Species (Family)
Aesculus hippocastanum L. (Hippocastanaceae)

Synonym(s)
Aesculus

Part(s) Used
Seed

Pharmacopoeial and Other Monographs
BHP 1996
ESCP 1999
Martindale 32nd edition
Mills and Bone
PDR for Herbal Medicines 2nd edition

Legal Category (Licensed Products)
GSL (for external use only)

Constituents
Coumarins
Aesculetin, fraxin (fraxetin glucoside), scopolin (scopoletin glucoside).

Flavonoids
Flavonol (kaempferol, quercetin) glycosides including astragalin, isoquercetrin, rutin; leucocyanidin (quercetin derivative).

Saponins
French pharmacopoeial standard, not less than 3% aescin. A mixture of saponins collectively referred to as 'aescin' (3–10%); α- and β-escin as major glycosides.

Tannins
Type unspecified but likely to be condensed in view of the epicatechin content (formed during hydrolysis of condensed tannins).

Other constituents
Allantoin, amino acids (adenine, adenosine, guanine), choline, citric acid, phytosterol.

Food Use
Horse-chestnut is not used in foods.

Herbal Use
Traditionally, horse-chestnut has been used for the treatment of varicose veins, haemorrhoids, phlebitis, diarrhoea, fever and enlargement of the prostate gland. The German Commission E approved use for treatment of chronic venous insufficiency in the legs.

Dosage
Fruit
0.2–1.0 g three times daily.

Preparations
Extracts equivalent to 50–150 mg triterpenes calculated as aescin.

Pharmacological Actions
Documented studies have concentrated on the actions of the saponins, in particular, aescin.

In vitro and animal studies
Anti-inflammatory and anti-oedema effects
Anti-inflammatory activity in rats has been documented for both a fruit extract and the saponin fraction. Anti-inflammatory activity in the rat has been reported to be greater for a total horse-chestnut extract compared to aescin. In addition, an extract excluding aescin also exhibited activity, suggesting that horse-chestnut contains anti-inflammatory agents other than aescin. No difference in activity was noted when the horse-chestnut extracts were administered prior to and after dextran (inflammatory agent). It has been proposed that aescin affects the initial phase of inflammation by exerting a 'sealing' effect on capillaries and by reducing the number and/or diameter of capillary pores.

Effects on venous tone
Horse-chestnut extract (16% aescin, 0.2 mg/mL) and also aescin (0.1 mg/mL) induced contractions in isolated bovine and human veins. Concentration-dependent contractions of isolated canine veins were observed with a horse-chestnut extract (16% aescin, 5 x 10^-4 mg/mL). A standardised extract (16% aescin, 50 mg, given intravenously) increased femoral venous pressure in anaesthetised dogs, and decreased cutaneous capillary hyperpermeability in rats (200 mg/kg, given orally).
In addition, the saponin fraction of horse-chestnut has been reported to exhibit analgesic and antigranulation activities in rats,\(^3\) to reduce capillary permeability,\(^6\) and to produce an initial hypotension followed by a longer lasting hypertension in anaesthetised animals.\(^4\) Prostaglandin production by venous tissue is thought to be involved in the regulation of vascular reactivity.\(^7\) Prostaglandins of the E series are known to cause relaxation of venous tissues whereas those of the F\(_x\) series produce contraction. Increased venous tone induced by aescin in vitro was found to be associated with an increased PGF\(_{2\alpha}\) synthesis in the venous tissue.

**Other activities**  
In vitro, aescin has been documented to inhibit hyaluronidase activity (IC\(_{50}\) 150 \(\mu\)mol/L).\(^{G2}\)

A saponin fraction of horse-chestnut has been reported to contract isolated rabbit ileum.\(^3\)

Antiviral activity in vitro against influenza virus (A\(_2\)/Japan 305) has been described for aescin.\(^8\)

Metabolism studies of aescin in the rat have concluded that aescin toxicity is reduced by hepatic metabolism.\(^9\)

Flavonoids and tannins are generally recognised as having anti-inflammatory and astringent properties, respectively.

**Clinical studies**

**Chronic venous insufficiency** Several studies have assessed the effects of horse-chestnut seed extract in patients with chronic venous insufficiency, a common condition which causes oedema of the lower leg.

A systematic review of randomised, double-blind, controlled trials of horse-chestnut seed extract in chronic venous insufficiency included 13 studies (eight placebo-controlled trials and five studies comparing horse-chestnut seed extract with reference medication or compression therapy).\(^{10}\)

Generally, trials involved the administration of horse-chestnut seed extract 100 or 150 mg daily for 3–12 weeks. The results of all the placebo-controlled studies indicated that horse-chestnut seed extract was superior. Four comparative studies indicated that horse-chestnut seed extract was as effective as O-(\(\beta\)-hydroxyethyl)-rutosides in relieving symptoms of chronic venous insufficiency; one study suggested that horse-chestnut seed extract was as effective as compression therapy. It was concluded that horse-chestnut seed extract is effective as a symptomatic, short-term treatment for chronic venous insufficiency, but that further well-designed clinical trials are required to confirm this.\(^{10}\)

**Other effects** Glycosaminoglycan hydrolysates are enzymes involved in the breakdown of substances (proteoglycans) that determine capillary rigidity and pore size (thus influencing the passage of macromolecules into the surrounding tissue). Proteoglycans also interact with collagen, stabilising the fibres and regulating their correct biosynthesis.\(^{11}\) The activity of these enzymes was found to be raised in patients with varicosis, compared with healthy patients. In a study involving 15 patients with varicosis treated with horse-chestnut extract (900 mg daily) for 12 days, the activity of these enzymes was significantly reduced.\(^{11}\) It was proposed that horse-chestnut may act at the site of enzyme release, exerting a stabilising effect on the lysosomal membrane.\(^{11}\)

In a randomised, double-blind, placebo-controlled study involving 70 healthy individuals with haematomas, a topical gel (2% aescin) reduced sensitivity to pressure on affected areas.\(^{G2}\)

The cosmetic applications of horse-chestnut have been reviewed;\(^{12}\) these effects are attributed to properties associated with the saponin constituents.

**Side-effects, Toxicity**

Two incidences of toxic nephropathy have been reported and were stated as probably secondary to the ingestion of high doses of aescin.\(^{13}\) In Japan, where horse-chestnut has been used as an anti-inflammatory drug after surgery or trauma, hepatic injury has been described in a male patient who received an intramuscular injection of a proprietary product containing horse-chestnut.\(^{14}\) Liver function tests showed a mild abnormality and a diagnosis of acute renal failure was made. Other side-effects stated to have been reported for the product include shock, spasm, mild nausea, vomiting and urticaria.\(^{14}\)

The effect of aescin, both free and albumin-bound, on renal tubular transport processes has been studied in the isolated, artificially perfused frog kidney.\(^{15}\) Aescin was found to primarily affect tubular, rather than glomerular, epithelium and it was noted that binding to plasma protein (approximately 50%) protects against this nephrotoxicity. Aescin was thought to be neither secreted nor reabsorbed in the tubules, and the concentration of unbound aescin filtered through the kidney (13%) was considered to be too low to have toxic effects. The authors commented that the symptoms of acute renal failure in humans are caused primarily by interference with glomeruli and in view of this, the nephrotoxic potential of aescin is probably only relevant when the kidneys are already damaged and also if the aescin is displaced from its binding to plasma protein.\(^{15}\)
A proprietary product containing horse-chestnut (together with phenopyrazone and cardiac glycoside-containing plant extracts) has been associated with the development of a drug-induced auto-immune disease called 'pseudolupus syndrome' in Germany and Switzerland.\(^{(16,17)}\) The individual component in the product responsible for the syndrome was not established.

It has been noted that death occurs rapidly in animals given large doses of aescin, due to massive haemolysis. Death is more prolonged in animals given smaller doses of aescin.\(^{(4)}\)

LD\(_{50}\) values for aescin have been estimated in mice, rats and guinea-pigs and range from 134 to 720 mg/kg (by mouth) and from 1.4 to 15.2 mg/kg (intravenous injection).\(^{G49}\) The total saponin fraction has been reported to be less toxic in mice (intraperitoneal injection) compared to the isolated aescin mixture (LD\(_{50}\) 46.5 mg/kg and 9.5 mg/kg, respectively).\(^{3}\) The haemolytic index of horse-chestnut is documented as being 6000, compared with 9500 to 12 500 for aescin.\(^{G62}\) Daily doses in rats (100 mg/kg, orally) of a standardised extract of horse-chestnut (16% aescin) did not produce teratogenic effects, and the extract was negative in the Ames test with Salmonella typhimurium TA98 without actuation.\(^{G52}\)

**Contra-indications, Warnings**

Horse-chestnut may be irritant to the gastrointestinal tract due to the saponin constituents. Saponins are generally recognised to possess haemolytic properties, but are not usually absorbed from the gastrointestinal tract following oral administration. Horse-chestnut may interfere with anticoagulant/anticoagulant therapy (coumarin constituents). Aescin, the main saponin component in horse-chestnut, binds to plasma protein and may affect the binding of other drugs. Horse-chestnut should be avoided by patients with existing renal or hepatic impairment.

**Pregnancy and lactation** The safety of horse-chestnut during pregnancy and lactation has not been established. In view of the pharmacologically active constituents present in horse-chestnut, use during pregnancy and lactation is best avoided.

**Pharmaceutical Comment**

Horse-chestnut is traditionally characterised by its saponin components, in particular aescin which represents a mixture of compounds. However, horse-chestnut also contains other pharmacologically active constituents including coumarins and flavonoids. The traditional use of horse-chestnut in peripheral vascular disorders has largely been substantiated by studies in animals and humans, in which anti-inflammatory and capillary stabilising effects have been observed. There is evidence from randomised, double-blind, controlled clinical trials to support the use of horse-chestnut seed extract in the treatment of symptoms of chronic venous insufficiency.

Many of the documented activities can probably be attributed to the saponin and flavonoid constituents in horse-chestnut.

**References**

*See also General References G2, G9, G16, G22, G31, G36, G37, G43, G48, G49, G50, G52, G56, G59, G62 and G64.*


