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BERBERINE AS A COMPLEMENTARY THERAPY FOR DIABETES MELLITUS: INTEGRATION WITH CONVENTIONAL TREATMENTS – A REVIEW

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Abstract
Diabetes mellitus (DM) is a prevalent metabolic disorder posing significant challenges to global public health. Despite advancements in conventional treatments, such as oral hypoglycemic agents and insulin, achieving optimal glycemic control remains elusive for many patients due to efficacy limitations and concerns regarding adverse effects. Herbal medications, particularly those from traditional Chinese medicine, have shown promise in addressing these shortcomings. Berberine, a compound found in various plants including Berberis species, has gained attention for its antihyperglycemic effects. This review discusses the therapeutic potential of berberine in managing diabetes mellitus, focusing on its mechanisms of action such as modulation of glucose metabolism, antioxidant and anti-inflammatory properties, regulation of lipid metabolism, and influence on gut microbiota. Berberine offers a holistic approach to diabetes management with fewer adverse effects compared to conventional medications, making it a promising adjunct or alternative therapy for diabetes mellitus.

Keywords: Berberine, Diabetes Mellitus, Hypoglycaemic, Traditional Chinese medicine

1. Introduction

Diabetes mellitus (DM) is an endocrine system metabolic disorder. As to the data provided by the International Diabetes Federation (IDF), the prevalence of diabetes mellitus (DM) among people aged 20-79 years was 8.3% worldwide in 2013. The anticipated number of patients worldwide was 382 million, with an expected rise to approximately 592 million by 2035 [1]. The high prevalence of DM poses a serious threat to public health since it has a substantial effect on both the financial burden of the healthcare system and people's quality of life [2]. Ninety to ninety-five percent of people with diabetes worldwide suffer from type 2 diabetes mellitus (T2DM), the most common kind of the disease [3,4]. A balanced diet, sensible exercise, the use of oral hypoglycemic medications, and/or subcutaneous insulin injections are all part of the usual treatment for type 2 diabetes [5]. Despite significant advancements in antidiabetic medications such as oral hypoglycemic agents (OHA) and insulin, there are still certain deficiencies. The antidiabetic medicines were only 41% effective in attaining optimum glycemic control, which was considered unsatisfactory [6,7]. Additionally, none of the treatments could sustain stable blood glucose control over a long period of time [8]. Furthermore, an increasing number of patients are worried about the possible toxicity and side effects of antidiabetic medications, including weight gain, bone loss, and a higher risk of cardiovascular events [9]. The potential adverse effects of sulfonylureas include hypoglycemia,

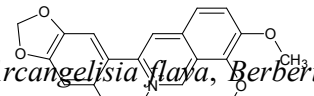
weight gain, and cardiovascular damage. Metformin is mainly associated with gastrointestinal discomfort. Pioglitazone use has been linked to increased risks of bladder cancer, edema, and distal bone fractures in postmenopausal women. Chemical or biochemical treatments like metformin are contraindicated in diabetes individuals with renal impairment, hepatic illness, or cardiac insufficiency [10].

Chinese herbal medications have shown a small but considerable antihyperglycemic impact. Long-term usage of these herbal medicines may help alleviate some diabetes problems. Moreover, combining herbal therapy with Western pharmaceuticals allows for reduced medication dosages and less frequent administration, leading to less unwanted effects and improved efficacy. Chinese herbal medicines, with their multiple ingredients, offer holistic regulation by targeting various mechanisms in the body. This approach can effectively alleviate metabolic disorders like obesity, hypertension, and dyslipidemia, as well as improve diabetic symptoms and quality of life. Herbal treatments have lower toxicity and adverse effects compared to Western medicine, and they are also more cost-effective. Herbal medicine might serve as a viable alternative or complement to Western hypoglycemic medications for managing diabetes mellitus [11–13]. There are 86 herbal remedies are often used in traditional Chinese prescriptions for T2DM and related comorbidities.

The genus *Berberis*, belonging to the Berberidaceae family, has a vast number of deciduous shrubs distributed throughout. The most famous species, *Berberis vulgaris* L., is extensively grown and used in Middle Eastern and Mediterranean cooking. Berberine is an ammonium salt categorized among benzylisoquinoline alkaloids, chemically identified as 5,6-dihydro 9,10-dimethoxybenzo(g)-1,3-benzodioxolo(5,6-a) quinolizinium. It is the primary active component of Berberis species and is typically administered orally for conditions such as diabetes (hyperglycemia), elevated cholesterol or other lipids in the bloodstream (hyperlipidaemia), and hypertension. Berberine, with a chemical formula of $C_{20}H_{18}NO_4$ and a molar mass of 336.36 g/mol, is obtained in its purified form as a yellow powder. It has a melting point of 145 °C, is odourless, and has a distinctive alkaloid bitterness. It has low solubility in water, moderate solubility in ethanol or methanol, but the salt form is rather soluble in water. It is also referred to as umbellatine, 5,6-dihydro-9,10-dimethoxybenzo1,3-benzodioxolo, and quinolizinium. Berberine can be easily extracted from various medicinal plants belonging to different plant families, primarily found in high-altitude regions. These families include Annonaceae (e.g., *Xylopia L.*), Berberidaceae (e.g., Berberis L.), Menispermaceae (e.g., *Tinospora Miers*), Papaveraceae (e.g., *Argemone* L.), Ranunculaceae (e.g., *Coptis Salisb*.), and Rutaceae (e.g., *Zanthoxylum* L.), or it can be synthesized entirely [14]. The genus Berberis, with 595 species, is widely spread and serves as a valuable source of the alkaloid berberine, found in many parts of the plant such as barks, leaves, twigs, branches, rhizomes, roots, stems, and flowers. This genus is often found in Europe, the USA, and Asia [14].

2. Chemical Characteristics and Source of Berberine

BBR, with a molecular mass of 336.36122 g/mol, is a plant quaternary ammonium salt belonging to the isoquinoline alkaloid (2,3-methylenedioxy-9,10-dimethoxeprotoberberine chloride; $C_{20}H_{18}NO_4$ +) group [15] (**Fig. 1**). Many plants may be used to isolate it, including



Arcangelisia flava, *Berberis aquifolium* (Oregon grape), *Berberis aristata* (Tree Turmeric), *Berberis vulgaris* (Barberry), and *Coptis chinensis* (Coptis or Goldthread) [16].

Fig. 1: Structure of Berberine

3. Mechanisms of action of Berberine on Ant-Diabetic

Traditional Chinese and Ayurvedic medicine have utilized BBR to treat bacterial diarrhea due to its antimicrobial, antiprotozoal, and antidiarrheal properties [16]. Numerous studies have provided evidence that BBR exhibits a wide range of therapeutic activities. It has the potential to be efficacious in the treatment of various chronic ailments, such as cardiovascular diseases (anti-hyperlipidaemia and antihypertension), cancer (cytotoxic effect, inhibition of proliferation and reproduction of specific tumorigenic microorganisms and viruses), depression (anti-inflammatory activity), and diabetes (anti-hyperglycaemia) [17]. In 1986, the antihyperglycemic effects of BBR were initially identified [18]. BBR potentially controls glucose metabolism via various pathways and mechanisms. These include modulating gut microbiota, inhibiting gluconeogenesis in the liver, stimulating glycolysis in peripheral tissue cells, promoting intestinal glucagon-like protein-1 (GLP-1) secretion, upregulating hepatic low-density lipoprotein receptor mRNA expression, and stimulating adenosine monophosphate-activated protein kinase (AMPK) pathway activity [17,19].

4. Therapeutic Potential of Berberine in Diabetic Mellitus

Berberine, a natural alkaloid compound found in various plants such as Berberis species, has garnered significant interest in recent years due to its potential therapeutic effects on diabetes mellitus. Several studies have explored its mechanisms of action and its efficacy in managing diabetes. **Fig. 2** illustration of Different methods for the treatment of Diabetes.

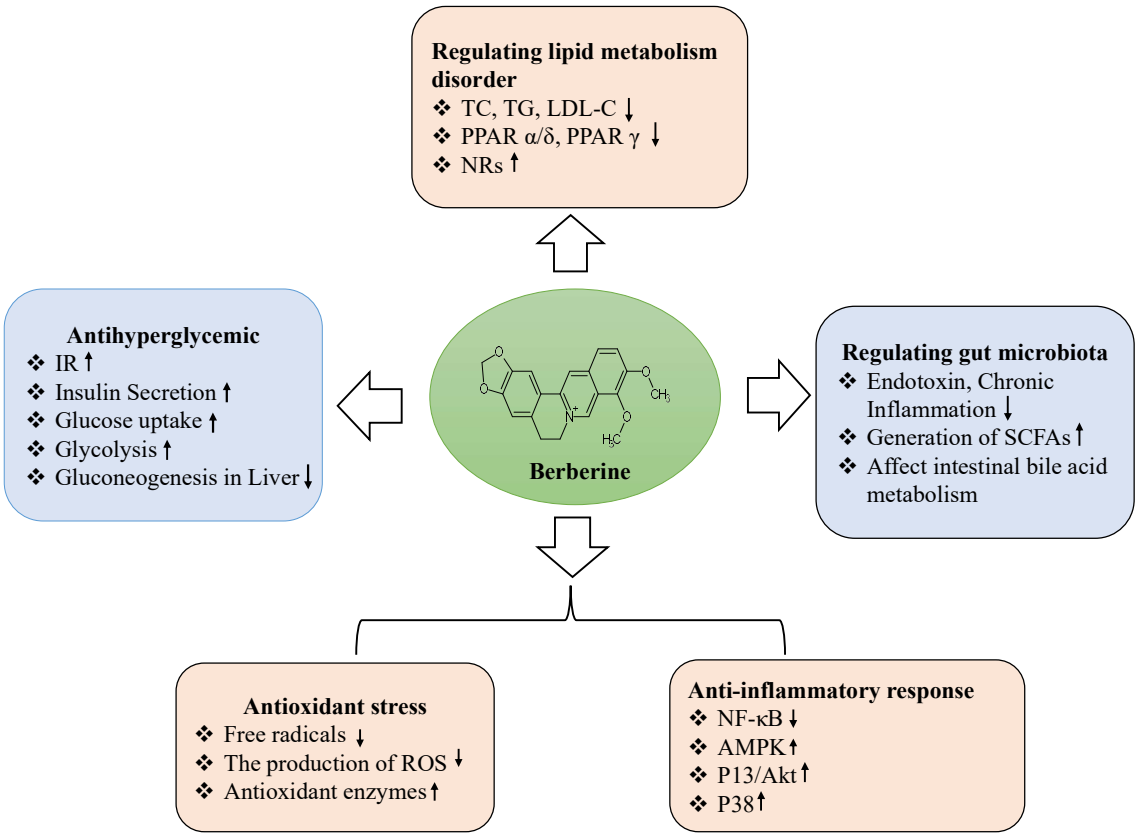


Fig. 2: Different methods for the treatment of Diabetes.

4.1 Berberine as an Anti-Hyperglycemic Agent

Berberine influences the metabolism of glucose by inducing glycolysis via AMPK activation-mediated glucokinase activity, increased insulin production, and inhibition of hepatic gluconeogenesis and adipogenesis [20–22]. The insulin response system comprising of Protein Kinase B (Akt), Phosphoinositide 3-kinase (PI3K), and Insulin receptor substrate 1 (IRS-1) is disrupted in the insulin resistance condition. Berberine increases Akt phosphorylation via AMPK activation. As a result, Akt becomes active and may promote the control of GLUT4 (glucose transporter type-4) expression and translocation to the plasma membrane. Therefore, the cell is able to accept and digest glucose. In this instance, berberine may boost an insulin-resistant cell's absorption of glucose [23].

4.2 Antioxidant stress and anti-inflammatory response

According to recent research, BBR reduces inflammation and oxidative stress, which has a therapeutic impact on type 2 diabetes mellitus (T2DM) and its consequences. Numerous studies in the literature shown the tight connection between oxidative stress and inflammation. They share a number of signaling pathways. IR will be exacerbated by the two's vicious cycle. Similarly, low-grade inflammation, oxidative stress, and IR are all caused by an imbalance of the gut flora in diabetes patients, and vice versa. Berberine may have anti-inflammatory properties in a variety of metabolism-related tissues and cells by downregulating the production

of major proinflammatory cytokines such as TNF-α, interleukin-6 (IL-6), and interleukin-1β (IL-1β). Similarly, studies showed that BBR controlled antioxidant enzymes and oxidative stress indicators to have a crucial impact on antioxidant stress [24]. BBR inhibited oxidative stress and inflammation by an incredibly intricate method that included many signaling pathways, such as AMPK, NFκB, nuclear factor erythroid-2-related factor-2 (Nrf2)/oxygenase, and MAPKs pathway, in addition to other cell kinases [25,26].

4.3 Regulating the Lipid Metabolism Disorder

Accumulation of fat significantly influences the onset and progression of insulin resistance (IR). Several tests have shown that BBR plays a crucial function in controlling adipose tissues. BBR may enhance the transformation of liver cholesterol into bile acids, promoting their quick excretion into bile to reduce lipid buildup and the release of free fatty acids. Levels of LDL-C, TGs, and serum total cholesterol fell considerably, whereas levels of high-density lipoprotein cholesterol and NO rose dramatically, indicating enhanced lipid catabolism. BBR can stabilize LDLR mRNA by increasing LDLR expression via ERK, which helps control LDL-C levels [27,28].

PPARs have a crucial role in regulating both fat metabolism and differentiation processes as the primary transcription factor for both functions. Experiments showed that PPARc mRNA expression decreases considerably following BBR treatment, leading to the inhibition of PPARc transcriptional activity and fat synthesis. BBR specifically elevated PPAR α/δ and ATP binding cassette transporter A1 levels, decreased PPAR c and PPARc co-activator-1 levels, and activated the c-Jun N-terminal kinases, AMPK-p38 MAPK-GLUT4, and PPARs pathways to control lipid metabolism. The presence of NR enzyme in feces might serve as a biomarker for tailoring hyperlipidemia therapy with BBR. Reports indicate that the intestinal bacteria's NR is crucial for enhancing BBR intestinal absorption. BBR may regulate NR activity in the gut as one of its strategies for decreasing cholesterol levels [29].

4.4 Regulating Gut Microbiota

The ecological balance of the intestinal flora has a significant impact on the therapeutic effect of drugs. Drug prototypes and their metabolites can influence the number and abundance of the intestinal flora, leading to changes in intestinal homeostasis, which in turn affects disease occurrence and development. Recent studies indicate a close relationship between metabolic syndrome and the role of intestinal flora, with abnormal metabolism of substances mediated by intestinal flora being a significant pathological mechanism of metabolic syndrome. Due to the low bioavailability of BBR, the classical pharmacokinetic theory may not fully explain its hypoglycaemic effect. Therefore, many scholars suggest that the hypoglycemic effect of BBR occurs in the intestine rather than after absorption [30].

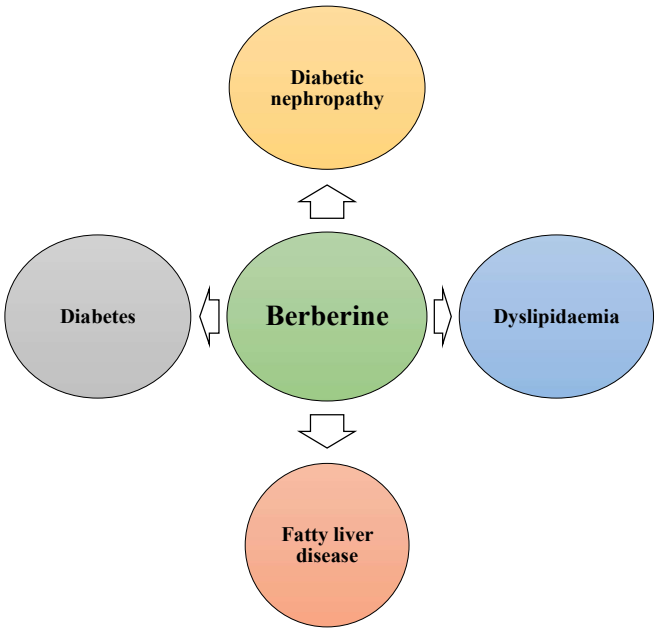


Fig. 2: The therapeutic benefits of berberine in living organisms.

Table 1: BBR's antihyperglycemic effects on diabetes mellitus-affected.

Authors	***In-vivo/In-vitro* Model**	**Dose**	**Effect of Berberine**	**Outcomes**	**References**
Wu YS *et al.,* (2020)	*In-vivo*	100 or 300 mg/kg/d	Improving insulin sensitivity and reducing insulin resistance	It was shown that BBR not only reduced inflammation under IR, but also improved glucose metabolism and insulin signal transduction on HepG2-IR cells by upregulating PPM1B levels and reducing cAMP/PKA signaling to lessen the stimulation of high glucose.	[31]
Zhou JY *et al.,* (2008)	*In-vivo*	75, 150, 300 mg/kg/d		Research indicates that berberine activates PPARs and enhances conditions such as hyperglycemia, hyperlipidemia, hepatic	[32]

				glycogenic degeneration, steatosis, and histopathologic changes in T2DM rats. These rats were made to be diabetic using a combination of 35 mg/kg STZ and a high-carbohydrate/high-fat diet.	
Bai M *et al.,* (2018)	*In-vitro*	0, 0.5, 2.5, 5 and 10 μM for 1 h	Promoting the release of insulin	The findings suggest that the reduction in insulin production in islets is closely associated with the slowing of glucose oxidation caused by berberine, regardless of AMPK activation. Additionally, the impact of berberine on insulin secretion may possibly be attributed to the suppression of fatty acid synthesis.	[33]
Jiang Y *et al.,* (2017)	*In-vivo*	100 mg/kg/d		In conclusion, CCE and Ber showed similar efficacy in treating T2MD rats, likely due to stimulating insulin secretion and protecting islet β-cells by increasing proliferation and PARP-1 protein expression.	[34]
Wei ShengNan WS *et al.,* (2016)	*In-vivo*	40 or 160 mg/kg/d	Suppressing gluconeogenesis in the liver	Author supports HNF-4α and miR122 as potential therapeutic targets for treating Type 2 Diabetes by regulating	[35]

				hepatic gluconeogenesis and lipid metabolism.	
Xiao Y *et al.,* (2018)	*In-vitro*	10 μM	Stimulating glycolysis	Metformin and berberine increase the metabolism of glucose via stimulating glycolysis, which may or may not be connected to AMPK activation.	[36]
Xu M *et al.,* (2014)	*In-vitro*	0, 2, 5, 10 and 20 μM		The findings indicate that berberine and metformin enhance glucose metabolism via boosting glycolysis through the inhibition of mitochondrial respiratory chain complex I, regardless of AMPK activation.	[37]

5. Berberine Phospholipid Complexes for Genetic Diabetes Management

Berberine is a compound found in several plants, including goldenseal, barberry, and Oregon grape [38]. It has been studied for its potential therapeutic effects on various conditions, including diabetes. Berberine has been shown to have several mechanisms of action that can benefit individuals with diabetes, such as improving insulin sensitivity, reducing glucose production in the liver, and enhancing glucose uptake in cells [39]. Phospholipid complexes, on the other hand, are formulations where berberine is combined with phospholipids, which are essential components of cell membranes [40].

These complexes are often used to enhance the bioavailability and absorption of berberine in the body. In the treatment of genetic disorders related to diabetes, such as maturity-onset diabetes of the young (MODY) or neonatal diabetes, berberine phospholipid complexes may offer several potential advantages:

Enhanced Absorption: Phospholipid complexes can improve the absorption of berberine, potentially leading to higher and more sustained levels of the compound in the bloodstream [40]. This improved absorption can be particularly beneficial for individuals with genetic disorders that may affect the absorption or utilization of nutrients.

Targeted Delivery: Phospholipid complexes can help target berberine to specific tissues or cells affected by the genetic disorder. This targeted delivery may enhance the effectiveness of berberine in modulating insulin sensitivity and glucose metabolism in these tissues [41].

Reduced Side Effects: By improving absorption and bioavailability, phospholipid complexes may allow for lower doses of berberine to be used while maintaining therapeutic efficacy. This could potentially reduce the risk of side effects associated with higher doses of berberine [42].

Synergistic Effects: Phospholipids themselves have been studied for their potential benefits in diabetes management, including improving insulin sensitivity and reducing inflammation [43]. Combining berberine with phospholipids in a complex may provide synergistic effects that further enhance the therapeutic outcomes for individuals with genetic disorders related to diabetes.

6. Conclusion

In conclusion, diabetes mellitus (DM) presents a significant global health challenge, with the prevalence expected to continue rising in the coming years. Conventional treatments for diabetes, while effective to some extent, often fall short in providing optimal glycemic control and may be associated with adverse effects. In this context, the therapeutic potential of herbal medications, particularly berberine, has garnered increasing attention. Berberine, derived from various plant sources including Berberis species, exhibits multifaceted pharmacological effects that make it a promising agent for the management of diabetes mellitus. Its mechanisms of action involve modulation of glucose metabolism, antioxidant and anti-inflammatory properties, regulation of lipid metabolism, and influence on gut microbiota. By targeting these diverse pathways, berberine offers a holistic approach to diabetes management. Moreover, berberine's relatively low toxicity and favorable safety profile make it an attractive option for long-term use. Combining herbal therapy with conventional medications may offer synergistic benefits, allowing for reduced medication dosages and minimizing adverse effects while improving efficacy. In conclusion, berberine holds promise as a viable alternative or complementary therapy for diabetes mellitus, offering a potentially safer and more cost-effective approach to diabetes management. Further research and clinical trials are warranted to fully elucidate its therapeutic effects and optimize its use in clinical practice.

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