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Berberine: A Promising Treatment for Type 2 Diabetes Mellitus and Its Associated Dementia – A Review

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ABSTRACT:

Introduction and objective: Berberine (BBR) is an isoquinoline alkaloid extracted from various plants. It has been utilized for millennia in traditional Chinese and Ayurvedic medicine. A growing body of evidence supports the beneficial effects of BBR in the treatment of type 2 diabetes mellitus (T2DM) and in reducing the risk of developing related complications. The aim of this study is to review the existing knowledge on the efficacy and safety of BBR in the treatment of T2DM and associated dementia, based on the available scientific literature.

Material and Methods: A review of the literature available in the PubMed database was conducted using the following search terms: Berberine; Diabetes Mellitus Type 2; Vascular Dementia; Alzheimer Disease.

Current knowledge: The pharmacological treatments of both T2DM and AD have been associated with relatively low efficacy, a high financial burden, and numerous complications that significantly impact patients' daily lives. The exact mechanisms of action of berberine remain unclear.

Summary: BBR may be an attractive option for the treatment of T2DM and associated dementia, with therapeutic effects similar to oral hypoglycemic agents, promising neuroprotective properties, a reduced risk of adverse reactions and lower cost. Moreover, BBR improves cerebral blood flow and memory in the rat model of AD. Further scientific research is required to determine the long-term outcomes of this treatment.

Key words: Berberine; Diabetes Mellitus Type 2; Vascular Dementia; Alzheimer Disease.

INTRODUCTION AND OBJECTIVE

Type 2 diabetes mellitus (T2DM), according to the World Health Organization (WHO), is recognized as a chronic metabolic disease characterized by elevated blood glucose levels. [1] The pathomechanism of T2DM primarily involves two factors: pancreatic β-cells secrete an insufficient amount of insulin, and peripheral tissues become increasingly insulin-resistant. [2] Over time, oxidative stress and chronic inflammation lead to the progressive loss of pancreatic β-cell function, resulting in increasingly difficult glycaemic control. [3] Genetic and environmental factors, particularly obesity and aging of the population, play a role in the pathogenesis of T2DM. [2,4] The majority of cases of diabetes are attributed to T2DM, accounting for over 90% of all cases and therefore representing the most common type of the disease. According to the International Diabetes Federation (IDF), T2DM was responsible for

4.2 million deaths worldwide in 2019. [1,5] It is estimated that approximately 45% of patients remain undiagnosed, and by 2045, the number of people with diabetes is expected to reach 783 million. [6] Therefore, this condition poses a significant challenge to healthcare systems.

BBR is extracted from the rhizomes, roots, and stems of various plants, including Berberis vulgaris, Hydrastis canadensis, Coptis chinensis, Berberis aristata, and Berberis aquifolium. It has traditionally been employed in the treatment of gastrointestinal infections. Numerous reports suggest its wide range of therapeutic properties. Recent scientific findings indicate that BBR possesses a broad spectrum of therapeutic applications. It has been demonstrated to positively affect glucose metabolism, lipid metabolism, cardiovascular function, and to exhibit neuroprotective effects. Furthermore, BBR is distinguished by its anti-inflammatory, antioxidant, antimicrobial, and anticancer properties. [7] This multifaceted action indicates that BBR may be one of the most promising natural substances in the field of medicine.

The main aim of this review is to systematise and update the knowledge on the impact of BBR in the treatment of type 2 diabetes and its potential in the treatment of associated dementia.

MATERIALS AND METHOD

A review of the literature was conducted by searching the Pubmed database. The combination of the following key words was used in the search**:** Berberine; Diabetes Mellitus, Type 2; Dementia, Vascular; Alzheimer Disease, Insulin Resistance. The terms “Berberine and Alzheimer disease” and “Berberine and type 2, diabetes mellitus” were used to identify a significant proportion of articles. Additional sources were included to provide a more comprehensive introduction and deeper understanding of T2DM and AD, focusing on their pathophysiology and treatment. A total of 45 articles were included, 29 of which were published between 2020 and 2024. 80% of the articles were published after 2016.

STATE OF KNOWLEDGE

Maintaining blood glucose levels within the appropriate range is crucial in the therapeutic process of T2DM, as it reduces the risk of mortality and complications. [8,9] These complications include diseases affecting both large vessels (stroke, coronary artery disease, peripheral artery disease) and small vessels (retinopathy, peripheral neuropathy, diabetic kidney disease), dementia, infections, and liver diseases. [9] The cornerstone of

therapy is lifestyle modification; however, if this is insufficient, oral hypoglycemic agents (OHA) and/or insulin are also introduced. [2, 8] The use of these substances is associated with certain side effects and does not always result in satisfactory glycemic control, as only 41% of cases achieve this. [8] Metformin is typically introduced as the drug of choice in the early stages of T2DM, but after three years of use, approximately 30% of patients require an additional hypoglycemic drug due to insufficient efficacy. [10] The use of metformin is most commonly associated with gastrointestinal disturbances. Insulin, on the other hand, may lead to the development of breast, pancreatic, liver, or colorectal cancers. [8] There are also reports that pioglitazone may increase the risk of bladder cancer and lead to heart failure or distal bone fractures in postmenopausal women. Sulfonylureas are primarily associated with weight gain and hypoglycemia. [11] All of this underscores the need for new, safer, and better-tolerated treatment regimens, [8] as well as providing appropriate and long-term patient care. [5]

An increasing number of scientific publications suggests that T2DM is associated with an elevated risk of developing cognitive impairment and dementia, [12,13,14,15] although the causal relationship is still poorly understood. [16] This is probably due to the overlapping effects of many processes associated with T2DM and its comorbidities, as well as mechanisms that cause dementia. [15]

Among the types of dementia, Alzheimer's disease (AD) is the most common, [17] affecting approximately 5% of the population over 65 years of age, [18] along with vascular dementia (VaD). [17,19] Over 80% of patients diagnosed with AD have T2DM or abnormal blood glucose levels, suggesting that the pathomechanisms of the two conditions are likely to overlap. [20]

AD is a neurodegenerative and multifactorial disease, and its exact pathomechanism is not fully understood. However, a hallmark of AD is the accumulation of beta-amyloid (Aβ) and hyperphosphorylation of tau protein in brain tissue. [17] Other pathological processes that occur in AD include synapse loss, hypometabolism, brain atrophy and neuroinflammation. There are two main theories as to how T2DM might contribute to the development of AD. The first theory suggests that T2DM leads to small vessel disease in the cerebral circulation. The second theory suggests that T2DM may lead to brain dysfunction directly or through numerous interactions with key AD pathways and proteins (tau and Aβ). [16]

Aβ is generated as a result of improper processing of the amyloid precursor protein (APP). Aβ then aggregates into oligomers that form amyloid plaques in the extracellular space,

leading to brain dysfunction. In the early stages of AD, these plaques are found mainly in the frontal and parietal lobes; in later stages, they spread to the neocortex, hippocampus, basal nuclei, brainstem and cerebellum. [21] The highly phosphorylated tau protein creates intracellular insoluble aggregates called neurofibrillary tangles (NFTs), [7] which can have a detrimental effect on nearby neurons. [21] NFTs can cause inflammation, which promotes the formation of Aβ and further phosphorylation of tau protein. [7] Insulin resistance also promotes Aβ and hyperphosphorylated tau deposition through activation of glycogen synthase kinase 3β (GSK3β). [17] A potential link between AD and T2DM is also suggested by defects in the insulin-degrading enzyme (IDE), which is responsible for both insulin and Aβ metabolism. This relationship creates a vicious cycle which, for better understanding is illustrated in fig. 1 below.

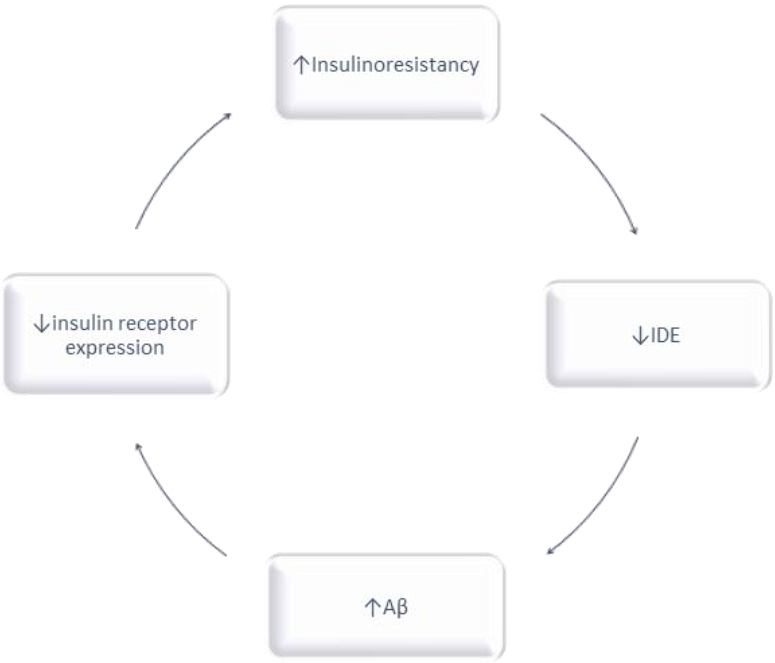

Figure 1. Link between AD and T2DM including IDE.
Source: own elaboration based on data from [20]

A reduction in the levels of insulin and insulin receptors has been demonstrated in the cerebrospinal fluid (CSF) of individuals diagnosed with AD. This is most likely due to chronic hyperinsulinemia and impaired insulin transport across the blood-brain barrier (BBB). [16,20] Experimental studies suggest that high blood glucose levels may induce the formation of reactive oxygen species, leading to inflammation within neural tissue and significant

neuronal damage in areas such as the hippocampus. In addition, chronic hyperglycemia affects the activity of acetylcholinesterase (AChE) and acetylcholine transferase (ChAT), whose proper functioning is important for the central nervous system. [14] The above mechanisms suggest a strong link between AD and T2DM.

AD is characterised by a late onset, with the first symptoms usually appearing after the age of 60. [22] However, the interpretation of AD studies is challenging because hyperphosphorylated tau and Aβ protein deposition occurs up to about 15 years before the onset of symptoms. [16] The main symptoms include progressive memory loss and difficulty with the simplest daily tasks. [22]

Treatment consists mainly of acetylcholinesterase (AChE) inhibitors, such as donepezil, rivastigmine and galantamine, and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. [18] However, these drugs have only a symptomatic effect and are not able to completely stop the progression of the disease. [17] On the other hand, their use is associated with unpleasant side effects for patients. In the case of AChE inhibitors, these most commonly include nausea, vomiting, loss of appetite, muscle spasms, diarrhoea or gastrointestinal bleeding. [23] The use of memantine is frequently associated with the possibility of hallucinations, hypertension, somnolence, anxiety, confusion, headache and dizziness. [24] As AD is a multifactorial disease, its treatment requires a broader view and a strategy of combining drugs that target different pathomechanisms. [21]

BERBERINE AS A TREATMENT FOR T2DM

A substantial body of evidence from animal models and human studies has established the antidiabetic properties of BBR. [11,25] The mechanisms through which BBR contributes to lowering blood glucose levels are numerous and varied. These include increasing glycolysis in peripheral tissues, [11] enhancing glucokinase activity, stimulating insulin secretion, supporting the regeneration of the islets of Langerhans, and reducing insulin resistance. [8,11,26] Another investigation has indicated that BBR is capable of facilitating the upregulation of the insulin receptor. [8] Furthermore, BBR has been demonstrated to reduce glucose absorption in the intestines by inhibiting α-glucosidase activity. [11,27] It is also noteworthy that BBR has an impact on the gut microbiome, which is capable of regulating metabolism. [27,28] It is significant that gut bacteria can enhance the bioavailability of BBR by converting it into dihydroberberine, a metabolite that is absorbed at a rate up to five times faster by the intestines than BBR itself. [21]

Additionally, BBR has been demonstrated to mitigate oxidative stress and inflammation, which are hallmarks of T2DM. [11] Patients with T2DM exhibit significantly elevated levels of interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). Chronic inflammation leads to a decrease in the expression of several enzymes responsible for drug metabolism, resulting in reduced efficacy and poorer outcomes in T2DM treatment. BBR therapy resulted in a reduction in the levels of IL-6, TNF-α [29] and CRP. [29,30] Furthermore, BBR exerts its anti-inflammatory and insulin-sensitizing effects by acting as an agonist of sirtuin 1 (SIRT1). [25]

In studies conducted on an animal model of T2DM, BBR was observed to inhibit gluconeogenesis in the liver in a manner analogous to that of the pharmaceutical metformin. This inhibitory effect was found to be mediated by the activation of AMP-activated protein kinase (AMPK). [8]

The presence of elevated glucose concentrations within pancreatic β-cells has been observed to stimulate the production of ATP, which in turn results in the closure of ATP-dependent potassium channels. [31] BBR functions as an inhibitor of the potassium voltage-gated channel KCNH6, thereby prompting the islets of Langerhans to secrete insulin. Nevertheless, these reactions do not occur at low glucose concentrations (2.8 mM). This is a notable distinction from the current insulin secretagogues, such as sulfonylureas and glinides, as BBR does not reduce blood glucose levels in hypoglycemic conditions, which suggests enhanced safety. [32]

A meta-analysis published in 2014 revealed that BBR exhibits a comparable therapeutic effect to oral hypoglycemic agents (OHA). Furthermore, the combined utilisation of BBR and OHA yielded more favourable outcomes compared to OHA therapy alone. Moreover, the combination of lifestyle modifications with BBR supplementation resulted in more pronounced reductions in fasting plasma glucose (FPG), postprandial glucose (PPG), and glycated hemoglobin (HbA1c) levels compared to lifestyle intervention or placebo alone. In addition to its beneficial effects on glucose metabolism, BBR has also been shown to have a positive impact on conditions associated with the metabolic syndrome, including hypertension, [26] hyperlipidemia [26,33] and obesity. [27] Furthermore, it stimulates the postprandial secretion of glucagon-like peptide-1 (GLP-1), an insulinotropic hormone that inhibits glucagon secretion and stimulates insulin secretion under hyperglycemic conditions, while also reducing hunger. [34]

These factors are all significant in a holistic approach to the treatment of T2DM. It is unfortunate that the efficacy of BBR may diminish over the course of treatment. [25]

NEUROPROTECTIVE EFFECTS OF BERBERINE

BBR has demonstrated promise in improving cognitive function in animal models of AD. [35] Studies in rodents have shown that BBR is able to cross the blood-brain barrier (BBB) by increasing the expression of claudin-5, a membrane protein. It therefore has the potential to affect the central nervous system. [22] However, as other work has exhibited, BBR transport across the BBB is inefficient, whereas this process can be aided by the use of specific transporters (microglia-derived exosomes). [36] The results suggest that BBR has neuroprotective, neurotrophic, [7] and anti-inflammatory effects, improves cholinergic neurotransmission, enhances cerebral blood flow, reduces tau protein hyperphosphorylation and facilitates Aβ clearance. [17]

Inhibition of oxidative stress

Reactive oxygen species (ROS) have been implicated in neurodegenerative diseases, causing oxidative stress and leading to a variety of tissue damage. BBR is thought to protect neurons from ROS by acting as a free radical scavenger and antioxidant. [37] However, its mechanism of action in AD is not well understood. [7,37] As shown in a study in a rat model of T2DM, chronic treatment with BBR (at doses of 50 and 100 mg/kg) caused a significant increase in superoxide dismutase (SOD) activity, one of the major antioxidant enzymes, and also reduced levels of nitrite and lipid peroxidation products. BBR also stimulates glutathione (GSH) synthesis, which protects cells from damage. [37] Moreover, BBR is responsible for inhibiting monoamine oxidase B (MAO-B), which mediates the dopamine pathway and generates free radicals such as hydrogen peroxide. Additionally, BBR activates nuclear erythroid-derived transcription factor type 2 (Nrf2), which has antioxidant properties. [22]

Anti-inflammatory effects

One of the principal characteristics observed in patients with AD is chronic neuroinflammation. [36] Microglia play a pivotal role in the progression of AD, particularly during the initial stages. They are responsible for repairing damaged tissues and for inhibiting

Aβ accumulation. [18,20] BBR facilitates the passage of bone marrow-derived mononuclear macrophages through the BBB, which then stimulate microglia to remove senile plaques and produce inflammatory factors. [18] Nevertheless, prolonged activation of microglia in T2DM gives rise to an overproduction of nitric oxide (NO), ROS and pro-inflammatory cytokines. This impairs the normal functioning of microglia and results in neuronal dysfunction and death. [38] A study employing a rat model of AD indicates that BBR may have a beneficial therapeutic effect. In the vicinity of the senile plaque, which is constituted by Aβ, microglia and astroglia demonstrate activity, and there is overexpression of a number of inflammatory factors that can damage neurons. These include interleukin-1beta (IL-1β), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS) and tumour necrosis factor-α (TNF-α). The study demonstrated that intragastric administration of berberine chloride at a dose of 50 mg/kg for 14 days resulted in an improvement in spatial memory in rodents. The animals exhibited a markedly superior performance in the Morris water maze test when compared to the control group ($p < 0.01$). It is noteworthy that, in contrast to the findings of previous studies on this topic, an increase in the expression of IL-1β and iNOS was observed in the hippocampus of the rats. The authors posit that these disparate outcomes may be attributable to the different routes of BBR administration, with intragastric administration exhibiting diminished absorption into the bloodstream relative to other routes such as intraperitoneal or intravenous. This discrepancy may give rise to disparate immune system responses and, consequently, the production of disparate inflammatory factors. The anti-inflammatory properties of BBR may also be attributed to the downregulation of cyclooxygenase-2 (COX-2) [18] and the Nuclear Factor kappa B (NF-κB) transcription factor expression. [22] Furthermore, BBR displays promise in its capacity to regulate mitochondrial bioenergetics and to mitigate the dysfunction of the primary energy and glutathione metabolism pathways in an AD cell model. Moreover, it has been demonstrated to suppress basal respiration and reduce the production of pro-inflammatory cytokines in activated microglial cells. [39]

Enhancement of cholinergic neurotransmission

A deficiency in cholinergic neurotransmission has been associated with symptoms of Alzheimer's disease. [17] BBR has the potential to enhance cholinergic neurotransmission by inhibiting the activity of acetylcholinesterase (AChE) [22,36,40] and butyrylcholinesterase (BChE). [22] This results in increased neurotransmitter levels, which may directly contribute

to enhanced memory function. [36,40] Furthermore, reduced AChE activity also inhibits neuronal entry into the apoptosis pathway. [22] Aβ has been demonstrated to decrease both acetylcholine (ACh) uptake and release. [32]

Inhibition of tau protein hyperphosphorylation and Aβ removal

Several studies have demonstrated that BBR administration inhibits the production and accumulation of Aβ. [21,22,41] In an in vitro study, BBR demonstrated the capacity to reduce Aβ levels by 30% in comparison to the control group. [22]

Furthermore, BBR has been observed to act as an agonist of AMP-activated protein kinase (AMPK), which results in the reduction of BACE1 expression, the primary β-secretase responsible for Aβ formation. [21,36,42] However, one publication demonstrated that BBR was unable to inhibit BACE1 activity. [22]

By inhibiting Aβ formation, BBR also exhibits indirect potential in limiting hyperphosphorylation of tau protein, as Aβ blocks proteasomal degradation of hyperphosphorylated tau protein. [7]

THE EFFECT OF BERBERINE ON VASCULAR DEMENTIA

Impairment of the blood supply to brain tissues is also observed during the course of T2DM, which may be related to cognitive decline, the occurrence of AD, or vascular dementia (VaD). [7] VaD usually develops as a result of reduced or blocked cerebral blood flow, which may be caused by hyperglycemia [19] and atherosclerotic vascular changes. [7] A study conducted on a rat model of T2DM demonstrated that the administration of BBR resulted in a notable improvement in cerebral blood flow in the right and left posterior cerebral arteries, which supply the hippocampus, when compared to rats that received saline treatment. [7]

Furthermore, several studies have indicated that BBR may possess anti-atherosclerotic properties. This is presumably achieved by inhibiting the proliferation of vascular smooth muscle cells. [7] Moreover, BBR has been proven to reduce cholesterol levels in a manner distinct from that of statins. [18] Additionally, it has been shown to stabilise atherosclerotic plaque by reducing oxidative stress in endothelial cells. [7]

It can therefore be concluded that BBR supplementation can be used both to inhibit the progression of neuronal loss and damage and to repair already existing brain tissue perfusion abnormalities. [22]

SIDE EFFECTS OF BBR THERAPY

The potential side effects of BBR therapy remain poorly understood. Since the 1950s, it has been employed as an over-the-counter antidiarrheal agent, thereby exemplifying its pervasive utilisation. [32] A meta-analysis conducted in 2014 revealed that the majority of studies did not report any significant adverse effects at doses ranging from 0.6 to 2.7 grams per day. If any side effects were observed, they were predominantly gastrointestinal in nature and included nausea, diarrhea, constipation, abdominal discomfort, flatulence, and, on rare occasions, hypoglycemia. No discontinuation or dose reduction of BBR was necessary, as patients on this therapy were able to tolerate the aforementioned side effects. Furthermore, the findings indicated that toxicity is dose-dependent. [26] Further investigation is required to elucidate the optimal dosage. This is evidenced by a research group's study on a transgenic AD mouse model, in which it was demonstrated that a lower dosage (25 mg/kg) often yielded superior results compared to a higher dosage (100 mg/kg). [22] This may be associated with potential reports of mitochondrial and NMDA receptor-dependent neurotoxicity. [43]
Additionally, several studies have documented cases of jaundice and phototoxicity, with the severity of these effects being dependent upon the dosage, the method of administration, and the duration of exposure. [44] A hypothesis has been put forth suggesting that BBR's inhibitory action on α-glucosidase may contribute to the emergence of gastrointestinal symptoms. [45] This side effect has been reported with particular frequency when BBR is used in conjunction with metformin or acarbose, the use of which is also associated with gastrointestinal side effects. Consequently, when both drugs were administered concurrently, the dose of BBR was reduced to 0.3 g three times a day to mitigate the occurrence of bloating and diarrhoea. [6] The safety of berberine chloride use is also evidenced by the lack of significant changes in Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT), [6] blood urea nitrogen (BUN) [30,32] and serum creatinine (Scr) levels. [6,25]

CONCLUSIONS

Based on the current evidence, it can be posited that due to beneficial properties, safety, and evidence of efficacy, BBR may represent an attractive option for the treatment of T2DM. BBR has been shown to exhibit comparable therapeutic effects to oral hypoglycaemic agents, with a reduced incidence of adverse effects and lower costs. Furthermore, the combination of herbal medications with standard pharmacotherapy and lifestyle modifications enables the use of lower doses and/or less frequent administration of drugs. Moreover, BBR has been demonstrated to possess neuroprotective properties, enhance cholinergic neurotransmission, reduce inflammation, and has been associated with diminished levels of beta-amyloid and hyperphosphorylated tau protein. The potential of BBR in the prevention of dementia is worthy of note, as it may arise from both the direct prevention of brain damage and improvement in cognitive function, as well as indirectly reducing the risk factors associated with type 2 diabetes. This review examines the multifaceted benefits of BBR in the management of T2DM and the prevention of related cognitive disorders. Despite the encouraging outcomes of ongoing research into berberine's efficacy, further scientific investigation is required to ascertain the long-term effects of this treatment.

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