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Sanguinaria canadensis L.
Bloodroot

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Bloodroot - *Sanguinaria canadensis* L.

1. Taxonomy

Sanguinaria canadensis L. (Family Papaveraceae).
Common names: Bloodroot, pucoon, red pucoon, Indian paint, tetterwort, coonroot, pauson, redroot, snakebite
Synonyms: *Sanguinaria australis* Greene, *S. dilleniana* Greene, *S. rotundifolia* Greene

2. Botany, distribution

S. canadensis is a small ephemeral herbaceous perennial attaining a height of up 30cm. The distinctive solitary white flowers with yellow stamens appear on the forest floor very early in the spring, lasting only for a number of days. The flower bud is initially enclosed in the curled leaf, which gradually opens out to expose the flower, while the leaves develop a distinctive palmately lobed shape with a dark green, leathery surface. Flowers have 8-10 petals arranged in rows, in contrast to other Papaveraceae flowers which have four petals only (Predny and Chamberlain, 2005). Flowers mature to produce elongated seed-bearing capsules divided into two valves.

One unique feature of the species is the production of an appendage on the seed – the elaisome – that is favored ant food. By moving seeds to their nest in order to eat the elaisome in comfort, the ants are unwittingly assisting the seed dispersal into a natural seedbed - hence encouraging future propagation (Hendershott, 2002; Predny and Chamberlain, 2005).

The natural distribution of *S. canadensis* encompasses large tracts of the North American continent, however its preference is for rich deciduous woodlands typical of the Appalachian region.

Part used

Dried rootstock, harvested in early spring, late summer or fall.

Figure 1. Reproduced from *A Manual of the Medical Botany of North America* by Lawrence Johnson. William Wood & Co. 1884

3. Traditional uses

Traditional Uses in Appalachia

In addition to its common uses as a dye for clothing and skin decoration, *S. canadensis* has long been used for medicinal uses in Appalachia, In small doses, it is considered soothing to the digestive tract, however when taken in too large a dose, it can reportedly cause nausea, vertigo and vomiting severe enough to dispel worms from the stomach (Millspaugh, 1974). A powerful medicine when administered by skilled hands, it is commonly used for colds, coughs and sore throats, being regarded as a systemic expectorant (Bass, 1990). When dried and powdered, it is often administered to fungal infections and ulcers of the skin (Erichsen-Brown, 1979) and as a snuff for nasal polyps (Elliot, 1976). One of the common names "tetterwort" derives from the common usage for treating blister-like skin lesions (Elliot, 1976).

As a topical treatment, it is regarded by many as one of the most effective medicines for cancerous growths. When applied as a paste, it is reputed to burn away the growth, and the cancer along with it. The same treatment was applied to warts, boils & polyps (Howell, 2006).

Traditional uses outside of Appalachia

Native American

American Indians used the root of *S. canadensis* for arthritis, asthma, bronchitis, lung ailments, laryngyitis and fevers, while the brightly colored juice from the root was applied to warts (Foster & Duke, 2000; Redmond, 2003). The juice was also used for face painting (Tyler, Brady, & Robbers, 1988) and applied as a love potion (Elliot, 1976; Foster & Duke, 2000). Iroquois used a

tea from rhizomes for stomachache and the roots for earache. For sore throats the juice was added to maple syrup (Arnarson, Hebda, & Johns, 1981). Iroquois women used it for reproductive disorders as well as for wounds and ulcers (Montgomery 2000). The Malecites used the roots for consumption with hemorrhage (Arnarson, Hebda, & Johns, 1981).

Folklore & Home

The traditional family physician and folkloric use of *S. canadensis* centered mainly on the so-called "moving effects", being regularly used as an emetic (inducing vomiting), diuretic (increasing urine flow), emmenagogue (stimulating menstrual flow), sialagogue (stimulating saliva and gastric juices) or cathartic (laxative effect) (Gardner & Aylworth, 1836).

Physiomedical

Early Thomsonian and Physiomedical practitioners appear to have largely avoided the use of *S. canadensis*. Samuel Thomson was a fierce advocate of 'non-poisonous' herbs (Thomson, 1835), and aside from *Lobelia inflata* L. there are notably few references to alkaloid containing species in the early physiomedical literature. However William Cook, who helped modernize the Physiomedical system in the second half of the nineteenth century, favored the use of this remedy for acute *and* chronic bronchitis, for restoring bronchial secretions when out of balance, and soothing mucus membranes that are dry, itchy and irritable (Cook, 1869). Albeit Cook believed it was too harsh an emetic to be used singly, and recommended it be used in combination with milder agents to ease the response.

Eclectic

S. canadensis has been shown to be quite versatile, having been used successfully for a variety of ailments in a dose dependent fashion. In small doses, it was used as a stimulant and tonic for the digestive tract, as an emetic and for atonic dyspepsia (Felter & Lloyd, 1898). Conversely, in larger doses it was shown to be, "sedative to the heart, reducing the pulse, causing nausea, and consequently diaphoresis, increased expectoration, and gentle diuresis, at the same time stimulating the liver to increased action." (Felter & Lloyd, 1898). It was particularly employed towards the hepatic system, working as a reliable cholagogue in suppressed or lethargic states (Felter, 1898). Scudder (1870) favored higher doses to address mucus membrane balance with variable secretions in both the respiratory tract in the stomach and liver. Smaller doses had a profound effect on the lungs, with indications of, "cough with dryness of the throat and air passages, feeling of constriction in the chest, difficult and asthmatic breathing, with sensation of pressure. In the same doses it is a stimulant to the vegetative system of nerves, and under its use there is an improvement in the circulation, in nutrition, and secretion", as a powerful circulatory and moving tonic (Scudder, 1870).

Regulars (allopathic & practicing physicians)

S. canadensis was often used in pulmonary diseases, bleeding of the lungs and in malignant scarlet fever. In the form of a snuff it was effective against nasal polyps. The root decoction was beneficial in pneumonia with expectoration of blood-streaked mucus (Beach, 1851). Other actions attributed to the species were emetic, cathartic, emmenagogue and sialagogue, and it was used as a snuff for catarrhal conditions (Gardnerm & Aylworth, 1836). As a stimulating expectorant is was used for treatment of subacute and chronic bronchitis (Wilcox, 1907). It was listed in the *United States Pharmacopoeia* from 1820-1910 and in the *National Formulary* from 1925-1965.

4. Scientific Research

Phytochemistry

The name 'bloodroot' refers to the red latex found in the rhizome. This latex is rich in the isoquinoline class of alkaloids, in particular several of the benzophenanthridine subclass. These include sanguinarine, chelerythrine, sanguilutine, chelirubine, sanguirubine and chelilutine. Sanguinarine consists of up to 50% of the total alkaloids by weight (see Table 1). While sanguinarine in its ionic form is colorless, it readily forms salts (chlorides, sulfates) which exhibit the distinctive red color (Tyler, Brady, & Robbers, 1988). A dimeric alkaloid named sanguidimerine consisting of two dihydrosanguinarine moieties has also been found (Tin-Wa Fong, Abraham, Trojanek, & Farnsworth, 1972). In addition *S. canadensis* contains low levels of other isoquinoline alkaloids namely protopine, allocryptine and berberine (Thorne et al 1986; Salmore and Hunter 2001).

Table 1: Benzophenanthridine alkaloids and their relative percentage in *S. canadensis* rhizome extracts (Thorne et al., 1986)

ALKALOID	RELATIVE PERCENTAGE
Sanguinarine	50
Chelerythrine	25
Sanguilutine	15
Chelirubine	4
Sanguirubine	4
Chelilutine	2

The diverse commercial applications of *S. canadensis* extracts from dental and skin care products to a weight gain stimulant for farm animals, have led to development of more sensitive analytical methods based on ion-pairing high-performance liquid chromatography (HPLC), capable of quantifying levels of sanguinarine in blood, body fluids and other biological matrices at micromolar levels (Reinhart, Harkrader, Wylie, Yewey, & Van Horne, 1991). For *in vitro* and *in vivo* experiments, submicromolar levels of detection are required, hence Kosina and co-workers found this could be achieved with the addition of a fluorescence detector to the ion-pairing HPLC apparatus (Kosina et al., 2003). While it was less sensitive than fluorescence detection, an alternative capillary electrophoresis (CE) method was also found to be effective.

Alkaloidal composition in *S. canadensis* has been found to be both genetically and environmentally determined. There have been numerous studies demonstrating the influence of eco-physiological factors on levels of sanguinarine and other constituents. One such study concluded benzophenanthridine alkaloid content of bloodroot rhizomes decreases with elevation, although there is no such correlation for the protopine group (Salmore and Hunter 2001). Variation in alkaloid content was also found between sites irrespective of elevation.

Other factors influencing alkaloid content were season of harvest and moisture content of rhizomes (Salmore and Hunter, 2001). Concentration of sanguinarine is highest between the period of flower maturation and fruit development (Bennett et al., 1990; Campbell, Affolter, and Randle, 2007). Alkaloids are typically concentrated in certain plant sections – in the case of bloodroot sanguinarine concentrations are highest in the rhizome followed by the roots, while aerial parts have low levels only (Campbell, Affolter, and Randle 2007) Graf et al., (2007) showed that levels of sanguinarine and chelerythrine were slightly lower in shade cultivated *S. canadensis* compared to wildcrafted, however the levels of the two alkaloids were more consistent for the cultivated specimens over the harvest period (May-November).

Pharmacology

Most of the experimental research is based around sanguinarine, an alkaloid with a broad range of biological activity; these include interactions with DNA and a variety of enzymes and signaling molecules (Kosina et al., 2003; Lopus & Panda, 2006).

Antimicrobial

S. canadensis alkaloids as represented by sanguinarine have broad antimicrobial activity including against gram negative and gram positive bacteria as well as fungi; it is particularly active against oral plaque bacteria (MIC ranges 1-32ug/mL) (Godowski 1989). The alkaloids are retained in the bacterial bioform associated with oral plaque for at least three hours (Moretti, Abdo, Carvalho, Machado, & da Silva, 2009). Methanolic extracts of *S. canadensis* and the alkaloids sanguinarine, chelerythrine and protopine were shown to inhibit *Heliobacter pylori in vitro*, sanguinarine being the most active (Mahady, Pendland, Stoia, & Chadwick, 2003). Three different potencies of homeopathic preparations (6CH, 12CH and 30CH) of *S. canadensis* significantly inhibited growth of the bacteria *Streptococcus mutans in vitro* (Giorgi, Carvalho, Passetti, & Valentim, 2006).

Antiproliferative effects

Studies with human epidermal carcinoma cells and revealed that sanguinarine provided dose dependent antiproliferative and antiapoptotic effects on carcinomas, but far milder effects on normal keratinocytes (Ahmad, Gupta, Husain, Heiskanen, & Mukhtar, 2000). Further studies showed these effects are initiated by damage to the mitochondria such that endogenous mechanisms of apoptosis were induced (Adhami, Aziz, Mukhtar, & Ahmad, 2003), while similar mechanisms were demonstrated in human breast cancer cells (Kim et al., 2008). Cell cycle blockage and apoptosis of prostate carcinoma cells by sanguinarine was associated with modulation of the cycline kinase cascade (Adhami et al., 2004). Both sanguinarine and chelerythrine induced apoptotic and necrotic cell death in uveal melanoma cells (Kemény-Beke et al., 2006), and acted as DNA intercalating agents when tested against B16 melanoma cells (De Stefano et al., 2009). Sanguinarine also showed antiproliferative and antiangiogenic effects in immunodeficient mice with induced human melanomas (De Stefano et al., 2009). Other investigators have uncovered a novel antiproliferative mechanism, whereby low concentrations of sanguinarine induced tubulin binding and depolymerized cellular microtubules in HeLa cells, thereby blocking the cell cycle at different stages (Lopus & Panda, 2006). Significantly it was also effective against multidrug resistant HeLa cells.

While sanguinarine has been touted as a potential drug for various forms of cancer (Adhami et al., 2004; Kemény-Beke et al., 2006) and for hyperproliferative skin disorders (Adhami, Aziz, Mukhtar, & Ahmad, 2003) there are few such studies based on *S. canadensis* itself. In one investigation *S. canadensis* extracts diminished proliferation of human leukemia cells as well as peripheral blood mononuclear cells (Senchina, Flinn, McCann, Kohut, & Shearn, 2009). In an anti-cancer screening program using malignant neuroblastoma cells, *S. canadensis* extracts were found to have strong tumoricidal effects (Mazzio & Soliman, 2009).

Immune modulating effects

The pro-inflammatory protein nuclear factor NF-κB is a key target for anti-inflammatory drug development, and sanguinarine is a known inhibitor. Using a variety of cell lines Chaturvedi et al. (1997) showed that sanguinarine blocked the phosphorylation and degradation of an inhibitory subunit of NF-κB, and the inhibition was selective for the inducible rather than the constitutive form of the protein (Chaturvedi et al., 1997).

The effects of *S. canadensis* extracts on immune cells were tested in a recent Iowa-based study (Senchina et al., 2009). The strongest effects were seen with the pro-inflammatory cytokines TNF and IL-1β, and they were mostly stimulatory, although the authors could not rule out the possible influence of endotoxin in these results. The alcohol rhizome extract significantly decreased the production of IL-8 from macrophages while other extracts had no effect, and flower and root extracts augmented IFN-γ production. Interestingly the isolated alkaloids sanguinarine and chelerythrine failed to showed significant immunomodulatory effects in these experiments, and the water extracts tested were generally superior to those containing ethanol (Senchina et al., 2009). These findings seem to indicate that a group of non-alkaloidal constituents are mainly responsible for the immunomodulatory effects of *S. canadensis.*

Cardiovascular effects

The alklaloid sanguinarine has long been known to produce positive inotropic (digitalis-like) effects on heart muscle, and investigations conducted in the 1970s confirmed these effects in frogs and guinea pigs (Moore & Rabovsky, 1979; Seifen, Adams, & Riemer, 1979). Sanguinarine inhibits Na^+, K^+ - ATPase activity in a similar way to cardiac glycosides, and may interact with the same cardiac receptors (Seifen et al., 1979). The main site of action appears to be the sodium pump, where sanguinarine produces a K^+ - like effect (Moore & Rabovsky, 1979).

Clinical studies

Human research on *S. canadensis* and sanguinarine is centered on their use in dentistry. Long known for its antibacterial and anti-inflammatory properties, extracts of the herb and the alkaloid itself have been used in various proprietary dentifrices and mouthwashes, the most notable being Viadent® toothpaste and oral rinse products distributed by Colgate-Palmolive. Numerous studies have confirmed beneficial short- and long-term effects on plaque formation and gingivitis in periodontal patients taking sanguinarine based dentifrices (Wennström & Lindhe, 1985; Hannah, Johnson, & Kuftinec, 1989; Tenenbaum, Dahan, & Soell, 1999), although some studies found no benefit at all (Cullinan, Powell, Faddy, & Seymour, 1997).

Despite the mostly positive clinical findings, the use of sanguinarine based dentifrices has declined over the last decade due to a possible association with leukoplakia (see below), and it has been removed from the Viadent® product (see Predny and Chamberlain, 2005 and Natural

Standard, 2011 for reviews). Notwithstanding these findings, a Brazilian group investigated the benefits of a chewing gum containing a tincture of *S. canadensis* on 48 young adult subjects, and found significant reduction in dental plaque scores and bacteria bioform that contained *Streptococcus* colony forming units (CFUs) at very low doses, equivalent to 4.2 mg dried herb equivalent per day (Moretti et al., 2009). This is of a similar to the human exposure to sanguinarine following use of Viadent® products

Toxicology

A safety review based on the numerous toxicological studies conducted in the 1980s and 1990s – including studies on humans by the Essex Testing Clinic Inc. - concluded that *S. canadensis* is a relatively non-toxic herb, safe for use in oral rinse and toothpaste products (Frankos et al., 1990). Acute oral LD_{50} values in rats for sanguinarine and *S. canadensis* extracts are well over 1000 mg/kg (Keller & Meyer, 1989; Frankos et al., 1990) which is higher than aspirin. Studies in rats and rabbits demonstrated no selective effects (defined as an adverse effect below the dose that would produce general toxicological effects) on fertility, reproduction or fetal and neonatal development (Keller & Meyer, 1989). Cytotoxic studies on human cells derived from oral tissues showed sanguinarine cytotoxicity increased with increasing pH, presumably as the alkaloid converts from the iminium form to the more lipid soluble alkanolamine form (Babich, Zukerbraun, Barber, Babich, & Borenfreund, 1996).

In 1999 a retrospective review of 88 patients with leukoplakia of the maxillary vestibule (white or red patches that may be precancerous – especially in smokers) revealed that 81% had used Viadent® products, while in a randomly selected group of adults only 3% reported using the product (Damm, Curran, White, & Drummond, 1999). However the methodology of this investigation was highly questionable, leading to a highly spirited defense of the use of *S. canadensis* in oral health products along with a comprehensive review of all the toxicological data available at that time (Munro, Delzell, Nestmann, & Lynch, 1999). Using computerized image analysis and biomarker immunohistochemical assays to compare the pathology changes in groups of *S. canadensis* based dentifrice users and a control group, Eversole, Eversole, and Kopcik, (2000) confirmed the existence of "Sanguinaria-associated oral leukoplakia" exhibiting characteristics of mild dysplasia, but with no reported cases of progression to carcinoma. In light of the authors' recommendation that *Sanguinaria*-based products be avoided until the risk of 'malignant transformation' was determined (Eversole, Eversole, and Kopcik, 2000), there has been a dramatic decline in the use of *S. canadensis* in dentifrice products. In a 2003 report the FDA proposed a safe level of *Sanguinaria* extract in oral rinse and dentifrice products at 0.03-0.075%, however this was opposed by many specialists in the oral pathology field (Gallagher, 2003).

The epidemic dropsy syndrome in farm animals has been linked to ingestion of plant-based oils contaminated with *Argemone mexicana* L. seeds. *A. mexicana* is in the same family as *S. canadensis* and it too contains benzophenanthridine alkaloids. Given the use of *S. canadensis* in veterinary proprietary weight gain formulas, concerns have been raised about its' safety (Kosina et al., 2004). In experiments with pigs in which they were fed doses up to 5mg/kg body weight of the alkaloids sanguinarine and chelerythrine, no toxicological signs were observed (Kosina et al., 2004).

The use of *S. canadensis* in escharioticsalves for treatment of skin cancers is widely disseminated across the Internet, often accompanied by personal testimonials (eg. http://www.blacksalveinfo.com/). There is little toxicological data available to support or refute such applications, however dermatologists generally oppose the use of these salves, and in one report four cases were described where a salve was used in lieu of surgery for treatment of basal cell carcinoma, three of which led to severe adverse reactions (scarring, residual tumor formation, metastatized lesion) (McDaniel & Goldman, 2002). In 2005 an MD in Georgia had her medical license revoked for providing pain management to clients of an unlicensed practitioner being treated for breast cancer with a bloodroot paste (Composite State Board of Medical Examiners {Georgia}, 2005). Bloodroot extracts and various black salves are also included an FDA list of fake cancer cures (FDA, 2009).

5. Modern Phytotherapy

The 1983 edition of the British Herbal Pharmacopoeia (BHP) lists *S. canadensis* as being useful for treating asthma and bronchitis, "deficient capillary circulation" and as a snuff for nasal polyps (BHMA, 1983). There is, however, no entry in the 1996 edition of the BHP suggesting a decreasing use in modern European herbal practice. Naturopathic use in North America indicates similar patterns of application. *Naturae medicina and Naturopathic Dispensatory* (Kuts-Cheraux 1953) lists *S. canadensis* as being used "as a frequent remedy in respiratory diseases" as well as for stimulating the circulation and digestion. In recent decades it has been rarely used in naturopathy for such indications, most likely due to concerns about toxicity. Modern use is generally relegated to oral hygiene products and incorporation into escharotic salves. Along with zinc chloride and galangal it is a key ingredient in the 'black salve' used by some lay people and promoted by a few physicians for treating internal and external tumors (Naiman, 1997), however the use of escharioticsalves remains controversial and is not widely accepted within the herbal community (see above).

Table 2: Modern phytotherapeutic uses of *S. canadensis*

ACTIONS	
Expectorant	Cathartic
Antibacterial	Anti-inflammatory
Local anaesthetic	Topical irritant, escharioticsalves
Spasmolytic	cardioactive
THERAPEUTIC INDICATIONS	
Bronchitis, asthma, croup, laryngitis, nasal polyps	
Skin infections, epithelial tumors, warts, chillblains, corns, ringworm	
Prevention of dental caries, peridontal disease, gingivitis	

Deficient capillary circulation

(BHMA, 1983; Wren, 1988; Skenderi, 2003).

Specific indication
Asthma and bronchitis with peripheral feeble circulation (BHMA, 1983).

Combinations
With *Lobelia inflata* L. in bronchial asthma. With *Salvia officinalis* L. and *Capsicum* spp as a gargle in pharngytis (BHMA, 1983).

Preparations and dosage
Dried rhizome. 0.06-0.5g, three times daily
Tincture 1:5. 0.3-2ml, three times daily (BHMA, 1983)
Extract for use in dentifrices 0.03-0.75% according to the U.S. Food and Drug Administration (FDA).

Toxicity and contraindications
The *Botanical Safety Handbook* classifies *S. canadensis* in Class 2(b): "Not to be used during pregnancy" and Class 2(d) "may cause nausea and vomiting" (McGuffin, Hobbs, Upton, & Goldberg, 1997). *S. canadensis* should not be consumed in the raw state. Signs of acute oral toxicity include severe mucus membrane irritation, intense thirst, diarrhea, abdominal cramping, vertigo and collapse (Natural Standard, 2011). Chronic use as a dentifrice may cause oral leukoplakia (see above). Topical application may result in staining, irritation, ulceration, and formation of an esdchar (Natural Standard, 2011).

Regulation
S. canadensis is regulated by FDA as a 'New Drug' under section 201(p) of the Act [21 U.S.C. § 321(p)].

6. Sustainability considerations
The USDA plant database lists New York and Rhode Island as the only states listing *S. canadensis* as a plant of concern or RTE (rare, threatened or extirpated) status (see Table 3). In 2002, the national status was N5, indicating that it is considered secure in its natural range (Predny & Chamberlain, 2005). According to Predny & Chamberlain (2005) the U.S. Yellow Creek Botanical Institute and Tuckasegee Valley Ginseng were attempting to grow *S. canadensis* commercially (70 acres) but this was not a large enough effort to offset over-harvesting of wild populations. Wild harvesters are encouraged to replant a budded portion of the rhizome, but Braly (2007) noted areas where entire patches of *S. canadensis* were removed completely by those gathering the rhizomes to sell.

Another concern for the sustainability of *S. canadensis* in Southern states is the loss of as much as 70% of native ant populations as a result of the spread of fire ants (Predny & Chamberlain, 2005). As mentioned in Section 2 above, ants play an important role in the seed dispersal for this species (Hendershott 2002).

Table 3. Ecological status-RTE status

Region	status	Url reference
Global	G4 G5 (RI-2007)	MD RTE 2010 http://www.dnr.state.md.us/wildlife/Plants_Wildlife/rte/pdfs/rte_Plant_List.pdf
MD	S2 threatened	MD Rare, threatened & Endangered 2010 http://www.dnr.state.md.us/wildlife/Plants_Wildlife/rte/pdfs/rte_Plant_List.pdf
RI	special concern	RI - 6 known populations, c - critical Rhode Island Rare Plants, 2007 Accessed http://www.rinhs.org/wp-content/uploads/ri_rare_plants_2007.pdf
NY	exploitably vulnerable	2011 http://www.dec.ny.gov/regs/15522.html Regulations, Chapter II-Lands and Forests, Part 193.3: Protected Native Plants, Section e: exploitably vulnerable. Department of Environmental Conservation.

Harvesting & Collection regulations

Where harvesting is allowed in national forests, permits are required to collect *S. canadensis* (Braly, 2007).

New York State: It is a violation for any person, anywhere in the State, to pick, pluck, sever, remove, damage by the application of herbicides or defoliants, 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 (NYSDEC, 2011).

Canada: No person shall damage or destroy the residence of one or more individuals of a wildlife species that is listed as an endangered species or a threatened species, or that is listed as an extirpated species if a recovery strategy has recommended the reintroduction of the species into the wild in Canada (CDOJ, 2011).

Market data - Harvesting impact, tonnage surveys

According to Strategic reports (2003), in 2001 sales of *S. canadensis* were handled by a very small group of brokers who represented many small suppliers, primarily in Appalachia.

Table 4. Aggregate harvest of fresh and dried plants for 1997–2005 (in pounds)

		1998	1999	2000	2001	2002	2003	2004	2005
Dried	wild	N/S	N/S	48,674	41,236	26,473	39,590	11,487	5,328
	cultiv	N/S	N/S	0	19	26	20	0	0
Fresh root	wild	N/S	N/S	458	150	52	38	41	23
	cultiv.	N/S	N/S	0	0	0	0	0	0

http://www.ahpa.org/Portals/0/members/04-05_AHPATonnageReport.pdf

The Strategic Reports data indicates an increase in consumption between 2000 and 2001, where the US aggregate reported harvest shows the beginning of a downturn in harvested amounts. Overall the reported consumption of *S. candensis* (Strategic Reports, 2003) appears to be more than double the aggregate harvest according to AHPA (2007). This discrepancy may indicate the use of plant materials obtained from sources that did not report their harvests to AHPA. In 2001 *S. canadensis* supply exceeded demand with a resultant increase in value such that sales doubled from one million dollars in 2000 to two million dollars in 2001 (Strategic Reports, 2003)

Dried root sold for $5-$9/pound in 1995-2000 increasing to $12-$16/pound by 2002-2004 with the primary consumers coming from Europe and China (Strategic Reports, 2003). Nursery prices for live plants were $1.00-$1.50 per plant for volume purchases with individual plants available for $4 (Greenfield & Davis, 2004; Predney & Chamberlain, 2005). In general, prices of *S. canadensis* in 2011 have doubled for all forms when compared to 2000 (See Table 4 for current prices).

Table 4. Selection of prices for various forms of *S. Canadensis,* August, 2011.

Source	Dried root	Live Plant	Powder	Seeds
EBAY - Desert Botanicals	$48.17/pound			
Pacific Botanicals www.pacificbotanicals.com	1-4 lbs $29.00 5-24 lbs $27.00 25-99 lbs $23.00 100+ lbs $20.00			
Mountain Rose www.mountainroseherbs.com	$29.00/pound		$29.00/pound	
Prairie Moon Nursery www.prairiemoon.com				$2.00/20 seeds
Horizon Herbs www.horizonherbs.com				$9.95/packet fresh
Easy wildflowers http://www.easywildflowers.com/quality/san.can.htm		$8.00/plant		
Horizon herbs http://www.horizonherbs.com/group.asp?grp=51&pgNUM=2		$5.00/plant		

S. canadensis was the primary ingredient in Viadent toothpaste until 2001 when it was removed from the formula (Strategic Reports, 2003). In 2001, however, marketing interest remained high since it was beginning to be used as an additive for European livestock feed to replace banned synthetic antibiotics (Strategic Reports, 2003). It is currently included in Sangrovitm, a product

marketed in seventy countries by Phytobiotics, GMBH (2011). Initially Phytobiotics, GMBH (2011) utilized wild harvests from the United States buying over 40 metric tons in 2000 (Strategic Reports, 2003), but in 2004 they established their own production in Germany and currently produce all of their own *S. canadensis* commercially.

The European Food Safety Authority (EFSA, 2011) lists *Potentilla erecta* as the bloodroot approved for use in feed while the European Union Register of Feed Additives pursuant to regulation (EC) no. 1831/2003 (2011) lists *S. canadensis* as bloodroot and regulates *Potentilla erecta* as Tormentil tincture, so caution in identification of the species may be essential.

Live plants were sold for gardening and ornamental purposes (Strategic Reports, 2003). Easy Wildflowers Native Plant Nursery (http://www.easywildflowers.com/quality/san.can.htm) listed potted specimens for $8.00/plant. There is interest in a beautiful cultivar, *S. canadensis multiplex* with doubled flowers, however since the reproductive parts are no longer present, this plant can only be reproduced vegetatively (see: http://www.sanguinaria.nl/indexEN.html).

Cultivation

Habitat:

Hardy to Zone 3, *S. canadensis* can grow in a variety of light conditions, from full sun to deep shade depending on light and moisture, but appears to prefer semi-shaded well-drained northern slopes in hardwood forests (Braly, 2007; Albrecht, 2006; Predny & Chamberlain, 2005). This species favors soil that is rich in humus and organic material, primarily a heavy layer of leaf matter (Gladstar & Hirsch, 2000; Predny & Chamberlain, 2005). Braly (2007) found that plants growing in disturbed areas were smaller both in plant stature and in rhizome size.

Propagation

S. canadensis can be propagated from seeds or by division of rhizomes (Davis, 2011).

Seed Propagation

About 4-5 weeks after the flowers have died back, seeds form in a small two-chambered pod (from 3-51 seeds/pod) which explodes when ripe ejecting the seeds as far as ten feet (Braly, 2007). Glick (2004) and Greenfield & Davis (2004) advise using small cotton or cheesecloth bags to allow the seeds to ripen until the seed capsules explode naturally.

The seeds are collected by ants which feed on the oil-rich elaiosome (Albrecht, 2006; Braly, 2007). It is thought that by removing this elaiosome, which inhibits germination, the ants enhance the propagation throughout its natural habitat (Greenfield & Davis, 2004; Predney & Chamberlain, 2005), however Albrecht (2006) found that in laboratory trials, seeds with eliasomes had an increased germination rate over those where the eliasomes were removed.

Fresh seeds should be planted (Montgomery, 2000) in the fall and can be expected to germinate after 1-2 seasons. Albrecht (2006) found that seeds on semi-shady northern slopes had higher rates of germination. The seed coat swells before splitting (Cech, 2002) and the radicle (root) emerges in 10-30 weeks followed by the cotyledon (seed leaves) at 38-42 weeks (Albrecht,

2006). Leaf litter has been noted to improve germination (Predny & Chamberlain, 2005) and Greenfield and Davis (2004) caution that the seed should never dry out.

Seed emergence can be stimulated through a phased chilling cycle such that seeds are held at 0/15 ºC for twelve weeks, followed by four weeks at 20/10 ºC the temperature is lowered to 15/6 ºC for four weeks, lowered again to 5 ºC and held for twelve weeks and then brought up to 15/6 ºC with germination then occurring during a final six weeks (Albrecht, 2005).

A grower may expect to harvest *S. canadensis* grown from seed 6-8 years after planting seeds (Greenfield & Davis, 2004; Predny & Chamberlain, 2005).

Rhizome propagation

Rhizomes should be planted about six inches apart with the bud facing up, about four inches below the soil surface and covered with 1-3 inches of hardwood mulch (Greenfield & Davis, 2004). The branching rhizome forms horizontally with a single bud for each branch, some rhizomes may branch up to twelve times with one flower for each branch (Greenfield & Davis, 2004; Cech, 2002). Plants propagated via rhizomes will be harvestable in 3-6 years (Greenfield & Davis, 2004).

Plant growth

Both field (Albrecht, 2006) and woods (Braly, 2007) cultivation may be possible for those wishing to propagate *S. canadensis.* Field plants should be shaded and well mulched and watered during dry periods (Greenfield & Davis, 2004). If a three-sided shade is used have the opening facing north, as Braly (2007) found that plants grew best facing north. Plants have been known to go into dormancy during droughts and can survive winter temperatures as low as minus forty degress Fahrenheit (Greenfield & Davis, 2004).

Fertilizers should not be used in plants to be sold for medicinal purposes. Braly (2007) cited a study that found that rhizome size diminished with increased fertilizer use and increased light exposure (Marino, Eisenberg, & Cornell, 1997). Sanguarine content for plants with good drainage increased with availability of water (Braly, 2007; Salmore, 2001).

Seed fertilization occurs through pollination by honeybees and syphid flies (Braly, 2007) however if insect pollination does not occur it will self-pollinate (Braly, 2007; Albrecht, 2006).

Pests/Diseases

Deer, groundhogs, and turkey are threats to the above ground portions of *S. canadensis* plants. *Cercospora sanguinariae,* Cylindrosporium *circinans, Gloeosporium sanguinariae*, and *Phyllosticta sanguinariae* are leaf spot diseases affecting bloodroot. Alternaria leaf blight and Botrytis are also common threats to bloodroot patches (Davis, 2011; Greenfield & Davis, 2004).

When the ground is moist, slugs can be a problem. Overly saturated soil can increase the incidence of fungal diseases such as *Pythium parecandrum* which attacks the roots (Greenfield & Davis, 2004; Persons, 2005).

Harvesting

Gladstar & Hirsch (2000) advise harvesting in the fall, but other authors note that sanguinarine content is highest in the spring and suggest harvesting at that time (Greenfield & Davis, 2004; Braly, 2007). However harvesting in the spring could have a negative impact on population sustainability, as the plants would not mature and set seed at that time of year (Graf et al., 2007).

Rhizomes are dug using a fork or spade (Greenfield & Davis, 2004). They should be dried whole on screens with good ventilation, and care must be taken that the rhizomes do not re-absorb water or they will tend to rot during storage (Montgomery, 2000). The roots are easily chopped or powdered after drying, but caution should be taken as the powder has been known to cause irritation of the nasal passages (Montgomery, 2000).

7. Summary – some possibilities moving forward

More than just about any other comparable species, demand for *S. canadensis* has fluctuated dramatically – most notably a decade ago following its removal from Viadent® products. Given the multiple potential applications for this herb, is would be safe to assume it is only a matter of time until demand peaks again. Conservation measures and cultivation projects should therefore be encouraged.

Unfortunately analytical and experimental research has focused largely on sanguinarine and alkaloids in general, despite evidence that other active principles are present. Immunoassay-linked chromatography (LCMS) techniques could help isolate and identify water soluble active principles. Increasing the aqueous content of menstruum used in commercial extracts could also alleviate potential toxicity by reducing alkaloid content. Clearly there is an ongoing need for further acute and chronic toxicity studies for *Sanguinaria* extracts, be they designed for topical applications or to be taken orally.

8. References

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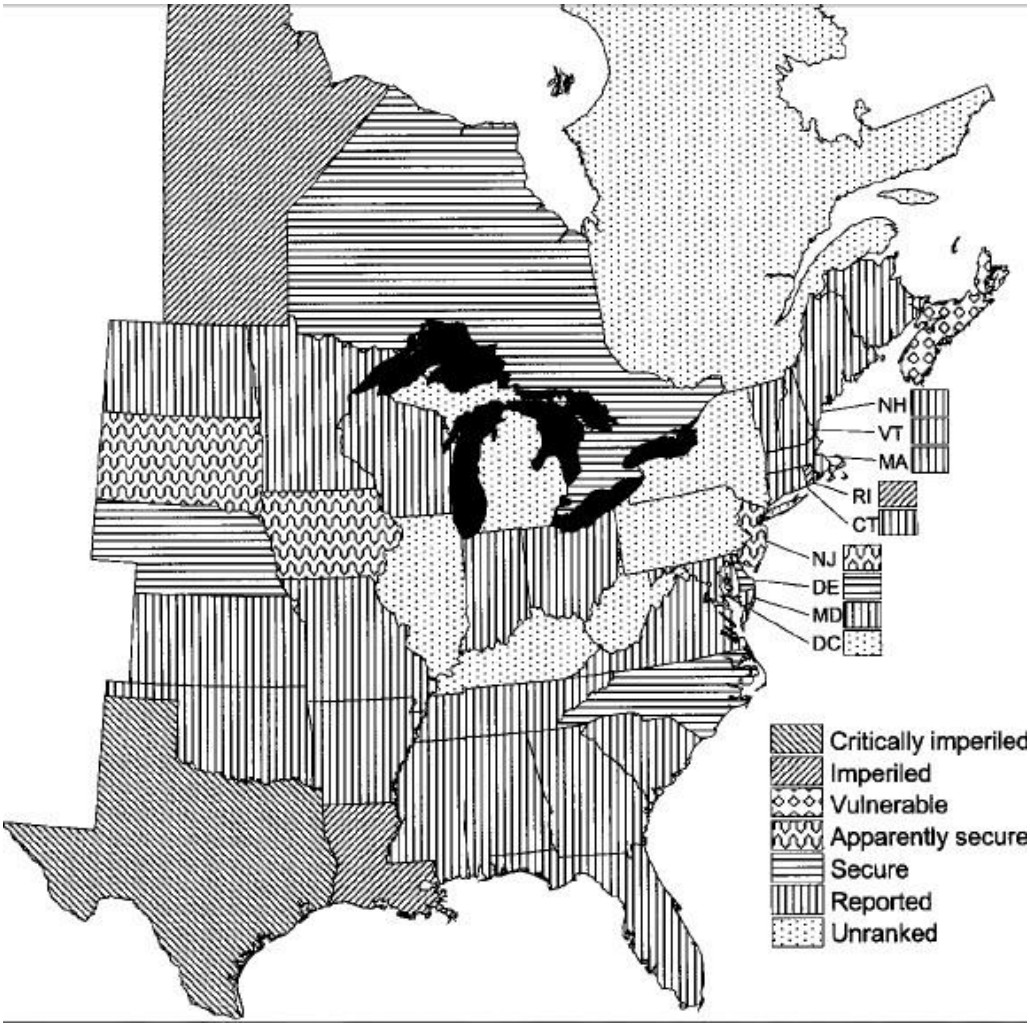
Appendix I - Bloodroot range and distribution (2001-2002). Adapted from Predny & Chamberlain (2005)



Appendix II. 2011 update of companies listed in 2003 (Strategic Reports, 2003) as providing or using *S. canadensis*

Company	Comments	Website url
Advanced Labs	Exporters - Powder & Extract	http://www.advancedlabs.com/biotanicals.php
Alfa Chem, New York	no longer lists *Sanguinaria*	http://www.alfachem1.com/
Alpha Omega Labs, Ecuador	Bloodroot paste, toothpaste, Black salve	http://www.altcancer.com/
Amitco International, NJ	Bulk supplier - no *Sanguinaria* listed - supplier pf botanicals and animal feed	http://www.amitco.com/en
Blue California, CA	Could not find listing for *Sanguinaria*	http://www.bluecal-ingredients.com/index.php
Botanicals International, CA	teas, extracts& powders- no *Sanguinaria*	http://www.botanicals.com/
California Energy Nutraceuticals	no longer available	"www.ridopain.com
Chart Corp., Inc., NJ	could not find website - extracts	No website
Ecuadorian Rainforest LLC, NJ	powdered *Sanguinaria*	http://www.intotherainforest.com/
Energique Inc.	extract of *Sanguinaria*	http://www.energiqueherbal.com/
Falcon Trading International	*Sanguinaria* is not listed	http://www.falconti.com/
FCC Products Inc	*Sanguinaria* is not listed	http://www.fccproducts.com/
Frontier Natural Products	wild-crafted - capsules & Cut and Sift	http://www.frontiercoop.com/
Gaia Herbs	*Sanguinaria* is not listed	http://shop.gaiaherbs.com/
GCI Nutrients Italy	*Sanguinaria* is not listed	http://www.gcinutrients.com/#
Gourmet Nutrition FDB Inc.	Bulk powder	http://www.gourmetfb.com/default.aspx
Kingchem Inc.	*Sanguinaria* is not listed	http://www.kingchem.com/
Klickitat Organics	*Sanguinaria* is not listed (good desriptions)	http://herbs.interposy.com/
Ministar International Inc	*Sanguinaria* is not listed	http://www.ministar.com/
Natural Herbs	Ayurvedic feeds - herbs not listed sep.	http://www.naturalherbs.co.in/Default.aspx
NHK Laboratories, Inc.	Testing & packaging	http://www.nhklabs.com/
Northwest Botanicals Inc.	now specializing in Mushrooms	http://www.nwbotanicals.org/nwb/nwbsales.htm
Phytobiotics GmBH Germany	Produces its own Sanguinaria	http://www.phytobiotics.com/en/phytobiotics-home.html
Productos de Origen Natural SL	trading company- mostly rosemary	no website
RIA International LLC	offers *Sanguinaria canadensis*	http://www.riausa.net/
Ridge Runner Trading	ginseng dealer	no website - Anthony J. Hayes PO Box 391, Boone, NC 28607 (828) 264-3615
Ruger Chemical Co., NJ	*Sanguinaria* is not listed	http://www.rugerchemical.com/
Scandinavian Formulas Inc	individual herbs not listed-proprietary	http://www.scandinavianformulas.com/
Starwest Botanicals Inc.	whole dried root $48.17/lb	http://www.starwest-botanicals.com
To Your Health	liquid formulas & extracts -no ingredients	http://www.toyourhealthcomplete.com/#
US Nutraceuticals LLC/Valensa	formulas - no ingredient listing	http://www.valensa.com/
Vitality Works Inc. , NM	no product listing - extracts	http://www.vitalityworks.com/
Zhejiang Medicines & Health Products	*Sanguinaria* is not listed	http://www.zhejiang-pharma.com/

Appendix III. Sample list of suppliers currently offering bulk quantities of *S. canadensis* that were not listed by Strategic Reports in 2003.

Company	Product availability in 2011	Website url
Vege Tech, CA & China	Sanguinaria extract	http://www.vegetech.com/products.htm
Carrubba Inc., CT	Bloodroot extract - CAS 84929-48-6	http://www.carrubba.com/index.html
Grau Aromatics	Sanguinaria extract HS 2778 G	http://www.grau-aromatics.de/en/home/
Pacific Botanicals	Bloodroot available as wildcrafted roots in dried or powdered forms	http://www.pacificbotanicals.com/
Mountain Rose Herbs	Wild harvested bloodroot, root and powder	http://www.mountainroseherbs.com/bulkherb/b.html
Herbal Remedies.com	Bloodroot tincture. (no source of origin listed) The powder has been discontinued	http://www.herbalremedies.com
Texas Naturals Supply	Bloodroot as cut & sift and powder Tincture offered is Herb Pharm	http://www.texasnaturalsupply.com
Herb Pharm	Bloodroot extract - prepared from shade-dried rhizomes from certified organic, forest-grown plants in eastern Kentucky.	http://www.herb-pharm.com/store/product_info.php?products_id=45
Sunrise Botanicals: Austral Suppliers	Wildcrafted bloodroot powder Place of origin: America	http://australherbs.com.au

Appendix IV. Voucher specimen lodged at the Claude E. Phillips Herbarium, Delaware State University. Specimen collected from Ohio Botanical Sanctuary, via Rutland Ohio, May 2011.