

Berberis aquifolium (Oregon grape)



Berberine

Description

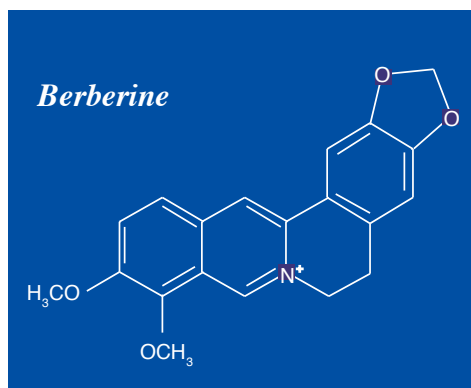
Berberine is a plant alkaloid with a long history of medicinal use in both Ayurvedic and Chinese medicine. It is present in many plants, including *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (Coptis or goldenthrum), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), and *Berberis aristata* (tree turmeric). Berberine can be found in the root, rhizome, and stem bark of the plants. Berberine extracts and decoctions have demonstrated significant antimicrobial

activity against a variety of organisms, including bacteria, viruses, fungi, protozoans, helminths, and chlamydia. Currently, the predominant clinical uses of berberine include bacterial diarrhea, intestinal parasite infections, and ocular trachoma infections.¹

Mechanisms of Action

The pharmacologic actions of berberine include metabolic inhibition of certain organisms, inhibition of bacterial enterotoxin formation, inhibition of intestinal fluid accumulation and ion secretion, inhibition of smooth muscle contraction, reduction of inflammation, platelet aggregation inhibition, platelet count elevation in certain types of thrombocytopenia, stimulation of bile and bilirubin secretion, and inhibition of ventricular tachyarrhythmias.^{1,2}

In vitro studies utilizing human cell lines demonstrate berberine inhibits activator protein 1 (AP-1), a key transcription factor in inflammation and carcinogenesis.³ In another study utilizing human peripheral lymphocytes, berberine exerted a significant inhibitory effect on lymphocyte transformation; the authors concluded berberine's anti-inflammatory action might



be due to inhibition of DNA synthesis in activated lymphocytes.⁴ A third study noted that during platelet activation in response to tissue injury, berberine had a direct effect on several aspects of the inflammatory process, which include dose-dependent inhibition of arachidonic acid release from cell membrane phospholipids, inhibition of thromboxane A2 from platelets,⁵ and inhibition of thrombus formation.⁶

Berberine has demonstrated a number of other beneficial effects, including immunostimulation via increased blood flow to the spleen, macrophage activation, elevation of platelet counts in cases of primary and secondary thrombocytopenia, and increased excretion of conjugated bilirubin in experimental hyperbilirubinemia.¹ In addition, berberine may possess anti-tumor properties as evidenced by inhibition of COX-2 transcription and N-acetyltransferase activity in colon and bladder cancer cell lines,^{7,8} and transient, but marked, inhibitory action on the growth of mouse sarcoma cells in culture.⁹

Clinical Applications

Bacterial Diarrhea

Diarrhea caused by *Vibrio cholera* and *Escherichia coli* has been the focus of numerous berberine studies, and results indicate several mechanisms that may explain its ability to inhibit bacterial diarrhea. An animal study found berberine reduced the intestinal secretion of water and electrolytes induced by cholera toxin.¹⁰ Other studies have shown berberine directly inhibits some *V. cholera* and *E. coli* enterotoxins,¹¹ significantly reduces smooth muscle contraction and intestinal motility,² and delays intestinal transit time in humans.¹² Berberine sulfate has also been found to be directly bacteriocidal to *V. cholera*.¹³ In the case of *E. coli*, *in vitro* research indicates berberine sulfate inhibits bacterial adherence to mucosal or epithelial surfaces, the first step in the infective process. This may be a result of berberine's inhibitory effect on fimbrial structure formation on the surface of the bacteria.¹⁴

Intestinal Parasites

Berberine extracts and salts have demonstrated growth inhibition of *Giardia lamblia*, *Entamoeba histolytica*, *Trichomonas vaginalis*,¹⁵ and *Leishmania donovani*,¹⁶ with crude extracts being more effective than berberine salts.¹⁷

In tropical climates *Giardia lamblia* infestation (giardiasis) is a common occurrence, particularly in pediatric populations.¹⁸ In clinical trials conducted in India, berberine administration improved gastrointestinal symptoms and resulted in a marked reduction in *Giardia*-positive stools. In comparison to metronidazole (Flagyl®), a popular giardiasis medication, berberine was nearly as effective at half the dose.¹⁹

Both *in vivo* and *in vitro* studies of berberine's effects on *E. histolytica* indicated berberine sulfate was amoebicidal and caused encystation, degeneration, and eventual lysis of the

trophozoite forms.²⁰ Berberine sulfate inhibited the growth of *Trichomonas vaginalis* via formation of large autophagic vacuoles that eventually result in lysis of the trophozoite forms.¹⁵

Studies show berberine markedly decreases parasitic load and rapidly improves hematologic parameters in infected animals. *In vitro* results indicate berberine inhibits multiplication, respiration, and macromolecular biosynthesis of amastigote forms of the parasite, interferes with nuclear DNA of the promastigote form, and inhibits organism maturation.¹⁶

Ocular Trachoma Infections

A clinical study of aqueous berberine versus sulfacetamide for the treatment of *Chlamydia trachomatis* infection was conducted on 51 subjects in an outpatient eye clinic. It was determined that while sulfacetamide eye drops produced slightly better clinical results, conjunctival scrapings of these patients remained positive for the infective agent, and relapses occurred. In contrast, the conjunctival scrapings of patients receiving berberine chloride eye drops were negative for *C. trachomatis* and there were no relapses, even one year after treatment. It was also concluded that, while berberine chloride had no direct anti-chlamydial properties, it seemed to cure the infection by stimulating some protective mechanism in the host.²¹ A second clinical study found berberine chloride superior to sulfacetamide in both the clinical course of trachoma and in achieving a drop in serum antibody titers against *C. trachomatis*.²²

Hypertension and Arrhythmias

Clinical trials and animal research indicate berberine administration prevents ischemia-induced ventricular tachyarrhythmia, stimulates cardiac contractility, and lowers peripheral vascular resistance and blood pressure.^{23,24} The mechanism for berberine's antiarrhythmic effect is unclear, but an animal study indicated it might be due to suppression of delayed after-depolarization in the ventricular muscle.²⁵ An animal study suggested, in addition to affecting several other parameters of cardiac performance, berberine might have a vasodilatory/hypotensive effect attributable to its potentiation of acetylcholine.²³

Side Effects and Toxicity

Berberine is not considered toxic at doses used in clinical situations, nor has it been shown to be cytotoxic or mutagenic. Side effects can result from high dosages and may include gastrointestinal discomfort, dyspnea, lowered blood pressure, flu-like symptoms, and cardiac damage.

Dosage

The therapeutic dosage for most clinical situations is 200 mg orally two to four times daily.¹

Warnings and Contraindications

Berberine usage should be avoided in pregnancy, due to potential for causing uterine contractions and miscarriage, and in jaundiced neonates because of its bilirubin displacement properties.

References

1. Birdsall TC, Kelly GS. Berberine: Therapeutic potential of an alkaloid found in several medicinal plants. *Altern Med Rev* 1997;2:94-103.
2. Akhter MH, Sabir M, Bhide NK. Possible mechanism of anti-diarrhoeal effect of berberine. *Indian J Med Res* 1979;70:233-241.
3. Fukuda K, Hibiya Y, Mutoh M, et al. Inhibition of activator protein 1 activity by berberine in human hepatoma cells. *Planta Med* 1999;65:381-383.
4. Ckless K, Schlottfeldt JL, Pasqual M, et al. Inhibition of *in vitro* lymphocyte transformation by the isoquinoline alkaloid berberine. *J Pharm Pharmacol* 1995;47:1029-1031.
5. Huang CG, Chu ZL, Yang ZM. Effects of berberine on synthesis of platelet TXA2 and plasma PGI2 in rabbits. *Chung Kuo Yao Li Hsueh Pao* 1991;12:526-528.
6. Wu JF, Liu TP. Effects of berberine on platelet aggregation and plasma levels of TXB2 and 6-keto-PGF1 alpha in rats with reversible middle cerebral artery occlusion. *Yao Hsueh Hsueh Pao* 1995;30:98-102.
7. Lin JG, Chung JG, Wu LT, et al. Effects of berberine on arylamine N-acetyltransferase activity in human colon tumor cells. *Am J Chin Med* 1999;27:265-275.
8. Fukuda K, Hibiya Y, Mutoh M, et al. Inhibition by berberine of cyclooxygenase-2 transcriptional activity in human colon cancer cells. *J Ethnopharmacol* 1999;66:227-233.
9. Creasey WA. Biochemical effects of berberine. *Biochem Pharmacol* 1979;28:1081-1084.
10. Swabb EA, Tai YH, Jordan L. Reversal of cholera toxin-induced secretion in rat ileum by luminal berberine. *Am J Physiol* 1981;241:G248-G252.
11. Sack RB, Froelich JL. Berberine inhibits intestinal secretory response of *Vibrio cholera* and *Escherichia coli* enterotoxins. *Infect Immun* 1982;35:471-475.
12. Yuan J, Shen XZ, Zhu XS. Effect of berberine on transit time of human small intestine. *Chung Kuo Chung Hsi I Chieh Ho Tsa Chih* 1994;14:718-720.
13. Amin AH, Subbaiah TV, Abbasi KM. Berberine sulfate: antimicrobial activity, bioassay, and mode of action. *Can J Microbiol* 1969;15:1067-1076.
14. Sun D, Abraham SN, Beachey EH. Influence of berberine sulfate on synthesis and expression of Pap fimbrial adhesin in uropathogenic *Escherichia coli*. *Antimicrob Agents Chemother* 1988;32:1274-1277.
15. Kaneda Y, Torii M, Tanaka T, Aikawa M. *In vitro* effects of berberine sulfate on the growth and structure of *Entamoeba histolytica*, *Giardia lamblia*, and *Trichomonas vaginalis*. *Ann Trop Med Parasitol* 1991;85:417-425.
16. Ghosh AK, Bhattacharyya FK, Ghosh DK. *Leishmania donovani*: amastigote inhibition and mode of action of berberine. *Exp Parasitol* 1985;60:404-413.
17. Kaneda Y, Tanaka T, Saw T. Effects of berberine, a plant alkaloid, on the growth of anaerobic protozoa in axenic culture. *Tokai J Exp Clin Med* 1990;15:417-423.

18. Nair KP. Giardiasis in children. *Pediatric Clinics India* 1970;5:45.
19. Choudhry VP, Sabir M, Bhide VN. *Indian Pediatrics* 1972;9:143-146.
20. Subbaiah TV, Amin AH. Effect of berberine sulphate on *Entamoeba histolytica*. *Nature* 1967;215:527-528.
21. Babbar OP, Chhatwal VK, Ray IB, Mehra MK. Effect of berberine chloride eye drops on clinically positive trachoma patients. *Indian J Med Res* 1982;76:S83-S82.
22. Khosla PK, Neeraj VI, Gupta SK, Satpathy G. Berberine, a potential drug for trachoma. *Rev Int Trach Pathol Ocul Trop Subtrop Sante Publique* 1992;69:147-165.
23. Chun YT, Yip TT, Lau KL, Kong YC. A biochemical study on the hypotensive effect of berberine in rats. *Gen Pharmac* 1978;10:177-182.
24. Marin-Neto JA, Maciel BC, Secches AL, Gallo L. Cardiovascular effects of berberine in patients with severe congestive heart failure. *Clin Cardiol* 1988;11:253-260.
25. Wang YX, Yao XJ, Tan YH. Effects of berberine on delayed afterdepolarizations in ventricular muscles *in vitro* and *in vivo*. *J Cardiovasc Pharmacol* 1994;23:716-722.