

# Goldenseal

*Hydrastis canadensis* L.

[Fam. *Ranunculaceae*]

## OVERVIEW

Goldenseal is ranked among the top herbal supplements sold in natural food stores in the U.S. and is often combined with echinacea. In 2000, sales of goldenseal ranked 12th in the natural food trade. In 1998, sales of products that contain both goldenseal and echinacea ranked fifth in mainstream stores at \$69.7 million. Despite goldenseal's popularity, clinical studies have been conducted only on its alkaloid, berberine. The fact that goldenseal is not widely used in Europe may account for the lack of clinical research. Goldenseal's medicinal value is believed to be due primarily to the alkaloidal constituents berberine and hydrastine.

## PRIMARY USES

[EDITORS' NOTE: Since there are no published clinical trials scientifically documenting the safe and effective use of goldenseal preparations in humans, despite significant *empirical* data, the editors have refrained from suggesting any primary uses.]

### Berberine

- Diarrhea
- Ocular trachoma infections (external)

## OTHER POTENTIAL USES

### Goldenseal

- Dyspepsia
- Gastritis
- Menorrhagia
- Eyewashes (external, diluted non-alcoholic extracts)

## PHARMACOLOGICAL ACTIONS

Anti-diarrheal; anti-microbial; antiparasitic; decreases systemic and pulmonary vascular resistance and left ventricular end-diastolic pressure; increases stroke index, cardiac index and left ventricular ejection fraction; suppresses ventricular premature contractions (VPC) without severe side effects.

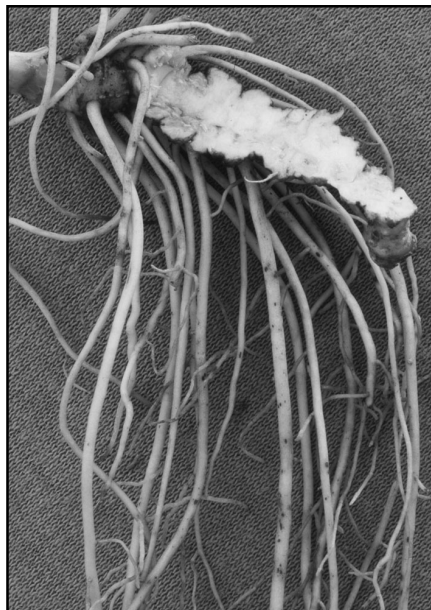


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## DOSAGE AND ADMINISTRATION

It may take up to a few days to a week for the herb to produce benefits.

### Internal

DRIED RHIZOME AND ROOT: 0.5–1.0 g, 3 times daily.

TINCTURE: 2–4 ml [1:10, 60% ethanol].

FLUID EXTRACT: 0.3–1 ml [1:1, 60% ethanol].

### External

EYEWASH: 2 drops in each eye, 3 times daily [0.2% sterile aqueous berberine solution, or aqueous non-alcoholic goldenseal preparation].

## CONTRAINDICATIONS

Goldenseal should not be used in cases of kidney disease, including kidney failure, due to inadequate urinary excretion of its alkaloids. It should be avoided in acute inflammation of the stomach, based on a

case report in which a bitters formula enhanced gastric acid secretions. Contraindicated in cases of jaundice in newborns.

PREGNANCY AND LACTATION: Not for use during pregnancy. Berberine can increase bilirubin in neonates, possibly leading to neonatal jaundice. It may also have uterine stimulant activity. Although there are no known contraindications during lactation, use of goldenseal or berberine during nursing should be avoided until further research has been conducted.

## ADVERSE EFFECTS

At recommended doses, goldenseal is considered nontoxic; berberine has also been well-tolerated in therapeutic doses.

## DRUG INTERACTIONS

Goldenseal can potentially antagonize the anticoagulant activity of heparin. Studies in mice and rats have indicated hemodynamic properties of berberine, including an increase in the number of thrombocytes, decrease in the activity of factor XIII, and the promotion of blood coagulation.

**CLINICAL REVIEW**

Although modern controlled clinical studies on goldenseal are lacking, there have been studies published on one of its principal alkaloids, berberine. Five clinical studies on berberine that included a total of 465 participants all demonstrated positive effects for indications including diarrhea, ocular infections, and cardiovascular conditions, although the safety of cardiac conditions (e.g., ventricular arrhythmias) is not adequately established. Human studies on berberine have shown that it is poorly absorbed from the small intestines, and therefore its antimicrobial action is only locally effective (i.e. in the gut). Since berberine is

excreted in the urine, it may have an antimicrobial effect in the kidneys or urinary tract. In clinical evaluations, berberine has been shown to be efficacious at stimulating bile and bilirubin secretion, improving symptoms of chronic cholecystitis, and normalizing elevated tyramine levels in persons with cirrhosis of the liver. Berberine is reportedly effective as an adjunct to cancer therapy. Clinical studies on berberine have confirmed that it is effective for acute diarrhea. Externally, it has been shown to be useful as an eyewash in treating trachoma, an infectious eye disease.



# Goldenseal

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## OVERVIEW

Goldenseal is ranked among the top herbal supplements sold in natural food stores in the U.S. and is often combined with the herb echinacea (*Echinacea* spp.). In 1998, sales of products that contain both goldenseal and echinacea ranked 5th in mainstream stores at \$69.7 million. In 2000, sales of goldenseal ranked 12th in the natural food trade. Goldenseal's medicinal actions are thought to be due to its primary active constituents, berberine and hydrastine. Goldenseal is often used by consumers for self-medication of upper respiratory tract infections associated with cold and flu although there is no scientific data to support this use.

## PRIMARY USES OF BERBERINE

**Internal**  
Diarrhea

### External

Ocular (eye) trachoma infections (in special preparations usually in developing countries).

## POTENTIAL USES OF GOLDENSEAL

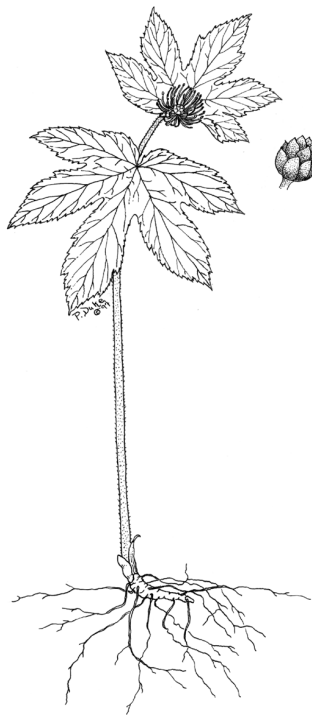
[EDITORS' NOTE: Since there are no published clinical trials scientifically documenting the safe and effective use of goldenseal preparations in humans, despite significant *empirical* data, the editors have refrained from suggesting any primary uses.]

### Internal

Stomach upset (dyspepsia, gastritis).

### External

Eyewashes (using water or glycerine-based, diluted non-alcoholic preparations).



## DOSAGE

**NOTE:** It may take up to a few days to a week for the herb to produce benefits.

**DRIED RHIZOME AND ROOT:** 0.5–1.0 g, 3 times daily.

**TINCTURE:** 2–4 ml [1:10, 60% ethanol].

**FLUID EXTRACT:** 0.3–1 ml [1:1, 60% ethanol].

**EYEWASH:** 2 drops in each eye, 3 times daily [0.2% sterile aqueous (non-alcoholic) berberine solution, or non-alcoholic, water-based goldenseal liquid preparations].

## CONTRAINDICATIONS

Goldenseal should not be used in cases of kidney disease, including kidney failure due to inadequate urinary excretion of its alkaloids. It should be avoided in acute inflammation of the stomach. It is contraindicated in cases of jaundice in newborns.

**PREGNANCY AND LACTATION:** Not for use during pregnancy. Berberine can increase bilirubin in newborn babies, possibly leading to neonatal jaundice. It may have a stimulant effect on the uterus. Although there are no known contraindications during breast-feeding, use of goldenseal and berberine should be avoided during breast feeding until further research has been conducted.

## ADVERSE EFFECTS

At recommended doses, goldenseal is considered nontoxic; berberine has also been well-tolerated in therapeutic doses.

## DRUG INTERACTIONS

Goldenseal may antagonize the anticoagulant (blood-thinning) activity of heparin.

## Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.



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# Goldenseal

*Hydrastis canadensis* L.

[Fam. *Ranunculaceae*]

## OVERVIEW

Goldenseal is ranked among the top herbal supplements sold in natural food stores in the U.S. (Blumenthal *et al.*, 1998) and it is often combined with echinacea (*Echinacea* spp.). In 2000, sales of goldenseal products ranked 12th in the natural food trade (NBJ, 2001). In 1998, sales of products that contain both goldenseal and echinacea, ranked fifth in mainstream stores, at \$69.7 million (Blumenthal, 2001). Despite goldenseal's popularity, clinical studies have been conducted on only one of its principal alkaloids, berberine. Berberine, hydrastine, and related isoquinoline alkaloids are the primary constituents thought responsible for goldenseal's medicinal activity. Goldenseal is not used widely in Europe, and this may be the reason for the lack of clinical research (Tyler, 1998). Ethnomedical use dates to the Cherokee Indians, who used goldenseal root to treat skin diseases and sore or inflamed eyes. The Iroquois used the root for diarrhea, digestion, whooping cough, and pulmonary problems (Foster, 1996; Moerman, 1998). In the latter part of the 19th century, Eclectic physicians used goldenseal preparations primarily for acute or subacute inflammation of the mucous membranes (Felter and Lloyd, 1898), chronic inflammation of the stomach, and atonic dyspepsia associated with alcoholism (Blumenthal, 2001). Goldenseal root was official in the *United States Pharmacopeia* starting from 1860 (Lloyd, 1929), and up to five different preparations were listed in the USP until the 10th revision in 1926 (Boyle, 1991).



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Due to its relatively high price, some “goldenseal” products sold in the U.S. may contain “goldenseal herb”, made with the leaves of the plant containing approximately 10% of the alkaloid levels usually found in the root. Some products have been known to be adulterated with the low cost goldthread root (*Coptis chinensis*) from China, a plant containing significant levels of berberine. Wild goldenseal was named a “threatened” species by CITES

(Convention in Trade in Endangered Species) in 1997, thereby limiting its trade in international commerce (Bannerman, 1997). About 15–30% of domestic supplies of goldenseal are derived from cultivated sources within the U.S. (McGuffin, 1999).

## DESCRIPTION

Goldenseal consists of the root and rhizome of *Hydrastis canadensis* L. [Fam. *Ranunculaceae*]. Its name derives from the seal-like scars on the rhizomes that are yellow or golden in color (Lloyd and Lloyd, 1884–85). The *United States Pharmacopeia* stipulates that the root and rhizome material must contain no less than 2.0% hydrastine and no less than 2.5% berberine (USPF, 2000).

## PRIMARY USES

[EDITORS' NOTE: Since there are no published clinical trials documenting scientifically the safe and effective use of goldenseal preparations in humans, despite significant *empirical* data, the editors have refrained from suggesting any primary uses.]

### Berberine (Pharmaceutical Preparations)

#### Internal

Gastrointestinal

- Diarrhea (Gupte, 1975; Khin *et al.*, 1985; Rabbani *et al.*, 1987)

#### External

Ophthalmic

- Ocular trachoma infections (Babbar *et al.*, 1982; Kholsa *et al.*, 1992; Mohan *et al.*, 1982)

## OTHER POTENTIAL USES

### Goldenseal

#### Internal

Gastrointestinal

- Dyspepsia (Bradley, 1992; Upton, 2001)
- Gastritis (Bradley, 1992)

Gynecology

- Menorrhagia (Bradley, 1992)

#### External

- Eyewashes (Bradley, 1992)

## DOSAGE

### Internal

DRIED RHIZOME AND ROOT: 0.5–1.0 g, 3 times daily (Bradley, 1992).

TINCTURE: (1:10, 60% ethanol), 2–4 ml (Bradley, 1992).

FLUID EXTRACT: (1:1, 60% ethanol), 0.3–1 ml (Bradley, 1992).

### External

EYEWASH: (0.2% sterile aqueous [non-alcoholic] berberine solution) 2 drops are placed in each eye, 3 times daily (Kholsa *et al.*, 1992).

## DURATION OF ADMINISTRATION

It may take up to a few days to a week for the herb to produce benefits. No known limitations on use (Tierra, 1998).

## CHEMISTRY

The active ingredients of goldenseal are isoquinoline alkaloids, mainly hydrastine and berberine (Bruneton, 1999). Other constituents include canadine, canadine, hydrastidine, isohydrastidine, (S)-corypalmine, (S)-isocorypalmine, berberastine, 1- $\alpha$ -hydrastine, and chlorogenic acid (Bradley, 1992; Upton, 2001).

## PHARMACOLOGICAL ACTIONS

The following actions are primarily related to berberine, a constituent of goldenseal, and therefore, depending on berberine content, the pharmacological actions of goldenseal products may vary from those actions listed below.

### Humans (berberine)

**ANTI-DIARRHEAL:** In cholera patients, berberine reduced cyclic adenosine by 77% (Khin *et al.*, 1985). In diarrhea due to *Vibrio cholerae* and *Escherichia coli*, berberine reduced stool volume 30–50% without side effects (Rabbani, 1996).

**ANTIPARASITIC:** In children with giardiasis, berberine demonstrated effectiveness compared with metronidazole without side effects (Gupte *et al.*, 1975).

**CARDIOVASCULAR:** Decrease in systemic and pulmonary vascular resistance and left ventricular end-diastolic pressure; increase in stroke index, cardiac index, and left ventricular ejection fraction (Marin-Neto *et al.*, 1988); suppression of ventricular premature contractions without severe side effects (Huang, 1990b).

### Animal (berberine)

Stimulates immune function (Rehman *et al.*, 1999); antiparasitic in hamsters with *L. donovani* amastigotes (Ghosh *et al.*, 1985); anti-chlamydial effects in ocular trachoma (Babbar *et al.*, 1982); positively inotropic and mild vasodilating effects in anesthetized dogs with ischemic left ventricular failure (Huang *et al.*, 1992); anti-inflammatory, inhibits vascular permeability and swelling induced by drugs (Zhang and Shen, 1989).

### In vitro (goldenseal)

The total extract of goldenseal demonstrated bactericidal activity against six strains of microorganism, including *Staphylococcus aureus*, *Streptococcus sanguis*, *Escherichia coli*, *Pseudomonas aeruginosa*, with a killing time of 4–30 minutes against all of the examined strains (Scazzocchio *et al.*, 2001).

### In vitro (berberine)

Berberine is antimicrobial (Scazzocchio *et al.*, 1998); inhibits smooth muscle contraction (Baldazzi *et al.*, 1998); anti-inflammatory, inhibits platelet aggregation, platelet adhesion induced by ADP, and arachidonic acid; inhibits thrombus formation, inhibits collagen-induced thromboxane A<sub>2</sub> release from platelets, and lowers plasma level of PGI<sub>2</sub> in rabbits (Ckless *et al.*, 1995; Wu and Liu, 1995; Huang *et al.*, 1991; Muller and Ziereis, 1994; Misik *et al.*, 1995).

Antiparasitic, amoebicidal at 0.5–1.0 mg/ml; preliminary results indicate cysticidal activity (Subbaiah and Amin, 1967); cardiovascular antiarrhythmic and proarrhythmic action in the cardiac muscle of dogs (Riccioppo, 1993); increases coronary artery flow (Huang, 1990a); bacteriostatic at low doses and a bactericide at higher doses (Bruneton, 1999).

## MECHANISM OF ACTION

The following mechanisms primarily describe the action of berberine:

- Increases antigen-specific immunoglobulin (IgM) production *in vivo*, demonstrated in goldenseal (Rehman *et al.*, 1999).
- Blocks  $\alpha_1$  and  $\alpha_2$ . These receptors mediate smooth muscle contraction (Baldazzi *et al.*, 1998).
- Anti-diarrheal activity may result from the inhibition of intestinal ion secretion, inhibition of toxin formation, and inhibition of smooth muscle contraction in addition to antimicrobial effects (Birdsall and Kelly, 1997).
- Inhibits ventricular tachyarrhythmias through potassium channel blocking effects (Hua and Wang, 1994).
- Anti-trachomal through stimulating protective mechanism in the host (Babbar *et al.*, 1982).
- Stimulates bile secretion and bilirubin discharge (Birdsall and Kelly, 1997).

## CONTRAINDICATIONS

Goldenseal should not be used in cases of kidney disease, including kidney failure due to inadequate urinary excretion of its alkaloids. It should probably be avoided in acute inflammation of the stomach, based on a case report in which a bitters formula enhanced gastric acid secretions. It is contraindicated in cases of jaundice in newborns. One study in rats found berberine displaced bilirubin from serum albumin which may lead to kernicterus (nuclear jaundice) (Brinker, 2001).

**PREGNANCY AND LACTATION:** Not for use during pregnancy (Brinker, 2001; McGuffin *et al.*, 1997). Berberine can increase bilirubin in neonates, possibly leading to neonatal jaundice (Hobbs, 2000; Upton, 2001). It may also demonstrate uterine-stimulant activity, since this has been demonstrated in its constituents berberine, canadine, hydrastine, and hydrastinine (Farnsworth, 1975). There are no known contraindications during lactation, but goldenseal's use should be avoided during lactation until further research has been conducted.

## ADVERSE EFFECTS

At recommended doses, goldenseal is considered nontoxic; berberine has also been well-tolerated in therapeutic doses (De Smet *et al.*, 1992; Newall *et al.*, 1996).

## DRUG INTERACTIONS

Goldenseal can potentially antagonize the anticoagulant activity of heparin. Studies in mice and rats have indicated hemodynamic properties of berberine, including an increase in the number of thrombocytes, decrease in the activity of factor XIII, and the promotion of blood coagulation (Ziablitskii *et al.*, 1996).

## AMERICAN HERBAL PRODUCTS ASSOCIATION (AHPA) SAFETY RATING

**CLASS 2B:** Not to be used during pregnancy (McGuffin *et al.*, 1997).

## REGULATORY STATUS

The following apply to goldenseal preparations, not berberine:

CANADA: Acceptable as a drug but unacceptable as a non-medicinal ingredient in oral use products (Health Canada, 1995a; HPB, 1993). Not permitted as single-ingredient Traditional Herbal Medicine (THM) and may not be used at over 300 mg/day as component of multi-ingredient THMs (Health Canada, 1995b). Acceptable indications: Bitter digestive in multiple ingredient products (up to 75 mg/day), and as mild antiseptic in topical THM multiple-ingredient products (up to 15%) (HPB, 1993). As a single active ingredient, not acceptable for internal use except in homeopathic dilution (HPB, 1993; Health Canada 2001)

FRANCE: Official in *French Pharmacopoeia* (Bradley, 1992; Newall *et al.*, 1996; Reynolds *et al.*, 1989).

GERMANY: Dried underground parts official in German *Homöopathisches Arzneibuch* (HAB 1) containing no less than 3.0% alkaloids, calculated as berberine (GHP, 1993). Homeopathic indications: D1–D4 for chronic nasal catarrh; uterine hemorrhages, leucorrhea, and tonic (Roth *et al.*, 1984).

SWEDEN: Natural product for external use (De Smet *et al.*, 1993). No products containing goldenseal are presently registered in the Medical Products Agency's (MPA) "Authorized Natural Remedies," "Homeopathic Remedies," or "Drugs" listings (MPA, 2001a, 2001b).

SWITZERLAND: In homeopathic dilutions, approved as a component of multi-ingredient homeopathic drugs classified by the *Interkantonale Kontrollstelle für Heilmittel* (IKS) as List D medicinal products with sales limited to pharmacies and drugstores, without prescription (Morant and Ruppner, 2001; Ruppner and Schaefer, 2000).

U.K.: *General Sale List*, Schedule 1 (requires full Product License), Table A (internal or external use) (Bradley, 1992; Newall *et al.*, 1996).

U.S.: Dietary supplement (USC, 1994). Subject of botanical monograph in development for the *U.S. National Formulary* containing no less than 2.0% hydrastine and no less than 2.5% berberine (USP, 2002). The 1X mother tincture of rhizome and roots, 65% alcohol *v/v*, is a Class C over-the-counter drug official in the *Homeopathic Pharmacopoeia of the United States* (HPUS, 1996).

## CLINICAL REVIEW

Although modern, controlled clinical trials on goldenseal are lacking, some studies have been published on the alkaloid berberine. It is not generally possible or prudent to attempt to explain the activity of an herb based on the research on one of its primary active constituents. However, in the case of goldenseal, where no modern human trials are available in the literature, the research on the isolated alkaloid is indicative of the proposed activity of goldenseal and is consistent with the herb's empirically-determined uses. Five studies are outlined in the following table, "Clinical Studies on Berberine," including a total of 465 participants. All of these studies demonstrated positive effects for indications including diarrhea, ocular infections, and cardiovascular conditions. However, there may be questions regarding the safety of *intravenous* administration of berberine for cardiac conditions (e.g., ventricular arrhythmias) due to occurrence of *torsades de pointes* in 4 of 12 patients receiving 0.2mg/kg berberine *i.v.* (Marin-Neto *et al.*, 1988). A comprehensive review of the car-

diovascular effects of berberine suggest possible clinical usefulness in the treatment of arrhythmias and/or heart failure (Lau *et al.*, 2001). There is no evidence that this issue is related to the oral use of lower goldenseal. Human studies on berberine have shown that it is absorbed poorly from the small intestines. Therefore, its antimicrobial action is only effective locally, *i.e.*, in the gut. Berberine is excreted in the urine, so it may have some antimicrobial effect in the kidneys or urinary tract (Bergner, 1996). Berberine has also been tested clinically and shown to be efficacious at stimulating bile and bilirubin secretion, improving symptoms of chronic cholecystitis, and normalizing elevated tyramine levels in persons with cirrhosis of the liver (Watanabe *et al.*, 1982). Berberine is reportedly effective as an adjunct to cancer therapy (Liu *et al.*, 1991). Clinical studies on berberine have confirmed that it is effective for acute diarrhea (Sack and Froehlich, 1982; Kamat, 1967). Externally, it has been shown useful as an eyewash in treating trachoma, an infectious eye disease (Mohan *et al.*, 1982).

## BRANDED PRODUCTS

Studies on berberine were conducted with generic, not specific, products.

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## Clinical Studies on Berberine

### Diarrhea

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Rabbani <i>et al.</i> , 1987	Diarrhea	R, C n=165 adult males with <i>E. coli</i> or <i>Vibrio cholerae</i> diarrhea	24 hours	400 mg berberine sulfate in a single dose	Berberine sulfate, or berberine sulfate and tetracycline, or tetracy- cline	In <i>E. coli</i> bacterial diarrhea, during 24 hours, berberine demonstrated a 48% reduction in mean stool volumes compared to control ( $p < 0.05$ ). Also reduced liquid diarrheal stools by 42% in treated group and 20% in control. <i>V. cholerae</i> diarrhea patients who received berberine alone had significantly reduced stool volume ( $p < 0.05$ ) over control group. <i>V. cholerae</i> patients receiving both berberine and tetracycline did not show a significant decrease in stool volume compared to patients treated with tetracycline alone.
Gupte, 1975	Giardiasis (documented)	C, Cm n=137 children ages 5 months–14 years on berberine vs. 242 patients on metroni- dazole	5 or 10 days berberine; 5–7 days metronidazole	5 or 10 mg/kg/day of berberine vs. 20 mg/kg/day of metronida- zole	Berberine or metronidazole	90% of children who received berberine in the 10 mg/kg/day dose had negative stool specimens after 10 days; 83% remained negative one month later. This compared closely to the effect of metronidazole at 95% after 10 days and 90% after one month. The author concluded berberine is an appropriate choice due to ease of administration and freedom from side effects common with metronidazole.

### Ocular Infections

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Babbar <i>et al.</i> , 1982	Ocular trachoma infections	C n=51	3 weeks, follow-up after 1 year	0.2% berber- ine chloride eye drops, or 0.2% berber- ine chloride with 20% sul- facetamide, or 20% sulfac- etamide	Berberine chloride or sulfacetamide	Subjects taking only 20% sulfacetamide had slightly better improvement in the areas of conjunctival congestion, pupillary reaction, and follicle number. But subjects still tested positive for <i>C. trachomatis</i> . Subjects with 0.2% berberine either by itself or combined with sulfacetamide demonstrated symptom improvement and tested negative for <i>C. trachomatis</i> , with no relapse one year later.

### Cardiovascular Effect

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Marin-Neto <i>et al.</i> , 1988	Refractory congestive heart failure	C n=12	30 minutes	0.02 and 0.2 mg/kg per minute	Berberine intravenous infusion	No significant response in lower dose. The dose of 0.2 mg/kg per minute decreased systemic (48%) and pulmonary (41%) vascular resistance, 28% decrease in right atrium, and 32% decrease in left ventricular end-diastolic pressure. Increases were observed in the cardiac index (45%), left ventricular ejection fraction (56%), and stroke index (45%). <i>Torsades de pointes</i> observed in 4 patients, concluding more research required before berberine can be recommended in i.v. cardiac therapy.
Huang, 1990b	Ventricular tachyarrhyth- mias	OB n=100 healthy volunteers	24–48 hours monitoring	Not stated	Berberine, route of administration not stated	65% of patients had 50% or greater, and 38% of patients had 90% or greater suppression of premature ventricular contractions (PVC's). No severe side effects were noted. However, mild gastrointestinal symptoms were reported by some patients.

**KEY:** C – controlled, CC – case-control, CH – cohort, CI – confidence interval, Cm – comparison, CO – crossover, CS – cross-sectional, DB – double-blind, E – epidemiological, LC – longitudinal cohort, MA – meta-analysis, MC – multi-center, n – number of patients, O – open, OB – observational, OL – open label, OR – odds ratio, P – prospective, PB – patient-blind, PC – placebo-controlled, PG – parallel group, PS – pilot study, R – randomized, RC – reference-controlled, RCS – retrospective cross-sectional, RS – retrospective, S – surveillance, SB – single-blind, SC – single-center, U – uncontrolled, UP – unpublished, VC – vehicle-controlled.