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ORIGINAL RESEARCH

Real-world effectiveness of a phlebotonic formulation combining diosmin, *Ruscus*, *Melilotus* and *Vitis vinifera* on symptoms and quality of life in patients with chronic venous and lymphatic disease: results from the VIVEMA Stasis observational study

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Abstract

Background: Chronic venous disease and lymphoedema frequently coexist, leading to significant symptom burden and impaired quality of life (QoL). Phlebotonic agents, such as diosmin, *Ruscus aculeatus*, *Melilotus officinalis* and *Vitis vinifera*, have demonstrated complementary anti-inflammatory, venotonic and lymphokinetic effects. However, real-world evidence on their combined use remains limited.

Methods: The VIVEMA Stasis study was a retrospective observational analysis conducted in a real-world clinical setting. Adult patients with lower limb venous and/or lymphatic oedema received a 30-day treatment with a standardized formulation containing diosmin, *R. aculeatus*, *M. officinalis* and *V. vinifera* extracts, in addition to compression therapy. The primary endpoint was improvement in health-related QoL, assessed using the CIVIQ-14 questionnaire. Secondary endpoints included changes in symptom burden and limb circumference measurements.

Results: Fifty-one patients (mean age 54.0 years; 84.3% female) were included. After 30 days, significant improvements were observed in QoL (global CIVIQ-14 score: $p<0.001$), with reductions in pain, sleep disturbance and functional limitations. Objective measurements showed significant reductions in both ankle and calf circumferences (median reduction: 0.40 cm and 0.50 cm, respectively; $p<0.001$). Symptom burden scores improved significantly (median increase from 19.0 to 25.0; $p=0.002$), especially for swelling, heaviness and fatigue. No adverse events were reported.

Conclusion: In this real-world setting, a short-term integrative treatment with a phlebotonic formulation combining diosmin, *R. aculeatus*, *M. officinalis* and *V. vinifera* significantly improved QoL, symptom burden and oedema in patients with chronic venous and lymphatic disease. These findings support the therapeutic potential of combined phlebotonic therapy alongside standard care.

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Keywords: chronic venous disease (CVD), CIVIQ-14, lymphoedema, phlebotonics, quality of life (QoL), symptom burden.

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Introduction

Chronic venous disease (CVD) represents an umbrella term encompassing a spectrum of venous disorders ranging from mild conditions, such as telangiectasias and reticular veins, to more advanced stages, including varicose veins, chronic venous insufficiency, skin changes and venous ulceration.[1] The overall estimates of the prevalence of CVD may vary and can reach 20–40% in the adult population of industrialized countries, with increasing prevalence in women and with age.[1,2] The clinical severity of CVD is classified according to the CEAP system (Clinical–Etiological–Anatomical–Pathophysiological), which stratifies patients into classes C0–C6, where C0 indicates no visible or palpable signs, C1 the presence of telangiectasias or reticular veins, C2 varicose veins, C3 oedema, C4 skin and subcutaneous changes (e.g. pigmentation or lipodermatosclerosis), C5 healed venous ulcers, and C6 active venous ulcers.[3] The management of CVD is multimodal and includes lifestyle interventions and compression therapy (elastic stockings or multilayer bandaging) as the cornerstone of treatment, and pharmacological options such as venoactive drugs (e.g. flavonoids), which reduce inflammation, improve venous tone and alleviate symptoms.[4] In advanced cases or when conservative therapy fails, interventional procedures, such as endovenous thermal ablation, sclerotherapy or phlebectomy, may be indicated to correct venous reflux and prevent disease progression.[5]

Venous hypertension and microcirculatory changes in CVD lead to increased interstitial fluid leakage and a higher demand on lymphatic drainage. In such conditions of lymphatic flow impairment, lymph stasis can occur, leading to chronic tissue inflammation and lymphoedema, with progression to phlebolymphatic oedema (or phlebolymphoedema) in some cases.[6,7] Indeed, CVD is widely recognized as a major cause of secondary lymphoedema.[8] Lymphoedema can be classified into primary lymphoedema, which results from congenital or hereditary abnormalities, such as lymphatic hypoplasia, aplasia or hyperplasia and secondary lymphoedema, which arises due to external factors, including surgery, radiotherapy, trauma, infection or CVD.[6,7] Globally, an estimated 250 million people are affected by lymphoedema, which significantly reduces quality of life (QoL) and psychosocial well-being.[9–11] Standard treatment for lymphoedema, whether primary or secondary, includes physical rehabilitation measures, such as manual lymphatic drainage, functional bandaging, elastic compression and skin care, often combined with pharmacological or surgical approaches.[7] Amongst pharmacological treatments, flavonoids, particularly diosmin, are widely prescribed to alleviate venous symptoms, reduce oedema and improve microvascular function.[4] Additional natural agents, including *Ruscus aculeatus*, *Melilotus officinalis* and *Vitis vinifera* extracts, have complementary anti-inflammatory, venotonic and lymphokinetic effects.[12–16] Despite its prevalence, our understanding of the role of chronic inflammation in the pathogenesis and progression of lymphoedema remains incomplete, and targeting the inflammatory microenvironment represents an area of active therapeutic research.[17] Overall, this overlap between venous and lymphatic dysfunction requires a combined management strategy.

Diosmin (7-O-rutinoside), a glycoside obtained from citrus peels or plant-derived hesperidin, is one of the most studied venotonics. Clinical studies showed that micronized purified flavonoid fraction (1000 mg once daily or 500 mg twice daily) and non-micronized diosmin (600 mg once daily) significantly improved symptoms and QoL in patients with venous insufficiency, with comparable efficacy over both 1-month and 6-month treatment durations.[4] Additional phytotherapeutics, such as *R. aculeatus*, *M. officinalis* and *V. vinifera*, exhibit complementary mechanisms. *Ruscus* saponins stimulate venous and lymphatic smooth muscle contraction, improving lymphatic return and reducing oedema.[12] *Melilotus* extracts exert lymphokinetic activity and modulate inflammatory pathways, including downregulation of NF-κB and cytokine production (e.g. IL-6, TNF and COX2), with evidence of increased macrophage recruitment and proteolytic clearance of interstitial proteins.[13] *V. vinifera*-derived proanthocyanidins — oligomeric flavanols with strong antioxidant activity — offer endothelial protection, scavenging free radicals and reducing capillary permeability, providing a reduction in leg circumference, subjective symptoms (heaviness, fatigue, cramps) and improved microcirculation.[14–16]

Based on this rationale, integrative therapies combining these compounds may provide synergistic benefits in patients with venolymphatic disease. Indeed, this multimodal approach leverages the anti-inflammatory and venotonic properties of diosmin, the venous and lymphatic smooth muscle contraction induced by *R. aculeatus*, the lymphokinetic and anti-inflammatory effects of *M. officinalis*, and the antioxidant and endothelial-protective actions of *V. vinifera*. However, real-world data evaluating the clinical effectiveness of such combinations remain limited.

The VIVEMA Stasis observational study was designed to evaluate the symptom burden, oedema reduction and QoL in patients with CVD, lymphoedema and/or phlebolymphatic oedema treated with a phlebotonic formulation containing diosmin, *R. aculeatus*, *M. officinalis* and *V. vinifera*, combined with functional bandaging and elastic compression therapy.

Patients and methods

Study design and setting

This was a retrospective observational study conducted at the Angiology Unit of the Azienda Ospedale-Università di Padova, Italy. The study included adult patients with lower limb oedema CVD, lymphoedema and/or phlebolymphatic oedema, who were commonly treated in clinical practice with functional bandaging, elastic compression therapy and active compounds targeting the venolymphatic system, such as diosmin and extracts of *V. vinifera*, *R. aculeatus* and *M. officinalis*, administered in addition to standard of care, and were evaluated between May 2024 and February 2025 for CVD and associated venolymphatic oedema. Eligible patients were identified from outpatient records and were included if they were between 18 and 80 years of age, had a confirmed clinical and instrumental diagnosis of lower limb oedema due to CVD, post-thrombotic syndrome or lymphoedema, and were undergoing treatment with a standardized phlebotonic formulation containing diosmin (500 mg), *R. aculeatus* (dry extract, 200 mg of which ruscogenin 20 mg), *M. officinalis* (dry extract, 50 mg of which coumarin 10 mg) and *V. vinifera* (dry extract, 200 mg of which proanthocyanidins 190 mg) with a dosage of one tablet per day. Patients with active thrombosis, active venous and phlebolymphatic ulcers, severe peripheral arterial disease (ankle-brachial index <0.6), decompensated heart failure, cancer, pregnancy, severe liver or kidney failure, or known allergy to the study compounds were excluded. Data were collected at baseline and at a follow-up visit, approximately 30 days later.

The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and Good Clinical Practice guidelines. As a retrospective observational study, it was approved by the institutional ethics committee of the Azienda Ospedale-Università di Padova (project code CET-ACEV: 6215/AO/25). Informed consent for the retrospective analysis was obtained via email, and participants were contacted by telephone to confirm eligibility and willingness to participate. All participants provided informed consent for the use of their anonymized clinical data for research purposes.

Study measures

The primary endpoint of the study was the improvement in health-related QoL, assessed using the validated CIVIQ-14 questionnaire (Supplementary Material; available at: https://www.drugsincontext.com/wp-content/uploads/2026/01/dic.2025-10-1-Suppl.pdf). This tool evaluates patient-reported outcomes across multiple domains, including pain, physical limitations, sleep disturbance and psychological distress. Each item is scored on a 5-point Likert scale with higher scores indicating greater impairment (Supplementary Material).

Secondary endpoints included clinical and subjective evaluation of oedema and symptom burden. Objective measurements of lower limb oedema were obtained using circumferential tape measurements at standardized anatomical landmarks: 1 cm above the medial malleolus (ankle) and 1 cm below the popliteal fold (calf). Improvement was defined as a reduction in ankle/calf circumference (lateralized right/left, maximum, mean and limb with the largest circumference at the first visit) between the two visits, greater than 0. Symptom burden was assessed using a self-administered 6-point Likert scale evaluating five specific symptoms: calf swelling, heaviness, fatigue, sensation of heat and nocturnal cramps with pain. Each item was rated from 1 (very severe) to 6 (none), allowing quantification of symptom intensity and tracking of improvement over time. Safety data were also collected.

All assessments were conducted during scheduled outpatient visits. Additional clinical evaluations included anamnestic data, CEAP classification for venous insufficiency, International Society of Lymphology (ISL) staging for lymphoedema (stage 0: subclinical, stage I: reversible with elevation, stage II: irreversible with fibrosis and stage III: lymphostatic elephantiasis) and venous Duplex ultrasonography using a Philips Elite/EpiQ 5 system.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics and clinical variables, including mean, standard deviation and frequency distributions. Paired comparisons between baseline and follow-up measurements were performed using the Student's *t*-test for normally distributed continuous variables, and the Wilcoxon signed-rank test or signed-rank test for non-parametric data. Categorical variables were compared using Fisher's exact test. Correlations between clinical and patient-reported outcomes were explored using Pearson or Spearman correlation coefficients, as appropriate.

Changes in QoL and symptom scores between the two timepoints were analysed to assess the direction and significance of treatment effects. Graphical representations included histograms for continuous data and bar or mosaic plots for categorical data. All analyses were performed using standard statistical software with significance defined as $p<0.05$.

Results

Baseline characteristics of patients

A total of 51 patients were included in the analysis. The mean age was 54.0 years (SD ±13.3) with a predominance

of women (*n*=43; 84.3%). Most patients did not have a history of deep vein thrombosis (100%) or thrombophlebitis (92.2%), whilst 74.5% reported a family history of chronic venous insufficiency. Hypertension and dyslipidaemia were present in 21.6% and 19.6% of patients, respectively, whilst diabetes was rare (2.0%) (Table 1). The distribution of patients across the CEAP and ISL classifications at baseline showed that 52.9% were categorized as CEAP C1, 41.2% as C2 and 5.9% as C3. According to the ISL staging, 52.9% were classified as stage 0.0, 39.2% as stage 0–1 and 7.8% as stage 1.0. The full details of patient baseline characteristics are reported in Table 1.

Improvement in health-related quality of life

A total of 51 patients were available for the analysis of the CIVIQ-14 questionnaire at both visits. Results revealed a significant improvement across several domains of QoL following the 30-day treatment period (global index score: $p<0.001$; Table 2). In detail, pain-related symptoms improved, with the proportion of patients reporting minimal or no leg pain (score 1) increasing from 9.8% at baseline to 41.2% at follow-up ($p<0.001$); sleep disturbances related to venous symptoms decreased

Table 1. Baseline characteristics of the study population (*n*=51).

Characteristic	Value
Age (years), mean ± SD	54.0 ± 13.3
Female sex, *n* (%)	43 (84.3%)
BMI, median (range)	24.6 (22.5–26.0)
Hypertension, *n* (%)	11 (21.6%)
Diabetes, *n* (%)	1 (2.0%)
Dyslipidaemia, *n* (%)	10 (19.6%)
Family history of CVI, *n* (%)	38 (74.5%)
History of DVT, *n* (%)	0 (0.0%)
History of thrombophlebitis, *n* (%)	4 (7.8%)
Phlebosurgical treatments, *n* (%)	8 (15.7%)
CEAP classification (%)	C1: 52.9% C2: 41.2% C3: 5.9%
ISL stage (%)	0.0: 52.9% 0–1: 39.2% 1.0: 7.8%

BMI, body mass index; CEAP, Clinical–Etiological–Anatomical–Pathophysiological; CVI, chronic venous insufficiency; DVT, deep vein thrombosis; ISL, International Society of Lymphology; SD, standard deviation.

Table 2. Distribution of responses to CIVIQ-14 items at baseline and follow-up (*n*=51).

Item (domain)	Responses		*p* value
	Baseline (%)	Follow-up (%)	
1. Pain in legs (pain)	1: 9.8% 2: 45.1% 3: 25.5% 4: 17.7% 5: 2.0%	1: 41.2% 2: 31.4% 3: 25.5% 4: 2.0% 5: 0%	<0.001
2. Discomfort in daily activities (physical)	1: 7.8% 2: 54.9% 3: 17.7% 4: 19.6% 5: 0%	1: 44.0% 2: 36.0% 3: 16.0% 4: 4.0% 5: 0%	<0.001
3. Sleep disturbed by symptoms (pain)	1: 41.2% 2: 33.3% 3: 19.6% 4: 3.9% 5: 2.0%	1: 60.8% 2: 31.4% 3: 7.8% 4–5: 0.0%	<0.001
4. Climbing stairs (physical)	1: 33.3% 2: 31.4% 3: 23.5% 4: 11.8% 5: 0%	1: 47.1% 2: 31.4% 3: 15.7% 4: 5.9% 5: 0%	0.020
5. Kneeling down (physical)	1: 31.4% 2: 31.4% 3: 15.7% 4: 19.6% 5: 2.0%	1: 43.1% 2: 29.4% 3: 15.7% 4: 11.8% 5: 0%	0.018
6. Walking briskly (physical)	1: 37.3% 2: 31.4% 3: 19.6% 4: 9.8% 5: 2.0%	1: 64.7% 2: 17.7% 3: 9.8% 4: 5.9% 5: 2.0%	<0.001
7. Attending social events (psychological)	1: 67.4% 2: 12.2% 3: 16.3% 4: 4.1% 5: 0%	1: 74.0% 2: 14.0% 3: 8.0% 4: 4.0% 5: 0%	0.2
8. Practising sports (physical)	1: 44.0% 2: 24.0% 3: 20.0% 4: 6.0% 5: 6.0%	1: 62.5% 2: 16.7% 3: 10.4% 4: 8.3% 5: 2.1%	0.080
9. Feeling nervous/tense (psychological)	1: 78.0% 2: 22.0% 3–5: 0%	1: 90.0% 2: 10.0% 3–5: 0%	0.020
10. Feeling like a burden (psychological)	1: 100% 2–5: 0%	1: 100% 2–5: 0%	*

(*Continued*)

Table 2. (Continued)

Item (domain)	Responses		*p* value
	Baseline (%)	Follow-up (%)	
11. Feeling ashamed (psychological)	1: 78.2% 2: 22.0% 3–5: 0%	1: 82.0% 2: 18.0% 3–5: 0%	0.300
12. Feeling irritable (psychological)	1: 92.0% 2: 8.0% 3–5: 0%	1: 94.0% 2: 6.0% 3–5: 0%	>0.900
13. Feeling disadvantaged (psychological)	1: 100% 2–5: 0%	1: 100% 2–5: 0%	*
14. Avoiding going out (psychological)	1: 100% 2–5: 0%	1: 100% 2–5: 0%	*

Responses are coded from 1 (no impact) to 5 (maximum impact). Statistical significance based on McNemar's test or the Wilcoxon signed-rank test. *Items 10, 13 and 14 had no variation and were excluded from statistical comparison.

substantially, with the percentage of patients scoring 1 rising from 41.2% to 60.8% ($p<0.001$). Functional limitations also showed significant reductions: difficulty climbing stairs and kneeling both improved ($p=0.020$ and $p=0.018$, respectively), and brisk walking was notably less impaired at follow-up ($p<0.001$; Table 2).

The item assessing nervousness or tension showed a modest but significant improvement, with 90.0% of patients reporting no such feelings after treatment compared to 78.0% at baseline ($p=0.020$; Table 2). Other psychological items, such as feeling ashamed, irritable or disadvantaged, showed little to no variation and remained stable over time, with some items (e.g. feeling like a burden, avoiding going out) exhibiting ceiling effects (Table 2). At the same time, the overall standardized psychological score resulted improved ($p=0.008$).

Clinical evaluation of oedema

Objective limb circumference measurements revealed a significant reduction in both ankle and calf diameters after the 30-day treatment. The median reduction in the maximum ankle circumference was 0.40 cm (IQR 0.20–0.70), whilst that for the calf was 0.50 cm (IQR 0.20–1.00) (both $p<0.001$). Overall, 78.0% of patients showed a reduction in ankle circumference and 80.9% in calf circumference on the more affected side at baseline. Notably, 84.0% experienced improvement in the maximum ankle measurement and 83.0% in the maximum calf measurement, irrespective of laterality.

Assessment of symptom burden

Overall, the cumulative Likert symptom score increased from 19.0 to 25.0 points ($p=0.002$), indicating reduced symptom burden. In particular, median scores for swelling, heaviness and fatigue improved from 3 or 4 to 5 across visits ($p=0.002$, $p<0.001$ and $p<0.001$, respectively). Improvements in cramps and heat sensation were also reported, even if they were not statistically significant. Internal consistency of the scale improved markedly between baseline (Cronbach's $\alpha=0.78$) and follow-up ($\alpha=0.95$), suggesting enhanced reliability in patient-reported improvements.

No adverse events were reported within the study.

Discussion

The use of flavonoid-based and other botanical formulations as complementary therapies to standard care is emerging as a promising area of clinical interest. Findings of the VIVEMA Stasis observational study provide real-world evidence supporting the clinical benefit of an integrative phlebotonic treatment combining diosmin, *R. aculeatus*, *M. officinalis* and *V. vinifera* in patients with CVD and lymphoedema, adding to the growing body of real-world evidence highlighting the value of integrative strategies in the management of this condition. In particular, after 30 days of treatment, significant improvements were observed in health-related QoL, as measured by the CIVIQ-14, with marked reductions in pain and physical limitations and a smaller but meaningful improvement in psychosocial well-being. The global index score decreased significantly ($p<0.001$), with some domains showing four-fold to five-fold improvements compared with baseline, especially for pain, discomfort in daily activities and sleep disturbances. Symptom burden, evaluated with a 6-point Likert scale, also improved substantially ($p=0.002$) with swelling, heaviness and fatigue showing the most notable improvements, reaching up to two-fold to six-fold reductions compared to baseline.

Objective reductions in both ankle and calf circumferences were observed in more than 80% of patients, confirming the decongestive action of the treatment with a median reduction of 0.40 cm at the ankle and 0.50 cm at the calf ($p<0.001$). Although the enrolled patients presented with varying underlying conditions – CVD, lymphoedema or phlebolymphoedema – these disorders share common pathophysiological pathways, such

as microcirculatory dysfunction, chronic inflammation and fluid retention. This overlap supports the rationale for an integrated therapeutic approach targeting both venous and lymphatic components. These results were consistent with previous studies investigating the individual components of the formulation. Cazaubon et al.[4] reported that diosmin significantly improved symptoms and QoL in patients with chronic venous insufficiency. Similarly, Guex et al.[12] demonstrated the clinical benefits of *R. aculeatus* in the management of chronic venous disorders. Zhou[13] highlighted the anti-inflammatory properties of *M. officinalis*, particularly through modulation of cytokine pathways. Furthermore, clinical trials by Kiesewetter et al.[15] and Schaefer et al.[16] reported that *V. vinifera* extracts exert antioxidant and endothelial-protective effects, leading to improved microcirculation and reduction of venous symptoms. Taken together, our findings align with this body of evidence, supporting the therapeutic rationale for combining these agents in an integrative approach.

The rapid clinical benefit observed within 30 days suggests that combined phlebotonic therapy may offer an effective complement to standard compression therapy, accelerating symptom relief and improving patient QoL.[5] Although the psychological domains of the CIVIQ-14 showed limited change, likely due to a ceiling effect at baseline, these findings emphasize the importance of targeting both physical and psychosocial aspects in the long-term management of venolymphatic disorders.

Despite the limitations of this retrospective, non-randomized study with a short period of follow-up and the absence of a control group, the relatively small and heterogeneous patient population, the consistency of results across subjective and objective measures supports the therapeutic potential of this formulation. Moreover, its real-world setting and the use of validated tools, such as the CIVIQ-14 questionnaire, to evaluate health-related QoL must be recognized as strengths of the study.

Taken together, our results suggest that this phlebotonic formulation may represent an effective complement to standard therapies, providing rapid symptom relief and measurable improvements in patient-reported outcomes. Future randomized trials with longer follow-up are warranted to confirm these findings, assess the sustainability of benefits, compare this formulation with other standard treatments or supplements, and explore the role of such integrative treatments in patients with more advanced disease or significant psychosocial burden.[3] Moreover, future comparative studies are needed to determine whether the combined formulation offers superior benefit over monotherapy.

Conclusion

In this real-world observational study, a short-term treatment with a phlebotonic formulation containing diosmin, *R. aculeatus*, *M. officinalis* and *V. vinifera* was associated with significant improvements in QoL, symptom burden and objective measures of oedema in patients with chronic venous and lymphatic disease. These findings provide promising evidence supporting the effectiveness of an integrative phlebotonic formulation in the management of CVD and lymphoedema. Future research, particularly well-designed randomized controlled trials with longer follow-up, is warranted to better define the optimal role of such supplements in the long-term management of venolymphatic disorders.

Supplementary Material available at: https://www.drugsincontext.com/wp-content/uploads/2026/01/dic.2025-10-1-Suppl.pdf

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Data availability: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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