



Biotex Hesperidin+ for Varicose-Vein-Associated Symptoms: A Hesperidin-Centered Review of Venoactive, Endothelial and Microvascular Evidence

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ABSTRACT

Varicose veins are a common manifestation of chronic venous disease (CVD) in which venous reflux and sustained venous hypertension interact with endothelial dysfunction, inflammation, oxidative stress, vein-wall remodelling, and increased microvascular permeability. These processes contribute to clinically important symptoms including leg heaviness, aching, swelling, cramps, and discomfort. Venoactive flavonoids are recognised in contemporary vascular guidelines as supportive options for symptom management in selected patients, although they do not correct the underlying anatomical reflux. Hesperidin+ is a multi-ingredient nutraceutical developed by Biotex Life Solutions Pvt. Ltd. containing hesperidin 500 mg, Bambusa arundinacea crystals (tabasheer/Vanshlochan; the contemporary literature also identifies the source as Bambusa bambos) 200 mg, rutin 100 mg, Citrus limon fruit extract 50 mg, Rubia cordifolia root extract 50 mg, and Punica granatum fruit extract 50 mg. This narrative review evaluates the venous-health rationale for this formulation, with emphasis on human vascular evidence for hesperidin; endothelial-barrier and inflammatory evidence for rutin; complementary vascular evidence for the botanical components; and the clinical literature supporting flavonoid-based venoactive therapy. The strongest clinical evidence derives from micronised purified flavonoid fraction (MPFF) and hydroxyethylrutin, not from isolated hesperidin or the finished Hesperidin+ formulation. Hesperidin and rutin nevertheless provide a biologically coherent flavonoid platform, while lemon, pomegranate, and Rubia cordifolia offer complementary phytochemical support. Current evidence provides an ingredient-level rationale for investigating Hesperidin+ as a supportive venous-health formulation; direct clinical efficacy for varicose veins remains unestablished, and the formulation should not be represented as reversing valvular incompetence or eliminating established varicosities.

Keywords: hesperidin; Hesperidin+; varicose veins; chronic venous disease; venoactive flavonoids; rutin; MPFF; venous tone; edema; microcirculation

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INTRODUCTION

Varicose veins are dilated, tortuous superficial veins arising within the spectrum of chronic venous disease (CVD). Their clinical importance extends beyond cosmetic appearance: symptomatic patients may experience aching, heaviness, swelling, night cramps, burning, itching, and impaired quality of life. Contemporary vascular guidelines classify varicose veins within a broader disease process that can progress from symptoms without visible signs to oedema, skin changes, healed or active venous ulceration^[1,2]. The therapeutic objective therefore depends on disease stage, venous anatomy, symptom burden, and patient preference.

The underlying biology is multifactorial. Venous reflux and/or obstruction generate venous hypertension, which alters shear stress and vein-wall tension. Endothelial activation, leukocyte recruitment, matrix metalloproteinase

activity, oxidative stress, and chronic inflammatory signalling contribute to progressive wall and valve remodelling^[3,4]. These mechanisms also increase microvascular permeability and interstitial fluid accumulation, providing a mechanistic link between venous hypertension and symptoms such as swelling and heaviness.

Definitive treatment of clinically important reflux may involve compression, sclerotherapy, endovenous ablation, or surgery. Oral venoactive therapy occupies a different role: symptom-oriented support. The 2023 Society for Vascular Surgery, American Venous Forum, and American Vein and Lymphatic Society guideline suggests MPFF for selected symptomatic patients with varicose veins who are not candidates for intervention, are waiting for intervention, or remain symptomatic after intervention. The same guideline also recognises hydroxyethylrutin for pain, heaviness,

night cramps, and swelling, albeit with lower certainty^[1]. The ESVS guideline similarly supports consideration of venoactive drugs for symptomatic CVD^[2].

Hesperidin+ is a six-component nutraceutical centred on 500 mg hesperidin. This review examines whether the pharmacology and clinical literature on hesperidin-related and rutoside-related flavonoids provide a scientifically defensible rationale for supporting venous comfort in people with varicose-vein-associated symptoms. Antiviral, anticancer, and unrelated systemic claims are outside the scope of this review.

Review Approach

This concise narrative review prioritised peer-reviewed publications from 2016 through September 2026 and high-authority clinical guidelines. Earlier studies were retained only when they provided unusually direct evidence that is not duplicated in the recent literature, such as human varicose-vein tissue studies or foundational endothelial-barrier experiments. PubMed/MEDLINE-focused searches used combinations of 'varicose veins', 'chronic venous disease', 'chronic venous insufficiency', 'hesperidin', 'rutin', 'rutosides', 'micronised purified flavonoid fraction', 'venoactive drugs', 'venous tone', 'edema', 'endothelial dysfunction', and the botanical names of the complementary Hesperidin+ ingredients. Systematic reviews, meta-analyses, randomised trials, guidelines, and mechanistic reviews were prioritised over isolated in vitro reports. Evidence from MPFF, hydroxyethylrutosides, or other chemically distinct preparations was treated as class-level or contextual evidence and was not presented as direct proof for Hesperidin+. Because this was a narrative review, a formal PRISMA study-selection process and study-level GRADE assessment were not undertaken.

Varicose-Vein Pathophysiology Relevant to Nutraceutical Support

Normal lower-limb venous return depends on competent valves, patent venous pathways, and the calf-muscle pump. When reflux develops, ambulatory venous pressure remains abnormally high. Progressive dilation may further impair valve-leaflet coaptation and perpetuate reflux. Raffetto identified venous hypertension as the fundamental hemodynamic disturbance connecting varicose veins with later manifestations of CVD^[4].

Hemodynamic stress initiates biological responses. Low or disturbed shear stress and increased wall tension are associated with endothelial activation, leukocyte adhesion, cytokine signalling, extracellular matrix turnover, and matrix metalloproteinase activity. Mansilha and Sousa emphasised the interplay between endothelial dysfunction and inflammation and the relevance of these processes to venoactive-drug targets^[3]. Accordingly, an intervention that modulates endothelial oxidative-inflammatory signalling may plausibly affect symptoms or microcirculatory consequences without correcting the primary structural reflux.

Microvascular leakage is especially relevant to a nutraceutical positioning strategy. Increased hydrostatic pressure in the venous microcirculation promotes filtration and interstitial fluid accumulation. Oedema and tissue congestion contribute to the sensation of heaviness, tightness, aching, and swelling. The clinically realistic targets of supportive therapy are therefore venous tone, capillary permeability, endothelial integrity, inflammatory balance, lymphatic drainage, and symptom burden—not anatomical eradication of varicosities.

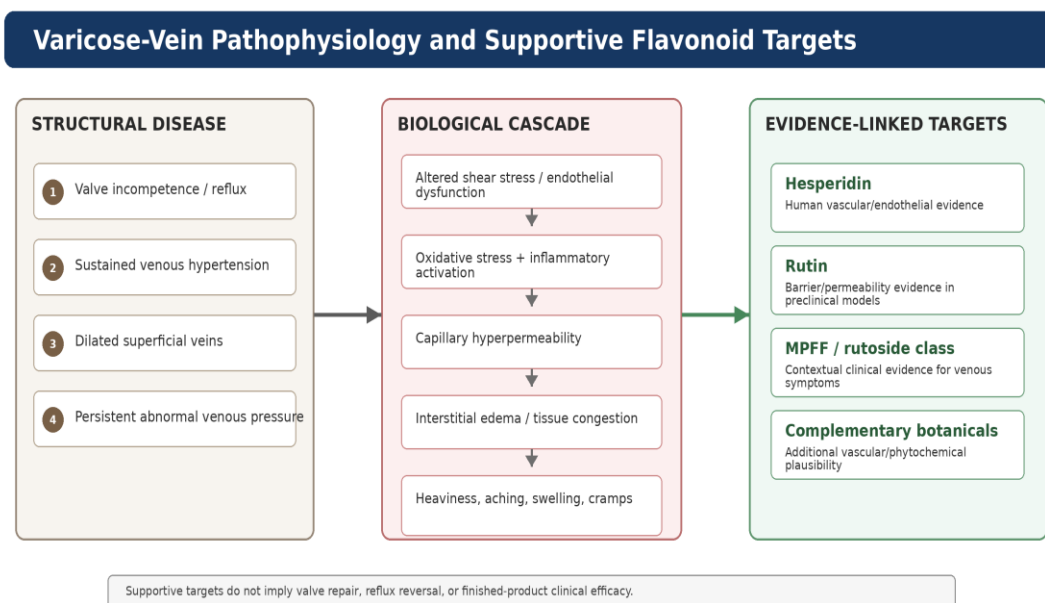


Figure 1: Pathophysiological sequence relevant to varicose-vein-associated symptoms and evidence-linked supportive targets. Structural venous reflux and hypertension lead to endothelial dysfunction, oxidative-inflammatory activation, capillary hyperpermeability, and oedema-related symptoms. The evidence-linked targets shown are contextual and do not imply correction of venous reflux, valve repair, or direct efficacy of the complete Hesperidin+ formulation.

Hesperidin: Principal Pharmacological Rationale

Hesperidin is a citrus flavanone glycoside that is metabolised to hesperetin and conjugated metabolites after intestinal and microbial transformation. Bioavailability varies substantially with the food matrix, gut microbiota, particle size, and formulation. This limitation is important when translating evidence between conventional hesperidin, citrus extracts, and micronised flavonoid products.

Human evidence supports systemic antioxidant and anti-inflammatory effects at the 500 mg/day dose used in Hesperidin+. In a randomised double-blind placebo-controlled trial in adults with type 2 diabetes, 500 mg/day hesperidin for six weeks improved total antioxidant capacity and reduced malondialdehyde and oxidative DNA-damage markers^[5]. A companion randomised trial using the same dose reported reductions in inflammatory markers and blood pressure together with increased antioxidant capacity^[6]. These populations were not patients with varicose veins, so the studies demonstrate biological activity at a formulation-relevant dose rather than direct venous efficacy.

A systematic review and meta-analysis of randomised trials found that hesperidin supplementation significantly reduced VCAM-1, whereas effects on several other inflammatory markers were inconsistent^[7]. This pattern is relevant because leukocyte-endothelial adhesion and inflammatory amplification participate in CVD, but it does not justify claiming that hesperidin broadly suppresses all inflammatory pathways in the human venous wall.

Human vascular studies add an important ingredient-level layer. Morand and colleagues used a randomised crossover protocol showing that a hesperidin-containing intervention produced a measurable short-term increase in endothelium-dependent microvascular responsiveness after ingestion^[19]. This is relevant to CVD because microvascular endothelial responsiveness is mechanistically closer to venous microcirculatory function than generic antioxidant biomarkers, although the study population consisted of healthy volunteers rather than patients with varicose veins.

The Citrus study subsequently evaluated hesperidin-containing and hesperidin-enriched orange juice in 159 adults with elevated blood pressure or stage-1 hypertension. Across the 12-week Citrus trial program, hesperidin exposure was associated with changes in vascular hemodynamic measures, and a separate analysis documented a favourable change in endothelial responsiveness^[20,21]. These studies again do not demonstrate treatment of venous reflux, but they strengthen the proposition that orally delivered hesperidin can exert measurable human vascular and endothelial effects at clinically relevant exposures.

Why MPFF Evidence Is Relevant—but Not Interchangeable

The strongest clinical flavonoid evidence in CVD concerns micronised purified flavonoid fraction (MPFF). Contemporary guidelines describe MPFF as a venoactive preparation with effects on venous tone, the vein wall and valve, capillary leakage, lymphatic drainage, hemorheology, antioxidant pathways, inflammatory reactions, and endothelial function^[1]. A 2018 systematic review and meta-

analysis of randomised double-blind placebo-controlled trials reported improvements across several CVD symptoms and signs^[8].

MPFF is, however, predominantly diosmin and is specifically micronised to enhance absorption; hesperidin constitutes only a minor portion of the preparation. Therefore, MPFF should be used to establish the clinical relevance of the venoactive-flavonoid class and the plausibility of shared pathways—not as direct proof that isolated hesperidin 500 mg or Hesperidin+ reproduces MPFF outcomes.

Clinical Evidence for Venoactive Flavonoids in Symptomatic CVD

The highest-level evidence supporting oral symptom-oriented therapy comes from guidelines and systematic reviews. A Cochrane review of phlebtonics concluded that these agents probably reduce lower-leg oedema slightly; evidence for some other outcomes was less certain, and gastrointestinal adverse events occurred somewhat more often than with placebo^[9]. The review included extensive rutoside experience, making it particularly relevant to the rutin-containing Hesperidin+ formulation.

Recent MPFF analyses have expanded the evidence base. A 2025 systematic review and meta-analysis covering CVD across all stages reported consistent reductions in major venous symptoms including pain, heaviness, discomfort, cramps, feeling of swelling, and burning^[10]. A companion analysis of clinical signs reported significant decreases in ankle and calf circumference and improvements in oedema-related and severity measures, although heterogeneity was frequently high and some included studies carried a high risk of bias^[11].

Patient-centred outcomes are also increasingly represented. A 2026 systematic review and meta-analysis reported improvements in global and domain-specific quality of life with MPFF, together with reductions in pain, heaviness, and discomfort^[12]. An additional 2026 analysis in early C0s-C1 disease found reductions in pain and heaviness and improved quality of life; the authors also noted high heterogeneity and risk-of-bias concerns in part of the evidence base^[13].

These analyses support clinically meaningful symptom improvement with selected flavonoid-based venoactive therapies. However, reductions in symptoms or oedema-related measures do not imply reversal of venous reflux, restoration of valve competence, or anatomical disappearance of varicose veins.

The broader evidence hierarchy is consistent with a 2025 review in the *Journal of Vascular Surgery: Venous and Lymphatic Disorders*, which concluded that venoactive compounds can provide symptom benefit in CVD and identified MPFF among the preparations with the most developed evidence^[22]. A network meta-analysis of pharmacological therapies for CVD also supports a measurable symptomatic effect of several venoactive drug classes, while emphasising heterogeneity among compounds, outcomes, and study quality^[23].

Preclinical work also demonstrates that flavonoids can engage mechanisms that are directly relevant to venous

hypertension. Casili and colleagues examined a flavonoid-based intervention in endothelial, isolated-vessel, and experimental venous-disease systems and observed modulation of pathways linked to vascular inflammation and function^[24]. The study did not test Hesperidin+ or isolated

hesperidin, but it provides mechanistic support for treating the venoactive-flavonoid class as biologically active in venous disease rather than relying solely on symptom scores.

Table 1: Composition of Hesperidin+ and evidence relevance to varicose-vein-associated symptoms.

Ingredient	Amount	Potentially relevant biology	Evidence boundary	Role in venous rationale
Hesperidin	500 mg	Citrus flavanone; antioxidant/endothelial-inflammatory modulation	Human biological activity at 500 mg/day; direct isolated-hesperidin varicose-vein trials limited	Primary
Bambusa arundinacea crystals/tabasheer (literature also: Bambusa bambos)	200 mg	Silica-rich biomineral matrix	Recent characterization/safety evidence; no established direct venotonic efficacy	Ancillary
Rutin	100 mg	Flavonol glycoside; capillary/microvascular rationale	Rutoside class supported in CVD; conventional rutin not equivalent to hydroxyethylrutosides	Primary complementary
Citrus limon fruit extract	50 mg	Eriocitrin/other citrus polyphenols depending on extract	Antioxidant/inflammatory support; no direct dose-specific varicose-vein trial	Complementary
Rubia cordifolia root extract	50 mg	Quinones and other phytochemicals	Predominantly preclinical antioxidant/anti-inflammatory evidence	Complementary
Punica granatum fruit extract	50 mg	Ellagitannins/polyphenols depending on extract	Human inflammation/endothelial biomarker evidence; no direct varicose-vein efficacy	Complementary

Table 2: High-value clinical and guideline evidence relevant to Hesperidin+ venous-health positioning.

Source	Design	Population	Main finding	Translation to Hesperidin
Gloviczki et al., 2023/2024	SVS/AVF/AVLS guideline	Symptomatic varicose veins	Suggests MPFF for pain/heaviness/swelling; hydroxyethylrutosides for pain/heaviness/cramps/swelling in selected patients	Direct guidance for venoactive symptom management; not product-specific
De Maeseneer et al., 2022	ESVS clinical practice guideline	Lower-limb CVD	Venoactive drugs may be considered for venous symptoms and oedema	High-authority European guidance
Martinez-Zapata et al., 2020	Cochrane systematic review	Venous insufficiency	Phlebotonics probably reduce oedema slightly; adverse-event profile mainly GI.	Class-level evidence
Kakkos & Nicolaides, 2018	Systematic review/meta-analysis of DB placebo-controlled trials	CVD	Improvement in multiple venous symptoms/signs with MPFF	MPFF-specific; contextual for hesperidin
Nicolaides et al., 2025 Part I	Systematic review/meta-analysis	C0s-C6 CVD	Improvement in pain, heaviness, discomfort, cramps, swelling sensation, burning.	Large contemporary MPFF evidence base; heterogeneous designs
Nicolaides et al., 2025 Part II	Systematic review/meta-analysis	C0s-C6 CVD	Reduced ankle/calf circumference and improved signs	Supports edema/sign outcomes; heterogeneity high
Santiago et al., 2026	Systematic review/meta-analysis	CVD	Improved quality of life and venous symptoms	Patient-centred MPFF evidence; some industry affiliations
Bouskela et al., 2026	Systematic review/meta-analysis	Early C0s-C1 CVD	Reduced pain/heaviness; improved QoL	Relevant to early symptomatic support; not Hesperidin+

For reproducibility, product characterisation is strengthened by reporting certificate-of-analysis specifications for active raw materials, including hesperidin assay/purity and citrus source, rutin assay and source, extract ratios or marker

compounds for *C. limon*, *P. granatum* and *R. cordifolia*, and physicochemical or elemental specifications for tabasheer. These quality-control parameters do not constitute efficacy

evidence but improve interpretation of ingredient-level literature.

Contribution of the Other Hesperidin+ Components

Rutin

Rutin is the most clinically relevant complementary constituent because the rutoside family has a long history in CVD. The current US guideline identifies hydroxyethylrutosides as an option for selected symptomatic patients and summarises their pharmacological profile as involving venous tone, capillary leakage, lymphatic drainage, hemorrheology, antioxidant activity, and inflammatory modulation^[1]. The Cochrane phlebotonics review also includes substantial rutoside evidence^[9].

Hydroxyethylrutosides are chemically modified, standardised derivatives and should not be treated as equivalent to 100 mg conventional rutin. For Hesperidin+, they provide class-level support for a capillary and microvascular rationale rather than direct dose-equivalent proof.

Rutin itself has preclinical properties that map closely onto CVD microvascular pathology. In endothelial-cell experiments supported by in vivo permeability testing, rutin preserved barrier integrity during inflammatory challenge and attenuated permeability changes together with adhesion-molecule-dependent monocyte interactions^[25]. These effects are particularly relevant to oedema formation because increased endothelial permeability is one mechanism linking venous hypertension to interstitial fluid accumulation.

A separate endothelial model linked rutin exposure with lower Nox4-associated oxidative signalling and reduced activation of the ROS-responsive NLRP3 pathway, consistent with protection of endothelial function^[26]. Together, these studies provide direct mechanistic support for the 100-mg rutin component as a vascular-barrier and endothelial-support constituent, but they remain preclinical and do not establish that the dose used in Hesperidin+ is clinically effective in varicose veins.

Citrus limon, Punica granatum and Rubia cordifolia

Citrus limon contains eriocitrin and other flavonoids whose abundance depends on fruit part and extraction method. A contemporary review documents antioxidant and anti-inflammatory properties but does not establish efficacy for a generic 50 mg lemon fruit extract in varicose veins^[14].

Pomegranate is rich in ellagitannin-derived polyphenols. A systematic review and meta-analysis of randomised trials reported reductions in selected inflammatory biomarkers, including hs-CRP, IL-6 and TNF-alpha, although several endothelial markers were unchanged^[15]. These findings support complementary vascular-inflammatory plausibility but are not evidence of a venotonic or anti-varicose effect.

Rubia cordifolia contains quinones, flavonoids, and other constituents with reported anti-inflammatory, antioxidant and antiplatelet activities; however, a 2022 comprehensive review emphasised that most pharmacological evidence is preclinical and that clinical safety and pharmacokinetic data remain limited^[16].

For the lemon component, eriocitrin is a particularly relevant candidate marker because it is a characteristic flavanone of Citrus limon. A 2022 review in Biomedicine & Pharmacotherapy summarised antioxidant and anti-inflammatory activities of eriocitrin, while pharmacokinetic work demonstrated systemic formation and tissue distribution of orally administered eriocitrin metabolites in vivo^[27,28]. This supports specifying eriocitrin or another validated citrus-flavonoid marker for the product raw material; it does not establish a direct venous effect of the current 50-mg lemon extract.

Pomegranate also has human vascular evidence relevant to the formulation rationale. A 2025 clinical meta-analysis reported beneficial changes in some measures related to endothelial and inflammatory status after pomegranate interventions, while other vascular biomarkers showed no consistent effect^[29]. In a randomised controlled trial in hemodialysis patients, pomegranate peel extract was also evaluated for inflammatory and endothelial-function biomarkers^[30]. These data justify classifying pomegranate as complementary endothelial-support evidence, but the studied preparations and populations differ from the 50-mg fruit extract in Hesperidin+.

Rubia cordifolia also has vascular-model evidence beyond general antioxidant activity. In zebrafish vascular assays, a characterised Rubia cordifolia preparation produced changes consistent with less thrombus formation and greater vascular growth, accompanied by alterations in signalling markers relevant to circulation^[31]. This is useful preclinical support for a circulation-related biological role, but the model is not chronic venous insufficiency and should not be converted into an antithrombotic or varicose-vein claim for the finished product.

Tabasheer / Vanshlochan

The bamboo-derived crystals in Hesperidin+ should be considered separately from polyphenol-rich bamboo leaves or shoots. Recent material characterisation identifies Vanshlochan from Bambusa bambos as a silica-rich biomineral and provides reassuring acute/subacute toxicological data^[17]. No contemporary evidence establishes a direct venotonic, capillary-permeability, or varicose-vein symptom effect. It should therefore be presented as an ancillary mineral matrix rather than a co-equal venoactive constituent.

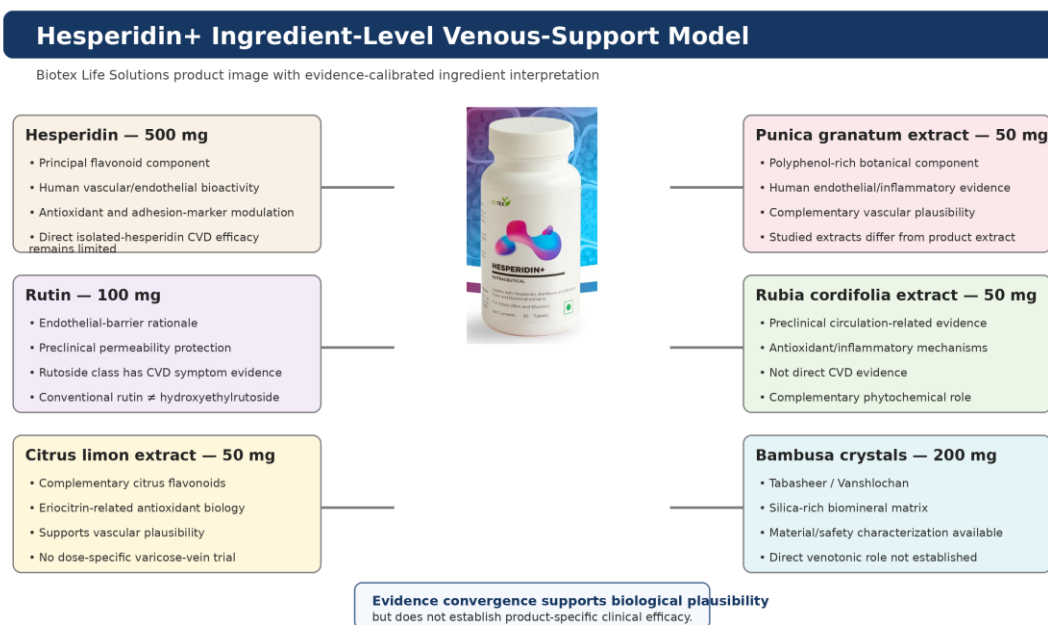


Figure 2: Ingredient-level evidence model for Hesperidin+ using the Biotex Life Solutions product image. Hesperidin and rutin form the principal flavonoid platform. Citrus limon, Punica granatum, and Rubia cordifolia provide complementary vascular or phytochemical plausibility, whereas tabasheer is represented as a silica-rich biomineral matrix with no established direct venotonic action. The model represents evidence convergence rather than demonstrated formulation synergy or finished-product clinical efficacy.

Table 3: Expanded ingredient-level clinical and preclinical evidence relevant to venous-health plausibility.

Ingredient/evidence class	Study/model	Key vascular finding	Evidence level	Relevance to varicose veins	Citation
Hesperidin	Randomised crossover human study	Improved microvascular endothelial reactivity in a hesperidin-containing intervention	Human vascular	Supports endothelial/microvascular plausibility; not CVD efficacy	[19]
Hesperidin	12-week randomised Citrus study	Dose-related vascular effects; companion analysis reported endothelial-function improvement	Human vascular	Strengthens oral vascular bioactivity; not venous reflux treatment	[20,21]
Diosmin-hesperidin	Primary human varicose-vein wall study	Apoptotic-marker changes across treatment arms; the study's statistically significant finding concerned calcium dobesilate, not the diosmin-hesperidin arm	Direct human venous tissue	Human venous-wall design is valuable, but the reported significant apoptotic effect belongs to calcium dobesilate; diosmin-hesperidin's own effect on these markers was not independently significant.	[18]
Rutin	HUVEC + in vivo permeability models	Reduced hyperpermeability, CAM expression and leukocyte adhesion/migration	Preclinical vascular	Directly relevant to endothelial barrier and oedema mechanisms	[25]
Rutin	Endothelial dysfunction model	Modulated Nox4/ROS-sensitive NLRP3 signaling	Preclinical vascular	Supports oxidative-inflammatory endothelial mechanism	[26]
Citrus limon / eriocitrin	Review + oral pharmacokinetics	Antioxidant/inflammatory activity; systemic metabolites after oral dosing	Preclinical/translational	Supports marker standardisation and systemic plausibility; no direct CVD evidence	[27,28]
Punica granatum	Clinical meta-analysis + RCT	Effects on selected endothelial/inflammatory biomarkers	Human vascular	Complementary endothelial support; preparation differs from Hesperidin+ extract	[29,30]

Ingredient/evidence class	Study/model	Key vascular finding	Evidence level	Relevance to varicose veins	Citation
Rubia cordifolia	Zebrafish thrombosis/vascular model	Antithrombotic and pro-angiogenic activity with vascular signalling changes	Preclinical vascular	Circulation-related plausibility only; not evidence of CVD efficacy	[31]
Venoactive flavonoid class	Vascular Pharmacology multi-model study	Flavonoid intervention affected endothelial/vascular pathways in experimental CVI.	Preclinical CVD	Supports class-level mechanistic relevance	[24]
Venoactive drugs	2025 vascular review + 2021 network meta-analysis	Symptom benefit varies by compound; MPFF among best-supported preparations	Clinical evidence synthesis	Supports context, not direct Hesperidin+ efficacy	[22,23]

Translational Positioning of Hesperidin+

The available evidence does not indicate that all six Hesperidin+ ingredients are equally venoactive or that their combination has demonstrated pharmacological synergy. Rather, hesperidin and rutin form the principal flavonoid platform, while selected botanical polyphenols add complementary redox and inflammatory support. This architecture is biologically coherent with CVD pathophysiology but remains an ingredient-level evidence-convergence model.

A clinically appropriate pathway is: venous reflux and hypertension → endothelial activation and oxidative-inflammatory stress → microvascular leakage and oedema → heaviness, aching, swelling and discomfort. The formulation rationale therefore centres on ingredient-level evidence relevant to endothelial redox balance, inflammatory modulation, and capillary/microvascular function rather than on correction of the anatomical cause of reflux.

Table 4: Claim translation framework for a product-focused review.

Potential wording	Assessment	Evidence basis	Recommended handling
Supports venous comfort	Defensible	Consistent with symptom-oriented venoactive framework	Phrase as support, not treatment
May help reduce sensations of heaviness/swelling	Plausible but indirect for finished product	MPFF/rutoside clinical evidence; no Hesperidin+ trial	Use 'may support' or 'designed to support'
Supports microvascular/endothelial health	Defensible ingredient-level rationale	Hesperidin/rutin plus complementary polyphenol evidence	Avoid implying demonstrated product-specific endothelial outcome
Improves venous tone	Context-dependent	Established for some venoactive preparations; not directly measured for Hesperidin+	Prefer 'supports venous function' unless product data exist.
Relaxes varicose veins	Not recommended	Venous relaxation can imply increased capacitance/dilatation	Replace with 'relief of varicose-vein-associated symptoms'
Reverses varicose veins/repairs valves	Unsupported	No nutraceutical evidence	Do not use
Clinically proven for varicose veins	Unsupported	No finished-product clinical trial identified	Do not use

Evidence Hierarchy for Hesperidin+ in Varicose-Vein-Associated Symptoms

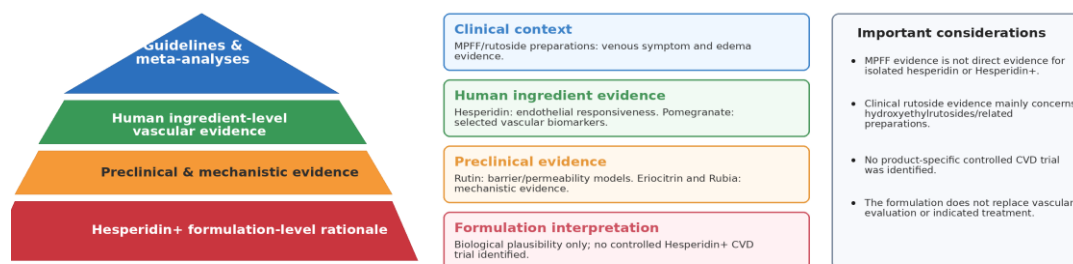


Figure 3: Evidence hierarchy for interpretation of Hesperidin+ in varicose-vein-associated symptoms. Clinical guidelines and meta-analyses of established venoactive preparations provide contextual clinical evidence; human ingredient-level vascular evidence is strongest for hesperidin and selected pomegranate outcomes; rutin, eriocitrin, and Rubia cordifolia are supported mainly by preclinical or class-level evidence. The finished formulation remains an evidence-convergence rationale because no controlled hesperidin + chronic venous disease trial was identified.

Safety, Evidence Boundaries and Clinical Context

The Cochrane review found that phlebotonics were associated with somewhat more adverse events than placebo, predominantly gastrointestinal effects, while serious safety concerns were not the dominant signal^[9]. Nevertheless, the safety of an individual venoactive drug cannot automatically establish the safety of a multi-ingredient product in all clinical settings.

No product-specific drug-interaction study was identified. Accordingly, use alongside prescription medicines should be considered under professional supervision, particularly in patients receiving complex or narrow-therapeutic-index regimens. Botanical authentication, extract specification, heavy-metal testing, microbial quality, and quantitative marker analysis are important for product reproducibility. *Rubia cordifolia* warrants particular attention to anthraquinone/quinone characterisation and long-term safety data.

A clear distinction is required between supportive symptom management and vascular diagnosis. Duplex ultrasound is recommended as the diagnostic test of choice to evaluate venous reflux in symptomatic patients^[1]. Sudden unilateral swelling, marked pain, suspected thrombosis, bleeding, ulceration, or progressive venous disease requires medical assessment rather than reliance on nutraceutical self-management.

Limitations of the Evidence

A principal limitation is the absence of a peer-reviewed controlled clinical trial evaluating the complete Hesperidin+ formulation in patients with varicose veins or CVD. The evidence base therefore combines direct clinical information from other venoactive preparations with ingredient-level biological evidence. MPFF is not hesperidin: it is predominantly diosmin, and its micronisation alters pharmacokinetics. Hydroxyethylrutosides are not conventional rutin. Likewise, standardised eriocitrin-rich lemon preparations, pomegranate juice or punicalagin-rich extracts, and chemically characterised *Rubia* preparations cannot be assumed equivalent to unspecified commercial extracts. Ingredient-level evidence strengthens mechanistic and translational support, particularly for hesperidin-associated endothelial responsiveness and rutin-associated barrier protection; however, the complete Hesperidin+ formulation remains untested in a controlled CVD trial.

Recent large MPFF meta-analyses provide useful contemporary evidence but frequently report high heterogeneity, and several include authors affiliated with or supported by the manufacturer of MPFF^[10-13]. These studies remain important, but a balanced product review should disclose these features and avoid presenting observational and single-arm data as equivalent to randomised placebo-controlled evidence.

Finally, biological plausibility should not be labelled as synergy. Demonstrating synergy requires direct combination experiments or appropriately designed clinical studies of the finished formulation.

CONCLUSION

Varicose-vein symptoms arise within a pathophysiological continuum involving venous reflux and hypertension, endothelial activation, oxidative-inflammatory signalling, altered vein-wall biology, microvascular leakage, and oedema. Contemporary guidelines and systematic reviews support a symptom-oriented role for selected venoactive flavonoid preparations, particularly for pain, heaviness, swelling, cramps, and related CVD manifestations.

Hesperidin+ has a coherent ingredient-level rationale for venous support. Hesperidin 500 mg is the principal component and has demonstrated human antioxidant and anti-inflammatory activity at the same nominal daily dose used in the formulation. Rutin provides the strongest complementary vascular rationale because the rutoside class has recognised relevance to CVD symptom management. Citrus limon, *Punica granatum*, and *Rubia cordifolia* contribute complementary phytochemical evidence, whereas tabasheer is more appropriately regarded as a silica-rich matrix with no established direct venotonic effect.

The available literature provides an ingredient-level biological rationale for Hesperidin+ in the context of venous comfort and microvascular health, but it does not establish finished-product efficacy for varicose-vein-associated symptoms. The formulation should not be claimed to repair incompetent valves, reverse reflux, eliminate established varicosities, or substitute for indicated vascular treatment.

Declarations

Conflict of Interest

All authors are employees of Biotex Life Solutions Pvt. Ltd., the developer of Hesperidin+. This employment relationship and the company's commercial interest in the reviewed product are disclosed as potential conflicts of interest. The authors declare no other competing interests.

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Author Contributions

All authors contributed to the conception and scope of the review, literature evaluation, interpretation of the evidence, drafting and critical revision of the manuscript, and approval of the final version for submission.

Data Availability

No new datasets were generated or analysed for this narrative review. All information discussed is derived from the cited literature.

Ethics Approval and Consent to Participate

Not applicable. This article is a narrative review of published literature and did not involve new research with human participants or animals.

Consent for Publication

Not applicable.

Abbreviations

CVD, chronic venous disease; ESVS, European Society for Vascular Surgery; MPFF, micronised purified flavonoid fraction; ROS, reactive oxygen species; SVS/AVF/AVLS, Society for Vascular Surgery/American Venous Forum/American Vein and Lymphatic Society; VCAM-1, vascular cell adhesion molecule-1.

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