

Botanicals for Chronic Venous Insufficiency

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Abstract

Chronic venous insufficiency (CVI) is a disorder that affects 5–35% of the United States population. CVI arises in a state of chronic venous hypertension that alters the permeability of the skin's microcirculation. Leakage of protein and other matter from the blood vessels leads to edema and inflammation-induced tissue injury. The end result is fibrotic and edematous skin, with damage to capillaries involved in nutrient supply and gas exchange. The mainstay of allopathic treatment of CVI is compression therapy to control edema and venous hypertension. In Europe, botanicals are commonly added to this as adjunctive therapy for CVI, and have shown great benefit. The botanicals used include *Ruscus aculeatus* (butcher's broom) root, *Aesculus hippocastanum* (horse chestnut) seed, *Centella asiatica* (gotu kola) herb, *Vitis vinifera* (grape) leaf, and oligomeric proanthocyanidins such as Pycnogenol.[®]

Introduction

Chronic venous insufficiency (CVI) is a disorder that affects 5–35% of the United States population.^{1,2} The major clinical features of CVI are dilated veins, edema, leg pain, and changes in the skin of the legs. Edema begins in the ankle region and ascends up the leg as fluid continues to accumulate. The leg pain or discomfort is usually described as heaviness or aching, and often occurs after prolonged standing. The discomfort may be relieved by elevating the leg(s). When the deep venous system is involved, venous claudication or intense leg cramping with ambulation may occur. Advanced CVI can cause lymphedema and slow-healing ulcers.²

CVI arises in a state of chronic venous hypertension that alters the permeability of the skin's microcirculation.² The movement of protein and other matter from the blood vessels into the interstitium causes injury to nutrient and exchange capillaries, white blood cell chemotaxis, and inflammation-induced injury. The end result is fibrotic and edematous skin.

The mainstay of allopathic treatment for CVI is the use of compression therapy to control edema and venous hypertension.² In Europe, botanicals are commonly added to this as adjunctive therapy, and have shown great benefit. Given the prevalence of the disorder, poor patient follow-through with compression therapy, and the complete lack of established drug protocols for CVI, botanicals should be much more widely prescribed in the United States for patients who have this disorder.

Most of the herbs used for CVI are rich in interesting flavonoids and other substances that protect capillaries. The herbs' mechanisms of action vary, but all of these substances activate venous and lymphatic return. The use of herbs in CVI is supported by research showing that they improve venous tone, venous blood flow, capillary permeability, and lymphatic drainage.

Butcher's Broom Root

Ruscus aculeatus (butcher's broom) is a prickly, berry-producing shrub in the Liliaceae family. It has a wide growth range (from Egypt and Turkey through the Mediterranean countries up through France, Spain, and England) and prefers to grow on the outskirts of dry woods. It thrives on moist, uncultivated ground, especially where the soil contains chalk. The berries are reported to be somewhat toxic. Although the plant could easily be cultivated in many parts of the United States, most of the butcher's broom available in commerce is imported. Butchers at one time used branches of the shrub to clean meat stalls and keep flies at bay, giving rise to its common name. The whole plant contains steroidal saponins known as ruscigenins, which are the compounds deemed most active in butcher's broom, but only the dried rhizomes are used medicinally.

Ancient Greek physicians used butcher's broom as a laxative and diuretic. In Europe, a decoction of the root in wine was used as a diuretic, to remove urinary obstruction, kidney stones, and renal "gravel." The plant was also used to regulate menses and ameliorate jaundice and headache, and a poultice of the berries was used to help heal broken bones and dislocated joints. In South America, the root was roasted, ground, and drunk like coffee for prostate tumors. Today, the plant is little used for most of these indications.

Instead, butcher's broom is now frequently used to relieve symptoms of CVI such as edema of the ankles, itching, tension and

cramping of the legs, and related symptoms. Both animal and human studies support this plant's benefit in CVI, and the German Commission E has affirmed the value of butcher's broom as an adjunctive treatment for this condition.³

The human studies of butcher's broom in CVI are shown in Table 1. All of the studies showed the plant to have a positive effect, and in one multicenter study butcher's broom efficacy in CVI was rated as "excellent" by 81.6% of the treating physicians and as "good" by the

Table 1. Studies on Butcher's broom in Chronic Venous Insufficiency (CVI)

Study	# of participants	Type	Product	Focus	Result	Length
Cappelli et al. ^a	40	Double-blind, crossover, placebo-controlled, prospective	2 capsules of (16.5 mg ruscogenins, 75 mg hesperidin & 50 mg ascorbic acid) 3 times/day	CVI, varicosities	Itching, edema, and paraesthesia reduced	2 months, with a 15-day washout and 2-month crossover
Rudofsky ^b	141 + 20 healthy volunteers	Randomized, double-blind, multicenter	2 capsules ^h 3 times/day for 4 weeks; 2 capsules 2 times/day for 8 weeks	CVI	Continuous decreases in foot and ankle volume, decrease in leg swelling, improved venous pumping	2 weeks wash-out followed by 12 weeks treatment
Haas et al. ^c	20	Placebo-controlled, double-blind	1 capsule (150 mg ruscus & 150 mg methylhesperidin chalcone) 3 times/day	CVI stages I and II, patients scheduled for surgery	Significantly increased fibrinolytic activity of removed great saphenous vein	14 days
Kiesewetter et al. ^d	30	Random selection, noncontrolled	3 x 2 ruscus capsules for 5 weeks then 2 x 2 capsules/day; amount of ruscus not stated	CVI	Reduced circumferences of lower legs, malleoli & subjective complaints; greater rheologic improvement in patients with advanced stages of CVI	5 months
Beltramino et al. ^e	80	Open-label, randomized, multicenter	2 capsules/day of 150 mg ruscus, 150 mg hesperidin methylchalcone, & 100 mg ascorbic acid; control was 2 tablets of 500 mg hydroxyethyl rutoside/day	CVI (heavy, tired, swollen or painful legs)	Significant reduction of symptoms, reduction in limb circumference; physicians & patients had more favorable opinion of ruscus than of rutoside	90 days
Le Devehat, et al. ^f	60 + 7 healthy volunteers	Randomized, double-blind, placebo-controlled	2 capsules/day of 150 mg ruscus, 150 mg hesperidin methylchalcone, & 100 mg ascorbic acid	CVI; blood samples drawn from foot before & after provoked venous stasis	Improved blood viscosity disturbances caused by venous stasis	4 weeks
Seydewitz et al. ^g	36	Randomized, double-blind, placebo-controlled	3 capsules (150 mg ruscus & 150 mg trimethylhesperidin chalcone)	Stage IV varicosities with stage I or stage II CVI, scheduled for vein stripping.	Increase in enzyme activity in the proximal segment of the vein, distinctly higher incidence of subjective reduction of symptoms	4 weeks

^aRef. 5; ^bRudofsky G. Efficacy of *Ruscus* extract in venolymphatic edema using foot volumetry. In: Vanhoutte PM, ed. Return Circulation and Norepinephrine Paris: John Libbey Eurotext, 1991; ^cRef. 6; ^dKiesewetter H, Scheffler P, Jung F, et al. Effect of *Ruscus* extract in chronic venous insufficiency stage I, II, and III. In: Vanhoutte PM, ed. Return Circulation and Norepinephrine Paris: John Libbey Eurotext, 1991; ^eBeltramino R, Penenory A, Buceta AM. An open-label, randomized multicenter study comparing the efficacy and safety of Cyclo 3 Fort versus hydroxyethyl rutoside in chronic venous lymphatic insufficiency. *Angiology* 2000;51:535-544; ^fLe Devehat C, Khodabandehlou T, Dougny M. The effects of Cyclo 3 Fort treatment on hemorheological disturbances during a provoked venous stasis in patients with chronic venous insufficiency. *Clin Hemorheol* 1994;14:S53-S63; ^gSeydewitz V, Berg D, Welbers P, Staubesand J. Biochemical investigations on the action of *Ruscus* extract and trimethylhesperidin chalcone (TMHC). In: Vanhoutte PM, ed. Return Circulation and Norepinephrine Paris: John Libbey Eurotext, 1991.

^hNot clearly stated but appeared to be using a capsule containing 150 mg of ruscus, 150 mg of hesperidin methylchalcone, and 100 mg of ascorbic acid.

other 18.4%.⁴ Even though the products used and the quality of the studies vary, a clear picture emerges from clinical and in vitro studies showing that butcher's broom improves venous circulation, perhaps most strongly when that circulation is deficient. However, some researchers caution that if butcher's broom is to have benefit, CVI should not have progressed to a point at which the activity of alpha-adrenergic receptors in the venous wall has been compromised.⁵

In one study, veins from patients treated with butcher's broom prior to vein-stripping surgery showed greater fibrinolytic activity than did the veins of placebo controls.⁶ In another trial, patients with CVI and healthy subjects were given butcher's broom in a random, double-blind fashion, and were then subjected to treatment simulating venous stasis. By comparison with the healthy subjects, the patients with CVI had

Case Study

A 53-year-old postmenopausal woman with low-normal blood pressure had a history of gastric-bypass surgery and arthroscopic surgery on both knees, and had seasonal affective disorder (SAD) for which she was taking a serotonin-specific reuptake inhibitor (SSRI)—type antidepressant. Her upper body was slender, and she had a small waist and flat stomach. However, her legs were quite stocky and swollen, as also were the tops of her feet and toes. Her ankle bones were not visible, and the skin from the midcalf to the ankle of both legs was a mottled red, and pitting edema was present.

Even the smallest scratch on the patient's legs caused leakage of a clear fluid that persisted for hours, completely wetting her socks. The leakage could eventually be stopped by applying continuous pressure. The patient did a lot of physical work, loved to garden, and felt fine as long as she was moving. She could not sit for more than very short periods because resting caused her cramping or pain, which was worsened when she elevated her legs. She had had restless leg syndrome in the past and described her current symptoms as entirely different from those of the syndrome. Her greatest pain came from her right ankle and radiated over the top of the foot. Her physician had told her that she would simply have to get used to her current circumstances. She had been prescribed full-leg compression stockings, which provided her with some relief, but which apparently fit poorly, with the tops of the stockings tending to slide down from the patient's waist to her hips, for which reason she no longer used them.

The patient's diet was small and not optimal. She primarily ate Lean Cuisine meals, little meat or fish, and not many vegetables, although she did consume a spinach drink and 100% vegetable juice. She ate few sweets but did consume some nuts and seeds, used alcohol only minimally, and drank water liberally. She was not taking any supplements. As her naturopathic physicians, we discussed the need for her to increase her intake of flavonoids and other antioxidants by eating as many fruits and vegetables as possible. She was unwilling to take tinctures and unable to spend a great deal of money on supplements.

Initial treatment involved:

- Pycnogenol^{®a}—100 mg once daily
- *Ruscus aculeatus* (butcher's broom)—470 mg (1 capsule)/day
- *Aesculus hippocastanum* (horse chestnut) cream—This consisted of horse chestnut seed and bark extract standardized to 20% aescin, and which also contained butcher's broom, *Hamamelis virginiana* (witch hazel), *Quercus alba* (white oak), *Commiphora myrrha* (myrrh) gum, and *Rosmarinus officinalis* (rosemary) extracts, with parabens as a preservative. The treatment was gentle topical application to the lower limb twice daily.

In a telephone conversation with us after 1 week, the patient reported that she was taking Pycnogenol every other day because of its cost, and that disliked the horse chestnut cream, complaining that it ran and was green, sticky, and messy. Her treatment was thereupon modified to consist of:

- Pycnogenol: 100 mg every other day
- Butcher's broom: 470 mg (1 capsule)/day
- Horse chestnut, 250 mg seed extract standardized to 20% aescin, 1 capsule/day

In a visit made 3 weeks after modification of her therapy, the patient reported making an effort to include more vegetables and fruit in diet, and felt that she was improving. At another visit at 5 weeks after modification of the patient's treatment, her ankle and calf circumferences had decreased and the tops of her feet and toes were no longer swollen. Her ankle bone was now visible. However, her leg continued to leak fluid when scratched, and still showed some pitting edema. She reported feeling much better and being able to fit into pants that she had previously become unable to wear because her knees and calves were too large (she wears loose men's pants). She continued to have pain when sitting or being still, and reported that the pain increased when she elevated her legs. She agreed to try a pair of air boots and subsequently reported that they enabled her to sit comfortably and completely without ankle pain. However, the boots are of a single size designed to fit all wearers ("one-size-fits-all") and she described them as sometimes being too snug for her. Her skin was still mottled but had not worsened or shown signs of skin or tissue breakdown.

	Initial	5 weeks		Initial	5 weeks
Right ankle	10.75"	10"	Right calf	17.25"	16.5"
Left ankle	10.25"	9.75"	Left calf	15"	14.5"

^aPycnogenol is an extract from French maritime *Pinus maritimus* (pine bark), manufactured by Horphag Research, Geneva, Switzerland.

hematologic abnormalities (e.g., disturbances in parameters of blood viscosity) that were exacerbated in conditions of venous stasis,⁷ and butcher's broom significantly reduced these abnormalities. A number of in vitro studies of animal veins confirm that butcher's broom and its ruscigenes have a vasoconstrictive effect and reduce vascular permeability.⁸ In other studies, butcher's broom protected human endothelial cells from hypoxia,⁹ and in yet another study exhibited significant antielastase activity in vitro.¹⁰ A review of 24 pharmacologic studies concluded that butcher's broom should be the treatment of choice for CVI.¹¹

Butcher's broom is generally considered a safe herb, although it does occasionally cause gastrointestinal (GI) distress.^{3,12} Side effects have not been noted in most clinical studies of butcher's broom. However, one study of 124 patients with hemorrhoids noted a 2.4% incidence of GI symptoms (primarily epigastric burning and pain),¹³ and in a study of lymphedema, 3.5% of the participants experienced significant nausea and abdominal pain.¹⁴ In addition, recent reports in the French medical literature suggest that butcher's broom may cause lymphatic colitis in some patients.^{15–17} We have not been able to review these reports, but we suggest that practitioners discontinue the use of butcher's broom if severe or persistent GI symptoms occur with its use. It might also be wise to advise patients not to combine butcher's broom with nonsteroidal anti-inflammatory medications that may cause lymphatic colitis and other adverse GI effects.



Ruscus aculeatus (butcher's broom) root.

Table 2. Dosing and Potential Safety Concerns of Herbs Used to Treat Chronic Venous Insufficiency

Herb	Dose	Potential safety concerns
<i>Ruscus aculeatus</i> (butcher's broom) root	Dried root: 300–450 mg/day; in most studies, butcher's broom is paired with trimethylhesperidin chalcone and ascorbic acid (see Table 1) Tincture: 2–3 mL t.i.d.	May cause GI upset, should be taken with meals; may cause lymphatic colitis (rare), should not be combined with NSAIDs. <i>Theoretical:</i> May interact with MAO-inhibiting drugs (there are no references supporting theory); herb's action may be decreased when combined with alpha-adrenergic- or calcium-antagonists; not sufficiently studied in pregnancy but appears to be safe based on existing data
<i>Aesculus hippocastanum</i> (horse chestnut) seed	Dried seed: 250–300 mg b.i.d. (100 mg aescin/day) Fresh seed: 120–180 mg q.i.d., (120 mg of aescin/day); dose may be cut in half after the first 8-week period Tincture: 2–3 mL t.i.d.	Should be used with caution in chronic kidney failure; should not be applied topically to broken or ulcerated skin; may cause GI upset and should be taken with meals <i>Theoretical:</i> Concern that the herb may affect the actions of anticoagulant drugs
Pycnogenol, ^{®a} extract from maritime pine or grape seeds	50–350 mg/day	Not recommended in pregnancy or lactation; may cause mild GI upset <i>Theoretical:</i> concern that, as an immune enhancer, the herb should not be combined with immunosuppressive therapies
<i>Centella asiatica</i> (gotu kola) herb	Dried herb: 90–180 mg/day Tincture: 2–4 mL t.i.d.	No known contraindications
<i>Vitis vinifera</i> (red grape) leaf	Dried herb, 370–720 mg/day	No known contraindications

GI, gastrointestinal; NSAIDs, nonsteroidal, anti-inflammatory drugs; MAO, monoamine oxidase.

^aPycnogenol is an extract from French maritime *Pinus maritimus* (pine bark), manufactured by Horphag Research, Geneva, Switzerland.

The authors of one book caution against the use of butcher's broom in patients using alpha-adrenergic antagonist therapy for benign prostatic hypertrophy (BPH) or hypertension, and against the plant's use in patients taking monoamine oxidase (MAO)-inhibiting medications.¹⁸ The authors cite no references for these recommendations, but they may be based on the theoretical possibility that the tyramine contained in butcher's broom might precipitate a hypertensive crisis, reduce the effectiveness of alpha-adrenergic blocking antihypertensive drugs, or reduce the effectiveness of treatment of BPH. While one in vitro study showed that alpha-adrenergic agents and calcium-antagonists reduced the vasoconstrictive effect of butcher's broom, no studies have shown that butcher's broom diminished the action of those drugs.

In fact, in one very small study, butcher's broom reduced edema of the ankles and legs edema caused by calcium-channel-blocker therapy for hypertension. Although the description of this latter study is poor, 4 of the 9 patients nevertheless had complete improvement with butcher's broom, and no adverse effects were noted. While caution is needed when combining herbs and pharmaceutical medications, it is also important to remember that botanicals can counteract the adverse effects of drugs and sometimes improve their actions. Many cases of edema are found in patients who are also hypertensive, and butcher's broom should not automatically be ruled out as a treatment for patients who are medicated for hypertension.

The abovementioned authors also caution against the use of butcher's broom in pregnancy and lactation, owing to lack of proof of its safety in these circumstances¹⁸; however, most authors who write on the topic consider butcher's broom safe in pregnancy and lactation.^{3,12} Although not large enough to be conclusive, an open study of 20 pregnant women taking butcher's broom daily for venous insufficiency followed both fetal and post-birth indices, finding no embryotoxic effects, and post-birth indices were normal in all instances.¹⁹ We reviewed two studies of the use of butcher's broom in pregnancy-related venous insufficiency, and both showed improvement in maternal symptoms without any adverse effects on the fetus.^{19,20} Two other European studies, one a multicenter study of 124 patients, reported a similar improvement of symptoms in pregnant women.^{21,22}

While these studies do not conclusively establish the safety of butcher's broom in pregnancy, both animal and human studies indicate that the plant has a high degree of safety. Nevertheless, a few cases of hypersensitivity to the ruscogenins of butcher's broom have been reported,²³ and there is one reported case of a severe allergic reaction to butcher's broom.²⁴

Butcher's broom is a sustainable medicine, largely obtained from cultivated sources. The dried root is dosed at 300–450 mg per day (in most studies, butcher's broom is paired with trimethylhesperidin chalcone and ascorbic acid; see Table 1). Dosing of the tincture of butcher's broom is 2–3 mL thrice daily.

Horse Chestnut Seed

Introduced to Europe as a botanical medicine in the 1600s, *Aesculus hippocastanum* (horse chestnut), like butcher's broom, is a widely used treatment for CVI, and is gaining in popularity in the United States for this purpose and as a treatment for varicose veins. In Germany, horse chestnut is the most widely prescribed botanical

for venous edema and has been approved by the German Commission E for CVI including heaviness, nocturnal leg cramping, itching, and swelling of the legs.³ A recent Cochrane Review of the use of horse chestnut found it to be an efficacious and safe short-term treatment for CVI.²⁵

Two of the main constituents of horse chestnut are aesculin, a coumarin derivative, and aescin. Aescin comprises the total saponin content of the seeds, which actually consists of more than 30 derivatives of triterpenoids, protoaescigenin, and baringtogenol C. It also contains a number of flavones. The renowned German phytotherapist R.F. Weiss stated that the antiedematous effect of horse chestnut was 600 times that of rutin in animals.²⁷

In studies, horse chestnut was found to be antiedematous²⁸ and to improve vein function, inhibit vasodilation, modulate inflammation, and act as an antioxidant.³ The herb reduced lysosomal enzymes that break down mucopolysaccharides (e.g., hyaluronidase) in the region of the capillary wall, and inhibited the filtration of small molecules, electrolytes, and water into the interstitium by reducing vascular permeability.²⁹ In one study horse chestnut inhibited induced leg edema in patients with CVI.³⁰

The ABC Clinical Guide to Herbs lists 18 studies of the use of horse chestnut in CVI.³¹ These range in duration from 6 to 12 weeks and uniformly show a reduction in ankle circumference and improvement in symptoms. In an observational study of more than 5000 patients, horse chestnut reduced all of the symptoms investigated, including pain, tiredness, tension and swelling of the leg, and itching, and had the advantage over compression stockings of better patient compliance.³² In one systematic review of clinical trials, horse chestnut reduced leg volume, reduced the likelihood of leg pain by 4-fold, and reduced itching and edema by 1.5-fold. It was found to be safe and to have no adverse effects.³³ As with butcher's broom, horse chestnut appears to be far more effective in the early stages of CVI. Thus, one study found the herb effective in stage I but far less effective in stage III of the disease.³⁴ Another study found that after 8 weeks, the dose of horse chestnut could be cut in half and still maintain its effect.³⁵

In rare cases, horse chestnut may cause pruritus, nausea, and gastric complaints. One of the herb's constituents may slow gastric emptying. There is speculation that horse chestnut may interfere with anticoagulants, but this may pertain only to a compound found in the bark and not in the seeds, which are the part of the plant used medicinally. There are no known contraindications to the use of horse chestnut in pregnancy and lactation, and it has been used in some studies involving pregnant women without reports of adverse effects.³¹ The potential toxicity of injected aescin has been associated with significant problems, but these are of no relevance when using the whole plant extract orally.

Horse chestnut is a highly sustainable medicine that grows readily in many temperate climates, and harvesting the seed does not harm the tree. Dosing of the dried seed is 250–300 mg twice daily (100 mg aescin daily); dosing of the fresh seed is 120–180 mg four times daily (120 mg aescin daily); and dosing of the tincture is 2–3 mL thrice daily. The dose may halved after the first 8-week period of treatment.

Gotu Kola

An herb of increasing interest and use in CVI is *Centella asiatica* (gotu kola). There is evidence that gotu kola is effective in venous insufficiency and, given the apparent ability of the herb to promote wound healing, adding gotu kola to a regimen containing either butcher's broom or horse chestnut (or both) may prove synergistic in preventing or healing venous ulcers.

Most of the clinical studies have been on the isolated total triterpenic fraction of gotu kola. In a test using a vacuum suction chamber that produces swelling when applied to the ankle skin, subjects with CVI had a relatively slow reabsorption of the fluid compared to controls. However, after taking gotu kola for 2 weeks, the time required to reabsorb the leaked fluid improved significantly.³⁶ In another small study with patients taking either 90 or 180 mg of gotu kola per day for 4 weeks, vein function according to various measurements improved in a dose related fashion. Another study compared 60 and 120 mg, again finding a dose-related reduction in discomfort, edema, and sense of leg heaviness.³⁷ The plant's triterpenic fraction prevented microcirculatory changes in adults with mild to moderate superficial venous disease during flights lasting over 3 hours.³⁸

Gotu kola is well known for its wound-healing abilities. The herb and its constituents are beneficial in promoting wound healing and have been used to treat people with keloids,³⁹ phlebitis and venous hypertension,^{40,41} leprosy,⁴² stretch marks in pregnancy,⁴³ and a variety of other ailments. In wound studies, gotu kola increased antioxidants in newly formed tissue while greatly reducing toxic lipid peroxide levels.⁴⁴ Gotu kola and its flavonoids increased tensile strength, collagen content, and epithelialization in many types of wounds when used internally or topically.^{45–47} Gotu kola had different actions at different stages of wound healing, and consistently increased collagen synthesis at wound sites.^{48,49} Most herbalists think that gotu kola should be used or prepared fresh for optimal effectiveness. It has no known adverse effects.

Gotu kola grows in tropical areas and is readily cultivated. Though the entire plant is often harvested to make medicine, it is sufficiently easy to grow that it is for the most part very sustainable. The dosing is as follows: dried herb, 90–180 mg per day; tincture 2–4 mL t.i.d.

Oligomeric Proanthocyanidins

Oligomeric proanthocyanidins (OPCs) are found in the heartwood and bark of some trees as well as in some seeds and most berries, ranging from *Crataegus* spp. (hawthorn) berries to *Vaccinium* spp. (blueberries), in which the OPC composition varies among plants. The most common sources of OPCs on the market are extracts of grape seeds or of *Pinus maritimus* (maritime pine bark). Pycnogenol® (Horphag Research, Geneva, Switzerland), extracted from French maritime pine bark, has been relatively well researched in CVI.

OPCs are primarily known for their antioxidant activity. However, they also appear to have anti-inflammatory, antiallergic, and vasodilatory actions. In addition, these substances have been found to inhibit lipid peroxidation, platelet aggregation, and capillary

permeability and fragility, and to affect enzyme systems including cyclo-oxygenase, and lipoxygenase.⁵⁰ These findings suggest that OPCs may be useful components in the treatment of a number of conditions including venous insufficiency, varicose veins, capillary fragility, and diabetic retinopathy.

When individual OPC molecules bind together, they yield what are collectively called procyanidolic oligomers (PCOs). These have a broad range of pharmacologic activity through increasing vitamin C levels, decreasing capillary permeability and fragility, scavenging free radicals, and inhibiting destruction of collagen. The last-named effect occurs through the crosslinking of collagen fibers, preventing free-radical damage, inhibiting enzymatic cleavage of collagen, and preventing the synthesis and release of inflammatory mediators.

In an open, controlled comparative study, horse chestnut seed extract at 600 mg per day was compared with Pycnogenol at 360 mg per day in 40 patients with CVI over a treatment period of 4 weeks. The study monitored circumference of the lower legs and subjective rating of symptoms of pain, cramps, night-time swelling, the sensation of "heaviness" in the lower legs, and reddening of the skin of the legs. Pycnogenol significantly reduced the circumference of the lower legs and significantly improved subjective symptoms. It also significantly decreased blood cholesterol and low-density lipoprotein (LDL) levels, while levels of high-density lipoprotein (HDL) remained unaffected. Horse chestnut did not significantly reduce the circumference of the lower limbs and marginally reduced symptoms. Horse chestnut seed and Pycnogenol were equally well tolerated.

Unlike butcher's broom and horse chestnut, Pycnogenol has been shown to provide a benefit in advanced stages of CVI. A study of 39 patients with severe CVI found that Pycnogenol in a dose of 50 mg taken 3 times daily improved capillary filtration and symptomatic score, and reduced edema.⁵¹

In another study, 86 patients with severe CVI were given either 150 mg or 300 mg of Pycnogenol or 1000 mg of Daflon—a micronized, purified flavonoid mixture. Ankle swelling was measured early in the morning, before becoming affected by standing, and again after 30 minutes of resting with the feet elevated. Measurements were made at the beginning of the study and again after 4 and 8 weeks of treatment. Each patient recorded a composite, analogue score based on signs and symptoms (edema, pain, restless limbs, subjective swelling, and skin alterations/redness), and an independent physician made a separate evaluation of edema. After 8 weeks of treatment, Pycnogenol decreased ankle swelling by 35%, while Daflon decreased it by 19%. Pycnogenol also decreased the composite score for edema and other symptoms in the lower legs by 64%, whereas Daflon was only half as effective, reducing the score by 32%. Additionally, Pycnogenol was found to have significantly increased tissue oxygen and to have reduced CO₂, which were measured transdermally with small sensors attached to the skin, suggesting a considerable improvement in blood circulation to the legs. Daflon, in contrast, did not yield any significant effect on tissue oxygenation, indicating that it apparently does not improve blood circulation to the legs. In this study, only the composite edema score reflected a benefit of the higher dose of Pycnogenol.⁵²



Vitis vinifera (grapes).

Like butcher's broom, Pycnogenol has shown the ability to offset edema secondary to treatment with calcium-channel-blocking or angiotensin-converting enzyme (ACE) –inhibiting drugs.⁵³

The trees from which Pycnogenol is obtained are grown on plantations, and its use is therefore sustainable. Dosing of Pycnogenol is 50–350 mg per day.

Grape

While the seed of *Vitis vinifera* (grapes) is used as a source of OPCs and a substitute for Pycnogenol in practice, little research has been done on the use of the grape seed in CVI. We located a French study in which a dose of 45 mg per day of grape OPCs reduced symptoms of CVI in 108 patients—particularly the symptom of heaviness of the lower legs.⁵⁴ However, extracts of grape leaf have also been used as a treatment for CVI. A 12-week, double-blind, placebo-controlled study of 219 individuals with CVI who were given either 360 mg/day or 720 mg per day grape leaf extract found both doses to be significantly more effective than placebo in reducing edema as well as easing pain and other symptoms. The researchers who conducted the study concluded that the higher dosage produced slightly greater, more sustained improvement.⁵⁵

Benefits were also seen in a much smaller study of 39 patients taking grape leaf extract at 360 mg/day divided into two doses. A significant improvement in subjective criteria as well as in lower leg volume was seen after 2 weeks of treatment.⁵⁶ In a crossover study of 71 patients with CVI, a daily dose of 360 mg grape leaf extract decreased leg circumference and increased microvascular blood-flow values.⁵⁷ In the double-blind study of 219 patients described above,⁵⁵ side effects were largely limited to mild GI distress and occasional reported headaches. Blood tests and physical examination did not reveal any harmful effects.⁵⁵ However, grape leaf has not yet been subjected to comprehensive safety studies, and is not at present recommended for pregnant or nursing women or individuals with severe liver or kidney disease.

Grapes, as well as their seeds and leaves, are widely available and highly sustainable. Dosing of the dried botanical product is 370–720 mg per day.

Conclusion

The herbs discussed in this paper are useful both for treating CVI and preventing its worsening. Because many different flavonoids appear to have a beneficial effect on CVI, patients taking the flavonoid-containing products described in this article should be advised to also increase their dietary intake of berries, as well as of other fruits and vegetables. Where patients are willing, better progress can be made if these treatments are combined with the use of compression therapy, frequent elevation of the legs, appropriate exercise, and when needed, weight loss. □

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