

# Angelica

## Species (Family)

*Angelica archangelica* L. (Apiaceae/Umbelliferae)

## Synonym(s)

*Archangelica officinalis* Moench and Hoffm.

## Part(s) Used

Fruit, leaf, rhizome, root

## Pharmacopoeial and Other Monographs

BHP 1996<sup>(G9)</sup>

Complete German Commission E<sup>(G3)</sup>

PDR for Herbal Medicines 2nd edition<sup>(G36)</sup>

## Legal Category (Licensed Products)

GSL<sup>(G37)</sup>

## Constituents<sup>(G2,G22,G32,G41,G48,G57,G58,G64)</sup>

The literature mainly refers to constituents of the root.

**Coumarins** Over 20 furanocoumarins, including angelicin, archangelicin, bergapten, isoimperatorin and xanthotoxin.<sup>(1,G2)</sup> Also the coumarins osthol (major constituent in rhizome/root, 0.2%) and umbelliferone.<sup>(G2)</sup> The root also contains the furanocoumarins 2'-angeloyl-3'-isovaleryl viginat, <sup>(2)</sup> heraclenol-2'-O-senecioate and heraclenol-2'-O-isovalerate.<sup>(3)</sup>

**Volatile oils** 0.35–1.3% in root and fruit. 80–90% monoterpenes, including  $\alpha$ - and  $\beta$ -phellandrene,  $\alpha$ - and  $\beta$ -pinene, sabinene,  $\alpha$ -thujene, limonene, linalool, borneol<sup>(1,4)</sup> and four macrocyclic lactones.

**Other constituents** Archangelenone (a flavonoid), palmitic acid, caffeic and chlorogenic acids, sugars (fructose, glucose, sucrose, umbelliferose).

## Food Use<sup>(1,G32)</sup>

Angelica is widely used in foods. Angelica is listed by the Council of Europe as a natural source of food flavouring (stem: category 1; other parts and pre-

parations: category 4, with limits on coumarin and furanocoumarin) (see Appendix 23).<sup>(G17)</sup> In the USA, angelica is listed as GRAS (Generally Recognised As Safe).<sup>(G41)</sup>

## Herbal Use<sup>(1,G32)</sup>

Angelica is stated to possess antispasmodic, diaphoretic, expectorant, bitter aromatic, carminative, diuretic and local anti-inflammatory properties. It has been used for respiratory catarrh, psychogenic asthma, flatulent dyspepsia, anorexia nervosa, rheumatic diseases, peripheral vascular disease, and specifically for pleurisy and bronchitis, applied as a compress, and for bronchitis associated with vascular deficiency.<sup>(G2,G7,G49,G64)</sup> The German Commission E monograph states that angelica can be used for lack of appetite and dyspeptic complaints such as mild stomach cramps and flatulence.<sup>(G4)</sup> Many related species, including *A. sinensis* (dong quai) are traditionally used in Chinese medicine.<sup>(G57)</sup>

## Dosage

**Dried leaf** 2–5 g by infusion three times daily.<sup>(G7)</sup>

**Leaf liquid extract** 2–5 mL (1:1 in 25% alcohol) three times daily.<sup>(G7)</sup>

**Leaf tincture** 2–5 mL (1:5 in 45% alcohol) three times daily.<sup>(G7)</sup>

**Dried rhizome/root** Daily dose 4.5 g<sup>(G2)</sup> or 1–2 g by infusion three times daily.<sup>(G4,G7)</sup>

**Rhizome/root liquid extract** 0.5–2.0 mL (1:1 in 25% alcohol) three times daily.<sup>(G7)</sup>

**Rhizome/root tincture** 0.5–2 mL (1:5 in 50% alcohol) three times daily.<sup>(G7)</sup>

**Fruit** 1–2 g.<sup>(G49)</sup>

## Pharmacological Actions

### *In vitro* and animal studies

Minimal anti-inflammatory activity (1% inhibition of carrageenan-induced rat paw oedema) has been documented for fruit extracts (100 mg/kg body

weight by mouth) given 45 minutes before eliciting oedema.<sup>(5)</sup> This was compared with 45% inhibition by indomethacin (5 mg/kg by mouth). Angelica is reported to possess antibacterial and antifungal properties.<sup>(G41,G46)</sup> Antibacterial activity against *Mycobacterium avium* has been documented, with no activity exhibited against *Escherichia coli*, *Bacillus subtilis*, *Streptococcus faecalis* or *Salmonella typhi*.<sup>(6)</sup> Antifungal activity was reported in 14 of 15 fungi tested.<sup>(6)</sup>

A methanolic extract of *A. archangelica* root showed antispasmodic activity against spontaneous contractions of circular smooth muscle (IC<sub>50</sub> 265 µg/mL) and inhibited acetylcholine- and barium chloride-induced contractions of longitudinal smooth muscle (IC<sub>50</sub> values 242 and 146 µg/mL, respectively).<sup>(7)</sup>

Extracts of *A. archangelica* root exhibit calcium channel-blocking activity.<sup>(8)</sup> A series of isolated coumarins showed activity, the most active being archangelicin with an IC<sub>50</sub> 1.2 µg/mL (verapamil 2.0 µg/mL) as a calcium channel antagonist as assessed by inhibition of depolarisation in GH<sub>4</sub>C<sub>1</sub> rat pituitary cells.<sup>(9)</sup>

Sixteen coumarin compounds isolated from *A. archangelica* were tested for activity in cyclooxygenase 1 (COX-1) and 5-lipoxygenase (5-LO) inhibition assays *in vitro*.<sup>(10)</sup> None of the compounds demonstrated activity against COX-1, but osthol and oxypeucedanin isovalerate were active in the 5-LO assay.

In rabbits, a uterotonic action has been documented for Japanese angelica root following intraduodenal administration of a methanolic extract (3 g/kg).<sup>(11)</sup> *A. sinensis* is reported to have induced uterine contraction and relaxation.<sup>(G57)</sup>

### Clinical studies

None documented for angelica (*A. archangelica*). The furanocoumarin constituent bergapten (5-methoxypsoralen) has been used in the PUVA (psoralen (P) and high-intensity long-wavelength ultraviolet irradiation) treatment of psoriasis.<sup>(G45)</sup>

### Side-effects, Toxicity

Both angelica and the root oil have been reported to cause <sup>(G32)</sup> photodermatitis and phototoxicity, respectively, following external contact.<sup>(6,G22,G33,G58)</sup> Angelica contains furanocoumarin constituents which are known to cause photosensitisation. Concern has been expressed at the possible carcinogenic risk of the furanocoumarin bergapten. Seven species of plants known to cause dermatitis were analysed for psoralen, 8-methoxypsoralen (xanthotoxin) and 5-methoxypsoralen (ber-

gapten). The highest total yield was obtained from *A. archangelica*.<sup>(12)</sup>

The root oil has been reported to be non-irritant and non-sensitising on animal and human skin.<sup>(6)</sup>

Root and fruit oils obtained by steam distillation are claimed to be devoid of furanocoumarins, although extracts may contain them.<sup>(G41)</sup>

Toxicity studies have been documented for the root oil.<sup>(6)</sup> Acute LD<sub>50</sub> values have been reported as 2.2 g/kg body weight (mouse, by mouth) and 11.16 g/kg (rat, by mouth). Death was attributed to liver and kidney damage, although animals surviving for three days completely recovered with a reversal of organ damage. An acute LD<sub>50</sub> (rabbit, dermal) value was reported to be greater than 5 g/kg. Subacute toxicity studies, lasting eight weeks, suggested that the tolerated dose in the rat was 1.5 g/kg, although at lower doses the animals weighed less than the controls.<sup>(6)</sup>

Furanocoumarins isolated from a related Chinese species, *Angelica koreana*, have been reported to affect the hepatic metabolism of hexobarbitone. The compounds were found to cause a marked inhibition of drug metabolism in the first phase and an acceleration in the second phase, and were thought to be drug-metabolising enzyme inhibitors rather than enzyme inducers. Furanocoumarins investigated included imperatorin and oxypeucedanin, which are also documented as constituents of *A. archangelica*. It has been reported that a related Chinese species, *Angelica sinensis*, may be hepatoprotective and prevent the reduction of hepatic glycogen.

### Contra-indications, Warnings

Angelica may provoke a photosensitive allergic reaction because of the furanocoumarin constituents. In addition, excessive doses may interfere with anticoagulant therapy because of the coumarin constituents.

The use of bergapten in cosmetic and suntan preparations is stated to be ill-advised by some regulatory authorities,<sup>(G45)</sup> in view of the concerns regarding the risk of skin cancer. The International Fragrance Association recommends that angelica root oil be limited to a maximum of 0.78% in products applied to skin which is then exposed to sunshine.<sup>(G58)</sup>

**Pregnancy and lactation** Angelica root is reputed to be an abortifacient and to affect the menstrual cycle. In view of this and the photosensitising constituents, the use of angelica during pregnancy and lactation in amounts exceeding those used in foods should be avoided.

## Pharmaceutical Comment

The chemistry of angelica is well documented. Although the traditional use of Chinese angelica species, such as *A. sinensis* and *A. acutiloba*, is well established in oriental medicine, there is limited documented pharmacological information available for *A. archangelica*, the species most commonly used in Europe, to justify its herbal uses. In view of the presence of known pharmacologically active constituents, especially bergapten, consumption of amounts exceeding normal human dietary intake should be avoided. Angelica contains furanocoumarins which are known to possess photosensitising properties.

The related species *A. sinensis* (dong quai) is popular in traditional Chinese medicine (TCM) and occurs in about 70% of all TCM prescriptions to treat dysmenorrhoea, postnatal disturbances, anaemia, constipation and chronic pelvic infections.<sup>(13)</sup> Western naturopaths recommend the use of dong quai in hypertension, for modification of high blood sugar concentrations, regulation of the immune system, liver detoxification, anaemia and to relieve allergic conditions. Several unlicensed over-the-counter (OTC) products containing dong quai are readily available.

The chemistry of dong quai is similar to that of *A. archangelica*, with coumarins and volatile oil being major components.<sup>(13)</sup> In addition, a series of phthalides (e.g. ligustilide, butylphthalide, butylidenephthalide) have been isolated. Pharmacological investigations have shown that phthalides and coumarins have antispasmodic activity. The volatile constituents generally exert a hypotensive effect. A polysaccharide component is active against Ehrlich ascites tumours in mice and has immunostimulating activity,<sup>(14)</sup> and protects the gastric mucosa against ethanol- and indomethacin-induced damage.<sup>(15)</sup> Clinical investigation has failed to support the claims for relieving menopausal symptoms.<sup>(16)</sup> *A. sinensis* has been reported to be effective in improving abnormal protein metabolism in patients with chronic hepatitis or hepatic cirrhosis.<sup>(17)</sup>

The furanocoumarins are phototoxic and have photocarcinogenic potential, but need ultraviolet (UV) light for activation. An extract of dong quai administered subcutaneously to rabbits did not affect prothrombin time given alone, but did after concurrent administration of a single dose of warfarin.<sup>(18)</sup> Elevation of prothrombin time was noted in a patient stabilised on warfarin who began taking dong quai.<sup>(19)</sup> Coagulation values returned to normal one month after discontinuing use of dong quai.

## References

See also General References G2, G3, G9, G10, G16, G22, G31, G33, G36, G37, G41, G44, G48, G49, G57, G58 and G64.

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