

The Longwood Herbal Task Force

(<http://www.mcp.edu/herbal/>) and

The Center for Holistic Pediatric Education and Research

(<http://www.childrenshospital.org/holistic/>)

## Horse Chestnut (*Aesculus hippocastanum*)

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**Principal Proposed Use:** Treatment for chronic venous insufficiency

**Secondary Proposed Use:** Reduction of edema caused by trauma or surgery, reduction of cerebral edema, prevention of thrombosis, treatment of hemorrhoids

### *Overview*

Horse chestnut seed extract (HCSE) is used in Europe as a treatment for chronic venous insufficiency. Randomized double blind, controlled studies support its use when used alone or in adjunct with compression stocking therapy in decreasing lower extremity peripheral edema caused by venous insufficiency. HCSE also decreases post-operative and post-traumatic edema. Allergic reactions, including anaphylaxis, do occur but are rare. Patients have reported minimal side effects, which include nausea, vomiting, diarrhea, dizziness, itching, headache and weakness. There is a wide margin of safety between therapeutic and toxic dosing; overdoses may cause acute renal failure.

### *Historical and Popular Uses*

*Aesculus hippocastanum*, commonly known as horse chestnut, is not the same as the edible sweet chestnut, *Castanea vesca*. Raw horse chestnuts are poisonous, but after special preparation to remove the toxins, they are relatively safe to use<sup>1</sup>. An ancient superstition of carrying a horse chestnut seed around in one's pocket to prevent or cure arthritis still exists in some countries<sup>1, 2</sup>. The seeds have been used as an analgesic, antipyretic, narcotic, tonic, and vasoconstrictor. They have been used to treat backache, sunburn, neuralgia, rheumatism, whooping cough and hemorrhoids<sup>1, 3</sup>. The bark has been used as a tonic, narcotic, antipyretic and to induce sneezing. The flowers have been used as an anodyne, astringent, tonic and

vulnerable<sup>1</sup>.

Today horse chestnut seed extract is the most widely prescribed medication in Germany for chronic venous insufficiency and edema<sup>2, 4</sup>. HCSE reduces vascular fragility by acting upon the connective tissue barrier between the blood vessels and the tissues, thereby inhibiting exudation and edema development<sup>5</sup>.

## ***Botany***

*Medicinal species: Aesculus hippocastanum*

*Common names:* Horse chestnut, Spanish chestnut, buckeye, seven leaves tree

*Botanical family:* Hippocastanaceae

*Plant description:* Horse chestnut is a deciduous tree up to 35 meters high with a large regular crown, five to seven digitate leaves and erect racemes of flowers with a yellow or reddish spot at the base of the white petals. The fruit is a spiny capsule containing up to three shiny, reddish brown seeds with a light-colored hilum<sup>6, 7</sup>.

*Where it's grown:* Horse chestnut is widely cultivated as an ornamental tree, especially in northern Europe and North America. It is indigenous to the mountains of Greece, Bulgaria, the Caucasus, northern Iran and the Himalayas<sup>7</sup>.

## Biochemistry

### Horse Chestnut: Active Chemical Constituents

- Aescin (aka escin), a complex mixture of triterpenoid saponin glycosides
- Coumarin derivatives: aesculin, fraxin, scopolin
- Flavonoids: quercetin, kaempferol, astragalín, isoquercetrin, rutin, leucocyanidine
- Essential oils: oleic acid, linoleic acid
- Other: amino acids (adenosine, adenine, guanine), allantoin, argyrim, carotin, choline, citric acid, epicatechin, leucodelphinidin, phyosterol, resin, scopoletin, tannin, and uric acid<sup>2, 3, 8</sup>

The principal extract and medicinal constituent of horse chestnut seed is *aescin*, a mixture of triterpenoid saponin glycosides. Its components include protoaescigenin, barringtonol C, allantoin, sterols, leucocyanidin, leucodelphinidin, tannins, and alkanes<sup>3, 4, 7, 8</sup>. It can be fractionated into beta-aescin, an easily crystallizable mixture, and alpha-aescin, which is water-soluble<sup>2</sup>.

Aescin decreases the transcapillary filtration of water and proteins<sup>2, 5</sup>. It has been used to treat a wide variety of inflammatory and edematous conditions, to reduce swelling associated with bruises, fractures, brain trauma, post-operative and post-traumatic soft tissue swelling, and acute thrombophlebitis<sup>5, 9</sup>. Aescin reduces lysosomal enzyme activity by stabilizing lysosomal membranes and limiting enzyme release<sup>10, 11</sup>. Aescin also improves venous tone by enhancing the constricting effect of noradrenaline. Arterial vessels are not constricted and diastolic blood pressure is not affected<sup>12</sup>.

Orally administered aescin is either sparingly absorbed by the gastrointestinal tract or undergoes a substantial first-pass effect. It has an absorption half-life of about one hour, peak serum levels in two to three hours, peak response in terms of vascular protection in 16 to 20 hours, and an elimination half-life of about 20 hours. Aescin is filtered through the glomerula and is neither reabsorbed nor excreted in the tubules. It binds to plasma proteins, preventing nephrotoxicity. The amount of free aescin excreted through the glomerula is small, and the concentration too low to have cytotoxic effects on the tubular epithelium<sup>13</sup>. Aescin is fully dialyzable<sup>14</sup>.

The coumarin *aesculin* has a moderate diuretic effect. Aesculin is reported to possess microvasculokinetic activity, and is used in the treatment of cellulitis and hair loss<sup>15</sup>.

### ***Experimental Studies***

#### **Horse Chestnut: Potential Clinical Benefits**

1. Cardiovascular: Treatment for chronic venous insufficiency and peripheral edema, antilipemic
2. Pulmonary: Expectorant
3. Renal and electrolyte balance: Diuretic
4. Gastrointestinal/hepatic: Prevention of gastric ulcers, antispasmodic
5. Neuro-psychiatric: Reduction of cerebral edema
6. Endocrine: Adrenal stimulant, hypoglycemic agent
7. Hematologic: Antithrombotic
8. Rheumatologic: none
9. Reproductive: none
10. Immune modulation: Anti-inflammatory, reduction of hematomas and inflammation from trauma or surgery
11. Antimicrobial: Antiviral, antifungal
12. Antineoplastic: none
13. Antioxidant: none
14. Skin and mucus membranes: Treatment of hemorrhoids, reduction of cellulite, sunblock
15. Other/miscellaneous: none

1. **Cardiovascular:** Treatment for chronic venous insufficiency and peripheral edema, antilipemic
  - a. Treatment for chronic venous insufficiency and peripheral edema
    - i. *In vitro data:* Sodium aescinate dose-dependently inhibited two important steps in the activation of endothelial cells exposed to hypoxic conditions, by decreasing the ATP content and increasing the activity of phospholipase A2, an enzyme responsible for the release of inflammatory mediator precursors. Aescin strongly inhibited the

adherence of neutrophil-like cells to umbilical veins incubated in hypoxic conditions. The researchers theorize that aescin may prevent venous wall damage by preventing neutrophil recruitment, adherence and activation during blood stasis in the lower extremities<sup>16</sup>.

Aescin stimulated the release of prostaglandins (PGF<sub>2</sub>-α) in the perfused isolated rat lung, and induced prostaglandin-mediated contractions in the isolated portal vein of rats and rabbits<sup>17</sup>. In canine and human saphenous veins, aescin increased venous tone and had a contracting effect on the valves in a dose-dependent fashion<sup>18</sup>. The maximum contraction was similar to that achieved with serotonin or dihydroergotamine, less than that achieved by norepinephrine or histamine, and greater than that of acetylcholine or vasopressin<sup>19</sup>.

- ii. *Animal data:* Orally-administered HCSE normalized the increased permeability caused by vasoactive agents or irritant chemicals in rats and rabbits, and normalized the decreased capillary resistance caused by Vitamin C deficiency in guinea pigs<sup>18</sup>. In the hind limb of rabbits, lymphatic flow was dose-dependently increased by intra-arterial PGE<sub>1</sub>; aescin decreased the PGE<sub>1</sub>-enhanced lymphatic flow by 45-91%, whereas indomethacin decreased the lymph flow by 13-68%<sup>20</sup>.

In the treatment of lymphatic and inflammatory edema in rats, whole HCSE was 100 times more effective than the same extract with the aescin removed<sup>18</sup>. In rats with experimentally induced pleurisy, HCSE suppressed plasmatic extravasation and leukocyte emigration into the pleural cavity and decreased connective tissue formation<sup>18</sup>. In rats with serous peritonitis and pleurisy, aescin inhibited the exudation of large molecules in a dose-dependent manner<sup>21</sup>. In dogs, HCSE increased thoracic lymphatic flow by up to 70%<sup>18</sup>.

- iii. *Human data:* A case series involving more than 5,000 patients with chronic venous insufficiency treated with standardized horse chestnut extract reported decreased subjective complaints<sup>22</sup>. Another case series of 1183 patients with chronic venous insufficiency receiving an aescin preparation over five months demonstrated a clear reduction in objective and subjective symptoms with few side effects<sup>23</sup>.

The use of horse chestnut seed in the treatment of chronic venous insufficiency has also been supported by placebo-controlled studies. A review article analyzing eight double-blind, randomized controlled trials including 20 to 240 chronic venous insufficiency patients found that patients taking 600 mg HCSE (equivalent to 100 mg/day of aescin) over 2 to 12 weeks experienced significant clinical improvement over those receiving placebo. Benefits of HCSE included objective data (decreased lower leg volumes, reduction in leg circumference at the calf and ankle, and reduced transcapillary filtration coefficients) and subjective improvements (decreased leg pain, pruritis, fatigue and tenseness<sup>24</sup>).

Six of these studies were randomized, partially blinded, placebo controlled, parallel studies comparing the efficacy of HCSE to other treatments of chronic venous insufficiency. HCSE was as effective as compression stockings, and slightly less effective (2%) than oxyruten, in the treatment of lower extremity edema<sup>24</sup>.

A double-blind study of foot and ankle edema in 19 healthy subjects following a long-distance flight showed significant edema reduction in the subjects who took 600 mg of HCSE prior to the flight<sup>26</sup>.

Healthy volunteers and varicose vein patients given HCSE had increased venous tone demonstrated by plethysmography and radioactive measurement of blood flow velocity<sup>12</sup>. In another study, subjects who received 600 mg of HCSE had a 22% reduction in the transcapillary filtration coefficient<sup>4</sup>.

b. Antilipemic

i. *In vitro data*: none

ii. *Animal data*: HCSE given to hypercholesterolemic rats lowered serum blood cholesterol in a dose-dependent manner<sup>27</sup>.

iii. *Human data*: none

2. **Pulmonary:** Expectorant. Plants containing saponins have been used as expectorants. There are no studies evaluating the efficacy of horse chestnut as an expectorant.

3. **Renal and electrolyte balance:** Diuretic

i. *In vitro data*: none

ii. *Animal data*: In saline-loaded rats, aesculin had a moderate diuretic effect, significantly

increasing the renal loss of sodium, chloride and potassium. Only high doses of aescin had the same diuretic effect as aesculin<sup>28</sup>.

iii. *Human data:* none

4. **Gastrointestinal/hepatic:** Prevention of gastric ulcers, antispasmodic

a. Prevention of gastric ulcers

i. *In vitro data:* none

ii. *Animal data:* In rats, aescin significantly inhibited the increased gastric acid secretion normally induced by histamines and carbachol. Aescin prevented ethanol-induced gastric ulceration in rats; the protective effect was not associated with an increased amount of gastric mucus or glycoproteins. In rats, oral pre-treatment with aescin reduced the number and severity of gastric ulcers induced by pylorus-ligation and absolute ethanol. Pretreatment with indomethacin before aescin administration reversed the protective effects of aescin in rats, suggesting an inhibition of prostaglandin biosynthesis. Aescin did not enhance PGE<sub>2</sub> levels<sup>29, 30</sup>.

iii. *Human data:* none

b. Antispasmodic

i. *In vitro data:* HCSE applied to guinea-pig ileum significantly reduced the spontaneous contractions of circular smooth muscle and inhibited acetylcholine and barium chloride-induced contractions of longitudinal smooth muscle<sup>31</sup>.

ii. *Animal data:* none

iii. *Human data:* none

5. **Neuro-psychiatric:** Reduction of cerebral edema

a. Reduction of cerebral edema

i. *In vitro data:* none

ii. *Animal data:* none

iii. *Human data:* In a case series of 11 patients with pseudotumor cerebri, treatment with high-dose i.v. aescin (20 mg every 8 hours for 3 days) caused a significant drop in intracranial pressure (ICP) in seven of the patients; four of the patients had no change in ICP. Oral treatment of the aescin-responsive group was continued at the same dosage for 20 to 30 days; follow-up in one year showed no recurrence in any of the patients<sup>32</sup>.

In a controlled study of 142 accident victims with severe cranio-cerebral trauma, intravenous treatment with sodium aescinate administered over several days considerably reduced the rise in intracranial pressure, shortened the duration of unconsciousness, and decreased total mortality in comparison with the control group receiving traditional corticosteroid therapy. Follow-up examinations two to three years later showed a significantly higher rehabilitation rate in the group treated with aescinate<sup>33</sup>.

A double-blind trial in geriatric patients suffering impaired cerebral function due to stroke compared the use of Apoplectal retard<sup>®</sup> (a formulation of buphenine, etofylline and HCSE) to placebo. The group receiving Apoplectal retard (two capsules given three times daily for four weeks) had significant improvement of cerebral and psychic functions, while the placebo group worsened<sup>34</sup>.

6. **Endocrine:** Adrenal stimulant, hypoglycemic agent

a. Adrenal stimulant. Aescin's adrenal stimulating effect may partially explain its anti-inflammatory effect.

i. *In vitro data*: none

ii. *Animal data*: Beta-aescin caused a 10-fold increase in plasma ACTH and a 20-fold increase in plasma corticosterol levels in rats. Beta-aescin did not have an anti-inflammatory effect in adrenalectomized or hypophysectomized animals<sup>35</sup>.

iii. *Human data*: none

b. Hypoglycemic agent

i. *In vitro data*: none

ii. *Animal data*: Oral aescin inhibited glucose absorption by suppressing the transfer of glucose from the stomach to the small intestine and by inhibiting the glucose transport system at the small intestinal brush border in glucose-loaded rats. It had had neither an insulin-like nor an insulin-releasing activity. Serum glucose levels were not decreased<sup>36, 37</sup>. Aescin had an inhibitory effect on ethanol absorption in rats<sup>36</sup>.

iii. *Human data*: none

7. **Hematologic:** Antithrombotic

i. *In vitro data*: none

ii. *Animal data*: none

iii. *Human data:* In one controlled study in 200 post-operative patients, intravenous aescin (Reparil<sup>®</sup>) decreased the rate of subclinical thrombosis from 27% to 16%<sup>38</sup>; however, eight other randomized, controlled studies failed to show any thrombotic prophylactic effect from aescin in postoperative gynecological patients<sup>39</sup>.

In a case series of 15 patients with thrombotic inflammation of tibial superficial veins, Essaven gel (which contains aescin, heparin and essential phospholipids) decreased pain, edema, warmth and flushing of the involved area in 12 of the patients<sup>40</sup>. In a multi-center, double blind, randomized placebo controlled trial in patients with superficial thrombophlebitis, Vasotonin N forte<sup>®</sup> (HCSE and mofebutazone) relieved subjective complaints after three weeks of treatment<sup>41</sup>.

8. **Rheumatologic:** none

9. **Reproductive:** none

10. **Immune modulation:** Anti-inflammatory

i. *In vitro data:* HCSE prevented histamine-induced edema of the skin, post-ischemic edema of the muscle, and cerebral edema provoked by cold injury<sup>42</sup>.

ii. *Animal data:* Aescin significantly increased plasma adrenocorticotrophic hormone and corticosterol levels in rats [Hiai, 1981 #171]. In one study using the rat ear model, intravenous administration of aescin did not reduce traumatic edema<sup>43</sup>. However, aescin inhibited the increase of vascular permeability induced by acetic acid in mice, histamine in rats, and serotonin in rats; it also inhibited rat paw edema induced by carrageenan<sup>44</sup>.

In rats with induced thermal edema, aescin increased acid protease activity levels and edema formation in the extracellular fluid of the skin within 24 hours after injury; it also reduced the maximum swelling volume and improved the rate of edema resolution<sup>45, 46</sup>.

iii. *Human data:* A case series, with no controls, of 70 post-mastectomy patients receiving topical 1-thyroxine and aescin (Somatoline<sup>®</sup>) demonstrated decreased lymphatic edema when treatment occurred prior to fibrosis formation<sup>47</sup>.

In a controlled trial in patients undergoing hand surgery, those treated with aescin (Reparil<sup>®</sup> 10 mg I.V. twice daily for six days) had an increase in hand temperature for only two days postoperatively, whereas the control group had elevated skin temperatures

for four days<sup>48</sup>.

In a double blind, randomized trial, a single application of topical 2% aescin gel decreased tenderness at the site of experimentally induced injection hematomas<sup>49</sup>.

**11. Antimicrobial:** Antiviral, antifungal

- i. *In vitro data:* Aescin has antiviral activity against *influenza virus*<sup>8</sup> and fungistatic activity against *Trichoderma viride* *G in vitro*<sup>50</sup>.
- ii. *Animal data:* none
- iii. *Human data:* none

**12. Antineoplastic:** none

**13. Antioxidant:** none

**14. Skin and mucus membranes:** Treatment of hemorrhoids; reduction of cellulite; sunblock

- a. Treatment of hemorrhoids: Ointments containing HCSE are used topically for hemorrhoids, but there are no data on the transdermal absorption of aescin, or the effectiveness of local HCSE in the treatment of hemorrhoids<sup>2</sup>.
- b. Reduction of cellulite
  - i. *In vitro data:* none
  - ii. *Animal data:* none
  - iii. *Human data:* A double-blind study in 40 subjects of a multi-ingredient cream containing aescin demonstrated a regression in the clinical stage of cellulite in over 80% of the test subjects and a 4% reduction in thigh circumference after using the test product; no reduction took place in the placebo group<sup>51</sup>.
- c. Sunblock
  - i. *In vitro data:* Extracts of horse chestnut seed incorporated into a 2% solution of synthetic sunscreen increased the SPF value<sup>52</sup>.
  - ii. *Animal data:* none
  - iii. *Human data:* none

**15. Other/miscellaneous:** none

## ***Toxicity and Contraindications***

*All herbal products carry the potential for contamination with other herbal products, pesticides, herbicides, heavy metals and pharmaceuticals.*

*Allergic reactions can occur to any natural product in sensitive persons.*

*Allergic reactions:* Isolated cases of contact dermatitis have occurred following topical application of horse chestnut seed extract<sup>53</sup>. Anaphylactic reactions have occurred following i.v. administration of aescin<sup>7</sup>.

*Potentially toxic compounds in horse chestnut:* Alkaloids, aesculin, saponins, quercetin, quercitrin, rutin, and shikimic acid<sup>3</sup>.

*Acute toxicity:* Although poisonings and death have occurred after ingestion of whole chestnut seeds, cases are rare due to the bitterness of the seed and the large quantity required. Symptoms of poisoning included muscle twitching and weakness, lack of coordination, dilated pupils, vomiting, diarrhea, depression, paralysis, and stupor. Treatment of poisoning may include gastric lavage, activated charcoal, diazepam for spasms, atropine for colic, electrolyte replenishment, and sodium bicarbonate infusions for acidosis. Intubation and oxygen therapy may also be necessary<sup>7</sup>.

The side effects from therapeutic doses of HCSE in eight placebo-controlled studies cited in a review article included gastrointestinal symptoms, dizziness, nausea, headache and pruritus in 0.9% to 3.0% of subjects. In three of these studies, side effect rates were not significantly different from the placebo group<sup>24</sup>.

Overdoses of aescin may be nephrotoxic. Acute renal failure has occurred in children who received high doses of aescin (two to three times the recommended dose for an average of four days) post-operatively<sup>5</sup>. Animal and *in vitro* studies suggest that high doses of aescin may contribute to existing nephrotoxicity only if the aescin is displaced from albumin<sup>13</sup>.

In acute toxicology tests in animals, HCSE and aescin had no adverse effects with doses as high as eight times therapeutic levels<sup>4</sup>.

The drug Venocuran<sup>®</sup>, which contains HCSE, phenopyrazone and cardiac glycoside-containing plant extracts, has been implicated in several cases of pseudo-lupus;

phenopyrazone appears to be responsible for these effects<sup>54, 55</sup>.

There is one reported case of a man who presented with symptoms consistent with drug-induced hepatic injury two months after receiving one 65 mg Venoplast<sup>®</sup> IM injection<sup>56</sup>.

*Chronic toxicity:* Animal studies over 34 weeks have shown no chronic toxic effects, teratogenicity or embryotoxicity from HCSE; there are no data on mutagenicity or carcinogenicity<sup>4, 57</sup>.

*Limitations:* Some herbalists suggest that HCSE should be used cautiously in patients with hepatic or renal impairment<sup>8</sup>. However, toxicology studies have not demonstrated hepatotoxicity or nephrotoxicity<sup>13</sup>.

Some herbalists recommend that patients who have bleeding disorders or are anticipating surgery avoid horse chestnut because the constituent aesculin may theoretically increase bleeding times<sup>58</sup>.

*Interactions with other herbs or pharmaceuticals:* It is theorized that the antithrombin activity of aesculin, a coumarin derivative, may interact with anticoagulant therapy resulting in increased bleeding time<sup>8, 58</sup>. Aescin binds to plasma protein and may affect the binding of other drugs.

*Safety during pregnancy and/or childhood:* The safety of HCSE during pregnancy and lactation has not been established<sup>8</sup>. In animal tests, there were neither cumulative effects nor any evidence of embryotoxic or teratogenic effects<sup>57</sup>.

## ***Typical Dosages***

*Provision of dosage information does NOT constitute a recommendation or endorsement, but rather indicates the range of doses commonly used in herbal practice.*

*Doses are given for single herb use and must be adjusted when using herbs in combinations.*

*Doses may also vary according to the type and severity of the condition treated and individual patient conditions.*

### *Adult doses*

*Tea:* 1-2 tsp. of dried seed infused for 10-15 minutes in 1-2 cups water, drunk three

times per day or used as a lotion<sup>59</sup>.

*Tincture:* 1-4 ml three times per day<sup>59</sup>.

*Powdered root extract:* 250-500 mg of standardized powdered extract three times per day<sup>4</sup>. Most studies have used oral doses of 600 mg per day of HCSE (equivalent to 100 mg/day of aescin), in two divided doses<sup>24</sup>.

Beta-aescin is given intravenously in Europe; adult doses are not to exceed 20 mg per day. This preparation is not available in the United States<sup>5</sup>.

*Topical use:* 1% to 2% aescin gel may be applied several times daily.

*Pediatric dosages:* Intravenous beta-aescin is used in pediatric patients in Europe. The daily maximum dose of I.V. beta-aescin for children up to three years is 0.1 mg/kg/day; for children ages 3 to 10 years it is 0.2 mg/kg/day<sup>5</sup>.

*Availability of standardized preparations:* Horse chestnut seed extract is standardized to a triterpene glycoside content of 16-21%, calculated as anhydrous aescin.

Controlled release preparations cause less stomach upset than standard forms<sup>4</sup>.

*Dosages used in herbal combinations:* Variable

*Proprietary names:* Common European preparations include Reparil<sup>®</sup> (aescin) and Venoplant<sup>®</sup> or Venostasin<sup>®</sup> (whole chestnut seed extracts)<sup>5</sup>. American brands include GNC Herbal Plus Standardized Horse Chestnut, Nature's Way Standardized Horsechestnut Extract, and Natrol Horse Chestnut, all standardized to 20% aescin. Horse chestnut seed preparations are also available in gels and ointments for external use on varicose veins; European products include Venostasin N<sup>®</sup> ointment (containing HCSE)

*Multi-ingredient preparations containing horse chestnut seed extract:* Many horse chestnut seed products also contain other ingredients including rutin and B vitamins. The European preparation Veno-Reparil<sup>®</sup> contains aescin and bioflavonoids. Essaven gel contains aescin, heparin and essential phospholipids<sup>5</sup>. Other products include Apoplectal, Bioglan Fingers & Toes, Bioveinal, Climaxol, Ginkgo Plus, Hemorrogel, and Herbal Capillary Care.

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