Berberine

Subjects: Others

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Berberine is a plant metabolite belonging to the group of isoquinoline alkaloids with strong biological and pharmacological activity. Currently, berberine is receiving considerable interest due to its anticancer activity based on many biochemical pathways, especially its proapoptotic and anti-inflammatory activity. Nonetheless its influence on metabolic disorders and related diseases seems to be equally important and promising.

berberine, metabolic diseases, clinical trials

Cardiovascular and Metabolic Diseases

Neurodegenerative and Neuropsychiatric Disorders

1. Berberine in Cardiovascular and Metabolic Diseases

1.1. Cholesterol-Lowering Effect

Berberine has been clinically examined quite extensively as regards its beneficial influence on the cardiovascular system. Berberine has an antiarrhythmic effect, improves ejection fraction and enhances the function of the leftventricle and general physical capacity in congestive heart failure [1]. Berberine decreases blood pressure by reducing cholesterol via several mechanisms, e.g., it stimulates the capture of cholesterol in serum by liver, stimulates the disposal of LDL-C from blood [2][3], reduces the absorption of cholesterol in bowels, enhances cholesterol excretion in excrements and stimulates liver exchange of cholesterol and the formation of bile acid [4]. It also stimulates AMPK (protein kinase activated by 5′ adenosine monophosphate), which may limit fatty acid synthesis [5]. Reduced TC, TG and LDL-C concentration and an increased HDL-C concentration were noted after three months of application of the compound [6]. In HepG2 cells, i.e., a human hepatoma cell line in primary hepatocytes, berberine inhibited the synthesis of cholesterol and triglyceride. It also lowers cholesterol levels in vivo [2].

1.2. Antidiabetic Action

In type 2 diabetes mellitus, berberine was first reported in 1986 [7]. Indirect clinical investigations of the effect of berberine proved that it reduced alanine and aspartate transaminase levels in diabetic patients [7]. It was reported as a successful agent alleviating insulin resistance [8]. The hypoglycemic effect of berberine is comparable to metformin. Berberine, likewise to metformin, regulates a variety of effectors, such as AMPK and MAPK (mitogen activated protein kinase) [9]. Hyperinsulinemia and insulin resistance, typical for type 2 diabetes are crucial in polycystic ovary syndrome pathogenesis [10]. Hence, berberine is considered effective in polycystic ovary syndrome, but this issue needs further investigation [11]. It has been clinically confirmed that berberine enhances

ovulation in polycystic ovary syndrome by reducing insulin resistance][12]. Moreover, the effect of berberine on the lipid profile in women with polycystic ovary syndrome is highly beneficial. The intake of 500 mg berberine for 3 months significantly improved the profile in treated patients. A higher pregnancy rate and a lower incidence of severe ovarian hyperstimulation syndrome were noticed as well [13]. In addition, the treatment with berberine instead of metformin entailed fewer adverse effects and reduced lipid parameters and BMI (Body Mass Index) [8].

1.3. Antiobesity Action

As mentioned previously, berberine is a potential drug for treatment of obesity. It acts by downregulation of adipogenesis and lipogenesis. This antiobesity activity is connected with the fact that berberine strongly decreased the size and number of droplets of lipid in the 3T3-L1 adipocyte cell line. The mitigation of high glucose-induced podocyte apoptosis after berberine treatment described currently is equally promising for diabetic patients. In this case, the alkaloid modulates autophagy and it proceeds via the mTOR/P70S6K/4EBP1 pathway [9]. A long-term body weight loss effect is observed after expousure to berberine. The effect is exerted through enhancing ATGL expression (AMPK-mediated) and increases the basal lipolysis state of triglycerides in adipocytes.

Crucial for the transcription factor of adipogenesis is PPARγ. Berberine inhibits adipocyte differentiation via PPARγ and C/EBPα pathways. Besides, berberine inhibits the proliferation and differentiation of preadipocytes [8]. With its regulatory function in insulin resistance and dyslipidemia, berberine can be a potential agent in metabolic syndrome. However, the overall effect of berberine in metabolic syndrome has not been systemically tested, partly because the preclinical models for metabolic syndrome are limited [14].

The anticancer activity of berberine via an effect on kinases, described in the further part of the article, is possibly also related to its effects on kinase-mediated lipid metabolic pathways. Insulin resistance development in obesity involves JNK kinases [15] and neurotransmitter excitotoxicity in ischemic conditions. [16]. Hong et al. described that berberine reduced the phosphorylation of JNK in gastric cancer cells [17], but the influence of berberine on kinases is strongly dependent on many conditions [18][19][20].

2. Berberine in Neurodegenerative and Neuropsychiatric Disorders

The ability to ameliorate hyperlipidemia and hyperglycemia make berberine supportive in neurologic disease [21][22]. Recent studies have shown that berberine exerts a protective effect on the central nervous system, which makes it a promising agent in disorders such as Alzheimer’s disease, cerebral ischemia, mental depression, anxiety and schizophrenia [23][24]. Berberine exerts a neuroprotective effect by regulating early immune activation of peripheral lymphocytes and immunotolerance in vivo [25]. However, this is not fully understood and there are reports on berberine exacerbating neurodegeneration [26].

Berberine also significantly decreases the production of kynurenine, which when increased, is metabolized to neurotoxic compounds (for example quinolinic acid), and influences glutamatergic neurotransmission [1][27]. It has

been described that berberine inhibits the effects of reward after abuse of drugs such as cocaine, morphine and ethanol. It proceeds through downregulation of tyrosine hydroxylase expression or other mechanisms [21][28][29]. Researchers suggest that alkaloids may rapidly act like antidepressants; hence, it is indicated as a potential substance for the treatment of patients with major depression. Berberine, like other antidepressant drugs, affects sigma receptor 1. Studies also show that berberine can act as an antidepressant via the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathway, which is activated by oxidative stress. This berberine antidepressant effect also results from its impact on the brain-derived neurotrophic factor—cAMP-response element—binding protein pathway. This well-known antidepressant pathway is crucial for the antidepressant action of drugs. Berberine acts by elevation of neurotrophic factor levels and restores the decreased level of its mRNA [1][27]. Berberine easily crosses the blood–brain barrier after systemic administration, which enhances its potential in treatment of neurological diseases [21][22].

3. Berberine in Clinical Trials

Due to the wide range of effects and safety, berberine has been assessed clinically. There are many ongoing trials and even more interesting ones are going to start soon. Berberine was clinically assessed in schizophrenia and its metabolic and cardiovascular effects were assessed in the metabolic syndrome, obesity, diabetes mellitus type 2 and insulin-resistance. The compound was clinically assessed in non-alcoholic fatty liver disease, dyslipidemia and hypercholesterolemia. It was also clinically assessed in cases of colorectal adenoma, gastric ulcer, chronic gastritis and gastric cancer [30]. There are many completed trials assessing berberine. The main target is its activity lowering cholesterol and glucose levels. The nutraceutical potential of berberine combined with some natural compounds seems to be very interesting. In patients with type 2 diabetes mellitus berberine significantly improved the level of fasting blood glucose, the level of postprandial blood glucose and the level of glycosylated hemoglobin and decreased insulin resistance. It has been estimated that berberine exerts a beneficial effect on blood glucose control comparable to that of metformin. Berberine appears to have an advantage over rosiglitazone in improving the level of fasting blood glucose. The combination therapy of berberine with oral hypoglycemic drugs may arouse high hopes. However, the efficacy of berberine should be further evaluated in a larger patient population of patients with type 2 diabetes mellitus [31]. As a nutraceutical, berberine with chromium picolinate, inositol, curcumin and banaba was clinically assessed in patients with fasting dysglycemia. It was reported to be helpful in improving glyco-metabolic compensation and total cholesterol and triglyceride value and in reducing inflammatory status in patients with dysglycemia. Reduced fasting and post-prandial level of glucose in plasma was observed after administration of the nutraceuticals. There was also a decrease in the level of fasting plasma insulin and in the level of glycated hemoglobin. Moreover, in patients with fasting dysglycemia after 3 months of application of combined nutraceutical therapy, the level of high-sensitivity C-reactive protein was reduced [32]. Furthermore, berberine was clinically assessed in metabolic syndrome. In metabolic syndrome in schizophrenia, the effect of berberine administration on insulin secretion, insulin sensitivity and metabolic syndrome was evaluated. A significant decrease in waist circumference and remission of the presence of metabolic syndrome was noted in patients after the administration of berberine. A marked decrease in systolic blood pressure, triglycerides, area under the curve of glucose, area under the curve of insulin and insulinogenic index and an increase in the Matsuda

index were reported. According to the clinical trials, administration of berberine abolishes the metabolic syndrome and decreases waist circumference. It also decreases insulin secretion and the levels of triglycerides Simultaneously, it increases insulin sensitivity in patients with metabolic syndrome in schizophrenia [33]. Additionally, the hypoglycemic effect of berberine and bifidobacterial administration in patients with prediabetes or diabetes mellitus was assessed and it was proved that berberine and bifidobacteria may be supportive in the treatment of diabetes [34]. An important and clinically assessed aspect of berberine activity is its cholesterol lowering effect. The efficacy and safety of a nutraceutical combination consisting mainly of red yeast rice extract, berberine and policosanols were assessed in patients with low to moderate risk of hypercholesterolemia. This combination associated with a hypolipidemic diet reduced total cholesterol and LDL-C levels [35]. Assessed in non-alcoholic fatty liver disease, comparison of berberine supplementation to lifestyle intervention and berberine treatment plus lifestyle intervention resulted in a strong reduction of hepatic fat content accompanied by improvement in serum lipid profiles and body weight. Berberine reduced body weight and the lipid profile more effectively than pioglitazone. The adverse events were mild and mainly affected the digestive system. Berberine was clinically proved to improve parameters in patients with non-alcoholic fatty liver disease and related metabolic disorders. Its therapeutic effect may involve regulation of hepatic lipid metabolism [36]. The compound has also been evaluated clinically in menopausal women at risk of dyslipidemia. In combination with compounds of plant origin such as chlorogenic acid and tocotrienols, a reduction in LDL and total cholesterol levels was observed after three months of supplementation; however, the influence of berberine on menopausal symptoms requires further research [37].

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