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**Review**

# Natural treatment approaches for varicose veins: A brief review of the literature

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**Abstract:** Chronic venous insufficiency (CVI) is a widespread condition affecting millions worldwide. Each year, approximately 150,000 new patients are diagnosed with CVI, and nearly $500 million is used in the care of these patients. The venous system has sturdy valves and muscle pumps that keep blood flowing back to the heart against gravity. The inadequacy of these systems leads to difficulties in blood circulation, blood pooling, and venous hypertension, all which have the potential to lead to the development of varicose veins, edema, discomfort, alterations in the skin, and potentially even the formation of ulcers. Conditions that induce CVI are genetic predisposition, obesity (body mass index greater than 30), continuous standing/sitting work, age, pregnancy, gender, and lifestyle. Conventional venous insufficiency treatments include compression therapy, surgical interventions like vein stripping, and sclerotherapy. Venoactive drugs used in conservative treatment have the potential to enhance both varicose veins and symptoms associated with chronic venous disorders throughout all stages of venous insufficiency. In addition to synthetic drugs, naturally derived coumarins, flavonoids, rutin derivatives, pycnogenol, micronized purified flavonoid fraction, and saponosides are essential in the treatment. Medicinal plants and natural compounds are highly preferred for treating CVI and varicose veins due to their biological activities, such as anti-inflammatory, antioxidant, and vascular tone improvement. The present review provides a concise overview of the utilization of natural compounds and plant extracts in treating varicose veins, both in medical practice and traditional folk medicine.

**Özet:** Kronik venöz yetmezlik (KVY), dünya çapında milyonlarca kişiyi etkileyen yaygın bir durumdur. Her yıl yaklaşık 150.000 yeni hastaya KVY tanısı konulur ve bu hastaların bakımına yaklaşık 500 milyon dolar harcanmaktadır. Venöz sistemde, kanın yer çekimine karşı kalbe geri akmasını sağlayacak sağlam kapakçıklar ve kas pompaları vardır. Bu sistemlerin yetersizliği kan dolaşımında zorluklara yol açarak kanın birikmesine ve venöz hipertansiyona neden olur. Yukarıda belirtilen durum varisli damarların gelişmesine, ödeme, ciltte değişikliklere ve hatta potansiyel olarak ülser oluşumuna yol açabilir. KVY genetik yatkınlığını tetikleyen koşullar arasında, obezite (vücut kitle indeksi 30'dan büyük), sürekli ayakta/oturup çalışma, yaş, hamilelik, cinsiyet ve yaşam tarzı yer almaktadır. Geleneksel venöz yetmezlik tedavileri arasında kompresyon tedavisi, damar soyulması gibi cerrahi müdahaleler ve skleroterapi yer alır. Konservatif tedavide kullanılan venoaktif ilaçlar, hem varisli damarları hem de venöz yetmezliğin tüm aşamalarında kronik venöz bozukluklarla ilişkili semptomları iyileştirme potansiyeline sahiptir. Tedavide sentetik ilaçların yanı sıra doğal olarak elde edilen kumarinler, flavonoitler, rutin türevleri, piknogenol, mikronize saflaştırılmış flavonoit fraksiyonu ve saponozitler önemlidir. Tıbbi bitkiler ve doğal bileşikler, anti-enflamatuvar, antioksidan ve damar tonusunu iyileştirme gibi biyolojik aktivitelerinden dolayı KVY ve varisli damarların tedavisinde oldukça tercih edilmektedir. Bu derleme, hem tıbbi uygulamada hem de geleneksel halk hekimliğinde varisli damarların tedavisinde doğal bileşiklerin ve bitki esktrelerinin kullanımına kısa bir genel bakış sunmaktadır.

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## Introduction

The term varicose comes from the Latin word "varix" meaning "twisted". Varicose veins and chronic venous insufficiency (CVI) can be summarized under the term "chronic venous disorders", which includes the entire spectrum of morphological and functional abnormalities of the venous system. Lower extremity CVI is a condition that occurs due to venous hypertension and includes some signs and symptoms such as pain, heaviness, leg ulcers, itching, burning, and swelling (Somers & Knaapen 2006, Partsch 2009). In order to enable blood to be returned to

the heart against gravity, the venous system's blood flow depends on strong muscular pumps and valves. Venous flow normally flows in a caudal to cranial direction, from the superficial vein to the deep system and proximally to the central veins. When completely functional, the valves in superficial, deep, and perforating veins preserve cerebral flow and stop reflux (Callam 1994). With the insufficiency of the systems, complications occur in the blood flow and cause backward flow of blood, pooling of blood, and venous hypertension. In addition, venous hypertension, and enlargement and swelling of the veins occur, which causes venous insufficiency in varicose veins (Callam 1994, Beebe-Dimmer *et al.* 2005, Youn & Lee 2019). Various symptoms in the lower extremities, including heaviness, swelling, pain, aching, restless legs, cramping, itching, and tingling are frequently attributed to varicose veins (Bradbury *et al.* 1999). Leg ulcers, stasis changes, infection, and thrombosis are all potential complications (Raetz *et al.* 2019). The prevalence of lower extremity varicose veins is estimated to be between 1-40% in men and 1-73% in women. Varicose veins with or without edema, classified as C2 and C3 according to clinical, etiological, anatomical, and pathophysiological (CEAP) criteria, are the most common type of CVI due to saphenous vein insufficiency (Eberhardt & Raffetto 2014, Azhdari *et al.* 2020). Genetic predisposition, obesity (body mass index higher than 30), continuous standing/sitting work, age, pregnancy, gender, and lifestyle can be counted among the responsible conditions causing CVI (Lim & Davies 2009). Several studies have reported that varicose veins can occur in people without any identifiable risk factors, suggesting that some intrinsic genetic factors may contribute to their formation (Aslam *et al.* 2022).

In the United States, the population-based cost of treating problems related with CVI is estimated to be $3 billion per year, and venous stasis ulcers are responsible for more than 2 million lost work days annually (Oklu *et al.* 2012). Treatment options for varicose veins are divided into conservative treatment and surgical intervention. Asymptomatic patients with varicose veins can be treated with medication, compression therapy, and lifestyle changes. Surgical interventions are performed in patients with symptomatic varicose veins with more advanced disease (Gao *et al.* 2022). In a systematic review, 38 researches which used different treatment methods for varicose veins were screened, and invasive treatments (surgical and endoluminal) were concluded to be superior to conservative treatment (Murad *et al.* 2011). However, it is known that venoactive drugs used in conventional treatment improve varicose veins and symptoms of CVI. Medicines, including calcium dobesilate, hydroxyl-ethyl rutosides, and the micronized purified flavonoid fraction (MPFF) have anti-inflammatory properties and can improve venous tone (Mansilha & Sousa 2019, De Maeseneer *et al.* 2022).

Although the pathogenesis of varicose veins is not fully known, oxidative stress, inflammation, and vascular damage are the primary pathophysiological disorders observed in varicose veins (Castro-Ferreira *et al.* 2018). Medicinal plants and natural compounds are highly preferred for treating CVI and varicose veins due to the biological activities of their secondary metabolites, such as anti-inflammatory, antioxidant, vitamin P activity (mainly flavonoids), and anti-edema (Lichota *et al.* 2019). The decrease in antioxidant potential and the formation of reactive oxygen species (ROS) result in dysfunction of the vascular endothelium and loss of vascular elasticity. Other factors associated with changes in vein structure are thought to be proinflammatory cytokines and related inflammation. Chronic inflammation can cause progressive vascular damage, varicose veins, and atheromas in the arteries. Blood stasis and accompanying hypoxia lead to metabolic disturbance resulting in the breakdown of adenosine triphosphate (ATP) and the release of excess superoxide radicals and other ROS due to the formation of hypoxanthine/xanthine by conversion of xanthine dehydrogenase to xanthine oxidase (Phan *et al.* 1992, Zweier *et al.* 1994, Guzik *et al.* 2011, Castro-Ferreira *et al.* 2018, Orhan & Deniz 2020, Kekilli *et al.* 2021). It has been noted that the damage to the endothelium and the entire vein wall is a result of the action of ROS as well as proteolytic enzymes released from active neutrophils (Michiels *et al.* 1993, Lichota *et al.* 2019). Collagenase, hyaluronidase, and elastase enzymes cause damage to venous structures in cases where proteoglycan synthesis is reduced. Inhibitors of these enzymes can also be used as wound healing and anti-inflammatory agents in addition to their cosmetic attributes, such as their capacity to reduce wrinkles (Kozachok *et al.* 2020, Deniz *et al.* 2020, Deniz *et al.* 2021). Studies have shown that matrix metalloproteinases (MMP) like elastase and collagenase are increased in the venous blood of the lower extremities in patients with varicose veins, so it has been suggested that the increase in MMP can be considered as an essential mediator of venous insufficiency (Alsaigh *et al.* 2011, Kucukguven & Khalil 2013, Pizzorno *et al.* 2016). The products of the lipoxygenase enzymes (LOXs), one of the proinflammatory enzymes, are known as mediators of inflammation, including atherosclerosis and varicose veins. High LOXs activity also causes an increase in the formation of peroxyl radicals and other free radicals. Moreover, an investigation revealed that veins from subjects with varicose veins generated elevated levels of prostaglandin E2 in contrast to veins from patients without varicose veins, suggesting the significance of the cyclooxygenase (COX) pathway in the walls of varicose veins (Seo *et al.* 2021). For this reason, collagenase, hyaluronidase, elastase, LOXs, COX, and xanthine oxidase inhibition can be used to investigate the mechanisms of active plant extracts and natural compounds for treating of varicose veins.

In the 2018 L'Union Internationale de Phlébologie (UIP) guideline, MPFF, diosmin, rutin, troxerutin flavonoids, *Aesculus hippocastanum* L. (horse chestnut) escin, *Ruscus aculeatus* L. (butcher's broom) saponosides have a recommendation level of 1, while recommendation level of *Vaccinium myrtillus* L. (bilberry) anthocyanins and *Pinus pinaster* Aiton. (maritime pine) proanthocyanidins is stated as 2C (Köksal *et al.* 2010, Lichota *et al.* 2019, Yun 2021). Typically, prescribing of many venoactive medications at the same time is advised. The 2018 UIP guideline explicitly indicates that combining several venoactive pharmaceuticals in a single prescription is not suitable. Although most venoactive drugs have common effects on swelling, pain, and spasms, effects may vary from drug to drug, as reported by some clinical guidelines and systematic reviews. Therefore, the use of combined venoactive drugs is expected to create a complementary effect by relieving different symptoms (Yun 2022).

This review evaluated the therapeutic effects of natural compounds and medicinal plants used in CVI and the potential effects of plants used to treat varicose veins in folk medicine.

## Ethnobotanical Studies

The literature survey revealed the utilization of plants, whether internally or externally in the treatment of varicose veins. The medicinal plants used in the treatment of varicose veins in different countries are given in Table 1.

**Table 1.** Some plants used in the treatment of varicose veins.

| Scientific name | Part | Preparation | Application | Country | Reference |
|---|---|---|---|---|---|
| *Crataegus monogyna* subsp. *monogyna* | Leaves, fruits | Infusion | Drink 2-3 glasses daily | Türkiye | (Korkmaz *et al.* 2016) |
| *Athyrium filix-femina* (L.) Roth | Roots | Decoction | Drink one time in a one-day | Türkiye | (Karaköse 2022) |
| *Brassica oleracea* L. | -[a] | Decoction | Wrap on leg | Türkiye | (Karcı *et al.* 2017) |
| *Plantago major* L. subsp. *major* | Leaves | Infusion | Externally | Türkiye | (Kalankan *et al.* 2015) |
| *Plantago lanceolata* L. | Leaves | Infusion | Externally | Türkiye | (Kalankan *et al.* 2015) |
| *Astragalus noaeanus* Boiss. | Root | Crushed | Applied by wrap-ping in a cloth | Türkiye | (Han & Bulut 2015) |
| *Urtica dioica* L. | Aerial parts | Decoction | Externally | Türkiye | (Kültür 2007) |
| *Sesamum indicum* L. | Seed oil | - | Internally | Türkiye | (Sargin & Büyükcengiz 2019) |
| *Peganum harmala* L. | Seed | - | - | Türkiye | (Sarı *et al.* 2010) |
| *Lamium album* L. | Leaves, flowers | - | Externally | Türkiye | (Akan & Sade 2015) |
| *Capsella bursa-pastoris* (L.) Medik | Leaf, Stem, Flower | - | - | Türkiye | (Aksoy *et al.* 2016) |
| *Helichrysum plicatum* DC. subsp. *plicatum* | Aerial parts | - | - | Türkiye | (Korkmaz & Karakurt 2015) |
| *Picea abies* (L.) H. Karst | Bark | Decoction | - | Romania | (Papp *et al.* 2022) |
| *Pinus sylvestris* L. | Bark | Decoction | - | Romania | (Keszeg 1981, Papp *et al.* 2022) |
| *Chiliadenus glutinosus* Fourr | - | Infusion | Internally | Spain | (Las Heras Etayo *et al.* 2021) |
| *Achillea maritima* L. | Leaves | Infusion | - | Syria | (Khatib *et al.* 2021) |
| *Calendula arvensis* M.Bieb. | Aerial parts | Infusion | - | Syria | (Khatib *et al.* 2021) |
| *Cupressus sempervirens* L. | Cypress oil | - | Externally | Syria | (Khatib *et al.* 2021) |
| *Pteridium aquilinum* (L.) Kuhn | Roots | Decoction | - | Syria | (Khatib *et al.* 2021) |
| *Silybum marianum* (L.) Gaertn. | Seeds | Decoction | - | Syria | (Khatib *et al.* 2021) |
| *Taraxacum officinale* L. | Whole plant | - | Externally | Syria | (Khatib *et al.* 2021) |
| *Convolvulus arvensis* L. | - | - | - | Libya | (El-Mokasabi *et al.* 2018) |
| *Cupressus sempervirens* L. | - | - | - | Libya | (El-Mokasabi *et al.* 2018) |
| *Juniperus phoenicea* L. | - | - | - | Libya | (El-Mokasabi *et al.* 2018) |

**Table 1.** Some plants used in the treatment of varicose veins (Continued).

| Scientific name | Part | Preparation | Application | Country | Reference |
|---|---|---|---|---|---|
| *Lavandula multifida* L. | - | - | - | Libya | (El-Mokasabi *et al.* 2018) |
| *Lolium rididum* Gaudin. | - | - | - | Libya | (El-Mokasabi *et al.* 2018) |
| *Plantago major* L. | - | - | - | Libya | (El-Mokasabi *et al.* 2018) |
| *Agave americana* L. | Leaves | - | Externally | Spain | (Benítez *et al.* 2010) |
| *Lithodora fruticosa* (L.) Griseb. | Flowery plant | - | Internally | Spain | (Benítez *et al.* 2010) |
| *Paronychia argentea* Lam. | Aerial part | Infusion/decoction | Internally | Spain | (Benítez *et al.* 2010) |
| *Paronychia suffruticosa* (L.) Lam. | Flowery plant | Infusion | Internally | Spain | (Benítez *et al.* 2010) |
| *Equisetum ramosissimum* Desf. | Aerial part | Infusion | Internally | Spain | (Benítez *et al.* 2010) |
| *Rosmarinus officinalis* L. | Flowery plant | Decoction | Internally | Spain | (Benítez *et al.* 2010) |
| *Digitalis obscura* L. | Aerial part | Decoction | Externally | Spain | (Benítez *et al.* 2010) |
| *Urtica dioica* L. | Aerial part | - | Externally | Spain | (Benítez *et al.* 2010) |
| *Urtica urens* L. | Aerial part | - | Externally | Spain | (Benítez *et al.* 2010) |
| *Castanea sativa* Mill. | Flowers, fruits | Fresh | - | Serbia | (Janaćković *et al.* 2019) |
| *Tuberaria lignosa* Samp. | Aerial part | Infusion | Externally | Portugal | (Novais *et al.* 2004) |
| *Aloe arborescens* Miller. | Leaves | Direct application | Externally | Portugal | (Novais *et al.* 2004) |
| *Stellaria media* (L.) Vill. | Fresh plant | Infusion | Internally | Italy | (De Feo *et al.* 1992) |
| *Senecio vulgaris* L. | Whole plant | Decoction | Externally | Italy | (De Feo *et al.* 1992) |

-[a] : Unexplained

**Natural treatment of varicose veins**

Venous reflux, venous hypertension, and vascular insufficiency all result from the weakening and relaxing of the vascular walls (Schuller-Petrovic *et al.* 1997). Venous hypertension causes pressure on the vessel wall (e.g., hypoxia, mechanical stretching, and low shear stress), endothelial damage, and leukocyte activation. Changes in the vascular wall include hyperplasia, collagen/elastin, and matrix metalloproteinase/tissue inhibitor of metalloprotease-1 imbalance, proliferation of smooth muscle cells, migration, apoptosis, and decrease in venous tone (Haviarova *et al.* 1999, Lim & Davies 2009). Since all these stages trigger each other, a vicious circle occurs, making it challenging to sequence pathological events correctly (Raffetto & Khalil 2021). To prevent the complications caused by these events, phlebotonic drugs with properties such as reducing inflammation, vascular permeability, and improving venous tone are used in pharmacological treatment.

*Micronized purified flavonoid fraction (MPFF)*

A product known as MPFF primarily consists of diosmin and hesperidin. In patients with primary varicose veins, the incidence of adverse effects (such as ecchymosis, hematoma, thrombophlebitis, and heat-induced thrombosis) was found to be lower in the group that received a 1000 mg daily dose of MPFF (7.6%) compared to the group that did not receive venoactive agents (15%) (Bogachev *et al.* 2019). Inflammation, micro-vessel permeability, valve and vessel wall remodeling, and reflux in microvalves are a few pathophysiological processes that MPFF helps. Therefore, MPFF is strongly recommended according to international guidelines on managing CVI (Lurie & Branisteanu 2023). In placebo-controlled clinical studies, MPFF has been shown to improve patient's quality of life and symptoms with CVI (Rabe *et al.* 2015, Kakkos & Nicolaides 2018). In addition, no clinical difference was found between the micronized form and the added form of hesperidin of non-micronized diosmin in CVI disease (Cazaubon *et al.* 2021).

*Aesculus hippocastanum* L.

Horse chestnut (*A. hippocastanum*) seed extract, standardized to contain escin is used in CVI due to its anti-inflammatory and antiedema properties. The efficacy of horse chestnut seed extract/escin activity has been documented in numerous randomized clinical trials (Dudek-Makuch & Studzińska-Sroka 2015). In studies on its efficacy, horse chestnut seed has been reported to be as effective as compression stockings and reference drugs such as *O*-(*β*-hydroxyethyl)-rutoside (Pittler & Ernst 1998). When the mechanisms of action in chronic

venous insufficiency are evaluated, horse chestnut seed extract/escin inhibits phospholipase A2, which is responsible for the production of lysosomal enzymes (elastase, collagenase), neutrophil adhesion and aggregation, and hyaluronidase enzyme. It also prevents the decrease in ATP content and reduces capillary permeability (Dudek-Makuch & Studzińska-Sroka 2015). The protective effect of escin on vascular permeability is attributed to its ability to prevent hypoxia-induced impairment in the normal expression and distribution of platelet endothelial cell adhesion molecule-1. Escin causes the vascular smooth muscles to become selectively sensitive to calcium ions, which decreases capillary sealing and venous tension (Gallelli 2019). Its anti-edematous characteristic is explained by the sensitization to ions and other chemicals, such as serotonin (5 hydroxytryptamine, 5-HT), which increases venous contractile activity (Unal *et al*. 2018). In a clinical study, patients with CVI (n=87) used 50 mg *A. hippocastanum* tablet twice a day for 8 weeks. At the end of the observation period, a decrease in symptoms including ankle and lower leg edema, pain, itching, and burning was observed (Dickson *et al.* 2004).

*Ruscus aculeatus* L.

*Ruscus aculeatus* is widely used to treat CVI, varicose veins, hemorrhoids, and orthostatic hypotension. Ruscogenin and neoruscogenin, which are responsible for the effect of its content, have vasoconstriction and venotonic effects (Masullo *et al.* 2016). *Ruscus aculeatus* extract (Fagorutin® Ruscus Kapseln) has been shown to provide effective results in leg volume, heaviness, tension, and tingling sensations in the lower legs compared to placebo (Vanscheidt *et al.* 2002a). It was suggested that ruscogenins suppress leukocyte migration by regulating both protein and mRNA (Ionescu *et al* 2021). *Ruscus aculeatus* reduces venous hypertension through vasoconstrictive activity related to α-1 and α-2 receptor agonism in the vessel wall. It also prevents histamine-induced increased vascular wall permeability. Its anti-elastase activity reduces vascular wall permeability. Its anti-inflammatory effect is explained by its role on activation of adhesive molecule expression and suppression of leukocyte migration (Urbanek 2017). *Ruscus* extract acts on veins, capillaries, and lymphatic vessels, according to pharmacodynamic *in vitro, ex vivo*, and *in vivo* research (Krasiński & Krasińska 2023). In clinical studies conducted with combined preparations of hesperidin, vitamin C, and *R. aculeatus* extracts, a significant reduction in pain, cramps, lower extremity and edema was observed (Monjotin & Tenca 2022). It has also been reported that the pleiotropic effect of *R. aculeatus* extract consists of its effect on the mobilization of calcium ions, which are involved in the pathophysiology of CVI (Woroń 2022).

*Pycnogenol*®

Pycnogenol is a French maritime pine bark extract produced from the outer bark of *P. pinaster*. Its potent antioxidant, anti-inflammatory, vasodilating activities, and antithrombotic effects provide essential advantages in treating CVI (Gulati 2014). In a randomized, double-blind study, approximately 60% of patients treated with Pycnogenol experienced a complete reduction in edema and pain at the end of treatment, while almost all patients experienced a reduction in leg weight (Arcangeli 2000). In addition, the efficacy of preparations containing diosmin/hesperidin combination (Daflon®) and horse chestnut seed extract (Venostasin®) were compared with Pycnogenol, and it was concluded that Pycnogenol was more effective than both of them (Koch 2002, Cesarone *et al.* 2006a).

*Vitis vinifera* L.

*Vitis vinifera* folium (AS 195) contains characteristic components, the flavone(ol)-glycosides and glucuronides (quercetin-3-*O*-*β*-D-glucuronide and isoquercitrin (quercetin-3-*O*)-*β*-glucoside). In clinical studies, AS 195 (hard gelatin capsules) demonstrated anti-edema and symptom-relieving properties in patients with CVI (Stücker *et al.* 2019). AS 195 (Antistax® film-coated tablets) was found to have a curative effect on all subjective symptoms (tired, heavy legs, feeling of tension in the legs, tingling sensation in the legs, pain in the legs) (Schaefer *et al.* 2003). The consumption of AS 195 was found to enhance cutaneous oxygen supply and microcirculation in patients with CVI. Considering the fact that patients with microvascular diseases exhibit elevated oxidative stress, which restricts the availability of NO, it is hypothesised that AS 195 enhances NO bioavailability through the reduction of ROS and boosting antioxidant capability (Grau *et al.* 2016).

*Centella asiatica* L.

It was reported that *C. asiatica* significantly improved microcirculation parameters, and patients treated with *C. asiatica* showed significant improvement in CVI symptoms such as leg weight, pain, and edema (Cesarone *et al.* 1994, Chong & Aziz 2013). *Centella asiatica* extract has a regulatory effect on the metabolism in the connective tissue of the vascular wall (Arpaia *et al.* 1990). The total triterpenic fraction of *C. asiatica* is active on connective tissue modulation, improving the synthesis of collagen and other tissue proteins by modulating the action of fibroblasts in the vein wall and stimulating collagen remodeling in and around the venous wall (Incandela *et al.* 2001).

*Ginkgo biloba* L.

Ginkor Fort, a venotropic drug composed of *G. biloba* extract, troxerutin and heptaminol, has been shown to prevent the activation of endothelial cells under hypoxic conditions both in cell culture and in a fully perfused saphenous vein (Arnould *et al.* 1998). In CVI, *G. biloba* extracts (Ginkgoselect®, Phytosome®) are effective in treating edema, although it is not statistically significant in reducing the feeling of heaviness in the legs (D'alessandro *et al.* 2015). Table 2 shows the pharmacological effects of some venoactive drugs.

**Table 2.** Pharmacological effects of natural-origin venoactive drugs.

| Class | Natural Compounds | Action Mechanism | Bioactive properties | References |
|---|---|---|---|---|
| Synthetic flavonoid | Hesperidin methyl chalcone | • Increases the expression and activity of nuclear factor erythroid 2-related factor 2 (Nrf2), an endogenous regulator of cellular resistance to oxidants and the anti-inflammatory and analgesic pathway.<br>• Inhibition of proinflammatory cytokines, oxidative stress, TRPV1, and NFκB signaling. | • Anti-inflammatory<br>• Anti-analgesic | (Martinez *et al.* 2016, Borghi *et al.* 2023) |
| Flavonoid derivatives | Oxerutin and rutoside | • Decreases capillary permeability<br>• Reduces free radical | • Swelling and improving hemodynamic venous function | (Lichota *et al.* 2019) |
| Flavonoid | Diosmin | • Prevents the activation of NF-κB pathways and inhibits the expression of proinflammatory cytokines by reducing T cell receptors.<br>• TNF, IL-6, VEGF-C, VEGF-A, and FGF2 expression are all down-regulated<br>• Angiostatin expression is up-regulated. | • Anti-inflammatory<br>• Reducing angiogenesis | (Feldo *et al.* 2018, Huwait & Mobashir 2022) |
| Triterpenic saponoside | Escin | • Decreases vascular permeability in inflammated tissues<br>• Prevents hypoxia-induced disruption in regular expression and distribution of platelet endothelial cell adhesion molecules<br>• Involves disturbances in cholesterol homeostasis that cause cytoskeletal problems and a reduction in NF-B activation.<br>• Inhibition of lysosomal enzymes | • Anti-edema<br>• Protective effect on blood vessel permeability<br>• Vascular anti-inflammatory | (Domanski *et al.* 2016, Gallelli 2019) |
| Steroidal saponoside | Ruscogenin | • Anti-elastase<br>• Inhibition of TNF-α<br>• Suppression of NF-kB activation | • Protecting vascular tone with elastic fibers<br>• Anti-inflamatuar | (Facino *et al.* 1995, Huang *et al.* 2008) |
| Coumarin | Esculetin | • Inhibits the proliferation of NF-κB dependent proinflammatory cytokines<br>• Prevents transport, infiltration, and activation of inflammatory cells<br>• Cyclooxygenase and lipoxygenase enzyme inhibition<br>• Free radical scavenging activity<br>• Increases the expression of antioxidant enzymes and non-enzymatic antioxidants<br>• Inhibition of superoxide anion formation | • Anti-inflammatory<br>• Antioxidant | (Lichota *et al.* 2019, Zhang *et al.* 2022) |

## Discussion

Varicose veins represent a disease condition that affects many people, with prevalence rates generally ranging from 29.5 to 39.0% in women and 10.4 to 23.0% in men (Gawas *et al.* 2022). Since varicose veins are so common and many complications (changes in skin, venous ulcer, etc.) occur in the advanced stages of the disease, different strategies and combinations are applied in the treatment. Several venoactive drugs constitute an essential step in its pharmacological treatment (Mansilha & Sousa 2018). The use of medicinal plants or phytochemicals isolated from natural sources as venoactive drugs is common. Anthocyanidins (delphinidin, cyanidin, malvidin), proanthocyanidin of *V. vinifera* seed extract, diosmin, rutin derivatives, pycnogenol, horse chestnut extract, escin, *R. aculeatus*, asiaticoside (*C. asiatica*), *Mammea africain* Sabine extracts, fraxin, ginkgolide B, *G. biloba* leaves are active

natural sources and ingredients used in inflammation and CVI (Lichota *et al.* 2019). In addition to using these components alone in treatment, their combinations are also used to increase the effectiveness of the treatment (Auteri *et al.* 1994, Vanscheidt *et al.* 2002b). In comparative studies, the pycnogenol and a combination of diosmin/hesperidin were evaluated, and most patients in the pycnogenol group showed significant improvement after four weeks of treatment (Cesarone *et al.* 2006b). In the study that compared the effects of pycnogenol (*P. maritima* extract), Antistax (*V. vinifera* extract), and stocking, ankle circumference, induration, pain, and edema were decreased more in the pycnogenol-treated groups than in the other groups. Transcutaneous PO2 was increased more with pycnogenol (Belcaro 2015). In a comparison of the efficacy of venostasin (horse chestnut seed extract) and pycnogenol (French maritime pine bark extract), pycnogenol reduced the symptoms of CVI more than venostasin (Koch 2002). In line with these studies, it can be said that pycnogenol is more effective than treatment with MPFF, *V. vinifera* extract, and horse chestnut extract in CVI disease. This shows the necessity of intensifying clinical studies and elucidating the action mechanism of pycnogenol. Comparing leg compression stockings with oral horse chestnut seed extract treatment, lower leg volume decreased by 43.8 mL with horse chestnut seed extract and 46.7 mL with compression treatment (Diehm *et al.* 1996). In one study, hydroxyethylrutoside was more effective than escin (Rehn *et al.* 1996), whereas in another, escin was more effective than hydroxyethylrutoside (Erler & Welt 1991). Two other studies revealed no differences (Frick & Frick 2000; the second study). When the efficacy of diosmin/hesperidin (Daflon) and oxerutin (Venoruton) in the treatment of CVI was evaluated, the venous-related quality of life was found to be significantly higher in oxerutin groups (Cesarone *et al.* 2006b). In another study, there was no significant difference in microcirculation parameters between patients using Venoruton and Daflon, whereas symptomatic improvement was better with Venoruton (Belcaro *et al.* 2002). In previous two studies, the diosmin/hesperidin combination was less effective in reducing the symptoms of CVI than pycnogenol and oxerutin. When the studies in the literature are evaluated, the combined use of natural components/plant extracts, which are accepted to be effective in CVI, appeared to increases the effectiveness of the treatment. In comparative studies, however, pycnogenol appears advantageous in relieving CVI symptoms.

In ethnobotanical studies, on the other hand, it was noted that extracts prepared from different parts of plants for treating varicose veins were used internally or externally (Table 1). Ethnobotanical studies constitute an important step in discovering medicine from a plant. Significant advantages are obtained in the planning and implementing experimental research by identifying candidate plants according to ethnobotanical field studies (Süntar 2020). Therefore, it is crucial to carry out *in vitro/in vivo* studies related to varicose veins on medicinal plants used in the treatment in folk medicine.

## Conclusion

Medicinal plants or natural compounds have the potential to effectively and reliably treat CVI, specifically varicose veins, by decreasing capillary permeability and enhancing connective tissue integrity with their biological activities such as anti-inflammatory, antioxidant, vasoconstrictive, anti-exudative, and anti-edematous. These bioactivities can enhance blood circulation, suppress inflammation, and improve venous tone, hence reducing the risk of developing varicose veins. In addition to medicinal plants and natural compounds that have a place in treatment of CVI, plants utilized in traditional medicine, which were identified in the light of ethnobotanical studies, might serve as a source of inspiration for novel researches to discover new active compounds.

**Ethics Committee Approval:** Since the article does not contain any studies with human or animal subject, its approval to the ethics committee was not required.

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