic neuropathy, autonomic nervous system is negatively affected and normal function of internal organs such as bladder muscles, cardiovascular system and genital organs are impaired. The proximal neuropathy also affects legs, hips and thighs and it is also called diabetic amyotrophy.

Brain and neurons are negatively affected by DM. There are some major underlying mechanisms responsible for neuropathy during DM that oxidative stress, inflammation and apoptosis are among them. Therapeutic agents targeting these molecular mechanisms can be

Table 2
AMPK signaling, β cell function and cell death.

Protective agents	In vitro/ In vivo	Cell line/ Animal model	Study design	Signaling networks	Remarks	Refs
–	In vitro	INS-1 cells	–	Adiponectin/ AMPKα1	Enhancing insulin secretion capacity of β cells and preventing apoptosis Adiponectin induces AMPKα1 for exerting its protective impacts	[146]
Phenylchromane derivative	In vitro	INS-1E cells	5, 10 and 25 μM	LKB1/AMPK	Increasing insulin secretion ability of β cells in a time- and concentration-dependent manner Inducing AMPK signaling via LKB1 upregulation	[147]
Metformin	In vitro	INS-1 cells	1, 5, 10, 20, and 40 μmol/L	AMPK/SIRT1/ PGC-1α	Inducing AMPK phosphorylation to promote SIRT1 levels Upregulation of PGC-1α to enhance irisin level Preventing apoptosis and inducing autophagy in enhancing survival and function of β cells	[148]
Ficus carica	In vitro In vivo	MIN6 cells Mice	20, 40, 60 and 80 μmol/L 2 g/kg	AMPK/JNK/ caspase-3	Inhibition of AMPK/JNK/caspase-3 axis prevents apoptosis and oxidative stress in β cells and promotes their survival rate	[149]
Compound K	In vitro	MIN6 cells	0–32 μM	AMPK/JNK	Decreasing JNK expression via inhibiting AMPK signaling leads to apoptosis inhibition in β cells	[150]
Visfatin	In vitro	RINm5F cells	1–1000 ng/mL	–	Enhanced phosphorylation of AMPK by visfatin in preventing apoptosis	[151]
Epigallocatechin gallate	In vitro	RINm5F cells	0–10 μM	–	Inducing AMPK signaling to improve mitochondrial function and prevent activity of lipogenic enzymes	[152]
–	In vitro	MIN6 cells	Not reported	AMPK/mTOR	Asprosin induces apoptosis in β cells and significantly decreases their survival Asprosin inhibits autophagy to sensitize β cells to apoptosis Asprosin induces mTOR signaling via AMPK down-regulation to suppress autophagy	[153]

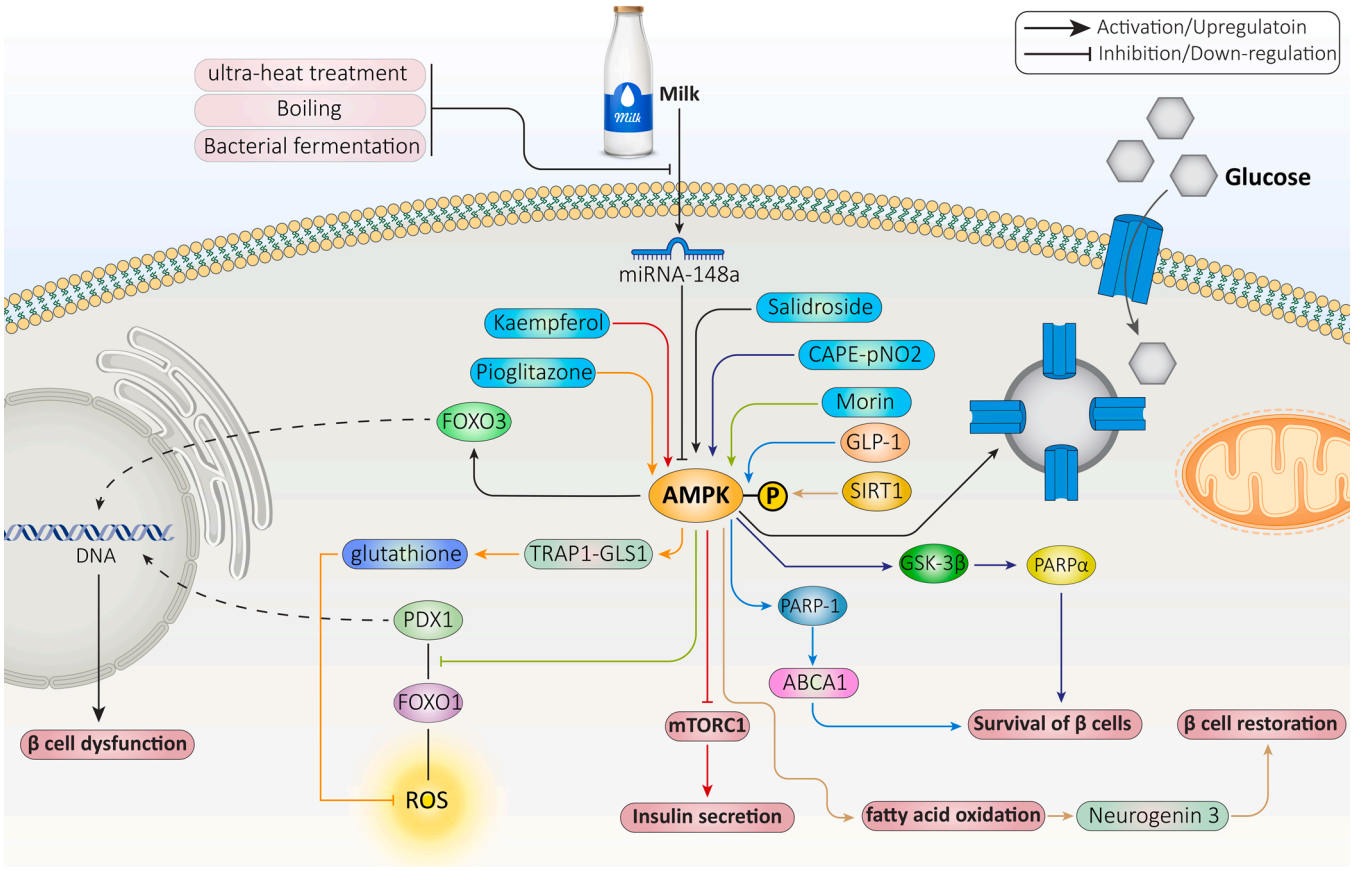

Fig. 4. AMPK signaling in center of regulating β cell function and survival.

advantageous in ameliorating diabetic neuropathy. The purpose of current section is to investigate AMPK signaling function in regulating diabetic nephropathy. The down-regulation of AMPK is correlated with brain damage in diabetic animal models. The Cdk5 is capable of phosphorylating AMPK at Thr485 to reduce its activity and aggravate brain damage. The mutation of Thr485 to alanine prevents AMPK down-regulation by Cdk5 and paves the way for alleviating diabetic nephropathy [162]. There have been efforts in recognition of agents with ability to target AMPK signaling in DM. The berberine administration (20 and 40 mg/kg) diminishes aldose reductase, glycated hemoglobin, serum insulin, hepatic cholesterol and triglyceride levels. Furthermore, berberine decreases oxido-nitrosative stress and enhances Na-K-ATPase and Ox levels. To exert such protective effects and decreasing diabetic neuropathy, berberine promotes AMPK expression level [163].

Hyperglycemia in TIID patients promotes risk of death in stroke [164,165]. Furthermore, TIID patients mainly demonstrate signs of cerebral ischemic/reperfusion (I/R) injury [166]. Chikusetsu saponin IVa (CHS) seems to be effective in alleviating cerebral I/R injury in DM. CHS decreases infarct size and prevents cell injury in I/R. CHS inhibits apoptosis and significantly decreases caspase-3, malondialdehyde (MDA), TNF-α and Bax levels in ameliorating cerebral I/R injury in DM. In this way, CHS enhances adiponectin levels to enhance AdipoR1 expression, leading to overexpression of AMPK and its downstream target GSK-3β [167]. Therefore, the chance of stroke is completely high in DM and its management and treatment are of importance. The non-mitogenic fibroblast growth factor 1 (nmFGF1) improves glucose and metabolic alterations to prevent stroke and brain damage in DM. Furthermore, nmFGF1 promotes AMPK expression to stimulate angiogenesis [168]. These impacts significantly reduce brain damage in DM and prevent stroke.

One of the impediments that modulates entrance of agents to brain is blood-brain barrier. This barrier has been composed of endothelial cells that have tight junction among them and are tough impediment against entrance of agents to brain [169–171]. The pre-clinical and clinical experiments have revealed that DM can impair proper function of BBB via inducing oxidative stress [172,173]. The epoxyeicosatrienoic acids (EETs) show protective impacts on BBB and their degradation by soluble epoxide hydrolase (sEH) enzyme which can induce BBB impairment. High levels of sEH and low levels of EETs enhance vascular permeability of BBB. T-AUCB as inhibitor of sEH, maintains BBB integrity in DM. Mechanistically, t-AUBC induces AMPK signaling to enhance HO-1 levels, leading to a significant decrease in ROS generation and promoting EETs levels to prevent BBB dysfunction in DM [174]. An interesting experiment has shown that mitochondrial dysfunction is in prior to AMPK down-regulation in mediating neuropathy in DM. The high glucose levels impair normal and appropriate function of mitochondria to reduce p-AMPK and Akt levels (AMPK/Akt axis). The loss of mitochondrial component and insulin resistance occur that mediate metabolic alterations and neuropathy in DM [175]. Based on these studies, AMPK signaling activation is of interest in decreasing diabetic neuropathy (Table 3) [176,177].

4.2. Nephropathy

Another diabetic complication is nephropathy that impairs normal function of kidneys. Targeting AMPK signaling seems to be beneficial in alleviating nephropathy in DM. A recent experiment has exploited klotho for ameliorating nephropathy in mice and the molecular pathway is unique. Klotho reduces ROS generation, glucose levels in serum and obesity to prevent development of diabetic complications. Klotho improves mitochondrial recovery in renal tubular cells and reduces albuminuria. Mechanistically, klotho induces AMPK phosphorylation in a LKB1 manner to upregulate PGC-1α expression, resulting in suppression of mTOR/TGF-β signaling. These signaling networks prevent

Table 3
Targeting AMPK signaling in alleviating diabetic neuropathy.

Protective agent	In vitro/ In vivo	Cell line/ Animal model	Study design	Signaling network	Remark	Ref
Donepezil	In vivo	Mice	1, 2 and 4 mg/kg	–	Preventing neuronal degeneration and inflammation Ameliorating swollen myelin sheath Inducing AMPK signaling among molecular pathways	[178]
Gentiopicroside	In vivo	Rat	50 mg/kg	PPAR-γ/AMPK/ACC	Decreasing hyperalgesia and prolonged paw withdrawal latency to heat and cold stimuli Decreasing dyslipidemia Improving nerve blood flow, MNCV and SNCV Enhancing AMPK expression via PPAR to inhibit ACC	[179]
–	In vivo In vitro	RatDRG neurons	–	IGF-1/AMPK	IGF-1 induces AMPK signaling to improve mitochondrial function and enhance axonal outgrowth Protecting against diabetic neuropathy	[180]
Metformin	In vivo	Rat	300 mg/kg	–	The activation of AMPK signaling by metformin exerts anti-inflammatory activity and significantly reduces levels of IL-6 and TNF-α	[181]
J147 (curcumin derivative)	In vivo In vitro	RatRSC96 cells	10 μM	AMPK/ TRPA1	Improving diabetic nephropathy via inducing AMPK signaling to reduce TRPA1 levels	[182]
Quercetin	In vitro In vivo	RatRSC96 cells	30 and 60 mg/kg	AMPK/PGC-1α	Preventing mitochondrial abnormality and improving diabetic nephropathy via AMPK upregulation and subsequent overexpression of PGC-1α	[183]

mitochondrial damage and oxidative stress in renal cells [184]. Oxidative stress and inflammation during DM can result in renal fibrosis. To decrease oxidative stress, 4-O-methylhonokiol (MH) induces Nrf2/SOD2 axis. The activation of AMPK signaling enhances PGC-1α expression, resulting in CPT-1B overexpression and preventing lipid dysfunction. This axis not only reduces oxidative stress, but also induces fatty acid oxidation to mediate lipid metabolic improvement [185]. Overall, preventing apoptosis and oxidative stress, and inducing protective autophagy are of importance for ameliorating diabetic nephropathy. Such mechanism is followed by cinacalcet in DM treatment. For this purpose, cinacalcet enhances Ca^{2+} levels in cells to induce AMPK phosphorylation in a CaMKKβ-LKB1 manner. Then, an increase occurs in levels of eNOS, Bcl-2 and SOD to prevent stress in renal cells including podocytes and HGECs. By affecting this signaling network, cinacalcet decreases albuminuria without affecting glucose levels and significantly inhibits oxidative damage and apoptosis [186]. However, it should be noted that high Ca^{2+} levels in renal cells may induce apoptosis. Therefore, cinacalcet should be utilized at an optimal concentration for ameliorating diabetic nephropathy.

One of the mechanisms responsible for reducing oxidative stress is Nrf2 signaling [187,188]. Noteworthy, AMPK can function as upstream mediator of Nrf2 in enhancing antioxidant defense system and preventing oxidative damage [189,190]. The activation of Nrf2 signaling significantly diminishes oxidative DNA damage in diabetes. In this case, upregulation of AMPK by AICAR is vital. Then, overexpression leads to raptor phosphorylation at Ser792 that is beneficial in inducing Nrf2 signaling, resulting in OGG1 upregulation and preventing oxidative damage in renal cells [191]. Based on experiments, AMPK signaling activation is advantageous in reducing both oxidative stress and inflammation in kidney. Geniposide shows protective impact in diabetic mice and prevents nephropathy. Geniposide diminishes albuminuria, podocyte loss, glomerular and tubular injury, inflammation and fibrosis in diabetic animal models. To exert these protective impacts, geniposide induces AMPK signaling to significantly enhance ULK1 expression, leading to autophagy induction. Furthermore, AMPK overexpression suppresses AKT function to prevent oxidative stress, inflammation and fibrosis in kidney of diabetic mice [192]. Another study reveals that AMPK signaling can prevent synthesis of NADPH via inhibiting H6PD to ameliorate diabetic nephropathy [193]. Overall, experiments highlight the fact that overexpression of AMPK is beneficial in reducing diabetic nephropathy mainly via decreasing oxidative stress, inflammation and fibrosis (Table 4) [194–196].

4.3. Liver diseases

Another organ that is negatively affected by DM is liver. Similar to other tissues, inducing AMPK signaling is beneficial in ameliorating injury. Tangshen formula (TSF) significantly decreases lipid deposition in hepatic cells. TSF prevents development of hepatic steatosis via inducing AMPK signaling. Then, AMPK promotes SIRT1 expression to

Table 4
The involvement of AMPK signaling in diabetic nephropathy and its protective impact.

Protective compound	In vitro/ In vivo	Cell line/ Animal model	Study design	Signaling network	Remark	Ref
Vitexin	In vivo	Mice	15, 30 and 60 mg/kg	AMPK/ACC	Enhancing AMPK levels to reduce ACC expression, ameliorating diabetic nephropathy	[197]
Empagliflozin	In vivo	Mice	10 mg/kg	AdipoR1/ AMPK/p-ACC	Reducing lipid deposition fibrosis and renal tubular atrophy Empagliflozin enhances protein levels of AdipoR1 Inducing AMPK signaling to enhance p-ACC and inhibiting ACC levels	[198]
–	In vitro In vivo	BUMPT cells Mice	–	STC-1/AMPK/ SIRT3	The protective role of STC-1 in alleviating diabetic nephropathy Decreasing oxidative stress Inducing AMPK/SIRT3 axis to reduce BNIP3 expression	[199]
Glycyrrhizic acid	In vivo	Mice	15 mg/kg	AMPK/SIRT1/ PGC-1α	Preventing oxidative stress and kidney damage Stimulation of AMPK signaling and its downstream targets including SIRT1 and PGC-1α	[200]
Cyclocarya paliurus	In vivo In vitro	Diabetic rat HK-2 cell	40 and 160 mg/kg	AMPK/mTOR/ autophagy	AMPK upregulation decreases mTOR expression, leading to autophagy and preventing apoptosis and renal cell injury	[201]
Polysaccharide derived from okra	In vivo	Mice	200 and 400 mg/kg	AMPK/SIRT/ PGC-1α	Decreasing apoptosis via Bcl-2 upregulation, and caspase-3 and Bax down-regulation Improving antioxidant activity of enzymes including SOD, GSH and CAT Preventing oxidative stress The induction of AMPK/SIRT1/PGC-1α induces Nrf2/HO-1 axis in preventing kidney damage	[202]
Huayu Tongluo	In vivo	Rat	4.59 and 13.5 mg/kg	AMPK/Nrf2	Decreasing oxidative stress and inflammation Enhancing Nrf2 expression via inducing AMPK signaling	[203]
Resveratrol	In vivo	Mice	40 mg/kg	AMPK/NOX4/ ROS	Resveratrol enhances AMPK expression to down-regulation NOX4, leading to ROS production inhibition	[204]
Salidroside	In vivo	Rat	100 mg/kg	AMPK/SIRT1	Preventing ROS generation Decreasing acetylation of p53 and FOXO-1Enhancing GSH and Bcl-2 levels Salidroside induces AMPK signaling to enhance SIRT1 expression	[205]

stimulate autophagy and ameliorate liver steatosis in DM in vitro and in vivo [206]. Another experiment also advocates protective role of autophagy in alleviating diabetic complications by focusing on a unique molecular pathway. Dapagliflozin triggers autophagy to decrease liver steatosis. In this way, dapagliflozin induces AMPK signaling to decrease mTOR expression for stimulating autophagy and improving liver steatosis [207]. As it was mentioned, AMPK can function as upstream regulator of SIRT1 in decreasing liver injury [206]. Notably, SIRT1 can also function as upstream mediator of AMPK in DM. The fucoidan with low molecular weight has shown capacity in ameliorating liver injury in diabetic mice. Fucoidan enhances activity of antioxidant enzymes including SOD and catalase to ameliorate hepatic oxidative stress. Besides, fucoidan promotes lipid peroxidation and adiponectin as anti-inflammatory factor. These hepatoprotective impacts of fucoidan in DM are mediated via enhancing SIRT1 expression to induce AMPK signaling, leading to PGC-1α down-regulation and subsequent resolution of oxidative stress and inflammation [208].

It is worth mentioning that insulin resistance and TIID are risk factors for development of NAFLD [209–211]. An experiment has revealed protective impact of salidroside in alleviating high fat-induced NAFLD. Salidroside decreases obesity, alters glucose level and lipid accumulation, and enhances insulin sensitivity. Salidroside is beneficial in reducing oxidative stress and inflammation in DM. To exert such protective impacts, salidroside induces AMPK signaling to significantly reduce expression level of TXNIP and its downstream target of NLRP3 inflammasome [212]. Besides, AMPK can recover glucose homeostasis in diabetic liver. Sonchus oleraceus Linn (SOL) diminishes plasma levels of glucose by 23%. SOL inhibits AMPK/Akt axis to down-regulate GSK-3β that is in favor of restoring insulin sensitivity [213]. This experiment provides new insight about role of AMPK signaling and shows that AMPK down-regulation is of importance in insulin sensitivity. Therefore, more studies are required to confirm results of this experiment [213].

The glycogen synthesis and glucose uptake demonstrate positive association in physiological background [214,215]. However, glycogen synthesis shows a decrease in insulin resistance that prevents conversion of circulating glycogen [216]. Furthermore, high hepatic glucose generation by gluconeogenesis leads to hyperglycemia in insulin resistance conditions [217]. Therefore, targeting both glucose synthesis and gluconeogenesis is of importance in DM treatment. Oleoylethanolamide (OEA) shows potent antidiabetic activity via stimulating glucose synthesis and suppressing hepatic gluconeogenesis. Mechanistically, OEA upregulates LKB1 expression to induce AMPK signaling in TIID [218]. Therefore, interaction between AMPK and molecular pathways and mechanisms provides its hepatoprotective impact in DM and most of the experiments have shown beneficial impact of AMPK signaling induction (Table 5) [219–224].

4.4. Cardiovascular diseases

The risk of cardiovascular diseases seems to be high in DM and several mechanisms including oxidative stress and inflammation among others, have been identified to be involved in heart injury. Targeting AMPK signaling is advantageous in ameliorating heart injury and cardiomyopathy in DM. NLRP3 inflammasome is responsible for inducing inflammation and injury in heart during DM. After NLRP3 inflammasome upregulation, an increase occurs in levels of IL-1β, IL-6 and IL-8 to stimulate inflammation. Furthermore, NLRP3, ASC and pro-caspase-1 complex can induce caspase-1 expression. The dapagliflozin and ticagrelor as antidiabetic agents are able to significantly enhance AMPK expression to down-regulate NLRP3, leading to inflammation resolution and preventing cardiomyopathy in DM [232]. Both antioxidant and lipid-lowering impact of AMPK signaling have made it an appropriate option in DM treatment. To exert its antioxidant activity, AMPK signaling enhances Nrf2 expression. Noteworthy, FGF21 functions as upstream mediator to elevate Akt2 expression, leading to GSK-3β down-regulation. Then, an increase occurs in Fyn expression to stimulate Nrf2 signaling for exerting antioxidant activity and preventing oxidative damage in heart. The CAT, HO-1, NQO1 and SOD-1 are among antioxidant enzymes activated by AMPK/Akt/Nrf2 axis to protective heart against oxidative damage. The AMPK activation by FGF21 inhibits CD36/FATP and induces ACC phosphorylation to prevent lipid deposition and increase of fatty acid β-oxidation that are beneficial for decreasing cardiac apoptosis and alleviating inflammation, hypertrophy and fibrosis in heart [233].

Hyperglycemia can induce endothelial dysfunction as a risk factor for cardiovascular disease development in DM. Endothelial cells preserve cardiovascular homeostasis and they are responsible for providing an impediment between lumen and wall of vessels. However, the oxidative stress resulting from hyperglycemia can induce endothelial cell dysfunction [234–236]. The aldose reductase (AR) meditates oxidative stress and ROS overgeneration in impairing endothelial cell function and promoting Bax/Bcl-2 ratio and caspase-3 expression. Mechanistically, silencing AR results in SIRT1 upregulation to promote AMPKα1 phosphorylation, leading to a significant decrease in mTOR phosphorylation [237].

DM and its positive association with myocardial inflammation can lead to pyroptosis [238,239]. Pyroptosis is a kind of cell death with

Table 5
AMPK signaling and its hepatoprotective impact in DM.

Protective agent	In vitro/ In vivo	Cell line/ Animal model	Study design	Signaling network	Remark	Ref
Irbesartan	In vivo	Mice	50 mg/kg	AMPK/Akt/mTOR	Decreasing lipid level in serum and liver Preventing hepatic steatosis Autophagy induction via upregulation of AMPK and subsequent inhibition of Akt/mTOR axis	[225]
Linggui Zhugan Decoction	In vivo	Rat	4.625, 9.25 and 18.5 g/kg/day	PI3K/Akt/mTOR/ S6K1/AMPK/PGC-1α	Decreasing blood glucose and recovering its homeostasis Decreasing fasting insulin Reducing total cholesterol, triglyceride, and low-density lipoprotein cholesterol Improving inflammation Decreasing TNF-α and IL-6 Restoring tissue structure of liver and pancreas	[226]
Red pepper	In vivo	Mice	200 mg/kg	–	Inducing AMPK phosphorylation is partially involved in antidiabetic impact and decreasing fasting glucose and inflammation	[227]
PSTi8	In vivo	Mice	2 and 5 mg/kg	GRP78/AMPK	PSTi8 induces AMPK signaling via GRP78 upregulation Mediating insulin sensitivity Decreasing inflammation and hyperglycemia	[228]
Ficus carica leaf	In vivo In vitro	Mice HepG2 cells	1 g/kg	–	Decreasing blood glucose Activation of AMPK signaling to decrease levels of PGC-1α, HNF-4α, FOXO1, PEPCK and G6Pase	[229]
Black ginseng extract	In vivo	Mice	20–25 g	–	Inducing AMPK signaling to prevent gluconeogenesis	[230]
Guava leaf	In vivo	Rat	100, 200 and 400 mg/kg	AMPK/ACC	Inhibiting gluconeogenesis Enhancing glycogen synthesis Inducing AMPK phosphorylation at Thr172Promoting ACC phosphorylation to prevent hyperlipidemia and hyperglycemia	[231]

differences from apoptosis and necrosis that occurs due to upregulation of cytokines and presence of pro-inflammatory immune cells [240–242]. The overexpression of extendin-4 can be beneficial in protecting against cardiomyocyte pyroptosis via decreasing inflammatory cytokines. Mechanistically, extendin-4 decreases ROS production to promote AMPK phosphorylation, resulting in a significant decrease in expression of TXNIP. Then, levels of caspase-1, IL-1β and IL-18 decrease to prevent pyroptosis in myocardial cells [243]. Therefore, activating AMPK signaling can dually suppress both inflammation and oxidative stress in preventing heart injury in DM. Fortunellin promotes AMPK phosphorylation to induce Nrf2 signaling, resulting in a significant decrease in oxidative stress via upregulating SOD, CAT and HO-1 as antioxidant factors. Furthermore, AMPK/Nrf2 signaling activation improves inflammation via down-regulating NF-κB [244]. Pterostilbene also uses a similar pathway in preventing cardiac injury in DM. Pterostilbene induces AMPK signaling to promote Nrf2 expression for upregulating HO-1 and subsequent decrease in oxidative stress and inflammation [245]. As it was mentioned previously, DM can predispose to development of I/R. It has been reported that berberine induces AMPK and PI3K/Akt molecular pathways to prevent I/R-induced apoptosis in myocardial cells and improve DM condition [246]. Hence, AMPK can be a promising target and is under focus in preventing cardiovascular disease development during DM (Table 6 **and** Fig. 5) [247–250].

5. Clinical studies

The incidence rate of DM is increasing in modern world due to lifestyle and consumption of high fat diet. The management of DM in clinical course is of importance and a variety of antidiabetic drugs have been utilized in this case. In the current section, our aim is to provide a discussion of AMPK signaling targeting for DM management in clinical course. Neurological diseases commonly occur due to DM. A recent clinical trial conducted an experiment on 80 patients and randomly divided them into two groups including metformin group and insulin group. After two weeks of treatment with metformin, neurological indexes were evaluated and it was shown that metformin improves neurological functions scores and alleviates oxidative stress. In order to determine underlying mechanisms responsible for these protective impacts of metformin in diabetic patients, rat model of DM was generated and metformin was utilized. The results showed that metformin induces AMPK signaling to reduce mTOR expression and improve neurological indexes in diabetic rats. Therefore, AMPK/mTOR axis can be considered as underlying pathway responsible for protective effect of metformin in DM patients [258]. Another experiment focuses on 27 patients including 13 overweight/obese patients and 14 control patients. This study reveals activation of AMPK signaling during exercise in TIID patients as an adaptation to exercise. However, there was no association between exercise, AMPK and insulin signaling. In fact, AMPK signaling is essential for adaptation to exercise [259]. In both healthy and diabetic patients, exercise can induce AMPK signaling. Based on this statement, there is a question that is there any different between AMPK activation in healthy and diabetic patients? An experiment conducted investigations on 12 TIID patients, 8 obese patients and 8 lean subjects. Based on the results of this study, TIID patients should perform exercise in higher intensity compared to lead subjects to activate AMPK signaling [260]. Hence, if physicians are going to recommend exercise as a therapeutic strategy for diabetic patients, they should consider intensity of exercise.

Another experiment attempts to reveal AMPK phosphorylation status in healthy and diabetic patients. Based on the results of this study, subjects with normal glucose tolerance demonstrate enhanced AMPK phosphorylation, while these alterations do not occur in diabetic patients [261]. Another randomized clinical trial reveals that creatine supplementation is associated with AMPKα upregulation and promoting glucose uptake in TIID [262]. Overall, clinical trials highlight the fact that AMPK possesses antidiabetic potential in diabetic patients and novel therapeutics in near future can focus on this pathway and also, related signaling networks [263,264]. Fig. 6 demonstrates an overview of clinical trial results about role of AMPK signaling in diabetic patients.

6. Conclusion and remarks

DM shows an increasing trend and due to COVID-19 pandemic and alterations in lifestyle, more new cases of DM will be diagnosed in future. Therefore, countries and world should be worried about such disease and precautions can be considered for providing novel therapeutics. Overall, DM patients show high level of glucose in their blood, known as hyperglycemia which can induce oxidative stress and inflammation in cells and tissues, leading to organ dysfunction. The diabetic complications are neuropathy, nephropathy, liver fibrosis, infertility and cardiovascular diseases among others, that reduce life quality of DM patients. Hence, the current review article was designed to provide an updated discussion of AMPK signaling targeting in DM treatment.

The β-cell death is responsible for development of TID and the patients are not able to secrete insulin to decrease glucose levels in blood circulation. The oxidative stress induces apoptosis and inflammation can also stimulate cell death and impair proper function of these cells. The maturation and proper function of β cells depends on mTOR to AMPK

Table 6
The participation of AMPK signaling in reducing diabetes-mediated heart injury.

Protective agent	In vitro/ In vivo	Cell line/ Animal model	Study design	Signaling network	Remark	Ref
–	In vitro In vivo	Diabetic mice Heart cells	–	FGFG19/ AMPK/Nrf2/ HO-1	Upregulation of AMPK by FGF19 Inducing Nrf2/HO-1 axis Preventing oxidative damage	[251]
Niacin-bound chromium	In vivo	Rat	Mixing 4 mg chromium with 1 kg of rat chow	AMPK/GLUT4	The overexpression of AMPK promotes GLUT4 translocation in preventing myocardial injury	[252]
Cinacalcet	In vivo	Rat	5 and 10 mg/kg	–	Autophagy induction Improving mitochondrial function Triggering AMPK signaling	[253]
Mulberry granules	In vivo	Mice	10, 20 and 30 mg/kg	AMPK/Nrf2	Improving cardiac function Decreasing myocardial infarct size Reducing blood glucose, lipid and fasting blood insulin levels Reducing oxidative stress Enhancing activities of GSH, SOD and CAT Inducing Nrf2 signaling via AMPK overexpression	[254]
Metformin	In vivo	BALB/c mice	100, 200 and 400 mg/ kg	–	Metformin induces AMPK to reduce inflammation via reducing TNF-α, IL-6 and IL-1β levels Decreased levels of MPO, CK-MB and BNP	[255]
4-O-methylhonokiol	In vivo	Mice	0.1 mg/kg	AMPK/SIRT1	MH induces AMPK signaling to upregulate SIRT1 expression Enhancing lipid metabolism and preventing inflammation and oxidative stress	[256]
UCF-101	In vivo	Mice	7.15 mg/kg	–	Enhancing AMPK phosphorylation at Thr172 Improved contractile function Down-regulating PP2A and PP2C in preventing AMPK degradation	[257]

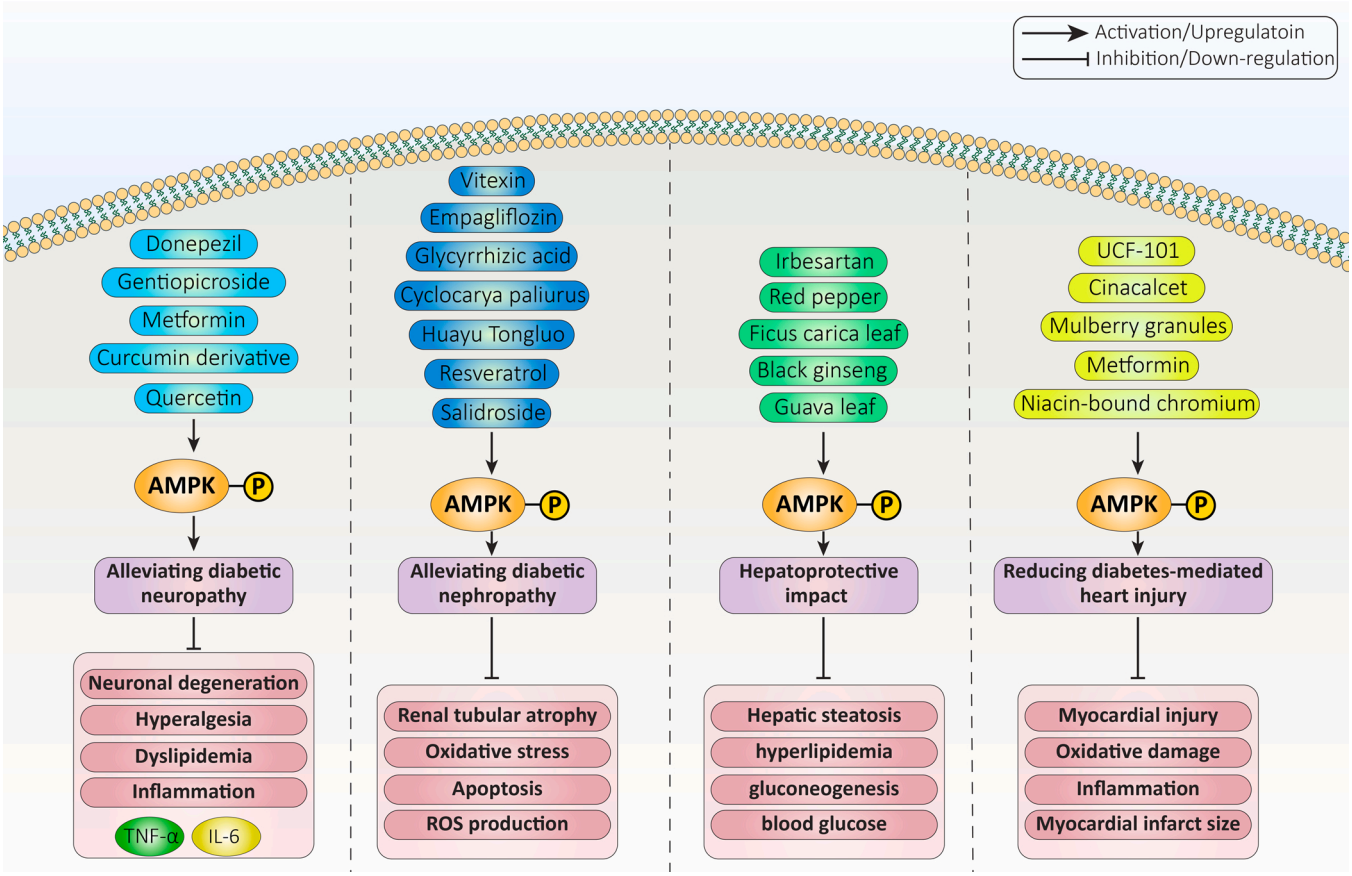

Fig. 5. The AMPK signaling targeting in alleviating diabetic complications.

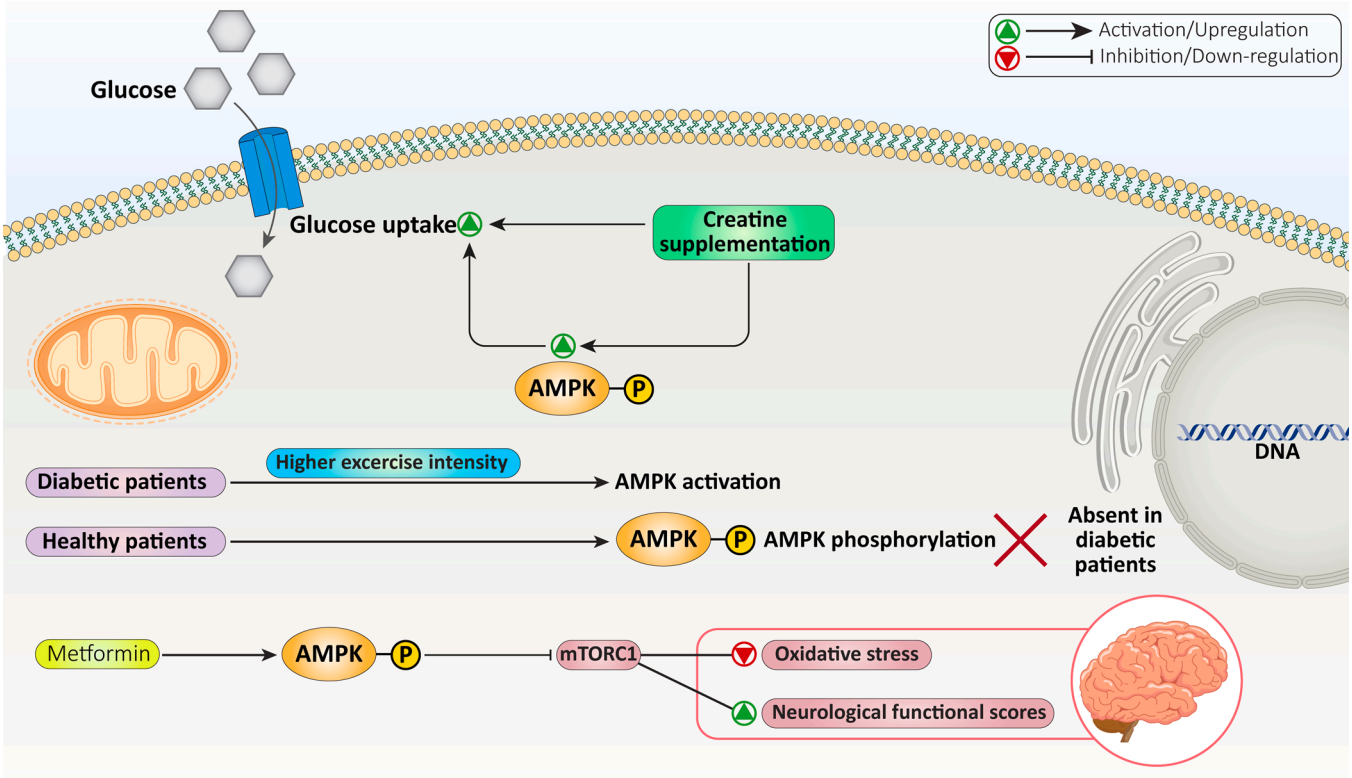

Fig. 6. The role of AMPK signaling in clinical studies for treatment of diabetic patients.

signaling switch. The clinical importance of this pathway is that exosomal miRNA-148a present in milk can prevent β cell death maturation and proper function via inhibiting mTOR-to-AMPK switch. Therefore, milk should be boiled to degrade exosomal miRNA-148a. Furthermore, AMPK signaling activation prevents oxidative stress and apoptosis in β cells partially via FOXO1 down-regulation. Besides, AMPK is vital for ameliorating ER stress in β cells and enhancing their survival and viability. Based on these statements, triggering AMPK signaling is beneficial in preventing TID development via protecting β cells.

Based on experiment and main text of this review, AMPK signaling targeting is also beneficial in treatment of TIID patients. The glucose levels are high in TIID and its metabolism is interrupted. AMPK signaling can significantly enhance glucose uptake in muscle and other cells to reduce serum glucose levels via upregulating GLUT1 and GLUT4 as its transporters. Furthermore, AMPK signaling is beneficial in enhancing glucose metabolism in cells via inducing SIRT1 and promoting PGC-1α expression. Therefore, triggering AMPK signaling significantly decreases glucose levels in serum. Noteworthy, AMPK signaling activation promotes insulin sensitivity of cells. So, both enhanced glucose metabolism and insulin sensitivity jointly participate in decreasing glucose levels in serum. The clinical studies have also shown role of AMPK signaling in treatment of DM patients. In order to improve understanding about AMPK signaling role in DM, we described AMPK role in diabetic complications. Activating AMPK signaling significantly diminishes nephropathy, neuropathy, liver diseases, cardiovascular diseases and so on. However, there are some limitations that should be addressed. Most of the therapeutics developed for targeting AMPK signaling are phytochemicals. The plant derived-natural products significantly suffer from poor bioavailability and have low therapeutic impacts in clinical course [265–269]. Therefore, future experiments can focus on their delivery by nanostructures in DM treatment via targeting AMPK signaling. Furthermore, as AMPK signaling is a druggable target, its binding sites have been recognized and medicinal chemistry can be exploited for developing novel small molecules capable of regulating its expression.

Based on the aforementioned discussions, AMPK signaling induction is an ideal strategy in reducing insulin resistance, improving glucose and lipid metabolism as well as ameliorating diabetic complications. However, two important notes should be mentioned. Although no specific drug designed for targeting AMPK signaling has been applied in clinical trials, it seems that already utilized drugs in treatment of DM have the capacity in regulating AMPK expression [270]. For instance, metformin is a well-known choice in treatment of DM and this drug diminishes blood glucose levels via AMPK upregulation [271]. Therefore, small molecule regulators of AMPK signaling can be developed in near future in treatment of diabetic patients. The second note is that AMPK signaling may exert harmful impacts in treatment of DM. For instance, AMPK signaling activation can lead to degradation of amyloid-beta plaques in diabetic patients and alleviate diabetic neuropathy [272]. However, excessive induction of AMPK signaling may result in enhanced amyloid-beta depositions and mediate pathogenesis in neurological disorders such as Alzheimer's disease. Furthermore, AMPK signaling is a regulator of autophagy. Excessive AMPK signaling activation may induce autophagic cell death instead of providing pro-survival autophagy. Therefore, caution should be made in targeting AMPK signaling for DM treatment [273].

CRediT authorship contribution statement

I confirm that the all authors have contributed at least in the part of preparing this research and preparing the manuscript. I also paid attention to the Authorship Roles.

Conflict of interest statement

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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