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EFFECTIVENESS OF MICRONIZED PURIFIED FLAVONOID FRACTION AS ADJUNCTIVE THERAPY IN PATIENTS WITH VARICOSE VEINS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Varicose veins are a common manifestation of chronic venous disease (CVD) and are associated with symptoms such as pain, edema, heaviness, and impaired quality of life (QoL). Micronized purified flavonoid fraction (MPFF), a venoactive agent composed primarily of diosmin and hesperidin, has been widely used for symptomatic management of CVD because of its venotonic, anti-inflammatory, and microcirculatory effects.

Objective: To evaluate the prescribing patterns, clinical outcomes, and safety of MPFF in patients with varicose veins receiving pharmacological management and/or surgical intervention.

Methods: A prospective longitudinal observational study was conducted among 120 patients with varicose veins (CEAP classes C2–C6) attending the Department of Vascular Surgery at Sheth H.J. Mahagujarat Hospital, Nadiad, India. Patients were managed either conservatively or surgically according to clinical indications and were further categorized based on MPFF use. Clinical outcomes were assessed using the Venous Clinical Severity Score (VCSS), Visual Analogue Scale (VAS) for pain, ulcer healing status, and quality of life (QoL) at baseline and during follow-up visits over a 3-month period. Safety outcomes were documented throughout the study.

Results: The study included 120 patients with a mean age of 50.6 ± 19.6 years, of whom 50% were male. Thirteen patients received conservative treatment (MPFF, n=10; non-MPFF, n=3), while 107 underwent surgical intervention (MPFF, n=82; non-MPFF, n=25). Patients receiving MPFF demonstrated greater improvements in VCSS and VAS pain scores during follow-up compared with those not receiving MPFF. Complete ulcer healing was observed in surgical patients treated with MPFF, whereas limited improvement was noted in the non-MPFF group. Quality-of-life scores showed clinically meaningful improvement among MPFF-treated patients. Reported adverse events during follow-up included itching, dizziness, and weakness; however, causality with MPFF treatment could not be definitively established.

Conclusion: MPFF administered at a daily dose of 1000 mg for three months was associated with improved clinical outcomes, including reduced symptom severity, enhanced ulcer healing, and better quality of life in patients with varicose veins. These findings support the use of MPFF as an adjunctive venoactive therapy in the management of chronic venous disease. Nevertheless, larger controlled studies with longer follow-up are warranted to confirm these observations.

KEYWORDS: Varicose veins; Chronic venous disease; Micronized purified flavonoid fraction; Venoactive therapy; Venous ulcer healing; Quality of life.

INTRODUCTION

Varicose veins represent one of the most common manifestations of chronic venous disease (CVD) and are characterized by dilated, elongated, and tortuous superficial veins, predominantly affecting the lower extremities. The pathogenesis of varicose veins is multifactorial and involves venous hypertension resulting from valvular incompetence, venous wall remodeling, inflammatory processes, extracellular matrix alterations, and disturbed hemodynamics. These pathological changes contribute to venous reflux, impaired venous return, and progressive deterioration of venous function.1–3

Varicose veins constitute a significant public health concern worldwide, affecting approximately 10–30% of the adult population. The reported prevalence increases substantially when reticular veins and telangiectasias are included, reaching up to 80% in certain populations.4–6 Epidemiological studies have demonstrated considerable geographical variation, with prevalence estimates ranging from 25–30% among women and 10–20% among men in Western countries.7,8 The disease imposes a substantial clinical and socioeconomic burden due to chronic symptoms such as pain, heaviness, swelling, fatigue, itching, and nocturnal cramps, which adversely affect daily activities and quality of life. Furthermore, advanced disease may lead to complications including skin changes, lipodermatosclerosis, and venous ulceration, resulting in increased healthcare utilization, loss of productivity, and considerable economic costs.9–11

The management of varicose veins encompasses both conservative and interventional approaches aimed at symptom relief, prevention of disease progression, and improvement of quality of life. Conservative management includes lifestyle modifications such as regular physical activity, weight management, leg elevation, and graduated compression

therapy.12,13 Compression therapy remains a cornerstone of treatment by improving venous return, reducing edema, and enhancing microcirculatory function.14 In patients with persistent symptoms, significant venous reflux, or complications, minimally invasive and surgical procedures such as sclerotherapy, endovenous thermal ablation (laser or radiofrequency), mechanochemical ablation, cyanoacrylate closure, microphlebectomy, and vein stripping are commonly employed.15–17 In addition to these therapeutic modalities, venoactive drugs have emerged as important adjuncts in the management of chronic venous disease. Among them, micronized purified flavonoid fraction (MPFF), consisting primarily of diosmin and hesperidin, has been extensively investigated and is recommended in several international guidelines for the treatment of CVD-related symptoms. MPFF exerts venotonic, anti-inflammatory, and vasculoprotective effects by reducing leukocyte activation, improving lymphatic drainage, decreasing capillary permeability, and enhancing venous tone.18–20 Clinical studies and systematic reviews have demonstrated that MPFF significantly reduces symptoms such as pain, heaviness, edema, and leg discomfort while improving quality of life in patients with chronic venous disease.18–20 Furthermore, experimental evidence suggests that MPFF may favorably influence microcirculatory function and venous wall inflammation, potentially contributing to delayed disease progression and improved healing of venous ulcers.18,21 Despite the growing body of evidence supporting MPFF therapy, real-world data regarding its utilization, prescribing patterns, and clinical outcomes in Indian patients with varicose veins remain limited. Therefore, the present study was conducted to evaluate the prescribing patterns, clinical effectiveness, and safety of MPFF in patients with varicose veins receiving conservative management and/or surgical intervention. The study also aimed to assess changes in symptom severity, pain, ulcer healing, and quality of life following treatment with MPFF over a three-month follow-up period.

MATERIALS AND METHODS

Study Design and Setting

This prospective, longitudinal, observational study was conducted at the Department of Vascular Surgery, Sheth H.J. Mahagujarat Hospital, Nadiad, Gujarat, India, over a period of three months. The study was designed to evaluate the prescribing patterns, clinical effectiveness, and safety of micronized purified flavonoid fraction (MPFF) in patients with varicose veins receiving conservative management and/or surgical intervention. Ethical approval was obtained from the Institutional Ethics Committee of Charotar University of Science and Technology (CHARUSAT) (Approval No. IEC/CHARUSAT/23/155), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Population

A total of 120 patients diagnosed with varicose veins were enrolled during the study period. Eligible participants included adults with Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification stages C2–C6, presenting with symptoms of chronic venous disease and duplex ultrasonographic evidence of venous reflux exceeding one second. Patients with CEAP class C1 disease, known thrombophilia, pregnancy, lactation, acute deep vein thrombosis, non-venous lower-limb pain, or any condition that could interfere with study assessments were excluded.

Treatment Allocation

Treatment decisions were made by the treating vascular surgeon based on clinical presentation, disease severity, duplex ultrasonography findings, and patient-specific considerations. Consequently, participants were allocated into either conservative management or surgical intervention groups.

The conservative management group consisted of 13 patients and was further categorized as follows:

- Group 1A: MPFF therapy (n = 10)
- Group 1B: Compression therapy without MPFF (n = 3)

The surgical intervention group consisted of 107 patients and was categorized as follows:

- Group 2A: Surgical intervention with adjunctive MPFF therapy (n = 82)
- Group 2B: Surgical intervention without MPFF therapy (n = 25)

Surgical procedures included radiofrequency ablation (RFA), mechanochemical ablation (MOCA), endovenous laser ablation (EVLA), and cyanoacrylate glue closure, selected according to standard clinical practice and individual patient characteristics.

Data Collection and Follow-up

Baseline demographic, clinical, and Doppler ultrasonographic data were collected for all participants. Recorded variables included age, sex, body weight, CEAP classification, pain severity, swelling, heaviness, fatigue, itching, nocturnal cramps, great saphenous vein (GSV) reflux, small saphenous vein (SSV) reflux, and venous diameters.

Patients were followed prospectively at predefined intervals of 7 days, 14 days, 1 month, 2 months, and 3 months after initiation of treatment or surgical intervention. The participant flow through the study is presented in Figure 1.

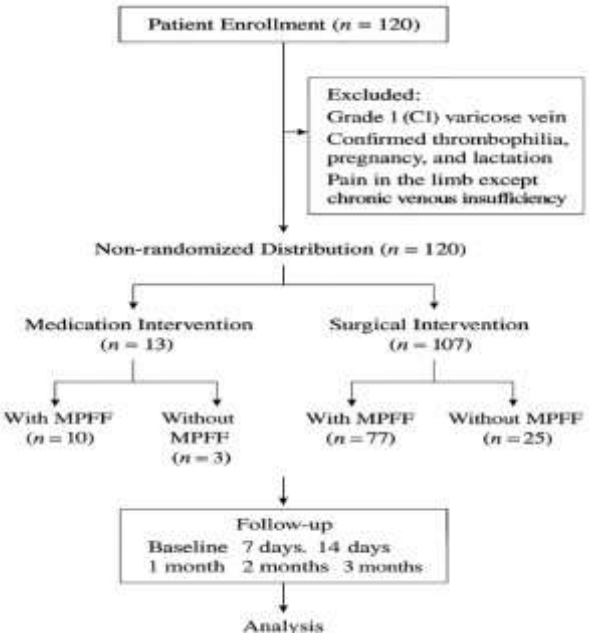

Figure 1: STROBE Participant Flow Diagram

Outcome Measures

The primary and secondary outcomes were assessed at baseline and follow-up visits using validated clinical measures:

1.Venous Clinical Severity Score (VCSS): Used to evaluate the severity of chronic venous disease and monitor clinical improvement over time.

2.Visual Analogue Scale (VAS): Used to assess pain intensity associated with varicose veins.

3.Ulcer Healing: Evaluated based on changes in ulcer size, progression, and complete healing during follow-up.

4.Quality of Life (QoL): Assessed using a standardized quality-of-life questionnaire.

5.Safety Assessment: All adverse events and treatment-related complaints reported during the study period were documented and evaluated.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software. Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons between treatment groups were performed using appropriate statistical tests. Changes in VCSS, VAS scores, ulcer healing outcomes, and quality-of-life measures over time were analyzed to evaluate treatment effectiveness. A p-value of less than 0.05 was considered statistically significant.

Study Limitations Related to Treatment Allocation

As this was an observational study, treatment allocation was based on clinical decision-making by the treating vascular surgeon rather than randomization. Therefore, the possibility of selection bias and confounding factors influencing treatment outcomes cannot be excluded.

RESULTS

Demographic and Clinical Characteristics

A total of 120 patients with varicose veins classified as CEAP stages C2–C6 were included in the study. The mean age of the study population was 50.6 ± 19.6 years, with the highest proportion of patients belonging to the 50–70 years age group. The study population comprised an equal distribution of males and females (50% each). The mean body weight was 100.8 ± 15.9 kg, and the majority of patients were within the 80–100 kg weight category. Detailed demographic and baseline clinical characteristics are presented in Table 1.

Table 1: Baseline Demographic Details of Varicose Vein Patients (N = 120)

Parameter	Group 1: Medication (n=13)	Group 2: Surgical (n=107)
Gender (M/F)	6/7	54/53
Mean Age (years)	50.6 ± 19.6	50.6 ± 19.6
Mean Weight (kg)	100.8 ± 15.9	100.8 ± 15.9
CEAP Classification		
C2 (Varicose veins)	10 (8.33%)	
C3 (Oedema)	6 (5%)	
C4 (Skin changes)	71 (59.16%)	
C5 (Healed ulcers)	17 (14.16%)	

C6 (Active ulcers)	16 (13.3%)

Baseline Symptom Profile

The clinical severity of chronic venous disease was evaluated using the Venous Clinical Severity Score (VCSS). The most frequently reported symptoms included pain, swelling, heaviness, itching, fatigue, walking discomfort, lipodermatosclerosis, and burning sensations. Moderate grades of pain (55.0%), swelling (62.5%), heaviness (64.1%), itching (70.0%), and lipodermatosclerosis (58.3%) were the predominant clinical manifestations observed among the study participants. The distribution of symptom severity is summarized in Table 2.

Table 2: Observed Symptoms of Chronic Venous Insufficiency (N=120)

Symptom	Absent	Mild	Moderate	Severe
Pain	6 (10%)	19 (15.83%)	66 (55%)	29 (24.16%)
Swelling	0	17 (14.16%)	75 (62.5%)	28 (23.33%)
Heaviness	0	18 (33%)	77 (64.1%)	25 (20.8%)
Walking discomfort	41 (34.16%)	29 (24.16%)	49 (40.83%)	1 (1%)
Fatigue	59 (14.16%)	20 (16.66%)	33 (27.5%)	1 (1%)
Itching	1 (1%)	12 (10%)	84 (70%)	23 (19.16%)
Lipodermatosclerosis	7 (11%)	31 (25.83%)	70 (58.33%)	12 (10%)
Burning	89 (74.16%)	20 (16.66%)	11 (9.16%)	0

Treatment Distribution

Based on clinical evaluation and disease severity, patients were managed either conservatively or surgically. Thirteen patients (10.8%) received conservative treatment, while 107 patients (89.2%) underwent surgical intervention. Among patients receiving conservative treatment, 10 received MPFF therapy and 3 received compression therapy alone. Among surgically treated patients, 82 received adjunctive MPFF therapy and 25 underwent surgery without MPFF.

Safety Outcomes

Adverse events reported during the study period are presented in Table 3. The most frequently reported events were itching (70.0%), dizziness (35.8%), weakness (31.6%), and acidity (26.6%). No serious adverse events requiring treatment discontinuation were reported during the follow-up period.

Table 3: Reported Side Effects (N=120)

Side Effect	Number of Patients	Percentage (%)
Itching	84	70
Dizziness	43	35.8
Weakness	38	31.6
Acidity	32	26.6
Vomiting	1	1

Changes in Venous Clinical Severity Score (VCSS)

A progressive reduction in VCSS scores was observed across all treatment groups during the three-month follow-up period. Patients receiving MPFF, either as conservative therapy or as an adjunct to surgical intervention, demonstrated greater improvement in VCSS scores compared with patients who did not receive MPFF. The difference in VCSS reduction between MPFF-treated and non-MPFF-treated groups was statistically significant ($p < 0.05$). Detailed changes in VCSS over time are illustrated in Figure 2.

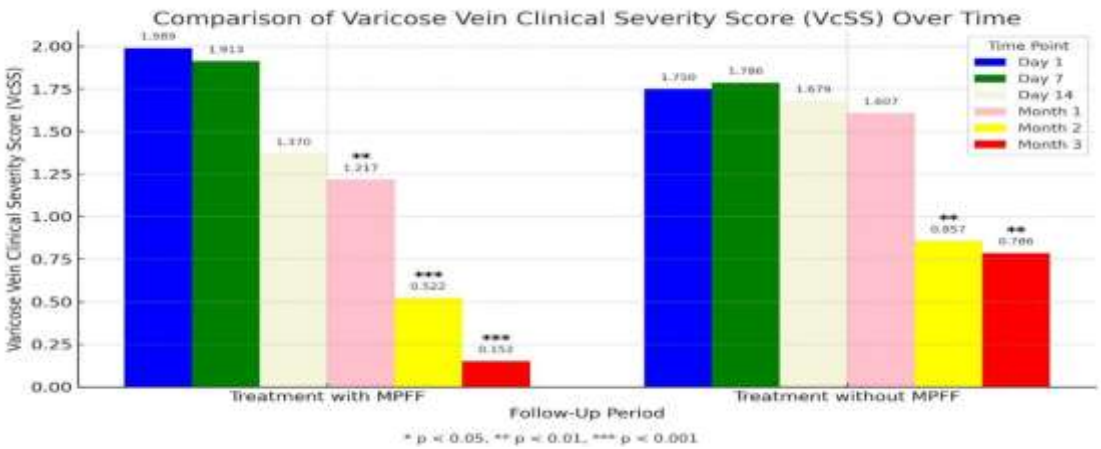

Figure 2: Venous Clinical Severity Score (VCSS) in both treatment groups.

Changes in Pain Severity (VAS Score)
Pain severity assessed using the Visual Analogue Scale (VAS) showed a significant decline throughout the study period. Patients receiving MPFF exhibited a greater reduction in pain intensity compared with those managed without MPFF. The improvement in VAS scores was statistically significant ($p < 0.001$). The temporal trend in VAS scores is presented in Figure 3.

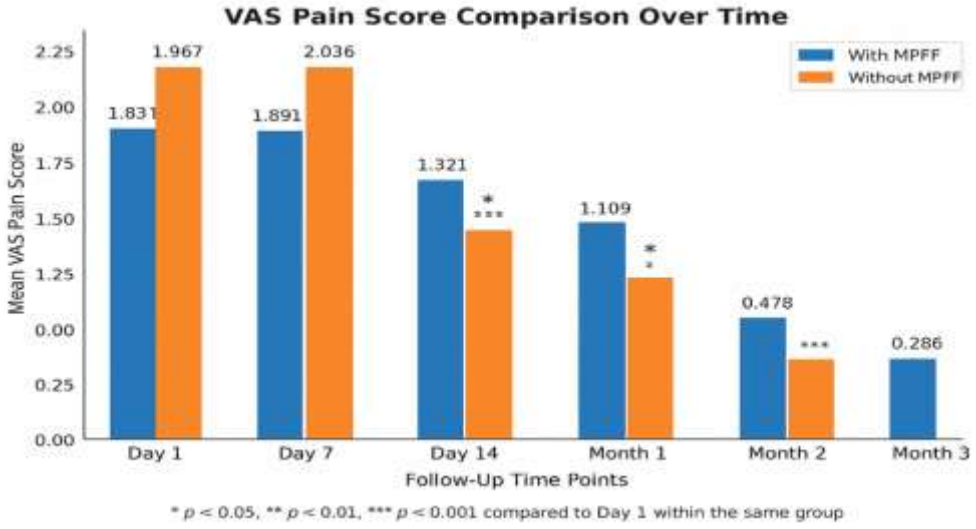

Figure 3: Visual Analogue Scale (VAS) in both treatment groups.

Ulcer Healing Outcomes
Among patients presenting with venous ulcers, those receiving MPFF in combination with surgical intervention demonstrated superior healing outcomes. Complete ulcer healing was observed in all ulcer patients receiving adjunctive MPFF therapy by the end of the three-month follow-up period, whereas limited improvement was observed among patients managed without MPFF.

Quality of Life Outcomes
Quality-of-life assessments demonstrated improvement across all treatment groups during follow-up. However, patients receiving MPFF showed greater improvement in quality-of-life scores, indicating reduced symptom burden and enhanced functional status compared with patients who did not receive MPFF.

Prescribing Pattern Analysis
Analysis of prescribing patterns revealed that Aceclofenac and Cefuroxime were prescribed to all patients. Other frequently prescribed medications included proton-pump inhibitors (Pantoprazole and Rabeprazole), multivitamin supplementation (Mbtron Plus), topical Clobetasol propionate ointment, and the venoactive combination of Diosmin and Hesperidin (MPFF). Detailed prescribing patterns according to treatment groups are presented in Table 4.

Table 4: Prescribing Pattern (N=120)

Drug	Medication without MPFF (n=3)	Medication with MPFF (n=10)	Surgery without MPFF (n=25)	Surgery with MPFF (n=82)
Aceclofenac	3 (100%)	10 (100%)	25 (100%)	82 (100%)
Cefuroxime	3 (100%)	10 (100%)	25 (100%)	82 (100%)
Acipant DSR (Pantoprazole (40 mg) + Domperidone (30 mg))	0	10 (100%)	23 (92%)	81 (99%)
Rabeprazole	0	0	25 (100%)	82 (100%)
Mbtron Plus (multivitamin and mineral supplement)	0	10 (100%)	23 (92%)	82 (100%)
Clobetasol propionate ointment	0	0	25 (100%)	82 (100%)
Diosmin + Hesperidin	0	10 (100%)	0	82 (100%)

DISCUSSION
The present prospective observational study evaluated the prescribing patterns, clinical outcomes, and safety of micronized purified flavonoid fraction (MPFF) in patients with varicose veins receiving conservative management and/or surgical intervention. The findings demonstrated that MPFF therapy was associated with significant improvements in symptom severity, pain scores, ulcer healing, and quality of life over a three-month follow-up period.

The demographic characteristics of the study population were generally comparable to those reported in previous studies. The mean age of participants was 50.6 ± 19.6 years, which is consistent with the findings of Hummel et al.23 who reported a mean age of 53.8 ± 12.37 years. However, Khryshchanovich et al.24 reported a younger study population with a mean age of 36.9 ± 4.1 years. The equal gender distribution observed in the present study differs from many epidemiological studies that have reported a higher prevalence of varicose veins among females.7 This variation may be attributed to differences in study populations, occupational exposure, and healthcare-seeking behavior.

Most participants presented with moderate clinical manifestations of chronic venous disease, including pain, swelling, heaviness, itching, and lipodermatosclerosis. These findings are consistent with previous reports indicating that symptom burden substantially affects daily functioning and quality of life in patients with chronic venous disease.9,25

One of the principal findings of the present study was the significant reduction in Venous Clinical Severity Score (VCSS) among patients receiving MPFF. Improvement in VCSS reflects an overall reduction in disease severity and symptom burden. These findings are consistent with the prospective comparative study by Khryshchanovich et al., which demonstrated significant clinical improvement following MPFF-based venoactive therapy after endovenous intervention.24 Furthermore, systematic reviews and meta-analyses have reported that MPFF significantly improves symptoms, functional discomfort, and quality of life in patients with chronic venous disease.18,20 The beneficial effects of MPFF may be attributed to its ability to improve venous tone, reduce venous hypertension, decrease capillary permeability, and attenuate inflammatory responses within the venous microcirculation.19,21

Similarly, patients treated with MPFF experienced significant reductions in pain intensity as assessed by the Visual Analogue Scale (VAS). Pain is one of the most common and disabling symptoms of chronic venous disease, and its reduction has a direct impact on patient well-being and functional capacity. The observed improvement may be explained by the anti-inflammatory and venotonic properties of MPFF, which reduce leukocyte activation, endothelial dysfunction, and microvascular inflammation.19,20 Recent European guidelines also recognize MPFF as one of the most extensively studied venoactive drugs for improving symptoms associated with chronic venous disease.26-29

Ulcer healing outcomes were notably better among patients receiving MPFF in conjunction with surgical intervention. Complete ulcer healing was observed in all surgically treated patients receiving MPFF by the end of follow-up. Previous studies have reported that MPFF improves microcirculatory function, reduces venous stasis, and enhances tissue repair, thereby facilitating wound healing in patients with chronic venous disease and venous leg ulcers.13,18,19

Quality-of-life assessment revealed substantial improvement among patients receiving MPFF. Chronic venous disease is known to adversely affect physical functioning, social activities, and emotional well-being. Improvement in quality-of-life scores observed in the present study is consistent with previous reports demonstrating that effective symptom control and reduction in disease severity contribute to better patient-reported outcomes.9,20,29

Analysis of prescribing patterns indicated frequent use of analgesics, antibiotics, proton-pump inhibitors, nutritional supplements, and topical agents in addition to MPFF therapy. The widespread utilization of MPFF observed in this study reflects increasing acceptance of venoactive drugs as adjunctive treatment options in chronic venous disease. The 2022 European Society for Vascular Surgery (ESVS) Clinical Practice Guidelines concluded that MPFF improves leg symptoms, functional discomfort, quality of life, and ankle circumference in patients with chronic venous disease and support its use as part of comprehensive disease management. 26-29

The safety profile observed in this study was generally acceptable. Although itching, dizziness, weakness, and acidity were reported during follow-up, no serious adverse events requiring treatment discontinuation were documented. However, causality assessment was not performed, and therefore these events cannot be definitively attributed to MPFF therapy. Further controlled studies are required to better characterize the safety profile of MPFF in routine clinical practice.

Strengths and Limitations

A major strength of this study is the prospective evaluation of multiple clinically relevant outcomes, including symptom severity, pain, ulcer healing, quality of life, and prescribing patterns in a real-world clinical setting. However, several limitations should be acknowledged. The study was conducted at a single center with a relatively small sample size and unequal distribution of participants across treatment groups. Treatment allocation was based on clinical judgment rather than randomization, introducing the possibility of selection bias and confounding. Furthermore, the follow-up period was limited to three months, preventing assessment of long-term outcomes, recurrence rates, and sustained treatment benefits.

Future Directions

Future multicenter studies with larger sample sizes, randomized treatment allocation, and longer follow-up durations are warranted to validate these findings and further establish the long-term effectiveness and safety of MPFF in the management of chronic venous disease and varicose veins.

CONCLUSION

Micro flavonoids (MPFF) as an adjuvant therapy demonstrated significant benefits in the management of varicose veins. Their use alongside surgical or pharmacological treatment reduced symptom severity, improved quality of life, and lowered the incidence of venous ulcers. A daily dose of 1000 mg for three months was particularly effective in early-stage disease and post-procedural care. These findings provide supportive evidence for incorporating MPFF into standard treatment protocols, although further studies are warranted to confirm these outcomes.

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