Berberine: Therapeutic Potential of an Alkaloid Found in Several Medicinal Plants

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Abstract

Berberine-containing plants are used medicinally in virtually all traditional medical systems, and have a history of usage in Ayurvedic and Chinese medicine dating back at least 3,000 years. Berberine has demonstrated significant antimicrobial activity against bacteria, fungi, protozoans, viruses, helminths and chlamydia. In addition, berberine's actions include: antagonism of the effects of cholera and E. coli heat-stable enterotoxin, inhibition of intestinal ion secretion, inhibition of smooth muscle contraction, inhibition of ventricular tachyarrhythmias, reduction of inflammation, elevation of platelet count in patients with primary and secondary thrombocytopenia, and stimulation of bile secretion and bilirubin discharge. Berberine's most common clinical uses include: bacterial diarrhea, intestinal parasites, and ocular trachoma infections. Evidence also suggests intravenous berberine administration can play a role in preventing the onset of reentrant ventricular tachyarrhythmias and sudden coronary death after myocardial ischemic damage.

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Berberine is an alkaloid present in a number of clinically-important medicinal plants, including *Hydrastis canadensis* (goldenseal), *Coptis chinensis* (coptis or goldenthread), *Berberis aquifolium* (Oregon grape), *Berberis vulgaris* (barberry), and *Berberis aristata* (tree turmeric) (See Table 1 for a list of these plants and the part used medicinally). Extracts and decoctions of these plants have been used in Ayurvedic and Chinese medicine for at least 3000 years. Berberine has been shown to exhibit significant antimicrobial activity against a variety of bacteria,[1-7] fungi,[1,8,9] protozoans,[1,10-16] helminths,[17] chlamydia,[18-20] and viruses.[21] In addition to this antimicrobial activity, berberine has been found to have numerous pharmacological effects.

Amin et al screened a total of 54 microorganisms for sensitivity to berberine, and found the alkaloid possesses antimicrobial activity against gram-positive and gram-negative bacteria, fungi, and protozoa (see Table 2). In addition to those listed, *Mycobacterium tuberculosis*, *Trichophyton mentagrophytes*, and some strains of *Escherichia coli*, *Klebsiella pneumoniae*, and *Cryptococcus neoformans* exhibited moderate sensitivities. Berberine has been shown to inhibit HIV-1 reverse transcriptase.[21]

Bacterial Diarrhea

Much of the research on berberine has focused on its use in cases of diarrhea, including that caused by *Vibrio cholerae*[1-4] and *Escherichia coli*.[2,3,5,6] Studies have demonstrated a direct antibacterial effect of berberine against *V. cholerae*,[1] and berberine has been shown to inhibit the intestinal secretory response caused by *E. coli* heat-stable enterotoxin (ST)[22] and *V. cholerae*

Table 1. Selected Berberine-Containing Plants and Part of Plant Used Medicinally

Latin Name	Common Name	Part Used
Berberis aquifolium	Oregon Grape	Rhizome, Roots
Berberis aristata	Tree Turmeric	Root
Berberis vulgaris	Barberry	Outer Bark of Stem, Root
Coptis chinensis	Coptis or Goldenthread	Rhizome
Hydrastis canadensis	Goldenseal	Rhizome, Root

enterotoxins.[2-4] In addition to its direct antimicrobial action, berberine has also been shown to block the adherence of *Strep. pyogenes*[6] and *E. coli*[7] to erythrocytes and epithelial cells. Thus, it is possible berberine exerts an antibiotic effect, even against organisms that do not exhibit *in vitro* sensitivity to the alkaloid.

A series of 63 adult males with enterotoxigenic *E. coli* (ETEC) diarrhea of similar clinical characteristics were serially assigned to either an experimental group or a control group by use of a random number table. Thirty-three people were given a single dose of 400 mg berberine sulfate (BS) orally. The control group received no treatment. Both groups received IV rehydration therapy, and were observed for a period of 24 hours. During the total observation period, the experimental group had a 48% reduction in mean stool volumes compared with the controls ($p<0.05$). Also, when compared with the control group, significantly more of those receiving BS stopped having liquid diarrheal stools during the observation period (42% vs. 20%, $p<0.05$).[2]

Berberine has been shown to inhibit the intestinal secretory response due to cholera toxins. Using a ligated rabbit intestinal loop model, Sack and Froehlich[3] were able to demonstrate a significant suppression of the intestinal secretory response following exposure to *V. cholerae* crude enterotoxin. This effect was similar whether the berberine was administered immediately prior to the cholera toxin, or as long as four hours after exposure ($p<0.02$), and did not require direct mucosal contact to be effective. In discussing their results, the authors note, "...it is also of clinical importance the berberine has not been reported to have significant side effects at the doses used clinically in humans (5 to 10 mg/kg per day orally)..."[3]

In patients with cholera, analysis by factorial design equations revealed a reduction in diarrheal stools by one liter and a reduction in cyclic adenosine monophosphate concentrations in stools by 77% in the groups given berberine.[23] In other studies of diarrhea due to *Vibrio cholerae* and ETEC, berberine (200 mg) reduced stool volumes 30-50% in diarrheal patients without significant side effects.[24] Berberine's effectiveness in reducing

Chemical Structure of Berberine

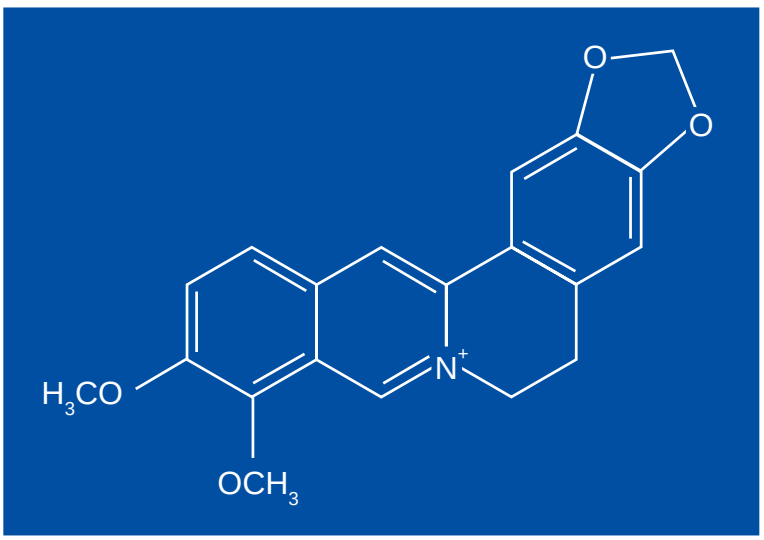

Table 2. Microorganisms Sensitive In Vitro To Berberine[1,9,10,13,14]

Bacillus pumilus
B. cereus
B. subtilis
Corynebacterium diphtheriae
Shigella boydii
Staphylococcus aureus
S. albus
Streptococcus pyogenes
Vibrio cholerae
Candida utilis
C. albicans
C. tropicalis
C. glabrata
Sporotrichum schenkii
Entamoeba histolytica
Giardia lamblia
Trichomonas vaginalis
Leishmaniasis sp.

water and electrolyte secretions induced by ST and cholera toxin appear to be enhanced in a dose-dependent manner.[3,5]

While the precise mechanism of action of berberine remains to be elucidated, in addition to the direct bacteriocidal action, several other mechanisms may account for its ability to inhibit infectious diarrhea. Metabolic inhibition of certain organisms,[1] inhibition of the formation of toxins, direct antagonism of the toxins,[25] inhibition of intestinal ion secretion, [26,27] and inhibition of smooth muscle contraction[27-29] may all play a role in this plant extract's antidiarrheal activity.

The antidiarrheal properties of berberine may be mediated, at least in part, by its ability to delay small intestinal transit time.[30-32] Berberine has been shown to block muscarinic receptors [33] and to exhibit a noncompetitive inhibition of the contractile response induced by acetylcholine, thus acting to inhibit spontaneous peristalsis in the intestine.[34] In animal studies, the transit of the small intestine was significantly delayed at 15 and 100 minutes after the highest doses of BS.[31] In humans, 1.2 grams of berberine significantly delayed small intestine transit time after an oral dose.[32]

Intestinal Parasites

Berberine sulfate has been shown to possess growth inhibitory activity against *Giardia lamblia, Trichomonas vaginalis*, and *Entamoeba histolytica* in axenic culture.[13] It was observed the crude extract was more effective than the salt. The greater inhibitory activity of the crude extract may be due to the cumulative contributions of berberine along with other alkaloids and pharmacologically active constituents.[12]

Subbaiah and Amin reported that BS was effective against the protozoan *Entamoeba histolytica* in a study that evaluated both *in vitro* and *in vivo* outcomes. *In vitro* testing indicated berberine "...is amebicidal at a concentration of 0.5-1.0 mg/ml, and that it acts rapidly." After addition of berberine, morphological changes could be observed in the trophozoites, including encystation, degeneration, and lysis. Preliminary results also indicated berberine may be cysticidal as well.[10]

Golden hamsters were given either 3 or 5 mg/kg body weight of BS orally three times at 4-hour intervals. The initial dose was given prior to intrahepatic infection with *E. histolytica*, the second at the time of infection, and the third 4 hours later. At 5 mg/kg, 100% of the animals showed normal livers upon necropsy four days later with no trophozoites found, while at 3 mg/kg, 33% showed small hepatic abscesses. In the control group, 75% of the animals demonstrated liver abscesses with trophozoites. Similar results were found in rats infected with *E. histolytica* via the intestinal tract, where the control group developed intestinal amebiasis while the berberine group did not.[10]

Giardia lamblia, another common protozoan infecting humans, has also been found to be sensitive to berberine. Nearly 20 years ago, Choudhry et al reported on 40 children (ages 1-10 years) infected with Giardia, who received either B-vitamin syrup (which they termed "a placebo"), berberine (5 mg/kg/day) or metronidazole (10 mg/kg/day). The substances were administered in three divided doses for 6 days. Following the placebo, 15% of the subjects became symptom-free and 25% demonstrated no Giardia in the stool. After taking berberine, 48% became asymptomatic and 68% were Giardia-free upon stool analysis. All of those receiving metronidazole showed no Giardia remaining, but only 33% of them had resolution of symptoms.[16]

In another study, a total of 137 children (ages 5 months to 14 yr, mean age 5 yr) with documented giardiasis were given either 5 mg/kg/day or 10 mg/kg/day of berberine in divided doses, for a period of either 5 or 10 days. They were then compared with 242 subjects placed on conventional therapy, including 88 who received metronidazole (20 mg/kg/day for 5-7 days). Ninety percent of those receiving berberine (10 mg/kg/day for 10 days) had negative stool specimens after 10 days, and 83% remained negative one month later, which compared favorably with those treated with metronidazole (95% and 90%, respectively). The author concludes by citing berberine's "...convenience of administration and freedom from unpleasant side effects."[11]

In visceral leishmaniasis, berberine has also shown significant effectiveness. One percent BS inoculated intralesionally on four occasions at weekly intervals was found to be highly effective against cutaneous leishmaniasis in domestic dogs.[35] Berberine was evaluated in golden hamsters infected with *L. donovani* amastigotes in two separate trials. In the 8-day model, berberine was administered intraperitoneally at 50 and 100 mg/kg/day for 4 days beginning on the third day following infection, and compared with infected controls. On necropsy, the liver parasite burden was determined: the 50 and 100 mg/kg/day berberine groups showed 0.86 +/- 0.09 and 0.65 +/-0.10 cells x 10^8 respectively, compared with infected controls which showed 1.67 +/- 0.63 cells x 10^8 ($p<0.05$).[15]

In an extended 60-day model, uninfected hamsters, infected controls, and infected animals treated with berberine were observed. The experimental group was administered berberine intraperitoneally (50 mg/kg/day) for 5 days, beginning 1 month after infection. After a five-day interval the berberine course was repeated. Upon evaluation, the berberine group was found to have a reduction in both liver and spleen parasite burden of 90% compared to infected controls ($p<0.001$). In addition, leukocyte counts were normalized: normal hamsters = 9343 +/- 1627; infected controls = 2862 +/- 534; berberine group = 7112 +/- 13.7 cells/mm3 ($p<0.001$). "*In vivo*, berberine was found to be as effective as pentamidine and had the advantage of being better tolerated."[15]

Ocular Trachoma Infections

Aqueous solutions of berberine have also been employed in cases of ocular infections, especially those resulting from *Chlamydia trachomatis*.[18-20] Fifty-one people attending an out-patient eye clinic having stage I or stage II trachoma lesions were recruited into the study. Subjects were divided into three groups: Group I received 0.2% berberine chloride eye drops, 2 drops per eye 3 times daily for 3 weeks; Group II received eye drops containing 0.2% berberine chloride plus 20% sulfacetamide according to the same schedule; Group III received eye drops containing only 20% sulfacetamide.

After 3 weeks, subjects in Group III had a slightly better clinical improvement as judged by conjunctival congestion, number of

follicles and papillary reaction. The conjunctival scrapings of all subjects in Group III still tested positive for *C. trachomatis*, and these subjects were likely to have a relapse of symptoms. Subjects in Groups I and II showed a significant improvement in symptoms compared to their initial examination, and following the experimental period had only very mild symptoms remaining. All subjects in Groups I and II had conjunctival scrapings which were negative for *C. trachomatis*. Those in Groups I and II had no incidence of relapse up to one year later.[19]

To further determine if these anti-trachoma effects were related to direct anti-chlamydial properties of berberine or to host-mediated factors, a series of *in vitro* and *in vivo* experiments were carried out using chick embryos. Three different *C. trachomatis* isolates were incubated in vitro with 0.2% berberine chloride prior to inoculation into chick embryos. A different set of embryos was initially infected with the *C. trachomatis* isolates, and then subsequently given 3 doses of 0.2% berberine chloride. The *in vitro* incubation of *C. trachomatis* with berberine had no effect in reducing the lesion scores or mortality of the organism, whereas administration of the berberine to infected embryos resulted in elimination of both lesion and mortality. This suggests that, with *C. trachomatis*, berberine's method of action is by "...stimulating some protective mechanism in the host."[19]

The clinical serological response to topical treatment of trachoma with berberine was studied in 32 microbiologically confirmed cases. Efficacy of berberine 0.2% when compared to sulfacetamide 20% was found to be superior in both the clinical course of trachoma and in achieving a fall in serum antibody titers against *Chlamydia trachomatis*.[36]

Cardiovascular Effects

Experimental results in animals and clinical trials in humans suggest intravenous berberine may be effective in preventing the onset of reentrant ventricular tachyarrhythmias and sudden coronary death after myocardial ischemic damage.[37]

In vitro, berberine increases, in a concentration-dependent manner, the action potential duration in canine Purkinje and ventricular muscle fibers without effecting other parameters of the action potential. The authors suggest, "...berberine exerts Class III antiarrhythmic and proarrhythmic actions in cardiac muscle of the dog *in vitro*."[38]

In 18 dogs with ischemic left ventricular failure, berberine was able to improve impaired left ventricular function by its positive inotropic effect and mild systemic vasodilation.[39] Berberine increased coronary artery flow of anesthetized open-chest canines and isolated guinea pig hearts. Rabbits were protected by berberine from ischemic ECG changes caused by posterior pituitary hormones. Spasm of isolated swine coronary arterial rings was prevented and treated effectively by berberine.[40]

In humans, 12 patients with refractory congestive heart failure were studied before and during berberine intravenous infusion at rates of 0.02 and 0.2 mg/kg per min for 30 minutes. The lower infusion dose produced no significant circulatory changes, apart from a reduction in heart rate (14%). The 0.2 mg/kg per min dose elicited several significant changes. A 48% decrease in systemic and a 41% decrease in pulmonary vascular resistance, along with a 28% decrease in right atrium and 32% decrease in left ventricular end-diastolic pressures were observed. Measurable increases in cardiac index (45%), stroke index (45%), and left ventricular ejection fraction (56%) were found. Also noted were increases in hemodynamic and echocardiographic indices of left ventricular performance and a decrease in arteriovenous oxygen uptake (28%) with no changes in total body oxygen uptake, arterial oxygen tension, or hemoglobin dissociation properties.[41]

The effects of berberine on 100 individuals with ventricular tachyarrhythmias observed with 24 to 48 hour ambulatory monitoring has also been reported. The results indicate 62% of patients had 50% or greater, and 38% of patients had 90% or greater suppression of ventricular premature contractions (VPC). No severe side effects were observed; however, mild gastroenterologic symptoms were reported by some patients.[42]

Several mechanisms have been proposed to explain the observed effects of berberine. Zhou observed berberine works as a Ca^{2+} channel agonist,[43] while Hua and Wang suggest the antiarrhythmic action of berberine might be due to its potassium channel blocking effects.[44] Experiments on the rat fundus indicate berberine inhibits the entry of extracellular calcium into the cell.[45] Evidence also suggests berberine, by reducing tyrosine hydroxylase activity, has an inhibitory effect on catecholamine biosynthesis.[46]

Anti-inflammatory

Among berberine's multiple pharmacological actions is anti-inflammatory activity. *In vitro*, a consistent and progressive inhibitory influence of berberine with increasing concentrations was identified with all mitogens and was most pronounced with pokeweed mitogen.[47] Berberine (20 mg/kg/d) inhibited platelet aggregation and platelet adhesion induced by ADP, arachidonic acid, and collagen in rats. The same dose of berberine also inhibited thrombus formation.[48]

Berberine may inhibit the release of arachidonic acid from cell membrane phospholipids and exerts an effect on arachidonic acid metabolites. Berberine dose-dependently inhibits collagen-, ADP-, and arachidonic acid (AA)-induced thromboxane A2 release from platelets. Berberine given intravenously lowers rabbit plasma level of PGI2.[49] While an extract of the bark from *Berberis aquifolium* has been shown to inhibit 5-lipoxygenase with an IC50 value of 50 microM,[50] berberine has not been shown to exert a significant inhibitory effect.[50,51]

In experimental animals, berberine has been shown to reduce the purging effects of castor oil or *Cassia angustifolia* leaf, significantly inhibit drug-induced vascular permeability, and inhibit drug-induced swelling in a dose-dependent manner.[52] Berberine has shown an inhibitory effect against induced ear edema in experimental animals.[53]

Other Effects

Berberine also has other immunostimulatory effects. Sabir and Bhide have reported berberine stimulates blood flow to the spleen.[29] Berberine has been shown to activate macrophages.[54] Berberine sulfate has demonstrated antipyretic effects in experimentally-induced fevers in rats. This effect has been found to be approximately three times greater than the antipyretic effect of sodium salicylate.[55]

In vitro, experimental, and clinical results indicate that berberine is an excellent disinfectant for infective deciduous root canal.[56] Because of its ability to block adhesion of *E. coli* and to suppress synthesis and assembly of fimbriae by uropathogenic organisms, berberine may be beneficial in *E. coli*-induced urinary tract infections.[6]

Berberine sulfate, given as monotherapy and in combined treatment 3 times a day for 15 days in a dose of 5 mg 20 minutes before meals, increases platelet count in patients with primary and secondary thrombocytopenia.[57]

Results indicate berberine has antinephritic effects partly due to antiplatelet action and improved renal hemodynamics. Berberine at doses of 0.5, 1.0 and 5.0 mg/kg/day, i.p., was effective in inhibiting urinary protein excretion, elevation of serum

cholesterol and creatinine levels, and glomerular histopathological changes. In addition, berberine given orally at 20 mg/kg/day inhibited urinary protein excretion throughout the experimental periods. Berberine inhibited platelet aggregation in both *in vitro* and *in vivo* assays, and inhibited the decline of renal blood flow. Berberine also inhibited an increase in thromboxane B2 formation, and increased the formation of 6-keto-prostaglandin F1 alpha in platelets and isolated glomeruli.[58]

The excretion of bilirubin has been found to be stimulated by the acute administration of berberine, although the effect diminished with chronic administration.[59] Berberine, *in vitro*, has been shown to be a potent displacer of bilirubin. *In vivo* administration of berberine to adult rats resulted in a significant decrease in mean bilirubin serum protein binding, due to a displacement effect and a persistent elevation in steady-state serum concentrations of unbound and total bilirubin, possibly due to inhibition of metabolism.[60]

The accumulation of tyramine and its derivatives in individuals with cirrhosis is associated with lowered peripheral resistance, high cardiac output, reduced renal function, and cerebral dysfunction. Berberine (600-800 mg/day) was shown to correct the hypertyraminemia in patients with liver cirrhosis, thus indicating its possible use as an adjunctive supplement.[61]

Experimental evidence suggests berberine increases the concentration of polar drugs in the skin when applied concurrently as a topical preparation; it also enhances skin permeation in a manner similar to surfactants.[62]

Dosage and Toxicity

Berberine is generally considered to be nontoxic at doses used in clinical situations. Berberine shows no genotoxic activity; is unable to induce significant cytotoxic, mutagenic or recombinogenic effects; and it is not a potent mutagenic agent in dividing cells.[63] The LD_{50} of berberine sulfate in mice is approximately 25 mg/kg, while intravenous administration of berberine to dogs at doses up to 45 mg/kg does not produce gross toxic effects.[29] High doses of berberine can result in the following side effects: lowered blood pressure, dyspnea, flu-like symptoms, gastrointestinal discomfort, and cardiac damage. Most berberine-containing plants are considered uterine stimulants or emmenogogues, so historically it has been recommended they be used with care during pregnancy. Because of these considerations and because of berberine's ability to displace bilirubin, the use of berberine should be avoided in pregnant women, as well as jaundiced neonates.

The therapeutic dose of berberine for conditions responsive to oral supplementation is typically 200 mg two to four times daily.

Summary

Berberine-containing plants have been used in traditional and folk medicine around the world for centuries. Many of these uses have centered around conditions caused by various micro-organisms, including bacteria and parasites. Current scientific research has not only validated these historic applications, but also provided valuable insight into the mechanisms by which this alkaloid acts on organisms and tissues. Because of the wide variety of pharmacologic actions of berberine, it is likely future research will identify other clinical conditions which are responsive to supplementation of berberine-containing plants or with the alkaloid berberine.

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