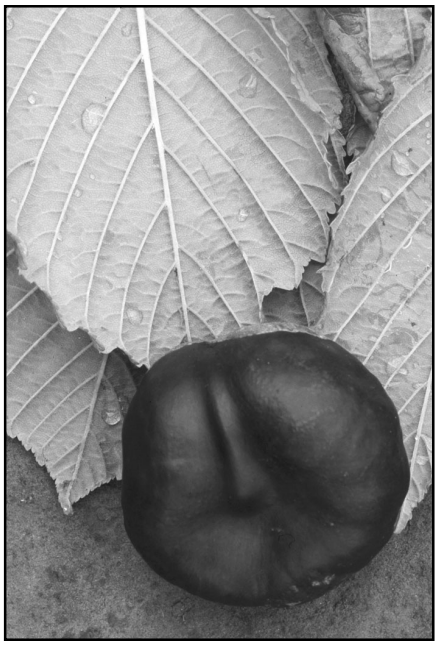
Horse Chestnut

Aesculus hippocastanum L.

[Fam. *Hippocastanaceae*]

Overview

Horse chestnut seed extract (HCSE) is relatively new to the U.S. botanical market. This phytomedicine is gaining popularity due to the high quantity of clinical evidence from Europe documenting its safety and efficacy as a treatment for varicose veins, chronic venous insufficiency (CVI), and related vascular disorders. Europeans have used HCSE for these conditions since the late 16th century. Horse chestnut seeds can be toxic when unprocessed and are unrelated to sweet chestnuts (*Castanea sativa*), which can be eaten without precautions. Standardized and purified preparations of horse chestnut seeds are available.



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Primary Uses

Internal

- Venous insufficiency (chronic)
- Varicosis, lower veins

External

- Blunt traumas, especially painful hematomas, post-traumatic and postoperative soft tissue swelling
- Injuries with hematomas
- Symptoms associated with varicose veins such as swollen legs (edema), pain and heaviness in the legs, and calf pain

Other Potential Uses

- Severe cranio-cerebral trauma
- Prevention and treatment of postoperative edema
- Traumatic head injury, intracranial pressure, and edema
- Hemorrhoids
- Leg ulcers

Pharmacological Actions

Antiedemic; reduces transcapillary filtration; venoactive effect.

Dosage and Administration

Internal

There is little information about the long-term, internal use of horse chestnut. However, in one clinical trial, horse chestnut was given for 56 weeks without adverse effect.

TINCTURE: 20–30 drops (0.5–0.7 ml), with water at mealtimes, 3 times daily [1:2.6 (*w/v*), 65 vol.-% alcohol].

DRY EXTRACT FROM DRIED SEED (standardized): 250–312.5 mg, 2 times daily with meals, in delayed-release form corresponding to 100 mg escin daily [5–8:1 (*w/w*), 16–20% triterpene glycosides].

DRY EXTRACT FROM FRESH SEED (standardized): 2 enteric coated tablets containing 63–90 mg dry native extract each, 3 times daily with water, at mealtimes, corresponding to 120 mg escin daily [5.0–6.1:1 (*w/w*)]. After 1–2 weeks reduce to 1 tablet, 3 times daily.

NOTE: Unprocessed horse chestnut seeds should not be eaten or made into tea because they contain toxins, including esculin, which are removed in processing.

External

There are no external horse chestnut preparations available in the U.S. at this time.

Contraindications

Internal

Not generally recommended for children or for individuals with chronic renal failure. However, an authoritative clinical review found no clinical basis for contraindications.

External

The gel or ointment should not be applied to broken or ulcerated skin. HCSE is contraindicated in cases of thrombosis or risk of embolism and for application to open wounds or mucous membranes.

PREGNANCY AND LACTATION: There are no known restrictions during pregnancy or lactation. HCSE has been used in some clinical studies involving pregnant women, with some studies excluding those in the third trimester.

Adverse Effects

Rare adverse effects include pruritus, nausea, gastric complaints, and irritation of the gastric mucous membranes and reflux. Escin Ib isolated from horse chestnut might partially delay or even inhibit gastric emptying. This potential adverse effect can be minimized by taking the extract in an enteric-coated tablet form with the main meal. Anaphylactic shock, toxic nephropathy, and renal failure have been reported following intravenous administration of isolated escin, but these reactions are not associated with oral ingestion of HCSE preparations. One case of horse chestnut-related contact dermatitis has been reported, but this does not pertain to the oral dosage form.

Drug Interactions

Horse chestnut extracts or derivatives, specifically escin, may interfere with the effects of anticoagulants. Escin, the main saponin component in horse chestnut, binds to plasma protein and may affect the binding of other drugs (speculative).

Clinical Review

Out of 23 clinical studies on horse chestnut that included a total of 4,339 participants, all of the 20 studies investigating its use in venous disorders demonstrated positive effects. Of the venous disorder studies, 4 were randomized, double-blind, placebo-controlled (R, DB, PC), parallel group (PG) studies, 5 were R, DB, PC, cross-over studies, 4 were R, DB, comparison, PG studies, one was a R, PC, single-blind design, another was a DB, PC, multicenter study, one was an uncontrolled, multicenter study with 71 participants, one was DB design, and three were surveillance studies. The main outcome measure for most studies was reduced leg volume or ankle circumference.

A systematic review of 13 R, DB clinical trials from 1976–1996 involving nearly 1,100 patients using HCSE in the treatment of venous disorders concluded that HCSE was superior to placebo. HCSE was as effective as rutosides (the conventional treatment) in five studies. Adverse effects were mild and infrequent.

A randomized, cross-over study found bioequivalence (phytoequivalence) in two different forms of HCSE. A R, DB, PC study of 70 subjects using HCSE topical gel showed significant reduction in tenderness with experimentally induced hematomas. Subjects with severe cranio-cerebral trauma regained consciousness more quickly and experienced reduced intracranial pressure with purified escin i.v., followed by HCSE tablets, compared to placebo.

Horse Chestnut

Aesculus hippocastanum L.
[Fam. *Hippocastanaceae*]

Overview

Horse chestnut is relatively new to the U.S. herbal products market. However, it is gaining popularity because of numerous clinical studies showing that it is safe and effective for treating varicose veins, inadequate vein strength, and related disorders.

Uses

Venous insufficiency (chronic); varicose veins (legs); symptoms associated with varicose veins such as swollen legs, pain and heaviness in legs, and calf pain; injuries with hematomas (bruises).

Dosage

Internal

DRY EXTRACT FROM DRIED SEED (standardized to 16–20% triterpene glycosides): 250–312.5 mg, 2 times daily, equivalent to 100 mg escin daily.

DRY EXTRACT FROM FRESH SEED (standardized): 2 tablets containing 63–90 mg, 3 times daily, equivalent to 120 mg escin daily. After 1–2 weeks reduce to 1 tablet, 3 times daily.

NOTE: Unprocessed horse chestnut seeds should not be eaten or made into tea because they contain toxins, including esculin, which are removed in processing.

External

There are no external horse chestnut preparations available in the U.S. at this time.

Contraindications

Consult with a healthcare provider before giving oral preparations to children or individuals with chronic kidney failure. The gel or ointment should not be applied to mucous membranes, or broken or ulcerated skin. Consult with a healthcare provider before giving preparations in cases of thrombosis (clots) or risk of embolism.

PREGNANCY AND LACTATION: None known.

Adverse Effects

Rare adverse effects can include pruritus (severe itching), nausea, stomach complaints, irritation of the stomach's lining, and reflux. An isolated horse chestnut seed chemical, escin Ib, might partially delay or even inhibit emptying of the stomach. This possible adverse effect can be minimized by taking the extract in an enteric-coated tablet form with the main meal. In one case report, horse chestnut was linked to contact dermatitis (red, itchy skin), but this did not involve oral preparations (e.g., capsules, tablets).

Drug Interactions

The effects of anticoagulant (blood-thinning) drugs may be increased by certain components of horse chestnut, specifically escin.

Comments

When using a dietary supplement, purchase it from a reliable source. For best results, use the same brand of product throughout the period of use. As with all medications and dietary supplements, please inform your healthcare provider of all herbs and medications you are taking. Interactions may occur between medications and herbs or even among different herbs when taken at the same time. Treat your herbal supplement with care by taking it as directed, storing it as advised on the label, and keeping it out of the reach of children and pets. Consult your healthcare provider with any questions.

AMERICAN BOTANICAL COUNCIL

Horse Chestnut

Aesculus hippocastanum L.

[Fam. *Hippocastanaceae*]

Overview

Europeans have used horse chestnut seeds for medicinal purposes since at least the late 16th century when the plant was introduced into Northern Europe from the Near East (Blumenthal *et al.*, 2000; McCaleb *et al.*, 2000). Extracts from horse chestnut seeds were used in France in the early 1800's. Publications from 1896 to 1909 report success in its use for hemorrhoids (Schulz *et al.*, 2000). Although horse chestnut seed extract (HCSE) is relatively new to the U.S. botanical market, it is gaining in popularity due to the significant quantity of clinical evidence from Europe documenting its safety and efficacy as a treatment for varicose veins, chronic venous insufficiency, and related vascular disorders. Horse chestnut seeds can be toxic when unprocessed and are unrelated to sweet chestnuts (*Castanea sativa*), a plant in the family *Fagaceae*, which can be eaten without precautions (McCaleb *et al.*, 2000). Standardized and purified preparations of horse chestnut seeds are available. HCSE is the most widely prescribed oral remedy for venous edema in Germany (Schulz *et al.*, 2000).

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Description

Horse chestnut preparations produced from the dried seed of *Aesculus hippocastanum* L. [Fam. *Hippocastanaceae*], containing not less than 3% triterpene glycosides, calculated as anhydrous escin (also spelled aescin), with reference to the dried seed (DAB, 1999). HCSE is a dry extract manufactured from German pharmacopeia-grade horse chestnut seed and is normalized to contain no less than 16%, and no more than 20%, triterpene glycosides, calculated as anhydrous escin (DAB, 1999). The typical drug-to-extract ratio for the native dry extract falls within the range of 5–8:1 (*w/w*), depending on the chemical composition of the starting material, and the subsequent yield of soluble extractive (Blumenthal *et al.*, 2000).

Primary Uses

Internal

- Venous insufficiency, chronic (Geissbühler and Degenring, 1999; Shah *et al.*, 1997; Diehm *et al.*, 1996; Rehn *et al.*, 1996; Diehm *et al.,* 1992; Erler, 1991; Pilz, 1990; Steiner, 1990; Steiner and Hillemanns, 1990; Erdlen, 1989; Kalbfleisch and Pfalzgraf, 1989; Rudofsky *et al.,* 1986; Lohr *et al.*, 1986; Bisler *et al.*, 1986)

  NOTE: The German Commission E also approved HCSE for venous insufficiency, usually of the legs, including pain and sensation of heaviness in the legs, nocturnal systremma (cramps in the calves), pruritus, and swelling of the legs (Blumenthal *et al.*, 1998)
- Varicosis, lower veins (Kreysel *et al.*, 1983; Friederich *et al.,* 1978; Neiss and Böhm, 1976)

External

- Blunt traumas, especially painful hematomas, post-traumatic and postoperative soft tissue swelling (Schilcher, 1997)
- Injuries with hematomas (Calabrese and Preston, 1993)
- Symptoms associated with varicose veins, such as swollen legs (edema), pain and heaviness in the legs, and calf pain (Morant and Ruppanner, 2001)

Other Potential Uses

- Severe cranio-cerebral trauma (Put, 1979)
- Prevention and treatment of postoperative edema (Reynolds *et al.*, 1989)
- Traumatic head injury, intracranial pressure, and edema (McCaleb *et al.,* 2000)
- Hemorrhoids (Mills and Bone, 2000)
- Leg ulcers (Weiss and Fintelmann, 2000)

Dosage

Internal

Crude Preparations

TINCTURE: 1:2.6 (*w/v*), 65 vol.-% alcohol, adult dose 20–30 drops (0.5–0.7 ml), with water at meal times, 3 times daily (Morant and Ruppanner, 2001).

Standardized Preparations

DRY EXTRACT FROM DRIED SEED: 5–8:1 (*w/w*), 16–20% triterpene glycosides: 250–312.5 mg, 2 times daily in delayed-release form, corresponding to 100 mg escin daily. One dose in the morning and another in the evening, with ample liquids during meals (Blumenthal *et al.*, 1998).

DRY EXTRACT FROM FRESH SEED: 5.0–6.1:1 (*w/w*), adult dose: 2 enteric coated tablets containing 63–90 mg dry native extract each, 3 times daily taken with water at mealtimes, corresponding to 120 mg escin daily. After 1–2 weeks reduced to 1 tablet, 3 times daily (Morant and Ruppanner, 2001).

PURIFIED ESCIN (intravenous preparation in the form of sodium escinate): 5.1 mg sodium escinate, 1–2 times daily, maximum adult dose: 20 mg (Reynolds *et al.*, 1989; Weiss, 1988); children 3–10 years: 0.2 mg/kg body weight, infants up to 3 years: 0.1mg/kg body weight (Weiss, 1988) (not available in the U.S.).

NOTE: Unprocessed horse chestnut seeds should not be eaten or made into tea because they contain toxins, including esculin, which are removed in processing (McCaleb *et al*, 2000).

External

Standardized Preparations

GEL: 1 g contains 54–177 mg dry extract standardized to 2% escin. Applied to affected area 2 times daily (Morant and Ruppanner, 2001).

OINTMENT: Contains aqueous extract. Applied to affected area. The type of ointment base contributes to efficacy, as does the use of occlusive dressings (Schilcher, 1997).

Purified Escin Preparation

ESCIN GEL NRF: 23.1 (*Aescini mucilago*), 1% water-soluble escin, a thin layer applied to skin, several times daily as needed. Not for use on open wounds (NRF 3, 1986) (not available in the U.S.).

DURATION OF ADMINISTRATION

Internal

There is little scientific information about the long-term use of horse chestnut; however, one clinical trial administered horse chestnut for 56 weeks without adverse effect (Put, 1979). HCSE is widely used for long-term therapy in German clinical practice, without reports of adverse events (Schulz *et al.*, 2000).

CHEMISTRY

Horse chestnut seed contains 3–6% of a complex mixture of triterpenoid saponins collectively referred to as escin (aescin) (Morgan and Bone, 1998), including the triterpene oligoglycosides escins, Ia, Ib, IIa, IIb, and IIIa (Yoshikawa *et al.,* 1996); the acylated polyhydroxyoleanene triterpene oligoglycosides escins IIIb, IV, V, and VI, and isoaescins Ia, Ib, and V (Yoshikawa *et al.*, 1998); 0.2–0.3 % flavonoids (Wagner, 1967), including flavonol oligosaccharides (Hübner *et al.*, 1999); coumarin derivatives (esculetin and esculin) (Fugmann *et al.*, 1997); sterols (stigmasterol, α-spinasterol, and β-sitosterol); and fatty acids (linolenic, palmitic, and stearic acids) (Leung and Foster, 1996). The sapogenols hippocaesculin and barringtogenol-C are produced by hydrolysis (Konoshima and Lee, 1986).

PHARMACOLOGICAL ACTIONS

Human

Anti-edemic (Geissbühler and Degenring, 1999, Shah *et al.,* 1997, Diehm *et al.*, 1996); reduces transcapillary filtration (Blumenthal *et al.*, 1998; Schilcher, 1997); venoactive (BHP, 1996).

Animal

Anti-edemic (Guillaume and Padioleau, 1994); improved vein compliance; inhibits vasodilation (Guillaume and Padioleau, 1994); anti-inflammatory (Guillaume and Padioleau, 1994; Matsuda *et al.*, 1997; Tsutsumi and Ishizuka, 1967); antioxidant (Bombardelli and Morazzoni, 1996); diminished cutaneous capillary hyperpermeability (Guillaume and Padioleau, 1994); isolated escin demonstrated anti-exudative and vasoconstricting effects (Blumenthal *et al.*, 1998).

In vitro

Antitumor (Konoshima and Lee, 1986); isolated hippocaesculin and barringtogenol-C-21-angelate have antitumor activity (Chandler, 1993; De Meirsman and Rosselle, 1980); isolated escin, and to a lesser extent escinol, inhibits activity of hyaluronidase (Facino *et al.*, 1995); antioxidant (Bombardelli and Morazzoni, 1996); anti-inflammatory and immunomodulatory (Brokos *et al.*, 1999).

MECHANISM OF ACTION

Human

- HCSE reduced lysosomal enzyme activity (Kreysel *et al.*, 1983) elevated in chronic pathological conditions of the veins, thereby preventing breakdown of glycocalyx (mucopolysaccharides) in the region of the capillary wall. Through a reduction of vascular permeability, the filtration of small molecule proteins, electrolytes, and water into the interstitium is inhibited (Blumenthal *et al.*, 1998).
- Inhibited experimentally induced leg edema in patients with chronic venous insufficiency by reducing transcapillary filtration (Pauschinger, 1987).

In vitro

- Decreased free radical generation by granulocytes, thereby indicating potential anti-inflammatory activity (Brokos *et al.*, 1999).
- Inhibited lipid peroxidation *in vitro* (Guillaume and Padioleau, 1994).
- Lowered the rate of lymphocyte proliferation while recruiting lymphocytes to mitotic cycle (Bronkos, 1999).
- Elevated B and NK cells influencing the induction/suppression-balance in the immune system (Bronkos, 1999).

CONTRAINDICATIONS

Internal

Not recommended for children (Morant and Ruppanner, 2001; ESCOP, 1999) or with chronic renal failure (Morant and Ruppanner, 2001). An authoritative clinical review found no clinical basis for contraindications (Schulz *et al.,* 2000).

External

The gel or ointment should not be applied to broken or ulcerated skin (NRF 3, 1986). Contraindicated in cases of thrombosis or risk of embolism and for application to open wounds or mucous membranes (Morant and Ruppanner, 2001).

PREGNANCY AND LACTATION: There are no known restrictions according to the Commission E (Blumenthal *et al.*, 1998). HCSE has been used in some clinical studies involving pregnant women, with some studies excluding those in the third trimester. No adverse effects have been reported (ESCOP, 1999).

ADVERSE EFFECTS

The Commission E noted that in rare cases, pruritus, nausea, and gastric complaints may occur after oral intake (Blumenthal *et al.*, 1998). In rare cases, irritation of the gastric mucous membranes and reflux may occur. Escin Ib isolated from horse chestnut might partially delay or even inhibit gastric emptying. The inhibition of gastric emptying might be mediated by capsaicin-sensitive sensory nerves (CPSN), stimulation of the synthesis and/or release of dopamine, or through the central dopamine2

receptor, which in turn causes the release of prostaglandins (Matsuda and Yoshikawa, 2000). This possible adverse effect can be minimized by taking the extract in an enteric-coated, time-release tablet with the main meal (Morant and Ruppanner, 2001). After *intravenous* administration of *isolated escin*, anaphylactic shock, toxic nephropathy, and renal failure have been reported (Leung and Foster, 1996; Grasso and Corvaglia, 1976), but these reactions are not associated with oral ingestion of the chemically complex HCSE preparations. One case report (Comaish and Kersey, 1980) linking horse chestnut with contact dermatitis has been documented, but this does not pertain to HCSE in internal dosage forms.

Drug Interactions

Some sources have theorized that horse chestnut extractives may interfere with the effects of anticoagulants (Ernst, 2000), specifically escin (Madaus AG, 2000). However, another source suggests that this activity pertains to the compound esculetin, found in the *bark*, not the seeds (Brinker, 2001). Escin, the main saponin component in horse chestnut, binds to plasma protein and may affect the binding of other drugs (speculative) (Newall *et al.*, 1996).

American Herbal Products Association (AHPA) Safety Rating

No rating. NOTE: The herbs evaluated by AHPA in its *Botanical Safety Handbook* were based on an earlier AHPA publication (Foster, 1992) listing the names of approximately 550 of the most commonly-sold herbs in U.S. commerce during the early 1990s (McGuffin *et al.*, 1997). Horse chestnut preparations were not readily available in the U.S. at that time.

Regulatory Status

CANADA: Horse chestnut is listed in Appendix II of the "List of Herbs Unacceptable as Non-medicinal Ingredients in Oral Use Products" (Health Canada, 1995b) and is also listed in Appendix I of the "Herbs that are Restricted or not Accepted as Medicinals in Traditional Herbal Medicines" (Health Canada, 1995a). However, it is permitted as a component of homeopathic drugs (Health Canada, 2000).

FRANCE: Official in the *French Pharmacopoeia* (ESCOP, 1999; Ph.Fr. X, 1982–1996). Nonprescription drug used in self-medication for circulatory stabilization (Goetz, 1999; Noël, 1997).

GERMANY: HCSE is an approved drug in the German Commission E monographs (Blumenthal *et al.*, 1998). Dried seed containing not less than 3.0% triterpene glycosides and HCSE containing 16–20% triterpene glycosides are official in the *German Pharmacopoeia* (DAB, 1999). Escin-Gel is an official preparation in the *German Formulary* (NRF 3, 1986). Fresh-peeled seeds, the mother tincture, and liquid dilutions are official preparations of the *German Homeopathic Pharmacopoeia* (HAB 1, 1978–1985).

SPAIN: Official in the *Spanish Pharmacopeia* (Newall *et al.*, 1996; Reynolds *et al.,* 1989).

SWEDEN: As of January 2001, no horse chestnut products have been listed in the Medical Products Agency (MPA) "Authorised Natural Remedies" (MPA, 2001).

SWITZERLAND: Positive classification (List D) by the *Interkantonale Konstrollstelle für Heilmittel* (IKS) and corresponding sales category D with sale limited to pharmacies and drugstores, without prescription (Morant and Ruppanner, 2001; WHO, 1998). One horse chestnut Anthroposophical preparation, 19 phytomedicines preparations, and 5 mainly-botanical combination preparations, are listed in the *Swiss Codex 2000/01* (Ruppanner and Schaefer, 2001).

U.K.: Medicinal product specified in the *General Sale List*, Schedule 1 (subject of full Product License), Table B (external use only) (GSL, 1994).

U.S.: Oral preparations regulated as dietary supplement (USC, 1994).

Clinical Review

Twenty-three studies are outlined in the following table, "Clinical Studies on Horse Chestnut," including a total of 4,339 participants. All of the 20 studies that investigated the use of HCSE in venous disorders demonstrated positive effects. Of the 20 studies, four were randomized, double-blind, placebo-controlled, parallel group (R, DB, PC, PG), studies (Diehm *et al.*, 1992; Lohr *et al.*, 1986; Pilz, 1990; Rudofsky *et al.*, 1986), five were R, DB, PC, cross-over (CO) studies (Bisler *et al.*, 1986; Friederich *et al.*, 1978; Neiss and Böhm, 1976; Steiner, 1990; Steiner and Hillemanns, 1990), four were R, DB, comparison, PG design studies (Erdlen, 1989; Erler, 1991; Kalbfleisch and Pfalzgraf, 1989; Rehn *et al.*, 1996), one was a R, PC single-blind design (Diehm *et al.*, 1996), another was a DB, PC, multicenter (MC) study (Shah *et al.*, 1997), one was an uncontrolled, multicenter study with 71 participants (Geissbühler and Degenring, 1999), one was a DB design (Kreysel et al., 1983), three were surveillance studies (Masuhr *et al.*, 1994; Knoche and Knoche, 1978; Rossi *et al.*, 1977). The main outcome measure for most studies was reduced leg volume or ankle circumference. A systematic review of 13 R, DB clinical trials from 1976–1996, using HCSE in the treatment of venous disorders, and involving nearly 1,100 patients, concluded that HCSE was superior to placebo (Pittler and Ernst, 1998). HCSE was as effective as rutosides (the conventional treatment in Europe) in five studies. Adverse effects were mild and infrequent.

A R, CO study found bioequivalence (phytoequivalence) in two different forms of HCSE (Oschmann *et al.*, 1996). A R, DB, PC study of 70 subjects using HCSE topical gel, showed significant reduction in tenderness with experimentally induced hematomas (Calabrese and Preston, 1993). Subjects with severe craniocerebral trauma regained consciousness more quickly and experienced reduced intracranial pressure with purified escin i.v., followed by HCSE tablets, compared to placebo (Put, 1979).

Branded Products*

Aesculaforce® Venen-Gel: Bioforce AG / CH-9325 Roggwil TG / Switzerland / Tel: +41 71 454 61 61 / Fax: +41 71 454 61 62 / www.bioforce.com / Email: info@bioforce.ch. One g of gel contains 54–117 mg dry extract prepared from fresh horse chestnut seed (Hippocastani semen recent extr. Sicc. 5.0–6.1:1) standardized to contain 2% escin.

Aesculaforce® Venen-Tabletten: Bioforce AG. Film-coated tablets (to prevent gastric irritation) contain 63–90 mg dry extract prepared from fresh horse chestnut seed (Hippocastani semen extr. Sicc. 5.0–6.1:1), corresponding to 20 mg escin. Extraction solvent: 60% (*m/m*) ethanol.

Reparil® Dragées: Madaus AG / Ostermerheimer Strasse 198 / Köln / Germany / Tel: +49-22-18-9984-76 / Fax: +49-22-18-9987-21 / Email: b.lindener@madaus.de. One coated tablet contains 20 mg escin amorphosed with adjuvants: polyvidone,

magnesium stearate, talc, gum arabic, polyethyl acrylate, methacrylic acid, Macrogol 8000, sodium hydoxide, carmellose sodium, triethyl citrate, dimethicone, titanium dioxide, lactose, colloidal silicon dioxide, sucrose, natural waxes.

Venoplant® retard S: Dr. Willmar Schwabe Pharmaceuticals / International Division / Willmar Schwabe Str. 4 / D-76227 Karlsruhe / Germany / Tel: +49-721-4005 ext. 294 / www.schwabepharma.com / Email: melville-eaves@schwabe.de. Each sustained-release tablet contains 263.2 mg dry extract from horse chestnut seeds (4.5–5.5:1), adjusted to 50 mg triterpene glycosides, calculated as anhydrous aescin; extraction agent: ethanol 50% (*w/w*).

Venostasin® Retardkapsel: Klinge Pharma GmbH / Postfach 80 10 63 / D-81610 Munich / Germany / Tel: +089 45 44 – 01 / Fax: +089 45 44 - 13 29 / www.klinge.com, www.fujisawa.com. Each 300 mg capsule contains 240–290 mg native dry extract normalized to contain 50 mg triterpene glycosides, calculated as escin. Extract is standardized by diluting with 10–60 mg dextrin.

*American equivalents, if any, are found in the Product Table beginning on page 398.

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Clinical Studies on Horse Chestnut (*Aesculus hippocastanum* L.)

Chronic Venous Insufficiency (CVI)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Geissbühler and Degenring, 1999	Venous insufficiency	U, MC n=71 patients (61 women and 10 men) with chronic venous insufficiency and edema	6 weeks	Morning and evening massage gel into lower leg including ankles and the inner side of the thighs	Aesculaforce® Venen-Gel (1g of gel contains 54–117 mg dry extract standardized to 2% escin)	After 6 weeks of treatment, ankle circumference was reduced significantly ($p<0.001$) by 0.7 cm compared with baseline. Patients symptoms score also decreased significantly ($p<0.001$) by 60%. Over 85% of the cases reported good to medium efficacy. [Note: the principal author was employed by the manufacturer.]
Shah *et al.*, 1997	Venous insufficiency	DB, PC, MC n=52 males and females with CVI (mean age test group 54 years; mean age placebo group 56 years)	6 weeks	2 tablets 3x/day (120 mg escin/day)	Aesculaforce® tablet (Each enteric coated tablet contains 63–90 mg native dry extract standardized to 20 mg escin per tablet)	After 2 weeks treatment there was significant ($p<0.05$) reduction in edema of the ankles and venous filling rate ($p=0.03$). There was no significant improvement in subjective symptoms. HCSE was well tolerated. [Note: the principal author was employed by the manufacturer.]
Diehm *et al.*, 1996	Venous insufficiency	R, SB, PC, Cm, PG n=240 men and women with CVI (mean age 52 years)	12 weeks preceded by a 2-week placebo run-in	1 capsule 2x/day (100 mg escin/day) vs. mechanical compression with bandages and class II elastic stocking	Venostasin® retard extract capsule (Each capsule contains 240–290 mg native dry extract standardized to 50 mg triterpene glycosides, calculated as escin, with 10–60 mg dextrin)	Lower-leg volumes were significantly reduced in both HCSE ($p=0.005$) and compression therapy ($p=0.002$) groups. HCSE decreased lower-leg volume by an average of 43.8 ml compared to 46.7 ml with compression therapy and an increase of 9.8 ml with placebo. HSCE was well-tolerated (98% compliance), whereas compression treatment was reported as uncomfortable, inconvenient and subject to poor (90%) compliance.
Rehn *et al.*, 1996	Grade II CVI	R, DB, Cm, MC, PG n=137 postmenopausal patients with grade II chronic venous insufficiency	12 weeks, preceded by 1 week placebo run-in, follow-up period of 6 weeks without treatment	One 300 mg capsule 2x/day (100 mg escin/day) vs. 1,000 mg/day O- (β-hydroxyethyl)-rutosides for 4 weeks, then 500 mg/day for 8 weeks	HCSE capsules standardized to 50 mg escin each or oxerutin (brand not stated)	Both HCSE and oxerutin significantly reduced leg volume compared to baseline with mean leg volume reduction of 100 ml after 12 weeks. HCSE alleviated subjective symptoms. After 6-week follow-up period both treatments exhibited substantial carry-over effect. Authors concluded that both therapies are effective in treatment of CVI.
Masuhr *et al.*, 1994	Venous insufficiency	S n=4,113 (treated in 842 practices)	87 days	Two, 100 mg tablets per day (100 mg escin/day)	Venoplant® retard, with 100 mg dry extract adjusted to 50 mg escin	In more than 84% of the patients, symptoms either improved or disappeared, with the "good" tolerance in 90% of the cases. The authors concluded that CVI can be successfully treated with a symptom-based therapy using horse chestnut seed extract.
Diehm *et al.*, 1992	Venous insufficiency	R, DB, PC, PG n=39 men and women with venous edema in chronic deep-vein incompetence	6 weeks	One, 300 mg capsule 2x/day (150 mg escin/day)	HCSE capsules standardized to 75 mg escin each (brand not stated)	Compared with baseline, HCSE significantly reduced ($p<0.01$) leg volume by an average 84 ml compared to 4 ml with placebo. HCSE caused dramatic improvement in feelings of heaviness, tension, fatigue, and paresthesia in the legs. Itching was not helped. Authors conclude that HCSE is a safe and effective adjunct to compression therapy.

KEY: C – controlled, **CC** – case-control, **CH** – cohort, **CI** – confidence interval, **Cm** – comparison, **CO** – crossover, **CS** – cross-sectional, **DB** – double-blind, **E** – epidemiological, **LC** – longitudinal cohort, **MA** – meta-analysis, **MC** – multi-center, **n** – number of patients, **O** – open, **OB** – observational, **OL** – open label, **OR** – odds ratio, **P** – prospective, **PB** – patient-blind, **PC** – placebo-controlled, **PG** – parallel group, **PS** – pilot study, **R** – randomized, **RC** – reference-controlled, **RCS** – retrospective cross-sectional, **RS** - retrospective, **S** – surveillance, **SB** – single-blind, **SC** – single-center, **U** – uncontrolled, **UP** – unpublished, **VC** – vehicle-controlled.

Clinical Studies on Horse Chestnut (*Aesculus hippocastanum* L.) (cont.)

Chronic Venous Insufficiency (CVI) (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Erler, 1991	Venous insufficiency	R, DB, Cm, PG n=40 patients with CVI and peripheral venous edema	2 months	One, 300 mg capsule 2x/day (150 mg escin/day) vs. 2000 mg/day O-(β-hydroxyethyl)-rutosides	HCSE capsules standardized to 75 mg escin each (brand not stated)	Compared with baseline, HCSE significantly protected calf and ankle from edema provocation. Both HCSE and rutin preparations were comparable in reducing edema, but HCSE had a more pronounced protective effect.
Pilz, 1990	Venous insufficiency	R, DB, PC, PG n=28 patients with CVI	20 days	One, 300 mg capsule 2x/day (100 mg escin/day)	HCSE capsules standardized to 50 mg of escin (brand not stated)	HCSE treatment caused significant reduction ($p<0.05$) of 0.08 cm in leg circumference and decreased edema compared with placebo. Subjective symptoms were also significantly decreased ($p<0.05$).
Steiner, 1990	Venous insufficiency	R, DB, PC, CO n=20 female patients with varicosis during pregnancy	2 weeks	One, 300 mg capsule 2x/day (100 mg escin/day)	Venostasin® Retardkapsel	Compared to placebo, HCSE caused significant reduction ($p=0.009$) of 114 ml in leg volume. Leg circumferences and subjective symptoms were also significantly reduced ($p<0.05$) during HCSE treatment period. HCSE was rated as significantly better than placebo by physicians ($p<0.01$) and patients ($p<0.05$).
Steiner and Hillemanns, 1990	Edema due to venous insufficiency	R, DB, PC, CO n=52 pregnant women with edema due to CVI	20 days	One, 300 mg capsule 2x/day (100 mg escin/day)	Venostasin® Retardkapsel each capsule contains 240–290 mg native dry extract standardized to 50 mg triterpene glycosides, calculated as escin, with 10–60 mg dextrin	Significant reductions ($p<0.01$) in foot volume before and after edema provocation and greater resistance to edema provocation demonstrated in HCSE group compared with placebo. Reductions in foot circumference and less severe subjective symptoms of pain, fatigue, swelling, and itching were also significant in HCSE group.
Erdlen, 1989	Venous insufficiency	R, DB, Cm, PG n=30 patients with CVI	1 month	One, 300 mg capsule 2x/day (100 mg escin/day) or reference medication (type not clearly indicated, presumably rutosides)	HCSE capsules standardized to 50 mg escin each (brand not stated)	HCSE significantly reduced ankle circumference by 0.4 cm and improved subjective symptoms compared with baseline.
Kalbfleisch and Pfalzgraf, 1989	Venous insufficiency	R, DB, Cm, PG n=30 (33) patients with CVI	2 months	One, 300 mg capsule/day (50 mg escin/day) vs. 500 mg O- (β-hydroxyethyl)-rutosides/day	HCSE capsules standardized to 50 mg escin each (brand not stated)	HCSE reduced ankle and calf circumference by 0.2 and 0.18 cm, respectively, compared to baseline. Values were not significantly different from the rutoside.
Rudofsky *et al.*, 1986	Venous insufficiency	R, DB, PC, PG n=39 patients (67% women) with grade I or II chronic venous insufficiency	1 month	One, 300 mg capsule 2x/day (100 mg escin/day)	HCSE capsules standardized to 50 mg escin each (brand not stated)	HCSE treatment resulted in statistically significant ($p<0.001$) reduction by 78 ml in leg volume compared with 34 ml increase with placebo. At 28 days, HCSE caused a significant change in calf and foot circumference ($p<0.01$). Additionally, significant improvement in subjective parameters (pain, tiredness, tension, and pruritus in legs) were reported. No difference with respect to venous capacity or venous drainage when leg was elevated.

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Clinical Studies on Horse Chestnut (*Aesculus hippocastanum* L.) (cont.)

Chronic Venous Insufficiency (CVI) (cont.)

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Lohr *et al.*, 1986	Venous insufficiency	R, DB, PC, PG n=74 patients (57 women and 17 men) with CVI	2 months (preceded by a 12-day washout phase with placebo)	One, 300 mg capsule 2x/day (morning and evening) (100 mg escin/day)	Venostasin® Retardkapsel	HCSE treatment resulted in leg volume reduction of 16.5 ml compared to 3.8 ml reduction with placebo. Formation of edema was decreased (– 21.0 ml) with HCSE and increased (+ 0.2) ml with placebo during edema-provoking period. Authors concluded that HCSE therapy showed statistically significant activity in inhibiting progression of edematous disease conditions and was well-tolerated.
Bisler *et al.*, 1986	Venous insufficiency	R, DB, PC, CO n=22 patients with CVI	Single dose of HCSE or placebo followed by 4-week study period	Two, 300 mg capsules/day (100 mg escin/day)	Venostasin® Retardkapsel	Three hours after administration, an acute dose of HCSE had an anti-edematous effect with a statistically significant (p=0.006) decrease (22%) in the capillary filtration coefficient compared with placebo, which caused an increase. Authors conclude that HCSE inhibits edema in CVI of leg by reducing transcapillary filtration.
Kreysel *et al.*, 1983	Varicosis	DB n=15 varicose patients	12 days	One, 300 mg capsule 3x/day (150 mg escin/day)	Venostasin® Retardkapsel	After 12 days of treatment, significant reduction in activity of glycosaminoglycan hydrolase enzymes. Serum activity of 3 lysosomal glycosaminoglycan hydrolases were significantly reduced by 29.1%, 25.7%, and 28.7% respectively, compared to placebo. The authors hypothesize that HCSE acts at the site of enzyme release, exerting a stabilizing effect on the lysosomal membrane.
Friederich *et al.*, 1978	Venous insufficiency or varicosis	R, DB, PC, CO n=95 patients with varicosis or CVI	20 days	One, 300 mg capsule 2x/day (100 mg escin/day)	HCSE capsules standardized to 50 mg escin each (brand not stated)	HCSE caused significant reduction ($p<0.05$) in CVI-related symptoms including calf spasm, pain, fatigue, and tenseness compared to placebo. No effect on pruritus.
Knoche and Knoche, 1978	Venous complaints	S n=61	9 months	One, 100 mg tablet 2x/day	Venoplant® retard standardized to 50 mg escin and 15 mg milk thistle (*Carduus marianus*) extract	A reduction in lower leg pain was demonstrated as early as 3 days after treatment. Edema formation declined after 7-14 days. Only 3 patients complained of minor side effects, including stomach complaints and dizziness.
de Rossi et al., 1977	Venous complaints (varicosis, thrombophlebitis, phlebothrombosis)	S n=1,236	28 days (average)	One, 100 mg tablet 2x/day	Venoplant® retard tablet containing 100 mg horse chestnut and 15 mg milk thistle (providing 50 mg escin and 7.5 mg silymarin per tablet)	Rapid effect (21% reported improvement by day 4, 52% by day 8, and 70% by day 10) and good gastric tolerance were emphasized by 90% of the physicians.
Neiss and Böhm, 1976	Varicosis	R, DB, PC, CO n=226 (233) predominantly women with varicosis	20 days	One, 300 mg capsule 2x/day (100 mg escin/day)	HCSE capsules standardized to 50 mg escin each (brand not stated)	Compared to placebo, HCSE caused significant ($p<0.05$) reduction in edema, leg pain, and pruritus.

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Clinical Studies on Horse Chestnut (*Aesculus hippocastanum* L.) (cont.)

Other

Author/Year	Subject	Design	Duration	Dosage	Preparation	Results/Conclusion
Oschmann *et al.*, 1996	Bio-equivalence as determined by pharmaco-kinetics	R, CO n=24	3 days each phase with 1-week washout between pases	Single dose of one tablet or one capsule (50 mg escin)	Venoplant® retard 263.2 mg tablet or Venostasin® retard 240–290 mg capsule (providing 50 mg escin per tablet or capsule)	Bioequivalence was established between the 2 dosage forms.
Calabrese and Preston, 1993	Experimentally induced injury with hematomas	R, DB, PC n=70 healthy volunteers	9-hour study period	1 time acute topical application	Topical gel containing HCSE standardized to 2% escin (brand not stated)	Using tonometric sensitivity measurements, escin gel significantly reduced ($p<0.001$) tenderness to pressure of experimentally induced hematomas. The effect was observed from 1 hour after treatment lasting until the end of the 9-hour study period.
Put, 1979	Severe cranio-cerebral trauma	C, Cm n=142 accident victims with severe cranio-cerebral trauma	Treatment periods varied on an individual basis from 1–56 weeks with follow-ups at 2–3.5 years after accident and treatment	Days 1–5: 20 mg/day escin i.v.; Days 6–9: 10 mg/day escin i.v.; Beginning on day 10: 1 tablet/day vs. corticosteroid i.v. (type not specified)	Purified escin i.v. in the form of sodium escinate (first 10 days) followed by Reparil®-coated tablets	Regaining of consciousness was more rapid in the escin group than the corticosteroid group. Escin was more effective than steroid therapy at reducing intracranial pressure and lowering mortality rates. Follow-up examinations 2–3.5 years after the accident showed significantly higher rehabilitation rate in escin group (49 of 71) compared with steroid group (36 of 71).

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