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Chimaphila umbellata (L.) NUTT. **Pipsissewa**

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Pipsissewa – *Chimaphila umbellata* (L.) NUTT.

1. Taxonomy

Family: Pyloraceae. Previously placed in the Ericaceae family.

Common names: pipsissewa, from Native American name pipsiskeweu meaning ‘it breaks into small pieces’. Prince’s pine, bitter wintergreen, fragrant wintergreen, ground holly, king’s cure.

Similar species: *Chimaphila maculata* L. – spotted pipsissewa, spotted wintergreen. It is considered to have similar medicinal properties.



Figure 1. *C. umbellata*. Reproduced with permission from Peggy Duke.

2. Botanical description and distribution

C. umbellata is an evergreen perennial growing to 10 inches, with dark green, leathery oblanceolate leaves with toothed margins, which form a pseudo-whorl that has the appearance of a small basal rosette when in the vegetative state (Minore, n.d.). The species has a slender creeping rhizome allowing the plant to form extensive colonies on the forest floor. Flowering stems bear terminal umbel-like corymbs consisting of 3-10 symmetrical, drooping flowers, 10-15mm wide. There are five pink-white petals, five sepals and 10 stamens; the ovary is superior maturing to produce an erect capsule (Minore n.d.; Brown & Brown, 1984; Haber, 1992).

C. umbellata favors deep mulch adjacent to trees or logs in dry coniferous and hardwood forests throughout the Northern hemisphere, and has a wide distribution in U.S.A. (Krochmal, Walters and Doughty 1969). It is a protected species in Germany (Gruenwald, 2000). *C. maculata* has a more restricted global distribution, however it is the more common species in parts of Appalachia.

Part used

Dried aerial parts, leaves.

Chimaphila.

N. Chimaphila, Pipsissewa, Prince's Pine.—**O.** Leaves of *Chimaphila umbellata*; *Ericaceae*. The leaves alone should be used, but twigs are always admixed.—**H.** North America, Nova Scotia to



Fig. 207.

Georgia, west to the Pacific.—**D.** The illustration gives a good idea of the drug, natural size; the leaves are cuneate-lanceolate, or oblanceolate, with margin serrate at apex and entire near the base, coriaceous, smooth, dark-green to brown, with little odor and a bitterish, slightly astringent taste.—**C.** Chimaphilin, arbutin, a small proportion of tannic acid, etc.—**U.** Alterative, astringent

Figure 2. Reproduced from *Handbook of Pharmacognosy* by Otto A. Wall 1917. C.V. Mosby Co., St. Louis

3. Traditional uses

Traditional uses in Appalachia

According to legendary Appalachian herbalist Tommie Bass pipsissewa has been used ‘ever since time’ for treating rheumatism, as well as for kidney and liver disorders (Crellin & Philpott, 1990). When combined with mullein (*Verbsacum* spp.) it relieved bedwetting in children. Considering Bass lived in Southern Appalachia, the species he referred to is most likely *C. maculata* (Crellin & Philpott, 1990). This species is still used in Appalachia for its’ diuretic, tonic and astringent properties, having a wide range of applications, from skin eruptions through to cancer (Jacobs & Burbage, 1958; Krochmal, Walters & Doughty, 1969). In northern Appalachia the *umbellata* species is more often used – with numerous indications including chronic kidney diseases, ascites and strangury (Jacobs & Burbage, 1958).

Traditional uses outside of Appalachia

Native American use

Topically, the leaf infusion was used to heal blisters and as an eye wash for dry and irritated eyes (Moerman, 1919). Leaves were also smoked as a tobacco substitute (Foster & Duke, 2000). It has been reported that the Wasco people of Oregon used whole plant decoctions to treat tubercular infections (Hostettmann, Gupta, & Marston, 1999). The Ojibwa of Canada used it as a tea for stomach problems, in a root decoction for treating sore eyes and as an ingredient of a formula used for gonorrhea. Other First Nations people of Eastern Canada used it for rheumatic conditions, kidney disorders, head colds and tuberculosis (Arnason, Hebda, & Johns, 1981).

Folklore & Home

C. umbellata was used as a tonic for promoting strength and appetite, and when drunk regularly it was said to cure cancers. It was taken as a diuretic for strangury, dropsy and other kidney disorders (Child, 1837).

Physiomedical

C. umbellata was primarily used as a tonic to strengthen debilitated kidneys, and for depleted tone in the urinary tract (Cook, 1869). Lyle (1897) recommended it be used in place of the popular urinary tract antiseptic *Arctostaphylos uva-ursi* (L.) Spreng., particularly for vaginal and uterine weaknesses, leucorrhea and spermatorrhea. Clymer (1904) regarded the tincture as a standby for “dropsy” and other kidney disorders, particularly when associated with scanty urine containing blood or purulent discharge.

Eclectic

C. umbellata was used as a urinary antiseptic herb, especially for elderly subjects exhibiting “chronic cystitis with a pinkish or reddish sediment of mucus, pus, blood and brick dust in the urine”. It was also used for symptoms of prostatitis (Felter, 1922). Felter and Lloyd give the following indication; “Atonic and debilitated states of the urinary organs, giving rise to lingering disorders, with scanty urine, but excessive voiding of

mucus, muco-pus, or bloody muco-pus, offensive or non-offensive in character; smarting or burning pain with dysuria; chronic irritation of the urethra and prostate; chronic relaxation of the bladder walls; chronic prostatitis, with vesical catarrh.”

(Felter & Lloyd, 1898).

Regulars

C. umbellata was formerly used by physicians for urinary tract infections and calculi (Foster & Duke, 2000). As already noted by Lyle (see above) it was often used in a similar way to *Arctostaphylos uva-ursi* (Wall, 1884).

4. Scientific Research

Phytochemistry

Quinones

Phytochemical analysis of *C. umbellata* was carried out as long ago as 1860, when the neutral crystalline substance named chimaphilin was isolated (Fairbank, 1869), although the chemical formula was not ascribed until 1892 (Peacock, 1892). The molecular structure was confirmed by Di Modica et al. in the 1950s, and found to be 2,7-dimethyl-1,4-naphthoquinone, a compound previously synthesized from coal tar in 1919 (Hausen and Schiedermaier, 1988). Biosynthetic studies revealed the precursor to the quinonoid moiety in chimaphilin to be the amino acid tyrosine (Bolkart & Zenk, 1968), while mevalonic acid is precursor to the substituted benzene ring (Bolkart, Knobloch, & Zenk, 1968). Chimaphilin is found in other species of the Pyloraceae families (Sheth, Catalfomo, Sciuchetti, & French, 1967), while the chlorinated derivative chlorochimaphilin is found in *Moneses uniflora* (L.) A. Gray, a Canadian species of the Pyloraceae (Saxena, Farmer, Hancock, & Towers, 1996).

Several alkylated benzohydroquinones have also been reported, including the antimicrobial toluquinol and the glycoside renifolin (Inouye & Inoue, 1985; Duke, 2001; Pedersen, 2002)

Simple phenols and phenolic glycosides

Simple phenols including methyl salicylate and salicylic acid methyl ester are reported (Duke, 2001); these give the leaves a slight wintergreen-like odor when rubbed. Phenolic glycosides arbutin and isohomoarbutin, widely distributed in the Ericaceae and Pyloraceae families, also occur (Duke, 2001). The glycosides are hydrolyzed in the human body to yield hydroquinone, an antiseptic to the urinary system (Pengelly, 2004).

Polyphenols

C. umbellata leaves contains (4-5%) tannins, including hydrolysable and condensed tannins such as epicatechin gallate. Sheth et al. (1967) isolated quercetin, which was verified by UV and IR spectrometry. Leaves and flowers are reportedly rich in other flavonoids, including hyperoside, kaempferol and avicularin (Gruenwald, 2000; Duke, 2001).

Terpenes and sterols

In a comprehensive investigation of the species, Sheth et al. (1967) isolated the free triterpenes taraxerol and ursolic acid using column chromatography, and by tracing the concentrated fractions via thin layer chromatography (TLC) also isolated the sterol β -sitosterol. However, they were unable to isolate the triterpene β -amyrin previously reported in the species (Sheth et al., 1967).

Other

C. umbellata contains, starch, gum, pectin, resin, a lignan, mineral salts (Fairbank, 1869; Duke, 2001) as well as the hydrocarbons nonacosane and hentriacontane (Sheth et al., 1967).

Pharmacology

Antimicrobial

Constituents of *C. umbellata* including chimaphilin and arbutin have long been reported to have antimicrobial properties. 1,4-naphthaquinones are substituted with OH or Cl groups on the quinine moiety; these attract electrons enabling a short-circuiting of the electronic transfer system in cells, a means by which they inhibit growth of microorganisms (Holmes et al., 1964; Ambrogi et al., 1970). A 70% ethanol extract of *C. umbellata* inhibited the growth of *S. aureus*, *E. coli*, *C. albicans* and *Trichophyton mentagrophytes in vitro* (Sheth et al., 1967). Mechanisms for antifungal activity of these compounds are particularly well documented (Gershon & Shanks, 1975; Steffen & Peschel, 1975). Chimaphilin from *Moneses uniflora* demonstrated potent inhibitory activity against *S. aureus*, *Bacillus subtilis* and *C. albicans* but with no significant effects on *Mycobacterium* species (Saxena et al., 1996).

In a survey of potential antifungal herbs used by First Nations People of Eastern Canada, *C. umbellata* was clearly the most potent of the 26 species tested, with an average growth inhibition zone of 19.9 mm for the six species of human pathogenic fungi analyzed (Jones et al., 2000). Using bioassay-guided isolation Galvin et al., (2008) confirmed that chimaphilin was the main antifungal constituent of *C. umbellata*, and using a chemical-genetic screening method determined that chimaphalin interferes with cell wall, mitochondrial, transcription and other cellular functions.

Antioxidant activity

C. umbellata is a component of the proprietary formula Eviprostat[®] that is used in Japan and Europe for treatment of benign prostatic hyperplasia (BPH). When components of the formula were tested for biological activity, *C. umbellata* was found to be a potent inhibitor of oxygen radicals generated in the xanthine/xanthine oxidase system, and hydroxyl radicals produced in the Fenton-type reaction system (Oka, Tachibana, et al., 2007). The crude extract also demonstrated good antioxidant activity via the DPPH assay (Galvin et al., 2008). Recently *C. umbellata* (but not its individual components) was shown to suppress oxidative stress markers in rats with surgically induced bladder outlet obstruction (Oka, Fukui, et al., 2009).

Anti-inflammatory activity

Studies in this area are based on Eviprostat[®] or its components. These components, along with different combinations of them, were tested by the carrageenan-induced paw edema method in rats. While individual components had no significant effect, all combinations that included *C. umbellata* suppressed the edema (Oka, Tachibana, et al., 2007).

Eviprostat[®] suppressed pro-inflammatory cytokines and reduced bladder weight in rats with surgically induced bladder outlet obstruction (Oka, Fukui, et al., 2009), as well as stromal predominance (stromal: epithelial ratio), gene expression and pro-inflammatory cytokines in a rat model of nonbacterial prostatitis (Tsunemori et al., 2011).

Clinical studies

In one study regular and double-strength formulations of Eviprostat[®] were randomly assigned to a group of 92 patients with BPH (Tamaki et al., 2008). Clinical efficacy was evaluated by the International Prostate Symptom Score (IPSS) and a Quality of Life (QOL) score, and both treatments provided benefits that were comparable to conventional BPH agents (compared with data from other studies) and were well tolerated (Tamaki et al., 2008).

Toxicology

Various anecdotal reports that contact with *C. umbellata* leaves could cause dermatitis and vesiculation (White, 1887) led Hausen & Schiedermaier (1988) to investigate the skin sensitizing potential of the active constituent chimaphilin on female guinea pigs. Using the open epicutaneous (OET) and Freund's complete adjuvant techniques (FCA), chimaphilin showed weak sensitizing potency in the OET and moderate sensitizing capacity in the FCA method. The authors posit the sensitizing effect is linked to nucleophilic attack at the 3rd carbon atom of the quinoid ring of chimaphilin (Hausen & Schiedermaier, 1988).

5. Modern Phytotherapy

Modern therapeutic use of *C. umbellata* reflects traditional indications, although the species is used sparingly in modern clinical herbal medicine. It is, however, admired by the British herbalist Andrew Chevallier, whose list of indications includes urinary tract infections, gonorrhoea, kidney stones, rheumatism and gout (Chevallier, 1996).

Naturae medicina and Naturopathic Dispensatory (Kuts-Cheraux 1953) states, "It stimulates the removal of catabolic wastes, and is a renal antiseptic and tonic...". It also states *C. umbellata* is useful for cystitis as well as early stages of pyelitis. Renowned U.S. herbalist Michael Moore (2003) says of it, "Similar in use and pharmacology to Uva Ursi... It is much less astringent than Uva Ursi, with a stronger diuretic action and less irritating to the intestinal linings". Moore also suggests it is useful for resolving a variety of skin disorders.

Table 1. Modern phytotherapeutic uses of *C. umbellata*.

ACTIONS	
Diuretic	Rubifacient

Astringent	Vescicant
Antimicrobial	Febrifuge
Alteratives	

THERAPEUTIC INDICATIONS

Acute and chronic cystitis, prostatitis, urethritis

Odema, kidney weakness, urinary calculi

Benign prostatic hyperplasia

Chronic mild nephritis

Bleeding wounds, skin reuptions

Rheumatoid arthritis, gout

(Foster & Duke, 2000; Gruenwald, 2000; Moore 2003; Skenderi, 2003; Chevallier, 2000).

Preparations and dosage

Dried herb. 2g per day as powder or tea (Gruenwald, 2000)

Fluid Extract 2.5-5ml (Wren, 1988), 1-4ml (Gruenwald, 2000)

Toxicity and contraindications

Leaves applied directly to the skin may induce redness and blisters (Foster & Duke, 2000).

6. Sustainability

Last reviewed in 2001, *Chimaphila umbellata* is considered globally secure (Natureserv, 2010). Of the three North American subspecies, *acuta* (last reviewed in 2002) is listed as “apparently secure” globally, while *cisatlantica* (last reviewed in 1998) and *occidentalis* (last review in 1991) are both considered globally secure (Natureserv, 2010).

In the United States *C. umbellata* is listed as endangered in Illinois (Illinois DNR, 2011), threatened in Ohio (Ohio DNR, 2011) and protected as “exploitably vulnerable” in New York (NYDEC, 2011). In Iowa, Horton (2006) summarized ten reviews from 1977 through 1998 and found *C. umbellata* listed as endangered from 1977 to 1989, then changed to threatened in the 1994 and 1998 reports. Horton (2006) also notes that Iowa law states that a review of endangered species be conducted every two years, but Iowa has canceled such reviews following public protest. The Indiana Department of Natural Resources (2010) lists the subspecies *C. umbellata ssp cisatlantica* as imperiled (S2) but not *C. umbellata*. According to Price (1960), both *C. maculata* and *C. umbellata* were once common in Delaware and Maryland (See Appendix I).

C. umbellata is classified as a slow-growing native perennial that is sensitive to harvesting pressures, ecological disturbances, fire and foot traffic (Everett, 1997; Matthews, 1994).

Harvesting & Collection regulations

According to New York regulations:

"It is a violation for any person, anywhere in the State, to pick, pluck, sever, remove, damage by the application of herbicides or defoliant, or carry away, without the consent of the owner, any protected plant. Each protected plant so picked, plucked, severed, removed, damaged or carried away shall constitute a separate violation" (NYDEC, 2011).

Market data - harvesting impact, tonnage surveys

Gray, Enzer & Kuzel, (2001) conducted a regeneration study of wild-harvested *C. umbellata* and concluded that the Pacific Northwest should not be open for commercial harvest. The Center for Non-timber Forest Products (CNTFP, 2009) and Tilford (1998) both note that *C. umbellata* regenerates too slowly for regular commercial harvesting. Tilford (1998) noted that areas of the Cascades had been denuded of *C. umbellata*. Matthews (1994) reports that loss of tree stands from the mountain pine beetles has resulted in serious population decline in *C. umbellata* – reportedly absent in areas where the forests are cleared and burned.

The AHPA does not include *C. umbellata* in its tonnage surveys.

There is commercial interest in *C. umbellata* as a medicinal herb as well as a soft drink flavoring (Thomas & Schuman, 1993). Extracts of the leaves are used commercially for flavoring and in formulations for skin astringents: CAS¹ # 89997-56-8 and FEMA² GRAS³ # 2914 (De Rovira, 2008).

In 1911 the plants brought \$0.04 /lb. (Henkel, 1911), by 1993 Thomas & Schuman (1993) list \$1.90/lb, in 2007 Northwest Botanicals was offering 1,500 pounds at \$2.65/lb (Miller, 2007) and by 2011 the pricing ranged from \$10.50 to \$47.94 per pound (Table 2).

Table 2. Availability and wholesale cost of Wild-crafted *Chimaphila umbellata*

Company	Cut/sift	Powdered	Seeds	Source
Monterey Bay Spice Co	\$12/lb.			http://www.herbco.com/c-269-pipsissewa.aspx
Herbs for Health	cert.kosher US origin			http://herbshealth.com/catalog/index.php?main_page=product_info&products_id=3801

1 Chemical Abstract Service

2 Flavor and Extract Manufacturers Association.

3 Generally Recognized as Safe

	\$47.94/lb			
Mountain Rose Herbs	\$10.50/lb. US origin	\$12.00/lb.		http://www.mountainroseherbs.com/bulkherb/p.php
Horizon Herbs			\$3.95/each pkt 500 seeds/pkt	

Cultivation

Habitat

Native in Zones 2-8 in North America, Europe, and Asia (Kartesz, 2011; Cullina, 2000), *C. umbellata* is a slow growing perennial with evergreen leaves that may persist for seven or eight years (Matthews, 1994; Minore, 2008). It can be found in a wide variety of soils including shady pine woods, gravel, rocky and sandy soils (Crellin & Philpot, 1990, Tilford, 1998; Matthews, 1994). The plants require loose uncompacted soil and do not thrive where there is a lot of trampling (Buhner, 2000; Matthews, 1994). This is a shade loving species which prefers protection from direct sunlight (Matthews, 1994) and well-drained to moist, acid humus with a pH between 4-5 (Plants for a Future, 2010; Miller, 1977; Cullina, 2000; Birdseye & Birdseye, 1951, reprint 1972).

Propagation

In its natural habitat, *C. umbellata* reproduces both sexually and vegetatively by offshoots from its creeping rhizomes (Tilford, 1998; Matthews, 1994). Several authors note that the plants are difficult to propagate from seed (Buhner, 2000; Tilford, 1998) because the *C. umbellata* may depend on a symbiotic relationship with mycorrhiza, bacteria etc. for seedling survival (Miller, 1977; Tilford, 1998; Cullina 2000).

Seed propagation

Forest cultivation

Horizon Herbs (2011) recommends mixing the seeds in sawdust and sowing them along a conifer dripline or in dry, acid woodland (Cullina, 2000).

Greenhouse cultivation

For greenhouse propagation, Plants for a Future (2010) suggests mixing the fresh seeds with soil from a local stand of *C. umbellata* with moist sphagnum as soon as the seeds are ripe. Seedlings are then transplanted into individual pots and grown under shade for at least one winter. One year old seedlings can be planted in late spring after the last frost or early summer, taking care not to disturb the roots (Plants for a Future, 2010; Cullina, 2000). Minore (2008) found that seedlings germinated in the spring when soil from *C. umbellata* habitat was sifted then stored outdoors all winter. While no pre-germination treatments are known, stratification of fresh seeds in soil inoculated with local soil suggests some potential success (Minore, 2008).

Vegetative propagation

Cuttings taken just as the plant begins to grow in the spring can be planted 1-2 inches below the soil surface as only rhizomes near the surface will produce shoots (Matthews, 1994; Plants for a Future, 2000). Mix soil from the gathering site in with your growing medium (Miller, 1977; Buhner, 2000). The slender rhizomes grow between 2-5 inches

deep and should be disturbed as little as possible (Matthews, 1994; Plants for a Future, 2000). Cullina (2000) recommends adding a granular fertilizer for thick growth and notes that *Mitchella repens* is a good companion plant.

Mature plants may be replanted into new areas but care must be taken to include a large root ball so that the fibrous roots are protected, as they may die if disturbed (Buhner 2000).

Reproduction

C. umbellata flowers from June to August (Matthews, 1994), usually after 7-8 whorls of leaves have been produced following 3-4 growing seasons (Minore, 2008). Natural pollinators include bumblebees and staphylinid beetles (Matthews, 1994; Minore, 2008). Between 45-50% of the flowers reportedly produced seed. (Matthews, 1994; Minore, 2008; Helenurm & Barrett, 1987). When the seed capsules begin to open (dehisce) the seeds can be collected into a jar or bag; collecting the closed capsules is not recommended because the seed may not be fully mature (Minore, 2008).

Harvest

When harvesting *C. umbellata* no more than the top third of the plant should be taken (Buhner, 2000; CNTFP, 2009). Always work from the periphery of wild or woods-grown plants to avoid damaging the fibrous roots and compacting the soil (Tilford, 1998; Buhner, 2000).

Pests/Diseases

White-tailed deer and Roosevelt elk have been known to eat *C. umbellata* during the fall, winter and spring (Matthews, 1994).

7. Summary and moving forward

C. umbellata is a characteristic herb of the Appalachian woods, however it is also an international herb both in terms of natural distribution and for its recognition as an effective complementary medicine for urinary and prostate disorders - particularly in Europe and Japan. Although herbalists in the USA have historically used it for similar indications, it is not widely used by contemporary practitioners. This is due at least in part to a presumption the species will not likely tolerate commercial exploitation in this country. Any proliferation of experimental and clinical research will need to be matched by increased cultivation programs and sustainability studies.

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Appendix- I. Ecological Status of *C. umbellata*

Authority	Status	Source
Global	G5T5	(Natureserv, 2010).
Federal	no threatened rating	(Natureserv, 2010)
Indiana	S2 -imperiled ssp cisatlantica	Indiana Department of Natural Resources (2010)
Illinois	Endangered	Illinois Endangered Species Protection Board. (2011)
Iowa	endangered/ threatened	Horton (2006)
New York	Exploitably vulnerable	Department of Environmental Conservation. 2011. Protected native plants . Division of Land and Forests, New York (2011)
Ohio	threatened	Division of Natural Areas and Preserves. 2011.
MD	S3 current rank improved from	MD RTE 2010 http://www.dnr.state.md.us/wildlife/Plants_Wildlife/rte/pdfs/rte_Plant_

