BERBERINE AND ITS RELEVANCE IN ANTI -DIABETIC ACTIVITY

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ABSTRACT

Berberine has been the basis of many traditional medicines throughout the world for thousands of years and continues to provide new remedies to mankind. Berberine have many medicinal properties that have attracted the attention of researchers over the time. According to several studies, Berberine exhibited anti-inflammatory, antioxidant, anticonvulsant, antidepressant, anti-Alzheimer, anti-cancer, anti-arrhythmic, antiviral, antibacterial and anti-diabetic effects in both in vitro and in vivo experiments. Diabetes mellitus has appeared as a threat to public health all over the world in the last few decades. Berberine plays an important role in lowering the blood glucose level as that of metformine and rosiglintazone. This review provides a summary regarding the pharmacokinetic and pharmacodynamic features of berberine, with a focus on the aspect of antidiabetic activity.

Keywords: *Berberine , Berberis aristata, Pharmacology, anti -diabetic activity.*

Introduction

Berberine is a plant alkaloid with a protracted history of medicinal use in both Ayurvedic and Chinese medication. It is present in Hydrastis Canadensis (goldenseal), Coptis chinensis (Coptis or goldenthread), Berberis aquifolium (Oregon grape), Berberis vulgaris (barberry), and Berberis aristata (tree turmeric). The berberine alkaloid can be foundwithin the roots, rhizomes, and stem bark of the plants.. Berberine extracts and decoctions have incontestible important antimicrobial activity against a range of organisms as well as microorganism, viruses, fungi, protozoans, helminths, and chlamydia.(Chander, Aswal, Dobhal, & Uniyal, 2017) Berberine(5,6-dihydro-9,10-dimethoxybenzo[g]-1,3-benzodioxolo[5,6-a]quinolizinium) is a nonbasic and quaternary benzylisoquinoline alkaloid, a relevant molecule in medicine and medicative chemistry. Indeed, it's called as a very important natural alkaloid for the synthesis of several bioactive derivatives by means of condensation, modification, and substitution of functional groups in strategic positions for the design of new, selective, and powerful drugs. (Neag et al., 2018) Berberine is a quaternary ammonium salt from the protoberberine group of benzylisoquinoline alkaloids found in such plants as Berberis, such as Berberis vulgaris (barberry), Berberis aristata (tree turmeric). BBR has been used in the clinic for hyperlipidemia, diabetes, neuroprotective and cardiovascular diseases, suggesting its potential in future. BBR showed anti-hyperlipidemia effect of lowering total cholesterol (TC), triglyceride (TG), low-density-lipoprotein cholesterol (LDL-c) levels in patients. Besides hyperlipidemia, BBR has also been reported to be effective in anti-diabetes. In 1988, the hypoglycemic effect of berberine was firstly reported when berberine was prescribed to treat diarrhea in diabetic patients. Moreover, several clinical and preclinical studies demonstrate ameliorative effect of berberine against several disorders together with metabolic, neurological and cardiological problems. Numerous literatures had been published by various authors exploring the phytochemical and pharmaceutical aspects beside ancient uses nevertheless there's no way more literature regarding to date the importance of Berberine, that is very important constituent of this species. Berberine is understood as antidiabetic drug since long and may be tagged as ‘herbal metformin’.

Berberis aristata

Berberis aristata DC. (Berberidaceae) is one of the herbs mentioned in all ancient scriptures of Ayurveda, Charaka and Susruta have mentioned it’s different properties along with various used for the treatment of numerous illnesses. The genus Berberis represents the around 12 genera and 600 species worldwide and about 77 species have been reported from India. In Indian Himalayan ecosystem most of the species have reported from Nilgiri hills at

an altitude of 1,000–3,000 mASL. Among the various species of Berberis genus Berberi aristata DC is one of the most important species due to its wide medicinal properties and its occurrence has reported from sub-tropical areas (1800-3000 m ASL) of the mountain state of Uttarakhand and Himachal Pradesh. It is used in various crude drug formulations and in different ayurvedic and homeopathic medicines since ancient times. (Chander et al., 2017) There are 12 –13 like genus Berberis asiatica, Berberis lycium, Berberis vulgaris, Berberis nepalensis etc. The root and wood are rich in a yellow alkaloid berberine, a bitter substance, which dissolves in acids and forms salts of the alkaloid. The root contains 2 additional alkaloids. A protoberberine alkaloid karachine is isolated and characterized, and taxalamine is also isolated. A protoberberine alkaloid karachine –isolated and characterized and also taxila mine isolated.Berberis aristata DC. is an erect acanthoid bush, usually found in little patches on the bill slopes. it's one amongst terribly necessary medicative plants. Virtually each a part of this plant has some medicative value. Its roots, stem, bark and fruits are used in several ayurvedic preparations. (Mazumder Papiya Mitra 1, *Das Saumya 2, Das Sanjita 2, 2011)

Phyto-chemical Examination Study

Berberis aristata contains protoberberine and bisisoquinoline type of alkaloid. Root of plant B. aristata contains alkaloid which are berbamine, Berberine, oxycanthine, epiberberine, palmatine, dehydrocaroline, jatrorhizine and columbamine, karachine, dihyrokarachine, taximaline, oxyberberine,aromoline. Four alkaloids, pakistanine, 1-Omethylpakistanine, pseudopalmatine chloride and pseudoberberine chloride were also isolated from Berberis aristata. A secobisbenzlisoquinoline or simple isoquinoline alkaloid was isolated from B. aristata. The major alkaloid found in B. aristata is Berberine having yield of 2.23% followed by palamatine. (Komal, Ranjan, Neelam, Birendra, & Kumar, 2011) Variation of Berberine content in root and stem of Berberis aristata with altitude determined. It has been found that plants growing at lower altitude have additional Berberine content. Berberine content in plant is additionally influenced by potassium and moisture content of soil . HPTLC fingerprinting of Berberine in Berberis aristata was done to quantify the amount of Berberine. Total alkaloidal content of Berberis aristata was also done. (Review, 2018) Berberine is reported as the major active constituent in almost all Berberis species. Although it has been reported unanimously by all the research groups that maximum berberine content is accumulated in root part (1.6–4.3 %) in most of the Berberis species and low altitude plants contain more berberine in comparison to higher altitude plants. Higher berberine content in B. asiatica Roxb (4.3 %) in comparison to B. lycium Royle (4.0 %) andB. aristata DC (3.8 %) whereas another researcher reported higher content in B. aristata DC (2.8 %) in comparison to B. asiatica Roxb (2.4 %)48,49. Maximum yield of berberine in the roots (2.76 %) and stem bark (1.76 %) of B. pseudumbellata Parker harvested in summer season contrary to this higher berberine content (1.86 %) was reported in the winter samples in the roots of B. aristata DC (Chander et al., 2017)

Ethno-pharmacology

B. aristata DC, the official species of Ayurvedic Pharmacopeia of India has a niche over reported pharmacological and clinical uses. Attention has been paid to the antioxidant and anti-inflammatory activity of natural products and compounds isolated from natural products which are often characterized by high efficacy and low adverse effects. Berberine is an isoquinoline alkaloid, widely present in different medicinal herbs, especially in the genus Berberis. It is mainly used as antidiarrhoeal, antibacterial, antifungal, and antiprotozoal agent. However, current research has also highlighted on its beneficial role in neurodegenerative diseases, mainly due to its powerful antioxidant effect. The therapeutic potential of Berberine in different neurodegenerative diseases such as Alzheimer, Parkinson and Huntington disease has been brought to evidence by numerous studies. (Ahamad J, Mir SR, 2012).According to Ayurvedic pharmacopeia of India Berberis

aristata DC is also used in diabetes. Diabetes mellitus is one of the most common chronic diseases and is associated with hyperlipidemia and co-morbidities such as obesity and hypertension. The use of medicinal plants for the treatment of diabetes mellitus dates back from the Ebers papyrus of about 1550 B.C.

A multitude of herbs spices and other plant materials have been described for the treatment of diabetes throughout the world. The medicinal plants might provide a useful source of new oral hypoglycemic compounds for development of pharmaceutical entities or as a dietary adjunct to existing therapies. (Pari L SR., 2003) Few of the plants used for the treatment of diabetes have received scientific or medicinal scrutiny. The maximum reduction in serum glucose levels was seen in methanolic extract of Berberis aristata DC at the dose of 500 mg/kg. Hence the methanolic extract of Berberis aristata DC had a beneficial effect on carbohydrate metabolism in diabetic condition.

Diabetes Mellitus

The term diabetes is the shortened version of the full name diabetes mellitus. Diabetes mellitus is derived from the Greek word diabetes meaning siphon - to pass through and the Latin word mellitus meaning honeyed or sweet.

Diabetes mellitus is a spectrum of metabolic disorders arising from myriad pathogenic mechanisms, all resulting in hyperglycemia. Both genetic and environmental factors contribute to its pathogenesis, which involves insufficient insulin secretion, reduced responsiveness to endogenous or exogenous insulin, increased glucose production, or abnormalities in fat and protein metabolism. The resulting hyperglycemia may lead to both acute symptoms and metabolic abnormalities. Major sources of the morbidity of diabetes are the chronic complications that arise from prolonged hyperglycemia, including retinopathy, neuropathy, nephropathy, and cardiovascular disease. These chronic complications can be mitigated in many patients by sustained control of the blood glucose and treatment of comorbidities such as hypertension and dyslipidemia. There are now a wide variety of treatment options for hyperglycemia that target different processes involved in glucose regulation or dysregulation. (Brunton, 2015)

Classification systems dividing DM into primary (idiopathic) and secondary types, juvenile-onset and maturity-onset types, and insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) types

Type 1 DM. It constitutes about 10% of cases of dm. It was previously termed as juvenile-onset diabetes (jod) due to its occurrence in younger age and was called insulin-dependent dm (IDDM) because it was known that these patients have an absolute requirement for insulin replacement as treatment. However, in the new classification, neither age nor insulin-dependence is considered as absolute criteria. Instead, based on underlying aetiology, type 1 dm is further divided into 2 subtypes: subtype 1a (immune-mediated) dm characterised by autoimmune destruction of β-cells which usually leads to insulin deficiency. Subtype 1b (idiopathic) dm characterised by insulin deficiency with a tendency to develop ketosis but these patients are negative for autoimmune markers.

Type 2 DM. This type comprises about 80% of cases of dm. It was previously called maturity-onset diabetes, or non-insulin-dependent diabetes mellitus (NIDDM) of obese and non-obese type. Although type 2 dm predominantly affects older individuals, it is now known that it also occurs in obese adolescent children; hence the term mod for it is inappropriate. Moreover, many type 2 dm patients also require insulin therapy to control hyperglycaemia or to prevent ketosis and thus are not truly non-insulin-dependent contrary to its former nomenclature. (Mohan, 2010)

Current scenario of Diabetes

According to recent estimates, the number of diabetics worldwide in 2019 was 463 million. That number is expected to grow until at least the year 2045. The projected number of diabetics is expected to reach 700 million by that time. With an increased number of diabetics, the prevalence of diabetes is also projected to increase to almost 11 per cent by 2045.

The prevalence of diabetes in India has remained at 11.8% in the last four years, according to the National Diabetes and

Diabetic Retinopathy Survey report released by the health and family welfare ministry. Males showed a similar prevalence of diabetes (12%) as females (11.7%). Known diabetics comprised 67.3% participants, while 32.7% were new diabetics. The highest prevalence of diabetes was observed in the 70-79 years age group at 13.2%. Nearly 40% of known diabetes was diagnosed 1-4 years back while 5.3% of known diabetes cases reported diagnosis within the past one year.

Therapy of Diabetes

Non-pharmacologic Therapy for Diabetes
The patient with diabetes should have educated about nutrition diet and exercise and aimed at lower the glucose level in plasma. The non-pharmacologic treatment in the person having DM 1 should have control on calories intake and insulin dosing. The treatment in the person having DM 2 should have a diet directed to the weight loss and the reduction in lowering the blood pressure and Monitoring your blood sugar

Pharmacologic Therapy for Diabetes

The person who has type 2 diabetes can achieve their target blood sugar levels with diet and exercise alone, but many also need diabetes medications or insulin therapy. The decision about which medications are best depends on many factors, including your blood sugar level and any other health problems. There are several combinations of drugs from different classes to help you control your blood sugar in several different ways. The possible treatments for type 2 diabetes include: Metformin (Glucophage, Glumetza, others), Sulfonylureas, Meglitinides, Thiazolidinedione, DPP-4 inhibitors, GLP-1 receptor agonists, SGLT2 inhibitors, insulin, Bariatric surgery

Herbal and Natural Remedies for Diabetes

Many herbs and spices are claimed to have blood sugar lowering properties that make them useful for people with or at high risk of type 2 diabetes. A number of clinical studies have been carried out in recent years that show potential links between herbal therapies and improved blood glucose control, which has led to an increase in people with diabetes using these more 'natural' ingredients to help manage their condition. Plant-based therapies that have been shown in some studies to have anti-diabetic properties include Aloe Vera, Bilberry extract, Bitter melon, Cinnamon, Fenugreek, Ginger, Okra. Herbs that have been studied, and may have positive effects for diabetic patients include Berberine, Cinnamomym tamala, Curry, Eugenia jambolana, Gingko, Phyllanthus amarus, Pterocarpus marsupium, Solanum torvum and Vinca rosea.

Berberine

Mode of Action of Berberine

Berberine is known as an AMP-activated protein kinase (AMPK) activator. Its insulin-independent hypoglycemic effect is related to inhibition of mitochondrial function, stimulation of glycolysis and activation of the AMPK pathway. Additionally, berberine may also act as an α-glucosidase inhibitor. The effect of AMPK activation is the stimulation of hepatic fatty acid oxidation and ketogenesis, inhibition of cholesterol synthesis, lipogenesis (the formation of fat), triglyceride synthesis, inhibition of adipocyte lipolysis, stimulation of skeletal muscle fatty acid oxidation, muscle glucose uptake and modulation of insulin secretion by pancreatic beta cells. Phosphorylation of Thr-172 within the catalytic domain of α subunit (AMPKα) is necessary for AMPK activity. B. vulgaris inhibited α-glucosidase enzyme activity provides an effective way for diabetes treatment. The inhibition of α -glucosidase activity is one of therapeutic approaches for reducing postprandial hyperglycemia. α-Glucosidase inhibitor is effective in delaying absorption of carbohydrates and suppressing postprandial hyperglycemia which contribute to the decrease in hemoglobin A1C (HbA1c). The decreasing of HbA1c could reduce the incidence of chronic vascular complication in diabetic patients (Yibchok-anun S, Jittaprasatsin W, Somtir D, Bunlunara W, 2009). Various studies demonstrate that berberine is a strong inducer for Thr-172 phosphorylation of AMPK. Liver kinase B1 (LKB1) and Ca2 calmodulin-dependent kinase II (CaMKK II) are two major upstream kinases for AMPK activation. Berberine may activate AMPK through increasing AMP/ATP ratio,

which is mediated by inhibition of ATP biosynthesis in mitochondria. (Chander et al., 2017)

Pharmacokinetics and Pharmacodynamics of Berberine

BBR can be absorbed by the gut wall and reach an effective treatment concentration. Bao showed that after oral administration of BBR chloride (300 mg, single dose), a maximum concentration of 0.39 mg/l was reached, sufficient for healing cardiac arrhythmia. This study demonstrates that BBR can be absorbed by humans. BBR is a quaternary amine alkaloid, which can bind easily to proteins, affecting disposition and action intensity (Ye, Fu, Pi, & He, 2009) Berberine gets metabolized in the liver by cytochrome P450 by phase 1 metabolism and gets accumulated by mitochondria on K1735-M2 melanoma cells, arresting cell proliferation, causing mitochondrial fragmentation, depolarization, oxidative stress and a decrease in ATP levels. It inhibits the mitochondrial respiration and a decrease in calcium loading capacity through induction of the mitochondrial permeability transition (MPT) 50. It also inhibits the cholinesterase (ChE) activity and increase glucagon-like peptide (GLP1) release and break down the memory molecule acetylcholine, a neurotransmitter that is crucial for the important memory activities of focus and concentration58. It has strong potential to regulate glucose homeostasis through decreased gluconeogenesis and oxidative stress and the root extract (250 mg/kg) reduced lipid peroxidation (41.6%) (Chander et al., 2017)

Effect of berberine on diabetic patients

Numerous clinical report about the hypoglycemic action of berberine can be found in Chinese literature. Berberine was claimed to have comparable activity to sulphonylureas or Metformin in reducing blood glucose, although most of the studies were not well designed. Up to now, berberine has been tested in several clinical trials. The administration of berberine (0.5gt.i.d.) at the beginning of each meal was able to reduce fasting blood glucose (FBG) and postprandial blood glucose (PBG) in patients with newly-diagnosed type 2 diabetes. In poorly-controlled diabetic patients with insulin injection, berberine reduced HbA1c by 0.8%.In addition to the hypoglycemic action, plasma triglycerides, total cholesterol and low-density lipoprotein (LDL) were decreased with berberine treatment (Yin, Ye, & Jia, 2012). Ni reported that fasting plasma glucose concentrations in 60 patients with type 2 diabetes were reduced from 11.6 to 6.6mmol/liter for 1–3 months when treated with berberine (0.3–0.5 g, three times daily). Xie et al. found that when berberine (0.3–0.5 g, three times daily) was administrated to 40 type 2 diabetic patients for 2 months without change in their previous therapy, fasting and postprandial plasma glucose concentrations were reduced by 21 and 27%, respectively. (Y. Zhang et al., 2008)A study published by the American Diabetes Association found that berberine not only lowered blood glucose levels, but it also lowered levels of haemoglobin A1C, triglycerides, and insulin in people with type 2 diabetes. A1C is a two- to three-month average of blood sugar levels and a test used to diagnose diabetes

Berberine on glucose metabolism in animals

Berberine was shown to decrease blood glucose, enhance Insulin sensitivity and reduce weight gain in both dietary and genetic rodent model soft type 2 diabetes. In high-fat diet-induced obese rats, berberine decreased FBG, PBG, fasting insulin, homeostasis model of assessment-insulin resistance (HOMA-IR) and body weight. In the low dose of streptozotocin (STZ) and high-fat diet-induced type 2 diabetic rats, berberine treatment significantly decreased FBG and improved insulin tolerance. In leptin receptor-deficient dB/dB mice, glucose tolerance was improved and body weight was reduced with berberine (Yin et al., 2012)

Anti-Inflammatory Activity of BBR in the Treatment of Diabetes Mellitus

In current medicine, it is generally accepted that DM is usually associated with chronic subclinical inflammation, and the roles of inflammation in the pathogenesis of T2DM and its vascular complications have been confirmed by several researches (W. Xie and L. Du, 2011). The anti-inflammatory activity of BBR was observed both in vitro and in vivo and was

noted by the reduction of proinflammatory cytokines as well as acute phase proteins such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), prostaglandins (PGs), inducible nitric oxide synthase (iNOS), matrix metalloprotease 9 (MMP9), monocyte chemoattractant protein-1 (MCP-1), C-reaction protein (CRP), and cyclooxygenase-2 (COX-2). BBR treatment could inhibit the expression of proinflammatory cytokines as well as acute phase proteins, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), prostaglandins (PGs), inducible nitric oxide synthase (iNOS), matrix metalloprotease 9 (MMP9), monocyte chemoattractant protein-1 (MCP-1), C-reaction protein (CRP), and cyclooxygenase- 2 (COX-2) . In a research, the insulin sensitizing effect of BBR was also associated with its anti-inflammatory activity. Lou et al. showed that BBR significantly increased insulin-mediated tyrosine phosphorylation of insulin receptor substrate-1 (IRS-1) in HepG2 cells with a decrease of cytokine production and serine phosphorylation.(Pang et al., 2015)In animal models, the anti-inflammatory activity of BBR was observed in different tissues like serum, liver, adipose tissue, and kidney and was associated with its effect against insulin resistance or diabetes mellitus .Mechanisms for these properties of berberine were complex and involved multiple cellular kinases and signaling pathways such as AMP activated protein kinase (AMPK), mitogen activated protein kinase (MAPKs), nuclear factor erythroid 2 related factor (Nrf2) pathway and nuclear factor kappa beta (Nf-kappa beta) pathway. Probably there may be other mechanisms for these properties of berberine which would need further studies(Patil, Patil, Patil, & Patil, 2015)

Antioxidant Activity of BBR in Treating Diabetes Mellitus

Oxidative stress and inflammation are associated with the pathogenesis of DM and its complications. Recent studies showed that BBR could also regulate glucose homeostasis through decreasing oxidative stress by changing oxidative stress markers, antioxidant enzymes, and pro inflammatory cytokines (Z. Li, Y.N. Geng, J. D. Jiang, 2014). BBR administration could reduce malondialdehyde (MDA) content and increase the contents of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and glutathione (GSH) in diabetic animals, which help to seek for excessive free radicals and protect oxidative stress. Wang et al. indicated that the levels of MDA and SOD of the diabetic animals did not have significant difference statistically compared with those of the normal control animals, suggesting that the effect of BBR on oxidative stress was not obvious. Therefore, further researches are needed to explore this mechanism. BBR has a good therapeutic efficacy for DN. Liu et al. found that BBR ameliorated renal injury in streptozotocin-induced Wistar rats by inhibiting aldose reductase and oxidative stress. After the treatment with oral administration of BBR (200 mg·kg−1·d−1), FBG, blood urea nitrogen (BUN), serum creatinine (Cr), and 24 h urinary albumin (24 h-UAlb) were significantly decreased, and serum SOD activity was increased, while the content of MDA, aldose reductase (AR) activity, and the expression of AR mRNA and protein in the kidney were markedly decreased compared with control group. Lan et al. showed that the ratio of kidney weight to body weight decreased, and synthesis of TGF-β1 was suppressed after BBR treatment. The antioxidant effect was also observed in rat mesangial cells cultured with high glucose-containing media, and the mechanisms that BBR ameliorated renal injury possibly were related to suppression of sphk-s1p signaling pathway as well as aldose reductase (AR) activity in vitro. (Pang et al., 2015)

Effect of berberine on pancreatic b-cells

Type 2 diabetes mainly results from insulin resistance and b-cell dysfunction. b-cell failure is responsible for the progressive loss of metabolic controlling type 2 diabetic patients and the eventual need for insulin treatment. Therefore, agents to protect b-cell function might be a better choice for diabetic treatment. Berberine treatment could promote pancreatic b cell regeneration and functional recovery. Berberine reduced the fasting serum insulin of diabetic rats and decreased the blood sugar by

improving the insulin sensitivity of insulin receptors, rather than by stimulating the pancreatic b cells to secrete insulin. This might reduce the burden on the islet b-cells and play a protective role for islet b cells. However, interestingly, Koetal.13 reported that berberine can cause glucose-stimulated insulin secretion in Min 6islet b-cell lines, and promote pancreatic b-cell proliferation, and activation of cell regulatory proteins(ERK1/2), so that the insulin receptor substrate IRS-2 expression increases activation of the insulin/ insulin-like growth factor signalling cascades, which serve to reduce blood sugar(M. Zhang & Chen, 2012)

Case study

Diabetic cardiomyopathy

Cardiovascular complications are major causes of morbidity and mortality in diabetic patients. Berberine show positive effct (30 mg/kg/day, i.g. for 6 weeks) on cardiac dysfunction were evaluated in the rat model of hyperglycemia and hypercholesterolemia. Hyperglycemia and hypercholesterolemia were induced by feeding high-sucrose/fat diet (HSFD) consisting of 20% sucrose, 10% lard, 2.5% cholesterol, 1% bile salt for 12 weeks and streptozotocin (30 mg/kg, i.p.). The plasma sugar, total cholesterol, and triglyceride levels were significantly increased (422, 194 and 82%, respectively) in the HSFD/streptozotocin-treated rats, when compared with control animals receiving normal diet and vehicle. Berberine treatment reduced the plasma sugar and lipid levels by 24–69% in the rat model of hyperglycemia and hypercholesterolemia. Cardiac functions signed as values of cardiac output, left ventricular systolic pressure, the maximum rate of myocardial contraction (+dp/dtmax), left ventricular end diastolic pressure and the maximum rate of myocardial diastole (− dp/dt max) were injured by 16–55% in the hyperglycemic/hypercholesterolemic rats. Berberine increased cardiac output, left ventricular systolic pressure and + dp/dtmax by 64, 16 and 79%, but decreased left ventricular end diastolic pressure and −dp/dtmax by 121 and 61% in the rats receiving HSFD/streptozotocin, respectively, when compared with the drug-untreated rats of hyperglycemia and hypercholesterolemia. Berberine caused significant increase in cardiac fatty acid transport protein-1 (159%), fatty acid transport proteins (56%), fatty acid beta-oxidase (52%), as well as glucose transporter-4 and peroxisome proliferator-activated receptor-γ (PPARγ), but decrease in PPARα mRNA and protein expression in hyperglycemic/hypercholesterolemic rats. These results indicated that berberine exerted protective effects on cardiac dysfunction induced by hyperglycemia/hypercholesterolemia through alleviating cardiac lipid accumulation and promoting glucose transport.(Shi-Fen Dong Ying Hong Ming LiuYing-ZhiHaoHai-ShiYuYangLiuJian-NingSun, 2011)

Diabetic nephropathy

Diabetic nephropathy is one of the most relevant diabetic complications. In the last decade, diabetic nephropathy has become the main cause of the end-stage renal disease (ESRD) in the Western world. In case study ,done by using streptozotocin (STZ)-induced in vivo model of DN and high glucose (HG)-induced podocytes as an in vitro model to investigate the protective effect of BBR on DN and its possible molecular basis. The study demonstrated that Berberine reduced renal injury in STZ-induced DN rat model, as evidenced by the decrease in fasting blood glucose, ratio of kidney weight to body weight, 24-h urinary protein, serum creatinine, and blood urine nitrogen. BBR attenuated the systemic and renal cortex inflammatory response and inhibited TLR4/NF-κB pathway in STZ-induced DN rats and HG-induced podocytes. Also, HG-induced apoptosis of podocytes was lowered by BBR administration. Furthermore, blockade of TLR4/NF-κB pathway by resatorvid (TAK-242) or pyrrolidine dithiocarbamate aggravated the inhibitory effect of BBR on HG-induced inflammatory response and apoptosis in podocytes. (Zhu, Liping, Jaikai han, Lei xue, 2018)

Diabetic neuropathy

Diabetic neuropathy is the incessant complication of diabetes mellitus and up to 50% of patients with type 1 and type 2diabetes mellitus have neuropathy. Control of blood

glucose is one of the most effective methods of preventing the formation and development of DN. Currently, multiple strategies had been used to treat diabetic neuropathy, such as multivitamins includingB1, B2, B6, B12. Recently, aldose reductase inhibitors, such as inositol have been applied to treat diabetic neuropathy. However, there are very few drugs available to directly treat diabetic neuropathy. Recent results indicate that berberine could remarkably improve the nerve conduction velocity. BBR (100 mg/kg) can significantly decrease the concentration of fasting blood glucose in diabetic rats, and a large dosage of BBR can ameliorate nerve pain in DN rats to some extent (Al, 2008).It also significantly increases the nerve conduction velocity in diabetes complicated with DN in rats(Guo HW et al., 2001). In addition, BBR is reported to inhibit glycosylation, in particular glycosylation in brain tissue, reducing the formation of advanced glycation end-products in brain tissue and inhibiting calcium overload to reduce the damage to nerve cells that these induce. BBR particularly protects the mitochondria of the hippocampus, and this might be the basis of its prevention of DN(Lu JH et al, 2006). It is worth noting that AChE and butyrylcholinesterase activity was significantly higher in the serum of type 2 diabetes rats complicated by AD compared with normal rats(Wang KF et al., 2006). Using berberine to treat diabetic neuropathy in rat induced by STZ and in diabetic patients demonstrated that berberine could significantly improve the median nerve, peroneal in nerve conduction velocity(NCV). In 2010 and 2012, a study from Lu group reported that berberine suppressed neuroinflammatory responses through AMPK activation in BV-2 microglia and astrocytes, which suggested an anti-neuro inflammatory effect of berberine. However, the mechanism of treatment of diabetic neuropathy by berberine needs further study (M. Zhang & Chen, 2012)

Other research universities in India also studied the medicinal properties of Berberis aristata along with effects of berberine as active componentin various studies of the anti-diabetic activity of the plant, diabetic rats treated with the ethanol extract of the roots showed a significant reduction of serum glucose level, however, it also showed a significant increase in the level of HDL cholesterol. Additional research must be conducted to determine if thehypolipidemic properties of the plant could serve as a protective mechanism against the development of atherosclerosis (Atherosclerosis; also known as arteriosclerotic vascular disease or ASVD) is a specific form of arteriosclerosis in which an arterywall thickens as a result of invasion and accumulation of white blood cells (WBCs), which is usually associated with diabetes(M. Zhang & Chen, 2012)

Conclusion

As per the current review- B. aristata found within the temperate and sub-tropical regions of Asia, Europe, and America and is native to the Himalayas in India and in Nepal. It is a customary therapeutic plant utilized in Ayurvedic, Chinese and other restorative frameworks on the planet for quite a while. All aspects of this plant has picked up significance for its extraordinary drug exercises. The foremost important pharmaceutical properties of this plant incorporate medicinal drug, inhibitor, antiepileptic drug, medicament, anti-Alzheimer, anti-cancer, anti-arrhythmic, antiviral, medicine and anti-diabetic. Regarding aldohexose reducing capability berberine few common medical specialty activities therefore berberine can be known as as flavoring antidiabetic varied medical specialty examinations have shown the symptom impact of BBR on T2DM improve internal secretion sensitivity and promote internal secretion secretion BBR regulates aldohexose and lipoid metabolism in liver. BBR reduces internal organ absorption of glucose; BBR possesses inhibitor activities geared toward diabetic complications. New formulations of berberine will be the next major task for the research scientist. Berberine remains a promising new drug in the treatment of diabetes and its complications.

Conflict of Interests

The authors have no conflict of interests in this paper.

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