REVIEW

DOI: http://dx.doi.org/10.15403/jgld-6306

The Combination of Fluocinolone Acetonide and Ketocaine Hydrochloride in the Conservative Management of Symptomatic Hemorrhoidal Disease: An Overview of Preclinical and Clinical Data

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Received: 26.05.2025
Accepted: 23.07.2025

ABSTRACT

Hemorrhoidal disease (HD) is a prevalent anorectal disorder that affects up to 36% of the general population. It is characterized by symptomatic enlargement and displacement of anal cushions, frequently associated with pain, bleeding, and reduced quality of life. The pathophysiology of HD includes vascular congestion, venous stasis, and vascular dilatation, promoted by increased nitric oxide activity. Inflammatory responses are considered crucial in HD, with NF-κB playing a major role. Treatment strategies for HD vary from conservative approaches to office-based and surgical interventions. Conservative therapies, such as topical agents and flavonoid-based systemic treatments, serve as the mainstay of low-grade HD management, while invasive procedures are reserved for refractory cases. Topical formulations containing fluocinolone acetonide (FLA) and ketocaine hydrochloride (KH) combine anti-inflammatory and anesthetic effects, providing rapid and sustained relief from pain, itching, and inflammation. FLA exerts potent anti-inflammatory effects by inhibiting NF-κB and induces vasoconstrictive activity by reducing nitric oxide levels, while KH provides localized analgesia by blocking sodium channels. Collectively, these agents mitigate vascular congestion, inflammation, and HD symptoms. Clinical evidence supports the efficacy of this combination in alleviating acute symptoms, reducing recurrence, and improving patient outcomes. The FLA/KH formulation provides targeted local action with minimal systemic absorption and predominantly mild and transient adverse events. Treatment with FLA/KH is an effective and well-tolerated option for managing acute HD. Furthermore, its combination with flavonoid-based supplements, which improve venous tone and reduce capillary permeability, may aid in preventing recurrence. This combined approach leverages the rapid symptom relief provided by topical agents and the long-term benefits of systemic therapies, promoting comprehensive HD management and reducing the risk of recurrence.

Key words: fluocinolone acetonide – ketocaine hydrochloride – hemorrhoidal disease – treatment – corticosteroids – local anesthetics – combined treatment.

Abbreviations: ADMA: asymmetric dimethylarginine; CRC: colorectal cancer; FLA: fluocinolone acetonide; GC: glucocorticoid; HD: hemorrhoidal disease; IL: interleukin; iNOS: inducible nitric oxide synthase; KH: ketocaine hydrochloride; MMP: matrix metalloproteinase; MPFF: micronized purified flavonoid fraction; NO: nitric oxide; TNF-α: tumor necrosis factor-alpha; VEGF: vascular endothelial growth factor.

INTRODUCTION

Hemorrhoidal disease (HD) is a prevalent anorectal disorder characterized by the symptomatic enlargement and displacement of normal anal cushions. This condition often arises from degenerative changes in supporting connective tissue, disrupted blood flow, and abnormal dilatation of the hemorrhoidal plexus [1, 2]. Diagnosis involves a detailed clinical history, digital rectal examination, and anoscopy [3, 4]. Constipation and prolonged straining at stool are common precipitating factors, underscoring the importance of a gentle, skilled digital rectal examination in diagnosing a comorbid functional evacuation disorder [5].

Hemorrhoids are classified as internal, occurring above the dentate line and typically associated with painless bleeding and mucous discharge [6], external, located below the dentate line with symptoms, such as pain and itching [7], and mixed (internal-external) [8]. Internal hemorrhoids are further graded from I to IV based on the degree of protrusion and

persistence of prolapse beyond the anal verge [9, 10]. Common symptoms of external hemorrhoids include bleeding, pain, discomfort, fecal leakage, and mucus secretion [9,11].

Hemorrhoidal disease is frequently encountered in general practice, although its true prevalence remains difficult to determine because of underreporting [12, 13]. Nevertheless, it is estimated to affect 36% of the general population, with higher rates observed among middle-aged people of high socioeconomic status [8]. Additionally, it is reported that 50% of individuals will experience symptomatic HD at some point in their lifetime [8, 14], with higher prevalence noted among postpartum women [11]. Hemorrhoidal disease is associated with comorbidities, including hypertension, diabetes, and depression [15, 16]. If left untreated, HD can lead to complications such as prolapsed hemorrhoids, thrombosis, chronic bleeding with anemia, and reduced quality of life due to pain, depression, and social embarrassment [1, 17–23]. The most feared complication is intravascular thrombosis of external hemorrhoids, in which the clot tends to be intravascular, causing tense swelling of the vascular space with unbearable pain, often requiring surgical intervention [24]. Moreover, thrombosed hemorrhoidal syndrome can occasionally evolve into chronic proctalgia, adversely affecting the patient's quality of life [25]. Although HD and colorectal cancer (CRC) may present with similar symptoms, such as rectal bleeding and bowel changes, HD does not cause CRC. However, a 10-year study recently published by Wu et al. [26] reported an increased risk of CRC [26]. This study showed that individuals with HD had a higher CRC risk than those without; the overall incidence was 2.39 times greater in the HD group. The mechanisms underlying this association remain unclear. Some authors suggest that chronic inflammation associated with HD may play a role in increasing the risk of CRC. However, it is also possible that the more frequent evaluations and screenings prompted by HD symptoms may increase the detection rate of CRC in these patients [26].

Beyond its impact on quality of life, HD contributes significantly to healthcare costs due to frequent consultations, diagnostics, and treatment [27]. Hemorrhoidal disease management varies according to severity and includes conservative approaches, office-based procedures, and surgical interventions. Conservative measures, such as dietary modifications, topical therapies, and flavonoid-based systemic treatments, are employed to address the symptoms of low-grade disease [28]. Symptomatic HD should initially be managed with conservative measures focused on improving bowel habits, including dietary advice to increase fluid intake (6–8 glasses of fluids daily) and fiber consumption (20–30 g daily). Moreover, patients should be advised against delaying bowel movements or spending prolonged periods on the toilet, including activities such as reading or using a cellphone. For patients who are unable or unwilling to increase dietary fiber intake (e.g., those with comorbid irritable bowel syndrome), laxatives such as macrogol or docusate may be considered [29]. While supporting evidence remains limited, conservative measures are strongly recommended because of their potential to address the underlying pathophysiology and their lower risk of complications compared with office-based procedures. In addition, sitz baths with warm water, which are traditionally used to alleviate anal tension, are commonly recommended for various benign anal diseases, including HD. Although randomized controlled trials to support this measure are lacking, anecdotal evidence suggests mild pain relief [30].

Office-based procedures like rubber band ligation and infrared photocoagulation are used in mild to moderate cases, while surgery is reserved for severe or recurrent disease [4, 31, 32]. Compared with office-based procedures, conventional hemorrhoidectomy is associated with greater pain, increased blood loss, and a longer recovery period, although it has significantly lower recurrence rates [33, 34]. Hemorrhoidal artery ligation may be effective for grade II or III hemorrhoids, as patients may experience less pain and recover more quickly [35]. Given the potential risks and discomfort associated with invasive procedures, it is recommended to prioritize safer, non-invasive measures for managing refractory HD. Topical treatments, known for their favorable safety profiles, include various local anesthetics, corticosteroids, and anti-inflammatory agents [36]. Supplements containing bioflavonoids such as hidrosmin, diosmin, hesperidin, and rutosides (rutin) enhance venous tone and reduce capillary permeability. Therefore, they are commonly used for the symptomatic relief of HD, including bleeding, inflammation, and pruritus [37]. Cream or suppository formulations containing 0.1 mg/g of fluocinolone acetonide (FLA), a corticosteroid, and 10 mg/g of ketocaine hydrochloride (KH), an anesthetic, are indicated for the treatment of internal and external hemorrhoids [38]. The FLA/KH combination has demonstrated significant efficacy in the conservative management of HD, providing rapid relief from pain, itching, and inflammation through its anti-inflammatory and local anesthetic properties [39]. Furthermore, its favorable safety profile is supported by extensive clinical and post-marketing data, underscoring its suitability for prolonged use. Adverse events are mainly limited to mild and transient local irritation [40, 41]. Additionally, systemic flavonoids may complement topical treatments of HD. This combined approach might leverage the rapid symptom relief of topical agents along with the long-term benefits of systemic therapies, thereby promoting comprehensive HD management and reducing recurrence risk [42–45].

This review aims to present a comprehensive narrative review of the pathophysiology of HD, focusing on the established and potential mechanisms of action of the FLA/KH combination in treating this condition. Moreover, it seeks to elucidate the rationale behind the combined use of these active ingredients.

Relevant articles were identified through PubMed database searches using various combinations of pertinent keywords (hemorrhoids; "hemorrhoids complications"; hemorrhoids AND angiogenesis; hemorrhoids AND vasodilation; hemorrhoids AND vascular congestion; flavonoids AND hemorrhoids; hemorrhoids AND inflammation; hemorrhoids AND NF-κB; corticosteroids AND vasoconstriction; corticosteroids AND inflammation; corticosteroids AND NF-κB; corticosteroids AND nitric oxide; fluocinolone AND vasoconstriction; fluocinolone AND NF-κB; "fluocinolone tolerability"; ketocaine AND analgesia; "ketocaine tolerability").

PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS

Currently, it is believed that the etiology of HD is primarily driven by constipation, which leads to prolonged straining and the passage of hard stools. These factors contribute to the degeneration of supportive tissues in the anal canal and distal downward displacement of anal cushions. Risk factors for HD include conditions that increase intra-abdominal pressure, such as pregnancy, obesity, sedentary lifestyle, prolonged sitting, chronic diarrhea or constipation, straining during defecation, extended toilet sitting, and inflammatory bowel disease. Although the associated risk is lower than in other conditions, repeated use of the Valsalva maneuver (e.g., for back pain relief in ankylosing spondylitis) and chronic cough can still promote the development of HD [46–49]. The sliding anal canal or cushion theory is the most widely accepted explanation for the development of HD. This theory identifies displacement of the anal cushions as the primary pathophysiological mechanism behind HD, suggesting that HD develops when the supporting tissues of the anal cushions disintegrate or deteriorate [8, 50]. Conversely, alternative theories such as vascular hyperplasia, proposing that hemorrhoids resemble erectile tissue, and internal anal sphincter hypertonia provide only partial explanations for HD pathogenesis [8]. Hypervascularization of the anorectum appears to contribute to hemorrhoid growth, rather than merely being a consequence of the disease [51].

Vascular congestion and venous stasis are critical mechanisms in the development and progression of HD. Vascular congestion increases pressure and distension within the vascular structures, promoting the enlargement of hemorrhoidal cushions. This congestion is typically triggered by factors such as prolonged straining during defecation, chronic constipation, or increased intra-abdominal pressure (e.g., due to pregnancy or obesity) [52]. Venous stasis occurs when venous return is impaired, leading to blood to pool in the hemorrhoidal veins. This stagnation may result from a weakened venous system or elevated venous pressure, hindering drainage. Venous stasis not only exacerbates vascular congestion but also promotes local inflammation, thrombosis within the hemorrhoidal vessels, ulceration, and deterioration of the vascular architecture [53]. The coexistence of HD and chronic venous insufficiency in over half of the study population emphasizes the need for screening for chronic venous insufficiency in patients with HD, especially when shared risk factors are present. A chronic increase in venous pressure, typical in constipated patients, contributes to both lower extremity chronic venous insufficiency and HD, which are often associated [54]. Ischemia from traction and constriction of the microvascular system induces inflammation in surrounding connective tissues [55].

Hemorrhoidal disease symptoms, including pain, redness, swelling, anal discomfort, and thrombosis, are closely related to inflammation. Recent studies suggest that inflammatory pathways significantly contribute to the development and exacerbation of HD. Among these, NF-κB has garnered attention for its role in regulating inflammatory responses. Upon activation, NF-κB translocates to the nucleus, inducing the expression of pro-inflammatory cytokines such as interleukin (IL)-1β, IL-6, tumor necrosis factor-alpha (TNF-α), and other mediators such as cyclooxygenase-2, inducible nitric oxide synthase (iNOS), and matrix metalloproteinases (MMPs) [56]. These molecules promote vasodilatation, increase vascular permeability, and attract immune cells, contributing to the swelling, pain, and irritation commonly associated with HD [57, 58].

NF-κB contributes to vascular tone deregulation by promoting an imbalance between vasodilating and vasoconstricting agents, leading to vasodilatation [59]. Specifically, NF-κB regulates the expression of iNOS, which, under pathological conditions, stimulates the expression of high levels of nitric oxide (NO), promoting excessive vasodilatation [60]. Studies have shown that hemorrhoids exhibit significantly elevated levels of nitric oxide synthase (NOS1 and NOS3) and NO, a potent vasodilator [59, 61]. Conversely, the levels of asymmetric dimethylarginine (ADMA), the primary endogenous inhibitor of NOS, are reduced [62]. Gokce et al. [62] suggest that this imbalance between NO and ADMA leads to vascular dilation, exacerbating HD symptoms such as bleeding or swelling. Consequently, as a potent NOS inhibitor, ADMA is considered a potential therapeutic target for HD management [62].

Hemorrhoidal disease is characterized by the disintegration or deterioration of tissues displaying disorganized connective fibers, fragmentation of the anal subepithelial muscle and elastin components, and fibrous tissue hypertrophy, resulting in the loss of elasticity. These structural changes are accompanied by vascular alterations such as abnormal venous dilatation and thrombosis [8, 58]. Levels of MMP-9 are elevated in internal hemorrhoid tissue compared with normal anal cushions [61], contributing to the breakdown of elastic fibers [63]. Alongside MMP-2, MMP-9 promotes the angioproliferative activity of transforming growth factor β [64], suggesting that neovascularization might be another important phenomenon in HD. Furthermore, Chung [65] and Han et al. [61] demonstrated that angiogenesis-related proteins, including vascular endothelial growth factor (VEGF), are highly expressed in HD. This growth factor contributes to the increased microvascular density observed in hemorrhoidal tissue [66]. Although dysregulation of vascular tone leads to the formation of new microvessels and hyperperfusion of the hemorrhoidal plexus [67], this does not translate into improved oxygenation. Instead, the hypoxic environment established contributes to inflammation [55].

A schematic representation of the pathophysiology of HD is depicted in Fig. 1.

FLUOCINOLONE ACETONIDE AND KETOCAINE HYDROCHLORIDE

Various topical treatments are available for the temporary relief of HD, frequently combining two or more active ingredients [32]. Among these, the active ingredients fluocinolone acetonide (FLA) and ketocaine hydrochloride (KH) are known to reduce pain and inflammation, improve local blood flow, and promote healing of the affected tissue. This section presents the mechanism of action of each ingredient individually, explores their synergistic activity, details the

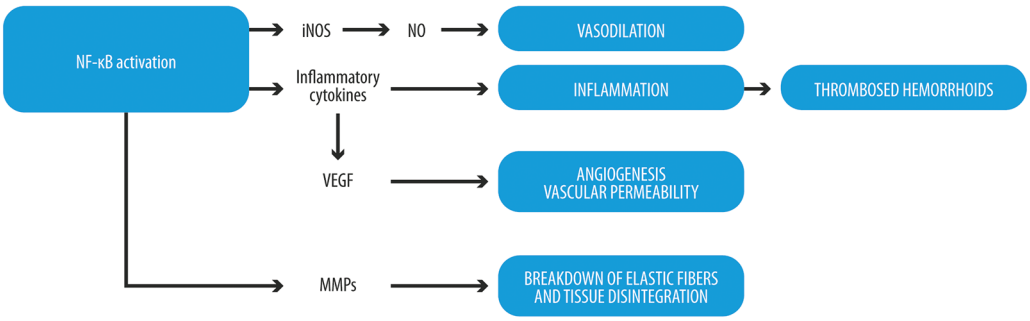

Fig. 1. Role of NF-κB in the pathogenesis of HD. Activated NF-κB enhances the expression of iNOS, leading to increased levels of NO, which, in turn, triggers vasodilatation. NF-kB triggers the expression of inflammatory molecules, which, besides leading to inflammation and promoting the formation of thrombosed hemorrhoids, also promote VEGF expression and the subsequent angiogenetic process and vascular permeability. NF-κB also elicits the expression of MMPs, which degrade elastic fibers and contribute to tissue degeneration. MMPs: metalloproteinases; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; VEGF, NO: nitric oxide; iNOS: inducible nitric oxide synthase; VEGF: vascular endothelial growth factor.

safety profile of the formulation, and discusses the potential synergism between the FLA/KH combination and systemic flavonoid-based treatments.

Mechanism of Action of FLA

Fluocinolone acetonide is a synthetic fluorinated corticosteroid with immunosuppressive, anti-inflammatory, antipruritic, vasoconstrictive, and antiproliferative properties. It has been used for several dermatological and mucosal conditions [68–70] and is considered promising for treating various inflammatory conditions [71]. Similar to other glucocorticoids (GCs), FLA induces the expression of Annexin A1 (lipocortin), a protein that inhibits phospholipase A2, thus blocking the release of arachidonic acid. This inhibition leads to a reduction in pro-inflammatory prostaglandins and leukotrienes, which are involved in iNOS activation and NO production. Additionally, GCs inhibit NF-κB activation and, as a result, upregulate the anti-inflammatory IL-10 [72]. This mechanism also suppresses the production of cytokines such as IL-1, IL-6, and TNF-α, which are known to stimulate iNOS expression [72, 73]. Through the reduction of cytokine levels, FLA indirectly limits iNOS induction and, consequently, NO production. This mechanism helps control the excessive vasodilatation, tissue damage, and the perpetuation of inflammation driven by high NO levels [74, 75]. Furthermore, dilution in petrolatum has been shown to enhance the vasoconstrictive activity of FLA, thereby amplifying its beneficial effect in HD [76]. Fluocinolone acetonide also decreases VEGF expression and TNF-α-induced angiogenesis through its GC receptor activity [77]. In HD, clinical unpublished data have reported that FLA, administered in cream or suppository formulations, resulted in complete symptom resolution in 77% of cases within 3 weeks and 94% relief of anal itching. Significant improvements were also observed in post-operative cases [78].

Mechanism of Action of KH

Ketocaine hydrochloride is a local anesthetic that blocks nerve signals by inhibiting sodium channels in nerve endings, effectively interrupting pain transmission in affected areas. This mechanism provides rapid relief from pain and itching [79], which are common and distressing symptoms of HD. The local anesthetic properties of KH have been documented in several clinical studies involving 412 patients. These studies revealed that KH acts rapidly, within minutes of application, and provides long-lasting relief (2–3 hours). Adverse events are generally mild and manageable, and systemic absorption is very low [80–85]. Topical application of KH produced sufficient levels of analgesia for split-skin graft procedures. Aside from redness and edema, no significant adverse effects were reported. These findings support the use of KH as a local anesthetic in HD management, given its rapid onset of action and targeted relief of pain and discomfort [83, 84]. This makes KH particularly effective for alleviating the acute symptoms of HD, such as pain and itching, which are often the most distressing for patients. Its topical application is well-tolerated, with minimal systemic absorption, thereby reducing the risk of adverse effects and ensuring localized action. This profile supports its role as a first-line component in combination therapies for HD symptomatic relief [78]. Furthermore, experimental studies have shown that KH can alter oxygen consumption in tissues with predominantly anaerobic metabolism and inhibit the mitotic activity of phytohemagglutinin-stimulated human lymphocytes [86]. These effects suggest that KH may also contribute to inflammation control. Additionally, local anesthetics, including KH, are recognized for inhibiting excessive inflammatory responses without significantly compromising host immunity [87]. This property further supports the therapeutic role of KH in HD management.

Synergism between FLA and KH in HD treatment

Some GCs produce delayed therapeutic effects because they rely on gene expression. Consequently, combining them with fast-acting local anesthetics enhances symptom relief in HD [88, 89]. Notably, the synergistic combination of an anti-inflammatory agent and an anesthetic has demonstrated superior symptom relief in HD compared with using individual

components. Clinical trials have shown that patients treated with the FLA/KH combination experienced significant improvements in symptom severity scores, including those who underwent hemorrhoidectomy. Among the studied population, complete symptom remission was achieved in 91% of patients. Specifically, 91% reached full remission with the ointment alone, 86% with suppositories alone, and 98% with the combined use of ointment and suppositories. Pain resolution, whether spontaneous or triggered by defecation or endoscopic maneuvers, was observed rapidly (within 4–30 minutes). The analgesic effect persisted 2–7 hours, with some cases lasting up to 12 hours. Fig. 2 shows the improvements in total clinical scores after 10 days of treatment with the FLA/KH combination, administered as a cream, suppository, or a combination of both formulations.

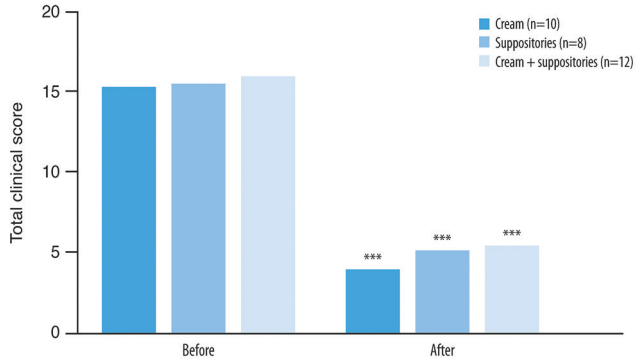

Fig. 2. Total clinical score after 10 days of treatment with the FLA/KH combination in cream or suppository formulations or their combination, in 30 patients. The following parameters were assessed: nodule volume, spontaneous or defecation/endoscopic maneuver-induced pain, tenesmus, burning sensation, itching, eczematization, and bleeding.*** p<0.001 vs baseline (Student's t-test for paired data). Data taken from [115–118].

In two controlled clinical studies [90, 91], the FLA/KH combination demonstrated superiority over placebo in alleviating key symptoms of HD (burning, pain, bleeding, and hemorrhoidal nodule size). Notably, the combination showed particularly significant improvements in pain and burning sensation (Figs. 3 and 4).

Importantly, the low concentration of FLA in these topical formulations makes them safer than other GC-based treatments [92].

The tolerability and safety of the FLA/KH combination have been extensively demonstrated. The combination is particularly effective because of its synergistic pharmacological properties in the treatment of HD, resulting from their complementarity. When combined, the anti-inflammatory properties of FLA and the local anesthetic action of KH provide rapid symptom relief and long-lasting anti-inflammatory effects. The reduction in pain and discomfort often leads to a decrease in the need for analgesics, which are typically required for symptomatic HD patients. Moreover, the FLA/KH combination has been shown to reduce the recurrence rate of acute HD flares [39]. In addition, the combined formulation of these active ingredients simplifies treatment compliance by eliminating the need for separate application of a GC and a local anesthetic. The fixed

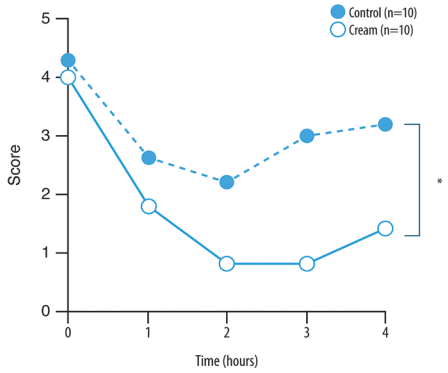

Fig. 3. Score on continuous pain. Comparison of continuous pain scores after 1 day of treatment with the cream formulation of the FLA/KH combination (10 patients) or placebo (control group, 10 patients). * p<0.05 vs control group (two-way ANOVA). Source: Perelli M. et al. 1969 [91]. Reproduced with permission from Minerva.

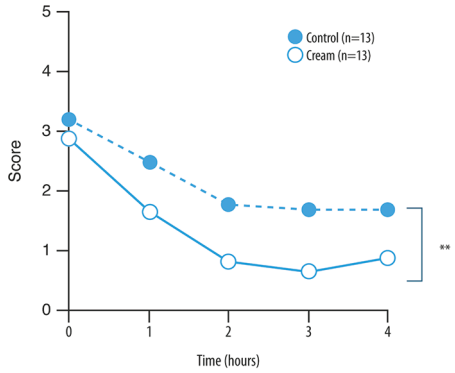

Fig. 4. Score on burning. Comparison of burning sensation scores after 1 day of treatment with the cream formulation of the FLA/KH combination (13 patients) or placebo (control group, 13 patients). ** p<0.01 vs control group (Two-way ANOVA). Source: Perelli M. et al. 1969 [91]. Reproduced with permission from Minerva.

dosage in the combination preparations guarantees that each active ingredient is delivered in the intended proportions, ensuring consistent therapeutic effects. An additional benefit of the FLA/KH combination is its capacity to provide localized anti-inflammatory action while minimizing systemic exposure, which supports prolonged use with a low side-effect profile [78]. Schematic representation of the activity of the FLA/KH combination in HD is depicted in Fig. 5. This dual-action combination enhances overall symptom control and is particularly beneficial in reducing hemorrhoidal prolapse, bleeding, and discomfort during defecation, offering a more comprehensive management approach than using either agent alone.

Safety Profile of the FLA/KH Combination

The FLA/KH combination has been marketed in Italy for over 50 years, with an estimated 39 million patients having used the product during this period. Despite this widespread use, side effects have been infrequent, as demonstrated by extensive post-marketing surveillance.

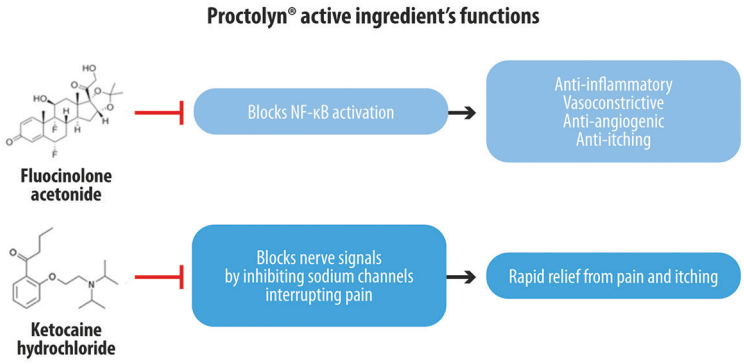

Fig. 5. Schematic representation of the activity of the FLA/KH combination in HD. FLA inhibits NF-κB, a key molecule involved in HD pathogenesis, thereby reducing inflammation, angiogenesis, and itching, while also displaying a vasoconstrictive effect. KH blocks sodium channels, providing relief from pain and itching. HD: hemorrhoidal disease; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells.

From 1969 to 2024, a total of 46 adverse reactions were recorded in 25 patients. Among these, only two cases were classified as serious (contact dermatitis and hives), while the remaining reactions were non-serious, including itching, application site pain, and anorectal discomfort. Less common events involved burning sensation, rash, and pain.

These side effects are generally mild, consistent with those observed in topical corticosteroid therapy, and rarely necessitate treatment discontinuation.

In summary, clinical and post-marketing data confirm that the FLA/KH combination, in both cream and suppository formulations, is safe and well-tolerated.

COMPLEMENTARY STRATEGIES FOR ACUTE HD TREATMENT AND RECURRENCE PREVENTION

In addition to topical therapies, oral preparations containing phlebotonic drugs are widely prescribed for HD treatment because of their proven efficacy in chronic venous insufficiency [37, 93]. Their use for symptomatic HD is further supported by a high level of moderate-quality evidence and endorsed by specific guidelines from the Italian Society of Colorectal Surgery (SICCR) [30] and the Italian Society of Colon-Proctology (SIUC) [94]. These agents comprise a heterogeneous class of compounds, including plant-derived flavonoids and synthetic substances. Although their precise mechanism of action is not fully elucidated, phlebotonics are known to enhance venous tone, regulate capillary permeability, and promote lymphatic drainage [95]. Evidence suggests that phlebotonics not only provide therapeutic benefits in HD reducing bleeding and overall symptoms, with minimal safety concerns, but also improve recovery after hemorrhoidectomy [28, 96–100]. Among phlebotonics, diosmin exhibits anti-inflammatory and antioxidant properties, alongside its phlebotonic and vasoactive effects [101]. To enhance the bioavailability and therapeutic efficacy, a new micronized formulation of diosmin has been developed specifically for HD treatment [102]. Furthermore, Ginkgo biloba-based preparations are employed as oral supplements to provide vascular support in HD [103]. Moreover, oral supplementation with natural extracts including *Aesculus hippocastanum, Ruscus aculeatus, Centella asiatica, Hamamelis virginiana,* and *Vitis vinifera,* when combined with bioflavonoids, has been shown to prevent complications associated with varicose veins and hemorrhoids [104]. This effect is particularly enhanced when used in combination therapy [105].

Venoactive drugs are often combined with other pharmacological agents in patients with symptoms of HD. A recent study demonstrated that adding micronized purified flavonoid fraction (MPFF) to topical hemorrhoid treatments significantly improved bleeding and health-related quality of life in patients with acute hemorrhoids [106]. Although clinical studies have demonstrated the efficacy of topical treatment in managing acute episodes of HD [107], systemic therapies are critical for long-term maintenance and prevention of recurrence. However, it is worth noting that the venotonic effects of MPFF can only minimize secondary venous bleeding after hemorrhoidectomy, but not arterial bleeding from the pedicle of excised hemorrhoids [108]. Topical and systemic therapeutic approaches are complementary, where topical agents provide immediate symptom relief, while systemic treatments ensure long-term management. For hemorrhoid pain, systemic treatment with MPFF is recommended alongside non-narcotic analgesics, local anesthetics, and topical combination treatments. Furthermore, MPFF therapy is advised for thrombosed hemorrhoids (with or without inflammation in the surrounding soft tissues) and hemorrhoidal bleeding [108–110]. Thus, the combined use of systemic flavonoids and topical treatments represents a synergistic strategy in HD management, targeting both systemic and local factors. This integrated approach enhances symptom relief and improves patient outcomes.

EXPERT OPINION

Symptomatic HD is a prevalent and disabling anorectal disorder that accounts for a considerable proportion of

consultations in both primary and secondary care [24]. However, many patients remain undiagnosed, opting for self-management and seeking medical or pharmacist advice only when complications arise, such as secondary fecal incontinence [111]. To maximize therapeutic effectiveness, patients with HD should receive practical lifestyle recommendations. These include maintaining a high-fiber diet, ensuring adequate hydration, and engaging in regular physical activity. Additional strategies, such as synchronizing defecation in the morning to take advantage of the synergistic effect of the orthocolic and gastrocolic reflex, avoiding postponement of defecatory urges, achieving a normal fecal consistency (Bristol Stool Scale types 3–5), and minimizing prolonged straining on the toilet, are also beneficial [112]. In both acute and chronic HD, the most concerning symptoms for the patients are anal pain and bleeding, which often prompt emergency care visits, leading to high medical expenses and reduced quality of life. Notably, severe anal pain caused by inflamed hemorrhoidal tissue can sometimes drive patients toward invasive treatment, even in the absence of complicated disease [113]. In cases of uncomplicated disease, the primary therapeutic goal should be pain management to enable timely and appropriate intervention. In this context, the early use of the FLA/KH combination such in the case of Proctolyn® [38], is recommended for symptomatic HD, given its effective blend of analgesic and anti-inflammatory properties. Furthermore, the safety profile of the FLA/KH combination allows for self-management in case of recurrent HD disease, especially when medical consultation is not readily accessible (e.g., during travel in a foreign country). Once complicated HD is ruled out through appropriate diagnostic testing, treatment with the FLA/KH combination may contribute to decreasing the patient's request for unnecessary invasive treatment, thereby minimizing the risk of fecal incontinence associated with such interventions [114].

CONCLUSIONS

This review highlights the role of the NF-κB pathway in regulating inflammation, contributing to the development of HD by promoting the production of pro-inflammatory cytokines and mediators such as NO. Additionally, the imbalance between vasodilators and their inhibitors (e.g., ADMA) is discussed as a key factor contributing to vascular dilatation, bleeding, and swelling. This review further explores the conservative topical treatment of HD using the FLA/KH combination, which has been shown to effectively relieve symptoms such as pain, itching, and mild bleeding. Its mechanism involves inhibition of inflammation and angiogenesis, promotion of vascular constriction, and potentially support for tissue healing. Current evidence suggests that the FLA/KH combination represents a good option for the conservative management of HD, particularly in the early stages of the disease. It displays a rapid onset of action and a favorable safety profile, with minimal adverse events localized to the anal region. The safety profile of the FLA/KH combination is suitable for long-term use and is particularly beneficial for patients who may not be candidates for more invasive HD treatments. Furthermore, the joint use of the FLA/KH combination with flavonoid-based supplements appears to be ideal for managing acute hemorrhoids, preventing recurrence, and maintaining long-term symptom control.

Conflicts of interest: M.B. has been a consultant for GE Healthcare, Aboca, Diadema, Norgine, Alfasigma, Agave, Polifarma, Recordati, Mayoly, Pharmanutra. G.C. received fees for Speaking/Consulting by Dompé Farmaceutici, Coloplast, Errekappa Farmaceutici, Laborie, Mayoly, Recordati, Schwabe Pharma. C.L. and S.L.P. declare no potential conflicts of interest.

Authors' contributions: G.C. conceived and designed the study. G.C., M.B. and C.L. performed the literature search and collected data. G.C. drafted the manuscript. C.L. and S.L.P. edited the manuscript. All the authors read and approved the final version of the manuscript.

Acknowledgements: Medical writing, editorial assistance, English editing and graphic support were provided by Lara Vecchi, Valentina Attanasio, Aashni Shah and Massimiliano Pianta (Polistudium Srl, Milan, Italy). This assistance was supported by Recordati.

REFERENCES

1. Sneider EB, Maykel JA. Diagnosis and management of symptomatic hemorrhoids. Surg Clin North Am 2010;90:17–32. doi:10.1016/j.suc.2009.10.005
2. Brillantino A, Marano L, Grillo M, et al. Lower pain, less itching, and faster healing after ultrasound scalpel-assisted hemorrhoidectomy using an intimate cleaner containing chlorhexidine, acid hyaluronic acid, and natural anti-inflammatories: a multicenter observational case-control study. Ann Coloproctol 2024;40:602-609. doi:10.3393/ac.2024.00570.0081
3. Yetkin E, Ozturk S, Cuglan B, Turhan H. Symptoms in Dilating Venous Disease. Curr Cardiol Rev 2020;16:164-172. doi:10.2174/1573403X16666200312101245
4. Jacobs D. Clinical practice. Hemorrhoids. N Engl J Med 2014;371:944-951. doi:10.1056/NEJMcp1204188
5. Chiarioni G, Lambiase C, Whitehead WE, et al. Difficult defecation in constipated patients: Diagnosis by minimally invasive diagnostic tests. Dig Liver Dis 2024;56:429-435. doi:10.1016/j.dld.2023.06.004
6. Madoff RD, Fleshman JW; Clinical Practice Committee, American Gastroenterological Association. American Gastroenterological Association technical review on the diagnosis and treatment of hemorrhoids. Gastroenterology 2004;126:1463-1473. doi:10.1053/j.gastro.2004.03.008
7. Cengiz TB, Gorgun E. Hemorrhoids: A range of treatments. Cleve Clin J Med 2019;86:612–620. doi:10.3949/ccjm.86a.18079
8. Lohsiriwat V. Hemorrhoids: from basic pathophysiology to clinical management. World J Gastroenterol 2012;18:2009-2017. doi:10.3748/wjg.v18.i17.2009
9. Ganz RA. The evaluation and treatment of hemorrhoids: a guide for the gastroenterologist. Clin Gastroenterol Hepatol 2013;6:593–603. doi:10.1016/j.cgh.2012.12.020
10. Davis BR, Lee-Kong SA, Migaly J, Feingold DL, Steele SR. The American Society of Colon and Rectal Surgeons clinical practice guidelines for the management of hemorrhoids. Dis Colon Rectum 2018;61:284–292. doi:10.1097/DCR.0000000000001030
11. Sheikh P, Régnier C, Goron F, Salmat G. The prevalence, characteristics and treatment of hemorrhoidal disease: results of an international

web-based survey. J Comp Eff Res 2020;9:1219-1232. doi:10.2217/cer-2020-0159
12. Tournu G, Abramowitz L, Couffignal C, et al. Prevalence of anal symptoms in general practice: a prospective study. BMC Fam Pract 2017;18:78. doi:10.1186/s12875-017-0649-6
13. Abramowitz L, Benabderrahmane M, Pospait D, Philip J, Laouénan C. The prevalence of proctological symptoms amongst patients who see general practitioners in France. Eur J Gen Pract 2014;20:301-306. doi:10.3109/13814788.2014.899578
14. Lohsiriwat V. Treatment of hemorrhoids: A coloproctologist's view. World J Gastroenterol 2015;21:9245-9252. doi:10.3748/wjg.v21.i31.9245
15. Mao L, Ma L, Liu N, et al. Self-reported health problems related to traditional dietary practices in postpartum women from urban, suburban and rural areas of Hubei province, China: the 'zuò yuèzi'. Asia Pac J Clin Nutr 2016;25:158-164. doi:10.6133/apjcn.2016.25.2.03
16. Poskus T, Buzinskienė D, Drasutiene G, et al. Haemorrhoids and anal fissures during pregnancy and after childbirth: a prospective cohort study. BJOG 2014;121:1666-1671. doi:10.1111/1471-0528.12838
17. Fontem RF, Eyvazzadeh D. Internal Hemorrhoid. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537182/
18. Ali SA, Shoeb MFR. Study of risk factors and clinical features of hemorrhoids. Int Surg J 2017;4:1936–1939. doi:10.18203/2349-2902.isj20172051
19. Ibrahim AM, Hackford AW, Lee YM, Cave DR. Hemorrhoids can be a source of obscure gastrointestinal bleeding that requires transfusion: report of five patients. Dis Colon Rectum 2008;51:1292-1294. doi:10.1007/s10350-008-9376-3
20. Jongen J, Bach S, Stübinger SH, Bock JU. Excision of thrombosed external hemorrhoid under local anesthesia: a retrospective evaluation of 340 patients. Dis Colon Rectum 2003;46:1226-1231. doi:10.1007/s10350-004-6719-6
21. Akkoca M, Kocaay AF, Tokgoz S, et al. Psychiatric Symptoms, Aggression, and Sexual Dysfunction Among Patients With Benign Anal Conditions. Am Surg 2023;89:4297-4304. doi:10.1177/00031348221074225
22. Kostev K, Konrad M, Smith L, Krieg S. Hemorrhoids are associated with an increased risk of depression in Germany: A retrospective cohort study in primary care outpatients. J Psychiatr Res 2024;175:381-385. doi:10.1016/j.jpsychires.2024.05.028
23. Rørvik HD, Davidsen M, Gierløff MC, Brandstrup B, Olaison G. Quality of life in patients with hemorrhoidal disease. Surg Open Sci 2023;12:22-28. doi:10.1016/j.sopen.2023.02.004
24. Keighley MRB, Sagar P, Williams NS, et al. (Eds). Keighley & Williams' Surgery of the Anus, Rectum and Colon, Fourth Edition: Two-volume set (4th ed.). CRC Press; 2018. doi:10.1201/9781351105040
25. Carrington EV, Popa SL, Chiarioni G. Proctalgia Syndromes: Update in Diagnosis and Management. Curr Gastroenterol Rep 2020;22:35. doi:10.1007/s11894-020-00768-0
26. Wu EB, Sung FC, Lin CL, Wu KL, Chen KB. Colorectal Cancer Risk in Patients with Hemorrhoids: A 10-Year Population-Based Retrospective Cohort Study. Int J Environ Res Public Health 2021;18:8655. doi:10.3390/ijerph18168655
27. 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;114:798-803. doi:10.14309/ajg.0000000000000143
28. 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;10:1549. doi:10.3390/jcm10081549
29. Wald A, Bharucha AE, Limketkai B, al. ACG Clinical Guidelines: Management of Benign Anorectal Disorders. Am J Gastroenterol 2021;116:1987-2008. doi:10.14309/ajg.0000000000001507
30. Gallo G, Martellucci J, Sturiale A, et al. Consensus statement of the Italian society of colorectal surgery (SICCR): management and treatment of hemorrhoidal disease. Tech Coloproctol 2020;24:145-164. doi:10.1007/s10151-020-02149-1
31. Rivadeneira DE, Steele SR, Ternent C, et al; Standards Practice Task Force of The American Society of Colon and Rectal Surgeons. Practice parameters for the management of hemorrhoids (revised 2010). Dis Colon Rectum 2011;54:1059-1064. doi:10.1097/DCR.0b013e318225513d
32. Mounsey AL, Halladay J, Sadiq TS. Hemorrhoids. Am Fam Physician 2011;84:204-210.
33. MacRae HM, McLeod RS. Comparison of hemorrhoidal treatment modalities. A meta-analysis. Dis Colon Rectum 1995;38:687-694. doi:10.1007/BF02048023
34. Picchio M, Greco E, Di Filippo A, Marino G, Stipa F, Spaziani E. Clinical Outcome Following Hemorrhoid Surgery: a Narrative Review. Indian J Surg 2015;77(Suppl 3):1301-1307. doi:10.1007/s12262-014-1087-5
35. Mott T, Latimer K, Edwards C. Hemorrhoids: Diagnosis and Treatment Options. Am Fam Physician 2018;97:172-179.
36. Lawrence A, McLaren ER. External Hemorrhoid. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500009/
37. Alonso-Coello P, Zhou Q, Martinez-Zapata MJ, et al. Meta-analysis of flavonoids for the treatment of haemorrhoids. Br J Surg 2006;93:909-920. doi:10.1002/bjs.5378
38. Proctolyn®, RCP. https://api.aifa.gov.it/aifa-bdf-eif-be/1.0.0/organizzazione/107/farmaci/21925/stampati?ts=RCP.
39. Boccaccio Soy A. (Direttore Clin. Dermat. Univ. Genova) - Relazione sulla sperimentazione clinica eseguita con il preparato Proctolyn supposte e Proctolyn pomata. Certificato Clinico, Genova, 30 Novembre 1970.
40. Montoro V, Asensio C, Martínez Á, et al. Efficacy and safety of fluocinolone acetonide 0.025% otic solution in patients with otic eczema: a randomized, double-blind, placebo-controlled clinical trial. J Int Med Res 2018;46:4050-4060. doi:10.1177/0300060518765333
41. Recordati, 1984, Relazione farmacologica e tossicologica sull'uso del Proctolyn. Unpublished data.
42. Lorenc Z, Gökçe Ö. Tribenoside and lidocaine in the local treatment of hemorrhoids: an overview of clinical evidence. Eur Rev Med Pharmacol Sci 2016;20:2742-2751.
43. Borghi SM, Mizokami SS, Pinho-Ribeiro FA, et al. The flavonoid quercetin inhibits titanium dioxide (TiO2)-induced chronic arthritis in mice. J Nutr Biochem 2018;53:81-95. doi:10.1016/j.jnutbio.2017.10.010
44. Verri WA Jr, Vicentini FT, Baracat MM, et al. Chapter 9 – Flavonoids as anti-inflammatory and analgesic drugs: mechanisms of action and perspectives in the development of pharmaceutical forms. Stud Nat Prod Chem 2012;36:297-330. doi:10.1016/B978-0-444-53836-9.00026-8
45. Gwozdzinski L, Pieniazek A, Gwozdzinski K. Factors Influencing Venous Remodeling in the Development of Varicose Veins of the Lower Limbs. Int J Mol Sci 2024;25:1560. doi:10.3390/ijms25031560
46. Talley NJ, Lasch KL, Baum CL. A gap in our understanding: chronic constipation and its comorbid conditions. Clin Gastroenterol Hepatol 2009;7:9-19. doi:10.1016/j.cgh.2008.07.005

47. Caglayan M, Türkoğlu A, Oktayoglu P, et al. Evaluation of the incidence of haemorrhoidal disease in patients with ankylosing spondylitis. Clin Rheumatol 2015;34:511-514. doi:10.1007/s10067-014-2732-x
48. Negri E, Pagano R, Decarli A, La Vecchia C. Body weight and the prevalence of chronic diseases. J Epidemiol Community Health 1988;42:24-29. doi:10.1136/jech.42.1.24
49. Ravindranath GG, Rahul BG. Prevalence and risk factors of hemorrhoids: a study in a semi-urban centre. Int J Surg 2018;5:496–499. doi:10.18203/2349-2902.isj20180339
50. Yang H. The pathophysiology of hemorrhoids. In: Hyung KY (Ed.). *Hemorrhoids*. Berlin Heidelberg: Springer-Verlag; 2014:15–24. doi:10.1007/978-3-642-41798-6_3
51. Aigner F, Bodner G, Gruber H, et al. The vascular nature of hemorrhoids. J Gastrointest Surg 2006;10:1044-1050. doi:10.1016/j.gassur.2005.12.004
52. Ekici U, Kartal A, Ferhatoglu MF. Association Between Hemorrhoids and Lower Extremity Chronic Venous Insufficiency. Cureus 2019;11:e4502. doi:10.7759/cureus.4502
53. Hardy A, Cohen CR. The acute management of haemorrhoids. Ann R Coll Surg Engl 2014;96:508-511. doi:10.1308/003588414X13946184900967
54. Godeberge P, Sheikh P, Zagriadskiĭ E, 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;35:577-585. doi:10.1111/jgh.14857
55. Morgado PJ, Suárez JA, Gómez LG, Morgado PJ Jr. Histoclinical basis for a new classification of hemorrhoidal disease. Dis Colon Rectum 1988;31:474-480. doi:10.1007/BF02552621
56. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. Signal Transduct Target Ther 2017;2:17023. doi:10.1038/sigtrans.2017.23
57. Lohsiriwat V. Approach to hemorrhoids. Curr Gastroenterol Rep 2013;15:332. doi:10.1007/s11894-013-0332-6
58. Serra R, Gallelli L, Grande R, et al. Hemorrhoids and matrix metalloproteinases: A multicenter study on the predictive role of biomarkers. Surgery 2016;159:487-494. doi:10.1016/j.surg.2015.07.003
59. Lohsiriwat V, Wilson VG, Scholefield JH, Dashwood MR. Regional Distribution of Nitric Oxide Synthase in Human Anorectal Tissue: A Pilot Study on the Potential Role for Nitric Oxide in Haemorrhoids. Curr Vasc Pharmacol 2020;18:43-49. doi:10.2174/1570161116666180730101532
60. Jones E, Adcock IM, Ahmed BY, Punchard NA. Modulation of LPS stimulated NF-kappaB mediated Nitric Oxide production by PKCepsilon and JAK2 in RAW macrophages. J Inflamm (Lond) 2007;4:23. doi:10.1186/1476-9255-4-23
61. Han W, Wang ZJ, Zhao B, et al. Pathologic change of elastic fibers with difference of microvessel density and expression of angiogenesis-related proteins in internal hemorrhoid tissues. Zhonghua Wei Chang Wai Ke Za Zhi 2005;8:56-59.
62. Gokce AH, Gokce FS, Durmus S, et al. The effect of nitric oxide, endothelial nitric oxide synthetase, and asymmetric dimethylarginine in hemorrhoidal disease. Rev Assoc Med Bras (1992) 2020;66:1128-1133. doi:10.1590/1806-9282.66.8.1128
63. Zhou M, Jin W, Li P, Wang R, Guo X. Traditional Chinese Medicine in the treatment of hemorrhoids-a review of preparations used and their mechanism of action. Front Pharmacol 2023;14:1270339. doi:10.3389/fphar.2023.1270339
64. Yoon SO, Park SJ, Yun CH, Chung AS. Roles of matrix metalloproteinases in tumor metastasis and angiogenesis. J Biochem Mol Biol 2003;36:128-137. doi:10.5483/bmbrep.2003.36.1.128
65. Chung YC, Hou YC, Pan AC. Endoglin (CD105) expression in the development of haemorrhoids. Eur J Clin Invest 2004;34:107-112. doi:10.1111/j.1365-2362.2004.01305.x
66. Palumbo VD, Tutino R, Messina M, et al. Altered Gut Microbic Flora and Haemorrhoids: Could They Have a Possible Relationship? J Clin Med 2023;12:2198. doi:10.3390/jcm12062198
67. Aigner F, Gruber H, Conrad F, et al. Revised morphology and hemodynamics of the anorectal vascular plexus: impact on the course of hemorrhoidal disease. Int J Colorectal Dis 2009;24:105-113. doi:10.1007/s00384-008-0572-3
68. Pauporte M, Maibach H, Lowe N, et al. Fluocinolone acetonide topical oil for scalp psoriasis. J Dermatolog Treat 2004;15:360-364. doi:10.1080/09546630410023566
69. Youngnak-Piboonratanakit P, Dhanuthai K, Thongprasom K, et al. Expression of IFN-gamma before and after treatment of oral lichen planus with 0.1% fluocinolone acetonide in orabase. J Oral Pathol Med 2009;38:689–694. doi:10.1111/j.1600-0714.2009.00805.x
70. Dhavale RP, Nadaf SJ, Bhatia MS. Quantitative structure property relationship assisted development of Fluocinolone acetonide loaded transfersomes for targeted delivery. J Drug Deliv Sci Technol 2021;65:102758. doi:10.1016/j.jddst.2021.102758
71. ELhabal SF, El-Nabarawi MA, Hassanin SO, et al. Transdermal fluocinolone acetonide loaded decorated hyalurosomes cellulose acetate/polycaprolactone nanofibers mitigated Freund's adjuvant-induced rheumatoid arthritis in rats. J Pharm Investig 2024;55:113–132. doi:10.1007/s40005-024-00693-8
72. Smart N, Mojet MH, Latchman DS, Marber MS, Duchen MR, Heads RJ. IL-6 induces PI 3-kinase and nitric oxide-dependent protection and preserves mitochondrial function in cardiomyocytes. Cardiovasc Res 2006;69:164-177. doi:10.1016/j.cardiores.2005.08.017
73. Schuerwegh AJ, Dombrecht EJ, Stevens WJ, Van Offel JF, Bridts CH, De Clerck LS. Influence of pro-inflammatory (IL-1 alpha, IL-6, TNF-alpha, IFN-gamma) and anti-inflammatory (IL-4) cytokines on chondrocyte function. Osteoarthritis Cartilage 2003;11:681-687. doi:10.1016/s1063-4584(03)00156-0
74. Ingawale DK, Mandlik SK. New insights into the novel anti-inflammatory mode of action of glucocorticoids. Immunopharmacol Immunotoxicol 2020;42:59-73. doi:10.1080/08923973.2020.1728765
75. Radomski MW, Palmer RM, Moncada S. Glucocorticoids inhibit the expression of an inducible, but not the constitutive, nitric oxide synthase in vascular endothelial cells. Proc Natl Acad Sci U S A 1990;87:10043-10047. doi:10.1073/pnas.87.24.10043
76. Guin JD, Wallis MS, Walls R, Lehman PA, Franz TJ. Quantitative vasoconstrictor assay for topical corticosteroids: the puzzling case of fluocinolone acetonide. J Am Acad Dermatol 1993;29:197-202. doi:10.1016/0190-9622(93)70167-r
77. Ayalasomayajula SP, Ashton P, Kompella UB. Fluocinolone inhibits VEGF expression via glucocorticoid receptor in human retinal pigment epithelial (ARPE-19) cells and TNF-alpha-induced angiogenesis in chick chorioallantoic membrane (CAM). J Ocul Pharmacol Ther 2009;25:97-103. doi:10.1089/jop.2008.0090
78. Recordati, 1984. Relazione Clinica sull'uso del Proctolyn®. Unpublished data.
79. Woolfson D, McCafferty. Percutaneous Local Anaesthesia. CRC Press; 1993:88.
80. Antonelli A. Relazione sulle applicazioni in clinica O.R.L. di un nuovo anestetico locale. La Clinica O.R.L. 1967;1:24-41.

81. Piccolo A. - Studio clinico sperimentale su un nuovo anestetico locale: il Rec 7/0518 (Chetocaina Recodarti). Reconstructive Medica 1965;4:583-585.
82. Filippone G, Köllinell G. Sperimentazione comparativa sulla anestesia corneale da instillazione tra una soluzione di Rec 7/0518 al 0.5% ed una soluzione di cocaina al 4%. Ann Oftalm Clin Oculistica 1967;22:212-221.
83. Pettersson LO. Percutaneous anaesthesia for taking split skin grafts. Scand J Plast Reconstr Surg 1977;11:79-82. doi:10.3109/02844317709025501
84. Pontén B, Ohlsén L. Skin surface application of ketocaine to provide local anaesthesia for cutting split skin grafts. Br J Plast Surg 1977;30:251-254. doi:10.1016/0007-1226(77)90110-2
85. Sandahl B, Ulmsten U, Andersson KE. Local application of ketocaine for treatment of referred pain in primary dysmenorrhea. Acta Obstet Gynecol Scand 1980;59:259-260. doi:10.3109/00016348009155407
86. Galatulas I, Andreani A, Rambaldi M, Bonazzi D, Bossa R. New alkylating agents: butyrophenone derivatives. Anticancer Res 1986;6:853-855.
87. Weinschenk S, Weiss C, Benrath J, von Baehr V, Strowitzki T, Feißt M. Anti-Inflammatory Characteristics of Local Anesthetics: Inhibition of TNF-α Secretion of Lipopolysaccharide-Stimulated Leucocytes in Human Blood Samples. Int J Mol Sci 2022;23:3283. doi:10.3390/ijms23063283
88. Stratta E, Gallo G, Trompetto M. Conservative Treatment of Hemorrhoidal Disease. Rev Recent Clin Trials 2021;16:87-90. doi:10.2174/1574887115666201021150144
89. Williams JA, Evans JC. An assessment of anesthetic-steroid suppositories: a controlled trial following rubber-band ligation of hemorrhoids. Dis Colon Rectum 1972;15:66-68. doi:10.1007/BF02587675
90. Seghezzi R, Ercoli A, Bordonaro L. Trattamento antinfiammatorio delle emorroidi e delle ragadoi anali. Minerva Chir 1968;23:1296-1306.
91. Perelli Ercolini M, Sforza M, Buffa E, Paoli GDE. Sperimentazione clinica di un nuovo farmaco antiemorroidario. Minerva Chir 1969;24:794-813.
92. Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 2014;71:116-132. doi:10.1016/j.jaad.2014.03.023
93. Ulloa JH. Micronized Purified Flavonoid Fraction (MPFF) for Patients Suffering from Chronic Venous Disease: A Review of New Evidence. Adv Ther 2019;36(Suppl 1):20-25. doi:10.1007/s12325-019-0884-4
94. Brillantino A, Renzi A, Talento P, et al. The Italian Unitary Society of Colon-Proctology (Società Italiana Unitaria di Colonproctologia) guidelines for the management of acute and chronic hemorrhoidal disease. Ann Coloproctol 2024;40:287-320. doi:10.3393/ac.2023.00871.0124
95. Martinez-Zapata MJ, Vernooij RW, Simancas-Racines D, et al. Phlebotonics for venous insufficiency. Cochrane Database Syst Rev 2020;11(11):CD003229. doi:10.1002/14651858.CD003229.pub4
96. Ferraz CR, Carvalho TT, Manchope MF, et al. Therapeutic Potential of Flavonoids in Pain and Inflammation: Mechanisms of Action, Pre-Clinical and Clinical Data, and Pharmaceutical Development. Molecules 2020;25:762. doi:10.3390/molecules25030762
97. Grassi D, Desideri G, Croce G, Tiberti S, Aggio A, Ferri C. Flavonoids, vascular function and cardiovascular protection. Curr Pharm Des 2009;15:1072-1084. doi:10.2174/138161209787846982
98. Xiao ZP, Peng ZY, Peng MJ, Yan WB, Ouyang YZ, Zhu HL. Flavonoids health benefits and their molecular mechanism. Mini Rev Med Chem 2011;11:169-177. doi:10.2174/138955711794519546
99. Perera N, Liolitsa D, Iype S, et al. Phlebotonics for haemorrhoids. Cochrane Database Syst Rev 2012;2012:CD004322. doi:10.1002/14651858.CD004322.pub3
100. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines According to Scientific Evidence. Part I. Int Angiol 2018;37:181-254. doi:10.23736/S0392-9590.18.03999-8
101. 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;33:1595-1600. doi:10.1007/s00384-018-3102-y
102. Russo R, Chandradhara D, De Tommasi N. Comparative Bioavailability of Two Diosmin Formulations after Oral Administration to Healthy Volunteers. Molecules 2018;23:2174. doi:10.3390/molecules23092174
103. EGb 761: ginkgo biloba extract, Ginkor. Drugs R D 2003;4:188-193. doi:10.2165/00126839-200304030-00009
104. MacKay D. Hemorrhoids and varicose veins: a review of treatment options. Altern Med Rev 2001;6:126-140.
105. Gravina AG, Pellegrino R, Facchiano A, Palladino G, Loguercio C, Federico A. Evaluation of the Efficacy and Safety of a Compound of Micronized Flavonoids in Combination With Vitamin C and Extracts of Centella asiatica, Vaccinium myrtillus, and Vitis vinifera for the Reduction of Hemorrhoidal Symptoms in Patients With Grade II and III Hemorrhoidal Disease: A Retrospective Real-Life Study. Front Pharmacol 2021;12:773320. doi:10.3389/fphar.2021.773320
106. Mokhtare M, Pakravan R, Rafieemanesh M, et al. The Efficacy of Adding Daflon to the Conventional Treatment on the Improvement of Symptoms and Health Related Quality of Life in Patients with Acute Hemorrhoids: A Randomized Clinical Trial. EC Gastroenterol Dig Syst 2019;6:44-51.
107. Kestřánek J. Hemorrhoid management in women: the role of tribenoside + lidocaine. Drugs Context 2019;8:212602. doi:10.7573/dic.212602
108. 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;10:801-813. doi:10.2217/cer-2021-0038
109. Shelygin YA, Frolov SA, Titov AY, et al. The Russian Association of Coloproctology clinical guidelines for the diagnosis and treatment of hemorrhoids. Koloproktologia 2019;18:7-38. doi:10.33878/2073-7556-2019-18-1-7-38
110. Froehner Junior I, Kotze PG, Rocha JG, et al. Postoperative topical analgesia of hemorrhoidectomy with policresulen and cinchocaine: a prospective and controlled study. Rev Col Bras Cir 2014;41:92-98. doi:10.1590/s0100-69912014000200004
111. Savarino EV, Chiarioni G. Improved diagnosis of faecal incontinence in the gastroenterology domain: The time to act has come. United European Gastroenterol J 2024;12:425-426. doi:10.1002/ueg2.12546
112. Bellini M, Tonarelli S, Barracca F, et al. Chronic Constipation: Is a Nutritional Approach Reasonable? Nutrients 2021;13:3386. doi:10.3390/nu13103386
113. Tarasconi A, Perrone G, Davies J, Coimbra R, Moore E, Azzaroli F, et al. Anorectal emergencies: WSES-AAST guidelines. World J Emerg Surg 2021;16:48. doi:10.1186/s13017-021-00384-x
114. Bocchini R, Chiarioni G, Corazziari E, et al. Pelvic floor rehabilitation for defecation disorders. Tech Coloproctol 2019;23:101-115. doi:10.1007/s10151-018-1921-z

115. Varini G. Nota preliminare su di un nuovo farmaco ad azione antiflogistico-analgesica nel trattamento delle emorroidi. Riv Gastroenter 1967;XIX(1):25.
116. Baccaredda Boy A. Relazione sulla sperimentazione clinica eseguita con i preparati Proctolyn supposte e Proctolyn pomata-Certificato clinico, Genova, 30 Novembre 1970.
117. Resti M. Trattamento topico delle flogosi acute emorroidarie con un nuovo preparato ad azione antiflogistica ed analgesica. Riv Gastroenter 1966;XVIII(2):66.
118. Parravicini F, Frezzini L. Sperimentazione clinica di un nuovo farmaco antiemorroidario. Gazz Med Lombarda 1968;11:31-35.