MONOGRAPH
FROM NATURAL STANDARD

Catherine Ulbricht, PharmD, Column Editor

Horse Chestnut: A Multidisciplinary Clinical Review

Natasha Tiffany, MD
Catherine Ulbricht, PharmD
Steve Bent, MD
Michael Smith, MRPharmS, ND
Cathi Dennehy, PharmD
Heather Boon, BScPhm, PhD
Ethan Basch, MD
E. P. Barrette, MD
David Sollars, MAc, HMC
Philippe Szapary, MD

Catherine Ulbricht is affiliated with the Natural Standard Research Collaboration (www.naturalstandard.com), 1130 Massachusetts Avenue, Cambridge, MA 02138-5204 (E-mail: kate@naturalstandard.com).

Natasha Tiffany, Heather Boon, Catherine Ulbricht, Ethan Basch, Steve Bent, E. P. Barrette, Michael Smith, David Sollars, Cathi Dennehy, and Philippe Szapary conducted this review for the National Standard Research Collaboration.

The authors would like to thank Mr. John Martinson for his support of this monograph and the ongoing research of the Natural Standard Research Collaboration. The authors also acknowledge the efforts of Michelle Nhuch, Nicole Halpenny, Charles Holmes, Paul Hammerness, and the Natural Standard research staff, which were invaluable to the compilation and analysis of research materials.

The Natural Standard Research Collaboration is an ongoing privately funded multidisciplinary project. Natural Standard employs evidence-based criteria to analyze complementary therapies, and to create decision-support materials for clinicians and patients.

ABSTRACT. Horse chestnut seed extract (HCSE) is widely used in Europe for the management of chronic venous insufficiency (CVI). Although traditionally recommended for a variety of medical conditions, CVI is the only indication for which there is strong supportive scientific evidence. Review of the literature reveals 14 randomized controlled trials, of which seven are methodologically of high quality, albeit limited by small sample sizes and short durations. These studies support the superiority of HCSE over placebo, and suggest equivalence to compression stockings and to oral oxerutins. In the future, a longer and adequately powered randomized trial is warranted to compare HCSE to standard of care, and to further assess safety and long-term efficacy. There are no data to suggest that horse chestnut flower, raw seed, branch bark, or leaf are effective for any indication, and it is recommended that these products not be used, as they are known to be toxic when ingested.

KEYWORDS. Aescin, aesculus, escin, HCSE, Hippocastanaceae, hippocastanum, horse chestnut seed extract, rosskastanie, rutin, oxerutins, venastat, venoplant, venostasin

INTRODUCTION

Horse chestnut is a member of the genus *Aesculus* and family Hippocastanaceae. The plant has pink and white flowers, and its thick-husked fruit contains one to six seeds (Figure 1). Indigenous to the mountains of Greece, Bulgaria, the Caucasus, northern Iran and the Himalayas, horse chestnut is now cultured internationally, particularly in Europe and Russia.

Horse chestnuts have been used medicinally for centuries. Indians roasted, peeled and mashed the seeds, then leached them in lime in order to render them less toxic. In European folk medicine, carrying the fruit in pockets was believed to prevent or cure arthritis.

Currently, horse chestnut seed extract (HCSE) is widely accepted in Germany for the management of chronic venous insufficiency (CVI), a syndrome characterized by incompetent veins in the lower extremities which cause edema, pain, atrophic skin changes and ulcerations. Based on German sales alone, HCSE products were the third best selling

FIGURE 1. Horse Chestnut

Photo provided free, courtesy of UK Safari <www.uksafari.com>

herbal extracts in 1996 (behind Ginkgo biloba and St. John's wort), accounting for 51 million U.S. dollars.[9]

Based on available studies, there is strong evidence to suggest that HCSE is superior to placebo in the treatment of mild to moderate CVI, and may be equivalent to compression stockings. Although the majority of trials have been small (fewer than 1500 patients studied total) and short in duration, the weight of the evidence suggests that HCSE is a viable alternative for patients suffering from CVI. An adequately powered randomized trial with long-term follow-up would strengthen the case further for this therapy.

HCSE and other forms of horse chestnut have historically been used for a myriad of other indications, for which there is insufficient human clinical trial data supporting efficacy. These include biliary diseases (cholecystitis, cholelithiasis, colic), benign prostatic hypertrophy, bladder disorders (incontinence, urinary retention), bruising (topical preparation), cough, diarrhea, dizziness, dysmenorrhea, fever, hemorrhoids (topical preparation), kidney diseases, liver (hepatic) congestion, nocturnal leg cramps, osteoarthritis, pancreatitis, phlebitis, post-operative or post-traumatic soft tissue swelling (topical preparation), rheumatoid arthritis, tinnitus, ulcers, and whooping cough.

Due to increased risk of hypoglycemia with HCSE, caution is advised in children and diabetics. There are no data to suggest that horse chestnut flower, raw seed, branch bark, or leaf are effective for any indication, and it is recommended that these products not be used, as they are known to be toxic when ingested.

METHODOLOGY

Electronic searches were conducted in Medline, EMBASE, AMED, International Pharmaceutical Abstracts, CISCOM, and the Cochrane library. Hand searches were conducted of 25 selected journals published since 1975, and of bibliographies from 50 selected secondary references. Search terms included "aescin," "*Aesculus hippocastanum*," "escin," "HCSE," "horse chestnut," "*rosskastanie*," and "Venastat" (Table 1). No restrictions were placed on language or quality of publications. Studies examining combination products were excluded. Ten researchers in the field of complementary and alternative medicine were consulted for access to additional references or ongoing studies. Blinded review was conducted on the completed monograph by nine clinician-researcher faculty in the area of complementary and alternative medicine, at major academic centers. Inclusion of studies in Table 3 was restricted to trials with scores greater than three on a validated scale described by Jadad,[1] considered to correlate r with higher-quality studies. These criteria are listed in Table 2.

PHARMACOLOGY

Horse chestnut seed contains 3-6% of a triterpene saponin mixture called escin (or aescin), flavonoids, condensed tannins, quinines, sterols and fatty acids (including linolenic acid, palmitic acid and steric acid), and coumarins (including aesculetin, fraxin [fraxetin glucoside], and

TABLE 1. Synonyms, Common Names, Brands, Related Substances

Aescin, aescine, aescule, *Aesculus hippocastanum* L., buckeye, bongay, chestnut, conkers, Conquerors, eschilo, escin, escine, fish poison, graine de marronier d'Inde, *H. vulgare* Gaertnhestekastanje, Hippocastabi folium, Hippocastani semen, horse chestnut, Marron Europeen, Marronier, Roβkastaniensamen, rosskastanie, Spanish chestnut, Venastat®, Venoplant®, Venostasin®

TABLE 2. Jadad Score Calculation[1]

Item	Score*
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described *and* appropriate (table of random numbers, computer-generated, etc.)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described *and* appropriate (identical placebo, active placebo, dummy, etc.)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described *and* it was *inappropriate* (patients were allocated alternately, or according to date of birth, hospital number, etc.).	0/−1
Deduct one point if the study was described as double blind but the method of blinding was *inappropriate* (e.g., comparison of tablet vs. injection with no double dummy).	0/−1

*Points are added, and a score ≥4 is considered high quality methodologically.

scopolin [scopoletin glucoside]). The main active ingredient is considered to be escin, which acts on capillary membranes to normalize vascular permeability. Purified escin has been shown to decrease histamine and serotonin-induced capillary hyperpermeability, and to decrease chemically-induced inflammation in rats.[2,3]

HCSE inhibits enzymes that are implicated in the pathogenesis of CVI.[4] It has been found to dose-dependently contract canine[3] and human[5] isolated saphenous veins *in vitro*, possibly due to preferential formation of the vasoconstrictive eicosanoid $PGF_{2\alpha}$.[6] HCSE has also been shown to increase femoral venous pressure and flow;[3] to decrease the formation of edema induced in rat paw models; and to suppress plasmatic extravasation and leucocyte emigration into the pleural cavity in an experimental rat model of pleurisy.[3] Additionally, the extract has been reported to have antioxidant effects.[3,7] In aggregate, these findings suggest that HCSE increases venous tone, improves venous return, and reduces vascular permeability, all which lead to the clinical benefit of dependent edema reduction.

Oral escin is not well absorbed, and undergoes substantial first-pass effect. Half-life is 10 to 20 hours.[8] Peak plasma levels occur 2-3 hours after ingestion.[9]

Horse chestnut contains a hydroxycoumarin component esculin that may have antithrombin activity. Esculin is found in the bark, buds and

TABLE 3. High Quality Trials (Jadad Score ≥4)[1]

Evidence/Study Type*	Author, Year	N	Statistically Significant Results?	Quality of Study: (Maximum score: 5)	Magnitude of Benefit (how strong is the effect?)	Duration of Treatment†	Comments
Systematic review	Pittler, 1998	13 trials	Yes	NA	Small-moderate reductions in ankle circumference, leg volume. Decreased leg pain, pruritis, fatigue, "tenseness."	NA	Well-designed, comprehensive. Did not include low-quality Alter (1973) trial.
RCT, placebo-controlled	Friederich, 1978	118	Yes	4	Reduction in lower leg pain and spasm in therapy group vs. placebo.	3 weeks.	1 tablet (50 mg escin) twice daily. Large number of dropouts (19%).
RCT, placebo controlled	Bisler, 1986	24	Yes	5	Capillary filtration coefficient reduced by 22% with HCSE vs. slight rise with placebo.	NA	2 tablets (50 mg escin each) once daily. Small trial, which only looked at acute effects post 1 dose.
RCT, placebo controlled	Rudofsky, 1986	40	Yes	5	Leg volume reduction of 44 mL compared with increased volume in placebo.	4 weeks.	1 tablet (50 mg escin) twice daily. Small trial.
RCT, placebo-controlled	Pilz, 1990	30	Yes	4	Leg circumference decreased 0.8 cm in treatment group, vs. 0.1 cm in placebo.	3 weeks.	1 tablet (50 mg escin) twice daily. Small trial.
RCT, placebo controlled	Diehm, 1992	40	Yes	4	Leg volume reduced by 84 mL with HCSE compared with reduction of 4 mL in placebo group.	6 weeks.	1 tablet (75 mg escin) twice daily. Small trial.
RCT, compared with oxerutins	Rehn, 1996	137	Yes	4	HCSE equivalent to oxerutins at 4 weeks in reducing leg edema and symptoms.	12 weeks.	1 tablet (50 mg escin) twice daily. No power calculation conducted towards equivalence.
RCT, compared with oxerutins	Kalbfleisch, 1989	33	No	4	Lower leg circumference decreased 0.18 cm, no significant difference from oxerutins.	8 weeks.	1 tablet (50 mg escin) once daily. Small trial. No power calculation conducted towards equivalence.

*RCT = Randomized controlled trial †NA = Not applicable

other parts of the fruits, but should not be present in properly extracted HCSE.

ADULT DOSING (AGE ≥18)

Oral: Horse chestnut seed extract products are generally standardized to contain 16-20% triterpene glycosides calculated as escin content. Although a range of doses are noted in the literature, clinical trial data suggest that it is necessary to ingest a product standardized to escin content that provides approximately the equivalent of 50-75 mg escin every 12 hours to obtain benefit.

Topical: A trial of topical 2% escin gel (applied 3-4 times daily) vs. placebo for experimentally induced hematoma aimed to demonstrate reduction in tenderness, but the results were not statistically significant.[10] Therefore, at this time no specific topical concentration or dose can be recommended.

Intravenous: There is no reliable data to support the use of HCSE intravenously for any indication, and anaphylactic shock has been reported.[11]

PEDIATRIC DOSING (AGE < 18)

There are no data supporting the use of HCSE in children, and chronic venous insufficiency is generally seen only in adults. It is recommended that children not take HCSE due to its potential for toxicity. Children drinking tea from leaves, twigs or eating raw horse chestnut seeds have been poisoned, and death has been reported.[12]

TOXICOLOGY

Due to known toxicology of horse chestnut, only preparations of HCSE standardized to escin content should be ingested. Eating the seed itself, the nut, leaves, bark, or any other part of the chestnut, which may contain esculin, is likely to be associated with significant toxicity or death. Teas made from any part of the chestnut, other than the horse chestnut seed extract, should be avoided. Horse chestnut poisoning can cause vomiting, diarrhea, headache, stupor, coma, and paralysis. It may also cause weakness, muscle fasciculation, and malcoordination.[13]

The LD_{50} of the water-soluble portion of a non-standardized alcoholic extract of horse chestnut seeds given as a single dose has been calculated as 10.6 mg/g body weight in chicks and 10.7 mg/g body weight in hamsters.[13] However, dried, powdered seeds were found to be nontoxic when fed to chicks and hamsters at a dose of 80 mg/g body weight.[13]

Aflatoxins, which are considered to be potent carcinogens, have been identified in commercial skin products containing horse chestnut,[14] but not in HCSE.

ALLERGY

HCSE should be avoided in patients with known allergy to HCSE, or to any of its ingredients (flavonoids, biosides, trisides of quertins, and oligosacharides including l-ketose and 2-ketose). Intravenous administration of horse chestnut has been reported to cause anaphylactic shock.[11] Horse chestnut pollen can cause allergic sensitization in children.[15]

ADVERSE EFFECTS

Standardized HCSE is generally believed to be safe. An observational study of > 5000 subjects found the incidence of adverse effects to be 0.6%,[16] and is up to 3.0% in the 14 available randomized trials. Gastrointestinal tract upset and calf spasm are the most common symptoms, while headache, nausea and pruritis are less frequent.

- *Dermatologic:* Pruritis has been rarely documented in the available HCSE randomized trials, and is likely similar in incidence to placebo. Contact dermatitis has been reported following topical application of HCSE.[17]
- *Gastrointestinal:* Mild nausea and dyspepsia have been documented amongst few subjects in HCSE trials.[18]
- *Hepatic:* Horse chestnut leaf has been associated with hepatitis after intramuscular injection.[19] A 69-year-old woman taking Venocapsan® containing horse chestnut leaf experienced hepatotoxicity which resolved after discontinuing the product.[20]
- *Renal:* There have been case reports of nephrotoxicity associated with high parenteral doses of escin (HCSE).[21,22]

- *Neurologic:* Occasional headache and dizziness have been reported with HCSE, although the exact frequency is not clear in published clinical trials. One trial (n = 62) reported a composite adverse event rate of 3.2%, in which headache and transient dizziness were listed.[18]
- *Musculoskeletal:* Calf spasm has been reported by a small number of subjects in an observational study involving > 5000 patients with CVI taking HCSE.[16]
- *Hematologic:* Horse chestnut theoretically may increase the risk of bleeding due to the hydroxycoumarin content of esculin. Properly extracted HCSE should not contain esculin, and therefore should not carry the same interaction risks.

PREGNANCY AND LACTATION

HCSE is generally not recommended during pregnancy or nursing due to lack of information regarding toxicity. However, Steiner et al. conducted a placebo controlled, double-blind study of 52 pregnant women with leg edema associated with pregnancy-induced venous insufficiency, and failed to observe any serious adverse effects following two weeks of therapy. The study was a crossover design, in which women were given one capsule twice daily of Venostasin® retard, each tablet containing 300 mg of standardized extract (240-290 mg of HCSE with 50 mg of escin).[23]

INTERACTIONS

- *Anticoagulants:* Due to its esculin constituents, horse chestnut (but not HCSE, which when properly prepared does not contain esculin) may theoretically increase the risk of bleeding when taken with anticoagulants (warfarin, heparin) or anti-platelet drugs (including aspirin, clopidogrel, ticlopidine, and non-steroidal anti-inflammatory drugs). However, our literature review has revealed no documented clinical cases of bleeding in such patients. Horse chestnut may also have additive effects with herbs considered to predispose to bleeding via effects on platelets, bleeding time, or the coagulation cascade. These include: angelica, anise, arnica, asafoetida, bogbean, boldo, capsicum, celery, clove, chamomile, danshen, fenugreek, feverfew, garlic, ginger, ginkgo, gymnestra,

horseradish, licorice, meadowsweet, prickly ash, onion, papain, passionflower, poplar, quassia, red clover, turmeric, wild carrot, wild lettuce, and willow.

- *Protein-binding drugs:* Escin may interfere with protein-bound drugs such as phenytoin, warfarin or amiodarone, although literature review has revealed no documented reports.
- *Hypoglycemic agents:* HCSE has been noted to inhibit the normal increase of serum glucose levels in glucose loaded rats.[24] HCSE may have an additive effect when taken together with drugs that can cause hypoglycemia, including sulfonylureas, insulin or metformin. Herbs that can lower blood sugar, such as bitter melon, panax ginseng and American ginseng (*Panax quinquefolius*), should be used cautiously with horse chestnut seed extract, as there may be an additive effect. However, literature review has revealed no documented interactions in humans.

REVIEW OF THE EVIDENCE

Review of the literature identified 14 randomized controlled trials of HCSE for CVI.[18,23,25-36] All but one of these[25] was identified in a well-designed 1998 systematic review by Pittler and Ernst,[37] which followed established standards for locating studies, rating quality, abstracting data, and pooling results.

The one trial not identified in the systematic review claimed a double-blind placebo-controlled design of HCSE in 96 patients for three weeks.[25] Results showed a decrease in lower leg edema, pain, and pruritis. However, this study was methodologically flawed with limited description of randomization, outcomes measurement, or dropouts.

Of the remaining 13 trials, five were placebo-controlled, and eight were compared with reference medications. In general, the placebo-controlled trials found statistically significant decreases in lower leg and ankle circumference, leg volume, and symptoms of leg pain, pruritis, fatigue and "tenseness." HCSE doses included one tablet taken twice-daily or two tablets taken once-daily (standardized to 50-75 mg escin/tablet). The most common reference medication in the remaining trials was a derivative of the flavonoid rutin used in Germany for CVI, which most trials found to be equivalent to HCSE.

Using a validated methodological quality rating scale described by Jadad (Table 2),[1] seven trials were found to have a score of 3,[23,25,28-30,33,34] felt to correlate with lower quality. The remaining trials, felt to be

of higher methodological quality, are described in Table 3. Selected studies are discussed below.

Preliminary evidence stemmed from trials by Friedrich et al.[31] and Bisler et al.[26] The Friedrich group examined symptoms of CVI in a crossover trial of 118 subjects, in which patients received 50 mg of escin twice daily for three weeks. Statistically significant reductions in pain, lower leg spasm, and fatigue were found vs. placebo. However, this study was limited by a 19% dropout rate, without ample follow-up or examination of dropouts. In the Bisler trial, 22 patients with documented CVI were randomized to receive a 1200 mg dose of Venostasin® (a German preparation of HCSE containing 100 mg of escin) or placebo, then to crossover. This double-blind study found a statistically significant 22% decrease in the capillary filtration coefficient three hours after taking HCSE. The authors concluded that Venostasin® may have an inhibitory effect on edema formation via a decrease in transcapillary filtration.

Rudofsky conducted a well-designed (albeit small) randomized, double-blind, placebo controlled study using a parallel design.[36] This trial compared HCSE (Venostasin® retard, containing 50 mg escin, one tablet twice daily) vs. placebo over 4 weeks in 40 subjects (67% women). The results demonstrated a statistically significant reduction in leg volume of 44 mL from baseline as measured by liquid plethysmography, vs. the placebo group which experienced an increase in volume from baseline. While this study failed to show a significant effect on venous capacity, it did demonstrate a statistically significant change in both calf and foot circumference ($p < 0.01$). At 28 days, HCSE treated patients had a mean decrease in ankle circumference of 6.5 mm as compared to a l mm increase in placebo treated patients. In addition, there were significant improvements in pain, pruritus, fatigability and fullness in the HCSE treated group by a five-point Likert scale.

Pilz conducted a randomized controlled trial in which HCSE subjects ingested 50 mg escin twice daily for three weeks, and were found to have a statistically significant reduction in ankle circumference of 0.7 cm vs. placebo.[35] This study was limited by its small size ($n = 30$), and unclear level of compliance. Diehm et al. followed this trial with a well-designed placebo-controlled study of 40 patients with chronic venous insufficiency.[27] Subjects received either placebo or HCSE (75 mg escin twice daily) for 6 weeks. Patients who received HCSE had significantly decreased leg volume both at rest and after edema provocation (allowing legs to hang down while patients sat for 15 minutes). Patients

in the treatment group also had significantly fewer symptoms of chronic venous stasis (feeling of heaviness, leg fatigue, numbness).

The same group of authors conducted a second larger randomized, partially double blinded study comparing leg compression stockings to oral HCSE (50 mg escin twice daily) and placebo in 240 patients with CVI.[28] The trial was partially blinded by necessity, since those subjects randomized to compression stockings were aware of their treatment assignment, while subjects receiving HCSE or placebo were blinded. As a result, this trial is considered to be of lesser methodological quality, revealing the difficulty of blinding patients using compression stockings. After 12 weeks of therapy, mean lower leg volume decreased by 53.6 mL with HCSE and by 56.6 mL with compression stocking treatment, when compared to the placebo group. HCSE and compression stocking treatment had comparable effects and were well tolerated. Compliance with compression stockings in this trial was 90% compared to 98% compliance with HCSE. Notably, the compliance with compression stockings outside of a clinical trial has been reported to be 47%,[28] which makes HCSE an even more attractive option in the treatment of symptomatic CVI. Although some authors have challenged the leg volume measurements used in this study,[38,39] the results lend support to the claim that HCSE can be beneficial in the treatment of venous insufficiency.

Rehn et al. conducted the longest duration randomized double-blind study of patients with CVI.[18] Subjects (n = 137) were randomized to three treatment arms, two with oxerutins and one with HCSE (100 mg escin per day). Outcomes were assessed at 12 weeks and at six weeks after ceasing treatment. Patients receiving HCSE experienced a 28 mL mean decrease in leg volume at 12 weeks (compared with mean reductions of 57.9 mL and 40.2 mL in the two control groups). Although results were stated as statistically significant, p-values were not reported. Oxerutins were also compared to HCSE in a small (n = 33) trial conducted by Kalbfleisch and Pfalzgraf.[32] Over an eight-week period, 50 mg of escin/day was compared with 500 mg/day of oxerutins. No statistically significant difference was found between the groups, both experiencing reductions in lower leg circumference of 0.18-0.20 cm. In review of these two trials,[18,32] it is not clear that either was adequately powered to assess the equivalence of the treatments. A follow-up study using a power calculation in its methodology would provide further support of these results.

CONCLUSION

Horse chestnut seed extract is used medicinally for multiple conditions, but chronic venous insufficiency is the only indication for which there is strong supporting evidence from randomized controlled trials. There is preliminary evidence suggesting equivalence to compression stockings, and several studies demonstrating equivalence to oxerutins. While the majority of trials have been small and of short duration, the weight of evidence to date suggests that HCSE is a viable medical alternative in the treatment of this often disabling condition. Since CVI is a chronic condition, presumably requiring long-term treatment with HCSE, a longer and adequately powered randomized controlled trial comparing HCSE to compression stockings is needed to assess safety and to establish continued efficacy of HCSE. Such a study could also better evaluate symptomatology, walking distance, time to ulceration or surgery, and validated quality-of-life scores.

The most common dosing in clinical trials is one tablet twice-daily or two tablets one-daily of HCSE (standardized to 50-75 mg escin/tablet). Brands used in statistically significant clinical trials include Venostasin® retard (Klinge Pharma, standardized to contain 50 mg escin per capsule), Venoplant® (Schwabe), and Venastat® (Pharmaton). The U.S. equivalent of the most commonly recommended European brands is Venastat Supro Caps® (Pharmaton).

REFERENCES

1. Jadad, A. R., Moore, R. A., Carroll, D., Jenkinson, C., Reynolds, D. J., Gavaghan, D. J., and McQuay, H. J. Assessing the Quality of Reports of Randomized Clinical Trials: Is Blinding Necessary? Control Clin Trials 1996;17(1):1-12.

2. Matsuda, H., Li, Y., Murakami, T., Ninomiya, K., Yamahara, J., and Yoshikawa, M. Effects of Escins Ia, Ib, IIa, and IIb From Horse Chestnut, the Seeds of *Aesculus hippocastanum* L., on Acute Inflammation in Animals. Biol Pharm Bull. 1997;20(10):1092-5.

3. Guillaume, M. and Padioleau, F. Veinotonic Effect, Vascular Protection, Anti-inflammatory and Free Radical Scavenging Properties of Horse Chestnut Extract. Arzneimittelforschung 1994;44(1):25-35.

4. Kreysel, H. W., Nissen, H. P., and Enghofer, E. A Possible Role of Lysosomal Enzymes in the Pathogenesis of Varicosis and the Reduction in Their Serum Activity by Venostasin. Vasa 1983;12(4):377-82.

5. Brunner, F., Hoffmann, C., and Schuller-Petrovic, S. Responsiveness of Human Varicose Saphenous Veins to Vasoactive Agents. Br J Clin Pharmacol. 200l;51(3): 219-24.

6. Longiave, D., Omini, C., Nicosia, S., and Berti, F. The Mode of Action of Aescin on Isolated Veins: Relationship with PGF2 Alpha. Pharmacol Res Commun. 1978;10(2):145-52.

7. Masaki, H., Sakaki, S., Atsumi, T., and Sakurai, H. Active-Oxygen Scavenging Activity of Plant Extracts. Biol Pharm Bull. 1995;18(l):162-6.

8. Schrader, E., Schwankl, W., Sieder, C., and Christoffel, V. [Comparison of the Bioavailability of Beta-Aescin After Single Oral Administration of Two Different Drug Formulations Containing an Extract of Horse-Chestnut Seeds]. Pharmazie 1995; 50(9):623-7.

9. Schulz, V., Hansel, R., and Tyler, V. (eds.) Rational Phytotherapy. Third Edition. Berlin: Springer 1998.

10. Calabrese, C. and Preston, P. Report of the Results of a Double-Blind, Randomized, Single-Dose Trial of a Topical 2% Escin Gel versus Placebo in the Acute Treatment of Experimentally-Induced Hematoma in Volunteers. Planta Med. 1993;59(5): 394-7.

11. Jaspersen-Schib, R., Theus, L., Guirguis-Oeschger, M., Gossweiler, B., and Meier-Abt, P. J. [Serious Plant Poisonings in Switzerland 1966-1994. Case Analysis from the Swiss Toxicology Information Center]. Schweiz Med Wochenschr 6-22-1996; 126(25):1085-98.

12. Hardin, J. Human Poisoning from Native and Cultivated Plants. Durham, NC: Duke University Press 1974;(2).

13. Williams, M. C. and Olsen, J. D. Toxicity of Seeds of Three *Aesculus* spp. to Chicks and Hamsters. Am J Vet Res. 1984;45(3):539-42.

14. el Dessouki, S. Aflatoxins in Cosmetics Containing Substrates for Aflatoxin-Producing Fungi. Food Chem Toxicol. 1992;30(11):993-4.

15. Popp, W., Horak, F., Jager, S., Reiser, K., Wagner, C., and Zwick, H. Horse Chestnut (*Aesculus hippocastanum*) Pollen: A Frequent Cause of Allergic Sensitization in Urban Children. Allergy 1992;47(4 Pt 2):380-3.

16. Greeske, K. and Pohlmann, B. K. [Horse Chestnut Seed Extract–An Effective Therapy Principle in General Practice. Drug Therapy of Chronic Venous Insufficiency]. Fortschr Med. 5-30-1996;114(15):196-200.

17. Comaish, J. S. and Kersey, P. J. Contact Dermatitis to Extract of Horse Chestnut (Esculin). Contact Dermatitis 1980;6(2):150-1.

18. Rehn, D., Unkauf, M., Klein, P., Jost, V., and Lucker, P. W. Comparative Clinical Efficacy and Tolerability of Oxerutins and Horse Chestnut Extract in Patients with Chronic Venous Insufficiency. Arzneimittelforschung 1996;46(5):483-7.

19. Takegoshi, K., Tohyama, T., Okuda, K., Suzuki, K., and Ohta, G. A Case of Venoplant-Induced Hepatic Injury. Gastroenterol Jpn. 1986;21(1):62-5.

20. De Smet, P. A. G. M., van den Eertwegh, A. J. M., Lesterhuis, W., and Stricker, B. H. Hepatotoxicity Associated with Herbal Tablets. BMJ 1996;313:92.

21. Klose, P. and Pistor, K. [The Post-Traumatic Renal Failure in 2 Children Following Therapy with BetaEscin]. MMW Munch Med Wochenschr 5-28-1976;118(22): 719-20.

22. Grasso, A. and Covaglia, E. Two Cases of Suspected Toxic Tubluonephrosis Due Escine. Gass Med Ital. 1976;135:581-4.

23. Steiner M. Untersuchungen Zur Odemvermindernden Und Odemportektiven Wirking Von Ro Kastaniensamenextrakt. Phlebol Prokto 1990;19:239-42.

24. Yoshikawa, M., Murakami, T., Yamahara, J., and Matsuda, H. Bioactive Saponins and Glycosides. XII. Horse Chestnut. (2): Structures of Escins IIIb, IV, V, and VI and Isoescins Ia, Ib, and V, Acylated Polyhydroxyoleanene Triterpene Oligoglycosides, from the Seeds of Horse Chestnut Tree (*Aesculus hippocastanum* L., Hippocastanaceae). Chem Pharm Bull. (Tokyo) 1998;46(11):1764-9.

25. Alter, H. Zur Medlkamentosen Therapie Der Varlkosis. Z Allg Med 1973; 49(17):1301-4.

26. Bisler, H., Pfeifer, R., Kluken, N., and Pauschinger, P. [Effects of Horse-Chestnut Seed Extract on Transcapillary Filtration in Chronic Venous Insufficiency]. Dtsch Med Wochenschr 8-29-1986;111(35):1321-9.

27. Diehm, C., Vollbrecht, D., Amendt, K., and Comberg, H. U. Medical Edema Protection–Clinical Benefit in Patients with Chronic Deep Vein Incompetence. A Placebo Controlled Double Blind Study. Vasa 1992;21(2):188-92.

28. Diehm, C., Trampisch, H. J., Lange, S., and Schmidt, C. Comparison of Leg Compression Stocking and Oral Horse-Chestnut Seed Extract Therapy in Patients with Chronic Venous Insufficiency. Lancet 2-3-1996;347(8997):292-4.

29. Erdlen, F. Klinische Wirksamkeit Von Venostasin Retard Im Doppelblindversuch. Med Welt 1989;40:994-6.

30. Erler, M. Rokastaniensamenextrakt Bei Der Therapie Peripherer Venoser Odeme: Ein Klinischer Therapievergleich. Med Welt 1991;43:593-6.

31. Friederich, H. C., Vogelsberg, H., and Neiss, A. [Evaluation of Internally Effective Venous Drugs]. Z Hautkr. 6-1-1978;53(11):369-74.

32. Kalbfleisch, W. and Pfalzgraf, H. Odemprotektiva: Aquipotente Dosierung: Rokastaniensamenextrakt Und O-Beta-Hydroxyethylrutoside Im Vergleich. Therapiewoche 1989;39:3703-7.

33. Lohr, E., Garanin, P., Jesau, P., et al. [Anti-Edemic Therapy in Chronic Venous Insufficiency with Tendency to Formation of Edema]. Munch. Med Wochenschr 1986;128:579-81.

34. Neiss, A. and Bohm, C. [Demonstration of the Effectiveness of the Horse-Chestnut-Seed Extract in the Varicose Syndrome Complex]. MMW. Munch Med Wochenschr 2-13-1976;118(7):213-6.

35. Pilz, E. Odeme Bei Venenerkrankungen. Med Welt. 1990;40:1143-4.

36. Rudofsky, G., et al. Odemprotektive Wirkung Und Klinische Wirksamkeit Von Ro Kastaniensamenextrakt Im Doppeltblindversuch. Phleb Prokto. 1986;15:47-54.

37. Pittler, M. H. and Ernst, E. Horse-Chestnut Seed Extract for Chronic Venous Insufficiency. A Criteria-Based Systematic Review. Arch Dermatol. 1998;134(11): 1356-60.

38. Vayssairat, M., Debure, C., Maurel, A., and Gaitz, J. P. Horse-Chestnut Seed Extract for Chronic Venous Insufficiency. Lancet 4-27-1996;347(9009):1182.

39. Simini, B. Horse-Chestnut Seed Extract for Chronic Venous Insufficiency. Lancet 4-27-1996;347(9009):1182-3.