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Recent Advances in Clinical Trials

Efficacy of Aesculus hippocastanum (Horse Chestnut) and Combination Therapies in Improving Clinical Outcomes of Hemorrhoidal Disease: A 60-Day Prospective Controlled Trial

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ABSTRACT

Background: *Hemorrhoids are prevalent, affecting up to 39% of adults, with venous wall failure as a key pathological factor. Limited pharmacological options target this mechanism, necessitating novel therapies.*

Objective: *To evaluate the safety and efficacy of Aesculus hippocastanum combined with Polygonum punctatum, Smilax papyracea, and rutin over 60 days in managing symptoms of Grade I–III hemorrhoids.*

Methods: *In a self-controlled design, 120 participants were assessed at baseline (Visit 1) and Day 60 (Visit 2) using the visual analogue scale (VAS), hemorrhoidal disease symptom score (HDSS), adapted Short Health Scale, physician and patient assessment scores, ease of swallowing, adherence, and safety monitoring.*

Results: *Significant improvements ($p<0.05$) were observed in all efficacy endpoints at Visit 2, with no grade differences and near-100% adherence. The combination was well-tolerated.*

Conclusion: *This 60-day regimen appears safe and effective for hemorrhoid symptom relief, independent of severity grade, with high swallowability potentially aiding adherence. ClinicalTrials.gov: NCT06705777.*

Keywords
Hemorrhoids, *Aesculus hippocastanum, Polygonum punctatum, Smilax papyracea* and rutin, self-controlled clinical trial.

Introduction
Hemorrhoids are a longstanding clinical challenge, with no curative pharmacological treatments available. Evidence from ethnopharmacology dates back to antiquity, supporting the use of plant species for symptomatic management. Over the past 50 years, certain plants have been repositioned through modern techniques and clinical research for venous wall failure syndromes [1]. This original self-controlled clinical trial aimed to demonstrate the efficacy and safety of a combination comprising horse chestnut (*Aesculus hippocastanum*), sarsaparilla (*Smilax papyracea*), dotted smartweed (*Polygonum punctatum*), and rutin for symptomatic control of hemorrhoids.

Pharmacology of the Tested Combination
Aesculus hippocastanum (horse chestnut), native to western Asia (Hippocastanaceae family), has been used ethnopharmacologically for venous insufficiency due to its escin content, which enhances vascular tone [2-6]. Side effects include gastrointestinal upset, dizziness, and pruritus [7,8]. *Smilax papyracea* (sarsaparilla) may address inflammation via antioxidant effects, with no known adverse reactions [9,10]. *Polygonum punctatum* (dotted smartweed) is traditionally used for circulatory issues, without reported side effects [10,11]. Rutin, derived from *Dimorphandra mollis*, supports venous health in conditions like hemorrhoids, with a favorable safety profile [10,12,13].

Hemorrhoids
Hemorrhoids involve symptomatic enlargement and/or distal displacement of anal cushions. Prevalence ranges from 4.4% to 39%, peaking at ages 45–65 years, with about 55% asymptomatic [14]. Risk factors include straining, obesity, pregnancy, chronic diarrhea, anal intercourse, cirrhosis with ascites, and low-fiber diets [15,16]. Pathophysiology encompasses elevated venous pressure, variceal dilations, sliding anal cushions, and venous engorgement leading to edema [14-16].

Hemorrhoids are classified as internal (above dentate line) or external (below) [14,15]. Internal grades (Goligher): I (asymptomatic outgrowth), II (spontaneous reduction), III (manual reduction) and IV (irreducible) [15,17]. Symptoms vary: Grade I (painless bleeding, soiling) and Grades II–IV (prolapse, visible bulges) [14]. External: pruritus and pain (thrombosed) [15].

Treatment for internal hemorrhoids: Grades I–II (diet, conservative measures, flavonoids, procedures) and Grades III–IV (surgery) [14,15]. External: treat if symptomatic or thrombosed [14].

Methods and Materials
This self-controlled trial evaluated *Aesculus hippocastanum* 10 mg, *Polygonum punctatum* 10 mg, *Smilax papyracea* 40 mg, and rutin 20 mg as one coated tablet three times daily for 60 days in patients with Grade I–III hemorrhoids (n=120). Endpoints included:

1. VAS (0=no symptoms, 100=worst symptoms)
2. HDSS (pain, itching, bleeding, soiling)
3. Adapted Short Health Scale (severity, interference, concern, well-being)
4. Physician and patient assessment scores (poor=10 to very good=40)
5. Ease of swallowing (0=very easy, 100=very difficult)
6. Adherence (% returned tablets)
7. Safety assessed via adverse events (AEs) at Visit 2, coded per MedDRA v21.0.

Study Medication
The tested combination corresponds to a pharmaceutical product commercially registered in Brazil under the name VASTONIC® (Makrofarma Química Farmacêutica Ltda., Rio de Janeiro, Brazil; ANVISA registration No. 111990032; regulatory category: *Específico*). This product has been authorized for commercialization in Brazil since 1994 and remains valid until December 2032. Each coated tablet contains *Aesculus hippocastanum* L. 10 mg, *Polygonum punctatum* 10 mg, *Smilax papyracea* 40 mg, and rutin 20 mg. The product has been available in the national market for over 40 years, with established safety and pharmacological use for chronic venous insufficiency and related conditions. To the best of our knowledge, this is the first clinical study specifically designed to evaluate the efficacy and safety of this registered combination in patients with hemorrhoids.

Participants were outpatients from Rio de Janeiro State, Brazil (Table 1). Enrollment: October 22, 2024, to March 15, 2025; last treatment: April 30, 2025. Coordinated by Centro Universitário Serra dos Órgãos Medical School (UNIFESO); IRB approval No. 7.078.287. Conducted per Helsinki Declaration; registered at ClinicalTrials.gov (**NCT06705777**). No patient compensation; informed consent obtained.

Inclusion: Grade I–III hemorrhoids; ages 18–65 (contraception for reproductive-age females). Exclusion: Concomitant hemorrhoid medications, gallbladder stones, hypertension (>145/100 mmHg), hypersensitivity, gastritis. Pre-study screening: clinical/laboratory. Data recorded in forms. Efficacy: paired comparisons V2 vs. V1. Statistics: Power and Precision v. 4.1; paired t-tests (p<0.05).

Concomitant drugs (no interactions): allopurinol, alprazolam, there were no interactions among the tested combination and other drugs previously taken by the participants. Sitz baths allowed. Labs: blood count, liver tests, etc. Abnormalities: leukocyturia (n=1), mild hyperglycemia (n=1), hyperuricemia (n=1).

Results

Participant demographics showed a mean age of 46±13 years, with female predominance (Table 1). Significant reductions (p<0.05) occurred in VAS (mean from 51.8 to 14.3), HDSS (19.6 to 7.2), and Short Health Scale (3.9 to 2.2) at Visit 2, consistent across grades and genders (Tables 2-4; Figures 1-3). Physician and patient scores reached "very good" in ~50% (Tables 5-6). Ease of swallowing: mean 6.6/100 (Table 7); adherence: 96.6%. Safety: 46 patients reported 48 mild–moderate AEs, mostly gastrointestinal (Table 9). No vital sign changes (Table 8). No discontinuations due to AEs; two lost to follow-up.

Table 1: Participant Demographics.

Characteristic	Females (N=75)	Males (N=45)	Total (N=120)
Height (cm, mean ± SD)	162 ± 4	174 ± 4	166 ± 8
Weight (kg, mean ± SD)	64.5 ± 9	78.3 ± 9	69.6 ± 11
BMI (kg/m², mean ± SD)	24.6 ± 3	25.9 ± 3	25.1 ± 3
Age (years, mean ± SD)	-	-	46 ± 13
Ethnicity (n)	-	-	White: 50; Mixed: 42; Black: 23; Asian: 5
Hemorrhoid Grade* (n)	I: 14; II: 40; III: 21; IV: 0	I: 6; II: 25; III: 14; IV: 0	I: 20; II: 65; III: 35; IV: 0

*Goligher Classification. [17].

Table 2: Vas Scores by Grade and Gender (mean; p<0.05 for all v1 vs. V2 comparisons).

Grade	Visit 1 female	Visit 1 male	Visit 2 Female	Visit 2 Male
I	36.5	38.6	5.9	5.9
II	48.7	49.4	13.5	13.2
III	68.1	63.3	19.7	19.7
Mean	51.8	51.8	14.1	14.4

Table 3: HDSS Scores by Grade and Gender (Mean; P<0.05 For All V1 VS. V2 Comparisons).

Grade	Visit 1 Female	Visit 1 Male	Visit 2 Female	Visit 2 Male
I	13.5	14.5	4.2	1.5
II	19.8	17.2	7.5	6.3
III	25.8	24.4	10.1	10.5
Mean	19.9	19.2	7.6	6.7

Table 4: Short Health Scale Scores by Grade and Gender (MEAN; P<0.05 FOR ALL V1 VS. V2 Comparisons).

Grade	Visit 1 Female	Visit 1 Male	Visit 2 Female	Visit 2 Male
I	3.4	3.7	1.7	1.5
II	4.0	3.9	2.2	2.1
III	4.3	4.4	2.3	2.4
Mean	3.8	4.0	2.2	2.1

Table 5: Assessment Scores in Visit 2 (Number of Individuals).

Score	Physician (Male/Female/Total)	Patient (Male/Female/Total)
10	2/4/6	2/4/6
20	3/5/8	2/3/5
30	15/31/46	14/34/48
40	23/35/58	25/34/59

Table 6: Assessment Scores Vs. Disease Severity in Visit 2 (Number of Individuals).

Grade	Physician Score: 10/20/30/40	Patient Score: 10/20/30/40
I	0/1/5/14	6/0/0/14
II	3/3/28/29	3/2/25/32
III	3/4/13/15	3/2/25/30

Table 7: Ease of Swallowing Scores at Visit 2 (Mean; P<0.05 VS. Worst Score of 100).

Group	Score
Male	5.1
Female	7.4
Total	6.6

Table 8: Physical Exam Parameters (Mean ± SD; No Significant Changes, P>0.05).

Parameter	Visit 1	Visit 2
Heart Rate (bpm)	71 ± 6	70 ± 6
Respiratory Rate (ipm)	13 ± 1	13 ± 1
Blood Pressure (mmHg)	123±9 / 80±9	122±10 / 79±9

Table 9: Adverse Events by System (N=48 Episodes).

System	Events (Frequency)
Gastrointestinal	Nausea (7), Flatulence (6), Distension (6), Diarrhea (4), Cramps (3), Reflux (2), Discomfort (2), Eructation (1), Dyspepsia (1), Epigastralgia (1)
Neurological	Vertigo (3), Migraine (1)
Behavioral	Anxiety (4)
Skin	Pruritus (1)
Other	Asthenia (1), Thirst (1), Inappetence (1), Insomnia (1)

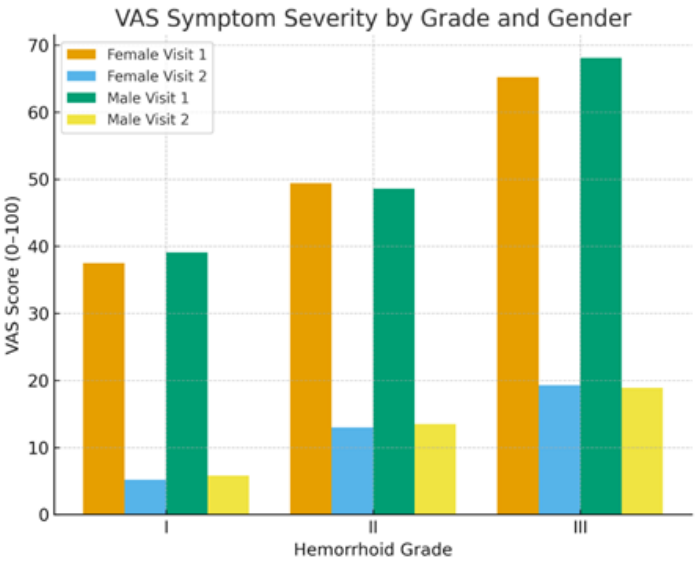

Figure 1: Vas Symptom Severity Scores at Baseline (Visit 1) and After 60 Days (Visit 2), By Hemorrhoid Grade and Gender.

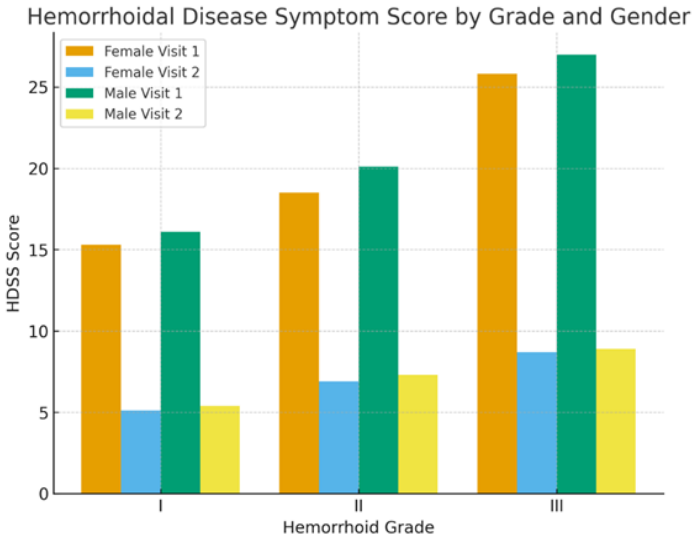

Figure 2: Hemorrhoidal Disease Symptom Scores (HDSS) Before and After Treatment, By Grade and Gender.

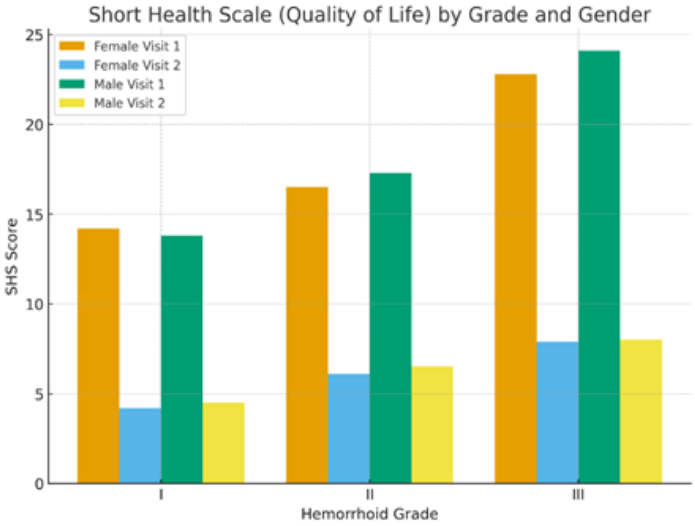

Figure 3: Short Health Scale (SHS) Scores Reflecting Quality of Life, Before and After Treatment, By Hemorrhoid Grade and Gender.

Discussion

Hemorrhoids remain a significant clinical challenge despite centuries of herbal use for venous disorders. To our knowledge, the present study is the first *prospective controlled* clinical trial evaluating VASTONIC®, a Brazilian-registered phytopharmaceutical (ANVISA No. 111990032) with over 40 years of market use for chronic venous insufficiency and related conditions, specifically in the context of hemorrhoidal disease. The results reinforce the therapeutic value of this traditional formulation when applied to hemorrhoids, expanding its evidence-based indications.

Symptomatic relief observed aligns with the known venotonic (escin), anti-inflammatory (*Smilax*, *Polygonum*), and capillary-stabilizing (rutin) pharmacological properties of the components [2-18].

Limitations include:

- Open-label design, introducing potential placebo or expectation bias — though reflective of real-world clinical practice where patient-reported outcomes are central.
- Gender imbalance (73% female), limiting generalizability.
- Absence of an active comparator (e.g., flavonoids).

Adverse events were mild and predominantly gastrointestinal, consistent with escin's known profile, and did not lead to study withdrawals. Future double-blind, randomized controlled trials comparing VASTONIC® to standard phlebotonics (e.g., diosmin/hesperidin) are strongly recommended [16].

Conclusion

This 60-day regimen of VASTONIC® (*Aesculus hippocastanum* L. 10 mg, *Polygonum punctatum* 10 mg, *Smilax papyracea* 40 mg, and rutin 20 mg) was safe, well-tolerated, and effective in reducing symptoms and improving quality of life in Grade I–III hemorrhoids, independent of disease severity. High swallowability and >96% adherence suggest excellent patient acceptability.

This trial provides the first structured clinical evidence for a long-marketed, ANVISA-registered phytopharmaceutical in hemorrhoidal disease, supporting its role in conservative management while paving the way for confirmatory RCTs.

Funding

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Conflict of Interest Statement

The sponsor (Makrofarma) provided study medication and partial funding but had no role in study design, data collection, analysis, interpretation, manuscript preparation, or decision to publish. The authors declare no other conflicts of interest.

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