S Afr Gen Pract. 2024;5(1):36-44
https://doi.org/10.36303/SAGP.0299

S Afr Gen Pract
ISSN 2706-9613 EISSN 2706-9621

REVIEW

The role of flavonoids in the pharmacological treatment of haemorrhoids

SS Singh, MA Strydom, M Balmith, C Megaw, MJ Nell

Department of Pharmacology, School of Medicine, University of Pretoria, South Africa
Corresponding author, email: *morne.strydom@up.ac.za*

Ethnopharmacological relevance: Flavonoids have been used for many years by traditional medical practitioners. Flavonoids possess a variety of beneficial effects, namely anti-inflammatory and analgesic properties used to treat typical haemorrhoidal disease (HD) symptoms, such as pain, bleeding, and inflammation.

Aim of the study: The aim of the study was to investigate the therapeutic potential of flavonoids in the conservative treatment of HD by analysing the safety and efficacy of flavonoids in the treatment and post-treatment remission of HD and determining if flavonoids are more effective on their own or when combined with other treatments.

Materials and methods: Five databases were searched to conduct this narrative review. The search was conducted using the following keywords namely, "haemorrhoids", "haemorrhoidal disease", "flavonoids", "safety and efficacy", "clinical trial", "treatment" and "therapy". Articles were filtered based on the inclusion and exclusion criteria. Data from 35 selected articles were charted and included in the qualitative synthesis of this narrative review.

Results: Flavonoids were found to be more effective when used in combination with other treatments such as sclerotherapy (SCL) and rubber band ligation (RBL); as well as in combination with other flavonoids. Micronised purified flavonoid fractions (MPFF), such as Daflon® were the most prescribed flavonoids due to their high efficacy in alleviating symptoms quickly for lower grades of HD. Some studies followed a two-phase dosing system in order to prevent relapse. Flavonoids administered orally displayed minimal side-effects in comparison to conventional conservative treatments.

Conclusion: Flavonoids have shown to be an effective and safe therapy in the treatment of acute, internal lower grades of HD. Flavonoids can be used synergistically with other conservative measures and procedures. They have been shown to avert relapses, decrease symptoms linked to HD, escalate the recovery time post-surgery, and often act as a bridge therapy.

Keywords: flavonoids, micronised purified flavonoid fraction, haemorrhoidal disease, treatment, clinical trials

Introduction

Haemorrhoid physiology and pathology

Haemorrhoids are normal anatomical vascular structures found in all individuals. They are anal cushions situated in the canal of the anus, as well as the surrounding tissue.[1,2] In a clinical setting "haemorrhoid" refers to a diseased state, known as haemorrhoidal disease (HD), which refers to the pathogenicity thereof. HD affects nearly 40% of adults, with a higher incidence rate in women as compared to men.[2] It places a significant burden on an individual's quality of life, causing discomfort and resulting in financial implications. In 2014, it was estimated that United States insured individuals racked up a $770 million bill for haemorrhoid care; including claims on outpatient facility use, physician visits, and prescription medications.[3] Yet, despite the common prevalence of HD and the substantial costs associated with symptom management, there is still a stigma attached to it, resulting in many people not seeking medical care. This could be due to the sensitive nature and location of HD.

Haemorrhoids are made up of connective tissue, blood vessels, and some muscle, and function in controlling the movement of stool and gas.[4] HD develops when the anal cushions of the submucosa become inflamed, enlarged, and displaced from their original position.[5,6] Pregnancy and menstruation may predispose an individual to symptomatic haemorrhoids.[7] However, other factors contributing to the development of the disease include a diet that is inadequate in vegetables, limited water intake, age, malnutrition due to poverty, diarrhoea, heavy lifting, oral contraceptives, an inactive lifestyle, and desk-bound jobs to name but a few.[5,8] These factors, singularly or in combination may result in increased pressure on the anal cushions due to increased intra-abdominal pressure.[5,9] This may prevent venous return, resulting in the enlargement of the haemorrhoidal plexus.[8] Haemorrhoids can present in two different forms, namely internal and external haemorrhoids.[4]

Haemorrhoidal disease classification

Internal haemorrhoids are found above the dentate line of the anorectum and are generally painless, resulting in minimal discomfort. Pain may be caused if it has prolapsed into the opening of the anus.[10] Many internal HD cases go undetected due to a lack of pain; however, bleeding may occur during bowel movements due to straining.[10,11] Therefore, it is advisable to contact a physician should blood be present in the stool. Internal HD cases are classified using a grading system that ranges between 1 and 4.[8] This is based on the enlargement of the anal cushions, as well as the extent to which the anal cushions have descended into the canal of the anus.[1,11] This system is known

as Goligher's classification, which only considers the extent of prolapse; therefore external haemorrhoids are excluded from being graded using this system.[12] The classification of internal HD is important in dictating which treatment will be appropriate, based on grading.[12] Grades 1–3 classifications can be treated using conservative measures while Grade 4 classifications require surgical intervention.[13] Goligher's classification of haemorrhoids is shown in Table I.

Table I: The four different grades of HD and their associated characteristics

Clinical grades of internal HD[8]	
First-degree (Grade 1)	Symptoms of bleeding but no prolapse is observed
Second degree (Grade 2)	Marked by straining on the toilet which results in prolapse, but may diminish on its own
Third degree (Grade 3)	Classified based on prolapse due to straining, that requires manual reinsertion
Fourth degree (Grade 4)	Occurs when the prolapse permanently hangs out of the anus and cannot be diminished

HD: haemorrhoidal disease

External haemorrhoids are located below the dentate line, under the skin surrounding the anus, and can emanate from the external plexus.[10] Innervation of the somatic nerves in this area may cause pain.[9,10]

Common symptoms in both internal and external haemorrhoids include swelling and inflammation of the anus, as well as itching in the anal region.[8] These symptoms may be more prevalent during bowel movements and are often treated conservatively, through regular exercise, changes in the diet by increasing the fibre content, stool softeners, improved anal hygiene and sitz baths.[11,13]

Common treatment options

Fibre is a popular conservative treatment for haemorrhoids as it is easily incorporated into the diet or taken as a supplement. Fibre prevents constipation by increasing bowel volume, resulting in the retention of water. This makes the stool softer and easier to pass, thus decreasing the potential for straining, which exacerbates HD.[14]

Good gut health is also dependent on fibre intake and a healthy balanced diet. If good gut health is not maintained, it may lead to altered gut motility and constipation.[15] Prioritising gut health, as well as a healthy diet is considered a conservative treatment.

Pharmacological interventions are generally recommended when conservative treatment measures fail and include medications such as anti-inflammatories, corticosteroids, and local anaesthetics. These medications can be applied in the form of topical creams and suppositories.[6]

Corticosteroids such as hydrocortisone are often used and can be applied topically or as a suppository; however, if used too often it can cause thinning of the skin around the anus.[16] People frequently self-medicate rather than seeking medical guidance, which may result in the overuse of hydrocortisone leading to a relapse of HD.[8] Topical creams and suppositories are often used for Grades 1–2 haemorrhoids,[11] while other treatment options include rubber band ligation (RBL) (nonsurgical intervention), haemorrhoidectomy (generally advised in Grade 4 haemorrhoids), sclerotherapy (SCL) and cryotherapy. Despite the relatively low rates of HD reoccurrence, these therapies are often invasive, have a long duration of recovery, and are extremely painful and expensive.[10] The glaring crack in the use of topical medications in treating HD is the lack of concrete evidence to support their use.[17] As such there is a need to explore evidence-based alternatives or complementary options, such as flavonoids. Flavonoids can exhibit diverse chemical structures, as seen in Figure 1.

Flavonoid efficacy

Flavonoids belong to the heterogenous class known as phlebotonics, which are often used to treat the milder stages of first- and secondary-degree haemorrhoids.[13,19] Flavonoids may act as an alternative oral therapy in the treatment of haemorrhoids.[11] Flavonoids are secondary phytochemical metabolites found in various fruits, vegetables, and flowers; and belong to the polyphenol group.[20] They are venoactive and play a role in increasing lymphatic drainage, venous tone, and the strength of the surrounding vessels.[13,20] Flavonoids such as rutin, possess anti-inflammatory properties due to the inhibition of vital enzymes involved in the inflammatory response and can also be used to treat inflammatory bowel disease (IBD).[5] IBD causes an alternation between constipation and diarrhoea, making it a possible culprit in the development of HD.[5] Flavonoids can be beneficial in the treatment of HD and help relieve its associated symptoms. There is a wide variety of known flavonoids; however, one of the most common flavonoids used in the treatment of

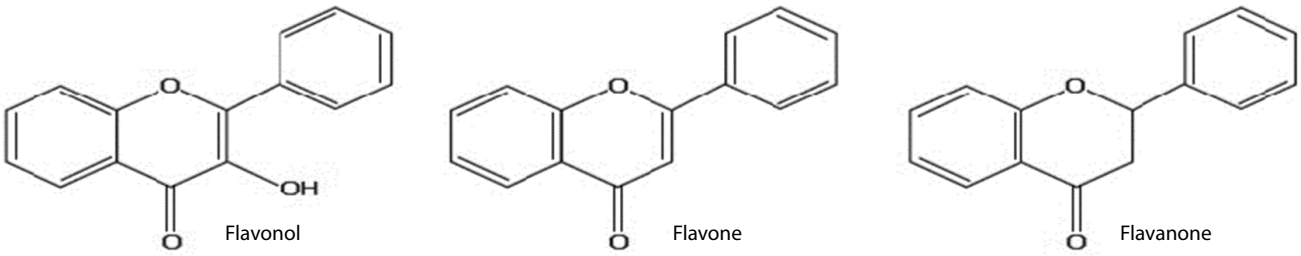

Figure 1: The chemical structures of three flavonoids[18]

HD is the micronised purified flavonoid fraction (MPFF), which is a mixture comprised of micronised diosmin and hesperidin.[1] MPFF has been shown to avert relapse and decrease the period of time in which chronic HD flare-up is present, as well as the aggressiveness of chronic HD.[1]

Flavonoids have been shown to decrease bleeding and itching associated with HD, as well as mitigate postoperative symptoms linked to haemorrhoidectomy.[17] Flavonoid agents have shown tremendous effects on clinical symptoms seen in HD. Studies have shown that treatment with flavonoids does not present with adverse reactions and had beneficial effects on the treatment of Grades 3 and 4 haemorrhoids as a post-surgical intervention.[5,17] The use of flavonoids in conjunction with conservative treatments, such as dietary fibre, has shown great benefits in mitigating symptoms, as well as preventing the reoccurrence of HD.

Thus, this study aimed to investigate the therapeutic potential of flavonoids in the conservative treatment of HD by analysing the safety and efficacy of flavonoids in the treatment and post-treatment remission of HD and determining if flavonoids are more effective alone or in combination with other treatments.

Methods

Database search

The following databases were searched when conducting this narrative review namely: Cochrane Library, Medline, PubMed, Scopus, and Web of Science. The following keywords were used namely: "haemorrhoids", "haemorrhoidal disease", "flavonoids" "safety and efficacy", "clinical trial", "treatment", and "therapy". The search terms used that provided the most relevant results included ([haemorrhoids OR hemorrhoids OR hemorrhoidal disease OR haemorrhoidal disease] AND [flavonoids OR bioflavonoids] AND [treatment OR therapy]).

Inclusion and exclusion criteria

Articles were screened according to the inclusion and exclusion criteria. The inclusion criteria consisted of articles from 2000–2023 in order to keep research current, majority of newer studies also mention older studies. Articles written in the English language, scoping, systematic, and observational reviews, as well as randomised control trials (RCT) and/or clinical studies about the use of flavonoids in the treatment of HD were included. In total 35 studies were data charted (Figure 2); 24 of those were RCT, comparative, prospective and observational studies which were included in Table II and included in the qualitative synthesis of this narrative review. The remaining 11 articles were review type articles, included in the background of this review.

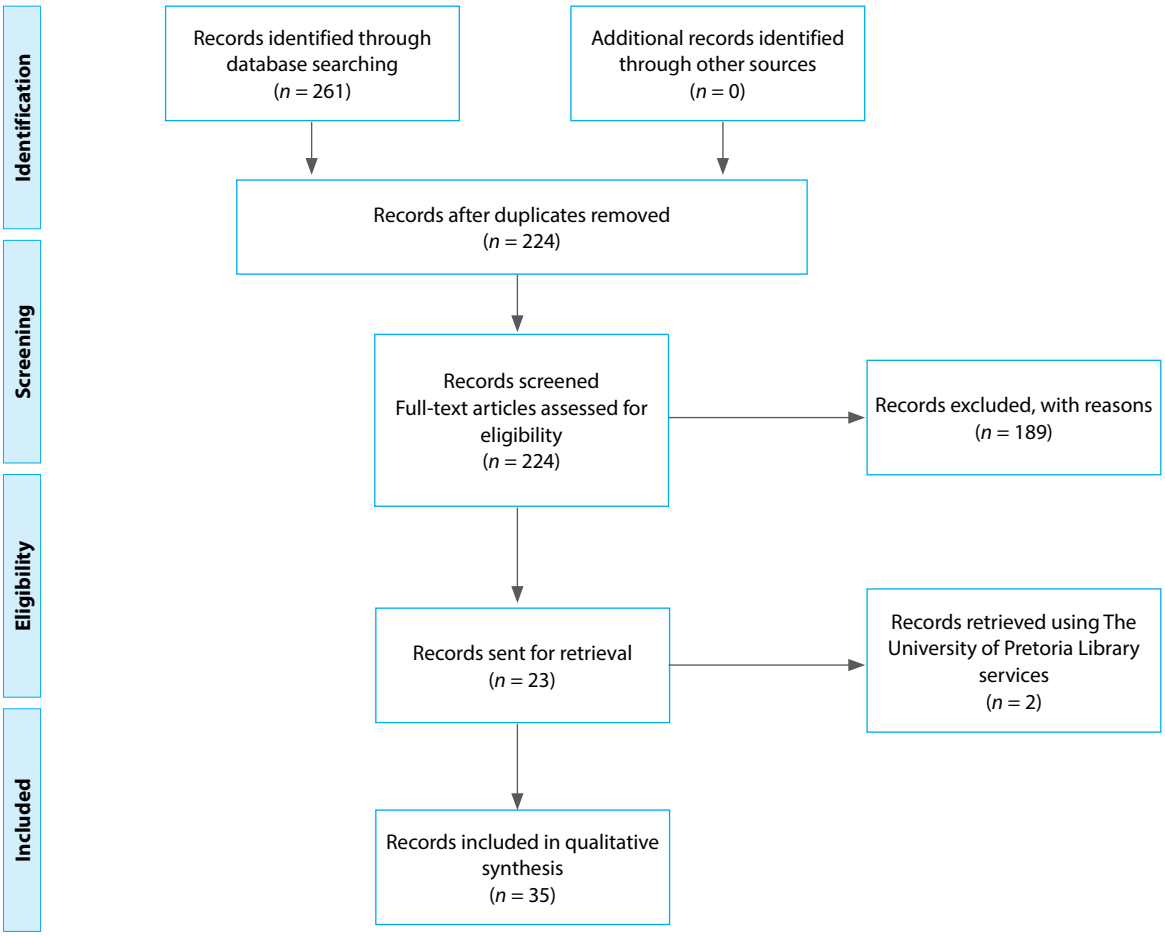

Figure 2: Workflow diagram for study inclusion

Results and discussion

Common types, doses, and administration of flavonoids

The most commonly prescribed flavonoid among the RCTs was a MPFF, also known as Daflon® (which is made up of 90% micronised diosmin and 10% hesperidin) at a dosage of 500 mg per tablet.[21] Prescribed flavonoids followed a trend of dose tapering. This can be seen in the common standard dosage given for Daflon® among the studies, which is three, 500 mg tablets twice a day for the first x number of days, followed by two tablets twice a day for x amount of time. "X" refers to any number of days/weeks depending on study. This was seen in a study conducted by Changazi et al. (2020), where one group was administered six Daflon® tablets everyday (equivalent to three tablets twice a day) for Week 1.[22] In Week 2, patients were administered four tablets daily, and in Week 3, they were administered two tablets daily.[22] Studies conducted by Gaetano et al. (2019) and Ho et al. (2000) looked at flavonoid use in combination with non-surgical therapies, such as RBL. Daflon® was administered with the same standard dosing mentioned, with the only variation being the number of days the tablets were taken.[23,24] This difference in the number of days may be attributed to the needs of individual patients. Some studies included in Table II, followed a two-phase approach where Phase one (first set dose of flavonoids) was generally administered to treat the symptoms associated with HD, and Phase 2 (subsequent doses thereafter) was used to prevent relapse.[25] Oral tablet formulations of flavonoids were mostly administered; however, some sublingual preparations and ointments/creams were also used. [26] Ointments and creams containing flavonoids were generally used in combination with other oral flavonoids to increase their efficacy.[27] Flavonoid lotion was seen to be a great alternative to topical chemical medications like anti-haemorrhoid ointments. In addition to being effective and safe, it is also inexpensive to produce and readily accessible to patients.[28]

Safety and efficacy of flavonoids

According to a longitudinal study conducted by Gaetano et al. (2019), a week-long treatment with MPFF following a RBL procedure decreased the intensity of bleeding during the first 30 days. Additionally, the combined treatment had a synergistic outcome in reducing pruritus acutely.[23] Flavonoids showed a positive effect in preventing bleeding and anal discomfort and proved more beneficial in alleviating HD symptoms as compared to traditional conservative treatments.[29] It is evident from the studies reviewed that flavonoids are generally used as a stepping stone treatment to symptomatically treat pathology of lower grades of internal HD prior to haemorrhoidectomy.[26,30] A few studies showed that flavonoids, such as MPFF were effective in preventing relapse and worsening of HD symptoms (namely bleeding) as compared to a placebo.[25,31] Similarly, a study conducted by Zagriadskiĭ et al. (2018) showed that flavonoids such as MPFF were helpful in avoiding relapse of advanced HD patients and fostering optimal postoperative conditions.[6] Flavonoids resulted in a decrease in hospitalisations caused by severe signs and symptoms of HD and was shown to prevent future acute HD outbreaks.[32] On their own, flavonoids can effectively manage the symptoms of lower grades of HD; however, cannot mitigate higher grades of HD (some Grades 3 and 4). Studies that aimed to assess the efficacy and safety of flavonoids, demonstrated its clinical efficacy and limited side-effects.[21,26,33-35] Notably, a mild side-effect of gastrointestinal symptoms was reported in one study.[36] As seen in Table II, flavonoids proved to be more effective than placebo in treatment of HD.[37]

Combined versus single flavonoid use

The majority of the RCT studies looked at the use of flavonoids alone in the treatment of acute HD. Flavonoids may also be effective in combination with other procedures, such as SCL and RBL.[38,39] This combination of flavonoids and SCL resulted in a decrease of HD symptoms more significantly as compared to the treatments alone.[40] Any symptoms associated with these non-surgical procedures have also shown to be effectively managed with flavonoid administration. SCL involves the injection of a chemical solution near the vicinity of the haemorrhoid, causing a scarring reaction, resulting in the gradual shrinkage of the haemorrhoid over time. This procedure is commonly used for internal Grades 1 and 2 HD. RBL is a procedure in which a rubber band is used to tie off the base of a haemorrhoid thereby cutting off blood flow in this area. This procedure is typically reserved for internal HD. Flavonoid use is favoured over these procedures, especially in lower grades of HD, as well as in cases where practitioners are not sufficiently trained to perform these procedures and in cases where proper equipment is inaccessible or not available.[24] It is recommended that flavonoids be used in conjunction with an increase in fibre and water intake, in order to accelerate the recovery process and decrease symptoms associated with HD, such as bleeding.[24] A double blind RCT study conducted by Squadrito et al. (2000), evaluated the efficacy of the combined use of troxerutin and carbazochrome and showed that the coaction between the two active ingredients is able to better control the signs and symptoms associated to HD, compared to each product alone.[41] Corsale et al. (2018), conducted a study to assess the effectiveness of a novel flavonoid mixture (diosmin, troxerutin, rutin, hesperidin, and quercetin) in reducing bleeding associated with Grades 1–3 HD. The use of this flavonoid mixture proved to be a safe and effective way to mitigate bleeding.[13] Some studies have used a combination of multiple flavonoids together for the treatment of HD. Such combinations include MMDH (micronised mixture of diosmin and hesperidin) and Emospid;[42] troxerutin and carbazochrome;[41] diosmin, troxerutin and hesperidin.[43] The general trend is that flavonoids are more efficient in alleviating HD symptoms quicker, with a minimal chance of relapse when combined with other non-surgical interventions or when combined with more than one type of flavonoid.

Limitations and recommendations

A few common limitations were identified when reviewing the current literature. A lack of patient compliance could be attributed to the long time period of treatment and cost of Daflon®. As such, decreasing the cost of the drug is

Table II: RCT, comparative and prospective studies on the clinical use of flavonoids in treating HD

Author/ Year	Study design	Study aims/objectives	Grade of HD	Type of flavonoid	Dosage	Findings
Ho et al. (2000)[24]	Prospective, RCT	To assess the role of MPFF in the management of bleeding non-prolapsed HD	Internal	MPFF (combined with RBL)	Daflon® 500 mg, 3 tabs twice daily/5 days, subsequently 2 tabs twice daily/3 weeks	No statistically significant advantage was shown over RBL
Squadrito et al. (2000)[41]	Double-blind, RCT	To evaluate efficacy of this combination treatment regimen compared to carbazochrome alone	Acute	Troxerutin and carbazochrome	150 mg troxerutin and 1.5 mg carbazochrome twice daily/ 7 days	This combination is safe and effective in controlling the signs and symptoms associated to HD, compared to the product alone
Misra et al. (2000)[25]	RCT	To examine if MPFF is effective in promptly halting the bleeding and preventing a relapse of HD	Internal	MPFF	450 mg diosmin and 50 mg hesperidin	MPFF was effective in halting bleeding. The average duration and relapse of bleeding in MPFF group was lower than the placebo
Meshikhes (2002)[36]	Prospective clinical study	To prove the value of Daflon® in the management of HD symptoms in Saudi patients	Grades 1–4	Daflon®	Two tabs twice daily/4 weeks	Daflon® is safe and effective in the treatment of HD symptoms. Minor gastrointestinal symptoms observed as a side-effect
Meshikhes (2004)[44]	Multicentre non-randomised observational study	To confirm the efficacy of Daflon® in the treatment of haemorrhoidal symptoms		Daflon®	Four tabs/day, in 2 divided doses/4 weeks	Daflon® showed to be effective in alleviating HD symptoms and improving the proctoscopic appearance of haemorrhoids
Pushpinder et al. (2004)[34]	Randomised comparative study	To compare the (dis)advantages, safety and efficacy of RBL and flavonoids in the treatment of HD, while looking at the compliance and acceptability in patients	Acute internal	Daflon® (90% diosmin and 10% hesperidin)	500 mg	Daflon® provides quick relief from symptoms associated with HD as compared to RBL
Dimitroulopoulos et al. (2005)[40]	Prospective, RCT, observer-blinded trial	To compare the efficacy of infrared photocoagulation (IRP) and oral MPFF versus each treatment alone on bleeding cessation	Grades 1, 2, and 3 acute internal haemorrhoids	MPFF	Not reported	Combining MPFF with IRP significantly reduced bleeding status in these study patients with Grades 1 and 2 acute internal haemorrhoids compared with each treatment used alone
Belcaro et al. (2010)[32]	RCT	To evaluate the efficacy and the tolerability of high-dose oral Pycnogenol® on symptoms/signs of acute haemorrhoidal episodes	Acute	Pycnogenol®	Group A: Pycnogenol® 300 mg daily/4 days, 150 mg daily/ 3 days Group B: placebo Group C: topical Pycnogenol® cream combined with Pycnogenol® oral treatment Group D: same as Group B	Pycnogenol® treatment decreased intensity/duration of pain and bleeding in acute HD. Resulted in a decrease in hospitalisations caused by severe signs/ symptoms and prevent future acute HD outbreaks
Di Pierro et al. (2011)[42]	RCT	To compare the clinical efficacy of MMDH with Emospid® in patients during an acute HD crisis	Acute	MMDH (micronised mixture of diosmin and hesperidin) and Emospid®	Emospid®: 1 tab every 8 hours/ 7 days MMDH: 2 tabs every 8 hours/7 days	Patients with acute haemorrhoidal crisis may be treated with Emospid® in order to avoid/delay, invasive procedures. Emospid® shows to be more effective, if compared with MMDH

Author/ Year	Study design	Study aims/objectives	Grade of HD	Type of flavonoid	Dosage	Findings
Aggrawal et al (2014)[21]	Multicentric randomised open labelled study	To determine the safety and compare the efficacy of Roidosanal® vs. Daflon® on symptomatic HD	Grades 1 to 3	Roidosanal® and Daflon®	Daflon® – 500 mg twice daily. Roidosanal®: 2 caps twice daily	Roidosanal® was found to be as effective as Daflon® in improving signs and symptoms of HD. No considerable adverse events were seen with the use of either product
Giannini et al. (2015)[43]	Prospective, triple blind, RCT	To assess the efficacy of a Triade H (diosmin, hesperidin and troxerutin) mixture in improving acute symptomatic HD	Acute	Diosmin, troxerutin and hesperidin	One sachet of powder with 300 mg of each flavonoid in water 3 times daily/3 days; 1 sachet twice daily/2 days and 1 sachet once daily/7 days. Treatment was switched to tabs after the 13th day, (diosmin 300 mg, troxerutin 300 mg, hesperidin 100 mg); one tab daily/1 month	The mixture is safe to use and can significantly aid management of common symptoms. Improvement was quicker and more consistent in patients receiving the active medications, as seen by changes in symptoms
Miškulin et al. (2018)[31]	Prospective cohort epidemiological study	To determine the efficiency of ointment with propolis extract in relief and suppression of the symptomatic internal HD Grades 1 and 2	Grades 1 and 2	Propolis extract (galangin)	Propolis extract (containing minimally 115 mg/kg of flavonoid galangin) 3 times daily	Ointment with propolis extract was effective in treating symptoms of the HD
Zagriadskiĭ et al. (2018)[6]	Multicentre, non-interventional study	To determine the effect of phlebotropic therapy on the evolution of clinical symptoms in patients with different degrees of internal haemorrhoids	Internal, Grades 1–3	MPFF	Not mentioned	MPFF was advantageous in alleviating HD symptoms in most Grades 1 and 2 patients and prevents relapse in advanced HD patients along with promoting optimal postoperative conditions
Corsale et al. (2018)[13]	Double-blind multicentre prospective comparative study	To evaluate the efficacy of a flavonoid's mixture, Fleben®: (diosmin, troxerutin, rutin, hesperidin, quercetin) to reduce bleeding in 1-3 degree HD in short/ medium time	Grades 1–3	Fleben® (diosmin, troxerutin, rutin, hesperidin, quercetin)	Study group: Flavonoid Fleben® 1 ampoule every 24 h/20 days. Control group: Daflon® 1 tab every 12 h/20 days	The use of Fleben® is a safe and effective way to manage bleeding associated with HD and minimal adverse events are reported
Gaetano (2019)[23]	Longitudinal cohort study	To compare the efficacy of common non-surgical interventions, either in combination or alone	Grades 1–3	Daflon®	500 mg Daflon®/7 days, 3 tabs twice daily/first 3 days, followed by 2 tabs twice daily from day 4–7. RBL. (RBL+MPFF group) underwent RBL, followed by Daflon® 500 mg for 7 days (at the same dose as above)	A week-long use of MPFF after RBL subsided the intensity of bleeding. The combined treatment was clinically valuable for decreasing the severity of all HD symptoms
Andarkhor et al. (2019)[35]	Double blind placebo RCT	To evaluate the safety and efficacy of *T. chebula* on haemorrhoids	Grades 1 and 2	*Terminalia chebula*	Four times daily on an empty stomach for 4 weeks	The study showed that *T. chebula* may be effective for HD and could be used as an additive treatment
Chiaretti et al. (2020)[5]	RCT	To compare the clinical effects of flavonoids and Centella to a control group in HD patients	Grades 1–4	Flavonoids (*Borago officinalis*,) *Rutin*) and Centella	Group A: 300 mg oral tablets of flavonoids twice daily/15 days. Topical ointment (bromelain, *B officinalis*, *A hippocastanum, H virginiana,* ruscogenine) once/ day. Group B: Oral 60 mg Centella tablets, twice daily/15 days, and 3 g of ointment (*C Asiatica*, Arnica, Aloe)	Both phlebotonic treatments are more effective than traditional treatments

Author/ Year	Study design	Study aims/objectives	Grade of HD	Type of flavonoid	Dosage	Findings
Changazi et al. (2020)[22]	RCT	To compare the efficacy of calcium dobesilate vs. flavonoids in the treatment of early HD	Grades 1–2	Daflon®	Group A: 6 500 mg flavonoid tabs, daily for the first week, 4 tabs daily in the second week and 2 tabs daily in the third. Group B: 2X 500 mg calcium dobesilate capsules twice daily/3 weeks	Flavonoid therapy was more effective than calcium dobesilate in improving symptoms of disease (frequency and amount of bleeding)
Giua et al. (2021)[45]	Multicentre prospective survey	To determine the efficacy of sucralfate ointment on the quality of life (QoL) and symptom frequency in treatment of HD from pharmacies in Italy	Grade not specified. Haemorrhoidal symptoms only	Calendula, witch hazel leaf (*hamamelis*), chamomile	Sucralfate ointment and other herbal extracts, such as calendula, witch hazel leaf (*hamamelis*) and chamomile	Improves QoL, decreases symptoms, and deemed safe for use in symptoms associated with HD
Orefice et al. (2021)[26]	Prospective observational study	To determine efficacy and safety of two different phlebotonic therapies, used preoperatively and in advanced HD patients awaiting surgery	Grades 3–4, advanced HD	MPFF (Group A) or sublingual nano-emulsion flavonoid (Group B)	Group A: X2 MPFF doses twice daily/4 weeks Group B: 1 sublingual sachet of micronised diosmin twice daily/4 weeks	Flavonoids have a potential role in treating patients with advanced HD. It was safe and well tolerated. Both phlebtonic therapies represented a valid "bridge-therapy" for patients awaiting surgery
Zobeiri et al. (2021)[33]	Double-blind placebo RCT	To evaluate the efficacy and safety of Hemoheal cream (anti-haemorrhoid herbal preparation)	Symptomatic HD	*Allium ampeloprasum*, *sesamum indicum*	Topical application of cream twice daily/3 weeks	The findings demonstrated the potential effect of Hemoheal cream
Romano et al. (2022)[30]	Observational single centre trial	To determine the efficacy of Mioven 700® (diosmin 500 mg, esperidine 90 mg, ruscogenin 100 mg) in improving symptoms of patients with haemorrhoidal disease	Grades 2–4, acute HD	Diosmin, hesperidin, ruscogenin	Group (A): 2 tabs daily/ 10 days of Mioven 700®, one daily tab/20 days, and one daily administration of macrogol/ 30 days. Group (B): one daily macrogol/ 30 days	Mioven 700® significantly improves symptoms and clinical conditions in patients with HD, and can be used to manage pathology, in patients waiting for surgical intervention
Mahmoudi et al. (2023)[37]	Double-blind placebo RCT	To evaluate the efficacy of *A. millefolium* ointment for treatment of internal haemorrhoids	Grades 1–2	*A. millefolium*	1 g of the ointments 3 times daily/10 days	Improvement of the symptoms treated with flavonoid ointment was greater than placebo
Razdar et al. (2023)[28]	RCT	To produce a mixture of flavonoids in the form of a lotion to determine their healing potential and possible side-effects compared to the standard of care treatment creams	Grades 2–4	Honey propolis, olive oil	Control group: Anti-HD lotion applied twice daily/1 month. 100 mg flavonoid lotion containing 70% flavonoid components	Flavonoid lotion can be a good substitute to topical chemical medications. Safe, effective and affordable

HD: haemorrhoidal disease; RCT: randomised controlled trials; SCL: sclerotherapy; RBL: rubber band ligation

recommended to ensure that these treatment options are accessible and affordable to individuals.[34] A lack of compliance was also seen, as some participants failed to attend weekly proctoscope examinations which is required to ascertain their level of improvement.[44] Another limitation identified was the small sample size/number of patients, which limits the extrapolation of data, hence a larger population size is recommended.[2335] Some studies were not randomised and did not have control groups, making it challenging to draw conclusions regarding the effectiveness of flavonoid therapy.[36,45] Potential bias may exist if researchers were not blinded, which can also be introduced through the qualitative self-assessment of patients' progress as improvement may be subjective.[23] The observed improvement in symptoms may not be entirely attributed to flavonoid therapy, as some patients had previously used other anti-haemorrhoidal medication prior to the study being conducted.[44] A longer follow-up period is recommended to validate the role flavonoids play in preventing the relapse of HD and to determine if there are any long-term effects.[44] The brief duration of patient follow-up can also be seen as a limitation. A three week follow-up does not allow for proper evaluation of symptomatic relapses or show the preventive role of flavonoids.[33] It is recommended that flavonoids be allocated as a bona fide medication.[5] Further research is recommended to explore the possibility of increasing the total amount of Daflon® with the aim of subsequently reducing the duration of treatment.[44] Further controlled studies are recommended to validate the results obtained.[45] Even though flavonoids have shown to be relatively safe, there is insufficient data available to assess its role in pregnant women. Therefore, the possible teratogenic effects of flavonoids are unknown.[13] In addition, no objective measurement was taken for haemorrhoid mass size, therefore future research should incorporate the use of a measuring device to delineate the improvement made using flavonoid therapy.[35]

Conclusion

In light of these findings, medical practitioners should consider the potential benefits of incorporating flavonoids, particularly MPFF, into their treatment approaches for HD. While current evidence suggests promising outcomes in managing lower grades of HD and preventing relapse, additional research is crucial to establish optimal dosing strategies and validate these clinical findings. Given the controversial evidence surrounding conventional HD treatments, exploring the potential efficacy of venoactive drugs like MPFF in routine clinical practice may offer a valuable alternative for medical practitioners seeking evidence-based interventions for their patients with HD.

Funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We would like to acknowledge the University of Pretoria Library services for assisting us with the retrieval of full-text articles used to compile this review.

ORCID

SS Singh https://orcid.org/0009-0000-4676-2658
MA Strydom https://orcid.org/0000-0001-8144-4970
M Balmith https://orcid.org/0000-0002-9209-7318
C Megaw https://orcid.org/0000-0003-1855-336X
MJ Nell https://orcid.org/0000-0001-9014-2333

References

1. Godeberge P, Sheikh P, Lohsiriwat V, Jalife A, Shelygin Y. Micronized purified flavonoid fraction in the treatment of hemorrhoidal disease. J Comp Eff Res. 2021;10(10):801-13. https://doi.org/10.2217/cer-2021-0038.
2. Hong YS, Jung KU, Rampal S, et al. Risk factors for hemorrhoidal disease among healthy young and middle-aged Korean adults. Scientific Reports. 2022;12(1):129. https://doi.org/10.1038/s41598-021-03838-z.
3. Yang JY, Peery AF, Lund JL, Pate V, Sandler RS. Burden and cost of outpatient hemorrhoids in the United States employer-insured population, 2014. Am J Gastroenterol. 2019;114(5):798-803. https://doi.org/10.14309/ajg.0000000000000143.
4. Alonso-Coello P, Zhou Q, Martinez-Zapata MJ, et al. Meta-analysis of flavonoids for the treatment of haemorrhoids. Br J Surg. 2006;93(8):909-20. https://doi.org/10.1002/bjs.5378.
5. Chiaretti M, Fegatelli DA, Pappalardo G, Venti MDS, Chiaretti AI. Comparison of centella with flavonoids for treatment of symptoms in hemorrhoidal disease and after surgical intervention: a randomized clinical trial. Sci Rep. 2020;10(1):8009. https://doi.org/10.1038/s41598-020-64772-0.
6. Zagriadskiĭ EA, Bogomazov AM, Golovko EB. Conservative treatment of hemorrhoids: results of an observational multicenter study. Adv Ther. 2018;35(11):1979-92. https://doi.org/10.1007/s12325-018-0794-x.
7. Quijano CE, Abalos E. Conservative management of symptomatic and/or complicated haemorrhoids in pregnancy and the puerperium. Cochrane Database Syst Rev. 2005;2005(3):Cd004077. https://doi.org/10.1002/14651858.CD004077.pub2.
8. Lohsiriwat V. Hemorrhoids: from basic pathophysiology to clinical management. World J Gastroenterol. 2012;18(17):2009-17. https://doi.org/10.3748/wjg.v18.i17.2009.
9. Margetis N. Pathophysiology of internal hemorrhoids. Ann Gastroenterol. 2019;32(3):264-72. https://doi.org/10.20524/aog.2019.0355.
10. Sandler RS, Peery AF. Rethinking what we know about hemorrhoids. Clin Gastroenterol Hepatol. 2019;17(1):8-15. https://doi.org/10.1016/j.cgh.2018.03.020.
11. Lohsiriwat V. Treatment of hemorrhoids: A coloproctologist's view. World J Gastroenterol. 2015;21(31):9245-52. https://doi.org/10.3748/wjg.v21.i31.9245.
12. Sobrado Júnior CW, Obregon CA, De Silva e Sousa Junior AH, et al. A new classification for hemorrhoidal disease: the creation of the "BPRST" staging and its application in clinical practice. Ann Coloproctol. 2020;36(4):249-55. https://doi.org/10.3393/ac.2020.02.06.
13. Corsale I, Carrieri P, Martellucci J, 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):1595-600. https://doi.org/10.1007/s00384-018-3102-y.
14. Garg P. Hemorrhoid treatment needs a relook: more room for conservative management even in advanced grades of hemorrhoids. Indian J Surg. 2017;79(6):578-9. https://doi.org/10.1007/s12262-017-1664-5.
15. Palumbo VD, Tutino R, Messina M, et al. Altered gut microbic flora and haemorrhoids: could they have a possible relationship? J Clin Med. 2023;12(6). https://doi.org/10.3390/jcm12062198.
16. England N. Hydrocortisone for piles and itchy bottom - Cream, ointment and suppositories 2020. Available from: https://www.nhs.uk/medicines/hydrocortisone-for-piles-and-itchy-bottom/.
17. Rabelo FEF, Lacerda-Filho A, Mansur ES, de Oliveira FH, de Queiroz FL, Fet al. Benefits of flavonoid and metronidazole use after excisional hemorrhoidectomy: a randomized double-blind clinical trial. Tech Coloproctol. 2021;25(8):949-55. https://doi.org/10.1007/s10151-021-02465-0.
18. Maggioli A. Chronic venous disorders: pharmacological and clinical aspects of micronized purified flavonoid fraction. Phlebolymphology. 2016.

19. Perera N, Liolitsa D, Iype S, et al. Phlebotonics for haemorrhoids. Cochrane Database Syst Rev. 2012(8):Cd004322. https://doi.org/10.1002/14651858.CD004322.pub3.
20. Thilakarathna SH, Rupasinghe HP. Flavonoid bioavailability and attempts for bioavailability enhancement. Nutrients. 2013;5(9):3367-87. https://doi.org/10.3390/nu5093367.
21. Aggrawal K, Satija N, Dasgupta G, et al. Efficacy of a standardized herbal preparation (Roidosanal®) in the treatment of hemorrhoids: A randomized, controlled, open-label multicentre study. J Ayurveda Integr Med. 2014;5(2):117-24.
22. Changazi SH, Bhatti S, Choudary A, Sr., et al. Calcium dobesilate versus flavonoids for the treatment of early hemorrhoidal disease: a randomized controlled trial. Cureus. 2020;12(8). https://doi.org/10.7759/cureus.9845.
23. Gaetano AC, Cunha C, Arroja B, Costa D, Rolanda C. Role of a micronized purified flavonoid fraction as an adjuvant treatment to rubber band ligation for the treatment of patients with hemorrhoidal disease: a longitudinal cohort study. Annals of Coloproctology. 2019;35(6):306-12. https://doi.org/10.3393/ac.2018.09.18.
24. Ho YH, Tan M, Seow-Choen F. Micronized purified flavonidic fraction compared favorably with rubber band ligation and fiber alone in the management of bleeding hemorrhoids: randomized controlled trial. Dis Colon Rectum. 2000;43(1):66-9. https://doi.org/10.1007/BF02237246.
25. Misra MC, Parshad R. Randomized clinical trial of micronized flavonoids in the early control of bleeding from acute internal haemorrhoids. Br J Surg. 2000;87(7):868-72. https://doi.org/10.1046/j.1365-2168.2000.01448.x.
26. Orefice R, Litta F, Parello A, et al. A prospective study on the efficacy of two different phlebotonic therapies as a bridge to surgery in patients with advanced hemorrhoidal disease. J Clin Med. 2021;10(8). https://doi.org/10.3390/jcm10081549.
27. Amaturo A, Meucci M, Mari FS. Treatment of haemorrhoidal disease with micronized purified flavonoid fraction and sucralfate ointment. Acta Biomed. 2020;91(1):139-41.
28. Razdar S, Panahi Y, Mohammadi R, Khedmat L, Khedmat H. Evaluation of the efficacy and safety of an innovative flavonoid lotion in patients with haemorrhoid: a randomised clinical trial. BMJ Open Gastroenterol. 2023;10(1). https://doi.org/10.1136/bmjgast-2023-001158.
29. Chiaretti M, Fegatelli DA, Pappalardo G, Venti MDS, Chiaretti AI. Comparison of Centella with flavonoids for treatment of symptoms in hemorrhoidal disease and after surgical intervention: a randomized clinical trial. Scientific Reports. 2020;10(1):8009. https://doi.org/10.1038/s41598-020-64772-0.
30. Romano L, Nervini A, Stia S, Schietroma M, Giuliani A. A combination of diosmin, hesperidin, and ruscogenin: Clinical effects in symptomatic hemorrhoidal disease. Formosan J Surg. 2022;55(4):129-33. https://doi.org/10.4103/fjs.fjs_79_22.
31. Miškulin M, Lalić Z, Dumić A, et al. New topical treatment of symptomatic internal hemorrhoids in a general practice setting. Journal of Health Sciences. 2018;8(3):148-53. https://doi.org/10.17532/jhsci.2018.454.
32. Belcaro G, Cesarone MR, Errichi B, et al. Pycnogenol treatment of acute hemorrhoidal episodes. Phytother Res. 2010;24(3):438-44. https://doi.org/10.1002/ptr.3021.
33. Zobeiri M, Parvizi F, Rahimi R, et al. Efficacy and safety of Hemoheal cream in patients with hemorrhoids: a randomized double-blind placebo controlled clinical trial. J Trad Chin Med. 2021;41(2):301-7. https://doi.org/10.1155/2021/6634115.
34. Pushpinder Skaram S. A randomized comparative study of micronised flavonoids and rubber band ligation in the treatment of acute internal haemorrhoids. Indian Journal of Surgery. 2004;66(5):281-5.
35. Andarkhor P, Sadeghi A, Khodadoost M, et al. Effects of Terminalia chebula Retz. in treatment of hemorrhoids: A double-blind randomized placebo-controlled clinical trial. Eur J Integr Med. 2019;30. https://doi.org/10.1016/j.eujim.2019.100935.
36. Meshikhes AW. Efficacy of Daflon in the treatment of hemorrhoids. Saudi Med J. 2002;23(12):1496-8.
37. Mahmoudi A, Seyedsadeghi M, Miran M, et al. Therapeutic effect of Achillea millefolium on the hemorrhoids; A randomized double-blind placebo-controlled clinical trial. J Herbal Med. 2023;39. https://doi.org/10.1016/j.hermed.2023.100657.
38. Yuksel BC, Armagan H, Berkem H, et al. Conservative management of hemorrhoids: A comparison of venotonic flavonoid micronized purified flavonoid fraction (MPFF) and sclerotherapy. Surg Today. 2008;38(2):123-9. https://doi.org/10.1007/s00595-007-3582-9.
39. Caetano AC, Cunha C, Arroja B, Costa D, Rolanda C. Role of a micronized purified flavonoid fraction as an adjuvant treatment to rubber band ligation for the treatment of patients with hemorrhoidal disease: A longitudinal cohort study. Annals of Coloproctology. 2019;35(6):306-12. https://doi.org/10.3393/ac.2018.09.18.
40. Dimitroulopoulos D, Tsamakidis K, Xinopoulos D, et al. Prospective, randomized, controlled, observer-blinded trial of combined infrared photocoagulation and micronized purified flavonoid fraction versus each alone for the treatment of hemorrhoidal disease. Clin Ther. 2005;27(6):746-54. https://doi.org/10.1016/j.clinthera.2005.06.016.
41. Squadrito F, Altavilla D, Oliaro Bosso S. Double-blind, randomized clinical trial of troxerutin-carbazochrome in patients with hemorrhoids. Eur Rev Med Pharmacol Sci. 2000;4(1-2):21-4.
42. Di Pierro F, Spinelli G, Monso G, et al. Clinical effectiveness of a highly standardized and bioavailable mixture of flavonoids and triterpenes in the management of acute hemorroidal crisis. Acta Bio-Medica : Atenei Parmensis. 2011;82(1):35-40.
43. Giannini I, Amato A, Basso L, et al. Flavonoids mixture (diosmin, troxerutin, hesperidin) in the treatment of acute hemorrhoidal disease: a prospective, randomized, triple-blind, controlled trial. Techniques in Coloproctology. 2015;19(6):339-45. https://doi.org/10.1007/s10151-015-1302-9.
44. Meshikhes AW. Daflon for haemorrhoids: a prospective, multi-centre observational study. Surgeon. 2004;2(6):335-8,61. https://doi.org/10.1016/S1479-666X(04)80032-5.
45. Giua C, Minerba L, Piras A, Floris N, Romano F. The effect of sucralfate-containing ointment on quality of life in people with symptoms associated with haemorrhoidal disease and its complications: The results of the Emocare Survey. Acta Biomed. 2021;92(1):1-7.