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Recommendations for the medical management of chronic venous disease: The role of Micronized Purified Flavanoid Fraction (MPFF)

Recommendations from the Working Group in Chronic Venous Disease (CVD) 2016

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Abstract

Scope: A systematic review of the clinical literature concerning medical management of chronic venous disease with the venoactive therapy Micronized Purified Flavonoid Fraction was conducted in addition to an investigation of the hemodynamics and mechanism of chronic venous disease.

Methods: The systematic review of the literature focused on the use of Micronized Purified Flavonoid Fraction (diosmin) which has recently become available in the US, in the management of chronic venous disease. The primary goal was to assess the level of evidence of the role of Micronized Purified Flavonoid Fraction in the healing of ulcers, and secondarily on the improvement of the symptoms of chronic venous disease such as edema. An initial search of Medline, Cochrane Database for Systematic Reviews and Google Scholar databases was conducted. The references of articles obtained in the primary search, including a Cochrane review of phlebotonics for venous insufficiency, were reviewed for additional studies. Studies were included if patients had a diagnosis of chronic venous disease documented with Doppler and Impedance Plethysmography. Studies excluded were those that had patients with arterial insufficiency (Ankle Brachial Index $< .6$), comorbidity of diabetes, obesity, rheumatological diseases, or if other causes of edema were present (congestive heart failure, renal, hepatic or lymphatic cause), or if the patient population had recent surgery or deep vein thrombosis, or had been using diuretics (in studies of edema). Other elements of the study design were to note specifically the type of compression therapy used in conjunction with Micronized Purified Flavonoid Fraction.

Results: The literature review yielded 250 abstracts, 65 of which met criteria for further review and 10 papers were selected for consideration in the systematic review.

Conclusion: In summary, the general level of evidence supports the recommendation that the use of medical therapy with Micronized Purified Flavonoid Fraction has beneficial outcomes without serious adverse events. In the United States, diosmiplex is the only available prescription formulation of Micronized Purified Flavonoid Fraction. It is derived from the rinds of oranges and is categorized as a medical food and not as a drug; and may be a particularly attractive therapy for many chronic venous disease patients because of its favorable safety profile. The Working Group for chronic venous disease concurs with previous guidance by the International European Society for Vascular Surgery in 2015 which recommended the use of Micronized Purified Flavonoid Fraction for the healing of venous ulcers, alone and adjunctive to compression therapy, and for the reduction in symptoms of chronic venous disease such as edema.

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Introduction and background

Chronic venous disease (CVD) is the term used to describe signs and symptoms of any pathology associated with the venous system (CEAP guidelines C1–C6). The term "chronic venous insufficiency" (CVI) is used to characterize the findings associated with advanced venous pathology (C4–C6).[1]

The use of "venoactive drugs" as part of the medical management of CVD has been explored in previous reviews (2009) and guidelines (2008 and 2009), especially flavonoids such as Micronized Purified Flavonoid Fraction (MPFF).[2–4] Only recently has a standardized formulation MPFF been available in the United States (Vasculera®—Primus Pharmaceuticals, Inc.). Most physicians have limited knowledge of MPFF in regard to mechanism of action and potential use as adjunct therapy for the management of CVD.

A panel of leading experts in the field of venous disease participated in numerous meetings and discussions (The Working Group in CVD) to investigate the potential benefits of MPFF in the treatment CVD, since it has recently become available by prescription in the US. The participating members were Ronald Bush, MD, FACS, (Chair), Anthony Comerota, MD, FACS, Mark Meissner, MD, FACS, and Joseph D. Raffetto, MD, FACS.

In order to establish recommendations and guidance on the usage of MPFF in the management of patients with CVD, a systematic review of the literature was conducted focusing on the use of MPFF across all categories of CVD. The following summary and comprehensive literature review are the findings of the Working Group in CVD in regards to the use of MPFF in venous disease.

Part 1: Introduction to chronic venous disease

One of the most commonly reported chronic medical conditions is varicose veins and CVD. Prevalence is higher in Western developed countries, and increases with age. Therefore, with the aging of the US population, the prevalence of CVD can be expected to increase over the coming years. In the US, over 25 million people have some type of "CVD", with more than 6 million having advanced disease or "CVI".[5] More recent epidemiologic studies have reported prevalence as high as 10–35% of US adult population and 60% worldwide, according to the Vein Consult Program, which was a prospective survey of global venous disease across geographies and CEAP classifications.[6]

The terminology used to refer to the long term presence of abnormalities of the venous system includes both "CVD" and "CVI". As defined by the Vein Term Meeting in 2008 "CVD" is the preferred term that captures the full range of the venous system's abnormal signs and/or symptoms of long duration, ranging from CEAP classifications of 0 to 6.[1] "Chronic venous insufficiency" is used to refer to more advanced venous disease, defined as CEAP Class 3 (moderate to severe edema) to CEAP Class 6 (active venous ulcer). About 20% of people with CVD will have leg ulcers, while overall prevalence of ulcers both active and healed is less than 1% of the adult population.[7]

The higher prevalence of CVI or more advanced disease varies by gender and by age, with a higher prevalence, as noted in Edinburgh Vein, Framingham, Vein Consult Program, and San Diego studies, in older adults (age 54–65). The Vein Consult Program showed a difference in prevalence by gender, based on CEAP status, with a higher prevalence of CEAP 0–3 in women and equal prevalence between men and women in CEAP 4–6, with prevalence increasing with advancing age.[6] The RELIEF study (Reflux assEssment and quality of lIfe improvEment with micronized Flavonoids) showed a correlation between more advanced disease or CVI and the presence of reflux. The prevalence of reflux in the RELIEF study varied between men and women, with 9.6% of women with reflux and 8.7% of men with more advanced disease.[8]

Part 2: Pathophysiology of CVD

The rationale for the use of flavonoids like MPFF in the management of CVD is well grounded in the understanding of the pathophysiology of CVD. The process for the development and progression of CVD has two principal factors: the mechanical effects of ambulatory venous hypertension (increased venous pressure) and the cellular and biochemical molecular effects caused by increased venous pressure.

Venous hypertension: A key pathophysiological mechanism of CVD

When venous pressure increases, return of the blood is impaired. A normal functioning venous system depends on the ability of the muscle pumps to channel blood

through intact valves supported by healthy walls. In the erect position, the muscle pump must pump blood against gravity, and valves make sure that the blood flows only in the cephalad direction. Immediately after walking, pressure in the veins of the legs is low, because they have already been emptied by the muscular pump action. Relaxation of the muscle pump allows the blood to flow back in from the surrounding tissue. Standing for a long time can lead to the distention of the veins, which allows the valves to open and distal pressure to increase. Contraction of the muscle pump will again empty the veins and reduce venous pressure. Venous hypertension, an abnormal increase in venous pressure, results from two processes: valvular dysfunction or incompetence and muscle pump dysfunction. Dysfunction of valves in the superficial venous system causes reflux, and valvular dysfunction in the superficial or deep system can lead to CVD. Dysfunction of the deep valves has been shown to increase the rate of progression in CVD to ulceration.[9,10]

Whether venous hypertension (or low shear from reflux, obstruction, and calf muscle pump dysfunction) is the result or part of the cause of complex cellular and microvascular reactions may depend on whether it is primary or secondary, but the inflammatory molecules produced by these reactions have been shown to be responsible for damage to the vein endothelium and lymphatic channel, which in turn leads to skin damage, ulcer and edema (Figure 1).[9,10]

Predisposition to CVD based on environmental or genetic factors

Environmental factors and genetic factors, such as weight, amount of standing time, family history of CVD and comorbidities play an initial role in promoting shear stress on the vein walls and valves (Table 1). The relative impact of specific environmental risk factors has been demonstrated across multiple large studies.[9,10,12–14] In a survey which used CEAP classification to categorize responses from more than 40,000 patients in Poland, men and women who spent a longer time standing were more likely to have more advanced CVI.[14] Those in the CVI group were also more likely to

Table 1. Genetic and environmental risk factors for CVD.[12–18]

Family history	Long periods of standing or sitting
Obesity	Constipation
Older age	Female Gender
Pregnancy	History of deep vein thrombosis (DVT) or previous leg injury

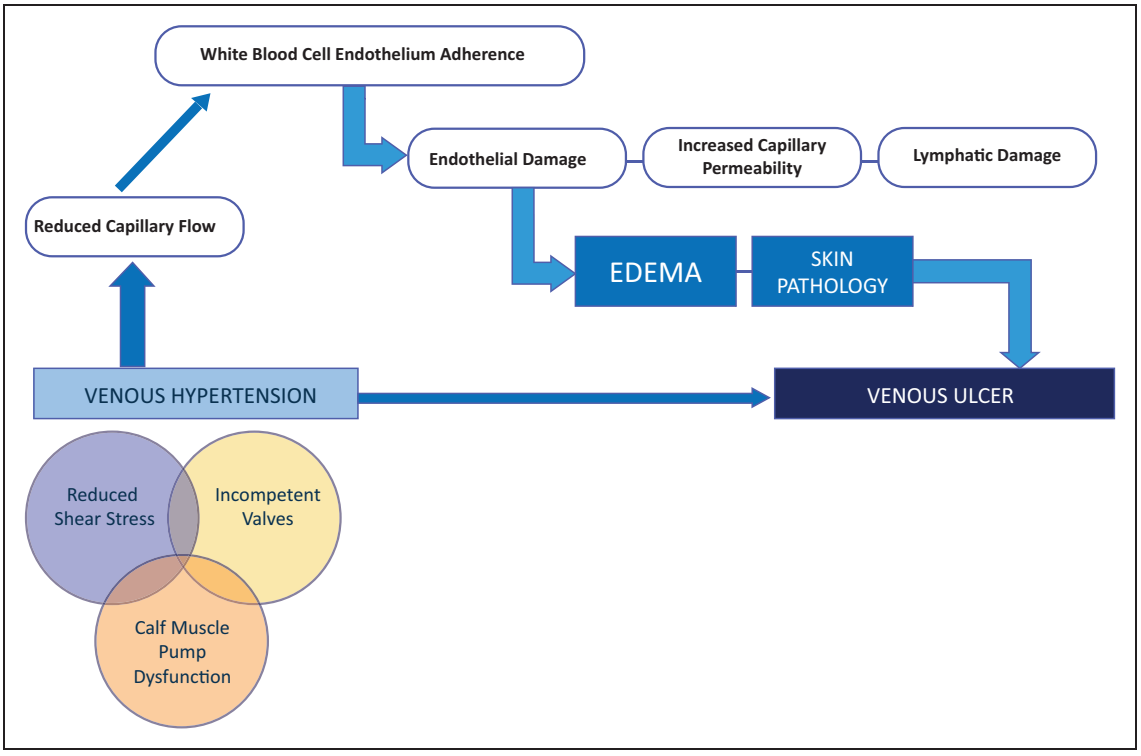

Figure 1. Contributing factors to skin pathology and edema. Adapted from Dabiri et al. *International Wound Journal* 2015.[11]

be obese and have a sedentary lifestyle compared to those in the non-CVI group. In the Edinburgh Vein Study,[15] lack of fiber and constipation were associated with varicose veins but only in men, while in the Polish study, greater frequency of constipation was more prevalent only in women in the CVI group.[14]

In both the San Diego Study and the Bonn Study,[16,17] older age emerged as a most important risk factor for varicose veins and CVI. In several European studies, mildly symptomatic CVD was more frequent in men and C2–C3 more frequent in women, but C4–C6 did not differ between men and women.[14,15,17,18] A body mass index (BMI) of >30 was correlated to increased risk for CVI.[14–17]

Risk factors such as family history and long periods of standing create a predisposition for the cellular and molecular reactions that ultimately result in the skin pathology and edema of CVD.[12,15–18] There are several historical studies that have demonstrated the cascade of interactions that correlate to increased venous pressure and capillary perfusion: white cell adhesion and migration, activation of leukocytes in the endothelium, capillary permeability, increased vascular proliferation and impaired lymphatic flow.[9,19–21]

Leukocyte trapping and skin pathology

In CVD patients, circulating leukocytes show greater levels of activation. In a study of venous hypertension induced in rats (Table 2),[19] venous hypertension was associated with increased myeloperoxidase (MPO) activity, which suggested that leukocytes may be mediators of skin pathology.

These data demonstrated that venous hypertension alone increases leukocyte tissue concentration. This supports the ''leukocyte trapping theory'' in venous hypertension, that the pressure difference is reduced between the arteriolar and venular ends of the capillary circulation, which reduces the shear force on the leukocytes in the endothelium, and makes them more likely to adhere. Leukocyte adhesion causes the endothelial cells to express cell adhesion molecules (CAMs), which promote further leukocyte adhesion and activation. Once leukocytes have been activated, they degranulate and release toxins that damage the surrounding tissues. These leukocytes may also migrate through the vessel wall into the extravascular space.

Table 2. MPO activity in rats after induced venous hypertension.[19]

	Sham (Negative Pressure)	Ligated (Increased Pressure)	*p*-value
Pressure (mmHg)	9.9	26.2	<0.05
MPO activity (leukocyte trapping)	0.77	4.77	0.05

Venous hypertension causes leukocyte adhesion which initiates cellular infiltration and protease production (increased matrix metalloproteinases [MMPs], decreased TIMP, increased TGFB, Figure 2).[9,10] In a human study designed to investigate endothelial activity in normal versus CVD patients with induced venous hypertension, this activity was demonstrated through tracking the presence of *L-selectin*, a WBC adhesion molecule which increases when WBC are activated and *CD-11b*, an integrin that allows adhesion to the endothelium, which decreases with WBC adhesion.[9]

Blood samples were taken from foot veins in 25 normal patients, 30 with CVD (15 with varicose veins and skin changes, 15 with varicose veins without skin changes) (Table 3). Leukocyte trapping was confirmed by calculating the white cell to red cell ratio. In both normal and the patients with CVD with venous hypertension, the white cell to red cell ratio fell, as evidence of leukocyte trapping and ICAM-1, VCAM-1 and ELAM-1 rose. Basal levels of all three adhesion molecules were significantly higher in the CVD patients compared to the normal controls.[9] This signifies chronic stimulation of the endothelium of CVD patients and therefore increased likelihood of leukocyte adhesion.

This study's finding that the concentration of soluble L-selectin rose during venous hypertension, was considered an indication that endothelial leukocyte binding had occurred. The plasma levels of ELAM-1 (endothelial leukocyte adhesion molecule-1), ICAM-1 (intercellular adhesion molecule-1), VCAM-1 (vascular cell adhesion molecule-1), and von Willebrand factor (vWf) with the venous hypertension were significantly higher in the CVD group with skin changes vs. the group without skin changes. Patients with lipodermatic skin (LDS) changes exhibited increased VCAM-1, which is a counterligand for receptors expressed by monocytes and lymphocytes and could signify that these cells may be more important in CVD skin changes.

Increased capillary permeability

Reduced fluid shear stress and the presence of inflammatory agonists enhance entrapment of leukocytes in capillaries. The entrapped leukocytes completely fill the vessel lumen, and can obstruct the capillaries.[10] Entrapment of neutrophilic leukocytes in the microcirculation reduces local capillary perfusion and trigger oxygen-free radical formation and the delivery of proteolytic enzymes, which can enhance tissue degradation (Figure 4).[12]

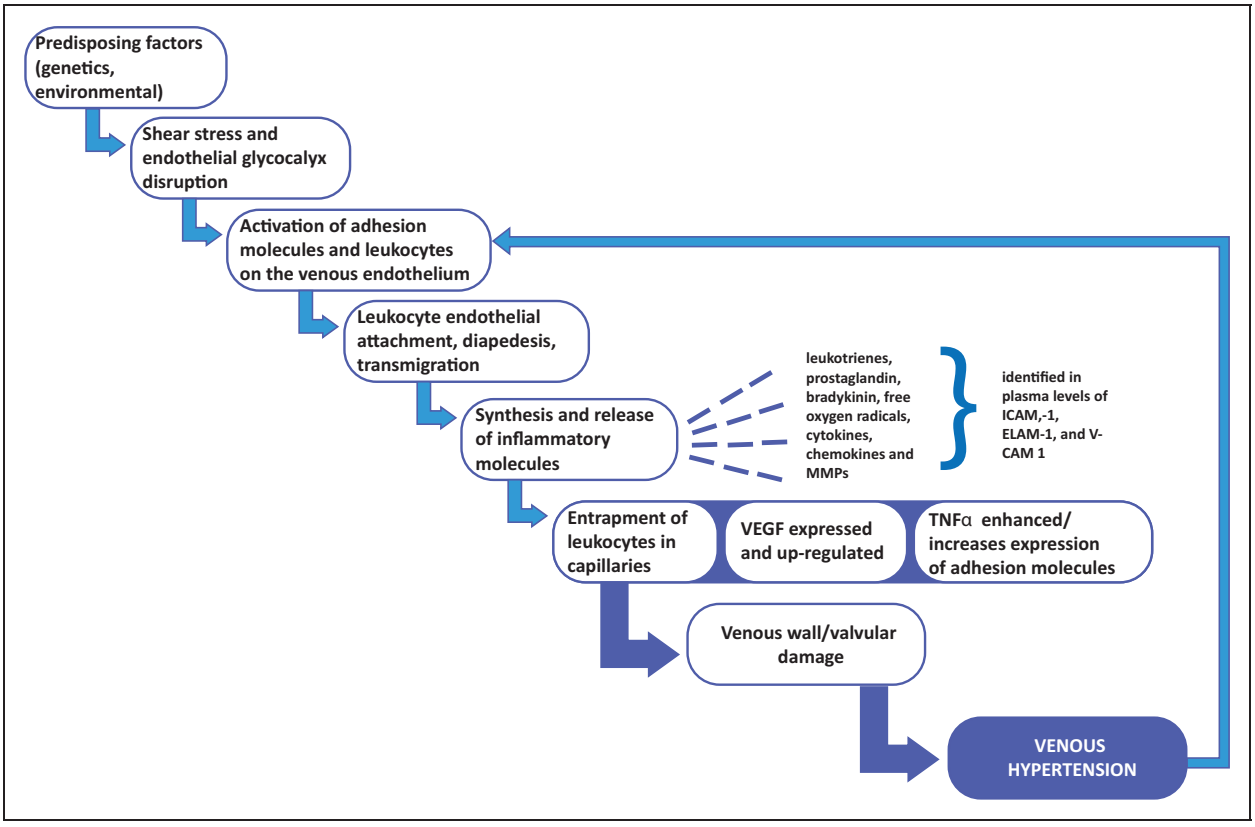

Figure 2. Cellular molecular pathway of venous hypertension.
Adapted from Saharay et al. (1998)[9] and Bergan and Shortell (2006).[10]
Note: Primary and secondary venous incompetence are distinctly different. Primary venous incompetence can cause the activation of adhesion molecules and leukocytes on the venous endothelium, while secondary (post-thrombotic) venous disease is likely to be the result of lumen obstruction and subsequent direct valve damage.

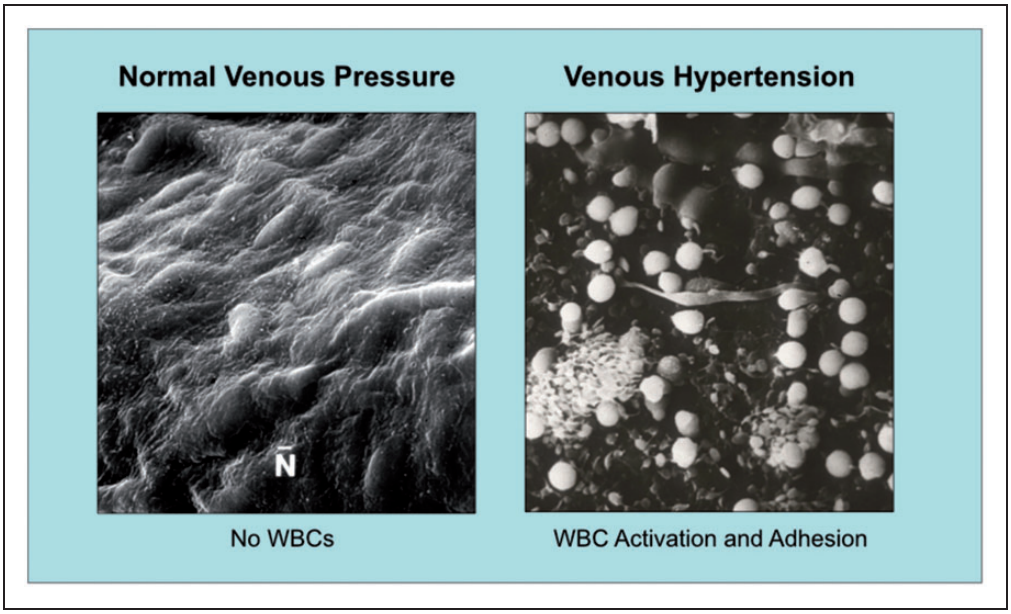

Figure 3. WBC adhesion with venous hypertension.
Original research, unpublished, reprinted with permission of the author/researcher, Anthony Comerota, MD.

The impact of a change in blood pressure and fluid shear stress on microvascular inflammatory reaction can be seen in less than an hour in both the endothelium and on circulating cells. The mechanical stimulus that instigates an inflammatory reaction is fluid shear stress.[12]

The connection between inflammation and skin changes is thought to be through MMPs and serine proteinases. MMP levels are found to be significantly higher in fluid of chronic wounds compared to acute wounds, and are reduced during wound healing.[9,10]

Tumor necrosis factor-α (TNF-α), whose expression is enhanced in many inflammatory reactions, stimulates the expression of membrane adhesion molecules, the synthesis and release of other cytokines, and the chemotactic migration of neutrophils and macrophages. Expression of TNF-α is upregulated in patients with venous ulcers, and reduced levels of TNF-α accompanies healing of the ulcer.[2,10]

In recent years, there has been growing recognition of the angiogenetic factors that stimulate the growth of blood vessels, such as vascular endothelial growth factor (VEGF), which have been studied in the skin samples of patients with and without CVD.[12]

Vascular proliferation is noted in patients with CVD. VEGF, is expressed and is up-regulated during inflammatory reactions. Patients with CVI and skin changes (CEAP 4–6) have been shown to have higher levels of VEGF than those in CEAP Classes 2 and 3 and normal.[10,12]

Table 3. Changes from baseline for L-selectin and CD-11b found in blood samples of CVD patients.[9]

Baseline	Standing (30 min)	*P*-value
L-selectin (WBC activation)	+20%	0.02
CD-11b[a] (endothelial adhesion)	−29%	0.02

[a]CD-11b is considered a marker of neutrophil activation.

Part 3: Effect of MPFF on basic mechanisms of CVD

The cascades of inflammatory molecules that are released by leukocyte trapping include leukotrienes, prostaglandins, bradykinins, oxygen free radicals and cytokines. Cytokines maintain the inflammatory state, and the result is an upregulation of inflammatory factors like TNF-α and VEGF, which are correlated to capillary permeability, impaired lymphatic flow, and vascular proliferation. Therefore, it should be possible to reduce progression of venous disease by a reduction of leukocyte activation and infiltration through the use of compression and anti-inflammatory medication.[2,10,12]

Reduction in WBC adhesion and leukocyte migration with MPFF

Animal models have been used to replicate CVD in humans in order to establish the role of venoactive therapy on leukocyte migration and adhesion as well as protein leakage. In one study (Table 4),[20] rats with 60

Table 4. Leukocyte migration and adhesion in post-ischemia rat cremasteric muscle.[20]

	Control (non-ischemic)	Vehicle (I/R)[a]	MPFF 500 (I/R)[a]
WBC adhesion (#/UM venule)	7	9	17
WBC emigration (#/FIELD)	2	16	6
Microvascular protein leak (%)	25	75	51

[a]I/R = ischemic/reperfusion.

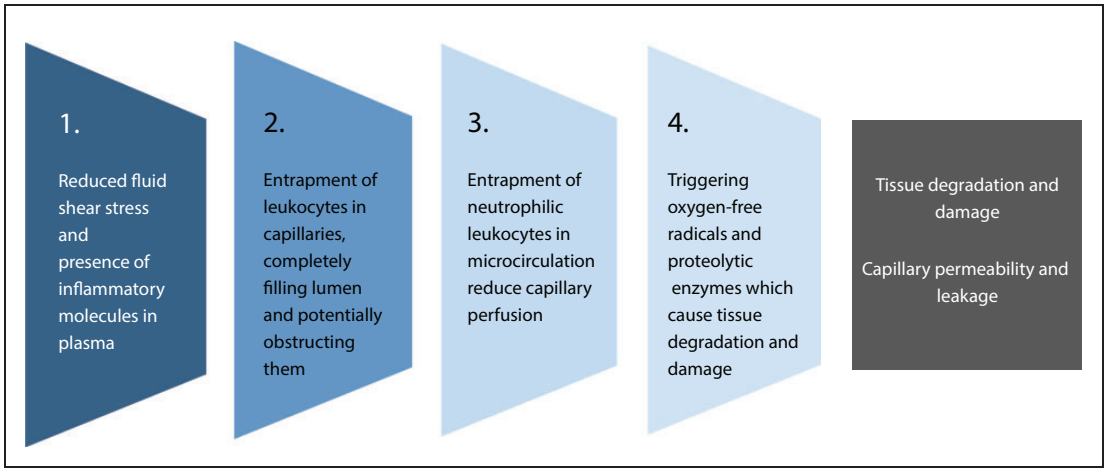

Figure 4. Process of leukocyte trapping to tissue degradation.

minutes of ischemia, and 60 minutes following of reperfusion were given either MPFF 500 mg for 2 days or a placebo, with tissue evaluations made through intravital microscope. The ischemia/reperfusion resulted in an increased number of adherent and migrating leukocytes, which was greatly reduced in the rats treated with the MPFF.

There was significant increase in adherent and migrated leukocytes in the presence of ischemia/reperfusion. It is thought that leukocyte adhesion and migration leads to edema due to microvascular barrier dysfunction, and that I/R may increase capillary pressure due to the adhesion of leukocytes occluding the lumen of the vessels.[10,20] This study not only demonstrated the increase in leukocyte migration and adherence in the presence of reperfusion but also that it is possible to inhibit the adherence of these molecules with medical therapy.[20]

The effect of MPFF on lymphatic flow had been investigated through a canine model which tracked the pulsatile activity of MPFF on the lymphatic system.[21] The lymphatic system is a transport system for interstitial fluid, intracellular fluid, extracellular matrixes, transport proteins, cytokines, immunoglobins, and macromolecules. It is thought that the release of inflammation mediators such as cytokines, oxygen radicals and nitric oxide products eventually lead to cell apoptosis, degradation of extracellular matrix proteins and basement membranes and an accumulation of extracellular tissue fragments.[10] Lymphatic flow is compromised, so that the accumulated tissue fragments cannot be cleared. With venous hypertension, the lymphatic flow becomes greater than the lymphatic transport capability.[10]

In the experiment, lymphatic volume was measured every two hours through the thoracic lymphatic duct of anesthetized dogs. The dogs were given three doses of MPFF: 3.125, 6.25, and 12.5 mg/kg.[21]

The results demonstrated an increase in pulsatile activity with MPFF which indicated an increase in lymphatic flow and demonstrated a dose response (Table 5). The maximum effect was observed in 20–25 minutes, and the duration of the response lasted from 90 to 180 minutes and was dose dependent.

The maximal 10-minute period lymphatic flows were 191% (12.5 mg/kg), 171% (6.25 mg/kg), and 91% (3.125 mg/kg); MPFF was shown to induce an increase of the pulsatile component of intralymphatic pressure (MPC). The MPC was correlated with the increase in lymph flow ($r = 0.877$).[21]

These findings are consistent with another study of the effects of MPFF on lymphatic flow, conducted through the observation of sheep's lymphatic systems before and after the administration of 500 mg of MPFF, both in vivo and ex vivo.[22] Lymphatic flow may be modulated by either modifying the rate of lymph formation or by modifying the contractility of the lymph ducts. This study demonstrates how MPFF works on lymphatic vessels, which have contractility to pump lymph. The ex vivo examination of the MPFF-treated sheep's lymphatic system showed significant increase in the frequency of spontaneous contractions compared to pre-treatment, with nearly double the contraction frequency at the highest dose studied. In live sheep, one group was given MPFF, and the other given a sham treatment, and their lymphatic flow was measured twice daily for 5 days. At the 5-day measurement, the lymph flow was compared to the pre-treatment flow, and the results showed that the flow after treatment with MPFF was significantly higher than in the pre-treatment period ($p < 0.024$).[22]

In an attempt to further understand the potential effectiveness on MPFF, experiments were conducted to study, under local acidosis conditions (pH 7.4–6.4), the interaction of MPFF and norepinephrine in human veins.[23] Varicose veins and normal veins were obtained from patients undergoing surgery. Histological tests were performed following each pharmacological intervention on both the normal and abnormal veins. In both the normal and varicose veins treated with MPFF, the EC_{50} value (concentration producing 50% of the maximal contraction) was lower than in the vehicle-treated veins. This study demonstrated that MPFF potentiated norepinephrine in acidotic conditions, with the greater effect in the more pathological veins (Table 6).

Leukocytes present in the vein wall and valves indicate the presence of an inflammatory response. Along with the inflammatory response is the body's reparative processes, such as the stimulation of growth factors such as VEGF to initiate angiogenesis of healing.[10,24]

Table 5. Effect on lymphatic flow.[21]

Increase in lymphatic flow (ml/kg/10 min)			
Control	3.125 mg/kg	6.25 mg/kg	12.5 mg/kg
0	2.1X	2.7X	3.1X

Table 6. Comparison of MPFF and vehicle treated normal and varicose veins (EC_{50}).[23]

Interaction with norepinephrine		
	Normal (n = 24)	Varicose (n = 27)
Vehicle	7.4×10^{-7} M	6.6×10^{-7} M
MPFF 500 mg	5.8×10^{-7} M	3.8×10^{-7} M
	p = NS	$p < 0.05$

It is due to the expression of adhesion molecules such as ICAM-1 responsible for lymphocyte/neutrophil binding and VCAM-1, binding lymphocytes and monocytes which leads to MHC-II and GMP-140 expression. It is GMP-140 which binds platelets, which in turn increases platelet-activating factor, and expresses more adhesion molecules, which are known to be increased in CVD. There is an up-regulation of VEGF in the skin and plasma of CVD patients, especially in those with C4 disease.[9,10,12] In studies where venous hypertension had been induced, it was correlated to increased VEGF levels.[10,25]

The purpose of a study of 20 patients with CVD, dosed with MPFF 500 mg BID for 60 days, was to evaluate the effect of MPFF on markers of endothelial activity in CVD. Blood samples were taken immediately before starting treatment and less than one week before stopping treatment, in patients with CVD classification ranging from C2 to C5 (patients with C6 or active ulceration were excluded) who all wore Class II support stockings throughout the study.[24] There were equal numbers of patients ($n = 10$) with and without skin changes, and the study results showed differences in the markers found. In both groups, there was a significant reduction in ICAM-1 and VCAM-1 ($p < 0.001$) prior and after treatment with MPFF 500 mg. Following treatment with MPFF, there was a significant reduction in lactoferrin, E-selectin levels and VW factor only in the group with skin changes.[24]

Proliferation of microvessels in the skin of patients and accumulation of pericapillary fibrin cuffs has been recognized in patients with CVD classified as C4 disease. In a study of the effect of MPFF on CVD patients with and without skin changes, the pre-treatment median VEGF values of patients with C4 disease were significantly higher ($p \leq 0.02$) than in patients with C0–C2 disease.[25] In CVD patients with skin changes, VEGF levels decreased significantly after 60 days of treatment with MPFF 500 mg BID. This effect was seen in both standing and supine positions. However, in CVD patients with earlier stage disease (categorized C1–C3) there was no significant reduction in VEGF levels (Table 7).

Table 7. VEGF levels pre and post treatment with MPFF in CVD patients.[25]

VEGF PG/ML	Pre-RX	60 days of MPFF	*p*-value Within group
All patients	47	29	<0.05
C2-C3	9	10	NS
C4	98	57	<0.02
p-value Between groups	<0.001	<0.001	

It is thought that the lack of significant reduction in the C0–C2 population is due to the fact that the predominant activity in early stages (<C4) is leukocyte activation and adhesion and the reparative processes like VEGF production and vascular proliferation do not occur until the later stages of disease or damage.[25]

Effect of MPFF on capillary permeability

In CVI, along with morphological and functional changes to the deep veins, there are also changes to the skin capillaries, which is stage-dependent. Capillary convolution is associated with more severe stages of CVD such as lipodermatosclerosis and healed leg ulcers. There is a decrease in capillary density in C3, and through microscopy ''halo formations'' are detected which indicate pericapillary edema due to capillary leakage. MPFF works to inhibit the production of inflammatory molecules which cause damage to the endothelium and increase capillary permeability.[2]

In a double-blind, placebo-controlled randomized study, 30 patients with idiopathic cyclic edema syndrome were dosed with MPFF 1 g/d for 6 weeks. There was evidence at 6 weeks of a reduction: capillary permeability (as evidenced by Landis isotope test). In addition, symptoms and signs of edema were improved.[2]

Skin blood flow and $TcPO_2$

There is evidence of microvascular dysfunction in CVI which can be measured through laser Doppler and the presence of carbon dioxide and oxygen in the skin. In CVI patients with skin lesions and lipodermasclerosis, transcutaneous oxygen pressure ($TcPO_2$) at the ankle is often reduced. Lipodermasclerosis is characterized by hardened skin, atrophie blanche, edema, and hyperpigmentation. In lipodermasclerosis, $TcPO_2$ is <35 mm, and resting laser Doppler flux (LDF, a measure of microvascular perfusion) is raised higher than in healthy subjects due to an increase in erythrocyte concentrations. In addition, in patients with healed ulcers, the flow was 6–7 times higher than in healthy controls.[2]

Part 4: Evidence-based recommendations for the use of MPFF in the management of CVD

Based on the studies of the pathophysiology of CVD and an ongoing review and assessment of the clinical evidence, guidelines have been developed and updated as needed for the management of CVD of the lower extremities. Guidance on the evaluation of the evidence comes through consensus from experts in venous disease.[26–28] Recommendations are weighted by two factors: Classes of recommendation (Classes 1,

2, 3—Table 8a) and level of evidence (Level A, B, C—Table 8b).[26]

The American Venous Forum and the Society for Vascular Surgery developed the Grade System for guidance on for the management of leg ulcers. The AVS/SVS guidelines employ both class of recommendation and level of evidence in their grading system (Table 8c).[28]

In addition to the classification of recommendation and the level of evidence, it is essential to have standardized terminology based on the VEIN TERM Consensus on the definition of the 33 most widely used clinical venous terms, and CEAP classification for proper categorization of disease progression, etiology, anatomy, and pathophysiology.

Guidelines are developed based on the current understanding of the pathophysiology of CVD, which can be summarized as follows. Experts, in developing guidelines, and in an attempt to discover the evidence that shapes their creation, developed a list of questions to be answered in order to consider including a therapy like flavonoids in recommendations. Some of the questions experts have considered to include MPFF in the recommendations are:

Table 8a. Classifications for recommendations.[26]

Class of recommendation	Definition
I	General agreement or evidence that a therapy/procedure is effective, beneficial, and useful
II	Divergent opinion or evidence of the effectiveness/usefulness of a therapy or procedure
IIA	Weight of evidence/opinion is in favor of usefulness/effectiveness of therapy or procedure
IIB	Usefulness/effectiveness is less well established
III	Evidence or general agreement that the given therapy/procedure is not useful or effective, and may be harmful

Table 8b. Levels of evidence in support of recommendation.[26]

Level of evidence	Definition
A	Data derived from multiple randomized clinical trials or meta-analysis
B	Data derived from a single randomized trial, or large non-randomized studies
C	Consensus of opinion of the experts, and/or small studies, retrospective studies or registry studies

How does MPFF impact the pathophysiology of disease?
How does MPFF help manage venous hypertension?
–In which symptoms?
–In which patients?
What type of recommendation can be made for use of MPFF in chronic CVD?
What evidence exists to support the recommendation?

There is precedent for guidelines that discuss the use of MPFF for the management of chronic CVD, developed by experts in both the US and internationally.[26–28]

Part 5: Systematic review of the use of micronized purified flavonoid fraction

Goal and methodology of the review

The goal of the systematic review was to examine the existing literature on the use of MPFF (diosmin, Daflon®, hidrosmin) for effectiveness and safety in the treatment of CVD. A literature review was conducted using the search strategy (Table 10) using Medline, Cochrane Database for Systematic Reviews, Google Scholar and references from identified articles. The focus of the review was on CEAP stages 2, 3, 5, and 6 (Table 11). Abstracts and articles were independently reviewed by two authors Hahn and Freeman. The initial search yielded 250 abstracts, 65 of which met criteria for further review and 10 papers were selected for consideration in the systematic analysis (Table 12).

Previous systematic reviews

The use of these agents has been the subject of previous systemic reviews and meta analyses.[29–33] These reviews have examined the evidence for the benefit of a spectrum of pharmacological and medical food ''phlebotonic'' agents across three objective clinical outcomes: ulcer healing, reduction of lower limb edema and trophic changes, and the spectrum of subjective symptoms associated with CVD and CVI. The most recent Cochrane review of randomized placebo controlled trials with acceptable low levels of potential bias studying the spectrum of phlebotonic agents concluded that there is moderate quality evidence for effectiveness in reducing edema, improving trophic changes and relieving cramps, restless legs, swelling and paresthesias compared with placebo, but no effect in speeding or achieving ulcer healing.[32] Phlebotonics were associated with a greater risk of non-serious adverse effects, principally gastrointestinal. The Cochrane study concluded

Table 8c. Grade system from AVF/SVS.[28]

Grade	Description	Benefit vs. risk	Quality of evidence	Implications
1A	Strong recommendation, high quality evidence	Benefits clearly outweigh risk or vice versa	RCTs without limitations, or overwhelming evidence from observational studies	Strong recommendations, can apply to most patients, without reservation
1B	Strong recommendation, moderate quality evidence	Benefits clearly outweigh risks or vice versa	RCTs with limitations[a] or exceptionally strong evidence from observational studies	Strong recommendation can apply to most patients without reservation
1C	Strong recommendation, low quality or very low quality evidence	Benefits clearly outweigh risks or vice versa	Observational studies or case series	Strong recommendation, but may change when higher quality evidence becomes available
2A	Weak recommendation, High quality evidence	Benefits closely balanced with risks	RCTs without limitations, or overwhelming evidence from observational studies	Weak recommendation, may differ by circumstances or patient or societal values
2B	Weak recommendation, moderate quality evidence	Benefits closely balanced with risks	RCTs with limitations[a] or exceptional evidence from observational studies	Weak recommendation, may differ by circumstances or patient or societal values
2C	Weak recommendation, low quality evidence	Uncertainty in estimates of benefits vs. risks; risks/benefits may be closely balanced	Observational studies or case series	Very weak recommendation, other alternatives may be reasonable

Adapted from O'Donnell et al. (2014).[28]
[a]Inconsistent results, methodological flaws, indirect or imprecise.

Table 9. US and European Guideline Recommendations that include flavonoids and MPFF.[3,26–28]

Guidelines for management of CVI/CVD	Level of recommendation	Description
2008 International Angiography	*A*	MPFF for healing of venous ulcers and for symptoms of CVD
Antithrombotic and thrombotic therapy: American Academy of Chest Physicians—2008	*2B*	MPFF for healing of persistent venous ulcers
Management of venous leg ulcers: Clinical practice guidelines of the Society of Vascular Surgery and the American Venous Forum 2014	*1B*	MPFF for long standing or large venous ulcer, in combination with compression therapy
Clinical Practice Guidelines for the European Society for Vascular Surgery (ESVS) 2015	*2A*	MPFF was most effective in reducing symptoms of edema and restless legs. MPFF helped in healing of venous ulcerations and was useful in the treatment of cramps and swelling

Table 10. Search strategy.

- Databases searched: Medline, Cochrane Database for Systematic Reviews, Google Scholar
- References from identified articles
- Search terms: chronic venous disease or chronic venous insufficiency or venous insufficiency or venous disease or varicose veins or leg ulcers or venous ulcers or CVD ulcers or CVI or post-thrombotic syndrome or post-thrombotic syndrome or PTS or thrombophlebitis or post-phlebitic syndrome or post-thrombotic or varicose ulcer or venous thromboembolism or venous thrombosis or thrombophlebitis) and (diosmin or bioflavonoids or flavonoids or MPFF)
- English language or English alphabet

Table 11. Inclusion criteria.

- Indication: Chronic Venous Disease, CEAP 2,3,5,6
- Treatment: MPFF; diosmin
- Primary outcome: healing of ulcers (either time to healing or rate healed)
- Secondary outcomes: symptoms, edema
- Validation of diagnosis: CVD documented by Doppler and Impedance Plethysmography

Table 12. Result of initial search.

Abstracts reviewed	250
Placebo trials	20
Observational studies	9
Comparison studies	16
Meta-analyses	4
Reviews	16
Questionable/rejected studies	132
Papers selected for review	65
Papers included in final analysis	10

that MPFF specifically (diosmin and hidrosmin) had evidence supporting benefit in edema, trophic changes, cramps, swelling, heaviness, and global benefit without evidence for greater adverse effects than placebo. In contrast to the Cochrane review which indicated inconclusive findings for ulcer healing, two other meta-analyses of MPFF,[29,30] one of which included data from unpublished studies supplied by the manufacturer of Daflon 500[30] which were not made available for this review, supported effectiveness in healing venous ulcers.

Phlebotonics were associated with a greater risk of non-serious adverse effects, principally gastrointestinal. The Cochrane study concluded that MPFF specifically (diosmin and hidrosmin) had evidence supporting benefit in edema, trophic changes, cramps, swelling, heaviness, and global benefit without evidence for greater adverse effects than placebo.[31]

Evidence for effect of MPFF in chronic venous insufficiency

Study design and outcomes. The outcomes of interest in evaluating the effects of MPFF on CVI can be divided meaningfully into those which can be measured objectively, i.e. edema, ulceration and trophic changes; and those which are subjective, i.e. pain, sensations of heaviness and swelling, nocturnal cramps, paresthesias, heat or burning and erythema or cyanosis. Only randomized, placebo controlled, double-blind studies were considered in evaluating the effect of MPFF on subjective symptoms. Some studies included in the assessment compared the effect of MPFF with standard compression treatment on the objective outcomes of edema, ulcers and trophic changes.

Objective outcomes

Ulcer healing. Two high quality, published randomized, double-blind, placebo controlled trials were available to evaluate the effect of MPFF on ulcer healing. The earliest, conducted in 1992, is a small study of 34 patients, eight of whom did not complete the study.[34] The dose used, 200 mg of hidrosmin [sic] three times per day, was less than the typical 500 mg of comparable products given twice daily. Subjects had Doppler documented insufficiency and varicose veins. The study focused on subjective symptoms but reported rates of ulcer healing. Among the patients who completed the study, three of the 16 subjects on hidrosmin and one of 12 subjects on placebo had ulcers at the beginning of the study. One of the three subjects in the active treatment arm experienced ulcer healing and the one patient with an ulcer in the placebo group did not. The risk ratio for not healing in the treatment vs. placebo treatment in this study was 1.5 (95% CI 0.15–14.68). Although the risk of not healing on active treatment was higher than that for the placebo group, the 95% confidence interval for the risk ratio encompasses "1" and thus the risk of not healing while on treatment is not significantly different from the risk of not healing on placebo.

The other randomized, double-blind, placebo controlled study, published in 1997, used 500 mg of MPFF and included 105 subjects.[35] All subjects in this study had venous ulcers of 3-month duration despite treatment; patients with arterial insufficiency (arm/ankle ratio ≤ 0.8) or skin grafting were excluded; patients with diabetes were not. The randomization was stratified by ulcer size ($\leq$10 cm and $>$10 cm); the largest ulcer was used if there were more than one, and

patients with circumferential ulcers were excluded. All patients used compression and received standardized local treatment. Patients in the active treatment arm received a tablet containing 450 mg of diosmin and 50 mg of flavonoid extract expressed as hesperidin (micronized diosmin) twice daily. Patients were monitored every 2 weeks and treated for 2 months. Among all subjects, 14/53 of those in the active treatment arm (26.4%) and 6/52 of those on placebo (11.5%) achieved complete ulcer healing. The risk ratio of not healing in the active treatment arm compared to placebo for all subjects was 0.83 with a 95% CI that encompasses 1 (0.69–1.0), and is therefore not significant. However, among subjects with ulcers of $\leq$10 cm, 14/44 of those receiving treatment (31.8%) and 6/47 (12.8%) of those on placebo achieved ulcer healing. The resulting risk ratio of not healing in subjects with ulcers of $\leq$10 cm was 0.78 (95% CI 0.62–0.98) and therefore demonstrated significant benefit. None of the subjects with ulcers >10 cm achieved complete healing. Time to healing among patients with ulcers $\leq$10 m was reported to be significantly shorter ($P = 0.036$) by survival analysis, but median time to healing for the two groups was not reported.

Two randomized, but unblinded studies also report on the effect of MPFF on venous ulcer healing.[36,37] Both examined the effect on ulcers between 2 and 10 cm, comparing the effect of treatment with MPFF plus compression and local treatment to compression and local treatment alone for a period of 6 months. Overall rates of ulcer healing were higher in both of these studies of longer duration, 46.5%[36] and 64.6%[36,37] in the MPFF treatment arms compared to 27.5% and 41.2% respectively in the compression and local treatment alone group (relative risks of 0.74; 95% CI 0.57–0.96 and 0.60; 95% CI 0.42–0.86), both of which indicate relative effectiveness for MPFF. Median time to complete healing was measured in one of the unblinded randomized controlled trials (RCTs) and was faster in subjects receiving MPFF (137 vs. 166 days, $P = 0.04$).[37]

Although high quality data are limited, overall, the available RCTs evaluating the effect of MPFF on venous ulcer healing indicate relative benefit compared to compression and local treatment alone. The larger of two randomized, placebo-controlled trials and both of the unblinded RCTs demonstrated a beneficial effect as did a meta-analysis which included two unpublished studies and one published in Russian that were not available for this review. Benefit was most evident for ulcers of <10 cm diameter and less than five-year duration.

Trophic disorders. Four studies assessing the effect of MPFF on trophic changes were cited in the Cochrane review,[34,38–40] three of which were available for this review.[34,38,39] One (Table 13),[34] the same small study described previously, that showed a statistically nonsignificant disadvantage to the use of MPFF in healing ulcer, also showed a nonsignificant and near equivalent effect on trophic changes (RR = 1.05, 95% CI 0.36–3.05).[34] As previously mentioned this was a short duration (2 months) study. Two studies (Table 13[38,39]) showed significant benefit in resolution of persistent trophic changes and results for the third study (Table 13) were not statistically significant.[40] The Cochrane Review meta-analysis of the pooled data favored treatment with MPFF (RR of persistent trophic changes on treatment compared to

Table 13. Effect of MPFF on trophic changes – Cochrane review.

Study	Design	MPFF n/N, %	Placebo n/N, %	Significance
Fermoso 1992[a]	RCT, MPFF (hidrosmin) vs. Placebo	6/20 30.0%	4/14 28.5%	RR = 1.05 (CI 0.36–3.05)
Gilly 1994[b]	RCT, MPFF (S 5682) vs. Placebo	66/80 82.5%	76/80 95.0%	RR = 0.87 (CI 0.78–0.97)
Laurent 1988[c]	RCT, MPFF vs. Placebo	86/100	96/100	RR = 0.90 (CI 0.82–0.98)
Planchon 1990[d]	RCT, MPFF vs. Placebo	32/55	40/55	RR = 0.80 (CI 0.61–1.05)
Cochrane Review Pooled RCTs	Pooled Data	255	249	RR = 0.87 (CI 0.81–0.94)

[a]Four weeks of treatment; use of compression not described; six of 34 did not complete study; ulcers size not described.
[b]Compression previously used for 3 months was continued; 77 had SX but no SVI (40 active treatment/37 placebo); 24 had post-phlebitic syndrome (12 active treatment/12 placebo); 59 had I^0 varicose veins (28 active/31 placebo).
[c]Subjects had "organic" (n = 83) or "functional" (n = 117) venous disease (terms not operationally defined). Other treatments were not specified; the implication was that there were none.
[d]Data from Cochrane review, study not available.

Table 14. CVI Symptom Assessment.[38]

Symptom	MPFF (S 5682) Mean[a] @ 8 weeks (S.D.); Change in mean	Placebo Mean[a] (S.D.); Change in mean	Difference in mean change; P[b]
Functional discomfort	0.5 (0.1); 1.2	1.2 (0.1); 0.6	0.6; <0.001
Heaviness	0.7 (0.1); 1.3	1.3 (0.1); 0.6	0.7; <0.001
Pain	0.6 (0.1); 1.0	0.9 (0.1); 0.4	0.6; 0.027
Nocturnal cramps	0.3 (0.1); 0.6	0.7 (0.1); 0.3	0.3; 0.002
Paresthesia	0.4 (0.1); 0.6	0.5 (0.1); 0.4	0.2; NS
Sensation of swelling	0.5 (0.1); 1.3	1.3 (0.1); 0.5	0.8; <0.001
Redness/cyanosis	0.4 (0.1); 0.6	0.7 (0.1); 0.2	0.4; NS
Heat/burning	0.3 (0.1); 0.9	0.7 (0.1); 0.5	0.4; 0.006

[a]Scale: O = no symptom; 1 = moderate without impact on daily activities; 2 = "appreciable" but permitting ADLs; 3 = severe symptom, causing discomfort or hampering daily activities.
[b]Two-way analysis of variance for difference between initial and final mean score.

placebo = 0.87, 95% CI 0.81–0.94).[31] Overall, these data support a role for MPFF in the treatment of trophic disorders.

Edema. Lower extremity edema has been evaluated in four randomized, placebo controlled trials of MPFF. All four studies demonstrated significant reduction in edema. Two used change in ankle circumference,[38,41] one used "improved vs. not improved"[31] and one (Planchon et al.) used both metrics.[40] Results of Planchon et al. were only available through a report in the Cochrane meta-analysis[31] as was also the case for one of the studies reporting ankle circumference alone.[41] Difference in mean reduction in ankle circumference at the end of treatment ranged from −5.70 to −9.00 cm with a pooled difference mean reduction of −5.98 (95% CI −7.78 to 4.18).[31] Both of the studies reporting improvement vs. non-improvement in ankle edema showed a beneficial effect; the pooled risk ratio of non-improvement compared to improvement was 0.63 (95% CI 0.46–0.68). These studies support the benefit of MPFF in reducing lower extremity edema.

Subjective outcomes: Symptoms. Assessment of the impact of MPFF on subjective symptoms is, of necessity, restricted to randomized, placebo controlled double-blind trials. Both quantitative and qualitative outcome measures have been used to assess subjective symptoms. One study provides the most robust assessment of the spectrum of symptoms associated with CVI.[38] This study included 160 participants, 150 of whom completed the study (76 in the treatment group and 74 in the placebo group); 26 were male and 134 females. All subjects had "symptomatic disturbances of the veno-lymphatic system," but participants were diverse in etiology: 77 had symptoms without CVI (40 active [a], 37 placebo [p]); 83 had CVI (40 a, 43 p); 24 post-phlebitic syndrome (12 a, 12 p); and 59 had bilateral primary varicose veins (28 a, 31 p). Potential participants were excluded if they had other vascular disease, edema [sic] from cardiac, renal or hepatic disease, symptoms or signs of arterial, metabolic or orthopedic origin, pregnancy, recent surgery or deep or superficial thrombosis in the previous 6 months. Patients were treated with 1000 mg of MPFF daily for 8 weeks and were allowed to continue compression which had been in place for 3 months prior to beginning the study. Eight symptoms of CVI (Table 14) were assessed using a four-point scale at weeks 0, 4, and 8. The symptom scale was anchored with both severity and functional impairment descriptors such as: O = no symptom; 1 = moderate without impact on daily activities; 2 = "appreciable" but permitting ADLs; 3 = severe symptom, causing discomfort or hampering daily activities. Results of ulcer healing, improvement in trophic changes and decrease in lower extremity edema from the Gilly et al. study have been described above.[38]

Of the eight symptoms of CVD, all but paresthesias and redness/cyanosis showed greater improvement in the treatment group than in the placebo arm. These differences were significant at week 4 for functional discomfort, sensation of heaviness, nocturnal cramps, and sensation of swelling. It is worth noting that change in the subjective sensation of swelling correlated with change in objectively measured decrease in ankle circumference ($r = 0.56$, $P < 0.001$).[38]

Several other studies examined cramps using a dichotomous metric comparing rates improvement between groups.[34,40,42] (One of which was Planchon,[40] whose results were only available through the Cochrane review.) Although all three showed that most patients improved in cramping, none of the studies individually reached significance. However, pooled analysis performed by the Cochrane authors demonstrated a

statistically significant benefit in reducing cramping; the risk ratio of non-improvement on MPFF compared to placebo was 0.83 (the 95% CI 0.70–0.98 does not include 1.0 indicating a statistically significant difference).[31] Pain was assessed using dichotomous metric (improved not improved) in four studies,[34,40,42,43] one of which (Planchon et al.) demonstrated a significant benefit[40]; pooled analysis in the Cochrane review indicated that for this qualitative assessment of pain, there was no significant benefit for MPFF.

Taken together, these randomized placebo controlled double-blind studies for the assessment of symptoms demonstrate that MPFF has a significant benefit across an array of symptoms associated with CVD. An ordinal metric that anchors assessment of pain with a combination of severity and functional impairment descriptors appears to be more sensitive than the dichotomous measure of improvement.

Quality of Life. Research addressing the effect of MPFF on quality of life is sparse. Perhaps the most useful albeit limited study was conducted by Rabe et al.[43] This randomized placebo controlled double blind study was designed to assess the impact of MPFF on "vesperal edema" but failed to do so because the volume displacement method used to assess edema was determined by the authors to be unreliable. The authors repurposed their study by performing a post-hoc analysis of the impact of MPFF on pain and quality of life among symptomatic patients who presented with a visual analog pain scale (VAS) value of $\geq$4.0 cm out of 10 cm, not stratified as such at randomization. (VAS used in this study was in fact a 10 cm line upon which the respondent makes a mark. The investigators measure the actual distance marked off.) The study was multinational, conducted in Europe and South America that recruited 1291 patients with CVI stages C3 or C4a, enrolling 1137 who were randomized to MPFF (579) and 558 to placebo. There were 592 patients with VAS pain scores of $\geq$4.0, 296 in both the placebo and treatment groups. Quality of life was assessed using the 20-item version of the Chronic Venous Insufficiency Questionnaire (CIVIQ).[43–45] This instrument has four subscales: psychological repercussions, physical repercussions, pain repercussions and social repercussion and an overall quality of life score. After four months of treatment with 1000 mg of MPFF daily, the treatment group had a 3.1 ± 1.5 point higher (better) change in CIVIQ score from baseline ($P = 0.04$; 95% CI = 0.1–6.1). The difference in change in VAS pain score (−0.5, 95% C1 −0.9 to −0.01) also favored the use of MPFF. Although the treatment and placebo groups had similar baseline characteristics, the strength of evidence provided by this study is nevertheless compromised by the nonrandomized allocation to treatment vs. placebo as a consequence of post hoc subgroup analysis design.

Adverse effects

Diosmin and hidrosmin are generally very well tolerated. The Cochrane analysis pooled eight randomized placebo controlled studies[34,38–40,42,46,47,48] reporting adverse effects with equal frequency in both the treatment (50/424, 11.8%) and placebo arms (49/413, 11.9%); risk ratio 1.01, 95% CI 0.70–1.44).[31] In these eight studies, 12 patients withdrew from treatment in the treatment arms and 11 in the placebo. In additional studies reviewed, there were no safety concerns.

Summary

This review of studies on the effects of MPFF in venous disease and venous insufficiency reveal moderate quality evidence that MPFF is of benefit in improving objectively observable signs including ulcers, edema and trophic changes as well as many of the subjective symptoms of CVI. Taken together, the consistently observed beneficial effect of MPFF in reducing many of the manifestations of CVD provides substantial support for its efficacy for this condition. The risk of adverse effects appears minimal. To date, the evidence demonstrating an impact on quality of life remains weak.

Discussion

The pathophysiology of venous disease provides the rationale for utilizing venoactive therapies in the management of CVD. Venous hypertension is considered to be the major component of CVD that includes the mechanical and functional failure of calf muscle pump, venous valvular incompetence and luminal obstruction, as well as complex molecular and cellular reactions that create a chronic inflammatory condition. What initiates the inflammatory reaction in the vein walls and valves is not clear, but it is maintained by leukocyte–endothelial interaction. Along with the inflammatory reactions, the body's reparative response to the compromise of the veins and valves can increase expression of VEGF which can increase vascularization and capillary permeability. The cellular and molecular pathway of venous hypertension results in damage to venous tissue and obstruction of the lymph drainage and fluid accumulation, which in turn, leads to skin ulceration and edema.

MPFF (diosmin) is known to play a role in the inhibition of leukocyte trapping, which in turn can reduce the release of the inflammatory molecules such as cytokines, bradykinins, chemokines, and

leukotrienes. The formulation of diosmiplex manages venous inflammation, accumulation of polymorphonuclear leukocytes, platelets and other thrombotic components as well as edema caused by a deterioration of venous vessel walls. Alka4-complex in diosmiplex works as a buffer and manages blood pH to affect local metabolic acidosis in veins.[49]

The recent availability in the US of diosmiplex (marketed as ''Vasculera'' by Primus Pharmaceuticals, Scottsdale, AZ) which consists of a specially formulated proprietary blend of micronized, highly purified 600 mg of diosmin glycoside in combination with 30 mg alkaline granules (alka4-complex),[49] led the members of the Working Group to initiate a comprehensive literature review. The purpose of the review is to investigate the evidence for support of a recommendation for the use of MPFF in the US for the management of CVD.

The systematic review of studies on the effects of MPFF in venous disease and venous insufficiency reveals moderate quality evidence of benefit in improving objectively observable signs including ulcers, edema and trophic changes as well as many of the subjective symptoms of venous insufficiency, while the risk of adverse effects is minimal.

MPFF is a venoactive therapy commonly used in Europe, where it is available in a formulation of 95% diosmin. It is ranked as a Class 2A-A recommendation in the 2015 ESVS International Guidelines to be used alone or in combination with compression, for the healing of venous ulcers and the reduction of edema in CVD. Recent clinical studies have demonstrated benefits for relief of symptoms in patients with CVD C4–6, and the guidelines recommend that they should be considered part of a range of treatment options.[26–28]

Diosmin is derived from hesperidin, which is found in orange peel (about 12.2–25.4 mg per 100 g of orange peel) and for a patient to achieve a similar dose would require ingestion of 25–50 oranges with their peels per day. Therefore, in the United States, diosmiplex meets the criteria for designation as ''medical food''. Medical foods are for diseased populations, not healthy populations. People with serious medical conditions such as CVD, are often candidates for the nutritional management offered by a medical food, because it can fill a deficiency that could only be addressed by ingesting excessive, indigestible quantities of a specific food. Because these patients are under management for a serious disease, the medical food cannot be dispensed without a physician's supervision, therefore requiring a prescription. Although the FDA monitors medical foods, they are not required to go through the same approval process as prescription drug therapy.

Table 15. Recommendations for the use of MPFF in the management of chronic venous disease.

1. Hemodynamic pathophysiology leads to major cellular and enzymatic pathologic mechanisms
2. Inflammation is central to symptoms/signs of CVD
3. Pharmacologic treatment with Micronized Purified Flavonoid Fracture—MPFF
   - Reduces microvascular inflammation
   - Improves pain and edema in patients with C_2–C_4 disease
   - Improves ulcer healing and reduces ulcer healing time in patients with C5–C6 disease
4. Only available MPFF in US formulation of 95% purified flavonoid is diosmiplex
   - Dosed once daily
   - Addition of Alka-4 complex may address GI upset with the high dose of diosmin and potentially as a buffer for the acidic environment

Diosmiplex has received a designation as ''Generally Recognized As Safe'' (GRAS), which indicates that as a food additive/substance, it is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use.[50] Diosmiplex is produced under pharmaceutical general manufacturing processes (cGMPs), and is indicated for the clinical dietary management of the metabolic aspects of CVI.

The significant differences seen in objective assessments of reduction in edema and in ulcer healing, from well-designed RCTs provided the rationale for the 2A-A recommendation from the 2015 International ESVS Guidelines, and merits consideration for a similar recommendation in the US (Table 15).

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RB.

Contributorship

RB, AC MM, and JDR have researched the literature to provide the overview of the pathophysiology and the criteria for recommendations. RB, AC, MM, and JDR collectively developed the visualizations of the cellular and molecular processes involved in CVD, and AC provided visual evidence of White Blood Cell adhesion. SH and KF conducted the systematic review, under the guidance of MM for the inclusion and exclusion criteria. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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