

Prickly Ash, Northern

Species (Family)

Zanthoxylum americanum Miller (Rutaceae)

Synonym(s)

Toothache Bark, Xanthoxylum, Zanthoxylum

Part(s) Used

Bark, berry

Pharmacopoeial and Other Monographs

BHP 1983^(G7)

Martindale 32nd edition^(G43)

PDR for Herbal Medicines 2nd edition^(G36)

Legal Category (Licensed Products)

Northern prickly ash is not included in the GSL.^(G37)

Constituents^(G6,G41,G64)

Alkaloids Isoquinoline-type. Lauriflorine and nitidine (major constituents), candicine, chelerythrine, magnoflorine and tembetarine.

Coumarins Xanthyletin, xanthoxyletin, alloxanthoxyletin and 8-(3,3-dimethylallyl)alloxanthoxyletin.

Other constituents Resins, tannins and acrid volatile oil.

Other plant parts Two furoquinoline alkaloids (γ -fagarine and skimmianine) have been isolated from the leaves.

Food Use

Prickly ash is listed by the Council of Europe as a natural source of food flavouring (category N3). This category indicates that prickly ash can be added to foodstuffs in the traditionally accepted manner, but that there is insufficient information available for an adequate assessment of potential toxicity.^(G16) In the USA, prickly ash is listed as GRAS (Generally Recognised As Safe).^(G65)

Herbal Use

Prickly ash is stated to possess circulatory stimulant, diaphoretic, antirheumatic, carminative and sialagogue properties. Traditionally, it has been used for cramps, intermittent claudication, Raynaud's syndrome, chronic rheumatic conditions, and specifically for peripheral circulatory insufficiency associated with rheumatic symptoms. The berries are stated to be therapeutically more active in circulatory disorders.^(G6,G7,G64)

Dosage

Dried bark 1–3 g or by decoction three times daily.^(G6,G7)

Bark, liquid extract 1–3 mL (1:1 in 45% alcohol) three times daily.^(G6,G7)

Bark, tincture 2–5 mL (1:5 in 45% alcohol) three times daily.^(G6,G7)

Dried berry 0.5–1.5 g.^(G6,G7)

Berry, liquid extract 0.5–1.5 mL (1:1 in 45% alcohol).^(G6,G7)

Pharmacological Actions

In vitro and animal studies

None documented for northern prickly ash. See Southern Prickly Ash for activities of alkaloid constituents (e.g. chelerythrine and nitidine).

Side-effects, Toxicity

The alkaloid constituents are potentially toxic (see Southern Prickly Ash).

Contra-indications, Warnings

Excessive ingestion may interfere with anticoagulant therapy in view of the coumarin constituents (see Southern Prickly Ash).

Pregnancy and lactation The safety of northern prickly ash has not been established. In view of the

pharmacologically active constituents the use of northern prickly ash during pregnancy and lactation should be avoided.

Pharmaceutical Comment

Northern prickly ash contains similar alkaloid constituents to the southern species but varies with respect to other documented components. No pharmacological studies documented specifically for northern prickly ash were located. However, activities have been reported for individual alkaloid con-

stituents and the monograph for southern prickly ash should be consulted. There is limited scientific evidence to support the traditional herbal uses. In view of the pharmacologically active constituents and potential toxicity associated with the alkaloids, excessive use of northern prickly ash should be avoided.

References

See General References G6, G7, G10, G16, G31, G36, G37, G41, G43 and G64.

Prickly Ash, Southern

Species (Family)

Zanthoxylum clava-herculis L. (Rutaceae)

Synonym(s)

Toothache Bark, Xanthoxylum, Zanthoxylum

Part(s) Used

Bark, berry

Pharmacopoeial and Other Monographs

BHC 1992^(G6)

BHP 1996^(G9)

Martindale 32nd edition^(G43)

Legal Category (Licensed Products)

GSL^(G37)

Constituents^(G6,G41,G45,G64)

Alkaloids Isoquinoline-type. Chelerythrine and magnoflorine (major constituents), candicine, lauriflorine, nitidine, *N*-acetylanonaine⁽¹⁾ and tembetarine.

Amides Cinnamamide, herculin and neoherculin.

Lignans (–)-Asarinin, (–)-sesamin, γ,γ -dimethylallyl ether of (–)-pluviatilol.⁽¹⁾

Other constituents Resins, tannins and an acrid volatile oil (about 3.3%).

Food Use

Southern prickly ash is listed by the Council of Europe as a natural source of food flavouring (category N3). This category indicates that prickly ash can be added to foodstuffs in the traditionally accepted manner, but that there is insufficient information available for an adequate assessment of potential toxicity.^(G16)

Herbal Use

Southern prickly ash is stated to possess circulatory stimulant, diaphoretic, antirheumatic, carminative and sialogogue properties. Traditionally, it has been

used for cramps, intermittent claudication, Raynaud's syndrome, chronic rheumatic conditions, and specifically for peripheral circulatory insufficiency associated with rheumatic symptoms. The berries are stated to be therapeutically more active in circulatory disorders.^(G6,G7,G8,G64)

Dosage

Dried bark 1–3 g or by decoction three times daily.^(G6,G7)

Bark, liquid extract 1–3 mL (1:1 in 45% alcohol) three times daily.^(G6,G7)

Bark, tincture 2–5 mL (1:5 in 45% alcohol) three times daily.^(G6,G7)

Dried berry 0.5–1.5 g.^(G6,G7)

Berry, liquid extract 0.5–1.5 mL (1:1 in 45% alcohol).^(G6,G7)

Pharmacological Actions

In vitro and animal studies

Southern prickly ash has been reported to act as a reversible neuromuscular blocking agent. Activity was associated with a neutral fraction of the bark that was thought to act primarily by blockade of endplate receptors.⁽²⁾

Various activities have been documented for the benzophenanthridine alkaloids (e.g. chelerythrine, nitidine) present in southern prickly ash. Hypotensive properties in mice have been documented for nitidine chloride, a single dose of 2 mg/kg body weight lowered the blood pressure by 20% within 90 minutes and persisted for 6 hours.⁽³⁾ Nitidine was also found to antagonise the effects of angiotensin-induced hypertension.⁽³⁾ Antileukaemic activity has been documented for nitidine, although preclinical toxicity prevented further investigations.^(4,5)

Anti-inflammatory activity in rats has been documented for chelerythrine (10 mg/kg by mouth) comparable to that achieved with indomethacin (5 mg/kg by mouth).⁽⁶⁾ Chelerythrine has also been reported to potentiate the analgesic effect of morphine, prolong

barbiturate-induced sleep, and cause temporary hypertension followed by hypotension in cats, mice and rabbits.⁽⁷⁾

Significant antimicrobial activity towards Gram-positive bacteria and *Candida albicans* has been documented for chelerythrine, although conflicting activities have been reported regarding Gram-negative bacteria.⁽⁶⁾ Chelerythrine has been shown to interact with Na⁺K⁺ ATPase and to inhibit hepatic L-alanine and L-aspartate aminotransferases in the rat, while nitidine has been reported to inhibit tRNA methyltransferase and catechol-O-methyltransferase.⁽⁵⁾

The lignan component, asarinin, has been reported to possess antitubercular activity.^(G41) Neoherculin is reported to possess insecticidal and sialogic properties.⁽¹⁾

Pharmacological activities, including anti-inflammatory, cardiovascular and antibacterial properties have been documented for various other *Zanthoxylum* species (or *Fagara/Xanthoxylum* species).⁽⁵⁾ For example, the root of *Zanthoxylum zanthoxyloides*, a Nigerian species, is commonly used as a chewing stick. These sticks are believed to possess antimicrobial properties and extracts were found to exhibit antimicrobial activity towards more than 20 organisms, including Gram-positive and Gram-negative bacteria, and *Candida* species.⁽⁵⁾ Anti-inflammatory activity (carrageenan rat paw oedema test) has been described for fagaramide (piperonyl-4-acrylic isobutylamide), isolated from *Z. zanthoxyloides*.⁽⁸⁾ The activity, approximately 20 times less potent than indomethacin, was thought to be partially mediated by inhibition of prostaglandin synthesis.⁽⁸⁾

The essential oil obtained from the Indian species *Zanthoxylum limonella* has been reported to exhibit *in vitro* anthelmintic activity against earthworms, tapeworms and hookworms that was stated to be superior to that of piperazine phosphate.⁽⁹⁾

Side-effects, Toxicity

None documented in humans. Ingestion of southern prickly ash by cattle, chicken and fish has proved lethal. This was attributed to the neuromuscular blocking properties of the bark.⁽²⁾ Neoherculin is reported to be the major ichthyotoxic principle in an extract of southern prickly ash bark.

The acute and chronic toxicity of chelerythrine in mice is reported to be low.⁽⁴⁾ LD₅₀ values were stated as 18.5 mg/kg body weight (intravenous injection) and 95 mg/kg (subcutaneous injection). Oral administration of 10 mg/kg for three days followed by 5 mg/kg for seven days produced no adverse effects.

Contra-indications, Warnings

None documented for southern prickly ash. Chelerythrine has been reported to interact with Na⁺K⁺ ATPase which may interfere with cardiac glycoside therapy. However the clinical relevance of this with respect to prickly ash is unknown. Hypotensive and sedative activities have been documented in animals. Both chelerythrine and nitidine have been reported to inhibit various hepatic enzymes (*see In vitro* and animal studies). The alkaloid constituents in southern prickly ash are potentially toxic.

Pregnancy and lactation The safety of southern prickly ash has not been established. In view of this and the pharmacologically active compounds, the use of southern prickly ash during pregnancy and lactation is best avoided.

Pharmaceutical Comment

The chemistry of southern prickly ash is well documented and particularly characterised by the alkaloid constituents. Limited pharmacological information has been documented for southern prickly ash, although several properties have been described for individual constituents. With the exception of anti-inflammatory and analgesic properties few data have been documented that support the herbal uses. Limited toxicity data are available and some benzophenanthridine alkaloids are associated with cytotoxicity. In view of this, excessive use of prickly ash should be avoided. Northern prickly ash has been used for similar herbal uses but has a different chemical composition compared to the southern species (*see Northern Prickly Ash*).

References

See also General References G6, G9, G10, G16, G31, G37, G41, G43 and G64.

- 1 Rao KV, Davies R. The ichthyotoxic principles of *Zanthoxylum clava-herculis*. *J Nat Prod* 1986; 49: 340-342.
- 2 Bowen JM, Cole RJ. Neuromuscular blocking properties of southern prickly ash toxin. *Fedn Proc* 1981; 40: 696.
- 3 Addae-Mensah I *et al.* Structure and anti-hypertensive properties of nitidine chloride from *Fagara* species. *Planta Med* 1986; 52(Suppl.): 58.
- 4 Krane BD *et al.* The benzophenanthridine alkaloids. *J Nat Prod* 1984; 47: 1-43.
- 5 Simánek V. Benzophenanthridine alkaloids. In: Brossi A, ed. *The Alkaloids*, vol 26. New York: Academic Press, 1985: 185-240.
- 6 Lenfield J *et al.* Antiinflammatory activity of

- quaternary benzophenanthridine alkaloids from *Chelidonium majus*. *Planta Med* 1981; 43: 161–165.
- 7 Preininger V. In: Manske RHF, ed. *The Alkaloids*, vol 15. New York: Academic Press, 1975: 242.
- 8 Oriowo MA. Anti-inflammatory activity of piperonyl-4-acrylic isobutyl amide, an extractive from *Zanthoxylum zanthoxyloides*. *Planta Med* 1982; 44: 54–56.
- 9 Kalyani GA *et al*. *In vitro* anthelmintic acitivity of essential oil from the fruits of *Zanthoxylum limonella*. *Fitoterapia* 1989; 60: 160–162.