

EVIDENCE BASED STATEMENT

DOMAIN **12**, Statement **03**

TOPIC: “**Supplements for venous-lymphatic disease patients.**”

SEARCH TERMS & SOURCES

(supplement) AND (venous)

(supplement) AND (lymphatic)

INCLUSION CRITERIA

- Lower limb only
- Systematic Reviews, Meta-Analysis, Reviews, RCT
- Publication < 10 years, only ENG

SEARCH RESULT BEFORE - AFTER SELECTION

133/9 ; 63/1

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. [Dietary supplements: US Food & Drug Administration https://www.fda.gov/food/dietary-supplements](https://www.fda.gov/food/dietary-supplements)
2. Raposo A, Saraiva A, Ramos F, Carrascosa C, Raheem D, Bárbara R, Silva H. The Role of Food Supplementation in Microcirculation-A Comprehensive Review. *Biology (Basel)*. 2021 Jul 2;10(7):616.
3. Raposo A, Saraiva A, Ramos F, et al. The Role of Food Supplementation in Microcirculation-A Comprehensive Review. *Biology (Basel)*. 2021 Jul 2;10(7):616
4. Michelini S, Cestari M, Michelini S, Camilleri G, De Antoni L, Sonna WN, Bertelli M. Study of a supplement and a genetic test for lymphedema management. *Acta Biomed*. 2020 Nov 9;91(13-S):e2020013
5. Sato Y. [Study of Formulation Development Based on the Pharmacokinetic Properties of Functional Food Components]. *Yakugaku Zasshi*. 2019;139(3):341-347.
6. Olas B. Dietary Supplements with Antiplatelet Activity: A Solution for Everyone? *Adv Nutr*. 2018 Jan 1;9(1):51-57.
7. Ronis MJJ, Pedersen KB, Watt J. Adverse Effects of Nutraceuticals and Dietary Supplements. *Annu Rev Pharmacol Toxicol*. 2018 Jan 6;58:583-601.
8. Schmitz SM, Lopez HL, MacKay D. Nutravigilance: principles and practices to enhance adverse event reporting in the dietary supplement and natural products industry. *Int J Food Sci Nutr*. 2014 Mar;65(2):129-34.
9. Bauer JD, Isenring E, Waterhouse M. The effectiveness of a specialised oral nutrition supplement on outcomes in patients with chronic wounds: a pragmatic randomised study. *J Hum Nutr Diet*. 2013 Oct;26(5):452-8.

EVIDENCE BASED STATEMENT

Domain 12; Statement 3

IDENTIFIED REFERENCES

1. de Souza T, Monteiro JDC, Curioni CC, et al. Nutrients with Antioxidant Properties and Their Effects on Lower-Limb Ulcers: A Systematic Review. *Int J Low Extrem Wounds*. 2022 Jan 24;15347346221074861.
2. Olas B, Urbańska K, Bryś M. Saponins as Modulators of the Blood Coagulation System and Perspectives Regarding Their Use in the Prevention of Venous Thromboembolic Incidents. *Molecules*. 2020 Nov 6;25(21):5171.
3. Peng L, Dong Y, Fan H, et al. Traditional Chinese Medicine Regulating Lymphangiogenesis: A Literature Review. *Front Pharmacol*. 2020 Sep 3;11:1259.
4. 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.
5. Robertson NU, Schoonees A, Brand A, et al. Pine bark (*Pinus* spp.) extract for treating chronic disorders. *Cochrane Database Syst Rev*. 2020 Sep 29;9(9):CD008294.
6. Bignamini AA, Matuška J. Sulodexide for the Symptoms and Signs of Chronic Venous Disease: A Systematic Review and Meta-analysis. *Adv Ther*. 2020 Mar;37(3):1013-1033.
7. Cholewa J, Trexler E, Lima-Soares F, et al. Effects of dietary sports supplements on metabolite accumulation, vasodilation and cellular swelling in relation to muscle hypertrophy: A focus on "secondary" physiological determinants. *Nutrition*. 2019 Apr;60:241-251.
8. Kakkos SK, Nicolaidis 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
9. Kakkos SK, Allaert FA. Efficacy of Ruscus extract, HMC and vitamin C, constituents of Cyclo 3 fort®, on improving individual venous symptoms and edema: a systematic review and meta-analysis of randomized double-blind placebo- controlled trials. *Int Angiol*. 2017 Apr;36(2):93-106.
10. Ye J, Mani R. A Systematic Review and Meta-Analysis of Nutritional Supplementation in Chronic Lower Extremity Wounds. *Int J Low Extrem Wounds*. 2016 Dec;15(4):296-302.

EVIDENCE BASED STATEMENT

Domain 12; Statement 3

TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 12, Statement 03, TOPIC: “**Supplements for venous-lymphatic disease patients.**”

The health market is flooded by nutritional supplements claiming benefits too often not properly demonstrated and moreover from products not properly validated. Differently from medications, supplements are regulated post-market with no regulatory body assessing the contents and safety before the selling to the consumer. The typical example is offered in the United States by the Dietary Supplement Health and Education Act for which the Food and Drug Administration consider the supplements as food. The Food and Drug Administration gets involved in supplements only in case a supplement has already caused a health issue (<https://www.fda.gov/food/dietary-supplements>).

The topic is of significant importance considering over 70% of the United States population take some supplement regularly and that potential serious side effects have been already reported

[Ronis MJJ, Pedersen KB, Watt J. Adverse Effects of Nutraceuticals and Dietary Supplements. Annu Rev Pharmacol Toxicol. 2018 Jan 6;58:583-601].

Properly produced and tested nutrients with anti-oxidant properties have recently demonstrated potentials in improving ulcer healing. Among these ones, omega-3 fatty acids, magnesium, zinc, vitamins A, C, D, probiotics and resveratrol. The benefit has been reported to be more evident in case of an initial deficiency. Nevertheless, because of several investigations biases, further studies are needed before recommending their use in the clinical practice.

[de Souza T, Monteiro JDC, Curioni CC, et al. Nutrients with Antioxidant Properties and Their Effects on Lower-Limb Ulcers: A Systematic Review. Int J Low Extrem Wounds. 2022 Jan 24:15347346221074861].

Preliminary data are suggesting potential effects of an anti-oxidant, anti-bacterial and anti-inflammatory supplement (hydroxytyrosol) on lymphedema, but also in this case more robust literature is needed to counteract inappropriate prescriptions.

[Michelini S, Cestari M, Michelini S, et al. Study of a supplement and a genetic test for lymphedema management. Acta Biomed. 2020 Nov 9;91(13-S):e2020013].

“Nutravigilance” is a term indicating “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects related to the use of a food, dietary supplement, or medical food”: its practice is of pivotal importance in all medical specialties and related scientific societies.

***[Schmitz SM, Lopez HL, MacKay D. Nutravigilance: principles and practices to enhance adverse event reporting in the dietary supplement and natural products industry. Int J Food Sci Nutr. 2014 Mar;65(2):129-34].**

EVIDENCE BASED STATEMENT

Domain 12; Statement 3

STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 12, Statement 03

“Up to the knowledge of this experts panel, no food, drink or supplement has scientifically demonstrated to improve venous-lymphatic circulation. Relying to the expert physician is of paramount importance before using whatever supplement”.

SELECTED REFERRENCES

1. Ronis MJJ, Pedersen KB, Watt J. Adverse Effects of Nutraceuticals and Dietary Supplements. Annu Rev Pharmacol Toxicol. 2018 Jan 6;58:583-601
2. de Souza T, Monteiro JDC, Curioni CC, et al. Nutrients with Antioxidant Properties and Their Effects on Lower-Limb Ulcers: A Systematic Review. Int J Low Extrem Wounds. 2022 Jan 24:15347346221074861
3. Michelini S, Cestari M, Michelini S, et al. Study of a supplement and a genetic test for lymphedema management. Acta Biomed. 2020 Nov 9;91(13-S):e2020013
4. *Schmitz SM, Lopez HL, MacKay D. Nutravigilance: principles and practices to enhance adverse event reporting in the dietary supplement and natural products industry. Int J Food Sci Nutr. 2014 Mar;65(2):129-34

identified LITERATURE BIAS

lack of properly conducted large studies on the different supplements

SUGGESTED NEXT LINES OF RESEARCH

RCT including objective validated outcome measures