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Objective and subjective effects of a nutraceutical fixed combination in patients with symptoms suggestive of early chronic venous disease: a prospective observational pilot study

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Abstract

Early chronic venous disease may significantly impair quality of life even in the absence of overt varicose disease, and effective conservative strategies are needed to relieve symptoms and possibly slow disease progression.

This prospective observational pilot study evaluated the effectiveness and tolerability of a nutraceutical fixed combination with venotropic, anti-inflammatory and draining activity in adults with symptoms suggestive of early-stage chronic venous disease (CEAP C0s-C1s). Sixty patients aged 35-70 years were enrolled, and 40 completed the 90-day follow-up; the 33.3% drop-out/non-completer rate is explicitly reported as a major real-world limitation. Participants received one tablet daily containing micronized flavonoids (µsMIN® Plus; 570 mg, including diosmin 450 mg), *Boswellia serrata* (Bospure®), bromelain (Bromeyal®), hesperidin, *Melilotus officinalis*, pineapple extract, and vitamin C. The primary endpoint was the change in ankle circumference from baseline to day 90. Secondary endpoints included patient-reported symptoms assessed by visual analogue scales for pain, heaviness/warmth, itching,

nocturnal cramps, self-perceived edema/swelling, visible varicosity, and self-perceived quality of life.

Of the 60 enrolled patients, 40 completed the study, corresponding to a 33.3% drop-out/non-completer rate (20/60). Eight patients were lost to follow-up and 12 did not consistently take the tested product (adherence <70%). This high drop-out rate substantially limits the statistical analysis and the value of the final outcomes. In the completer population, mean ankle circumference significantly decreased from 23.1±1.8 cm at baseline to 21.4±1.4 cm at Day 90, corresponding to a mean reduction of 1.7±0.5 cm ($p=0.023$). Significant improvements were also observed in all subjective parameters except visible varicosity, with benefits already detectable at Day 45 and maintained or enhanced at Day 90. No adverse events leading to treatment discontinuation were reported.

In this real-world cohort of patients with symptoms suggestive of early chronic venous disease, the tested nutraceutical combination was associated with significant improvements in both objective and subjective outcomes and was well tolerated. However, given the uncontrolled observational design and the 33.3% drop-out/non-completer rate, these findings should be considered preliminary and not definitive evidence of a causal treatment effect.

Key words: chronic venous disease; nutraceutical; diosmin; venotropic; self-perceived swelling; quality of life.

Introduction

Chronic venous disease represents one of the most common circulatory disorders of the lower limbs, characterized by impaired venous return, primarily due to valvular incompetence and, in some cases, venous obstruction. This mechanism may lead to venous hypertension and a broad spectrum of symptoms and clinical signs, with potential impairment of patients' Quality of Life (QoL).[1,2] Patients frequently report heaviness, leg fatigue, a swelling sensation, itching, nocturnal cramps, throbbing or burning pain, and diffuse aching of the legs. These symptoms typically worsen with prolonged standing or sitting.[1,2]

Globally, the prevalence of chronic venous disease across its spectrum varies considerably depending on geographic location, diagnostic criteria, and age distribution.[3] Longitudinal data from the Edinburgh Vein Study reported an incidence of 9.2% over a 13-year follow-up, corresponding to an annual rate of 0.7%, with higher rates among older and obese individuals.[4] Established risk factors include prolonged standing, obesity, pregnancy, genetic predisposition, and sedentary lifestyle.[5]

From a clinical perspective, the CEAP classification provides a standardized framework for reporting chronic venous disorders. In brief, C0 indicates no visible or palpable signs of venous disease, C1 indicates telangiectasias or reticular veins, C2 varicose veins, C3 edema, and C4-C6 skin changes and venous ulceration.[6]

Early symptomatic disease is clinically relevant despite the absence of advanced signs. Symptomatic C0 patients represent a sizeable proportion of patients seeking care for venous symptoms, and even mild disease can impair QoL and motivate conservative treatment.[3,7]

Management of mild chronic venous disease typically involves lifestyle interventions such as regular physical activity, weight control, leg elevation, and, when appropriate, compression therapy.[8] Conservative pharmacological or nutraceutical approaches may include venotropic agents, particularly flavonoid-based compounds such as diosmin and hesperidin, which act on several venous and microvascular morpho-functional features, including permeability, inflammation, microcirculatory function, and symptom perception.[3,9,10]

In light of these considerations, the present study aimed to evaluate the effectiveness and safety of a nutraceutical fixed combination containing registered raw materials and active ingredients selected for venotropic, anti-inflammatory, and draining activity: micronized flavonoids (µsMIN® Plus; 570 mg, including diosmin 450 mg), bromelain (Bromeyal®), *Boswellia serrata* (Bospure®), hesperidin, *Melilotus officinalis*, pineapple extract, and vitamin C, in patients presenting with symptoms suggestive of early-stage chronic venous disease (CEAP C0s-C1s).

Materials and Methods

The study was conducted at the Hypertension and Cardiovascular Risk Research Center of the Department of Medical and Surgical Sciences, Alma Mater Studiorum University of Bologna.

The study fully adhered to the ethical guidelines outlined in the Declaration of Helsinki and the International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP). The protocol received approval from the Ethical Committee of the University of Bologna (code: LLD-RP2018), and all participants provided written informed consent.

A total of 60 patients aged 35-70 years spontaneously reporting symptoms suggestive of early chronic venous disease were enrolled. The main clinical inclusion criterion was CEAP clinical class C0s or C1s, namely C0 or C1 clinical staging associated with patient-reported venous symptoms. Thus, by definition, patients with clinically evident edema (CEAP C3) were not included. Inclusion criteria also required patients to understand the study objectives and sign an informed consent form.

Exclusion criteria included diagnosed chronic venous disease at C2 stage or higher, clinically evident lower-limb edema (CEAP C3), obesity (Body Mass Index ≥30 kg/m²), acute or subacute heart failure, malignancies, major psychiatric disorders, ongoing treatment with venotropic agents, glycosaminoglycans, calcium-channel blockers, alpha-blockers, or systemic corticosteroids, pregnancy, or known intolerance to the ingredients of the tested supplement.

Following the enrolment visit (T0), participants were instructed to take one tablet of the nutraceutical product daily for 90 days. Two follow-up visits were scheduled, at 45 days (T45) and at 90 days (T90). Concomitant venous-directed treatments were assessed at screening. No protocol-driven compression therapy, topical cream, glycosaminoglycan, venotropic drug, or other adjunctive treatment was initiated during the study, and patients were instructed not to start new venous-specific treatments or drugs potentially affecting edema during follow-up.

Each tablet contained the following active ingredients and registered raw materials: i) micronized flavonoids (μsMIN® Plus), 570 mg (including diosmin 450 mg); ii) *Boswellia serrata* (Bospure®), 200 mg; iii) bromelain 2400 GDU/g (Bromeyal®), 150 mg; iv) hesperidin 50 mg; v) *Melilotus officinalis* dry extract, 25 mg; vi) vitamin C, 12 mg; vii) *Ananas comosus* (Pineapple) extract, 10 mg.

The primary study endpoint was the reduction of ankle circumference (cm), compared with baseline, at the end of the study. Secondary exploratory effectiveness variables were patient-reported signs and symptoms assessed using an 11-point VAS scale (0: no signs/symptoms; 10: maximal signs/symptoms). Evaluated items were pain, heaviness/warmth, itching, nocturnal cramps, self-perceived edema/swelling, visible varicosity, and QoL. Because patients were C0s-C1s, the edema item should be interpreted as subjective swelling perception rather than clinically evident CEAP C3 edema.

Continuous variables were expressed as mean ± Standard Deviation (SD) or Standard Error (SE), as specified, whereas categorical variables were summarized as counts and percentages. Given the within-subject design of the study, changes in continuous variables across the three study time points (T0, T45, and T90) were evaluated in the completer population using repeated-measures analysis, with *post hoc* pairwise comparisons versus baseline when the overall time effect was significant. In the event of a non-normal distribution, the corresponding non-parametric repeated-measures approach was considered. Changes in categorical patient-reported symptom trajectories were summarized descriptively. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant. Given the pilot, observational nature of the study, all analyses were considered exploratory.

Results

Out of the 60 enrolled patients, 40 completed the study, corresponding to a 33.3% drop-out/non-completer rate (20/60). Eight patients were lost to follow-up, and 12 did not consistently take the tested product (adherence to treatment <70%). This high rate of non-completion reflects a relevant real-world issue in mild symptomatic disease

and significantly limits the statistical analysis and the value of the final outcomes. No subject interrupted the treatment because of adverse events. The final sample comprised 8 men and 32 women aged 36-68 years (mean 56±4 years). Among female participants, 25 had undergone at least one pregnancy, and 18 were in menopause. The mean Body Mass Index was 26.8±2.1 kg/m².

Regarding physical activity, 25% reported no activity, 39% minimal, 33% moderate, and 3% intense. Occupational risk was present in 43% of cases, family history of varicose veins or thromboembolism in 52%, postural problems in 39%, recent venous thrombosis in 4%, and coagulation abnormalities in 2%. Most patients (70%) were classified as CEAP C0s, and 30% as C1s.

At objective evaluation, ankle circumference significantly decreased from 23.1±1.8 cm at T0 to 21.6±1.5 cm at T45 and 21.4±1.4 cm at T90, corresponding to a mean reduction of 1.7±0.5 cm at the end of the study ($p=0.023$).

The treatment resulted in significant improvements in all evaluated subjective parameters at T45 and T90, except for visible varicosity (Table 1).

The analysis of symptom changes from baseline to the end of the study showed improvements in most patients, with a lower percentage of subjects declaring no improvement, and no significant number declaring worsening of symptoms (Figure 1).

No adverse events were reported during the study.

Discussion

The results of this study suggest that the tested nutraceutical fixed combination was associated with a significant reduction in subjective symptoms of early-stage chronic venous disease, particularly pain, heaviness/warmth, nocturnal cramps, and self-perceived edema/swelling. The observed improvements are consistent with the

venotropic, anti-inflammatory, and antioxidant properties of the active ingredients. The reduction in ankle circumference further supports a possible effect on fluid retention and venous stasis, although causality cannot be inferred from the uncontrolled design.

These data were partly expected. The flavonoid component of the tested combination is represented by micronized flavonoids (μsMIN® Plus; 570 mg, including diosmin 450 mg) and hesperidin 50 mg. Therefore, evidence on diosmin/hesperidin-based Micronized Purified Flavonoid Fractions (MPFF) is relevant as mechanistic and clinical background for the present study, although it cannot be considered direct evidence for the tested fixed combination.

MPFF and related diosmin/hesperidin preparations have been shown to improve symptoms, edema, and self-perceived QoL in chronic venous disease, and ESVS guidelines recognize venoactive/venotropic drugs, including flavonoid fractions, among symptomatic conservative strategies.[1,3,11]

In early symptomatic disease, Greco and Bissacco recently reported improvement of venous symptoms in C0s-C1s patients treated with a multicomponent diosmin-based preparation, supporting the plausibility of investigating similar strategies in this setting.[12]

Moreover, μsMIN® Plus has been developed to improve diosmin bioavailability. Clinical and pharmacokinetic data on micronized/modified diosmin formulations suggest improved absorption and potential symptom benefits, but these data should be interpreted as supportive rationale rather than definitive proof of efficacy of the present combination.[13-15]

The anti-edema and anti-pain effects observed during treatment may also be partly explained by the known inhibitory effect of *Boswellia serrata* extract, and particularly

of beta-keto-boswellic acid derivatives, on lipoxygenase pathways.[16] *Boswellia serrata*, included as Bospure®, is a selective extract designed to maximize anti-inflammatory activity while minimizing pro-thrombotic concerns.[17-22] These effects may contribute to capillary stability and edema control in a multi-component venotropic strategy; more broadly, nutritional aspects have also been discussed in venous and lymphatic disorders.[23]

Bromelain also exerts a well-known anti-edema and proteolytic effect, confirmed in systematic reviews and meta-analyses of randomized clinical trials.24 Bromelain, included as Bromeyal®, is a purified extract standardized to 2400 GDU/g. Its potential relevance in chronic venous disease is related to anti-inflammatory, anti-edema and fibrinolytic mechanisms, including modulation of bradykinin/eicosanoid pathways and leukocyte-endothelium interactions.[25-29]

One of the main strengths of this study is the combined use of objective and subjective outcome measures in a real-world early-stage population. The CEAP stage of the included population deserves specific clarification: C0 indicates no visible or palpable signs of venous disease, whereas C1 indicates telangiectasias or reticular veins. Neither C0 nor C1 includes clinically evident edema, which is classified as C3. Therefore, the VAS item labelled as edema should be interpreted as self-perceived swelling or fluid retention, not as objectively evident CEAP C3 edema. This also explains why ankle circumference was used as a pragmatic objective measure.

Despite its promising findings, this study has important limitations. First, the drop-out/non-completer rate was high: 20 of 60 enrolled patients (33.3%) did not complete the study or did not meet the predefined adherence threshold. This is a relevant real-world finding in mild symptomatic disease, but it substantially limits statistical power, increases the risk of attrition bias, and reduces the value of the final outcomes. Second,

the lack of a placebo-controlled group limits the ability to attribute improvements solely to the tested product, as a placebo effect cannot be ruled out. Third, the relatively small completer sample and short study duration may not capture long-term benefits or late-onset adverse effects. Most importantly, because of the single-arm observational design and the absence of a placebo or active control group, the present findings are hypothesis-generating only and do not allow definitive causal conclusions regarding the effectiveness of the tested nutraceutical combination.

Conclusions

This study showed an improvement in symptoms associated with early-stage chronic venous disease after supplementation with the tested nutraceutical fixed combination. The intervention was associated with reductions in heaviness/warmth, self-perceived swelling, pain, itching, and cramps, with improvement in patients' self-perceived QoL. This study sets the scene for further clinical research on nutraceutical fixed combinations in symptomatic C0s-C1s patients. Larger randomized, placebo-controlled trials with lower attrition, predefined management of concomitant treatments, and longer follow-up are required to confirm these preliminary findings.

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Funding: no external funding was received for the statistical analysis and writing of this manuscript. The commercial name of the final product was removed from the main text; registered raw material names are reported only to allow full reproducibility of the tested formulation. The manufacturer of the tested product had no role in data analysis, interpretation of the results, or writing of the manuscript.

Ethics approval and consent to participate: the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice principles. The protocol was approved by the Ethical Committee of the University of Bologna (code: LLD-RP2018).

Informed consent: all participants provided written informed consent before enrolment.

Patient's consent for publication: the patients gave their written consent to use their personal data for the publication of this paper and any accompanying images.

Availability of data and materials: the data used to support the findings of this study are available from the corresponding author upon request.

Table 1. Patient self-evaluation Visual Analogue Scale (VAS) score for signs and symptoms.

	T0 (mean±SE)	T45 (mean±SE)	T90 (mean±SE)
Pain	2,7±0,8	2,3±0,5*	2,2±0,4*
Heaviness/warmth	4,3±0,9	3,6±0,7*	3,2±0,4*
Itching	2,7±0,3	2,4±0,3*	2,1±0,2*
Nocturnal cramps	4,8±1,0	2,9±0,7*	2,4±0,9*
Visible varicosity	2,2±0,4	2,2±0,4	2,2±0,5
Self-perceived edema/swelling	3,3±0,4	2,6±0,5*	2,4±0,5*
Quality of Life	4,5±0,9	6,9±1,0*	7,8±0,8*

*$p<0.05$ *vs* baseline

SE, Standard Error

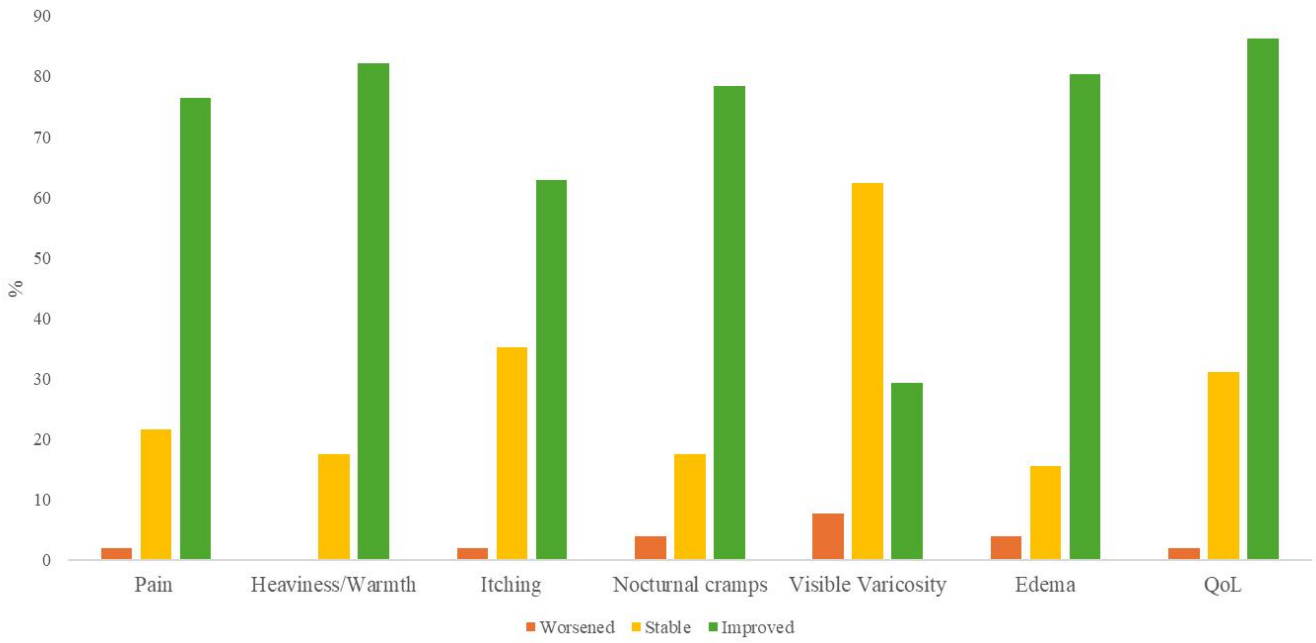

Figure 1. Percentage of patients declaring worsening, no improvement or improvement of signs and symptoms at the end of the study.