Original article

doi:10.5633/amm.2026.0411

TEN-YEAR TRENDS IN THE USE OF BIOFLAVONOIDS IN THE TREATMENT OF HEMORRHOIDAL DISEASE AND CHRONIC VENOUS INSUFFICIENCY

Mišel Mutlag[1], Goran Stanojević[2,3], Zoran Damnjanović[2,4]

[1]University of Niš, Faculty of Medicine, doctoral studies, Niš, Serbia

[2]University of Niš, Faculty of Medicine, Department of Surgery and Anesthesiology and Reanimatology, Niš, Serbia

[3]University Clinical Center Niš, Clinic for Digestive Surgery, Niš, Serbia

[4]University Clinical Center Niš, Clinic for Vascular Surgery, Niš, Serbia

Contact: Zoran Damnjanović

81 dr Zorana Djindjića Blvd., 18000 Niš, Serbia

E-mail: zoran.damnjanovic@medfak.ni.ac.rs

Bioflavonoids are well-studied active compounds that can improve clinical outcomes in patients with hemorrhoidal disease and chronic venous insufficiency, including reducing pain and edema and enhancing quality of life. This study aimed to analyze the ten-year use of venoprotective bioflavonoids in Serbia, focusing on consumption trends and costs from 2014 to 2023. Data were obtained from the official database of the Medicines and Medical Devices Agency of Serbia. Results showed a significant increase in the total consumption of diosmin and troxerutin, while the diosmin/hesperidin combination also demonstrated a steady rise, especially in recent years. Statistical analysis confirmed a significant upward trend for all analyzed drugs ($p = 0.0013$; Tau = 0.82). The increase in use of venoprotective bioflavonoids may be associated with higher disease prevalence and the proven efficacy and safety of these therapies. These findings highlight

the need for further research and continuous evaluation of therapeutic protocols to optimize treatment strategies.

Key words: venoprotective bioflavonoids, hemorrhoidal disease, chronic venous insufficiency, consumption trends

Originalni rad

doi:10.5633/amm.2026.0411

DESETOGODIŠNJI TRENDOVI U PRIMENI BIOFLAVONOIDA U LEČENJU HEMOROIDALNE BOLESTI I HRONIČNE VENSKE INSUFICIJENCIJE

Mišel Mutlag[1], Goran Stanojević[2,3], Zoran Damnjanović[2,4]

[1]Univerzitet u Nišu, Medicinski fakultet, student doktorskih studija, Niš, Srbija

[2]Univerzitet u Nišu, Medicinski fakultet, Katedra za hirurgiju i anesteziologiju sa reanimatologijom, Niš, Srbija

[3]Univerzitetski klinički centar Niš, Klinika za digestivnu hirurgiju, Niš, Srbija

[4]Univerzitetski klinički centar Niš, Klinika za vaskularnu hirurgiju, Niš, Srbija

Kontakt: Zoran Damnjanović

Bulevar dr Zorana Đinđića 81, 18000 Niš, Srbija

E-mail: zoran.damnjanovic@medfak.ni.ac.rs

Bioflavonoidi su dobro proučene aktivne supstance koje mogu poboljšati kliničke ishode kod pacijenata sa hemoroidalnom bolešću i hroničnom venskom insuficijencijom, uključujući smanjenje bola i edema, kao i unapređenje kvaliteta života. Cilj ove studije bila je analiza desetogodišnje primene venoprotektivnih bioflavonoida u Srbiji, sa fokusom na trendove potrošnje i troškove u periodu od 2014. do 2023. godine. Podaci su preuzeti iz zvanične baze Agencije za lekove i medicinska sredstva Srbije. Rezultati su pokazali značajan porast ukupne potrošnje diosmina i trokserutina, dok je kombinacija diosmin/hesperidin takođe beležila kontinuirani rast, posebno u poslednjim godinama. Statistička analiza potvrdila je značajan uzlazni trend za sve analizirane lekove ($p = 0,0013$; $Tau = 0,82$). Porast upotrebe venoaktivnih bioflavonoida može biti povezan sa većom prevalencom ovih oboljenja, kao i sa dokazanom efikasnošću i bezbednošću ovih terapija.

Ovi nalazi ukazuju na potrebu za daljim istraživanjima i kontinuiranom evaluacijom terapijskih protokola u cilju optimizacije terapijskih strategija.

Ključne reči: venoprotektivni bioflavonoidi, hemoroidalna bolest, hronična venska insuficijencija, trendovi potrošnje

INTRODUCTION

Hemorrhoidal disease (HD) and chronic venous insufficiency (CVI) are two highly prevalent conditions which, owing to their characteristic symptoms, can markedly impair patients' quality of life and impose considerable social and economic burdens (1). It is well established that HD and CVI share a number of common risk factors. In the case of CVI, the most relevant include age, family history, obesity, constipation, female gender, and occupations that involve prolonged standing (2), while for HD, the risk factors encompass constipation, diarrhea, a low-fiber diet, pregnancy, age, family history, and activities that increase intra-abdominal pressure (3).

It is considered that HD and CVI may have a related underlying cause associated with the loss of vascular integrity (4). Observational studies confirm the association between HD and CVI, with patients who have undergone surgical treatment for HD showing a higher incidence of CVI (5). The association between HD and CVI is further emphasized by the shared pharmacotherapeutic approach for both conditions. Pharmacological therapy, particularly the use of venoactive (venoprotective) drugs, has shown effectiveness in reducing venous inflammation and improving microcirculation (6). Bioflavonoids, such as diosmin, hesperidin, and troxerutin, represent well-studied active components with the potential to improve clinical outcomes, including pain reduction, edema control, and enhancement of quality of life, in patients with both HD and CVI (7,8).

The aim of this study is to analyze the ten-year use of venoprotective bioflavonoids, specifically diosmin, hesperidin, and troxerutin, in the treatment of HD and CVI in Serbia. The study will focus on the analysis of material costs, through the quantity and price of these medications, as well as on monitoring the frequency of their use over the period from 2014 to 2023.

MATERIAL AND METHODS

Data on the consumption of bioflavonoids used in the treatment of HD and CVI in the Republic of Serbia for the period from 2014 to 2023 were obtained from the official website of the Agency for Medicines and Medical Devices of Serbia (ALIMS) (9–18).

The internationally recognized and widely accepted methodological framework for drug utilization analysis is based on the Anatomical Therapeutic Chemical (ATC) Classification System and the Defined Daily Dose (DDD). However, bioflavonoids belong to a group of drugs for which a

DDD has not yet been defined, so for the analysis of drug utilization, changes in material costs were monitored on an annual basis over a ten-year period within the relevant ATC drug groups.

Within the ATC classification system, active substances are organized in a hierarchical structure consisting of five different levels. The system comprises fourteen main anatomical/therapeutic groups, representing the 1st level. Each ATC main group is further divided into a 2nd level, which may represent pharmacological or therapeutic group. The 3rd and 4th levels represent chemical, pharmacological, or therapeutic subgroups, while the 5th level is the chemical substance. The second, third, and fourth levels are frequently used to define pharmacological subgroups when this is considered more appropriate than therapeutic or chemical subgroups.

The following section presents the ATC codes and their corresponding categories related to bioflavonoids in the treatment of cardiovascular diseases, with a particular focus on vasoprotective agents and capillary-stabilizing drugs (Table 1).

Table 1. ATC classification of diosmin, troxerutin, and diosmin/hesperidin

C	Cardiovascular system	**C**	Cardiovascular system	**C**	Cardiovascular system
C05	Vasoprotective agents	**C05**	Vasoprotective agents	**C05**	Vasoprotective agents
C05C	Capillary-stabilizing agents	**C05C**	Capillary-stabilizing agents	**C05C**	Capillary-stabilizing agents
C05CA	Bioflavonoids	**C05CA**	Bioflavonoids	**C05CA**	Bioflavonoids
C05CA03	Diosmin	**C05CA04**	Troxerutin	**C05CA53**	Diosmin/hesperidin

The first anatomical level is represented by a capital letter. Medicines are classified into 14 main groups according to the organ or system on which they primarily act. According to the ATC classification, drugs acting on the cardiovascular system belong to group C. The second level is represented by two digits and indicates the main therapeutic group to which a given drug belongs (vasoprotective agents). The third level consists of a single letter and describes in detail the therapeutic-pharmacological subgroup (capillary-stabilizing agents). The fourth level consists of a single letter and indicates the pharmacological-chemical subgroup (bioflavonoids). The fifth (chemical) level consists of two digits and identifies the specific drug.

Data on drug consumption (diosmin, hesperidin, troxerutin) were collected for the period from 2014 to 2023. Each year includes data on the quantity of drugs sold, calculated as the product of quantity and price, and will be presented in tabular form for each year within the specified period. The data were statistically analyzed and processed using descriptive statistics, as well as appropriate tests of statistical significance, presented in tables and graphs. The database was created in Microsoft Excel, and statistical processing was performed using the Python software package. For the analysis of changes in drug consumption over time, the Mann–Kendall test was applied. This non-parametric test is used to detect trends in time series of data without assuming normality of the data distribution. The test assesses whether there is a statistically significant trend in drug consumption over the analyzed period. All statistical tests will be considered significant if the null hypothesis was equal to or less than 5%.

RESULTS

The consumption of vasoprotective drugs and venoactive bioflavonoids (quantity × price) is expressed in RSD for each year over the period from 2014 to 2023, in relation to the group of vasoprotective agents. This amount represents the total value of the quantities of diosmin, troxerutin, and diosmin/hesperidin consumed during each individual year, calculated based on the unit price and the quantity of drugs sold.

Table 2. Consumption of venoprotective bioflavonoids, capillary-stabilizing agents, and vasoprotective drugs (quantity × price) for each year in the period from 2014 to 2023

Year	**C05** (quantity x price in RSD)	**C05C** (quantity x price in RSD)	**C05C/C05**	**C05CA03** (quantity x price in RSD)	**C05CA04** (quantity x price in RSD)	**C05CA53** (quantity x price in RSD)
2014	790570738.56	232916001.80	**29.46%**	174639151.80	/	58276850.00
2015	924745857.00	336584078.60	**36.40%**	208219163.60	1494450.00	12687046.00
2016	956986715.60	377048002.40	**39.40%**	215216502.40	/	161831500.00
2017	972060841.10	338606361.50	**34.83%**	214798466.40	18724160.00	105083735.10
2018	1060042260.30	458239832.11	**43.23%**	237125645.90	27325903.71	193788282.50
2019	1113610984.32	455560476.72	**40.91%**	236450259.40	29257582.32	189852635.00
2020	1101918905.00	401945127.00	**36.48%**	197304079.40	29964350.00	174676697.60
2021	1204925559.00	502739903.06	**41.72%**	237196188.30	40453712.00	225090002.80
2022	1365084918.00	606455623.90	**44.43%**	292722734,40	38634593,76	275098295.70
2023	1387846874.00	747816923.90	**53.88%**	359839304,40	46538639,46	341438980.00

*RSD – official international abbreviation for the Serbian currency (dinar)

The data show a significant increase in the total consumption of this group of drugs, with a particular emphasis on the rising consumption of diosmin (C05CA03) and troxerutin (C05CA04)

over the years, while the consumption of the diosmin/hesperidin combination (C05CA53) also showed a steady increase, especially in the recent years. The share of vasoprotective bioflavonoids within the C05C group (capillary-stabilizing agents) varied throughout the analyzed period. In 2014, the share of vasoprotective bioflavonoids in the total consumption of the C05C group was 29.46%, and by 2023 it increased to 53.88%. This increase of 24.42 percentage points indicates a growing use of vasoprotective bioflavonoids in relation to the overall group of capillary-stabilizing agents.

The annual growth rate of venoactive bioflavonoid use was calculated using the following mathematical formula:

$$\text{Growth rate (2023 vs. 2014)} = \left(\frac{\text{total consumption in 2023}}{\text{total consumption in 2014}} - 1 \right) \times 100 = 220.1\%$$

The annual growth rate of venoactive bioflavonoid use, expressed as the percentage change between 2023 and 2014, amounts to 220.1%. This result indicates that the total expenditure on venoactive bioflavonoids (diosmin, hesperidin, and troxerutin) in 2023 was 220.1% higher than in 2014.

Figure 1. presents the share of venoprotective bioflavonoids in the total consumption of the C05C group – Capillary-stabilizing agents over the period from 2014 to 2023. The data refer to the share of diosmin (C05CA03), troxerutin (C05CA04), and the diosmin/hesperidin combination (C05CA53) in the total consumption of this drug group.

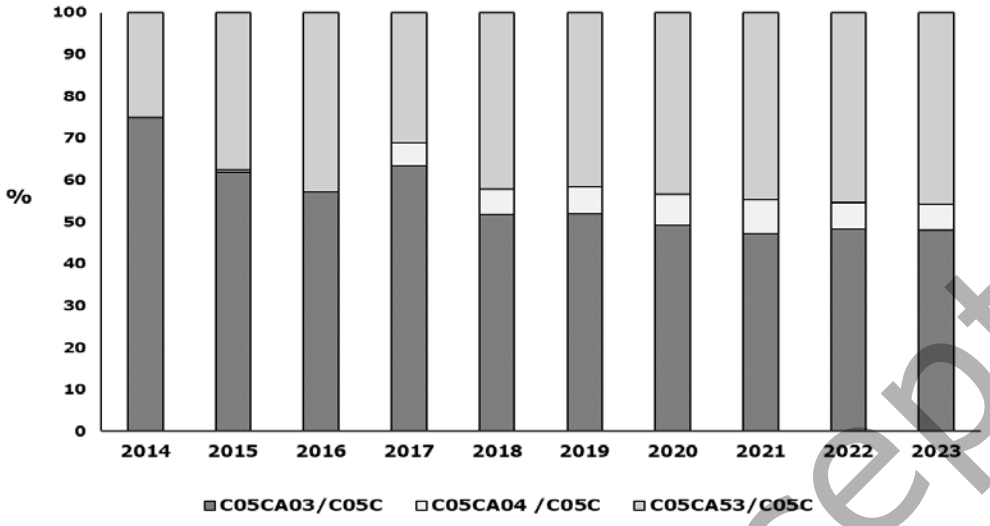

Figure 1. Share of venoprotective bioflavonoids (%) in relation to the group of capillary-stabilizing agents over the period from 2014 to 2023

Diosmin (C05CA03) was the most widely used throughout the entire period, with a share varying from 74.98% in 2014 to 48.12% in 2023. Although there was a decrease in the share of diosmin, it remained the most commonly used bioflavonoid within this group. Troxerutin (C05CA04) had a smaller but still notable share in the total consumption of venoprotective bioflavonoids. The share of troxerutin gradually increased from 0% in 2014 (no data available) to 6.22% in 2023. This indicates an increase in the use of troxerutin over the observed period, which may reflect changes in therapeutic approaches or new treatment recommendations for these conditions. The diosmin/hesperidin combination (C05CA53) showed a relatively stable share during the observed period, increasing from 25.02% in 2014 to 45.66% in 2023. This rise suggests an increasing popularity of combination therapies, which may indicate their efficacy and wider use in the treatment of HD and CVI.

To analyze trends in drug consumption over time, the Mann–Kendall test was applied, and the results of this statistical analysis are presented in Table 3.

Table 3. Trend analysis of the use of venoprotective bioflavonoids

Metric	All	Diosmin C05CA03	Troxerutin C05CA04	Diosmin, hesperidin C05CA53
p-value	0.0013	0.0073	0.00046	0.00236
Tau	0.82	0.69	0.89	0.78
Slope	40.6M	12.4M	5.4M	25.7M
z-score	3.22	2.68	3.50	3.04

The results of the conducted study indicate the presence of a statistically significant increasing trend for all drugs over the analyzed time period ($p = 0.0013$; Tau = 0.82). All analyzed drugs (diosmin, troxerutin, and the diosmin/hesperidin combination) demonstrate a statistically significant upward trend in consumption over the last 10 years, with diosmin and troxerutin showing the greatest increase. Troxerutin exhibits the fastest growth, while the diosmin/hesperidin combination showed the most pronounced increase in the recent years. Overall, venoactive bioflavonoids represent a significant segment of consumption in the treatment of HD and CVI, with a very strong and rapid increase in consumption over the observed period.

DISCUSSION

Among pharmacological approaches, venoactive drugs may act on the underlying causes of both symptomatic hemorrhoids and CVD through their beneficial effects on venous tone, inflammatory processes, and microcirculatory permeability. Early introduction of these agents may play a role in preventing or slowing the development and recurrence of symptoms and signs of both HD and CVD (4). Venoactive drugs have demonstrated various benefits in patients with CVD and HD (19,20). This group of drugs is widely prescribed in Europe and other parts of the world and is currently available mainly over the counter (OTC) or as dietary supplements. Most venoactive drugs are plant-derived compounds, and the most extensively studied and commonly used in practice are bioflavonoids with venotonic activity, such as diosmin, troxerutin, and the diosmin/hesperidin combination (21). However, it is important to note that the lack of homogeneity within the group of venoactive bioflavonoids in terms of their biological and molecular characteristics may also correspond to potential differences in their clinical efficacy (22), and consequently in their use in everyday clinical practice.

Bioflavonoids with venoactive properties are widely used in the treatment of CVD symptoms (23). Thanks to their anti-inflammatory and vasoprotective effects, diosmin, hesperidin, and troxerutin may have beneficial effects on objective indicators of leg edema, as well as on symptoms and signs associated with CVI, such as pain, cramps, restless legs, a sensation of swelling, paresthesia, and trophic changes (level of evidence IIB) (24).

On the other hand, the acute clinical manifestation of hemorrhoidal disease is characterized by pain, bleeding, itching, prolapse, edema, and often thrombosis (25). This condition is commonly referred to as a “hemorrhoidal crisis.” The mechanism of action of bioflavonoids on HD symptoms is based on the improvement of venous tone, reduction of capillary permeability, enhancement of lymphatic drainage, and anti-inflammatory effects, leading to a significant and rapid reduction in anal pain, bleeding, and itching (26). The European Society of ColoProctology has developed comprehensive guidelines for the management of HD, which support the use of venoactive bioflavonoids to improve symptoms (particularly anal bleeding) and reduce recurrence (27).

The consumption of venoactive drugs is increasing, driven by the growing prevalence of HD and CVI associated with population aging, obesity, and other risk factors for these diseases, such as: genetic predisposition, prolonged standing or sitting, physical inactivity, pregnancy, and others (28). Venoactive bioflavonoids therefore become a key therapy in the management of these chronic conditions, but it is important that, due to differences in their biological activity, their use is adapted to the specific needs of the patient. The dose and duration of venoactive drug administration depend on the type of disease. In HD, therapy is usually shorter and administered at lower doses, whereas in CVI longer treatment courses with higher doses are required to achieve long-term symptom control (22, 29).

According to the available literature data, this study represents the first comprehensive investigation and analysis of the consumption of venoactive bioflavonoids (diosmin, hesperidin, and troxerutin) over a 10-year period, with a particular focus on monitoring material costs and statistical analysis of consumption trends, thereby contributing new insights into the pharmacoeconomic and therapeutic dynamics of this class of drugs. The results of the conducted study show a significant increase in the total consumption of venoactive drugs, particularly in recent years, with a marked rise in the consumption of diosmin (C05CA03) and troxerutin (C05CA04), as well as the diosmin/hesperidin combination (C05CA53) (Table 2). The increase in

consumption of venoactive bioflavonoids is directly related to the rising prevalence of CVI and HD, as well as with the fact that this is a group of drugs with a favorable safety profile, often prescribed for long-term use, thereby contributing to symptom control and overall improvement in quality of life (30–32). Analyzing trends in the total consumption of venoactive bioflavonoids, an increase of 220.1% was observed in 2023 compared to 2014. As previously noted, this increase may be the result of various factors, including increased drug consumption due to wider therapeutic application in HD and CVI, a growing number of patients, and/or an increase in drug prices over the ten-year period (9–18).

When observing the share of individual venoactive bioflavonoids over the analyzed ten-year period (Figure 1), it was noted that diosmin continues to dominate consumption throughout the entire study period. However, a significant increase in the use of troxerutin, as well as in the share of the diosmin/hesperidin combination, was also observed. In addition, the results of the conducted study indicate the presence of a statistically significant increasing trend for all analyzed drugs over the last 10 years ($p = 0.0013$; Tau = 0.82; Table 3). These findings show that diosmin, troxerutin, and the diosmin/hesperidin combination all demonstrated a statistically significant increase in consumption, suggesting changes in therapeutic practices and an increased use of venoactive drugs in the treatment of HD and CVD.

The obtained results may indicate changes in therapeutic practices. Furthermore, the decrease in the share of diosmin in total consumption may suggest an adaptation of therapeutic approaches and the selection of appropriate drugs in accordance with patient needs, as well as new guidelines for the treatment of CVD and HD. These changes indicate the development and improvement of therapeutic approaches aimed at optimizing treatment and enhancing clinical outcomes (33,34).

This study has several potential limitations. First, the research is limited by heterogeneous data encompassing two different conditions, HD and CVI, which share similar etiological factors of development, but differ in clinical characteristics, as well as by the lack of specific results related to the use of troxerutin and the diosmin/hesperidin combination, particularly in HD and CVI separately. Additionally, the study was conducted in the territory of Republic of Serbia, meaning that the results cannot be directly generalized to other countries or healthcare systems with different demographic, socioeconomic, and healthcare characteristics. Nevertheless, this study is

the first to provide a comparative analysis of the use of venoactive bioflavonoids, and further research on a broader geographic sample may contribute to better validation and application of the findings in a global context. Moreover, the lack of a defined daily dose for bioflavonoids, as well as changes in drug prices over time, prevent standardized comparison with other studies, thereby limiting the pharmacoepidemiological interpretation of the data.

CONCLUSION

Venoactive bioflavonoids represent a significant segment of consumption in the treatment of HD and CVI. The consumption of these drugs has shown a very strong and rapid increase, which may be associated with the increased prevalence of these diseases, as well as with their efficacy and safety in long-term use. This trend indicates the need for further research and adaptation of therapeutic protocols in order to ensure optimal treatment for patients with these conditions, along with continuous evaluation of new therapeutic protocols. The results of this study provide a basis for future research focused on global monitoring of venoactive bioflavonoid consumption, as well as comparison with other drugs, which would contribute to the improvement of therapeutic approaches and the development of better tailored and cost-effective strategies for patients with HD and CVI. In order to achieve the highest treatment efficacy, it is necessary to continuously monitor and analyze the use of these drugs, as well as to evaluate their impact on individual symptoms, which may contribute to a more personalized approach in the treatment of patients with HD and CVI.

REFRENCES

1. Lee ML, Kao YW, Yang YT, Chen MC, Shia BC, Huang SY, et al. The bidirectional association between hemorrhoidal disease and varicose veins: a nationwide population-based cohort study. Int J Colorectal Dis 2025;40(1):91. doi: 10.1007/s00384-025-04889-8. https://pubmed.ncbi.nlm.nih.gov/40210792/
2. Taengsakul N. Risk Factors for and Treatment of Chronic Venous Disease in Thai Patients. Vasc Health Risk Manag 2022;18:667-76. doi: 10.2147/VHRM.S382726. https://pubmed.ncbi.nlm.nih.gov/36065282/
3. Pata F, Sgró A, Ferrara F, Vigorita V, Gallo G, Pellino G. Anatomy, Physiology and Pathophysiology of Haemorrhoids. Rev Recent Clin Trials 2021;16(1):75-80. doi: 10.2174/1574887115666200406115150. https://pubmed.ncbi.nlm.nih.gov/32250229/
4. Godeberge P, Sheikh P, Zagriadskiĭ E, Lohsiriwat V, Montaño AJ, Košorok P, et al. Hemorrhoidal disease and chronic venous insufficiency: Concomitance or coincidence? Results of the CHORUS study (Chronic venous and HemORrhoidal diseases evalUation and Scientific research). J Gastroenterol Hepatol 2020;35(4):577-85. doi: 10.1111/jgh.14857. https://pubmed.ncbi.nlm.nih.gov/31512275/
5. Ekici U, Kartal A, Ferhatoglu MF. Association Between Hemorrhoids and Lower Extremity Chronic Venous Insufficiency. Cureus 2019;11(4):e4502. doi: 10.7759/cureus.4502. https://pubmed.ncbi.nlm.nih.gov/31249764/
6. Lee ML, Kao YW, Yang YT, Chen MC, Shia BC, Huang SY, et al. The bidirectional association between hemorrhoidal disease and varicose veins: A nationwide population-based cohort study. Int J Colorectal Dis 2025;40(1):91. doi: 10.1007/s00384-025-04889-8. https://pubmed.ncbi.nlm.nih.gov/40210792/
7. Ekici U, Kartal A, Ferhatoglu MF. Association Between Hemorrhoids and Lower Extremity Chronic Venous Insufficiency. Cureus 2019;11(4):e4502. doi: 10.7759/cureus.4502. https://pubmed.ncbi.nlm.nih.gov/31249764/
8. Miguel CB, Andrade RS, Mazurek L, Martins-de-Abreu MC, Miguel-Neto J, Barbosa AM, et al. Emerging Pharmacological Interventions for Chronic Venous Insufficiency: A Comprehensive

Systematic Review and Meta-Analysis of Efficacy, Safety, and Therapeutic Advances. Pharmaceutics 2025;17(1):59. doi: 10.3390/pharmaceutics17010059. https://pubmed.ncbi.nlm.nih.gov/39861707/

9. Agency for Medicines and Medical Devices of Serbia. Marketing and consumption of medicinal products for human use in the Republic of Serbia in 2014. Belgrade: Agency for Medicines and Medical Devices of Serbia, 2015.
10. Agency for Medicines and Medical Devices of Serbia. Marketing and consumption of medicinal products for human use in the Republic of Serbia in 2015. Belgrade: Agency for Medicines and Medical Devices of Serbia, 2016.
11. Agency for Medicines and Medical Devices of Serbia. Marketing and consumption of medicinal products for human use in the Republic of Serbia in 2016. Belgrade: Agency for Medicines and Medical Devices of Serbia, 2017.
12. Agency for Medicines and Medical Devices of Serbia. Marketing and consumption of medicinal products for human use in the Republic of Serbia in 2017. Belgrade: Agency for Medicines and Medical Devices of Serbia, 2018.
13. Agency for Medicines and Medical Devices of Serbia. Marketing and consumption of medicinal products for human use in the Republic of Serbia in 2018. Belgrade: Agency for Medicines and Medical Devices of Serbia, 2019.
14. Agency for Medicines and Medical Devices of Serbia. Marketing and consumption of medicinal products for human use in the Republic of Serbia in 2019. Belgrade: Agency for Medicines and Medical Devices of Serbia, 2020.
15. Agency for Medicines and Medical Devices of Serbia. Marketing and consumption of medicinal products for human use in the Republic of Serbia in 2020. Belgrade: Agency for Medicines and Medical Devices of Serbia, 2021.
16. Agency for Medicines and Medical Devices of Serbia. Marketing and consumption of medicinal products for human use in the Republic of Serbia in 2021. Belgrade: Agency for Medicines and Medical Devices of Serbia, 2022.

17. Agency for Medicines and Medical Devices of Serbia. Marketing and consumption of medicinal products for human use in the Republic of Serbia in 2022. Belgrade: Agency for Medicines and Medical Devices of Serbia, 2023.
18. Agency for Medicines and Medical Devices of Serbia. Marketing and consumption of medicinal products for human use in the Republic of Serbia in 2023. Belgrade: Agency for Medicines and Medical Devices of Serbia, 2024.
19. Gloviczki P, Lawrence PF, Wasan SM, Meissner MH, Almeida J, Brown KR, et al. The 2023 Society for Vascular Surgery, American Venous Forum, and American Vein and Lymphatic Society clinical practice guidelines for the management of varicose veins of the lower extremities. Part II: Endorsed by the Society of Interventional Radiology and the Society for Vascular Medicine. J Vasc Surg Venous Lymphat Disord 2024;12(1):101670. doi: 10.1016/j.jvsv.2023.08.011.
https://pubmed.ncbi.nlm.nih.gov/37652254/
20. Giannini I, Amato A, Basso L, Tricomi N, Marranci M, Pecorella G, et al. Flavonoids mixture (diosmin, troxerutin, hesperidin) in the treatment of acute hemorrhoidal disease: a prospective, randomized, triple-blind, controlled trial. Tech Coloproctol 2015;19(6):339-45. doi: 10.1007/s10151-015-1302-9.
https://pubmed.ncbi.nlm.nih.gov/25893991/
21. Mansilha A, Sousa J. Pathophysiological Mechanisms of Chronic Venous Disease and Implications for Venoactive Drug Therapy. Int J Mol Sci. 2018;19(6):1669. doi: 10.3390/ijms19061669.
https://pubmed.ncbi.nlm.nih.gov/29874834/
22. Gloviczki ML, Kakkos SK, Urbanek T, Chuback J, Nicolaides A. The role of venoactive compounds in the treatment of chronic venous disease. J Vasc Surg Venous Lymphat Disord 2025;13(5):102258. doi: 10.1016/j.jvsv.2025.102258.
https://pubmed.ncbi.nlm.nih.gov/40348378/
23. Martinez-Zapata MJ, Vernooij RW, Simancas-Racines D, Uriona Tuma SM, Stein AT, Moreno Carriles RMM, et al. Phlebotonics for venous insufficiency. Cochrane Database Syst Rev 2020;11(11):CD003229. doi: 10.1002/14651858.

https://pubmed.ncbi.nlm.nih.gov/33141449/

24. De Maeseneer MG, Kakkos SK, Aherne T, Baekgaard N, Black S, Blomgren L, 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(2):184-267. doi: 10.1016/j.ejvs.2021.12.024.
https://pubmed.ncbi.nlm.nih.gov/35027279/
25. Dekker L, Han-Geurts IJM, Grossi U, Gallo G, Veldkamp R. Is the Goligher classification a valid tool in clinical practice and research for hemorrhoidal disease? Tech Coloproctol 2022;26(5):387-92. doi: 10.1007/s10151-022-02591-3.
https://pubmed.ncbi.nlm.nih.gov/35141793/
26. Picciariello A, Rinaldi M, Grossi U, Verre L, De Fazio M, Dezi A, et al Management and Treatment of External Hemorrhoidal Thrombosis. Front Surg 2022;9:898850. doi: 10.3389/fsurg.2022.898850.
https://pubmed.ncbi.nlm.nih.gov/35592120/
27. van Tol RR, Kleijnen J, Watson AJM, Jongen J, Altomare DF, Qvist N, et al. European Society of Coloproctology: guideline for haemorrhoidal disease. Colorectal Dis 2020 Jun;22(6):650-662. doi: 10.1111/codi.14975.
https://pubmed.ncbi.nlm.nih.gov/32067353/
28. Rabe E, Berboth G, Pannier F. Epidemiologie der chronischen Venenkrankheiten [Epidemiology of chronic venous diseases]. Wien Med Wochenschr 2016;166(9-10):260-3. doi: 10.1007/s10354-016-0465-y.
https://pubmed.ncbi.nlm.nih.gov/27277219/
29. Corsale I, Carrieri P, Martellucci J, Piccolomini A, Verre L, Rigutini M, et al. Flavonoid mixture (diosmin, troxerutin, rutin, hesperidin, quercetin) in the treatment of I-III degree hemorroidal disease: a double-blind multicenter prospective comparative study. Int J Colorectal Dis 2018;33(11):1595-1600. doi: 10.1007/s00384-018-3102-y.
https://pubmed.ncbi.nlm.nih.gov/29934701/
30. Huwait E, Mobashir M. Potential and Therapeutic Roles of Diosmin in Human Diseases. Biomedicines 2022;10(5):1076. doi: 10.3390/biomedicines10051076.

https://pubmed.ncbi.nlm.nih.gov/35625813/

31. Godeberge P, Csiki Z, Zakharash M, Opot EN, Shelygin YA, Nguyen TT, et al. An international observational study assessing conservative management in hemorrhoidal disease: Results of CHORALIS (aCute HemORrhoidal disease evALuation International Study). J Comp Eff Res 2024;13(10):e240070. doi: 10.57264/cer-2024-0070.
https://pubmed.ncbi.nlm.nih.gov/39132755/
32. Santiago F. Quality of Life in Chronic Venous Disease: Bridging the Gap Between Patients and Physicians. Clin Drug Investig 2023;43(Suppl 1):3-8. doi: 10.1007/s40261-023-01264-9.
https://pubmed.ncbi.nlm.nih.gov/37162624/
33. Wittens C, Davies AH, Bækgaard N, Broholm R, Cavezzi A, Chastanet S, et al. Editor's Choice - Management of Chronic Venous Disease: Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg 2015;49(6):678-737. doi: 10.1016/j.ejvs.2015.02.007.
https://pubmed.ncbi.nlm.nih.gov/25920631/
34. Hawkins AT, Davis BR, Bhama AR, Fang SH, Dawes AJ, Feingold DL, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Hemorrhoids. Dis Colon Rectum 2024;67(5):614-23. doi: 10.1097/DCR.0000000000003276.
https://pubmed.ncbi.nlm.nih.gov/38294832/