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Review Article

Comprehensive Review on Hemorrhoids: From Epidemiology to Preclinical Assessment of Anti-hemorrhoidal Agents

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ABSTRACT

The review discusses the etiology, epidemiology, classification, risk factors, assessment, the role of biomarkers in the development of hemorrhoids, operative and non-operative treatment options, post-operative complications of hemorrhoids, preclinical evaluation methods of anti-hemorrhoidal drugs, and different medicinal plants that exhibit anti-hemorrhoidal activity. The dilation and dislocation of normal anal cushions characterizes hemorrhoids. One of the most significant discoveries regarding hemorrhoids is the atypical enlargement and distortion of blood vessels, along with damage and modifications to the anal cavity's supporting connective tissue. Hemorrhoids are categorized into different classifications based on various factors, Golingher's classification commonly used, which divides the hemorrhoidal condition into four grades according to prolapse and the development of hemorrhoids. Hemorrhoids are recognized as one of the leading causes of morbidity, affecting millions of populations worldwide and also increasing the economic burden on the healthcare system. Current treatment options for hemorrhoids often involve conservative approaches, including fiber supplements, anti-inflammatory medications, lifestyle changes, and venotonic medicines. Additionally, operative treatments like rubber band ligation, hemorrhoidectomy, and injection sclerotherapy are utilized. Various biomarkers are responsible for the occurrence of hemorrhoids, such as matrix metalloproteinase (MMP), vascular endothelial growth factor (VEGF), inducible nitric oxide synthase (iNOS), and C-reactive protein (CRP). These biomarkers hold potential as targets for developing new anti-hemorrhoidal agents.

Introduction

The word "hemorrhoid" originated from the Greek terms "haema" and "rhoos," which refer to the flow of blood.[1] It is an anorectal disease that shows the symptoms of growth and distal eviction of typical rectoanal cushions. Anal cushions comprise connective tissue housing blood-filled vascular structures commonly found within the anal passage. These anal cushions support anal continence and safeguard the sphincters when perfused during defecation.[2] Anal cushions that are distally displaced and swollen are symptoms of hemorrhoids or piles. At 39% of the general population, it is one of the most prevalent anorectal conditions. Furthermore, symptomatic hemorrhoids affect roughly 45% of individuals.[3,4] There are significant medical and social issues impacting millions worldwide. Hence, nowadays, hemorrhoids are recognized as a significant contributing factor of morbidity and influence the society's economy and social structure.[5] It affects social interactions and lifestyle choices like eating, sleeping, and hygiene. It also increases economic overload on the health care system. Because hemorrhoidal illness causes sensitive symptoms, including anal bleeding, pain, and itching, it greatly lowers patients' quality of life and causes them to feel physically and psychologically uncomfortable.[6] The formation of hemorrhoids can be linked to several factors, like constipation and extended straining. A significant characteristic of the hemorrhoidal condition involves the atypical enlargement and deformation of the vascular channel, accompanied by a detrimental change

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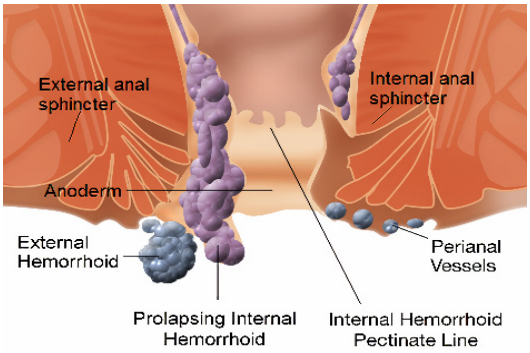

Fig. 1: Hemorrhoid: Internal and external[14]

in the supportive connective tissue within the anal cushion.[7] Hemorrhoids exhibit indications of blood vessel hyperplasia[8] and inflammatory reactions.[9]

Pathophysiology

Hemorrhoids are considered to be a natural component of the anal canal's structure. Found inside the submucosal area, they are cushions of densely vascularized tissue. There are three primary rectal padding or support tissue positioned in the right anterior, left lateral, and right posterior locations in the anal canal. Blood veins, elastic tissue, smooth muscle, and supportive tissue are all in these hemorrhoidal cushions. These tissues collectively account for 15 to 20% of the anorectal resting pressure. Each cushion contains the arteriovenous connections that link the end terminals of the upper and central anorectal arteries to the upper, lower, and medium rectal veins.[10,11] Anal cushions provide a number of crucial purposes in the anorectal canal. They aid in maintaining anal continence and preventing stool leaks while sniffling, straining, or wheezing by filling with blood and closing the anal canal. These cushions guard the anorectal muscular valves during defecation when they are engorged with blood. Additionally, this tissue is vital to the sensory capabilities required to distinguish between liquid, solid, and gas.[10-12] Constipation, low-fiber diet, prolonged straining, lack of valves within the hemorrhoidal vessels, pregnancy, intense exercise, elevated intraperitoneal pressure, genetics, unsteady bowel movements (constipation/diarrhea), gravity, and aging are some of the factors that lead to pathological alterations inside the hemorrhoidal cushions.[12] These elements raise the pressure inside the submucosal arteriovenous plexus, which in turn causes the cushions to enlarge, the supporting connective tissue to become loose, and the cushions to expand into and through the anal canal.[13] Depending upon connection to the dentate line is divided into internal and external hemorrhoids (Fig. 1).

General Incidence and Prevalence of Hemorrhoids

Hemorrhoids is one of the major prevalent anorectal illnesses. It has been found to impact 4.4 to 36.4% of the population. The age group of 45 to 65 is found more prevalent; approximately one-third of hemorrhoid sufferers consult a physician. Several studies showed that between 5 and 10% of people with hemorrhoids do not respond to conservative measures; in these instances, surgery is the recommended course of treatment.[15] It is estimated that 40,723,288 individuals in India suffer from hemorrhoids. Every year, one million new cases are recorded, with an increasing rate as people age (47 per 1000).[16] According to current estimates, about half of all people on the planet will suffer from hemorrhoids in one way or another, especially after they turn fifty.[17] Hemorrhoidal illness is claimed to be more common in some categories, like pregnant or postpartum women, where the occurrence ranges from 12 to 41%.[18] One of the leading prevalent anorectal conditions in normal practice is hemorrhoidal illness. However, the real frequency in the general community is poorly known, in part because a large number of patients choose not to pursue therapy.[19]

Assessment/Clinical Evaluation of Hemorrhoids

It includes a physical examination, a comprehensive medical history, and diagnostic tests.

Medical history

With the use of a therapeutic history, the physician can identify the patient's symptoms and general health. This often includes questions on the patient's food and bowel habits. Additionally, the patient could be questioned about how often they exercise and whether they currently take any medications. The patient has to disclose if any blood relations have ever experienced colon polyps or cancer.[20]

Physical examination

Throughout the physical check-up, the patient is requested to recline on a table. At that time, he or she will be examined for signs of enlarged hemorrhoids and additional issues. It takes very little time to complete the exam. Most of the time, it is not pleasant or challenging. The physical examination consists mostly of an anoscopic examination, a computerized rectal test, and a visual test.[20]

Diagnostic tests

To be sure that the symptoms aren't caused by other conditions, such as polyps or colorectal cancerous development, diagnostic testing is helpful. One of the tests included in these is a fecal occult blood test, which looks for blood that has been hidden in the feces. Certain tests may be required to look into the colon. Sigmoidoscopy, colonoscopy, and barium enema are a few tests. [21]

Sigmoidoscopy

The test performed to examine the sigmoid colon, or lower part of the colon, is called a sigmoidoscopy. This section of the colon is close to the anus and rectum. A tissue test can also be performed using a sigmoidoscopy. It is also frequently used to remove hemorrhoids or polyps. It also serves as a screening test for colorectal cancer. To perform

Table 1: Different classification of hemorrhoids[27]

S. No.	*Year*	*Classification*	*Description*
1	1919	Miles	Based on anatomical features, Miles *et al* . categorized internal hemorrhoids into three stages. were two signs that a patient needed operation for internal hemorrhoids: persistent, severe blood loss, and irrevocable sagging.
2	1975	Goligher	Goligher developed a classification that divided internal hemorrhoid prolapse into four grades.
3	1988	Japanese colonoscope	Morgado P. J. proposed that hemorrhoids are a typical part of human tissue, and they are not necessarily a disease if they don't cause any symptoms and are classified as hemorrhoids based on symptoms.
4	2000	Fabio Gaj classification	Gaj *et al* . classified hemorrhoids based on anatomy and symptoms, and considerations include external and internal hemorrhoids, degree of prolapse, and the rate of sudden onset (thrombosis and edema).
5	2004	Lunniss classification	Another additional categorization was developed by Lunniss *et al* . in 2004 from a therapeutic perspective. The morphology, primary symptoms (prolapse and bleeding), comorbidities, patient age, internal hemorrhoid size, and treatment recommendations are taken into consideration when classifying a patient
6	2006	Position acute tone external system (PATE 2006)	This classification uses quality of life and objective markers to assess patients with hemorrhoids. The sum of the points adds up to the final result.
7	2007	Videoanoscopy	Harish *et al* . The red corpuscular sign, the size and quantity of hemorrhoids, and other factors are evaluated.
8	2008	Prolapsed hemorrhoid classification algorithm	In 2008, Gerjy and colleagues presented an algebraic grading system for hemorrhoids that prolapse. According to patient self-report, the algorithm was first divided into two groups. Following a three- to six-month follow-up, patients who did not get therapy were further divided depending on the results of the pre- and post-surgical proctoscopic examination. The quantity and distribution of these lesions in the perianal region will determine the next level of classification for patients with external hemorrhoids. The findings suggest that this anatomically based method may accurately identify prolapsed and recurrent hemorrhoids.
9	2009	Hemorrhoid severity score (HSS)	P. O. Nyström and colleagues developed the hemorrhoid severity score (HSS) questionnaire as a means to evaluate the symptoms experienced by patients with hemorrhoids. This questionnaire, comprising five questions, aims to gauge various aspects of discomfort and incontinence among patients. Specifically, it encompasses inquiries into the recurrence of hemorrhoid-related symptoms like pain, itching, profuse discomfort, prolapse, and anal flow. Through patient responses to these questions, the HSS questionnaire provides valuable insights into the extent of pain associated with mucosal anal prolapse.
10	2015	Proctological symptom scale (PSS)	Matthias and colleagues played a significant role in developing the proctological symptom scale (PSS) questionnaire, designed to assess the severity of symptoms related to benign rectal diseases.
		The Sodergren score	In 2015, Pucher and colleagues introduced the Sodergren score evaluation tool as a means to evaluate both the intensity of signs and the impact on comfort levels among patients suffering from hemorrhoids. This tool serves multiple purposes, including facilitating comparisons between various therapeutic approaches, monitoring the progression of the condition over time, and aiding clinicians in making informed decisions regarding surgical interventions.
		The single pile classification (SPC)	A novel tool was created by Elbetti et. al. who combined the Goligher classification and also examined 197 patients, the authors discovered that the new categorization could provide more detailed descriptions of symptoms that the previous classification was unable to. The Goligher classification does not provide anatomical information impedes the occurrence of hemorrhoidal diversity and actual severity.
11	2018	Hemorrhoidal disease symptom score (HDSS) and short health scale adapted for hemorrhoidal disease (SHSHD)	Roverik *et al* . analyzed to evaluate the responsiveness, accuracy, and authenticity of patient self-disclosed ratings for prolapse, pain, itching, bleeding, and soiling (also referred to as the hemorrhoidal illness symptom score). The HDSS was modified from the HSS, with the score depending on the patient's sentiments during the previous two to three months and a different scale. Furthermore, the short health scale HD, a tool for assessing the health-focused living standard of hemorrhoid-ill persons, was assessed for responsiveness and reliability.
		Hemohorrids fissures quality of life (HEMO-FISS-Qol)	To evaluate the total effect of anal fissures and hemorrhoids on patients' everyday life, Abramowitz *et al* . designed a questionnaire. The findings showed that in those with hemorrhoids, the HEMO-FISS-QoL score intensified as symptom severity rose. It is the first thorough psychological creation of an assessment for hemorrhoids and anal fissures that is known to exist.

12	2020	Prolapse; Numbers; Relation; Bleed (PNR- bleed)	Khan *et al* . introduced a classification based on several key factors: the extent of hemorrhoidal prolapse, the volume of bleeding, and the number of major hemorrhoidal columns involved.
		Anatomical/ clinical-therapeutic classification (A/CTC)	Naldini *et al* . give the categorization which comprises an evaluation of the hemorrhoid's anatomical characteristics (external and internal prolapse), the symptoms (swelling, pain, bleeding, prolapse, etc.), the frequency of symptoms, and potential challenges and treatment modality contraindications, which can help reduce the risk of surgery.
		Bleeding; Prolapse; Reduction; Skin tag: Thrombosis (BPRST)	In 2020, Sobrado Junior *et al* . developed the BPRST classification for hemorrhoids. he considered not just prolapse but also other symptoms like thrombosis and external hemorrhoids in classification.
13	2022	Patient reported outcome measure-hemorrhoidal impact and satisfaction score (PROM- HISS)	Kuiper *et al* . Through extensive literature research and expert panel discussions, PROM-HISS was created. It evaluates how hemorrhoidal symptoms like bleeding, prolapse, discomfort, itching, soiling affect day-to-day functioning and measures how satisfied patients are with their medical care.

sigmoidoscopies, a flexible tube called a sigmoidoscope is utilized. The small pipe has a small light and a camera in it. After being installed into the anal passage, the tube is gradually passed into the rectal canal and the lower part of the colon, and the air is blown into the colon using a tube, slightly expanding it to increase visibility.[22]

Colonoscopy

The goal of a colonoscopy is to find any alterations or defects in the colon and rectum. During a colonoscopy, a prolonged, versatile catheter (colonoscope) is introduced inside the anorectal canal. Through a small camera placed at the bottom of the tube, the physician can examine the colon. If required, polyps and other aberrant tissue types can be removed during a colonoscopy using the scope. Moreover, tissue samples, or biopsies, may be obtained during a colonoscopy.[23]

Barium enema

A radiographic test that is barium enema can identify alterations or variances in the colon. The method is also known as a colon X-ray. An enema involves inserting a fluid through a tiny tube into the rectum. In this case, the fluid covers the colon's lining with a metallic material called barium. Generally, an X-ray shows a low image of sensitive tissues, but the barium coating produces an outline of the colon that is usually clear. During a barium enema test, the colon may be siphoned with air. The colon expands with the air, which enhances image quality. This type of barium enema is known as an air-contrast or two-fold contrast. The doctor will advise the patient to completely empty their colon before receiving a barium enema.[24,25]

Classification of Hemorrhoids

Since the eighteenth century, researchers have studied hemorrhoids extensively. Hemorrhoidal conditions have been classified using a variety of techniques that take into account anatomy, etiology, pathophysiology, and related Indications. The position and form of the piles plexus are objective indicators of hemorrhoids, but signs and their perceived effect on a person's quality of life (QoL) are

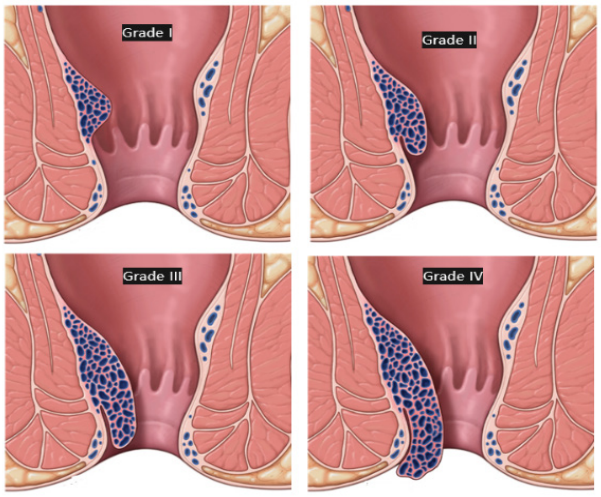

Fig. 2: Degree of hemorrhoids[30]

subjective. The majority of hemorrhoid categorization systems now in use have their drawbacks and limitations since they only take into account objective or subjective features. The most popular approach is still the Goligher classification.[26] Different classifications of hemorrhoids are summarized in Table 1.

Hemorrhoids are categorized on the basis of their connection to the dentate line, which is based on the implicated 'parent' hemorrhoidal plexus. External hemorrhoids begin away from the dentate line, but internal hemorrhoids begin proximally.[28] Internal hemorrhoids are referred to in the traditional Goligher staging of hemorrhoidal illness [29] and they are categorized into 4 degrees (Fig. 2).

- First-degree hemorrhoids are those bulging into the anal passage without prolapsing;
- second-degree hemorrhoids that prolapse outside the anal passage but spontaneously reduce;
- third-degree hemorrhoids that bulge outside the anal passage upon pushing and necessitate manual realignment.
- Fourth-degree hemorrhoids are unavoidable and continuously prolapse.

Table 2: Role of biomarkers in the development of hemorrhoids

Protein/Biomarker	*Role*
Nitric oxide synthase (NOS)	High nitric oxide synthase (NOS) can contribute to the development of hemorrhoids through increased nitric oxide (NO) production, which leads to relaxation of the anal sphincter muscle. This relaxation can result in increased pressure within the hemorrhoidal veins, leading to engorgement and the development or exacerbation of hemorrhoids. Additionally, excessive NO production can impair vascular tone regulation, further contributing to venous congestion and hemorrhoid formation[36,37]
Matrix metalloproteinase (MMP)	Matrix metalloproteinases (MMPs) are enzymes responsible for the remodeling and breakdown of the extracellular matrix, which is the structural framework that supports anal cushions. MMPs may contribute to tissue degradation and weakening of the vascular wall in the hemorrhoidal veins. Specifically, MMPs can degrade collagen, elastin, and additional elements of the extracellular matrix, leading to structural changes in the vein walls. This degradation can weaken the integrity of the veins and make them more susceptible to dilation and rupture, which are characteristic features of hemorrhoids. Additionally, MMPs may also be involved in the inflammatory process associated with hemorrhoids. They can promote the discharge of Pro-inflammatory signaling molecules and also promote the migration of inflammatory cells to the site of injury or inflammation[38,39].
CRP	C-reactive protein (CRP) is an indicator of inflammation and shows the presence of inflammation in the body. Although CRP itself doesn't directly cause hemorrhoids, its level is elevated in hemorrhoidal conditions which reflects the inflammatory response associated with the condition, which contributes to its development and progression[40]
Vascular endothelial growth factor (VEGF)	Vascular endothelial growth factor (VEGF) is responsible for the progression of hemorrhoids by promoting angiogenesis. Increased VEGF expression promotes new blood vessel formation, which can exacerbate venous congestion and contribute to the enlargement and engorgement of hemorrhoidal veins. This angiogenic process may further compromise the structural integrity of the veins, making them more prone to dilation and rupture, characteristic features of hemorrhoids[41,42,43]

As a result, this classification has clinical ramifications and affects future management. Goligher's classification scheme for hemorrhoids is the most extensively used of the others that have been developed.[31,32]

Risk Factors for Hemorrhoids

The growth of hemorrhoids has been associated with multiple risk factors, including pregnancy, age, and abdominal obesity.[33] On the other hand, it is seen by most that certain circumstances associated with elevated tension in the abdomen, such as bowel obstruction and continuous straining, are responsible for hemorrhoids due to impaired venous drainage of the hemorrhoid plexus.[34] Fiber-deficient diet, alcohol, and peppery foods are among the dietary and lifestyle choices that have been linked to the progression of hemorrhoids and the exacerbation of acute hemorrhoid symptoms.[35]

Role of Biomarkers in Hemorrhoids

Biomarkers such as NOS, MMP, CRP, and VEGF show a significant role in the development of hemorrhoids (Table 2) so we can consider these biomarkers proteins as a promising target for the discovery of novel potential medication for the management of hemorrhoidal condition.

Treatment

Dietary modifications

It is best to try non-operative techniques first if the hemorrhoids are not prolapsing. It is best to encourage patients to take care of the straining of stools. This advice is typically taken in conjunction with methods to enhance bowel function, such as using laxatives or consuming more water and fiber. According to a meta-analysis, the population that consumed fiber primarily ispaghula had a 50% lower relative risk (RR) of blood loss when it came to treating hemorrhoid symptoms.[44]

Topical agents

Many OTC and prescription externalized ointments, suppositories, and creams are accessible to cure hemorrhoidal problems. Mild-dose tranquilizers, astringents, steroids, antiseptics, and protectants are frequently found in these superficial medications,[45] and many people have reported relief from their anal discomfort after utilizing these topical treatments. Medical therapies include both conventional and contemporary medications, which come in a range of formats, such as pills, suppositories, creams, and wipes. Flavonoids are commonly utilized to treat acute symptoms, either in a pure form or as a component of a Ginkgo tree derivative. In addition to their anti-inflammatory properties, they may reduce capillary permeability, elevate vascular tension, and promote lymphatic clearance. Calcium dobesilate, nitrates, and nifedipine are also efficient and well-tolerated when treating hemorrhoids.[46] For first-degree hemorrhoids, other treatment options include injectable sclerotherapy and rubber band ligation, which can provide more rapid symptom alleviation. These more intrusive treatments should only be used for patients who are unresponsive to non-operative measures.[47] Some commonly used drugs or phytoconstituents in the management of hemorrhoids are given in Table 3.

Table 3: Drugs/Phytoconstituents used in the management of hemorrhoids

S. No.	*Drugs*	*Category*
1	Benzocaine	Local anesthetic
2	Cinchocaine	Potent amino amide local anesthetic
3	Docusate	Stool softener
4	Hydrocortisone valerate	Corticosteroid
5	Ibuprofen	NSAID
6	Lidocaine	Local anesthetic
7	Methyl hesperidin	Flavanone glycoside
8	Rutin	Flavonoid glycoside

Rubber band ligation

It is a majorly utilized non-operative intervention and the method of choice for second-degree hemorrhoids. About 90% of surgeons in recent research stated that RBL was the first course of treatment for low-grade hemorrhoidal illness.[48] Using a proctoscope, the focus of rubber band ligation (RBL) is on the pectinate line and other areas with muscular nerves, specifically targeting the tip of the anorectal cushion upside of the pectinate line. Incorrect positioning of the band, too low, can result in immediate discomfort for the patient and requires removal. The procedure aims to induce cauterization at the apex of the hemorrhoid. The tissue impacted by the elastic band undergoes necrosis and sheds off (Fig. 3). Typically, in several days, it prevents the hemorrhoidal tissue from engorging and prolapsing.[49,50]

RBL has an around 70% short-term success rate. Remember that RBL is easily repeatable also frequently provided as an option as opposed to an isolated therapy. In a meta-analysis comparing the effectiveness of RBL against injectable sclerotherapy as monotherapy for hemorrhoid treatment across 18 studies, RBL demonstrated superior performance. This was evidenced by a similar incidence of complications between the two treatments. Moreover, individuals subjected to RBL exhibited a diminished probability of necessitating supplementary therapeutic interventions when contrasted with those undergoing sclerotherapy.[51] Although long-term RBL results are less well-publicized, a recent systematic analysis found that bleeding recurrence rates ranged from 10 to 46%.[52]

Injection sclerotherapy

Sclerotherapy involves the infusion of a sclerosant (5% phenol in almond oil) using a custom-made Gabriel syringe, with 2 to 3 mL injected into all hemorrhoidal sites together. The hemorrhoid pedicle's underlying mucosa is where the sclerosant is inserted at the intersection of the cushion's purplish mucosa and the typical pink rectal mucosa. The end effect is localized inflammation, which gradually causes a decrease in blood flow in hemorrhoids. Fibrosis in the region causes a slight protrusion back into the anal canal, just like RBL does.[53]

Injection sclerotherapy appears to help decrease hemorrhoidal bleeding in the short term, but its long-term results are not very good. In a single randomized experiment, injection sclerotherapy did not improve hemorrhoidal symptoms at six months compared to the patient receiving bulk laxative alone.[54] Less than one-third of patients in another trial that examined the intermediate to long-term results after high-dose injectable sclerotherapy reported being cured at the 4-year follow-up; most patients said their symptoms had either worsened or remained unchanged. Due to its unsatisfactory long-term results, injectable sclerotherapy still has a limited role.[55]

Hemorrhoidectomy

Traditionally, hemorrhoids of the third degree have been removed by hemorrhoidectomy. Many methods have been reported; however, some have been dropped. At current times, there are two widely used hemorrhoidectomy techniques: The Ferguson closed hemorrhoidectomy and the Milligan and Morgan open excision. The fundamental idea of both procedures is to take out the enlarged hemorrhoid tissue from both the inside and outside of the anal canal while leaving enough anoderm and mucosa in place to allow the anal canal to continue functioning. A hemorrhoidectomy can be carried out using diathermy or scissors[56] but more recently, ultrasonic technology (also known as a harmonic scalpel),[57] lasers,[58] and radiofrequency devices have been used. There have been reports that these more recent technologies result in minimal post-surgical pain and enable a quick recovery to regular activity.[59]

- *Open (Milligan-Morgan) hemorrhoidectomy*

Under general anesthesia, the individuals are subjected to the dorsolithotomy position, and the operation is carried out. The location of the hemorrhoid(s) that need to be removed is confirmed by using a Pratt retractor to examine the anal canal. Grip the skin-covered outside portion of the hemorrhoid that needs to be removed with artery forceps. Pull it down and out to reveal the bottom tip of the mucosal-covered portion of the hemorrhoid. Using a second artery clip, the mucosal component of each hemorrhoid is then grabbed and pulled out, exposing the entire hemorrhoid. Next, a V-structured cut is created in the anorectal area, deepening and extending over the anal canal's mucocutaneous junction. After that, the hemorrhoid is meticulously detached from the internal sphincter within and the ring of external sphincter muscle at the anal edge. This leads to the development of a hemorrhoidal pedicle, which has its base in the upper anal canal. The pedicle is removed with scissors after being ligated and fixated with a thick absorbable suture. At every other hemorrhoid location, the process is repeated.

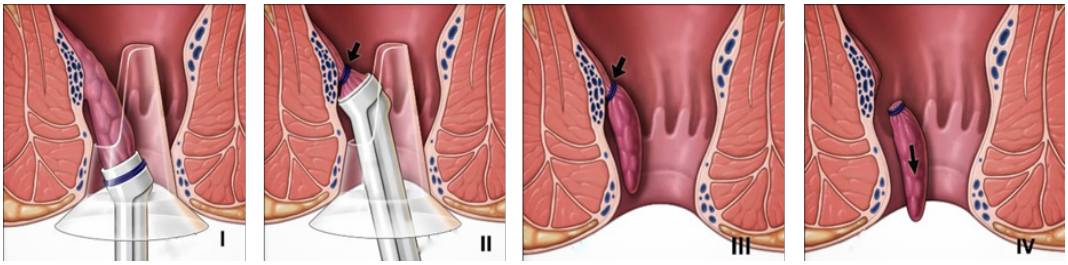

Fig. 3: Rubber band ligation[30]

It takes care to maintain enough mucocutaneous bridges between each incision site.[60,61]

- *Closed (Ferguson) hemorrhoidectomy*

researchers and surgeons argue that the closed hemorrhoidectomy technique reduces the risk of stenosis, which could impede recovery by unintentionally reopening large anal sores. The hemorrhoid is removed in the same way as an open hemorrhoidectomy. Unlike the open approach, a running soluble suture closes the resultant defect. To stop additional, prolapse, suturing ends at the summit, where the anorectal mucosa attaches to the lower muscles. Small muscle bites can also be used to fix the anal mucosa to the internal sphincter. A 5 mm drainage hole is left as the suturing proceeds outward onto the perianal skin to create a transversal suture line. The process continues until all hemorrhoids are addressed. At every succeeding site, less tissue is invariably removed, and once more, tremendous care is taken to retain anoderm to facilitate tension-free wound closure.[62]

Post-operative Complications

Bleeding

Considerable post-operative bleeding may arise from submucosal vessels, which can be incised, cauterized, or ligated during the surgical intervention. The causes of bleeding may include the improper suture ligature, malfunction of energy sealants or staple devices, or local trauma incurred during bowel movements. There is a 2% chance of hemorrhaging after surgery either immediately, early, or delayed. Sometimes the bleeding may stop on its own, and clotting may be encouraged by physical pressure or packing the anal canal. Suture ligation may often be done at the patient's bedside with sufficient exposure and cooperation, but more often than not, it necessitates a journey back to the operating room. The use of blood-thinning medications like aspirin, Plavix, or warfarin does raise the risk of bleeding.[63]

Urinary retention

Urinary retention has been reported to be the most common adverse effect post hemorrhoid surgery; in certain series, up to 34% of cases have been documented. Because of their near closeness to the rectum, the pelvic nerves that are connected to the bladder are often inflamed during hemorrhoidectomy procedures. The choice of anesthetic can also have an impact on the sacral nerve roots, especially in cases of spinal or caudal block. Sphincter spasm is caused by extreme discomfort, and post-operative fluid excess may make things worse.[64]

Wound infections

The blood flow, frequent bacterial contact, and the ensuing effect on local immunity all likely play a part in post-surgery wound infections. Taking warm showers or sitz procedures following bowel movements aids in maintaining the cleanliness of the wounds. Hemorrhoidectomy can very rarely result in pelvic or perineal sepsis. Any patient who is immunosuppressed by medicine (transplant patients) or who has concomitant conditions (diabetes patients) should always be treated with caution. Early identification, followed by wide-spectrum antibiotic treatment, local debridement, and seldom, fecal diversion, is crucial for management.[65]

Anal stricture and ectropion

These days, problems are rare of consist of the development of anal strictures and ectropion. This is probably the result of surgical skills improving throughout time, with people learning from the long-term results of their ancestors. In a three-column hemorrhoidectomy, the risk of strictures can be reduced by leaving at least 1-cm of anoderm between the specimens. Strictures can still arise from infection or extensive tissue excision.[66]

Preclinical Evaluation of Anti-hemorrhoidal Activity

To screen the anti-hemorrhoidal activity, two animal models are commonly used in various research papers.

- Croton oil-induced hemorrhoid:
- Jatropha oil-induced hemorrhoid:

Croton oil-induced hemorrhoid

- *Mechanism of croton oil*

The vesicant and irritant effects of croton oil, derived from *Croton tiglium* L. are attributed to its constituent phorbol esters, notably 12-O-tetradecanoylphorbol-13-acetate. Studies indicate that this compound activates protein kinase C, leading to inflammation *via* the liberation of cytokines such as TNF-α, IL-1β, and IL-6 along with other inflammatory factors. Additionally, phorbol esters induce

vasodilation and the infiltration of polymorphonuclear leukocytes. Investigations have revealed that these esters generate soluble substances, including nitric oxide, cytokines, prostaglandins, leukotrienes, kinins, chemokines, and bradykinins, which contribute to inflammation. This inflammatory response involves the modulation of Indigenous cells such as matrix-producing cells, mastocyte, endothelial cells, and macrophages, also the recruitment of inflammatory cells like neutrophils, monocytes, eosinophils, and lymphocytes, either individually or collectively.[67,68]

Grouping of animals

Wistar albino rats, either male or female, having body weight between 180 to 200 g are divided into six groups each containing six animals; group I serves as normal control, group II serves as negative control, group III serves as standard, groups IV, V, VI serve as treatment 1, treatment 2, treatment 3, respectively.[69]

Induction

All the rats are kept for fasting overnight. Initially, inject the Evans blue (EB) dye *via* the tail vein, this Evans blue dye acts as an indicator for judgment of the development of hemorrhoid.

After one and half hours of EB injection, hemorrhoids were developed by the application of croton oil preparation (mixture of deionized water, pyridine, diethyl ether, and 6% croton oil in diethyl ether in the ratio of 1:4:5:10). The application of croton oil preparation is done by soaking the sterile cotton swab having diameter 4 mm into 100 µL of croton oil preparation and then insert into anal opening upto 20 mm deep. In 7 to 8 hours after application, linear development of edema is observed and edema lasting up to 12 hours is considered a hemorrhoid. due to Evans blue dye anal region appears bluish. After 24 hours of induction, give relevant treatment to all the groups for five days. On the 5th day, scarify (with an overdose of CO2) rats 1 hr after relevant treatment for histopathological observation to determine recto-anal coefficient (RAC), and collect the blood sample from the retro-orbital route for biochemical evaluation. Extract the Evans blue dye from rectoanal tissue for estimation of plasma exudation.[70]

Jatropha oil-induced hemorrhoid

Wistar albino rats either male or female, having body

Table 4: Different plants which show anti-hemorrhoidal activity

S. No.	*Botanical name*	*Family*	*Extraction*	*Plants part*	*Activity/MOA*	*Author/ref.*
1	*Nigella sativa* L	Ranunculaceae	water-ethanol extracts	Seeds	Potent anti-inflammatory action by reduction of pro-inflammatory mediators like PG and LT. Immunomodulatory effect by enhancing natural killer cell and T cell-mediated immune response Antimicrobial activity Antioxidant (DPPH radical scavenging activity, Lipid peroxidation inhibition) vasoconstriction effects Significant anti-hemorrhoidal effect	Omar Said *et al* .[74]
2	*Conyza bonariensis*	Asteraceae	water-ethanol extracts	branches and flowering parts	Vasoconstriction effects antioxidant (DPPH) radical scavenging	Durre Shahwar *et al* .[75] Omar Said *et al* .[74]
3	*Alchemilla vulgaris*	Rosaceae	water-ethanol extracts	Leaves and root	vasoconstriction effects Radical scavenging activity COX enzyme inhibition, Antimicrobial activity	Omar Said *et al* .[74]
4	*Dolichandrone falcata*	Bignoniaceae	ethanolic leaf extract	Leaves	Anti-hemorrhoidal activity by the decrease in the elevated expression of pro-inflammatory cytokines like TNF- α, IL-1β, and IL-6, inhibit degradation of anal tissue antioxidant (Decrease NO and LPO)	Suhas R. Dhaswadikar *et al* .[68] Saddam Shaikh Chand *et al* .[76]
5	*Acacia ferruginea* DC	Mimosaceae	hydroalcoholic extract	Bark	Reduce IL-6, TNF-α, PGE2, nitric acid, and bradykinin also inhibit cyclo-oxygenase (COX) enzyme	Samriti Faujdar *et al* .[77]
6	*Cistus laurifolius* L	Cistaceae	aqueous and ethanolic	Leaves	Anti-inflammatory and antinociceptive	Esra Kupeli *et al* .[78]
7	*Acokanthera schimperi Schweinf*	Apocynaceae	Methanol extract	Leaves	Wound healing effect. Antioxidant Anti-inflammatory	Belete Kassa Alemu *et al* .[79]
8	*Solanum melongena* L.	Solanaceae	Methanolic extract	Dark green Calyx parts	Reduce Serum TNF-α, VEGF Anti-inflammatory Antioxidant	Ceylan Donmez *et al* .[80]

9	*Pandanus fascicularis* Lam.	Pandanaceae	Ethanolic extract	leaves	suppressed LPS-induced synthesis of the pro-inflammatory cytokines TNF- α, IL-1β, and IL-6, also show the Analgesic effect.	Sun-Yup Shim *et al* . [81]
10	*Macrotyloma uniflorum* (lam.) Verdc.	Fabaceae	Seed oil	Seeds	Reduces Inflammatory mediators such as bradykinin, substance P, and prostaglandins as well as pro-inflammatory cytokines like TNF- α, IL-1β, IL-6, and IL-8	Javed Ashraf [82]
11	*Solanum anguivi* Lam.	Solanaceae	hydroalcoholic extract	Fruit	Antioxidant Anti-inflammatory	Aisha Musaazi Sebunya Nakitto *et al* . [83]
12	*Tapak Liman (Elephantopus Scaber)* leaves	Asteraceae	Ethanolic extract	Leaves	Inhibit the COX-2 Diminish inflammatory agents such as prostaglandins, TNF, leukotrienes, nitric oxide, and bradykinin derived from arachidonic acid. antioxidant	Riski Sulistiarini *et al* . [84]
13	*Achillea millefolium* L	Asteraceae	hydroalcoholic extract	Leaves	anti-secretory and gastroprotective, Antiulcerogenic antioxidant	Aynaz Mahmoudi *et al* . [85]
14	*Aesculus hippocastanum* L	Sapindaceae	glycerolic extract	Seed	anti-inflammatory, venotonic, and vascular protective effects and antioxidant activity	Dragos Paul Mihai *et al* .[86] Ismail Küçükkurt *et al* . [87]
15	*Vitis vinifera* L	Vitaceae	Ethanolic	leaves	analgesic and antipyretic effects, antioxidant effects	Dragos Paul Mihai *et al* .[86] Nassiri-Asl. M. *et al* . [88]
16	*Bryonia alba* L.	Cucurbitaceae	methanolic	Root	Anti-inflammatory and antinociceptive	Mert Ilhan *et al* . [89]
17	*Juniperus sabina* L	Cupressaceae	Ethanolic extract	Seed and leaves	Anti-inflammatory (inhibit COX enzyme as well as LOX, significantly reduce the PG level and other inflammatory mediators antioxidant and analgesic	Jun Zhao *et al* .[90]
18	*Aloe vera* (L.) Burm. f.	Liliaceae	Methanolic extract	Gum	anti-viral, anti-fungal properties analgesic, antipyretic, and anti-inflammatory	Mehdi Mohammadian Amiri *et al* . [91]
19	*Tridax procumbens*	Asteraceae	Ethanolic extract	Whole Plant	Decreases pro-inflammatory mediators like TNF-α, IL-1ß, IL-6 also show venotonic activity (decrease iNO) and anti-oxidant activity	Nallajerla *et al* . [92]
20	*Annona muricata* L.	Annonaceae	Ethanolic extract	Leaves	Reduce COX-2 and TNFα Anal tissue protective Anti-inflammatory, analgesic, antioxidant	Nurul Qurrota Ayun *et al* . [93]
21	*Amorphophallus paeoniifolius*	Araceae	Methanolic extract	Tuber	Reduce blood levels of cytokines (TNF-α and IL-6), as well as suppress myeloperoxidase activity and lipid peroxidation in anorectal tissue.	Yadu Nandan Dey *et al* . [94]
22	*Capsella bursa-pastoris*	Brassicaceae	Ethanolic extract	flowers, leaves, and stalk	Decreases the production of COX-II and soluble factors such as IL-6, kinins, lipid metabolites, TNF-α, and nitric oxide.	Betul Apaydin Yildirim *et al* [95]
23	*Graptophyllum pictum* (L.) Griff.	Acanthaceae	ethanolic extract	Leaves	antioxidant, anti-inflammatory, and hemostatic properties suppression of IL-6, IL-8, and TNF-α activity	Idha Kusumawati *et al* . [70] Yulia Ratnasari.[96]
24	*Blumea lacera* (Burm.f.) DC.	Asteraceae	ethanolic extract	Leaves	Reduce interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) levels. Enhance Superoxide Dismutase (SOD) Activity and show antioxidant effect Reduce plasma exudation in anal tissue	Tarkeshwar Dubey *et al* . [97]
25	*Lawsonia inermis*	Lythraceae	ethanolic extract	Leaves	notable decrease in plasma neutrophils, IL-6, TNF-α, and other serum proinflammatory mediators	Sai Krishna Nallajerla *et al* . [72]

weight between 180 to 200 g are divided into six groups, each containing six animals (normal control, induction control, reference standard, treatment 1, 2, and 3)

The application of jatropha is done by soaking a sterile cotton bud in Jatropha oil and insert into the anus (about 20 mm deep) of a rat and keep for 20 seconds in all groups (except normal control). This application is given for five days. A day after induction, all groups will be subjected to their relevant treatment for the next five days (Once a day). On the 5th day, 1-hour after relevant treatment, record the body weight of all rats, then sacrifice rats (with an overdose of CO_2) for histopathological observation and recto-anal coefficient (RAC) determination and collect the blood samples from the retro-orbital route for biochemical evaluation.[71]

Parameters

- Body weight
- Severity score
- Recto-anal coefficient (RAC)

RAC is calculated by weighing the rectoanal tissues and comparing the resultant value to the body weight of each individual rat. This process helps in determining the degree of inflammation and it is accomplished by applying the following formulas:

Rectoanal coefficient = wt. of rectoanal tissue (mg)/ Body weight (g).[72]

- Quantitative evaluation of plasma exudation (Evans blue dye) Three hours after treatment, the rats are euthanized by deep thiopental sodium anesthesia, and their rectoanal tissues, measuring about 20 mm, are removed and weighed. The tissues were then exposed to EB dye extraction using 2 mL of formalin. The absorbance of the sample at 620 nm was measured using a UV-visible spectrophotometer to estimate the amount of EB dye.[73]
- Serum inflammatory cytokines (PEG-2, TNF-∝, IL-6)
- Histopathological examination (inflammation, congestion, hemorrhage, vasodilation and necrosis).

Anti-hemorrhoidal Activity by Medicinal Plants

Different medicinal plants belonging to different families show anti-hemorrhoidal activity in experimental animals. Their mechanism of action, extraction, and part of the plant are summarized in Table 4.

Conclusion

Hemorrhoid is a colorectal disease characterized by inflammation, elongation, and distal dislocation of anal cushions that affects millions of individuals worldwide. It leads to the main cause of morbidity in the majority of society. Most commonly, hemorrhoids are classified according to Golingher's classification, which divides hemorrhoids into four different grades. First-degree hemorrhoids are typically managed with a pharmacological approach, utilizing anti-inflammatory agents, local anesthetics, NSAIDs, flavonoids, and venotonics, which are available in various formulations such as oral pills, ointments, creams, and suppositories. In contrast, operative interventions like RBL, hemorrhoidectomy and injection sclerotherapy are commonly employed for prolapsing hemorrhoids. However, these surgical modalities are associated with potential post-operative complications, including but not limited to bleeding, irritation, urinary retention, wound infection, anal stenosis, and ectropion. For the preclinical evaluation of drugs or compounds which show anti-hemorrhoidal activity two preclinical models were used, namely Croton oil-induced hemorrhoids and Jatropha oil-induced hemorrhoids.

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