

EVIDENCE BASED STATEMENT

DOMAIN **8**, Statement **4**

TOPIC: “RUSCUS ACULEATUS IN THE CHRONIC VENOUS DISESES TREATMENT”

SEARCH TERMS & SOURCES

(ruscus) OR (cyclo 3)

PubMed, Embase and Cochrane Library

INCLUSION CRITERIA

Indexed Journal, English Language, lower limb,
<10 y.

SEARCH RESULT BEFORE - AFTER SELECTION

39 (before) - 10 (after selection)

PERTINENT LITERATURE NOT IDENTIFIED BY THE LITERATURE SEARCH

1. Nicolaidis A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. Int Angiol. 2018 Jun;37(3):181-254.
2. Chudek J, Mikosiński J, Kobielski A, et al. Patients' satisfaction with therapy methods of advanced chronic venous disease Int Angiol. 2016 Feb;35(1):98-107

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IDENTIFIED REFERENCES

1. Carpentier P, Allaert FA, Chudek J, Mosti G. Womens Health (Lond). Phlebotonic and compression stocking therapy in venous edema management: an overview of recent advances with a focus on Cyclo 3 Fort® and progressive compression stockings. 2013 Jul;9(4):325-33.
2. 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
3. Jawien A, Bouskela E, Allaert FA, Nicolaïdes AN. The place of Ruscus extract, hesperidin methyl chalcone, and vitamin C in the management of chronic venous disease. Int Angiol. 2017 Feb;36(1):31-41
4. Raully-Lestienne I, Heusler P, Cussac D, Lantoine-Adam F, de Almeida Cyrino FZG, Bouskela E. Contribution of muscarinic receptors to in vitro and in vivo effects of Ruscus extract. Microvasc Res. 2017 Nov;114:1-11.
5. de Almeida Cyrino FZG, Balthazar DS, Sicuro FL, Bouskela E. Effects of venotonic drugs on the microcirculation: Comparison between Ruscus extract and micronized diosmine. Clin Hemorheol Microcirc. 2018;68(4):371-382.
6. Kakkos SK, Bouskela E, Jawien A, Nicolaides AN. New data on chronic venous disease: a new place for Cyclo 3® Fort. Int Angiol. 2018 Feb;37(1):85-92
7. Kakkos SK, Guex JJ, Lugli M, Nicolaides AN. CEAP clinical classes C0S-C4: differences, similarities and role of Ruscus + HMC + vitamin C in patients with chronic venous disease. Int Angiol. 2020 Apr;39(2):118-124.
8. de Souza MDGC, Cyrino FZGA, Sicuro FL, Bouskela E. Effects of Ruscus extract on muscarinic receptors: Is there a role for endothelium derived relaxing factors on macromolecular permeability protection and microvascular diameter changes? Clin Hemorheol Microcirc. 2021;77(4):443-459
9. 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.
10. Monjotin N, Tenca G. Lymphotonic activity of Ruscus extract, hesperidin methyl chalcone and vitamin C in human lymphatic smooth muscle cells. Microvasc Res. 2022 Jan;139:104274.

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TEXT FOR INCLUSION IN THE DOCUMENT

DOMAIN 8, Statement 4 TOPIC: “RUSCUS ACULEATUS EXTRACT EVIDENCE BASED MEDICINE SUPPORTED USE IN THE CHRONIC VENOUS DISEASES SYMPTOM AND SIGN TREATMENT

Ruscus aculeatus extract contains saponins, flavonoids, sterols, tyramine, cumarine, triterpenes and benzofurane. Ruscus extract can be used as a solid treatment or in the combination with other molecules including the flavonoid hesperidin methyl chalcone (HMC) and ascorbic acid. Ruscus extract possess venotonic activity related to the direct activation of α 1- and α 2 adrenergic receptors located in the smooth muscle cells as well as an indirect effect via the noradrenalin release. In the studies an increase of the lymphatic tone was also documented. Among other important proprieties of ruscus extract, the microcirculation protection (including, endothelial cell protection, inhibition of their activation and endothelial layer permability decrease), as well as inflammation reduction should also be mentioned. As documented in the recent studies the anti-inflammatory and protective effects of ruscus on the capillaries are, at least in part, mediated via muscarinic receptors. HMC used in the combined drugs containing ruscus extract (eg. Cyclo 3 Fort) potentially lowers the capillary filtration rate and has venoconstrictive properties (additive to ruscus own proprieties). **de Souza MDGC et al. Effects of Ruscus extract on muscarinic receptors: Is there a role for endothelium derived relaxing factors on macromolecular permeability protection and microvascular diameter changes? Clin Hemorheol Microcirc. 2021;77(4):443-459**

According to the systemic review and meta-analysis of 10 RCTs ruscus extract in combination with HMC and vitamin C shows significant efficacy on the CVD individual symptom improvement, including pain, heaviness, fatigue, feeling of swelling, cramps, itching and paresthesia. Regarding objective assessment of leg oedema ruscus compared with placebo significantly reduced ankle circumference as well as foot volume. **Kakkos et. al. 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; 36(2):93-106**

An overview of the available evidence evaluated in the Guidelines According to the Scientific Evidence position ruscus extract + HMC + ascorbinic acid among the drugs with the high level of evidence in regard to the CVD symptoms reduction (level A of evidence for pain, heaviness, filling of swelling and paresthesia decrease) as well as leg swelling decrease. **Nicolaidis A, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. Int Angiol. 2018 Jun;37(3):181-254.**

Despite the successful use of ruscus treatment in the patients with various advancements of the CVD (in the range from C0s to C4), there is lack of the high quality evidence on the clinical efficacy of ruscus and ruscus containing drugs in the VLU healing. **Kakkos SK, Guex JJ, Lugli M, Nicolaidis AN. CEAP clinical classes C0S-C4: differences, similarities and role of Ruscus + HMC + vitamin C in patients with chronic venous disease. Int Angiol. 2020 Apr;39(2):118-124.**

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STATEMENT FOR PUBLIC EVIDENCE-BASED AWARENESS

DOMAIN 8, Statement 4

“Ruscus aculeatus demonstrated to be potentially beneficial in chronic venous disease related symptoms improvement as well as in chronic venous disease oedema treatment”

4 SELECTED REFERENCES

- 1.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
- 2.Jawien A, Bouskela E, Allaert FA, Nicolaïdes AN. The place of Ruscus extract, hesperidin methyl chalcone, and vitamin C in the management of chronic venous disease. *Int Angiol.* 2017 Feb;36(1):31-41
3. Kakos SK, Guex JJ, Lugli M, Nicolaides AN. CEAP clinical classes C0S-C4: differences, similarities and role of Ruscus + HMC + vitamin C in patients with chronic venous disease. *Int Angiol.* 2020 Apr;39(2):118-124.
4. Raully-Lestienne I, Heusler P, Cussac D, Lantoine-Adam F, de Almeida Cyrino FZG, Bouskela E. Contribution of muscarinic receptors to in vitro and in vivo effects of Ruscus extract. *Microvasc Res.* 2017 Nov;114:1-11

identified LITERATURE BIAS

Heterogeneity of the studies performed with ruscus extract only as well as with ruscus in combination with HMC and vitamin C

SUGGESTED NEXT LINES OF RESEARCH

Timing and dosage protocols in early and advanced stages of CVD,
Efficacy in lymphatic drainage improvement in phlebolympheoedema and lymphoedema