Article

Berberine in China: History, pharmacological research, clinical trials, industrialization application and market consumption

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Received 20 March 2026; *Accepted 26 March 2026*; *Published online 30 March 2026*; *Published 1 December2027*

Abstract

Berberine (the hydrochloride salt is commonly called *Huangliansu* in clinical practice) is a bioactive natural isoquinoline alkaloid that has been used in traditional Chinese medicine for over 2000 years. This comprehensive review systematically synthesizes up-to-date preclinical and clinical evidence to summarize berberine's pharmacological properties, diverse therapeutic potentials, and existing bottlenecks for clinical translation. Extensive studies confirm that berberine exerts multiple biological activities including antibacterial, anti-inflammatory, hypoglycemic, lipid-regulating, wound healing-promoting, and cardiovascular protective effects, with promising clinical value for managing type 2 diabetes, metabolic syndrome, vascular diseases, chronic wounds, and gastrointestinal infections. However, its large-scale clinical application is still limited by extremely low oral bioavailability, significant quality variation among commercial preparations, and a lack of large-scale standardized clinical trials. Future research directions include optimizing novel drug delivery systems to improve bioavailability and verifying long-term efficacy and safety through high-quality clinical trials. This review provides a systematic reference for the further development and clinical utilization of berberine as a low-cost, safe natural therapeutic agent.

Keywords berberine; berberine hydrochloride; matural isoquinoline alkaloid; pharmacological activity; therapeutic potential

Network Pharmacology
ISSN 2415-1084
URL: http://www.iaees.org/publications/journals/np/online-version.asp
RSS: http://www.iaees.org/publications/journals/np/rss.xml
E-mail: networkpharmacology@iaees.org
Editor-in-Chief: WenJun Zhang
Publisher: International Academy of Ecology and Environmental Sciences

1 Introduction

Berberine (BBR), commonly known as berberine hydrochloride or *Huangliansu* (黄连素) in clinical practice, is a natural isoquinoline alkaloid mainly extracted from medicinal plants such as *Coptis chinensis* (*Huanglian*, 黄连) and *Phellodendron chinense* (*Chuanhuangbai*, 川黄柏), which have been used in traditional Chinese medicine (TCM) for over two thousand years (Zhang, 2017a-d; Zhang and Liu, 2019). In modern pharmacology, BBR was first recognized as a safe antibacterial agent for gastrointestinal infections, and over the past decades, accumulating basic and clinical studies have revealed a wide range of pharmacological

activities, including anti-inflammatory, glucose-lowering, lipid-regulating, and anti-tumor effects, making it a research hotspot in natural product drug development (Yiling Pharmaceutical, 2023; Chinese Pharmaceutical Association, 2020; Zhang, 2017a-d; Zhang and Wei, 2023). As a low-cost natural product with proven safety, BBR has attracted extensive attention from both academia and the pharmaceutical industry for its potential to prevent and treat multiple chronic diseases that are highly prevalent globally. This comprehensive review systematically summarizes the discovery history, latest research progress in different biological activities, completed and ongoing clinical trials, current industrialization and market status, and future research directions of BBR, to provide a systematic reference for its further research and clinical application.

Berberine has a molecular formula of $C_{20}H_{18}NO_4$, with a quaternary ammonium structure that gives it high polarity and low oral bioavailability (less than 1% of the oral dose is absorbed into systemic circulation). Most of the ingested BBR remains in the intestinal tract, which underlies its prominent effects on intestinal-related diseases. Berberine hydrochloride is the most common clinical formulation, which is stable and easy to produce at large scale.

2 Discovery and Historical Development of Berberine

2.1 Early Application in Traditional Chinese Medicine

The earliest record of *Coptis chinensis*, the main source of BBR, can be traced back to Shennong Ben Cao Jing (Divine Farmer's Materia Medica; 神农本草经) compiled around 200 AD, where it was recorded as a drug for "removing heat, drying dampness, and stopping diarrhea" (Zhang & Wang, 2001). For centuries, preparations of *Huanglian* and related herbs have been widely used to treat various gastrointestinal disorders, fever, and infectious diseases in TCM clinical practice, forming a solid foundation of empirical application for modern research.

2.2 Isolation and Early Modern Research

In 1826, pure berberine was first isolated from *Berberis vulgaris* by European chemists, and its complete chemical structure was elucidated by the 1920s. Since the 1950s, synthetic berberine hydrochloride was mass-produced and entered the global pharmaceutical market as an over-the-counter (OTC) anti-diarrheal drug, due to its broad-spectrum antibacterial activity against most Gram-positive and Gram-negative enteric pathogens. From the 1980s, research on the extra-antibacterial effects of BBR began to boom, with a series of studies exploring its effects on diabetes, cardiovascular diseases and cancer (He et al., 1991). This laid the foundation for the modern redevelopment of this traditional natural product.

3 Recent Advances in Pharmacological Research and Scientific Findings

3.1 Pharmacological Effects in Gastrointestinal Diseases

Gastrointestinal tract is the main site of action of BBR due to its low oral bioavailability, so most of its well-documented effects are related to gastrointestinal health.

3.1.1 Intestinal Microbiota Regulation

One of the core mechanisms of BBR's multiple effects is its regulation of intestinal microbiota homeostasis. Multiple studies have confirmed that low-dose BBR does not cause intestinal dysbiosis, unlike many broad-spectrum antibiotics; instead, it reduces the abundance of conditional pathogens such as Enterococcus and *Escherichia coli*, and promotes the growth of beneficial commensal bacteria, which contributes to the maintenance of intestinal barrier function and reduces systemic metabolic inflammation (Baishideng Publishing Group, 2023). This microbiota-modulating effect explains why BBR is effective for both infectious and non-infectious intestinal diseases.

3.1.2 Functional Gastrointestinal Disorders

For diarrhea-predominant irritable bowel syndrome (IBS-D), BBR has shown promising therapeutic effects in basic and clinical studies. Its mechanisms include reducing intestinal mucosal inflammation, regulating abnormal intestinal motility, and reducing visceral hypersensitivity, which are core pathological features of IBS-D (Hans Publishers, 2024).

3.1.3 Helicobacter pylori Infection and Chronic Gastritis

Recent in vitro studies on chronic gastritis have confirmed that BBR can significantly reduce the viability of *H. pylori*-infected gastric cells, regulate the expression of inflammatory factors including IL-1β, IL-8, and apoptosis-related protein Bax, and promote apoptosis of abnormal infected cells, suggesting its potential as an adjuvant agent for *H. pylori* eradication (Chinese Society of Integrated Traditional and Western Medicine, 2025).

3.1.4 Inflammatory Bowel Disease and Colorectal Cancer Prevention

BBR has shown significant anti-inflammatory activity in animal models of inflammatory bowel disease (IBD), reducing intestinal mucosal inflammation and damage and improving disease activity. For colorectal cancer (CRC) chemoprevention, multiple studies have confirmed that BBR can inhibit proliferation of CRC cells, induce cancer cell apoptosis, and reduce the recurrence of colorectal adenomas, which are the main precancerous lesions of CRC (Chinese Pharmaceutical Association, 2020).

3.2 Pharmacological Effects in Metabolic Diseases

The anti-diabetic effect of BBR has been studied for over 40 years. Early clinical observations published in 1988 found that BBR showed significant glucose-lowering effects in 60 patients with T2DM, with an overall effective rate of over 70% (Zhang & Wang, 2001). The main mechanisms of BBR's glucose-lowering effect include improving peripheral tissue insulin sensitivity, increasing glucose uptake in muscle and adipose tissue, inhibiting hepatic gluconeogenesis, and regulating gut microbiota to reduce metabolic endotoxemia. Besides glucose lowering, BBR also has moderate lipid-lowering effects, reducing total cholesterol and low-density lipoprotein cholesterol levels in patients with hyperlipidemia, making it beneficial for patients with T2DM combined with dyslipidemia.

3.3 Other Pharmacological Activities

Preclinical studies have also shown that BBR has hepatoprotective effects in non-alcoholic fatty liver disease, anti-atherosclerotic effects by reducing vascular inflammation, and neuroprotective effects in animal models of neurodegenerative diseases such as Alzheimer's disease. These effects are still in the early basic research stage, and have not yet been verified by large-scale clinical trials.

4 Clinical Trials and Therapeutic Efficacy

4.1 Clinical Trials for Gastrointestinal Indications

4.1.1 Irritable Bowel Syndrome

A randomized double-blind placebo-controlled clinical trial included 196 patients with IBS-D, and the results showed that BBR treatment significantly improved the overall clinical response rate, reduced the frequency of diarrhea and abdominal pain scores, compared with placebo, without increasing the incidence of adverse events (Hans Publishers, 2024). This trial provides high-level clinical evidence for the use of BBR in IBS-D treatment, and supports its clinical application as a low-cost safe option for IBS-D management.

4.1.2 Colorectal Adenoma Recurrence Prevention

A landmark large-scale clinical trial conducted by Professor Fang's team, published in The Lancet Gastroenterology & Hepatology, demonstrated that long-term low-dose BBR treatment reduced the recurrence rate of colorectal adenoma after endoscopic polypectomy by approximately 20% compared with placebo. This finding is a major breakthrough for CRC chemoprevention, and provides a low-cost preventive option for

populations at high risk of colorectal cancer (Chinese Pharmaceutical Association, 2020). This study has drawn wide attention in the international oncology community, and has been included in several expert consensuses on colorectal cancer prevention.

4.1.3 Chronic Gastritis and H. pylori Infection

The 2025 Chinese Expert Consensus on Chronic Non-Atrophic Gastritis notes that BBR has shown consistent in vitro and preliminary clinical activity against *H. pylori*, and can be used as an adjuvant treatment option for patients who cannot tolerate standard quadruple therapy due to antibiotic intolerance. However, further large-scale randomized controlled trials are still needed to confirm its clinical efficacy and optimal dosage (Chinese Society of Integrated Traditional and Western Medicine, 2025).

4.2 Clinical Trials for Type 2 Diabetes

A systematic review of all existing clinical trials of BBR for T2DM concluded that current available data suggests that BBR has a mild glucose-lowering effect when used alone or in combination with conventional oral hypoglycemic agents, and is well tolerated by most patients. However, the methodological quality and reporting quality of most existing clinical studies are generally low, with common issues such as small sample size, unclear randomization and blinding procedures, and short follow-up periods. Therefore, high-quality large-scale multi-center randomized controlled trials are still needed to further confirm its long-term efficacy and safety for T2DM management (Li & Wang, 2014).

4.3 Safety Profile and Adverse Effects

Most clinical studies have shown that BBR is well tolerated at the recommended clinical doses (0.5-1.5g per day for adults). The most common adverse effects are mild gastrointestinal reactions such as constipation, nausea, and mild abdominal discomfort, which usually resolve spontaneously within a few weeks without discontinuation of treatment. No serious adverse events have been reported in large clinical cohorts, confirming BBR's good safety profile for long-term use at recommended doses (Zhang & Wang, 2001).

5 Industrialization Application and Market Consumption

5.1 Current Approved Indications and Industrial Status

Berberine hydrochloride has been registered as an OTC drug for the treatment of acute gastrointestinal infectious diarrhea for decades in China and many other countries, with very mature extraction and synthesis production processes, and extremely low production cost. Currently, China is the world's main producer and exporter of BBR active pharmaceutical ingredient (API) and finished preparations, with dozens of domestic pharmaceutical enterprises producing BBR-related products. In recent years, with the continuous discovery of new pharmacological effects of BBR, many domestic pharmaceutical companies have invested in the research and development of new BBR preparations and new indications. It should be noted that new drug development of BBR follows the standard global pharmaceutical regulatory pathway, which generally requires preclinical research, clinical trial approval, phase I to III clinical trials, and final production approval, with large R&D investment, long development cycles, and high regulatory requirements (Yiling Pharmaceutical, 2023). At present, most new indication development projects of BBR are still in different stages of clinical research, and have not yet obtained official marketing approval for new indications.

5.2 Market Consumption Status

Due to its low price, high safety, and expanding clinical application scenarios, the global market size of BBR has shown a steady growth trend over the past decade. In addition to traditional pharmaceutical use as an anti-diarrheal drug, BBR is also widely used as a dietary supplement in North America, Europe, and other developed regions, driven by consumer demand for natural products for glucose and lipid management. This dietary supplement segment has become the main growth driver of global BBR consumption in recent years. In

China, BBR is also commonly used as an adjuvant treatment for metabolic diseases and chronic gastrointestinal diseases in integrative medicine clinical practice, with a large annual clinical usage.

6 Future Perspectives and Challenges

Berberine, as a natural product with thousands of years of empirical application and decades of modern research, has shown great potential for the prevention and management of multiple chronic diseases. However, there are still several key challenges that need to be addressed in future research:

First, the quality of existing clinical evidence for most new indications of BBR is still insufficient. Especially for T2DM and metabolic syndrome, high-quality large-scale multi-center randomized double-blind placebo-controlled trials are urgently needed to confirm long-term efficacy and provide high-level evidence for updating clinical guidelines (Li & Wang, 2014).

Second, the molecular mechanisms of BBR's multiple pharmacological effects are still not fully elucidated. Although the microbiota-modulating effect is widely recognized, the detailed interaction between BBR and host signaling pathways, and the causal relationship between microbiota regulation and BBR's systemic effects, still need further in-depth basic research.

Third, the low oral bioavailability of BBR is a major limitation for its application in systemic diseases. The development of new optimized dosage forms such as liposomes, nanoparticles, and lipid-soluble prodrugs to improve BBR's oral absorption and bioavailability is an important research direction for further improving its clinical efficacy.

Fourth, the landmark finding that BBR reduces colorectal adenoma recurrence opens a new direction for low-cost cancer chemoprevention. Further validation of this finding in larger cohorts of different ethnic groups will promote its widespread translation into clinical practice, which will benefit millions of people at high risk of colorectal cancer globally (Chinese Pharmaceutical Association, 2020).

Overall, BBR is a very promising natural drug candidate with unique advantages of low cost and high safety. With further in-depth research and standardized clinical development, BBR is expected to play a more important role in the prevention and treatment of chronic non-communicable diseases in the future.

References

Baishideng Publishing Group. 2023. Research progress of traditional Chinese medicine on intestinal mucosal injury. World Journal of Gastroenterology, 29(9): 449

Beijing University of Chinese Medicine. 2022. Introduction to Scientific Research Platform of Beijing University of Chinese Medicine. Beijing University of Chinese Medicine, China

Chinese Pharmaceutical Association. 2020. Highlights of research on traditional Chinese medicine and natural medicines from 2015 to 2020. Journal of Traditional Chinese Medicine and Materia Medica. https://html.rhhz.net/YXXB/html/20201201.htm. Access on 15 March 2026

Chinese Society of Integrated Traditional and Western Medicine. 2025. Expert Consensus on Integrative Medicine Diagnosis and Treatment of Chronic Non-Atrophic Gastritis (2025). Bejing, China

Hans Publishers. 2024. Research progress of berberine in the treatment of intestinal diseases. Hans Journal of Pharmaceutical Sciences

He LH, Xu FM, Zhang ZD. 1991. Progress in pharmacological studies of berberine. Pharmaceutical Practice and Service, 4. https://yxsj.smmu.edu.cn/article/1991/4. Access on 15 March 2026

Institution of Chinese Materia Medica, China Association of Chinese Medicine. 2024. Guidelines for the diagnosis and treatment of liver cirrhosis with traditional Chinese medicine. Journal of Clinical Hepatology.

https://www.lcgdbzz.org/cn/article/doi/10.12449/JCH240305. Access on 15 March 2026

Li X, Wang Y. 2014. Systematic review of the efficacy and safety of berberine in the treatment of type 2 diabetes mellitus. Chinese Journal of Clinical Pharmacology. http://dianda.cqvip.com/Qikan/Article/Detail?id=40518300. Access on 15 March 2026

Ministry of Science and Technology of the People's Republic of China. 2014. Collection of scientific and technological resources and achievements of national science and technology programs (population health field). Ministry of Science and Technology of the People's Republic of China, China

Yiling Pharmaceutical. 2023. 2023 Interim Report of Yiling Pharmaceutical. https://vip.stock.finance.sina.com.cn/corp/view/vCB_AllBulletinDetail.php?stockid=002603&id=9462417. Access on 15 March 2026

Zhang L, Wang H. 2001. Pharmacological effects of traditional Chinese medicine against diabetes. Chinese Journal of Integrated Traditional and Western Medicine. http://www.cjim.cn/zxyjhcn/zxyjhcn/ch/reader/view_abstract.aspx?file_no=20010446&st=alljournals. Access on 15 March 2026

Zhang WJ. 2017a. Network pharmacology of medicinal attributes and functions of Chinese herbal medicines: (I) Basic statistics of medicinal attributes and functions for more than 1100 Chinese herbal medicines. Network Pharmacology, 2(2): 17-37. http://www.iaees.org/publications/journals/np/articles/2017-2(2)/basic-statistics-of-medicinal-attributes-and-functions.pdf

Zhang WJ. 2017b. Network pharmacology of medicinal attributes and functions of Chinese herbal medicines: (II) Relational networks and pharmacological mechanisms of medicinal attributes and functions of Chinese herbal medicines. Network Pharmacology, 2(2): 38-66. http://www.iaees.org/publications/journals/np/articles/2017-2(2)/networks-and-mechanisms-of-medicinal-attributes-and-functions.pdf

Zhang WJ. 2017c. Network pharmacology of medicinal attributes and functions of Chinese herbal medicines: (IV) Classification and network analysis of medicinal functions of Chinese herbal medicines. Network Pharmacology, 2(3): 82-104. http://www.iaees.org/publications/journals/np/articles/2017-2(3)/classification-and-network-analysis-of-medicinal-functions.pdf

Zhang WJ. 2017d. Network pharmacology of medicinal attributes and functions of Chinese herbal medicines: (III) Canonical correlation functions between attribute classes and linear eignmodels of Chinese herbal medicines. Network Pharmacology, 2(3): 67-81.

http://www.iaees.org/publications/journals/np/articles/2017-2(3)/canonical-correlation-functions-between-attribute-classes.pdf

Zhang WJ, Liu GH. 2019. Naturalness and preference for species selection of Chinese medicinal seed plants. Network Pharmacology, 4(1-2): 1-5. http://www.iaees.org/publications/journals/np/articles/2019-4(1-2)/naturalness-and-preference-for-species-selection-of-Chinese-medicinal-plants.pdf

Zhang WJ, Wei QS. 2023. Information system of attributes and functions of Chinese herbal medicines. Network Pharmacology, 8(3-4): 27-63. http://www.iaees.org/publications/journals/np/articles/2023-8(3-4)/information-system-Chinese-herbal-medicines.pdf