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Review Article

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The Role of Medicinal Herbs in Endothelial Tissue and their Function in Veins Health

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Abstract

The inflammatory control of veins is crucial for vascular health, with endothelium being a key organ in the physiology of blood vessels. The endothelium regulates the function of the vascular barrier, coagulation pathways, and motor tone, performing essential roles during infections and injuries due to its wide distribution throughout the body and constant interaction with circulating blood. One of the diseases that most affect endothelial function is the cardiovascular disease. This occurs due to decreased inflammatory control through metabolic changes, mainly in the hormone insulin. Some clinical studies have already demonstrated that combinations of certain ingredients from natural sources can improve endothelial function due to their synergistic effects when administered together, enhancing both inflammatory control and the production of free radicals in the endothelium, such as PPARs expression, nuclear factor kappa- beta (NF-kβ), tumor necrose factor alpha (TNF-α) and interleukin - 6 (IL-6) activity, and superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activity respectively. In this review, we evaluated several studies on how medicinal plants can help in vascular treatments, separately or collectively, especially when it comes to diseases that affect the veins and the possibility of future treatment.

Keywords: Vein, Endothelium, Oxidative Stress, Inflammation, Medicinal Herbs.

Introduction

Veins are blood vessels that collect oxygen-poor blood (venous blood) and return it to the heart. Approximately 70% of the blood in the human body is present in the veins [1]. By working in unison with other blood vessels and the heart to maintain the blood in motion, veins are part of the circulatory system. The main functions of veins are to act as conducting vessels in transporting blood from the body's organs and tissues back to the heart (i.e., venous return); and act as capacitance vessels, accommodating large volumes of blood [2]. Venous structures contain around two-thirds of the total blood volume and act as blood reservoirs in the human body [3]. As they have thinner walls and larger diameters than arteries, and with less muscle and elastic tissue, giving veins the ability to have high vascular compliance, 30 times ampler than that of arteries, with the rate of volume variation in response to higher pressure producing relatively small changes in venous distension pressure [4]. In other words, veins are highly distensible, easily expanding to accommodate large volumes of blood allowing them to be used as arterial bypass grafts.

The inflammatory control of veins is crucial for vascular health. In inflammatory processes of the veins, also known as phlebitis, the wall of the superficial blood vessel becomes inflamed, mainly in the leg region (thigh, calf, knee, foot, ankle) [5]. In the case of acute inflammation in an intact vein, it is called thrombophlebitis [6]. Varicophlebitis (inflammation of the varicose vein) is the most common inflammation in this type of tissue [6]. Any inflammation of the veins must be treated as quickly as possible and can last from a few days to several weeks, otherwise, the inflammation of the blood vessels can cause thrombosis (blood clot) putting the patient at serious risk of death [7]. The decrease in blood fluidity contributes to an increased risk of inflammation in the veins [8]. The blood in varicose veins flows more slowly than normal, which increases the likelihood of vein inflammation [9].

Phlebitis and Thrombophlebitis

Phlebitis leads to increased discomfort for patients, longer hospital stays, and higher healthcare costs [10]. It is characterized by inflammation of the vein wall. It may be accompanied by symptoms such as edema, pain, and erythema near the catheter insertion site or along the affected vein [10, 11]. These processes can progress to palpable venous cords, intense redness, tenderness, and fever [11]. Numerous factors affect the incidence of phlebitis and can be classified as sex, age, underlying health conditions such as infectious or hypertensive disease, and surgery [12]. Chemical factors are one example and may also alter

the condition of phlebitis, such as the osmolality of the injected medication some medications the type of antibiotics and the method of medication injection [13-16]. Similarly, mechanical factors are also considered, such as catheter dwell time catheter insertion site and catheter size [14, 17, 18]. On the other hand, infectious factors such as healthcare professionals' hand hygiene and nurses' skill in administering intravenous injections need to be considered [19, 20]. Hospital data have shown that orthopedic patients with phlebitis have a longer average length of stay when compared to those without phlebitis [11]. According to Lee et al. (2019), negligent control of phlebitis leads to longer periods of hospitalization, which increases the patient's suffering and economic burden [21]. Normally, hospitalized orthopedic patients undergo surgical treatment and receive antibiotics for therapeutic and/or preventive purposes, which end up irritating the blood vessels, lowering the pH, and causing chemical phlebitis [22].

Thrombophlebitis is another process associated with pain and the appearance of inflammatory signs (swelling, redness, and heat) in the affected region, usually where there were previously visible varicose veins [6]. This is a prevalent condition in which thrombosis (blood clotting) occurs in a superficial vein causing an inflammatory reaction of the venous wall and neighboring tissues to a varying degree [23]. In an acute phase, in conjunction with the manifestation of local symptoms, thrombophlebitis can suffer complications, progressing to deep vein thrombosis, in turn with an associated risk of pulmonary thromboembolism [24, 25]. The first [deep vein thrombosis] mainly affects the venous drainage of the lower limb; the second [pulmonary thromboembolism] is associated with compromised respiratory function, which may even be a fatal event [26]. Therefore, phlebitis is characterized by inflammation of the vessel wall that occurs as a result of damage to the endothelial lining [27].

The Role of the Endothelium in Blood Vessels

The endothelium is a monolayer of endothelial cells that constitutes the inner cellular lining of blood vessels, such as arteries, veins, and capillaries as well as the lymphatic system, and is therefore in direct contact with blood/lymph and circulating cells (Fig 1) [28, 29]. Endothelium is an important element in the control of blood fluidity, platelet aggregation, vascular tone, regulation of immunoinflammatory processes, angiogenesis, and endocrine metabolism [28]. Endothelial cells control vascular tone and therefore blood flow by synthesizing and releasing relaxation and contraction factors such as nitric oxide, arachidonic acid metabolites through the cyclooxygenases, lipoxygenases, and cytochrome P450 pathways, various peptides such as endothelin, urotensin, CNP and adrenomedullin, adenosine, purines, reactive oxygen species (ROS) and so on [29, 30]. Furthermore, endothelial ectoenzymes are necessary steps in generating vasoactive hormones such as angiotensin II [28]. Therefore, endothelial dysfunction can explain the appearance of several pathologies, especially cardiovascular ones [31].

The function of the vascular barrier, coagulation pathways, and motor tone is dynamically regulated by the endothelium [32]. These play important roles during infections and injuries, due to their wide distribution throughout the body and their constant interaction with circulating blood [33]. Although they are not classified as classical immune cells, endothelial cells express innate immune receptors, including Toll-like receptors (TLRs), which activate intracellular inflammatory pathways mediated by nuclear factor kappa-beta (NF-κβ) and mitogen-activated protein kinase (MAPK) [33, 34]. The expression of inflammatory mediators in microvascular endothelial cells can be regulated by TLR agonists such as lipopolysaccharides (LPS) and bacterial lipopeptides [35-37]. Interestingly, the permeability of microvascular endothelial cells and the expression of coagulation pathway intermediates can also be changed by TLR activation [33]. It has been hypothesized that microvascular thrombi trap microorganisms, thereby limiting the spread of infection [38]. However, the unregulated activation of endothelial inflammatory pathways may lead to problems such as coagulopathy as well as increased vascular permeability, promoting organ failure induced by sepsis [33].

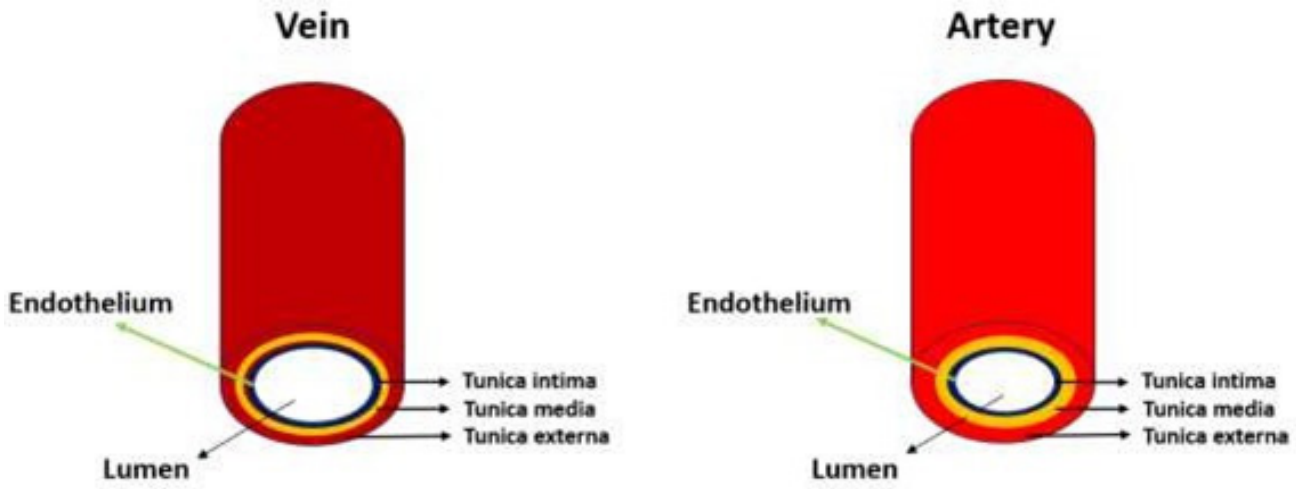

Figure 1: The endothelium is a monolayer of endothelial cells that constitutes the inner cellular lining of blood vessels, such as arteries, veins, and capillaries as well as the lymphatic system, and is therefore in direct contact with blood/lymph and circulating cells

The growth of blood vessels to meet tissue oxygen demand depends on the control of vascular endothelial growth factor (VEGF) [39]. In the absence of oxygen in any cell type, an increase in intracellular concentrations of the active form of the gene regulatory protein called hypoxia-inducible factor 1 (HIF-1) is observed (Fig 2) [40]. HIF stimulates not only the transcription of the VEGF gene but also several other genes whose products are necessary when there is a shortage of oxygen [41]. The VEGF protein, when secreted, diffuses through the tissue to act on nearby endothelial cells [42]. The endothelial cell response includes at least four components, among them the production of proteases to digest their way through the basal lamina of the parent capillary or venule, migration toward the source of the signal, proliferation, and tube formation [42]. The action of VEGF occurs selectively in endothelial cells, stimulating not only the production of proteases to digest their way through the basal lamina of the parental vessel (venule), but also directing these cells to the source of the signal for proliferation and tube formation [43]. As new vessels form, there is a greater concentration of blood in the tissue, consequently increasing oxygen concentrations and resulting in a decrease in HIF-1 activity, resulting in the interruption of VEGF production alongside angiogenesis [44].

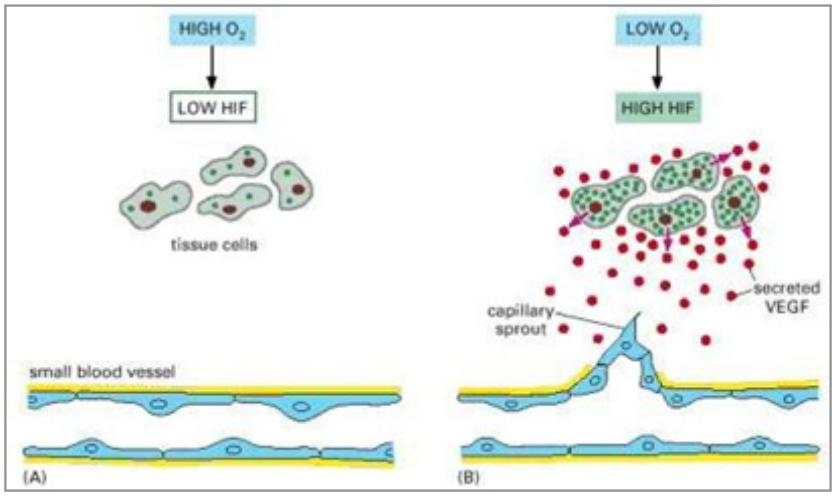

Figure 2: The regulatory mechanism controlling blood vessel growth according to a tissue's need for oxygen

Molecular Biology of the Cell 4th edition.

Estrogen and its Impact on Endothelial Tissue

The biosynthesis of estrogens as well as several other steroid hormones occurs through neurohormonal releases from the hypothalamic-pituitary-gonadal axis using cholesterol as a substrate for their production [45, 46]. However, in both men and women, estrogen production depends on the intermediate testosterone, which through the action of aromatase can be converted into estrone and estradiol, the latter being the main form of circulating estrogen in women. In female individuals, testosterone levels are much lower compared to testosterone levels in male individuals [47]. On the other hand, in men, circulating estrogen levels are much lower than in women, with testosterone and dihydrotestosterone predominating, which is the main circulating androgen [47, 48]. Because the enzymes aromatase and 5-α reductase (the enzyme that converts testosterone to dihydrotestosterone) are found in various tissues, circulating hormone levels may not reflect those found in tissues [49, 50]. In a study on the use of aromatase inhibitors in young men, Lew et al. (2003) demonstrated a decrease in endothelial vasodilator function, providing evidence that the conversion of testosterone into estradiol can contribute to the regulation of peripheral circulation in men [51]. In another study, Karim et al. (2008) showed that circulating concentrations of free 17β estradiol, free testosterone, and sex hormone binding globulin (SHBG) may be more predictive of changes in carotid intimal thickening in contrast to the concentrations of each of these hormones individually [52].

Although the effects of estrogen on the arteries are well elucidated, the same cannot be said regarding the estrogenic effects on the veins. It has been established that estrogen regulates and modulates vascular function, mainly in potential mechanisms of induced vasodilation [53]. However, many ambiguous results are found in scientific literature. Studies suggest that estrogen reduces atherosclerosis by reducing low-density lipoproteins (LDL) as well as inflammatory processes in the vasculature [53]. Other studies state that estrogen acts as an antioxidant, improving vascular function concerning oxidative stress [54]. Among other benefits of estrogen on blood vessels is its action as a vasodilator and hypotensive, which can induce vascular relaxation on top of the release of vasodilatory substances derived from the endothelium, such as nitric oxide (NO) or even acting directly on vascular smooth muscle (MSV) [47]. On the other hand, estrogen, in the clinical setting, is mainly used for contraception and hormone replacement therapy, causing a risk of arterial and venous thrombosis [55].

Venous thromboembolism (VTE) of the deep veins of the legs or pulmonary vessels is the most common condition of estrogen-related thrombosis [55]. For this reason, women at high risk of thrombosis need to be carefully monitored regarding contraception, pregnancy, menopausal hormone therapy, and other types of estrogen-related treatments, to reduce the risk of thrombosis [56]. The scientific community suggests that more investigations are necessary to understand the action of estrogen-on-estrogen receptor alpha (ERα) and beta (ERβ) in the endothelium. Conversely, As the influence of estrogen on vascular function

is multifactorial, researchers have been directing scientific investigations pursuing a deeper understanding of the mechanisms of estrogen in its receptors to maximize its beneficial effects and minimize its side effects which can be lethal in many cases [47].

Although estrogen receptor alpha (ERα) and beta (ERβ) are expressed in both the endothelium and smooth muscle cells of human coronary arteries, ERα is responsible for mediating most of the vascular protective effects of E2 [57]. In addition to ERα acting as a gene transcription factor, it also exerts extranuclear actions, activating membrane-initiated steroid signaling, as demonstrated specifically in the endothelium [58]. As in aging, alterations in estrogen receptors are part of a physiological process, such as a decrease in their expression, and low signaling in parallel with a decline in the hormone itself, this situation could lead to a deficiency in the protection of blood vessels, compromising the cardiovascular system [59]. Therefore, understanding the interaction of estrogen and its regulation in ERs, especially in ERα in the aging cardiovascular system is fundamental for the development of new therapeutic strategies [57].

Medicinal Herbs and Other Nutraceuticals

Cardiovascular diseases are practically associated with endothelial dysfunction caused by a lack of inflammatory control through metabolic changes, mainly the hormone insulin [60]. This condition, also known as metabolic syndrome, can promote drastic changes in the endothelium, causing serious damage to these types of cells [61]. However, because monotherapies are limited to the complexity of multifactorial pathways, the use of natural products as alternative treatments has attracted the attention of the scientific community [62]. Some clinical studies have already demonstrated that combinations of certain ingredients from natural sources can improve endothelial function [63]. Another interesting factor is the synergistic effects when some ingredients are administered in conjunction, enhancing both inflammatory control and the production of free radicals in the endothelium [62]. Several studies have focused on different biochemical markers for evaluating treatments, including the production of ROS, nuclear factor erythroid 2–related factor 2 (Nrf-2) heme oxygenase-1 (HO-1) peroxisome proliferator-activated receptors (PPARs) MAPK, phosphatidylinositol-3 kinases (PI3K), tumor necrosis factor-α (TNF-α), NF-κβ, nicotinamide adenine dinucleotide (NAD) and superoxide dismutase (SOD) [64-69]. This may highlight how alternative therapies can become a promising path in vascular treatments.

Many medicinal plants as well as several nutraceuticals have already demonstrated promising results in treating blood vessels, especially when they are administered in tandem [70]. The synergy of some compounds seems to have responded more effectively to metabolic processes [71]. Whenever a pathology is addressed, trying to control inflammatory processes and oxidative stress is very difficult with one single ingredient [72]. Therefore, the combined use of two or more nutraceutical ingredients has become a useful tool in cardiovascular treatments [73]. Alternatively, a number of studies showed that some ingredients such as astaxanthin diosgenin lutein and Vitis vinifera also showed promising results even when administered independently in endothelial treatments [74-77].

Luteolin, for example, is a flavonoid with antioxidant properties that have already been scientifically proven to be related to inflammatory, tumor, and cardiovascular processes [78]. In a study by Assunção et al. (2021), the authors investigated luteolin in rat venous endothelial cell cultures [79]. The authors observed a significant increase in intracellular nitric oxide (NO) levels additionally to a decrease in ROS after 10 minutes of luteolin incubation. The 3-nitrotyrosine (3-NT) residues were also evaluated, showing significant reductions in their expression. However, an increase in the release of prostacyclin (PGI2) was also observed, demonstrating that luteolin is effective in reducing ROS, thus improving the availability of NO in venous endothelial cells [79]. In another study, Zhang et al. (2019) showed that the combination of curcumin (1 μM) and luteolin (0.5 μM) synergistically inhibited TNF-α-induced monocyte adhesion to human EAhy926 endothelial cells, whereas ingredients, when administered individually, had no such effect [80]. This study also revealed that TNF-α-enhanced protein expressions of vascular cell adhesion molecule 1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1), and NF-κβ translocation were synergistically reduced by combined curcumin and luteolin in EAhy926 cells. At the same time, individually they did not show this inhibitory effect. Still in the same study, the authors showed that a 2- week administration of combined curcumin (500 mg/kg) and luteolin (500 mg/kg) in C57BL/6 mice synergistically prevented TNF-α-stimulated adhesion of mouse monocytes to the ex vivo aortic endothelium, combined with TNF-α increased aortic protein expression of MCP-1 and VCAM-1 [80]. This demonstrates that curcumin and luteolin combined at physiological concentrations synergistically inhibit TNF-α-induced monocyte adhesion to endothelial cells and MCP-1 and VCAM-1 expression through suppression of NF-κβ translocation to the nucleus.

Curcumin has also demonstrated synergistic effects with resveratrol on EAhy926 endothelial cells [81]. In studies by Zhou et al. (2021), the authors demonstrated that the combination of curcumin with resveratrol produced synergistic protection against changes induced by H2O2, caspase-3 activity, and ROS production. SOD activity, as well as NAD activity, were also significantly increased in the presence of curcumin with resveratrol. This study also established a ratio of 8:2 concerning curcumin and resveratrol respectively were the ones that obtained the most significant results. The authors concluded that the combination of curcumin with resveratrol in this proportion may act as a more potent agent than the individual components in protecting the vascular endothelium against oxidative stress. According to the authors, this mechanism was mediated, at least partially, by the activation of Nrf2-HO-1 [81].

Another combination that demonstrated promising results was chitin-glucan (CG), an insoluble fiber with prebiotic properties, with pomegranate peel extract (PPE) [82]. In the study by Neyrinck et al. (2019) the administration of CG together with PPE was shown to improve endothelial and inflammatory disorders in a model of cardiovascular disease (CVD) in mice, modulating the intestinal microbiota. This study was carried out in male Apolipoprotein E (ApoE -/-) knock-out mice fed a high-fat (HF) diet [82]. Consequently, the mice developed significant endothelial dysfunction evidenced by atherosclerotic plaques.

Supplementation combined with CG + PPE in the high-fat diet reduced inflammatory markers in both the liver and visceral adipose tissue not to mention the reduction of hepatic triglycerides [82]. Furthermore, there was an increase in endothelial NO synthase activity in mesenteric arteries and blood levels of heme-nitrosylated hemoglobin (Hb-NO) compared to HF-fed ApoE -/- mice. The authors suggested an increase in the ability of the mesenteric arteries to produce nitric acid [82]. It appears that the intestinal bacteria Lactobacillus and Alistipes may be implicated in the treatment of endothelial and inflammatory dysfunctions associated with CVD, suggesting that the role of nutrition in modulating these bacteria may be fundamental for vascular health [83].

The possible associations of medicinal plants in vascular health go even further. The combination of Astragalus membranaceous and Angelica sinensis, used in Traditional Chinese Medicine to treat diabetes mellitus has shown promise in endothelial dysfunction [84]. As vascular endothelial dysfunction is an essential and early sign of diabetic macroangiopathy Yin et al. (2020) proposed a study of the combination of the granular form of the extract produced from the dried root of Astragalus membranaceous with the granular form of the extract produced from dried Angelica sinensis in a ratio of 3:2 respectively in diabetic macroangiopathy and its underlying mechanism [84, 85]. The study was carried out on human umbilical vein vascular endothelial cells (HUVECs) induced by high glucose administration. The results demonstrated that in HUVECs induced with high glucose, the combination of Astragalus membranaceous with Angelica sinensis increased cell viability, decreased the percentage of apoptotic cells and the expression of the pro-apoptosis protein caspase 3, additionally reducing the proportion of cells in the G0/G1 phase [84]. The result also diminished ROS levels, provided an increase in cell migration and invasion, and reduced the level of 8-iso-prostaglandin F2alpha. The authors of this study suggest that the combination of Astragalus membranaceous with Angelica sinensis can act as a targeted drug in the therapy of diabetes mellitus induced by high glucose and complications of macroangiopathy [84]. However, more studies must be carried out to clarify the molecular mechanisms of this type of treatment, which are still unclear.

In isolated supplementation, astaxanthin demonstrated promising results in endothelial cells when induced to increase levels of homocysteine [74]. Research has already demonstrated in vivo and in vitro, that astaxanthin presented cardioprotective activity against homocysteine-induced cardiotoxicity [86]. In the study by Wang et al. (2019), astaxanthin significantly inhibited homocysteine-induced cytotoxicity by enhancing migration, invasion, and tube formation of HUVEC [74]. The authors attributed this result to the mechanisms of effective inhibition of ROS generation by astaxanthin, which was significantly increased when homocysteine levels were induced. The high homocysteine negatively regulates the expression of VEGF, phosphorylated receptor 2 (p) -Tyr-VEGF (VEGFR2), and p-Tyr397-focal adhesion kinase (FAK) [74, 87]. The results of this study suggested that astaxanthin may be a great ally in inhibiting homocysteine- induced endothelial dysfunction, suppressing homocysteine-induced activation of the VEGF-VEGFR2- FAK signaling axis, which indicates a new therapeutic potential in the treatment of cerebrovascular diseases. mediated by homocysteine [74].

Another ingredient of great relevance for vascular health is urolithin A (UA), a metabolite produced by the intestinal microbiota from ingested ellagic acid [87]. Although the effect of ellagic acid intake on improving vascular endothelial function has already been well elucidated, the effect of UA intake on vascular endothelial function is still enthusiastically investigated by the scientific community. Improvement in the function of the intestinal barrier along with the intestinal microbiome may have improved vascular endothelial function as a result [88]. In a study by Han et al. (2016), the authors investigated the protective effect of urolithin A (UA) on endothelial dysfunction induced by ox-LDL (in which ox-LDL is oxidized low-density lipoprotein). UA markedly reduced the expressions of intercellular adhesion molecule 1 (ICAM-1) and MCP-1 in addition to further attenuating the cell adhesion of THP-1 (human acute monocytic leukemia cell line) [87]. Furthermore, UA suppressed the expressions of TNF-α, IL-6, and endothelin 1 (ET1), and increased the expression of PPAR-γ (peroxisome proliferator-activated receptor gamma) mRNA. In the same study UA also significantly downregulated phosphorylated ERK1/2 (where ERK is extracellular signal-regulated kinase), while decreasing the level of interleukin - 6 and elevating PPAR-γ [87]. These results demonstrate that UA can alleviate oxLDL-induced endothelial dysfunction partially by modulating the expression of miR-27 and the ERK/PPAR-γ pathway.

Diosgenin has also engaged the interest of the scientific community. In a study by Liu et al. (2012) on HUVECs, Diosgenin significantly reduced the phosphorylation of inhibitor of nuclear factor kappa-β kinase subunit beta (IKKβ) and NF-κβ increased by palmitate with inhibition of the production of TNF-α and Interleukin - 6 (IL-6) in endothelial cells, demonstrating its potent anti-inflammatory activity [89]. In the same study, diosgenin attenuated palmitate-induced serine phosphorylation (S307) of insulin receptor substrate 1 (IRS-1) and restored tyrosine phosphorylation of IRS-1 in response to insulin. Beneficial modulation of IRS-1 serine/tyrosine phosphorylation by diosgenin contributed to improved insulin signaling along the phosphatidylinositol-3-kinase pathways (PI3K/Akt) and nitric oxide synthase (NOS), thus increasing insulin-mediated NO production. Diosgenin also notably inhibited the production of ET-1 and plasminogen activator inhibitor-1 (PAI-1) in endothelial cells and markedly restored the loss of insulin- mediated vasodilation in the presence of palmitate [89]. Likewise, studies by Esfandiarei et al. (2015) demonstrated that diosgenin had positive effects on vascular smooth muscle cells (SMC) [90]. In this study, diosgenin caused a significant decrease (40%) in SMC viability. This process occurred due to a decrease in the phosphorylation of the Akt protein. In cell culture, the pro-apoptotic effect of diosgenin on aortic SMCs was associated with a significant reduction in Akt phosphorylation and a marked increase in caspase-3 cleavage [90]. The authors reported a causal relationship between decreased Akt activity and increased apoptosis in SMCs treated with diosgenin.

A notable flavonoid also known as diosmin has been drawing the attention of the scientific community due to its biological activity in improving microcirculation and increasing venous tone besides venous elasticity [91]. Diosmin is found in citrus fruits and the Rutaceae family. Studies suggest that diosmin, in addition to improving lymphatic drainage, increases capillary resistance, and reduces capillary filtration in conjunction with

capillary hyperpermeability [92, 93]. In studies by Imam et al. (2015), diosmin presented an anti-inflammatory effect by inhibiting the expression of proinflammatory cytokines by blocking the activation of NF-κβB pathways and reduction of T cell receptors [94]. Likewise, in the studies by Feldo et al. (2018), diosmin showed antioxidant properties by controlling the formation of H2O2 while increasing the activity of the enzymes SOD, catalase (CAT), and glutathione peroxidase (GPx) in endothelium cells [95]. These studies suggested that flavonoids restored the activity of cellular antioxidant enzymes and reduced the level of malondialdehyde (MDA) upregulated by exposure to H2O2. These results place diosmin as a promising flavonoid in the prevention of oxidative stress in endothelial cells, potentially protecting against the development and progression of disorders related to oxidative stress in the endothelium.

Table 1

S no.	Ingredients	Endothelial Interaction	Reference
1	Curcumin & Luteolin	TNF-a, NF-kB, MCP-1, VCAM-1	Zhang et al.(2019)
2	Diosgenin	IKKB, NF-kB, TNF-a, IL-6	Liu et al. (2012)
3	Resveratrol	TNF-a, NAD(P)Hox, Enos	Zhang et al. (2009)
4	Astaxanthin	VEGF-VEGFR2-FAK	Wang et al.(2019)
5	Diosmin	MDA, CAT, SOD, GPX	Feldo et al. (2018)
6	Astragalus m. & Angelica s.	8-iso PGF2a & caspase 3	Yin et al. (2020)
7	Chitin-glucan & Pomegranate	NO synthase & Hb-NO	Neyrinck et al. (2019)
8	Urolithin A	ox-LDL, miR-27, ERK/PPAR-Y	Ham et al. (2016)
9	Vitis vinifera	Ob-Ra, Lrp2, clu/Apoj, NF-kB, NO	Ardid-Ruiz et al. (2020)
10	Beta-caryophyllene	CB2R, PPAR-Y, VCAM-1, eNOS/INOS	Yussef et al. (2019)
11	Centella asiatica & Lipoic acid	p44/42 MAPK, NF-kB p65	Tomo et al. (2015)

Discussion

There is a direct relationship between endothelial tissue and blood vessel health. Endothelial dysfunction is associated with several pathologies in the cardiovascular system. Some authors state that the endothelium directly participates in the vascular barrier and coagulation pathways as well as motor tone, which is also dynamically regulated by the endothelium [32]. Because Endothelial cells also express innate immune receptors, such as TLRs, which activate intracellular inflammatory pathways mediated by NF-κβ and MAP kinases [33, 34], several studies observed in this review demonstrated that the focus of medicinal plants was, in most inflammatory markers. Assunção et al. (2021), for example, observed a significant increase in intracellular NO levels in tandem with a decrease in ROS in rats venous endothelial cell cultures [79]. Similarly, Zhou et al. (2021) reported that the combination of curcumin with resveratrol protected endothelial cells against H2O2, caspase-3 activity, and ROS production and promoted an increase in SOD and NAD activity [81].

A fact that drew attention in this review was the synergistic relationship between some plants observed by some authors. For example, the combination of Astragalus membranaceous with Angelica sinensis, used in Traditional Chinese Medicine has shown promise in endothelial dysfunction in a ratio of 3:2 respectively [84]. Although we do not have a combined study regarding some ingredients mentioned in this review, a synergy between astaxanthin and UA could be of great value for endothelial treatment. In the study by Wang et al. (2019), astaxanthin significantly inhibited homocysteine-induced cytotoxicity by enhancing migration, invasion, and tube formation of HUVEC [74]. According to the author, this result was attributed to the control of ROS production exerted by astaxanthin supplementation. Astaxanthin acts as a protection on mitochondrial membrane potential (MMP), enhancing the flow of electron transfer, and generating less ROS production leading to the recovery of mitochondrial ATP production, also blocking the release of cytochrome c activating MAPK signaling. This role of astaxanthin promotes an increase in the level of anti-apoptotic Bcl-2, protecting the cell from apoptosis [96]. On the other hand, in a study by Han et al (2016), UA suppressed the expressions of TNF-α, IL-6, and ET-1, and increased the expression of PPAR-γ mRNA [87]. This anti-inflammatory combination of UA with the oxidative control exerted by astaxanthin could, in theory, enhance endothelial treatments. Astaxanthin and UA, in addition to being notable modulators of PPARs, are able to decrease NF-kβ activity by controlling inflammatory cytokines in the endothelium.

The same way can be attributed to the possible synergy between diosmin and diosgenin. In a study by Liu et al. (2012) in HUVECs, diosgenin inhibited the production of TNF-α and IL-6 in endothelial cells, demonstrating its potent anti-inflammatory activity [89]. The beneficial modulation of IRS-1 serine/tyrosine phosphorylation by diosgenin also contributed to improving insulin signaling along the PI3K/Akt and NOS pathways, thus increasing the production of NO-mediated by insulin itself [89]. As in the studies by Feldo et al. (2018), diosmin showed antioxidant properties by controlling the formation of H2O2 while increasing the activity of the enzymes SOD, CAT, and GPx in endothelial cells, the authors suggested that diosmin restored the activity of cellular antioxidant enzymes and reduced the level of MDA upregulated by exposure to H2O2. These results together with diosgenin, in theory, can place a promise in the prevention of oxidative stress in endothelial cells and possible inflammatory control, protecting against the development and progression of disorders related to oxidative stress and inflammation in the endothelium [95]. Controlling the activity of SOD, GPx, and CAT scan positively modulate the results presented in endothelial tis-

sue derived from certain pathologies. Both aspects of phosphorylation control of pro- inflammatory cytokine by diosgenin and oxidative control by diosmin can, in theory, be also a promising path in vascular treatments.

Conclusion

The scientific community considers endothelium to be more than a simple barrier between blood and tissues, they consider it an endocrine organ. Therefore, preserving endothelial function against inflammatory processes and oxidative stress is crucial to maintaining the physiological functions of veins, arteries, and capillaries. The orchestration of specific receptors, notably PPARs, assumes a pivotal role in governing inflammatory cascades associated with certain pathologies, such as phlebitis and thrombophlebitis. Phlebitis, characterized by vessel wall inflammation resulting from endothelial lining damage, underscores the significance of regulating endothelial inflammatory markers as a promising avenue for therapeutic intervention. In this context, the modulation of inflammatory markers like NF-kB, IL-6, and TNF-a becomes a targeted strategy, and herbal medicines emerge as potential agents with the ability to influence these markers, as expounded in this review. The exploration of nutraceuticals in vascular health unveils encouraging outcomes in diverse vascular treatments. Importantly, the comparative analysis reveals a favorable safety profile of these herbal remedies when juxtaposed with conventional pharmaceuticals, offering a prospect of reduced side effects for patients. Nevertheless, the translation of these findings from preclinical studies to clinical applications necessitates comprehensive human trials to definitively validate the efficacy of herbal medicines in promoting vascular health. The ongoing pursuit of such clinical validation is indispensable to establish herbal interventions as credible and effective components in the armamentarium against vascular diseases.

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