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Review

Study progress of berberine for treating cardiovascular disease

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Abstract

Berberine (BBR) is a natural alkaloid isolated from the *Coptis chinensis*. While this plant has been used in Chinese medicine for more than 2500 years, interest in its effects in treating cardiovascular disease has been growing in the last decade. Recent researches showed that BBR had the effect of anti-heart failure, anti-hypertension, anti-hyperlipidemia, anti-insulin resistance, anti-arrhythmias, and anti-platelet aggregation.

Keywords: Berberine; Cardiovascular disease; Mechanism; Progress

Berberine (BBR) is a natural alkaloid with a bright yellow color isolated from the plant *Coptis chinensis*. It is widely used in Chinese medicine as an antimicrobial for treating dysentery and infectious diarrhea.[1] While this plant has been used in Chinese medicine for more than 2500 years, interest in its effects in treating cardiovascular disease has been growing in the last decade. Recent research has shown that berberine has an effect of protecting heart failure, hypertension, hyperlipidemia, insulin resistance, arrhythmias, and platelet aggregation.

Berberine chemical characteristics and pharmacokinetics

BBR is a plant quaternary ammonium salt from the group of isoquinoline alkaloids (2, 3-methylenedioxy-9, 10-dimethoxyprotoberberine chloride; $C_{20}H_{18}NO_4^+$) with a molar mass of 336.36122 g/mol (Fig. 1). BBR is yellow in color, which is why in earlier times Berberis species were used to dye wool, leather, and wood. As a natural dye, berberine has a color index of 75160.[2]

Berberine has low bioavailability and shows poor absorption through the gut wall (<5%) and bowel P-glycoprotein appears to contribute to its poor absorption, actively expelling the alkaloid from the lumen mucosal cells.[3]

In a rat noncompartmental model,[4] unbound berberine is transported to bile through active transport

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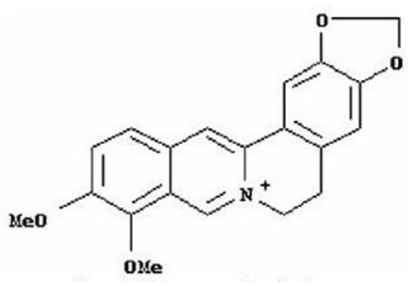

Fig. 1. Chemical structure of berberine.

and it is metabolized by a p450 enzyme system in the liver, with phase I demethylation and phase II glucuronidation. Berberine has four main metabolites identified in rats: berberrubine, thalifendine, demethyleneberberine and jatrorrhizine (Fig. 1), all of which have glucuronide conjugates.[5] Intestinal bacterial flora takes a role in enterohepatic circulation of berberine and its conjugated metabolites.[4] On the other hand, a very small amount of unchanged berberine is eliminated in urine.[6] Berberine may inhibit CYP2E1-like and CYP1A2, which is not related to a significant increase in the pharmacological interaction since most available drugs are not metabolized by these enzymatic systems.[7]

Standard doses of berberine are generally well tolerated and eventual adverse events are rare and mild. On the contrary, high doses have been associated with arterial hypotension, dyspnea, flu-like symptoms, gastrointestinal discomfort, constipation, and cardiac damage.[8] The most studied side effects are those in the gastrointestinal system. Berberine and derivatives can also produce gastric lesions.

The safety issue of berberine mostly involves the risk of some pharmacological interaction. In fact, berberine displaces bilirubin from albumin about 10-fold better than phenylbutazone, thus any herb containing large amounts of berberine should be avoided in jaundiced infants and pregnant woman.[9] Berberine displaces warfarin, thiopental, and tolbutamide from their protein-binding sites, increasing their plasma levels (Fig. 2).[10]

Effects of berberine on heart failure

Recent studies suggested that the mechanism of BBR for improving cardiac function may be related to increasing the concentration of calcium in cardiac muscle cells. The augmented cardiac contractile force is induced by progressively increasing the concentration of cyclic adenosine monophosphate (cAMP) in cardiac muscle cells by increasing an inward current carried by calcium ions in the intracellular of cardiac muscle mediated through alteration of cAMP.[11] BBR increases high energy phosphate in heart failure and prevented ventricular fibrillation due to its effects on potassium channels,[12,13] increased intracellular calcium,[14] and suppressed the delay of depolarization partly due to sodium influx.[15] On the other hand, BBR has a sympathetic activity-modulated effect on myocardium. In rats with experimentally induced cardiac hypertrophy by suprarenal aortic constriction, BBR decreased plasma noradrenaline and adrenaline levels and adrenaline in ventricular tissue, improved cardiac contractility with a shortened time to reach the maximum rate from the beginning of contraction and reduced the size of the left ventricular myocardium.[16,17] In a dog ischemic heart failure model, intravenous berberine administration increased cardiac output, decreased left ventricular end-diastolic pressure and systemic vascular resistance.[18] This activity was also confirmed in other animal models.[19]

Examination of hemodynamic parameters in humans reveals similar results with an increased cardiac index, increased left ventricular ejection fraction, decreased systemic and pulmonary vascular resistance and left ventricular end-diastolic pressures.[20] In a clinical trial carried out on chronic heart failure patients, BBR decreased the frequency and complexity of ventricular premature complexes and increased the left ventricular ejection fraction.[21]

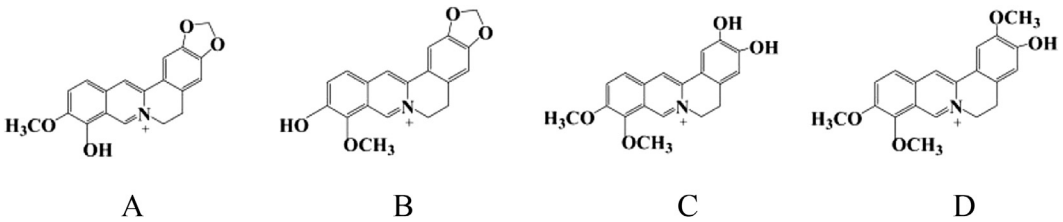

Fig. 2. (A) Berberrubine, $C_{19}H_{16}ClNO_4$; (B) Thalifendine, $C_{19}H_{16}NO_4$; (C) Demethyleneberberine, $C_{19}H_{18}NO_4$; (D) Jatrorrhizine $C_{20}H_{20}ClNO_4$.

BBR has been recognized as being capable of decreasing cardiovascular through reducing oxidative stress, low-density lipoprotein (LDL), triglycerides, and insulin resistance and improving the mood.[22] A multicenter randomized trial showed BBR reduced LDL-c levels as well as total cholesterol/HDL-c and ApoB/ApoA1 ratios, while increasing Apo A1, all of which are improvements in cardiovascular risk indicators.[23]

Effect of berberine on regulating blood pressure

Systolic and diastolic blood pressures are correlated with cardiovascular events. A consistent theme in the literature has confirmed that there is a close correlation between blood pressure and atherosclerosis.[24]

BBR can competitively block the α_1 receptor of VSMC, inhibit activity of the cholinphospholipid enzyme, and enhance the effect of acetylcholine. So BBR can dilate blood vessels and decrease blood pressure.[25] It is reported that BBR can act on both endothelium and the underlying vascular smooth muscle to induce relaxation.[19] Nitric oxide released from endothelium might primarily account for the BBR-induced endothelium-dependent relaxation, while activation of 4-aminopyridine and Ba^{2+}-sensitive K^+ channels, inhibition of intracellar Ca^{2+} release from caffeine-sensitive pools, or a direct relaxant effect are likely responsible for the BBR-induced endothelium-dependent relaxation. Mechanisms related to either Ca^{2+} influx or protein kinase C activation may not be involved. Both vasorelaxant and antiproliferative effects may contribute to a long-term benefit of BBR in the vascular system.

Effects of berberine on regulating blood lipids

In lipid metabolism, the lipid-lowering effect of BBR appears to be mainly due to the stabilization of the hepatic LDL-C receptors (LDLR) by an extracellular signal regulated kinase (ERK)-dependent pathway and also by increasing transcriptional activity of the LDLR promoter by a c-Jun N terminal kinase (JNK) pathway.[26,27] In addition, in 3T3-L1 cells leptin, transcription factors like sterol regulatory element binding protein-1c (SREBP-1c) and CCAAT enhancer-binding protein-α (C/EBP-α), peroxisome-proliferator activated receptor-γ (PPAR-γ), fatty acid synthase, acetyl-coenzyme A (acetyl-CoA) carboxylase, acyl-CoA synthase, and lipoprotein lipase are reduced by berberine treatment.[28] Moreover, in addition to LDLR upregulation, berberine activates 5′ adenosine monophosphate (AMP) kinase (AMPK), while blocking the mitogen-activated protein kinase (MAPK)/ERK pathway, resulting in inhibition of lipid synthesis: its action on AMPK is eliminated by MEK inhibitors, suggesting a link between these two pathways.[29] Other research showed BBR could counteract hyperlipidemia partially via upregulating LDLR and apoE mRNA levels and suppressing HMGR gene expression.[30]

The antihyperlipidemic effects of BBR have also been confirmed in humans by some small clinical trials. One study evaluated the effects of 500 mg BBR twice a day in a hyperlipidemic group of 32 Asian patients without any other drug use for three months and compared the results with 11 patients using a placebo. The BBR significantly reduced the total cholesterol by 29%, triglycerides by 35%, and LDL-C by 25%.[31] These results have been then confirmed in a larger trial carried out on 116 hyperlipidemic type 2 diabetic patients randomized to treatment with berberine 0.5 g thrice daily or a placebo. Beyond a similar decrease in plasma lipids, the berberine-treated patients also experienced a significant decrease in glycohemoglobin, and in both fasting and two-hour postprandial glucose levels compared with the placebo group.[32]

A randomized controlled study provides evidence that the addition to diet and lifestyle changes of a patented combination of natural nutraceuticals, based on red yeast rice extract and berberine, can significantly improve the lipid profile versus diet alone in dyslipidemic subjects in whom a hypolipidemic therapy is not yet indicated or not well tolerated or contraindicated.[33]

Effects of berberine on insulin resistance

Beyond a direct effect of berberine on lipid metabolism, recent preclinical and clinical evidence suggest that it increases insulin receptor expression and improves glucose utility.[34]

It has been observed that berberine acts as an insulin-sensitizing agent,[35] therefore its activity has been compared with metformin in different animal models. In a rat model of type 2 diabetes, berberine showed better fasting plasma glucose and LDL-C lowering and better homeostasis model assessment of insulin resistance (HOMA-IR) than metformin by a mechanism involving retinol binding protein-4 (RBP-4) and glucose transporter-4 (GLUT-4).[36] However, in another study, berberine was not inferior to metformin as an insulin-sensitizer.[37]

Beyond the large preclinical literature, data on human glucose metabolism are really preliminary.

However, a study carried out on subjects affected by type 2 diabetes, showed that 500 mg of berberine three times a day was associated with a significant reduction in hemoglobin-α1 (HbA1) (−2%), fasting plasma glucose (−44%), postprandial glucose (−45%), fasting plasma insulin (−28%), and HOMA-IR index (−44.7%).[38] In this study, berberine also significantly reduced the plasma total and LDL-C levels. Another study showed a nutraceutical containing berberine and chlorogenic acid was able to increase insulin-sensitivity and liver parameters for the short-term in overweight patients with mixed hyperlipidemia.[39]

Berberine anti-arrhythmia effects

Recent studies indicate that BBR may significantly prolong the duration of the action potential and the effective refractoriness of the cardiac cells and may improve cardiac reentry rhythm by modifying the unidirectional conduction block to a bidirectional conduction block or delaying the duration of the reentrant pathway.[40] It has been demonstrated that berberine may protect the cardiac cellular membrane from interference by hydroxyl radicals and intracellular calcium overload. By its action, BBR may abolish the delay after depolarization induced by intracellular calcium overload and may thereby terminate arrhythmias associated with triggered activation.[41] In addition, one study has found that the effects of berberine on I(K1)/Kir2.1 may be an important mechanism for producing anti-arrhythmic effects.[42] In the 24−48 h ambulatory monitoring of 100 patients with ventricular tachyarrhythmia, berberine caused a 50% or greater reduction in ventricular premature contractions in 62% of patients and a 90% or more reduction in 38% of patients.[43]

Berberine anti-platelet aggregation effects

Some studies show that BBR has a significant anti-platelet effect,[44] explained by inhibition of arachidonic acid metabolism and calcium influx,[45] but also by a partial agonistic effect on plateletα_2 adrenoreceptors.[44] BBR inhibited thromboxane synthesis induced by collagen, adenosine diphosphate and arachidonic acid, and it might inhibit arachidonic acid metabolism in platelets and endothelial cells.[20] BBR can cause potassium channel blockade resulting in prolongation of the action potential in cat ventricular monocytes.[46] On the other hand, recent evidence suggests that BBR can also have prothrombotic effect-enhancing tissue factor activity.[47]

Conclusion

BBR is usually thought of as a traditional Chinese medicine, and recent discoveries have provided novel evidence that it may be considered a promising tool to counteract cardiovascular disorders. We believe that after further research, BBR will show a more important role in the treatment of cardiovascular disease.

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