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Berberine: A Medicinal Compound for the Treatment of Bacterial Infections

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Abstract

Berberine is an isoquinoline alkaloid mainly extracted from Rhizoma Coptidis, which is an efficient therapeutic agent to combat bacterial infections. However, bioactive assay manifested that berberine exhibited poor effect on antibacterial properties. In the present paper, we reviewed the multiple activities of berberine, including inhibition of biofilm formation, anti-inflammation effect, and clinical trials, which indicate the possible mechanism of berberine in the treatment of bacterial infections.

Keywords: Berberine; Bacterial infections; Antibacterial; Biofilm; Anti-Inflammation

Introduction

Berberine is a natural isoquinoline alkaloid isolated from various Chinese herbs, including Hydrastis canadensis, Berberis aristata, Coptis chinensis, Coptis rhizome, Coptis japonica, Phellondendron amurense and Phellondendron chinense schneid. In clinical practice, berberine has been used in the treatment of enteritis for thousands of years in China [1]. More importantly, synergy of berberines enhanced the inhibitory efficacy of other antibacterial [2,3]. However, the role of berberine in antibacterial action has not been extensively studied. In this review, we gain insights into the possible mechanisms of berberine in the treatment of bacterial infection diseases, mainly focusing on the inhibition of biofilm formation and anti-inflammation activities.

Antibacterial activity

The natural isoquinoline alkaloid berberine has been employed in Chinese and Ayurvedic Medicine for hundreds of years in the treatment of bacterial infections. Many clinical trials have shown that berberine is effective in treating acute diarrhea (Table 1) [4-7]. A study of one hundred and twenty-seven children with diarrhea in the age group 1 month to 6 years shows that, 68.5% children responded to the berberine therapy with no complications [7]. In addition, four hundred adults presenting with acute watery diarrhoea were entered into a clinical trial of berberine. During the clinical observation, berberine significantly reduced the number of motions (p<0.05), duration of diarrhea in hospital (p<0.001), volume of required intravenous (p<0.001) and oral fluid (p<0.001). However, it is mentioned that berberine did not reduce the excretion of vibrios in the stools, which suggested that berberine exhibited poor effect on antibacterial properties [8]. A study for investigating the potential of berberine and enrofloxacin against *E. coli, E. ictaluri and S. dysgalactiae* shows that, minimal inhibitory concentrations of berberine against those three bacteria were 300, 400 and 150 μg/ml, while the enrofloxacin were 0.025, 0.025 and 0.8 μg/ml [9]. Another evidence revealed that the low concentration of berberine would

promote the growth of *B. subtilis*, only a high concentration showed inhibitory activity (the IC_{50} is 952.37 μg/mL) [10]. Thus, we believed that there might be other mechanisms in the antibacterial action of berberine.

Disease	Dispose	Case number	Effect	
			Cure rate	**Total efficency**
Acute watery diarrhea	Berberine (oral)	88	77.2%(68)	-
Infantile infectious diarrhea	Berberine (oral)	57	68.4% (39)	96.5% (55)
Infantile diarrhea	Berberine(oral)	127	68.5%(87)	89.8%(114)
	Berberine (clyster)	274	-	96.4% (264)
	Berberine (oral)	195	62.6% (122)	82.6% (161)
	Berberine (clyster)	377	87.0% (328)	96.0% (362)
	Berberine hydrochloride and Smecta (clyster)	60	88.3% (53)	96.6% (58)
	Berberine (clyster) / Ampicillin (i.v)	50	68.0% (34)	92.0% (46)
	Berberine (clyster) / Virazole (oral)	50	60.0% (30)	98.0% (49)

Table 1: Overview of berberine in treating diarrhea

Inhibition of biofilm formation

The pathogens are usually found as communities. Although the pathogens that cause acute infection are generally free, those chronic bacterial forms that stick around for decades long ago evolved ways to join together into communities called biofilms. Bacterial biofilm is defined as "a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface" [11]. Biofilm formation process can be divided into attachment, maturation and detachment. The first step is the adherence and attachment of planktonic bacteria to the surfaces or interfaces, such as food, domestic and indwelling medical device. The next step is the maturation of biofilm which contains division, differentiation and recruitment of biofilm inhabitants, secretion of the extracellular matrix and reformation of the biofilm architecture according to the environment [12-16]. During the initial attachment, the matrix will induce bacteria to produce extracellular polymeric substance (EPS) [17]. Meanwhile, the bacteria can utilize the matrix nutrition to divide and differentiate into sessile cells, which will move to the biofilm surface via water channel [13].

These bacteria encase themselves in a hydrated matrix that is a shield against antibiotics, allowing them to grow rapidly [18-21]. Susceptibility tests in vitro have shown that the survival of bacterial biofilms after treatment with antibiotics at concentrations hundreds or even a thousand times the minimum inhibitory concentration of the bacteria measured in a suspension culture [18]. In vivo, antibiotics might suppress symptoms of infection by killing free-floating bacteria shed from the detachment, but fail to eradicate those bacteria still embedded in the biofilm. When the antibacterial treatment stops, the biofilm can act as a nidus for recurrence of infection. Infections usually persist until the surface with biofilm is surgically removed from the body [19].

Recent study has shown that berberine could significantly inhibit *Staphylococcus (S.) epidermidis* adhesion at the concentration of 45 mg/ml. Higher concentrations (>30 mg/mL) of berberine can prevent the formation of *S. epidermidis* biofilm [22]. More importantly, berberine has also been proved to be effective in inhibiting biofilm formation in clinical isolates of *Klebsiella pneumoniae* [23]. We suppose that berberine might affect the attachment during biofilm formation. As mentioned above, bacteria can join together on essentially any surface and start to form a protective matrix. The matrix is made of polymers composed of molecules with repeating structural units that are connected by chemical bonds, in which polymerized phenol soluble modulins (PSMs) play an important role in stabilizing the biofilm architecture [24,25]. PSMs are a family of protein toxins that are produced in all methicillin-resistant *Staphylococcus aureus* strains, and which are thought to be a possible cause of severe infections. PSMs share a similar β-sheet structure with amyloid-β peptide (Aβ) in Alzheimer's disease (AD). The accumulation of Aβ derived from amyloid precursor protein (APP) is a triggering event leading to the pathological cascade of AD. It has been proved that berberine can reduce Aβ by modulating APP processing in human neuroglioma H4 cells at the range of berberine concentration (0.1-100 μM) [26]. Thus, we believed that berberine could bind to the amyloid proteins in bacterial biofilm EPS that share a similar β-sheet structure, such as PSMs in *S. epidermidis* and *S. aureus* biofilm, Curli in Escherichia coli biofilm, TasA in Bacillus subtilis biofilm, and Fap fimbriae in *Pseudomonas aeruginosa* biofilm [27-30].

This hypothesis might better explain the effects of berberine in the combinatory therapeutic applications with antibiotics. For example, berberine could enhance the in vitro inhibitory efficacy of antibacterial agents' azithromycin (AZM) and levofloxacin (LEV) against 10 clinical isolates of Methicillin-Resistant *Staphylococcus aureus* (MRSA) [3]. According to our theory, berberine might bind to the β-sheet structure of PSMs produced by MRSA, and affect the aggregation of PSM peptides into amyloid-like fibers, results in the biofilm abrogation [31-38]. The free-floating bacteria shed from the fractured biofilm can be easily killed by the antibiotics. Thus, berberine might enhance the antibacterial activity of antibiotics through affecting the stability of bacterial biofilm (Figure 1).
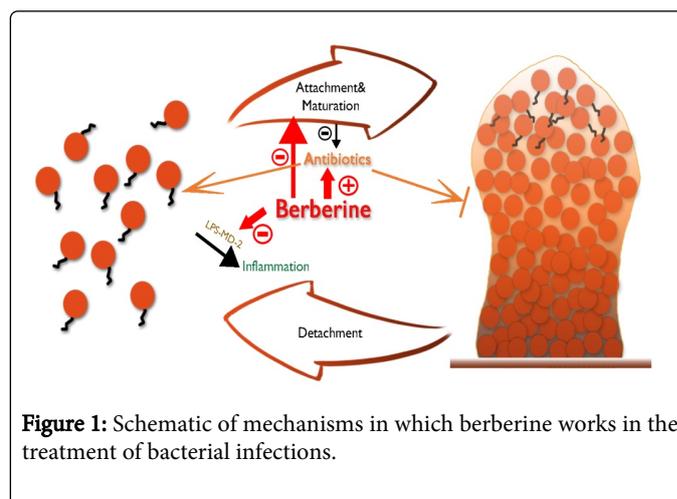

Figure 1: Schematic of mechanisms in which berberine works in the treatment of bacterial infections.

Anti-inflammation activity

The bacteria in a biofilm are protected by a matrix; the host immune system is less likely to mount a response to their presence [12]. But if planktonic bacteria are periodically released from the biofilm, each time single bacterial forms enter the tissues, the immune system suddenly becomes aware of their presence. It may proceed to mount an inflammatory response that leads to heightened symptoms. The periodic release of planktonic bacteria from some biofilms may be what causes many chronic relapsing infections. The symptoms of infection include abdominal pain, cramping, dehydration, diarrhea and fever, which are mainly caused by the bacterial endotoxin infection. Endotoxin is used synonymously with the term LPS, which interacts with specific receptors on immune cells such as monocytes, macrophages, dendric cells. LPS consists of a hydrophobic anchor, known as lipid A, a repeating O-antigen polysaccharide, and an inner core oligosaccharide [39,40]. Many of the immune activating abilities of LPS can be attributed to the lipid A unit, which binds to the toll-like receptor 4 (TLR4), and activates the host defence effector system by rapidly triggering pro-inflammatory processes [41-44]. TLR4 alone does not directly bind LPS and requires its coreceptor myeloid differentiation protein (MD-2). MD-2 has a unique hydrophobic cavity which can directly bind the lipid A unit [45,46]. The combination between LPS and TLR4/MD-2 receptor complex can cause intense innate immune response [1,47-49]. Recently, our group has just proved that berberine can act as an antagonist to compete against LPS in binding with TLR4/MD-2 receptor, results in blocking the LPS/TLR4 signaling transduction, and disrupt the body's immune response to LPS [1]. In a study with non obese diabetic mice, berberine supplementation for 14 weeks significantly decreased the expression

ratios of pro-/anti-inflammatory and/or Th1/Th2 cytokines, protecting the spleen, liver and kidney from spontaneous chronic inflammation [50]. We believe that further study on the berberine will aid in our ability to design effective interventions and treatments for bacterial infection diseases.

Conclusion

Berberine might function in the treatment of bacterial infections in two mechanisms. On the one hand, berberine could bind to amyloid proteins in biofilm, thus interrupt its stability and enhance the antibacterial activity of antibiotics. On the other hand, berberine could compete with LPS for binding to TLR4/MD-2, which inhibits the inflammation in the infection (Figure 1).

Acknowledgment

Conflict of Interest

The authors declare no conflict of interest.

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