Berberine

Lian-Hua Fang, Jin-Hua Wang, and Guan-Hua Du

Abstract Berberine is a quaternary ammonium salt that is found in some plants such as huanglian (*Rhizoma coptidis*), huangbo (*Phellodendri Chinensis Cortex*), and sankezhen (*Berberidis Radix*). Berberine hydrochloride has extensive pharmacological effects, such as antibacterial, antiviral, anti-inflammatory, analgesic, anticancer, hyperglycemic, antilipidemic, antihypertensive, anti-arrhythmic, anti-heart failure, and so on. Therefore, berberine hydrochloride is mainly used to treat gastroenteritis, bacterial diarrhea, intestinal infection, conjunctivitis, and suppurative otitis media. In the future, it is necessary for researchers to focus on its structural optimization and mechanisms of action, and a large number of long-term clinical studies are needed to further confirm its role in the clinical treatment process and curative effect of berberine hydrochloride.

Keywords Berberine · Alkaloid · Antibacterial · Diarrhea

Alias: Berberine, berberine hydrochloride, umbellatine
Origin: *Coptis chinensis* (Fig. 1)
Chemical name (Fig. 2)

Benzo[G]-1,3-benzodioxolo[5,6-α]quinolizinium, 5,6-dihydro- 9,10-dimethoxy

Molecular formula, $C_{20}H_{18}NO_4$; **MW**, 336.36; **CAS**, 2086-83-1
Derivatives

Berberine hydrochloride, $C_{20}H_{20}NO_4Cl$; MW, 371.82; CAS, 633-65-8

L.-H. Fang · J.-H. Wang · G.-H. Du (✉)
Beijing Key Laboratory of Drug Targets Identification and Drug Screening, Centre for Pharmaceutical Screening, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China
e-mail: dugh@imm.ac.cn

G.-H. Du, *Natural Small Molecule Drugs from Plants*,
https://doi.org/10.1007/978-981-10-8022-7_62

Properties

Appearance: Berberine is odorless and yellow crystalline powder. *Solubility*: Berberine is soluble in hot water, slightly soluble in water or ethanol and in chloroform, and insoluble in ether. *Melting point*: Melting point of berberine is about 204–206 °C. Berberine is heat labile.

Dosage Forms and Indications

This product was recorded in the *Pharmacopoeia of the People's Republic of China* (2015), the *British Pharmacopoeia* (2017), the *Japanese Pharmacopoeia* (17th ed.), the *European Pharmacopoeia* (9th ed.), and the *Korea Pharmacopoeia* (10th ed.).

Berberine hydrochloride is commonly used in clinic as tablet and capsule forms. It was mainly used to treat gastroenteritis, bacterial diarrhea, intestinal infection, conjunctivitis, and suppurative otitis media.

Literature

Coptis chinensis was widely used in China as a folk medicine by Shennong around 3000 BC. *Coptis chinensis* was firstly described in the ancient Chinese medical book *The Divine Farmer's Herb-Root Classic*. *Coptis chinensis* was used to treat intestinal bacterial infections and antipyretic analgesic for thousands of years ago.

Coptis chinensis also called zhilian, chuanlian, weilian, jizhualian, shanglian, and xuanlian in Chinese history. *Coptis chinensis* was accepted by most physicians, and the Chinese pharmacopoeia also uses *Coptis chinensis* as its official name [1]. *Coptis chinensis* mainly grows in Anhui, Hunan, Sichuan, and Yunnan and has been cultivated in Sichuan since the Ming dynasty, which has a long history of cultivation. Other species of *Coptis chinensis* from different places were used as medicine. However, commodity circulation of wild *Rhizoma coptidis* has not been formed [1]. *Coptis chinensis* is national three level protection plants at present and majorly produced in Shizhu of Chongqing, West Hubei, Shanxi, and Gansu.

Berberine is a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids. It is found in some plants such as huanglian 黄连 (*Rhizoma coptidis*), huangbo黄柏 (*Phellodendri Chinensis Cortex*), sankezhen三颗针 (*Berberidis Radix*), and so on.

The components of *Coptis chinensis* which have antibacterial and anti-inflammatory effects are original alkaloid berberine class, including berberine, coptisine, palmatine, epiberberine, columbamine, jatrorrhizine, worenine, and magnoflorine, with berberine having the highest content (5–8%).

History of R&D

Berberine is often used in the form of quaternary ammonium alkali. The solubility of berberine in water is lower, for example, berberine hydrochloride is 1:500, and berberine sulfate is 1:30. In 1926, berberine was first separated from bark of *Zanthoxylum clava*. Modern pharmacology study showed that berberine has defined structure and is a monomer of traditional Chinese medicine. Berberine can be obtained from many sources and is used in clinics, with reliable pharmacological effects and various and unique mechanisms.

Berberine sulfate injection was created by Sichuan medical pharmaceutical factory in1958, but the intramuscular dose is too low and cannot achieve intravenous bacteriostatic concentration; at the same time, intravenous injection of berberine can induce Adams-Stokes syndrome and kidney failure. The injection was eliminated because the curative effect was not accurate and was replaced by other products by the Ministry of Public Health of China on September 4, 1982 [2].

At present, berberine can be synthesized by industrial biosynthesis. A series of derivatives can also be synthesized by structure modification, and the pharmacological activities of these derivatives have been tested. A lot of information of structure-activity relationship was obtained. These results indicated that berberine derivatives had many pharmacological activities, such as anti-Alzheimer's disease, antibacterial, antitumor, and antiviral [3]. The berberine derivatives included tetrahydroberberine, dihydrogen isoquinoline berberine, four hydrogen isoquinoline berberine, and phenethylamine berberine. The derivatives of berberine have many kinds of biological activity through a variety of targets. However, none of them was approved as a drug.

Pharmacology

Berberine hydrochloride has extensive pharmacological effects, such as antibacterial, antiviral, anti-inflammatory, analgesic, anticancer, hyperglycemic, antilipidemic, antihypertension, anti-arrhythmic, anti-heart failure, and so on. Experimental study and clinical reports demonstrate that berberine has therapeutic effect on the endocrine system, circulatory system, nervous system, digestive system, and respiratory system and other diseases.

The clinical indication of berberine is intestinal bacterial infectious diarrhea, which is confirmed by years of clinical application. Berberine hydrochloride exerts effect on intestinal infection, eye conjunctivitis, and suppurative otitis media induced by *Shigella dysenteriae*, *Escherichia coli*, and *Staphylococcus aureus* and ameliorates gastritis and combined gastric and duodenal ulcers. Berberine hydrochloride also has curative effect on acute lung injury, pneumonia, and other respiratory diseases; peptic ulcer, colitis, and other digestive system diseases; pregnancy, urinary, and reproductive system infections; and other urinary tract and reproductive system diseases.

Recent research found that berberine has many pharmacological effects. However, it wasn't approved as drug. Berberine (560 mg/kg/day, 7 days) reduced body weight and caused a significant improvement in glucose tolerance without altering food intake in db/db mice. Similarly, berberine (80 mg/kg/day, for 2 weeks, i.g.) reduced body weight and plasma triglycerides and improved insulin action in high-fat-fed Wistar rats. Berberine downregulated the expression of genes involved in lipogenesis and upregulated those involved in energy expenditure in adipose tissue and muscle. Berberine (5 μg/L) treatment resulted in increased AMP-activated protein kinase (AMPK) activity in 3T3-L1 adipocytes and L6 myotubes, increased GLUT4 translocation in L6 cells in a phosphatidylinositol 3′ kinase–independent manner, and reduced lipid accumulation in 3T3-L1 adipocytes [4].

In cultured human liver cells, berberine (7.5 μg/ml) enhanced the identification of insulin receptor (InsR) messenger RNA (mRNA) and protein expression in a dose- and time-dependent manner. Berberine increased InsR expression in the L6 rat skeletal muscle cells as well. Berberine induced InsR gene expression through a protein kinase C (PKC)-dependent activation of its promoter. Inhibition of PKC abolished berberine-caused InsR promoter activation and InsR mRNA transcription. In animal models, treatment of type 2 diabetes mellitus rats with berberine (75 or 150 mg/kg/day, twice a day, 2 weeks) lowered fasting blood glucose and fasting serum insulin, increased insulin sensitivity, and elevated InsR mRNA as well as PKC activity in the liver [5].

Berberine hydrochloride has antilipidemic, antihypertensive, anti-arrhythmic, anti-heart failure, antiplatelet aggregation, and other cardiovascular system effects. In patients with hyperlipidemia taking berberine (0.5 g each time, twice a day, for 3 months), cholesterol was decreased by 29%, triglyceride was decreased by 35%, and low-density lipoprotein was decreased by 25% [6], the mechanism of which includes raising liver low-density lipoprotein receptor, reducing the synthesis of triglyceride and cholesterol and inhibiting adipocyte differentiation. The mechanism of antihypertensive is to block alpha receptors, causing vasodilatation and enhancing stimulation of acetylcholine receptors.

Berberine plays a role in blood lipid regulation. Berberine significantly upregulates the expression of low-density lipoprotein receptor (LDLR) in hepatocytes in vitro. Further studies have shown that berberine plays a role at posttranscriptional levels through the activation of cells outside the extracellular signal-regulated kinase, and the mechanism is totally different from statin. Clinical applications showed that curative effect of berberine used in the treatment of hyperlipidemia patients was good, and security of berberine in treating patients with liver dysfunction is good without the side effects of statins. The results of the study were confirmed by many European and American research institutes and hospitals, which made berberine a promising drug for reducing cholesterol.

A low (25 mg/kg per day) or a high dose of berberine (100 mg/kg per day) were administered in a 2-month-old TgCRND8 mice by oral gavage until 6 months old, and the treatment significantly ameliorated learning deficits, long-term spatial memory retention, as well as plaque load [7]. Berberine ameliorates β-amyloid pathology, hyperphosphorylation of tau, the formation of tangles, and anti-

inflammatory, antioxidant, and inhibiting activities of AchE and MAO via the PI3K/AKT/GSK3 signaling pathway.

Berberine has drawn more attention for its antineoplastic effects. It can suppress the growth of a wide variety of tumor cells, such as in ovarian cancer, endometrial cancer, cervical cancer, breast cancer, lung cancer, liver cancer, colorectal cancer, renal carcinoma, bladder cancer, and prostatic cancer. The mechanisms included inducing cell apoptosis, affecting the activity of COX-2 and NF-κB, suppressing the production of PGE2 and expression of IL-8, inhibiting the activity of telomerase, downregulating bcl-2 expression, and upregulating bax expression.

Similar compounds as berberine contains jatrorrhizine, coptisine, palmatine, and other isoquinoline alkaloids, which all have quaternary ammonium groups. The main pharmacological effects include antibacterial, antiviral, antifungal, anti-inflammatory, antipyretic and analgesic, anticancer, hypoglycemic, lipid-lowering, blood pressure-lowering, anti-arrhythmic, and anti-heart failure.

Bioavailability of berberine is low, and is not easy to be absorbed after oral administration. Absorption rate of the intestinal wall is only 5%, and intestinal p-glycoprotein can increase the efflux effect of alkaloids [8]. After the injection berberine immediately distribute to various organs and tissues, but the concentration of plasma was maintained for a short time. The concentration of plasma of berberine after intramuscular injection is lower than the minimum bacteriostatic concentration. Drug distribution is wide, and the concentration in the heart, bone, lung, and liver is high. Retention time in tissues is short, most of the drugs were metabolized and cleared after 24 h, and the drug that exits the body unchanged only accounts less than 5% of dosage. In the atrioventricular model in rats, the non-conjunction type of berberine active transport to bile, metabolized by p450 enzyme system in the liver, the first stage is demethylation, and the second stage is glucosidation. In a rat model, four main metabolites are all glucuronide, such as berberrubine, thalifendine, demethyleneberberine, and jatrorrhizine.

Clinical Application

Rhizoma coptidis, as the digestive tract disease medication, has a history of more than 3000 years in China and India. Berberine, as a cathartic nonprescription drug, is mainly used in the treatment of intestinal infection clinically. Clinical research showed that berberine has hypoglycemic effect and has very good prevention and treatment for diabetic patients with complications such as hypertension, hyperlipidemia, thrombosis, and inflammation.

There are few oral side effects of berberine hydrochloride, accidentally appears nausea, vomiting, rash, and fever, which can disappear after withdrawal of drug. In patients with hemolytic anemia and lack of glucose-6-phosphate dehydrogenase, it was forbidden to be used. Berberine if used intravenously is toxic, but is only suitable for oral drug delivery [9].

Discussion

Berberine hydrochloride has extensive pharmacological activity and therapeutic effects for each system diseases in clinic. At the same time, berberine has been widely used as a medicine source which has the advantages of low cost, less adverse reaction, and the value of popularization and application, but the mechanism of berberine is still not clear. In recent years, researches were mainly focused on antitumor, Alzheimer's disease, diabetes, and cardiovascular complications. But at present, the study on antitumor mechanism of berberine is confined to the cellular and molecular level of modern medicine. In the future, it is necessary for research to focus on its structural optimization, mechanism of action, or targets of the research around the above three aspects, and a large number of long-term clinical studies are needed to further confirm the role of the clinical treatment process and curative effects of berberine hydrochloride.

Fig. 1 *Coptis chinensis*

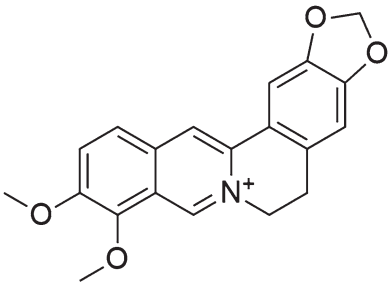

Fig. 2 Chemical structure of berberine

References

1. Zhao BL, Liu XY. Literatures of rhizoma coptidis. J Chin Med Mater. 2013;36(5):832–5.
2. Editorial office of Chinese journal of hospital pharmacy. Answers to questions about the drug elimination. Chin J Hosp Pharm. 1983;3(4):187–8.
3. Huang ZJ, Zeng Y, Lan P, et al. Advances in structural modifications and biological activities of berberine: an active compound in traditional Chinese medicine. Mini Rev Med Chem. 2011;11(13):1122–9.
4. Lee YS, Kim WS, Kim KH, et al. Berberine, a natural plant product, activates AMP-activated protein kinase with beneficial metabolic effects in diabetic and insulin-resistant states. Diabetes. 2006;55(8):2256–64.
5. Kong WJ, Zhang H, Song DQ, et al. Berberine reduces insulin resistance through protein kinase C-dependent up-regulation of insulin receptor expression. Metabolism. 2009;58(1):109–19.
6. Kong W, Wei J, Abidi P, et al. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat Med. 2004;10(12):1344–51.
7. Durairajan SS, Liu LF, Lu JH, et al. Berberine ameliorates β-amyloid pathology, gliosis, and cognitive impairment in an Alzheimer's disease transgenic mouse model. Neurobiol Aging. 2012;33(12):2903–19.
8. Pan GY, Wang GJ, Liu XD, et al. The involvement of p-glycoprotein in berberine absorption. Pharmacol Toxicol. 2002;91(4):193–7.
9. Qiu F, Zhu Z, Kang N, et al. Isolation and identification of urinary metabolites of berberine in rats and humans. Drug Metab Dispos. 2008;36(11):2159–65.