EVIDENCE BASED STATEMENT

DOMAIN 8, Statement 2

TOPIC: "MPFF EVIDENCE-BASED USE IN CHRONIC VENOUS DISEASE MANAGEMENT"

SEARCH TERMS & SOURCES

(micronized purified flavonoid fraction) OR (diosmin[MeSH Terms])

PubMed, Embase and Cochrane Library

INCLUSION CRITERIA

Indexed Journal, English Language, lower limb

Reviews.

<10 y

SEARCH RESULT BEFORE - AFTER SELECTION

30 (before) - 26 (after selection)

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Nicolaides AN. The Benefits of Micronized Purified Flavonoid Fraction (MPFF) Throughout the Progression of Chronic Venous Disease. Adv Ther. 2020 Feb;37(Suppl 1):1-5.
2. Lurie F. Advanced Stages of Chronic Venous Disease: Evolution of Surgical Techniques and Advantages of Associated Medical Treatment. Adv Ther. 2020 Feb;37(Suppl 1):6-12.
3. Mansilha A. Early Stages of Chronic Venous Disease: Medical Treatment Alone or in Addition to Endovenous Treatments. Adv Ther. 2020 Feb;37(Suppl 1):13-18
4. Gavrilov SG, Moskalenko YP, Karalkin AV. Effectiveness and safety of micronized purified flavonoid fraction for the treatment of concomitant varicose veins of the pelvis and lower extremities. Curr Med Res Opin. 2019; 35(6): 1019-1026.
5. Gianesini S, Onida S, Obi A, et al. Global guidelines trends and controversies in lower limb venous and lymphatic disease: Narrative literature revision and experts' opinions following the vWINter international meeting in Phlebology, Lymphology & Aesthetics. Phlebology. 2019, Vol. 34(1S) 4–66

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IDENTIFIED REFERENCES

1. Chaitidis N, Kokkinidis DG, Papadopoulou Z, et al. Management of Post-thrombotic Syndrome: A Comprehensive Review. Curr Pharm Des. 2022;28(7):550-559.
2. Gerges SH, Wahdan SA, Elsherbiny DA, El-Demerdash E. Pharmacology of Diosmin, a Citrus Flavone Glycoside: An Updated Review. Eur J Drug Metab Pharmacokinet. 2022 Jan;47(1):1-18.
3. Cazaubon M, Benigni JP, Steinbruch M, et al. Is There a Difference in the Clinical Efficacy of Diosmin and Micronized Purified Flavonoid Fraction for the Treatment of Chronic Venous Disorders? Review of Available Evidence. Vasc Health Risk Manag. 2021 Sep 16;17:591-600.
4. Li KX, Diendéré G, Galanaud JP, et al. Micronized purified flavonoid fraction for the treatment of chronic venous insufficiency, with a focus on postthrombotic syndrome: A narrative review. Res Pract Thromb Haemost. 2021 May 8;5(4):e12527.
5. Pompilio G, Nicolaides A, Kakkos SK, Integlia D. Systematic literature review and network Meta-analysis of sulodexide and other drugs in chronic venous disease. Phlebology. 2021 Oct;36(9):695-709.
6. Kitchens BP, Snyder RJ, Cuffy CA. A Literature Review of Pharmacological Agents to Improve Venous Leg Ulcer Healing. Wounds. 2020 Jul;32(7):195-207.
7. Martinez-Zapata MJ, Vernooij RW, Simancas-Racines D, et al. Phlebotonics for venous insufficiency. Cochrane Database Syst Rev. 2020 Nov 3;11(11):CD003229.
8. Zheng Y, Zhang R, Shi W, et al. Metabolism and pharmacological activities of the natural health-benefiting compound diosmin. Food Funct. 2020 Oct 21;11(10):8472-8492.
9. Mansilha A. Early Stages of Chronic Venous Disease: Medical Treatment Alone or in Addition to Endovenous Treatments. Adv Ther. 2020 Feb;37(Suppl 1):13-18.
10. Lurie F. Advanced Stages of Chronic Venous Disease: Evolution of Surgical Techniques and Advantages of Associated Medical Treatment. Adv Ther. 2020 Feb;37(Suppl 1):6-12.
11. Nicolaides AN. The Most Severe Stage of Chronic Venous Disease: An Update on the Management of Patients with Venous Leg Ulcers. Adv Ther. 2020 Feb;37(Suppl 1):19-24.
12. Mansilha A, Sousa J. Benefits of venoactive drug therapy in surgical or endovenous treatment for varicose veins: a systematic review. Int Angiol. 2019 Aug;38(4):291-298.
13. Lichota A, Gwozdzinski L, Gwozdzinski K. Therapeutic potential of natural compounds in inflammation and chronic venous insufficiency. Eur J Med Chem. 2019 Aug 15;176:68-91.
14. Ulloa JH. Micronized Purified Flavonoid Fraction (MPFF) for Patients Suffering from Chronic Venous Disease: A Review of New Evidence. Adv Ther. 2019 Mar;36(Suppl 1):20-25.
15. Rabe E, Carpentier P, Maggioli A. Understanding lower leg volume measurements used in clinical studies focused on venous leg edema. Int Angiol. 2018 Dec;37(6):437-443.
16. Jindal R, Dekiwadia DB, Krishna PR, Khanna AK, Patel MD, Padaria S, Varghese R. Evidence-Based Clinical Practice Points for the Management of Venous Ulcers. Indian J Surg. 2018 Apr;80(2):171-182.
17. Mansilha A, Sousa J. Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. Int J Mol Sci. 2018 Jun 5;19(6):1669.

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18. Radak D, Atanasijević I, Nešković M, Isenovic E. The Significance of Pain in Chronic Venous Disease and its Medical Treatment. Curr Vasc Pharmacol. 2019;17(3):291-297.
19. Kakkos SK, Nicolaides AN. Efficacy of micronized purified flavonoid fraction (Daflon®) on improving individual symptoms, signs and quality of life in patients with chronic venous disease: a systematic review and meta-analysis of randomized double-blind placebo-controlled trials. Int Angiol. 2018 Apr;37(2):143-154.
20. Bush R, Comerota A, Meissner M, Raffetto JD, et al. Recommendations for the medical management of chronic venous disease: The role of Micronized Purified Flavanoid Fraction (MPFF). Phlebology. 2017 Apr;32(1_suppl):3-19.
21. Martinez-Zapata MJ, Vernooij RW, Uriona Tuma SM, et al. Phlebotonics for venous insufficiency. Cochrane Database Syst Rev. 2016 Apr 6;4(4):CD003229.
22. Pascarella L, Shortell CK. Medical management of venous ulcers. Semin Vasc Surg. 2015 Mar;28(1):21-8.
23. Lattimer CR. CVD: a condition of underestimated severity. Int Angiol. 2014 Jun;33(3):222-8.
24. Bogucka-Kocka A, Woźniak M, Feldo M, et al. Diosmin-isolation techniques, determination in plant material and pharmaceutical formulations, and clinical use. Nat Prod Commun. 2013 Apr;8(4):545-50.
25. Scallon C, Bell-Syer SE, Aziz Z. Flavonoids for treating venous leg ulcers. Cochrane Database Syst Rev. 2013 May 31;(5):CD006477.
26. Allaert FA. Meta-analysis of the impact of the principal venoactive drugs agents on malleolar venous edema. Int Angiol. 2012 Aug;31(4):310-5.

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TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 8, Statement 2, TOPIC: "MPFF EVIDENCE-BASED USE IN CHRONIC VENOUS DISEASE MANAGEMENT"

Micronized purified flavonoid fraction (MPFF) consists of diosmin 90% and 10% of an additional flavonoid fraction (ie, diosmetin, hesperidin, linarin, isorhoifolin). The micronization is a method to reduce the particles diameter with the aim of improving intestinal absorption.

MPFF has been the most investigated venous active drug (VAD) currently on the market and it's positioned as the most recommended in several international guidelines.

*[**Gianesini S, Onida S, Obi A, et al. Global guidelines trends and controversies in lower limb venous and lymphatic disease: Narrative literature revision and experts' opinions following the vWINter international meeting in Phlebology, Lymphology & Aesthetics. Phlebology. 2019, Vol. 34(1S) 4–66**].

It shows an anti-inflammatory mechanism of action, including endothelial phenotype expression modification with reduction of capillary permeability and leukocyte adhesion.

[**Mansilha A, Sousa J. Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. Int J Mol Sci. 2018 Jun 5;19(6):1669**]

Clinically, MPFF demonstrated its potentials in chronic venous disease signs and symptoms management in all the disease stages.

In particular, it showed control of chronic venous disease (CVD) related pain, heaviness, swelling, functional discomfort, cramps, paresthesia, burning, pruritus, redness, skin changes and edema.

Its use was also associated with an improvement in the patient quality of life.

Recent data confirmed its potentials also in post-venous procedural pain relief, hematoma and hyperpigmentation reduction, CVD related symptoms improvement.

MPFF demonstrated to facilitate healing of venous leg ulcers.

[**Nicolaides AN. The Benefits of Micronized Purified Flavonoid Fraction (MPFF) Throughout the Progression of Chronic Venous Disease. Adv Ther. 2020 Feb;37(Suppl 1):1-5**].

Preliminary data also suggest its potentials in pelvic venous refluxes associated symptoms management.

[**Gavrilov SG, Moskalenko YP, Karalkin AV. Effectiveness and safety of micronized purified flavonoid fraction for the treatment of concomitant varicose veins of the pelvis and lower extremities. Curr Med Res Opin. 2019; 35(6): 1019-1026**].

The above mentioned results refer specifically to MPFF use. Further studies are needed to properly compare MPFF versus non-micronized diosmin, as well as the role of eventual prescription variations in terms of dosages and timing. Particular caution must be used in the comparison of different VAD effects on CVD patients, avoiding grouping different quality of evidence together. Properly conducted randomized comparative trials and meta-analysis should be taken into consideration before proceeding with guidelines or consensus documents recommendations. It should be strongly emphasized that the results of the MPFF studies should not be directly extrapolated to the non-micronized diosmin group which is currently available in many countries in the form of drugs or dietary suplements. The evidence about this molecules (non-micronised diosmin) remains limited.

EVIDENCE BASED STATEMENT

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STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 8, Statement 2

"Micronized Purified Flavonoid Fraction (MPFF) demonstrated to be potentially beneficial in all chronic venous disease clinical classes, improving several signs and symptoms"

4 SELECTED REFEREENCES

1. ***Gianesini S, Onida S, Obi A, et al. Global guidelines trends and controversies in lower limb venous and lymphatic disease: Narrative literature revision and experts' opinions following the vWINter international meeting in Phlebology, Lymphology & Aesthetics. Phlebology. 2019, Vol. 34(1S) 4–66**
2. **Mansilha A, Sousa J. Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. Int J Mol Sci. 2018 Jun 5;19(6):1669**
3. **Nicolaides AN. The Benefits of Micronized Purified Flavonoid Fraction (MPFF) Throughout the Progression of Chronic Venous Disease. Adv Ther. 2020 Feb;37(Suppl 1):1-5**
4. **Gavrilov SG, Moskalenko YP, Karalkin AV. Effectiveness and safety of micronized purified flavonoid fraction for the treatment of concomitant varicose veins of the pelvis and lower extremities. Curr Med Res Opin. 2019; 35(6): 1019-1026**

identified LITERATURE BIAS

Lack of correlations between hemodynamic and quality of life outcomes

SUGGESTED NEXT LINES OF RESEARCH

Timing and dosage protocols and related clinical and cost-effectiveness