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Targeting AMPK signaling: The therapeutic potential of berberine in diabetes and its complications

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ABSTRACT

Introduction: Berberine (黄连素, huáng lián sù) is a time-honored remedy in Traditional Chinese Medicine (TCM) that is found in various medicinal herbs and used to treat diabetes mellitus (DM), infections, diarrhea, and dysentery. Berberine, the major active component of *Coptidis rhizome* (黄连, huanglian), *Phellodendri cortex* (黄柏, huangbai), and *Mahoniae caulis* (亮叶十大功劳, Gong Lao Mu), exhibits several pharmacological activities, including antioxidant, anti-inflammatory, anti-apoptotic, cardioprotective, antineoplastic, antimicrobial, and antidiabetic effects. Antidiabetic effects of berberine are partly attributed to the activation of AMP-activated protein kinase (AMPK), which is a key mechanism and a potential treatment strategy for DM and its complications. This review discusses recent studies on the significant roles of berberine in activating AMPK for treating DM and its complications.

Method: We have comprehensively searched online databases like Scopus, PubMed, and Google Scholar for articles published in English between 2016 and 2025 using different permutations of these keywords: "Berberine", "AMPK", "Diabetes Mellitus", "Diabetic nephropathy", "Diabetic neuropathy", "Diabetic retinopathy", "Diabetic cardiomyopathy", "Diabetic hepatic steatosis," "Diabetic bone diseases", "Diabetic atherosclerosis", "Diabetic cognitive dysfunction", "Diabetic lung injury" and "Other diabetic complications" to compile this narrative review. Out of 1750 initially retrieved articles, 183 were included based on their relevance to treating DM or its complications through the AMPK signaling pathway, pharmacokinetics, and translational potential. Non-English articles and studies not focused on AMPK activation by berberine and that did not address DM and its complications were excluded.

Results: The literature review found that berberine consistently activates AMPK across various preclinical studies of DM. The activation of AMPK is frequently mediated by pathways involving LKB1 and CAMKKβ. Berberine's activation of AMPK positively impacts glucose uptake, insulin sensitivity, lipid metabolism, oxidative stress, and inflammatory responses. Evidence from animal models demonstrated its efficacy in ameliorating complications such as diabetic nephropathy, neuropathy, retinopathy, cardiomyopathy, hepatic steatosis, bone diseases, atherosclerosis, cognitive dysfunction, and lung injury. Clinical trials reported significant reductions in fasting blood glucose (FBG), HbA1c, and lipid levels, with minimal side effects, at standard doses.

Discussion: AMPK activation by berberine plays a central role in cellular energy homeostasis, modulating key processes such as gluconeogenesis, lipogenesis, oxidative stress, and inflammation, which contribute to its therapeutic efficacy in metabolic dysfunction and DM-related complications. However, challenges remain

Abbreviations: ACC, acetyl-CoA carboxylase; AMD, age-related macular degeneration; AMPK, AMP-activated protein kinase; ATGL, adipose triglyceride lipase; C/EBPβ, CCAAT/enhancer-binding protein beta; CPT-1, carnitine palmitoyltransferase 1; CypD, cyclophilin D; DCM, diabetic cardiomyopathy; DM, diabetes mellitus; DN, diabetic neuropathy; DPN, diabetic nephropathy; DR, diabetic retinopathy; eNOS, endothelial nitric oxide synthase; ERK, extracellular Signal-regulated Kinases; GSK3β, glycogen synthase kinase 3β; HIF-1α, hypoxia-Inducible Factor 1-alpha; IR, insulin resistance; IRS-1, insulin receptor substrate-1; LKB1, Liver Kinase B1; mTOR, mechanistic target of rapamycin; NAFLD, non-alcoholic fatty liver disease; NEU1, Neuraminidase-1; Nrf2, nuclear factor (erythroid-derived 2)-related factor 2; NF-?B, nuclear factor kappa-light-chain-enhancer of activated B cells; OA, osteoarthritis; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1a, peroxisome proliferator-activated receptor ? coactivator 1 a; PI3K, phosphatidylinositol 3-kinases; RA, rheumatoid arthritis; ROS, reactive oxygen species; Runx2, Runt-related transcription factor 2; SCD1, stearoyl-CoA desaturase 1; SIRT-1, sirtuin-1; SIRT-3, sirtuin-3; SREBP-1c, sterol regulatory element-binding protein 1; TGF-ß1, transforming growth factor-beta 1; TORC2, target of rapamycin complex 2.

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regarding its poor bioavailability, potential drug interactions, and variability in clinical outcomes due to differences in formulations and dosing strategies. Combination with bioenhancers and novel delivery systems may help overcome these limitations. Further large-scale, well-controlled clinical trials and pharmacokinetic optimization studies are needed to fully establish the therapeutic potential of berberine and to develop clinical guidelines for its application.

1. Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized by abnormally high blood sugar levels, posing a significant global health challenge with potentially life-threatening complications [1,2]. It stems from insufficient insulin production, impaired cellular response to insulin, and/or disrupted glucose metabolism. There are various subtypes of DM, each associated with distinct etiologies, diagnostic criteria, and management strategies. The two primary forms are immune-mediated type 1 diabetes (T1D) and metabolism-mediated type 2 diabetes (T2D [3]. According to the International Diabetes Federation (IDF), approximately 537 million adults worldwide are living with DM, resulting in a death toll of 6.7 million and financial implications of about 966 billion dollars [4]. In China, the DM epidemic is particularly severe, with over 118 million individuals affected, which constitutes roughly 22 % of the global DM population [5]. Given the significant threat posed by DM to humanity, the development of effective therapeutic interventions to combat it remains a medical priority.

The pathogenic mechanisms underlying DM are complex, involving intricate networks associated with the disease that comprise various signaling pathways. Increasing evidence suggests that targeting these signaling networks with DM medications is an effective strategy for addressing DM and its associated complications [6,7]. One such biological pathway integral to maintaining energy and metabolic homeostasis is the 5′ adenosine monophosphate-activated protein kinase (AMPK) pathway. AMPK plays a crucial role in regulating glucose and lipid homeostasis by inhibiting anabolic processes and stimulating catabolic processes [8]. AMPK activation enhances glucose uptake, triggers fatty acid oxidation, and suppresses hepatic gluconeogenesis to improve insulin sensitivity and reduce hyperglycemia [9]. AMPK also mitigates lipotoxicity, oxidative stress, and inflammation, which play a crucial role in the progression of DM and its complications [10]. This underscores the importance of the AMPK signaling pathway as a significant therapeutic target for DM and its complications.

Berberine (5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo [5,6-a] quinolizinium) is a quaternary isoquinoline alkaloid belonging to the protoberberine group, with a molecular formula $C_{20}H_{18}NO_4^+$ and molecular weight 336.36 g/mol. It is characteristically yellow, bitter-tasting, and exhibits strong fluorescence under UV light [11]. Chemically, berberine exists as a cationic salt and is typically isolated in the form of berberine chloride or sulfate. It is known for its poor solubility in aqueous solutions but demonstrates notable stability under physiological pH conditions. Berberine is found in the rhizome, stem, and fruits of various plants belonging to families such as Berberidaceae (e.g., *Berberis* L.), Annonaceae (e.g., *Xylopia* L.), Menispermaceae (e.g., *Tinospora* Miers), Papaveraceae (e.g., *Argemone* L.), Ranunculaceae (e.g., *Coptis* Salisb.), and Rutaceae (e.g., *Phellodendron Rupr.*) [12] (Fig. 1). Berberine has been widely studied and was found to possess diverse pharmacological activities, including antioxidant and anti-inflammatory [13], anti-diabetes [14], anti-dyslipidemia [15], anti-obesity [16], antimicrobial [17], neuroprotection [18], and anti-cancer [19]. Previous studies on berberine have reported its safety profile [20] and suggested that the health effects observed in cellular and animal models demonstrate translational potential [21–23]. The popularity of berberine in treating various ailments in some parts of the world, particularly in regions where traditional medicine is prevalent, has increased since it is a phytoconstituent and owing to the perception among some patients that natural remedies are cheaper and more accessible alternatives to conventional pharmaceuticals [24].

Berberine is the major active component of *Coptidis rhizome* (huanglian), *Phellodendri cortex* (Huangbai), and *Mahoniae caulis* (Gong Lao Mu), and has been used as a traditional and cost-effective remedy for treating digestive system diseases for a long time. Berberine was commonly used in ancient times as an anti-infective and anti-inflammatory, as infectious diseases were more prevalent than DM at that time [25]. In TCM, berberine-rich herbs are classified as “heat--clearing, dampness-drying” agents used for dysenteric diarrhea, febrile and inflammatory disorders, and “Xiaoke” (wasting–thirst) syndromes, which is analogous to modern-day DM and its complications, even before the discovery of insulin [26]. Its broad therapeutic potential

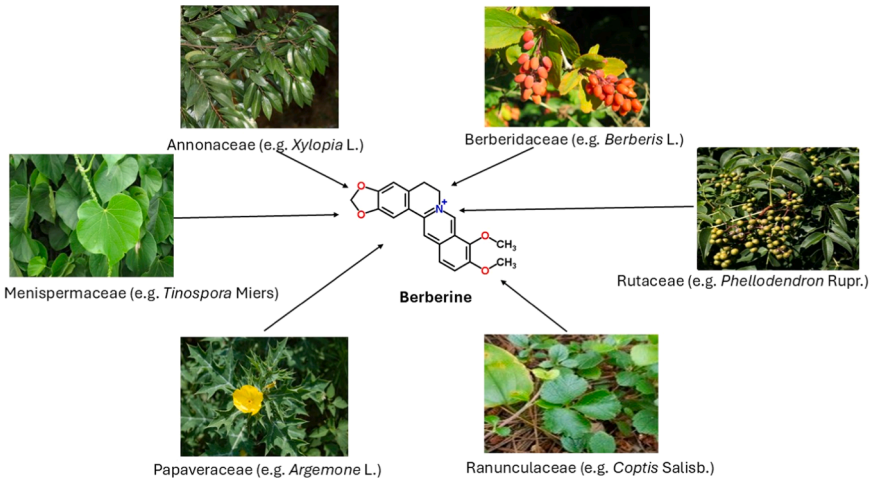

Fig. 1. Chemical structure of berberine and its various sources. Berberine, with a chemical name 5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a] quinolizinium, is an isoquinoline alkaloid found in the rhizome, stem, and fruits of various plants belonging to families such as Berberidaceae (e.g., Berberis L.), Annonaceae (e.g., Xylopia L.), Menispermaceae (e.g., Tinospora Miers), Papaveraceae (e.g., Argemone L.), Ranunculaceae (e.g., Coptis Salisb.), and Rutaceae (e.g., Zanthoxylum L.).

spans both glycemic control and the mitigation of diabetic complications. The first reports highlighting the therapeutic efficacy of berberine for T2D emerged in 1986 in studies involving mice [27] and in 1988, with diabetic patients [28].

Berberine is often combined with other herbs as an extract, decoction (Gegen Qin Lian) [29], granule (Jiao-Tai-Wan) [30], and capsule (Tianqi) [31] to enhance its therapeutic effects and address the holistic nature of diseases (Table 1). The combination of *Radix Astragali* (Huangqi) and *Rhizoma Coptidis* in antidiabetic formulae improves insulin resistance and glucose metabolism [32]. Tianqi capsule, a formula comprising *Coptidis Rhizoma* and nine other Chinese herbal medicines, has been shown to improve glycemic control in diabetic patients with impaired glucose tolerance [31]. Berberine in combination with other herbs is a major constituent in many Chinese patent medicines approved by the China Food and Drug Administration to treat Xiaoke syndrome, including Jinqi Jiangtang tablets and Xiaokeping tablets [33]. Moreover, modern medical research has also shown that berberine stimulates the AMPK signaling pathway to exert positive effects on diabetic complications, such as diabetic nephropathy (DNP), diabetic neuropathy (DN), and diabetic cardiomyopathy (DCM) [34,35]. AMPK is considered a more favorable therapeutic target than other pathways, such as mTOR or PI3K/Akt, for treating DM and its complications due to its central role in energy homeostasis and its ability to modulate multiple metabolic pathways [9,10]. Therefore, understanding the mechanisms in the traditional applications of berberine within TCM will provide valuable insights into its antidiabetic effects and underscore its role in bridging traditional remedies with contemporary therapeutic practices.

This article reviews and analyzes recent studies on the significant roles of berberine as a therapeutic phytocompound used in TCM for treating DM and its associated complications. We also discuss pharmacological aspects of berberine and the activation of AMPK as a key mechanism underlying the antidiabetic effects of berberine, alongside potential considerations for its clinical application in the management of DM and its complications. The promising results of these studies provide a strong theoretical basis for the potential of berberine in developing innovative and effective treatments against DM and its associated complications, offering hope for the future of DM management.

2. Methods

We have comprehensively searched online databases like Scopus, PubMed, and Google Scholar for articles published in English between 2016 and 2025 using different permutations of these keywords: “Berberine”, “AMPK”, “Diabetes Mellitus”, “Diabetic nephropathy”, “Diabetic neuropathy”, “Diabetic retinopathy”, “Diabetic cardiomyopathy”, “Hepatic steatosis,” “Diabetic bone diseases”, “Diabetic atherosclerosis”, “Diabetic cognitive dysfunction”, “Diabetic lung injury” and “Other diabetic complications” to compile this narrative review. This review adopts a rigorous methodology in literature selection, explicitly excluding irrelevant studies, duplicate publications, and potentially misleading data while ensuring comprehensive coverage of validated research findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [44]. Fig. 2 shows the literature-screening process.

Initially, a total of 1750 records were retrieved. After screening titles and abstracts for relevance, 282 studies were selected for full-text review. Articles were included if they (1) investigated the pharmacological properties of berberine or its derivatives in the context of treating DM or its complications through the AMPK signaling pathway, (2) clinical studies focusing on AMPK-dependent metabolic parameters that serve as reliable surrogates, and (3) were published in English. Studies were excluded if they were duplicates, did not focus on AMPK activation by berberine, did not address DM and its complications, or were centered on unrelated conditions (e.g., cancer, inflammatory diseases). Finally, 44 articles met the inclusion criteria and were analyzed qualitatively. A total of 183 articles were used for this review. This collection

Table 1
TCM preparations containing berberine for the management of DM and its complications.

S/N	TCM preparation	Berberine source	Use in TCM	References
1	Huang-Lian-Jie-Du (黄连解毒汤, Decoction)	*Rhizoma Coptidis* (*Coptis chinensis* Franch), *Radix Scutellariae* (*Scutellaria baicalensis* Georgi), *Cortex Phellodendri* (*Phellodendron chinense* Schneid), and *Fructus Gardenia* (*Gardenia jasminoides* Ellis)	Heat-clearing and detoxifying effects, treatment of DM and Alzheimer’s disease	[36]
2	Jiao-Tai-Wan (胶台湾, formular)	*Coptis chinensis* Franch., and *Cinnamomum cassia Blume.*	Treat insomnia and DM	[30,37]
3	Xiao-Ke-An (小可安, formular)	*Coptis chinensis* Franch., *Panax ginseng* C.A. Meyer, *Anemarrhena asphodeloides* Bge, *Salvia miltiorrhiza* Bunge, *Rehmannia glutinosa* Libosch, *Polygonatum odoratum* (Mill.) Druce, *Lycium chinense* Mill., *Lycium barbarum* L.	Treating T2D	[38]
4	Jiang Tang Xiao Ke (姜糖小克,granule)	*Coptis chinensis* Franch. *Rehmannia glutinosa, Cornus officinalis* Sieb. et Zucc., *Salvia miltiorrhiza* Bunge.	Treating T2D	[39]
5	Jiedu Tongluo Tiaogan (解毒通络调肝, formular)	*Coptis chinensis* Franch, *Rheum officinale* Baill, *Astragalus membranaceus* Bge, *Lonicera japonica* Thunb, *Bupleurum chinense* DC, *Salvia miltiorrhiza* Bunge, *Scrophularia ningpoensis* Hemsl, and *Reynoutria japonica* Houtt	Treat T2D by regulating the liver’s laxative function, unblocking Qi and blood meridians, eliminating toxins, and balancing Zang and Fu functions	[40]
6	Huangqi Guizhi Wuwu (黄芪桂枝五物, decoction)	*Astragalus membranaceus* (Fisch.) Bunge, *Cinnamomum cassia* Presl., *Paeonia lactiflora* Pall., *Zingiber officinale* Roscoe *and Ziziphus jujuba* Mill.	Harmonizing ying and wei	[41]
7	Tianqi (田七, capsule)	*Astragalus membranaceus* (Fisch), *Trichosanthes kirilowii* Maxim, *Coptis chinensis* Franch, *Panax ginseng* C.A. Mey., *Caulis Dendrobii, Eclipta prostrata* (L.) L.., *Lycium chinense* Mill., *.Ligustrum lucidum* W.T. Aiton., *and Cornus officinalis* Sieb. et Zucc.	To decrease hemoglobin A1c and blood glucose	[31]

(*continued on next page*)

Table 1 (*continued*)

S/N	TCM preparation	Berberine source	Use in TCM	References
8	Gegen Qin Lian (葛根芩连汤) decoction	*Puerariae Lobatae* Radix, *Scutellaria baicalensis Georgi.*, *Coptis chinensis* Franch, *and Glycyrrhiza uralensis* Fisch.	Treat internal and external symptoms of diarrhea	[29]
9	Jinqi Jiangtang (金芪降糖) Tablet	*Coptis chinensis* Franch, *Astragalus membranaceus* (Fisch.) Bunge *and Lonicera japonica* Thunb.	Treating DM and related complications	[42]
10	Xiaokeping (消渴平) mixtures	*Astragalus membranaceus* (Fisch.) Bge, *Dioscorea oppositifolia* L., *Rehmannia glutinosa* (Gaert.) Libosch. ex Fisch. et Mey., *Ophiopogon japonicus* (Linn. f.) Ker-Gawl., *Trichosanthes kirilowii* Maxim., *Salvia miltiorrhiza* Bunge, *Dendranthema morifolium* (Ramat.) Tzvel., *and Lycium barbarum* L.	Treating DM and its kidney damage	[43]

included original research articles, reviews providing new insights, and selected classical texts from TCM relevant to the traditional use of berberine. The data were synthesized with a focus on molecular mechanisms, pharmacokinetics, and limitations pertaining to clinical translation.

3. Overview of diabetes mellitus

DM, which is characterized by hyperglycemia, has emerged as one of the most significant public health challenges of the 21st century. The epidemiology of DM shows notable regional variations [45]. For instance, the International Diabetes Federation (IDF) reports that the number of DM patients in China has surpassed 110 million, while South Africa has about 4.3 million [5]. In several countries of the world, the rising prevalence and incidence of DM have been linked to lifestyle changes, including sedentary habits, unhealthy diets, and risk behaviors associated with urbanization. Moreover, differences in genetic backgrounds, dietary practices, and levels of physical activity among various populations further contribute to the regional disparities in DM risk [46].

T2D accounts for the majority of DM cases and is associated with complications, which are the main sources of morbidity and mortality, and the economic burden associated with DM management. Traditionally, complications have been divided into macrovascular diseases, like cardiovascular disease (CVD), stroke, and peripheral artery disease, and microvascular diseases, such as retinopathy (DR), DNP, and DN. However, this current classification of DM complications is considered outdated and requires revision to better reflect the complexities of the condition [47]. As DM progresses, several pathways become activated, including the polyol pathway, diacylglycerol/protein kinase C (PKC) activation, the hexosamine biosynthesis pathway, and the formation of advanced glycation end products (AGEs), which contribute to ROS generation and aggravate oxidative stress and inflammatory responses [48], leading to the pathogenic effects in DM and its complications. The AMPK signaling pathway represents a critical convergence point for oxidative stress and inflammation in DM. Therefore, activation of AMPK alleviates these pathogenic effects, indicating its therapeutic potential in DM and its associated complications [49].

4. Overview of AMPK signaling pathways

Maintaining energy homeostasis is an important biological process that takes place in all living cells. AMPK is a key regulator of energy homeostasis that is activated by various stimuli in response to reduced ATP production or increased ATP consumption under conditions of cellular stress [50]. The AMPK enzyme is composed of a heterotrimer structure that includes one catalytic subunit (α) and two regulatory subunits (β and γ) [51]. Each subunit has multiple isoforms (α1, α2, β1, β2, γ1, γ2, γ3), allowing for a total of 12 potential heterotrimer combinations. The kinase activity of the α subunit is activated over 100-fold upon the phosphorylation of a conserved threonine residue located on the kinase activation loop (Thr 172 in α1/α2). The primary upstream kinase responsible for this phosphorylation is a heterotrimeric complex composed of the liver kinase B1 (LKB1), mouse protein 25 (MO25), and the sterile-20-related adaptor (STRAD) [52]. Moreover, the Ca^{2+}/calmodulin-dependent protein kinase kinases (CaMKKs), especially CaMKKβ, have been identified as alternative enzymes that phosphorylate Thr172 in response to elevated intracellular Ca^{2+} levels [53]. Furthermore, research has suggested that transforming growth factor-β-activated kinase/mitogen-activated protein kinase 7 (TAK1/-MAP3K7), a member of the MAPKKK family, may also play a role in Thr172 phosphorylation [54]. Three complementary mechanisms, including promoting phosphorylation of AMPK by upstream kinases, protecting the enzyme from dephosphorylation via conformational changes that inhibit protein phosphatases, and inducing allosteric activation, can be employed to enhance the binding of AMP and/or ADP to the γ-regulatory subunit to activate AMPK in conditions where intracellular ATP concentrations are low [52].

Activating AMPK initiates a catabolic pathway to restore ATP levels and inhibits anabolic processes. For instance, AMPK activation not only triggers glucose utilization and fatty acid oxidation but also suppresses gluconeogenesis and lipid synthesis, thereby alleviating IR and reducing both blood glucose and lipid levels. AMPK elevates glucose transporter protein (GLUTs) concentrations to facilitate the uptake of glucose into cells and to further reduce blood glucose levels [33]. By its action on glucose uptake, fatty acid oxidation, and lipogenesis, AMPK reduces β-cell apoptosis and ultimately boosts insulin secretion and alleviates organ damage induced by DM [9,55]. AMPK inhibits cholesterol synthesis by inhibiting HMG-CoA reductase (HMGCR), and protein synthesis through the suppression of mTORC1 signaling via TSC2/Raptor phosphorylation to conserve ATP [56]. Moreover, AMPK activates the upstream kinase in mitophagy, Unc-51 like autophagy activating kinase 1 (ULK1) and peroxisome proliferator-activated receptor-γ (PPARγ) co-activator 1α (PGC1-α), respectively, to enhance mitophagy and mitochondrial biogenesis, thereby maintaining cellular and mitochondrial homeostasis [57]. These insights suggest that targeting the AMPK signaling pathway could lead to innovative strategies for managing DM and its associated complications.

5. Berberine

Berberine, colloquially known as Huangliansu, is a naturally occurring yellow crystalline hydrophobic cationic alkaloid that has been applied in TCM from time immemorial to treat various diseases [58]. Berberine is isolated and quantified from the rhizome, stem, and fruits of various plants belonging to families such as Berberidaceae (e.g., *Berberis* L.), Annonaceae (e.g., *Xylopia* L.), Menispermaceae (e.g., *Tinospora* Miers), Papaveraceae (e.g., *Argemone* L.), Ranunculaceae (e.g., *Coptis* Salisb.), and Rutaceae (e.g., *Zanthoxylum* L.) [12] (Fig. 1). Berberine was first recorded in the Divine Farmer's Classic of Materia Medica (Shen Nong Ben Cao Jing), an ancient book of TCM, which was compiled in

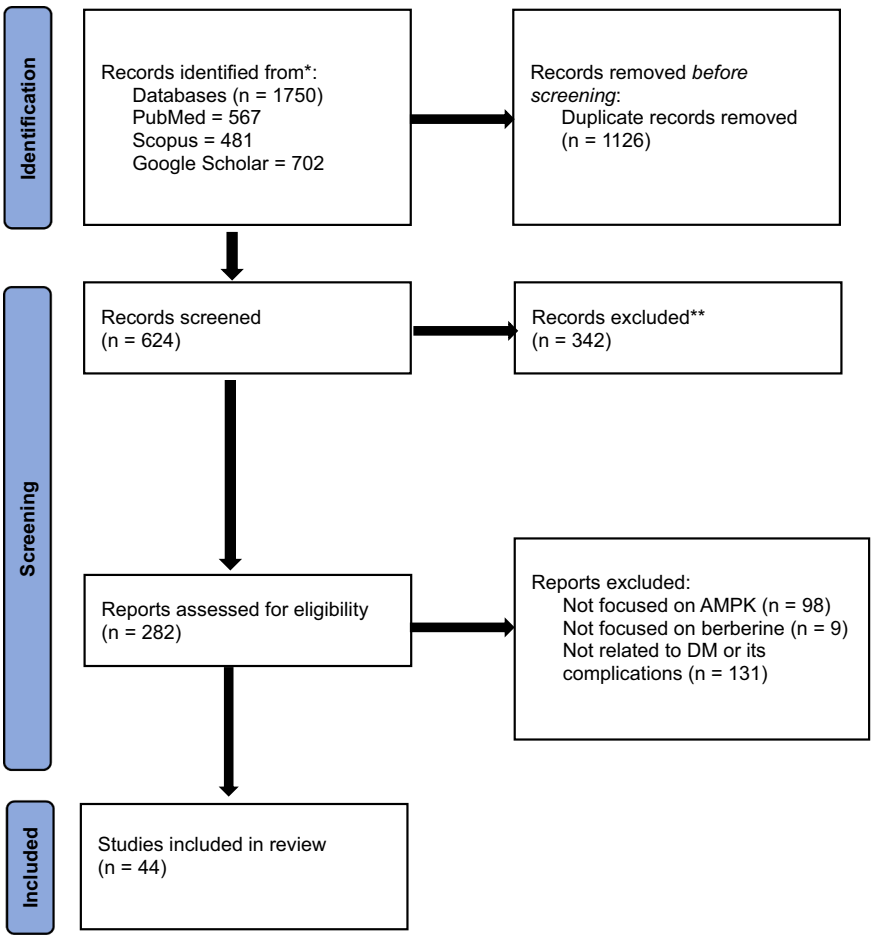

Fig. 2. PRISMA flow diagram.

200 A.D [59]. It has a long history of use as a nonprescription drug to treat gastrointestinal infections, such as diarrhea and bacillary dysentery, in the People's Republic of China. The Compendium of Materia Medica also recorded its use as a remedy for heat-clearing and detoxification [60]. The earliest mention of its use as an antidiabetic medication was recorded by Hongjing Tao in the Note of Elite Physicians approximately 1500 years ago [61].

A plethora of evidence from modern pharmacological studies has shown the antidiabetic effects of berberine [10,34,62,63]. Berberine increases insulin secretion, improves IR and dyslipidemia, and alleviates inflammation to exert its antidiabetic effects [64–66]. However, the concern of the toxicity of long-term administration of berberine remains a grey area that needs to be addressed [67]. Thus, a number of clinical trials are underway to confirm the clinical benefits, safety profile, and antidiabetic effects of berberine in a large number of human subjects [20,68] (Table 3).

5.1. Pharmacological aspects of berberine

The pharmacokinetic aspects of berberine, which include its absorption, distribution, metabolism, and excretion, are quite complex. Oral administration of berberine is plagued by the challenge of poor bioavailability, stemming from first-pass effects in the gut and rapid metabolism in the body, which causes it to be metabolized before reaching systemic circulation. At a dose range of 48.2–240 mg/kg, berberine has an absolute bioavailability of 0.37 %, T_{max} ~ 2.8 h, C_{pmax} ~4 μg/ml, V_d ~ 12–38 L, $T_{1/2}$ ~ 5–6 h [69]. Moreover, its characteristic poor permeability, hepatobiliary excretion, self-aggregation, and high affinity for P-glycoprotein further compound the bioavailability issue [70]. However, berberine is preferably administered orally, even though the parenteral route has increased plasma drug concentration owing to its associated problems of toxicity. Berberine is widely distributed across various tissues and organs after entering circulation and can still accumulate in plasma while maintaining a low concentration [69,70] (Fig. 3). According to findings, the tissue distribution of berberine after intragastric dosing was highest in the liver, followed by the kidneys, muscles, lungs, brain, heart, pancreas, and adipocytes [71]. Berberine has a rapid metabolic rate in vivo and undergoes transformation in the

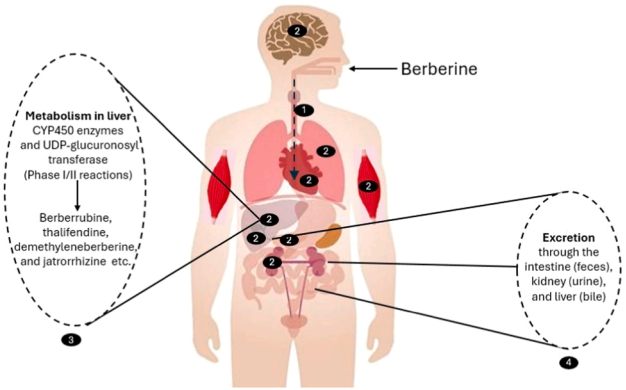

Fig. 3. The pharmacokinetics of berberine. Berberine exhibits complex pharmacokinetics characterized by poor oral bioavailability due to low intestinal absorption, extensive phase I/II metabolism, and significant first-pass elimination. Where 1, 2, 3, and 4 represent berberine absorption, distribution, metabolism, and excretion, respectively.

liver by cytochrome P450 enzymes and UDP-glucuronosyl transferase following oral administration into different phase I and II metabolites, including berberrubine, thalifendine, demethyleneberberine, and jatrorrhizine [72,73]. Berberine and its metabolites are primarily excreted through the bile, urine, and feces, with fecal excretion occurring at a higher rate than urinary and biliary excretion routes [74]. Consequently, research efforts have focused on enhancing the bioavailability and efficacy of berberine by developing various formulations to address the pharmacokinetic challenges associated with it [75,76].

Studies have shown that berberine lowers fasting plasma glucose (FPG), postprandial blood glucose, and glycated hemoglobin (HbA1c) levels, both as a single treatment and adjunctive therapy with other hypoglycemic agents [63,69,77]. Berberine, just like metformin, has pleiotropic antidiabetic mechanisms, including activation of AMPK, inhibition of gluconeogenesis, modulation of gut microbiota, and anti-inflammatory and antioxidant effects [65,78]. AMPK activation by berberine in various tissues alleviates systemic IR, β-cell dysfunction, oxidative stress, and inflammation, through enhancing insulin receptor expression and GLUTs translocation to promote glucose transport [79], suppressing NF-$_{K}$B signaling to reduce inflammation and oxidative stress [80], and regulating lipid metabolism to reduce hyperlipidemia [81].

AMPK-dependent mechanisms of berberine are both direct and indirect. In the direct effects, berberine induces the phosphorylation of Thr-172 in the α-subunit of AMPK in tissues such as skeletal muscles and adipose tissues, to alleviate IR, hyperglycemia, and dyslipidemia [82]. Moreover, in LKB1−/− cells with or without the CaMKKβ inhibitor STO-609, the effects of berberine in activating AMPK phosphorylation have been reported to be independent of either LKB1 or CaMKKβ [83], suggesting that berberine could improve metabolic functions through multiple signaling pathways, including calcium-dependent mechanisms [84]. On the other hand, indirect effects involve the activation of adenylosuccinate synthetase, and concurrent reversible suppression of AMP-deaminase and mitochondrial respiratory chain complex 1, causing an increase in AMP/ADP: ATP ratio, or by targeting sirtuins [8,83,85,86].

6. AMPK-mediated preventive and therapeutic effects of berberine in DM

Preclinical studies have shown that berberine activates AMPK and regulates metabolic pathways, making it a valuable therapeutic agent for DM by improving glucose metabolism, reducing lipid accumulation, and alleviating oxidative stress and inflammation (Table 2). The molecular targets and mechanisms underlying berberine-mediated activation of AMPK signaling in treating DM and its associated complications are shown in Fig. 4.

6.1. Regulation of glucose uptake and metabolism

Impaired glucose metabolism is a major challenge in DM management. Glucose metabolism depends on glucose uptake in the cells, which involves the activity of various enzymes and carriers, including GLUTs, to increase postprandial blood glucose levels [87]. Therefore, modulating the activity of these enzymes and carriers will have beneficial effects on postprandial blood glucose levels. Treatment with berberine significantly improved hyperglycemia, insulin resistance, and lipid profiles by enhancing GLUT4 expression and activating the IRS-1/PI3-K/AKT signaling cascade in an AMPK-dependent manner, resulting in increased glucose uptake both in vivo and in vitro [88]. This suggests the beneficial role of berberine in promoting insulin-independent glucose uptake in the cell membrane. Moreover, it has been reported that treatment with berberine enhances glucose uptake, suppresses gluconeogenesis by downregulating key gluconeogenic genes (PEPCK, G6Pase), and improves mitochondrial function by promoting sirtuin 3 (SIRT3) degradation through an AMPK-dependent mechanism both in hepatocytes [89] and ovarian cells [90]. This indicates the potential pharmacological value of mitochondrial-driven AMPK activation by berberine in addressing glycometabolic disorders in the liver and ovary.

The liver regulates systemic glucose homeostasis by enhancing glucose uptake to form glycogen and lipids, and by providing glucose through glycogenolysis and gluconeogenesis, both in the fed state and during fasting. Aberrant hepatic gluconeogenesis activation results in hyperglycemia in T2D. Therefore, the inhibition of hepatic gluconeogenesis with the rate-limiting enzymes, including glucose-6-phosphatase (G-6-Pase) and phosphoenolpyruvate carboxykinase (PEPCK), ensures the maintenance of glucose homeostasis. Previous reports have shown that berberine suppresses the expression of PEPCK and G-6-Pase in the liver through AMPK signaling [91,92]. Berberine inhibits gluconeogenesis by upregulating the expression of p-AMPK and LKB1, and downregulating p-TORC2, PEPCK, and G6Pase expression in skeletal muscles and adipose tissues in diabetic rats [93]. This suggests the metformin-like properties of berberine that activate AMPK and suppress TORC2 to inhibit gluconeogenesis through cAMP response element–binding protein (CREB)-dependent transcription of peroxisome proliferator-activated receptor-γ coactlvator-1α (PGC1α) [94], and hence, highlights the need to conduct long-term clinical trials to evaluate the sustained effects of berberine on glucose metabolism in diverse populations.

6.2. Regulation of lipid metabolism

AMPK regulates lipid metabolism in adipose tissue, promoting lipolysis and suppressing lipogenesis, with dysfunction in adipose tissues leading to inflammation that contributes to IR and T2D [95]. Therefore, regulating AMPK-mediated lipid metabolism and controlling lipid accumulation holds therapeutic promise in the prevention and management of T2D. Several studies have shown the antidiabetic effects of berberine by AMPK-mediated lipid-regulation [93,96]. In a study to evaluate the effect of berberine on IR before the onset of hyperglycemia, treatment with berberine improved skeletal muscle mitochondrial dysfunction and insulin-sensitivity without affecting blood glucose level in rats by activating AMPK and inhibiting mitochondrial cyclophilin D [97]. AMPK-mediated inhibition of cyclophilin D suggests the beneficial role of berberine as an early clinical intervention for IR by abrogating mitochondrial permeability transition pore-induced mitochondrial dysfunction. Berberine exerts renoprotective effects by alleviating mitochondrial damage and improving lipid metabolism in podocytes in the development of DNP [98]. Treatment with berberine improved metabolic alterations, including lipid accumulation, mitochondrial ROS generation, mitochondrial dysfunction, and disrupted fatty acid oxidation in clinical and experimental studies of DNP by activating AMPK/PGC-1α signaling [98]. AMPK coordinates cellular energy through the PGC-1α signaling pathway to enhance fatty acid oxidation and mitochondrial biogenesis [99]. This indicates that berberine may have a positive impact on DNP by improving the health of renal mitochondria and optimizing energy metabolism. Although the efficacy of berberine in improving the lipid profile of diabetics is evident, further studies should be geared towards optimizing bioavailability, long-term safety, and personalized dosing strategies.

6.3. Regulation of oxidative stress and inflammation

The accumulation of free radicals from oxidative stress and the accompanying inflammation are predisposing factors to cell and tissue damage. Prolonged hyperglycemia increases reactive oxygen species (ROS) generation and a variety of inflammatory markers, which reinforce each other in a vicious cycle to cause IR and β-cell apoptosis, and eventually lead to DM [55,100–102]. The AMPK signaling pathway represents a critical convergence point for oxidative stress and inflammation in DM. The activation of AMPK can elicit various therapeutic interventions to simultaneously reduce ROS production, inhibit

Table 2
Studies showing the efficacy of berberine in treating DM and its complications through AMPK signaling.

S/N	Disease condition	Molecular target(s)	AMPK-related pathway	Type of study	References
1	T2D	IRS-1/PI3K/AKT and Nrf2	Enhanced glucose uptake and suppressed oxidative stress	*In vitro/in vivo*	[88]
2	DM	AMPK/Akt/IRS-1 and GSK3-β	Improved glucose uptake and glycogen synthesis	*In vitro/in vivo*	[177]
3	Metabolic diseases	AMPK	Suppression of gluconeogenesis and lipogenesis	*In vitro*	[96]
4	Hepatic damage and steatosis	AMPK/mTOR	Autophagy	*In vivo*	[178]
5	T2D	HO-1, PI3K/Akt and AMPK	Activated glycogenesis and inhibited gluconeogenesis, apoptosis and oxidative stress	*In vitro/in vivo*	[179]
6	DM	AMPK and eNOS	Inhibition of endoplasmic reticulum stress and oxidative stress	*Ex vivo*	[180]
7	Obesity/T2D	AMPK/PGC-1α	Activation of mitochondrial biogenesis and function and inhibition of lipid deposition	*In vitro/ in vivo*	[181]
8	DM	AMPK, SIRT3 and PEPCK	Promotes glucose uptake and inhibits gluconeogenesis	*In vitro/in vivo*	[89]
9	PCOS	AMPK, SIRT3 and FoxO3a	Promotes glucose uptake and inhibits mitochondrial function	*In vitro*	[90]
10	T2D	LKB1, AMPK-TORC2	Inhibits gluconeogenesis in skeletal muscles and adipose tissues	*In vivo*	[93]
11	Inflammatory responses in macrophages	AMPK, SIRT1, and NF-κB	Suppression of proinflammatory cytokines	In vitro	[108]
12	Obesity	AMPK/NLRP3	Suppressed NLRP3 inflammasome activation activated autophagy	*In vitro/in vivo*	[105]
13	Insulin-resistant patients	AMPK/Akt, CypD	Increased insulin sensitization in muscles and inhibited lipolysis in adipose tissue	*In vitro/in vivo*	[97]
14	Obesity	AMPK, ATGL, and HSL	Increased lipolysis	*In vitro*	[182]
15	DNP	AMPK, ACC, and CPT-1	Reducing lipogenesis and enhancing lipolysis	*In vitro*	[183]
16	DNP	AMPK, PGC-1α, CPT1, ACOX1 and PPAR-α	Reducing lipogenesis and enhancing lipolysis	*In vitro/in vivo*	[112]
17	DNP	AMPK, mTOR, and TGF-β1	Promoting autophagy and inhibiting glomerular mesangial matrix expansion	*In vivo*	[110]
18	DR	AMPK/mTOR	Inhibiting apoptosis and stimulating autophagy	*In vitro*	[119]
19	DN	AMPK/PPARs	Suppression of proinflammatory cytokines	*In vivo*	[116]
20	DN	SIRT1/AMPKα/PGC1-α/NRF2	Positive effects on autophagy, inflammation, oxidative stress, and mitochondrial biogenesis	*In vivo*	[106]
21	DCM	AMPK/NLRP3/mTOR/mtROS	Improved NLRP3-dependent inflammation	*In vitro/in vivo*	[103]
22	DNP	AMPK/mTOR	Inhibited apoptosis and activated autophagy	*In vitro*	[109]
23	DNP	AMPK/NF-κB	Inhibited the activation of inflammatory pathways and regulated macrophage polarization	*In vitro/in vivo*	[111]
24	DN	AMPK/PKCε/TRPV1	Suppressing inflammatory pathway	*In vivo*	[115]
25	Heart failure	AMPK/PGC-1α signaling	Maintains mitochondrial homeostasis and prevents apoptosis	*In vitro/in vivo*	[127]
26	DCM	AMPK/mTOR	Enhance mitochondrial biogenesis and autophagy	*In vitro*	[128]
27	Ischemia–reperfusion injury	AMPK/AKT/GSK3β	Reduction of lipogenesis, apoptosis, and stimulation of glucose uptake	*In vivo*	[129]
28	Ischemia–reperfusion injury	AMPK/mTOR	Reduced myocardial autophagy and apoptosis	*In vitro/* clinical	[130]
29	DR	AMPK	Modulation of autophagy, apoptosis, oxidative stress, and inflammation	*In vitro*	[120]
30	AMD	AMPK activation	Inhibition of oxidative stress and apoptosis	*In vitro*	[123]
31	Atherosclerosis	AMPK/KLF16/PPARα	Increase insulin sensitivity and inhibit lipid accumulation and vascular inflammation	*In vitro/ in vivo*	[144]
32	Atherosclerosis	AMPK/NF-κB/galectin-3	Suppressed lipid accumulation and inflammatory cytokines	*In vitro/* clinical	[145]
33	Diabetic osteopathy	AMPK/Runx2/OPG	It improves insulin sensitivity, stimulates osteoblastogenesis, and inhibits osteoclastogenesis.	*In vivo*	[137]
34	OA	AMPK/SIRT3; AMPK/SIRT1/SIRT3	Limits oxidative stress and improves mtDNA integrity and function; Preserving mitochondrial biogenesis capacity and suppressing inflammation	*Ex vivo/in vivo*	[138,139]
35	RA	AMPK/mTORC1; AMPK/HIF-1α; AMPK/NF-κB	Reduced inflammatory response by shifting macrophage polarization from M1 to M2 phenotype	*In vitro/in vivo*	[140]; [141]; [142]
36	Osteoporosis	AMPK activation of multiple pathways	Enhancement of antioxidants, bone formation by osteoblasts, and inhibition of bone resorption by osteoclasts	*In vivo*	[143]
37	Diabetic cognitive dysfunction	AMPK/SIRT1/PGC-1α/GLUT4	Enhancing mitochondrial biogenesis, glucose uptake and reducing oxidative stress	*In vivo*	[146]
38	Diabetic lung injury	AMPK/NEU1/TGFβ1/Smad	Reduced glycemic and lipid levels, and inhibition of inflammation	*In vitro/in vivo*	[147]
39	NAFLD	AMPK/SIRT1	Regulates lipid metabolism, oxidate stress and inflammation	*In vivo*	[131]
40	NAFLD	AMPK-ERK-C/EBPβ and CD36	Fatty acid uptake and oxidation	*In vitro/in vivo*	[134]
41	NAFLD	AMPK-SREBP-1c-SCD1	Reduces hepatic triglyceride accumulation	*In vitro/ex vivo/in vivo*	[133]

ACC, acetyl-CoA carboxylase; AMD, age-related macular degeneration; AMPK, AMP-activated protein kinase; ATGL, adipose triglyceride lipase; Akt, Protein Kinase B; C/EBPβ, CCAAT/enhancer-binding protein beta; CPT-1, carnitine palmitoyltransferase 1; CypD, cyclophilin D; DCM, diabetic cardiomyopathy; DM, diabetes mellitus; DN, diabetic neuropathy; DNP, diabetic nephropathy; DR, diabetic retinopathy, eNOS; endothelial nitric oxide synthase; HO-1, heme oxygenase-1; IR, insulin resistance; IRS-1, insulin receptor substrate-1; LKB1, Liver Kinase B1; NAFLD, non-alcoholic fatty liver disease; Nrf2 nuclear factor (erythroid-derived 2)-related factor 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; OA, osteoarthritis; PEPCK, phosphoenolpyruvate carboxykinase; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1 α; PI3K, phosphatidylinositol 3-kinases; RA, rheumatoid arthritis; ROS, reactive oxygen species; SIRT-1, sirtuin-1; SIRT-

3, sirtuin-3; SREBP-1c, sterol regulatory element-binding protein 1; TGF-β1, transforming growth factor-beta 1; TORC2,target of rapamycin complex 2; T2D; type 2 diabetes mellitus.

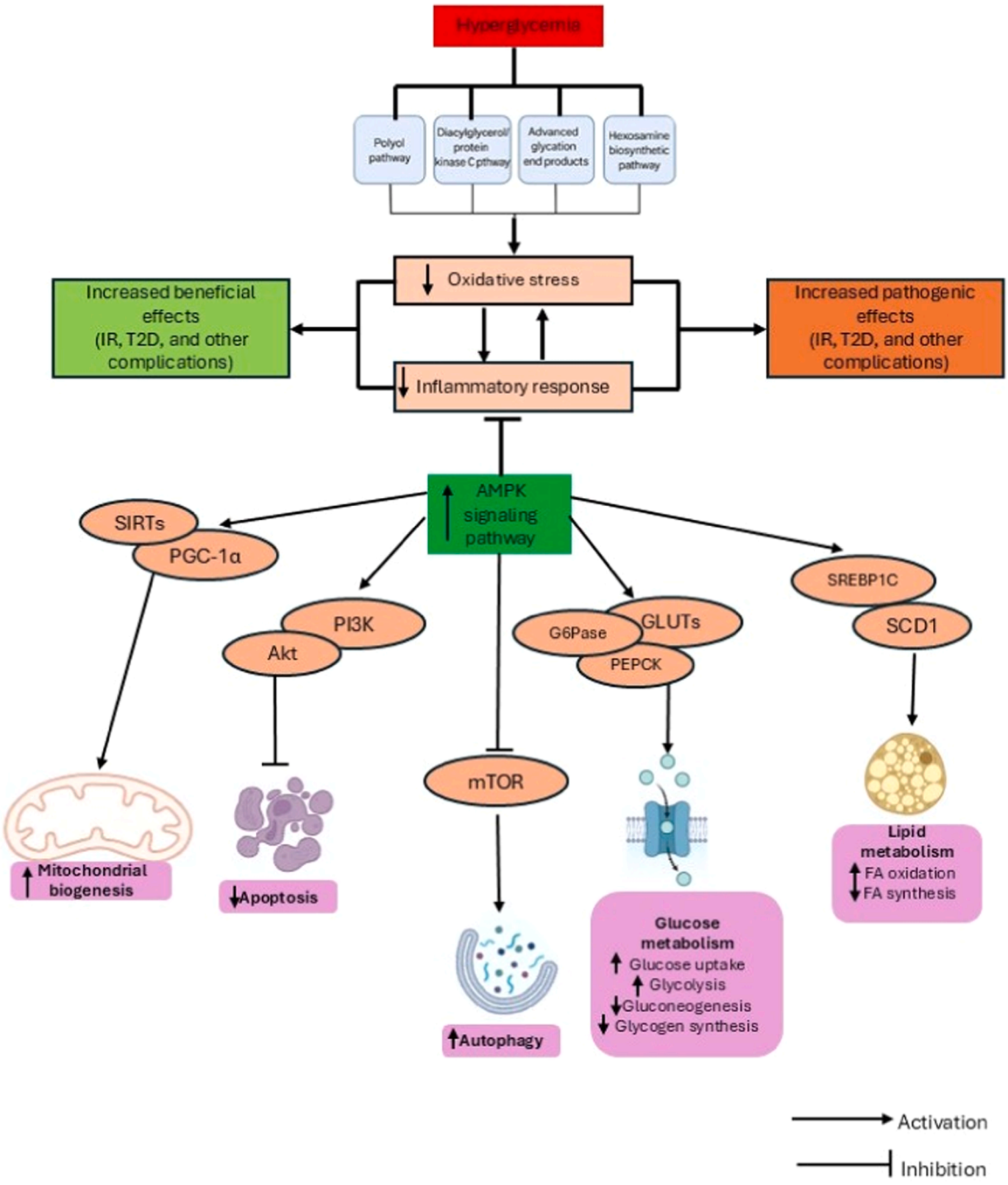

Fig. 4. A unified schematic diagram summarizing the therapeutic mechanisms of action of AMPK in diabetes and its complications.

inflammatory pathways, and improve glucose metabolism [100].

Berberine has been reported to inhibit mitochondrial ROS generation and suppress Nod-like receptor family pyrin domain containing 3 (NLRP3)-dependent inflammation via the AMPK/mTOR pathway to alleviate cardiac inflammation in DCM [103]. mTOR activation predisposes cells to myocardial injury by impairing autophagy, and AMPK/mTOR signaling-mediated autophagy attenuates NLRP3 inflammation in DCM [104]. Thus, this suggests the cardioprotective and anti-inflammatory effects of berberine are by improving autophagy, which is often dysregulated in DCM. Similarly, berberine prevents NLRP3 inflammasome activation and inhibits palmitate-stimulated interleukin-1β (IL-1β) expression through activating AMPK-dependent autophagy in macrophages [105]. Moreover, berberine mitigates oxidative damage and neuroinflammation in a mouse model of diabetic encephalopathy by modulating AMPK signaling [106]. Defective mitochondrial biogenesis plays a pathophysiological role in diabetic complications by suppressing PGC-1α expression in cells to inhibit Nrf2 expression [107]. By upregulating PGC-1α expression, berberine facilitates Nrf2-mediated antioxidant defense systems, thereby mitigating oxidative damage and neuroinflammation in peripheral neurons and

neuronal cells. Treatment with berberine not only reduces oxidative stress and neuroinflammation but also significantly ameliorates cognitive deficits and neuronal apoptosis. These effects were closely associated with the activation of the AMPK/Nrf2/PGC-1α pathway, indicating a mechanistic link between the metabolic and neuroprotective effects of berberine. The findings indicate the promising role of berberine not only in glycemic control but also in preventing or mitigating oxidative stress and neuroinflammation-mediated cognitive decline.

In another study, berberine was shown to improve hepatic insulin sensitivity by relieving oxidative stress in experimental diabetic models by enhancing the phosphorylation of AMPK and promoting nuclear translocation of Nrf2 [88], suggesting that berberine may help protect liver cells from oxidative damage and improve metabolic function in diabetic conditions. Berberine mitigated oxidative stress by elevating SOD and GPx activities, reducing ROS and MDA levels, and upregulating the expression of Nrf2, NQO1, and HO-1 in hepatic tissues. Moreover, berberine relieves inflammatory responses in macrophages by downregulating the expression of proinflammatory cytokines and suppressing NF-κB signaling through SIRT1-dependent mechanisms [108]. This suggests that berberine could target both metabolic and inflammatory pathways by regulating AMPK signaling upstream of SIRT1, thereby supporting its potential as a multifaceted therapeutic agent in DM management.

7. AMPK-mediated preventive and therapeutic effects of berberine in DM-related complications

A growing body of preclinical evidence shows the ability of berberine to activate AMPK and regulate metabolic pathways to protect against diabetic complications (Table 2). An overview of the molecular targets and mechanisms underlying berberine-mediated activation of AMPK signaling in alleviating DM and DM-associated complications is summarized in Fig. 5.

7.1. Diabetic nephropathy

Diabetic nephropathy is one of the most common microvascular complications in individuals with DM. Statistically, approximately 40 % of diabetic patients are affected by DNP, and it is the major risk factor for end-stage renal disease. Oxidative stress and chronic inflammation play a pathogenic role in the progression of DNP. Treatment with berberine exerts renoprotective effects by promoting autophagy through the AMPK/mTOR signaling pathway in mouse podocytes [109] and in animal models [110]. This suggests that by activating autophagy, berberine may alleviate oxidative stress and inflammatory damage in DNP, thereby improving kidney function and potentially abrogating clinical microalbuminuria, proteinuria, and renal fibrosis. Moreover, berberine reduces inflammatory response and protects renal cells from injury in a mouse model of uric acid nephropathy through the activation of AMPK and indirect inhibition of NF-κB signaling pathway [111]. AMPK and NF-$_K$B are known to share anti-inflammatory mechanisms in suppressing macrophage infiltration. Regulating AMPK/NF-$_K$B signaling pathway suggests the therapeutic benefits of berberine in maintaining the structure and function of the kidney. In addition, treatment with berberine suppresses elevated levels of uric acid, bilirubin, and creatinine, as well as macrophage infiltration in the kidney. This suggests that berberine has urate-lowering and anti-inflammatory effects, which may play a role in preventing nephrolithiasis and tubule-interstitial fibrosis associated with DNP. Berberine reduces tubule epithelial lipid accumulation and promotes fatty acid oxidation and mitochondrial function in T2D mice by enhancing AMPK activation and promoting PGC-1α expression [112], indicating a beneficial role in the onset and progression of DNP. Therefore, further mechanistic studies on the downstream effects of activating AMPK/PGC-1α signaling pathways, as well as assessing the

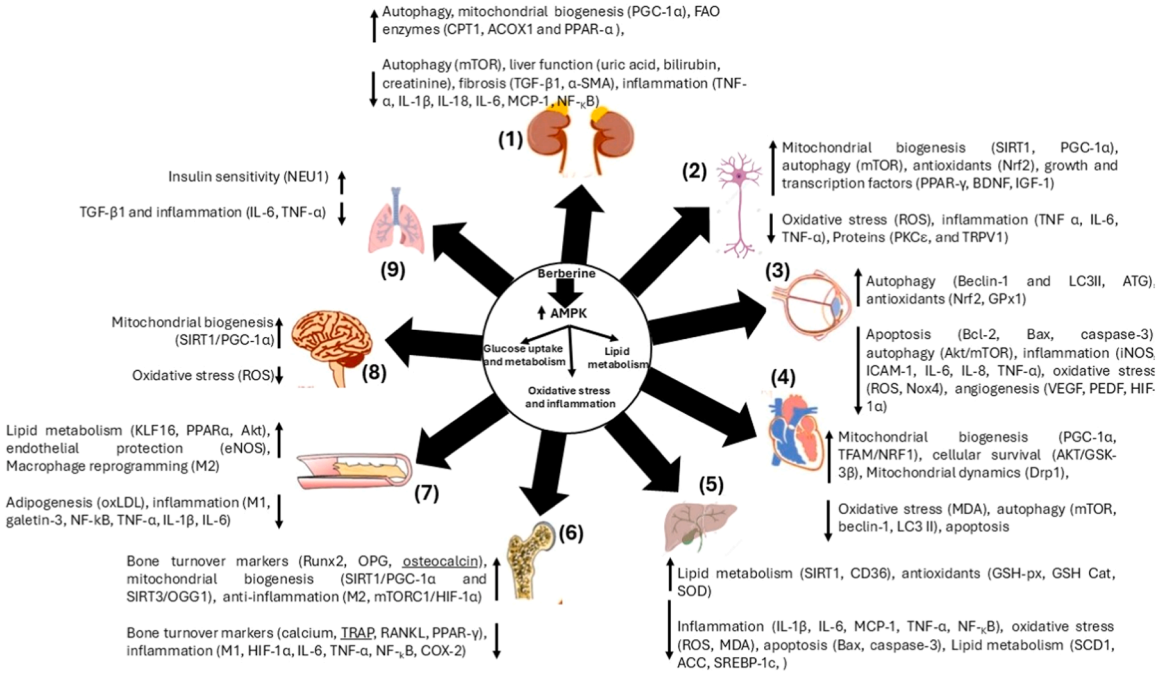

Fig. 5. Overview of multiple targets and pathways of AMPK activation by berberine for the management of diabetes and its complications. Berberine activates AMPK, a central regulator of cellular energy homeostasis, which impacts multiple metabolic processes such as autophagy, apoptosis, mitochondrial biogenesis, inflammation, oxidative stress, and fibrosis, involved in glucose uptake and metabolism, lipid metabolism, oxidative and inflammatory pathways, thereby alleviating diabetes and its complications. AMPK, AMP-activated protein kinase; CPT-1, carnitine palmitoyltransferase 1; eNOS; endothelial nitric oxide synthase; GSK3β, glycogen synthase kinase 3β; HIF-1α, hypoxia-Inducible Factor 1-alpha; IL-1, interleukin-1; mTOR, mechanistic target of rapamycin; NEU1, Neuraminidase-1; Nrf2, nuclear factor (erythroid-derived 2)-related factor 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1 α; ROS, reactive oxygen species; Runx2, Runt-related transcription factor 2; SCD1, stearoyl-CoA desaturase 1; SIRT-1, sirtuin-1; SIRT-3, sirtuin-3; SREBP-1c, sterol regulatory element-binding protein 1; TGF-β1, transforming growth factor-beta 1; TNF-alpha, tumor necrosis factor-alpha.

preventive effects of berberine on the early onset of renal tubular dysfunction in prediabetic or at-risk populations, are needed to understand its therapeutic potential.

7.2. Diabetic neuropathy

Diabetic neuropathy is a chronic microvascular complication of DM, which is characterized by hypersensitivity and intense pain that affects the central, peripheral, and autonomic nervous systems. It is a significant risk factor for foot ulceration, which accounts for 50–75 % of non-traumatic lower extremity amputations [113]. AMPK has been reported to play a crucial role in neuronal function, pain regulation, and neurodegeneration [114]. The neuroprotective effects of berberine have been reported in previous studies [106,115,116]. Mitochondrial dysfunction, particularly in nociceptors, is a critical etiological factor for neuropathic pain in diabetics [117]. Treatment with berberine reduces nociception associated with DN in diabetic rats by activating AMPK/PGC-1α signaling in peripheral neurons and neuronal cells to promote mitochondrial function [106]. The activation of this signaling pathway enhances mitochondrial biogenesis and autophagy to strengthen redox homeostasis and abrogates neuroinflammation, indicating that berberine could alleviate lower extremity pain transmission by preventing oxidative stress in peripheral nerves. Similarly, berberine has been reported to mitigate diabetic pain in animal models by blocking the release of proinflammatory factor TNF-α and protein kinase C epsilon (PKCε)-mediated suppression of transient receptor potential vanilloid subtype 1 (TRPV1) activation [115]. By inhibiting PKCε, it is argued that berberine could activate the expression of AMPK, leading to anti-allodynic effects, by reducing inflammation and sensory neuron excitability [114], and therefore, requires further preclinical and clinical data validation.

7.3. Diabetic retinopathy

Diabetic retinopathy is a common microvascular complication of DM and remains the leading cause of blindness in the elderly. Despite numerous investigations on the aetiology and pathology of DR, there are disappointingly few effective treatment options available [118]. Therefore, any treatment that could suppress the progression of DR would be immensely valuable, both to diabetic patients and society at large. AMPK activation by berberine reduces Müller cell injury by enhancing autophagy and relieving oxidative stress, inflammation, apoptosis, pro-angiogenesis, and glial cell activation in retinal cells [119,120]. This suggests the beneficial effects of berberine in targeting multiple interconnected pathological processes leading to the progression of DR. Berberine reduces the expression of HIF-1α and VEGF and improves DR by inhibiting the Akt/mTOR pathway in retinal endothelial cells [121]. Akt/mTOR and AMPK are two regulatory mechanisms that often oppose each other [122]. Thus, berberine reduces HIF-1α and VEGF expression, leading to the alleviation of retinal neovascularization and damage through an AMPK-dependent mechanism. Moreover, berberine protects retinal pigment epithelium cells against oxidative injury and cell death by suppressing mitochondrial apoptosis partially through the activation of AMPK signaling pathway in vitro [123], suggesting its protective role against age-related retinal pathophysiology.

7.4. Diabetic cardiomyopathy

DCM is a multifactorial disease and the leading cause of heart failure in diabetic patients, posing a significant medical challenge because of its complex pathophysiology and the absence of targeted therapies [124]. Chronic hyperglycemia and IR are the major predisposing factors to the condition, causing complex alterations in metabolic pathways within cardiomyocytes, which lead to deranged myocardial structure and myocardial dysfunction [125]. AMPK has been reported to play a beneficial role in regulating cardiac physiology [126].

Berberine improved cardiac function in a murine model of heart failure with preserved ejection fraction by maintaining mitochondrial homeostasis and preventing apoptosis through the activation of AMPK/PGC-1α signaling pathway [127]. Treatment with berberine inhibited apoptosis, suppressed ROS generation, and disrupted mitochondrial homeostasis by upregulating AMPK and PGC-1α expression both in vitro and in vivo, suggesting the cardiovascular benefits of berberine as an AMPK agonist. Berberine plays a pivotal role in mitigating cardiomyocyte hypertrophy and high glucose-induced cardiomyocyte injury in vitro by restoring mitochondrial function and autophagic flux through AMPK-dependent inhibition of dynamin-related protein 1 (Drp1) [128], suggesting its role in maintaining mitochondrial dynamics and health in cardiomyocytes. Treatment with berberine was reported to protect diabetic heart from ischemia–reperfusion injury and decrease arrhythmia in diabetic rats partly through suppressing myocardial autophagy and apoptosis via the AMPK/mTOR and AMPK/AKT/GSK3β signaling pathways in vivo and in vitro [129,130], suggesting its prospects as a therapeutic agent in improving cardiac health in diabetic patients. Hence, further preclinical and clinical evidence is needed to validate the protective effects of berberine on cardiomyopathy and promote its application to cardiovascular medicine.

7.5. Diabetic hepatic steatosis

Diabetic hepatic steatosis is a hallmark feature of nonalcoholic fatty liver disease (NAFLD), which can subsequently advance to non-alcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma when the liver exhibits aberrant inflammation. The pathophysiological mechanisms of NAFLD are complex and have not been completely elucidated; however, it is widely accepted to involve complex interactions among obesity, dyslipidemia, IR, inflammation, and oxidative stress [131,132]. The discovery of safe and effective hepatic lipid-lowering drugs aimed at mitigating NAFLD-related pathological conditions has been an area of active research.

Berberine has been shown to improve NAFLD-related hepatic lipogenesis primarily through the activation of AMPK, which disrupts the sterol-regulatory element binding protein-1c (SREBP-1c)-SCD1 lipogenic pathway in steatotic hepatocytes, both in vitro and in vivo [133]. The activation of AMPK enhanced the phosphorylation of SREBP-1c and inhibited the expression of SCD1 and fatty acid synthase (FAS), leading to a reduction in liver triglyceride synthesis and an improvement in hepatic steatosis in patients with NAFLD, as well as in experimental models. Similarly, Chen et al. [131] reported that berberine reduced hepatic lipid accumulation, oxidative stress, and inflammation, thereby improving both biochemical and histological parameters in db/db mice through AMPK/SIRT1-dependent mechanisms. However, treatment with berberine enhances CD36 expression and promotes fatty acid uptake and lipid accumulation in hepatocytes via ERK1/2–C/EBPβ signaling [134]. Collectively, these findings elucidate the molecular basis and the dual nature of berberine action in hepatic steatosis, which exerts hepatoprotective benefits through AMPK-dependent pathways, while also exhibiting context-dependent pro-lipogenic effects. Either way, the jury is still out but underscores the importance of investigating the precise molecular mechanisms underlying the pro-lipogenic effects of berberine, particularly in relation to the ERK1/2–C/EBPβ signaling pathway when using berberine to manage DM-related hepatic complications.

7.6. Diabetic osteopathy

Patients with diabetes are more susceptible to skeletal complications, commonly referred to as "diabetic osteopathy" or "diabetic bone disease." The most prevalent forms of diabetic bone disease include osteoporosis, an increased risk of fractures, and impaired bone healing properties. Bone tissues of diabetic patients with DM are characteristically prone to microstructure destruction, bone metabolism imbalance,

and reduced bone turnover rate [135]. AMPK signaling has favorable effects on both DM and bone fragility. AMPK activation enhances mineralization and differentiation of osteoblastic cells and increases the formation of trabecular bone nodules [136], suggesting its favorable effects on skeletal metabolism and bone physiology in diabetic conditions. Berberine reverses pioglitazone-induced bone loss and deterioration of bone microarchitecture in diabetic rats by restoring abnormal bone turnover markers through the activation of the AMPK signaling pathway [137]. Treatment with berberine increases bone resorption and decreases bone formation by increasing Runx2, OPG, and osteocalcin, as well as decreasing RANKL in an animal model of diabetic osteoporosis, suggesting the osteogenic role of berberine to improve bone physiology by maintaining bone remodeling processes.

Progressive cartilage degeneration is a predisposing factor of osteoarthritis, which results in permanent loss of joint function. Treatment with berberine alleviates age-related spontaneous cartilage degradation by preserving mitochondrial DNA integrity and function and preventing excessive oxidative stress in mice through the activation of AMPK/SIRT3 signaling pathway [138]. Similarly, activation of AMPK by berberine attenuated the progression of post-traumatic osteoarthritis by suppressing cartilage degradation, synovitis, and osteophyte formation, and improving pain sensitization in mice [139]. Moreover, the anti-arthritic effects of berberine have been reported in vivo through AMPK-mediated regulation of macrophage energy metabolism [140,141] and macrophage polarization [142]. While osteoarthritis currently lacks a definitive cure, these findings collectively underscore the chondroprotective effects of berberine, highlighting its potential as a therapeutic agent in the context of metabolic disorders like DM. However, Londzin et al. [143] reported that while berberine beneficially affects bone growth through the activation of AMPK, it did not sufficiently improve the quality of bone in diabetes-induced bone damage. This could be due to the multifactorial nature of diabetes-induced bone damage, which creates a barrier that AMPK activation alone cannot fully address. This, therefore, highlights the importance of further research and suggests a need for combination therapies that target multiple pathways simultaneously to combat diabetic bone disease effectively.

7.7. Other diabetic complications

The activation of AMPK by berberine shows significant promise beyond the common complications of DM, including diabetic atherosclerosis, diabetic cognitive dysfunction, and diabetic lung injury. Berberine improved lipid and glucose metabolic dysfunction to alleviate diabetic atherosclerosis and plaque vulnerability in vivo [144]. Treatment with berberine suppressed inflammation, monocyte adhesion to endothelial cells, and foam cell formation through AMPK-mediated activation of Krüppel-like factor 16 (KLF16)/PPARα signaling pathway. Macrophage-derived foam cells and galectin-3 expression have a critical regulatory role in the pathogenesis of atherosclerosis. Berberine significantly delayed the progression of atherosclerosis by downregulating galectin-3 expression through the modulation of the NF-κB and AMPK signaling pathways, thereby attenuating macrophage activation induced by oxidized LDL and reducing inflammation [145]. This suggests that the activation of AMPK by berberine contributes to the attenuation of the galectin-3-induced inflammatory response and delays the progression of atherosclerotic lesions and atherosclerotic plaque. Treatment with berberine mitigated aging-related reductions in cognitive ability and muscular function in aging rats by reversing glucose metabolism abnormalities and muscle mitochondrial dysfunction through the AMPK/SIRT1/PGC-1α signaling pathway [146], thereby highlighting the therapeutic benefit of berberine in mitigating cognitive deficits and muscle dysfunction associated with aging. Berberine suppresses lung inflammation and alveolar epithelial-mesenchymal transition in diabetic mice by activating AMPK/NEU1 Signaling and inhibiting TGF-β1 expression [147], suggesting a potentially beneficial role in preventing lung fibrosis. While berberine demonstrates promise in addressing diabetic complications through AMPK activation, further research is needed to fully comprehend its long-term effects and efficacy, particularly concerning lung-related issues, as well as a need for additional clinical studies to validate these benefits in human populations.

8. Clinical considerations and future perspectives

Although preclinical studies have established a strong link between the effects of berberine and the activation of AMPK, human clinical trials seldom measure AMPK activity directly. This is primarily due to the fact that measuring AMPK activity reliably requires tissue biopsies from muscle, liver, and fat, which are invasive [148–150]. Such procedures are not routinely performed in DM trials, where the primary focus tends to be on clinical outcomes, like levels of HbA1c, rather than the underlying molecular mechanisms.

Despite the fact that much of the existing knowledge regarding the activation of AMPK by berberine in DM treatment is based on in vitro and in vivo preclinical studies, some clinical trials focusing on complications where AMPK plays a central role, or AMPK-dependent metabolic parameters, served as reliable surrogates to validate the clinical significance of AMPK in the antidiabetic effects of berberine have been completed or are underway (ClinicalTrials.gov) (Table 3). For example, in the multi-center, randomized, double-blind, placebo-controlled study with the aim of determining the efficacy and safety profile of administering berberine (500 mg, bid) and bifidobacteria (700 mg, bid) for 16 weeks to newly diagnosed patients with pre-diabetes or DM (NCT03330184) [20], even though AMPK was not mentioned as an outcome, the study measured the changes in HbA1c and FPG, where AMPK activation is a key proposed mechanism. In another study focusing on non-alcoholic steatohepatitis, treatment with berberine ursodeoxycholate (HTD1801) (1000 mg, bid) has been shown to reduce lipogenesis and enhance fatty acid oxidation (NCT03656744) [68]. Although AMPK itself was not directly measured, the observed improvements in liver fat and liver-related enzymes suggest the core AMPK-mediated effects in alleviating the complications associated with NAFLD and DM.

Despite the promising therapeutic effects of berberine in managing DM and its complications, several concerns remain. The poor bioavailability and potential interactions with other medications pose significant pharmacokinetic challenges that hinder the approval of berberine as a clinical drug. The bioavailability of berberine can be influenced by its innate physicochemical properties and biological interactions in the systemic circulation. Berberine is a potent modulator of various cytochrome enzymes, such as cytochrome P450 enzymes [151,152] and drug transporters, including P-glycoprotein (P-gp) and organic anion transporting polypeptides (OATPs) [153,154]. It has been reported that berberine synergizes with statins to enhance its hepatic CYP3A4 inhibitory activity and to increase its cardiotoxicity [155] and induces OATP1B1 expression to improve the drug deposition [154], suggesting its potential role in affecting the pre-systemic metabolism and bioavailability. These interactions raise concerns regarding the possible effects of berberine on commonly prescribed medications, as they may elevate blood levels and increase the risk of toxicity for these co-administered drugs. Therefore, it is crucial to develop suitable formulations that enhance oral bioavailability by using bioenhancers and novel delivery systems such as nanocarriers, as well as modulating these proteins to mitigate the risks associated with berberine interactions. Common herbal bioenhancers, such as piperine, quercetin, curcumin, and naringin, which improve absorption, modulate drug metabolism, and interact with drug transporters, are used to enhance therapeutic outcomes and reduce the dosage of berberine [156]. The use of Brij-S20-modified nanocrystals significantly improved the intestinal transport and oral bioavailability of berberine. This formulation enhances the intracellular uptake by modulating P-gp function, leading to a 404.1 % increase in relative bioavailability compared to pure

Table 3
Some of the registered clinical trials of berberine using surrogates of AMPK in diabetes and related complications.

Condition	Study title	Intervention	Outcomes	Design	Study identifier	Status
T2D	A Phase 2 Study of Berberine Ursodeoxycholate (HTD1801) in Patients With Type 2 Diabetes Inadequately Controlled With Diet and Exercise	HTD1801 (1000 mg, bid po)	Change in HbA1c levels	Phase 2, double-blind, placebo-controlled, 12-week randomized clinical trial	NCT06411275	Completed
	Comparative Efficacy of Metformin and Berberine Among TCF7L2 (rs7903146) TT vs. CC Genotype Carriers With Type 2 Diabetes	Metformin (500 mg, bid po) and berberine (500 mg, tid po)	Change in HbA1c	Randomized open-label study	NCT06911983	Ongoing
pre-diabetes or DM	Effectiveness and Safety of Berberine Hydrochloride and *Bifidobacterium* in People With Abnormal Glucose Level	*Bifidobacteria* and berberine (500 mg, bid po)	Change of absolute value of FPG and HbA1c	Double-blind, randomized, and parallel-controlled study	NCT03330184	Completed
NAFLD	A Study of HTD1801 in Adults With Nonalcoholic Steatohepatitis (NASH) and Type 2 Diabetes Mellitus	HTD1801 (1000 mg, bid po)	Change in glycemic control, liver-associated enzymes, and weight loss	Randomized, double-blind, placebo-controlled, parallel-group study	NCT03656744	Completed
T2D	A Study on the Efficacy and Gut Microbiota of Berberine and Probiotics in Patients With Newly Diagnosed Type 2 Diabetes	Berberine hydrochloride tablets (600 mg, bid po) and Promets probiotics powder (400 mg, qN po)	Changes in HbA1c	Multicenter randomized, double-blind, placebo-controlled trial	NCT02861261	Completed
T1D	Effects of Berberine Plus Inulin On Diabetes Care in Patients With LADA	Berberine (600 mg, bid) and inulin (600 mg, bid po)	Change in HbA1c	Prospective, randomized, double-blind, placebo-controlled trial	NCT04698330	Ongoing
T2D and metabolic syndrome	Efficacy and Safety of Berberine in the Treatment of Diabetes with Dyslipidemia	Berberine (1000 mg, po)	Changes in plasma glucose and serum lipid levels	Randomized, double-blind, and placebo-controlled trial	NCT00462046	Completed

FPG, fasting plasma glucose; HbA1c, glycated hemoglobin A1c; HTD1801, berberine ursodeoxycholate; LADA, latent autoimmune diabetes in adults.

berberine [157]. Similarly, hyaluronate-based liposomes have been found to improve the entrapment efficiency and sustained release of berberine, resulting in enhanced bioavailability and faster absorption into the bloodstream [158]. Thus, further studies should be geared toward pharmacokinetic optimization of berberine to fully establish its therapeutic potential and clinical guidelines for its application.

Enhancing the absorption of berberine has garnered significant attention in research. For example, in a phase 2 randomized clinical trial, a novel derivative, HTD1801, was designed to improve the bioavailability of berberine in treating T2D [22]. A comparison between the results of this study and short-term studies of metformin indicates that equivalent doses of HTD1801 exhibited similar, albeit slightly reduced, potency. Specifically, metformin at the doses of 500 mg twice daily can lead to a reduction in HbA1c levels by 1.0 % to 1.5 %, while 1000 mg twice daily may achieve reductions of 1.5 % to 2.0 % over comparable time frames [159]. However, the glucose-lowering effects of HTD1801 are consistent with those of other FDA-approved antihyperglycemic medications, such as sodium-glucose cotransporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors [65], indicating a promising translational potential for the use of berberine.

Genetic polymorphisms in drug transporters and metabolic enzymes may contribute to interindividual variability in berberine pharmacokinetics and efficacy. Variants in ABCB1 (P-glycoprotein), such as C3435T and G2677T/A, can alter intestinal efflux, affecting berberine absorption and systemic exposure [160]. In addition, polymorphisms in CYP2D6, CYP1A2, and CYP3A4 affect oxidative metabolism, while alterations in UGT1A1 and UGT2B1 can reduce glucuronidation, potentially leading to increased plasma concentrations of berberine [161]. Polymorphisms in CYP2D6, the primary enzyme responsible for berberine metabolism, have sex-specific effects on the pharmacokinetics of berberine metabolism, particularly in females [162]. Altered SLC22A1 (OCT1) function due to polymorphism may modify hepatic uptake of its substrates and AMPK activation, thereby impacting their pharmacokinetics and therapeutic efficacy. Studies have shown that OCT1-mediated uptake is crucial for the pharmacological action of drugs like metformin, which also activates AMPK, suggesting a similar importance for berberine [163]. Moreover, ethnic differences in gut microbiota significantly impact the pharmacokinetics of berberine. Ethnic-specific allelic frequencies can lead to population-level differences in efficacy and tolerability of berberine, compounded by host genetic influences on gut microbiota-mediated conversion of berberine to dihydroberberine. For instance, individuals of African descent have shown higher Cmax and AUC values for berberine compared to their Chinese counterparts, which can be attributed to differences in gut microbiota composition. The Chinese population tends to have a higher abundance of certain bacterial genera, resulting in increased metabolism and reduced systemic exposure to berberine [164]. These variations highlight the importance of considering pharmacogenetics in optimizing berberine therapy.

Although berberine is classified as a phytocompound that is generally regarded as safe and well-tolerated, there still remain concerns of toxicity, including gastrointestinal effects such as diarrhea, constipation, flatulence, and stomach discomfort [21]. The dosage of berberine used in clinical trials ranges from 0.3 to 1.5 g/day, depending on the formulation and the target condition, with treatment durations lasting from a few weeks to several months [165]. It is noteworthy that adverse effects associated with berberine are primarily linked to overdosing, which is often done in an attempt to compensate for its poor bioavailability or with prolonged use [22,166]. However, a lower dose with long-term intake of berberine has been suggested to confer more substantial benefits for patients [167], suggesting a promising approach to mitigate berberine toxicity. Either way, this highlights the importance of comprehensively understanding and validating the long-term safety and efficacy of berberine through larger randomized controlled trials, compared to other antidiabetic agents.

Despite the evidence from meta-analyses and pooled trials showing significant reductions in fasting glucose, HbA1c, and lipid levels with berberine, many of these studies are small, short in duration, single-center, and utilize varying dosages and product types [168]. Therefore, large multicenter randomized controlled trials with standardized endpoints and long-term safety follow-up are still needed. Moreover, variability in formulations poses a significant limitation to the clinical

application of berberine, leading to inconsistencies in its safety and efficacy [169]. Despite the development of various formulations such as Berberine LipoMicel® [60], Berberine Phytosome™ [170], and berberine nanoformulations [171] aimed at enhancing absorption and therapeutic effects, challenges related to berberine formulations persist. For example, a quantitative analysis of 15 berberine-containing dietary supplements available in the U.S. market, using ultra-high-performance liquid chromatography tandem mass spectrometry, showed that the average berberine content across these products was 75 % ± 25 % of the amount claimed on the product labels. The potency of the products varied significantly, ranging from 33 % to 100 %, with 60 % of the tested products not meeting the potency standards of 90 % to 110 % of the labeled content claim [172]. The lack of reliable, standardized formulations that address the challenge of bioavailability complicates dosing strategies and undermines the validity of cross-trial comparisons. Therefore, there is a need for optimization of berberine formulations using a clinically proven, widely adopted enhanced delivery system with predictable pharmacokinetics to address these issues.

The future of berberine in managing DM and its complications requires strategic advancements that will focus on overcoming bioavailability limitations using delivery technologies, strategic combination regimens with current antidiabetics, and a concerted effort to establish rigorous quality standards and clear regulatory systems. Nano-delivery systems such as metallic, polymeric, lipid, and hybrid nanoparticles and nanocarriers could be used to enhance the solubility of berberine and address its pharmacokinetic barriers. These nanoplatforms could be functionalized with ligands to maximize the delivery of berberine to sites of diabetic complications, thereby minimizing systemic exposure and off-target effects [173]. Stimuli-responsive nanosystems could be designed in response to the diabetic microenvironment, such as high ROS, acidic pH, and overexpressed enzymes, to achieve controlled release of berberine and to potentiate its pharmacodynamic effects. Nano-phytosomes and lipid-based carriers, which have translational appeal because of relative manufacturing simplicity, could be used to improve membrane permeability and oral bioavailability of berberine. The phospholipid structures in phytosomes protect phytoconstituents from degradation by digestive enzymes and gut bacteria to ensure better therapeutic outcomes [174].

Berberine could be used as a complementary agent with standard antidiabetic medications. The multifaceted mechanisms of berberine present strong support for its use in combination with existing medications such as metformin, DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones (TZDs), and insulin secretagogues. The most promising area lies in the berberine–metformin combination, as clinical trials have suggested that this combination therapy leads to greater reductions in fasting plasma glucose, HbA1c, and triglyceride levels than either drug used alone, with potential for metformin dose reduction and improved gastrointestinal tolerability [175]. However, the future integration of berberine into these combinatorial treatment protocols requires careful attention to the pharmacokinetic interactions. Therefore, rigorous interaction studies, dose-optimization trials, and long-term safety evaluations will be needed prior to its widespread clinical adoption. It is worth mentioning that the development and acceptance of berberine as a therapeutic agent face regulatory and scalability challenges. Regulatory frameworks for products containing berberine differ across regions, reflecting varying safety and quality standards [176]. These challenges underscore the necessity for standardized regulations and stringent quality control measures. Addressing these obstacles requires collaborative efforts among researchers, regulatory authorities, and industry stakeholders to establish safety standards, improve bioavailability, and facilitate the large-scale implementation of berberine-based therapies.

9. Conclusion

Berberine is a popular plant-derived isoquinoline alkaloid used in TCM. In TCM, herbs that are high in berberine, specifically *Coptidis rhizoma* (Huang Lian), *Phellodendri cortex* (Huang Bai), and *Mahoniae caulis* (Gong Lao Mu), are categorized as "heat-clearing and dampness-drying" agents and are used to treat dysenteric diarrhoea, febrile and inflammatory disorders, as well as "Xiaoke" syndromes, which can be likened to modern-day diabetes mellitus and its complications, even before the discovery of insulin. Modern pharmacology has validated broad, anti-diabetic, antimicrobial, anti-inflammatory, metabolic, and cardiovascular actions of these medicinal herbs, with berberine recognized as a significant marker and effector compound. Berberine has shown promise as an adjunct or alternative therapy for DM and its complications by modulating AMPK signaling. The activation of AMPK, a key energy-sensing enzyme in the body, is frequently facilitated by pathways involving LKB1 and CAMKKβ. When berberine activates AMPK, it initiates a cascade of beneficial metabolic changes and modulates several critical processes, including gluconeogenesis, lipogenesis, oxidative stress, and inflammation. Evidence from animal models demonstrated its efficacy in ameliorating complications such as diabetic nephropathy, neuropathy, retinopathy, cardiomyopathy, hepatic steatosis, atherosclerosis, bone diseases, cognitive dysfunction, and lung injury. Despite these encouraging preclinical and clinical findings, a pressing need remains for further extensive, well-controlled trials, as well as improvements in pharmacokinetic profiles. Conducting large-scale randomized controlled trials involving diverse populations is essential to validate the efficacy and safety of berberine across various conditions. These trials should include clearly defined endpoints, such as changes in blood glucose levels, lipid profiles, and inflammatory markers. Future trials should include participants from various age groups, ethnic backgrounds, and health statuses to ensure the generalizability of findings. Such efforts are vital for validating the therapeutic potential of berberine and establishing comprehensive clinical guidelines for its optimal use in treating DM and its complications.

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Kingsley Chimaeze Mbara: Writing – review & editing, Conceptualization. **Poloko Stephen Kheoane:** Data curation. **Clemence Tarirai:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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