Synonyms

Hippocastani semen (Lat), Robkastaniensamen (Ger), graine de marronier d’Inde, aescule (Fr), eschilo (Ital), hestekastanja (Dan).

What is it?

The horsechestnut tree (*Aesculus hippocastanum* L.) is mainly grown as an ornamental in parks and gardens in Europe, although it is in fact a native of Asia Minor. Horsechestnut seeds and bark have been extensively used in European herbal medicine since the 16th century and a wine based on the flowers was imbibed for neuralgia and arthritis. The flowers and flower buds are now used to make two of the Bach Flower Remedies. However, this monograph will only describe the herbal use of the seed, principally for the improvement of vein health. Unlike true chestnuts, the seeds of the horsechestnut are not edible, although a specially prepared seed meal has been used as fodder. While it is sometimes regarded as a toxic herb, there is no suggestion from published trials that the normal use of the seed causes toxic effects.

Effects

Increases venous tone, improves capillary resistance, decreases capillary permeability, improves circulation by toning veins; decreases oedema resulting from lymphatic congestion or inflammation.

Traditional view

Horsechestnut seed (hereafter referred to as horsechestnut) was traditionally used in the treatment of rheumatism and neuralgia and conditions of venous congestion, particularly with dull, aching pain and fullness. Other major uses include rectal complaints (particularly haemorroids, rectal neuralgia and proctitis) and reflex conditions attributed to rectal involvement (including headache, spasmodic asthma, dizziness and disturbed digestion). It was regarded as a remedy for congestion and engorgement. Uneasy and throbbing sensations, with dull aching pain in any part of the body, but especially in the hepatic region, was one specific indication.1,2

Summary actions

Venotonic, anti-oedematous, anti-inflammatory.

Can be used for

Indications supported by clinical trials

Chronic venous insufficiency (high level evidence), varicose veins, varicose ulcer, oedema of the lower limbs. Prophylactic use to decrease the incidence of deep venous thrombosis following surgery (low level evidence). Topically for haematoma, contusions, non-penetrating wounds and sports injuries involving oedema (typically in combination).

Traditional therapeutic uses

Venous problems (especially varicose veins, haemorrhoids); rheumatism; neuralgia; rectal complaints; disease states associated with inflammatory congestion.

May also be used for

Extrapolations from pharmacological studies

To improve circulation by improving venous tone (peripheral vascular disorders, slow-healing leg ulcers); disorders where local tissue oedema may be involved (such as carpal tunnel syndrome, Bell’s palsy, congestive dysmenorrhoea, trigeminal neuralgia, intervertebral disc lesions, compression neuropathies); conditions requiring treatment in the early phase of inflammation, such as soft tissue injuries, swelling, minor surgery.

Other applications

Skin care products: for normal skin, baby skin, sensitive skin; to tone the skin; as an anti-inflammatory; to treat fragile capillaries, pimples, sunburn or cellulite.3 Topically for antiageing effects on skin.

Preparations

Decoction of dried or fresh seeds, tincture, liquid extract, capsules and tablets for internal use. Decoction, extract, cream, gel or ointment for topical use.

Dosage

- 1 to 2 g/day of dried seed
- Horsechestnut tablets or capsules (200mg of 5:1 concentrated extract, standardised to contain 40 to 50mg beta-escin): two to three tablets/day
- 2 to 6 mL/day of 1:2 liquid extract, 5 to 15 mL/day of 1:5 tincture
- Preparations containing at least 100 mg/day of beta-escin.

**Duration of use**

There is no suggestion that the long-term use of horsechestnut should be restricted.

**Summary assessment of safety**

Despite its inclusion in texts on poisonous plants, there is a very low risk associated with the oral or topical administration of horsechestnut seed.

**Technical data**

**Botany**

The horsechestnut, a member of the Hippocastanaceae (buckeye family), is a deciduous tree with grey bark that grows to 25 m. The leaves are opposite and palmate with five to seven strongly ribbed leaflets. The flowers are white with yellow to pink spots, contain five petals and are arranged in noticeable panicles up to 30 cm long. The fruit has a leathery, prickly capsule (the conker) and contains one to two brown seeds with large whitish scar.

**Adulteration**

No known adulterants.

**Key constituents**

- Saponins (3% to 6%), referred to as escin (which is a complex mixture of over 30 individual pentacyclic triterpene diester glycosides). Beta-escin is a subfraction of escin containing only 22-O-acetyl compounds
- Flavonoids, lipids, sterols.

Although from a phytochemical perspective escin and beta-escin are not equivalent, in most products and studies the ‘escin’ being referred to is actually beta-escin.

**Pharmacodynamics**

Escin (also spelt ‘aescin’) was a registered drug in Germany and is the active ingredient in a number of preparations used either topically or orally for the treatment of peripheral vascular disease, in particular that related to altered capillary permeability and resistance. (For conditions associated with oedema it is mainly administered by injection see under Clinical trials.)

**Venotonic, vascular protective and anti-oedema activity**

Most of the pharmacological research on horsechestnut and escin was conducted prior to 2000; hence a 2001 review still has relevance. This review noted research supporting three key pharmacological actions, namely anti-oedematous, anti-inflammatory and venotonic. The review suggested that all of these appear to be due to a basic molecular mechanism: selective vascular permeabilisation, allowing a higher sensitivity of calcium channels (for example) to molecular ions, resulting in increased venous and arterial tone. In a sense the
anti-oedematosus effect is a key feature of the anti-inflammatory activity of horsechestnut and underlies much of its value in conditions linked to local inflammation, with associated swelling and pressure on other structures.

The review goes on to state that these sensitising effects to ions and other molecules such as serotonin probably result in enhanced venous contractile activity, leading to the venotonic effect. In fact, escin can be used as a pharmacological tool to assess the sensitivity of vascular tissues to different agonists.

Escin reduced the localised oedema associated with inflammation probably by reducing capillary permeability to water, thereby decreasing exudation into intercellular spaces. It induced contraction of isolated portal vein and stimulated the generation and release of prostaglandin F2-alpha in vitro. Hence this antixudative activity of escin may be mediated by prostaglandin F2-alpha. Escin administered by injection inhibited oedema induced by several agents in rat paw, but was not effective in models representing the late reparative (proliferative) phase of inflammation. This suggests it acts more specifically on the initial stages of inflammation. In contrast, a study using carrageenan-induced paw oedema and induced capillary permeability in mice found that escin (2 mg/kg, by injection) was a potent and long-lasting anti-inflammatory agent without immunosuppressive activity. Parenteral administration of escin to rats indicated the antixudative activity resulted from an influence on the small pores of the capillary wall (through which fluid is exchanged).

Tests conducted on adrenalectomised and hypophysectomised animals indicated the normal production of corticosteroids is necessary for the anti-oedema activity. Escin thus mimics and relies upon the activity of corticosteroids and it exerts a synergistic anti-inflammatory effect with low doses of glucocorticoids in vivo and in vitro. Oral administration of escin demonstrated antixudative and anti-inflammatory activity in another in vivo study. The activity occurred in both prophylaxis and treatment and was due to a beneficial effect on permeability and diuresis. Topical application of escin also significantly inhibited exudation in vivo.

Additional studies have examined the endothelial cell protective activity of escin. Human vascular endothelial cells were exposed to cobalt chloride to mimic hypoxia and to Escherichia coli lipopolysaccharide to mimic inflammation. Pretreatment with escin prevented both the induced hypoxia and inflammation, as measured by factors such as the expression of vascular cell adhesion molecule 1 and the reduction of platelet endothelial cell adhesion molecule 1. Escin enhanced endothelium-dependent relaxation in rat aortic rings induced by acetylcholine when such relaxation had been reduced by pyrogallol, a generator of the superoxide radical.

The whole extract of the horsechestnut also shares these properties of escin. In fact, some writers suggest that the combination of escin with flavonoids, as found in the natural plant extract, is a superior treatment to escin alone. Horsechestnut extract demonstrated venotonic activity in vitro by inducing the contraction of isolated vein preparations. Perfusion with horsechestnut extract increased the venous pressure of normal veins and, with prior administration, pathological veins. During perfusion in the opposite direction to blood flow, a clear contractile effect on the valves was obtained. Horsechestnut extract (2.5, 5.0 mg/kg, iv) increased femoral venous pressure and flow, as well as thoracic lymphatic flow, with no change in arterial parameters. A more recent in vitro study found that horsechestnut extract dose-dependently contracted both veins and arteries, with veins being the most sensitive. ADP-induced platelet aggregation was also significantly reduced. Escin (as the sodium salt) in vitro also contracts blood vessels at lower concentrations (rat aorta).

Oral administration of a horsechestnut standardised extract (HCSE, 50 to 400 mg/kg, containing 70% escin) reduced cutaneous capillary hyperpermeability in rodents. It also increased skin capillary resistance in guinea pigs fed a vitamin C-deficient diet, as measured by the petechiae method. The extract (200 to 400 mg/kg) decreased the formation of oedema of lymphatic or inflammatory origin induced in rat hind paw, suppressed plasmatic extravasation and leucocyte migration into the pleural cavity in experimental pleurisy (200 to 400 mg/kg, oral, and 1 to 10 mg/kg, iv), and decreased connective tissue formation in subchronic inflammatory granuloma (400 mg/kg, oral, and 5 to 10 mg/kg, sc).

In a randomised, double blind, placebo-controlled crossover study, the influence of oral doses of horsechestnut on capillary resistance was tested in 12 healthy volunteers. After 7 days of treatment with a high dose of a HSCE (1500 mg/day, corresponding to 500 mg/day escin), capillary resistance was significantly improved (as measured by the petechiae test). There was no effect from the placebo.

Pharmacological and clinical studies indicate that oral administration of horsechestnut extract can improve connective tissue and circulation by toning the veins. In a double blind, placebo-controlled study, a decrease in the vascular capacity (as measured by increased flow) and filtration coefficients was observed in volunteers with healthy circulation treated with HCSE (600 mg/day, containing 100 mg escin). The anti-oedematosus activity demonstrated by HCSE in chronic venous insufficiency was mainly dependent on the inhibition of proteoglycan degradation and lysosomal enzyme activity, as determined in a human study after administration of 900 mg/day HCSE for 12 days.

The effect of oral HCSE (360 mg/day, containing 90 mg escin) in 14 healthy volunteers on the venous tone of a segment of the lower leg was compared with placebo controls. Horsechestnut resulted in significant reduction of the pressure-dependent vein capacity (p<0.02), which is an indication of reduced deformation of the veins and an increase in venous tone. An intravenous infusion of escin did not result in a noticeable change, suggesting other components of the extract had this activity. However, in a double blind, placebo-controlled trial involving 20 healthy volunteers, 100 mg of HCSE (containing 16% or 70% escin) demonstrated similar venotonic activity on peripheral venous pressure-volume curves to the placebo. This lack of a positive effect may reflect inadequate dosage.

In an uncontrolled trial, the velocity of blood in varicose veins was assessed after patients received HCSE for 12 days. Blood viscosity was significantly lowered and correlated to subjective improvement in 73% of cases. A single dose of...
HCSE (600 mg, containing 100 mg escin) prevented or significantly reduced the increase in ankle and foot oedema (p<0.05) in healthy humans during a 15 h air flight. The study was randomised, double blind design and the oedema was compared with preflight levels.36

Gastrointestinal activity

The inhibitory effects of oral doses of the saponin fraction of horsechestnut extract and its principal constituents escins Ia, Ib, Ia and Ib on gastric emptying were investigated in mice. Gastric emptying of a 1.5% carboxymethyl cellulose sodium salt meal was inhibited by 11.1% to 54.2%. Escins Ia to Ib (50 mg/kg) also inhibited gastric emptying of a 40% glucose meal by 21.1% to 23.5% (except for escin Ia), a milk meal by 18.4% to 33.1%, and a 30% ethanol meal by 13.5% to 15.9%.37 Further studies were conducted to assess the likely mechanism involved. Results suggested a possible involvement of capsaicin-sensitive sensory nerves (CPSN) stimulating the synthesis and/or release of dopamine to release prostaglandins (PGs) via central dopamine-2 receptors.38,39 Escins Ib and Ib also demonstrated enhanced absorption of magnesium at 12.5 and 25 mg/kg orally in mice, respectively. The mechanism was suggested to involve constitutive nitric oxide synthase (NOS), but not endogenous PGs or the sympathetic nervous system (SNS).40,41

Further to these investigations, the effect of oral pretreatment with escins Ia, Ia and Ia on ethanol-induced gastric mucosal lesions, and the roles of CPSN, endogenous NO, sulphhydrils, PGs, gastric secretion and the SNS, were studied in rats.42 Escins Ia to Ib (10 to 50 mg/kg) potently inhibited ethanol-induced gastric mucosal lesions, whereas their hydrolysed products desacylescins I and II showed no effect. Endogenous PGs, NO, capsaicin-sensitive afferent neurons and the SNS all participated in this activity.

Postoperative adhesions form after trauma through complex processes involving injured tissues and the peritoneum. Escin (0.45 to 3.6 mg/kg, iv, as the sodium salt) was administered in different rodent models to investigate its effect on inflammation, gastrointestinal transit and postoperative adhesion formation.43 It was shown that escin could inhibit acute inflammation and granuloma formation, accelerate gastrointestinal transit, help recover intestinal mobility and attenuate the formation of postoperative adhesions. The authors suggest that escin attenuated adhesion formation by inhibiting inflammation and promoting gastrointestinal transit. However, an invited commentary noted that the design of the study, for example the different animal species used, made the results difficult to interpret.44 Gastrointestinal transit acceleration from escin was postulated to involve constitutive NOS and the SNS.33,45

Antitumour activity

A few studies have examined the antitumour activity of escin, mainly in vitro. For example, beta-escin inhibited proliferation and induced apoptosis in human hepatocellular carcinoma cells by inhibiting STAT-3 (signal transducer and activator of transcription 3).46 At 1.4 and 2.8 mg/day, for 7 days, ip administration of escin inhibited hepatocellular carcinoma growth in mice.47 Escin was observed to chemosensitise human cancer cells in vitro through inhibition of NF-kappaB48 and beta-escin acted synergistically with 5-fluorouracil in human hepatocellular carcinoma cells.49

However, some retractions of published work in this area,50-52 and the fact that escin does not appear to be as active as other similar saponins,53 together with its limited oral bioavailability as such, all suggest that more attractive antitumour prospects exist elsewhere.

Oral doses of beta-escin do appear to have chemopreventive activity. The chemopreventative activity of dietary beta-escin on azoxymethane-induced colonic aberrant crypt foci (ACF) was evaluated in vivo.54 Rats were fed diets containing 0%, 0.025% or 0.05% beta-escin for 1 week. Treatment was then continued for 8 weeks after the addition of azoxymethane (15 mg/kg once weekly for 2 weeks). Both the 0.025% and 0.05% diets significantly suppressed total colonic ACF formation, up to around 40% (p<0.001) and 50% (p<0.0001), respectively, compared with the saline control. The same researchers observed that beta-escin induced cancer growth arrest in HT-29 human colon cancer cells at the G1-S phase, which was associated with induction of the cyclin-dependent kinase inhibitor p21.54

Dermatological activity

Contraction forces generated by non-muscle cells such as fibroblasts play important roles in determining cell morphology, vasoconstriction and/or wound healing. They can influence the morphology and mechanical properties of the skin, but few agents are known that can help generate such contraction forces. A screen of around 100 plant extracts found that horsechestnut extract induced the strongest contraction force in cultured human fibroblasts.55,56 A postulated mechanism was the formation of stress fibres accompanied by actin polymerisation.

Further to this, the effect of horsechestnut extract on various kinases involved in contraction force generation in fibroblasts was examined in vitro.57 Contraction forces induced in fibroblasts by stimuli such as lysophosphatidic acid and thrombin are accompanied by stress fibre formation, regulated by myosin light chain kinase and Rho kinase. Results suggested that horsechestnut extract produced force generation in fibroblasts via direct activation of Rho kinase through Rho protein, preceded by the formation of stress fibres.

Other activity

Horsechestnut extract demonstrated strong active oxygen-scavenging activity and protective activity in vitro against cell damage induced by active oxygen.58 HCSE (containing 70% escin) inhibited enzymatic and non-enzymatic lipid peroxidation in vitro and counteracted the deleterious effects of free radical oxidative stress in mice and rats (200 to 400 mg/kg, oral, and 25 mg/kg, iv, respectively).59

The inhibitory action of plant constituents on the activity of the connective tissue enzymes elastase and hyaluronidase were investigated in vitro. Saponin constituents from horsechestnut showed inhibitory effects on hyaluronidase. The
activity was mainly linked to escin and, to a lesser extent, its genin (aglycone). Triterpene saponins from horsechestnut (escin Ia, Ib, Iia and Iib) exhibited an inhibitory effect on ethanol absorption and a hypoglycaemic activity in the oral glucose tolerance test in rats. Saponins can inhibit absorption of small molecules that rely on transporter systems (see Chapter 2).

Beta-escin (15, 30 and 60mg/kg/day for 7 days, oral) was given to rats before induced ischaemia/reperfusion. Higher doses significantly decreased neurological deficit (p<0.05). Beta-escin potently inhibited caspase-3 activation and the release of cytochrome c, increasing the expression of Bcl-2 after cerebral ischaemia/reperfusion, supporting an inhibitory effect on apoptosis. Additional research by the same Chinese research group using a similar model of cerebral ischaemia/reperfusion injury identified that beta-escin (sodium salt) downregulated expression of adhesion molecules and subsequent migration of neutrophils and boosted antioxidant activity, while reducing infarct size and neurological deficit. Some years later, different Chinese investigators observed that escin (0.45, 0.9 and 1.8mg/kg/day for 3 days, iv) given post-ischaemia to mice improved learning and memory responses and reduced hippocampal injury relative to controls.

Beta-escin (1.0 to 6.0mg/kg/day, ip) exhibited potent anti-allergic activity and reduced airway inflammation in two mouse models. Its activity was comparable or superior to dexamethasone, a standard reference compound. An isolate from horsechestnut seeds rich in escin (100mg/kg/day for 5 weeks, oral) decreased leptin by 31.6% (p<0.05) in mice fed a high fat diet. Considerable variation was observed for the key pharmacokinetic parameters, leading the authors to suggest that these differences might be due to variations in the relative saponin concentrations from batch to batch (since escin is a complex mixture of many individual saponins). Hence the need was expressed for either specific validation of the RIA technique, or the use of an alternative analytical technology, to better understand the pharmacokinetics of this herb.

Studies indicate that escin is eliminated quickly following intravenous injection, with two-thirds excreted by the bile and one-third by renal elimination. Two studies of the bioavailability of beta-escin following oral doses of various horsechestnut preparations were conducted using healthy volunteers. Validated radioimmunosorbent assay (RIA) was used to determine levels of beta-escin in plasma. One study on two solid-dose preparations in 18 volunteers found a large variation in absorption parameters for beta-escin. Cmax after a dose containing 50mg escin varied from 0.19 to 45.1ng/mL, Tmax varied from 0.73 to 8.5h and the area under the curve (AUC, an assessment of concentration over time) varied from 24.6 to 389ng/h/mL. The second study, also of two solid-dose preparations (one sustained-release) and using 24 volunteers found more consistent results.

This may have been because a horsechestnut extract containing a defined dose of escin was used, rather than just escin alone. Parameters for the sustained-release tablet were superior. For example, after a dose containing 50mg escin, Cmax for the sustained-release tablet was 9.81±4.9ng/mL, Tmax was 2.23±0.9h and AUC averaged 187.1ng/h/mL. The half-life for both preparations was about 20h.

In a steady-state crossover study over 7 days in 18 healthy volunteers, the relative bioavailability of 100mg beta-escin after oral administration of an immediate release, enteric-coated test formulation of HCSE was evaluated against a sustained-release product. RIA was used for analysis. The two tested products were bioequivalent with Cmax around 16 to 18ng/mL for the first dose of the day (containing 50mg beta-escin) and 10 to 11ng/mL for the second, the difference apparently being due to food intake.

A review of the pharmacokinetic data published for HCSE up to 2000 identified five single- and four multiple-dose bioequivalence studies, including those reviewed above. Considerable variation was observed for the key pharmacokinetic parameters, leading the authors to suggest that these differences might be due to variations in the relative saponin concentrations from batch to batch (since escin is a complex mixture of many individual saponins). Hence the need was expressed for either specific validation of the RIA technique, or the use of an alternative analytical technology, to better understand the pharmacokinetics of this herb.

Since the review, the comparative bioavailability of beta-escin (from HCSE) was evaluated for two test products in two randomised, open label crossover trials using a multiple-dose treatment schedule in 18 healthy volunteers each. A normal and a sustained-release product were compared and shown to have similar bioavailability, as assessed using RIA. Peak serum concentrations were reached approximately 2 to 4h (Tmax) after dosing of 100mg of beta-escin and concentration/time profiles and steady-state concentrations were similar for the two formulations in both trials. Average Cmax concentrations ranged from 12 to 18ng/mL.

Saponins are large molecules containing highly polar groups and their intact bioavailability can be expected to be low after oral doses. This has been confirmed in all the above studies, since the pharmacokinetic parameters indicate absorptions of less than 1% of the administered oral dose of beta-escin. However, saponins can be hydrolysed by intestinal flora, leaving the less polar aglycone or sapogenin available for absorption. These sapogenins, or their hepatic metabolites, may in fact be the main active form of escin following oral doses. More studies are needed to clarify this issue.

Pursuing this line of reasoning, the effect of human intestinal bacterial enzymes on the biotransformation of escin Ia was examined, and structures of biotransformation products were determined in vitro. Escin Ia was incubated with crude enzymes or Lactobacillus brevis. Biotransformation products were isolated and structures determined by spectroscopic techniques. Results suggested that escin Ia is indeed a prodrug and was converted by both the enzymes and Lactobacillus. Biotransformation products included isoeiscin Ia, desacyleisin I, 21beta-O-tigloylprotoaescigenin and protoaescigenin. Of these, desacyleisin I showed inhibitory action on mouse sarcoma-180.

Pharmacokinetics

High concentrations of escin were measured in skin and muscle tissue underlying the site of topical application of radio-labelled sodium escinate, but low values were measured in internal organs, blood, urine, skin and musculature from other parts of the body. Between 0.5% and 1% of the applied dose was excreted in urine within 24h of administration. Total elimination (bile and urine) was calculated at 1% to 2.5% of the administered dose. Less than one half of this was excreted as escin, the remainder as metabolites. However, the true availability of escin to skin and muscle tissue may not be as high as reported in this study, since the radioactivity detected may have been carried by metabolites of escin, as well as by escin itself.

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tumour cell growth, hepatic carcinoma H(22) and lung carcinoma in vivo, thereby indicating biological activity.74

Clinical trials with escin

There are several early clinical studies where escin was mainly given by injection, for example to treat road accident victims with severe head injury. Here it reduced the dangerous rise in intracranial pressure, leading to a more favourable prognosis at iv doses of 10 to 20 mg/day.75 Escin has also been effective in the treatment of cerebral oedema following cranial fracture and cranial trauma (with or without retrograde amnesia), cerebral tumours, intracranial aneurysms, cerebral sclerosis, subdural haematoma, encephalitis, meningitis and cerebral abscess.76 Depending on the severity of the condition, disappearance of cephalgia, vertigo and general discomfort were observed within 3 to 16 days. Cerebral oedema due to acute vasomotor insufficiency was resolved quickly, while in chronic disease remission occurred slowly over a long period of administration.76 Other trials examined the value of intravenous escin during routine surgery. For example, in a placebo-controlled trial in patients undergoing surgery of the hand, iv administration of escin (20 mg/day) produced a fast reduction in postoperative inflammation and oedema.77 Oral escin was also used in some trials. For example a dose of 120 mg/day for up to 2 months markedly and significantly (p<0.01) improved symptoms, bleeding and swelling in an early, double blind, placebo-controlled trial involving 80 patients suffering from acute haemorrhoids.78 Recent studies on the clinical use of escin are as follows. The impact of escin was examined in patients experiencing cutaneous pruritus to test the traditional Chinese medicine theory that ‘wind’ should be treated by regulating blood disorder, and wind disappears after activating blood.79 A total of 51 patients were randomly divided into either an escin-treated group (n=30) or a loratadine-treated group (n=21) in an open label trial. The dose of escin was 300 mg twice daily for 4 weeks and that of loratadine 10 mg four times daily, both higher than average doses. After 4 weeks the effective treatment rate for escin and loratadine were 86.7% and 80%, respectively. No statistically significant difference was noted in total symptom scores, or specific scores of pruritus and lesion shape between the two groups (p>0.05). However, the score for lesion range was lower for the escin group compared with the loratadine group (p<0.05). The conclusion was that escin has a satisfactory effect in treating pruritus caused by ‘blood stasis and wind-dryness’. Note that, while this study refers to ‘escin’ as the treatment, the active agent might well have been HCSE (based on the incorrect attribution in other clinical studies from China of ‘escin’).

Following on from positive pharmacological studies (see earlier), an open label, controlled pilot trial was conducted in 64 abdominal surgery patients to assess the impact of escin (0.3 mg/kg, iv, immediately after surgery) on intestinal ileus.80 Times to first bowel sounds, passage of gas and defecation were all significantly less in the escin group, compared with a saline control treatment (p<0.01). Another pilot trial (of similar design, but undertaken by a different research team) in 72 postoperative colorectal cancer patients demonstrated a dose-response effect for escin (5, 15 and 25 mg, iv) on the above parameters, with the higher doses achieving statistical significance.80 A combination of oral escin (1250 mg/day) and the flavonoid derivative troxerutin (2250 mg/day) was assessed against the drug pentoxyphylline (600 mg/day) in 68 patients with inner ear perfusion disturbances.81 This 6-week, open label, controlled trial found that 23 of the 34 patients receiving the escin-troxerutin combination demonstrated a hearing increase of at least 10 dB, compared with only six of 34 in the drug control group (p<0.05).

The pathological mechanism involved in Bell’s palsy, the most common acute facial paralysis, is believed to involve inflammatory oedema and entrapment neuropathy. It has been postulated that the impact of beta-escin on local oedema and effusion suggests it could be a valuable treatment for Bell’s palsy.82

Topical use

Topical preparations containing escin have been successfully used for a variety of applications: treatment of oedema and haematoma in surgical practice,83 the prevention and treatment of sports injuries, including acute injuries, blunt injuries (non-penetrating wounds) and oedema.84-89 It has been used alone, or more typically in combination with heparin, buthephrin, diethylamine salicylate (DEAS) or polyunsaturated phosphatidylcholine in venous disorders (inflammation of veins, venous insufficiency, varicose veins),90-93 in combination with L-thyroxine for the treatment of hypertrophic scars, keloid scars, stretch marks and lymphoedema after mastectomy,94-96 and in combination with heparin and phospholipids for the treatment of joint and venous diseases.97-98 Anorectal varicose pathologies (particularly in gynaecology and obstetrics),99-101 postoperative treatment of episiotomies102 and during oral and periodontal surgery.103 Details of some more recent, larger and interesting studies follow.

In a randomised, double blind trial, 81 patients with contused traumas following limb injuries received treatment with a 2% escin and 5% salicylate gel or placebo gel for 9 days. Compared with placebo, the mobility of the injured extremity increased significantly in comparison to the uninjured extremity in those treated with the active gel (p<0.02). The circumferences of the lower extremities returned to almost normal (compared with the uninjured leg) in the treatment group, but remained unchanged in the placebo group. The active gel was also superior for reduction in lower leg swelling, subjective complaints and remission frequencies (p<0.05).104 A topically applied 2% escin gel was compared with a placebo in experimentally induced haematoma in a randomised, double blind trial. Efficacy was measured over 9 h after a single application of gel. The escin gel significantly reduced tenderness to pressure within 1 h and then at all other time points during the trial.105

The effect of topical escin on pain from blunt injuries caused by sports and leisure activities was examined in a double blind, placebo-controlled clinical trial.106 In all, 126 patients were randomly assigned to one of four groups: three active preparations (containing various amounts of escin, DEAS and sulphated escin) or a placebo. The gel was applied topically at 0, 4 and 8 h after injury and the variable measured was the pressure required at the centre of the lesion to elicit
a pain reaction at different time points up to 24 h after the injury. There was a significant difference observed for tenderness at 6 h (p = 0.0001) for all treatment groups compared with placebo, with similar findings after 24 h.

In a similar trial, the clinical efficacy and safety of an escin-containing gel was investigated on blunt impact injuries. Participants in various sports competitions were enrolled within 2 h of sustaining a strain, sprain or contusion and randomised to one of either two active treatment groups or a placebo group. Topical treatment occurred three times within a period of 8 h. The gels contained either 1% or 2% escin, together with 5% DEAS and heparin. A total of 156 patients were evaluated and results demonstrated that the active gels were significantly more effective than placebo at reducing tenderness (p = 0.0001 and p = 0.0002, respectively). Both active gel preparations produced more rapid pain relief than the placebo, as well as showing good safety and tolerability.

A proprietary escin-containing gel with 1% escin, 1% essential phospholipids and 10 000 IU sodium heparin has been developed for local treatment of venous and microcirculatory problems, sports injuries and varices in pregnancy. A review suggested that the gel is effective and safe, without contraindications or side effects. A series of small, placebo-controlled and somewhat repetitive clinical trials, all from the same research group, have observed benefits on microcirculation and other related parameters and symptoms in patients with venous hypertensive microangiopathy (with ulcers), diabetic microangiopathy and superficial vein thrombosis. Patient numbers ranged from 10 to 35 and treatment times varied from a single application to up to 8 weeks.

A few years later the same research team evaluated a similar topical escin plus phospholipids product, but without the heparin, in a series of four open label clinical trials involving patients with chronic venous insufficiency (hypertension). A 2-week trial in 15 patients compared with 15 normal controls found that the gel significantly increased transcutaneous oxygen levels (PO2) compared with baseline (p < 0.05). The three other 2-week tests tried the gel in similar patient numbers. Significant changes (p < 0.05) observed relative to baseline included improvements in skin flux (as measured by laser-Doppler flowmetry), plasma free radicals and transcutaneous carbon dioxide (pCO2).

**Clinical trials with horsechestnut**

**Chronic venous insufficiency**

Chronic venous insufficiency (CVI) is an imprecise term frequently referred to and not easily defined. It describes the impairment of venous return, usually from the legs, often with oedema and sometimes with stasis ulcers at the ankle. Other terms used are chronic deep vein incompetence, peripheral venous incompetence and chronic venous hypertension. According to more recent clinical, aetiological, anatomical and pathological elements, chronic venous disease has been classified into seven clinical classes, designated C0–6. These are defined as follows: C0: no visible sign of venous disease; C1: telangiectasia or reticular veins; C2: varicose veins; C3: oedema; C4a: pigmentation or eczema; C4b: lipodermatosclerosis; C5: healed ulcer; C6: active ulcer. Classes C4 to C6 have been designated as CVI. There have been a substantial number of clinical trials using various versions of HCSE in the management of CVI published over a time span of around 40 years. Most of these are reviewed below.

A meta-analysis of 16 trials was published in 2002. In all, 13 randomised, controlled trials (1051 patients) and three observational studies (10 725 patients) were identified as meeting the inclusion criteria (out of 75 studies located). Inclusion criteria included treatment of CVI with HCSE versus control (placebo or other therapies), duration of at least 20 days, and trials that permitted adequate data extraction. Examined objective outcomes were leg volume, ankle and calf circumference and oedema. Subjective outcomes were pain, sensation of tension, swelling, leg fatigue/heaviness, calf cramp and itching. Random and fixed effect models were used to pool outcomes and adverse events. Such models were applied separately for the randomised trials and the observational studies. Overall, results from the randomised trials indicated that HCSE improved signs and symptoms in patients with CVI. Leg volume was reduced by 46.4 mL compared with placebo (95% confidence interval (CI) 11.3 to 81.4) and likelihood of an improvement in leg pain was increased 4.1-fold (95% CI 0.98 to 16.8). Similarly, improvement probabilities were increased 1.5-fold (95% CI 1.2 to 1.9) for oedema and 1.7-fold (95% CI 0.01 to 3.0) for itching. Subjective improvement scores were transformed into a standardised scale before quantifying pooled effects (such as leg heaviness/fatigue and calf cramps). Treatment effects of HCSE were not as evident for these as the objective outcomes. Based on these results, the authors concluded that there is substantial evidence to support the efficacy, routine effectiveness and safety of HCSE in the treatment of CVI.

Subsequent to this analysis came the review from the Cochrane collaboration. This 2006 review was updated in 2010 with no changes to conclusions. Randomised, controlled clinical trials were included if they compared oral HCSE mono-preparations with placebo or a reference therapy in CVI. In all, 31 trials assessing HCSE in CVI were identified, including two unpublished trials, of which 17 met the inclusion criteria. Fourteen trials were excluded: two used topical application, eight assessed HCSE in combination with other active components, and four did not have appropriate clinical endpoints or were in healthy volunteers. Of the 17 trials included in the systematic review, 10 were placebo-controlled, two compared horsechestnut against treatment with compression stockings and placebo, four were controlled against a flavonoid derivative (beta-O-hydroxyethylrutoside) and one was controlled against pine bark extract. In all of the trials the extract was standardised to a defined level of escin and all the included trials bar one used a double blind design. Trials were scored for concealment of treatment allocation, where A = clearly concealed, B = unclear if concealed and C = clearly not concealed. Three trials scored A and the remaining 14 trials scored B. Methodological quality was evaluated using the scoring system developed by Jadad that measures the likelihood of bias inherent in a trial. The scale is from 1 to 5, where 5 denotes high quality with a low...
risk of bias. Nine of the 17 trials scored 4 or 5 and the average Jadad score for all the trials was 3.4. The majority of the included studies assessed clinical outcomes in terms of leg pain, oedema and pruritus. Other endpoints assessed included leg volume and circumference. For example, leg pain was assessed in seven placebo-controlled trials and six of these (543 patients) reported a statistically significant reduction (p<0.05) of leg pain using various measurement scales. Three other comparative studies reported no significant difference for horsechestnut extract relative to the reference treatments in terms of leg pain. Leg volume was assessed in seven placebo-controlled trials. Meta-analysis of six of these (502 patients) suggested a significant reduction in leg volume from HCSE versus placebo. One trial indicated that HCSE may be as effective as treatment with compression stockings. Adverse events were mild and infrequent. The evidence presented suggested that HCSE is an efficacious and safe short-term treatment for CVI. However, the authors noted that more and larger long-term trials are needed.

A brief summary follows of most of the clinical trials included in the above two studies.

In a double blind, placebo-controlled trial, 40 patients with leg oedema caused by chronic deep venous incompetence received either HCSE (738 to 824 mg/day, containing 150 mg escin) or placebo over 7 weeks. A significant reduction in average leg volume was observed for the treated group compared with placebo, both before and after an oedema provocation test (p<0.01). Leg pressure at rest was decreased (indicating better venous tone) and a pronounced alleviation of symptoms occurred in the treated group.124

A randomised, double blind, placebo-controlled trial assessed treatment with HCSE (600 mg/day, containing 100 mg escin) in 20 patients over a 4-week period. There was a significant improvement in volume changes of the foot and ankle (p=0.001) compared with the 20 patients treated with placebo. Symptoms such as oedema, pain, fatigue, feeling of tension and itching were also significantly improved (p<0.05). There were, however, no changes in venous capacity or calf muscle spasm.125

Seventy-four patients with CVI and lower leg oedema participated in a randomised, double blind, placebo-controlled trial. An anti-oedema effect was observed for those treated with HCSE (600 mg/day, containing 100 mg escin) over 8 weeks. Leg volume was reduced, while in the placebo group it increased. The progression of oedema was slowed in the treatment group, as were subjective symptoms.126 In a randomised, double blind, placebo-controlled, crossover trial involving 20 women with pregnancy-induced varicose veins or CVI, treatment with HCSE (containing 100 mg/day escin) for 4 weeks resulted in significant reduction in leg volume (p<0.01).127

The influence of HCSE (approximately 600 mg/day, containing 100 mg escin) for 4 weeks was tested in a randomised, placebo-controlled trial involving 30 patients with peripheral venous incompetence (CVI). Horsechestnut effected a reduction in leg circumference and improvement in subjective symptoms.128 In a double blind trial using the same dosage over 20 days involving 30 outpatients suffering from CVI, a significant reduction of leg circumference was demonstrated (p<0.05).129

One hundred and eighteen patients with varicose veins or CVI were treated for 40 days with 60 mg/day of HCSE (containing 70% escin) or placebo in a double blind trial. Significant improvements in symptoms (oedema, cramps, pain, fatigue, sensation of heaviness) were observed in the treated group (p<0.05).130 The dosage quoted for this trial is a low dose in comparison to the majority of trials conducted. Similar results were observed in a double blind, placebo-controlled, crossover trial (n=233) for patients treated with horsechestnut. Improvements were observed for oedema and pain (p<0.01), itchiness, fatigue and sensation of heaviness (p<0.05). Calf cramping, however, was not significantly improved.131

Treatment with HCSE (600 mg/day, containing 100 mg escin) for 2 weeks was superior to placebo in a trial in 20 pregnant women with oedema due to CVI. Significant reductions in oedema (p=0.009) and symptoms such as pain, fatigue and itching (p<0.05) were observed in the treatment group, and these patients also showed a greater resistance to oedema provocation. The trial was double blinded and crossover in design.132

In a randomised, partially blinded, placebo-controlled, parallel study published in The Lancet, 240 patients with CVI participated in a comparison of the efficacy of compression stockings class II with HCSE (600 mg/day, containing 100 mg escin) over 12 weeks. Lower leg volume decreased by a similar amount (43 to 47 mL) for both horsechestnut and compression therapy compared with placebo. A significant reduction in oedema was observed for horsechestnut (p=0.005) and compression (p=0.002) compared with placebo, and the two therapies were shown to be equivalent. Compression achieved high oedema reductions at the beginning of the study, while horsechestnut gradually decreased oedema volume, reaching a maximum by the end of the trial. (Patients allocated to compression treatment received a diuretic once daily during the first week of the trial to ensure the best possible stocking fit. Class II stockings provide a defined pressure.) Compliance was better for the herbal therapy.133

HCSE (720 to 824 mg/day, containing 150 mg escin) and beta-hydroxyethylrutinosides (2000 mg/day) both demonstrated an oedema-protective effect in a randomised, double blind trial involving 40 patients with CVI and peripheral venous oedema.134 In a multicentre, randomised, double blind trial, the comparative efficacy of oxerutins (beta-hydroxyethylrutinosides) and HCSE was investigated in 137 postmenopausal patients with grade II CVI. Patients received 600 mg/day of HCSE (containing 100 mg escin), 1000 mg/day of oxerutins for 12 weeks or 1000 mg/day of oxerutins for 4 weeks followed by 500 mg/day (of oxerutins) for 8 weeks. All treatments achieved a mean leg volume reduction of about 100 mL after 12 weeks of treatment, comparable to that achieved by compression therapy. A 6-week follow-up period without treatment indicated that both treatments also exhibited a substantial carry-over effect.135

HCSE (600 mg/day, containing 100 mg escin) was compared with a proprietary French maritime pine bark extract (360 mg/ day) in an open, controlled, comparative study in 40 patients over 4 weeks. Outcomes assessed were the circumference of lower legs and the subjective symptoms of pain, cramps, nighttime swelling, feeling of heaviness and reddening of the skin.
HCSE moderately (but not statistically significantly) reduced the circumference of the lower limbs and marginally impacted subjective symptoms compared to baseline, but was inferior to pine bark. Both treatments were well tolerated.\textsuperscript{136}

A previously unpublished study by Diehm and Schmidt from 2000 was reported by other authors in 2001.\textsuperscript{137} This was a 16-week, three-arm, randomised, double blind trial where HCSE (containing 100 mg/day escin) was compared with placebo or compression stockings in 355 patients with CVI. The drop-out rate was high at 69 patients. From intention-to-treat analysis, compression was significantly superior to placebo (p<0.001), whereas HCSE was not (p=0.115). Only in the per-protocol population (286 patients) did HCSE also demonstrate significance against placebo (p=0.018) for this parameter. Subjective symptoms favoured HCSE over compression, but the difference between the two treatments did not reach statistical significance.

Other published studies of interest that were not covered by, or were specifically excluded from, the Cochrane systematic review are discussed below.

HCSE (600 mg/day, containing 100 mg escin, for 3 weeks) significantly reduced subjective symptoms of patients with varicose veins (p<0.001) in a double blind, placebo-controlled trial.\textsuperscript{138} The impact of a single dose of HCSE was investigated in a randomised, double blind, placebo-controlled trial involving 22 patients with proven CVI. Three hours after taking 600 mg of horsechestnut extract (containing 100 mg escin), a significant decrease in the capillary filtration coefficient (22\%) was observed in the treated group.\textsuperscript{139}

In a case observation study involving more than 800 German general practitioners, more than 5000 patients with CVI were treated with HCSE and followed up at regular intervals. All the symptoms investigated (pain, tiredness, tension, swelling in the leg, itching and tendency towards oedema) improved markedly or completely disappeared. Horsechestnut extract was considered an economical, practice-relevant therapeutic tool which, in comparison with compression therapy, had the additional advantage of better compliance.\textsuperscript{140} In a postmarketing surveillance study, 1183 patients with CVI received the recommended dosage of HCSE over a 5-month period. A clear reduction in the objective and subjective symptoms was demonstrated.\textsuperscript{141}

A proprietary fresh plant extract of horsechestnut seed, available as an oral tincture, tablets and a topical gel was reviewed for its efficacy in CVI and varicose veins.\textsuperscript{142} Five clinical trials were reviewed, of which only one was randomised and placebo-controlled. The trial details were as follows. A daily dose of fresh plant tincture containing 39 mg escin was given to 40 patients with CVI in a prospective, uncontrolled, multicentre trial over 4 weeks. In all, 77\% of patients demonstrated a clinically relevant therapeutic result in terms of global efficacy, and more than 60\% of patients rated the treatment as ‘good’ to ‘very good’ for subjective symptoms such as leg swelling and pruritus. Tablets delivering 120 mg/day escin were examined in 60 patients with CVI in a randomised, placebo-controlled, multicentre, double blind trial. The primary outcome was changes in the circumference of the leg measured just above the ankle, and the treatment group achieved a clinically relevant, statistically significant reduction compared with placebo (p<0.05). A tablet dose containing 100 mg/day escin was assessed in 87 patients with CVI in an open trial design. The primary assessment variable was safety. Fifty-seven of the 87 patients reported 91 adverse events; all were non-serious and only four were judged to be actually from the trial medication. A gel containing 2\% escin was evaluated in 71 CVI patients in an open, uncontrolled, multicentre trial over 6 weeks. The primary trial outcome of ankle circumference decreased significantly (p<0.001). The fifth trial assessed tablets (60 mg/day escin) and the gel in 39 patients with varicose veins in an open, uncontrolled trial over 8 weeks. Trial outcomes were both subjective (by a visual analogue scale) and objective (reduction in ankle oedema). A significant improvement in heaviness and pain in the legs and blue discoloration was observed (p<0.0003) and a moderate rating was given by both therapists and patients for efficacy/satisfaction and tolerability.

**Chronic venous ulceration**

Fifty-four patients with venous leg ulcers were randomly assigned to treatment with HCSE tablets (containing 150 mg/day escin) or placebo in a parallel, triple blind, multicentre trial over 12 weeks.\textsuperscript{143} Assessment of ulceration was performed at 0, 4, 8 and 12 weeks using a wound assessment tool and the Alfred/Medseed Wound Imaging System. Primary outcomes measured were the number of healed leg ulcers, the change in wound surface area, depth, volume, pain and exudate. These variables were found not to be statistically significant between the treatment group and placebo. However, HCSE did have a significant effect on the percentage of wound slough over time (p=0.045) and the number of dressing changes at week 12 (p=0.009). Any assessable impact on the primary trial outcomes was limited by the small size of the trial.

The authors also conducted a 12-week cost–benefit analysis using the data from the above trial.\textsuperscript{144} The cost of HCSE, dressing materials, travel, staff salaries and infrastructure for each patient was taken into account. HCSE therapy combined with conventional therapy was found to be more cost-effective than conventional therapy alone, with an average saving of AUD 95 in organisational costs and AUD 10 in dressing materials per patient.

**Deep vein thrombosis**

A controlled trial involving 4176 patients with thrombosis, pulmonary infarction or pulmonary embolism investigated horsechestnut as a prophylactic treatment for thrombosis and embolism arising from surgery over a 3-year period. Patients received an intravenous injection of horsechestnut extract (10 mL/day), strophanthin or digitalis, vitamin B complex and vitamin C or a similar injection without the horsechestnut extract for 4 days prior to surgery and continuing for up to 7 days after the operation. Horsechestnut significantly reduced the incidence of deep venous thrombosis following surgery compared with the control group (p=0.01; other patients: p<0.001). It would be valuable to conduct a randomised, controlled trial of oral HCSE to assess its impact on this problem.
Topical use
A gel containing horsechestnut extract and heparin was found to be effective in the treatment of acute and chronic traumas and venopathies in an uncontrolled study. In particular, the gel quickly broke down haematomas. The tolerability and efficacy of a topical horsechestnut preparation were assessed in 15 patients with first- and second-degree CVI. The horsechestnut preparation contained 1.4% triterpene glycosides calculated as escin and was compared with a preparation containing heparin. Efficacy was assessed by the change in circumference of the lower, middle and upper leg and by changes in symptoms. Both treatments were well tolerated and the horsechestnut preparation showed a greater tendency to improvement than heparin. The effect of topical horsechestnut was investigated for its impact on skin ageing, based on pharmacodynamic studies suggesting the herb increased contraction forces in fibroblasts (see earlier). Clinical testing was carried out in 40 healthy women using a double blind, placebo-controlled design. The gel (containing 3% horsechestnut extract) was applied twice daily to the periphery of the eye for a total of 9 weeks. Outcomes were evaluated by visual scoring by a specialist, based on photo scales. The active gel showed significant wrinkle-smoothing efficacy at the corner of the eye and the lower eyelid compared with placebo (p < 0.05 and p < 0.001, depending on the site). Six weeks of treatment was deemed sufficient to have a significant wrinkle-smoothing effect.

Other uses
The impact of HCSE (containing 60 mg/day escin) on sperm quality was assessed against surgery or a control treatment (20 mg of vitamin E, together with 400 mg pentoxyphylline and 50 mg clomiphene) in an open label trial involving 219 patients with varicocele-associated infertility. Both surgery and HCSE were equally effective, and significantly superior to the control treatment, in terms of sperm density (p < 0.05). However, only surgery was significantly better than the control treatment in terms of sperm motility (p < 0.05). Patients with mild or moderate disease appeared to respond better to the HCSE treatment. Adverse effects were mild and infrequent.

The addition of HCSE to HIV treatment with indinavir was examined for its effect on delaying indinavir precipitation in urine, thereby preventing indinavir-associated nephrolithiasis. This pilot clinical trial was multicentre, randomised open label and controlled, with four crossover periods each of 4 weeks. One group of patients (n=22) received HCSE during the second and third treatment periods, the second (n=25) received HCSE during the first and fourth treatment periods. The dose used was 50 mg escin every 12h (from 300 mg of HCSE) in combination with highly active antiretroviral activity (HAART). Thirty patients out of the 47 enrolled completed the study. Urine samples were collected at the end of each 4-week period and tested for indinavir crystallisation. The mean time to crystallisation averaged 14.7 min with HCSE and 9.9 min without (p = 0.008). Urine and plasma concentrations of indinavir were unaffected by HCSE and no adverse effects were experienced.

These data demonstrate that horsechestnut seed extract has low oral toxicity. The substantially higher toxicity after ip or iv administration is probably a reflection of the low oral bioavailability of escin as such and its haemolytic activity.
No toxic effects were observed on the behaviour, growth, food consumption, haematological and biochemical tests or organ histology of rats fed horsechestnut seed extract at doses of 100 to 400 mg/kg/day for 34 weeks. The only toxic effect observed in dogs orally administered the extract (20 to 80 mg/kg/day, 5 days per week) for the same time period was vomiting in the highest dosage group at 8 weeks. This was eliminated by the use of enteric-coated tablets. No toxic effects were observed in rats after daily intravenous injection of 9 mg/kg of extract for 8 weeks. Lesions were primarily observed in the kidneys after administration of acutely toxic oral and intravenous doses.4

Oral administration of the sodium salt of escin (10 mg/kg, 70 mg/kg) to rats did not induce fatty degeneration of the liver.152 Intraperitoneal administration of escin (10 mg/kg) to juvenile male rats did not affect fertility or cause renal toxicity.153 Toxic effects in rodents following intravenous injection of high doses of escin were due to massive haemolysis. In contrast, continuous administration of escin (1.1 mg/kg/day) for 1 month was associated with minimal haemolysis in rabbits, only detectable by increased erythropoiesis.10,154 The route of administration was not clearly specified. However, as the dose was one-fifth of the LD50 of escin, it was probably administered by injection.

Horsechestnut seed extract demonstrated weak mutagenic activity in the Ames test in vitro. It was suggested that this effect might be due to the flavonoid quercetin.155 The potential genotoxicity of quercetin has been extensively studied and the results have been interpreted as being not relevant to human intake (see also Chapter 2).156

Contraindications

Because of the irritant effect of the saponins, horsechestnut should not be applied to broken or ulcerated skin. Do not use during pregnancy or lactation without professional advice.

Special warnings and precautions

Saponin-containing herbs are best kept to a minimum in patients with pre-existing cholestasis.

Interactions

A case of acute renal insufficiency after therapy with escin and the antibiotic gentamicin has been reported.157 (It is likely that the escin was administered by injection.) High doses of intravenous escin have been implicated in acute renal failure.158 (See the Overdosage section below.) Escin is a saponin that can cause haemolysis after injection. The liberated haemoglobin can deposit in the kidneys and cause renal failure. The risk of haemolysis after oral intake of horsechestnut is minimal because of the low absorption of saponins.

In vitro testing found that horsechestnut is quite a weak inhibitor of CYP3A4, which is unlikely to have clinical significance.159 It was also moderately active at inhibiting P-glycoprotein activity in vitro, a finding of uncertain clinical relevance.

Use in pregnancy and lactation

Category B3 – no increase in frequency of malformation or other harmful effects on the fetus from limited use in women. Evidence of increased fetal damage in animal studies exists, although the relevance to humans is unknown.

Standardised horsechestnut seed extracts have been successfully used in clinical studies127,132,138,160 to treat venous conditions in pregnant women at dosages of 600 mg/day (containing 100 mg escin) for 2 to 4 weeks. Some of these studies excluded women in the third trimester of pregnancy.127,132

Intravenous administration of standardised horsechestnut seed extract (9 and 30 mg/kg/day) to rats (days 6 to 15 gestation) and rabbits (days 6 to 18 gestation) did not result in teratogenicity or embryotoxicity. The same results were demonstrated in rats (100 and 300 mg/kg/day) and rabbits (100 mg/kg/day) after oral administration. Although no teratogenic effects were observed in rabbits orally administered very high doses of extract (300 mg/kg/day), fetal body weights were significantly reduced compared to controls.4

Horsechestnut is compatible with breastfeeding but caution should be exercised.

Effects on ability to drive and use machines

No adverse effects expected.

Side effects

A 2002 meta-analysis of adverse reactions found no significant difference between horsechestnut seed extract and placebo.121 Meta-analysis of three post-marketing surveillance studies, which included 10 725 patients, found an average of 1.51% of patients treated with horsechestnut seed extract reported mild adverse reactions.21 From 1968 until 1989 nearly 900 million individual doses of one brand of standardised horsechestnut seed extract were prescribed. In that time, only 15 patients reported significant side effects.160 Fourteen studies in the Cochrane review provided information on adverse events, which were usually mild and frequent. Gastrointestinal symptoms, dizziness, nausea, headache and pruritus were reported as adverse events in six studies. Four studies reported no adverse events and another four studies reported a good tolerability for the herbal treatment. The reviewers concluded that HCSE is a safe and effective treatment option for CVI and, according to available data, the risk/benefit ratio for treatment of CVI is positive.122

A case has been reported in Japan where pruritus, jaundice, elevated liver enzymes, liver cholestasis, centrilobular necrosis and mild eosinophilia developed 60 days after intramuscular injection of a product for pathological bone fracture containing horsechestnut extract. Drug-induced hepatic injury was suspected.162 The product has been in use in Japan since 1967 and only mild side effects such as nausea, vomiting, urticaria and, rarely, spasm and shock have otherwise been reported.162,163
A case of occupational asthma was reported where a 57-year-old man employed in the pharmaceutical industry developed bronchial asthma while working with products, including escin. Various tests were performed and other products eliminated, confirming escin as the causative factor. Characteristics of the asthma were suggestive of a non-IgE immunological mechanism, although an irritative mechanism secondary to long-term, low-level exposure could not be ruled out.164

Cases of pseudo-lupus (an autoimmune syndrome) after use of a product containing phenopyrazone, horsechestnut extract and cardiac glycosides have been reported.165 The ingredient or ingredients responsible for this reaction were not established. Urticaria and dyspnoea have been reported after the topical application of escin.10,166

As with all saponin-containing herbs, oral use may cause irritation of the gastric mucous membranes and reflux. However, the gastric irritation and reflux can be avoided by the use of enteric-coated preparations. Because of the irritant effect of the saponins, horsechestnut should not be applied to broken or ulcerated skin. Saponins and sapogenins in the bloodstream cause haemolysis but this effect is negligible at the oral doses used.

Overdosage

Very high doses will result in gastrointestinal irritation. If sufficient quantities of escin are absorbed through damaged or irritated gastrointestinal mucous membranes, haemolysis with associated kidney damage could possibly result.

Cases of acute renal failure have been reported which were suspected to have been caused by escin (510 to 540 μg/kg) administered intravenously for postoperative oedema.153,158

However, in trials designed to assess the effects of intravenous escin on renal function, no signs of impaired renal function developed in patients with normal renal function, and renal function did not worsen in patients with pre-existing renal impairment. Adults received intravenous escin (10 to 25 mg/day) for 3 to 10 days and two children with normal renal function were prescribed 0.2 mg/day for 3 to 10 days and two children with normal renal function did not worsen in patients with pre-existing renal impairment.10,166

In the USA, an analysis of 3099 cases of human exposure to plant parts from eight different Aesculus spp. from 1985 to 1994 found that no effect or a non-toxic effect was recorded in 76.6% of cases. Most exposures (49.2%) occurred in children aged 0 to 5 years. Analysis of the 1993 to 1994 subset (571 cases) found that no cases of serious toxicity were reported and gastrointestinal symptoms occurred in only 5% of cases.167

Safety in children

Poisonings in children due to the ingestion of horsechestnut seeds or infusions made from the leaves and twigs have been reported, including fatalities.168 However, in an analysis of human exposures to Aesculus spp. which included 1527 children aged 0 to 5 years, serious toxicity was not reported and no effect or a non-toxic effect occurred in the majority of cases.167 Cases of toxicity in children attributed to horsechestnut seed might have actually resulted from ingestion of the seed capsule (pericarp).

Regulatory status in selected countries

A draft monograph of horsechestnut is being prepared for the European Pharmacopoeia.169,170

Horsechestnut seed is covered by a positive Commission E monograph and can be used to treat symptoms of venous disorders and chronic venous insufficiency, such as pain and a feeling of heaviness in the legs, night cramps, itching and swelling.

Horsechestnut is included in the UK General Sale List. Horsechestnut products have achieved Traditional Herbal Registration in the UK with the traditional indication of relief of symptoms associated with CVI and varicose veins such as tired heavy legs, pain, cramps and swelling.

Horsechestnut does not have GRAS status. However, it is freely available as a ‘dietary supplement’ in the USA under DSHEA legislation (1994 Dietary Supplement Health and Education Act).

Horsechestnut is not included in Part 4 of Schedule 4 of the Therapeutic Goods Act Regulations of Australia and is freely available for sale.

References

PART THREE

Materia Medica


