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DIOSMIN – A POWERFUL FLAVONOID FOR CHRONIC VENOUS DISEASE

KEY WORDS: Diosmin, Flavonoid glycoside, Venoactive, Chronic venous disease

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ABSTRACT

Chronic venous disease (CVD) represents a prevalent public health issue that can impact approximately 80% of the adult population. This progressive condition is linked to venous hypertension, valvular insufficiency, and venous reflux. Common symptoms include leg pain, discomfort, heaviness, and a sensation of swelling, alongside clinical signs of CVD. Venoactive drugs form a diverse pharmacological category that includes both synthetic substances and those derived from plants. Flavonoids, a subgroup of polyphenolic compounds found in plants, have been suggested by numerous studies to be effective in treating symptomatic CVD. Diosmin, which is derived from citrus plants, varies in abundance depending on the species, tissue type, and maturity of the fruits, with immature fruits typically containing higher levels of Diosmin. It is commercially produced from hesperidin through a semi-synthetic process that involves the oxidation of hesperidin extracted from citrus fruits. These compounds primarily target the venous wall, exerting anti-inflammatory and antioxidant effects, which may be their primary mechanisms of action. The early administration of venoactive medications and the use of compression stockings are likely to be cost-effective strategies that could alleviate the increasing economic burden of CVD on healthcare systems. In this study, we examine the effectiveness of diosmin and emphasize its significance in the management of venous disease

INTRODUCTION

CVD is typically categorized using the Clinical – Etiology – Anatomy - Pathophysiology classification system, which spans from stage C0 (absence of visible or palpable signs of CVD) to C6 (presence of an active venous ulcer). [3] Standard first-line treatment options include compression stockings and venoactive drug therapy. [4-6] As the disease advances, venoactive medications may also be utilized alongside procedures such as endovenous ablation and other surgical interventions. The micronized purified flavonoid fraction (MPFF), consisting of 90% diosmin and 10% other active flavonoids (including hesperidin, diosmetin, linarin, and isorhoifolin), is the most extensively researched venoactive drug for CVD treatment[1,2] MPFF exhibits anti-inflammatory properties, diminishes endothelial activation and leukocyte adhesion, and enhances capillary resistance and integrity[1,7]

MPFF

Micronized purified flavonoid fraction (MPFF) is a venoactive drug based on flavonoids, exhibiting greater potency than pure diosmin due to the inclusion of additional flavonoids like hesperidin, diosmetin, linarin, and isorhoifolin.Moreover, the micronization of its active components enhances the dissolution and absorption rates of MPFF. This micronization process also increases exposure to the metabolites derived from MPFF, which are crucial for its pharmacological effects. The beneficial influence of micronization on the pharmacological efficacy of the purified flavonoid fraction has been validated through both animal studies and clinical pharmacological trials. MPFF enhances venous tone by influencing noradrenergic signalling and lowering norepinephrine metabolism. Additionally, MPFF offers protection against inflammation-related damage to valves by obstructing the interaction between leukocytes and the endothelium, reducing capillary permeability, enhancing capillary resistance, and promoting lymphatic drainage. The optimal dose-effect ratio is found at 1000 mg. As a significant treatment option for chronic venous disorders, MPFF alleviates symptoms across all stages, effectively reduces venous edema, and in more advanced cases, it can be combined with sclerotherapy, surgery, and/or compression therapy for patients undergoing stripping or endovenous procedures for varicose vein ablation. Furthermore, MPFF may serve as an adjunctive treatment for patients with active venous ulcers, particularly those with chronic large ulcers.[8]

SOURCES AND AVAILABLITY OF FLAVONOIDS

Polyphenolic compounds, such as flavonoids, are vital for the flavour and coloration of plants. They fulfil numerous important roles in plants, including the transport of auxins, promoting growth, attracting pollinators, facilitating reproduction, aiding in seed dispersal, and providing protection against both abiotic and biotic stresses, as well as deterring predators [10] . Flavonoids are found in abundance in various vegetables (like onions and lettuce), fruits (including apples, limes, and cherries), grains, legumes, and tea; they are also present in processed foods such as wine and dark chocolate [9] . The amount of flavonoids can differ based on the source, species, exposure to sunlight, time of harvest, and other influencing factors [11] . Physiologically, humans do not produce flavonoids and must obtain them from plant sources. In the human body, flavonoids are absorbed in the small intestine, where they undergo conjugation with glucuronic acid, sulfate, or O-methylation. This process varies considerably across different classes of flavonoids, yet the overall absorption rate remains high when these compounds are consumed as part of a balanced diet [12] .

FLAVONOIDS AND THEIR ROLE IN VASCULAR FUNCTION

A variety of vasoactive compounds are secreted by endothelial cells, playing a crucial role in regulating vascular structure and function in both normal and disease conditions. [13] Flavonoids, a diverse group of compounds, interact with numerous targets and exhibit a wide array of biological effects, indicating their potential for treating various diseases. While the antioxidant properties were believed to be the primary mechanism of action for flavonoids and polyphenols during the 1980s and 90s, recent studies have shed light on additional mechanisms. It is now understood that direct interactions with protein targets—especially kinases—can alter signalling pathways. Furthermore, one plausible explanation for the health benefits of flavonoids is their pro-oxidant activity, which stimulates antioxidant defence mechanisms, such as the expression of antioxidant enzymes and the upregulation of endogenous antioxidant pathways. [14]

Despite their ability to interact with multiple targets, flavonoids are remarkably safe, likely due to their long-standing incorporation into the mammalian diet, suggesting that evolved mechanisms exist to reduce toxicity. [15] Nitric

oxide (NO) is vital for maintaining vascular homeostasis, as it plays key roles in platelet aggregation, blood flow, vascular tone, and the regulation of vascular smooth muscle cell (VSMC) proliferation. Endothelial dysfunction, marked by reduced NO bioavailability, increased oxidative stress, impaired endothelium-dependent vasodilation, and a prothrombotic, pro-inflammatory state of the vascular wall, is significantly affected by disturbances in NO signalling pathways. [16]

HESPERIDIN AND DIOSMIN

Diosmin and Hesperidin are flavanone glycosides predominantly found in citrus fruits (Family Rutaceae). Hesperidin (Hesperitin 7-rhamnoglucoside, Hesperitin-7-rutinoside), $C_{28}H_{34}O_{15}$, appears as a yellow to brown powder with a molecular weight of 610.56. It is insoluble in water but soluble in pyridine, DMC, and NaOH. The melting point ranges from 250-255°C and exhibits a characteristic absorption spectrum at 285nm. Diosmin, a bioflavonoid and semi-synthetic drug (3, 5, 7-trihydroxy-4-methoxyflavone-7-rutinoside), $C_{28}H_{32}O_{15}$, is a yellow-brown to brown powder with a molecular weight of 608.54. It is also insoluble in water and soluble in organic solvents like DMSO and NaOH, with a melting point of 274°C and maximum absorption at 268nm.

Diosmin can be sourced from plants such as Teucrium gnaphalodes, citrus, vetches, and hyssop [17]. It has been reported to possess various activities but is most notably recognized for its neuroprotective effects [18]. Hesperidin, a flavanone glycoside, is abundantly derived from the Rutaceae family, particularly from citrus plants like grapefruit, lemon, orange, and tangerine, as well as from other species such as peppermint and Welsh onion [19,20]. Hesperidin has been associated with numerous activities, including antioxidant, anti-inflammatory, anti-viral, and anti-carcinogenic properties, and has been shown to protect against DNA damage and lipid peroxidation. When combined with other bioflavonoids like Diosmin, it is marketed as Daflon-500mg (Servier) tablets, which contain micronized flavonoids-hesperidin (50mg) and Diosmin (450mg)-to treat lymphedema and are primarily used for blood vessel disorders such as varicose veins, venous stasis, and hemorrhoids. In studies involving animal models, this combination was assessed for safety and toxicity, demonstrating good gastrointestinal acceptability of the micronized formulation with no genotoxicity or drug incompatibility [21] . However, Maher and Sabir have explored the effects of the Diosmin and Hesperidin combination on hypercholesterolemia and hyperglycemia in patients with type 2 diabetes mellitus. A decrease in glucose and cholesterol levels was reported without any adverse events, thus lowering the cardiovascular risk factor for diabetic patients [22] .

WHAT MAKES DIOSMIN AND HESPERIDIN HIGHLY SOUGHT AFTER FOR SUPPLEMENTS

In the changing realm of natural therapeutic compounds, diosmin and hesperidin are recognized as two of the most thoroughly studied flavonoids with important clinical uses. These complementary bioflavonoids, often combined as diosmin hesperidin complexes, present a fascinating focus in the fields of pharmaceutical and nutraceutical development. The synergistic interaction between these compounds has led to extensive research investigating how hesperidin and diosmin work together to achieve improved therapeutic results. The natural presence of these flavonoids in citrus fruits has made them readily available dietary elements with significant health benefits. Formulations that pair diosmin with hesperidin have shown notable effectiveness in maintaining vascular integrity, rendering them beneficial for circulatory issues. Recent studies have shed light on how these flavonoids influence inflammatory pathways, boost antioxidant defences, and enhance circulatory health through their complementary actions. As research continues to clarify their functions and uses, these flavonoids embody a blend of traditional herbal knowledge and evidence-based medicine, underscoring the lasting importance of plant-derived substances in tackling contemporary vascular health challenges [23] .

MARKET OVERVIEW

The global diosmin market was estimated to be valued at approximately USD 0.45 billion in 2024 and is expected to grow to USD 0.49 billion in 2025, further increasing to USD 0.9 billion by 2033, with a compound annual growth rate (CAGR) of around 8% from 2025 to 2033.The diosmin market is expanding due to consumer demand for flavonoid-based supplements and pharmaceuticals that assist in treating chronic venous insufficiency, as well as hemorrhoids and varicose veins. Bioflavonoid diosmin, derived from citrus fruits, is widely available in pharmaceuticals, dietary supplements, and cosmetics. Market growth is driven by a rising health consciousness among the population and an aging demographic that prefers natural supplements. Key market players are focusing on research activities, product development initiatives, and channel expansion strategies. North American and European countries dominate the market; however, the Asia-Pacific region is experiencing rapid growth. Market trends are influenced by the regulatory approval process and quality control standards. The sector shows a positive development trajectory as medical researchers are introducing new treatments alongside increasing product demand from customers [24] .

DISCUSSION

The existence of various methods for treating chronic venous disorders calls for a clinical evidence-based ranking to enhance patient care and treatment satisfaction. An optimal treatment should quickly and significantly alleviate symptoms, halt disease progression, address all aspects of the condition, safeguard against complications, maintain long-term effectiveness, and be well tolerated. The goal is to enhance the patient's quality of life as swiftly as possible. MPFF is the sole venoactive medication that has shown significant anti-inflammatory and venoprotective effects, setting it apart from other venoactive drugs by offering patients prompt and considerable symptom relief. Additionally, MPFF uniquely protects against complications by preserving the integrity of venous valves and walls. These attributes have been acknowledged in systematic reviews and both national and international guidelines, where MPFF is recommended as the top choice for first-line treatment of chronic venous disorder-related symptoms and edema at all stages, as well as an adjunctive therapy for venous ulcers. MPFF possesses several well-established mechanisms of action that render it an effective treatment for various symptoms related to all stages of cardiovascular disease (CVD); consequently, it is highly recommended by international guidelines on vascular access device (VAD) treatment . Recent studies indicate that its beneficial effects may be partially mediated through the inhibition of leukocyte adhesion, enhancements in venous tone and valvular competence, and reductions in reflux. These flavonoids, which show no signs of toxicity, are primarily consumed as dietary supplements and have a long-standing history of medicinal use. Various studies on Hesperidin and Diosmin have reported numerous protective potentials, including neuroprotective, cardioprotective, hepatoprotective, anti-inflammatory, antioxidant, lipid-lowering, and insulin-sensitizing properties. It is now established as a venoactive drug and is the most sought-after raw material in the international market. As it falls under the category of flavonoid glycosides, many plants and grains containing flavonoid glycosides have been utilized as therapeutic agents for improved health, serving as ingredients in medicine and supplements. The landscape has shifted, with many modern medicines incorporating natural phytoconstituents as primary ingredients, playing a significant role in promoting

good health. Notably, flavonoid glycosides have been employed as key ingredients in numerous contemporary medicines. In addition to their role as venoactive agents, Diosmin and Hesperidin can be taken as regular supplements to achieve overall good health.

CONCLUSION

Diosmin and Hesperidin belong to a group of flavonoids that are increasingly recognized worldwide for their potential health advantages, including the reduction of neurodegenerative symptoms, inflammation of blood vessels, and microbial activity, as well as enhancing cardiovascular health and serving as effective antioxidants, while also influencing immunomodulatory functions. Whether used individually or in combination, they can modulate the activities of various targets that are crucial for eliciting biological and therapeutic effects, which also depend on their physicochemical and structural characteristics.Hesperidin, found in citrus fruits, is the primary source for the synthesis of diosmin. The demand for Diosmin is projected to reach USD 0.9 billion by 2033, with a compound annual growth rate (CAGR) of approximately 8% from 2025 to 2033. Consequently, there will be a significant need for raw materials to produce Diosmin, positioning it as a leading compound within the flavonoid glycosides category.

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REFERENCES

1. Mansilha A, Sousa J. Pathophysiological mechanisms of chronic venous disease and implications for veno active drug therapy. Int J Mol Sci 2018; 19:1669.
2. Davies AH. The seriousness of chronic venous disease: a review of real-world evidence. Adv.Ther 2019;36(Suppl 1):5e12.
3. Lurie F, Passman M, Meisner M, et al. The 2020 update of the CEAP classification system and reporting standards. J Vasc Surg Venous Lymphat Disord 2020;8:342e52.
4. De Maeseneer MG, Kakkos SK, Aherne T, et al. Editor's choice - European society for vascular surgery (ESVS) 2022 clinical practice guidelines on the management of chronic venous disease of the lower limbs. Eur J Vasc Endovasc Surg 2022;63:184e267.
5. Eberhardt RT, Raffetto JD. Chronic venous insufficiency. Circulation 2014; 130:333e46.
6. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. Int Angiol 2018;37:181e254.
7. Maggioli A. Chronic venous disorders: pharmacological and clinical aspects of micronized purified flavonoid fraction. Phlebolymphology 2016;23:82e91.
8. Arnaud Maggioli, Chronic venous disorders: Pharmacological and clinical aspects of micronized purified flavonoid fraction .Phlebolymphology
9. Juliana C, Paula A, Erica A, Mario H, Alexandra C, Maria C. Flavonoid contents and antioxidant activity in fruit, vegetables and other types of food. Agric Sci. 2015;6(4):426-435. doi:10.4236/as.2015.64042
10. Shen N, Wang T, Gan Q, Liu S, Wang L, Jin B. Plant flavonoids: Classification, distribution, biosynthesis, and antioxidant activity. Food Chem. 2022; 383:132531. doi:10.1016/j.foodchem.2022.132531
11. Jaakola L, Hohtola A. Effect of latitude on flavonoid biosynthesis in plants. Plant Cell Environ. 2010; 33(8):1239-1247. doi: 10.1111/j.1365-3040.2010.02154.x
12. Ku YS, Ng MS, Cheng SS, et al. Understanding the composition, biosynthesis, accumulation and transport of flavonoids in crops for the promotion of crops as healthy sources of flavonoids for human consumption. Nutrients. 2020; 12(6):1717.
13. Cahill PA, Redmond EM. Vascular endothelium - Gatekeeper of vessel health. Atherosclerosis. 2016;248:97-109. doi: 10.1016/j.atherosclerosis.2016.03.007
14. Xi YD, Yu HL, Ding J, et al. Flavonoids protect cerebrovascular endothelial cells through Nrf2 and PI3K from -amyloid peptide-induced oxidative damage. Curr Neurovasc Res. 2012;9(1):32-41. doi: 10.2174/156720212799297092
15. Bellavite P. Neuroprotective potentials of flavonoids: Experimental studies and mechanisms of action. Antioxidants (Basel). 2023; 12(2):280. doi: 10.3390/antiox12020280
16. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascul Pharmacol. 2018; 100:1-19.
17. Marin, F., Ortuño, A., Benavente-Garcia, O., Del Rio, J.A., 1998. Distribution of Flavone Glycoside Diosmin in Hyssopus officinalis Plants: Changes During Growth. Planta Med, 64(2), pp.181-182.
18. Nabo, W.E.E., Oluwadamilola, O.A., Oyetunde, T.O., 2018. Cardioprotective Effects of Curcumin-Nisin Based Poly Lactic Acid Nanoparticle on Myocardial Infarction in Guinea Pigs. Sci Rep, 8, pp.16649.
19. Areias, F.M., Valento, P., Andrade, P.B., Ferreres, F., Seabra, R.M., 2001. Phenolic fingerprint of peppermint leaves. Food Chemistry, 73(3), pp.307–311.
20. Ren, H., Endo, H., Hayashi, T., 2001. Antioxidative and antimutagenic activities and polyphenol content of pesticide-free and organically cultivated green vegetables using water-soluble chitosan as a soil modifier and leaf surface spray. J Sci Food Agric, 81(15), pp.1426–1432.
21. Meyer, O.C., 1997. Angiology Safety and Security of Daflon 500 mg in Venous Insufficiency and in Hemorrhoidal Disease. Angiology, 45(6), pp.579 - 584.
22. Maher, S., Sabri, N.A., 2009. Evaluation of clinical activity and safety of Daflon 500 mg in type 2 diabetic female patients. Saudi Pharm J, 17(3), pp.199–207.
23. Reginald marzo, Nutri Avenue , March 21, 2025
24 Business research insights .Chemical and materials /diosmin market updated on 2nd June 2025