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# Comparative Efficacy and Safety of a Horse Chestnut Formulation vs. Diosmin-Hesperidin in Chronic Venous Insufficiency: Randomized Double-Blind Trial

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## Abstract

**Background:** Chronic venous insufficiency (CVI) is a prevalent and incurable condition that can be managed through both medical and surgical interventions. **Objective:** To compare the safety and efficacy of a combination of *Aesculus hippocastanum*, *Polygonum acre*, *Smilax papyracea*, and rutin (Group A; $n_A = 60$) versus a combination of diosmin-hesperidin (Group B; $n_B = 60$), over a 90-day treatment period, in patients with symptoms consistent with CVI. **Methods:** Efficacy and safety were assessed using both self-paired and comparative study designs. Study endpoints included: 1) Severity of venous symptoms measured by the Visual Analogue Scale (VAS), 2) Quality of life via the CIVIQ-20 score, 3) Physician's assessment score, 4) Patient's self-assessment score, and 5) Ease of swallowing the pharmaceutical form, assessed by VAS. Safety profiles were also evaluated. **Results:** The Group A combination was statistically non-inferior to the Group B combination across all study endpoints, including venous symptom severity, quality of life, and both physician



and patient assessments. Group A's formulation was reported to perform better on quality-of-life (CIVIQ-20 score-Visit 3) ($p < 0.05$) and was easier to swallow ($p < 0.05$). Both treatments were well tolerated. **Conclusion:** Both regimens were safe and effective, with Group A showing better general performance in relation to Group B.

## Keywords

Chronic Venous Insufficiency, *Aesculus hippocastanum* and Associations, Diosmin-Hesperidin

## 1. Introduction

CVI (chronic venous insufficiency) is a syndrome of ancient prevalence in medical history. Correspondingly, it is possible to point out evidence of the ethnopharmacological use of plant species since Antiquity, dedicated to CVI symptomatic management. Even in our time, CVI remains an important clinical and surgical challenge, for which there is no curative treatment. During the last 50 years, plant species have been repositioned through modern development techniques and clinical research, consolidating their efficacy and safety for CVI, already established for centuries. This randomized, double-blind clinical trial aims to demonstrate the non-inferiority of a new combination consisting of the species horse chestnut, sarsaparilla, dotted smartweed, and rutin (ANVISA 111990032 Vastonic®) against a reference combination of diosmin-hesperidin in the symptomatic control of CVI.

### 1.1. Pharmacology of Tested Substances

*Aesculus hippocastanum*. Horse chestnut is a species native to western Asia that belongs to the Hippocastanaceae family. It was introduced in the Balkans, spreading widely through European inhabited areas [1] [2]. The extraction of escin, its main pharmacologically active derivative, is obtained from the dried plant, usually through alcohol or hydroalcoholic solutions, maceration, decoction and percolation techniques [3]-[5]. In humans, the nut of *A. hippocastanum* is traditionally used for several indications, including CVI [6]-[10]. Reported side effects are gastrointestinal discomfort, dizziness, and itching. There are records of death after ingestion of the whole plant by children [11]-[13]. *Polygonum acre*. There are descriptions of the traditional use of *Polygonum* spp., including species of Asian origin such as *Polygonum acre* (dotted smartweed), for indications such as joint inflammation, hemorrhoids and circulatory problems. Aqueous and alcoholic extraction are the extraction technologies used for the species. Its leaves, stems and roots are all used in the form of infusions, tinctures and baths. There are no known side effects attributed to *Polygonum acre* [14]-[16]. *Smilax papyracea*. Sarsaparilla (*Smilax* sp.) is a genus that encompasses more than 200 species of plants prevalent

in Europe, Central and South America, among them *Smilax papyraceae* (sarsaparilla). Since its pharmacologically active components are traditionally administered for the management of joint inflammation, it is assumed that sarsaparillha might play a role in the inflammatory component of CVI. Due to the fact their active ingredients are saponins, the method of extraction for sarsaparillha is similar to that of horse chestnut. There are no known side effects attributed to *Smilax papyraceae* [15] [16]. *Rutin*. The term rutin comes from the name *Dimorphandra mollis* (fava d'anta), a species which contains the referred substance. Its physiological role includes the absorption of vitamin C in the digestive tract. In humans, there are descriptions of the traditional use of the substance in indications such as hemorrhoids, capillary fragility, and CVI [17]. Plant extraction methods are hot reflux extraction, ultrasound-assisted extraction, and microwave-assisted extraction. There are no known side effects attributed to rutin [16] [18]-[20]. *Diosmin-hesperidin*. Hesperidin is extracted from the peel of *Citrus aurantium* and other citrus species [16] [21]. Diosmin is obtained from hesperidin through reaction of the latter with water followed by chemical purification. Diosmin is a venotonic agent that increases lymphatic drainage and reduces capillary as well as vascular permeability [22]. It is indicated in the symptomatic treatment of CVI and, in some countries, acute hemorrhoidal crises as well. Reported side effects are gastric discomfort, diarrhea, insomnia, and lethargy [23]-[25].

### 1.2. Chronic Venous Insufficiency

Lower limbs CVI is defined as the inability of the superficial venous system, deep venous system, perforating veins and venous valves to return blood to the heart. There are several causes and predisposing factors for this disorder, such as older age, family history, hormonal factors (e.g., pregnancy and exogenous hormone therapy), obesity, labor orthostasis, and sedentarism. CVI etiopathogenesis is characterized by the following factors: 1) endothelial injury due to local hypoxia impairing the synthesis of cell proteins, 2) thickening of the endothelium basement membrane, 3) release of proinflammatory factors, 4) oxidative stress, and 5) microthrombogenicity [26] [27]. Venous hypertension, interstitial leg edema, and blood vascularity deficit secondary to extrinsic arterial and microvascular compression ensue. These changes result in pain (vascular parietal distension), a feeling of heaviness in the legs (edema), night cramps (arterial vascular compression), as well as thickening and hyperpigmentation of the skin (blood extravasation). Venous and/or valve incompetence finally lead to hypertension of the entire venous system, dilation, and varicosity [28] [29]. Physical exam reveals vascular parietal tortuosity and dilations, valvular incompetence, and blood reflux in the lower limbs. Doppler ultrasound shows vascular structural abnormalities, dilated diameters, and valve incompetence. Therapy consists of conservative (compressive socks, lower limbs elevation, scar creams, occlusive bandages), invasive (endovascular procedures, surgery), and vasodilating agents such as phosphodiesterase inhibitors (pentoxifylline) [26]-[29].

## 2. Methods and Materials

This was a double-blind, non-inferiority, and randomized study for efficacy and safety evaluation of *Aesculus hippocastanum* 10 mg + *Polygonum acre* 10 mg + *Smilax papyracea* 40 mg + rutin 20 mg as two tablets bid (Group A; $n_A = 60$) vs. diosmin 450 mg + hesperidin 50 mg as two tablets bid (Group B; $n_B = 60$), both in a 90-day regimen, in CVI of lower limbs. Study's objectives were to evaluate clinical efficacy according to the following endpoints: 1) venous symptom severity according to VAS (visual analogic scale) (0 = no symptoms; 100 = worst symptoms possible), 2) quality of life according to CIVIQ-20 score [chronic venous insufficiency quality of life questionnaire—20 parameters]) (0 = no symptoms; 2 to 5, according to symptomatic intensity), 3) physician's assessment score according to a categorical scale (Very Good, Good, Fair, or Poor), 4) patient's assessment score according to a categorical scale (Very Good, Good, Fair, or Poor), 5) pharmaceutical form swallowability according to VAS (0 = very easy to swallow; 100 = too difficult to swallow), and 6) adherence (measured as the quantity of delivered pills). Tolerability was determined by asking the participants in V2 (D30) and V3 (D90) regarding any adverse events (AEs) they might have noticed. The study design is depicted in **Figure 1**.

The study population consisted of outpatients from Rio de Janeiro State, Brazil. The first patient was enrolled on 11/6/2023, the last one on 3/28/2024, and the last day of treatment was 7/1/2024. The study was performed under the coordination of Centro Universitário Serra dos Órgãos Medical School (UNIFESO). Study protocol and related documents received approval from the Institutional Review Board (approval No. 5.963.063). The protocol was conducted according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) and is registered at ClinicalTrials.gov (ID NCT06579482). No financial compensation was provided. All patients signed a written informed consent before any study-related activity.

Patients were included according to the following criteria: 1) individuals of both sexes ranging from 18 and 65 years of age (reproductive-age females had to practice contraception during the study period), and 2) a clinical picture consistent with CVI of lower limbs. Patients were non-included according to the following criteria: 1) hypersensitivity to study medications, 2) gallbladder stone history, 3) gastritis history, 4) arterial blood pressure >145 × 100 mmHg, and 5) concomitant use of other CVI medications. Patients were randomized according to the order in which they arrived at the study center, using Random Allocation Software. The randomization code corresponded to the patient number and consisted of a sequential three-digit number (the first patient was 001, the second 002, and so on until the number of randomized patients reached 120). Randomization was performed sequentially for both groups, in blocks of four, with a 1:1 ratio between treatment groups. Patients were blinded to the identification of the treatment. No differences were observable in the packaging and labels of the study drugs. The identification of the drug was traceable through the respective label number. All

enrolled patients were submitted to clinical and laboratory screening before the study started. All data were recorded in the clinical research form.

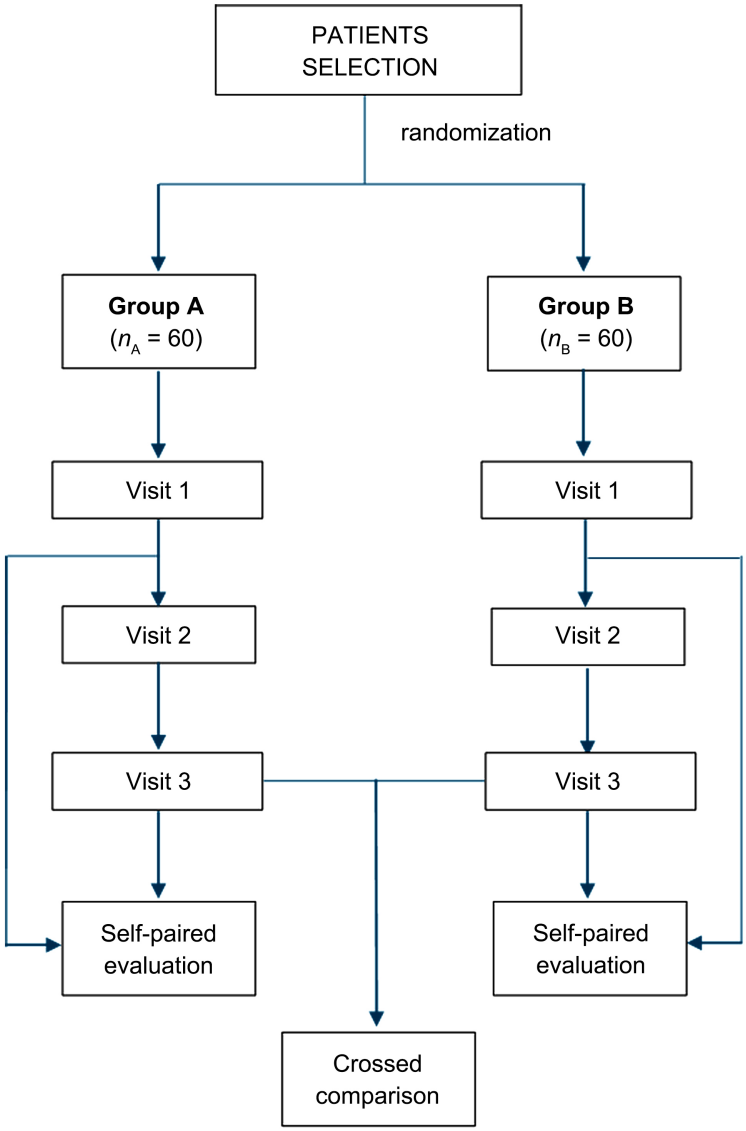


**Figure 1.** Diagram representing study design of *Aesculus hippocastanum* and combinations (Group A) vs. diosmin-hesperidin (Group B).

With a margin of non-inferiority set at 20 mm (VAS) and an estimated standard deviation of 30 for the primary outcome, the number of subjects required was 40 to obtain a power of 90% to ascertain non-inferiority of 20 mm with a unilateral significance level of 0.05. In a clinical study published by Steinbruch et al., a non-inferiority margin of 20 mm in VAS was established for the demonstration of noninferiority of nonmicronized diosmin in relation to micronized diosmin plus hesperidin [30]. Based on the above parameter, the investigators established 20 mm as the effect size for sample estimate. As major deviations of 33.3% were anticipated, the total number of patients required for randomization was 120. Sta-

tistical analysis of collected data was performed using Power and Precision statistical software (v. 4.1). Adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities version 21.0 (in Portuguese). Clinical efficacy and safety data were statistically analyzed by comparing the results of Visit 3 relatively to Visit 1, in a self-paired and comparative fashion. Results and safety data were processed in an intent-to-treat analysis.

## 3. Results

### 3.1. Population Profile

Participants' general profile is detailed in Table 1.

Table 1. Participants general profile.

| Participants Profiles | Group A | | Group B | |
|---|---|---|---|---|
| **Age** (mean) | 47.3 | | 47.9 | |
| **Gender** | 4 males | 54 females | 2 males | 53 females |
| **Height** (mean) (cm) | 162 | | 161 | |
| **Ethnicity** | 22 whites; 21 mixed; 13 black | | 27 whites; 7 mixed; 21 black | |
| **Reference leg** | left: 38 | right: 20 | left: 23 | right: 32 |
| **CEAP*** | C1: 15; C2: 22; C3: 21; C4: 0 | | C1: 21; C2: 25; C3: 9; C4: 0 | |

*Clinical, etiology, anatomy, pathophysiology. **C1:** clinical compromise of superficial venous system, no external signs of the condition; **C2:** reticular veins compromise as vascular spiders (no external signs of deep venous involvement); **C3:** superficial varicosities and perforating/deep veins changes (no external signs of deep venous involvement); **C4:** structural compromise of perforating vessels and deep venous system; edema formation that might have obscured abnormal superficial veins.

Table 2. Physical exam results at Visit 1 (pretreatment) and Visit 3 (end-of-study visit).

| Parameter | Visit 1 | Visit 3 |
|---|---|---|
| | mean (±SD) | mean (SD±)* |
| Weight | 66.2 ± 9.8 | 64.9 ± 6.6 |
| Body mass index (kg/cm$^2$) | 25.1 ± 2.9 | 24.9 ± 2.5 |
| Heart rate (bpm) | 71 ± 6 | 68 ± 6 |
| Respiratory rate | 14 ± 1 | 14 ± 1 |
| Mean blood pressure (mmHg) | 124.1 ± 9.6 | 123.5 ± 8.8 |

*No statistically significant difference in relation to Visit 1 parameters [$p > 0.05$ for all parameters (t test)].

Twenty patients reported concomitant treatments with proton bomb inhibitors, corticosteroids, antihypertensives, statins, benzodiazepines, hypoglycemic agents, and fibers. No substances belonging to these therapeutic classes were regarded as potentially interactive with either Group A or Group B combinations. No participants reported using CVI medications. Some patients were withdrawn from the study for the following reasons: lost to follow-up (three individuals), protocol violation (two individuals), clinical worsening (one individual), and other reasons (one individual). No significant changes in physical exam parameters were noted in Visit 3 in relation to Visit 1 in the general population (Table 2).

### 3.2. Tested Combinations Performance

Intragroup and comparative results of Group A and Group B combinations are depicted in Table 3.

Table 3. Intragroup and comparative consolidated study results per Visit per Group.

| Studied Groups | Visit 1 | Visit 2 | Visit 3 |
|---|---|---|---|
| **Venous symptom severity according to VAS** (mean ± SD) | | | |
| **Group A** | 49.7 ± 7.6 | 26.0 ± 7.6<br>95% CI* (23.9 - 28.6) | 17.4 ± 7.6<br>95%CI (15.3 - 19.4) |
| **Group B** | 46.0 ± 9.4 | 31.2 ± 12.9<br>95%CI (27.8 - 34.5) | 21.1 ± 12.7<br>95%CI (17.8 - 24.6) |
| One-sample t-test that proportion = specific value (two-tailed). Graphic representation of the above results is depicted in Figure 2. **Intragroup comparisons:** 1) Group A provided relief in V2 ($p = 0.05$), intensified in V3 ($p < 0.05$ in relation to V2), and 2) Group B provided relief in V2 ($p < 0.05$), intensified in V3 ($p < 0.05$). **Intergroup comparison:** Group A relieved symptoms in V2 and V3 better than Group B ($p < 0.05$). **Investigators' interpretation:** both Group A and Group B combinations were effective, but Group A combination was more effective. | | | |
| **CIVIQ-20 score** (percentual decrease) | | | |
| **Group A** | - | 20.4% | 30.7%<br>95%CI (0.20 - 0.43) |
| **Group B** | - | 17.6% | 24.2%<br>95%CI (0.23 - 0.39) |
| One-sample test that proportion = specific value (two-tailed). Graphic representation of the above results is depicted in Figure 3. **Intragroup comparisons:** 1) Group A performed better in V3 in relation to V2) ($p < 0.05$), and 2) Group B did not attain cutoff for null hypothesis rejection in V2 (>20% of percentual points decrease), turning V3-V2 comparison not warranted. **Intergroup comparison:** Group A performed better than Group B in V3 ($p < 0.05$). **Investigators' interpretation:** Group A combination was more effective than Group B combination. | | | |

**Continued**

| | | | |
|---|---|---|---|
| **Physician's assessment score** (mean ± SD) | | | |
| **Group A** | - | 28.6 ± 6.9 | 30.0 ± 7.6<br>95%CI (26.9 - 29.1) |
| **Group B** | - | 26.1 ± 6.5 | 30.0 ± 9.4<br>95%CI (28.0 - 31.0) |
| One-sample t-test that proportion = specific value (two-tailed). Graphic representation of the above results is depicted in Figure 4. A discrete value was attributed to each categorial item of the 4-item scale (poor = 10, fair = 20, good = 30, very good = 40). **Intragroup comparisons:** 1) Group A performed better in V3 in comparison to V2 ($p < 0.05$), and 2) Group B performed better in V3 in comparison to V2 ($p < 0.05$). **Intergroup comparison**: 1) Group A performed better in V2 in comparison to Group B ($p < 0.05$), and 2) Group A and Group B performed equally in V3. **Investigators' interpretation:** Group A and Group B were both effective (even though Group A provided earlier improvement). | | | |
| **Patient's assessment score** (mean ± SD) | | | |
| **Group A** | - | 28.7 ± 7.6 | 32.0 ± 8.4<br>95%CI (29.0 - 34.0) |
| **Group B** | - | 26.0 ± 7.2 | 29.6 ± 8.5<br>95%CI (26.0 - 31.0) |
| One-sample t-test that proportion = specific value (two-tailed). Graphic representation of the above results is depicted in Figure 5. A discrete value was attributed to each categorial item of the 4-item scale (poor = 10, fair = 20, good = 30, very good = 40). **Intragroup comparisons:** Group A and Group B performed better in V3 in comparison to V2 ($p < 0.05$). **Intergroup comparison**: Group A performed better in V2 and V3 in comparison to Group B ($p < 0.05$). **Investigators' interpretation:** Group A and Group B were both effective, Group A performing slightly better. | | | |
| **Pharmaceutical form difficulty to swallow according to VAS** (mean ± SD) | | | |
| **Group A** | - | | 2.3 ± 8.4** |
| **Group B** | - | | 36.1 ± 22.5 |
| One-sample t-test that proportion = specific value (two-tailed). Group A performed better than Group B ($p < 0.05$). **Investigators' interpretation**: pharmaceutical form was swallowed more comfortably in Group A than in Group B. | | | |

*Confidence interval. **A SD higher than the mean was due to the proximity of the latter to zero.

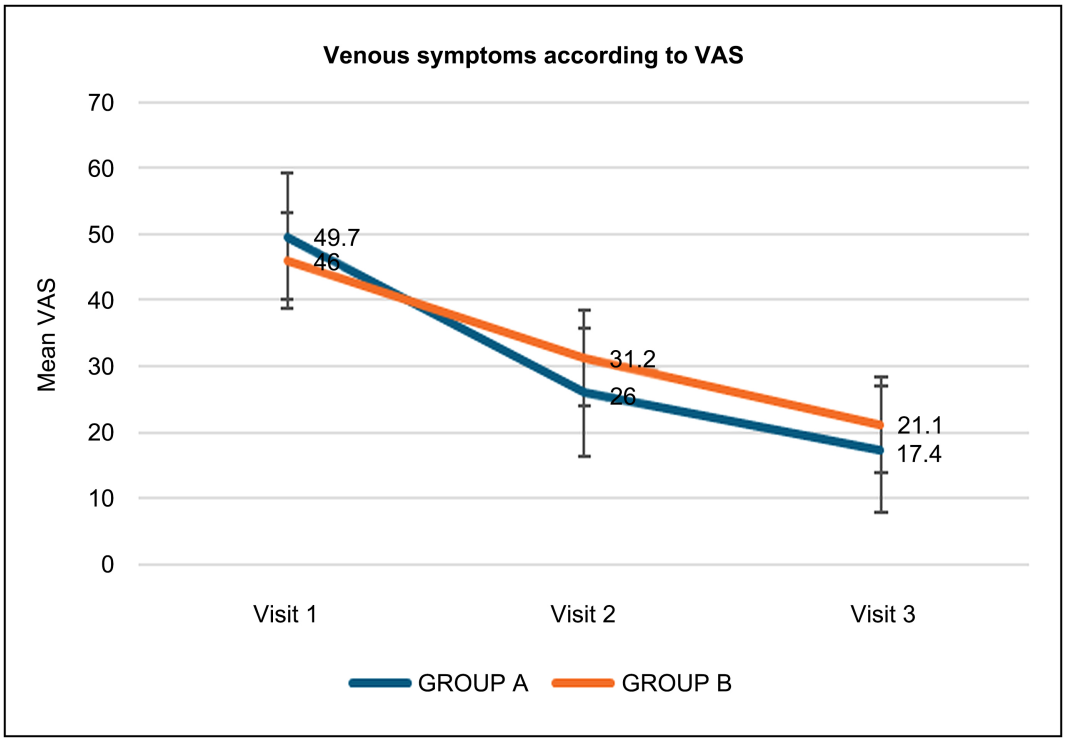


**Figure 2.** Graphic representation of the efficacy endpoint venous symptom severity according to VAS of Group A vs. Group B (mean ± SD [standard deviation]). Both Groups performed better in V3 in comparison to V1 ($p < 0.05$). Group A performed better than Group B for V2 ($p < 0.05$).

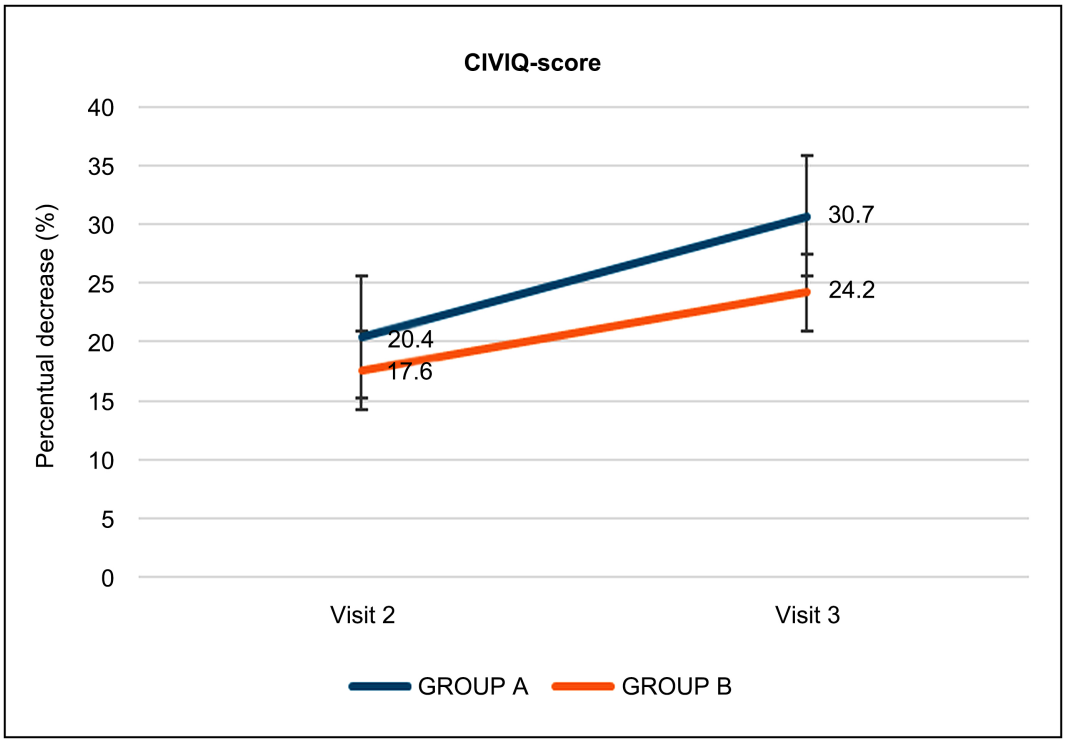


**Figure 3.** Graphic representation of the efficacy endpoint CIVIQ-20 score of Group A vs. Group B (percentual decrease). Group A performed better in V3 in comparison to V2 ($p < 0.05$). Group A performed better than Group B in V3 in comparison to V2 ($p < 0.05$).

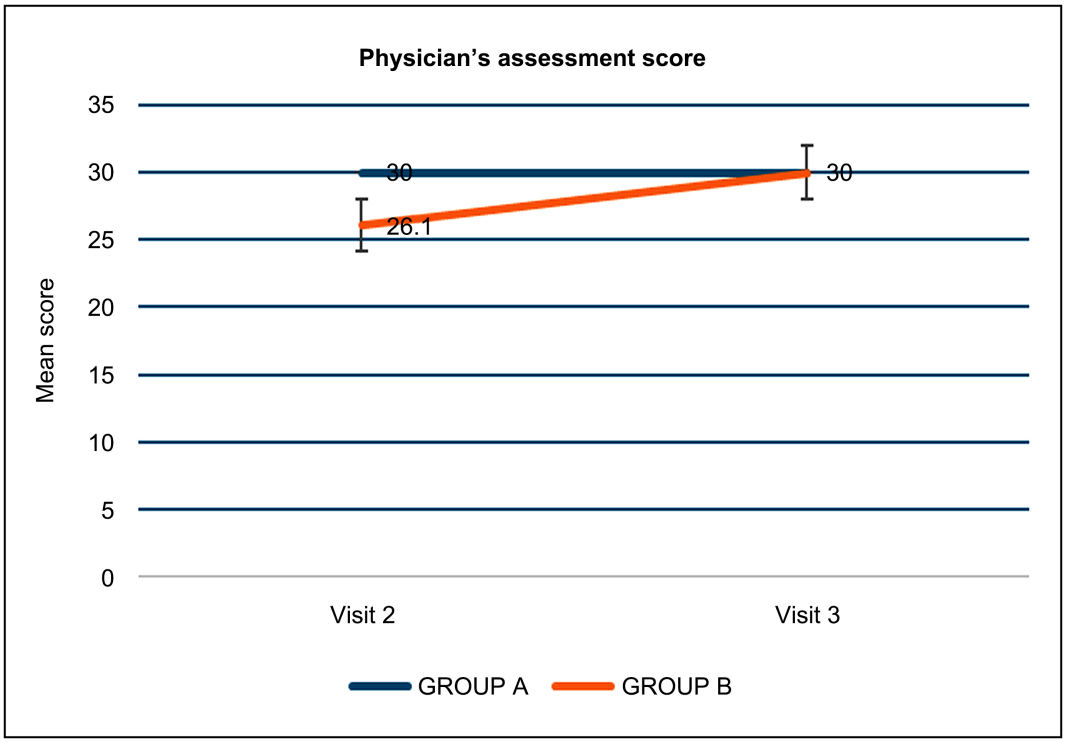


**Figure 4.** Graphic representation of the efficacy endpoint physician's assessment score of Group A vs. Group B (mean ± SD). Both Groups performed better individually in V3 in relation to V2 ($p < 0.05$) and Group A performed better than Group B in V2 ($p < 0.05$).

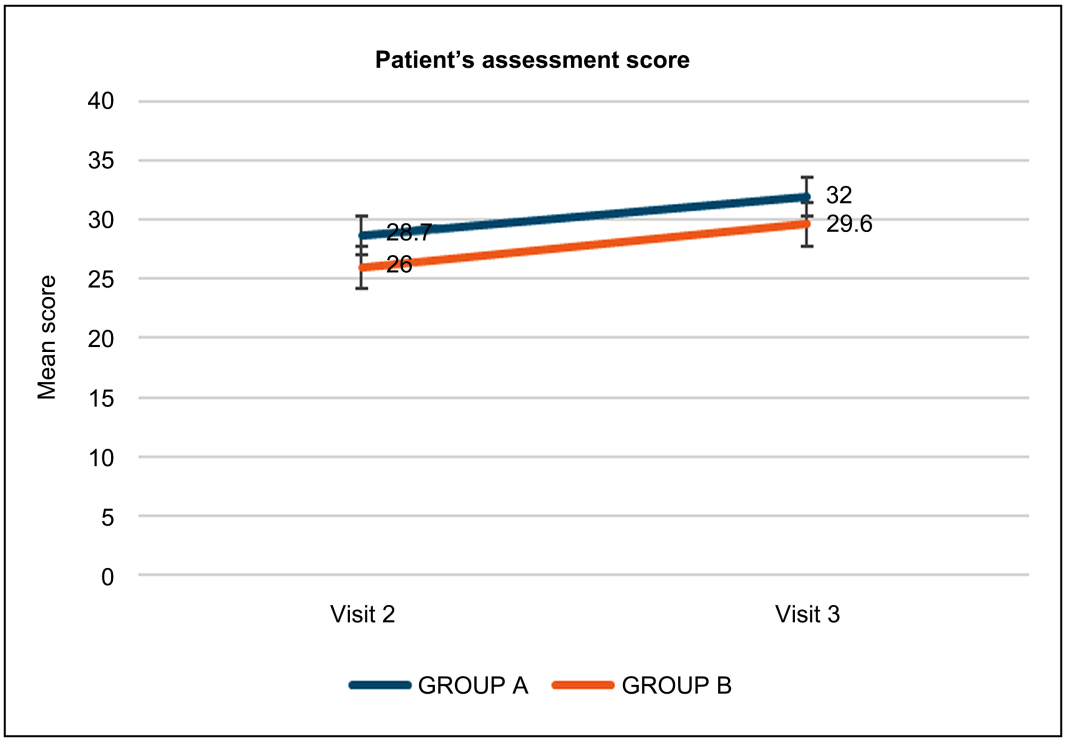


**Figure 5.** Graphic representation of the efficacy endpoint patient's assessment score of Group A vs. Group B combinations (mean ± SD). Both Groups performed better individually in V3 in relation to V2 ($p < 0.05$) and Group A performed better than Group B in V2 and V3 ($p < 0.05$).

The investigators were able to demonstrate Group A combination non-inferiority in relation to Group B combination regarding the following endpoints: 1) venous symptom severity according to VAS, 2) quality of life according to CIVIQ-20 score, 3) physician's assessment score, and 4) patient's assessment score. On the other hand, Group A showed superiority in relation to Group B in the endpoint of pharmaceutical form difficulty to swallow according to VAS. A trend towards improvement from V2 to V3 was noticed regarding the following endpoints, for both Groups: 1) venous symptom severity according to VAS, 2) CIVIQ-20 score, and 3) patient's assessment score. Adherence to therapy was 99% for both Groups (intention-to-treat analysis).

### 3.3. Safety

Twenty-four patients and 14 patients in Groups A and B, respectively, presented AEs (a total of 31.6% of all patients). Sixteen and 13 different AEs were demonstrated in Group A and Group B, respectively. All AEs were mild in severity, except for asthenia (moderate, not attributed to any of the tested substances, according to their respective literature), with no serious AEs recorded during the treatment period and no dropouts related to safety issues. In one episode in Group A the test combination had to be withdrawn, with resolution of the AE. Safety data from this study are detailed in Table 4.

Table 4. Number of patients presenting adverse events per Group (most common manifestations between brackets).

| Adverse Reactions | Group A | Group B |
|---|---|---|
| **Gastrointestinal** | 20 events (dyspepsia, nausea, bloating, abdominal discomfort) | 22 events (dyspepsia, nausea, bloating) |
| **Neurological** | 13 events (headache, insomnia, vertigo) | 12 events (headache, insomnia, vertigo) |
| **Total Events** | 33 | 34 |

## 4. Discussion

The medical management of symptoms in patients with mild to moderate chronic venous insufficiency (CVI) remains a frequent challenge in clinical practice. The limited availability of commercially accessible, orally administered pharmacological agents presents significant constraints for physicians, particularly in cases where surgical intervention is not indicated and long-term conservative therapy is the preferred approach. In this context, Aesculus hippocastanum, Polygonum acre, Smilax papyracea, Rutin, Diosmin, and Hesperidin—along with other botanicals and plant-derived compounds—have been re-evaluated and optimized through modern pharmaceutical technologies and clinical research, building upon

their long-standing tradition of efficacy and safety.

To the best of our knowledge, this is the first study in which the effectiveness and safety of *Aesculus hippocastanum* and associations is clinically tested. Additionally, study design was elaborated under a self-paired, randomized and comparative fashion, against a reference combination for CVI. Corresponding study findings are consistent with the general pharmacology described for the substances that compose both combinations, as documented in medical literature.

Investigators' findings were consistent with an equivalent efficacy of *Aesculus hippocastanum* and associations in relation to diosmin-hesperidin, with the additional observations:

1) both Groups demonstrated a consistent trend in clinical improvement of the tested endpoints across study Visits, with a slightly better general performance observed for *Aesculus hippocastanum* and associations, and

2) Group A tablet was more easily swallowed compared to the Group B tablet, an important factor regarding patient adherence in a chronic disease context.

Both treatment combinations were generally safe, with AEs being mild and limited to the gastrointestinal and nervous systems. Group B had a slightly higher incidence of AEs in general, in relation to Group A. Importantly, no severe AEs were reported, and no participants were withdrawn from the trial. A limitation of this study was gender bias due to female patients overrepresentation.

The overall impression of the investigators is that both combinations performed well, with Group A showing superior overall performance and better swallowability in relation to Group B.

## 5. Conclusions

The combination used in Group A (*Aesculus hippocastanum*, *Polygonum acre*, *Smilax papyracea*, and rutin) and Group B (diosmin-hesperidin) were both safe and effective in managing symptoms of CVI. Group A showed better general performance in relation to Group B as well more comfortable swallowability, an aspect that may enhance adherence in the treatment of CVI.

Further clinical studies are warranted to confirm and validate the efficacy and safety of Aesculus hippocastanum and combinations, and to more clearly define their therapeutic profile in the treatment and management of CVI.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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