THE CLINICAL EFFICACY OF *RUSCUS ACULEATUS* EXTRACT: IS THERE ENOUGH EVIDENCE TO UPDATE THE PHARMACOTHERAPY GUIDELINES FOR CHRONIC VENOUS DISEASE?

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ABSTRACT
The wide range of clinical presentations and patient complaints related to chronic venous disease often require complex treatments based on lifestyle modification, the use of compression stockings, pharmacotherapy, and/or surgical or other minimally invasive treatments.
According to most available guidelines, the main indication for pharmacotherapy in patients with chronic venous disease is the presence of symptoms related to venous hypertension, including leg pain and heaviness. Additional patient complaints that are indicators for venotrophic pharmacological treatment include leg edema and venous leg ulcers. Despite these suggested indications, the clinical evidence for the benefit of many available drugs remains questionable. The paper presents an overview of the available literature on *Ruscus aculeatus* extract and drugs containing *Ruscus* extract. The current literature and a recent systematic review and meta-analysis confirm the use of *Ruscus aculeatus* extract as a phlebotropic drug with evidence-based confirmation of its positive effects on complaints related to chronic venous disease. The variety of possibilities for the pharmacological treatment of chronic venous disease enables pharmacological intervention using various compounds that address different mechanisms of chronic venous disease-related pathology. The current evidence concerning *Ruscus aculeatus* as a component of combined treatment (with hesperidin methyl chalcone and ascorbic acid) suggests the need to upgrade the position of this drug in the current CVD pharmacotherapy guidelines.

Key words: *Ruscus aculeatus* extract, chronic venous disease, clinical efficacy, pharmacotherapy.

INTRODUCTION

Understanding the pathogenesis of chronic venous disease (CVD) and the clinical consequences of venous hypertension has motivated the search for successful treatments for this condition [1, 2]. The wide range of clinical presentations and patient complaints related to CVD often require complex treatments based on lifestyle modification, the use of compression stockings, pharmacotherapy, and/or surgical or other minimally invasive treatments [2].

Pharmacotherapy is an important component of CVD treatment, and a wide range of drugs is currently available [2, 3]. Despite the number of medications used and suggested for the treatment of CVD, the evidence-based confirmation of the efficacy of many of these drugs remains limited. A lack of properly designed trials and poor quality research cause significant difficulties in creating guidelines for proper CVD treatment. According to the guidelines proposed by the European Society for Vascular Surgery (2015), venoactive drugs should be considered as a treatment option for the swelling and pain caused by chronic venous disease [4]. The guidelines proposed by the American Venous Forum and the Society for Vascular Surgery published 4 years earlier suggest the use of this group of drugs for patients with pain and swelling due to chronic venous disease in countries where these drugs are available [5].

In a document published in 2014 (Management of the Chronic Venous Disease of the Lower Limbs: Guidelines According to the Scientific Evidence), Nicolaides *et al.* proposed using grades to recommend the use of venoactive drugs for the "relief of symptoms associated with

CVD in patients in CEAP classes C0s to C6s and those with venous edema (CEAP class C3)" [2].

Pharmacological treatment grading proposals have been suggested in 2005 in an International Consensus Statement by Ramelet *et al*. and in 2008 in a Guideline Document proposed by Nicolaides *et al.* [3, 6]. Based on previous guideline documents and the available literature, in new guidelines introduced in 2014, the quality of EBM studies was assessed as moderate for the use of micronized purified flavonoid fraction (MPFF), rutosides, red vine leaf extracts, calcium dobesilate, horse chestnut seed extract, and *Ruscus* extract, and the quality of evidence for the use of non-micronized or synthetic diosmins, *Ginkgo biloba*, and other venoactive drugs was assessed as poor [2]. Based on an evaluation of the literature, a strong recommendation (Grade 1B according to the GRADE system) was proposed only for MPFF, and a weak recommendation was given for the use of the other abovementioned drugs, with a grade 2B recommendation for rutosides, red vine leaf extract, calcium dobesilate, *Ruscus* extract and horse chestnut seed extract and a grade 2C recommendation for non-micronized or synthetic diosmins and *Ginkgo biloba* [2].

Ongoing research on CVD pathogenesis and new clinical data on pharmacological treatments and their efficacy change our understanding of the goals and possibilities of pharmacological treatment. From the clinical point of view, effects on vein tonus, decreased swelling due to improved lymphatic drainage and decreased permeability of microcirculatory vessel walls, endothelially protective effects, and anti-inflammatory and inflammation inhibitory effects are the primary components expected of many phlebotropic drugs [2, 3]. Despite laboratory data confirming some of these activities, the often subjective character of the reported symptoms related to CVD, as well as the variety of clinical presentations, cause difficulties when attempting to objectively document the positive clinical effects of a particular drug.

As new studies aiming to find new targets for pharmacological treatment are proposed, there is an urgent need for the unification of study outcome criteria and their assessment in the field of CVD research. Many currently available studies use CEAP classification as well as the VAS (visual analog scale) as bases for the evaluation of patients and disease states, but quality of life and symptom assessments are necessary for the more precise evaluation of the efficacy of pharmacological treatments. The use of more complex complaint-oriented scales including the VCSS (Venous Clinical Severity Score) or a dedicated quality of life evaluation such as CIVIQ or VEINES-QOL/Sym questionnaires has been proposed [2, 7]. In this context, when searching for evidence-based justifications for the use of a particular venotonic agent, the potential role of properly performed studies should be emphasized.

RUSCUS ACULEATUS EXTRACT AND RELATED COMPOUNDS: LABORATORY RESEARCH AND CLINICAL ACTIVITY

Ruscus aculeatus extract contains two major saponins: ruskogenin and neuroruskogenin. According to previous studies, the extract contains other saponins (including ruscin and ruscoside), many of which have described anticancer activities [8, 9]. Along with saponins, *Ruscus aculeatus* extract contains flavonoids, sterols (sitosterol, stigmasterol, and kempesterol), tyramine, coumarin, triterpens, lignoceric acid, glycolic acid, and benzofuranes [10-14]. *Ruscus aculeatus* extract has been used for many years to decrease sensations of leg heaviness and leg swelling. Among its confirmed activities, one of the major effects of *Ruscus* extract is the vasoconstrictive activity related to α-1 and α-2 receptor agonism in the vessel wall and the release of norepinephrine from adrenergic nerve endings [15-18]. Recently, new pathways of *Ruscus* extract activity have been discovered, suggesting a role for muscarinic receptor agonism. Acethylocholine muscarinic and nicotinic receptors are responsible for many different activities at the molecular and tissue levels, and muscarinic receptors are present on endothelial cells. As documented by Bouskela, muscarinic receptor agonism (expressed by *Ruscus* extract compounds) is at least partially responsible for venule vasoconstriction [19].

According to previous studies, *Ruscus* extract has effects not only on veins but also on the lymphatic and capillary vessels [15]. Various mechanisms for the activity of *Ruscus* extract in protecting microcirculation have been suggested, including vessel vasoconstriction leading to decreased venous hypertension and local protective activity related to endothelial cell protection and anti-inflammatory properties [15-17]. An important benefit of the administration of *Ruscus aculeatus* extract is the inhibition of histamine-induced increased vessel wall permeability [15, 20]. *Ruscus* extract also affects the early phase of inflammatory reactions, leading to the decreased rolling and adherence of leucocytes to the venous wall. According to recent research, both of the abovementioned processes are at least partially controlled by the muscarinic receptor pathway [15, 19]. In previous studies, the anti-inflammatory properties of *Ruscus* extract were also explained by an effect on the activation of adhesive molecule (ICAM-1) expression, and a role for *Ruscus* extract in the action of anti-elastase on decreased vessel wall permeability was suggested [21, 22]. Vasoconstrictive *Ruscus* activity appears to be hormone dependent; in a study by Miller *et al*., venous vasoconstriction increases in the presence of increased progesterone levels [23]. The benefits of *Ruscus* extract have also been documented in the lymphatic system and in lymphedema patients [15]. Among the suggested mechanisms for these benefits, along with the effect of *Ruscus* on decreased vessel

permeability, lymph vessel constriction and increased veno-lymphatic return have been suggested [24, 25].

Concerning the clinical efficacy of *Ruscus* extract, several studies have examined *Ruscus aculeatus* extract as an active compound of a therapeutic regimen, but few studies focus on *Ruscus* extract as a unique pharmacological treatment. In a randomized, placebo controlled study performed on a group of 148 patients with chronic venous disease (using solid *Ruscus* extract only) Vanscheidt (2002) evaluated the results of *Ruscus aculeatus* extract administration (in capsules containing 4.5 mg of pure roscogenin administered twice daily) over 12 weeks. The primary endpoint of the study was decreased foot and ankle volume. Secondary parameters were changes in the circumference of the lower leg and ankle, changes in subjective symptoms and quality of life, overall efficacy and tolerability, and safety parameters. The administration of *Ruscus aculeatus* extract resulted in significant differences between the treatment groups (*Ruscus* extract capsules vs. placebo) in leg volume as well as changes in ankle and leg circumferences after 8 and 12 weeks. Simultaneously, improvements in subjective CVD symptoms (heavy, tired legs and the sensation of tension) and their severity were observed in patients administered *Ruscus aculeatus* extract. A positive correlation between changes in leg volume and changes in the symptoms of heavy lower legs, the sensation of tension, and tingling sensations was documented [26].

RUSCUS ACULEATUS EXTRACT AS PART OF THE COMBINED PHARMACOLOGICAL TREATMENT OF CHRONIC VENOUS DISEASE

Ruscus aculeatus extract can be used as an individual treatment or as a mixture with other venotonic substances in combination therapies. In the current classification of venoactive drugs, *Ruscus aculeatus* extract is considered a saponin. However, as mentioned above, *Ruscus* extract also contains other biologically active substances, such as flavonoids [3].

Few studies focused on CVD symptom treatment are dedicated to the administration of *Ruscus* extract alone. Most of the currently available evidence focuses on the evaluation of a commonly used combination of drugs consisting of *Ruscus aculeatus* extract, hesperidin methyl chalcone (HMC), and ascorbic acid. Trimethyl hesperidin chalcone is a derivative of the flavonoid hesperidin that exhibits various venoprotective effects including a potential influence on the decrease of vessel wall permeability and venous tone [3, 27, 28]. The number of previously performed studies as well as the growing body of evidence concerning this combined treatment allow important clinical conclusions to be drawn.

The positive influence of the combined treatment (*Ruscus* extract + HMC + ascorbic acid) was confirmed in the laboratory and in clinical studies [15, 27, 28–30]. Similar to the activity of *Ruscus* extract, the combination of drugs including *Ruscus* has vasoconstrictive effects based not only on *Ruscus* activity but also on the properties of HMC [15, 17, 29]. Thebault, testing the activity of the combined treatment (*Ruscus* extract + HMC+ ascorbic acid; Cyclo 3 Fort, Pier Fabre, France), documented an additive vasoconstriction effect of HMC (the administration of *Ruscus* extract resulted in a 50% decrease in vein dilation, while the administration of HMC led to a 40% decrease in vein dilation) [30]. Jager conducted a duplex Doppler-based study dedicated to the effect of the same combined treatment (Cyclo 3 Fort) on the deep and superficial venous system and documented the presence of deep vein vasoconstriction with an increase in the flow parameters in the deep vein system of the leg after Cyclo 3 Fort administration [31].

The positive effects of the combined treatment were also confirmed at the microcirculatory level. Bouaziz *et al.* suggested an influence of the combined drug (*Ruscus aculeatus* extract, HMC, and ascorbic acid) on endothelial cell protection. In this study, *Ruscus* extract inhibited the hypoxia-induced activation of endothelial cells (resulting in decreased ATP content, phospholipase A2 activation, and increased neutrophil adherence to endothelial cells). According to this study, both *Ruscus* extract and HMC were able to reduce a hypoxia-induced decrease in ATP, and the effect of the combined treatment appears to be additive [32]. In another study, Bouskela *et al.* documented the influence of the abovementioned pharmacological treatment on the microvascular permeability induced by various agents in hamster cheek pouches [17]. The effect of the combined treatment (*Ruscus*, HMC, and ascorbic acid) on capillary wall permeability was also documented in diabetic patients [33].

Clinical plethysmographic studies have also produced interesting results. Bocccalon performed a double blind, placebo-controlled study with *Ruscus* extract, HMC, and ascorbic acid in 20 CVD patients and examined heat-induced vein distension and post-occlusion venous flow plethysmographically. According to the results of this study, the proposed pharmacological treatment decreased induced vein distention and improved normal vein drainage compared with the placebo group [34]. Improvements to venous tone and capillary sealing were confirmed after treatment with the combination of *Ruscus* extract, hesperidin methyl chalcone, and ascorbic acid in other studies [27, 28]. Rudofsky assessed venous capacity (VC) reduction and tissue volume decreases after the administration of the abovementioned treatment in healthy volunteers and documented a statistically significant decrease in both parameters [27]. In another clinical, prospective, capillaroscopy assessment-based study, in a group of 124 CVD patients treated pharmacologically for 8 weeks with the combined treatment, decreased CVD symptom severity (including heaviness, cramps, and edema) corresponded with decreased intracapil-

lary fluid collection, reduced efferent loop thickening, decreased pericapillary beds, and decreased megacapillaries upon capillaroscopic examination [35]. In another recently published prospective study, the combination of *Ruscus* extract, HMC, and ascorbic acid was used in a group of 65 women (class C2s and C3s), and significant improvements in the plethysmographically evaluated venous refilling time correlated with improvements in functional CVD symptom severity [36].

Several other studies have documented the positive influence of combined *Ruscus*-based drug therapy on CVD symptom severity and on decreased leg edema [15, 37, 38]. Rieger, in a randomized, controlled, double-blind study performed in an orthostatic position, documented a significant decrease of calf and foot swelling after treatment with *Ruscus* extract, HMC, and ascorbic acid [37]. Cluzan treated patients with secondary lymphedema of the upper limb after breast cancer therapy with Cyclo 3 Fort or placebo and documented an arm volume reduction of 12.9% after 3 months of therapy [25]. Di Pieri, in a placebo controlled study performed in Italy with *Ruscus aculeatus* extract, HMC, and ascorbic acid (Cyclo 3 Fort), reported a statistically significant improvement in CVD-related symptoms [39]. Guex *et al*., in a study performed on Latin American patients, observed a significant decrease in CVD clinical symptom severity and a significant improvement in the quality of life in C0s-C3 CVD patients [40]. A meta-analysis of the efficacy of the combination of *Ruscus* extract, HMC, and ascorbic acid for the treatment of chronic venous disease patients was presented by Boyle *et al.* [41]. In this analysis, the results of 20 placebo controlled randomized double blind studies and 5 randomized studies against a comparison drug in patients with CVD were evaluated (the study population included 10,246 patients). The combined treatment significantly reduced the severity of pain, heaviness, cramps, and paresthesia. A reduction in the severity of leg edema and decreases in calf and ankle circumference were also observed, but these differences were not statistically significant [41].

Very few head to head comparisons of phlebotropic drugs have been performed. In 1999, a comparison of Cyclo 3 Fort and hydroxyethylrutosides in chronic venous and lymphatic incompetence was performed by Beltramino *et al.* [42]. In this study, the symptoms of chronic venous lymphatic insufficiency, including heavy, tired, and swollen legs or leg pain were evaluated at baseline and after 30, 60, and 90 days of treatment. In both groups, a reduction in CVD complaints was observed, which was more rapid in the group of patients administered Cyclo 3 Fort. Both groups exhibited reduced swelling, but after 90 days of treatment, this reduction was observed only in the group treated with Cyclo 3 Fort [42]. In another study, the efficacy of the combined treatment (*Ruscus* extract, HMC, and ascorbic acid) was compared with the administration of micronized diosmin [43]. In this randomized study of 100 patients, the reduction of symptoms (heavy legs, cramps, breast tension, pelvic congestion, edema of the lower limbs) and reduced ankle circumference were found in both groups with equivalent efficacy, but the initial decrease in symptom severity was more rapid in patients taking a *Ruscus*-containing drug regimen (symptoms were evaluated when treatment began, and 15 and 60 days after the start of treatment).

To summarize the available EBM-based knowledge on the efficacy of *Ruscus aculeatus* extract, HMC, and ascorbic acid (constituents of Cyclo 3 Fort) in improving individual venous symptoms and edema, a systematic review and meta-analysis of randomized double-blind placebo-controlled trials was recently presented by Kakkos and Allaert. [44]. This meta-analysis focused on 10 RCTs including 719 patients with CVD symptoms; the influence of pharmacological treatment with Cyclo 3 Fort on patients with leg edema was also analyzed [25, 38, 44-51]. According to the results, *Ruscus* extract, HMC, and ascorbic acid were statistically superior to placebo in reducing all analyzed CVD symptoms, including both global symptoms and the number of symptoms in a qualitative analysis. When analyzing individual CVD-related leg symptoms, statistically significant reductions in leg pain, heaviness, fatigue, sensations of swelling, cramps, pruritus, and paresthesia were observed. *Ruscus*-based therapy was also found to be superior to placebo at significantly reducing objectively estimated venous edema. Observations based on qualitative evaluations confirmed a significant reduction in global symptoms, as well as in pain and heaviness, analyzed as both continuous and categorical variables. The severity of cramps, pruritus, and paresthesia were reduced when assessed as continuous variables but not when evaluated as categorical variables. In the treatment of leg edema, *Ruscus*-based therapy statistically significantly reduced ankle circumference in comparison with placebo. The authors of this meta-analysis conclude that based on the high-quality evidence available, *Ruscus* extract-based pharmacological treatment is highly effective at reducing objectively measured leg edema (ankle circumference and leg/foot volume) as well as CVD symptoms such as leg pain, heaviness, the feeling of swelling, fatigue, cramps, pruritus, and paresthesia, as well as global symptoms and the total number of venous symptoms in patients with CVD. As mentioned above, the meta-analysis performed by Kakkos was based on the evaluation of randomized prospective trials and on the selection of high-quality trials. The conclusion of this analysis is also supported by a number of prospective observational studies and laboratory research. *Ruscus aculeatus* extract (especially in combined treatment with HMC and ascorbic acid) is among those drugs with high-quality evidence for their clinical efficacy in CVD treatment. As in most studies, a wide range of CVD patients was enrolled, and future studies should focus on the selection of patients with the highest clinical benefit from the implementation of pharmacological treatment.

CONCLUSIONS

The variety of possibilities for the pharmacological treatment of chronic venous disease enables pharmacological intervention using various compounds that address different mechanisms of chronic venous disease-related pathology. Despite a relatively extensive theoretical background and previous laboratory research, the clinical efficacy of pharmacological treatment requires clinical proof based on properly performed clinical studies. The current evidence concerning *Ruscus aculeatus* extract as a component of combined treatment (with HMC and ascorbic acid) suggests the need to upgrade the position of this drug in the current CVD pharmacotherapy guidelines.

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