Golden Seal Root

Hydrastis canadensis

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NOMENCLATURE

Botanical Nomenclature

Hydrastis canadensis L.

Botanical Family

Ranunculaceae

Definition

Goldenseal root consists of the fresh or dried roots and rhizomes of Hydrastis canadensis L. containing not less than 2.0% hydrastine (C$_{21}$H$_{21}$NO$_{6}$) and 2.5% berberine (C$_{20}$H$_{18}$NO$_{4}$) calculated on a dry weight basis.

Common Names

United States: Goldenseal, yellow puccoon, yellow root (McGuffin and others 2000).
France: Hydrastis, racine orange, sceau d’or.
Germany: Kanadische Gelbwurzel.
Holland: Canadese Geelwortel.
Italy: Idraste.
Spain: Sello de Oro, hidrastis.

HISTORY

Goldenseal is an indigenous North American plant that has been widely used by Native Americans. The common name goldenseal was introduced by the Thomsonian medical practitioners in the middle 1800s in reference to the yellow-golden color of the rhizome interior and the wax seal-like scars that occur on its external surface. According to the renowned Eclectics John Uri and Curtis Gates Lloyd (1884-85), Linnaeus (1753), being only acquainted with the leaves of goldenseal which resembled those of Hydrophyllum, named the plant Hydrophyllus verum canadense. A few years later Linnaeus obtained a flower of the plant and, in his Systema Naturale (10th edition, 1759), being only acquainted with the leaves of goldenseal which resembled those of Hydrophyllum, named the plant Hydrophyllus verum canadense. A few years later Linnaeus obtained a flower of the plant and, in his Systema Naturale (10th edition, 1759), applied the genus name Hydrastis, naming John Ellis as the botanical authority though Ellis had never published a description of the plant. The name Hydrastis is derived from the Greek νερός which means “wet”, and δύαω, meaning “to act”. Thoughts differ as to whether the reference to wet alludes to the growth of the herb in moist locations, which is not typical, or its effect on the mucosa, which has traditionally been goldenseal’s primary indication. Asa Gray’s Manual of Botany of the Northern United States (1848) maintained that the name “allude[es] to the active properties of the juice”, an opinion disputed by the Lloyds. The species name canadensis refers to Canada.

The first report of Native American use of goldenseal root was made by Mr. Hugh Martin in 1782 before the American Philosophical Society. Mr. Martin reported on the relatively common use of goldenseal as a plant dye. The first reference to its medicinal use appears to have been made by medical botanist Benjamin Smith Barton in his Collections for a Vegetable Materia Medica of 1798. In this text, Barton reports on the use of “yellow root” as a medicine by the Cherokee for the treatment of what was thought to be cancer, as an eye wash for inflamed eyes, and as a bitter tonic (Lloyd 1908). Medicinally, it has additionally been used for skin disorders and respiratory illnesses. Goldenseal was widely employed against the infectious diseases introduced by Europeans. Among the Iroquois, goldenseal was used for whooping cough, diarrhea, fevers, pneumonia, stomach problems, and tuberculosis (Moerman 1986). Though goldenseal has historically been used by many different Native American tribes, it is currently most used by the Cherokee and Iroquois.

Despite a long tradition of goldenseal use in America and though goldenseal was mentioned in the records of Lewis and Clark in 1804, it was largely ignored in medical texts until Rafinesque’s Medical Flora of the United States in 1828. In that text, Rafinesque reported additional uses of the herb (“yellow puccoon”, “yellow eyeroot”) as a topical application for the treatment of leg sores and afflictions of the stomach and liver. In 1828, Rafinesque isolated a “golden principle” which he named hydrastine but was later found to be berberine, a compound isolated by Buchner in 1835 from barberry (Berberis vulgaris). Hydrastine, as we now know it, was isolated by Durand in 1851. A third alkaloid, canadine, was isolated by Hale in 1873 (Lloyd and Lloyd 1908).
Wooster Beach, founder of the Eclectic school of medicine, included goldenseal in his first edition of the American Practice of Medicine in 1833. This was followed by its inclusion in Professor John King’s and Robert Newton’s Eclectic Dispensatory of the United States (1852), which led to the widespread use of goldenseal among the Eclectics. Reporting that goldenseal “ranks among their best articles”, they used goldenseal predominantly for gastrointestinal complaints, jaundice, infections, as a bitter tonic to regulate bile production, and as a uterine tonic. For many of these purposes it was considered to have no equal. Other uses reported for goldenseal included the treatment of mouth ulcers and thrush, as well as inflamed mucous membranes and chronic gonorrhea (Jones and Scudder 1858).

Goldenseal was reportedly introduced to the British Isles in 1760 under the name of Warmera after botanist Richard Warner and was brought under cultivation at Kew Gardens in England, as well as in Edinburgh, Scotland and Dublin (Grieve 1931). According to the account of the Lloyd brothers, Warner was the first to provide a detailed description of the plant and they lamented the fact that the genus name of Warnera was not maintained. Philip Miller, in his Gardener’s Dictionary, reported that he had goldenseal under cultivation prior to Warner in 1759 (Lloyd and Lloyd 1884-85). In 1883, goldenseal was introduced into Germany where it was primarily used in gynecology and, in particular, for menorrhagia, metrorrhagia, and dysmenorrhea (Benigni and others 1971).

Goldenseal was briefly cited in the appendix of the second edition of Wood and Bache’s Dispensatory of the United States of America in 1834. Both the tincture and fluid extract of goldenseal were listed in most editions of the United States Pharmacopoeia (USP) from approximately 1830-1926 until being replaced by hydrastine (Boyle 1991). Goldenseal was also listed in the first edition of the National Formulary of the United States in 1888, and again from 1926-1960. After the advent of antibiotics, domestic interest in goldenseal waned although it remained a valued commodity among Europeans.

As domestic interest in herbal medicines has increased over the past two decades, goldenseal has regained popularity. Goldenseal is now one of the most popular medicinal plants used in America and remains a staple of most modern herbal practitioners. It is currently used primarily for its antimicrobial properties. It is taken orally for the treatment of upper respiratory infections, gastrointestinal disorders, and is applied topically as an antiseptic wash, fomentation, douche, eyewash, gargle, and salve. A monograph on goldenseal root has recently been published in the Pharmeuropa (1999) and the United States Pharmacopeial Forum (2000). In recent years, goldenseal has been listed in the pharmacopoeias of Brazil, Egypt, Italy, France, and Romania (Reynolds 1993).

**Identification**

**Botanical Identification**

_Hydrastis canadensis_ L. Herbaceous perennial from yellow rhizome. **Stem:** Erect, 2-5 dm tall, unbranched, pubescent. **Leaves:** Simple; basal leaf 1, early deciduous; cauline leaves 2, alternate, inserted near top of stem; blades palmately 3-9 lobed, cordate-orbicular, 3-10 cm across at anthesis, to 25 cm at maturity; palmately-veined; margin singly- or doubly-serrate. **Inflorescence:** Flowers solitary, terminal, peduncle 0.5-3.8 cm long. **Flowers:** Perfect, radially symmetric, 8-18 mm across; sepals 3, ovate to elliptic, 3.5-7 mm long, greenish-white, caducous; petals 0; stamens 50-75, exserted, white, 4-8 mm long; pistils 5-15, separate; styles short, stigmas 2-lipped. **Fruit:** Aggregate of 15 or fewer berries; berries dark red, sessile, ellipsoid to globose, 5-8 mm long, 1.5-5 mm wide, beaked, 1-2 seeded; seeds black, ellipsoid, smooth, lustrous. Chromosome number: 2n = 26.

**Distribution:** Native to the deep rich woods of the eastern and central United States, from Vermont west to Minnesota and Nebraska, south to Virginia, Georgia, and Arkansas. Flowers in spring (Bailey 1949; Ford 1997; Gleason and Cronquist 1991; Linneaus 1753 [original citation]).

Several analyses have suggested that _Hydrastis_ belongs in its own family (Hoot 1991; Tobe and Keating 1985, cited

**Table 1 Historical timeline of the medical use of goldenseal root (Hydrastis canadensis)**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1760</td>
<td>Introduced to the British Isles in 1760 under the name of Warnera, after Richard Warner.</td>
</tr>
<tr>
<td>1782</td>
<td>Hugh Martin reports on the Native American use of goldenseal as a plant dye.</td>
</tr>
<tr>
<td>1798</td>
<td>The first written reference to the medical use of “yellow root” by medical botanist Benjamin Smith Barton in his Collections for a Vegetable Materia Medica.</td>
</tr>
<tr>
<td>1828</td>
<td>Rafinesque recommends “yellow pucoon” for leg sores and for “liver and stomach afflictions” and isolates a yellow principle, naming it “hydrastine”.</td>
</tr>
<tr>
<td>1835</td>
<td>Buchner isolates berberine crystal from barberry extract.</td>
</tr>
<tr>
<td>1833-1858</td>
<td>Eclectics report on the use of goldenseal as a bitter digestive aid, for jaundice, to lower fever, as a uterine tonic, for mucosal inflammation, mouth ulcers, and chronic gonorrhea.</td>
</tr>
<tr>
<td>1850-1862</td>
<td>Hydrastine isolated by Durand; yellow principle of Rafinesque confirmed to be Buchner’s berberine.</td>
</tr>
</tbody>
</table>
in Ford 1997). However, other analyses have confirmed its position within the Ranunculaceae (Keener 1993; Locente and Estes 1989). A definitive placement of this genus awaits a more detailed molecular phylogeny.

**Macroscopic Identification**

Goldenseal rhizome and root are traded both fresh and dried, in whole, cut, and powdered forms. The fresh, full-grown rhizome is knotted and sub-cylindrical, 1-6.5 cm in length and 2-10 mm in diameter. Fibrous rootlets are sparsely distributed on the upper surface of the rhizome and are much thicker on the sides and lower surface. The roots make up approximately 70% and the rhizomes 30% of the underground portion. On average, the rhizome and roots of a single plant weigh 5-11 g. When freshly picked, they are a bright yellow both internally and externally.

When dry, the rhizome is subcylindrical, knotted, contorted, 1-5 cm in length, and 2-6 mm in diameter. The external surface is brownish-gray to yellowish-brown in color and rough due to the raised, circumferential growth rings which are spaced 1.5-3.1 mm apart. The upper surface has small, raised, annular scars where past stems emerged from the rhizome. These scars look like old wax seals, hence the common name. The fracture is short, brittle, clean, and resinous, revealing a smooth brownish-yellow or greenish-yellow internal surface and a yellowish-orange center. In cross section, the bark is approximately 0.5 mm thick. The wood, approximately 1 mm thick, is arranged radially with broad medullary rays. The pith is light yellowish-orange and is large in diameter compared to the wood.

The dry root is 4-7 cm in length and 0.2-0.4 mm in diameter. The external surface is brownish-gray to yellowish-brown in color. The fracture is brittle and short; when magnified it has the appearance of broken beeswax. The internal surface is bright yellow to orange-yellow in younger roots, changing to greenish-yellow or dark yellowish-brown in older roots. Occasionally there is a reddish hue to the central part of the root. The bark is thick and the wood is arranged in a quadrangular fashion.

**Aroma:** Characteristic and persistent. **Taste:** Acrid and astringent, possessing a marked and unique bitterness stimulating salivation.

**Powder:** Bright yellow to brownish-yellow.

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**Figure 2a-d** Botanical characteristics of goldenseal (*Hydrastis canadensis*)

a. Goldenseal in flower.

b. Goldenseal in fruiting stage.

c. Goldenseal in fruiting stage.

d. Goldenseal under cultivation.

Photograph credits: 2a-c, ©stevenfoster.com; 2d, Char Krautkramer, courtesy of Wisconsin Cultivated Goldenseal L.L.C, Athens, WI.
Figures 3a-g  Macroscopic characteristics of roots and rhizomes of goldenseal (Hydrastis canadensis) (fresh and dried)

a. Freshly wildcrafted goldenseal rhizome sliced open to reveal the bright yellow interior.

b. Freshly harvested cultivated goldenseal rhizome sliced open to reveal bright yellow interior.

c. Freshly wildcrafted goldenseal roots and rhizomes (note “seals”).

d. Freshly wildcrafted goldenseal roots and rhizomes.

e. Dried whole goldenseal roots and rhizomes.

f. Dried cut and sifted goldenseal roots and rhizomes.

g. Goldenseal root and rhizome powder.

Photograph credits: 3a-c ©stevenfoster.com; 3d, Martin Wall Photography, Pleasant Garden, NC; 3e-g, Joanne Snow, Santa Cruz, CA. © 2001 American Herbal Pharmacopoeia™.
Figure 4a-e  Common adulterants traded as goldenseal root

a. Goldenseal (Hydrastis canadensis) leaf: cut and sifted.
b. Chinese goldthread (Coptis sp.): whole, sliced, and ground.
c. Oregon grape root (Mahonia nervosa): whole and ground.
d. Yellow dock root (Rumex sp.): fresh whole and sliced.
e. Yellow root (Xanthorhiza simplicissima) with leaves: dried whole.

Photograph credits: 4a, Roy Upton, Soquel CA; 4b-e, Joanne Snow, Santa Cruz, CA ©2001 American Herbal Pharmacopoeia™.
Microscopic Identification

Rhizome: Preparation in chloral hydrate: Parenchyma tissue dominates the rhizome in cross section. The rhizome has a thin, yellowish-brown cork consisting of several thin-walled cell layers. The secondary phloem consists of parenchyma cells only; these are generally thin-walled, though in the outer regions they may be somewhat thickened. The cells are rounded or polygonal in cross section and elongated in longitudinal view, and frequently contain yellow-brown, granular masses. Close to the cambium, semicircular regions of smaller cells indicate the sieve tubes and companion cells. Interior to the cambium and associated with the phloem bundles are found narrow cuneiform groups of vessels separated by wide medullary rays. The vessels are small with numerous slit-shaped pits, bordered pits, or helical secondary walls. Many of the pitted vessels are filled with yellow, amorphous, granular masses. The thin-walled cells of the pith, as well as other parenchyma cells, contain single or compound starch granules with either a round or slit-shaped hilum. Calcium oxalate crystals, sclereids, and fibers are absent throughout.

Root: Preparation in chloral hydrate: Parenchyma tissue dominates the root in cross section. The root is covered by a hypodermis of a single cell layer. The cortex consists of parenchyma cells only and is separated from the stele by a conspicuous primary endodermis, the cells of which often have sinuous walls. The stele shows the typical structure of an oligarch radial bundle. Sclerenchymatous cells and crystals are absent.

The primary diagnostic characteristics are the pervading yellow color, the minute starch grains, the absence of calcium oxalate crystals, the nature of the elements of the wood, and the absence of sclerenchymatous cells.

Powder: Goldenseal root powder contains numerous, mostly single, nearly spheroidal starch grains from 2-15 µm in diameter, either free or in the parenchyma cells; fragments of the fibro-vascular bundles mostly associated with starch-bearing parenchyma; vessels with pitted (simple and bordered) or helical secondary walls; and occasional fragments of tabular cork cells with yellowish- or reddish-brown walls and occasional granular masses attached to them.

Powdered goldenseal root may be adulterated by goldenseal leaf. Goldenseal leaf powder is dark green and lacks the persistent characteristic odor and taste of the root. Pure goldenseal leaf or admixtures of root and leaf can be identified by the occurrence of leaf fragments with unicellular, thick-walled, acute trichomes (up to 600 µm in length) and epidermal cells with wavy or sinuous walls. On fragments from the lower epidermis, anomocytic stomata are often found. For the macroscopic and microscopic differentiation of goldenseal rhizome from other known adulterants, see Table 2.

Figure 5a Microscopic characteristics of goldenseal (Hydrastis canadensis) root and rhizome
1. Cortical parenchyma from the rhizome showing thickened walls (cross section).
2. Cortical parenchyma from the rhizome (longitudinal view).
3. Cork with attached granular material, from the rhizome (cross section).
4. Cork from rhizome (surface view).
5. Cork from root (surface view).
6. Root endodermis (tangential view).
7. Xylem vessels with attached parenchyma, from the rhizome (radial view).
8. Starch granules.

Microscopic drawings courtesy of Elizabeth Williamson, University of London.
Figure 5b  Microscopic characteristics of goldenseal (Hydrastis canadensis) root and rhizome
1. Rhizome (overview cross section) showing small xylem strands among broad medullary rays; the xylem strands end at the cambial line and the phloem bundles appear as groups of irregular cells in the cortical parenchyma.
2. Vessels in the rhizome (cross section).
3. Vessels in the rhizome (longitudinal section).
4. Young root showing the tetrarch arrangement of the primary xylem (overview cross section).
5. Older root (overview cross section).
7. Starch granules.
Microscopic images courtesy of Reinhard Länger, University of Vienna.

Figure 5c  Microscopic characteristics of goldenseal (Hydrastis canadensis) leaf
1. Upper epidermis.
2. Covering trichome and trichome base.
3. Lower epidermis with a hair base from a broken trichome.
4. Lower epidermis with anomocytic stoma.
Microscopic drawings courtesy of Reinhard Länger, University of Vienna.

Figure 5d  Microscopic characteristics of goldenseal (Hydrastis canadensis) leaf
1. Upper epidermis showing cells with wavy walls.
2. Lower epidermis showing cells with sinuous walls.
3. Spongy parenchyma showing large intercellular spaces.
Microscopic images courtesy of Alkemists Pharmaceuticals, Costa Mesa, CA (1-2), and Reinhard Länger, University of Vienna (3-4).
The majority of goldenseal is gathered from wild populations in Canada and the eastern and mid-western United States, including Illinois, Indiana, Missouri, Kentucky, Minnesota, North Carolina, Ohio, Virginia, and Wisconsin. Currently a transition is being made from wild to cultivated sources due to the threatened status of this species.

**Collection**

Wildcrafted goldenseal root and rhizome should be dug in the fall after the plants have set fruit and the aerial portions have died back (Sievers 1949) (hereafter, “root” will be used to refer to the root and rhizome together). Roots historically have also been harvested in the spring. Spring-harvested roots reportedly shrink considerably more in drying than fall-harvested roots due to their higher moisture content and, according to older references, are inferior to fall-harvested roots (Hardacre 1923; Lloyd and Lloyd 1884-85). Currently, wildcrafters are gathering goldenseal throughout the summer. When summer harvest occurs, care should be taken to harvest only after the seeds have matured and been released, allowing for natural regeneration. Contemporary data regarding the effect of harvest time on constituent yields are needed to help determine optimal harvest times for both wildcrafted and cultivated goldenseal root.

If the leaf is not senescent when the root is collected, it should be removed immediately upon harvesting to prevent the leaf from drawing moisture and nutrient reserves from the root. Small, undeveloped, or broken pieces of the root should be removed before processing.

**Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Goldenseal (Hydrastis canadensis)</th>
<th>Oregon Grape (Mahonia spp.)</th>
<th>Goldthread (Coptis spp.)</th>
<th>Yellow Dock (Rumex spp.)</th>
<th>Yellow Root (Xanthorrhiza simplicissima)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Macroscopic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size and form</td>
<td>Sub-cylindrical; 1-6 cm long, 2-9 mm diameter</td>
<td>Branched, cylindrical; variable length, to 1.5 cm diameter</td>
<td>Highly branched from apex, branches congested, descending, looking like a closed chicken’s foot; 3-6 cm long, 0.3-0.8 cm diameter</td>
<td>Fusiform; 10-20 cm long, 1-2 cm diameter</td>
<td>Thin, slender; 50-100 cm long, approximately 1 cm diameter</td>
</tr>
<tr>
<td>External surface</td>
<td>Yellow; rough, with circumferential growth rings and annular scars; with many wiry lateral rootlets (may be trimmed off)</td>
<td>Pale to dark yellow-brownish-brown; longitudinally wrinkled, rough</td>
<td>Gray to yellow or yellowish-brown; knotted, rough; with many wiry lateral rootlets (may be trimmed off)</td>
<td>Grayish- to reddish-brown; upper portion annulate, lower portion longitudinally wrinkled</td>
<td>Yellowish-brown; longitudinally wrinkled</td>
</tr>
<tr>
<td>Interior color and characteristics</td>
<td>Bright golden yellow (green if old or improperly dried); xylem distinctly radiate with a large pith</td>
<td>Light brown to light yellow; xylem distinctly radiate</td>
<td>Dull to bright orange; pith reddish-orange, sometimes hollow</td>
<td>Dingy brownish-yellow; thick cortical layer, xylem distinctly radiate with reddish medullary rays</td>
<td>Light to bright yellow; thin bark, small pith</td>
</tr>
<tr>
<td>Fracture</td>
<td>Short, waxy</td>
<td>Tough</td>
<td>Brittle, uneven</td>
<td>Short</td>
<td>Tough</td>
</tr>
<tr>
<td>Powder</td>
<td>Bright yellow-gold (brownish-yellow if old)</td>
<td>Brownish-yellow</td>
<td>Brownish-orange with orange flecks</td>
<td>Dark brown</td>
<td>Bright yellow</td>
</tr>
</tbody>
</table>

**Microscopic**

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Medullary rays</td>
<td>Wide, with thin-walled cells</td>
<td>Narrow, with thick-walled and pitted cells</td>
<td>Narrow, with thick-walled and pitted cells</td>
<td>Narrow, with thin-walled and pitted cells</td>
<td>Narrow, with thick-walled and pitted cells</td>
</tr>
<tr>
<td>Sclereids</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Fibers</td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Calcium oxalate crystals</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>

Note: Organoleptic differentiation of these species is difficult. The taste and smell of goldenseal rhizome is characteristic but difficult to describe. All of the species listed are bitter tasting and are only discernible from each other with experience.

Sources: Mansfield 1937; Sayre 1917; Yen 1992; Youngken 1930; microscopic data courtesy of Reinhard Länger, University of Vienna.

**COMMERCIAL SOURCES AND HANDLING**

The majority of goldenseal is gathered from wild populations in Canada and the eastern and mid-western United States, including Illinois, Indiana, Missouri, Kentucky, Minnesota, North Carolina, Ohio, Virginia, and Wisconsin. Currently a transition is being made from wild to cultivated sources due to the threatened status of this species.

Wildcrafted goldenseal root and rhizome should be dug in the fall after the plants have set fruit and the aerial portions have died back (Sievers 1949) (hereafter, “root” will be used to refer to the root and rhizome together). Roots historically have also been harvested in the spring. Spring-harvested roots reportedly shrink considerably more in drying than fall-harvested roots due to their higher moisture content and, according to older references, are inferior to fall-harvested roots (Hardacre 1923; Lloyd and Lloyd 1884-85). Currently, wildcrafters are gathering goldenseal throughout the summer. When summer harvest occurs, care should be taken to harvest only after the seeds have matured and been released, allowing for natural regeneration. Contemporary data regarding the effect of harvest time on constituent yields are needed to help determine optimal harvest times for both wildcrafted and cultivated goldenseal root.

If the leaf is not senescent when the root is collected, it should be removed immediately upon harvesting to prevent the leaf from drawing moisture and nutrient reserves from the root. Small, undeveloped, or broken pieces of the rhi-
zome should be kept moist and cool and set aside for replanting (Davis and McCoy 2000; Hardacre 1923). Rhizome crowns may also be replanted directly to aid in replenishing wild stocks.

Commercial dealers have reportedly created artificial price increases in the market by hoarding roots until higher prices can be demanded. This can result in the trade of significant amounts of old substandard material. In such roots, the brilliant golden color normally present in freshly harvested material deteriorates and turns a dull greenish brown.

**Species Conservation**

Due to its popularity and high market value, goldenseal root is subject to over-harvest throughout its range. As early as 1923, it was reported that every druggist in the country stocked goldenseal due to its popularity as a medicine (Hardacre 1923). A decline in plant populations had already been reported much earlier in 1884 (Lloyd and Lloyd 1884-85). In response to the over-harvest of wild populations, experimental cultivation began around 1899 and continued until the advent of sulfur drugs which significantly decreased domestic and international demand for goldenseal. With the recent resurgence in popularity of goldenseal, cultivation is once again in process. In 1997 and 1998, the annual usage of dried goldenseal root was estimated to be 90,000-135,000 kg. In 1998, approximately 122,175 kg of dried root was sold of which 97.5% (119,250 kg), came from wild sources. In 1998, approximately 140 acres of goldenseal were under cultivation. The area under cultivation is predicted to increase such that approximately 78% of the total root will be obtained from cultivated sources after 2003 (McGuffin 1999). The question has been raised as to whether such a projected increase in cultivated goldenseal justifies continued wildcrafting. To answer this question with any degree of accuracy, a population viability analysis of goldenseal needs to be done to determine long term population trends and sustainable harvest limits.

Of the approximately 27 states to which goldenseal is native, it is listed as “endangered” in 6 and is variously listed as “threatened”, “rare”, “vulnerable”, or of otherwise “special concern” in all but one of the others. It is similarly regarded as being threatened in Canada. Goldenseal is included in Appendix II of the Convention on International Trade in Endangered Species (CITES). CITES regulates the international trade of Appendix II species, which includes species considered to be at serious environmental risk. Appendix II species require a permit from the United States Fish and Wildlife Service for exportation of the plant. In addition, it requires that plants be 4 years of age prior to harvest, for both cultivated and wild sources. Various state laws further regulate the cultivation, wild harvesting, and trade of goldenseal root.

**Cultivation**

The threatened status of goldenseal, dwindling supplies of the root, and its increased economic value make goldenseal an ideal candidate for cultivation. In the wild, goldenseal typically prefers well-drained, moist, calcareous soils with a pH of 5.5-6.5. It grows under the canopy of hardwoods such as oak, tulip poplar, maple, sycamore, and basswood with a shade density of approximately 60% to 80%. It can be cultivated as a crop under shade cloth or other artificial or natural shade. The estimated cost of cultivation under shade cloth in 1999 was approximately $10,000 per acre, an expensive practice that current market prices can sustain. Current data regarding the potential market value of goldenseal root cultivation are lacking. According to early sources, intensive cultivation can yield 2250-2700 kg of fresh root and 675-900 kg of dried root per acre (Hardacre 1923; Sievers 1949).

Goldenseal is propagated by seed or rhizome divisions. Seeds mature at the end of June or beginning of July in most regions and are best sown immediately after collection. They may also be cleaned, kept cool and moist, and sown in the fall of the year before the first freeze for optimum germination. The seeds should not be allowed to dry out completely. According to one reference, artificial cold stratification of seeds may result in a 10%-90% loss of viability (Davis and McCoy 2000). However, other sources have found that seeds will only germinate with some cold treatment (Tim Blakley, personal communication to AHP; unreferenced). Seeds are best planted 15-20 cm apart in rows. The planted beds should be heavily mulched (several inches deep) for winter protection. This also helps the soil to retain moisture and reduces weed growth. Goldenseal is reportedly very hardy and requires little irrigation. However, during drought the plants will drop their foliage and go dormant earlier than usual. Goldenseal is relatively resistant to disease and pests, though normal control of slugs and moles is required. It should be noted that fungal disease incidence associated with artificial shade structures is increasing (Davis and McCoy 2000). When grown from seed, roots are best harvested at 5-7 years of age (CITES prohibits harvest prior to 4 years of age).

To propagate vegetatively, the mature rhizomes should be divided into three or more cuttings of approximately 1 g each; the rootlets should be left intact. The cuttings are then planted on 30 cm centers. Vegetative propagation in the spring or fall reportedly produces higher yields than propagation from seeds.

**Handling and Processing**

Freshly harvested roots should be freed of adhering soil and thoroughly cleaned using pressurized air or spray-washed without the use of brushes. Excessive washing can leech out desired constituents. A significant amount of commercial material in trade is poorly washed by the primary suppliers and may require additional washing by secondary processors. A ginseng root washer or a rotating drum with running water works well (Jeanine Davis, personal communication to AHP; unreferenced).

**Drying**

Data on optimum drying techniques for goldenseal are lacking. The noted Eclectic pharmacist John Uri Lloyd recognized that careless drying could lead to significant degradation...
tion of the material (Lloyd and Lloyd 1884-85). Hydrastine decomposes to hydastinine at temperatures at or above 126 °C and when subjected to steam and oxygen (Wisniewski and Gorta 1969). Hence, processes subjecting goldenseal to high temperatures are to be avoided. Various recommendations for drying have been made in the literature. It is generally believed that roots should be dried in a shaded well-ventilated area on drying racks or another clean surface with absorbent material, turning the material several times daily. Forced air dryers may be used. Roots that are dried outside must be protected from dew and rain. According to early bulletins of the United States Department of Agriculture, if outside temperatures are low, drying rooms should be heated to 27 °C to ensure proper drying (Hardacre 1923; Sievers 1949). Contemporary drying practices suggest optimal drying conditions to be 35 °C - 37.7 °C with approximately 40% humidity. Extra care must be applied when drying spring-harvested roots since they have a higher moisture content and are therefore subject to molding and fermentation. Fresh roots lose approximately 70% of their weight upon drying. Properly dried roots should snap cleanly upon breaking (Davis and McCoy 2000).

It has been reported that some gatherers quickly dry freshly harvested material in home ovens, on the dashboards of cars, or in direct sunlight. Such methods cause the brilliant golden color to turn a dull greenish brown and the roots and rhizomes become more brittle.

Storage

Follow general guidelines for storage of dry material by packing in air-tight containers protected from light, heat, moisture, and insect infestation. Storage temperature should be below 30 °C (NF 1946). Hydrastine is unstable, undergoing oxidative degradation into hydastinine (Wisniewski and Gorta 1969), whereas berberine is stable under a wide variety of storage conditions (Paul Schiff, personal communication to AHP; unreferenced).

Qualitative Differentiation

The interior of roots that are dried at too high a temperature or for overly long periods of time will turn brown or greenish-brown, signifying a degradation of the crude material. The same is true for roots that have been stored for several years.

Adulterants

Many species have been traded as goldenseal, a practice reported as early as 1912 by John Uri Lloyd. These include barberry (Berberis vulgaris), Oregon grape root (Mahonia aquifolium, M. nervosa, and M. repens), yellow dock root (Rumex spp.), bloodroot (Sanguinaria canadensis), yellow root (rhizome, leaf, stem) (Xanthorrhiza simplicissima), turmeric (Curcuma spp.), and Chinese and American goldthread (Coptis spp.). Of these species, bloodroot is easily distinguished from goldenseal by its deep red coloring when fresh and orange-red coloring when dried. In recent years, supplies described as "Chinese goldenseal" have entered into commerce. At least two samples obtained have been identified as Coptis chinensis. C. optis contains berberine, but does not contain hydrastine or canadine. Twin leaf (Jeffersonia diphylla) has historically also been cited as an adulterant, though it does not appear to be found in goldenseal trade today. Another common adulterant is the leaves and stems of goldenseal itself, which are often ground up with the root when it is traded as powder. Such an admixture will give the normally distinct yellow powder a greenish hue. The only other species in the genus Hydrastis is H. jeozensis Sieb. et Zucc., native to Japan. See Identification and Analytical sections for methods of distinguishing adulterants from true goldenseal.

Preparations

A variety of goldenseal root preparations are in commerce with various manufacturers preparing their products according to their own specifications using maceration or percolation of fresh and/or dried material. Goldenseal products include powders, capsules, tablets, teas, fluid extracts, tinctures, solid extracts, and salves. Authoritative information on the bioavailability of goldenseal and its compounds in these various preparations is lacking. The following guidelines for preparations are provided in the older literature.

Tincture (1:5 g/mL):

Prepare by percolation. Mix 200 g powdered goldenseal root with a sufficient quantity of menstruum (2:1 V/V alcohol [57%-63%] to water) to produce an even moistness. Allow to stand for 15 minutes and pack firmly in an appropriate percolator. Fill the percolator with a sufficient quantity of menstruum to saturate the powder. Cover the percolator. When the liquid is about to drip, close the lower orifice and allow to macerate for 48 hours. After 48 hours, allow to percolate slowly adding a sufficient quantity of menstruum to yield a total of 1000 mL of tincture. Mix thoroughly (NF 1946).

Fluid Extract (1:1 g/mL):

Mix 1000 g of coarsely ground goldenseal root with a sufficient quantity of menstruum (2:1 V/V alcohol to water) to produce an even moistness (approximately 600-800 mL). Follow the directions for the tincture. Reserve the first 850 mL of percolate, recover alcohol from the percolator, concentrate the residue to a soft extract below 60 °C. Dissolve the soft extract in the first 850 mL of percolate. Add enough menstruum to yield 1000 mL of finished extract. Mix thoroughly (NF 1946).

Powdered Extract:

Macerate in alcohol for 48 hours, percolating slowly. Evaporate the percolate to a soft extract at a temperature not greater than 21 °C. Add a mixture of 1 part magnesium oxide and 3 parts dry starch or other permitted diluent to the residue; the amount added should equal one-fifth of the weight of the percolate. Mix thoroughly and evaporate to dryness at a temperature not exceeding 21 °C. Reduce the residue to a fine powder. If necessary, mix the powder with a sufficient amount of...
diluent to make the final extract contain 9 to 11 g of the ether-soluble alkaloids (NF 1946).

Ocular Solution:
Prepare as a 0.2% solution by combining 0.1 mL of recently filtered goldenseal tincture (1:5) with 50 mL of sterilized distilled water. Prepare fresh. Make sure there is no precipitate in the extract. Do not store.

**CONSTITUENTS**

The primary constituents of interest in goldenseal root are the alkaloids berberine, canadine, and hydrastine. Goldenseal typically contains 2.5% to 6.0% total alkaloids (Betz and others 1998). Berberine is primarily responsible for goldenseal’s bitter taste and yellow color.

**Isoquinoline and Phthalideisoquinoline Alkaloids**
Hydrastine (β-hydrastine: 1.5% to 4%), berberine (0.5% to 6%), anhydrous ether-soluble alkaloids (2.5%), canadine (tetrahydroberberine: 0.5% to 1.0%), canadaline, hydrastidine (3′-O-demethyl-β-hydrastine), isohydrastine (4′-O-demethyl-β-hydrastine), l-β-hydrastine, 5-hydroxytetrahydroberberine, (S)-corypalmine, (S)-isocorypalmine, (S)-tetrahydropalmatine, berberastine (traces) (Caille and others 1970; Fulde and Wichtl 1994; Genest and Hughes 1969; Gentry and others 1998; Gillis and Langenhans 1931; Messana and others 1980). Recent laboratory research has found goldenseal root to have a berberine to hydrastine ratio of 1.5:3.5. Hydrastine and canadine are unique to goldenseal (Betz and others 1998).

Note: The above values should be taken as relative estimates since more recent constituent analyses are lacking.

**Other Constituents**
Chlorogenic acid; two quinic acid derivatives, hycandinic acid esters-1 and -2, 8-oxotetrahydrothalifendine (Gentry and others 1998); lipids (75% unsaturated and 25% saturated fatty acids), including the unsaturated fatty acids stearic acid (62%), palmitic acid (28.7%), and arachidonic acid (9.3%); linoleic acid, oleic acid, phytosterol from the unsaponifiable fraction, phytosterin, resin, starch, sugar, and a small amount of volatile oil (Benigni and others 1971).

**ANALYTICAL**

There are a variety of needs regarding the qualitative analysis of goldenseal due to the presence of numerous botanical adulterants in the marketplace. Most of these adulterants, like goldenseal, contain berberine. Therefore, appropriate physical and/or chemical analyses must be used to establish the identity of crude material. Physical examination is invaluable and should include botanical identification through an appropriate vouchering program or macro- and microscopic identification of whole crude material by trained personnel. Chemical analysis of hydrastine or canadine is required since these alkaloids are specific to goldenseal. However, the presence of either hydrastine or canadine in a product is insufficient to diagnose adulteration, since admixtures of goldenseal with other berberine-containing plants is a common occurrence in the market. The presence of alkaloids not found in goldenseal, such as coptisine, found in Coptis spp., or jatorrhizine, found in other berberine-containing plants, would therefore better serve as a chemical indicator of adulteration (Betz and others 1998) (Table 3). The absence or presence of palmatine in goldenseal has not been conclusively determined. According to one source (Betz and others 1998), palmatine occurs only in Coptis spp. However, another study which analyzed goldenseal root powder samples from three manufacturers (two lots per manufacturer), reported palmatine to be present in both lots from one of the manufacturers (Weber and others 2001). No indication was given that the samples were from botanically authenticated sources, leaving open the possibility that the powder may have been adulterated with a palmatine-containing species.

The presence of hydrastine or canadine is likewise not sufficient to discern admixtures of goldenseal root with goldenseal leaf, for the latter has an alkaloid profile that is identical to that of the root. To identify leaf and root mixtures, appropriate physical assessment (see Macroscopic and Microscopic Identification) or more detailed chemical analyses are required. The presence of hydastinine (a degradation product of hydrastine) in goldenseal is considered to be an indication that the material is old or has been improperly dried or handled.

The American Herbal Pharmacopoeia™ has adopted a
thin layer chromatography (TLC) method for the identification of goldenseal that analyses palmatine and hydrastinine in addition to berberine and hydrastine. Using this method hydrastine and hydrastinine were identified in all of the goldenseal samples tested (Figures 7-9), while neither compound occurred in any of the adulterants tested (Berberis vulgaris, Coptis sp., Mahonia nervosa, Rumex sp., Xanthorhiza simplicissima; Figure 9a-d). Palmatine was best visualized with 366 nm detection (Figure 9b and d) and was not present in any of the authentic goldenseal samples analyzed (Figures 7-9). At 366 detection, a yellow band at the position of the palmatine standard was present in M anhonia nervosa, Berberis vulgaris, Xanthorhiza simplicissima, and C optis sp. This band may be due to the presence of palmatine, or it may be due to another compound eluting at the same Rf and color as the palmatine standard (Figures 9b and d). Regardless, using 366 nm detection, a yellow band at the position of palmatine does serve as a marker for all of the adulterants analyzed except yellow dock (Rumex sp.) and goldenseal leaf. While the current method can distinguish between pure samples of the authentic goldenseal root and leaf (using ninhydrin reagent, white light detection; Figure 8c), the standards and/or methods of detection are not sufficient to distinguish mixtures of root and leaf. TLC analysis of chlorophyll may provide a means of identifying such mixtures, depending on detection limits.

Quantitative analyses of goldenseal target berberine due to its reported bioactivity and hydrastine as an identity marker. For the quantitative analysis of goldenseal, Pharmeuropa (1999) has proposed a spectrophotometric method for the quantification of hydrastine and has further called for submission of methods for the quantification of berberine. The high performance liquid chromatography (HPLC) method adopted by the American Herbal Pharmacopoeia™ quantifies berberine and hydrastine and has been proposed for inclusion in the National Formulary (USPF 2000). The method has been substantiated by American Herbal Pharmacopoeia™ collaborating laboratories.

### High Performance Thin Layer Chromatography (HPTLC) for the Identification of Goldenseal Root

#### Sample Preparation

In a test tube, 0.25 g of powdered drug is extracted in an ultrasonic bath at room temperature for 30 minutes with 4 mL of a methanol and water mixture (80:20). The suspension is filtered and the residue washed twice with 2 mL methanol. The filtrate and washings are combined and brought up to volume with methanol in a 20 mL volumetric flask. One mL of the solution is transferred into a small sample vial. This is the test solution. The solution is sensitive to light and heat and must be stored in the refrigerator in an amber vial.

#### Standard Preparation

In a 50 mL volumetric flask, 25.0 mg (1R,9S)-β-hydrastine HCl, 1.0 mg hydrastinine HCl, 1.2 mg palmatine chloride, and 1.2 mg berberine chloride are dissolved in methanol. After dissolution is complete, the solution is brought up to volume with methanol. One mL of this solution is transferred into a small sample vial. This is the reference solution.

Note: Hydrastine is light and heat sensitive and readily decomposes.
Discussion of Chromatograms

7a) UV 254 nm: The standard solution (Lane 6) shows 4 bands: hydrastinine gives a sharp fluorescent blue band at R_f = 0.06, hydrastine gives a broad dark band at R_f = 0.30, palmatine gives a very weak dark band at R_f = 0.38, and berberine gives a very weak dark band at R_f = 0.51. The chromatogram of the test solution (Lane 3) shows a weak dark (not fluorescent) band at the position of, but not corresponding to, hydrastinine. Two strong dark bands are present at R_f = 0.30 and R_f = 0.52 corresponding to hydrastine and berberine, respectively. There is another weak dark band at R_f = 0.17. The test solution shows a very faint band with the same R_f as palmatine.

7b) UV 366 nm: The standard solution (Lane 6) shows 4 bands. Hydrastinine gives a sharp fluorescent blue-white band at R_f = 0.06, hydrastine gives a broad dark blue band at R_f = 0.30, palmatine gives a yellow band at R_f = 0.38, and berberine gives an intensely yellow band at R_f = 0.51. The chromatogram of the test solution (Lane 3) shows an intensely blue band at R_f = 0.06 corresponding in R_f and color to hydrastinine, a faint blue band at R_f = 0.31 corresponding to hydrastine, and a strong yellow band corresponding in color and R_f to berberine. There is another faint yellow band at R_f = 0.67. The test solution shows a very faint band with the same R_f as palmatine.

7c) Ninhydrin reagent, white light: The standard solution (Lane 6) shows 3 bands. Hydrastinine gives a dark yellow band at R_f = 0.31, and palmatine and berberine give a faint yellow band at R_f = 0.38 and 0.51, respectively. Hydrastinine is not visible with ninhydrin reagent. The chromatogram of the test solution (Lane 3) shows a dark brown band representing an unknown compound occurring at or near R_f = 0.06. While this compound interferes with fluorescence of hydrastinine under UV 254 nm detection, it does not when UV 366 nm detection is used. In addition, the chromatogram shows a broad yellow band at R_f = 0.31 corresponding to hydrastine, 3 brown bands between R_f = 0.06 and 0.31, and a strong yellow band corresponding in color and R_f to berberine. There is also a faint yellow band at R_f = 0.67.

Discussion of Chromatograms

8a) UV 254 nm: All of the goldenseal test solutions show identical chromatograms with clearly resolved bands corresponding in color and R_f to hydrastinine, hydrastine, and berberine as described previously. The bands in the chromatogram of goldenseal leaf (Lane 5) are of lower intensity, especially with regard to the three alkaloids. The chromatogram of the mixture of goldenseal root and leaf is identical to that of the root alone, indicating that this method of
Detection is not sufficient for differentiating between pure root and mixed root and leaf. The concentration of the reference standards applied (Lane 7) was not sufficient for good visualization in this chromatogram.

8b) UV 366 nm: As described above, all of the goldenseal chromatograms are identical in appearance except for the relatively low intensity of bands corresponding to the alkaloids in goldenseal leaf (Lane 5). Clearly resolved bands corresponding in color and \( R_f \) to hydrastinine, hydrastine, and berberine are present. Palmatine is visible in the chromatogram of the standard solution (Lane 7).

8c) Ninhydrin reagent, white light: As described above, all of the goldenseal chromatograms are identical except for that of goldenseal leaf (Lane 5). Faint bands at the level of palmatine (\( R_f = 0.38 \)) are visible in the goldenseal samples but are not visible in the standard solution. In this figure, the band observed at the start position in each of the root extract solutions is lacking in the leaf test solution. The reference standards (Lane 7) are only faintly visible in this chromatogram. Hydrastinine is not visualized by ninhydrin reagent. All chromatograms except that of goldenseal leaf show a brown band occurring at or near the level of hydrastinine that corresponds to a compound eluting at the same \( R_f \) as hydrastinine. This compound does not interfere with fluorescence of hydrastinine under either UV 254 nm or UV 366 nm detection.

8d) Ninhydrin reagent, white light

Figures 9a-d HPTLC of goldenseal root and common adulterants

Lane 1: 5 µL of standard mixture: hydrastinine, hydrastine, palmatine, berberine (with increasing \( R_f \)).

Lane 2: Yellow dock root (Rumex sp.).

Lane 3: Oregon grape root (Mahonia nervosa).

Lane 4: Goldthread root (Coptis sp.).

Lane 5: Yellow root (leaf) (Xanthorrhiza simplicissima).

Lane 6: Goldenseal root (Hydrastis canadensis).

Lane 7: Yellow root (stem) (Xanthorrhiza simplicissima).

Lane 8: Yellow root (root) (Xanthorrhiza simplicissima).

Lane 9: Oregon grape root (Mahonia nervosa).

Lane 10: Barberry root (Berberis vulgaris).

Lane 11: 3 µL of standard mixture: hydrastinine, hydrastine, palmatine, berberine (with increasing \( R_f \)).

Discussion of Chromatograms

9a) UV 254 nm: Standard solution (Lanes 1 and 11): Hydrastinine gives a sharp fluorescent blue band at \( R_f = 0.06 \); hydrastine gives a broad blue band at \( R_f = 0.30 \); palmatine gives a weak dark band at \( R_f = 0.38 \); and berberine gives a weak dark band at \( R_f = 0.51 \).

Yellow dock root (Rumex sp.) (Lane 2): There are several weak bands in the upper third of the chromatogram. One of those bands is at the solvent front. There is a sharp band at \( R_f = 0.01 \) and another fainter band immediately above this. There are no bands matching the \( R_f \) of any of the standards.

Oregon grape root (Mahonia nervosa) (Lane 3): There is a dark band at \( R_f = 0.01 \) and a weak band at \( R_f = 0.49 \). There are no bands matching the \( R_f \) and color of any of the standards. The band at the position of hydrastinine (\( R_f = 0.06 \)) does not correspond in color to the hydrastinine standard. There is a weak band corresponding in \( R_f \) to berberine.

Goldthread root (Coptis sp.) (Lane 4): There is a dark band at \( R_f = 0.01 \) and a dark band present at \( R_f = 0.38 \) corresponding to palmatine. There is a strong dark band at \( R_f = 0.51 \) corresponding to berberine. Two weak bands are seen between berberine and palmatine. There is a band slightly below hydrastine believed to correspond to jatrorhizine (a reference standard was not included). There are no bands corresponding to hydrastine and hydrastinine; the band at the position of hydrastinine (\( R_f = 0.06 \)) does not correspond to the standard in color.

Yellow root (Xanthorrhiza simplicissima): The leaf (Lane 5) shows a strong band at \( R_f = 0.51 \) corresponding to berberine and a weak band slightly above the position of palmatine. There is a weak band close to the solvent front. The stem (Lane 7) is lacking the band
above the position of palmatine and shows a dark band corres-
ponding to berberine, as well as a band at \( R_f = 0.01 \). The root (Lane 8) shows a dark band corresponding to berberine and bands above and below berberine. A band at \( R_f = 0.02 \) is also present. There are no bands corresponding to hydrastine or hydastinine. The band at the position of hydastarine (\( R_f = 0.06 \)) does not correspond to the standard in color.

Goldenseal root (Hydrastis canadensis) (Lane 6): There is an intense dark band at \( R_f = 0.51 \) corresponding to berberine. A weak blue band corresponding to hydastrine is present at \( R_f = 0.30 \). There is a weak, dark, non-fluorescent band at \( R_f = 0.06 \) that corresponds to hydastinine and another broad band at \( R_f = 0.18 \).

Oregon grape root (Mahonia nervosa) and barberry root (Berberis vulgaris) (Lanes 9 and 10, respectively): These give almost identical profiles with double bands at \( R_f = 0.5 \), the upper band corresponding to berberine. There is a weak band at the same \( R_f \) as palmatine (\( R_f = 0.38 \)), a non-fluorescent band at \( R_f = 0.01 \), and one weak band close to the solvent front.

9b-c) UV 366 nm (normal and overexposed): Standard solution (Lanes 1 and 11): At normal exposure, hydastrine gives a sharp blue-white band at \( R_f = 0.06 \), hydrastine gives a broad dark blue band at \( R_f = 0.30 \), palmatine gives a yellow band at \( R_f = 0.38 \), and berberine gives a yellow band at \( R_f = 0.51 \). When overexposed, all reference compounds, with the exception of hydastrine, which is dark and barely perceptible, are more intense.

Yellow dock root (Rumex sp.) (Lane 2): At normal exposure no bands are observable. When overexposed, two blue and three brown bands are seen in the upper third of the chromatogram including a reddish brown band in the solvent front. There are no bands matching the \( R_f \) of any of the standards.

Oregon grape root (Mahonia nervosa) (Lane 3): At both exposures there are two yellow bands (darker under normal exposure), one corresponding in \( R_f \) and color to berberine and the other to palma-
tine. There is also a dark band at \( R_f = 0.01 \). When overexposed, there are four brown bands below \( R_f = 0.3 \). One of those bands matches the position but not the color of hydastrine.

Goldthread root (Coptis sp.) (Lane 4): At normal exposure there are strong yellow bands at \( R_f = 0.51 \) corresponding to berberine, at \( R_f = 0.38 \) corresponding to palmatine, and at \( R_f = 0.24 \) believed to be due to jatorrhizine (a reference standard was not included). There is also a faint brown band at the start position. When overexposed, these three primary yellow bands blur into each other. Additionally, there is a brown band directly above berberine and a blue band at \( R_f = 0.83 \). There are no bands corresponding to hydastrine or hydastinine, although clear yellow bands are visible at the start position and above the level of the hydastrine standard in the overexposed image.

Yellow root (Xanthorrhiza simplicissima): At normal exposure, the leaf (Lane 5) shows a yellow band at \( R_f = 0.51 \) corresponding to berberine and a lighter band below this. The stem (Lane 7) and root (Lane 8) show an additional yellow band immediately below berberine and a dark yellow band at \( R_f = 0.38 \), corresponding to palmatine. When overexposed, the leaf shows a strong yellow band at \( R_f = 0.51 \) corresponding to berberine and two weak bands below. There is a blue band at \( R_f = 0.83 \) in each of the chromatograms, though it is more pronounced in the stem and root. There is an additional brown band above the blue band in the leaf solution. The three yellow bands in the stem and root are much stronger than those in the leaf.

The stem and root also show a brown band at \( R_f = 0.01 \) and another non-fluorescent band at \( R_f = 0.06 \).

Goldenseal root (Hydrastis canadensis) (Lane 6): At both exposures, a sharp blue band corresponding to hydastrine at \( R_f = 0.06 \), a broader blue band at \( R_f = 0.30 \) corresponding to hydastrine, and a broad, bright yellow band corresponding to berberine at \( R_f = 0.51 \) are seen. When overexposed, there is additionally a weak blue band at \( R_f = 0.83 \).

Oregon grape root (Mahonia nervosa) and barberry root (Berberis vulgaris) (Lanes 9 and 10, respectively): Both profiles are identical. At normal exposure, these solutions show yellow bands corre-
sponding in color and \( R_f \) to berberine and palmatine. When overex-
posed an additional brown band at \( R_f = 0.01 \) and one blue band at \( R_f = 0.83 \) are seen.

9d) Ninhydrin reagent, white light: Standard solution (Lanes 1 and 11): Hydastrine gives a dark yellow band at \( R_f = 0.30 \), palmatine gives a very faint yellow band at \( R_f = 0.38 \), and berberine a very faint yel-
low band at \( R_f = 0.51 \). Hydastrine gives no reaction with ninhydrin.

Yellow dock root (Rumex sp.) (Lane 2): There is a yellow band close to the solvent front and four brown bands below \( R_f = 0.3 \). There are no bands matching the \( R_f \) of any of the standards.

Oregon grape root (Mahonia nervosa) (Lane 3): There are two very faint yellow bands matching in color and \( R_f \) to berberine and palmatine. There are four brown bands below \( R_f = 0.3 \), one at \( R_f = 0.06 \).

Goldthread root (Coptis sp.) (Lane 4): There are two yellow bands matching berberine and palmatine in color and \( R_f \). There is a third faint yellow band at \( R_f = 0.24 \), thought to be due to jatorrhizine (a reference standard was not included). There are four faint brown bands below \( R_f = 0.3 \), one at \( R_f = 0.06 \).

Yellow root (Xanthorrhiza simplicissima): The leaf (Lane 5) shows a very faint yellow band at \( R_f = 0.51 \) corresponding to berberine. There are four faint brown bands below \( R_f = 0.3 \), one at \( R_f = 0.06 \).

The stem and root also show a brown band at \( R_f = 0.01 \) and another non-fluorescent band at \( R_f = 0.06 \).

Goldenseal root (Hydrastis canadensis) (Lane 6): At both exposures, a sharp blue band corresponding to hydastrine at \( R_f = 0.06 \), a broader blue band at \( R_f = 0.30 \) corresponding to hydastrine, and a broad, bright yellow band corresponding to berberine at \( R_f = 0.51 \) are seen. When overexposed, there is additionally a weak blue band at \( R_f = 0.83 \).

Oregon grape root (Mahonia nervosa) and barberry root (Berberis vulgaris) (Lanes 9 and 10, respectively): These show yellow bands at \( R_f = 0.50 \) corresponding to berberine. There are four brown bands below \( R_f = 0.3 \), one at \( R_f = 0.06 \).
**Ninhydrin Reagent (optional)**

Ninhydrin reagent is prepared by dissolving 0.6 g ninhydrin in 190 mL isopropanol/5 mL acetic acid.

**Chromatographic Conditions**

**Stationary Phase:**

HPTLC plates 10 x 10 cm or 20 x 10 cm silica gel 60 F 254.

Note: HPTLC plates allow for better separation, shorter development times, and less solvent. Standard TLC plates can also be used under the same conditions.

**Solvent System:**


**Sample Application:**

5 µL test solution and 5 µL standard are applied each as a 8 mm band with 4 mm distance between bands. Application position should be 8 mm from lower edge of plate.

**Development:**

10 x 10 cm or 20 x 10 cm Twin Trough Chamber, chamber pre-saturated for 15 minutes, 5 mL or 10 mL, developing solvent, respectively, per trough. Developing distance 60 mm from lower edge of plate. Dry plate in a stream of cold air.

**Detection:**

- a) UV 254 nm.
- b) UV 366 nm.
- c) Ninhydrin reagent (optional): Immerse plate in or spray plate with reagent for 2 seconds, then dry in a stream of cold air. Heat plate to 120 °C for two minutes. Evaluate under white light.

**Rf Values:**

Compare to the chromatograms provided.

**High Performance Liquid Chromatography (HPLC) for Berberine and Hydrastine**

**Sample Preparation**

Place 1.0 g of accurately weighed finely powdered goldenseal rhizome and root into an extraction thimble. Connect soxhlet extractor to a 500-mL round bottom flask. Add 200 mL* of methanol to the powder and extract for 6 hours or until the solvent is clear. The volume of the thimble should be at least one-half the volume of methanol. Cool to room temperature and transfer the extract to a 250-mL volumetric flask. Rinse the extraction apparatus with methanol and transfer the rinsings to the volumetric flask, diluting with methanol to volume.

* The original method proposed by USP recommends 150 mL of methanol for extraction of goldenseal for the sample preparation. This amount was insufficient and was increased to 200 mL.

**Standard Preparation**

Dissolve accurately weighed quantities of berberine chloride and hydrastine hydrochloride in a 1:1 mixture of water and methanol to obtain a solution containing approximately 0.2 mg/mL of each standard. The standard solution must be prepared fresh daily. Reference standards are available from Chromadex Inc, Laguna Hills, CA and Phytocal, Little Falls, NJ, among others.

Note: To account for the concentration of chlorides, the concentrations of berberine and hydrastine in the standard solution are calculated by multiplying the concentration of each reference standard by correction factors of 0.905 and 0.913, respectively. The correction factor for berberine chloride dihydrate is 0.825.

**Chromatographic Conditions**

**Column:** Phenomenex Luna 2, C 18, 5 µm, 4.6 x 150 mm or equivalent.

**Column Temperature:** Ambient.

**Mobile Phase:** Isocratic: 27% acetonitrile, 73% 0.1M potassium dihydrogen phosphate.

**Flow Rate:** 1.8 mL/minute.

**Detection:** 235 nm.

**Injection Volume:** 10 µL

**Run Time:** 10 minutes.

**Calculation**

Measuring the areas under the major peaks, calculate the percentage of berberine and hydrastine using the following formula:

\[
100 \left( \frac{C V}{W} \right) \left( \frac{r_u}{r_s} \right)
\]

C = Concentration (mg/mL) of berberine or hydrastine in the reference standards used in the standard solution (calculated using the correction factors given above).

V = Final volume (mL) of the sample solution.

W = Weight (mg) of goldenseal sample used.

r_u = Peak areas for berberine and hydrastine obtained from the sample solution.

r_s = Peak areas for berberine and hydrastine obtained from the standard solution.

**System Suitability**

The capacity factor determined from hydrastine and berberine peaks should not be less than 3.0, the column efficiency should not be less than 2.0, and the relative standard deviation for replicate injections should not exceed 2.0%.

**Linearity Range**

The linearity range was 20% to 200% of the target concentrations of hydrastine and berberine. The correlation coefficient was > 0.999 for both compounds.

**Quantitative Standards**

**Foreign Organic Matter:** Not to exceed 2% (USP 2000).

**Total Ash:** Not to exceed 9% (USP 2000).

**Acid Insoluble Ash:** Not to exceed 5% (USP 2000).

**Loss of Moisture on Drying:** Not to exceed 12.0% determined on 2 g of powdered goldenseal dried at 100 °C for 5 hours (USP 2000).

* Calculated according to USP protocols.
**Figure 10** HPLC chromatogram for berberine and hydrastine

**Therapeutics**
Currently, the most common clinical use of goldenseal by herbal practitioners is as an antimicrobial and anti-secretory for a variety of infections affecting the mucosa, such as upper respiratory and sinus infections, intestinal infections, cystitis, vaginitis, and conjunctivitis. For these purposes it is used both internally and topically. Less commonly it is used as a bitter, though for this purpose more widely available bitters are preferred.

The pharmacologic activity of goldenseal root has not yet been fully elucidated and there are almost no data regarding its use in humans. There are likewise few animal and in vitro studies on the effect of crude goldenseal or the alkaloids directly extracted from it, namely berberine, hydrastine, canadine, and canadaline. What in vitro and animal data exist support goldenseal’s antimicrobial and smooth muscle spasmolytic and contractile effects. Additional in vitro research suggests that goldenseal possesses antitumor and antioxidant activities as well, though it is not currently widely used for these effects. The therapeutic relevance of such preclinical data is unknown.

Despite the paucity of pharmacologic and therapeutic research done on goldenseal, there is a plethora of data on the effects of berberine and its sulfate, chloride, and hydrochloride salts derived from other plants. A direct correlation of the results from these studies with effects of whole goldenseal cannot be made. Similarly, studies citing systemic effects of berberine administered through nonoral routes may be clinically irrelevant to the oral administration of berberine. In addition, from the information available it is clear that compounds other than berberine contribute to goldenseal’s effects. Given such limitations to the pharmacologic research presented below, it is not possible to extrapolate findings from pre-clinical studies using isolated compounds to the effectiveness of orally-administered goldenseal extract in humans. For this reason, studies using goldenseal and goldenseal products are generally presented separately from those using isolated compounds. Studies using isolated alkaloids are presented because they allow us to generate hypotheses concerning possible uses of goldenseal, many of which support traditional uses of this botanical.

**Pharmacokinetics of Berberine**
At this writing there does not appear to be human or animal data available regarding the pharmacokinetics of orally administered goldenseal or goldenseal alkaloids. There is, however, limited data available showing that the absorption and distribution of orally-administered berberine derived from other plants is minimal, though sufficient to elicit clinical activity in some studies.

**Human Clinical Studies**
In an uncontrolled study, Zeng and Zeng (1999) correlated the efficacy of berberine with berberine plasma concentration in treating arrhythmias associated with congestive heart failure (CHF). Fifty-six patients with CHF were treated orally (po) with 1.2 g berberine daily for 2 weeks, at which point cardiac function and plasma berberine levels were assayed. It was determined that berberine plasma concentration peaked 2.4 hours after administration with the concentration/elapsed time relationship fitting the one-compartment open model. Treatment resulted in two patient subgroups: patient group A presented peak plasma berberine levels of 0.07 ± 0.08 mg/L and patient group B presented peak plasma berberine levels of 0.08 ± 0.08 mg/L. Hence, only a fraction of the administered berberine was detectable in plasma with metabolism being the most likely fate. The clinical efficacy of berberine treatment was directly proportional to the plasma berberine concentration (more details presented under Cardiovascular Effects).

Prior to this report, the clinical pharmacokinetics of orally administered berberine had only been described in healthy volunteers, in whom it was shown that berberine could reach levels in the plasma resulting in the inhibition of the cellular transport of potassium (values not reported) (Li and others 1995; cited in Zeng and Zeng 1999).

In an earlier report, Miyazaki and colleagues (1978) found that only 0.043% of a 100 mg oral dose of berberine was recoverable from the urine of normal volunteers after 24 hours.

**Animal Studies**
The pharmacokinetics of orally-administered berberine was studied in healthy dogs (n = 5) (Sheng and others 1993; Table 4). Evaluation was conducted using four different dosages: 45 mg/kg, single dose (n = 4); 45 mg/kg twice daily (bid) for 1 week (n = 4); 280 mg/kg, single dose (n = 3); and 700 mg/kg, single dose (n = 2). Berberine was
Table 4  Mean pharmacokinetic parameters of orally administered berberine (280 mg/kg) in the plasma of beagles

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (± Standard Deviation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{1/2}$</td>
<td>0.63 h (± 0.14)</td>
</tr>
<tr>
<td>$T_{1/2}$ elimation</td>
<td>38.42 h (± 14.36)</td>
</tr>
<tr>
<td>$T_{max}$</td>
<td>3.71 h (± 0.95)</td>
</tr>
<tr>
<td>Peak concentration</td>
<td>15.46 µg/L (± 4.20)</td>
</tr>
<tr>
<td>AUC</td>
<td>777.29 µg/h/L (± 150.10)</td>
</tr>
<tr>
<td>Distribution</td>
<td>125.41 L (± 32.55)</td>
</tr>
<tr>
<td>Clearance rate</td>
<td>2.64/h (± 0.55)</td>
</tr>
</tbody>
</table>

Key: $T_{1/2}$ = half life; $T_{1/2}$ elimation = elimination half-life; $T_{max}$ = time to maximum concentration; AUC = area under the curve.

Source: Data from Sheng and others (1993).

undetectable in plasma after administration of both 45 mg dosages (limit of detection 10 µg/L) at 280 mg/kg, vomiting occurred within 1 hour; at 700 mg/kg, vomiting and diarrhea occurred. Even at these higher doses blood concentration of berberine was still extremely low. Following the 280 mg/kg dose, a concentration of 31.4 and 22.6 µg/L was seen at 2 and 3 hours, respectively. At the 700 mg/kg dose, berberine concentrations of 21.5, 44.9, 49.5, 36.4, 27.8, and 16.0 µg/L were recorded at 2, 3, 5, 7, 9, and 24 hours, respectively. Based on the average weight of the dogs, it was estimated that 2% of each administered dose of berberine was absorbed. This level of absorption is much lower than what the researchers claim is required to elicit a cardiovascular effect in vitro (1 mg/mL). These researchers also pointed out that clinical reports on effects of chronic ingestion of berberine are difficult to explain considering the relatively low plasma levels of berberine that are typically found and noted that further dose-effect studies were needed.

Chen and Chang (1995) used HPLC to measure berberine in the plasma, urine, and bile of healthy rabbits after iv bolus and intramuscular (im) administration of 2 mg/kg berberine sulfate. The cumulative urinary excretion of berberine over a 48 hour period after iv bolus administration was 4.93% of the administered dose. The cumulative biliary excretion over a 5.5 hour period after iv bolus administration was only 0.5% of the administered dose.

Utilizing nonspecific analytical techniques such as fluorometry and ultraviolet spectrometry in a healthy rat model, Schein and Hanna (1960) found that berberine accumulated in the heart, liver, omental fat, plasma, and most persistently, in the pancreas. The levels found in these respective tissues depended on administration route, with oral administration (at doses as high as 1.0 g/kg) resulting in the lowest concentrations of berberine in the various tissues. In another study, berberine sulfate was administered orally to healthy rabbits and those infected with cholera or treated with a cholera toxin (Bhide and others 1969). Berberine plasma levels peaked within 8 hours in all groups, remaining detectable for up to 72 hours. Berberine levels were lower in the heart and higher in the liver and kidney in infected animals compared to healthy ones. After im administration to healthy rabbits, berberine blood levels peaked at 4 hours with concentrations highest in the heart, followed by the kidney, then liver. It was noted that metabolism occurred in the liver and excretion was via the stools and urine.

A recent study by Baird and others (1997) hypothesized that the diseased state of the intestinal epithelium during illnesses with symptomatic diarrhea may affect the pharmacokinetics of berberine. In particular, the increase in epithelial permeability during diarrhea may allow for the improved absorption of orally or parenterally-administered berberine. Using isolated rat colon, these researchers found that tissues pretreated with cytochalasin D (which enhances paracellular permeability and was used to simulate the diseased state) significantly increased absorption of berberine compared to untreated tissues (P < 0.05). The inhibitory effect of berberine on ion exchange in secretory diarrhea was greater when berberine was applied to the serosal versus the mucosal side of the intestinal epithelium. Since berberine acts as an anti-secretory, it was suggested that its efficacy would be self-limiting since its absorption would decrease as symptoms improved.

Clinical Efficacy and Pharmacodynamics

Effects of Goldenseal Preparations

Because of the sparse human clinical data on the use of goldenseal preparations, it is difficult to ascertain the clinical value of this botanical. The available data support goldenseal’s local antimicrobial and contrasting spasmylic and contractile effects. The traditional use of goldenseal for the treatment of uterine hemorrhage has found mixed support. Less convincing data suggest that goldenseal may shorten antibody response time and stimulate the secretion of digestive enzymes.

Antimicrobial Effects

In Vitro Studies

There are no human clinical trials studying the antimicrobial effects of goldenseal products. Gentry and others (1998) screened crude extracts of commercial goldenseal root in an assay for activity against multiple drug resistant Mycobacterium tuberculosis and other organisms. The extract exhibited reproducible activity at 1000 µg/mL against Candida albicans, Klebsiella pneumoniae, M. smegmatis, and Staphylococcus aureus in a primary screen, and antitubercular activity against the more clinically relevant M. avium complex, M. intracellulare, and M. tuberculosis, as well as bacille Calmette-Guerin (BCG), in secondary screens. Bioassay-guided fractionation was undertaken to isolate and identify the active components of the extract. Several compounds were isolated including β-hydrastine, canadine, and 3 newly described compounds, but only purified berberine was found to be active. Isolated berberine, however, displayed weak activity compared to the activity of the total extract, implying that some additional mechanism accounts for the enhanced activity observed with the crude extract.
Scaccocchio and others (1998) characterized the in vitro antimicrobial activity of a goldenseal extract and the major alkaloids isolated therefrom (berberine, β-hydrastine, canadine, and canadaline) against 6 strains of bacterial pathogens (Table 5). Based on the data presented, and the conclusions of the researchers, compounds other than berberine contribute markedly to the antimicrobial activity observed. Moreover, they reported these same compounds were synergistic in eliciting activity on isolated organ tissues.

**D i g e s t i v e  E f f e c t s**

Goldenseal has historically been used as a bitter digestive stimulant. Bitters are primarily used to enhance bile secretion, improve digestion, and increase appetite. The two studies presented which investigated this effect are both dated and gave contrasting results.

**H u m a n  C l i n i c a l  S t u d i e s**

In 1956, Wolf and Mack attempted to understand what action, if any, bitters exert on digestion when administered directly through a gastrostomy opening in order to prevent stimulation of taste receptors. The experiment was carried out with a single individual and a total of 96 assays predominantly focusing on increased gastric acidity were conducted. Six bitter preparations were tested including a compound tincture of gentian (Gentiana spp.) and hydroalcoholic extracts of barberry (Berberis vulgaris), black haw (Viburnum prunifolium), blessed thistle (Cnicus benedictus), gentian, and goldenseal. Alcohol was used as a control and did not increase gastric acidity. All bitters increased gastric function after 30 or 60 minutes, though to variable degrees. The most consistent effect was observed with goldenseal fluid extract. When introduced directly into the stomach, an immediate salivary response was stimulated. The researchers concluded that the effect was due to a direct action on the stomach or duodenum.

**A n i m a l  S t u d i e s**

A series of experiments was performed to determine the potential appetite enhancing effect of goldenseal and other bitter herbs (black haw [Viburnum prunifolium], blessed thistle [Cnicus benedictus], and gentian [Gentiana lutea]) in rats. No differences in weight gain were observed between animals administered goldenseal powder at 0.5% of the diet and controls (Garb and Cattell 1956).

**Immunomodulatory E f f e c t s**

**Animal Studies**

Rehman and others (1999) studied the effect of continuous goldenseal treatment on immunological responses in rats. Rats were treated with 6.6 g/L of a glycerin-based goldenseal extract in their drinking water for 6 weeks in order to determine how such treatment modulates antigen-specific immunity. This was determined via continuous monitoring of immunoglobulin (Ig) production over the treatment period. Rats were injected ip with the novel antigen keyhole limpet hemocyanin on day 0 and again after 2 weeks, with re-exposure at the 4th week. The goldenseal-treated group had an

<table>
<thead>
<tr>
<th>Test Material</th>
<th>S. aureus (Atcc 25923)</th>
<th>S. aureus (Atcc P6538)</th>
<th>S. sanguis (Atcc 10556)</th>
<th>E. coli (Atcc 25922)</th>
<th>P. aeruginosa (Atcc 27853)</th>
<th>C. albicans (Atcc 3153)</th>
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<tbody>
<tr>
<td>Standard Extract</td>
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<tr>
<td>1 mL</td>
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<td>4</td>
<td>120</td>
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<tr>
<td>0.5 mL</td>
<td>15</td>
<td>30</td>
<td>8</td>
<td>120</td>
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<td>30</td>
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<tr>
<td>Canadaline</td>
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<td>3.0 mg/mL</td>
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<tr>
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<td>&gt; 120</td>
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<tr>
<td>β-hydrastine</td>
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</table>

augmented acute primary IgM response compared to controls during the first 2 weeks of treatment but failed to show any changes in IgG response. These researchers found that herbal treatment did not elevate maximal Ig levels but rather accelerated the response, causing antibody levels to increase more rapidly.

**Smooth Muscle Spasmolytic and Contractile Effects**

The animal and in vitro studies presented below have found contrasting contractile and spasmolytic effects of goldenseal on vascular tissue, the intestines, uterus, bladder, trachea, and prostate. Many of the studies have also investigated the effects of alkaloids isolated from goldenseal; for clarity, these are presented here along with results from whole extracts. These effects on smooth muscle tissue are thought to be due to the receptor binding effects of the various alkaloids found in goldenseal (see Receptor Binding Effects under Effects of Isolated Compounds).

**Animal and In Vitro Studies**

Recent work has focused on the in vitro relaxant effects of goldenseal and its major alkaloids on various smooth muscle models, including isolated guinea pig trachea and ileum, rat uterus, and rabbit aorta (Abdel-Haq and others 2000; Cometa and others 1996, 1998; Palmery and others 1993, 1996). In their 1998 study, Cometa and others found that goldenseal extract applied to carbachol-preconstricted isolated guinea pig trachea, induced dose-dependent relaxation (at doses 0.1-10 μg/mL; EC₅₀ 1.6 ± 0.943 μg/mL). Incubation with the β-blocker timolol (at doses sufficient to induce a total block of isoproterenol-induced tracheal relaxation) only partially inhibited relaxation induced by the extract (EC₅₀ 5.28 ± 0.653 μg/mL). This research group then investigated the relaxant effect of isolated alkaloids from goldenseal extract on the same model (Abdel-Haq and others 2000). Berberine, β-hydrastine, canadine, and canadaline had EC₅₀ values of 34.2 ± 0.6, 72.8 ± 0.6, 11.9 ± 1.2, 2.4 ± 0.8 μg/mL, respectively. Timolol antagonized canadine and canadaline only, while xanthine amine congener antagonized β-hydrastine and canadaline only. Though the mechanism of action of goldenseal and its alkaloids could not be determined conclusively, the researchers hypothesized an agonistic effect at β-adrenergic receptors, based on the ability of timolol to antagonize the relaxant activity of the extract and some of its alkaloids. They further hypothesized that other mechanisms may be at work as well, including an effect at adenosine receptor sites (based on the ability of xanthine amine congener to inhibit the relaxant effect of β-hydrastine and canadaline) and interaction with ion channels.

In another series of studies, the same research group (Palmery and others 1993, 1996) investigated the in vitro spasmolytic activity of goldenseal extracts and the alkaloids isolated therefrom on isolated rabbit aorta. Berberine, canadine, and canadaline applied singly inhibited the contractile response to lower epinephrine concentrations (4.5 x 10⁻⁶ M) but not to higher ones (5 x 10⁻⁵ M), while the total extract inhibited the contractile response to all epinephrine concentrations; β-hydrastine was inactive in this system (Palmery 1996). The alkaloid mixture (berberine, canadine, and canadaline) was of higher adrenolytic potency than either the single alkaloids or the total extract. The fact that the largest adrenolytic effect was observed with berberine applied singly at a dose of 1.2 x 10⁻⁴ M, indicated that the effects of the alkaloids were not additive. These researchers suggested that the difference in potency between the total extract and the alkaloid mixture was due to the presence of other compounds in the total extract (such as β-hydrastine) that counteract the adrenolytic activity of berberine, canadine, and canadaline. They speculated that these other compounds may be responsible for goldenseal's traditional use as a vasoconstrictor. In another study by the same research group using the same model, the total extract was found to have a dose-dependent vasoconstrictive effect at doses of 50 μL/mL or above (Palmery and others 1993). At doses of 1, 10, and 30 μL/mL, the total extract caused a dose-dependent inhibition of adrenaline-induced contractions. Given alone, berberine had a vasorelaxant effect, while hydrastine was inactive.

The spasmylocytic activity of goldenseal total extract has also been demonstrated in rabbit prostate strips (Baldazzi and others 1998) and rabbit bladder detrusor muscle (Bolle and others 1998). The non-selective β-blocker propanolol was 69% effective in blocking goldenseal extract's spasmylocytic effect on rabbit bladder detrusor muscle which these researchers suggested implies partially non-adrenergically mediated muscle relaxant effects in this tissue (Baldazzi and others 1998; Bolle and others 1999).

Cometa and others (1996) studied the contractile effect of alkaloids derived directly from goldenseal root (10 mg/mL canadine, β-hydrastine, canadaline, or berberine in dimethyl sulfoxide) in the perfused guinea pig ileum model. Both berberine and canadine stimulated contractile activity in a dose-dependent manner, canadine had little activity, and β-hydrastine was inactive in this system. Berberine was the most potent of the alkaloids assayed, followed by canadine and canadaline. The pharmacologic activity of canadine was further evaluated through the use of cholinergic receptor subtype-selective antagonists. The researchers proposed that canadine may cause contraction of guinea pig ileum by increasing acetylcholine release from postganglionic parasympathetic nerve endings by an unexplained interaction with muscarinic acetylcholine receptors.

The older literature contains contrasting opinions regarding the appropriateness of goldenseal for the treatment of uterine hemorrhage. In an early veterinary medicine report, Graf and Riebe (1931) reviewed the use of fresh goldenseal tincture and isolated goldenseal alkaloids for the treatment of uterine hemorrhage and bleeding during labor. The hemostatic effect of goldenseal was thought to be due primarily to localized vasoconstriction and secondarily to the stimulation of uterine contractions. Their review of the literature found contrasting examples of vasoconstrictive and vasodilatory effects, as well as uterine stimulant and relaxant effects. Hydrastine and hydrastinine generally acted
as vasoconstrictors and uterine stimulants. In their own experiments, the researchers found that these two alkaloids increased uterine tone with a variable increase in contraction strength. Gibbs (1947) also found that hydastine increased the rate of uterine contraction in rat uteri, with decreased tone and amplitude. Imaseki and others (1961) reported that berberine acts as a uterine stimulant in mice.

Other studies, however, have found an overall uterine relaxant effect of goldenseal extract and berberine applied singly. Gibbs (1947) found a relaxant effect of goldenseal and its alkaloids on rat uteri. Berberine applied alone to the uteri of rats caused a slow diminution of tone, amplitude, rate, and response to acetylcholine, while hydastine had the opposite effect (above). Administered together, however, berberine and hydastine caused a rapid decrease in tone and amplitude of uterine contractions akin to that produced by the total extract of goldenseal. Cometa and others (1998) and Haginawa and Harada (1962) also reported a relaxant effect of goldenseal on rat uteri. In the former study, goldenseal extract antagonized the contractile effects of oxytocin and acetylcholine. Given how dated four of the studies on uterine effects are, and given their contrasting results, more work needs to be done to determine under what conditions goldenseal acts as a uterine stimulant or relaxant and whether the traditional use of goldenseal to stop uterine bleeding is due to an effect on the uterine muscle or to a local, vasoconstrictive, hemostatic effect.

In summary, in vitro work on smooth muscle tissue has found that goldenseal elicits both a spasmodylitic and contractile effect. Further research is necessary to positively identify in what organs and under what conditions, goldenseal and alkaloids derived from it exert these different effects on smooth muscle.

Other Effects
Goldenseal is often cited as having an effect on lowering blood sugar levels for the treatment of diabetes. In one study, streptozotocin (200 mg/kg ip) was used to induce diabetes in adult male mice (Swanson-Flatt and others 1989). After 6 days, groups of mice were supplied ad libitum with traditional herbal treatments, including goldenseal (6.25%), added to standard Spratts Laboratory Diet I (Lillico Ltd, Reigate, UK). Control diabetic groups received only the standard pellet diet. While none of the botanical treatments tested produced a significant hypoglycemic effect, both hyperphagia and polydipsia attributed to diabetes were significantly reduced in goldenseal-fed mice. Silva and others (2000) investigated the antioxidant potential of the hydrogen donating antioxidants in goldenseal by testing their ability to scavenge the radical cation ABTS\(^+\). Goldenseal extract (ethanol/water 7:3, at a dilution of 1:1000) elicited antioxidant activity approximately similar to 40 \(\mu\)M of Trolox.

Goldenseal has been used for its alleged ability to interfere with tests for recreational drug use. This use apparently dates from the time when TLC of urine was used to test for morphine glucuronide (Morgan 1994). It was claimed that compounds in goldenseal could interfere with the TLC band identifying morphine glucuronide. Even if this were true, goldenseal would not interfere with immunoassay or gas chromatography-mass spectroscopy screening tests. One study was found that tested for the masking effects of goldenseal in morphine testing (Gorodetzky 1985). At a drug addiction center, a single dose of heroin (5 mg/70 kg iv), 4 goldenseal capsules (~530-575 mg per capsule po), and 72 ounces of water po were administered alone and in various combinations to 6 drug-free volunteers in an 8 week crossover study. Urine was collected 3 days after treatment and was pooled into four 8-hour samples. Morphine was tested for using EMIT, RIA-I\(^{135}\), and TLC. Goldenseal alone resulted in neither false positives nor false negatives. Water alone diluted the first 8-hour urine samples, but did not result in significant false negatives. Goldenseal and water administered together diluted the second 8-hour samples and resulted in significant false negatives during that period using the less sensitive screening tests (> 100 ng/mL total morphine).

Another study found that goldenseal had only minimal and selective interference with tests screening for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, and tetrahydrocannabinol (THC) (Wu and others 1995). Given the use of standard methods of detection, goldenseal is not considered to be effective for masking recreational drug use.

Conclusion: Goldenseal Preparations
The use of goldenseal as an antimicrobial and anti-secretory in the treatment of various kinds of mucosal infections is firmly established within the professional community of medical herbalists. Confirmation of such uses by well-designed human clinical trials is lacking. Two in vitro studies using goldenseal provide evidence that it is antimicrobial against many pathogens, with the total extract exhibiting a more potent action than isolated constituents in one of the studies. Goldenseal’s effectiveness as a bitter digestive stimulant has been demonstrated in one human study but was not supported by one animal study. One animal study showed that goldenseal increases antibody response. In vivo and ex vivo studies have reported both spasmodylitic and contractile activity of goldenseal extract and various of its alkaloids. More work needs to be done to determine when goldenseal acts as a contractant or a relaxant and what constituents are responsible for these activities. Other work suggests that goldenseal may alleviate some of the symptoms of diabetes and may act as an antioxidant. Lastly, goldenseal has been shown to be ineffective in interfering with tests for recreational drug use.

While the use of goldenseal will undoubtedly persist, additional well-developed human clinical trials are needed in order to determine its true clinical potential. Moreover, its threatened environmental status underscores the need to use goldenseal root judiciously until cultivated supplies are more widely available, relying on it for well-established uses in which other botanicals will not suffice.
Effects of Isolated Alkaloids

Many studies have investigated the pharmacology and clinical efficacy of berberine salts and other isolated alkaloids found in goldenseal. While the results of these studies may not be directly applicable to crude goldenseal products, they provide important data on possible mechanisms of action and clinical efficacy of this botanical. A large body of information from both clinical and preclinical studies supports the antimicrobial and anti-secretory effect of berberine and structurally related alkaloids found in goldenseal. Other studies have investigated their effects on the digestion and the heart. Still others investigate receptor binding activity as the mechanism by which the alkaloids act as smooth muscle contractants and relaxants.

Antimicrobial, Antiparasitic, Antifungal, and Anti-secretory Effects

By far, most clinical research on goldenseal constituents has investigated the use of berberine sulfate, tannate, chloride, or hydrochloride as antimicrobials and anti-secretories in infectious diarrhea. It has been reported that berberine-containing plants have been used for this purpose for more than 2000 years (Tang and Eisenbrand 1992). A more limited set of studies has investigated the use of berberine in treating trachoma. Various mechanisms of action for the antimicrobial effects have been proposed. These include direct cytotoxic and cytostatic activity through interference with macromolecular synthesis or various other cellular processes (Amin and others 1969; Ghosh and others 1985; Kaneda and others 1991; Schmeller and others 1997) as well as anti-adhesion activity through the release of adhesion lipoteichoic acid (LTA) from cell surfaces; this latter activity would limit the ability of bacteria to bind to host cell walls (Sun and others 1988a, 1988b). Anti-secretory effects are thought to result from alterations in ion transport across the mucosal epithelium.

Use of Berberine in Infectious Diarrhea: Antimicrobial and Anti-secretory Effects

Human Clinical Studies

Four-hundred adults presenting with acute watery diarrhea were enrolled into a randomized, double-blind, placebo-controlled clinical trial investigating the anti-secretory and vibriostatic effects of berberine derived from Berberis aristata (Khin and others 1985). The treatment group was given 1 berberine hydrochloride tablet (100 mg) and 1 placebo capsule 4 times daily (qid); the positive control group was given 1 tetracycline capsule (500 mg) and 1 placebo tablet qid; the combined treatment group was given 1 berberine hydrochloride tablet (100 mg) and 1 tetracycline capsule (500 mg) qid. The 2 placebo groups were given 1 placebo capsule and 1 placebo tablet qid. Patients were diagnosed as having cholera (n = 185) or non-cholera diarrhea (n = 215). Of the patients with cholera, those given tetracycline showed significantly reduced stool volume (P < 0.05), stool frequency (P < 0.05), duration of diarrhea (P < 0.001), and volume of required intravenous (iv) and oral rehydration fluids (P < 0.001, in both cases) compared to the placebo group. Berberine and tetracycline administered together did not show significant trends in any of the above outcomes except in the case of stool volume, where a significant reduction was found after 16 hours (P < 0.05) and at 48 hours (P < 0.001). Berberine given alone produced a small but not significant anti-secretory effect compared to placebo. None of the three treatments had any significant anti-secretory effects in patients with non-cholera diarrhea.

A controlled but unblinded study of 165 patients investigated the efficacy of berberine sulfate treatment for diarrhea due to enterotoxigenic E. coli (ETEC) (n = 63) and Vibrio cholerae (n = 102) (Rabbani and others 1987). ETEC patients received either a single oral dose of 400 mg berberine sulfate or no treatment. Cholera patients received 1 of 4 treatments: 400 mg of berberine sulfate in a single dose; 400 mg of berberine sulfate every 8 hours for 24 hours along with a single dose of 1 g tetracycline; a single dose of 1 g tetracycline alone; or no treatment. Twenty-four hours after treatment, ETEC diarrhea had stopped with a higher frequency in the berberine group (42%) compared to the control group (20%) (P < 0.05). Similarly, the group treated with a single dose of berberine had significantly reduced stool volumes for 3 consecutive 8-hour periods following treatment compared to controls (P < 0.05). In patients with cholera, the mean 8-hour stool volume was significantly lower in the second 8-hour period in the berberine sulfate group (mean of 2.22 L) compared to the non-treatment group (mean of 2.79 L; P < 0.05). Stool cultures were vibrio-positive 24 hours after treatment in all control patients and in all of the berberine sulfate-treated patients except one. Cholera patients who received berberine sulfate in conjunction with tetracycline did not have a significant reduction in stool volume compared to those who received tetracycline alone. Stool cultures were vibrio-negative after 24 hours in 80% of the patients administered tetracycline plus berberine and in 86% of the patients given tetracycline alone. No major side effects were noted in treatment groups receiving berberine sulfate, although some patients experienced transient nausea and abdominal discomfort. These results suggest that though the anti-secretory activity of berberine sulfate compared to no treatment is effective in reducing stool volume in both ETEC and cholera, it is the antimicrobial activity (greater in tetracycline than in berberine) that is paramount in the effective treatment of cholera.

In a controlled, open trial, Sharda (1970) studied the efficacy of berberine tannate in the treatment of acute diarrhea in 100 children (aged 2 months to 6 years). Subjects were equally divided into a berberine treatment group and a positive control group. In the berberine treatment group, infants 2-6 months were administered 25 mg po qid, while older children were given 50 mg for the first dose, followed by 25 mg qid. The control patients were given either sulfonamide plus bismuth-kaolin mixture, sulfonamide plus streptomycin, chloromycetin plus streptomycin, or a furazolidine preparation. All patients received supportive hydration and electrolyte replacement. Patients were classified as mild, moderate, or severe on the basis of stool number and hydration state. In the treatment group, recovery rate was
100% and 77% in mild and severe cases, respectively. In the positive control group, recovery rate was 100% and 74% in mild and severe cases, respectively, after 72 hours. The only side effect noted was in the berberine group and involved severe vomiting in 3 subjects which necessitated their withdrawal from the study. The results suggested that berberine treatment of acute diarrhea in children was as effective as treatment with the antibiotics used in the study. A follow-up study looking at between-group differences in recurrence rate was not performed.

An unblinded controlled study evaluated the efficacy and safety of berberine in 620 subjects with cholera or severe diarrhea (Lahiri and Dutta 1967). Children (12 years and under) and adults (13-50 years) were enrolled during 2 cholera epidemics in Calcutta in 1964 and 1965. Only results for the adults are presented because they were the only ones analyzed statistically. Patients were stratified according to type of diarrhea (cholera versus severe diarrhea) and presence of vibrios in stool culture (vibrio-negative versus vibrio-positive). Adults received 50 mg berberine hydrochloride upon admission, then 50 mg every 8 hours for 48 hours, followed by 50 mg twice daily until the fifth day or until hospital discharge. The positive control group received 250 mg chloramphenicol every 4 hours for the first 24 hours, then 250 mg every 6 hours for the second 24 hours, followed by 250 mg 3 times daily over the next 3 days. In addition, there was a small placebo control group (n = 10). Patients received hydration therapy as appropriate. Outcome measures included reduction in mortality and control of diarrhea. In patients with vibrio-negative cholera, mortality rate was significantly reduced in the berberine group compared to the chloramphenicol group (P < 0.05). However, conflicting results were found in the vibrio-positive patient group: in 1964, berberine was more effective than chloramphenicol in reducing mortality, whereas in 1965 there was no statistical difference between groups. In both the berberine and chloramphenicol groups, diarrhea was completely controlled by 48 hours. In the placebo control group, no reduction in diarrhea was observed over the course of 3 days. No side effects were reported. The presence in the gut of pathogens other than V. cholerae that may have influenced the outcome of the study was not addressed. In addition, a follow-up study looking at between-group differences in recurrence rate was not performed.

In an open clinical trial with pediatric patients (aged 5 months to 14 years, mean 5 years), the antiparasitic effect of berberine in the treatment of giardiasis was compared with 3 standard therapeutic agents (Gupte 1975). The percentage of patients with negative stool cultures at the end of the high dose berberine treatment (10 mg/kg daily) was lower than, but compared favorably to, the results from the antibiotic treatment groups (Table 6). Statistical analyses of results were not provided.

### Animal and In Vitro Studies
Several in vitro studies have investigated the mechanism of berberine’s anti-secretory effect. Fluid loss in secretory diarrhea can be a consequence of the osmotic imbalance due to excessive Cl- secretion by the intestinal epithelium. In order to maintain the cellular electrical potential required to support Cl- secretion, K+ must be recycled at the basolateral membrane of the epithelium (Barrett 1993). Taylor and others (1999) examined the effects of berberine on healthy human colonic mucosal epithelia and cultured monolayers of a human intestinal epithelial cell line (T84) in order to determine the mechanism of berberine’s in vivo anti-secretory effect. These researchers suggested that berberine exerts its anti-secretory action directly upon the epithelium via K+ channel blockade. Other researchers reported similar findings in animal models with berberine sulfate or hydrochloride (Guandalini and others 1987; Sack and Froehlich 1982; Zhu and Ahrens 1982).

Two other studies reported that mucosal berberine hydrochloride (1 mM) dose-dependently reduced cholera toxin-induced secretion of water, Na, Cl, and HCO3 in the rat ileum, while serosal berberine stimulated Na secretion (Swabb and others 1981; Tai and others 1981). Additionally,

### Table 6 Anti-giardial effects of berberine compared to standard treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose (mg/kg)</th>
<th>Duration (days)</th>
<th>N</th>
<th>On completion of treatment</th>
<th>One month post treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berberine</td>
<td>5</td>
<td>5</td>
<td>30</td>
<td>14 (47)</td>
<td>12 (40)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>10</td>
<td>36</td>
<td>20 (55)</td>
<td>16 (44)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>5</td>
<td>29</td>
<td>20 (68)</td>
<td>18 (62)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>10</td>
<td>42</td>
<td>38 (90)</td>
<td>35 (83)</td>
</tr>
<tr>
<td>Quinacrine HCl</td>
<td>5</td>
<td>7</td>
<td>46</td>
<td>46 (100)</td>
<td>43 (93)</td>
</tr>
<tr>
<td>Furazolidone</td>
<td>5</td>
<td>7</td>
<td>108</td>
<td>100 (92)</td>
<td>95 (90)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>20</td>
<td>5-7</td>
<td>88</td>
<td>85 (95)</td>
<td>80 (90)</td>
</tr>
</tbody>
</table>

Source: Modified from Gupte (1975).
mucosal cell villous tip edema due to cholera toxin was resolved following the administration of berberine. These results are of interest because they indicate that berberine can affect the mucosal side of the small intestine, in contrast to other anti-secretory drugs which only effect the serosal side (such as aspirin, somatostatin, α-adrenergic compounds, and neuroleptics). A more recent study, however, found that berberine had a more potent anti-secretory action when applied to the serosal side of isolated rat intestinal epithelium compared to when it was applied apically (Baird and others 1997). In order for anti-secretory drugs to work they must be delivered across the intestinal epithelium to the site of action. These researchers concluded that the diseased state of the intestines may enhance the delivery of otherwise poorly absorbed drugs to their site of action.

**Use of Berberine in Ophthalmic Infections**

**Human Clinical Studies**

Goldenseal has traditionally been used in the treatment of conjunctivitis and trachoma. The use of berberine for the treatment of trachoma, an eye infection caused by Chlamydia trachomatis, has been investigated in two studies. In the first of these, 32 microbiologically-confirmed cases of trachoma were enrolled in an open uncontrolled clinical trial comparing the serological response of trachoma to topical treatment with 0.2% berberine solution versus 20% sulfacetamide (Khosla and others 1992). The efficacy of the berberine solution was found to be superior to that of the standard treatment in both the clinical course of trachoma and in achieving a fall in the serum antibody titers against *C. trachomatis* in the treated patients (outcome measures not given).

Babbar and others (1982) conducted an open uncontrolled clinical trial investigating the use of berberine chloride in the treatment of trachoma patients with clinically active lesions. Patients were treated with either 0.2% aqueous berberine chloride ophthalmic solution (2 drops per eye, 3 times daily for 8 weeks), 20% sulfacetamide ophthalmic solution, or both. While the 20% sulfacetamide solution relieved clinical symptoms completely, it did not eradicate the pathogen, *C. trachomatis*. By the end of treatment in the berberine group, patients were symptom-free and tested negative for *C. trachomatis*. In 5 of seventeen patients in the sulfacetamide treatment group, symptoms recurred 4-6 months after treatment. None of the berberine-treated trachoma patients suffered from recurrence up to 1 year after treatment. The combination of berberine and sulfacetamide ophthalmic solutions provided only slightly better improvement than did berberine alone; this group was bacteria-free after treatment with no recurrent infections.

**General Antimicrobial Effects**

**Animal and In Vitro Studies**

Studies on the general antimicrobial effects of alkaloids contained in goldenseal have targeted a variety of organisms including bacteria, fungi, and various parasites. Two studies investigated the inhibitory effect of berberine on Helicobacter pylori. This bacterium produces a vacuolating toxin and toxicity-promoting urease which appear to mediate much of the pathogenesis of gastritis and peptic ulcer. The appearance of antibiotic resistant strains of *H. pylori* and the prevalence of adverse effects associated with many of the accepted medications led to in vitro screening of various herbal medicines against several strains of *H. pylori* (Bae and others 1998). Active extracts were subjected to bioassay-directed chromatography. Berberine, derived from Chinese goldthread root (*Coptis spp.*), was among the most potent of the *H. pylori*-inhibiting compounds, with a minimum inhibitory concentration (MIC) of 8-200 µg/mL. However, the researchers noted that the phytoecgenic antimicrobials were an order of magnitude less potent against *H. pylori* in vitro than standard antibiotics. In another study, Chung and others (1999) found that berberine (0.08-160 µM) dose-dependently inhibited *H. pylori* growth (mean percent inhibition at 0.8 and 160 µM was 8.9% and 80.2%, respectively). In addition, berberine inhibited arylamine N-acetyltransferase (NAT) activity in *H. pylori* cytosol and intact bacteria. This is important because NAT is capable of activating dietary and environmental exposure-derived aromatic amines into mutagens and carcinogens or deactivating them once formed. Repression of NAT activity in the liver is associated with several pathological processes including breast and bladder cancer. This may be especially noteworthy since the chronic gastritis often associated with *H. pylori* is now a recognized precursor of certain gastric cancers.

Pepeljnjak and Petricic (1992) noted significant in vitro antimicrobial effects of berberine chloride against *C. andida albicans*, *C. pseudotropicalis*, and *C. tropicalis*, but not against *C. krusei*. MICs were not reported. Minor antimicrobial effects were also noted against *Bacillus cereus*, *Corynebacteria diphtheriae*, *Klebsiella pneumoniae*, *Sarcinia lutea*, and *Staphylococcus aureus*. In addition, it was found that berberine chloride significantly inhibited the binding of *E. coli* to epithelial cells of the urinary tract (see Anti-adhesive Effects of Berberine).

In a study of the structure-activity relationships among antimalarial protoberberine alkaloids, Vennerstrom and Klayman (1988) tested for antimalarial activity in vitro against *Plasmodium falciparum* and in vivo against *P. berghei*. None of the protoberberine alkaloids were active in vivo, although berberine and two synthetic berberine derivatives were as potent as quinine in vitro. In a follow-up study, Vennerstrom and others (1990) investigated the efficacy of protoberberine alkaloids and their derivatives in treating leishmaniasis in golden hamsters. When assayed against *Leishmania donovani*, canadine was less toxic and more potent than berberine but was not as effective as *Glucantime* (meglumine antimonate) for leishmaniasis treatment. Of several compounds tested, only berberine and the semisynthetic derivative 8-cyanodihydroberberine showed significant activity (greater than 50% suppression of lesion size) against *L. braziliensis* panamensis. In the study of Ghosh and others (1983), it was found that berberine treatment reduced by 90% the number of parasitic amastigotes in hamster liver and spleen during long-term infections. Berberine was much better tolerated at dosage levels of 50...
and 100 mg/kg daily than the anti-leishmanial medication pentamidine. Both compounds interfered with macromolecular synthesis in prokaryotic and eukaryotic cells; in particular, berberine was shown to have a propensity to interact with nucleic acids (see Disruption of M acromolecular Synthesis and O ther C ellular Functions in Pathogens).

In an assay against a number of fungi isolated from the eyes of symptomatic patients (Mahajan and others 1982), 10-25 mg/mL of berberine sulfate was shown to repress the growth of Alternaria spp., A. flavus, A. fumigatus, C. albicans, C. uvarum, Drechslera spp., Fusarium spp., M. oryzae, Penicillium spp., Rhizopus oryzae, and Scopulariopsis spp. Concentrations of 50 mg/mL inhibited Syncephalastrum spp., while Aspergillus niger remained unaffected.

Berberine sulfate was shown to be bacterioidal to V. cholerae and bacteriostatic to S. aureus at concentrations of 35 µg/mL and 50 µg/mL, respectively (Amin and others 1969). While most strains of E. coli were resistant to berberine sulfate, enteropathogenic E. coli strain AL 26 and Shigella boydii, responsible for bacillary dysentery, were inhibited at concentrations of 50 µg/mL and 12.5 µg/mL, respectively. All Xanthomonas spp. were highly susceptible at concentrations of 6.25-12.5 µg/mL in a liquid medium. Salmonella and Pseudomonas spp. were resistant at these concentrations. Berberine sulfate (35 µg/mL) displayed more rapid antimicrobial activity in vitro against V. cholerae than tetracycline (10 µg/mL) or chloramphenicol (10 µg/mL) and was found to be antifungal against Candida albicans, C. tropicalis, Cryptococcus neoformans, M. interporum gypseum, Sporotrichum schenckii, and Trichophyton mentagrophytes. Antimicrobial activity was dependent upon inoculum size and media pH with maximal activity at pH 8. These workers noted that these characteristics were comparable to those of the sulfonamides and penicillins and that the effect of pH on activity was consistent with the supposition that berberine is the active compound.

In another early study, berberine sulfate was shown to be amoebicidal and amoebostatic to Entamoeba histolytica trophozoites in vitro at 0.5-1.0 mg/mL and 0.05-0.1 mg/mL, respectively, causing encystation, degeneration, and subsequent lysis of the trophozoites (Subbaiah and Amin 1967). Follow-up experiments demonstrated that berberine sulfate (2 mg/kg im or 3 mg/kg po) administered to golden hamsters in a regimen of 3 doses at 4-hour intervals (first dose before infection, second dose at time of infection, third dose 4 hours after infection) prevented hepatic amebiasis. Rats were infected intracereally with trophozoites of E. histolytica. The control group developed an intestinal form of amebiasis while berberine-treated animals did not.

Disruption of M acromolecular Synthesis and O ther C ellular Functions in Pathogens

Animal and In Vitro Studies

A number of studies have reported that berberine and related alkaloids act as antimicrobials by disrupting macromolecular synthesis and other cell functions (Amin and others 1969; Creasey 1979; Ghosh and others 1983; Kaneda and others 1991; Schmeller and others 1997; Ye and others 1989). A representative sampling of these are reviewed here.

Amin and coworkers (1969) found that berberine sulfate can interfere with nucleic acid synthesis. Berberine sulfate was shown to be bacterioidal to V. cholerae and bacteriostatic to S. aureus at concentrations of 35 µg/mL and 50 µg/mL, respectively. In both cases, RNA and protein synthesis were inhibited almost immediately after the addition of berberine sulfate; DNA synthesis was largely unaffected even at the highest concentrations. A decrease in RNA content by more than 50% was observed, suggesting at least a partial enzymatic degradation.

Kaneda and others (1991) found that berberine sulfate inhibited the growth of parasites E. histolytica, G. lamblia, and T. vaginalis in vitro, inducing morphological changes in the parasites. In berberine-treated E. histolytica, clumping of nuclear chromatin and the formation of autophagic vacuoles and aggregates of small vacuoles in the cytoplasm were noted. In G. lamblia, an irregularly-shaped vacuole appeared in the cytoplasm which enlarged during culture. The trophozoites became swollen and deposits of glycogen were seen in the cytoplasm. In T. vaginalis the number of autophagic vacuoles increased soon after treatment, with the characteristic appearance of one large vacuole. The increase in vacuolar size was associated with plasma membrane disruption in the parasite. A significant inhibition (P < 0.001) of growth was noted for all pathogens from 3-24 hours after treatment with 1 mg/mL berberine sulfate.

Ye and others (1989) suggested that o-hydrastine (present in goldenseal) might be useful in the treatment of hydatidosis, a cyst infestation caused by a larval stage of the dog tapeworm Echinococcus granulosus. o-hydrastine given to mice at a dosage of 3.75 mg/kg for 20 days was effective in dissolving E. granulosus cysts by disrupting Golgi complexes, organelles, microtubules, and mitochondria and by causing pits in the cyst membrane.

Anti-adhesin E ffects of B erberin e

In Vitro Studies

At least three studies have evaluated the anti-adhesin effects of berberine. Bacterial adhesins are surface molecules that mediate a bacterium’s adherence to host cells. Certain antimicrobial agents can block the binding of microorganisms to host cells at doses much lower than those needed to kill or inhibit growth of the infectious agent. Strategies that interrupt the adhesion of bacteria to the host cell before tissue invasion occurs may be an effective prophylactic approach against microbial infections. Sun and others (1988a) reported on the anti-adhesin activity of berberine sulfate on streptococci in vitro. Concentrations of berberine below its MIC showed an 8-fold increase in the release of lipoteichoic acid (LTA), the primary streptococcal adhesin, from the streptococci. Higher concentrations prevented or disrupted the formation of LTA-fibronectin complexes, thereby interfering with the adherence of streptococci to host cells.

Sun and others (1988b) also studied the influence of
berberine on the adhesion of uropathogenic E. coli to erythrocytes and epithelial cells in vitro. Though berberine had no effect on the growth or synthesis of major cell wall proteins by E. coli, it reduced adhesion in a dose-dependent manner. Pap fimbriae are adhesins mediating the adherence of uropathogenic E. coli to urinary tract epithelia. The decreased adhesion was accompanied by reductions in both the synthesis of fimbrial subunits and expression of assembled fimbriae on the cell surface. At berberine concentrations that inhibited growth by 10% or less (300 µg/mL), expression of fimbriae on the cell surface was completely suppressed, accompanied by pathological changes in the flagella as well. These effects only occurred in growing microbes; E. coli in stationary phase was unaffected. These workers suggested that selective repression of fimbrial protein synthesis and assembly in uropathogenic organisms by berberine explain the traditional medical use of berberine-containing plants for the prevention and treatment of urinary tract infections. In addition to this study by Sun and others (1988b), the aforementioned study of Pepeljnjak and Petricic (1992), also offers evidence that berberine inhibits the binding of E. coli to the epithelial wall of the urinary tract.

In summary, there is much evidence in support of the antimicrobial, antiparasitic, antifungal, and anti-secretory effects of berberine. Human clinical studies on the antimicrobial and anti-secretory effects of berberine in the treatment of infectious diarrhea gave varying results. Three unblinded studies found that berberine was as, or more, effective than control antibiotics in the treatment of acute diarrhea, cholera, or giardiasis (Gupte 1975; Lahiri and Dutta 1967; Sharda 1970). Two other unblinded studies found that berberine had a significantly greater effect against diarrhea compared to no treatment at all (Lahiri and Dutta 1967; Rabbani and others 1987). However, the best-designed study (randomized, double-blind, and placebo-controlled) showed no significant effect of berberine compared to placebo or antibiotics in the treatment of cholera (Khin and others 1985). Rabbani and others (1987) similarly found that berberine did not improve the effectiveness of antibiotics in the treatment of cholera. Two additional clinical studies found berberine to be as effective as antibiotics in eliminating trachoma (Babbar and others 1982; Khosla and others 1992).

Animal and in vitro studies have suggested that berberine's anti-secretory effect is due to its effect on ion transport (Swabb and others 1981; Tai and others 1981; Taylor and others 1999). The antimicrobial activity of berberine is apparently due to a direct local rather than a systemic action. Several mechanisms appear to be responsible for this activity. In particular, there is substantial evidence that pathogens are killed or their ability to grow and reproduce is limited by the interference of berberine with macromolecular synthesis, especially of nucleic acids, and other cell functions. In addition, there is strong evidence from a limited number of studies that berberine prevents adhesion of streptococci and E. coli to host cell walls, helping to prevent infection from occurring. Despite the relatively large number of studies supporting the antimicrobial activity of berberine, most are not well designed. Additionally, the amount of berberine administered in most studies exceeds the amount that would be derived from recommended dosages of crude goldenseal.

**Digestive Effects**

**Human Clinical Studies**

According to an abstract of one older, uncontrolled, clinical study (Turowa and others 1964), 225 patients with chronic cholecystitis were given berberine hydrochloride or sulfate at oral doses of 5-20 mg 3 times daily before meals for 1-2 days. This resulted in an increase of bile secretion and flow rate, the elimination of clinical symptoms, and a reduction of gall bladder bile volume (specific values and method of measurement not given). Bilirubin excretion was increased even when bile levels were low. In this study, berberine demonstrated some positive (though undefined) effects in patients with toxic hepatitis caused by industrial poisons. No side effects or changes in blood parameters were observed.

**Animal Studies**

According to an abstract of an older study (Velluda and others 1958), an extract was prepared from the stem bark of Berberis vulgaris and was characterized as containing 2% berberine and approximately 2% other alkaloids. Both the total extract and the individual alkaloids stimulated biliary secretion in an unspecified model. Berberine had the greatest effect, tripling bile secretion in 1.5 hours.

**Cardiovascular Effects**

Limited studies suggest that alkaloids contained in goldenseal may be of benefit in the treatment of congestive heart failure (CHF). In addition, there is some evidence that canadine acts as a platelet aggregation inhibitor. In vitro studies presented above found contrasting vasoconstrictive and vasorelaxant effects of goldenseal and its alkaloids (Palmer and others 1993, 1996; see Smooth Muscle Spasmolytic and Contractile Effects). In general, the total extract, berberine, canadine, and canadaline appeared to act as vasorelaxants, while hydrastine was inactive. However, in one of the studies, high doses of the total extract (at or above 50 µL/mL) had a vasoconstrictive effect (Palmer and others 1993).

**Human Clinical Studies**

In the uncontrolled trial of Zeng and Zeng (1999), the efficacy of berberine in alleviating the arrhythmias associated with CHF was correlated with its plasma concentration. Fifty-six patients (34 male, 22 female; age range 45-76 years) with severe chronic CHF were treated conventionally for 2 weeks, after which baseline cardiac function was determined by dynamic electrocardiogram and left ventricular ejection fraction (LVEF) measurements. The patients were then treated orally with berberine, 1.2 g daily for 2 weeks, at which point cardiac function was re-evaluated and plasma berberine levels assayed. Berberine treatment significantly improved the cardiac function in all patients, increasing LVEF (P < 0.05) and decreasing the complexity and frequency of ventricular premature beats (VPBs) (P < 0.01).
Two subgroups could be delineated after treatment: patient group B, presenting plasma berberine levels of 0.19 ± 0.08 mg/L, displayed a greater increase in LVEF and more significant decreases in VPBs compared to patient group A, which presented with lower plasma berberine levels of 0.07 ± 0.4 mg/L. There were no adverse reactions reported.

An open study investigated the cardiovascular effects of parenteral berberine by monitoring 12 CHF patients before and during berberine infusion (Marin-Neto and others 1988). Berberine was administered as an iv infusion at 0.02 or 0.2 mg/kg/minute for 30 minutes. At the lower infusion dose rate, the only significant change in circulatory status was a 14% reduction in heart rate. At the higher dosage rate, however, several statistically significant changes in cardiovascular status were elicited: decreases in systemic (48%, P < 0.01) and pulmonary vascular resistance (41%, P < 0.01), and in right atrium (28%, P < 0.05) and left ventricular end-diastolic pressure (32%, P < 0.01); increases in cardiac index (45%, P < 0.01), stroke index (45%, P < 0.01), and LVEF measured by contrast angiography (56%, P < 0.01); increases in hemodynamic and echocardiographic indices of LV performance such as peak measured velocity of shortening (45%, P < 0.01), peak shortening velocity at zero load (41%, P < 0.01), rate of development of pressure at developed isovolumic pressure of 40 mm Hg (20%, P < 0.01), percent fractional shortening (50%, P < 0.01), and the mean velocity of circumferential fiber shortening (54%, P < 0.01); and lastly, a decrease of arteriovenous oxygen difference (28%, P < 0.05), with no changes in total body oxygen uptake, arterial oxygen tension, or hemoglobin dissociation properties.

Animal and In Vitro Studies

The in vivo and in vitro effects of canadine on certain hemodynamic parameters were studied in animal models (Xuan and others 1994). Canadine inhibited the in vitro aggregation of rabbit platelets induced by arachidonic acid (AA) (IC_{50}: 0.86 mmol/L), adenosine diphosphate (ADP) (IC_{50} 1.31 mmol/L), and collagen (IC_{50} 1.10 mmol/L). It also reduced thromboxane B2 generation in rabbit platelet-rich plasma triggered by AA. Treatment of rats with canadine (30 mg/kg daily ip for 1, 3, or 5 days) inhibited AA-induced platelet aggregation ex vivo and a similar experimental protocol (30 mg/kg daily ip for 3 or 5 days) attenuated ADP-induced platelet aggregation. In vivo inhibition of venous thrombosis in rats was noted after iv treatment (15-30 mg/kg) with canadine. The researchers concluded that canadine is an effective inhibitor of platelet aggregation in vitro and in vivo.

According to the above open studies, there is limited evidence that orally administered berberine may be effective in the treatment of CHF (Marin-Neto and others 1988; Zeng and Zeng 1999). In vivo and in vitro anti-platelet effects have also been demonstrated for canadine with relatively large injected doses. The role of berberine as a hypotensive needs further investigation, since it has only been demonstrated in one study using large iv doses (Marin-Neto and others 1988).

Receptor Binding Effects

In Vitro Studies

In vitro studies of goldenseal and alkaloids derived from it have been found to have contrasting spasmylic and contractile effects on smooth muscle, including the vascular system, the intestines, the uterus, the trachea, and the prostate. It has been hypothesized that receptor binding effects may be at least partly responsible for these activities (see Smooth Muscle Spasmylic and Contractile Efects). In vitro research on berberine supports this view, suggesting that berberine may act as a partial agonist (or mixed agonist-antagonist) at α2-receptors and that it may also affect acetylcholine release in certain tissues. Hydrastine may act as a GABA(A) receptor antagonist.

Using the perfused guinea pig ileum model, Shin and others (1993) tested the hypothesis that berberine inhibits muscle contraction through its activity as an α2-adrenoceptor agonist. Contrary to expectation, these researchers found that berberine (10^{-6}-10^{-5} M) not only failed to inhibit, but actually increased the twitch response to transmural stimulation. They then did further studies in the same model both with and without transmural stimulation in order to determine if there was a cholinergic component to the alkaloid’s “paradoxical” activity. Utilizing chemoreceptor antagonists partially selective for nicotinic and muscarinic cholinergic receptors and α2-adrenoceptors, as well as an acetylcholine synthesis inhibitor (mecamylamine, atropine, xylazine, and hemicholinium, respectively), these workers demonstrated that muscarinic cholinergic receptors mediate berberine’s ability to enhance acetylcholine release from guinea pig ileum in vitro. The effects were proven not to be a result of berberine acting directly on muscarinic cholinergic receptors since acetylcholine depletion prior to assay nearly abolished this activity. These results support the hypothesis of Cometa and others (1996) from their work with goldenseal. Berberine treatment (10^{-6}-10^{-4} M) also inhibited cholinesterase in guinea pig ileum in vitro, and at a concentration of 10^{-5} M, it also antagonized xylazine-induced inhibition of the twitch response in transmurally-stimulated guinea pig ileum, presumably due to a concentration-dependent antagonist effect at α2-adrenoceptors.

Hui and others (1991), utilizing human platelets and α2-adrenoceptor ligands, reported that berberine is a partial agonist of human platelet α2-adrenoceptors with similar pharmacology to clonidine. Berberine inhibited the cyclic adenosine monophosphate (cAMP) accumulation induced by 10 μm prostaglandin E1 (PGE1) in a dose-dependent manner, acting as an α2-adrenoceptor agonist. When assayed against epinephrine, berberine blocked the inhibitory effect of epinephrine on PGE1-induced cAMP accumulation, behaving as an α2-adrenoceptor antagonist. These researchers propose that berberine’s activity as a partial agonist (or mixed agonist-antagonist) at α2-adrenoceptors may provide mechanisms for the sedative, hypotensive, and anti-secretory effects observed with berberine.

According to Schmeller and others (1997), previous pharmacological studies suggested that berberine is antagonistic at α2-adrenoceptors and is a cholinergic agonist, with...
the nature of the action at 5-HT receptors yet to be elucidated. They investigated the neuroreceptor binding affinities of berberine (displacement of radioligand, IC₅₀ in µM): α₁-adrenergic: 3.2 (against [¹²⁵I]-prazosine); α₂-adrenergic: 0.476 (against [¹²⁵I]-yohimbine); serotoninergic: 1.9 (against [¹²⁵I]-ketanserine); muscarinic: 1.0 (against [¹²⁵I]-quinuclidinyl benzilate).

Huang and Johnston (1990) reported on the preclinical pharmacology of (+)-hydrastine hydrochloride (HCl). (+)-Hydrastine has the same absolute configuration as the competitive γ-aminobutyric acid receptor subtype A (GABAₐ) antagonist bicuculline and was twice as potent as the latter as a convulsant in mice (CD₅₀ 0.16 mg/kg iv). These workers found that (+)-hydrastine HCl was a selective antagonist at bicuculline-sensitive GABAₐ receptors in the guinea pig isolated ileum with no activity at baclofen-sensitive GABA₈ receptors or acetylcholine receptors in this tissue. (+)-Hydrastine HCl (10 nM-1 mM) also failed to inhibit the binding of [³H]-(-)-baclofen to GABA₈ binding sites in rat cortical membranes. Displacement studies utilizing [³H]-muscimol binding to high affinity GABA₈ sites in rat cortical membranes demonstrated that (+)-hydrastine HCl (IC₅₀ 2.37 µM) was 8 times more potent than bicuculline. (+)-Hydrastine HCl antagonized activation of low affinity GABA₈ receptors as determined by its effects on GABA-induced stimulation of [³H]-diazepam binding in rat cortical membranes, being 5 times more potent (IC₅₀ 0.4 µM) than bicuculline in this regard.

In summary, there is evidence that berberine and hydrastine have receptor binding effects. Shin and others (1993) found that berberine acts as a mixed agonist-antagonist at α₂-adrenoceptors, causing contractility in the perfused guinea pig ileum model, explaining one mechanism by which goldenseal may act as a smooth muscle contractant. Huang and Johnston (1990) identified hydrastine as a GABA₈ antagonist.

Other Effects
Numerous other in vitro effects have been reported for berberine, most of which are of unknown relevance to the use of goldenseal. Briefly these include: antitumor activity (Zhang and others 1990; immunomodulatory effects with both stimulant and suppressive actions reported (Ivanovska and others 1999; Kumazawa and others 1984); inhibition of bone loss (Li and others 1999); protection against the hemotoxic effects of radiation exposure (Ziablitskii and others 1996); and antioxidant and lipoxigenase inhibitory activity with repression of the proliferative process in psoriasis (Misk and others 1995; Muller and others 1995); and the ability of berberine (pretreatment at 4 mg/kg twice daily for 2 days) to prevent acetaminophen- or CCl₄-induced hepatotoxicity (Janbaz and Gilani 2000). The use of berberine in psoriasis is consistent with the topical application of goldenseal in clinical herbal medicine.

Traditionally in China, berberine-containing Coptis chinensis was used to treat neonate jaundice. Though this practice is no longer recommended (see Safety Profile), an older study investigated the effect of berberine on biliary excretion in hyperbilirubinemic rats (Chan 1977). Acute doses of berberine (2.5 mg/kg) significantly enhanced bilirubin excretion in the first hour after administration compared to controls (P < 0.05). However, this effect did not occur when more continuous doses (2 and 5 days) were administered.

Berberine, employed in veterinary practice, has been used in various astringent, deodorant, and antiseptic powders for topical use on wounds and in the uterus. Veterinary applications of hydrastine include its use as an antitussive (of limited duration) in dogs, its topical application for indolent ulcers and chronic inflammations of mucous membranes (respiratory and genitourinary), its use as a uterine stimulant, a hemostatic, and a stomachic and chologogue, especially in hypochlorhydria (Rosoff 1974). Specific data regarding its relative level of efficacy in these uses and its clinical relevance to humans are lacking.

Conclusion: Isolated Alkaloids
The available data suggests that berberine is of value in the treatment of gastrointestinal and eye infections caused by a variety of pathogens including V. cholerae, H. pylori, various strains of C. candida, E. coli (both enteric and uropathogenic), E. histolytica, and C. trachomatis. Its antipathogenic effects appear to be mediated by cytostatic and cytoidal effects (functioning via the disruption of nucleic acid synthesis and other cell functions) as well as anti-adhesin effects, preventing the binding of bacteria to host cell walls. Berberine’s therapeutic use in infectious diarrhea and other infections of the mucosa is also due to its anti-secretory action. The multiple modes of action of berberine make it an ideal candidate for further study against drug resistant pathogens. In addition to its antimicrobial and anti-secretory effects, berberine may act as a chologogue, though the data regarding this activity is very limited. Cardiovascular and hemodynamic effects of berberine have been reported, the clinical relevancy of which is not known. Lastly, the receptor binding effects of goldenseal alkaloids appear to be responsible, at least in part, for goldenseal’s smooth muscle effects.

The results from studies using isolated compounds cannot be directly extrapolated to the clinical efficacy of goldenseal. This is especially true because most, but not all, of the studies used concentrations of berberine far higher than can be achieved with a therapeutic oral dosage of goldenseal itself.

Actions
Antimicrobial (antibacterial, antifungal, antiparastic, antiprotozoal, antiseptic) (Babbar and others 1982; Gupu 1975; Khosla and others 1992; Lahiri and Dutta 1967; Mahajan and others 1982; Rabbani and others 1987; Sharda 1970), anti-secretory (Gentry and others 1998; Scaccuzioch and others 1998; Taylor and others 1999), antibacterial (Baldazzi and others 1998; Bolle and others 1998; Cometa and others 1998; Palmer and others 1996), muscle con-
Medical Indications Supported by Clinical Trials: Berberine

Oral Administration: Gastrointestinal disorders, primarily infectious diarrhea, associated with microbial infection and secretory symptoms.

Local Application: Microbial infections of the conjunctiva (trachoma).

Medical Indications Supported by Traditional or Modern Experience: Goldenseal Root

Oral Administration: Since its introduction into western medical practice, goldenseal has been used as an antimicrobial agent for various kinds of infections, including respiratory tract infections such as whooping cough, gastritis, diarrhea, conjunctivitis, cystitis, bedsores, and gonorrhea. Traditionally, the most specific indication of goldenseal is for atonic mucous membranes with profuse secretion of thick yellowish or greenish mucus; this includes cases of mucoid diarrhea, especially following acute diarrhea or dysentery (Bloyer 1897; Felter 1922; Felter and Lloyd 1905; Locke and others 1895; Solis-Cohen and Githens 1928). In addition, it was used as a mild astringent, a bitter tonic (stomachic) and cholagogue (Scudder 1886), and a uterine vasoconstrictor. Modern herbalists report on its value in the treatment of irritable bowel syndrome though specific therapeutic protocols are lacking.

According to the experience of the Eclectic and modern medical herbalists, oral use of goldenseal is appropriate for the following conditions, especially when used in combination with other supportive agents such as myrrh (Commiphora myrrha), Echinacea spp., slippery elm (Ulmus rubra) or marigold (Calendula officinalis): chronic gastritis, dyspepsia, intestinal infections and/or inflammations, urinary tract infection, menorrhagia, and anorexia (as an appetite stimulant) (Felter and Lloyd 1905; Kuts-Cheraux 1953). Herbalists Mills and Bone (2000), report on the common use of goldenseal in the United Kingdom for gastric and duodenal ulcers, though another source indicates that normal doses of goldenseal may exacerbate both (Jonathan Treasure, personal communication to AHP; unreferenced). In order to help attenuate any irritation, demulcents are typically added to goldenseal when it is used in the treatment of ulcers.

Goldenseal's effects on digestive function were noted by Eclectic physician Dr Finely Ellingwood, who wrote, "If there is a marked atonicity, with inaction of the stomach and lack of nerve sensibility, the powdered drug in five grain doses is the most useful [1 grain = .0021 ounces]. This increases the tone, reduces abnormal secretion, stimulates the normal secretion, promotes the appetite, and increases the quantity of the digestive juices and thus favors the digestion." He further states that goldenseal stimulates liver function and helps to relieve chronic constipation when combined with mayapple (Podophyllum peltatum), leptandra (Veronicastrum virginica), or iris (Iris versicolor) (Lloyd 1908). He further stated that it superceded all known remedies for gastric ulcers. Another prominent Eclectic HW Felter joined Ellingwood in his use of goldenseal in biliary conditions including the treatment of gall stones (Ellingwood 1898). Ellingwood recommended goldenseal (combined with cayenne [Capsicum spp.]) for liver congestion due to alcoholism. The Eclectic Webster (1898) reported on the use of goldenseal for myalgic tenderness and soreness where the symptoms are masked by rest, but aggravated by pressure and motion and for skin disorders caused by gastrointestinal debility with impaired digestion. In these cases, topical applications were combined with internal usage.

Topical wash: Bedsores, acne, and eczema of the scrotum and anus. According to one early 20th century Eclectic physician, Byron Nellans, goldenseal needs to be used over an extended period of time, as it "is rather slow acting, but its effects once established are usually permanent" (Lloyd 1928). Localized use of goldenseal in septic wounds and on the mucosa (mouth, gums, throat, the vagina, cervix, and ocular mucosa) figures prominently among traditional herbalists. Modern herbalists have reported using goldenseal mixed with calendula and sterile water as an antiseptic wash around ileostomy stoma and for treatment of antibiotic-resistant staphylococcal infections, impetigo, trichomoniasis, and bedsores not responsive to conventional therapies.

Fomentation: Burns, abrasions, cuts, eczema, fungal infections.

Douche/bolus: In modern herbal therapies, goldenseal is used as an antiseptic solution for vaginal discharges, yeast infections, as adjunctive therapy for sexually transmitted diseases, and for vaginitis and leukorrhea. A douche or bolus of the root is used intra-vaginally for candidiasis, bacterial vaginosis, and as an adjunct for treatment of chlamydial and erosion of the cervix (Pizzorno and Murray, 1999). Eclectic physician E Howes (1904) reported on the local use of goldenseal for fibroid tumors. For this purpose, a tampon was saturated with a solution of equal parts of glycerin and goldenseal and inserted as high as possible resting against the posterior part of the neck of the uterus. A second unmedicated tampon was inserted to help in the retention of the first. This was done morning and evening followed by a douche of plain warm water. For leukorrhea, goldenseal can be combined with witch hazel (Hamamelis virginiana) and used as a douche or as a medicated tampon. For leukorrhea, Ellingwood recommended from 1-3 drams (1/8-3/8 oz), presumably of the powder, in a pint of hot water (Ellingwood 1898). A nasal douche or spray can be used for sinus infections, postnasal drip, and rhinitis. For this, Ellingwood recommended a nasal douche prepared from 10 minims (1 minim = 1 drop, equivalent to 1/60 of a fluid dram) of a fluid preparation (likely a glycerite) per ounce of water (Ellingwood 1898).

Gargle: Pharyngitis, laryngitis, uvulitis, tonsillitis, symptoms of pyorrhea, thrush, aphthous stomatitis, and gingivitis (mouthwash) (Felter and Lloyd 1905; Kuts-Cheraux 1953).

Rectal injection/suppository: Hemorrhoids, anal fissures.
Often mixed with astringent tonics such as white oak bark. Eyewash: Prepared in sterile aqueous or saline solution, goldenseal has historically been used for conjunctivitis (Webster 1898). This continues to be a common use of goldenseal. There is no standardized means for preparing the solution. The first recorded preparation for the eye was made by Captain Meriwether Lewis (1804) who reported on the use of a cold macerate (macerated for 6 hours) from freshly harvested, cleaned and dry roots for “violent inflammation of the eyes.” The water was applied to the eyes with a fine cloth. The Thomsonian Recorder (1833) reported on the use of a cold water macerate of the fresh roots for sore eyes (Lloyd and Lloyd 1884-85).

Some herbalists prepare an aqueous solution by decocting the root in water, straining it through a coffee filter, and applying it as a fomentation, by an eye dropper or eye cup. Others recommend that a few drops of tincture (1:5 or 1:6) be added to an eyecup of warm sterile water and the eye bathed for a period of 2-3 minutes. Ellingwood recommended 10 minims (likely of a glycerite) per ounce of water for inflamed eyes (Ellingwood 1898). For both childhood and adult contagious conjunctivitis, a solution can be prepared from goldenseal powder (1/2 tsp) and chamomile blossoms (1 tsp) by steeping in 1/2 cup of hot water in a covered vessel and filtering thoroughly. Let cool and apply every 2 hours to the corner of the eye with an eyedropper, or a sterile gauze. Improvement is usually seen within 12 hours with complete resolution of symptoms within 36 hours (Aviva Romm, personal communication to AHP; unreferenced). Other herbalists recommend application of goldenseal solution to be as hot as can be tolerated (Cascade Anderson-Geller, personal communication to AHP; unreferenced).

Salve: Cuts and wounds. In modern herbal medicine, goldenseal is often used as a primary ingredient in salves, most often combined with other botanicals such as marigold flowers (Calendula officinalis) and comfrey leaves (Symphytum officinalis).

Sitz bath: As a bath, goldenseal can be used for hemorrhoids, episiotomy incisions, anal pruritus, and rectal fissures (Kuts-C Heraux 1953).

Many modern herbalists have expressed concern over the use of wildcrafted goldenseal due to the plant’s environmentally threatened status. In many cases, other berberine-containing herbs such as the roots of Oregon grape and goldthread may be substituted for goldenseal. However, in other cases, such as in mucosal infections, goldenseal is often considered indispensable (Bergner 1996-7). In most cases, modern herbalists in the US only recommend goldenseal be used for relatively short periods of time (2-3 weeks), though others may recommend small amounts for long term use. In Australia and the United Kingdom, herbalists will prescribe substantial amounts for long-term use when specifically indicated for problems of the mucous membrane.

Substantiated Structure and Function Claim
Berberine has been shown to elicit anti-secretory effects on healthy human colonic mucosal epithelial cells via K+ channel blockade in vitro (Taylor and others 1999) and to improve biliary secretion in humans (Turova and others 1964).

Dosages
Powder: 2 g (NF 1946) daily.
Tincture (1:5): 8 mL (NF 1946) daily.
Fluid Extract (1:1): 2 mL (NF 1946) daily.
Ocular Solution: 2 drops each eye 3 times daily of a 0.2% sterile aqueous berberine solution (Babbar and others 1982; Khosla and others 1992).

Safety Profile
Classification of the American Herbal Products Association
The Botanical Safety Handbook of the American Herbal Products Association (AHPA) assigns goldenseal root the following classifications (McGuffin and others 1997):
Class 2b: Contraindicated in pregnancy unless otherwise directed by a qualified health professional expert in the use of this substance.
Class 2d: Not to exceed recommended dosage; fresh plant may cause mucous inflammation.

Side Effects
Claims that topical application of large doses of goldenseal can cause skin or membrane ulceration have been cited in both past and contemporary herbal literature (Duke 1985; Felter 1922; Foster and Duke 2000; Tierra 1990; Westbrooks and Preacher 1986). The Eclectic Hale reported that high but undefined doses of goldenseal resulted in dry, cracked, and bleeding mucous membranes. Ellingwood (1919) reported that local application of high but undefined concentrations of undiluted extracts of goldenseal may aggravate already existing mucosal inflammation, anal fissures, rectal ulcers, and proctitis (Felter 1922). He further stated that goldenseal powder (dose undefined) can cause extreme irritability of the stomach. According to a contemporary account, no negative effects have been seen with local application to the skin of up to 5 mL of a 1:2 tincture 3 times daily (Eric Yarnell, personal communication to AHP; unreferenced). One anecdotal report of goldenseal causing an exacerbation of a peptic ulcer was received (Jonathan Treasure, personal communication to AHP; unreferenced).

Goldenseal and other berberine containing plants should not be used by neonates or pregnant women. Throughout the 1970s and 80s, incidences of kernicterus (neonatal jaundice) were reported in Singapore, southern China, and neighboring regions. At the time, Chinese goldthread (Coptis chinensis [huang lian]) was a component of a number of traditional medicines used by expectant mothers for nausea and vomiting and was given to newborns.
as a general antimicrobial. The association of C. chinensis with kernicterus led to its use being banned in Singapore. It has since been shown that this botanical is capable of displacing bilirubin from binding to cord serum protein (Yeung and others 1990). Since many exogenous and endogenous factors are known which can displace bilirubin from serum albumin, thus increasing the risk of kernicterus, and since berberine is known to occur in C. chinensis, berberine was investigated in vitro and in vivo in rats for its bilirubin displacement effect (Chan 1993). Berberine was found to be 10 times more potent in vitro than phenylbutazone, a known displacer of bilirubin, and approximately 100 times more potent than papaverine, a representative protobberine alkaloid. Chronic administration of berberine (10 or 20 µg/g ip daily for 1 week) to adult rats resulted in a significant decrease in mean bilirubin serum protein binding due to a displacement effect. It also led to a persistent elevation in steady-state serum concentrations of unbound and total bilirubin. Based on the study results, the researcher noted that C. chinensis toxicity in infants is probably due, at least in part, to berberine acting as a potent bilirubin displacer and metabolism inhibitor. It has been estimated that the typical oral dose of berberine received from traditional Chinese herbal medicines containing high levels of berberine should be avoided in neonates and pregnant women.

**Contraindications**

Due to its potential to stimulate uterine contractions, goldenseal should not be used in pregnancy unless otherwise directed by an expert qualified in its use (MCGuffin and others 1997; Mills and Bone 2000). Neither pregnant women nor neonates should use goldenseal due to the potential ability of berberine-containing drugs to displace bilirubin from serum protein, thereby inducing neonate kernicterus (Chan 1993; see Side Effects).

**Interactions**

Goldenseal root: Goldenseal extract, at non-relaxant doses (0.01-0.1 µg/mL), potentiated the relaxant effect of isoprenaline on isolated guinea pig trachea (Abdel-Haq and others 2000). In vitro inhibition of human isoenzyme cytochrome P450 3A4 has been reported for both goldenseal tincture and berberine (Budzinski and others 2000; Janbaz and Gilani 2000). Of several botanicals in which this activity was investigated, goldenseal tincture (not characterized) exhibited the strongest inhibitory effects with an IC₅₀ of 0.03% (percent full strength extract) (Budzinski and others 2000). Therefore, there is a potential for goldenseal tincture and berberine preparations to alter the metabolism of medications metabolized by isoenzyme cytochrome P450 3A4*. An older reference states that goldenseal may potentiate the oxytocic effects of ergot (Solis-Cohen and Githens 1928). However, a more recent study by Cometa and others (1998) found that goldenseal extract antagonized the contractile effects of oxytocin.

**Berberine:** The IC₅₀ of berberine against cytochrome P450 3A4 was 5.72% nM, a moderate inhibitory ability ranking fifth among the 13 isolated herbal compounds tested (Budzinski and others 2000). Berberine has been reported to significantly potentiate pentobarbitone sleeping times in albino mice when given at doses of 4.5 mg/kg ip prior to pentobarbitone administration (35-40 mg/kg ip) (Janbaz and Gilani 2000; Shanbhag and others 1970). Preninger (1975) reported that berberine has an antagonistic effect on the anticoagulant activity of heparin, while other work has shown that berberine may interfere with the effectiveness of chemotherapeutic agents. According to these researchers, this is due to its ability to enhance the activity of multidrug resistance transporters (Lin and others 1999a; 1999b). Results from one study suggest that berberine may interfere with the virostatic effects of tetracycline in the treatment of cholera (Khin and others 1985). It is not known whether this or any of the other safety data pertaining to isolated alkaloids applies directly to goldenseal.

**Canadine:** Intraperitoneal administration of 40-65 mg/kg of canadine in mice significantly potentiated hexobarbital narcosis, reduced spontaneous activity, antagonized amphetamine-induced hyperactivity and toxicity, diminished the typical scratching response induced by mescaline, aggravated strychnine-induced convulsions, and slightly inhibited metrazole-induced convulsions. Some antagonistic action on apomorphine emesis in dogs has been observed (Chin and others 1962).

**Pregnancy, Mutagenicity, and Reproductive Toxicity**

Goldenseal is contraindicated during pregnancy due to its potential uterine stimulant and bilirubin displacing effects (see Contraindications and Side Effects). Pasqual and others (1993) found that berberine was unable to induce significant cytotoxic, mutagenic, or recombinogenic effects during treatments performed under nongrowth conditions. It also lacked genotoxic activity with or without metabolic activation in the SOS chromotest. However, in dividing cells, berberine induced crossing-over as well as frameshift and mitochondrial mutations in repair-proficient and repair-deficient S. cerevisiae strains. Berberine is reportedly a mitochondrial mutagen in yeast (De Smet and others 1992).

**Lactation**

No data available.

**Carcinogenicity**

No data available.

**Influence on Driving**

No data available. Based on a review of the data and the

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* It has been pointed out by Streser and others (2000) that there is dramatic qualitative and quantitative variability in the fluorometric assays used to screen for cytochrome P450 modulation and that all CYP3A4 inhibition data should be interpreted with caution.
experience of herbal practitioners, no negative effects are to be expected.

Precautions

According to a patent* on the use of goldenseal for ophthalmological use, a 0.25% or 2% solution of berberine at 3 drops per dose in the eye can dilate the pupil (M edow and G reco 1975).

* This patent incorrectly states that “no evidence has been found of the intentional topical application of hydrastis type compounds for any medicinal or pharmacological use.” Reports of the external application of goldenseal for medicinal purposes have been made since the late 1800s (Jones and Scudder 1858; King 1866; Lloyd and Lloyd 1884-85).

Oversdose

An anecdotal report of excessive use of goldenseal in two individuals was received. Both individuals reportedly consumed high, though undefined, doses of goldenseal (10 capsules and a 1:4 tincture) resulting in prolonged emesis (Paul Bergner, personal communication to AHP; unreferenced). High doses of goldenseal fluid extract have also been reported to cause gastric pain, nausea, faintness and giddiness, extreme weakness, headache, and visual hallucination followed by dyspnea and precordial distress, though no details were provided (Solis-Cohen and Githens 1928). An unreferenced report by Roth and others (1984) states that, in extremely high doses (amounts not defined) goldenseal may cause cardiac and respiratory depression.

* The most common commercially available dosages of goldenseal capsules contain from 535-575 mg. If a commercial product was used the estimated total dose would have been approximately 5.35-7.5 g. However, it is not uncommon for consumers to make their own preparations.

Treatment of Oversdose

In the event of poisoning, first aid should consist of administration of charcoal or an emetic gastric lavage, electrolyte supplementation, and balance of acidosis with sodium bicarbonate. Appropriate cardiac and respiratory stimulatory measures should be applied if necessary.

Toxicology

Data regarding the toxicity of crude goldenseal and its preparations in humans are lacking. The only toxicity data available from laboratory studies come from administration of isolated alkaloids to animals (Table 7). It should be borne in mind that safety data pertaining to isolated alkaloids may not apply to directly goldenseal.

Berberine: The oral LD50 of berberine in mice is approximately 3.29 mg/10 g (Haginawa and Harada 1962). In a report from 1895, it was stated that an oral dose of 2.75 g of berberine sulfate administered to dogs produced severe gastrointestinal irritation, watery diarrhea, salivation, tremors, and paralysis. After sacrifice, autopsies revealed that the intestines were contracted and inflamed (Phillips 1885). In cats, oral administration of 25 mg/kg of berberine sulfate caused depression beginning approximately 1 hour after treatment and lasting 6-8 hours. A 50 mg/kg oral dose of berberine promoted salivation and sporadic emesis. At 100 mg/kg, emesis lasting 6-8 hours was observed with death occurring in all animals 8-10 days later (Turova and others 1962). Shanbhag and others (1970) found that 1 mg/0.2 mL ip and 100 µg/0.2 mL iv of berberine HCl produced sedation in cats. Oral doses of 100 mg/kg of berberine sulfate reportedly were well tolerated by rats (Kulkami and others 1972). However, ip and intramuscular administration of berberine to rats resulted in an LD50 of 88.5 mg/kg and 14.5 mg/kg, respectively. Daily oral doses of 0.5 g/kg for 6 weeks produced no changes in tissues or organs (Kowalewski and others 1975). According to one report, when given at 100 mg/kg subcutaneously (equivalent to 50 times the effective dose), berberine exhibited no toxicity in rabbits (Subbaiah and Amin 1967). In long term studies with dogs and cats, 2 mg/kg of berberine were shown to depress cardiac function through dilation of the blood vessels and stimulation of the vagus nerve. At high doses, depression of respiration and stimulation of the smooth muscle of the intestines and uterus were also observed. Smaller doses were found to exert the opposite effect, stimulating cardiac activity and respiration while depressing intestinal peristalsis (Osol and others 1947).

Hydrastine: The LD50 of hydrastine iv in various models has been reported as follows: frog, 0.3 mg/g; mouse and rat, 1 mg/g; rabbit, 0.2 g/kg; cat and dog, 0.3 g/kg; pigeon, 0.1 g/kg (Solis-Cohen and Githens 1928). Intrapertoneal administration of hydrastine to rats (LD50 104 mg/kg) produced strychnine-like toxic convulsive effects (MacDoulgual as cited in Tice 1997). In a study by Huang and Johnston (1990), the dose of hydrastine HCl that induced convulsions in 50% of the test animals (mice) within one minute of iv injection (CD50) was 0.16 mg/kg for (+)-hydrastine HCl and 29.8 mg/kg for (-)-hydrastine HCl. However, in another study, β-hydrastine did not induce convulsions in mice even at lethal doses (Bartolini and others 1990).

Canadine: In mice, the LD50 of canadine is reported to be 566 mg/kg. Oral administration of 150 or 300 mg/kg in rats for 30 days produced no macroscopic changes in the viscera. Upon microscopic examination, a very slight degree of cloudy swelling was noticed in the heart. When injected into anesthetized cats, canadine produced a transient hypotension and tachycardia. Intravenous administration of 40 mg/kg of canadine in rabbits produced an analgesic effect (Chin and others 1962).
Table 7  LD_{50} of goldenseal alkaloids (mg/kg)

<table>
<thead>
<tr>
<th>Alkaloid</th>
<th>LD_{50}</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Berberine</td>
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<td></td>
</tr>
<tr>
<td>Mice</td>
<td>329 po</td>
<td>Tice 1997</td>
</tr>
<tr>
<td></td>
<td>18 sc</td>
<td>Tice 1997</td>
</tr>
<tr>
<td>Berberine sulfate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td>14.5 im</td>
<td>Kowalewski and others 1975</td>
</tr>
<tr>
<td></td>
<td>88.5 ip</td>
<td>Kowalewski and others 1975</td>
</tr>
<tr>
<td></td>
<td>205 ip</td>
<td>Kulkarni and others 1972</td>
</tr>
<tr>
<td></td>
<td>&gt;1000 po</td>
<td>Kowalewski and others 1975</td>
</tr>
<tr>
<td>Mice (albino)</td>
<td>24.3 ip</td>
<td>Sabir and Bhide 1971</td>
</tr>
<tr>
<td>Canadine</td>
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<td>Mice</td>
<td>566 ip</td>
<td>Chin and others 1962</td>
</tr>
<tr>
<td>Hydrastine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rats</td>
<td>104 ip</td>
<td>Tice 1997</td>
</tr>
</tbody>
</table>

**International Status**

**United States**
Regulated as a dietary supplement (USC 1994). Subject of botanical monograph in development for the National Formulary of the United States. Contains not less than 2.0% hydrastine and not less than 2.5% berberine (USPF 2000). The 1X tincture of the rhizome and roots, 65% alcohol V/V, is a Class C OTC drug official in the Homoeopathic Pharmacopoeia of the United States (1996).

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

**Council of Europe**
Subject of botanical monograph in development for the European pharmacopoeia. Contains not less than 2.5% hydrastine, calculated in reference to the dried drug (PharmEuropa 1999).

**France**

**Germany**
Official in the German Homöopathisches Arzneibuch (HAB 1). Contains not less than 3.0% alkaloids, calculated as berberine (GHP 1993). **Indications:** D1-D4 for chronic nasal catarrh, uterine hemorrhages, leukorrhea, and as a tonic (Roth and others 1984).

**Italy**

**Switzerland**
Goldenseal homeopathic dilution is 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 (AKS 2001; Codex 2000-1; WHO 1998).

**United Kingdom**


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