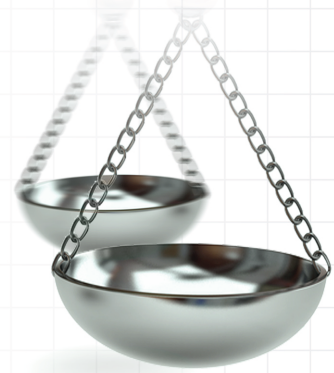
Systematic Review



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Micronized purified flavonoid fraction in the treatment of hemorrhoidal disease

Philippe Godeberge*[,1], Parvez Sheikh[2], Varut Lohsiriwat[3], Abel Jalife[4] & Yury Shelygin[5]

[1]Institut Mutualiste Monsouris, Paris, France
[2]Department of Colorectal Surgery, Saifee Hospital, Mumbai, India
[3]Division of Surgery, Department of Colorectal Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[4]Center of Medical Specialties & Investigation of Mexico, Mexico City General Hospital Surgery, Mexico City, Mexico
[5]State Scientific Center of Coloproctology, Ministry of Health of Russian Federation, Moscow, Russia
*Author for correspondence: Tel.: +33 156 616 301; p.godeberge@orange.fr

Hemorrhoidal disease (HD) is common in adults. Treatment is largely conservative, although more invasive procedures may be required. Venoactive drugs such as micronized purified flavonoid fraction (MPFF) are widely used, but a recent and comprehensive review of supporting evidence is lacking. In acute HD, MPFF can reduce HD symptoms such as bleeding, pain, anal discomfort, anal discharge and pruritus. In patients undergoing surgery, postoperative adjunct MPFF consistently reduces pain, bleeding duration and use of analgesia. MPFF treatment is appropriate and effective both as a first-line conservative treatment and as a postoperative adjunct treatment. MPFF reduces the duration of hospital stay following surgery, facilitating a return to normal activity and improving quality of life. MPFF may also prevent HD recurrence.

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Overview

Hemorrhoidal disease (HD) is a common problem for adults, although estimates of its prevalence vary [1–3]. In a colonoscopy-based screening program for colorectal cancer in adults, the prevalence of HD diagnosed by colorectal surgeons was 38.9%, though only 44.7% of these individuals complained of symptoms [3]. There are two types of HD: internal and external. Internal HD affects the anal cushions located above the dentate line in the anal canal, and is graded according to severity based on the extent to which the diseased anal cushions (hemorrhoids) descend, or prolapse, into the anal canal or exit the anus. In contrast, external HD affects the tissues and blood vessels beneath the skin surrounding the anus.

In most patients, the prolapse is not sufficient to require surgery or an outpatient procedure (e.g., rubber band ligation [RBL] or sclerotherapy), and conservative medical treatment is therefore an important first option in managing HD. This includes diet and lifestyle modification to increase fiber and fluid intake, increased physical activity, and avoidance of constipation and straining during defecation. Topical treatments, including creams containing anesthetics, corticosteroids and anti-inflammatory drugs, may be used to provide some relief for HD. Several venoactive drugs have been used to treat HD, but the clinical evidence for the efficacy of many of these treatments is unclear.

However, micronized purified flavonoid fraction (MPFF), which consists of micronized diosmin (90%) and other active flavonoids (hesperidin, diosmetin, linarin and isorhoifolin; 10%), has shown clinical efficacy in the treatment of chronic venous disease [4] and HD [5–7]. Diosmin, diosmetin, linarin and isorhoifolin are synthesized from hesperidin, which is extracted from *Citrus aurantinum* var *amara*, a type of small, bitter, immature orange. Experimental studies showed that MPFF is more potent than pure diosmin and each flavonoid present in MPFF contributes synergistically to its pharmacological effect [8,9]. Consistent with this synergy, MPFF increases venous tone, has free-radical scavenging properties, reduces capillary permeability (edema), improves lymphatic drainage,

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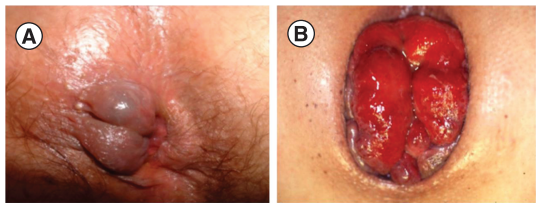

Figure 1. Hemorrhoids. (A) External hemorrhoids. **(B)** Internal prolapsed hemorrhoids.

reduces blood viscosity and/or erythrocyte aggregation, and acts on the inflammatory processes in veins by decreasing the expression of adhesion molecules by neutrophils and monocytes [10]. In this article, we review and summarize the clinical evidence for the efficacy of MPFF in the treatment of acute HD (appearing within the past 7 days [11]), and as an adjunct following hemorrhoidectomy or outpatient procedures. We also discuss the acceptability of MPFF and its position in current guidelines [12–16].

Hemorrhoid anatomy & pathophysiology

In their normal state, internal hemorrhoids (IHs) are anal cushions located in the anal canal as 2–4 (usually 3) thickened pads of blood vessels and fibrous connective tissue stroma that bulk into the lumen. IHs are surrounded by connective tissue and muscular fibers that issue from, and anchor them to, the internal sphincter. The subcutaneous hemorrhoidal plexus or external hemorrhoid (EH) is a small venous plexus under the skin at the margin of the anus. This plexus consists mainly of small interlacing veins separated by fibrous septa, giving the EH a honeycomb-like structure.

The many anastomoses in these structures make hemorrhoidal tissues susceptible to blood pooling. An imbalance between the arterial inflow and venous drainage has been proposed to explain the enlargement of the venous sinuses in IHs [17].

The exact pathophysiology of HD development remains undetermined, and the likely causes have been described in detail elsewhere [18]. These causes appear to involve mechanical injury to the anal cushions, venous stasis, vascular abnormalities within the hemorrhoidal plexus or at the anorectal region, and tissue inflammation [18]. Inflammatory reactions are especially evident in prolapsed or thrombosed lesions [18,19]. Inflammation could thus play a role in HD pathogenesis or in the aggravation of acute hemorrhoidal symptoms [20]. However, inflammatory changes in hemorrhoids may be a result of inflammatory responses to thrombosis in prolapsed tissue, mechanical injury to the anal cushions or venous stasis.

The signs & symptoms of HD

HD refers to all the acute and chronic symptoms related to the anal cushions (or IHs) or to EH. HD is characterized by several different symptoms, and there is often little correlation between HD anatomy and clinical signs. Acute signs (appearing within the last 7 days [11]) involve mostly external HD, while chronic signs (lasting longer than 7 days) generally involve only internal HD.

Acute symptoms usually start with continuous pain and may be accompanied by pruritus, rapidly followed by the appearance of a bluish lump located on the anal margin (Figure 1A). Swelling is the only clinical sign, and usually occurs suddenly. Usually, the pain spontaneously disappears within a few days, whereas edema and swelling resolve more slowly. Skin erosion may lead to the spontaneous evacuation of a clot and some bleeding. The swelling may gradually lead to the formation of a persistent fold of skin, known as a skin tag, which may be asymptomatic or cause some discomfort or soiling.

Chronic symptoms of internal HD typically include anal bleeding during defecation, which is painless and stops spontaneously at the end of straining to defecate. Because of arterialization of the venous blood, it is generally bright red, appears at the end of the evacuation, varies in volume, and may pulsate. Spontaneous bleeding and soiling of the clothing are signs of anatomically advanced HD.

Prolapse is the descent and externalization of the IH plexi (i.e., anal cushions; Figure 1B). Prolapse is usually not painful; thus, pain may indicate an anal fissure, suppuration or thrombosis. Extensive and persistent prolapse can lead to mucous discharge, pruritus and maceration, and can cause spontaneous bleeding between defecations.

Risk factors for HD

Risk factors for HD have been reported to include inadequate dietary fiber, chronic straining during defecation, prolonged sitting on the toilet, obesity, increasing age, pregnancy and a sedentary lifestyle [21–24]. Although recent

studies found significant relationships between HD and constipation [25–27], earlier studies found that diarrhea rather than constipation was linked to HD [2,22,28]. Other reported risk factors are depression [23], and a history of childbirth [22,27]. In younger individuals (aged <50 years), spicy diet, alcohol intake and reduced physical activity could lead to acute hemorrhoids [26]. In other studies, no clear correlation has been found between HD and education level, alcohol consumption, diabetes mellitus, hypertension, fat intake or physical activity [3,22].

The role of MPFF in the treatment of HD

The mode of action of MPFF

MPFF is a flavonoid-based venoactive preparation for oral use, composed of 90% micronized diosmin and 10% other active flavonoids (hesperidin, diosmetin, linarin and isorhoifolin), all of which contribute to its pharmacological effects [8,9]. It has a variety of significant anti-inflammatory, antioxidant and venoprotective actions, which form the basis of its beneficial clinical effects in HD [29–31]. In several animal models of venous hypertension, MPFF reduced venous inflammation by inhibiting leukocyte rolling, adhesion and migration [8,32,33]. In a chronic venous hypertension model induced by femoral arteriovenous fistula, MPFF decreased granulocyte and macrophage infiltration into the venous valves, thereby preventing their degeneration [34,35]. It has also been shown to inhibit the synthesis of prostaglandins and inflammatory mediators, including prostaglandin E_2, prostaglandin $F_{2\alpha}$ and thromboxane B_2 in rat granulomas [36]; to exhibit oxygen radical scavenging activity [37]; to reduce histamine-, bradykinin- and leukotriene B_4-induced ischemia [38]; and to protect endothelial cells from lipid peroxidation [30]. MPFF improves venous tone and lymphatic drainage by modulating noradrenergic signaling and reducing norepinephrine metabolism [39,40]; it also significantly reduces capillary hyper-permeability and improves capillary resistance in patients with abnormal capillary fragility, leading to further improvement of microcirculation [41,42]. Because venous pathologies and diminished venous return play prominent roles in HD, these actions of MPFF provide the rationale for its use in treating HD.

Clinical efficacy of MPFF

Patients with internal HD essentially have two main symptoms – bleeding and prolapse – but may also have minor symptoms of itching and pain, as well as complications of thrombosis, irreducibility and strangulation. Medical management cannot cure prolapse, irreducibility or strangulation, but bleeding can be controlled to a large extent by targeted medical therapy, along with supportive treatment that includes laxatives and dietary adjustment. Only 5–10% of patients will require hemorrhoidectomy because they have failed or are unable to tolerate conservative management [43]. Since most patients do not have prolapse to such an extent that necessitates surgery, medical treatment plays an important role in the management of HD.

We undertook a systematic literature search to identify articles investigating the clinical efficacy of MPFF treatment for HD. This systematic review was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [44]. We conducted the search using two online biomedical databases (Embase® and MEDLINE®) on 15 July 2020. Search terms included hemorrhoid, phlebotonic, flavonoid, bioflavonoid, hesperidin, diosmin, Daflon, MPFF and micronized purified flavonoid fraction, as well as synonyms and brand names for MPFF. There was no restriction on language or publication date.

After removing duplicates from the retrieved records, 60 publications were selected for further screening (see PRISMA flow diagram; Figure 2). Only studies comparing MPFF (alone or in combination with surgery or another procedure) versus placebo or no treatment were included; reviews and studies comparing MPFF versus an active compound (for acute HD), or versus surgery or procedures (for chronic HD) were excluded. Thirteen publications were identified for further analysis, and full texts were obtained for all selected articles. To identify additional potentially relevant trials, a manual search was conducted using a Servier internal database (Pharmanet), and a further four studies were identified. A total of 17 publications were included in the systematic literature review (see Supplementary Table 1 in the online supplementary information).

Clinical efficacy of MPFF in the management of acute HD

For many of the drugs currently used to treat HD, evidence of their effectiveness is weak. However, several placebo-controlled clinical trials have investigated the efficacy of MPFF in the management of acute hemorrhoids. In total, we identified eight studies that investigated MPFF treatment in acute HD patients. In 1992, Godeberge assessed the effectiveness of MPFF compared with placebo in 120 patients with an acute episode of hemorrhoids, and found that a dose of 1000 mg/day for 60 days had significant benefits [45,46]. Acute episodes were significantly less

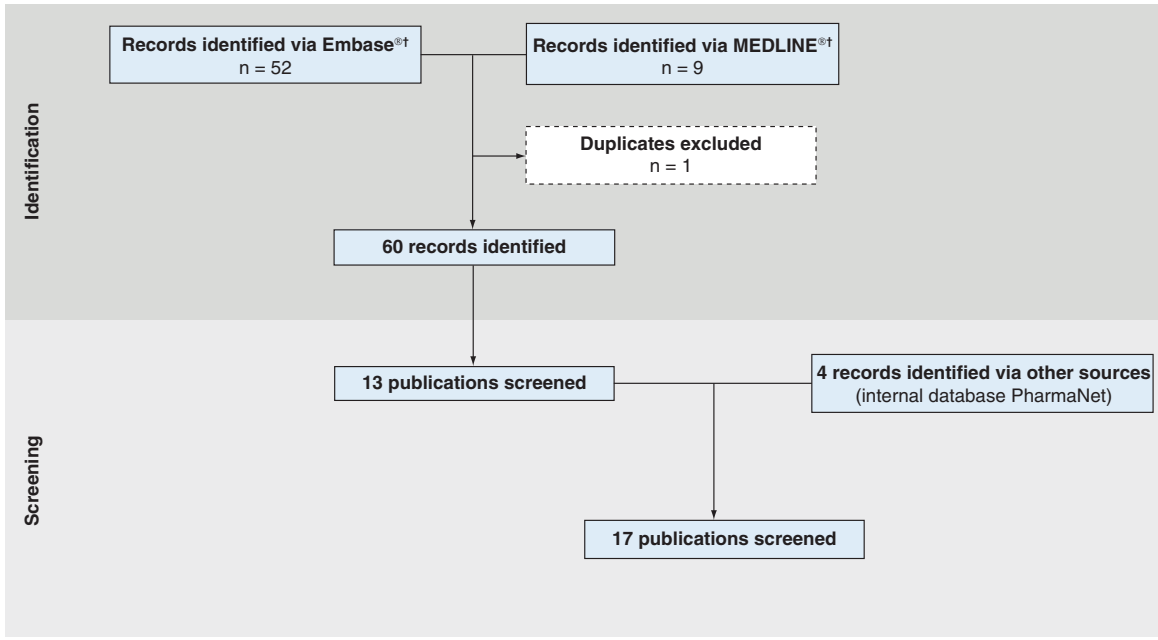

Figure 2. PRISMA flow diagram.
†via ProQuest®.

frequent, shorter and milder in the MPFF group ($p < 0.01$). The double-blind controlled period was followed by an open-label long-term tolerability and efficacy study in which 20 patients received MPFF for about 6 months.

In a randomized, placebo-controlled study in 100 patients with acute HD (grades I–III), also published in 1992, MPFF was used at a dosage of 6000 mg/day for 4 days, then 2000 mg/day for 10 days [45,46]. The overall improvement in symptoms with MPFF was significant at day 4 when compared with placebo ($p < 0.01$), but the difference between groups was not significant at day 14; this may be due to spontaneous improvement in symptoms with time.

Vajrabukka *et al.* compared the effects of MPFF (3000 mg/day for 4 days then 2000 mg/day for 3 days) versus placebo in patients with acute hemorrhoidal episodes. There was a significant difference in favor of MPFF in the evolution of discharge ($p = 0.038$), as well as beneficial effects on other symptoms that did not achieve statistical significance [47]. Using a similar treatment regimen, Panpimanmas *et al.* also found improvements in symptoms that were in favor of MPFF, but without reaching statistical significance [48].

In contrast, in another double-blind, placebo-controlled study in patients with acute HD, MPFF (3000 mg/day for the first 4 days, and 2000 mg/day for the next 3 days) was associated with significantly greater improvements in the anatomic lesions between baseline and day 7 versus placebo ($p < 0.001$) [7]. Moreover, the duration and intensity of the current attack compared with previous attacks were lower with MPFF than with placebo ($p < 0.001$ for both). Three-times more patients in the MPFF group (77.5 vs 24.5% for placebo) considered the duration of the current attack to be shorter, and twice as many (89.8 vs 38.8%) considered the current attack to be less intense. The signs and symptoms of anal bleeding, anal discomfort, pain and anal discharge in the MPFF group improved to a significantly greater degree than in the placebo group, beginning from day 2 onwards. Results were similar in another study employing the same 7-day dosing regimen, in which MPFF significantly reduced the frequency and intensity of bleeding, pain and edema [49]. Collectively, these results suggest that this MPFF regimen is effective for use in day-to-day clinical practice for the management of acute HD. MPFF tablets of either 500 or 1000 mg can be used [50].

Recurrent bleeding is a common problem in HD, and MPFF can decrease the incidence of relapse bleeding after an acute attack. In a randomized, double-blind study, treatment with MPFF was compared with placebo in 100 outpatients who presented with acute internal HD of less than 3 days duration [51]. Patients were randomized to receive MPFF (n = 50; 3000 mg/day for 3 days, followed by 2000 mg/day for 4 days) or placebo (n = 50). After 3 days of treatment, acute bleeding had stopped in significantly more patients who received MPFF (80%)

than in those who received placebo (38%; $p < 0.01$). The mean (±standard deviation) duration of acute bleeding was 4.9 ± 1.6 days with MPFF treatment, which was 2.1 days less than in patients who received placebo. Over a subsequent 83-day period in patients whose bleeding had stopped after 7 days, continued treatment with MPFF 1000 mg/day prevented relapse in 64% of patients compared with 40% who received continued treatment with placebo ($p < 0.05$).

Together, these results show that, after a 7-day regimen of high-dose MPFF (3000 mg/day reducing to 2000 mg/day) to treat an acute attack, a lower 'maintenance' dose of 1000 mg/day for 60–90 days may be beneficial for patients in whom recurrent hemorrhoids is a problem.

Venoactive drugs may be used in combination with other drugs in patients with symptoms of HD. A recent study demonstrated that the addition of MPFF to topical hemorrhoid treatment was associated with improvements in bleeding and health-related quality of life in patients with acute hemorrhoids. Patients were randomized to receive MPFF (n = 43; 3000 mg/day for 4 days, followed by 2000 mg/day for 3 days) in combination with topical antihemorrhoidal treatment, or topical treatment alone (n = 45). Two weeks after the end of treatment, the bleeding rate was significantly improved in the combination treatment group versus the topical-only group ($p = 0.045$). Additionally, improvements in the mean total Short Form-12 score, as well as in physical and general health domains, were significantly greater in the MPFF group than in the placebo group ($p = 0.048$, $p = 0.039$ and $p = 0.036$, respectively) [52].

Cospite reported that the consumption of analgesic tablets was significantly lower with MPFF than with placebo ($p < 0.013$), and that the use of topical analgesics was also significantly lower in the MPFF arm at days 3 ($p < 0.041$) and 7 ($p < 0.001$) [7]. The use of bulk laxatives combined with MPFF or placebo treatment has also been examined in patients with grade I or grade II HD. Swelling and congestion significantly improved by day 4 in the MPFF group ($p < 0.01$), but not in the placebo group [53].

Clinical efficacy of MPFF as an adjunct to surgical & nonsurgical procedures

Several clinical trials have investigated the benefits of MPFF treatment in combination with surgical or nonsurgical techniques to treat HD. From our systematic search of the literature, we identified ten studies that investigated MPFF treatment in patients who underwent surgery or other procedures such as RBL, infrared photocoagulation (IPC) or sclerotherapy.

MPFF treatment as an adjunct to surgical procedures

Ho *et al.* assessed the incidence of secondary postoperative bleeding within 14 days of Milligan–Morgan hemorrhoidectomy in 114 patients with grade IV hemorrhoids [54]. In the MPFF-treated group, MPFF was administered for 7 days at daily doses of 3000 mg for the first 3 days and 1500 mg for the next 4 days. Postoperative bleeding was observed in 0.9% of patients in the MPFF group and 6.1% of patients in the control (no MPFF) group ($p = 0.03$), indicating that MPFF reduces the risk of this complication. It is worth noting that the venotonic effects of MPFF could minimize only secondary venous bleeding after hemorrhoidectomy, but not arterial bleeding from the pedicle of excised hemorrhoids.

Lee *et al.* assessed the effects of MPFF compared with placebo on bleeding, pain, purulent discharge, and anal discomfort after closed hemorrhoidectomy [55]. Patients in the active treatment group (n = 27) received MPFF after surgery (3000 mg/day for 4 days then 2000 mg/day for 3 days). Eighteen days after surgery, rates of bleeding (11.1 vs 77.8%), pain (33.3 vs 74.1%) and purulent discharge (14.8 vs 63.0%) were significantly lower in the MPFF group than in the control group ($p < 0.005$ for all between-group comparisons). Rates of anal discomfort were not significantly different. These results suggest that postoperative MPFF therapy reduces the severity of symptoms, including bleeding, and shortens the recovery period.

Colak *et al.* assessed the severity of pain with or without MPFF treatment after hemorrhoidectomy using a 10-point visual analog scale [56]. Other outcomes included analgesic use, and overall treatment satisfaction on a scale of 1 (poor) to 4 (excellent) at 7 days after surgery. The study included 112 patients with grade III–IV chronic HD randomly allocated to receive MPFF (n = 56, 3000 mg/day for 4 days then 2000 mg/day for 3 days) or no add-on treatment (n = 56). On days 2, 3 and 7 after surgery, pain severity, the need for analgesics, and the number of patients requiring analgesia were significantly lower in the MPFF group than in the control group ($p < 0.05$). Treatment satisfaction at 1 week after hemorrhoidectomy was higher in the MPFF group: 'good' or 'excellent' ratings were selected by 89.3% of the MPFF group versus 64.3% of the control group, and there were no 'excellent' ratings in the control group.

La Torre *et al.* evaluated MPFF for relief of symptoms in 50 patients who underwent a Milligan–Morgan hemorrhoidectomy [57]. Patients were randomized to receive MPFF (n = 25) or no additional treatment (n = 25), with both groups receiving analgesic treatment for 5 days. Patients in the MPFF group received a nonstandard dosage regimen of 2000 mg/day for 10 days followed by 1000 mg/day for 20 days. On the third day after surgery, intensity scores for bleeding, pain, tenesmus and pruritus were significantly lower in the MPFF group than in the control group ($p < 0.0001$). Smaller but still significant differences were also observed on day 60 after surgery ($p < 0.001$).

Mlakar *et al.* enrolled consecutive patients with grade III–IV HD undergoing closed hemorrhoidectomy over a period of 2 years [58]. Patients were randomized to MPFF 3000 mg/day for 5 days plus standard analgesic therapy, or standard analgesic therapy alone. During the first week after the procedure, the duration of self-assessed bleeding on defecation was significantly shorter for the MPFF treatment group (3.5 days) than for the control group (4.7 days; $p < 0.05$), with no major complications in either group.

Finally, Mlakar and Kosorok compared treatment outcomes in patients who underwent stapled hemorrhoidopexy with or without adjunctive MPFF treatment (3000 mg/day for 5 days) after the procedure [59]. On day 7 after the procedure, there were no significant differences between the two groups in the duration of bleeding, the severity of pain or analgesic consumption. One possible reason for the lack of differences between the groups was that pain intensity was low in both groups: the stapled sutures were positioned above the sensitive area of the anal canal, leaving the IH plexus intact.

All of these studies reported that treatment outcomes in patients undergoing hemorrhoidectomy were significantly better for those who received MPFF than those who did not. These results indicate that MPFF is effective in the relief of bleeding and the main symptoms occurring in patients after hemorrhoidectomy.

MPFF treatment as an adjunct to nonsurgical procedures

MPFF has also been studied as an adjunct to nonsurgical procedures, including IPC, RBL and sclerotherapy, in patients with internal HD [60–62]. Dimitroulopoulos *et al.* [61] evaluated postprocedural bleeding in 351 patients with grade I–III hemorrhoids treated with IPC plus MPFF (3000 mg/day for 5 days), MPFF only or IPC only (117 patients each). The IPC plus MPFF group had significantly more patients without bleeding during defecation at 5 days after the procedure (74.8%) than either the MPFF-only group (59.6%, $p = 0.023$) or the IPC-only group (55.6%, $p = 0.004$). These results demonstrate that MPFF provides a significant benefit to patients treated with IPC.

Ho *et al.* evaluated treatment with MPFF, RBL and laxative (ispaghula husk; LAX) in 162 patients with grade I bleeding hemorrhoids [62]. Patients received LAX only (n = 66), LAX plus RBL (n = 57) or LAX plus MPFF (n = 39; 3000 mg/day for 5 days then 1000 mg/day for 21 days). The bleeding stopped earliest in the LAX/MPFF group (at a mean of 3.9 days, vs 5.6 days in the LAX/RBL group and 10.6 days in the LAX-only group). The difference between the LAX/MPFF and LAX-only group was statistically significant ($p = 0.043$), but differences between other group pairs were not. Groups also did not differ significantly in the rate of recurrence of hemorrhoid symptoms after 6 months of follow-up.

Shelygin *et al.* assessed the duration and severity of pain and discomfort after sclerotherapy in 124 patients with grade I–III hemorrhoids treated with or without adjunctive MPFF [60]. In the MPFF group (n = 63), patients received MPFF 1000 mg/day starting at 7 days before sclerotherapy, then received 2000 mg/day for 3 days and 1000 mg/day for 4 days after the procedure. The control group received no MPFF. On day 3 after sclerotherapy, pain was reported by 3% of patients in the MPFF group, versus 21% in the control group ($p < 0.001$), whereas discomfort was reported by 61% of patients in the MPFF group and 73% of patients in the control group (not significant). On day 7 after the procedure, no pain was reported in either group, but discomfort persisted in 7% of patients in the MPFF group and 37% of patients in the control group ($p < 0.001$). After 14 days, slight discomfort remained in 11% of patients of the control group. These findings suggest that MPFF treatment resulted in a statistically significant relief of pain by day 3 and of discomfort by day 7 after sclerotherapy.

Meta-analyses of MPFF treatment in HD

Several systematic reviews and meta-analyses have also found evidence for the efficacy of flavonoids, MPFF and other venoactive drugs in the treatment of HD [5,63,64]. Alonso-Coello *et al.* investigated various flavonoid treatments (including MPFF) for hemorrhoids and found that these treatments reduced the risk of persistent symptoms by 58% (relative risk: 0.42; 95% CI: 0.28; 0.61), and showed an apparent reduction in the risk of bleeding, persistent

pain, itching and recurrence [63]. A Cochrane meta-analysis found that venoactive treatments were associated with statistically significant improvements in bleeding and overall symptoms in acute HD, and improvements in bleeding after hemorrhoidectomy [64]. The odds ratio for bleeding in acute HD was 0.12 (95% CI: 0.04; 0.37; $p < 0.001$) favoring MPFF over placebo [64]. In a study by Aziz *et al.*, the risk ratio for reducing bleeding was 1.46 (95% CI: 1.10; 1.93; $p = 0.008$) in favor of MPFF treatment [5].

Recently, a systematic review and meta-analysis of randomized controlled clinical trials investigating MPFF treatment, specifically for acute HD and as an adjunctive treatment after hemorrhoidectomy, has been completed [11]. Quantitative analysis of pooled results indicated that 7 days of MPFF treatment was associated with a 90% reduction in the risk of bleeding ($p < 0.001$), significant reductions in discharge and leakage ($p < 0.001$) and a trend toward a reduction in pain ($p = 0.06$). Consistent and statistically significant quantitative evidence was also found for overall improvement in symptoms, as assessed by patients and investigators ($p < 0.001$).

Safety profile of MPFF

MPFF is extracted from a natural source (i.e., citrus fruit) and is generally well tolerated. Although adverse drug events (ADEs) have been monitored in most clinical trials investigating MPFF as HD treatment, no studies have been designed specifically to evaluate the safety and tolerability of MPFF. Some studies have cited infrequent mild gastrointestinal distress [7,49,51,55], whereas others have reported no adverse effects [46,47,54,56,57]. Overall, the frequencies of ADEs in groups treated with MPFF or with placebo appear to be similar. In two meta-analyses, results for MPFF were pooled with results for other flavonoids or other venoactive drug treatments; these studies therefore do not provide MPFF-specific safety information [63,64]. Nevertheless, in both studies, no significant differences in ADEs were found between the treatment and placebo groups, with a risk ratio of 1.22 (95% CI: 0.69; 2.15) in one study [63] and a risk difference of 0.00 (95% CI: -0.04; 0.04) in the other [64]. A recent pooled analysis of MPFF treatment in HD found no difference in the risk of ADEs between MPFF and control groups (risk ratio 0.62; 95% CI: 0.30; 1.27; $p = 0.71$) [5]. It should be noted that most of the studies used in these analyses were less than 3 months in duration; thus, the safety and tolerability of longer-term MPFF treatment are unknown.

Pharmacokinetic and toxicology studies in animals also indicate that MPFF has a good safety profile [65]. MPFF has a very high 50% lethal dose (LD_{50}: >3 g/kg) and is not mutagenic; additionally, 26 weeks of high-dose administration in mice at 35-times greater than the therapeutic dose in humans produced no detectable effects on fertility [65].

Data on MPFF treatment during pregnancy or in breastfeeding women are limited [66], and its use in these settings cannot be recommended.

MPFF in HD treatment guidelines

Although many national societies and associations have published guidelines for the treatment of HD, there are no international guidelines. The American Society of Colon and Rectal Surgeons recommends medical therapy as first-line treatment for Goligher's grade I–III hemorrhoids [14], citing the Cochrane review of Perera *et al.* and the meta-analysis of Alonso-Coello *et al.* as evidence for the efficacy of venoactive drugs and flavonoids in the treatment of HD [63,64]. The American Gastroenterological Association recognizes MPFF as the pharmacological treatment of reference, citing its efficacy in reducing the symptoms and signs of HD [15]. The French National Society of Coloproctology recommends MPFF (1000–2000 mg/day) as a short-term treatment for the symptoms of IHs (pain, prolapse and bleeding; grade B recommendation) [12].

In its clinical practice guidelines for the management of hemorrhoids, the Association of Colon & Rectal Surgeons of India (ACRSI) recommends MPFF as a first-line treatment for grade I–II and selected/minor grade III hemorrhoids [13]. MPFF treatment is strongly recommended (grade A), with an evidence level of 1 (indicating high-quality evidence from well-performed randomized trials). The recommended dosage of MPFF for the treatment of acute bleeding is 3000 mg/day for 4 days, followed by 2000 mg/day for 3 days. Thereafter, a maintenance dose of 1000 mg/day for at least 2 months is advised.

The Russian Association of Coloproctology gives MPFF a grade B (evidence level 1a) recommendation for the treatment of HD in its clinical guidelines for the diagnosis and treatment of hemorrhoids [16]. For hemorrhoid pain, systemic treatment with MPFF is recommended in combination with non-narcotic analgesics, local anesthetics and topical combination treatments. MPFF treatment is also recommended for thrombosed hemorrhoids (with or without inflammation in the surrounding soft tissues) and hemorrhoidal bleeding.

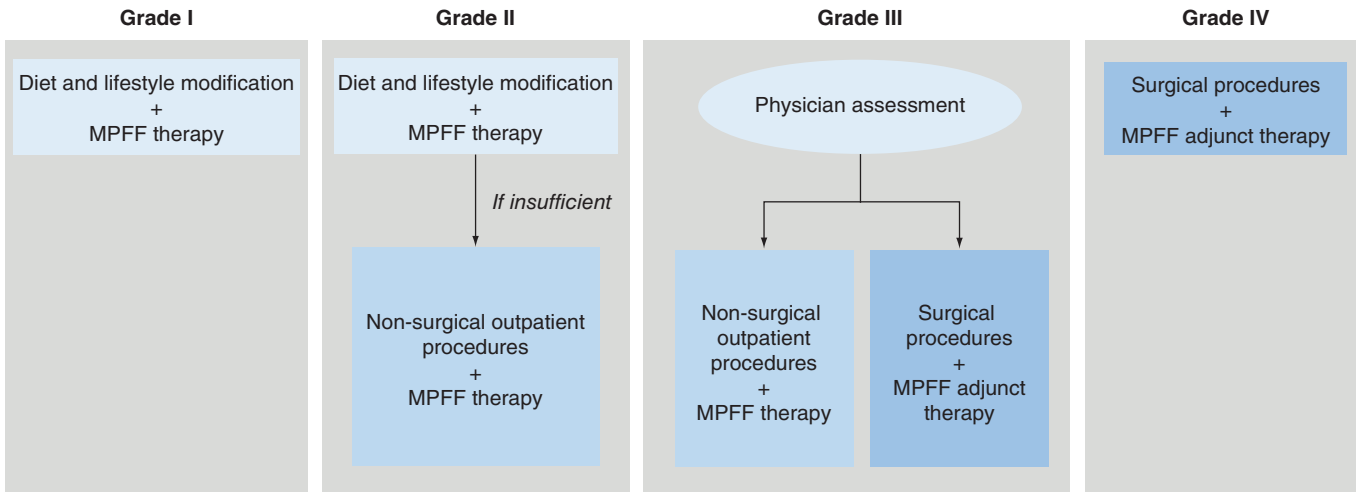

Figure 3. Management of hemorrhoidal disease with micronized purified flavonoid fraction.
MPFF: Micronized purified flavonoid fraction.

Conclusion

Based on the available clinical evidence, current national guidelines and extensive clinical experience in treating HD patients, it is our collective opinion that oral MPFF treatment is appropriate and effective for all grades of HD (Figure 3). MPFF can be administered as a first-line treatment, in combination with diet (increased fiber and fluid intake) and lifestyle modifications, for acute grade I/II HD; or as an adjunctive treatment to aid recovery from hemorrhoidectomy or outpatient procedures, which are usually performed for patients with grade II–IV HD.

In acute HD, bleeding can be effectively treated with MPFF at a dosage of 3000 mg/day for 4 days followed by 2000 mg/day for 3 days. A maintenance dose of 1000 mg/day could be recommended for a period of up to 2 months or more, at the physician's discretion [63,64]. MPFF treatment may also reduce pain, itching and recurrence. In patients undergoing open surgery, minimally invasive procedures or instrumental techniques to treat hemorrhoids, postprocedural adjunctive MPFF consistently reduces the duration of bleeding, pain, hemorrhoidal symptoms and the requirement for analgesics. These benefits could help patients return to normal activity sooner, resulting in improved quality of life.

In practice, most patients with HD are successfully managed with conservative measures, and do not need a medical procedure or surgery. However, even patients with more advanced disease can benefit from MPFF treatment after an invasive procedure to remove prolapsed hemorrhoids. This aspect of MPFF treatment should not be overlooked. Thus, MPFF plays an important role in the arsenal of medical treatment options available for the direct treatment of HD.

Future perspective

HD is a common medical problem affecting nearly 40% of adults. HD occurs as the consequence of several pathological mechanisms: inflammation, edema, circulatory abnormalities, alteration of the suspension fibers and mechanical trauma [3,17,18]. There are two types of HD: internal HD and external HD. Internal HD occurs when IHs become swollen and 'slide' toward the anus. The classification of internal HD is based on the degree of prolapse, with grade I indicating no prolapse, and grade IV indicating a permanent prolapse outside the anus. The symptoms of internal HD include bleeding, intermittent or permanent prolapse, and sometimes soiling; there is usually no pain, except in high grade HD and in rare cases of internal thrombosis. Symptoms of external HD include pain, permanent swelling and occasionally a little bleeding as a consequence of an expulsion of the clot through skin ulceration. Some patients may present with both internal and external HD, simultaneously or sequentially. Therefore, HD symptoms may not only vary between patients, but also in the same patient at different times during the day.

Diet and lifestyle modifications (e.g., adoption of a diet that includes adequate fiber and fluid intake, increased physical activity, avoidance of constipation and avoidance of straining during defecation) are among the conservative

treatment options for HD. Topical HD treatments include creams containing anesthetics or corticosteroids, and anti-inflammatory drugs. Venoactive drugs (phlebotonics), including MPFF, are also used in HD treatment [4–7].

Despite the prevalence and social significance of HD, it is unlikely that there will be any fundamental changes in treatment strategies in the coming years or even decades. Innovations of significance in the treatment of HD are now mainly procedural. Several minimally invasive surgery techniques (hemorrhoidal artery ligation with or without recto-anal repair and stapling hemorrhoidopexy) [67–71] as well as various energy-based therapies (LigaSure™, Harmonic Scalpel™, radiofrequency [Rafaelo®] and laser treatments) [72–75] have been developed over the last 25 years, and several well-designed randomized trials have been performed to compare these therapies. However, there has been no further innovation in strategic options for HD treatment.

Some possible reasons for the lack of innovation in HD treatment could be a lack of knowledge about the natural history of HD, the purely symptomatic nature of therapy, and the fact that most patients with HD need only medical treatment. Moreover, despite an impressive list of medicinal agents currently available for treating HD, only flavonoids have a systemic effect and influence, at least indirectly, on the pathogenesis of HD [63]. At the same time, the real evidence base for the efficacy of conservative therapy in HD is, in general, currently relevant only for MPFF. Further, studies have mostly focused on surgical techniques to treat HD, without significantly advancing our knowledge of the pathophysiology of HD. Therefore, scientific research in this area, from clinical presentation to postoperative management, is extremely relevant.

First, a better understanding of the natural history of HD through longitudinal research is needed to identify a more effective management strategy, as HD is most often benign, even when it significantly affects quality of life. The introduction of a specific score will allow a comparison of therapeutic strategies in the future.

Second, it is necessary to develop effective individualized therapeutic regimens that involve the use of MPFF for treating several types of HD, and introduce them into clinical practice.

Third, it is critical to develop a unified concept of classification, clinical manifestations, and therefore, treatment of HD; currently, all the classifications used in clinical practice are empirical, and by no means reflect all of the clinical and morphological forms of HD. Moreover, existing classifications do not follow the principles of modern typology, hierarchy and intersection. There are also no unified, validated scales for assessing the quality of life of patients with HD. Further, differences in the healthcare systems and pricing policies of insurance and medical companies make it difficult, even within the European Union, to estimate the cost of HD treatment. These challenges make it impossible to conduct a comprehensive meta-analysis, to formulate clinical guidelines of a high level of evidence, and to standardize approaches in the diagnosis and treatment of HD.

Overall, the lack of unified teaching on HD is currently an obstacle to the development of new therapies and treatment standards for HD. Scientific research and engagement by leading coloproctological centers in different countries, and active participation of specialists across several countries, can serve to educate the medical community regarding the major challenges in this area. This, in turn, will promote standardization of terminology, and lead to the adoption of a single global consensus on the classification, diagnosis and treatment of various forms of HD.

Executive summary

Overview

- Hemorrhoidal disease (HD) is prevalent in about 40% of adults.

The signs & symptoms of HD

- Internal HD occurs when the anal cushions become swollen and prolapsed. External HD involves the external perianal vasculature and the tissues lining the anal canal; the local occurrence of a clot (thrombosis) is associated with symptoms of pain, pruritus, and, very occasionally, bleeding.

Risk factors for HD

- Risk factors for HD include constipation, inadequate dietary fiber, diarrhea, obesity, increasing age, pregnancy and a sedentary lifestyle.

The role of MPFF in the treatment of HD

- Conservative HD treatments include dietary measures to avoid constipation, venoactive drugs and surgery.
- A systematic review of the literature indicates that micronized purified flavonoid fraction (MPFF) can reduce bleeding, pain, anal discomfort, anal discharge and pruritus in patients with acute HD, and can reduce pain, bleeding duration and the requirement for analgesics in patients undergoing surgery for HD.
- MPFF has been shown to be effective and well tolerated in all grades of HD, either as a first-line treatment in combination with dietary modifications, or as an adjunct in patients recovering from hemorrhoidectomy.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2021-0038

Author contributions

All authors were involved in the conception of the paper and commissioning the literature search, reading and revising the manuscript drafts, and approval of the final manuscript.

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