REVIEW
VASCULAR DISEASE

Diseases & Research

Efficacy of Venoactive Substances and Drugs in the Treatment of Chronic Venous Insufficiency and Varicose Veins: A Narrative Review

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Abstract: Chronic venous insufficiency (CVI) and varicose veins are common conditions that cause symptoms such as heavy legs, swelling (oedema), skin discolouration, lipodermatosclerosis, venous ulcers, venous congestion, and reflux. To gather information for this review, the following keywords were used in PubMed: "varicose veins," "chronic venous insufficiency," "venoactive compounds (VAC)," and "venoactive drugs (VAD)," and a narrative review was then conducted to assess the efficacy of venoactive agents. Treatment includes venoactive medications, with the investigated substances being micronized purified flavonoid fraction (MPFF), a combination of Ruscus aculeatus, hesperidin methyl chalcone (HMC) and vitamin C, rutosides, hydroxyethylrutosides (HR), Ruscus aculeatus, pycnogenol, aescin, red vine leaf extract, calcium dobesilate, pentoxifylline, topical agents, and sulodexide. Venotonic medications have similar effects on the venous endothelium, lymphatic drainage, oedema, venous tone, leukocyte adhesion, inflammatory mediators, blood viscosity, and red blood cell behaviour. Study results concerning symptoms like pain, cramps, heaviness, and swelling show some variation; however, micronised purified flavonoid fractions (MPFF) and ruscus extract combined with hesperidin methyl chalcone and ascorbic acid demonstrated the highest quality of evidence, primarily at level A. For venous leg ulcers, MPFF, sulodexide, and pentoxifylline were effective adjunctive treatments, also supported by level A evidence. Additionally, the concept of venous active drugs (VAD) has been introduced to prevent deterioration of venous status, including arterial vascular changes, and although study quality varies, recent research tends to be more positive. In conclusion, the efficacy of venoactive compounds and drugs (VAC/VAD) in treating CVI and varicose veins has been confirmed by several studies, and recent research has achieved a level of evidence that supports recommendations in international guidelines; nonetheless, there is a clear need for further high-quality studies.

Keywords: Chronic venous insufficiency; Varicose vein; Venoactive compounds; Venoactive drugs; Micronized purified flavonoid fraction; Aescin.

Introduction

Chronic venous insufficiency (CVI) is a common condition that causes leg discomfort, with symptoms including heaviness, swelling, changes in skin color, and venous ulcers[1]. Treatment options are classified as conservative or invasive. Conservative treatments involve medications and compression stockings, while invasive methods include high ligation, "Cure Conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire" (CHIVA), Endovenous Laser Ablation (EVLA), Radiofrequency Ablation (RFA), sclerotherapy, foam sclerotherapy, Mechano Chemical Ablation (MOCA), and Cyanoacrylate Embolisation (CAE)[2,3]. Venoactive medications are used for CVI and varicose veins based on the disease's severity: Diosmin/hesperidin (MPFF micronized purified flavonoid fraction), a combination preparation of Ruscus aculeatus, Hesperidin Methyl Chalcone (HMC), and Vitamin C, Rutin (also "rutoside"), a flavonoid glycoside from the flavonol class, Hydroxyethylrutosides (HR), semisynthetic derivatives of the flavonoid group, derived from rutin, Ruscus aculeatus (Butcher's broom), a medicinal plant, Pycnogenol, a standardized extract from the bark of the French maritime pine (Pinus pinaster), Aescin (also escin), an active ingredient from the seeds or bark of the horse chestnut (Aesculus hippocastanum), Red vine leaf, a standardized extract (e.g., AS195) from the leaves of Vitis vinifera (grapevine) with main constituents flavonoids such as quercetin-3-O-β-glucuronide, Isoquercitrin, Calcium dobesilate (a vasoprotective drug and calcium salt of dobesilic acid), Pentoxifylline (a methylxanthine derivative with rheological effects), Topical heparinoids, Sulodexide (a glycosaminoglycan).

The substances in question have similar effects on the venous endothelium, lymphatic drainage, edema, venous tone, leukocyte adhesion to venous walls and valves, inflammatory mediators, blood viscosity, and red blood cells. The results of studies concerning symptoms such as pain, cramps, heaviness, swelling, and edema are mixed. Micronized purified flavonoid fractions (MPFF) and ruscus extract, combined with hesperidin methyl chalcone and ascorbic acid, demonstrated the highest level of

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evidence, primarily at level A. For the treatment of venous leg ulcers, MPFF, sulodexide, and pentoxifylline are identified as the most effective adjunctive treatments, also supported by level A evidence. While the quality of the studies varies and they are only partially comparable, more recent studies have shown positive outcomes[4–6].

Methodology

The following keywords were entered into PubMed: "varicose veins"; "chronic venous insufficiency"; "venoactive compounds"; "venoactive drugs"; "mpff"; "rutosides"; "ruscus aculeatus"; "hydroxyethylrutoside"; "pycnogenol"; "aescin"; "calcium dobesilate"; "pentoxifylline"; "topical heparinoid"; "sulodexide"; "red wineleaf". After reviewing the results, a narrative review of the efficacy of venoactive agents in chronic venous insufficiency and varicose veins was conducted.

Results

Diosmin MPFF

Previous systematic reviews have questioned the efficacy of micronized purified flavonoid fraction (MPFF) for treating chronic venous insufficiency (CVI) and for promoting ulcer healing, due to limitations in the studies[7]. MPFF, which includes diosmin and hesperidin, improves venous tone, microcirculation, and reduces inflammation, pain, and edema. Despite its benefits, gastrointestinal disturbances and reduced bioavailability can affect patient responses, and data on long-term use (beyond 12 months) are limited[5,8]. MPFF is classified as a venoactive substance with a recommendation category of 1B[9]. It has been shown to reduce ankle and calf circumference and to improve quality of life in patients with CVI[10,11]. MPFF can enhance venous ulcer healing when combined with compression[12], and is noted for its effectiveness in reducing postoperative pain[13]. While MPFF has substantial evidence for improving chronic venous disease (CVD) patients' quality of life, gastrointestinal issues and allergic reactions may occur. Variability in dosages and study methodologies limits the robustness of the evidence[6].

Hesperidin, a flavonoid in citrus fruits, is converted to hesperetin in the body, impacting its bioavailability. It has been shown to lower triglycerides, total cholesterol, LDL cholesterol, TNF-alpha levels, and systolic blood pressure, while not affecting glycemic control. Prolonged use or higher doses can also reduce inflammatory markers like VCAM-1, TNF-α, IL-6, and CRP. It can lower triglycerides, total cholesterol, LDL cholesterol, TNF-alpha levels, and systolic blood pressure without affecting glycemic control[14,15]. Higher doses or prolonged use may reduce inflammatory markers like VCAM-1, TNF-α, IL-6, and CRP[16].

Rutin (Rutoside)

Rutin, or "rutoside," is a flavonoid glycoside used to treat venous diseases, swelling, chronic venous insufficiency, and post-thrombotic syndrome (PTS). It has demonstrated anti-inflammatory and antioxidant effects in animal models and in vitro[17]. While some studies show a non-significant improvement in PTS symptoms compared to placebo, there isn't enough evidence to prove it is better than placebo or compression therapy[18]. Combination therapies with enzymes and rutin may provide analgesic and anti-inflammatory effects. Side effects reported include headaches, flushing, skin rashes, and mild gastrointestinal issues[19].

Hydroxyethylrutosides (HR)

Hydroxyethylrutosides (HR) are semisynthetic derivatives of the flavonoid rutin, including mono-, di-, tri-, and tetrahydroxyethylrutosides. Common brands are Venoruton®, Relvène®, and Paroven®. HR are used to treat chronic venous insufficiency (CVI), which causes pain, cramps, heaviness, and edema. A systematic review found that HR treatment significantly reduces leg pain and other symptoms compared with placebo, with mild to moderate side effects[20]. However, the review noted variability in study designs and dosages, resulting in mostly moderate effects that aren't always statistically significant.

There is a notable lack of long-term data, particularly for specific patient groups like those with advanced venous disease, chronic venous insufficiency, and pregnant women[21]. Hydroxyethylrutosides, pycnogenol, and other plant flavonoids show effects similar to micronized purified flavonoid fraction (MPFF), improving blood flow, providing antioxidant benefits, and reducing pain. Recent studies favor pycnogenol and hydroxyethylrutosides, but issues like data heterogeneity and small sample sizes exist. Side effects are rare and generally mild, primarily gastrointestina[4,5].

Ruscus Aculeatus

Ruscus aculeatus, or butcher's broom, is a medicinal plant known for its beneficial effects, particularly in treating chronic venous insufficiency (CVI). Its rhizomes contain steroidal saponins, such as ruscogenin, and are often used with hesperidin methyl chalcone (HMC) and vitamin C (found in products such as Cyclo 3 Fort®) to alleviate symptoms such as swelling, heaviness, and pain[22]. This combination benefits patients by improving microcirculation, reducing inflammation, and relieving edema, with many experiencing symptom relief within two weeks.

Research indicates that the combination of Ruscus, HMC, and vitamin C shows significant improvements over placebo in various symptoms of CVI[23]. However, distinguishing the specific contributions of Ruscus alone is difficult because studies focus on combination therapies. While patient demographics and study methodologies vary, these treatments generally show good tolerability[24].

Compared with hydroxyethylrutoside, the combination of Ruscus, HMC, and ascorbic acid provides faster and more complete symptom relief[25]. After two weeks, significant reductions in pain, heaviness, cramps, and edema were noted, along with improved capillary microcirculation[26]. Overall, this combination has been proven to enhance symptom relief, reduce ankle circumference, and improve quality of life[27]. Additionally, it exerts a venoconstrictive effect on microcirculation and lymphatic circulation[22], making it a noteworthy option in evidence-based treatments for conditions like post-thrombotic syndrome[6].

Pycnogenol

Pycnogenol is an extract from the bark of the French maritime

pine (Pinus pinaster) and is commonly used as a dietary supplement for cardiometabolic health, skin aging, and cognitive function. Various randomized controlled trials (RCTs) and meta-analyses have evaluated its efficacy and safety. In a clinical trial on venous ulcers, Pycnogenol outperformed a combination of diosmin and hesperidin[28], and it was also more effective for chronic venous insufficiency (CVI)[29]. A meta-analysis showed significant improvements in health markers such as fasting blood glucose, blood pressure, Body Mass Index (BMI), and cholesterol levels[30,31], whereas a 2014 review reported contradictory results[32]. Additionally, Pycnogenol significantly reduced C-reactive protein (CRP) levels, indicating its anti-inflammatory properties[33].

Aescin

Aescin (or escin) is an active compound derived from the seeds and bark of the horse chestnut tree (Aesculus hippocastanum). It is primarily used as a venoactive agent to treat venous insufficiency, helping to reduce edema, strengthen capillary walls, and provide anti-inflammatory benefits. Its mechanisms of action include lowering capillary permeability, increasing venous tone, and inhibiting inflammatory mediators. Aescin has demonstrated effectiveness in treating postoperative chronic venous insufficiency-related edema and can be an alternative to compression therapy.

Studies show that Aescin, along with hydroxyethyl rutoside (HR) and Daflon, is safe and effective for chronic venous insufficiency. These phlebotonics help maintain Adenosintriphosphate (ATP) levels in venous endothelial cells during hypoxia and reduce inflammation and venous damage. Horse chestnut seed extract (HCSE) has been linked to decreases in leg volume and alleviation of symptoms such as leg pain and fatigue. Comparative studies suggest that HCSE and O-(β-hydroxyethyl) rutosides are equally effective, with mild side effects reported[34,35].

Red Vine Leaf

Red vine leaf extract, particularly AS195 (Antistax®), is derived from *Vitis vinifera* leaves and contains flavonoids like quercetin-3-O-β-glucuronide and isoquercitrin. It's primarily used to treat venous-related issues such as chronic venous insufficiency (CVI), heavy legs, and swelling. AS195 has shown significant reductions in lower leg volume and calf/ankle circumference in cases of mild-to-moderate CVI, along with improvements in symptoms like heaviness and pain. However, results vary across different studies[36,37].

Rabe et al.[38] studied an oral treatment (720 mg) for patients with chronic venous insufficiency stages 3-4a over 12 weeks, finding significant reductions in pain and leg volume. In randomized controlled trials, side effects were rare and mild, comparable to placebo. While benefits were noted in early and moderate stages of CVI, they were less pronounced in severe cases. Nonetheless, the need for further research is highlighted due to the lack of long-term data, study variability, and potential bias[37].

Calcium Dobesilate

Calcium dobesilate improves microcirculation, reduces capillary permeability, and alleviates edema, although gastrointestinal discomfort may occur as a side effect. Limitations include a small number of study participants, the necessity for combination therapy, and variability among products[5]. Its effects on lower extremity volume are only noticeable after prolonged treatment[39]. In animal and cell studies, it shows protective effects on the endothelium, reduces vascular permeability, enhances tight junction proteins, and inhibits pathways related to Nuclear Factor kappa B (NF-Kb) and oxidative stress[40]. This medication is effective for chronic venous insufficiency (CVI), diabetic retinopathy (DR), and other circulatory issues. Its benefits include improved symptoms of CVI compared to a placebo, supported by a meta-analysis of 10 randomized controlled trials[41]. Additionally, in vitro, it protects human varicose veins from oxidative stress[42].

In a double-blind study of 30 patients with chronic venous insufficiency (CVI), significant improvements in symptoms and volume were noted compared to placebo[43]. A controlled study with 40 patients showed notable clinical improvements[44]. A larger double-blind study with 256 patients indicated that calcium dobesilate (CaD) significantly reduced lower leg volume over eight weeks[39]. While CaD shows moderate effects on edema and symptoms, its benefits for ulcer healing remain unclear[5]. It has been reported to improve nocturnal cramps, discomfort, and other symptoms, with stronger effects observed in patients with severe disease[41]. One study found significant volume reduction in the dobesilate group after follow-up despite no initial differences[39]. Another trial indicated improvements in leg circumference and swelling within a short time frame[43]. A pilot study showed significant pain and swelling reduction in patients with leg ulcers[45]. Additionally, improved lymphographic findings indicated better lymph flow[46], and trials reported good tolerability with minimal serious adverse events[47].

Pentoxifylline

Pentoxifylline is a methylxanthine derivative that improves blood flow by enhancing microcirculation and reducing blood viscosity. It is commonly used for treating venous leg ulcers, peripheral arterial occlusive disease, and diabetic complications. The drug promotes wound healing, especially when combined with compression therapy, and exhibits anti-inflammatory effects by inhibiting cytokines. Potential side effects include gastrointestinal issues, and caution is needed for patients at risk of bleeding or with liver and kidney diseases. Studies show that a dosage of 1,200 mg of pentoxifylline significantly improves venous ulcer healing rates and reduces ulcer size, although it may increase gastrointestinal disturbances[48–50]. PTX significantly reduced levels of CRP, IL-6, TNF-α, and IL-8 compared to the control group but had no effect on IL-1β, ESR, or IL-10[51]. It lowered TNF-α and CRP without impacting blood pressure[52]. Some patients reported gastrointestinal issues like nausea and stomach upset[49]. Challenges arise from study heterogeneity, including varying dosages, differing definitions of "cure," and inconsistent durations.

Many studies fail to address long-term relapse rates[50]. PTX is an effective adjunct to compression therapy for venous leg ulcers, enhancing healing rates. However, no meta-analysis compares PTX directly with modern MPFF studies or other venoactive substances like flavonoids and diosmin. In network meta-analyses of chronic venous disease, PTX is included among several options but isn't always deemed first-line treatment[53].

Topical Heparinoids

Topical heparinoids, especially heparin, are used in dermatology to treat inflammatory skin conditions like burns, phlebitis, and atopic dermatitis. They provide local antithrombotic effects, enhance microcirculation, and reduce swelling and inflammation, improving skin perfusion. However, they do not penetrate deeper tissues and may cause local skin irritation[54–55]. In a study of 100 surgical patients with superficial thrombophlebitis, those using heparinoid cream reported quicker symptom relief compared to the placebo group[56]. A review of 20 studies with 1,055 patients showed that heparin gel (1,000 IU/g) was more effective than placebo in reducing symptoms like pain and edema for superficial vascular disorders.

A liposomal heparin formulation (2,400 IU/g) was as effective as subcutaneous low-molecular-weight heparin for localized symptoms[57]. Heparin gel (1,000 IU/g) outperformed placebo, and heparinoid-mucopolysaccharide creams (e.g., Hirudoid) effectively alleviated spontaneous pain, induced pain, edema, and feelings of heaviness[57].

Sulodexide

Sulodexide is a glycosaminoglycan used to treat venous insufficiency, hypertension, and for thrombosis prophylaxis. Research shows it is at least as effective as pentoxifylline and more effective for venous ulcers, with a meta-analysis indicating complete ulcer healing rates of 48% for sulodexide compared to 37% for pentoxifylline and 16% for MPFF. It significantly alleviates symptoms like pain, swelling, and heaviness[53]. Sulodexide's anti-inflammatory and antithrombotic properties improve capillary permeability and are beneficial in conditions like chronic venous disease. However, studies vary in quality, and there is a potential risk of bleeding[6,53,58–62].

A Cochrane analysis showed a 49.4% complete ulcer-healing rate with sulodexide compared to 29.8% in the control group receiving standard care. Most studies were of low to very low quality due to bias. Sulodexide was generally well tolerated, with rare mild side effects like headache and dizziness[61]. A systematic review of 13 studies involving 1,901 patients found significant reductions in pain, cramps, swelling, and edema, with no increased side effects compared to placebo[59]. An open-label study of 25 patients with chronic venous insufficiency reported significant improvements in symptoms and quality of life after 90 days[63]. In another study of 450 patients, all symptoms and quality-of-life measures improved after 3 months[60]. A larger prospective study of 2,263 patients reported symptom improvement in 99.2% within 15−20 days[64]. A meta-analysis found that sulodexide significantly reduced deep vein thrombosis incidence, with a bleeding rate of 0.28% compared to 1.60% in controls[65].

Summary

VAC (venoactive compounds) and VAD (venoactive drugs) have similar effects on the venous endothelium, lymphatic drainage, edema, venous tone, leukocyte adhesion to the walls and valves of veins, inflammatory mediators, blood viscosity, and red blood cells. However, the study results regarding symptoms such as pain, cramps, heaviness, swelling, and edema show some variability. Micronized purified flavonoid fractions (MPFF) and ruscus extract, when combined with hesperidin methyl chalcone and ascorbic acid, provided the highest quality of evidence, predominantly at level A. For venous leg ulcers, the most effective adjunctive treatments were MPFF, sulodexide, and pentoxifylline, all of which also had level A evidence. Additionally, the use of VAD has been introduced to prevent deterioration of venous status, including changes in arterial vascular conditions. While the quality of the studies varies and they are only partially comparable, more recent research has shown positive findings.

Conclusion

Studies have confirmed the efficacy of VAC and VAD in the treatment of chronic venous insufficiency (CVI) and varicose veins. The quality of these studies has been assessed differently; however, more recent studies have achieved a level of evidence that has led to recommendations in international guidelines. New, high-quality studies are still needed.

Abbreviations

ATP, Adenosine Triphosphate; BMI, Body Mass Index; CaD, Calcium Dobesilate; CAE, Cyanoacrylate Embolisation; CHIVA, Cure Conservatrice et Hémodynamique de l'Insuffisance Veineuse en Ambulatoire; CRP, C-reactive Protein; CVI, Chronic venous insufficiency; ESR, Erythrocyte Sedimentation Rate; EVLA, Endovenous Laser Ablation; HCSE, Horse chestnut seed extract; HMC, Hesperidin methyl chalcone; HR, Hydroxyethylrutosides; IL 1 b, Interleukin 1 beta; IL 10, Interleukin 10; IL 6, Interleukin 6; LDL, Low Density Lipoprotein; MOCA, Mechano Chemical Ablation; MPFF, Micronized purified flavonoid fraction; NFkB, Nuclear Factor kappa B; PTS, Postthrombotic Syndrome; PTX, Pentoxifylline; RCT, Randomized controlled trial; RFA, Radiofrequency Ablation; TNFalpha, Tumor Necrosis Factor alpha; VAC, Venoactive compounds; VAD, Venoactive drugs; VCAM-1, Vascular cell adhesion molecule 1.

Conflicts of interest

The author declares no conflicts of interest.

Authors' contributions

RH researched the keywords and wrote the first draft. NH read, checked the text and references and made corrections, contributed to the discussion and made style improvements.

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