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Original Research Article

Venifixe: phytovanoactive topical infused oil for healing and preventing epidermal and venous ailments

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ABSTRACT

Background: This study investigates Venifixe®, a cost-effective phyto-vanoactive infused oil, as an alternative treatment for epidermal and venous ailments (EVA). Venifixe® combines venoactive phyto-complexes, hydrophilic botanical extracts, essential oils, carrier oils, and epidermal care components. The study strives to offer a non-invasive and potentially more effective alternative to conventional treatments, aiming to improve or prevent various EVAs and enhance patients' quality of life. Despite the array of existing treatments, there remains a need for formulations offering enhanced efficacy, reduced invasiveness, and broader applicability.
Methods: Over twelve weeks, 250 participants (average age: 59.91±7.25 years), diagnosed with varicosities via ultrasonography, were included. Participants were divided into two groups: 142 received standard management (SM) for symptomatic EVA, and 108 received Venifixe® treatment. Both groups were assessed for EVA-related symptoms (pain, itchiness, restlessness, swelling/edema, heaviness, and leg cramps) and Venous Clinical Severity Score (VCSS) based on CEAP classification pre-and post-treatment.
Results: At twelve weeks, the Venifixe® group demonstrated a VCSS ROC curve (AUC=0.905, 95% CI: 0.89-0.92, $p<0.0001$), with 93.68% sensitivity, 61.11% specificity, and 75.43% accuracy, indicating favorable treatment outcomes. Significant reductions in VCSS risk ratios and associated symptom prevalence ($p<0.0001$) led to an improved NHS gradation scale from level 3 to level 2 compared to the SM group.
Conclusions: Venifixe®'s topical application provides a more effective phytotherapeutic approach for EVA compared to standard management, offering symptom relief and enhancing quality of life. These results, supported by ROC curves and NHS gradation improvements, warrant further clinical investigation.

Keywords: Botanical extracts, Chronic venous disease, Phyto-venoactive compounds, Skin health, Topical therapy, Venifixe®

INTRODUCTION

Epidermal and venous ailments (EVA), often classified under chronic venous disease (CVD), are characterized by the impairment of venous blood return from the legs to the heart. This condition frequently leads to complications such as swelling, pain, itchiness, restless legs syndrome, stasis dermatitis, and venous eczema. In more severe instances, patients may experience skin shrinkage (lipodermatosclerosis), scar-like patches around the ankles (atrophie blanche), and cramping in the legs.[1] The root cause of these symptoms is often weakened or damaged valves within the veins, which permit blood to flow in reverse. This backward flow leads to the development of enlarged, swollen, and twisted veins, commonly known as varicose veins. Additionally, spider veins, or telangiectasias, present as small, dilated blood vessels near the skin's surface, typically appearing as lines, clusters, or webs of red, blue, or purple hues.[2]

CVD, and particularly EVA, disproportionately affects women over the age of 50 due to hormonal fluctuations that relax the venous walls, increasing the susceptibility to valve leakage.[3] Other significant risk factors include smoking, chronic constipation, occupations involving prolonged standing, pregnancy, obesity, menopause, hereditary predispositions, leg injuries, abdominal straining, and venous or arteriovenous malformations.[4]

Historically, varicose vein treatment has evolved from rudimentary remedies to surgical interventions, with the introduction of the Trendelenburg ligation in 1890 marking a pivotal point.[5] Modern approaches to varicose vein management encompass both standard and interventional methods. Standard treatments generally focus on lifestyle adjustments, compression stockings, and the administration of phlebotonic medications and nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, to mitigate pain and inflammation. However, these approaches have demonstrated limited efficacy and come with notable adverse effects, such as gastrointestinal bleeding and superficial thrombophlebitis.[6] Additionally, there is insufficient evidence supporting the effectiveness of compression stockings for treating varicose veins, with their use recommended primarily for pregnant women and when interventional treatments prove ineffective.[7]

Interventional management techniques include vein stripping, ambulatory phlebectomy, cryosurgery, sclerotherapy, and various forms of endovenous thermal ablation, including laser, radiofrequency, and steam.[8] Despite their efficacy, these procedures are often expensive and carry risks such as hematomas, infections, nerve damage, pulmonary embolism, and aesthetic concerns. In light of these challenges, alternative treatments for EVA have garnered increasing public interest. One such alternative is Venifixe®, a cost-effective, phyto-vanoactive-infused oil designed as a treatment for EVA. This topical formulation incorporates venoactive ingredients, hydrophilic botanical extracts, essential oils, and carrier oils in well-defined proportions. Key components include Aescin, Triterpenes, Ruscogenin, Oligomeric Proanthocyanidins (OPCs), Diosmin-Hesperidin, Proanthocyanidins, Tannins, and Piperine, alongside botanical extracts from Allium sativum, Zingiber officinale, Aloe barbadensis, Rubia cordifolia, Vitex negundo, Withania somnifera, and Tinospora cordifolia.[9-23] The formulation also contains essential oils such as Melaleuca alternifolia, Cupressus sempervirens, Lavendula officinalis, and Salvia rosmarinus, along with carrier oils including Cocos nucifera and Triticum vulgare.[24-29]

The therapeutic effects of Venifixe® are rooted in the bioactive properties of its phytoconstituents. For instance, Aescin9 reduces inflammation, improves blood flow, and strengthens venous walls, while Triterpenes enhances skin healing and vein elasticity.[10] Similarly, Ruscogenin alleviates leg pain and reduces edema by promoting microcirculation, and OPCs provide potent antioxidant protection against oxidative stress and capillary damage.[11,12] Diosmin-Hesperidin improves venous tone and lymphatic drainage, while Tannins and Piperine offer astringent, antimicrobial, and analgesic properties.[13-16]

This study aims to evaluate the efficacy of Venifixe® in alleviating EVA symptoms and improving Venous Clinical Severity Scores (VCSS)[30]. By employing meta-analysis and receiver operating characteristic (ROC) curve analysis, this investigation explores the potential of Venifixe® as a cost-effective alternative to standard EVA management treatments.[31-32]

METHODS

This twelve-week observational study included 388 patients aged 45 to 75 years (78.82% female) treated at organic phyto therapeutic method (OPTM) health care (P) Ltd, Kolkata, India.

Study duration was between September 2023 and January 2024. Ethical approval for the study was obtained from the OPTM Research Institute Ethics Committee, and written informed consent was provided by all participants for physical and radiological assessments (duplex sonography) during the initial screening.

Exclusion criteria

Of the 388 participants, 138 were excluded based on the following criteria, cancer, diabetes mellitus, dyslipidemia, gout, arterial hypertension, vascular brain events, chronic obstructive pulmonary disease, mental disorders, chronic varicose ulcers, severe metabolic disorders, chronic renal failure, recent varicose vein surgery (within three months), and refusal to participate in physical or radiological evaluations or weekly follow-ups.

Study design

After exclusion, 250 eligible patients with radiologically confirmed varicose veins and telangiectasias experiencing severe pain impacting daily activities were included. Among them, 108 patients were assigned to the experimental group (Vanifixe group), receiving Venifixe® oil treatment, while 142 patients formed the control group, receiving standard management (SM) for varicose veins and telangiectasias.

Symptom evaluation

Symptoms such as telangiectasias, pain, swelling, inflammation, heaviness, restless legs syndrome, night cramps, superficial thrombophlebitis, and stasis dermatitis were assessed in both groups before and after treatment. The experimental group (108 patients, 199 legs) received Venifixe® oil, and the control group (142 patients, 223 legs) underwent standard treatment. Symptom improvement percentages were analyzed using radar charts at the end of the 12-week study.

CEAP classification and VCSS

The Clinical, Etiological, Anatomical, and Pathophysiological (CEAP) classification for Chronic Venous Disease (CVD) and the Revised Venous Clinical Severity Score (VCSS) were applied. VCSS parameters such as pain, varicose veins, venous edema, skin hyperpigmentation, inflammation, and induration were graded from zero (none) to three (severe). Parameters specific to varicose ulcers were excluded. ROC curve analysis was used to evaluate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for each VCSS parameter. Meta-analysis techniques, including Cochran's Q-test and the I-squared index, were utilized to assess heterogeneity and significance. Radar charts illustrated standardized means and percentage changes in risk factors and VCSS parameters for both the Varco and SM groups.

NHS varicose vein treatment grading system

The 'NHS Varicose Vein Treatment Grading System,' used to qualify patients for surgical treatment, was applied to assess patients' condition severity at week 12. This system categorizes varicose veins from Grade 1 (cosmetic thread veins) to Grade 5 (varicose veins with severe skin damage at the ankle). No Grade 6 patients (with varicose ulcers) were included in the study[33].

Topical phytotherapy management

Composition and acquisition of ingredients

Venifixe® oil contains 39.5-40.5% aqua Rosa, 16.5-17.9% venoactive phyto-complexes, 7.5-7.9% hydrophilic botanical extracts, 2.8-3.2% essential oils, 18.5-19.8% carrier oils, and 0.8-1.1% epidermal care components. All ingredients were sourced from certified suppliers and underwent quality analysis, including UV and HPLC profiling.

Effectiveness

Venifixe® oil's effects include fibrinolytic, anticoagulant, astringent, vasoconstrictor, and antioxidant properties[34]. These attributes support varicose vein symptom relief, tissue regeneration, and improved venous health.

Application method

Patients applied five milliliters of oil from the groin to the toes while in a supine position, and from the hip to back of the legs in a prone position, three times daily.

External study review

An independent panel reviewed cohort results and data to ensure the study's impartiality.

Statistical analysis

Descriptive statistics were used for continuous variables, while frequency tables were used for categorical variables. Non-parametric ROC curve analysis assessed the predictive accuracy of measurements for the experimental group's outcomes. Statistical analysis was conducted using IBM SPSS (version 20), with an alpha level of 5% (p-value < 0.05) considered statistically significant.

Ethical approval

The study protocol was approved by the OPTM Research Institute Ethics Committee. Informed consent was obtained from all participants for physical examinations and radiological assessments.

RESULTS

Enrolment and baseline characteristics of patients

Recruitment commenced on 1st August 2022, with the final follow-up data collected on 28th September 2022. Of the 501 patients approached, 334 were screened, and 250 (49.90%) met the inclusion criteria. Among these, 108 patients were allocated to the experimental group (Varco® group), and 142 to the control group (Standard Management or SM Group). Study flow chart according, to the consolidated standards of reporting trials (CONSORT), (n=number of subjects) as shown in Figure 1.

Analysis of attributed symptoms of varicosities

The attributed symptoms of varicose veins showed significant improvement in the Varco® group. Compared

to the control group, there was a remarkable reduction in symptom severity, with the greatest improvement observed in heaviness (83.78%), cramping (85.85%), and restless leg syndrome (82.60%). Other symptoms, including swelling, throbbing, pain, itching, and superficial thrombophlebitis, showed reductions between 79.95% and 64.76% (p<0.0001) (Figure 2). Risk ratios for all attributed symptoms were statistically significant (p<0.0001), as presented in figure 3.

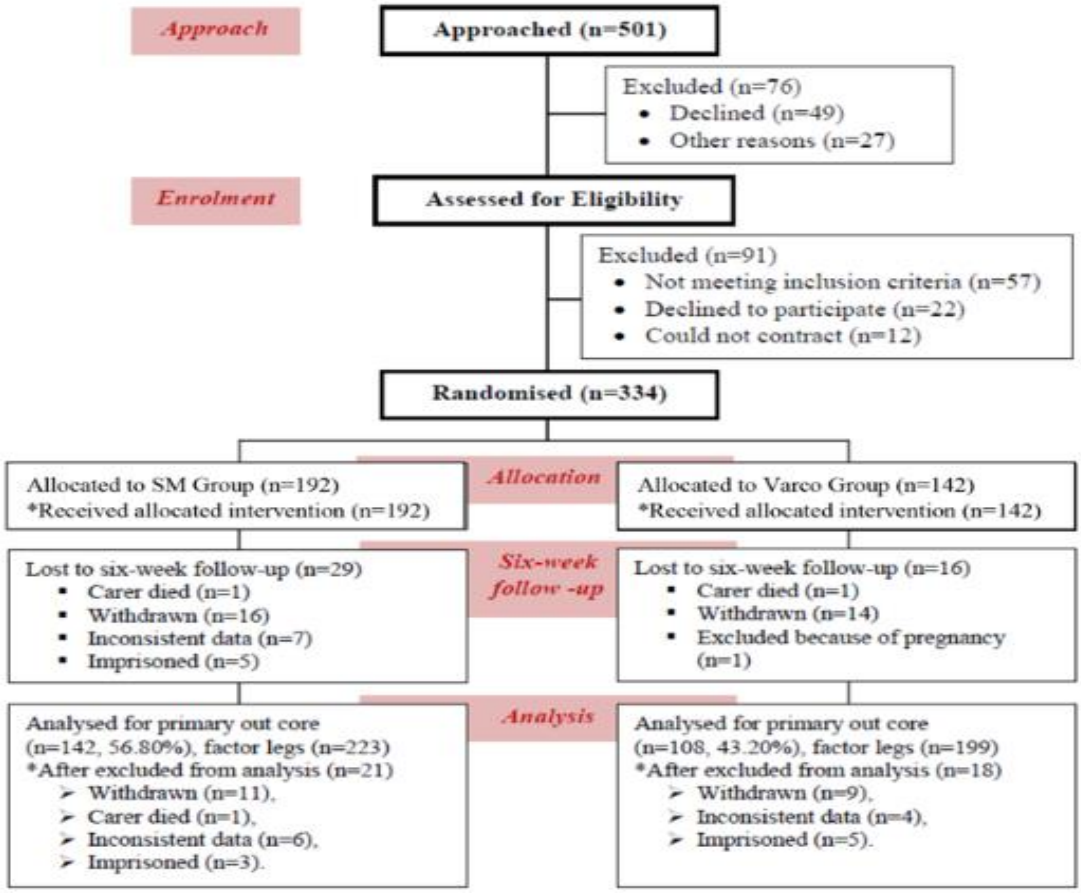

Figure 1: Study flow chart according, to the consolidated standards of reporting trials (CONSORT), (n=number of subjects).

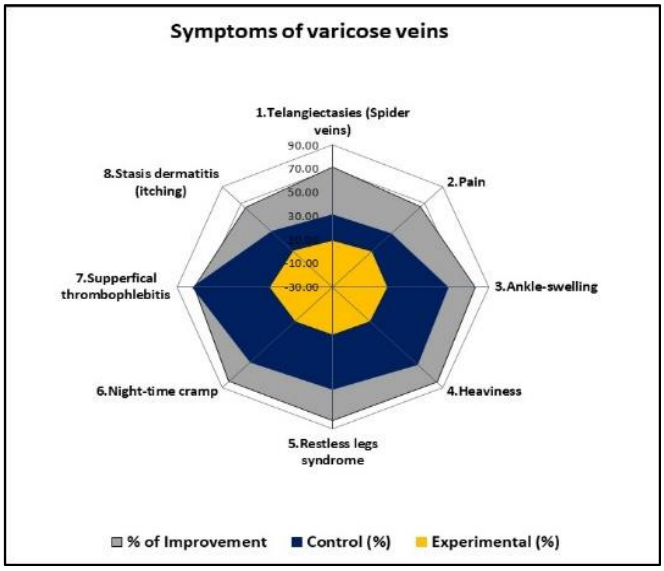

Figure 2: Radar chart showing the associated symptoms for % of experimental and control cohorts and their % of improvements at twelve-week.

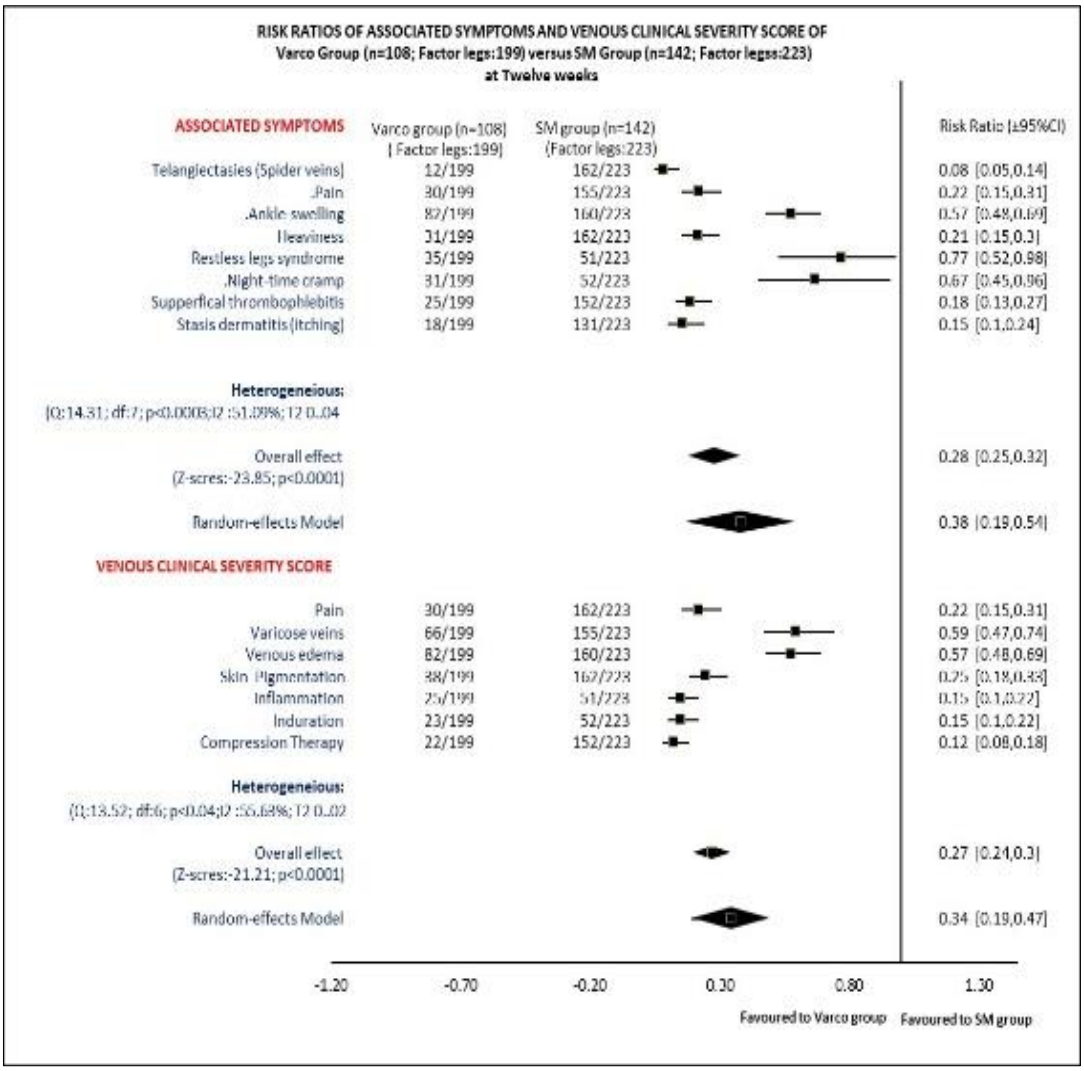

Figure 3: Risk ratios of associated symptoms and elements of venous clinical severity score (VCSS) at twelve-week experimental group (n=108; factor legs:199) versus control group (n=142; factor legs:223).

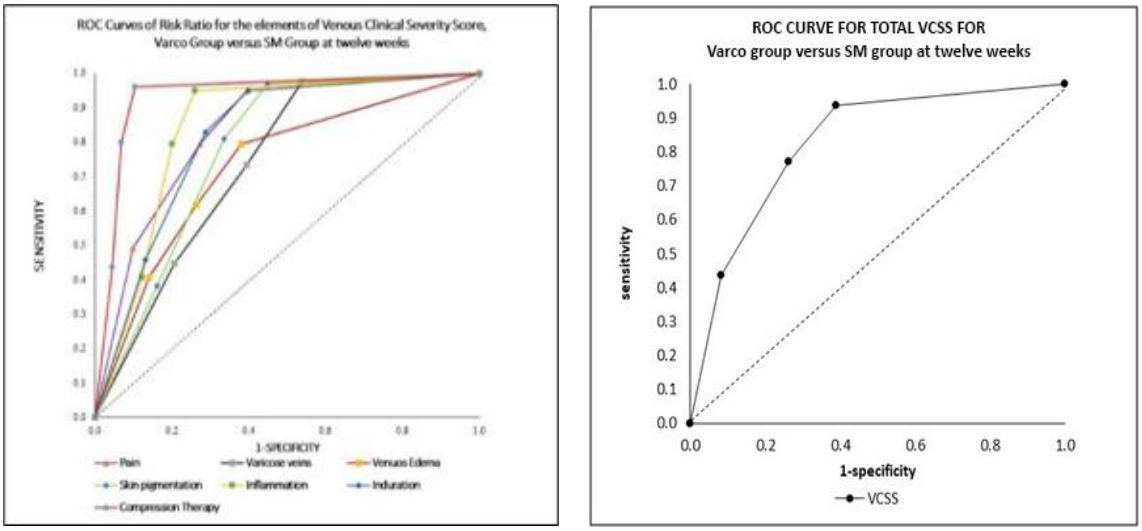

Figure 4: ROC curves of the elements of venous clinical severity score (VCSS) and total VCSS and their values thereon at week twelve of the experimental group (n=108; factor legs:199) versus the control group (n=142; factor legs:223).

Table 1: Analysis of receiver operating curves for patients of the varco group (n=108, factor legs: 199) versus the MS group (n=142, factor legs:223) at week twelve.

VENOUS clinical severity score [VCSS]								
Parameter	**AUC (95%CI)**	**Youden index (J) (%)**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**	**Cut-off value**
Pain	0.908 (0.88,0.94)	55.51	94.97	90.54	72.15	79.8	75.83	Mild
Varicose veins	0.832 (0.79,0.87)	43.68	97.49	46.19	63.18	73.77	67.77	Mild
Venous edema	0.846 (0.81,0.88)	41.28	79.4	61.88	67.58	68.33	68.01	Mild
Skin pigmentation	0.863 (0.83,0.9)	52.14	96.98	55.16	68.22	79.57	73.22	Mild
Inflammation	0.909 (0.88,0.94)	68.97	94.97	73.99	77.73	81.28	79.62	Mild
Indurations	0.897 (0.87,0.93)	55.06	94.97	60.09	72.05	82.38	76.78	Mild
Compassion therapy	0.969 (0.95,0.99)	85.67	95.98	89.69	91.38	83.87	86.97	Mild
Total VCSS	0.905 (0.89,0.92)	54.8	93.68	61.11	72.44	78.4	75.43	Mild

Table 2: Analysis of the NHS varicose vein grading system of patients under the SM group (N=142 Factor legs (n): 223) and Varco group (N=108; Factor legs (n): 199) at the baseline and week-12.

Varicose vein grading system	SM group				Varco group			
	Baseline		**At week-16**		**Baseline**		**At week-16**	
	N	%	N	%	N	%	N	%
Grade 1	10	4.48	5	2.24	4	1.79	55	24.66
Grade 2	35	13.45	23	10.31	32	14.35	74	33.18
Grade 3	71	30.49	60	26.91	62	27.80	51	22.87
Grade 4	68	27.80	61	27.35	72	32.29	25	11.21
Grade 5	59	23.77	68	30.49	53	23.77	18	8.07
Grade 6	0	0.00	6	2.69	0	0.00	0	0.00
Total	223	100.00	223	100.00	199	100.00	199	100.00

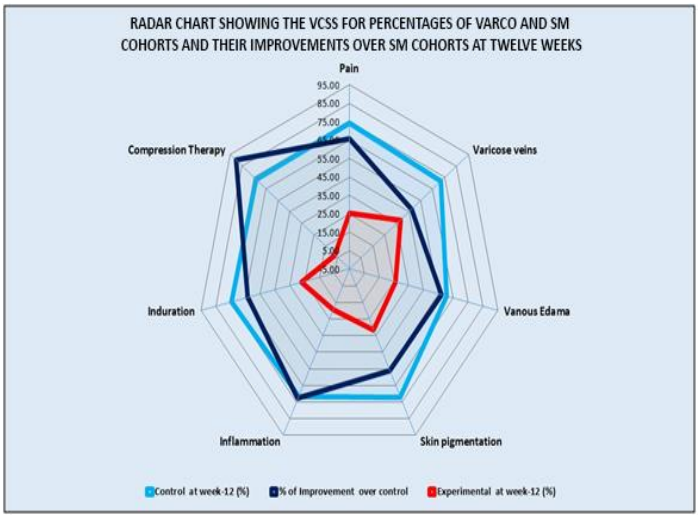

Figure 5: Radar chart showing the % of the elements of venous clinical severity score in the experimental group, control group and their % of improvements at twelve-week.

Analysis of clinical, etiological, anatomical, and pathophysiological classification (CEAP)

The Venous Clinical Severity Score (VCSS) parameters, such as pain, varicose veins, venous edema, skin pigmentation, inflammation, and induration, showed significant improvement in the Varco® group compared to the control group. The risk ratios for each parameter were highly significant ($p<0.0001$). The area under the curve (AUC) for compression therapy was the highest (0.969), followed by inflammation (0.909) and pain (0.908) (Figure 4 and Table 1). The overall AUC for the total VCSS improvement was 0.905 (Figure 4 and Table 1), and the improvement pattern at 12 weeks was clearly shown in the radar chart (Figure 5).

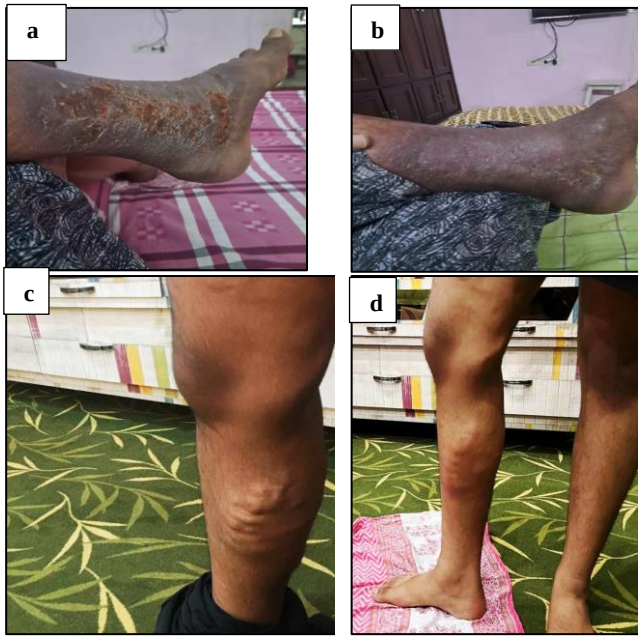

Figure 6 (a-d): Before and after images of patients with acute EVA, illustrating the treatment outcomes following twelve weeks of topical Venifixe® phyto-complexes-infused oil application.

Analysis of the NHS varicose vein treatment grading system

The NHS varicose vein treatment grading system demonstrated notable improvement in the Varco® group. Approximately 30% of patients upgraded from grades 3 and 4 to grade 2, and 42% improved from grade 5 to grade 4 after 12 weeks of treatment. In contrast, 1.52% to 2.51% of patients in the SM group experienced a downgrade in their condition from grades 2 and 3 to grades 4 and 5, respectively (Table 2).

Before and after images depicting the treatment outcomes of patients with acute varicose veins are shown in Figure 6.

Safety and cost evaluation

The topical use of Venifixe® phyto-complexes-infused oil was well tolerated, with no reported adverse events or safety concerns. The need for additional therapies, such as painkillers, physiotherapy, and compression stockings, was eliminated in the Varco® group, in contrast to the control group ($p < 0.05$). Additionally, the average cost of management, including treatment, diagnostics, and lost working days, was reduced by 94% ($p<0.05$) in the Varco® group compared to standard varicose vein management.

DISCUSSION

This study demonstrates that topical Venifixe® phyto-complexes-infused oil offers a promising alternative for managing epidermal and venous ailments, specifically chronic venous disease (CVD) characterized by varicose veins. A comprehensive analysis of symptoms and Venous Clinical Severity Score (VCSS) parameters showed that the topical application of Venifixe® oil led to significant improvements in patients' conditions compared to standard management (SM) practices. The unique formulation of Venifixe®, comprising venoactive phyto-complexes, hydrophilic botanical extracts, essential oils, carrier oils, and epidermal care components, appears to play a crucial role in its effectiveness.

Efficacy of Venifixe® in alleviating symptomatic factors

The radar chart analysis (Figure 2) and the ratio analysis (Figure 3) indicate a significant reduction in attributed symptomatic factors such as pain, swelling, heaviness, restless legs syndrome, cramping, throbbing, itchiness, and superficial thrombophlebitis. These results demonstrate the efficacy of Venifixe® oil in alleviating the discomfort associated with varicose veins. The observed improvements can be attributed to the synergistic effects of the phyto-compounds present in the formulation.

Mechanisms of action of bioactive components in Venifixe®

The bioactive components in Venifixe® exert their therapeutic effects through multiple molecular actions. Aescin, an anti-inflammatory saponin, targets leukocyte activation and endothelial dysfunction in venous disorders.[9] Triterpenes modulate cytokine production and promote collagen synthesis, enhancing wound healing and microcirculation.[10] Moreover, Li et al emphasized that Aescin may exert its therapeutic effects by targeting specific biomarkers, including PTGS2, SRC, MMP9, and MAPK1, subsequently influencing key signaling pathways such as TNF, TRP channels, and T-cell receptor signaling pathways, highlighting the multifaceted mechanisms through which Aescin contributes to the regulation and healing of venous and epidermal ailments.[35]

Ruscogenin improves venous tone by inhibiting leukocyte adhesion and modulating VEGF, thus reducing edema.[11] OPCs protect endothelial cells from oxidative stress, inhibit platelet aggregation, and enhance nitric oxide production, promoting vascular health.[12] Diosmin-Hesperidin improves venous tone and lymphatic drainage by reducing capillary permeability and enhancing lymphatic vessel contraction.[13] Proanthocyanidins protect collagen and elastin fibers, strengthen capillary walls, and scavenge free radicals.[14] Tannins exhibit antioxidant and astringent properties, modulating inflammatory cytokines and collagen degradation, while piperine enhances the absorption of bioactive compounds, inhibits inflammatory mediators, and improves skin penetration.[15,16]

Hydrophilic botanical extracts such as allicin in Allium sativum offer antimicrobial, anti-inflammatory, antioxidant, and vascular health-enhancing properties.[17] Gingerol, shogaol, and paradol in Zingiber officinale inhibit COX-2 and LOX enzymes, neutralize ROS, and modulate TRPV1 receptors, while acemannan, anthraquinones, and glycoproteins in Aloe barbadensis stimulate fibroblast activity, inhibit the arachidonic acid pathway, and have antimicrobial properties.[18,19] Rubiadin, purpurin, iridoids, and triterpenoids in Rubia cordifolia inhibit the NF-κB pathway, scavenge free radicals, and enhance detoxification.[20] Alkaloids, flavonoids, terpenoids, and essential oils in Vitex negundo inhibit COX and LOX pathways, modulate pain receptors, and have antimicrobial properties.[21]

Essential oils such as terpenes in Melaleuca alternifolia disrupt microbial cell membranes, reduce pro-inflammatory cytokines, and promote wound healing.[24] Monoterpenes, sesquiterpenes, flavonoids, and phenolic compounds in Cupressus sempervirens enhance vascular tone, inhibit microbial growth, and modulate inflammatory pathways.[25] Linalool, linalyl acetate, camphor, and 1,8-cineole in Lavandula angustifolia disrupt microbial cell walls, inhibit COX-2 and LOX pathways, and modulate GABAergic neurotransmission.[26] Carnosic acid, rosmarinic acid, 1,8-cineole, α-pinene, and camphor in Salvia rosmarinus scavenge free radicals, inhibit NF-κB and MAPK pathways, and inhibit microbial growth.[27]

Carrier oils like lauric acid, capric acid, caprylic acid, polyphenols, tocopherol, and proteins in Cocos nucifera disrupt microbial cell membranes, enhance skin hydration, and reduce inflammatory markers while tocopherol, linoleic acid, octacosanol, phytosterols, and squalene in Triticum vulgare provide high levels of vitamin E, enhance skin barrier repair, and promote collagen synthesis.[28.29] Epidermal care components such as ceramide restore the lipid barrier, enhance water retention, and modulate skin inflammation. Lactic acid promotes exfoliation, acts as a humectant, and maintains skin pH balance, while tocopherol (vitamin E) scavenges free radicals, reduces UV-induced inflammation, and promotes cellular regeneration. Collectively, these bioactive components target multiple molecular pathways, supporting the therapeutic efficacy of Venifixe® in treating and preventing epidermal and venous ailments.

Efficacy of Venifixe® in venous clinical severity score (VCSS)

The study's results in Figure 4 and Figure 5 demonstrate that Venifixe® oil provides considerable relief from the symptoms associated with EVA. The marked reduction in VCSS and the high sensitivity and accuracy highlighted by the ROC curve analysis indicate a robust therapeutic effect. The high sensitivity (93.68%) and considerable specificity (61.11%) suggest that Venifixe® is highly effective in detecting and managing EVA, although the specificity indicates room for improvement in distinguishing EVA from other conditions. The 75.43% accuracy reflects the overall effectiveness of Venifixe® oil in clinical settings, supporting its potential as a reliable treatment modality.

ROC curve analyses reinforce the effectiveness of Venifixe® oil, with the highest area under the curve (AUC) observed for parameters such as compression therapy, inflammation, and pain, suggesting substantial improvements in these areas. The elimination of compression stockings during treatment with Venifixe® highlights its potential to offer effective symptom relief without the need for adjunctive therapies. The CEAP classification system is essential for diagnosing venous conditions but lacks guidance for treatment gradation, unlike the Kellgren and Lawrence system for osteoarthritis.[36] The revised Venous Clinical Severity Scoring (VCSS) refines venous outcome assessment but does not establish varicosity grading.

In contrast, the NHS varicose vein treatment grading system, developed at the London Vein Centre, offers a more practical framework. Professor Vasquer from the Venous Institution of Buffalo highlighted the importance of comparative statistical evaluation for optimizing patient outcomes.[37] Meissner et al. emphasized evaluating treatment efficacy through disease progression, quality of life, and therapeutic outcomes via pre- and post-treatment assessments.[38] This study compares Venifixe® oil therapy (Vanifixe group) to standard management (SM group). Results show that more patients using Venifixe® progressed to higher varicosity grades, while conventional treatment patients experienced more deterioration (Table 1). This underscores Venifixe® oil therapy's potential effectiveness. Figure 6 illustrates significant improvements in acute EVA cases after 12 weeks of Venifixe® treatment.

Comparison with standard management

When compared to standard management practices, which often involve lifestyle modifications, compression

therapy, and pharmacological interventions, Venifixe® oil offers several advantages. Standard treatments, while effective to some extent, are often associated with limitations such as side effects and invasive procedures. The study's findings indicate that Venifixe® not only matches but in many cases surpasses the efficacy of standard management, providing a non-invasive, well-tolerated, and holistic approach to EVA treatment. The significant improvements in symptomatology and quality of life reported by participants using Venifixe® highlight its potential as a superior alternative, particularly for patients seeking less invasive and more natural treatment options.

Clinical implications and future directions

The promising results from this study warrant further clinical investigation to validate and expand upon these findings. Long-term studies with larger and more diverse populations are necessary to confirm the efficacy and safety of Venifixe® oil over extended periods. Additionally, exploring the mechanistic pathways through which Venifixe® oil exerts its therapeutic effects could provide deeper insights into its role in EVA management. Future research should also consider the cost-effectiveness of Venifixe® oil in comparison to conventional treatments. Given the growing interest in phytotherapeutic approaches and the increasing burden of EVA on healthcare systems, Venifixe® oil could represent a viable and sustainable option for managing this prevalent condition.

CONCLUSION

Our study suggests that Venifixe® shows significant potential as a phyto-vanoactive-infused oil for treating and preventing epidermal and venous ailments. The multi-faceted mechanism of action of its bioactive compounds, including venoactive phyto-complexes, hydrophilic botanical extracts, essential oils, and carrier oils, supports its efficacy in alleviating the symptoms of varicose veins and other venous disorders. The study's results suggest that Venifixe® oil offers a non-invasive and well-tolerated alternative to standard management practices, potentially eliminating the need for compression stockings and reducing dependence on pharmacological interventions. Further research is warranted to confirm these findings and explore the long-term efficacy and safety of Venifixe® oil in diverse patient populations.

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