Horse-chestnut

Summary and 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. Many of the documented activities can be attributed to the saponin and flavonoid constituents in horse-chestnut. The traditional use of horse-chestnut in peripheral vascular disorders is supported by data from preclinical studies 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 but confirmation from more robust studies is required. In view of the limited information on safety and toxicity, excessive use of horse-chestnut and use during pregnancy and lactation should be avoided.

Species (Family)

Aesculus hippocastanum L. (Hippocastanaceae)

Synonym(s)

Aesculus

Part(s) Used

Seed

Pharmacopoeial and Other Monographs

BHP 1996[G9]
ESCOP 2003[G76]
Martindale 35th edition[G85]
USP29/NF24[G86]

Legal Category (Licensed Products)

GSL (for external use only)[G37]

Constituents

The following is compiled from several sources, including General References G52, G59 and G62.

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-aescin 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.[G3]

Dosage

Dosages for oral administration (adults) for traditional uses recommended in older and contemporary standard herbal and/or pharmaceutical reference texts are given below.

Fruit 0.2–1.0 g three times daily.[G49]

Preparations Extracts equivalent to 50–150 mg triterpenes calculated as aescin, in divided doses.[G52]

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.[1–4] 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.[5] 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.[3]

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.[G52] Concentration-dependent contractions of isolated canine veins were observed with a horse-chestnut extract (16% aescin, 5×10^{-4} mg/mL).[G52] 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).[G52]

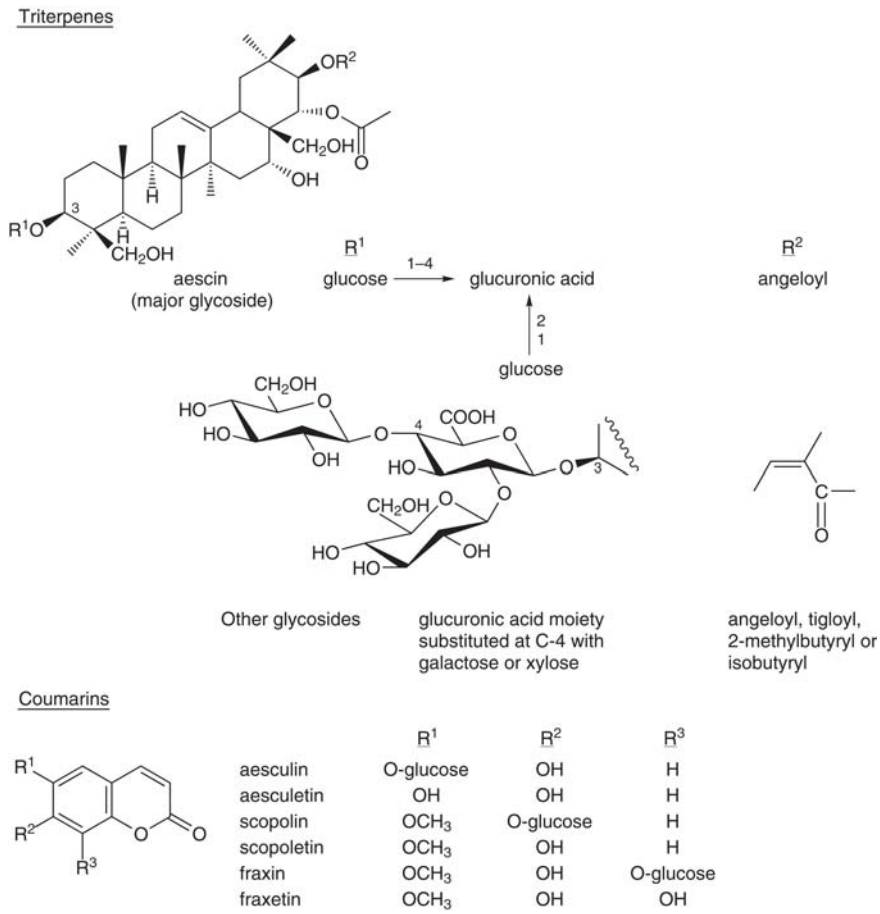

Figure 1 Selected constituents of horse-chestnut.

In addition, the saponin fraction 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_{α} 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 µmol/L).[G52]

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 Cochrane systematic review of randomised, double-blind, controlled trials of horse-chestnut seed extract in chronic venous insufficiency included 17 studies: ten placebo-controlled trials and seven studies comparing horse-chestnut seed extract with reference medication (*O*-β-hydroxyethylrutosides, pycnogenol) or compression therapy.[10] Trials involved the administration of horse-chestnut seed extract equivalent to 50–150 mg aescin daily for two to 16 weeks. Collectively, results of placebo-controlled studies indicated that horse-chestnut seed extract was superior to placebo with respect to leg pain (weighted mean difference (95% confidence interval (CI)) in 100 mm visual analogue scale scores: 42.40 mm (34.90–49.90; six trials), oedema and pruritus resulting from chronic venous insufficiency.[10] Trials comparing horse chestnut seed extract with other treatment approaches indicated that the herbal preparation was as effective in relieving symptoms of chronic venous insufficiency. The review concluded that horse-chestnut seed extract is an effective short-term treatment for symptoms of chronic venous insufficiency, but that because of methodological limitations of existing studies, further well-designed clinical trials are required for confirmation of the observed effects.[10]

Other effects Glycosaminoglycan hydrolyses 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] However, this observation requires confirmation in larger, robust clinical studies.

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.[G52]

The cosmetic applications of horse-chestnut have been reviewed;[12] these effects are attributed to properties associated with the saponin constituents.

Side-effects, Toxicity

Clinical data

There is a lack of clinical safety and toxicity data for horse-chestnut and further investigation of these aspects is required.

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 giant cell tumour of bone (grade 2) by bone biopsy was made. Other side-effects stated to have been reported for the product include shock, spasm, mild nausea, vomiting and urticaria.[14] However, a causal association with horse-chestnut use in this case has not been established.

Preclinical data

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 autoimmune disease called 'pseudolupus syndrome' in Germany and Switzerland.[15, 16] The individual component in the product responsible for the syndrome was not established.

The effect of aescin, both free and albumin-bound, on renal tubular transport processes has been studied in the isolated, artificially perfused frog kidney.[17] 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.[17]

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. As a precaution, horse-chestnut should be avoided by patients with existing renal or hepatic impairment.

Drug interactions None documented. However, the potential for preparations of horse-chestnut to interact with other medicines administered concurrently, particularly those with similar or opposing effects, should be considered. Horse-chestnut has coumarin constituents, although those detected so far do not

Figure 2 Horse-chestnut (*Aesculus hippocastanum*).

Figure 3 Horse-chestnut – dried drug substance (seed).

possess the minimum structural requirements for anti-coagulant activity. There is evidence from preclinical studies that aescin, the main saponin component in horse-chestnut, binds to plasma protein. However, it is not clear if this has clinical relevance in terms of affecting binding of other drugs.

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 should be avoided.

Preparations

Proprietary single-ingredient preparations

Argentina: Grafic Retard; Herbaccion Venotonico; Nadem; Venastat; Venostasin. *Austria:* Aesculaforce; Provenen; Venosin; Venostasin. *Belgium:* Venoplant. *Brazil:* Varilise; Venafort; Venostasin. *Chile:* Venastat. *Czech Republic:* Venitan. *Germany:* Aescorin Forte; Aescusan; Aescuven; Concentrin; Essaven; Heweven Phyto; Hoevenol; Noricaven; Plissamur; Sklerovenol N; Venalot novo; Venen-Dragees; Venen-Fluid; Venen-Tabletten; Venen-Tropfen N; Venentabs; Veno-biomo; Venodura; Venoplant; Venopyronum; Venostasin. *Hungary:* Venastat. *Italy:* Flebostasin. *Mexico:* Venastat. *Spain:* Plantivenol; Varicid. *Switzerland:* Aesculaforce; AesculaMed; Phlebostasin; Venavit N; Venostasin.

Proprietary multi-ingredient preparations

Argentina: Nadem Forte; Venoful; VNS 45. *Australia:* Bioglan Cirflo; Bioglan Zellulean with Escin; Extralife Leg-Care; Herbal Capillary Care; Proflo. *Austria:* Dilaescol; Heparin Comp. *Belgium:* Rectovasol. *Brazil:* Castanha de India Composta; Digestron; Hemorroidex; Mirorroidin; Novarrutina; Proctosan; Supositorio Hamamelis Composto; Traumed; Varizol; Venocur Triplex. *Chile:* Proctoplex. *Czech Republic:* Heparin-Gel. *France:* Arterase; Climaxol; Creme Rap; Evarose; Fluon; Hemorrogel; Histo-Fluine P; Intrait de Marron d'Inde P; Mediflor Tisane Circulation du Sang No 12; Opo-Veinogene; Phlebosedol; Phytomelis; Veinophytum; Veinostase; Veinotonyl. *Germany:* Aescusan; Amphodyn; Cefasabal; Cycloven Forte N; Diu Venostasin; Fagorutin Rosskastanien-Balsam N; Heparin Comp; Intradermi; PC 30 V; Sportupac M; Traumacyl; Varicylum-S; Venen Krauter NT; Venen-Salbe N; Venengel; Weleda Hamorrhoidalzapfchen. *Italy:* Capill Venogel; Capill; Centella Complex; Centella Complex; Centeril H; Centeril H; Flavion; Inflamase; Pik Gel; Proctopure; Varicogel; Venactive; Venoplus. *Mexico:* Almodin. *South Africa:* Stibium Comp. *Spain:* Contusin; Roidhemo; Ruscimel. *Switzerland:* Demoven N; Ipasin; Strath Gouttes pour les veines.

References

1 Farnsworth NR, Cordell GA. A review of some biologically active compounds isolated from plants as reported in the 1974–75 literature. *Lloydia* 1976; 39: 420–455.

2 Benoit PS *et al*. Biological and phytochemical evaluation of plants. XIV. Antiinflammatory evaluation of 163 species of plants. *Lloydia* 1976; 39: 160–171.

3 Cebo B *et al*. Pharmacological properties of saponin fractions from Polish crude drugs: *Saponaria officinalis*, *Primula officinalis*, and *Aesculus hippocastanum*. *Herba Pol* 1976; 22: 154–162.

4 Vogel G *et al*. Untersuchungen zum Mechanismus der therapeutischen und toxischen Wirkung des Rosskastanien-saponins aescin. *Arzneimittelforschung* 1970; 20: 699–705.

5 Tsutsumi S, Ishizuka S. Anti-inflammatory effects of the extract *Aesculus hippocastanum* and seed. *Shikwa-Gakutto* 1967; 67: 1324–1328.

6 De Pascale V *et al*. Effect of an escin-cyclonamine mixture on capillary permeability. *Boll Chim Farm* 1974; 113: 600–614.

7 Longiave D *et al*. The mode of action of aescin on isolated veins: Relationship with $PGF_2\alpha$. *Pharmacol Res Commun* 1978; 10: 145–153.

8 Rao SG, Cochran KW. Antiviral activity of triterpenoid saponins containing acylated β-amyrin aglycones. *J Pharm Sci* 1974; 63: 471.

9 Rothkopf M. Effects of age, sex and phenobarbital pretreatment on the acute toxicity of the horse chestnut saponin aescin in rats. *Naunyn-Schmied archpharm* 1977; 297 (Suppl. Suppl.): R18.

10 Pittler MH, Ernst E. Horse-chestnut seed extract for chronic venous insufficiency (Review). 2006, Issue 1. Art. No.: CD003230.10.1002/14651858.CD003230.pub2

11 Kreysel HW *et al*. A possible role of lysosomal enzymes in the pathogenesis of varicosis and the reduction in their serum activity by Venostasin^R. *Vasa* 1983; 12: 377– 382.

12 Proserpio G *et al*. Cosmetic uses of horse-chestnut (*Aesculum hippocastanum*) extracts, of escin and of the cholesterol/escin complex. *Fitoterapia* 1980; 51: 113–128.

13 Grasso A, Corvaglia E. Two cases of suspected toxic tubulonephrosis due to escine. *Gazz Med Ital* 1976; 135: 581–584.

14 Takegoshi K *et al*. A case of Venoplant^R-induced hepatic injury. *Gastroenterol Japonica* 1986; 21: 62–65.

15 Grob P *et al*. Drug-induced pseudolupus. *Lancet* 1975; ii: 144–148.

16 Russell AS. Drug-induced autoimmune disease. *Clin Immunol Allergy* 1981; 1: 57–76.

17 Rothkopf M *et al*. Animal experiments on the question of the renal toleration of the horse chestnut saponin aescin. *Arzneimittelforschung* 1977; 27: 598–605.