Rhizoma Hydrastis

Definition
Rhizoma Hydrastis consists of the dried rhizomes and roots of *Hydrastis canadensis* L. (Ranunculaceae) (*1–3*).

Synonyms
Hydrastis canadensis was formerly classified as a member of the family Berberidaceae.

Selected vernacular names
Eyebalm, golden seal, goldenseal, gorzknik kanadyjski, ground raspberry, hydraste, hydrastis, idraste, Indian dye, Indian paint, Indian turmeric, sceau d'or, warnera, wild curcuma, yellow puccoon (*4, 5*).

Geographical distribution
Indigenous to North America (*4, 6*).

Description
A perennial herb. Underground portion consists of a horizontal, branching rhizome bearing numerous long slender roots. Aerial part consists of a single radical leaf and a short stem 10–18 cm high, which bears near its summit two petiolate, palmate (five to seven lobes), serrate leaves and ends with a solitary greenish-white flower. Fruits are compound crimson berries somewhat similar to raspberries (*4*).

Plant material of interest: dried rhizomes and roots
General appearance
Rhizomes horizontal or oblique, subcylindrical, 1–6 cm long, 2–10 mm in diameter, occasionally with stem bases; numerous short upright branches terminating in cup-shaped scars and bearing encircling cataphyllary leaves. Externally, brown-greyish or yellowish-brown, deep longitudinal wrinkles, marked by numerous stem and bud-scale scars. From the lower

and lateral surfaces, arise many long, slender, brittle, curved, and wiry roots, frequently broken off to leave short protuberances or circular, yellow scars. Fracture short and resinous; fractured surface yellowish-orange at centre and greenish-yellow at margin with thick, dark yellow to yellowish-brown bark. Bright yellow, narrow xylem bundles separated by wide medullary rays; large pith. Roots numerous, filiform up to 35 mm long and 1 mm in diameter, curved or twisted. Fracture short and brittle, fractured surface yellowish-orange to greenish-yellow (*1, 3, 4*).

Organoleptic properties

Odour: faint, unpleasant; taste: bitter, persistent (*1, 4, 6*).

Microscopic characteristics

Rhizome cork yellowish-brown, polygonal cells with thin lignified walls; secondary cortex contains abundant thin-walled, polygonal to round or elongated, parenchymatous cells and some collenchyma, with abundant starch grains, simple or rarely compound with two to six components, spherical or ovoid with small, round or slit-like hilum. Parenchyma contains numerous masses of granular, orange-brown matter. Lignified tracheids present, usually small with slit-like pits, but occasionally large vessels with reticulate thickening. Root cork consists of a single layer of cells, irregularly elongated. Very occasional fragments of piliferous layer from young roots with root hairs; and a few thin-walled, lignified fibres associated with vessels present. Occasional fragments of epidermis of stem bases composed of cells with thick, lignified, beaded walls, slightly elongated in surface view (*1, 3, 4*).

Powdered plant material

Dark yellow to moderate greenish-yellow. Numerous spherical, simple starch grains, 2–15 µm in diameter, the larger grains exhibiting a central hilum; a few compound forms with two to six components. Fragments of starch-bearing parenchyma and fibrovascular tissue. Tracheal elements with simple and bordered pores, some with spiral thickenings and wood fibres, 200–300 µm long, thin-walled and with simple pores. A few fragments of cork tissue, the cells of which have reddish-brown walls. Calcium oxalate crystals absent (*3, 4*).

General identity tests

Macroscopic and microscopic examinations (*1, 3, 4*), and thin-layer chromatography (*1, 3*).

Purity tests

Microbiological

Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*7*).

Chemical

Not less than 2.0% hydrastine and not less than 2.5% berberine (*3*).

Foreign organic matter

Not more than 2% (*3*).

Total ash

Not more than 9% (*3*).

Acid-insoluble ash

Not more than 5% (*3*).

Water-soluble extractive

Not less than 14% (*1*).

Loss on drying

Not more than 12% (*3*).

Pesticide residues

The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*8*). For other pesticides, see the *European pharmacopoeia* (*8*), and the WHO guidelines on quality control methods for medicinal plants (*7*) and pesticide residues (*9*).

Heavy metals

For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*7*).

Radioactive residues

Where applicable, consult the WHO guidelines on quality control methods for medicinal plants for the analysis of radioactive isotopes (*7*).

Other purity tests

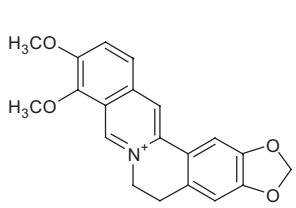
Sulfated ash and alcohol-soluble extractive tests to be established in accordance with national requirements.

Chemical assays

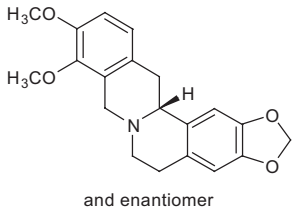
Contains not less than 2.0% hydrastine and not less than 2.5% berberine determined by high-performance liquid chromatography (*3*).

Major chemical constituents

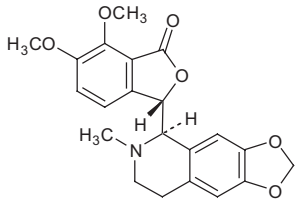
The major constituents are isoquinoline alkaloids (2.5–6.0%), principally hydrastine (1.5–5.0%), followed by berberine (0.5–4.5%), canadine (tetrahydroberberine, 0.5–1.0%), and lesser quantities of related alkaloids including canadaline, corypalmine, hydrastidine and jatrorrhizine (*5, 10–13*). The structures of hydrastine, berberine and canadine (a mixture of α-canadine (*R*-isomer) and β-canadine (*S*-isomer)) are presented below:



berberine



canadine



hydrastine

Medicinal uses

Uses supported by clinical data

None.

Uses described in pharmacopoeias and well established documents

Treatment of digestive complaints, such as dyspepsia, gastritis, feeling of distension and flatulence (*1*).

Uses described in traditional medicine

Treatment of cystitis, dysmenorrhoea, eczema, haemorrhoids, uterine haemorrhage, inflammation, kidney diseases, menorrhagia, nasal congestion, tinnitus and vaginitis. As a cholagogue, diuretic, emmenagogue, haemostat, laxative and tonic (*5*).

Pharmacology

Experimental pharmacology

Antimicrobial activity

A methanol extract of Rhizoma Hydrastis and berberine inhibited the growth of *Helicobacter pylori* (the bacterium associated with dyspepsia, gastritis and peptic ulcer disease) in vitro, median inhibitory concentration

range 0.625–40.00 µg/ml (*14, 15*). A 95% ethanol extract of the rhizomes, 1.0 mg/ml, inhibited the growth of *Staphylococcus aureus*, *Klebsiella pneumoniae, Mycobacterium smegmatis* and *Candida albicans* in vitro (*16*). Berberine was the active constituent of the extract, minimum inhibitory concentration 25.0–50.0 µg/ml against *Staphylococcus aureus* and *Mycobacterium smegmatis* (*16, 17*). Berberine inhibited the growth of *Bacillus subtilis* and *Salmonella enteritidis* in vitro at concentrations of 1.0 mg/ml and 0.5 mg/ml, respectively (*18*). Berberine, 150.0 µg/ml, also inhibited the growth of *Clostridium perfringens* in vitro and, at 1.0 mg/ml, significantly ($P < 0.001$) inhibited the growth of and induced morphological changes in *Entamoeba histolytica*, *Giardia lamblia* and *Trichomonas vaginalis* (*19*).

Effects on smooth muscle

A 70% ethanol extract of the rhizomes inhibited carbachol-induced contractions of isolated guinea-pig trachea in vitro, median inhibitory dose 1.6 µg/ml (*20*). In rabbit bladder detrusor muscle strips, an ethanol extract of the rhizomes inhibited contractions induced by isoprenaline, median effective concentration 40 nmol/l (*21*). An alcohol extract of the rhizomes reduced contractions induced by serotonin, histamine and epinephrine in isolated rabbit aortas (*22*). Investigations using the major alkaloids from the rhizomes assessed the antispasmodic mechanism of action in isolated guinea-pig tracheas (*23*). The median effective concentrations of berberine, β-hydrastine, canadine and canadaline were 34.2 µg/ml, 72.8 µg/ml, 11.9 µg/ml and 2.4 µg/ml, respectively. Timolol pretreatments antagonized the effects of canadine and canadaline, but not berberine or β-hydrastine (*23*).

Berberine, 1 µmol/l, induced relaxation of norepinephrine-precontracted isolated rat aortas (*24*). Berberine, 10^{-5} mol/l, induced relaxation in isolated precontracted rat mesenteric arteries (*25, 26*). Berberine, 0.1–100.0 µmol/l, suppressed basal tone and induced a concentration-dependent relaxation of phenylephrine-precontracted rabbit corpus cavernosum (*27*). Intracavernosal injection of 5.0 mg/kg of berberine to anaesthetized rabbits increased intracavernosal pressure from 12.7 mmHg to 63.4 mmHg, duration of tumescence ranging from 11.5 to 43.7 minutes (*27*). A hydroalcoholic extract of the rhizomes or berberine inhibited norepinephrine- and phenylephrine-induced contractions in isolated rabbit prostate strips with ED_{50} values of 3.92 µmol/l and 2.45 µmol/l, respectively (*28*).

Immunological effects

Intragastric administration of an extract (type not specified) of the rhizomes, 6.6 g/l in drinking-water, to rats for 6 weeks increased production of antigen-specific immunoglobulin M (*29*). Intraperitoneal administra-

tion of 10.0 mg/kg body weight (bw) of berberine per day for 3 days to mice before the induction of tubulointerstitial nephritis significantly ($P = 0.001$) reduced pathological injury, improved renal function, and decreased the numbers of CD3+, CD4+ and CD8+ T-lymphocytes (*30*).

Toxicology

The oral median lethal dose of berberine in mice was 329.0 mg/kg bw (*31*). Oral administration of 2.75 g of berberine to dogs produced severe gastrointestinal irritation, profuse watery diarrhoea, salivation, muscular tremors and paralysis; respiration was not affected. Postmortem examination showed the intestines to be contracted, inflamed and empty or containing mucous and watery fluid. Oral administration of berberine sulfate, 25.0 mg/kg bw, induced central nervous system depression in dogs lasting 6–8 hours; 50.0 mg/kg bw caused salivation and sporadic emesis; 100.0 mg/kg bw induced persistent emesis and death of all animals 8–10 days later (*31*).

Uterine stimulant effects

Hot aqueous extracts of the rhizomes, 1:200 in the bath medium, stimulated contractions in isolated guinea-pig uteri (*32*). However, an alkaloid-enriched extract of the rhizomes did not stimulate contractions in isolated mouse uteri (*33*). A 70% ethanol extract of the rhizomes inhibited spontaneous and oxytocin- and serotonin-induced contractions in isolated rat uteri, median inhibitory concentrations 10.0–19.9 µg/ml (*20*).

Clinical pharmacology

No controlled clinical studies available for Radix Hydrastis. While berberine has been shown to be effective for the treatment of bacterially-induced diarrhoea (*34–40*), ocular trachoma (*41*) and cutaneous leishmaniasis (*42–44*), the data cannot generally be extrapolated to include extracts of the rhizomes.

Adverse reactions

No information available on adverse reactions to Radix Hydrastis. However, high doses of hydrastine are reported to cause exaggerated reflexes, convulsions, paralysis and death from respiratory failure (*45*).

Contraindications

Radix Hydrastis is contraindicated in cases of known allergy to the plant material.

Warnings

No information available.

Precautions

General

Use with caution in patients with high blood pressure, diabetes, glaucoma and a history of cardiovascular disease.

Drug interactions

An ethanol extract of the rhizomes inhibited the activity of cytochrome P450 (CYP3A4) in vitro, median inhibitory concentration <1% (*46*). Concomitant administration of Radix Hydrastis with drugs metabolized via cytochrome P450 may therefore affect the metabolism of such drugs (*46*).

Carcinogenesis, mutagenesis, impairment of fertility

The genotoxic effects of berberine in prokaryotic cells were assessed in the SOS-ChromoTest in *Saccharomyces cerevisiae* (*47*). No genotoxic activity with or without metabolic activation was observed, and no cytotoxic or mutagenic effects were seen under nongrowth conditions. However, in dividing cells, the alkaloid induced cytotoxic and cytostatic effects in proficient and repair-deficient *Saccharomyces cerevisiae*. In dividing cells, the induction of frameshift and mitochondrial mutations and crossing over showed that the compound is not a potent mutagen (*47*).

Pregnancy: non-teratogenic effects

The safety of Rhizoma Hydrastis has not been established (*31*) and its use is therefore not recommended during pregnancy.

Nursing mothers

The safety of Rhizoma Hydrastis has not been established (*31*) and its use is therefore not recommended in nursing mothers.

Paediatric use

The safety of Rhizoma Hydrastis has not been established (*31*) and its use is therefore not recommended in children.

Other precautions

No information available on precautions concerning drug and laboratory test interactions; or teratogenic effects during pregnancy.

Dosage forms

Dried rhizomes and roots, dried extracts, fluidextracts, and tinctures (*1, 11*). Store dried rhizomes and roots in a tightly sealed container away from heat and light.

Posology

(Unless otherwise indicated)

Daily dose: dried rhizomes and roots 0.5–1.0 g three times, or by decoction; liquid extract 1:1 in 60% ethanol, 0.3–1.0 ml three times; tincture 1:10 in 60% ethanol, 2–4 ml three times (*1*).

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