Monograph

Aesculus hippocastanum (Horse chestnut)

Introduction

Aesculus hippocastanum (horse chestnut) is a large deciduous, rapidly-growing tree that can reach a height of 36 meters. It is native to the countries of the Balkan Peninsula, but because of its large, showy flower clusters the tree is cultivated worldwide for its beauty. Flowers are white or pink with a small red spot. Leaves are large, consisting of either five or seven leaflets and the fruit is round with a thick, green, spiny husk containing a glossy brown seed (chestnut or conker). While the common name for the tree is horse chestnut, it is also known as buckeye, and like other buckeyes, is a member of the Hippocastanaceae family, rather than the chestnut family (Castanea). The name, horse chestnut, is believed to be derived from the brown conkers that look similar to chestnuts and because a horseshoe shaped mark (complete with spots resembling horseshoe nails) is left on the twig when the leaves drop off in autumn.[1,2]

Historically, the seed extract was used as a treatment for many ailments, including rheumatism, rectal complaints,[3] bladder and gastrointestinal disorders, fever (first written account in 1720), hemorrhoids (as early as 1886),[4] and leg cramps.[5] Currently, horse chestnut seed extract (HCSE) is widely used in Europe for chronic venous insufficiency, hemorrhoids, post-operative edema, and topically for clearing skin conditions. In the United States, HCSE is gaining wider acceptance as an effective therapy for venous disorders and edema, based on the publication over the last two decades of numerous randomized controlled trials in prominent, peer-reviewed journals.[4]

Active Constituents

The primary active constituent found in horse chestnut seed extract is aescin. Aescin is actually a mixture of triterpene saponins present in two forms, α and β, which are distinguished by their water solubility and melting points. Other constituents include bioflavonoids (quercetin and kaempferol), proanthocyanidin A2 (an antioxidant), and the coumarins fraxin and aesculin.[6] In 1960, Lorenz and Marek determined the anti-edematous and vasoprotective properties observed after administering an extract from the horse chestnut were due exclusively to aescin. Of the two forms of aescin, β-aescin is the active component in the saponin mixture and the form found in most HCSE pharmaceuticals used for venous insufficiency.[7]

Mechanisms of Action

Aescin from HCSE has been shown to have anti-edematous, anti-inflammatory, and venotonic properties that may be attributable to decreased vascular permeability.[8]

Anti-edematous

HCSE administration increases sensitization to calcium ions, decreases permeability of small vessels, and enhances venous contractile activity, thereby improving venous tone and having a "sealing effect" at the sight of injury. The end result is decreased edema and swelling.[8,9] Aescin's anti-edematous property is also attributed in part to its inhibition of hypoxia and the resultant reduction of ATP content in endothelial cells. Reduced endothelial ATP levels initiate the release of prostaglandins, platelet activating factor, and neutrophil chemotaxis, leading to venous stasis and edema.[10-12] Aescin also reduces the adherence and activation of white blood cells, thereby inhibiting edema and protecting the vessels.[13]

Anti-inflammatory

The anti-inflammatory properties of aescin have been demonstrated in animal models and suggest it interferes with the release of inflammatory mediators by decreasing leukocyte activation and adhesiveness. In a rat model of pleurisy, aescin administration decreased leukocyte migration into the pleural cavity and inhibited the release of inflammatory mediators.[13] A human study of patients with chronic venous insufficiency showed 5 mg aescin given intravenously twice daily for a week resulted in a 33-percent reduction of leukocyte density, a 50-percent decrease in macrophage numbers, and a 46-percent increase in neutrophils in inflammatory exudates.[14]

Venotonic

Animal studies in dogs and *in vitro* studies using human saphenous veins demonstrated aescin's venotonic properties are linked to its ability to enhance production of prostaglandin F2. Prostaglandin F2 inhibits catabolism of venous tissue mucopolysaccharides and improves venous contractility.[4] In dogs, 25-50 mg injected aescin resulted in a dose-related increase in venous pressure of nearly 21 percent, with an increase in final maximum pressure of 30 percent compared to baseline.[13]

In the *in vitro* study using human saphenous veins, a dose-response curve demonstrated purified β-aescin increased venous tone by 10-20 percent at low concentrations that would correspond to reasonable oral dosing in humans.[15]

Clinical Indications

Chronic Venous Insufficiency

Chronic venous insufficiency (CVI) is the inability of the veins in the lower leg to carry blood back toward the heart and is usually attributed to either valve damage within the leg veins or deep vein thrombosis blockage, which results in blood leakage and pooling in the legs and feet.[16] CVI is characterized by a tired, "heavy," achy feeling in the lower legs, dry and/or discolored skin, swelling (edema), varicose veins, or leg ulcers. Some individuals experience pain upon walking or prolonged standing. CVI is typically classified according to severity as follows: stage I: edema; stage II: skin discoloration or varicose veins accompanying edema; and stage III: edema, skin changes, and the presence of leg ulcers (either open or healed).[17] Statistics indicate 20-25 percent of women and 10-15 percent of men suffer from CVI at some time in life, with the incidence increasing with age.[18]

Typically, CVI is treated with compression stockings or wraps to encourage blood flow up the leg; vascular surgery is used when compression stockings fail. With compression therapy, compliance is poor due to discomfort, and surgery is often not a desirable option. A combination therapy of compression stockings and medication to relieve swelling is currently the most typically used therapy in the United States. In Europe, where it has been studied extensively, HCSE is a more popular choice and has been shown in numerous clinical trials to be a highly effective therapy, equal to that of compression stockings.[19]

A criteria-based systematic review of double-blind, randomized, controlled trials utilizing oral horse chestnut extract for patients with chronic venous insufficiency was conducted by Ernst and Pittler in 1998[20] and updated in 2004.[21] Eighteen clinical trials with a total of 1,258 subjects and three observational studies with 10,725 subjects were reviewed.[22-24] Trial length ranged from 2-12 weeks with dosage between 100-150 mg aescin daily. Six of the 18 trials compared HCSE to other medications such as diosmin[25] or O-hydroxy-rutosides,[26-29] or to compression stockings,[29] while the remaining 12 trials compared HCSE to placebo. Overall, HCSE treatment was associated with a statistically significant improvement in the CVI symptoms. Compared to placebo, general findings were reductions in lower-leg

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volume, leg circumference at the calf and ankle, leg pain, itching, fatigue, and tenseness. Adverse effects were mild and comparable to placebo.[21]

In a randomized, partially blinded, placebo-controlled, parallel study, 240 patients with chronic venous insufficiency were treated for 12 weeks with compression stockings, HCSE, or placebo. In the more severely affected limb, lower leg volume decreased an average of 43.8 mL with HCSE and 46.7 mL with compression therapy, compared to an average increase of 9.8 mL with placebo. While this trial was included in the Pittler and Ernst meta-analysis, it is the only trial to date to compare HCSE with compression stockings, the most commonly used treatment for CVI in the United States. These results indicate that compression stocking therapy and horse chestnut therapy are equally effective for patients with chronic venous insufficiency and edema. Due to the low rate of side effects observed with HCSE, it seems likely that better patient compliance might be achieved with HCSE than with compression stocking therapy.[19]

Varicose Veins

Varicose veins are a result of CVI and usually manifest during stage II. Sclerotherapy, laser surgery, or surgical vein stripping are the recommended treatments. In a meta-analysis of five clinical studies on treatment of CVI with HCSE, Suter et al reported on one trial that explored the effect of HCSE on varicose veins. Thirty-nine patients with varicose veins took 1-2 tablets (20 mg aescin each) three times daily and also applied a two-percent aescin gel topically twice daily (average = 4.4 mL daily) for eight weeks. Fifty-eight percent of subjects reported good overall efficacy for the combination treatment. Blue skin discoloration, pain, edema, and leg heaviness were significantly improved at the end of the treatment period compared to baseline.[30]

Venous Stasis Ulcers

Venous stasis ulcers of the lower limb can occur when CVI is left untreated or is refractory to treatment. Because HCSE inhibits several aspects of CVI and has a "sealing effect" on venous tissue, it seems likely HCSE would be an effective treatment for venous stasis ulcers. To date, one clinical trial has been conducted. In a small, triple-blind, randomized, placebo-controlled trial conducted at a community nursing service in Southern Australia, 54 patients with venous stasis ulcers received either HCSE (n=27) or placebo (n=27) for 12 weeks. Ulcers were assessed at baseline, 0, 4, 8, and 12 weeks for wound dimensions, wound topography, dressing changes, and symptoms. Due to sample size the study was somewhat underpowered; however, statistically significant improvements were noted in two parameters. First the rate of wound slough from baseline to study completion in the subjects receiving HCSE decreased significantly compared to those receiving placebo. Second, subjects in the HCSE group experienced a significant decrease in dressing changes (2.1 per week at baseline improved to 1.1 per week) at week 12, compared to 2.4 per week at baseline and 2.5 per week at week 12 in the placebo group.[31]

Post-Operative Edema

Surgeries involving large limbs or lymph nodes often result in post-operative edema in the affected limb. Two clinical trials demonstrate HCSE given intravenously decreases skin temperature and edema in post-surgical patients. In the first trial, patients undergoing surgery for hernia repair (n=33), meniscus removal (n=24), or lower leg fracture (n=15), received intravenous aescin treatment (5-10 mg aescin twice daily) on the day prior to and three days after surgery. The primary endpoint of the trial was skin temperature comparison between the surgical area and the contralateral side. Skin temperature is a relevant indicator of circulation and swelling in the affected limb. In the post-surgical patients receiving intravenous aescin, skin temperature was lower in the operated side than in the post-surgical patients receiving no treatment.[32]

In the second trial, patients undergoing hand surgery received 10 mg intravenous aescin twice daily (n=27; duration unknown) or no treatment (n=26) and were assessed with infrared thermography until symptoms disappeared. In the patients receiving aescin, peak hand temperature difference (between treated side and contralateral side) was noted on the second post-operative day, indicating improvement in skin circulation and swelling, compared to subjects in the non-treated group for whom peak hand temperature difference was not observed until four days post-surgery.[33]

In addition to these two clinical trials, numerous open-label studies have been published (in German and French) exploring the use of aescin, some with oral dosing. Overall, more than 1,200 surgical patients (having various major surgeries) were involved, and most studies cited report therapeutic benefit from aescin treatment in the form of decreased edema. English full text of these published studies was not available for evaluation.[34]

Hemorrhoids

Hemorrhoids are characterized by congestion of internal and/or external veins around the anal canal. Hemorrhoids may be a result of straining during defecation, chronic constipation or diarrhea, anal intercourse, pregnancy, or aging. Two-thirds of healthy people reporting for physical examinations have hemorrhoids. Conventional treatments for hemorrhoids include topical anti-inflammatory agents, astringent creams, rubber band ligation, or surgery when severe.

While horse chestnut seed extract has been used effectively to treat hemorrhoids, supportive clinical research is limited. One double-blind, placebo-controlled trial, published in French (full text not available), demonstrated that HCSE (40-mg aescin tablet three times daily for two months) given to patients with acute symptomatic hemorrhoids significantly improved symptoms, endoscopic evaluation, and bleeding after less than a week of treatment. Of 38 patients receiving aescin, 31 (82%) reported significant improvement in symptoms (pain, itching, burning, swelling), compared to only 11 of 34 (32%) in the placebo group. Endoscopic evaluation revealed significantly decreased bleeding in 26 patients taking aescin compared to 13 in the placebo group, as well as decreased swelling in 29 patients taking aescin compared to 12 in the placebo group. Average time to symptom improvement was six days for the aescin group.[35]

Inner Ear Perfusion

Based on aescin's anti-inflammatory and venotonic properties and the vasoprotective antioxidant properties of troxerutin, a natural flavonoid derivative, researchers investigated whether the combination of the two would have an effect on treating inner ear disturbances. Many of these conditions and the resultant loss of hearing are known to be due to circulatory insufficiency in the inner ear.

In a randomized clinical trial of 68 people with inner ear disturbances and hearing loss, Siegers et al administered 25 mg aescin and 450 mg troxerutin orally five times daily (daily total of 125 mg aescin and 2,250 mg troxerutin) to 34 men and women (average age=59.7) for approximately six weeks. Thirty-four subjects (average age=57.7) in the control group received 600 mg pentoxifylline (a drug that improves blood flow, blood rheology, and inhibits inflammation) daily. The primary endpoint was hearing improvement of at least 10 decibels (dB) between baseline and the end of the study. Among subjects in the aescin/troxerutin group, 23 of 34 (68 percent) experienced greater than 10 dB hearing improvement, seven of which improved by more than 14 dB from baseline. In the control group (pentoxifylline) only six patients of 34 (18 percent) improved more than 10 dB. Both medications were well tolerated without major adverse events.[36]

Herb-Drug Interactions

It is possible that aesculin, a hydroxycoumarin, may potentiate the effect of anticoagulant medications. However, other research suggests this effect is only seen with aesculin, a bark constituent not found in HCSE.[37]

Due to lack of clinical research in pregnant or nursing women, HCSE is contraindicated in this patient population.

Side Effects and Toxicity

HCSE is associated with relatively few side effects and is generally considered to be safe when given at recommended dosages. Preclinical studies on the safety of HCSE showed no oral toxicity or mutagenic or teratogenic activity.[38] In clinical trials for CVI published to date, the rate of adverse events associated with HCSE administration is 0.9-3.0 percent, comparable to placebo.[4] The most frequently reported adverse events are gastrointestinal symptoms, dizziness, headaches, and itching. Gastrointestinal side effects are more often associated with high doses of HCSE.

In the case of topically applied aescin, rare incidences of acute anaphylactic reaction have been reported.[39] Lesser skin sensitivities to topical HCSE are characterized by redness and itching at the site of application.

Dosage

HCSE extracts are typically standardized to contain 16-20 percent aescin, but HCSE with 70-percent aescin is available and has been used in some clinical trials. Regardless of extract standardization, the oral dosage used in most studies is 100-150 mg aescin daily. Topical HCSE preparations are typically two-percent aescin and are usually applied 3-4 times daily.

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