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Review

Research progress on berberine with a special focus on its oral bioavailability

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ABSTRACT

The natural product berberine (BBR) has become a potential drug in the treatment of diabetes, hyperlipidemia, and cancer. However, the oral delivery of BBR is challenged by its poor bioavailability. It is necessary to improve the oral bioavailability of BBR before it can be used in many clinical applications. Understanding the pharmacokinetic characteristics of BBR will enable the development of suitable formulas that have improved oral bioavailability. The key considerations for BBR are how to enhance the drug absorption and to avoid the intestinal first-pass effect. This review summarizes the pharmacological activities of BBR and analyzes the factors that lead to its poor oral bioavailability. In particular, the therapeutic potential of BBR in new indications from the aspect of oral bioavailability is discussed. In conclusion, BBR is a promising drug candidate for metabolic disorders and cancer but faces considerable challenges due to its poor oral bioavailability.

Contents

1. Introduction

Berberine (BBR), a protoberberine alkaloid (Fig. 1), is present in several plant species such as *Coptis* (*Coptis chinensis* and *Coptis japonica*

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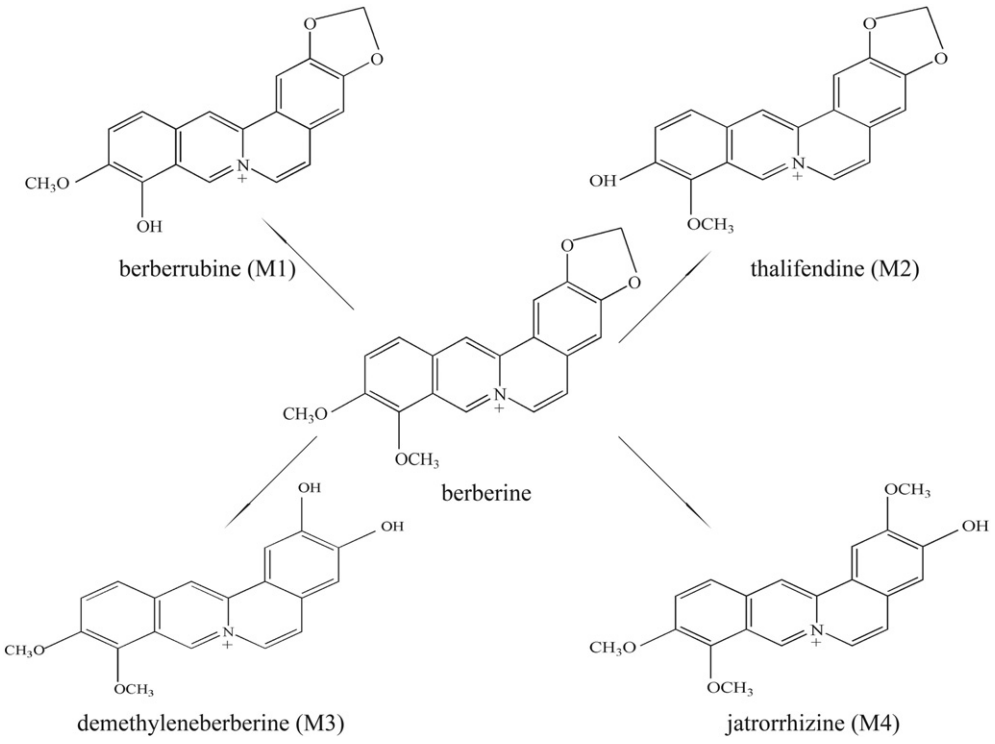

Fig. 1. Chemical structures of berberine (BBR) and its metabolites, berberrubine (M1), thalifendine (M2), demethyleneberberine (M3), and jatrorrhizine (M4).

Makino) and *Berberis* (*Berberis vulgaris* and *Berberis croatica* Horvat), which are common in the Eastern hemisphere [1]. Clinically, plants containing BBR have been used for centuries in many prescriptions to treat dysentery [2], diarrhea [3], stomatitis [4], and hepatitis [5] via its antiprotozoal, antimicrobial, and anti-inflammatory properties. BBR has been extensively used as a nonprescription drug to treat diarrhea caused by different sources since the 1950s in China [2].

In recent years, numerous studies have indicated that BBR may have many positive effects on some major medical pathologies, such as regulation of lipid and glucose metabolism [6,7], suppression of tumor cell proliferation [8], and induction of apoptosis [9]. However, the oral bioavailability of BBR appears to be very poor (below 1%) [10,11], indicating that such medical efficacy may never be obtained by patients taking BBR as a medical treatment. Therefore, the first purpose of this review was to summarize the effect of BBR on diabetes, hyperlipidemia, and cancer as well as to discuss its therapeutic potential for these diseases. In addition, we aimed to elaborate the pharmacokinetic characteristics of BBR and to discuss strategies to improve its oral bioavailability.

2. Pharmacological activities

2.1. Current medical uses

2.1.1. Antidiarrheal activity

BBR has been used as a nonprescription drug for diarrhea [12] and has shown a good efficiency in the clinic. A total of 132 patients with diarrhea-predominant irritable bowel syndrome were randomized for treatment with BBR (400 mg/twice daily) or placebo for 8 weeks. The patients treated with BBR had a reduction of diarrhea frequency, abdominal pain frequency, and urgent need for defecation frequency. These results were significantly more pronounced in the BBR group than in the placebo group. Furthermore, BBR was well tolerated [13]. The antidiarrheal property of BBR may be associated with the following mechanisms: (1) BBR inhibits the intestinal secretory response of bacterial enterotoxins. The secretion of water and electrolytes stimulated by cholera toxin and the related toxins of *Escherichia coli* has been found to be one of the major factors that causes diarrhea, while BBR has been shown to reverse this secretion [14]. (2) BBR regulates intestinal motility. Intestinal motility dysfunction is an important pathological characteristic of diarrhea. In humans, BBR has been shown to reduce intestinal smooth muscle contraction and to delay intestinal transit time [15,16]. (3) BBR restores intestinal barrier function in disease states. In Crohn's disease, epithelial barrier dysfunction leads to leak-flux diarrhea, but the damage of intestinal epithelial tight junctions could be ameliorated by BBR (100 μM) treatment, and such amelioration is related to inhibition of proinflammatory cytokines [17].

2.1.2. Antimicrobial activity

BBR has been found to display broad-spectrum antibacterial activities against *Staphylococcus epidermis*, *E. coli*, etc. [18–20]. For example, BBR inhibited oral pathogens in an in vitro tooth model, and the minimum inhibitory concentration (MIC) values against *Fusobacterium nucleatum*, *Prevotella intermedia*, and *Enterococcus faecalis* were 31.25 μg/mL, 3.80 μg/mL, and 500 μg/mL, respectively [21]. In another in vitro study, the antimicrobial effect of BBR was evaluated against 17 microorganisms based on the half maximal inhibitory concentration (IC_{50}), MIC, minimum microbicidal concentration (MMC), and minimum microbistatic concentration (MMS). The results showed that the IC_{50}, MIC, MMC, and MMS values of BBR for the most sensitive *Staphylococcus aureus* strain were 14.6, 212, 250, and >250 mg/L, respectively; while those values for *Trichoderma viride* (original green strain) were 809, 1345, 3000, and >3000 mg/L, respectively [22]. The values against other microorganisms, including *E. coli*, *Pseudomonas aeruginosa*, and *Bacillus subtilis*, fell in between [22]. The role of BBR as an antibacterial agent may be due to its inhibitory effect on enzymatic and/or endotoxic (e.g., lipopolysaccharide; LPS) activities of bacteria. For example, BBR can inhibit the activity of the bacterial surface protein sortase [23], a transpeptidase that mediates covalent binding between Gram-positive bacterial surface proteins and cell walls [24]. In addition, BBR has been shown to be a high-affinity LPS antagonist and decrease the interaction of LPS with specific receptors on host immune cells; therefore, it can be used to treat LPS-induced diseases [25].