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Therapeutic Potential of Berberine in Type 2 Diabetes: A Short Review

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ABSTRACT

Background: Type 2 Diabetes Mellitus (T2DM) is a multifactorial disease that is influenced by genetic, metabolic, and environmental factors. Genetic predisposition, obesity, low physical activity, and unhealthy diet are key risk factors for T2DM. Result: Type 2 diabetes is treated with various natural medicines, the most significant of which is berberine (BBR). Berberine, an isoquinoline alkaloid found in various medicinal plants, exhibits a wide range of pharmacological activities and (BBR) has the potential to treat various diseases, such as diabetes, cancer, and metabolic and cardiovascular diseases. Conclusion: It has been found to be effective in AMPK activation, regulation of blood glucose and lipids, stimulation of insulin secretion from pancreatic beta cells, inhibition of cancer cells, and reduction of fat formation.

1. INTRODUCTION

Diabetes is a metabolic condition characterized by hyperglycemia that persists without treatment. Diabetes can be caused by errors in insulin production or action as well as disruptions in carbohydrate, lipid, and protein metabolism.

Diabetes can lead to retinopathy, nephropathy, and neuropathy. Diabetes increases the risk of several disorders including heart disease, peripheral arterial and cerebrovascular disease, obesity, cataracts, erectile dysfunction, and nonalcoholic fatty liver disease. They are also more susceptible to infectious diseases including TB. The symptoms of diabetes include thirst, polyuria, blurred eyesight, and weight loss. Genital yeast infection is common. Ketoacidosis, a non-ketotic hyperosmolar condition, can cause dehydration, unconsciousness, and even death in the absence of treatment. In T2DM, symptoms may be mild or nonexistent because of the gradual progression of hyperglycemia. In the absence of biochemical testing, hyperglycemia can lead to long-term pathological and functional abnormalities, leading to diagnostic problems [1]. According to the World Health Organization, approximately 1.5 million people worldwide died of diabetes in 2019. Diabetes affects an estimated 537 million individuals worldwide. By 2045, this figure is predicted to

increase to almost 783 million people with diabetes, globally. Millions of individuals worldwide with diabetes lack access to diabetes care. People with diabetes require constant care and assistance to control their disease and avoid complications. Diabetes causes severe oxidative stress due to prolonged hyperglycemia, impairing antioxidant defenses and promoting free radical production. Recent studies have explored the potential of natural antioxidants in ameliorating diabetes mellitus (DM [2]). The global incidence of type 2 diabetes is rapidly increasing, prompting the development of new anti-diabetic medications. However, most antidiabetic medications cannot be used in patients with hepatic dysfunction, renal disease, or cardiac disease, which complicates the pharmacological therapy for type 2 diabetes [3]. Therefore, this study aimed to investigate the effects of berberine on type 2 diabetes.

2. DIABETES

Diabetes is a multifaceted condition characterized by elevated blood sugar levels, referred to as hyperglycemia. It encompasses a range of diseases, with hyperglycemia as a common factor. Various factors such as age at onset and insulin resistance have historically been used to differentiate between different types of diabetes. Precision medicine is increasingly used to improve diabetes management by tailoring treatments based on clinical and laboratory data. Laboratory tests can aid in categorizing diseases, identifying treatment targets, and predicting treatment responses for more individualized therapeutic approaches. Genetic factors can also have a significant effect on diabetes. Monogenic diabetes such as MODY is caused by genetic mutations, whereas polygenic diabetes is influenced by multiple genetic factors. The discovery of insulin has revolutionized our understanding of diabetes, revealing that it is a complex condition with various underlying causes rather than a singular disease entity [4].

2.1. Type of Diabetes

Type 1 and 2 diabetes mellitus are two major types of diabetes mellitus. However, it has become apparent that these types do not capture the full range of the disease, and there are other forms of diabetes, such as adult-onset autoimmune diabetes and maturity-onset diabetes, in the young [4].

Type 1 diabetes mellitus (T1DM) arises from autoimmune destruction of pancreatic β cells, resulting in insulin deficiency. It differs from type 2 diabetes mellitus, which is characterized by insulin resistance and reduced insulin secretion. T1DM is increasingly being diagnosed at a young age and is categorized into two types: type 1A (autoimmune) and type 1B (idiopathic). Genetic factors, such as specific genes in the major histocompatibility complex (MHC) region and insulin gene polymorphisms, contribute to genetic predisposition to T1DM. Environmental factors such as viral infections, diet, and gut microbiota also play a role in T1DM development. The autoimmune destruction of β cells progresses gradually over months to years, resulting in symptomatic hyperglycemia and diabetes [5].

Type 2 Diabetes Mellitus (T2DM) is a common metabolic condition caused by inadequate insulin production by pancreatic β-cells and insulin resistance in the tissues. This leads to hyperglycemia [6-8].

Genetic predisposition strongly affects susceptibility to type 2 Diabetes Mellitus (T2DM), as evidenced by genome-wide association studies, which underscore the complex polygenic character of the disease [9]. Mitochondrial dysfunction is a major factor in the development of T2DM, particularly age-related insulin resistance and accompanying comorbidities [3]. Obesity, a sedentary lifestyle, and poor dietary habits contribute significantly to an increased risk of developing T2DM, maintaining insulin dysfunction via a network of pathological alterations. T2DM is complex, with interactions between genetic, metabolic, and environmental variables, emphasizing the need to understand these linkages for effective treatment approaches and disease management [6].

2.2. Symptoms of Diabetes Type 2

Type 2 diabetes mellitus (T2DM) is characterized by high blood glucose levels due to insufficient insulin production and insulin resistance. Increased thirst, frequent urination, increased hunger, unexplained

weight loss, weariness, blurred vision, slow-healing wounds, and recurrent infections are the symptoms associated with type 2 diabetes. Furthermore, obesity, sedentary lifestyle, and high-calorie diet are frequently linked to type 2 diabetes mellitus (T2DM), which increases the prevalence and progression of the disease. The onset and maintenance of type 2 diabetes are significantly influenced by genetic predisposition, ethnicity, and environmental variables such as obesity, limited physical activity, and an unhealthy diet [6, 9-12]. For people with type 2 diabetes mellitus (T2DM), early identification and treatment of these symptoms are crucial to avoid complications and enhance the quality of life.

2.3. The Relationship of Oxidative Stress and Inflammation to Type 2 Diabetes

Inflammation and oxidative stress are important factors in the pathophysiology of type 2 diabetes. Oxidative stress is characterized by elevated levels of reactive oxygen species (ROS) and reactive nitrogen species (ROS), as well as enhanced lipid peroxidation [8]. Insulin resistance results from impaired insulin production and action, which contributes to the development of diabetic complications [6]. Inflammation and the development of cardiovascular problems are closely associated with diabetes [2]. Berberine, an antioxidant molecule, combats oxidative stress and inflammation in type 2 diabetes by suppressing reactive oxygen species (ROS) synthesis, lowering cytokine levels, and modifying antioxidant enzyme activity.

3. BERBERINE

Berberine is an isoquinoline alkaloid with the chemical formula $C_{20}H_{19}NO_5$, **Figure 1** shows the chemical structure of berberine (**Figure 1**). It is derived from various medicinal plants such as *Hydrastis canadensis*, *Berberis aristata*, and *Coptis chinensis* [3, 13]. It has a variety of pharmacological characteristics including antihypertensive, anti-inflammatory, antioxidant, depressive, anticancer, and antibacterial properties. Berberine has also demonstrated potential in the treatment of illnesses, such as type 2 diabetes, hypercholesterolemia, and congestive heart failure. Alkaloids have been clinically evaluated for numerous diseases and may be useful for the development of medications [14, 15].

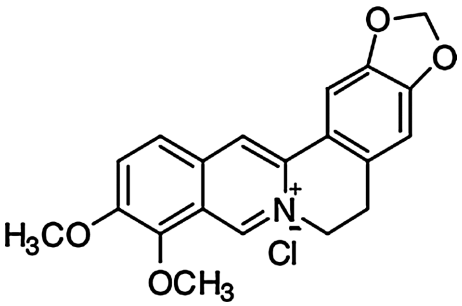

Figure 1. Structure of berberine [16].

3.1. Sources of Berberine

Plants belonging to the Euphorbiaceae, Ranunculaceae, and Papaveraceae families, including *Coptidis rhizoma*, Barberry, and *Scutellaria baicalensis*, are the source of berberine; because of their therapeutic qualities, they have long been used in China, India, and Iran. Among the protoberberine alkaloids, berberine has received the most attention, and plants belonging to the Euphorbiaceae, Ranunculaceae, and Papaveraceae families, including *Coptidis rhizoma*, Barberry, and *Scutellaria baicalensis*, are the source of berberine. Owing to their therapeutic properties, these plants have long been used in China, India, and Iran. Among protoberberine alkaloids, berberine has received the most attention [17, 18].

3.2. Berberine Derivatives

Because berberine has a relatively poor bioavailability, researchers are working to increase its use by

employing drug derivatives or cutting-edge delivery methods. One group produced two compounds: berberine and dihydroberberine. 8,8-dimethyldihydroberberine (Di-Me) and (dhBBR). Similar to berberine, berine increases glucose absorption, triggers AMPK, and inhibits mitochondrial respiration *in vitro*. dhBBR and Di-Me mitigated tissue triglyceride buildup, insulin resistance, and obesity in mice with diet-induced obesity [19].

The provided papers mention several derivatives of berberine, specifically coptisine, palmatine, epiberberine, and jatrorrhizine, which are known to exhibit pharmacological effects similar to those of berberine, particularly in modulating hyperglycemia and hyperlipidemia [20].

3.3. The Therapeutic Effects of Berberine

Berberine acts through several routes to produce therapeutic benefits. By suppressing pro-inflammatory cytokines and eliciting anti-inflammatory reactions, it exhibits potential as a treatment for gestational diabetes mellitus (GDM) [21]. Furthermore, berberine shows promise for the treatment of metabolic and cardiovascular disorders by modifying gut microbiota, lipid metabolism, and insulin resistance [22]. Additionally, studies have shown that it improves cardiac function, lowers peripheral vascular resistance, and has vasodilatory effects, all of which are beneficial to cardiovascular health [16]. Berberine is a possible option for managing diabetes because of its anti-diabetic properties, which are emphasized by its capacity to regulate blood glucose levels, promote insulin production, and prevent adipogenesis [8, 18]. These results indicate the potential of berberine as a therapeutic agent for various illnesses.

3.4. AMPK Activation

Berberine activates AMPK by inducing the phosphorylation of Thr172 on a subunit, increasing the AMP/ATP ratio by inhibiting ATP biosynthesis in the mitochondria, and inhibiting mitochondrial function associated with AMPK activation [3, 8, 19, 20].

AMPK activation is essential for several processes including enhancing insulin sensitivity, controlling mitochondrial activity, promoting glycolysis, reducing hepatic gluconeogenesis, and preventing adipogenesis. As berberine activates AMPK, there are improvements in glucose metabolism, increased glucose absorption in the skeletal muscle, lowered blood glucose levels, and decreased adiposity. Furthermore, the activation of AMPK by berberine has positive effects on insulin sensitivity, glucose homeostasis, and lipid metabolism without the assistance of upstream kinases, such as LKB1 or CaMKK.

3.5. Regulating Blood Glucose, Lipids

Berberine has demonstrated encouraging results in controlling blood sugar and fat levels. Increasing insulin sensitivity, encouraging insulin secretion, and decreasing the hepatic synthesis of glucose can lower blood sugar levels [7, 18]. Research has shown that berberine, similar to popular diabetes drugs, such as metformin, dramatically enhances glucose and lipid metabolism [23]. Berberine decreases mitochondrial activity, promotes glycolysis, and activates the AMPK pathway, all of which promote insulin secretion and sensitivity [8]. Additionally, berberine lowers triglyceride and total cholesterol levels in diabetic individuals, while lowering HbA1c, fasting plasma glucose, and postprandial glucose levels [19]. These results demonstrated the potential of berberine as a natural remedy for diabetes and its associated metabolic conditions.

3.6. Stimulate Insulin Secretion from Pancreatic Beta Cells

Berberine affects the ability of β-cells to secrete insulin in several ways. Insulin sensitivity and glucose uptake were improved by upregulating mRNA expression [8]. Furthermore, berberine can boost insulin secretion by stimulating important enzymes in insulin synthesis, such as glucokinase (GK) and nuclear factor 4-alpha (HNF-4a) [19] Additionally. Berberine has been shown to enhance islet activity, possibly restoring worn-out or injured beta cells, which in some diabetic circumstances, increases insulin secretion [2]. Berberine targets β-cell insulin secretion, making it a promising treatment option for diabetes. These activities

also help to improve insulin sensitivity and blood glucose regulation [23].

3.7. Inhibiting Cancer Cells

Berberine has demonstrated encouraging effects on cancer cells by disrupting many signaling pathways, inducing apoptosis, and limiting growth. Research has demonstrated that it is effective against many different types of cancer, such as those of the tongue, liver, lung, breast, and prostate [3, 13, 16]. The anticancer activity of berberine is partly attributed to its interaction with DNA, which can result in double-strand breaks and the modification of gene transcription [8, 21]. Berberine also increases the efficiency of chemotherapy and radiation by inhibiting tumor development and activating pro-apoptotic pathways. Berberine is a promising candidate for cancer treatment owing to its capacity to induce cell cycle arrest, promote cell death, and prevent cancer cell proliferation. Therefore, further studies and developments in this field are necessary.

3.8. The Relationships between Cancer Cells and Diabetes

Diabetes increases the risk of certain cancers, particularly type 2 diabetes mellitus (T2DM), owing to chronic inflammation and metabolic dysregulation. Insulin and insulin secretagogues, commonly used in diabetes management, may elevate the risk of developing breast, liver, pancreatic, and colorectal cancer. High blood glucose levels in diabetes can contribute to cancer cell proliferation as these cells often use glucose for energy. Therefore, careful management of blood glucose levels is crucial to mitigate the risk of cancer in patients [10, 24].

3.9. Reducing Fat Formation

It has been demonstrated that berberine inhibits the production of fat via a number of methods. Downregulation of important transcription factors required for adipogenesis, such as PPAR-γ, C/EBPα, and SREBP-1c, prevents adipocyte development [3, 14]. Berberine also reduces fat buildup by activating AMP-activated protein kinase (AMPK) and extracellular signal-regulated kinases, both of which are essential for fat and glucose metabolism [19]. According to clinical research, berberine reduces serum cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglyceride levels. It also prevents triglycerides from being deposited in organs, such as the liver and muscles, which helps lipid metabolism and reduces fat content. These results indicated that berberine can efficiently inhibit fat accumulation through a variety of mechanisms.

3.10. Effect on Blood Vessels and the Heart

Berberine has a profound effect on heart and blood vessels. Enhancing endothelial function, lowering atherosclerosis, and protecting against myocardial injury have beneficial effects on cardiovascular health [16, 21]. By boosting thrombolysis, preventing calcium influx, and interfering with adrenoreceptors to impair platelet activity, berberine protects blood vessels over the long term. Furthermore, it exhibits antiarrhythmic properties by adjusting the ion channels of the heart muscle and action potential duration. The cardioprotective properties of berberine are partly attributed to its ability to control lipid metabolism, reduce inflammation, and improve insulin sensitivity. Through a variety of molecular pathways, berberine generally demonstrates promise in the management of cardiovascular illnesses and promotion of heart health [3, 22].

3.11. Lowering Blood Pressure

Berberine has a considerable effect on blood pressure regulation through several processes. Their cardiovascular advantages are facilitated by their hypotensive and vasodilatory properties [16]. Because of its capacity to prevent the liver from synthesizing lipids and regulate its low-density lipoprotein receptor (LDLR), berberine helps lower cholesterol levels, which, in turn, can lower blood pressure [3, 23]. Furthermore, the anti-inflammatory properties of berberine may aid in lowering inflammation caused by hypertension [8].

Additionally, berberine can indirectly affect blood pressure management by increasing glucose metabolism and upregulating insulin receptors [2]. Berberine is a prospective drug for preserving cardiovascular health that may influence blood pressure management owing to its diverse pharmacological effects.

3.12. Side Effects of Berberine

The natural substance berberine has many positive effects, but can also have negative effects. According to previous studies, berberine may cause gastrointestinal distress such as nausea, vomiting, diarrhea, constipation, and abdominal discomfort [11, 15]. Furthermore, when berberine is consumed in large quantities, it can cause even more serious side effects, including liver and kidney damage, in addition to mild effects such as salivation and tremors in the muscles [18]. When considering the use of berberine supplements, it is important to be aware of possible adverse effects, particularly in people who already have medical concerns.

4. CONCLUSIONS

Berberine (BBR) has therapeutic potential for the treatment of several illnesses, including diabetes, cancer, and metabolic and cardiovascular diseases. Recommendations for overcoming difficulties such as poor oral absorption and drug interactions brought on by BBR's metabolism are to use sophisticated drug delivery systems and combine them with other medicines. When used with other diabetes drugs, berberine may enhance their ability to reduce blood sugar levels, according to the studies

Further research is needed to explore its full therapeutic potential and mechanisms of action.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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