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IMPACT OF PHARMACOLOGICAL TREATMENT OF CHRONIC VENOUS DISEASE ON PATIENTS' QUALITY OF LIFE AND SOCIAL FUNCTIONING

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ABSTRACT

Aim: The aim of this study was to review the literature on the efficacy of phlebotonics in the treatment of chronic venous disease (CVD) of the lower limbs, with particular emphasis on their impact on patients' quality of life, social functioning and daily activity.

Materials and Methods: A narrative literature review was conducted in PubMed/MEDLINE, Cochrane Library, Google Scholar and ScienceDirect, covering publications from 1992 to 2026. A total of 22 references were included – randomised controlled trials, systematic reviews, meta-analyses and review articles.

Results: Chronic venous disease significantly impairs patients' quality of life in both physical and psychosocial dimensions. Phlebotonics act primarily symptomatically, reducing pain, oedema and limb heaviness, which translates into improved daily functioning and social activity. Micronized purified flavonoid fraction (MPFF) has the best-documented efficacy in symptom reduction and quality of life improvement, assessed with the CIVIQ-20 questionnaire, with the highest level of evidence according to GRADE. Results of available studies are inconclusive and depend on the type of phlebotonic used and measurement tools applied.

Conclusions: Phlebotonics should not be treated as a homogeneous therapeutic class, as individual substances differ in efficacy profile and mechanism of action. Effective pharmacological management of CVD contributes to improved social functioning and health-related quality of life. Further clinical studies with longer observation periods and standardised quality of life tools are needed to better understand the full impact of these drugs on patients' everyday lives.

KEYWORDS

Chronic Venous Disease, Quality of Life, Social Functioning, Health-related Quality of Life, CIVIQ, Phlebotonics

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1. Introduction

Chronic venous disease (CVD) of the lower limbs is one of the most common health problems in the modern population. According to data from the Vein Consult Program, encompassing over 91,000 subjects from various regions of the world, the prevalence of CVD reaches 83.6% of the general population (Rabe et al., 2012). The disease affects both women and men, with stages C1-C3 being more frequent in women, while more severe clinical forms (C4-C6) occur with similar frequency in both sexes (Rabe et al., 2012).

The clinical picture of CVD is highly varied – ranging from telangiectasias and varicose veins, through oedema and skin changes, to difficult-to-heal venous leg ulcers. For standardised assessment of clinical disease severity, the CEAP classification (Clinical, Etiological, Anatomical, Pathophysiological) is widely used, developed by the International Ad Hoc Committee of the American Venous Forum and first published in 1995 (Porter & Moneta, 1995), then revised in 2004 (Eklöf et al., 2004). This classification enables precise description of disease severity and facilitates comparison of clinical study results. The pathophysiological basis of CVD is venous hypertension, leading to chronic inflammation of the vessel wall, increased capillary permeability and progressive tissue damage.

Symptoms of CVD – such as pain, heaviness of the legs, oedema, muscle cramps and aesthetic changes – significantly affect patients' daily functioning. The disease substantially reduces quality of life both in physical and psychosocial dimensions. For the assessment of quality of life in CVD patients, specific tools are used, among which a particularly important role is played by the CIVIQ-20 questionnaire (Chronic Venous Insufficiency Questionnaire), developed and validated by Launois et al. (1996). This questionnaire comprises 20 questions assessing four dimensions: pain, physical functioning, social functioning and the patient's psychological state.

In the conservative treatment of CVD, two methods play a key role: compression therapy and pharmacotherapy with phlebotonics. Phlebotonics are a heterogeneous group of drugs with vessel wall-sealing,

capillary permeability-reducing and anti-inflammatory properties. They include, among others, micronized purified flavonoid fraction (MPFF – diosmin with hesperidin), aescin, rutin and horse chestnut extracts. A meta-analysis conducted by Kakkos and Nicolaides (2018), encompassing 7 randomised trials involving 1,692 patients, demonstrated high efficacy of MPFF in reducing clinical symptoms and improving quality of life in CVD patients.

The aim of this study is to review the current literature on the efficacy of phlebotonics in the treatment of chronic venous disease of the lower limbs, with particular emphasis on their impact on patients' quality of life. An attempt was made to answer the question of whether these drugs modify the actual course of the disease, or whether their action is limited exclusively to the reduction of subjective symptoms.

2. Methods

This study is a narrative literature review on the efficacy of phlebotonics in the treatment of chronic venous disease of the lower limbs, with particular emphasis on their impact on patients' quality of life. Literature searches were conducted in the PubMed/MEDLINE, Cochrane Library, Google Scholar and ScienceDirect databases, covering publications from 1992 to 2026. The following keywords and their combinations were used: phlebotonic, venoactive drugs, chronic venous disease, chronic venous insufficiency, quality of life, CIVIQ, diosmin, hesperidin, MPFF, horse chestnut, Pycnogenol, calcium dobesilate, rutosides, aminaphthone.

The review included randomised controlled trials, systematic reviews, meta-analyses and narrative review articles concerning the mechanisms of action and efficacy of phlebotonics in the treatment of CVD. Articles concerning other methods of CVD treatment, studies devoted to other disease entities, publications in languages other than English and articles not available in full text were excluded. After applying the inclusion and exclusion criteria, 22 references were qualified for the final analysis.

3. Characteristics of Phlebotonics

Phlebotonics (venoactive drugs, VAD) constitute a heterogeneous group of pharmacological substances used in the conservative treatment of chronic venous disease. Despite their chemical diversity, all substances in this group share a number of common pharmacological properties: they seal the endothelial barrier, improve lymphatic drainage, reduce oedema, increase venous tone, inhibit leukocyte adhesion to the vessel wall and reduce the release of inflammatory mediators (Gloviczki et al., 2025). However, the mechanisms of action of individual representatives of this group differ significantly, which translates into different clinical efficacy profiles.

The pathophysiological basis of CVD is venous hypertension leading to leukocyte activation, vascular endothelial dysfunction and chronic inflammation of the venous wall. These processes result in progressive damage to venous valves, increased capillary permeability and oedema formation. Phlebotonics act on several of these mechanisms simultaneously, breaking the pathophysiological vicious cycle of CVD (Mansilha & Sousa, 2018).

3.1. Micronized Purified Flavonoid Fraction (MPFF)

Micronized purified flavonoid fraction (MPFF) is the most extensively studied of all phlebotonics. It contains 90% diosmin and 10% hesperidin in micronized form, which increases its bioavailability compared to non-micronized diosmin. The mechanism of action of MPFF is based on several mutually complementary molecular pathways. MPFF inhibits the degradation of noradrenaline by catechol-O-methyltransferase, leading to increased venous tone and improved venous return. At the same time, it exhibits potent anti-inflammatory activity by inhibiting leukocyte adhesion to the vascular endothelium, reducing the expression of adhesion molecules ICAM-1 and VCAM-1, and reducing the release of reactive oxygen species and pro-inflammatory cytokines. Furthermore, MPFF reduces capillary permeability by protecting collagen and elastin fibres of the vessel wall, which translates into oedema reduction and improved microcirculation (Mansilha & Sousa, 2018).

3.2. Aescin and Horse Chestnut Extract

Extract from the seeds of the common horse chestnut (Aesculus hippocastanum, HCSE – Horse Chestnut Seed Extract), standardised for aescin content, is a widely used phlebotonic of plant origin. Aescin acts by inhibiting the enzyme hyaluronidase responsible for the degradation of proteoglycans in the vessel wall, leading to reduced capillary permeability and oedema reduction. Additionally, aescin stimulates the release of prostaglandin F2α, leading to increased venous tone. Horse chestnut extract also exhibits anti-inflammatory properties by inhibiting NF-κB factor activation and reducing the expression of proteolytic enzymes that degrade the extracellular matrix (Mansilha & Sousa, 2018).

3.3. Pycnogenol

Pycnogenol is a standardised extract from the bark of maritime pine (Pinus pinaster), rich in proanthocyanidins, phenolic acids and other polyphenols. Its mechanism of action is based primarily on potent antioxidant properties – Pycnogenol neutralises reactive oxygen and nitrogen species, protecting the vascular endothelium from oxidative stress. Furthermore, it inhibits the enzymes collagenase and elastase responsible for the degradation of the extracellular matrix of the vessel wall, strengthening the vascular structure and reducing its permeability. Pycnogenol also stimulates the synthesis of nitric oxide by the vascular endothelium, leading to vasodilation and improved blood flow, and exhibits antithrombotic properties by inhibiting platelet aggregation (Gulati, 2014).

3.4. Calcium Dobesilate

Calcium dobesilate is a synthetic phlebotonic with a multidirectional mechanism of action. It exhibits antioxidant and angioprotective properties, acting at the microvascular level by reducing capillary permeability and decreasing blood viscosity. At the molecular level, calcium dobesilate inhibits the activity of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), reducing pathological angiogenesis and vascular permeability. The drug also exhibits anti-inflammatory properties by inhibiting the synthesis of prostaglandins and leukotrienes and inhibiting platelet aggregation (Liu et al., 2019).

3.5. Rutin and Oxerutins

Rutin and its semi-synthetic derivatives – oxerutins (hydroxyethylrutosides, HR) – belong to the group of flavonoids with capillary wall-sealing properties. Hydroxyethylrutosides act primarily on the microvascular endothelium, reducing its excessive permeability and decreasing oedema formation. Their mechanism of action involves inhibition of the enzyme hyaluronidase and reduction of capillary permeability, improvement of microcirculation by increasing transcutaneous partial oxygen pressure, and inhibition of erythrocyte aggregation and improvement of their deformability. Oxerutins also exhibit protective properties towards the vascular endothelium, reducing damage caused by reactive oxygen species (Wadworth & Faulds, 1992).

3.6. Aminaphthone

Aminaphthone is a synthetic phlebotonic with a documented mechanism of action at the cellular level. In vitro studies have shown that aminaphthone significantly reduces VEGF-induced vascular permeability and restores normal expression of VE-cadherin – a protein responsible for the integrity of endothelial intercellular junctions. Furthermore, aminaphthone stabilises capillary structures by protecting endothelial cells organised in three-dimensional vascular structures, which may explain its beneficial clinical effect in CVD (Felice et al., 2018).

4. Efficacy of Phlebotonics in the Treatment of CVD – Results of Clinical Studies

The assessment of the efficacy of phlebotonics in the treatment of CVD is based on a broad spectrum of clinical studies including randomised controlled trials (RCTs), meta-analyses and systematic reviews. In the assessment of therapeutic efficacy, both objective clinical parameters – reduction of oedema, decrease in ankle circumference or improvement of venous flow – and subjective endpoints, including symptom severity and patients' quality of life, are taken into account. For the assessment of quality of life in CVD patients, specific questionnaires are used, the most widely used of which is the CIVIQ-20, developed and validated by Launois et al. (1996). The results of available studies are inconclusive and depend on the type of phlebotonic used, dosage, duration of therapy and measurement tools applied.

4.1. Micronized Purified Flavonoid Fraction (MPFF) and Diosmin

MPFF has the largest evidence base among all phlebotonics. The meta-analysis by Kakkos and Nicolaides (2018) encompassing 7 randomised trials involving 1,692 patients demonstrated that MPFF compared to placebo significantly reduces pain (RR 0.53; $p=0.0001$), leg heaviness (RR 0.35; $p<0.00001$), oedema (RR 0.39; $p<0.00001$) and muscle cramps (RR 0.51; $p=0.02$). Regarding quality of life, the meta-analysis demonstrated a statistically significant improvement in the MPFF-treated group compared to placebo (SMD -0.21; 95% CI -0.37 to -0.04). The quality of available evidence was assessed as high in the GRADE system.

Maggioli and Carpentier (2019), in a post-hoc analysis focused on mild stages of CVD (C0s-C1), demonstrated that MPFF at a dose of 1,000 mg/day for 8 weeks significantly reduced limb discomfort, pain and heaviness measured by the VAS scale ($p<0.001$). A significant improvement in quality of life measured by the CIVIQ-20 questionnaire was observed in both dosage groups – the change in global index score was -16.53±14.18 in the MPFF 1,000 mg group and -18.78±18.14 in the MPFF 500 mg twice daily group ($p<0.001$). These results indicate that patients with mild symptoms also benefit from MPFF treatment.

Contrasting results were obtained by Danielsson et al. (2002) in a randomised double-blind placebo-controlled trial conducted in a group of 101 patients. No statistically significant superiority of MPFF over placebo was demonstrated regarding the global symptom score ($p>0.05$). The only significant therapeutic effect was a reduction in the frequency of nocturnal muscle cramps. An interesting secondary finding was a reduction in venous reflux time in patients with oedema in the MPFF group ($p=0.03$), however this result did not correlate with clinical improvement.

Serra et al. (2021) evaluated the efficacy of a new diosmin formulation (μsmin® Plus) at a dose of 450 mg/day in a randomised double-blind placebo-controlled multicentre trial in a group of 72 patients with CVD in CEAP classes C2-C4. It was demonstrated that from week 4 of treatment, diosmin significantly reduced limb oedema ($p<0.001$), and after 8 weeks of therapy improved VAS scores for pain ($p<0.05$) and global symptom severity indices GIS and VCSS ($p<0.001$). No treatment-related adverse events were recorded.

4.2. Horse Chestnut Seed Extract (HCSE)

The Cochrane systematic review conducted by Pittler and Ernst (2012), encompassing a series of randomised controlled trials, demonstrated that horse chestnut seed extract (HCSE) significantly reduces leg pain compared to placebo. In six out of seven analysed placebo-controlled trials, a statistically significant reduction in pain was observed in the HCSE group. The meta-analysis demonstrated a reduction in limb volume of on average 32.1 ml (95% CI 13.49-50.72) in favour of HCSE compared to placebo. One of the analysed trials suggested comparable efficacy of HCSE and compression therapy. Adverse events were rare and mild, confirming the good safety profile of the preparation.

4.3. Pycnogenol

Arcangeli (2000), in a randomised double-blind placebo-controlled trial conducted in a group of 40 patients with CVD, demonstrated that Pycnogenol at a dose of 300 mg/day for 2 months significantly reduced subcutaneous oedema and feelings of heaviness and leg pain both after 30 and 60 days of treatment. Complete resolution of oedema was observed in approximately 60% of patients treated with Pycnogenol, while no significant changes were observed in the placebo group.

Cesarone et al. (2006), in a prospective controlled trial in a group of 86 patients with severe CVD, demonstrated that Pycnogenol at a dose of 150-300 mg/day for 8 weeks was more effective than diosmin with hesperidin in improving microcirculation parameters, reducing oedema and improving tissue oxygenation. Significant improvement in the Pycnogenol group was visible after 4 weeks of treatment ($p<0.05$).

4.4. Calcium Dobesilate

Martínez-Zapata et al. (2008) conducted a large randomised double-blind placebo-controlled trial assessing the effect of calcium dobesilate on quality of life measured by the CIVIQ questionnaire as the primary endpoint in a group of 509 patients. It was demonstrated that calcium dobesilate did not significantly improve quality of life compared to placebo after 3 months of treatment (p=0.07), and no significant differences between groups were observed regarding clinical symptoms and oedema either. Only in a multifactorial analysis after 12 months of follow-up was a slight superiority of the drug over placebo observed regarding quality of life (p=0.02). These results suggest that the possible effect of calcium dobesilate on symptoms and quality of life may be delayed and requires long-term observation.

4.5. Comparison of Different Phlebotonics

Belczak et al. (2014), in a randomised double-blind placebo-controlled trial, compared the effect of four different phlebotonics on quality of life and clinical parameters in a group of 127 patients with CVD in CEAP classes C2-C5. It was demonstrated that the use of phlebotonics as a drug class was associated with a significant improvement in quality of life compared to placebo. Diosmin with hesperidin achieved the best results in reducing limb volume (reduction ≥100 ml more frequent than in the other groups), while aminaphthone showed the most favourable effect on quality of life. No differences in ankle joint range of motion were observed between groups.

4.6. Results of Systematic Reviews

The Cochrane systematic review encompassing 69 RCTs involving 7,690 patients presented the most comprehensive assessment of phlebotonic efficacy. It demonstrated that phlebotonics probably slightly reduce lower limb oedema compared to placebo (RR 0.70; 95% CI 0.63-0.78) and reduce ankle circumference (MD -4.27 mm; 95% CI -5.61 to -2.93 mm). Regarding quality of life, it was demonstrated that phlebotonics probably have little or no effect on QoL compared to placebo (SMD -0.06; 95% CI -0.22 to 0.10). At the same time, no significant effect on venous ulcer healing was demonstrated (RR 0.94; 95% CI 0.79-1.13). The quality of available evidence was assessed as moderate in the GRADE system (Martinez-Zapata et al., 2020).

The most recent review by Gloviczki et al. (2025) confirms that among available phlebotonics, the highest level of evidence (A according to GRADE) for symptom reduction and quality of life improvement is held by MPFF and Ruscus extract combined with hesperidin methyl chalcone and ascorbic acid. In the treatment of venous ulcers, where compression therapy remains the cornerstone of treatment (Gadzińska et al., 2026), the highest level of evidence as adjunctive treatment is held by MPFF, sulodexide and pentoxifylline (Gloviczki et al., 2025).

The results of available studies indicate that the effect of phlebotonics on clinical symptoms and quality of life is heterogeneous and depends on the type of drug used and the duration of therapy. Improvement in clinical symptoms does not always translate into a significant improvement in quality of life measured by standardised questionnaires, which raises the question of the actual impact of phlebotonics on patients' functioning in the psychosocial dimension.

5. Discussion

The results of the presented literature review indicate that phlebotonics exert primarily a symptomatic effect in the treatment of chronic venous disease, while the efficacy of individual substances differs significantly. Among available phlebotonics, MPFF has the best-documented efficacy both in terms of symptom reduction and quality of life improvement. The ambiguity of available study results stems from several important methodological factors that require critical evaluation.

The first and most important problem is the lack of standardisation of assessment tools used in clinical studies. Some studies use the CIVIQ-20 questionnaire, considered the gold standard for quality of life assessment in CVD (Launois et al., 1996), while others use clinical symptom severity scales such as VAS, GIS or VCSS. Although these scales reflect patients' subjective feelings, they do not encompass the psychosocial and functional dimensions that are an integral part of the concept of quality of life. This makes comparison of results between studies considerably more difficult and may lead to erroneous conclusions regarding the actual impact of phlebotonics on patients' quality of life (Martinez-Zapata et al., 2020).

Another important issue is the heterogeneity of the drug group referred to as phlebotonics. Analysis of available studies indicates that individual substances may differ significantly in their efficacy profile and

should not be treated as a homogeneous therapeutic class. The Cochrane review encompassing all phlebotonics as a group demonstrated no significant effect on quality of life (Martinez-Zapata et al., 2020), while the meta-analysis focused exclusively on MPFF documented high efficacy of this specific drug (Kakkos & Nicolaides, 2018). This suggests that averaging results for the entire class of phlebotonics may mask the actual efficacy of individual substances, and that the choice of a specific preparation should be based on individual clinical evidence rather than general recommendations for the entire group.

Addressing the research question of this study, available data suggest that phlebotonics act primarily symptomatically – reducing pain, oedema and feelings of limb heaviness – however, in the case of MPFF, there are indications of a possible disease-modifying effect. This is supported by the mechanism of action of MPFF, which includes inhibition of leukocyte adhesion, reduction of inflammation and protection of the vascular endothelium – that is, action on key elements of CVD pathophysiology (Mansilha & Sousa, 2018). The most recent data confirm the efficacy of MPFF as adjunctive treatment in venous ulcers at the highest level of evidence (Gloviczki et al., 2025), which further suggests that this drug may go beyond purely symptomatic action. For other phlebotonics, available evidence points mainly to symptomatic action without significant effect on disease progression – as evidenced by the lack of significant effect of phlebotonics as a group on venous ulcer healing demonstrated in the Cochrane review (Martinez-Zapata et al., 2020).

An important limitation of available studies is the short observation period – usually 8-12 weeks – which may be insufficient to capture the full therapeutic effect. The study by Martínez-Zapata et al. (2008) suggests that the effect of calcium dobesilate on quality of life may only become apparent after 12 months of treatment, indicating that short-term studies may underestimate the actual efficacy of phlebotonics. The heterogeneity of studied populations – different stages of CVD according to the CEAP classification, varying disease duration and comorbidities – further complicates the formulation of unambiguous conclusions and comparison of results between studies.

Despite certain limitations of available evidence, phlebotonics remain an important element of conservative CVD treatment, used as a complement to compression therapy and lifestyle modification, including regular physical activity whose role in improving venous function is increasingly well documented (Salwa et al., 2024). Future studies should focus on standardisation of assessment tools with widespread use of the CIVIQ-20 questionnaire as the primary endpoint, extension of the observation period to at least 12 months, and conducting direct comparative studies between different phlebotonics. This would enable the formulation of more precise clinical recommendations regarding the choice of the optimal drug for a specific patient.

6. Conclusions

Based on the conducted literature review on the efficacy of phlebotonics in the treatment of chronic venous disease of the lower limbs, the following conclusions were formulated:

Phlebotonics act primarily symptomatically – reducing pain, oedema and feelings of limb heaviness – and as a drug class do not demonstrate a clear disease-modifying effect in chronic venous disease.

Among available phlebotonics, micronized purified flavonoid fraction (MPFF) has the best-documented efficacy both in terms of symptom reduction and quality of life improvement, with the highest level of evidence according to the GRADE system.

Phlebotonics should not be treated as a homogeneous therapeutic class – individual substances differ significantly in their efficacy profile and mechanism of action, which should be taken into account when selecting therapy for a specific patient.

Phlebotonics remain an important element of conservative CVD treatment, used as a complement to compression therapy and lifestyle modification, however further high-quality clinical studies with longer observation periods and standardised quality of life assessment tools are needed.

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