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REVIEW ARTICLE

Micronized purified flavonoid fraction for the treatment of chronic venous insufficiency, with a focus on postthrombotic syndrome: A narrative review

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Abstract

Introduction: Postthrombotic syndrome (PTS) is a form of secondary chronic venous insufficiency (CVI) that occurs after deep vein thrombosis (DVT). Effective treatments for PTS are lacking. Micronized purified flavonoid fraction (MPFF) is a venoactive drug used in the treatment of CVI.

Objective: To determine whether MPFF is a good candidate to explore as a therapeutic agent for PTS.

Methods: We performed a narrative review in which we identified 14 systematic reviews, 33 randomized controlled trials, and 19 observational studies that discussed the use of MPFF in CVI, as well as studies that reported on the mechanistic action of MPFF in relation to the pathophysiology of PTS.

Results: MPFF targets a number of pathophysiologic components of PTS. Based on animal models and human studies investigating objective vascular and lymphatic measures, MPFF promotes venous recanalization after DVT, decreases venous remodeling and reflux, inhibits inflammatory processes, improves venous tone and stasis, improves lymphatic circulation, improves capillary hyperpermeability, and decreases tissue hypoxia. Furthermore, MPFF shows promise in improving clinical manifestations, quality of life, and objective venous parameters of CVI. Studies suggest good patient acceptability and tolerability with the use of MPFF in CVI.

Conclusion: MPFF is a good candidate to explore as a potential therapy for PTS. Confirmatory high-quality studies are still needed to reinforce the evidence supporting the use of MPFF in CVI. Double-blind randomized controlled trials with clinical endpoints are needed to assess the clinical efficacy of MPFF in the treatment of PTS.

KEYWORDS
diosmin, flavonoids, hesperidin, postthrombotic syndrome, venous insufficiency, venous thrombosis

Essentials

- Postthrombotic syndrome (PTS) is venous insufficiency occurring after deep vein thrombosis.
- Effective therapies for the PTS are lacking.
- Micronized purified flavonoid fraction (MPFF) targets its pathophysiological components.
- MPFF should be explored as a potential therapy for PTS.

1 | INTRODUCTION

Postthrombotic syndrome (PTS) refers to the clinical manifestations of chronic venous insufficiency (CVI) that occur after deep vein thrombosis (DVT). PTS is the most frequent complication of DVT.[1] Its clinical manifestations are variable, ranging from mild symptoms and signs such as mild pain, swelling, and hyperpigmentation, to more severe manifestations such as intractable pain, venous claudication, and leg ulceration.[2] Though it is not a lethal condition, PTS is burdensome. It is the main determinant of quality of life (QOL) after DVT.[3] Management options for PTS, preventive or therapeutic, are limited.[4] Recent large randomized controlled trials (RCTs) showed that the use of catheter-directed thrombolysis to prevent PTS after DVT was generally ineffective.[5-7] A 2017 Cochrane systematic review with meta-analysis concluded that the use of elastic compression stockings reduced the overall incidence of PTS following DVT (relative risk [RR], 0.62; 95% confidence interval [CI], 0.38-1.01; P = .05).[8] The evidence, however, remains of low quality considering the methodological limitations of the trials included, such as the lack of adequate blinding. Furthermore, there is very low-certainty evidence supporting the use of elastic compression stockings in the treatment of PTS.[9] New therapeutic targets are thus needed for the treatment of established PTS.[10]

One of the therapeutic options to explore is the use of venoactive drugs or phlebotonics.[11] Venoactive drugs comprise a heterogeneous group of medicinal products of plant or synthetic origin. While rarely used in North America, they are commonly used in Europe for the treatment of CVI.[11,12] A Cochrane meta-analysis, including 53 RCTs (n = 6013 participants), of the effectiveness of venoactive medications in the treatment of CVI reported a beneficial effect by venoactive drugs on edema (RR, 0.70; 95% CI, 0.63-0.78) and on some CVI symptoms, when compared with placebo.[13] However, as underlined by authors of this review, there is a lack of strong evidence supporting the use of venoactive drugs for the treatment of CVI in general and in established PTS.

Among venoactive drugs that could be tested in a high-quality trial for the treatment of PTS is micronized purified flavonoid fraction (MPFF), which appears to have a particularly favorable profile. MPFF is composed of micronized diosmin and flavonoids. Its flavonoid fraction can take many forms, including that of hesperidin, diosmetin, and linarin.[14] The proportion of micronized diosmin to flavonoids varies, with 9:1 being a commonly used ratio. MPFF acts on improving venous obstruction, valvular reflux, and inflammatory venous damage, which are key components contributing to the pathogenesis of PTS.[15] In this article, we review the mechanism of action of MPFF and its relevance in the treatment of the pathophysiologic components of PTS. Given that PTS presents as CVI after DVT, we review the clinical efficacy, tolerability, and acceptability of the use of MPFF in CVI, with a focus on PTS. Finally, we establish whether MPFF should be further explored as a potential new therapeutic agent for PTS.

2 | METHODS

We conducted a scientific literature search using PubMed, MEDLINE, Cochrane libraries (Cochrane Database of Systematic Reviews, Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and National Health Service Economic Evaluation Database), and ClinicalTrials.gov databases from inception to November 28, 2018, with the latest updated PubMed search on July 25, 2020, to retrieve the relevant articles reporting the use of MPFF in the treatment of CVI and PTS. We identified additional literature from reference lists of relevant articles, conference proceedings, abstracts, reports, presentations, online theses, journals, and books. We performed manual searches on the latter to identify potential articles missing from initial electronic searches. Given the heterogeneous nature of MPFF, we used a broad range of search terms to identify a wide array of studies that may be of relevance. The terms include registered commercial names of MPFF, drug categories such as phlebotonics under which MPFF falls, and individual components of MPFF such as diosmin and flavonoids. We performed updated PubMed searches using terms including *Alvenor*, *Ardium*, *Arvenum*, *Capiven*, *Daflon*, *Detralex*, *diosmetin*, *diosmin*, *diosmiplex*, *Elatec*, *Flavonoids*, *Flebotropin*, *hesperidin*, *isorhoifolin*, *linarin*, *micronized purified flavonoid fraction*, *phlebotonics*, *Variton*, *Venarus*, *Venitol*, and *veno-active drugs* in combinations with the following: *chronic venous disease*, *chronic venous insufficiency*, *phlebothrombosis*, *post-phlebitic disease*, *post-thrombotic syndrome*, *venous stasis* and *venous ulcer*.

An overview of our study selection is depicted in Figure 1. The studies retrieved and reviewed were restricted to systematic reviews, RCTs, observational studies, and articles discussing the mechanism of action of MPFF. First, we included studies describing the use of MPFF, which is composed of diosmin and an additional flavonoid fraction, in CVI or PTS. In these studies, MPFF treatment was compared with placebo, conventional treatment, baseline status in observational studies, or other agents such as aminaphthone, coumarin-toxerutin combination, or diosmin alone (Tables 1-3). Studies discussing an agent other than MPFF alone, without comparing it to MPFF, were excluded. Second, we also included studies on patients with venous thrombosis who did not have CVI at onset, assessing for MPFF's effect on clinical manifestations and objective

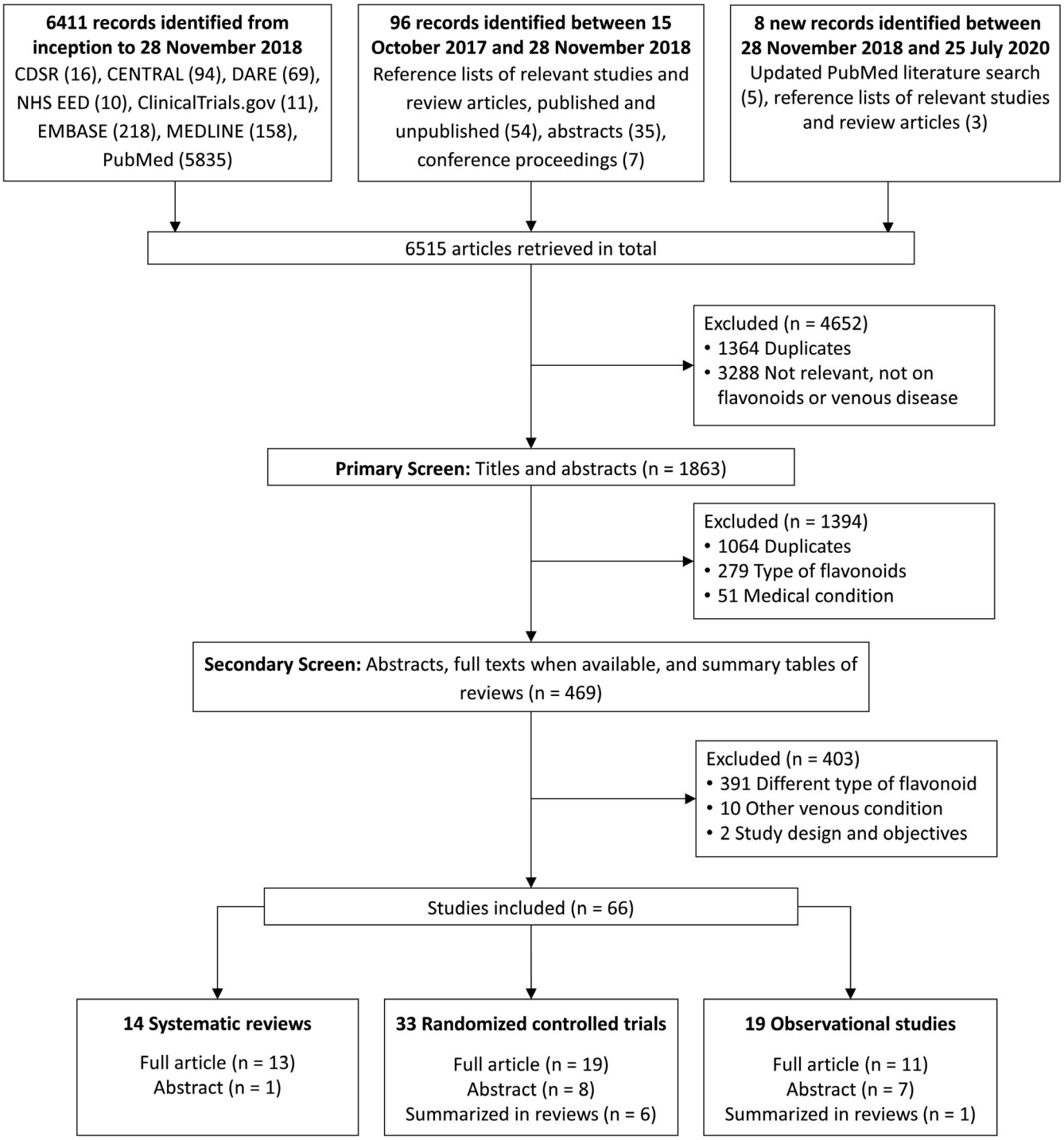

FIGURE 1 Flow diagram of study selection. CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; EMBASE: Excerpta Medica Database; NHS EED: National Health Service Economic Evaluation Database

venous changes related to CVI and PTS. Third, we included studies discussing the mechanistic action of MPFF on pathophysiological mechanisms underlying PTS, including those without clinical endpoints and those performed in animal models. All other studies included were performed in human subjects. Studies published in the English language and those translated to English were included. We excluded duplicate studies, studies not discussing venous disease, and studies discussing other types of venous disease. Among the systematic reviews, several were duplicates in that the same group of studies were meta-analyzed and identical results were presented, with minor addendums at times. They were thus considered as a single systematic review for the purposes of this narrative review to minimize multiple publication bias, unless a noticeable addition in content was noted. Similarly, we also treated duplications of RCTs

TABLE 1 Systematic reviews discussing the use of micronized purified flavonoid fraction in chronic venous insufficiency

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Boada, 1999[91]	Any CVI	Systematic review and meta-analysis 21 studies included (n=817) Included 3 RCTs with phlebotonics: • MPFF[80] • Hidrosmin[105,106] • Excluded 2 RCTs on MPFF[23,47]	At least 4 wk	*Efficacy:* Venoactive drugs, including MPFF: • Improved leg heaviness (pooled OR, 0.26; 95% CI, 0.17–0.39; chi-square, 4.04) • Could decrease limb perimeter and venous capacity and increase venous outflow*Acceptability and tolerability not reported in abstract*
Lyseng-Williamson, 2003[90]	Any CVI	Systematic review Included 7 RCTs on CVI[23,24,39,40,45,64,78] 10 to 170 participants in included RCTs Treatment duration from 2 to 12 months	2-12 months	*Efficacy:* MPFF: • Is a well-established and well-tolerated treatment option in patients with CVI, including those with venous ulcers • Is indicated as a first-line treatment of edema and symptoms of CVI • May be used, in advanced CVI, in conjunction with sclerotherapy, surgery and/or compression therapy, or as an alternative treatment when surgery is not indicated or is unfeasible • Accelerates healing of venous ulcers ≤10 cm in diameter *Acceptability not reported* *Tolerability:* In clinical trials: Similar to that of placebo Most frequent side effects: gastrointestinal and autonomic
Martinez, 2005[94]	Any CVI	Systematic review and meta-analysis Included 44 RCTs of oral phlebotonics: • 10 RCTs on MPFF (diosmine and hidrosmine)[23,106] • 1 ongoing RCT[94]4413 participants in total 2417 participants received a phlebotonic agent and 1996 received placebo Treatment duration from 2 to 6 months	2-6 months	*Efficacy:* Phlebotonics: • Heterogeneous results regarding signs and symptoms of CVI • Phlebotonics reduced edema (RR, 0.72; 95% CI, 0.65-0.81) • No quantifiable data on QOL • Not enough evidence to globally support the efficacy of phlebotonics for CVI • Limited current evidence, need for further RCTs, need for greater attention paid to methodological quality MPFF: • Results of the analyses of the dichotomous and continuous variables swelling and cramps were favorable to the diosmine and hidrosmine group • Dichotomous variables heaviness and global assessment by the participant were heterogeneous, and analyses of the continuous data were favorable • Lack of concordance between the results produces uncertainty • When studies with a Jadad score of ≥4 were assessed, the results of the variables trophic disorders, swelling, cramps, heaviness, and global assessment by the patient were not different than placeboAcceptability not reported *Tolerability:* Most frequently reported side effects were gastrointestinal disorders

(Continues)

TABLE 1 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Ramelet, 2005[93]	Any CVI	Systematic review Included 4 RCTs on MPFF[33,77,78,83] 40-160 participants in included studies	2-6 months	*Efficacy:* Grade A level of evidence for the use of MPFF Acceptability not reported Tolerability not reported
Coleridge-Smith, 2005[31,104]	Venous ulcers	Systematic review and meta-analysis Included 5 RCTs: • 3 published[39,75,77] • 2 unpublished 723 participants in total MPFF (Daflon) 500 mg BID for 2-6 months and conventional treatment (compression and local care) • vs conventional treatment plus placebo • or vs conventional treatment alone	2-6 months	*Efficacy:* MPFF was associated with: • Increased chances of ulcer healing (RRR, 32%; 95% CI, 3%-70%) at 6 mo • Shorter time to healing (16 vs 21 wk; $P = .003$) • Benefit was present from second months (RRR, 44%; 95% CI, 7%-94%) • Highest benefit present in subgroups of ulcers: of 5-10 cm^2 in area (RRR, 40%; 95% CI, 6%-87%) and present for 6-12 months (RRR, 44%; 95% CI, 6%-97%)MPFF may be a useful adjunct to conventional therapy in large and long-standing ulcers Acceptability not reported *Tolerability:* Adverse effects such as gastrointestinal disturbances were present in 10% of people
Nelson, 2008[98] Nelson, 2011[32]	Venous ulcers	Systematic review Part on flavonoids included 5 RCTs and 1 systematic review on these same RCTs[31,104] on which present review comments MPFF (Daflon) 500 mg BID for 2-6 months and conventional treatment (compression and local care) • vs conventional treatment plus placebo • or vs conventional treatment alone723 participants in total	2-6 months	*Efficacy:* • Uncertain whether MPFF plus compression is more effective at increasing ulcer healing rates (moderate-quality evidence) *Commenting on previous systematic review[31,104]:* • Using a fixed-effect model, MPFF increased ulcer healing by 44% (95% CI, 7%-94%) at 2 months • Using a random-effects model, MPFF increased ulcer healing by 54% (95% CI, 0%-137%) (varying results depending on model used)Review excluded 2 unpublished RCTs from the meta-analysis because of missing data at baseline, intermediate time points, or study incompletion; it is not clear what impact these RCTs would have had on the meta-analysis *Acceptability not reported* *Tolerability:* 10% of people reported gastrointestinal disturbances
Allaert, 2012[92]	Any CVI	Systematic review and meta-analysis 10 double-blind RCTs (1010 patients): • 4 RCTs on MPFF[23,46,78,107] • 2 RCTs on hydroxyethylrutoside • 4 RCTs on ruscus extracts	2-6 months	*Efficacy:* • Significantly greater reduction in ankle circumference with each venoactive drug vs placebo ($P < .0001$) • Significantly greater reduction in ankle circumference with MPFF vs any of other venoactive drug ($P < .0001$) • Mean reduction in ankle circumference was −0.80 ± 0.53 cm with MPFF (−0.58 ± 0.47 cm with ruscus extract, −0.58 ± 0.31 cm with hydroxyethylrutoside, −0.20 ± 0.5 cm with single diosmin, and −0.11 ± 0.42 cm with placebo) • As per authors, meta-analysis confirms the validity of the grade A given to the evidence supporting MPFF in the management of CVI in recent international guidelines*Acceptability and tolerability not reported*

(Continues)

TABLE 1 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Scallon, 2013[97]	Venous ulcers	Cochrane systematic review and meta-analysis 5 RCTs (723 participants) on MPFF: • 4 published RCTs[39,75,77] • 1 unpublished RCTSame RCTs as Nelson's[32,98] and Coleridge-Smith's[31,104] systematic reviews MPFF (Daflon) 500 mg BID for 2 months[77] or 6 months[39,75]	2-6 months	*Efficacy:* • More venous leg ulcers were healed in the MPFF groups than in the control groups (RR, 1.36; 95% CI, 1.07-1.74) • However, poor reporting in 4 of 5 RCTs • No benefit of MPFF in the most rigorously conducted trial, which was not published (RR, 0.94; 95% CI, 0.73-1.22) • Need to acknowledge possibility of publication bias in flavonoid trials • Trials with poor reporting, unclear risk of bias for randomization, allocation concealment, blinding, and methods for addressing incomplete outcome dataAcceptability not reported *Tolerability:* More side effects as compared to placebo (RR, 1.52; 95% CI, 1.01-2.3): 47/218 patients in the MPFF group and 30/213 patients in the control group Most commonly skin changes (including eczema), gastrointestinal disturbances (including diarrhea), and hypertension
Rabe, 2013[96]	Any CVI	Systematic review Included 3 double-blind RCTs On flavonoids (with MPFF)[77,83,105] 101-105 participants in RCTs MPFF 500 mg BID for 2 months or hidrosmin 200 mg TID for 45 d vs placebo	45-60 d	*Efficacy:* • Good evidence to recommend the use of flavonoids (including MPFF) in CVI • However, poor quality of older clinical trials • Further research, including long-term double-blind RCTs, needed to firmly establish clinical efficacy, indication, and method of use of flavonoids*Acceptability and tolerability not reported*
Martinez, 2016[13]	Any CVI	Systematic review and meta-analysis 53 RCTs (6013 participants): • 10 RCTs on MPFF[23,106] and 2 ongoing RCTs[108,109] • 28 RCTs on rutosides • 9 RCTs on calcium dobesilate • 2 RCTs on *Centella asiatica* • 2 RCTs on aminaftone • 2 RCTs on French maritime pine bark extract • 1 RCT on grape seed extract	Up to 12 months	*Efficacy:* No pooled results for MPFF Acceptability not reported *Tolerability:* • 50 adverse events in the MPFF group (50/424) and 49 (49/413) in the placebo group • Pooled results showed no statistically significant differences between phlebotonics and placebo (RR, 1.01; 95% CI, 0.70-1.44; I^2, 0%) • Gastrointestinal disorders were the most significant adverse events (heartburn and nausea): 12 cases in the MPFF group and 11 in the placebo group • 9 participants withdrew from the hidrosmine group and 11 from the placebo group as a result of adverse events
Varatharajan, 2016[95,103]	Any CVI	Systematic review and meta-analysis 1 systematic review on flavonoids including MPFF[97] with 723 participants. MPFF (Daflon) 500 mg at the usual dosage for 2-6 months	2-6 months	*Efficacy:* Flavonoids (including MPFF) may be effective adjuncts but methodological shortcomings and issues with bias limit the validity of results Acceptability and not reported *Tolerability:* Side effects of flavonoids: skin changes, gastrointestinal disturbances such as diarrhea, hypertension

(Continues)

TABLE 1 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Bush, 2017[89,110]	Any CVI	Systematic review 10 papers including a Cochrane review[13,23,39,47,48,71,75,77,78,80,106] 34-160 participants in each included study MPFF (Daflon) 500 mg BID for 4 wk to 6 months	4 wk to 6 months	*Efficacy:* • MPFF improves objectively observable signs including ulcers, edema, and trophic changes as well as many of the subjective symptoms of CVI • To date, the evidence demonstrating an impact on QOL remains weak. Acceptability not reported *Tolerability:* The risk of adverse effects appears minimal: • In the Cochrane review,[13] adverse effects were of equal frequency in both the treatment (50/424; 11.8%) and placebo arms (49/413; 11.9%) (RR, 1.01; 95% CI, 0.70-1.44). In the included studies, 12/424 patients withdrew from treatment in the treatment arms, compared to 11/413 in the placebo arms • In other studies, there were no safety concerns
Kakkos, 2018[88]	Any CVI	Systematic review and meta-analysis 7 double-blind RCTs (1692 patients)[24,71,72,78,79,80,83] with copublications[23,24]; MPFF compared with placebo	4 wk to 4 months	*Efficacy:* MPFF, compared to placebo, improved: • Leg pain (RR, 0.53; $P = .0001$; NNT, 4.2) • Heaviness (RR, 0.35; $P < .00001$; NNT, 2.0) • Feeling of swelling (RR, 0.39; $P < .00001$; NNT, 3.1) • Cramps (RR, 0.51; $P = .02$; NNT, 4.8) • Paresthesia (RR, 0.45; $P = .03$; NNT, 3.5) • Functional discomfort (RR, 0.41; $P = .0004$; NNT, 3.0) • Ankle circumference (SMD, −0.59; 95% CI, −1.15 to −0.02) • Leg redness (SMD −0.32; 95% CI, −0.56 to −0.07; RR, 0.50; $P = .03$; NNT, 3.6) • Skin changes (RR, 0.18; $P = .0003$; NNT, 1.6) • QOL (SMD, −0.21; 95% CI, −0.37 to −0.04)According to authors, MPFF is highly effective in patients with CVI when it comes to improving leg symptoms, edema, and QOL. This is based on high-quality evidence, in their opinion *Acceptability and tolerability not reported*
Mansilha, 2019[87]	Varicose veins, with endovenous, sclerotherapy, or surgical treatment	Systematic review 5 open-label studies[67,73,74,81,82] 60-245 patients in studies MPFF 1000-3000 mg daily	2 wk preop to 30 days postop, up to 90 days total	*Efficacy:* • 3 studies reported significantly less postprocedural pain with MPFF, 1 study with no significant effect • 2 studies reported significant postprocedural bleeding reduction with MPFF • 3 studies reported greater symptomatic improvement with MPFF • Adjunctive venoactive drug treatment to surgical, sclerotherapy, or endovenous therapy in varicose veins is promising, but high-quality placebo-controlled studies needed to unequivocally demonstrate benefits*Acceptability and tolerability not reported*

Note: Not reported: Information not reported in the full text of the manuscript. Not reported in abstract: Information not reported in the abstract and the full text of the manuscript is not available.

Abbreviations: BID: twice daily; CI: confidence interval; CVI: chronic venous insufficiency; d: day(s); months: month(s); MPFF: micronized purified flavonoid fraction; NNT: number needed to treat; OR: odds ratio; QOL: quality of life; RCT: randomized controlled trial; RR: relative risk; RRR: relative risk reduction; SMD: standardized mean difference; TID: 3 times a day; wk: week(s).

TABLE 2 Randomized controlled trials discussing the use of micronized purified flavonoid fraction in chronic venous insufficiency

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Biland, 1982[80]	Not available	Double-blind RCT 70 patients Included in meta-analyses[13,88,94]	4 wk	*Efficacy:* Objective improvement of venous disease as assessed by physician in the form of improvement of leg redness, edema, and skin changes Acceptability and tolerability not available
Amiel, 1987[99]	Includes patients with PTS	Double-blind RCT MPFF 500-mg 2 tablets daily Included in narrative review[111]	Not available	*Efficacy:* Positive effect on venous tone measured by plethysmography starting 1 h after administration Acceptability and tolerability not available
Chassignolle, 1987[24]	Any CVI	Double-blind RCT 40 patients MPFF (Daflon) 500-mg 2 tablets daily vs placebo for 2 months Included in meta-analysis[88] and systematic review[90]	2 mo	*Efficacy:* • MPFF significantly decreased all symptoms and signs of CVI (both $P < .001$) with similar trends for symptoms and signs • MPFF decreased measurements around calves and ankles • MPFF decreased venous capacity, venous distensibility, and venous drainage times and increased venous tone *Patient's satisfaction* • Very satisfied: 55% (n=11) in the MPFF group vs 10% (n=2) in the placebo group ($P < .05$). • No improvement: 10% (n=2) in the MPFF group vs 30% (n=6) patients in the placebo group *Clinician's satisfaction* • Very satisfied: 40% (n=8) in the MPFF group vs 5% (n=1) in the placebo group ($P < .05$)*Tolerability:* Well tolerated, with no side effects reported by the 18 patients who completed the trial
Laurent, 1988[47]	Organic or functional CVI	2 double-blind RCTs 200 patients MPFF (Daflon) 1000 mg daily for 2 months vs placebo Included in meta-analyses[13,94] and narrative review[107]	2 months	*Efficacy:* MPFF: • Significantly reduced symptoms and signs of CVI, whether organic or functional • Significantly improved venous hemodynamics on plethysmographyAcceptability: Good acceptability Tolerability not reported in abstract

(Continues)

TABLE 2 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Cospite, 1989[45] Potential duplicate of Amato, 1994[46]	Lower-limb CVI, functional CVI, varicose veins, PTS	Multicenter, double-blind, RCT 90 outpatients (including functional CVI, 39 patients; varicose veins, 32 patients; PTS, 17 patients) MPFF (5682 SE, Daflon) two 500-mg tablets a day vs single diosmin (900 mg) for 2 months Include in systematic review[90]	Up to 2 months	*Efficacy*: • As compared with diosmin, MPFF was at least 2 times more effective at improving CVI symptoms • The difference was statistically significant for most symptoms • There were more substantial decreases in the venous outflow parameters with MPFF than with diosmin Acceptability • Patient satisfaction: 95% in the MPFF group (vs 80% in the diosmin group; $P < .01$) • Clinician satisfaction: 79% in the MPFF group (vs n/a in the diosmin group) *Tolerability*: • Epigastric pain: 16.3% (n=7) (spontaneously resolved without any changes) in the MPFF group vs 11.1% (n=5) in the diosmin group • Dropout: 2.3% (n=1) in the MPFF group (nonmedical reason) and 2.3% (n=1) in the diosmin group (because of epigastric pain)
Tsouderos, 1989 and 1991[23,41]	*Crossover phase II trial* PTS *Pharmacoclinical trial* CVI without varicose, during pregnancy and PTS *Phase III clinical trial* Functional CVI	3 double-blind RCTs (including that of Chassignolle, at al 1987[24]) *Crossover phase II trial* 20 patients with PTS Single dose of MPFF (Daflon) 1000 mg vs placebo *Pharmacoclinical trial* 3 groups of 10 women each Daflon 500 mg two tablets daily for 1 wk *Phase III clinical trial* 2 parallel groups of 20 patients each MPFF (Daflon) 500 mg 2 tablets daily vs placebo for 2 months Included in meta-analyses[13,88,94] and systematic review[90]	2 h 1 wk 2 months	*Efficacy*: *Crossover phase II trial* MPFF decreased: • Venous capacity ($P < .001$) • Venous distensibility ($P < .001$) • Venous outflow time ($P < .001$) Modifications were observed 2 h after administration. No significant change observed in T50 outflow, cardiac index, capillary filtration index, blood pressure, cardiac or respiratory rate *Pharmacoclinical trial* • MPFF acutely increased venous tone. *Phase III clinical trial* MPFF, after 1 and 2 months of treatment: • Improved functional symptoms and edema • Lead to statistically significant increase in venous toneAcceptability not reported in abstract *Tolerability*: *Crossover phase II trial* 2 h after administration: no significant change in cardiac index, blood pressure, cardiac or respiratory rate *Pharmacoclinical trial:* Not reported in abstract *Phase III clinical trial:* Not reported in abstract
Planchon, 1990[79]	Any CVI	RCT 110 patients Included in meta-analyses[13,88,94]	2 months	*Efficacy*: MPFF significantly reduced: • Leg pain • Heaviness • Feeling of swellingCramps Acceptability and tolerability not available

(Continues)

TABLE 2 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Barbe, 1992[25] Potential duplicate of trials by Tsouderos[23,41]	Including PTS, functional CVI, pregnancy-related CVI	3 double-blind RCTs RCT 1: Patients with PTS RCT 2: Women with CVI −10 with functional CVI, −10 with pregnancy-related CVI −10 with postthrombotic CVI RCT 3: patients with functional CVI Included in narrative review[111,112]	Not available	*Efficacy:* MPFF led to: • Significant increase in venous tone. • Significant decreases in venous distensibility and venous emptying times • Effects occurred 1 h after a single dose of 1000 mg MPFF and lasted 4 h. After a 1-wk period of treatment, the effect lasted 24 h after a single doseAcceptability and tolerability not available
Chassignolle, 1994 and 1999[33,44] Potential duplicate of Chassignolle, 1987[24] and of trial by Tsouderos[23,41]	Functional CVI	Double-blind RCT 40 women (22-49) MPFF (Daflon) vs placebo for 2 months Plethysmographic and clinical outcomes included in meta-analyses[13,94]	2 months	*Efficacy:* As compared with placebo, MPFF improved: • Overall functional symptoms ($P < .001$) (discomfort, heaviness, tiredness, burning sensation). • Overall objective symptoms ($P < .05$) (ankle circumference). • Venous capacity, venous distensibility, and venous drainage *Acceptability:* Good acceptability in all 18 MPFF patients who completed study *Tolerability:* No reported side effects
Menyhei, 1994[70]	Any CVI including PTS, primary varicose veins	Multicenter, double-blind RCT 320 patients MPFF (Daflon) 500 mg BID vs 1000 mg once in the morning vs 1000 mg once in the evening for 2 months Included in systematic review[90] and narrative review[107]	2 months	*Efficacy:* As compared with baseline: • Significant improvement of all symptoms in each group • Decrease in ankle and calf edema for most affected leg ($P < .001$) • Significant improvement started to be noticed between days 15 and 30 for aboveNo difference between groups *Acceptability and tolerability not reported in abstract*

(Continues)

TABLE 2 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Gilly, 1994[42,43,78]	Symptomatic disturbance of veno-lymphatic system with or without CVI, including PTS	Two-center, double-blind RCT 160 outpatients MPFF (Daflon) 500 mg vs placebo for 8 wk Included in meta-analyses[13,88,94] and systematic reviews[90,93]	2 months	*Efficacy*: Significant improvement with MPFF in terms of: • Discomfort • Heaviness • Nocturnal cramps • Swelling • Pain • Sensation of burning or heat • Calf circumference • Ankle circumference Acceptability: Good acceptability. *Tolerability*: • 11.8% (n=9) with side effects in MPFF group vs 15% (n=12) in placebo group • Nausea (5% in each group), gastralgia (2.5% in each group), headaches, insomnia, and hypotension (1.3% in each group) • Side effects transient, mild, and did not lead to interruption of treatment, except in the case of nausea and hypotension
Amato, 1994[46] Potential duplicate of Cospite, 1989[45]	Any CVI stable for 1 y	Multicenter, double-blind RCT 90 patients MPFF (Daflon) 500 mg 2 tablets vs diosmin equivalent dose for 2 months	2 months	*Efficacy*: Statistically greater improvements in terms of clinical symptoms and plethysmographic parameters with: • Diosmin and MPFF, compared to baseline • MPFF, compared to diosmin Acceptability: Satisfaction: 95% in the MPFF group vs 80% in the diosmin group ($P < .01$) *Tolerability*: • Clinical tolerance satisfactory • 7 transient mild epigastric pain in MPFF group
Ibegbuna, 1997[26]	Symptomatic varicose veins in one leg and abnormal elastic modulus without varicosities in other leg	Open-label RCT 25 patients MPFF (Daflon) 500 mg 2 tablets daily vs no treatment for 4 wk	4 wk	*Efficacy*: MPFF significantly improved elastic modulus and venous tone in patients at risk of developing varicose veins when compared to no treatment Acceptability and tolerability not reported

(Continues)

TABLE 2 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Guilhou, 1997[40,77]	Any venous ulcer, including PTS related	Multicenter, double-blind, RCT 105 patients MPFF (Daflon) 500 mg 2 tablets daily and compression therapy vs placebo and compression for 2 months Included in meta-analyses[13,94,97,104] and systematic reviews[90,93,96]	2 months	*Efficacy*: As compared with placebo, MPFF led to: - Among patients with ulcer size ≤10 cm, greater and faster rate of ulcer healing (32% vs 13%; $P = .03$) and shorter duration of healing ($P = .04$) • Improvement in leg heaviness sensation ($P = .04$) • No difference in effect on ulcers >10 cm Acceptability: 2 patients withdrew consent in MPFF group (vs 4 in placebo group) for reasons unrelated to side effects *Tolerability*: • Rates of adverse events were similar in both groups • No adverse event could be clearly related to treatment
Glinski, 1999 and 2001[39,76]	Any venous leg ulcer, including PTS related	Multicenter, open-label RCT 140 patients Standard treatment (including compression) plus MPFF (Daflon) 2 tablets daily for 6 months vs standard treatment alone Included in meta-analyses[97,104] and systematic review[90]	6 months	Effectiveness: As compared with standard treatment alone, addition of MPFF was associated with: • Higher rates of ulcers healing (46.5% vs 27.5%; $P < .05$) whether ulcer was <3 cm in diameter (71% vs 50%) or 3-6 cm (60% vs 32%) (both $P < .05$). • Higher mean reduction in ulcer size (80% vs 65%; $P < .05$). • Better cost-effectiveness ratio per healed ulcer: 1026.2 in MPFF group vs 1871.8 in control group (cost per healed ulcer)Acceptability not reported *Tolerability*: Slightly more adverse effects in the control group, although no statistical difference in adverse effects between the groups; adverse effects not specified
Danielsson, 2002[83]	Symptomatic CVI	Double-blind RCT 101 patients MPFF 500 mg BID vs placebo for 60 d Included in meta-analyses[13,88,93,94] and systematic review[96]	60 d	*Efficacy*: MPFF did not significantly improve: • Symptoms of CVI, except night cramps • Foot-volumetric or ultrasonographic parameters Results might be more favorable to MPFF in subgroup of patients with edema: • Ultrasonographic reflux time significantly reduced in patients with edema of treatment group compared to those of control group ($P = .03$), without correlation to clinical symptoms Acceptability not reported *Tolerability*: • 2 withdrawals in each group, 1 in each group for nausea • Mild side effects: 12% in MPFF group vs 4% in placebo group

(Continues)

TABLE 2 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Belcaro, 2002[85] Cesarone, 2005 and 2006[37,38]	Severe CVI	RCT Group I 90 patients MPFF (Daflon) 500 mg every 8 h vs rutoside (0-[beta-hydroxyethyl]-rutosides, Venoruton) 2 g/d for 8 wk Group II (included additionally in Cesarone's publication)[38]: 122 patients: Comparable patients included in a registry following the same study format	8 wk	*Efficacy*: Rutoside significantly: • Decreased resting skin flux and rate of ankle swelling • Improved venous microangiopathy and edema both in the randomized study and in the pooled analysis[38] • Showed more effectiveness in the improvement of microcirculatory parameters, signs, and symptoms when compared to MPFF • Improved (46.8%; $P < .05$) Ve-QOL score to a greater extent when compared to MPFF (15.5%)Acceptability not reported *Tolerability*: No side effects and no dropouts observed; good compliance
Maruszynski, 2004[36,84]	Symptomatic CVI, CEAP C0-3	Multicenter, double-blind RCT 119 patients MPFF 500 mg BID vs diosmin 600 mg BID	28 d	*Efficacy*: • The drugs have similar effectiveness in reducing symptoms related to CVI • Effectiveness of both drugs already noticeable after 1 wk of treatment Acceptability not reported *Tolerability*: Both MPFF and diosmin were safe and well-tolerated: • No serious adverse events; adverse events led to a full recovery • 2 reactions in the diosmin group: calf, hands, and feet edema; body rash • 3 reactions in the MPFF group: calf edema, body rash and dryness of the mouth • 3 patients interrupted the study at their own request, after the occurrence of mild adverse events.
Roztocil, 2003[75]	Venous ulcers, including PTS related	RCT 150 patients MPFF (Daflon) 2 tablets daily and standard treatment including compression vs standard treatment alone for 6 months Included in meta-analyses[97,104]	6 months	*Efficacy*: MPFF significantly: • Increased rate of ulcer healing ($P = .004$) • Decreased ulcer surface ($P = .01$) • Improved heavy leg sensation from week 4 ($P < .05$)Acceptability: MPFF considered excellent by 85% of patients *Tolerability*: No treatment-related side effects reported; 99%-100% compliance during course of study
Cesarone, 2006[86]	Severe CVI, venous ulceration	RCT 86 patients MPFF (Daflon) 1000 mg daily vs pycnogenol 50 mg TID vs Pycnogenol 300 mg daily for 8 wk	8 wk	*Efficacy*: Pycnogenol significantly superior to MPFF in: • Reduction of edema • Venous score improvement • Microcirculation parameter (skin flux at rest, capillary filtration, pO_2, pCO_2) improvementAcceptability not reported *Tolerability*: Treatments well tolerated in all groups, no side effects reported, no dropouts

(Continues)

TABLE 2 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Veverková, 2005 and 2006[35,74]	Patients who underwent a stripping procedure of the great saphenous vein	Open-label, multicenter RCT 181 patients MPFF (Daflon) 500 mg 2 tablets daily from 14 d before to 14 d after stripping surgery (1 months total) vs control (not treated with MPFF)	14 d before to 14 d after procedure	*Efficacy*: MPFF significantly: • Reduced intensity of postoperative pain • Reduced size of postoperative hematoma • Improved symptoms of CVI • Improved QOL on CIVIQ *Acceptability not reported* *Tolerability*: No subject lost because of side effects or clinical problems All dropouts failed to follow the protocol or did not come to the control evaluation for nonmedical reasons[74]
Pokrovsky, 2007[73] Saveljev, 2008[34]	Varicose veins, undergoing phlebectomy	RCT 245 patients MPFF (Detralex) 1000 mg daily (n=200) vs no agent (n=45) 2 weeks before phlebectomy for varicose veins until 30 d after procedure Included in systematic review[87]	2 wk before to 30 d after the procedure	*Efficacy*: MPFF significantly decreased: • Pain before and after surgery • Leg heaviness before and after surgery • Area of subcutaneous hemorrhage • Subjective symptoms.MPFF improved orthostatic and exercise tolerance in the early postoperative period; it had no impact on QOL 30 d postoperatively Acceptability not reported *Tolerability*: Minor adverse effects (gastric irritation) of MPFF appeared in 4 cases (1.6%) during the first 2 wk of administration and resolved spontaneously
Bogachev, 2012[67]	CEAP C2-4 s, undergoing endovascular treatment	Open-label RCT 230 patients MPFF (Detralex) 1000 mg daily (n=126) vs compression therapy (n=104) from 14 d before procedure to 30 d after procedure Included in systematic review[87]	2 wk before to 30 d after procedure	*Efficacy*: MPFF: • Significantly decreased CVI severity on VCSS scale. • Improved QOL on CIVIQ-14 • *Acceptability and tolerability not reported in abstract*
Belczak, 2014[72]	CEAP C2-5	Double-blind, RCT 136 patients MPFF vs aminaphthone vs coumarin and troxerutin vs placebo (starch) for 30 d Included in meta-analysis[88]	Until 30 d after treatment	*Efficacy*: • Volume reductions ≥100 mL more frequent in the MPFF group than in any other group • QOL scores best in aminaphthone group • No differences in tibiotarsal joint range of motion Acceptability not reported *Tolerability*: 9 patient dropouts: • 3 lost to follow-up • 1 patient in aminaphthone group with headache • 2 patients in MPFF group with urolithiasis/urinary tract infection and diarrhea, respectively • 1 patient in troxerutin group with nausea and vomiting • 2 patients in placebo group with subjective worsening of leg pain

(Continues)

TABLE 2 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Stoiko, 2015[82]	CVI undergoing endovenous thermal ablation	Open-label RCT 60 patients MPFF 3000 mg on days 1-4, 2000 mg on days 5-7 vs control Included in systematic review[87]	7 d after procedure	*Efficacy*: • Significantly less pain (visual analog scale) in MPFF group on postoperative day 2 • Otherwise, no significant differences in pain, VCSS or QOL (CIVIQ)*Acceptability and tolerability not reported in abstract*
Rabe, 2015[71]	CEAP C3-4	Multinational, parallel group, double-blind RCT 1137 participants MPFF (Daflon) 500 mg 2 tablets administered at 1 dosing at lunchtime for 4 months vs placebo Included in meta-analysis[88]	6 months	*Efficacy*: MPFF significantly: • Reduced pain and leg heaviness (visual analog scale) (P = .03) at the end of the 4-months treatment period • Improved QOL (CIVIQ) over the treatment period (P = .04) Acceptability not reported *Tolerability*: • Mean overall compliance (treatment intake): 98% ± 12% • Treatment-emergent adverse event: 16.6% (MPFF) vs 19.3% (placebo) • Most frequent adverse events with MPFF: infectious (influenza, erysipelas, tonsillitis), gastrointestinal (abdominal pain, nausea, constipation, diarrhea) • Serious adverse events: 1.4% in MPFF group including 2 erysipelas, 1 hypertensive crisis, and 1 cataract extraction • 4 patients stopped treatment in MPFF group in the context of adverse events: pruritus, nausea, brittle nails, abdominal pain, erysipelas, depression
Kirienko, 2016[69]	CEAP C0-4	International, parallel-group, double-blind RCT 174 patients MPFF 1000 mg once daily vs MPFF 500 mg BID for 8 wk	8 wk	*Efficacy*: • Similar efficacy in both treatment regimens • Decrease in leg pain score starting as early as after 2 wk of treatment, with decrease over the whole duration of treatment Acceptability not reported in abstract *Tolerability*: • No serious adverse events reported • <4% (n=3) with mild adverse events (constipation, dyspepsia, allergic dermatitis) considered to be related to treatment in MPFF 1000-mg group; resolved at the end of treatment

(Continues)

TABLE 2 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Carpentier, 2017[68]	CEAP C0 s–4 s	International, parallel-group, double-blind RCT 1139 patients MPFF 1000 mg once daily vs MPFF 500 mg BID for 8 wk	8 wk	*Efficacy*: • Significant reduction in lower limb symptoms with MPFF • Noninferiority of MPFF 1000-mg oral suspension once daily compared to MPFF 500-mg tablet BID ($P < .0001$) for lower-limb discomfort (−3.33 cm for MPFF 1000 mg and −3.37 cm for MPFF 500 mg), leg pain (−3.27 cm for MPFF 1000 mg and −3.31 cm for MPFF 500 mg) and leg heaviness (−3.41 cm for MPFF 1000 mg and −3.46 cm for MPFF 500 mg) • QOL was improved by about 20 points on the CIVIQ scale in both groups (19.33 points for MPFF 1000 mg and 20.28 points for MPFF 500 mg) Acceptability not reported *Tolerability*: • Adverse events lead to premature withdrawal in 1.3% of patients: 6 patients (1.1%) in the MPFF 1000-mg group and 9 patients (1.6%) in MPFF 500-mg group • All emergent adverse events that led to discontinuation were resolved • 13.3% report at least 1 adverse event (12.9% of 1000-mg group, 13.7% of 500-mg group) • Most frequent from 1000-mg group: nausea, upper abdominal pain • Most frequent from 500-mg group: diarrhea, headache
Katseni, 2017[27]	CVI and lower-extremity venous ulcer	RCT 60 patients Group A: Elastic compression stockings Group B: MPFF 500 mg BID and elastic compression stockings Group C: MPFF 500 mg BID, antibiotics, and elastic compression stockings	40 d	*Efficacy*: • Ulcer healing time was significantly shorter in MPFF and MPFF combined with antibiotics groups when compared to the control group • No significant difference with the addition of antibiotics to MPFF • MPFF reduced white blood cell trapping rate in capillaries around the ulcer by half after 20 d of MPFF • MPFF is beneficial for capillary permeability and microcirculationAcceptability and tolerability not reported
Toledo, 2017[66]	Venous ulcers	Longitudinal prospective RCT 30 patients Group 1 (n=15): Pycnogenol 50 mg orally TID Group 2 (n=15): MPFF (diosmin/hesperidin) 450/50 mg orally BID for 90 d	90 d	*Efficacy*: Pycnogenol and MPFF: • Both had a similar effect on venous ulcer healing • Both led to a significant decrease in ulcer area over time • Both led to significant decrease in circumference of affected limbsAcceptability and tolerability not reported
Ignat'ev, 2018[65]	PTS of the lower extremities	Open prospective RCT 80 patients MPFF (Venarus) and conservative treatment (n=40) vs conservative treatment (n=40) alone	Not reported in abstract	*Efficacy*: • Significant improvement of clinical symptoms in MPFF group • MPFF improved tonicoelastic properties of the intact common femoral vein • MPFF improved healing of small trophic ulcers*Acceptability and tolerability not reported in abstract*

(Continues)

TABLE 2 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Lobastov, 2019[102]	Femoropopliteal DVT, investigating for development of PTS	Open-label RCT 60 patients MPFF 1000 mg daily and rivaroxaban vs rivaroxaban alone	6 months	*Efficacy*: In the MPFF group: • Mean Villalta score was significantly lower (2.9 ± 2.7 vs 5.8 ± 3.0; $P < .0001$) at 6 months • There was a greater reduction in the Marder score ($P < .0001$) and a faster rate of recanalization for the femoral vein ($P < .0001$) • There was no significant difference in rate of recanalization of the common femoral vein ($P = .130$) and popliteal vein ($P = .20$) compared to the control group • Full recanalization of the popliteal vein was obtained in more patients at 6 months (24 patients; 80%) compared to the control group (17 patients; 57%) ($P = .10$) • VCSS was lower (2.3 ± 1.9) compared to the control group (4.9 ± 1.9) ($P < .0001$) • PTS was diagnosed in 6 (20%) patients, compared to 17 patients (57%) in the control group Acceptability not reported *Tolerability*: • None of the 60 patients discontinued treatment during follow-up • 1 hemorrhoidal bleed and 1 rectal bleed in the MPFF group • 2 cases of macrohematuria and 1 epistaxis in the control group • No major bleeding in either group • 3 dyspeptic disorders in the MPFF group not requiring discontinuation
Saveliev, unpublished	CVI, including trophic ulcers	Open RCT: multicenter trial involving 3 centers in Russia 124 patients Group 1: MPFF (Detralex) 500 mg 2 tablets daily and standard local therapy with compression bandaging Group 2: standard therapy with elastic compression and local treatment alone Included in meta-analyses[97]	6 months	*Efficacy*: • Less time to achieve complete ulcer healing in the MPFF group • No significant difference in severity or intensity of pain and frequency of night cramps between the 2 groups Acceptability not available *Tolerability*: Adverse events: • MPFF group: 21.0% (13/62), including arterial hypertension (4.8%) and reduction in body mass (3.2%) • Standard therapy group: 11.3% (7/62), including reduction in body mass (1.6%)

Note: Not reported: Information not reported in the full text of the manuscript. Not reported in abstract: Information not reported in the abstract and the full text of the manuscript is not available. Not available: Neither the abstract nor the full text of the manuscript are available, and information not reported in other reviews.

Abbreviations: BID: twice daily; CEAP: Clinical-Etiology-Anatomy-Pathophysiology Comprehensive Classification System for Chronic Venous Disorders; CIVIQ: Chronic Venous Insufficiency Questionnaire; CVI: chronic venous insufficiency; d: day; DVT: deep vein thrombosis; h: hour(s); months: month(s); MPFF: micronized purified flavonoid fraction; PTS: postthrombotic syndrome; QOL: quality of life; RCT, randomized controlled trial; TID: 3 times a day; VCSS: Venous Clinical Severity Score; Ve-QOL: Venous Quality of Life Score; wk: week; y: year.

and observational studies as a single study. RCT publications presenting the results of multiple trials within the same publication were considered a single RCT-type publication.

Given the scarcity of the manuscripts accessible for detailed review of older studies and substantial heterogeneity between studies in terms of design, population, duration of treatment, and outcomes assessed, conducting a meta-analysis as part of a systematic review with statistical pooling was neither suitable nor feasible. Instead, a narrative review and descriptive presentation of findings was deemed methodologically appropriate. When the

TABLE 3 Observational studies discussing the use of micronized purified flavonoid fraction in chronic venous insufficiency

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Guillot, 1989[64]	Any CVI	Multicenter study 170 outpatients MPFF (Daflon) 2 tablets daily vs baseline Included in systematic review[90]	12 months	*Efficacy:* With MPFF, significant improvement in: • Signs and symptoms • Supra-malleolar and calf circumference • Functional discomfort • Evening edema • CrampsBenefits started from second month of treatment and increased with time Acceptability: Excellent or useful in 91% of cases (58% excellent, 33% useful, 9% nil) Tolerance: Mainly epigastric pain (4.1%, n=7)
Blume, 1992[63]	Any CVI, including PTS and varicose veins	20 patients: 9 PTS, 11 varicose veins Described in narrative review[107,113]	Every 2 wk	*Efficacy:* MPFF was associated with significant decrease in leg volume by optoelectronic method of the more affected lower leg of 263 mL (8%) in all patients and 392 mL (12%) in patients with varicose veins Acceptability and tolerability not available
Iablokov, 1996[62]	Severe CVI	76 patients MPFF (Detralex) 500 mg BID for 2 months	Not reported in abstract	*Efficacy:* MPFF relieved CVI symptoms in most cases Acceptability not reported in abstract *Tolerability:* Well tolerated
Jantet, 2000[68] and 2002[48,49]	Symptomatic CVI, CEAP C1-4	Prospective, controlled, multicenter, international study First consolidated data[48] Worldwide results[49] Intention-to-treat analysis (confirmed to have taken 2 tablets of MPFF): 3075 patients[48] 4527 patients[49] Per-protocol (adhered to all protocol conditions): 2395 patients[48] 3174 patients[49] MPFF (Daflon) 500 mg 2 tablets daily for 6 months. Instructions to not change their habits as to the wearing or not of compression stockings	6 months	*Efficacy:* MPFF significantly: • Improved pain, leg heaviness, sensation of swelling, and cramps (P = .0001) • Decreased edema measured by leg circumferences with the Leg-O-Meter (P = .0001) • Improved QOL scores (CIVIQ) • Improved CEAP classification: patients tended to move to a lower CEAP category Acceptability: • 79% of patients considered MPFF's effectiveness as good or excellent after 6 months of treatment • 91% of patients judged overall acceptability as good or excellentTolerability not reported
Ting, 2001[61]	Mild to moderate CVI	Prospective study 28 patients MPFF (Daflon) 500 mg oral BID for 6 months	6 months	*Efficacy:* MPFF significantly: • Decreased swelling and heaviness • Reduced mean pain score from 21.8 ± 19.3% to 10.4 ± 20.2% (P < .01) • Decreased mean calf circumference from 37.0 ± 4.3 to 36.4 ± 4.3 cm (P < .001)Improvement in cramps was not statistically significant. No significant change in venous filling index, ejection fraction, or residual volume fraction; clinical improvement without associated changes in venous hemodynamics as measured by air plethysmography Acceptability not reported *Tolerability:* No side effects encountered

(Continues)

TABLE 3 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Sirotin, 2003[60]	CEAP C0-4	14 patients MPFF (Detralex)	Not reported in abstract	*Efficacy:* MPFF led to: • Regression of clinical manifestations of CVI • Improvement of leg circulation and systemic microcirculation • Reduction of perivascular edema • Increase of number of functioning microvessels and flow acceleration within them • Lowering of intramuscular red blood cell aggregation*Acceptability and tolerability not reported in abstract*
Navratilova, 2010[59]	Symptomatic CVI with edema	Observational study 213 patients included 196 patients completed study in accordance with protocol MPFF (Daflon) 500 mg 2 tablets daily for 6 months	6 months	*Efficacy:* As compared with baseline, MPFF significantly: • Improved sensation of swelling, tension and pain, heavy leg sensation, and restless legs from the second month ($P < .001$) • Reduced edema from the second month ($P < .001$), in terms of leg perimeter and volume Acceptability: • No patients reported deterioration • 91% of patients satisfied or very satisfied • 82% decided to continue Daflon *Tolerability:* No side effects in relation to MPFF observed No changes in body weight, heart rate, or blood pressure Compliance 99%-100% during study
Pitsch, 2011[101]	Telangiectasia, with or without varicose veins and edema, undergoing sclerotherapy	Observational study 3202 patients MPFF (Daflon) 500 mg 2 tablets daily in patients undergoing sclerotherapy (microsclerosis with foam, liquid sclerosing agents or laser) from the first session to the last session of sclerotherapy, for 2 months	2 months	*Efficacy:* MPFF and sclerotherapy significantly: • Improved all CVI symptoms • Improved QOL (CIVIQ-14) • Acceptability:81% of patients satisfied or very satisfied with the combination of sclerotherapy and MPFF *Tolerability:* Side effects in 2.4% of patients: Mainly hematomas (0.4%), postprocedure pain (0.3%), and inflammation (0.3%)
Lenkovic, 2012[58]	Any CVI with at least 3 symptoms (pain, heaviness, swelling, night cramps) CEAP C0-C6	Prospective study 1212 patients MPFF (Daflon) 500 mg 2 tablets daily for 6 months	6 months	Effectiveness: As compared to baseline, regardless of stage of disease, MPFF significantly improved ($P < .05$): • Heaviness in legs • Swelling • Pain and crampsAcceptability and tolerability not reported
Gudymovich, 2013[100]	Any CVI	Observational study MPFF (Venarus)	At least 4 wk	*Efficacy:* MPFF: • Significantly improved QOL • Was effective in cohort, with maximum positive effect observed within the first 4 wk*Acceptability and tolerability not reported in abstract*

(Continues)

TABLE 3 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Zubarev, 2014[57]	CEAP C2	Observationnal study 19 patients MPFF (Detralex) 1000 mg daily for 3 months	3 months	Effectiveness: • All patients reported a positive clinical effect with decreased intensity of manifestations or disappearance of complaints • Tendency toward a decrease in the wall thickness and diameter of veins • Increase in the perivasal zones of elastographic homogeneity of tissues (ultrasound elastography) • Trend toward normalization of the elastographic pattern of the vessel*Acceptability and tolerability not reported in abstract*
Yanushko, 2014[56]	Symptomatic CVI	Prospective observational study 557 patients MPFF (Daflon) 500 mg 2 tablets daily for 2 months	6 months	*Efficacy:* Strong significant ($P < .01$) decrease in the number of patients with the following symptoms at the end of the second month of treatment: • Cramps (76%) • Itching (75%) • Pain along vein (66%) • Feeling of burning (81%) • Swelling (66%) • Leg pain (59%) • Feeling of leg heaviness (38%)6% reduction of patients with edema In terms of QOL improvement, the Global Index Score (GIS) decreased from 32.9±21.0 at baseline to 14.6±14.7 ($P < .0001$) after 2 months of treatment Acceptability: 94% of patients and 96% of physicians estimated efficacy of MPFF to be high or very high *Tolerability:* 4.2% of cases had adverse events on MPFF: Mostly gastrointestinal, appearing after 2-3 d and disappearing at the end of treatment; 1 case of urticaria reported
Son'kin, 2014[53]	PTS	Open multicenter retrospective study 110 patients MPFF (Venarus) with conventional PTS treatment or conventional treatment alone for 3 months at least	At least 3 months	*Efficacy:* MPFF lead to: • Greater improvement of PTS symptoms and QOL • Significant increase in psychological and social activityGreatest improvements occurred when MPFF was administered for at least 3 months Acceptability not reported in abstract *Tolerability:* No side effects noted during study
Zudin, 2014[30]	DVT without varicose disease, investigating for development of PTS	Prospective study 66 patients Group I (n=22): Angiotropic and metabolic infusion therapy, direct and indirect anticoagulant and elastic compression Group II (n=22): Same as Group I, with MPFF (Venarus) 1000 mg daily for 2 months every half year Group III (n=22): Same as Group I, with MPFF (Venarus) 1000 mg daily uninterrupted	18 months	*Efficacy:* • MPFF groups showed accelerated processes of recanalization by 15%-20% on average compared to non-MPFF group • Patients taking MPFF without interruption showed deceleration of the formation of vertical and horizontal veno-venous reflux, more adequate recanalization at the end of the duration of follow-up and decreasing CVI clinical manifestations*Acceptability and tolerability not reported in abstract*

(Continues)

TABLE 3 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Tsoukanov, 2015[28]	Subjective CVI, CEAP C0	Open-label prospective study 41 women MPFF (Daflon) 1000 mg once daily in the morning for 2 months	2 months	*Efficacy:* Significant improvement in: • Intensity of subjective symptoms of CVI (P = .000001) • QOL: CIVIQ−20 from 58 ± 7.63 at baseline to 70 ± 8.65 after 2 months of treatment (P = .000001)MPFF led to reduction of greater saphenous vein reflux in most treated patients and decrease in vein diameter Acceptability and tolerability not reported
Tsukanov, 2016[55]	PTS secondary to iliac thrombosis with small varicose pelvic veins, with impaired urination	Observational study 70 patients with acute iliac thrombosis, among which 24 patients received MPFF: those suffering most from the disease, that is, with urination impairment MPFF 1000 mg once daily for 1 months	1 months	*Efficacy:* MPFF: • Significantly reduced the severity of clinical manifestations • Significantly reduced varicose small pelvic vein dilation in 18 patients and normalized ultrasonic indices in the rest of the patients • Decreased the number of patients with bilateral varices from 10 to 2 • Decreased mean paraprostatic and parametrial vein diameter to near-normal values • Decreased the number of patients with pelvic pain from 8 to 1 • Decreased the number of patients with urination disorder from 24 to 9 • Improved retrograde flow and pelvic hemodynamicsAcceptability not reported *Tolerability:* No side effects noticed
Tsukanov, 2017[54]	Telangiectasia, reticular varices	Observational study 96 patients MPFF (Daflon) 1000 mg for 90 d	90 d	*Efficacy:* MPFF: • Eliminated transient venous reflux in most (92.5%) patients • Reduced greater saphenous vein diameter from baseline (P = .000001) • Eliminated leg heaviness in most (88.6%) patients • Reduced symptoms in 11.4% of patients • Improved QOL (CIVIQ)Acceptability and tolerability not reported
Bogachev, 2018[52]	CEAP C1 with dilated intradermal veins, undergoing sclerotherapy	Multicenter observational study 1150 patients: 905 took MPFF, remainder had sclerotherapy alone MPFF 1000 mg daily for 6 wk, beginning 2 wk before sclerotherapy	2 wk before sclerotherapy to 4 wk after sclerotherapy	*Efficacy:* • MPFF-treated group had more pronounced symptomatic improvement in visual analog scale score (such as in terms of leg heaviness and pain) compared to sclerotherapy alone • Greater QOL (CIVIQ-14) improvement with adjunctive MPFFAcceptability: Outcomes of treatment exceeded patient expectations, by Darvall questionnaire. *Tolerability:* No adverse events with MPFF; fewer sclerotherapy-induced hyperpigmentation with adjunctive MPFF compared to sclerotherapy alone

(Continues)

TABLE 3 (Continued)

First author Year of publication	Type of CVI	Study design Number of participants Dosage and duration of MPFF	Duration of follow-up	Main results and interpretations
Mazzaccaro, 2018[81]	Varicose veins treated with radiofrequency ablation, stripping, crossectomy, or phlebectomy	Observational study, case-controlled, comparing those who complied to venoactive drug vs those who did not 132 patients Compression therapy with venoactive drug (MPFF 500 mg BID or sulodexide 250 mg BID) for 90 d following procedure Included in systematic review[87]	90 d	*Efficacy:* No significant difference between patients who took a venoactive drug (MPFF or sulodexide) and those who did not in terms of: • Intensity of pain • Days of rest from daily activities • QOL assessed with Short Form–12 (Physical Component Summary–12 and Mental Component Summary–12) Acceptability not reported *Tolerability:* • One-third of patients did not comply to recommended venoactive drug therapy postoperatively • No side effects from sulodexide or MPFF • No major complications such as bleeding or infection

Note: Not reported: Information not reported in the full text of the manuscript. Not reported in abstract: Information not reported in the abstract and the full text of the manuscript is not available. Not available: Neither the abstract nor the full text of the manuscript are available, and information not reported in other reviews.

Abbreviations: BID: twice daily; CEAP: Clinical-Etiology-Anatomy-Pathophysiology Comprehensive Classification System for Chronic Venous Disorders; CIVIQ: Chronic Venous Insufficiency Questionnaire; CVI: chronic venous insufficiency; d: day(s); DVT: deep vein thrombosis; months: month(s); MPFF: micronized purified flavonoid fraction; PTS: postthrombotic syndrome; QOL: quality of life; wk: week(s).

information was retrievable, each article was described in terms of the type of CVI investigated, study design, number of participants, dosage, composition and duration of pharmacotherapy, duration of follow-up, main results, and interpretations. This information was summarized in Tables 1 through 3. Studies were then discussed in terms of their reports of the efficacy, acceptability, and tolerability of MPFF in the treatment of CVI. When the full manuscript or the abstract of a study was inaccessible but key findings were presented in other review articles, we instead used this source of information.

3 | RESULTS

3.1 | Description of studies

We identified 14 systematic reviews, 33 RCTs, and 19 observational study publications discussing the use of MPFF in CVI, including PTS (Figure 1). Tables 1 through 3 summarize the studies by study type. Obvious duplicate publications were cited and grouped together within a single row. Fifteen studies were retained as relevant to the discussion of the mechanistic action of MPFF in relation to the pathophysiology of PTS.[16-30]

Among studies we have identified on the use of MPFF in CVI, including PTS, there were two duplicate publications of systematic reviews.[31,32] One of these duplicates was a systematic review that was conducted in 2011, three years following the earlier review. The latter discussed the same RCTs when it comes to MPFF in CVI and differs only in the addition of a table presenting such studies.[32] There were 11 duplicate RCT-type publications,[33-43] including one duplicate of a publication discussing three separate RCTs[41] and two duplicates of a single RCT,[42,43] with the remaining being duplicates of distinct RCTs. A total of 11 RCT studies were duplicated at least once. It is important to note that although these duplicate publications discussed trials that were presented in another publication, some of them presented additional study groups or discussed additional content, such as QOL.[37,38] Additionally, two RCT publications[24,25] and a third RCT publication that also has a duplicate publication[33,44] seemed to be presenting trials similar to the ones published by Tsouderos.[23] The more recent Chassignolle RCT publications[33,44] also bear a resemblance to the original Chassignolle 1987 RCT[24]. Two other RCTs also seemed to be potential duplicate publications of each other.[45,46] The distant date of publication and resulting inaccessibility of the full manuscripts of studies prevented us from confirming these suspicions. Three RCT publications presented the results of several trials within the same publication.[23,25,47] There was a single duplicate publication of an observational study.[48] The preliminarily consolidated results of this study were first published in 2000,[48] whereas the worldwide results were subsequently published 2 years later.[49]

3.2 | Efficacy

3.2.1 | MPFF's mechanism of action and the pathophysiology of PTS

Following DVT, conventional treatment with anticoagulants prevents further thrombus extension without lysis of the thrombus, with the hope that the residual clot burden is cleared by endogenous thrombolysis. Unfortunately, residual thrombus often

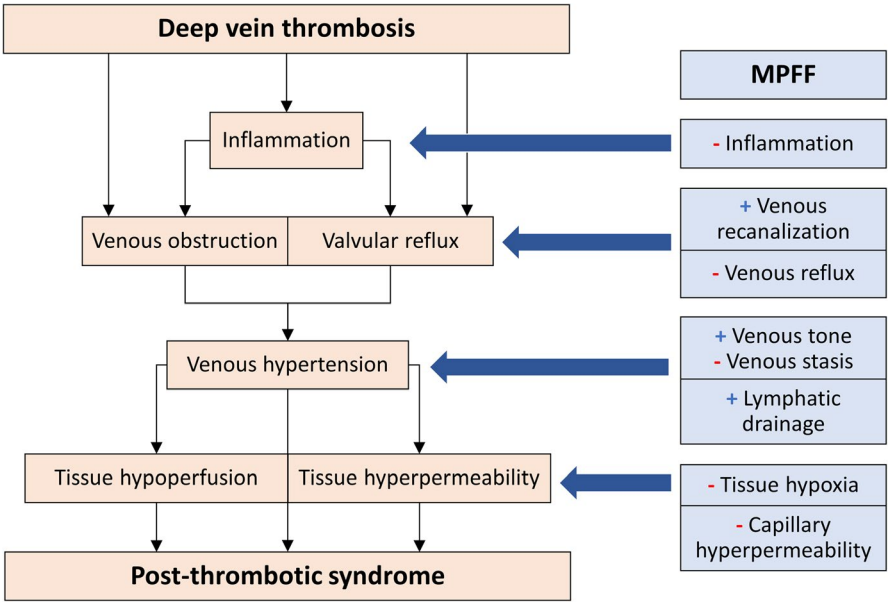

FIGURE 2 The pathophysiology of the postthrombotic syndrome (PTS) and the mechanism of action of micronized purified flavonoid fraction. The pathogenesis of PTS begins with venous obstruction and valvular reflux resulting from acute, then residual venous thrombosis. Inflammation can delay thrombus resolution, worsening both obstruction and reflux. As a consequence of persistent venous occlusion and reflux, venous hypertension results. Venous hypertension leads to tissue hypoperfusion and hyperpermeability, which together cause the clinical manifestations of PTS. MPFF improves venous recanalization following DVT and decreases venous reflux, acting on two key steps in the establishment of venous hypertension leading to PTS: venous obstruction and valvular reflux. MPFF has anti-inflammatory effects, which may prevent further obstruction and reflux resulting from inflammatory responses following deep vein thrombosis. MPFF increases venous tone, decreases venous stasis, and improves lymphatic circulation, further relieving venous hypertension. Finally, MPFF acts on the deleterious outcomes of venous hypertension: it decreases tissue hypoxia and capillary hyperpermeability. MPFF: micronized purified flavonoid fraction

remains.[50] The pathogenesis of PTS begins with venous obstruction and valvular reflux resulting from acute, then residual venous thrombosis (Figure 2). Inflammation can delay thrombus resolution, worsening both obstruction and reflux. As a consequence of persistent venous occlusion and reflux, venous hypertension results.[50] Venous hypertension leads to tissue hypoperfusion and hyperpermeability, which together cause the clinical manifestations of PTS: edema, hyperpigmentation, ulceration, heaviness, and pain. Studies support the relevance of the mechanism of action of MPFF in treating pathophysiological components of PTS, making it an interesting candidate for the potential management of PTS.

The pathophysiology of PTS and the relevance of the mechanism of action of MPFF are summarized in Figure 2. First, MPFF could favor venous recanalization after a DVT. In Zudin's[30] observational study of patients with DVT, those treated with MPFF in addition to conventional anticoagulant treatment achieved better and 15% to 20% faster rates of recanalization compared to patients not treated with MPFF.

Second, MPFF protects the venous wall from remodeling and reflux. In a model for venous hypertension induced by femoral arterial-venous fistula, male Wistar rats received MPFF 4 days before induction of the fistula, and venous reflux was measured by duplex ultrasound.[29] Rats who received MPFF had less venous reflux, valvular damage, and manifestations of leakage such as limb edema compared to their counterparts who did not receive the drug.[29] In a prospective observational study of female patients with CVI, MPFF decreased valvular reflux and vein diameter.[28]

Third, MPFF protects venous and capillary systems by inhibiting inflammatory processes. MPFF decreased granulocyte and macrophage venous valvular infiltration in the previously discussed rat model of venous hypertension.[29] In an observational study of patients with CVI, MPFF decreased expression of adhesion molecules by neutrophils and monocytes, inhibited the leukocyte-endothelium interaction, and decreased inflammatory mediator release.[51] In a RCT comparing MPFF to elastic compression stockings in patients with CVI, MPFF led to a decrease in white blood cell trapping around venous ulcers.[27]

Fourth, MPFF improves venous tone and reduces stasis. Double-blind placebo-controlled trials in patients with CVI showed that MPFF reduces venous hypertension by increasing venous tone and reducing venous capacitance, distensibility, and stasis.[23-26]

Fifth, MPFF improves lymphatic circulation, an important contributor to blood return, by increasing contractility of lymphatic capillaries.[22] In a prospective observational study of patients with severe CVI, MPFF improved lymphatic microangiopathy by increasing the number of functional lymphatic capillaries.[21]

Sixth, MPFF has a protective effect on the microcirculation with improvement of capillary hyperpermeability and resistance. In a model of increased microvascular permeability induced in male hamster cheek pouches by histamine, bradykinin, and leukotriene,[20] 10

days of MPFF decreased macromolecular permeability and reduced the number of leukocytes adhering to the venular endothelium.[20] In a double-blind RCT of patients with idiopathic cyclic edema syndrome, MPFF was associated with significant improvement in capillary hyperpermeability, significant reduction in the sensation of swelling, and significant weight loss.[19] A RCT of patients with abnormal capillary fragility treated with MPFF showed that MPFF improved capillary resistance and relieved symptoms of capillary fragility such as spontaneous ecchymosis and epistaxis.[18]

Finally, MPFF stimulates the microcirculation and prevents tissue hypoxia. This beneficial effect of MPFF was suggested by evidence of higher transcutaneous oximetry measurements in patients with CVI randomly assigned to MPFF when compared to placebo.[17] In an observational study of patients with CVI, MPFF improved venous microangiopathy and reduced capillary stasis by increasing red blood cell velocity in capillaries, compared to baseline.[16]

MPFF acts on the main steps of the pathophysiology leading to PTS (Figure 2). MPFF improves venous recanalization following DVT and decreases venous reflux, acting on two key steps in the establishment of venous hypertension leading to PTS: venous obstruction and valvular reflux. MPFF has anti-inflammatory effects, which may prevent further obstruction and reflux resulting from inflammatory responses following DVT. MPFF increases venous tone, decreases venous stasis, and improves lymphatic circulation, further relieving venous hypertension. Finally, MPFF acts on the deleterious outcomes of venous hypertension: It decreases tissue hypoxia and capillary hyperpermeability. Altogether, MPFF's mechanism of action makes it a relevant therapeutic agent to explore as therapy for PTS.

3.2.2 | Improvement of CVI signs and symptoms

A summary of the findings of efficacy, acceptability, and tolerability presented in systematic reviews, RCTs and observational studies are presented in Tables 1, 2, and 3, respectively. MPFF is a heterogeneous drug, and its manufacturing process varies. As a result, differences in the composition of the drug used may have led to variability of reported results. When available, we described the specific brand name and dose of MPFF used in studies (Tables 1-3). Among the studies we identified, 15 observational studies[28,64] totaling 8303 patients and 21 RCTs[23,24,80] totaling 4817 patients showed a benefit of MPFF in improving the clinical manifestations of CVI, while 1 observational study[81] and 2 RCTs [82,83] showed no improvement of CVI signs and symptoms with MPFF compared to no MPFF. Eight observational studies[49,54,55,56,58,59,61,64] totaling 6873 patients and 9 RCTs[44,69,71,73,75,77,78,79,83] totaling 2222 patients showed a benefit of MPFF in improving sensory and functional symptoms of CVI, such as leg pain, paresthesia, and feeling of swelling. One observational study[81] and 2 RCTs [82] (including the unpublished Saveliev RCT) showed no significant differences in pain improvement with MPFF compared to no treatment with MPFF. Three RCTs[68-70] totaling 1633 patients showed that there was no difference in symptom improvement among patients who took MPFF 1000 mg once daily compared to 500 mg twice daily and that both regimens improved clinical manifestations of CVI equally compared to baseline.

One RCT[72] found that MPFF was superior to aminaphthone and a coumarin-toxerutin combination in terms of leg volume reduction. Two RCTs,[45,46] which are similar and may represent duplicate publication, found MPFF to be superior to diosmin in improving CVI clinical manifestations. The RCTs compared MPFF, composed of 90% diosmin and 10% hesperidin, with diosmin alone. Although sparse, the limited evidence suggests that the addition of hesperidin, the purification of such a flavonoid fraction, the micronization, or any other processing step to obtain MPFF may confer additional pharmacologic benefit over diosmin alone. This must be explored in further studies, as one RCT reported that diosmin and MPFF had similar effectiveness.[84] One RCT found MPFF to be similar to pycnogenol in improving venous ulcer healing and limb circumference.[66] One RCT[85] found rutoside to be superior and another found pycnogenol[86] to be superior to MPFF in improving signs and symptoms of CVI.

Six systematic reviews[31,87,88,89,90,91] concluded that MPFF showed benefit in improving signs and symptoms of CVI. Two systematic reviews suggested grade A evidence for the use of MPFF in CVI.[92,93] One systematic review concluded that MPFF's effect on signs and symptoms of CVI were no different from placebo.[94] Five systematic reviews[94-98] reported uncertain benefit or that further higher-quality evidence was needed to support the use of MPFF in CVI.

3.2.3 | Improvement in venous ulcer healing

Seven RCTs[27,65,66,75,76,77] (including the unpublished Saveliev RCT) totaling 689 patients showed a benefit of MPFF in CVI ulcer healing. One RCT[77] showed no difference with MPFF compared to placebo in healing ulcers >10 cm. Four systematic reviews[31,89,90,97] reported improvement of ulcer healing with MPFF. One systematic review[97] pointed out flaws in the current evidence of MPFF use in CVI ulcers, including inadequate reporting in RCTs and potential publication bias. One systematic review[98] reported that good-quality evidence is lacking to show whether MPFF combined with compression therapy was superior to compression alone in improving ulcer healing.

3.2.4 | Improvement in objective venous measures

Studies reported on the effect of MPFF on objective venous measures related to CVI, including limb perimeter, plethysmographic parameters, elastic modulus, capillary permeability, venous capacity, venous outflow, venous tone, venous distensibility, venous emptying time, venous reflux, and other venous hemodynamic measures. Seven observational studies[28,54,55,57,60,61,63] totaling 288 patients reported improvement of objective venous measures with MPFF, while one observational study[61] reported no significant change in venous filling index, ejection fraction, residual volume fraction, or

venous hemodynamics despite clinical improvement of CVI with MPFF.

Ten RCTs[23,24,25,26,27,99] totaling 690 patients (excluding two RCTs[25,99] where the number of patients was unavailable) reported a benefit of MPFF in improving objective venous measures related to CVI. Two RCTs,[45,46] which may be duplicate publications, reported that MPFF was superior to diosmin in improving objective venous measures. One RCT[72] showed that leg volume reductions of ≥100 mL were more frequent with MPFF when compared to aminaphthone, coumarin in combination with troxerutin, and placebo. One RCT[83] showed no significant improvement of foot-volumetric or ultrasonographic parameters compared to placebo. One RCT[86] found pycnogenol to be superior, and one RCT[85] found rutoside to be superior to MPFF in improving objective venous measures of CVI.

Three systematic reviews[88,91,92] reported a benefit of MPFF in improving objective venous measures in CVI, and one systematic review[92] found MPFF to be superior to ruscus extract, hydroxyethylrutoside, diosmin, and placebo in reducing ankle circumference.

3.2.5 | Improvement in QOL

Eight observational studies[28,49,52,53,54,56,100,101] totaling 9683 patients (excluding one observational study[100]) and four RCTs[67,68,71,74] totaling 2687 patients showed improvement in QOL with MPFF in CVI. One observational study[81] and two RCTs[73,82] showed no significant impact of MPFF on QOL. One RCT[37] found rutoside to be superior, and another[72] found aminaphthone to be superior for QOL improvement in CVI when compared to MPFF. One systematic review[89] reported improved QOL with MPFF, while another systematic review[88] concluded that the evidence on the effect of MPFF on QOL in patients with CVI was weak.

In terms of the use of validated QOL assessment tools, six RCTs[67,68,71,73,74,82] and five observational studies[28,49,52,54,101] used the Chronic Venous Insufficiency Questionnaire, one RCT[37] used the Venous Quality of Life Score (Ve-QOL), one observational study used the Short-Form 12,[81] and one observational study[56] used the Global Index Score. The remaining studies either used an adapted QOL questionnaire[72] or did not report the method of measurement.[53,100]

3.2.6 | Improvement when MPFF was used with ancillary interventions

Two observational studies[52,101] found MPFF to be effective in improving symptoms and QOL in patients with CVI when combined with sclerotherapy. One observational study[30] found MPFF to be effective in decreasing CVI manifestations when added to angiotropic metabolic infusion therapy, anticoagulation, and elastic compression. Two RCTs[73,74] found that MPFF reduced signs and symptoms of CVI in patients undergoing venous surgery. One systematic review[90] concluded that MPFF could be used in combination with sclerotherapy, surgery, or compression therapy and could be considered as an alternative to surgery in CVI. Another systematic review[87] found promising results regarding the use of MPFF as an adjunct to sclerotherapy and surgical and endovenous therapy, but calls for the need for further placebo-controlled studies to confirm the benefits.

3.2.7 | Use of MPFF in patients with PTS

Three observational studies[53,55,63] totaling 300 patients reported that MPFF improved clinical manifestations or objective venous measures in patients with PTS. One observational study[30] reported faster venous recanalization, improved objective venous measures, and decreased clinical manifestations with MPFF combination therapy in patients with DVT compared to angiotropic metabolic infusion, anticoagulation, and elastic compression therapies without MPFF. Two RCTs[23,99] on MPFF showed improvement of objective venous measures in patients with PTS. One RCT[102] found that MPFF combined with rivaroxaban in femoropopliteal DVT improved Villalta score and Venous Clinical Severity Score and decreased the incidence of PTS in patients with DVT compared to rivaroxaban alone. A single RCT reported improvement of PTS symptoms with MPFF treatment compared to conservative treatment alone.[65]

3.3 | Patient acceptability

Six observational studies[49,52,56,59,64,101] and three RCTs[24,75,78] described good patient acceptability of MPFF, with patients reporting good to excellent effectiveness and satisfaction with MPFF. Two RCTs,[45,46] which are potential duplicate publications, found that more patients were satisfied with MPFF than with diosmin. Nonetheless, none of the systematic reviews we identified commented on patient acceptability, and very few RCTs and observational studies described patient opinion and perspectives on MPFF. Thus, when it comes to the description of patient acceptability, reporting bias cannot be excluded in individual observational studies and RCTs.

3.4 | Adverse effects

One systematic review found MPFF to be well tolerated,[90] and three systematic reviews[13,89,90] found MPFF's tolerability to be similar to that of placebo. One observational study[62] and four RCTs[24,46,84,86] reported that MPFF was well tolerated. One observational study[59] and three RCTs[71,75,85] reported good compliance with MPFF. Five observational studies[52,53,59,61,81] and two RCTs[85,86] reported no side effects with MPFF use. Two RCTs[71,78] reported fewer adverse events with MPFF compared to placebo, and one RCT[77] reported similar tolerability of MPFF and placebo. One systematic review[97]

and one RCT[83] found MPFF to have more side effects than placebo. One observational study[56] and six RCTs[68,69,73,78,83,84] reported mild or transient adverse effects with subsequent resolution. One RCT[71] reported serious adverse events, including erysipelas and hypertensive crisis, and four RCTs[68,71,78,83] reported adverse effects leading to treatment interruption, including nausea and hypotension.

In terms of specific adverse effects of MPFF, gastrointestinal side effects were the most common, as reported by two observational studies,[56,64] nine RCTs,[45,46,68,69,71,72,73,78,102] and six systematic reviews.[13,31,90,94,97,98] Other reported adverse effects included autonomic effects (one RCT[78] and one systematic review[90]), hypertension (the unpublished Saveliev RCT, one published RCT,[71] and one systematic review[97]), mucocutaneous side effects (one observational trial,[56] three RCTs,[69,71,84] and one systematic review[97]), insomnia (one RCT[78]), headaches (three RCTs[68,71,78]), urinary morbidity (one RCT[72]), sinopulmonary morbidity (one RCT[71]), bleeding (one observational study[101] and one RCT[102]), weight loss (the unpublished Saveliev RCT), postprocedural pain and inflammation in patients who underwent sclerotherapy (one observational study[101]) and depression (one RCT[71]).

TABLE 4 Overview of the Micronized Purified Flavonoid Fraction for the Treatment of Postthrombotic Syndrome (MUFFIN-PTS) trial

Micronized Purified Flavonoid Fraction for the Treatment of Post-Thrombotic Syndrome (MUFFIN-PTS) trial (NCT03833024)
Study design • Double-blind multicenter RCT
Objective • To describe the clinical effectiveness, the effect on QOL and the safety of MPFF in the treatment of PTS
Participant characteristics • Established PTS with a Villalta scale score >4 • ≥2 of the following manifestations of PTS daily: leg heaviness, cramps, pain, or edema
Study groups • 6-months regimen of MPFF (Venixxa) 500 mg oral twice daily, along with conventional PTS treatment • Placebo, along with conventional PTS treatment
Primary outcome • Proportion of patients showing improvement in Villalta score at 6 months
Secondary outcomes • Villalta scores and each individual component of the score • Proportion of patients with worsening Villalta score • Venous disease–specific QOL scores • PTS severity and PTS progression • Compliance • Patient satisfaction • Venous thromboembolism, death, and other serious adverse effects

Abbreviations: months: month(s); MPFF: micronized purified flavonoid fraction; PTS: postthrombotic syndrome; QOL: quality of life; RCT: randomized controlled trial.

4 | DISCUSSION

4.1 | MPFF as a potential therapeutic agent for PTS

As presented in this review, MPFF is an excellent candidate for further study as a therapeutic agent to treat PTS because the mechanism of action of MPFF is directly relevant to its pathophysiology, the clinical efficacy of MPFF in the treatment of CVI is promising, and high-quality studies directly investigating MPFF's clinical efficacy in PTS are lacking.

First, our review demonstrates that MPFF's mechanism of action is directly relevant to each stage of the PTS pathophysiology (Figure 2). MPFF helps relieve venous obstruction by promoting venous recanalization following DVT and decreases venous reflux. Its anti-inflammatory effects could help prevent further worsening of venous obstruction and reflux resulting from DVT-related inflammatory responses. By improving venous tone and stasis and promoting lymphatic drainage, MPFF can help relieve venous hypertension. Finally, MPFF can improve capillary hyperpermeability and tissue hypoxia, sequelae of venous hypertension following DVT. Thus, by the various elements of its mechanism of action, MPFF has potential as a therapeutic agent to treat PTS.

Second, MPFF has already shown promise in the treatment of clinical manifestations of CVI that are similar to that of PTS and include edema, hyperpigmentation, ulceration, leg cramps, limb heaviness, and pain. PTS and primary CVI also share objectifiable venous abnormalities such as abnormal venous tone, venous capacity, capillary permeability, and venous reflux. Common findings among studies of MPFF to treat CVI include improvement of signs and symptoms of CVI, objective venous measures, and QOL, leading many authors to recommend MPFF for the treatment of CVI.[90,92,93] However, uncertainty around such benefit has led others to call for higher-quality evidence.[94-98] The available evidence suggests that MPFF treatment is associated with good patient acceptability, but the level of evidence remains low. In terms of adverse effects, MPFF seems to be generally well tolerated.[13,89,90] Taken together, MPFF shows promise in its clinical efficacy, acceptability, and tolerability for the treatment of CVI, which supports its potential candidacy as a therapeutic agent for the treatment of PTS.

Third, although MPFF's mechanism of action and efficacy in CVI support its potential use in PTS, the literature directly investigating its clinical efficacy in PTS is sparse. Thus, there is a need for well-designed clinical trials studying MPFF, specifically in patients with PTS. While observational studies[30,53,55,63] described improvement in clinical manifestations and objective venous measures with the use of MPFF in patients with PTS, only a single RCT[65] used clinical endpoints to assess the use of MPFF as pharmacologic monotherapy in PTS.

Taken together, the relevance of MPFF's mechanism of action in the pathophysiology of PTS, the clinical efficacy of MPFF in CVI and the lack of RCTs rigorously assessing MPFF's clinical efficacy in PTS calls for a need for further research investigating the use of MPFF

as therapy in PTS, namely, in well-designed double-blind RCTs with clinical endpoints.

4.2 | Limitations of the evidence

Weaknesses in the quality of studies reviewed contributes to the suboptimal strength of the current evidence supporting the use of MPFF in CVI. First, studies potentially suffered from publication bias and poor methodology in reporting, randomization, allocation concealment, and blinding,[97] limiting the validity of results.[95,103] Second, many articles were duplicate publications, which potentially decreases the validity of published reviews, overestimating the magnitude of results presented. Third, several publications report funding from or author affiliation with the manufacturers of venoactive drugs or were published in journals overseen by pharmaceutical companies. This may have put certain studies at higher risk of bias stemming from potential conflicts of interest. Finally, language bias was apparent, with several studies identified published only in Russian, for example, which may have led to selection bias in reviews.

4.3 | Limitations of the current review

Only the abstract was available for 1 of 14 systematic reviews,[91] for 8 of 33 RCTs,[23,41,46,47,65,67,69,70,82] and for 7 of 19 observational studies,[30,53,57,60,62,64,100] with associated duplicate publications cited. Neither the abstract nor the full manuscript were available for 6 RCTs[25,33,44,79,80,99] (including the unpublished Saveliev RCT) and 1 observational study,[63] with their respective duplicate publications cited. This limits the current review in several ways. First, the analysis of such studies often depended on the reporting of review articles that included them. The review articles themselves carry intrinsic methodological limitations and errata could have been carried over into the present publication. Second, a detailed perusal of the study design, methodology, patient population, interventions, and outcomes were at times not possible, which limited our ability to assess the quality of many studies. Third, our literature review yielded unpublished studies included in other reviews,[97,104] which did not describe them in detail. Their full manuscripts were unavailable. One unpublished RCT by Saveliev was described as reporting partly negative findings. Such studies may have contributed to publication bias favoring the efficacy of MPFF in CVI management.[97]

5 | CONCLUSION AND NEXT STEPS

To the best of our knowledge, no systematic reviews have focused on the use of MPFF in PTS. In the current review, we provided rationale that MPFF should be evaluated as a new therapeutic agent for PTS. To accomplish this, we described the relevance of the mechanism of action of MPFF in the pathophysiology of PTS. As PTS manifests as CVI following DVT, we reviewed in a narrative fashion systematic reviews, RCTs, and observational studies investigating the use of MPFF in CVI and highlighted the current lack of clinical evidence supporting the use of MPFF in PTS. We explained that MPFF shows promise in terms of clinical efficacy, patient acceptability, and tolerability in CVI and that its therapeutic potential in patients with PTS should therefore be investigated in high-quality RCTs. For this purpose, we are conducting the Micronized Purified Flavonoid Fraction for the Treatment of Post-Thrombotic Syndrome (MUFFIN-PTS) trial (ClinicalTrials.gov identifier: NCT03833024), a double-blind multicenter RCT that will compare the clinical efficacy of a 6-month regimen of MPFF (Venixxa) 500 mg oral twice daily to that of placebo in conjunction with conventional PTS treatment in PTS patients (Table 4).

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RELATIONSHIP DISCLOSURE

J-PG received consulting fees from Servier, outside of this review article. All other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

KXL and GD performed the literature review and drafted the manuscript, tables, and Figure 1. KXL led the manuscript revisions and created Figure 2. J-PG and SRK conceived of the project and guided the literature review, manuscript, tables, and figures. All authors revised and approved the final version of the manuscript.

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