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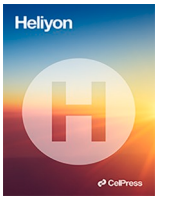

Review article

Addressing the preventive and therapeutic perspective of berberine against diabetes

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ABSTRACT

Diabetes has emerged as one the leading detrimental factors for human life expectancy worldwide. The disease is mainly considered as outcome of dysregulation in glucose metabolism, resulting in consistent high glucose concentration in blood. At initial stages, the diabetes particularly type 2 diabetes, is manageable by lifestyle interventions such as regular physical activity and diet with less carbohydrates. However, in advance stage, regular intake of external insulin dose and medicines like metformin are recommended. The long-term consumption of metformin is associated with several side effects such as nausea, vomiting, diarrhoea, lectic acidosis etc., In this scenario, several plant-based medicines have shown promising potential for the prevention and treatment of diabetes. Berberine is the bioactive compound present in the different plant parts of berberis family. Biochemical studies have shown that berberine improve insulin sensitivity and insulin secretion. Additionally, berberine induces glucose metabolism by activating AMPK signaling and inhibition of inflammation. A series of studies have demonstrated the antidiabetic potential of berberine at *in vitro*, pre-clinical and clinical trials. This review provides comprehensive details of preventive and therapeutic potential of berberine against diabetes.

1. Introduction

Diabetes mellitus (DM) popularly called as diabetes, is the one of the most common lifestyle diseases after obesity worldwide which equally affects men and women. In 2021, DM alone has affected more than 500 million people of age 20–79 year worldwide and approximately 800 million new cases of DM are expected in 2045 [1]. The burden of DM is higher in low and middle-income countries including India, Bangladesh, Indonesia, South Africa, and Iran [2]. Over the past few decades, DM cases are rising in India and approximately 69.9 million new DM cases are expected by 2025 [2]. This is really an alarming situation not only for developing countries but also developed ones. Several contributing factors such as intake of carbohydrate rich diet, lack of regular physical activities, stress, environmental and genetic mutations have been recognized for DM development. DM is now widely considered as life threatening disease as it has determinantal effects on the functioning of vital organs such as eye (retinopathy), kidney (nephropathy),

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heart (cardiomyopathy), brain (neuropathy) and reproductive potential (infertility) [3,4]. To curb these complications, oral hypoglycemic agents have been prescribed to DM patients which effectively reduce the blood glucose levels. Though effective, however their irregular use sometime leads to severe hypoglycemia which accounts for 4–10 % of DM related deaths [5]. Recently, use of artificial intelligence applications such as Siri integration for continuous glucose monitoring has been shown to improve glycemic control in legally blind patients with diabetes [6]. Further, long term practice of antidiabetic treatment such as insulin administration or oral intake of insulin secretagogues is a risk factor for the development of several type of cancer including liver, pancreatic, breast and colon cancer [7]. Considering the adverse effect of these synthetic drugs, the focus of general public as well as scientific community has shifted towards the novel preventive as well as drugs of natural origin which can delay or reverse diabetes or diabetes associated multiorgan complications. In this regard, plant-based medicines hold a great hope for the prevention and treatment of diabetes as well as its complications such as diabetic nephropathy [8,9], diabetic neuropathy [10], diabetic retinopathy [11] with minimal adverse effects. Berberine is the bioactive compound present mainly in rhizome, stem and fruits of plants of Berberidaceae, Ranunculaceae, Menispermaceae, Papaveraceae and Rutaceae [12,13]. The antibacterial activity of berberine dates back to traditional knowledge where the rhizome of *Coptis chinesis* (Ranunculaceae family) were used to treat diarrhoea. However, the reports showing the therapeutic efficacy of berberine against T2DM was first reported in 1986 in mice [14] and in 1988 in DM patient [15]. Thereafter, numerous studies have been done to evaluate antidiabetic activity of berberine at *in vitro* and *in vivo* [13,16–19]. In order to identify the cellular target of berberine, several *in silico* molecular docking, structure activity relationship assays and cell-based assays were performed [18–20]. The antidiabetic activity of berberine has been attributed to its pleotropic mechanisms involving activation of AMP-activated protein kinase (AMPK), inhibition of mitogen-activated protein kinases (MAPK), inhibition of PI3K/Akt signaling pathway, inhibition of aldose reductase, inhibition of inflammation, inhibition of oxidative stress and modulation of lipid metabolism. Based on the success demonstrated at preclinical stage, several clinical trials have been conducted to evaluate efficacy and safety of berberine and its subsequent use as a medicine to treat diabetes in humans. This chapter covers a comprehensive detail of mechanisms of action of berberine and its recent progress in drug development against diabetes.

1.1. Methodology adopted

We searched the different freely available databases i.e., PubMed, Scopus, Google scholar and Web of science using the keywords 'Berberine and diabetes mellitus', 'natural products and Diabetes', 'berberine and glucose metabolism', 'berberine and AMPK signaling', 'Berberine and Inflammation', and 'Berberine and Oxidative stress' for the period of 2003 to May 2023. We received an output of total 454 articles published in various journals (https://pubmed.ncbi.nlm.nih.gov/?

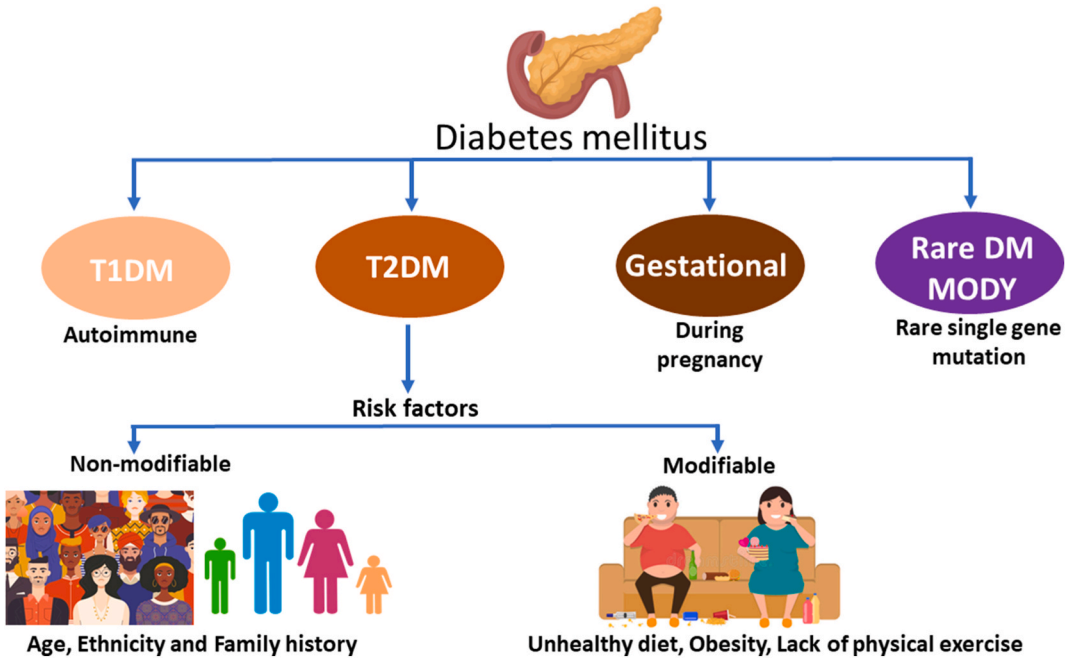

Fig. 1. Flow chart showing the major types of diabetes and their causal/risk factors. In T1DM, the insulin secreting β cells of islets of Langerhans are damaged by autoantibodies produced against them. This results in no or negligible insulin production in these patients. In T2DM, β cells are capable to secret insulin in response to enhanced glucose concentration, however several non-modifiable (age, ethnicity, and family history) and modifiable factors (unhealthy diet, lack of physical exercise) cause structural modifications in insulin receptor which hampers insulin binding and subsequent activation of glucose uptake in cells. Some women may also develop diabetes during pregnancy termed as gestational diabetes and is temporary. Moreover, some types of diabetes are termed as rare as the single gene mutation in insulin gene are rare (<5 %).

term=berberine+and+diabetes+mellitus&filter=years.2003-2023&size=200). However, articles published beyond the selected dates were also included based on their scientific merits. Primary relevance with the review topic was determined by the title of the searched articles. In order to keep the review relevant and precise, we further checked into the abstract and finalized the list to be included in the review. The article published with no full text available and published in languages other than English were excluded from this study. All the authors independently assessed and finalized various reference studies to be included in this review. Discrepancies, if any, among the authors were discussed thoroughly and resolved. Finally, full text articles were obtained for better quality assessment and completing manuscript.

2. Diabetes: pathophysiology, diagnosis, and treatment

An individual is diabetic when either blood glucose concentration remains ≥126 mg/dL or hemoglobin A1C levels is ≥ 6.5 %. Based on the etiology, DM is mainly categorised as T1DM, T2DM, Gestational and rare DM (Fig. 1). Of these, T1DM is manifestation of autoimmune reaction resulting in loss of β cell. On the other hand, T2DM is sporadic in nature and 90 % of the all diabetes cases reported globally fall in this category [21,22]. Gestational diabetes (GDM) represents another type of diabetes and is observed in approximately 7 % of pregnant women. In addition to commonly observed diabetes types, several rare types of diabetes have also been identified in humans which are caused by multiple mutations in insulin gene e.g., maturity-onset diabetes of the young (MODY) [23,24].

As the highest number of diabetes cases are contributed by type 2 diabetes, therefore it is worth to understand its pathophysiology so that effective treatment can be developed against this disease. The most clinical symptoms of types 2 diabetes are: polyurea, polydipsia, polyphagia, loss of body weight, fatigue, and vision impairment in severe conditions. Two major functional abnormalities are responsible for the development of diabetes. First one includes insulin resistance while in second condition β cells are not capable to produce insulin [25,26]. Insulin resistance (IR) is the common clinical feature of diabetes characterised by reduced or non-responsiveness of peripheral tissues such as muscles, adipose and liver for glucose consumption even in the presence of adequate insulin. Association of perturbation in several cellular signaling pathways and IR has been supported by multiple *in vitro* and preclinical studies [27,28]. During the early stage, in response to high blood glucose level, β cells in pancreas secret higher amount of insulin in blood (hyperinsulinemia) to maintain normoglycemia. Over the time, β cells start producing less insulin which subsequently becomes unable to compensate the reduced sensitivity of peripheral tissues for glucose. As a result, the absorption of blood glucose in peripheral

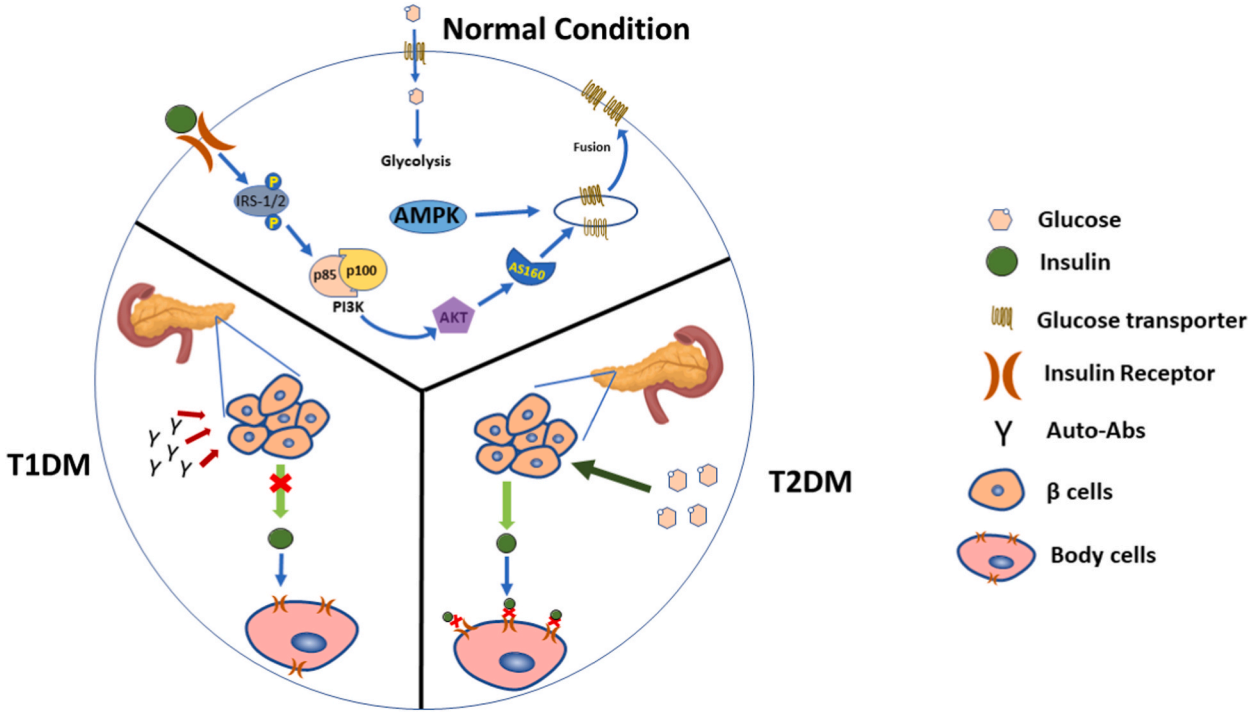

Fig. 2. Mechanism of action of insulin and glucose uptake in normal, T1DM and T2DM. In normal conditions, insulin induces translocation of GLUT4 transporters from vesicles to cell membrane of body cells (muscle, adipose, epithelial etc.). The enhanced expression of GLUT4 channels glucose into body cells and hence reduces blood glucose concentration. In T1DM, autoimmune antibodies generated against β cells of islets of Langerhans. This results in no or very little insulin release from pancreas which results in sustained high glucose concentration in blood. Conversely, in T2DM sufficient insulin is produced from β cells in blood to channel glucose to body cells from blood stream. However, due to prolonged insulin exposure, the insulin receptor no longer activates downstream signaling pathway for GLUT4 fusion to cell membrane. This renders target cells unable to uptake glucose from blood stream even in the presence of sufficient insulin, a condition called insulin resistance.

tissues (muscles, adipose and liver) decreases which in turn results in hyperglycemia. This condition when insulin is present though low in amount but still it is not consumed in peripheral tissue and stays in blood for longer period than usual is called insulin resistance (Fig. 2).

Currently, there are ten classes of orally available pharmacological agents to treat T2DM: 1) sulfonylureas, 2) meglitinides, 3) metformin (a biguanide), 4) thiazolidinediones (TZDs), 5) alpha glucosidase inhibitors, 6) dipeptidyl peptidase IV (DPP-4) inhibitors, 7) bile acid sequestrants, 8) dopamine agonists, 9) sodium-glucose transport protein 2 (SGLT2) inhibitors and 10) oral glucagon like peptide 1 (GLP-1) receptor agonists. These drugs can be prescribed alone (monotherapy) or in combination with other class of anti-diabetic drugs with different mechanism of action to treat severe/brittle diabetes [29]. Considering the side effects of current hypoglycemic drugs, a visible inclination towards plant-based medicine has been noticed. Subsequently, a huge growth in market with plant-based antidiabetic formulations and/or products can be seen. Berberine is one such natural product that possesses immense antidiabetic potential, particularly against type 2 diabetes. In the following section we will cover the different aspects of berberine e.g., its natural sources, evidence from pre-clinical studies and its efficacy through clinical trials.

3. Berberine: source and phytochemistry

Berberine ($C_{20}H_{18}NO_4^+$, Mol. Wt. 336.37) is a yellow crystalline isoquinoline alkaloid and possesses a bitter taste (Fig. 3) [30]. Due to its polar nature, free berberine is soluble in polar solvents (ethanol, methanol and water) and insoluble in non-polar solvents such as benzene and chloroform. However, the salt form i.e., berberine hydrochloride is less soluble in water as such but in boiling water it gets easily soluble. Further, salfate and phosphate salts of berberine are easily soluble in water and do not need a boiling step.

Several families of plants have been identified as source of berberine (Table 1). Berberine has been isolated from root, stem, leaf and fruits of source plant. Based on the local availability different plants have been used for isolation of berberine, the genus *Berberis* being the most common natural source. Considering the importance of the plant species and geographical conditions, berberine content varies greatly from 0.05 mg/g to 96.10 mg/g. The highest content of berberine is reported in *C. chinensis* to date, followed by *Coptis teeta* and *Berberis asiatica*. While reviewing the method utilized for berberine detection in a plant extract, it was found that high performance liquid chromatography (HPLC) is the most reliable method irrespective of plant extract prepared from leaf, stem bark, root etc., [31–37]. Several advancements in HPLC such as HPLC-DAD [38], HPLC-PDA [39] and UHPLC-Q-TOF-MS [40] have been made in recent years for enhanced detection of limit in small sample volume.

4. Molecular targets of berberine in diabetes

During the past three decades, a huge number of drugs have been approved to treat human diseases. Of these, approximately 70 % of drugs including metformin [51], artemisinin [52], taxol [53], etc., are inspired from natural compounds. Berberine is the main effective bioactive compound of several Tradition Chinese Medicine system [54] as well as Indian Ayurvedic formulations [55].

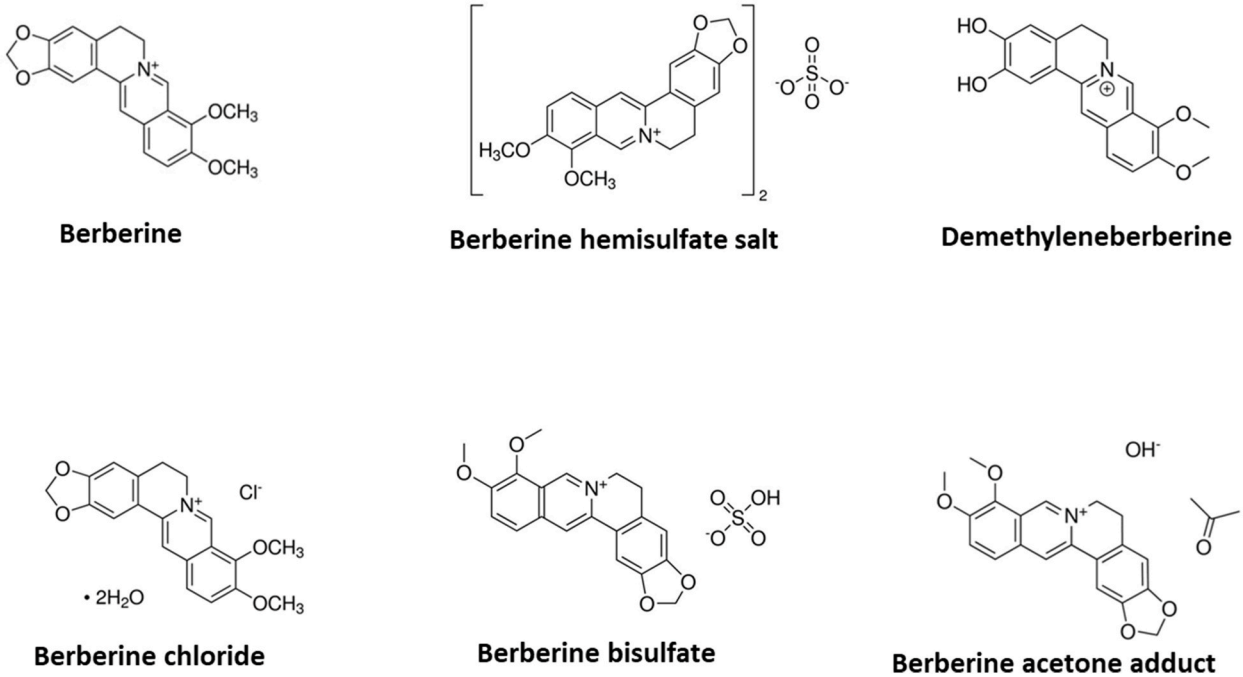

Fig. 3. Chemical structure of berberine and its derivatives.

Table 1
Natural source of berberine.

Sr. No.	Family	Plant species	Plant part used	Detection Method	Content (mg/g)	Reference
1.	Berberidaceae	(i) Berberis asiatica Roxb. Ex DC. (ii) Berberis vulgaris L. (iii) Berberis croatica Horvat (iv) Berberis pseudumbellata R.Parker (v) Berberis lycium Royle	Root	HPLC	8.2–59.00	[33,35], [36], [41]
		(i) Berberis asiatica Roxb. Ex DC (ii) Berberis pseudumbellata R.Parker (iii) Berberis kansuensis C·K.Schneid. (iv) Berberis dictyophylla Franch. (v) Berberis diaphana Maxim. (vi) Berberis vernae C·K.Schneid.	Stem Bark	HPLC	0.37–35.37	[32,33,36]
		(i) Berberis lycium Royle	Fruit	UPLC-DAD-ESI-QTOF-MS/MS	0.58	[37]
2.	Ranunculaceae	(i) Coptis chinensis Franch. (ii) Coptis deltoidea C·Y.Cheng et Hsiao (iii) Coptis teeta Wall. (iv) Coptis trifolia (L.) Salisb. (v) Hydrastis canadensis L.	Rhizome	HPLC	51.14–96.10	[32,42,43]
		(i) Thalictrum foliolosum DC	Root	HPTLC	5.09–11.10	[44]
3.	Menispermaceae	(i) Tinospora cordifolia (ii) Tinospora sinensis (Lour.) Merril (iii) Tinospora sinensis (iv) Coscinium fenestratum (Goetgh.) Colebr.	Stem	HPLC, TLC	0.97–33.70	[45–47]
4.	Papaveraceae	(i) Argemone mexicana L. (ii) Corydalis yanhusuo W.T. Wang	Whole plant, Tuber	TLC, HPLC-DAD-MS/MS	0.05–1.78	[48,49],
5.	Rutaceae	(i) Phellodendron amurense Rupr. (ii) Phellodendron chinense Schneid.	Bark	HPLC-DAD	0.69–25.75	[38,50]

Literature has documented the effectiveness of these traditional medicines against inflammation [56], tumor [57], hyperlipidemia [58] and diabetes [59]. Pharmacological studies have demonstrated berberine as a hyperglycemia-dependent glucose-lowering agent [19,60,61]. Further, berberine has been shown to target multiple signaling pathways to exert its antidiabetic effect (Fig. 4) [13,62,63]. Activation of AMPK signaling pathway is one of the well demonstrated mechanism of action of berberine to lower glucose concentration in blood [64]. Recently, berberine has been shown to acts as an insulin secretagogue by binding directly to KCNH6 potassium channels [65]. This results in prolonged glucose-dependent cell membrane depolarization which eventually stimulates insulin secretion. In order to decipher the precise mechanism of action and druggable targets of berberine through which it reduces glucose concentration in blood, berberine has been tested in several *in vitro* and pre-clinical studies (Table 2).

4.1. Activation of AMPK pathway

AMP-activated protein kinase (AMPK) pathway plays a key role in maintaining systemic homeostasis by acting as cellular energy (ATP/AMP ratio)/signaling system [84]. Berberine is well known activator of AMPK pathway, glycolysis stimulation and inhibition of mitochondrial function. Berberine mediated activation of AMPK pathway in different tissues including skeletal muscles and adipose tissues leads to insulin sensitivity and eventually reduces obesity [85]. Activation of AMPK pathway leads to a decrease in blood glucose concentration along with enhanced glucose uptake by skeletal muscles [86]. Berberine is reported to activate AMPK signaling pathway mainly by two routes: either by inhibiting respiratory complex I of the mitochondrion [87] or by targeting sirtuins, particularly SIRT1 in adipose [88] and SIRT3 in liver [89].

4.2. Phosphorylation of InsR and insulin receptor substrate 1 (IRS1)

Insulin receptor is the primary effector protein of insulin dependent signaling cascade. For insulin to have its intended physiological effects on target cell, the insulin receptor (InsR) must function properly. Berberine is capable to upregulate insulin receptor (InsR) mRNA expression in a protein kinase D (PKD)-dependent manner in muscle and liver cells [90,91]. This results in improved glucose uptake and regaining insulin sensitivity. Further, berberine treatment has been demonstrated to induce autophosphorylation of insulin receptor substrate 1 (IRS1) and Akt in diabetic rats [92]. Fibroblast growth factor 21 (FGF 21) is an important regulatory hormone of glucose concentration and lipid homeostasis in peripheral blood and tissue [93]. Interestingly, berberine is capable to activate FGF 21 in peripheral blood and adipose tissue as a mechanism to reduce insulin resistance [94,95]. Similarly, Lui et al. reported the inhibition of LPS/TLR4/TNF-α pathway by berberine as another mechanism of action for reducing blood sugar and tolerating insulin resistance [96].

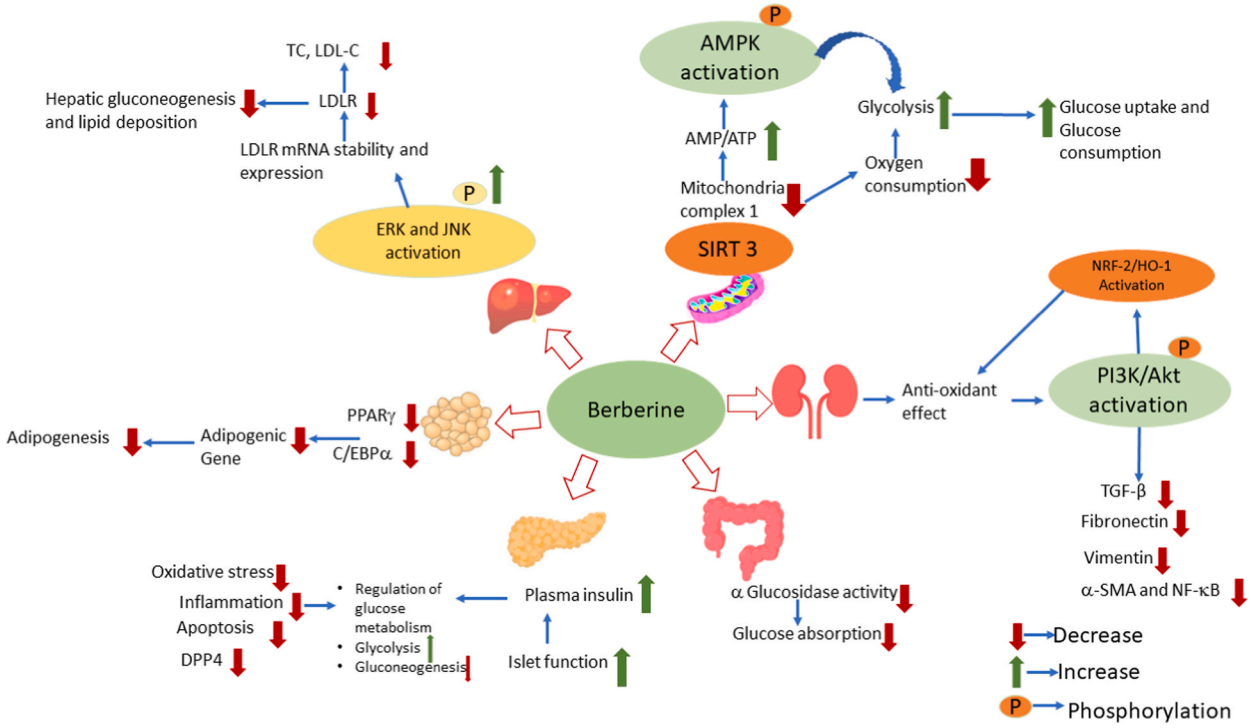

Fig. 4. Molecular targets and mechanism of action of berberine in T2DM and associated complications. BR suppresses adipogenesis by inhibiting PPARγ, C/EBPα, and downstream target genes. BR improves islet function via promoting glycolysis, plasma insulin, and decreases gluconeogenesis by reducing oxidative stress, inflammation, apoptosis and DPP4. Similarly, BR augments glucose uptake and glucose consumption through concomitantly increasing AMP-ATP-AMPK activation a consequence of inhibition of mitochondrial electron transport chain complex I and reducing oxygen consumption. BR can decrease hepatic gluconeogenesis and lipid deposition by enhancing low-density lipoprotein receptor (LDLR) mRNA stability and expression. BR showed protective attributes for diabetic nephropathy and also has anti-oxidant and anti-fibrotic effects via activating PI3K/Akt/NRF-2/HO-1 cascade and suppressing TGF-β/Fibronectin/Vimentin/α-SMA/NF-kB signaling. BR also helps in reducing intestinal glucose absorption by inhibiting α-glucosidase activity.

4.3. Enhancement of glucagon-like peptide-1 (GLP-1) level

Glucagon-like peptide-1 (GLP-1) is secreted by enteroendocrine L cells of intestinal tract and has diverse physiological roles such as stimulating the release of insulin, encouraging pancreatic beta-cell growth, and controlling glucose metabolism [97]. When blood glucose levels are high, berberine enhances the production and synthesis of GLP-1, boosting the release of insulin from β cells [98]. In a dose dependent manner, berberine therapy was effective in reducing endotoxemia, regaining intestinal permeability, and healing the injured mucous membrane via enhancing GLP-1 expression in diabetic rat model [99]. Berberine had these series of effects in rats fed a high-fat diet by boosting endocrine regulatory peptide (peptide, PYY), controlling the GLP-1 and GLP-2 secretions, stimulating the differentiation of L cells in the colon, and improving the intestinal peptide level [100,101].

4.4. Activation of GLUT1

Glucose uptake in insulin sensitive tissues like adipose and muscle cells depends upon the availability of glucose transporters (GLUTs). GLUT1 is ubiquitously expressed on all cells whereas GLUT4 is insulin responsive glucose transporter expressed in muscle, adipose and heart [102] Berberine has been found to enhance GLUT1-mediated glucose uptake in 3T3-L1 adipocytes, a result of AMPK stimulation [103,104]. Additionally, berberine enhances GLUT4 expression and translocation activity, which improved glucose absorption and raises the body's glucose availability. In adipocytes, berberine improved the IRS1-PI3-kinase-Akt signaling pathway to increase the number of GLUT4 in the membrane, which is advantageous for promoting glucose uptake [105]. Recently, Och et al. demonstrated an insulin independent mechanism of berberine for boosting glucose absorption in adipose tissue via the AMPK-p38-MAPK pathway [20].

4.5. Inhibition of PEPCK and G6Pase expression

Enhanced hepatic gluconeogenesis is a major contributor of hyperglycemia in diabetic patients and subsequent complications [106]. Glucose-6-phosphatase (G6 Pase) and phosphoenolpyruvate carboxykinase (PEPCK) are the two important rate limiting

Table 2
Summary of *in vitro* and *in vivo* studies for evaluation of berberine efficacy.

Cell type/animal model	Diabetes	Concentration	Mechanism/Target	References
Rat recirculating perfusion model	Type 1 diabetes	• 1.830 mg/ml	• Inhibition of alpha-glucosidase • Influences glucose absorption	[66]
Streptozotocin induced diabetes Rat model		• 187.5 and 562.5 mg/kg	• Augments insulin secretion and modules lipids.	[67]
Alloxan and a high-fat/high-cholesterol induced Rat model		• 100 and 200 mg/kg	• Hypoglycemic impact, • Modulating lipids metabolic effects • Scavenge free radical.	[68]
3T3-L1 preadipocytes	Type 2 diabetes	• 1, 10, and 100 μM	• Reduces lipid accumulation • Suppresses PPARgamma2 expression	[69]
3T3-L1 adipocytes, L6 myotubes, C2C12 myotubes, and H4IIE hepatocyte		• 2 g/kg	• Improves glucose metabolism via induction of glycolysis	[70]
Streptozotocin (STZ)-induced diabetic nephropathy rat model		• 100 and 200 mg/kg	• Regulation of the MMPs/TIMPs system	[71]
Streptozotocin- and high-carbohydrate/ high-fat diet-induced diabetic rats		• 75, 150, 300 mg/kg	• Increase insulin expression • β cell regeneration • Decreasing lipid peroxidation	[72]
3T3-L1 adipocytes		• 5 μM BBR for 48 h	• Enhance beige adipogenesis of through transcription-coupled post-transcriptional regulation	[73]
AML12 hepatocytes and 3T3-L1 adipocytes		• 10 μM, 50 μM, 100 μM, and 0.1 % by volume	• Alteration of BCAA catabolic enzymes	[74]
db/db mice		• 100 mg/kg	• Modulating gut microbiota and fecal metabolomics	[75]
BKS-Leprdb (db/db, T2DM model) and C57BLKS/JNju mice		• 136.5 mg/kg	• Modulate the composition of the gut microbiome • Reduce body weight • Blood glucose levels • Reduce intestinal inflammation	[76]
db/db mice		• 100 mg/kg	• Inhibition of lipogenesis • Induction of lipolysis in the liver	[77]
db/db mice		• 50 mg/kg	• Modulation of SIRT1 • Downregulating ER stress-associated proteins	[78]
db/db mice		• 250 mg/kg	• Improve insulin sensitivity	[79]
db/db mice		• 210 mg/kg	• Increased microbiome mediated DCA production • Up-regulated colonic TGR5 expression and GLP secretion	[75]
Streptozotocin (STZ)-induced diabetic nephropathy mice model		• 200 mg/kg	• Activating Nrf2 pathway • Inhibiting TGF-β/Smad/EMT signaling activity	[80]
Streptozotocin (STZ)-induced mice model		• 50 mg/kg	• Decreases blood glucose • Improves lipid metabolism	[81]
C57BLKS/J db/db diabetic kidney mice		• 200 and 300 mg/kg	• Restoration of PGC-1α activity and the energy homeostasis	[82]
Danio rerio (Zebrafish)		• berberine derivative 1 (10 μM)	• Improved the glucose uptake	[83]

enzymes of hepatic gluconeogenesis [107]. The adipogenic genes PEPCK, G6 Pase, and others whose expression depends on ATP are suppressed by berberine, which also suppresses mitochondrial function and gluconeogenesis [108]. Berberine slows down the gluconeogenesis rate in liver by impairing SIRT3 and causing PEPCK1 instability [109]. In type 2 diabetic mice, berberine inhibited the HNF-4/miR122 pathway, which in turn resulted in reduced gluconeogenesis [110]. Cappel et al. showed the contributing role of pyruvate carboxylase in hyperglycemia, insulin resistance and obesity [111]. Further, knockdown of hepatic pyruvate carboxylase prevented obesity and improved insulin sensitivity but caused oxidative stress and inflammation in liver. Berberine has been shown to improve glucose metabolism by inhibiting hepatic gluconeogenesis in diabetic rats [108] and fish [112,113] via suppressing expression of gluconeogenic genes including by PEPCK and G6Pase.

4.6. Inhibition of oxidative stress

Oxidative stress is the initial biochemical perturbation in most of human diseases including diabetes. Enhanced reactive oxygen species, reactive nitrogen species, increased lipid peroxidation and depletion of glutathione are the characteristics features of oxidative stress. In diabetes, increased oxidative stress is a poor prognostic marker of diabetes induced cardiomyopathy and atherosclerosis [114]. The incredibly intricate molecular process by which berberine combats oxidative stress and inflammation involves different cellular kinases as well as signaling pathways, such as NF-κB, AMPK, Nrf2/oxygenase, and MAPKs [115]. Nrf2 is a type of transcription factor that promotes the transcription of genes involved in antioxidant and anti-inflammatory processes [116]. Berberine is responsible for increasing the levels of the antioxidant enzymes SOD but decreased GSH, and GSH-Px in diabetic mice [117]. Moreover, berberine was shown to inhibit production of ROS as well as cytokines associated to inflammation such IL-1, IL-6, TNF-α, COX-2, and *i*NOS [118].

4.7. Regulation of lipid metabolism

Diabetic dyslipidemia is the common clinical symptom characterised by elevated levels of triglycerides, decreased high density lipoproteins cholesterol (HDL-C) and increased levels of low-density lipoprotein cholesterol (LDL-C) [119]. Long term consumption of statins by obese individuals is now new risk factor for developing diabetic dyslipidemia via modulating 3-hydroxy-3-methylglutaryl--coenzyme A (HMG CoA)-reductase activity [120]. Moreover, insulin resistance can perturb the systemic lipid metabolism which ultimately leads to the development of diabetic dyslipidemia [121] Berberine improved the fat-induced hepatic insulin resistance by downregulating the expression of sterol-regulatory proteins and PPARγ as well as by upregulating liver X receptor expression [105]. Additionally, berberine promotes insulin secretion through increased pancreatic β cell proliferation and PARP-1 protein expression [122,123]. Berberine controls the level of LDL-C via enhancing the LDLR expression, activated by ERK [58]. In order to moderate lipid metabolism, berberine upregulates the levels of PPAR and ATP binding cassette transporter A1 [124]. After berberine administration, PPARγ mRNA expression is drastically decreased, which inhibits PPARγ transcriptional activity and prevents the formation of fat. Berberine also downregulates the levels of PPARγ, and activates the *c*-Jun *N*-terminal kinases, AMPK-p38 MAPK-GLUT4 and PPARs pathways [125].

4.8. GLUT4 translocation and AMPK-GLUT4 interaction

GLUT4 is the essential for glucose transportation as it cannot enter the cell directly. Moreover, GLUT4 regulates the rate limiting step of insulin mediated signal transduction. Insulin stimulates the fusion of GLUT4 transporters from GLUT4 storage vesicles to the cell membrane and hence aid in glucose uptake from circulation [126]. Activation of p38 MAPK has been reported a preceding event during the insulin mediated translocation of GLUT4 to plasma membrane in muscle cells [127]. Berberine has been demonstrated to promote upregulation of AKT/GLUT4 pathway [128]. Conversely, berberine has been shown to activate GLUT4 via PI3K/AKT and suppressing the MAPK pathway in a mechanism to lower polycystic ovary syndrome (PCOS) pathophysiology and insulin resistance levels in murine model [129]. These contrasting evidence warrants further experimental proofs to fully elucidate the mechanism of action of berberine in stimulating GLUT4 translocation and thereby reducing hyperglycemia.

5. Therapeutic efficacy of berberine in pre-clinical studies

In drug discovery hierarchy, new entity should be assessed for its efficacy first using *in vitro* cell line-based model followed by *in vivo* studies carried on lab animals. To date, several *in vitro* and *in vivo* studies have been performed with berberine for diabetes at varying concentrations. Authors reported its beneficial effects by targeting different cellular and molecular mechanisms. Anti-diabetic potential of berberine was first time reported by Nakai et al. where they mentioned it as an aldose reductase inhibitor [130]. After this, from the last two decades, researchers extensively worked with berberine in the context to both diabetes. Several *in vitro* assays have been established and studied to understand the efficacy of berberine. These include 3T3-L1 adipocytes, L6 myotubes, C2C12 myotubes, and H4IIE hepatocyte. Similarly, for evaluation of *in vivo* potential, different chemical induced (streptozotocin, alloxan) and nutrition based (high fat diet) are used [131]. Moreover, special strain mouse models (db/db mice, ob/ob mice) have also been developed to study the pathophysiology of diabetes and antidiabetic potential of bioactive compounds [132]. The two most common strains are db/db mice have a mutation of the diabetes (db) gene encoding for the ObR whereas ob/ob mice possess mutation of the obese (ob) gene encoding leptin. Recently, *Danio rerio* i.e., Zebrafish has been demonstrated as an easy and excellent experimental model to study diabetes and obesity [133,134]. The detail of these studies is depicted in Table 2.

Though, berberine is known to have a hypoglycemic effect, several *in vitro* and *in vivo* studies along with interventional clinical trials have been carried to understand the exact molecular mechanism and appropriate dose of berberine. Zhou et al. reported that berberine treatment stimulated the glucose transport in 3T3-L1 preadipocytes through a mechanism distinct from insulin [135]. Moreover, Jia et al. showed enhanced pharmacokinetics and absorption of berberine at a dosage of 20 mg/kg in T2DM model rats versus normal rats [136]. Berberine assuaged hyperglycemia in diabetic db/db mice by targeting hepatic glucokinase at 210 mg/kg per day dosage for four weeks [137]. Chinese medicine has documented that berberine at the dose of 0.2–1.0 g/day in tablet and capsule forms for the treatment of several chronic disorders, particularly T2DM [138]. Zhang et al. (2008) verified in a clinical study that oral administration of berbeine at a dose of 1.0 g per day for 3 months is efficacious and safe in the treatment of T2DM and dyslipidemia [139]. Interestingly, a dose of 0.5 g t. i.d. Of berberine showed hypoglycemic effect as that of metformin [59]. Preclinical to clinical dosage conversion appears to be consistent with the scientific dose equivalence approach for animal-to-human dose estimations in the studies described above.

6. Therapeutic efficacy of berberine in clinical trials

Data regarding the safety of berberine in long term use was thoroughly examined and clinicaltrials.gov showed 89 clinical studies with 'berberine' keyword, out of which 52 are completed. These studies primarily reported extremely low bioavailability of berberine to be the main obstacle for clinical use and encouraged enhancement of bioavailability. Dong et al., 2012 also, a decade back, summarised, fourteen randomized trials using berberine, with 1068 participants, and observed that no serious (severe) adverse effects from berberine were reported during these trials [60]. Some of these trials reported moderate incidences of abdominal discomfort and nausea. The duration of the clinical trials investigated varied from 8 to 24 weeks. Similarly, Ye et al., 2021 reviewed 417 trials reporting clinical treatment data of berberine and observed berberine to be clinically safe and well-tolerated by the human body [140].

Table 3
Clinical trials of berberine in diabetes.

Sr. No.	Clinical trial/ Study	Type of trial	Disease	No. Of participant	Drug (Dose)	Duration	Outcomes	Reference
1.	NCT02861261 (PREMOTE Study)	randomized, double-blind, -placebo-controlled (Multicentric)	T2DM	409	Berberine (0.6 g twice daily before meal) + Probiotics (4 g once daily at bedtime)	12-week	• Reduced blood glucose levels by inhibiting DCA biotransformation by *Ruminococcus bromii*	[141]
2.	Pilot study	randomized, double-blind, -placebo-controlled trial (Unicentric)	T2DM	84	BBR (0.5 twice in day), Metformin (0.5 g twice in day)	3 months	• Fasting blood glucose decrease • Total cholesterol and low-density lipoprotein cholesterol (LDL-C) were decreased	[59]
3.	NCT03656744	Prospective, randomized, double-blind, placebo-controlled Phase 2 trial	non-alcoholic steatohepatitis and type 2 diabetes	100	Berberine ursodeoxycholate or BUDCA (1 g twice a day)	18 weeks	• Significant improvement in glycemic control • Reductions in liver-associated enzymes • Significant weight loss.	[142]
4.	NCT03972215	randomized, double-blind, placebo-controlled, two-period crossover, single-dose, phase 1 clinical trial	T2DM with obesity	15	Berberine (1 g)	2 weeks	• Significantly promotes insulin secretion under hyperglycemic state comparing with placebo treatment	[65]
5.	Hospital based	single-center, randomized (1:1), open, controlled study	T2DM	40	Metformin (0.5 g once daily) Berberine based-nutraceutical formulation (BHC, 0.5 g once daily)	12 weeks	• significant reduction in both glycated hemoglobin (HbA1c) and fasting blood glucose (FBG)	[143]
6.	NCT00462046	randomized, double-blind, placebo-controlled and multi-centeric trial	T2DM with dyslipidemia	116	berberine (1.0 g daily)	3 months	• fasting and post-load plasma glucose decreased • HbA1c decreased • Triglyceride, total cholesterol, and low-density lipoprotein-cholesterol levels decreased	[139]
7.	Hospital based trial	single-center, randomized, controlled study	T2DM	97	BBR (1 g per day), metformin (1.5 g per day), or rosiglitazone (4 mg per day)	2 months	• significantly lowered fasting blood glucose (FBG), hemoglobin A1c and triglyceride • percentages of peripheral blood lymphocytes that express Insulin receptor were significantly elevated after therapy	[144]
8.	Hospital based trial	single-center, randomized, controlled study	T2DM	114	berberine (0.4 g, 3 times a day)	6 months	• improvement of glycosylated hemoglobin (HbA1c), blood urea nitrogen (BUN), systolic pressure (SP), high sensitive *C*-reactive protein (hs-CRP)	[145]
9.	Hospital based study	Double blind, placebo-controlled trial	T2DM	136	Berberine (500 mg daily) and Sylimarin (105 mg daily)	52 weeks	• Improved fasting blood glucose and insulin, Insulin Resistance index • Homeostatic Model Assessment (HOMA-R), total, HDL and LDL	[146]

(*continued on next page*)

Table 3 (*continued*)

Sr. No.	Clinical trial/ Study	Type of trial	Disease	No. Of participant	Drug (Dose)	Duration	Outcomes	Reference
							cholesterol, triglycerides, uric acid were reduced	
10.	NCT00633282	randomized, parallel controlled, open-label clinical trial	T2DM with NAFLD	185	Pioglitazone (15 mg daily) + berberine (0.5 g twice in day)	16 weeks	• decreased liver fat content in women as compared to men	[147]

Few adverse reactions were reported in some of these studies, but no negative effect was observed on participants' diet. The promising results of antidiabetic properties of berberine obtained in various *in vitro* and *in vivo* studies have encouraged to conduct human clinical trials to evaluate its therapeutic efficacy as drug or adjuvant. In this regard, PubMed search was exercised with keywords: berberine and diabetes. Two filters i.e., clinical trial and randomized controlled trial were applied to articles published from 1994 to April 2023. Out of 24 filtered articles, 10 most relevant clinical trials were showing evaluation of berberine efficacy against T2DM and T2DM + other complications. These clinical trials have investigated efficacy of berberine at different dose and capacity to work as adjuvant with standard drugs such as metformin against diabetes. The details of each trial are given in Table 3.

Comparative efficacy of berberine with other available treatments was also determined from available literature. Yin et al. (2008) revealed that at 0.5 g t. i.d., berberine had a hypoglycemic effect comparable to that of metformin [59]. Similarly, Singh et al., 2019 discovered that when sulfonylureas and berberine were co-incubated in clinical patients, their metabolism was impacted; this could be due to competitive binding of the herb and medicine to the catalytic sites of the same isozymes [148]. In clinical investigations, Xie et al., 2022 discovered statistically significant improvements in fasting plasma glucose, glycosylated haemoglobin, and 2 h plasma blood glucose was observed with supplementation of berberine [61]. Furthermore, in the treatment of T2DM, berberine alone or in combination with oral hypoglycemic agents (metformin, sulfonylureas, glipizide, gliclazide, glimepiride, thiazolidinediones, pioglitazone, acarbose) did not significantly increase the incidence of total adverse events or the risk of hypoglycemia. When metformin is used early on, diarrhoea and other gastrointestinal problems are prevalent, and it is contraindicated in people with severe liver and renal disease. Overall, berberine can compensate for the shortcomings of present glucose-lowering medications and serve as a useful adjunct in the treatment of type 2 diabetes.

7. Conclusion

The ever-increasing burden of diabetes, particularly T2DM, has become a public health problem across the world. The root cause of T2DM is modified lifestyle characterised by intake of high carbohydrate diet and lack of routine physical exercise. Mother Nature is a treasure of medicinal plants which possess valuable bioactive compounds for developing new drugs. Berberine is one such bioactive compound that has shown immense potential to work as antidiabetic drug. This has been supported by a series of *in vitro*, *in vivo* and human clinical trials. Molecular and pharmacological studies have demonstrated pleotropic effect of berberine in different experimental model systems. The most widely supported mechanism of action of berberine is activation of AMPK signaling pathway and stimulation of glycolysis. In addition, berberine has been shown to optimize blood glucose levels by stimulating β cells of pancreas for insulin secretion. Berberine is also capable to act as α-glycosidase inhibitor especially in intestine and hence delays absorption of glucose. Substantial evidences have demonstrated that several drugs used in clinics stimulate adipogenesis and promote diabetic cardiovascular complications. Under such scenario, berberine could be a promising adjuvant as it inhibits adipogenesis by targeting PPRγ, SREBP1/2 and C/EBPα. In addition to diabetes, multiple studies have suggested the beneficial effects of berberine in other metabolic diseases such as cancer, obesity, non-alcoholic fatty liver diseases, hyperlipidemia, and gout. These reports collectively indicate that berberine is a potent oral hypoglycemic agent with modest effect on lipid metabolism. Berberine may serve a low-cost and new drug candidate for the management of diabetes.

8. Limitations

We believe this review to have some limitations. Firstly, a systematic literature search was carried out using the most widely used databases i.e., PubMed, Scopus, Google scholar and Web of science; and other less commonly used databases were not searched during the preparation of this review. Thus, some concerned studies might not have been included in this summary. Secondly, most of the studies included in this review are primarily available in English. However, some studies in the regional languages might have been missed, including those published in Chinese. Lastly, we did not include preprints from various preprint databases as their peer review process was not completed.

Future directions

Natural antidiabetic agents have a bright future. Berberine has been evaluated in multiple clinical trials for its efficacy in the treatment of diabetes. A low bioavailability and low toxicity associated with berberine has limited its approval from FDA as medicine

for diabetes. Therefore, studies are required especially in the development of berberine derivatives or modifications in berberine structure with improved not only its antidiabetic potentials but also pharmacokinetics and pharmacodynamics parameters. Additionally, more robust multicentric clinical trials in different ethnic groups are warranted to fully elucidate the efficacy, safety profile and clinical application of berberine.

Credit author statement

SS and AS: Wrote the first draft of manuscript. RB: collected the data on clinical trials related to berberine. NS, SS and SK: Editing of manuscript. SK: Conceived the idea, structure, refinement, finalization of manuscript.

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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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