

Update on pharmacological treatment for lymphedema

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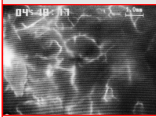
Disclosure

Chief Scientific and Clinical Advisor, VitasupportMD

Venoactive compounds improve lymphatic drainage

Example of Micronized Purified Flavonoid Fraction (MPFF) in severe Chronic Venous Insufficiency

- increases functional microlymphatic density
- improves microlymphatic drainage by decreasing microlymphatic diameter and pressure



Allegro C. et al. Lymphology 1998;31:124

COCHRANE REVIEW

Dietary supplements in lymphedema

GABRIELE BONETTI*, ANTONIANGI BIRELLI*, ANTONIO MANFREDINI*, SILVIA MICHIELINI*, SANDRO MICHELINI*, MAURIZIO BUCCHETTI*, ALESSANDRA CASALE*, MATTEO BERTHIELLO*, ...

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Benzopyrones are considered the most effective pharmacological treatment despite non-conclusive Cochrane 2004 review


A systematic review of pharmacologic and cell-based therapies for treatment of lymphedema (2010-2021)

- Poor quality studies with high risk of bias
- Some improvement with **Ketoprofen** (skin thickness and histopathological scores), **Selenium**, **Benzopyrones** and **Doxycycline** might be beneficial for secondary lymphedema after lymphatic filariasis infection

Walker J. et al. J Vasc Surg Venous Lymphat Disord 2022;10(4):666-675

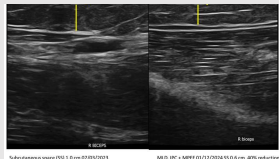
MPFF versus placebo for treatment of breast cancer-related lymphedema

- RCT with 6-months follow-up
- Subanalysis of 24 patients with severe lymphedema
 - Significant improvement of the lymphoscintigraphy migration speed (0.84±0.6 vs 0.14±0.26; p=0.005)
 - Δ half-life (10.3±3.07 minutes, p=0.034 vs 0.5±0.51, p=0.086)
 - Tendency for reduction of lymphedema volume in favor of MPFF



Photos: courtesy of G. E. Bar
 Paskalis A.P. et al. Angiology 1997;48(1):93-95

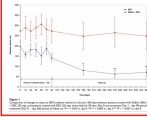
Example of a patient treated with MPFF



Subcutaneous speed (cm/s) 1.8 vs 0.95/2023
 MAGI, INC. - MPFF 02/22/2024 0101 cm MAGI-04/2024

Double-blind RCT (MPFF + DEC*) vs DEC in 26 patients with bancroftian filarial lymphedema

- Group DEC: no significant change (-9%) in edema volume
- Group MPFF + DEC: **63.8% reduction** in edema volume (day 360 vs day 0, p < 0.001)
- **MPFF (1000 mg daily) was safe and efficacious in reducing limb volume in filarial lymphedema.**



DEC = diethyltoluamide citrate (anti-parasitic drug)
 Das L. et al. Filaria Journal 2023, 3:5

Latest studies 2023-2024

- Rosiglitazone: Reduction in the overall quantity of PDGFRα+ cells (causing adipogenic and fibrogenic differentiation) and LipidTOX+ cells*
- Metformin: Anti-inflammatory and anti-fibrotic effects in lymphedema mouse models**

*Chen Z et al. JCI Insight. 2023 Dec 22;8(24):e165324
 **Wei JH et al. Plast Reconstr Surg. 2024 Feb 22;doi: 10.1097/PRS.00000000000011363. Online ahead of print.

HANDBOOK OF VENOUS AND LYMPHATIC DISORDERS
 71
 Lymphedema
 Medical and physical therapy
 Dana M. Nelson and Robert H. Dean

Consensus Statements 71.0 of the American Venous Forum on medical management of lymphedema

No.	Consensus Statements
71.1	The efficacy of chronic decongestive therapy (CDT) is supported by randomized controlled trials.
71.2	Patient compliance is important to maintain the volume loss achieved with phase 1 CDT.
71.3	Scientific evidence supports the clinical utility and cost benefit of pneumatic compression pumps.
71.4	Important lymphedema risk factors include obesity and chronic venous insufficiency.
71.5	Patients with lymphedema should follow appropriate preventative measures, including skin care and exercise.
71.6	Pharmacotherapies as adjuncts for the lymphedema patient should be considered.

NO treatment method has really undergone a satisfactory meta-analysis

The exact role for benzopyrones (rutinoids and bioflavonoids) as an adjunct is yet to be determined including appropriate formulations and dose

European Society for Vascular Surgery 2022 CVD Guidelines

European Society for Vascular Surgery 2022 CVD Guidelines

Meta-analysis in phlebolymphe'dema

Comparison of veno-active compounds' efficacy on malleolar edema (ankle circumference)

Compound	Z-score	Significance	Conclusion
MPFF versus placebo	18.9	P<0.00001	MPFF effective
Ruscus extract versus placebo	18.7	P<0.00001	Ruscus extract effective
Hydroxyethylrutinoid versus placebo	11.5	P<0.00001	Hydroxyethylrutinoid effective
MPFF versus ruscus extract	3.00	P<0.0001	MPFF effective
MPFF versus hydroxyethylrutinoid	5.38	P<0.00001	MPFF effective
Ruscus extract versus hydroxyethylrutinoid	0	P=NS	No difference
MPFF versus single diosmin	7.6	P<0.00001	MPFF effective
Ruscus extract versus single diosmin	4.6	P<0.00001	Ruscus extract effective
Hydroxyethylrutinoid versus single diosmin	8.7	P<0.00001	Hydroxyethylrutinoid effective
Placebo versus single diosmin	1.15	P=NS	No difference

Albers T-A, Int Angiol 2012;31:310-315

MPFF meta-analysis in phlebolymphe'dema

30 studies (15 RCTs, 15 non-RCTs)
 24,000 patients
 Mean reduction in ankle and calf circumferences -7.6 mm (P<0.001) and -7.9 mm (P<0.001)
 MPFF effective in phlebolymphe'dema

Venoactive compounds in phlebolymphe'dema

HANDBOOK OF VENOUS AND LYMPHATIC DISORDERS

GUIDELINES 24.0 OF THE AMERICAN VENOUS FORUM ON THE DRUG TREATMENT OF CHRONIC VENOUS DISEASE

Guideline	Strength of Recommendation	Quality of Evidence
24.1 We recommend compression (elastic bandages, stockings, hose, compression and/or socks), and exercise for patients with symptoms and edema due to chronic venous disease.	1	Very High
24.2 We suggest diosmin, ruscus extract, and red vine leaf extract for patients with symptoms and edema due to chronic venous disease.	2	Very High
24.3 We suggest rutinoids for patients with symptoms and edema due to chronic venous disease.	2	High

Gianfranceschi M, and Raffetto JD. Drug treatment for chronic venous disease. Handbook of Venous and Lymphatic Disorders, 3rd Ed.

Conclusion

- Pharmacotherapy using bio-nutrients and nutraceuticals (selenium, MPFF, diosmin...) as an adjunct therapy for the lymphedema patients should be considered
- RCTs and meta-analyses provided evidence of efficacy of veno-active compounds (MPFF, ruscus and hydroxyethylrutinoids) in phlebolymphe'dema

Thank you!