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Plant sources containing berberine with potential of control type 2 diabetes mellitus: A brief literature review

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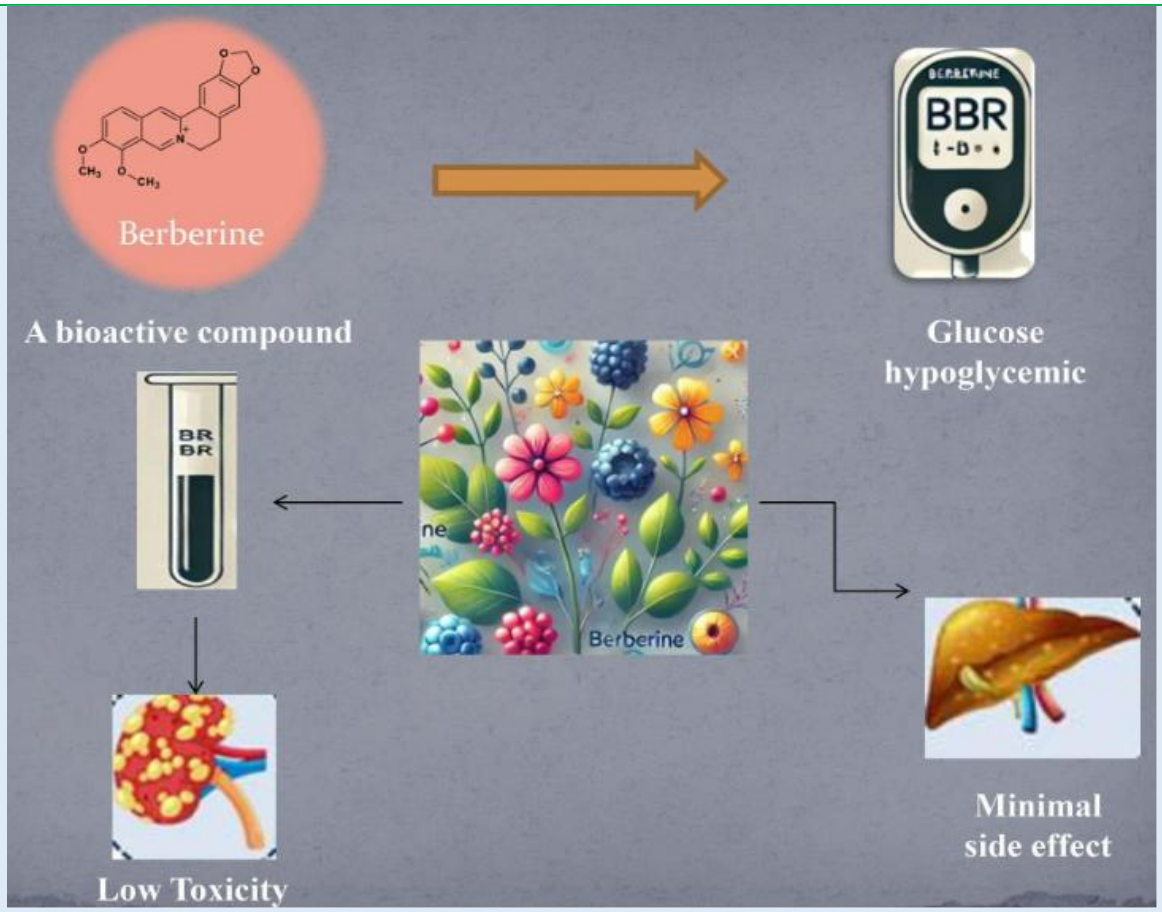
ABSTRACT

Berberine (BBR) is a bioactive compound found in some plants. Plants containing BBR are used as important functional food supplements, particularly for their potent oral hypoglycemic effects and beneficial impact on lipid metabolism. Another advantage of this bioactive compound is its low toxicity and/or minimal side effects, which has captured the attention of researchers. This review focuses on the structure and toxicity of BBR, as well as the best plant sources containing this compound, to investigate the mechanisms of its antidiabetic effects and clinical effectiveness.

Key Words: Berberine, Type 2 diabetes mellitus, Hypoglycemic, Metabolite, Plant sources, Clinical research

Graphical Abstract: Plant sources containing berberine with potential of control type 2 diabetes mellitus



INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by insufficient insulin secretion, elevated blood glucose levels, impaired glucose uptake, and abnormal lipid profiles [1,2]. The disease is further exacerbated by oxidative stress and the overproduction of reactive oxygen species (ROS), which contribute to complications like microvascular and cardiovascular diseases [3]. The global prevalence of DM continues to rise, fueled by aging populations, unhealthy lifestyles, obesity, and reduced physical activity. The International Diabetes Federation (IDF) reported that the number of people with diabetes is projected to increase from 537 million in 2021 to 643 million by 2030 and 783 million by 2045 [5]. In addition, the IDF estimated that over 6.7 million adults (aged 20–79) died from diabetes-related causes in 2021 [5].

While DM and its complications can be managed through lifestyle changes and medication, current antidiabetic drugs are not always effective, with only 41% of patients achieving optimal glycemic control [5]. Furthermore, these drugs are associated with side effects such as weight gain, gastrointestinal discomfort, and increased risks of cardiovascular events and cancer. They may also be contraindicated for patients with renal, cardiopulmonary, or hepatic issues [6].

In recent years, the medical community has shown interest in identifying of bioactive compounds in medicinal plants and food with antidiabetic effect. Herbal medicines containing phenolic compounds have

demonstrated effective antihyperglycemic effects [7]. Their long-term use as functional foods or dietary supplements may help reduce complications of diabetes. Because oxidative stress is a key factor in the progression of DM, research has focused on identifying plant-derived antioxidants for DM control. Countries like China and Iran have a long history of using traditional medicine to treat DM, identifying 86 and 33 herbal medicines, respectively, for this purpose [8-11].

Among these, berberine (BBR), a bioactive compound found in *Berberis* species and other plants, has garnered attention for its potent antihyperglycemic and antihyperlipidemic properties [8]. BBR has been used in traditional Chinese medicine and Ayurveda for its antiprotozoal, antidiarrheal, and antimicrobial activities, with its therapeutic applications extending to cancer, inflammatory diseases, cardiovascular conditions, and depression [9]. The antihyperglycemic effects of BBR were first reported in 1986, and subsequent studies have shown its ability to treat DM and its complications through anti-inflammatory and antioxidant mechanisms [9]. BBR effectively reduces blood glucose, LDL cholesterol, triglycerides, and total cholesterol in diabetic patients [10, 11].

Given the growing interest in functional foods, this study considered the bioactive substance BBR found in certain plants with nutritional and medicinal value. Notably, this is the first report of plant sources containing berberine which are widely available as a nutraceutical supplement with the potential to control DM. This review emphasizes the clinical potential of BBR, providing valuable insights for clinicians and traditional medicine practitioners on incorporating BBR-containing plants into DM management.

This study aims to explore the plant sources containing Berberine with potential for controlling Type 2 Diabetes. The results represent a significant breakthrough that is beneficial to millions of people, especially for future scientific studies in the area of functional food science.

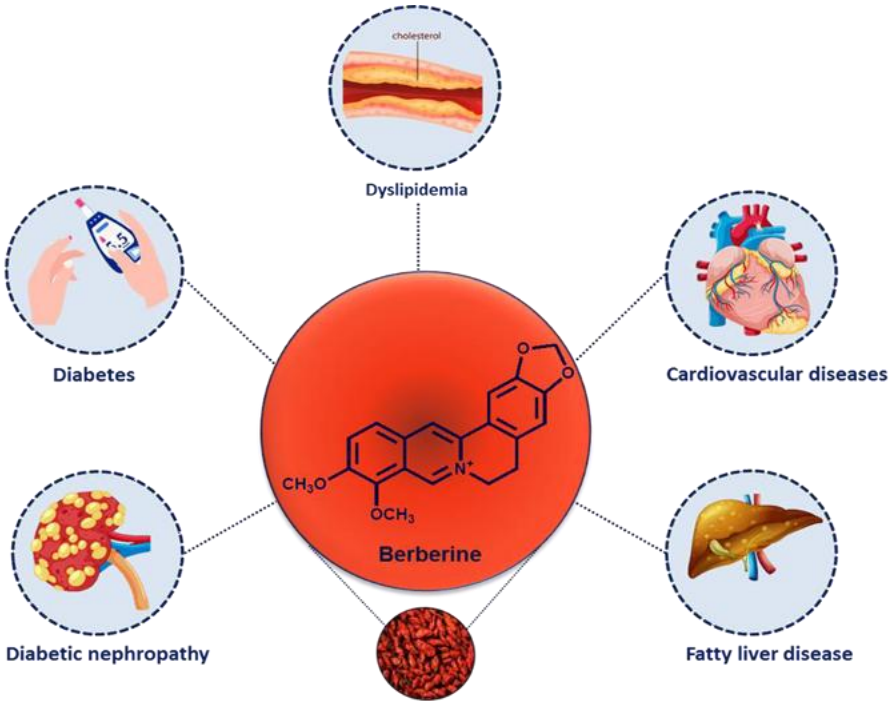


Figure 1. Therapeutic targets of berberine.

To investigate the role of BBR in diabetes management, a comprehensive literature search was conducted using the PubMedand FFHDJ databases. Keywords such as "Berberine," "diabetes," "metabolite," "plant source," "mechanism of action," "toxicity," "clinical research," and "combination therapy" were utilized. The article titles and abstracts were screened, followed by a detailed review of selected full-text articles to compile the manuscript.

Sources of Berberine: BBR is isolated from various plants, including *Coptis chinensis* (Coptis or Goldthread), *Hydrastis canadensis* (goldenseal), and *Arcangelisia flava*, as well as different species of *Berberis* such as *Berberis aristata* (Tree Turmeric), *Berberis aquifolium* (Oregon grape), and *Berberis vulgaris* (Barberry) [12]. These plants have the potential to be used as functional foods or food supplements. Given BBR's medical important, numerous research groups have evaluated its content in various plant sources using different analytical methods listed in Table 1 [13-25].

Shigwan and colleagues (2013) isolated BBR from the methanol extracts of stem barks of *Baptisia tinctoria* and *B. aristata* using a reversed-phase high-performance liquid chromatography (HPLC) method with a photo diode array detector. They reported BBR contents of 3.18% and 1.46% for *B. aristata* and *B. tinctoria*, respectively [13]. Analysis of methanol root extracts of *B. aristata* using HPLC with an ultraviolet (UV) detector showed 1.86% content of BBR in the plant source in winter, correlating with the highest antifungal activity [14]. Soxhlet extraction of *H. canadensis* root powder in various solvents displayed a 53.69% BBR content in the chloroform extract, confirmed by liquid chromatography-mass spectrometry (LC-MS) [15].

The ethanol extract of *Fibraurea tinctoria* Lour, analyzed using HPLC with a UV detector contained 25.8% of BBR [16]. Analysis of a 100-ppm ethyl acetate fraction from the aerial parts of *Acalypha indica* revealed a BBR concertation of 11.82030 µg/mL, which was determined by a HPLC separation system [17]. The highest concentration of BBR (840 mgL^{-1}) was found in the acetone extract of *Coptidis rhizoma*, an antioxidant plant using HPLC with UV detection [18]. Methanol extracts if BBR contained 282.90 µg/g, which was about 24 times higher than its ethyl acetate extract, as identified by the HPLC method [19].

A high-performance thin-layer chromatography (HPTLC) method at 350 nm was used to estimate of BBR in the hydroethanolic extract of *B. aristata* stem bark, revealing a BBR content of 12.08% in samples collected from Tamil Nadu [20]. Consistent with the HPTLC results, infrared spectroscopy, confirmed the presence of BBR in *B. aristata* alcoholic extract [20]. Using gas chromatography-mass spectrometry (GC- MS), researchers identified 34,53% BBR as the main bioactive component [21].

Ahn (2009) identified methanol as the most effective extraction method for isolating *Phellodendron amurense,* reporting a relative abundance of 81.3% for BBR using GC-MS analysis [22]. Chemical profiling of various parts of *Berberis petiolaris* was conducted using direct analysis in real time (DART) coupled with time-of flight mass spectrometry (TOF-MS), revealing that BBR was the most abundant in the root of *B. petiolaris* (336 m/z) [23]. Similarly, BBR was detected in the methanolic leaf extract of *Argemone mexicana* using thin-layer chromatography (TLC) after fractionation by column chromatography [24]. The BBR containing fraction was further purified using HPLC and its structure was confirmed using ^{1}H-NMR. All of the chromatographic techniques collectively confirm the presence of BBR in different plant sources. Additionally, a review has been highlighted the therapeutic effects of *B. vulgaris* on T2DM [25].

Table 1. Various plants containing berberine

Name of plant	Plant part	Identification method	Reference
Berberis aristata	Root and fruits	HPLC	[13-14]
Hydrastis canadensis	Root	HPLC, LC-MS	[15]
Fibraurea tinctoria	Root and stem	HPLC	[16]
Acalypha indica	Aerial part	HPLC	[17]
Coptidis rhizoma	Plant material	HPLC	[18]
Tinospora cordifolia	Whole plant	HPLC	[19]
Berberis aristata	Stem bark	HPTLC	[20]
Berberis tinctoria	Stem bark	GC-MS	[21]
Phellodendron ammurense	Heartwood	GC-MS	[22]
Berberis petiolaris	Root and stem	DART-TOF-MS	[23]
Argemone Mexicana	Leaves	TLC, HPLC, NMR	[24]

Structure of Berberine and Its Some Metabolites

BBR is a plant-derived quaternary ammonium alkaloid with a molar mass of 336.36122 g/mol, belonging to the family of isoquinoline alkaloids (5,6-Dihydro-9,10-dimethoxybenzo(g)-1,3- benzodioxolo(5,6-a) quinolizinium; $C20H18NO^{+}$) [26]. It is one of the most common alkaloids isolated from different parts of a Berberis plant (Fig. 2) [27]. Analogues of BBR, such as tetrahydroberberine, demethyleneberberine, palmatine, tetrahydropalmatine, coptisine, magnoflorine, jatrorrhizine, columbamine, 8-oxoberberine, dihydroberberine, berberrubine, and thalifendine, are also isolated from various plant sources (Fig. 2) [27].

The B, C and D rings in the BBR skeleton play an essential role in its antidiabetic activity (Fig. 2) [20]. The methylenedioxy substitution on ring B and the fused tetrahydroisoquinoline structure in rings C and D contribute to the hypoglycemic effect of BBR. However, alkylation or acylation of the E ring is beneficial for BBR's hypoglycemic activity and the bioavailability of derived compounds [28]. C8-alkylation and C8-bromoalkylation of ring D significantly increase the glucose-lowering effect of such molecules. Moreover, 9,11-dimethoxy-10-hydroxy substitutions on the E ring have exhibited potent glucose-reducing activity.

Palmatine, a naturally occurring isoquinoline alkaloid with 2,3-dimethoxy substitution on ring B, is found in some Tradiotional Chinese Medicines (TCMs) and has shown hypoglycemic and hypolipidemic effects [21]. Another key metabolite of BBR, demethyleneberberine (Figure 2), formed through the cleavage of the dioxole ring via demethylenation, has exhibited favorable hepatoprotective and hypolipidemic impacts [29].

The antidiabetic effect of other metabolites of BBR such as jatrorrhizine (2-methyl-3-hydroxy substitution), berberrubine (10-methoxy substitution), and columbamine (2,9,10-trimethoxy-3- hydroxy substitution), can be related to their antioxidant, anti-inflammatory, hepatoprotective and hypoglycemic activities (Fig. 2) [21]. Together, these metabolites of berberine contribute to the prevention and treatment of diabetes and its complications [20-21].

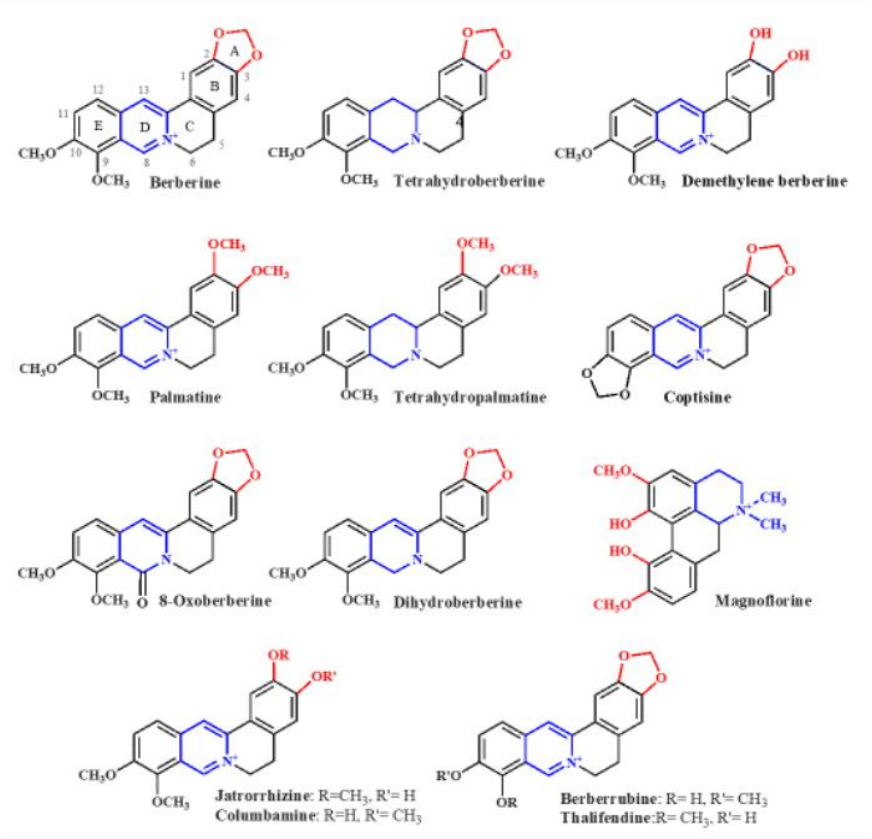


Figure 2. Structures of some of the main bioactive alkaloids are isolated from Berberis species.

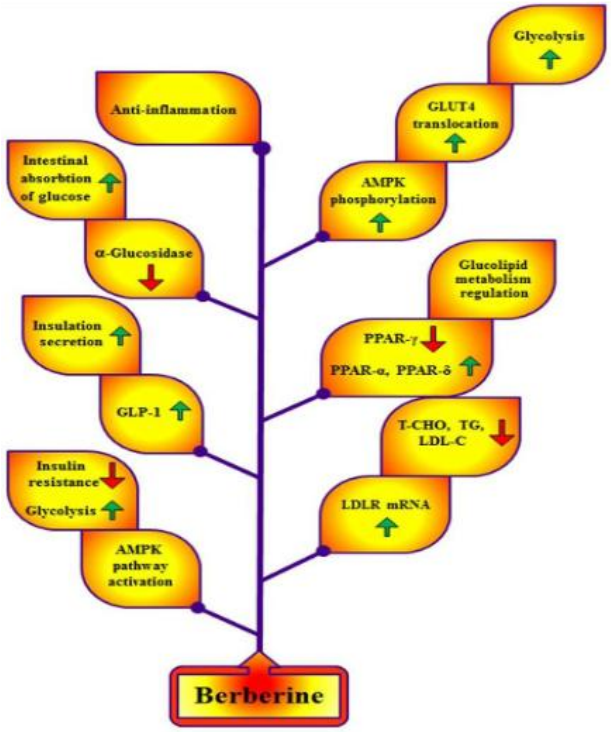


Figure 3. The main mechanisms of berberine in glucose and lipid metabolism. PPARs: peroxisome proliferator-activated receptors; AMPK: adenosine monophosphate-activated protein kinase; GLP-1: glucagon-likeprotein-1; GLUT4: glucose transporter type 4; LDLR mRNA: low-density lipoprotein receptor m ribonucleic acid; T-CHO: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol.

Mechanisms of Antidiabetic Effect of Berberine: Glucose metabolism is regulated by BBR through multiple signaling pathways and mechanisms. These include incrementing insulin sensitivity, modulating gut microbiota, activating the adenosine monophosphate (AMP)-activated protein kinase (AMPK) pathway, inhibiting gluconeogenesis in the liver, promoting intestinal glucagon-like protein-1 (GLP-1) secretion, increasing glucose transporter activity, and stimulating glycolysis in peripheral tissue cells [30]. The antihyperlipidemic effect of BBR was confirmed by lowering levels of T-CHO, triglycerides, and LDL-C through various mechanisms [30]. Figure 3 illustrates the main mechanisms of glucose and lipid metabolism affected by BBR.

Antihyperglycemic Effect of Berberine: BBR has a protective effect on islet function by enhancing insulin sensitivity in individuals with insulin-resistant T2DM [31]. It also has a protective effect on pancreatic islet cells through its antioxidant activity in late-stage Type 1 Diabetes T1DM and T2DM, promoting insulin secretion [11]. The Molecular mechanism of BBR against insulin resistance involves the reducing fasting serum insulin and fasting blood glucose (FBG) by upregulating insulin receptor (InsR) expression [32].

BBR has been shown to stimulate glucose uptake into muscle and adipose tissues through the upregulation of glucose transporter type 1 (GLUT1) expression [31], inhibiting retinol binding protein 4 (RBP-4) activity to enhance insulin sensitivity [8] and mimic insuline action by inhibiting phosphatase activity of protein tyrosine phosphatase 1B (PTP1B) [8]. By upregulating AMPK, BBR has shown its insulin-independent hypoglycemic effect, which is related to the stimulation of glycolysis and α-glucosidase inhibition, as well as the inhibition of mitochondrial function [33].

BBR can lower blood insulin levels by enhancing insulin sensitivity in individuals with type 2 diabetes. BBR may also improve insulin secretion by revitalizing exhausted islets in patients with weak β-cell function. For example, BBR can increase glycolysis by stimulating AMPK activation and promoting glucose transporter type 4 (GLUT4) translocation in 3T3-L1 adipocytes. This, in turn, could reduce blood glucose level at high concentrations of BBR.

BBR also interact with GLP-1 receptors, which are critical for islet cell survival. After being activated by GLP-1 receptors, adenylate cyclase produces cyclic AMP, enhancing intracellular Ca^{2+} and stimulating the migration and exocytosis of insulin granules [34]. BBR could enhance GLP-1 secretion, significantly increase insulin secretion, and modify the function of β-cells in the pancreas [35].

Berberine and Its Effects on Controlling Diabetes:

Intestinal Absorption of Glucose by Berberine: BBR inhibits α-glucosidase, an enzyme that digests carbohydrates into monosaccharides, thereby reducing intestinal glucose absorption. BBR can also suppress the expression of intestinal disaccharidases *in vitro* (Caco-2 cell) and *in vivo* (rats with diabetes), particularly in the duodenum [36].

Glucolipid Metabolism by Berberine: BBR directly suppresses hepatic gluconeogenesis and reduces blood glucose levels by reducing fatty acid synthase activity, enhancing hepatic steatosis, and increasing hepatic nuclear factor 4 alpha (HNF-4α) mRNA expression [10].BBR also affects the regulation of glucolipid metabolism in the liver through the reduction of intranuclear transcription factors such as carbohydrate response element-binding protein (ChREBP), sterol regulatory element-binding protein 1c (SREBP1), and forkhead transcription factor O1 (FoxO1) [8].

BBR enhances metabolic activities by modulating the expression of ligand-based transcription factors of peroxisome proliferator-activated receptors (PPARs) in the liver. PPARs, including PPAR-α, PPAR-δ, and PPAR-γ, play key roles in regulating essential gene expression in

glucolipid metabolism [8]. Specifically, BBR modulates glucolipid metabolism and reduces hepatic glycogen, likely by increasing the expression of PPAR-δ and PPAR-α proteins. Moreover, BBR enhances lipid metabolism by decreasing PPAR-γ expression in the liver [37].

Lipid Metabolism of Berberine: BBR has demonstrated antihyperlipidemic effects by reducing the levels of T-CHO, TG, and LDL-C [38]. It has also been indicated that BBR can upregulate hepatic low-density lipoprotein receptor (LDLR) expression, through a mechanism independent of sterol regulatory element binding proteins but dependent on extracellular signal-regulated kinase (ERK) activation [38]. BBR can activate the c-Jun N-terminal kinase (JNK1) pathway, enhancing the transcriptional activity of the LDLR promoter, ultimately lowering serum LDL levels. Additionally, BBR activates AMPK, leading to the inhibition of TG and T-CHO synthesis in human hepatocytes [38].

Anti-inflammatory and Antioxidant Effects of Berberine: DM is an inflammatory disease with chronic complications such as nephropathy, neuropathy, and retinopathy that are closely linked to oxidative stress [3]. The production of excessive ROS causes damage and apoptosis of pancreatic islet β-cells, leading to a decline in insulin secretion and accelerating in the progression of diabetes [39]. ROS also activates cellular signaling pathways, including protein kinase C (PKC), JNK, and nuclear factor-κB (NF-κB), interfering with the insulin signaling pathway and causing insulin resistance [40]. Proinflammatory cytokines like tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), produced by immunocytes and adipocytes in DM, further induce insulin resistance by promoting serine phosphorylation of insulin receptor substrate (IRS) through the activation of NF-κB or JNK pathway [40]. Additionally, islet dysfunction can be related to the overproduction of TNF-α and IL-6 in the pancreas [40].

BBR exhibits potent antioxidant and anti-inflammatory properties, which have been shown to counteract oxidative stress and inflammation in various tissues like adipose tissue, liver, pancreas, and kidney. The antioxidant and anti-inflammatory activities of BBR have been proven to contribute to its efficacy against T2DM and insulin resistance [40]. The mechanisms of these activities are intricate and involve many cellular kinases and signaling pathways that are fundamental routes for BBR in reducing oxidative stress and inflammation, such as the AMPK pathway, nuclear factor erythroid-2-related factor-2 (Nrf2) pathway, mitogen-activated protein kinases (MAPKs), and NF-κB pathway. [41].

In animal models of diabetes, BBR administration has resulted in notable changes in oxidative stress markers such as malondialdehyde (MDA) and glutathione (GSH). Antioxidant enzymes like superoxide dismutase (SOD), sirtuin 1 (SIRT1), and glutathione peroxidase (GSH-Px), and proinflammatory cytokines such as TNF-α, IL-6, IL-17, and interferon-γ (IFN-γ) have been observed [41]. MDA, a byproduct of lipid peroxidation, rises during oxidative stress, while GSH levels often decline during this phenomenon [41]. Administrating of BBR can help scavenge excessive free radicals by decreasing MDA content and increasing GSH content, thereby overcoming oxidative stress.

BBR can also inhibit oxidative stress by increasing levels of SOD, SIRT1, and GSH-Px enzymes [41]. The activity of BBR against oxidative stress is likely related to the upregulation of SOD mRNA expression in mice with diabetes and the enhancement of SIRT expression with antioxidant activity [42]. BBR efficiently prevents TNF-α and IL-6 production and improves the insulin signaling cascade, indicating that the insulin-enhancing potential of BBR is associated with its anti-inflammatory activity [42].

Toxicity of Berberine: The evaluation of the toxicity of BBR showed that subacute concentrations of BBR result in altered liver function, gastrointestinal disturbances,

hematological toxicity, hemorrhagic inflammatory consequences, immune cell damage, and apoptosis [43]. Despite these finding, BBR has shown satisfactory potential in the treatment of DM with low toxicity in several studies. Animal studies reported an LD50 of 713.57 mg/kg, with no mortality observed at doses of 156 mg/kg/day for three months [44]. It is notable that different administration routes affect the LD_{50} of BBR in mice [44]. The intravenous and intraperitoneal injection of BBR showed LD_{50} values of 9.04 and 57.61 mg/kg, respectively, whereas no LD_{50} was observed with oral administration. Overall, the benefits of BBR outweigh its minor side effects, supporting its use in diabetes management despite potential toxicity concerns.

Clinical Studies on Berberine: BBR has been evaluated for its antidiabetic, antihyperlipidemic, and cardioprotective effects. Zhang et al. (2008) found that taking 1.0 g of BBR daily for three months significantly reduced levels of FBG, postprandial glucose (PPG), and HbA1c levels [45]. Similarly, Yin et al. (2008) reported comparable hypoglycemic effects between BBR and metformin, with BBR reducing FBG, PPG, and HbA1c levels by over 30%, though 34.5% of patients experienced gastrointestinal side effects [46]. Rao (2017) observed significant reductions in HbA1c, FBG, and PPG with BBR adminsitered twice daily for three months without causing liver or kidney damage and hypoglycemia [47].

Another study administered *B. vulgaris* fruit extracts (1 mg of dry barberry fruit extract containing berberine) twice daily for eight weeks, resulting in reduced serum glucose and HbA1c levels [48]. Additionally, the use of *T. cordifolia* stem extract (500 mg) over a two-month period demonstrated its efficacy in managing dyslipidemia and dysglycemia in patients with type 2 diabetes [49]. In prediabetic individuals, taking BBR (HIMABERB®, 500 mg three times daily for 12 weeks) reduced FPG, HbA1c, HOMA-IR and 2- hour oral glucose tolerance test (OTGG) values to below prediabetic thresholds, suggesting that HIMABERB® may delay the progression of DM [50].

Incorporating quantum and tempus theories in functional food science can help scientist to find novel therapeutic or food agents with increased efficacy and minimized side effects by considering timing of consumption [51]. It is suggested that these theories maybe used to determine the suitable dosage and timing for consuming BBR or plants containing BBR.

Clinical Evaluation of Berberine (BBR) Compared to Metformin: A pilot study compared the antidiabetic effects of BBR and metformin, a chemical antidiabetic drug, in patients with type 2 diabetes. BBR, unlike metformin, significantly reduced lipid levels and blood glucose, including LDL-C and HDL-C. However, there were no considerable differences between the 1st and 13th weeks in the BBR group. Both BBR and metformin effectively regulated glucose metabolism markers such as HbA1c, postprandial glucose (PBG), FBG, and insulin levels. However, BBR outperformed metformin in lipid metabolism, by significantly lowering total cholesterol and triglycerides compared to metformin [46].

Meta-Analysis Findings: Meta-analyses of 14 randomized controlled trials (RCTs), including 1,068 participants with type 2 diabetes, revealed that BBR effectively treats dyslipidemia and hyperglycemia without adverse side effects [52]. Another meta-analysis, including 27 RCTs with 2,569 patients, showed that BBR was comparable to oral hypoglycemic agents in reducing HbA1c, FPG, and PPG levels, while also lowering TG and increasing HDL-C, with no serious adverse effects in any participant. [53]. Another meta-analysis involving 3,048 patients confirmed a glucose-lowering effect of BBR, which was correlated with baseline FPG and HbA1c levels. The addition of BBR to lifestyle changes or oral hypoglycemic drugs did not increase the risk of hypoglycemia or other adverse events [54]. Meta-analysis is an evidence-based method that offers greater statistical power, better accuracy, and more efficiency.

By providing a large amount of data without requiring excessive time, money, or resources, it allows scientists to identify potential successful paths for future research in the field of diabetes.

Combination Therapy: Combination therapy can be effective by using a mixture of bioactive compounds with the aim of increasing treatment efficacy, preventing drug resistance development, reducing dosage and toxicity, and shortening the duration of treatment, due to the synergy effect [55]. Several studies have reported the effect of combining BBR with antidiabetic agents on diabetes control. Di Pierro et al (2012) found that a combination of *B. aristat* extract (containing 85% BBR) and *Silybum marianum* extract improved glycemic and lipid profiles. This combination, known as Berberol®, also appeared to enhance statin efficacy and positively affect liver enzymes [56]. In another controlled pilot trial by Di Pierro et al. (2015) involving 45 patients with type 2 diabetes, Berberol® was found to be a safe and effective supplement for managing lipid and glycemic profiles [57]. Ming et al. (2018) demonstrated that combining BBR with bifidobacteria improved glucose control in patients with pre-diabetes and diabetes [58].

CONCLUSION

BBR, a key bioactive constituent found in traditional medicinal or nutritional plants, has shown promise as an oral hypoglycemic agent. Its primary mechanisms include stimulating glycolysis, inhibiting mitochondrial function, and activating the AMPK pathway. BBR has also demonstrated potential as an α-glucosidase inhibitor, reducing blood insulin levels by enhancing insulin sensitivity and improving insulin secretion in patients with poor β-cell function. BBR's cardiovascular benefits, particularly its cholesterol-lowering effects, are notable, making it a valuable option for patients with diabetes and associated complications. Furthermore, BBR's low cost and lack of serious side effects make it a suitable alternative for individuals with limited financial resources. BBR could potentially open exciting avenues for further research in diabetes management. Despite its potential, the clinical trials evaluating BBR have generally been of low methodological quality using small sample sizes. Therefore, further research involving well-designed clinical trials is needed to confirm BBR's efficacy and safety as a treatment for diabetes.

Moreover, this review article introduces traditional herbs containing BBR as a complementary approach to managing diabetes and improving patients' quality of life. Diabetic patients can include therapeutic or nutritional plants with proven effects on diabetes in their daily diet, depending on the specific plant flora in their country. Additionally, this article can be useful for nutrition consultants and traditional medicine practitioners in determining proper therapeutic diets, introducing therapeutic or nutritional plants, and advising on consumption methods of these plants as functional foods to help lower blood sugar levels and manage disease. Finally, using BBR and plants containing BBR as daily functional foods could potentially open up exciting avenues for further research in diabetes management.

Abbreviations: AMPK: Activation of 5’ AMP-activated protein kinase; FAS: Fatty acid synthase; FBG: Fasting blood glucose; FPG: Fasting plasma glucose; GLUT: Glucose transporter; GSH: Glutathione; HbA1c: Hemoglobin A1C; HDL: High-density lipoprotein cholesterol; HOMA-IR: Homeostatic model of assessment of insulin resistance; IFN-γ: Interferon-gamma; IL-6: Interleukin-6; ISI: Insulin sensitivity index; LDL: Low-density lipoprotein cholesterol; MDA: Malondialdehyde; NF-κB: Nuclear factor kappa-B; PBG: Postprandial blood glucose; PPAR: Peroxisome Proliferator-activated receptor; SOD: Superoxide dismutase; T2D: Type 2 diabetes; TG: Triglyceride; TNF-α: Tumor necrosis factor-α.

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Conflict of Interest: The authors declare no potential conflicts of interest.

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