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Therapeutic Potential of Berberine

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Abstract. Berberine, an alkaloid extracted from plants, is used in the treatment of many diseases, has many pharmacological effects, and is accompanied by a high safety profile, which is popular in drug development and has been applied in many diseases. It shows significant effects on cancer, type 2 diabetes mellitus, gastrointestinal diseases, and cholesterol reduction as the inherent properties of berberine have inhibitory effects on these conditions, some by targeting specific steps in the disease progression, and others by acting directly on the pathogens themselves. Additionally, berberine also has several side effects, and patients should be cautious to avoid exceeding the recommended dosage. Also, it may interact with certain medications, presenting both benefits and risks. Therefore, it is important to take berberine under medical supervision and follow the doctor's advice. This article summarizes several clinical trials, randomized controlled trials, and other experimental studies, including in vivo and in vitro experiments. During this review, it will focus on these four kinds of diseases, to explain the mechanism and description of the relationship between disease and berberine.

Keywords: Berberine, cancer, Type-II diabetes, Gastrointestinal disease, Cholesterol-lowering.

1. Introduction

Berberine(Figure 1.), a bioactive alkaloid extracted from plants such as barberry, goldenseal, and tree turmeric, has a wide range of pharmacological effects and can be used to treat various diseases, including cancer and inflammation [1]. Berberine has a distinctive yellow color, which gives the source plant material a yellow to golden appearance [2]. These effects are largely attributed to several key characteristics of berberine. Firstly, its anti-inflammatory and antioxidant properties help reduce inflammation and oxidative stress. Secondly, its antimicrobial activity allows it to act against fungi and viruses; berberine interacts directly with bacterial cells, inhibiting their growth and replication, thereby helping to balance microbial populations, such as the gut microbiota, and reducing intestinal permeability. Additionally, berberine can regulate glucose and lipid metabolism by activating AMP-activated protein kinase (AMPK), thereby enhancing insulin sensitivity, lowering blood sugar levels, and reducing cholesterol levels. This makes it commonly used in the treatment of type 2 diabetes [1]. Furthermore, berberine has protective effects on the cardiovascular system, which are linked to its aforementioned properties. It helps regulate blood pressure and maintain cardiovascular health [3]. Lastly, berberine is known for its safety and tolerability. According to most studies, berberine is considered highly safe when used at appropriate doses, although it may cause mild gastrointestinal discomfort in some individuals. Overall, the effects of berberine (BBR) are due to its specific actions on enzymes, receptors, and biological targets, as well as its general anti-inflammatory and antioxidant properties [2]. This review will provide a detailed description of four diseases that can be treated with berberine (BBR): cancer, type 2 diabetes, Gastrointestinal disease, and cholesterol-related diseases.

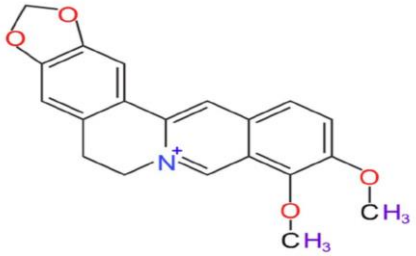

Figure 1. Structure of Berberine [1]

2. Cancer

Cancer, with its incidence rate continuously increasing over recent years, is characterized by the abnormal growth of cells. Typically, these abnormal cells need to reach a size of about 1 cm or consist of approximately one million cells before they can be detected [4]. Focusing on malignant tumor cells, which are also referred to as cancer, they exhibit high levels of invasiveness and metastatic potential, escaping the regulatory mechanisms that normally control cell growth [5]. Berberine (BBR) exhibits significant anti-proliferative and cytotoxic effects on cancer cells, inducing apoptosis and inhibiting cell cycle progression and invasion. Numerous studies have demonstrated its strong selectivity for cancer cells, with limited toxicity to normal cells. On one hand, BBR can activate pro-apoptotic factors in cancer cells, affecting the NF-kB signaling pathway and leading to its inactivation, which subsequently disrupts a series of cellular growth activities. Additionally, BBR suppresses this behavior of the transcription factor AP-1, resulting in a cascade of apoptotic events in various types of cancer cells, including human hepatocellular carcinoma, oral cancer, breast cancer, and colon cancer cells. On the other hand, BBR impacts the cell cycle, thereby affecting cellular viability and disrupting B-cell lymphomas. At low concentrations, BBR inhibits the growth of tumor cells in the G1 phase, thereby reducing cellular activity; at high concentrations, it induces growth arrest in the G2/M phase of the cell cycle in cancer cells [6]. Moreover, some studies suggest that BBR promotes the generation of reactive oxygen species (ROS) in tumor cells.

Liver cancer, as one of the leading causes of cancer-related deaths worldwide, has a high incidence rate, particularly among patients with liver cirrhosis, and is closely associated with personal habits, such as heavy alcohol consumption. Experimental studies have found that berberine (BBR) can effectively treat liver cancer to a certain extent. In a study involving mice, BBR was shown to reduce tumor burden in liver cancer and enhance the function of immune cells, particularly T cells. The mechanism of action involves BBR reducing the proportion of TCRbhiPD-1hiCD69+ CD27 + effector CD8+ T lymphocytes while increasing the proportion of Ly6ChiTCRb+ CD69+ CD27+ CD62L+ central memory CD8+ T lymphocytes [6]. Additionally, BBR modulates tumor immunity in liver cancer by influencing receptor-ligand interactions between immune cells. As research continues to advance, BBR is expected to show further promise in the treatment of liver cancer.

3. Type-II diabetes

Type 2 diabetes mellitus (T2DM) has nearly evolved into a pandemic, characterized by fasting and postprandial hyperglycemia, and can lead to many life-threatening complications and comorbidities. The pathophysiology of T2DM is primarily driven by insulin resistance in skeletal muscle, liver, and adipose tissue [7]. The primary cause of insulin resistance is the ectopic accumulation of lipids in insulin-sensitive tissues, such as the liver, skeletal muscle, and adipose tissue. This accumulation disrupts insulin signaling and response. Moreover, type 2 diabetes mellitus (T2DM) is often accompanied by obesity, which is associated with impaired adipocyte metabolism. Such impairment leads to excessive lipolysis and elevated levels of plasma free fatty acids. Consequently, abnormal adipose tissue metabolism in T2DM directly contributes to insulin resistance in target tissues by increasing lipid accumulation or by cytokine-mediated disruption of insulin signaling cascades in the liver and skeletal muscle [8]. Pancreatic β-cell failure is a hallmark pathological feature of T2DM

and, together with insulin resistance, is a prerequisite for hyperglycemia [9]. In Type 2 Diabetes Mellitus (T2DM), the majority of cases are associated with insulin resistance (IR). Berberine (BBR) has been experimentally confirmed to improve T2DM with IR, primarily through mechanisms involving the inhibition of mitochondrial function, acceleration of glycogenolysis, and activation of the AMP-activated protein kinase (AMPK) signaling pathway. The therapeutic effects of BBR on T2DM include enhancing insulin sensitivity by activating AMPK, which increases glucose uptake in skeletal muscle and reduces gluconeogenesis in the liver. BBR also reduces lipid accumulation and improves lipid metabolism by decreasing fat deposition in insulin-sensitive tissues such as the liver and muscle. It lowers plasma triglycerides and cholesterol levels, regulating lipid metabolism and promoting lipid oxidation. BBR's most notable anti-inflammatory effects are also evident here, as it inhibits the production of pro-inflammatory cytokines. Additionally, BBR modulates the gut microbiota, promoting the growth of beneficial bacteria, which improves glucose metabolism and enhances insulin sensitivity, helping to reduce postprandial blood glucose levels [7, 9].

4. Gastrointestinal disease

Helicobacter pylori, a common bacterium found in the human gastrointestinal tract, is a major culprit in gastritis and peptic ulcers, and in severe cases, it can lead to gastric cancer. It is prevalent worldwide, and in China, approximately 44.2% of the population is infected with H. pylori [10]. Moreover, the antibiotic resistance of H. pylori is increasing, and the eradication rate fluctuates between 70% and 85%. Therefore, there is a significant need for improvement in the medications used to treat H. pylori [10]. The primary habitat of **Helicobacter pylori** is located in the gastric mucosa and intercellular spaces. The thick mucus layer and acidic environment provide protection for *H. pylori*, reducing the effectiveness of many antimicrobial agents. A high bacterial load of *H. pylori* leads to severe infections, with large numbers of bacteria adhering to the gastric mucosa and forming biofilms, which further complicates treatment [11]. Berberine has shown significant inhibitory effects on multi-drug-resistant strains of Helicobacter pylori, directly targeting the bacteria itself. Clinical studies have found that berberine not only inhibits these strains but also reduces the incidence of adverse reactions in patients, demonstrating high safety and efficacy. In the treatment of H. pylori infections, berberine is often used in combination with antibiotics and other components, typically including bismuth. Bismuth primarily works by increasing sensitivity to resistant antibiotics and improving the eradication rate of H. pylori. However, with the use of berberine, bismuth may not be necessary, enhancing the safety profile of the treatment since bismuth is a metal element and prolonged use may pose some risk to the human body [12]. Berberine reduces the activity of H. pylori and is minimally affected by internal or external environmental factors. It has demonstrated excellent efficacy even against multi-drug-resistant strains. Specifically, berberine can restructure gut bacterial cells by inducing cell death in harmful gut bacteria and increasing the abundance of beneficial bacteria, such as Bifidobacterium ii and Lactobacillus acidophilus [2]. This effect has been noted by researchers to be similar to that of probiotics. Certain diseases, such as colitis and gut-related inflammation, can be treated or reversed by altering the gut microbiota. However, this also explains the side effects associated with berberine, such as diarrhea.

5. Cholesterol-lowering

5.1. high cholesterol

High cholesterol refers to a condition characterized by elevated levels of cholesterol in the blood, which significantly increases the risk of atherosclerosis [13]. This condition can be attributed to various factors, including unhealthy dietary habits, lack of physical activity, genetic predisposition, and smoking. High cholesterol not only poses significant health risks on its own but also elevates the risk of other diseases, such as heart disease and stroke. Therefore, maintaining cholesterol levels within a normal range is crucial. Berberine (BBR) is a lipid-lowering agent used to manage cholesterol levels. Experimental results indicate that patients receiving oral berberine show

significant reductions in serum cholesterol and triglycerides after three months. Additionally, similar findings have been observed in rodent models, where serum cholesterol levels were also decreased [14]. The mechanism of action of berberine involves stabilizing mRNA post-transcriptionally, thereby enhancing the expression of LDL receptors (LDLR) [14]. Specifically, berberine acts on the 5' proximal region of the 3' untranslated region (UTR) of LDLR mRNA.

5.2. cardiovascular diseases

Berberine not only lowers cholesterol levels but also inhibits related diseases, such as cardiovascular diseases associated with cholesterol. Sex hormones have long been considered to be related to lipid reduction and anti-inflammatory effects in the treatment of such conditions. The mechanism of action of berberine is not yet fully understood, but there are currently two proposed mechanisms: Firstly, similar to its effect in treating type 2 diabetes, berberine may activate AMP-activated protein kinase (AMPK), which coordinates energy balance and lipid synthesis. Secondly, berberine may inhibit Aldo-Keto Reductase Family 1 Member C3 (AKR1C3), an enzyme involved in the regulation of steroid hormones [15]. Despite the unclear mechanism, experimental results indicate that berberine is effective against this disease, with a greater impact observed in females compared to males.

6. Conclusion

In conclusion, this review describes the four diseases mentioned above and introduces the mechanisms of action of berberine (BBR). It is evident that berberine possesses broad and effective pharmacological properties. The diseases discussed are associated with high and continually rising incidence rates, impacting individuals, families, and society at large. Berberine offers a promising treatment approach, providing a greater likelihood of effective and safer therapeutic options for these conditions. As technological advancements continue, it is hoped that the potential of berberine will be further explored, paving the way for a brighter future in human health and safety.

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