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Review article

Euphorbia Prostrata - A Clinically Proven Drug in Hemorrhoids – Multiple Pharmacological Actions Targeting Pathological Processes

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ABSTRACT

Hemorrhoids are one of the most common anorectal disorders. They affect millions of people around the world and represent a major medical & socioeconomic problem. The pathogenesis of hemorrhoids can be explained on the basis of the "sliding anal canal lining theory". The abnormal dilatation & distortion of the vascular channels, together with destructive changes in the supporting connective tissue within the anal cushion leading to downward displacement of the anal cushion, forms the essence of hemorrhoidal pathogenesis. Bleeding per rectum, anal discharge, itching, pain, feeling of heaviness & discomfort are the most common symptoms of a hemorrhoidal patient. Medical management forms an important part in the treatment of a patient. They are used as a part of conservative management or as an adjuvant to invasive outpatient or surgical procedures. *Euphorbia Prostrata* (Flavonoids, Phenolic Compounds, Tannins) has been proven to be effective in the management of symptomatic hemorrhoids. It provides excellent relief in symptoms like bleeding per rectum, pain, itching & pruritus, feeling of heaviness & discomfort due to its multiple activities. These pharmacological actions enable the drug to act at every level of the hemorrhoidal pathogenesis to provide quick relief & improve quality of life of the patients.

KEY WORDS: *Euphorbia Prostrata*, Flavonoids, Hemorrhoids, Phenolic Compounds, Piles, Tannins.

INTRODUCTION

Hemorrhoids are one of the most common anorectal disorders encountered in the general population as well as in clinical practice. They affect millions of people around the world and represent a major medical & socioeconomic problem.Hemorrhoids are defined as the symptomatic enlargement and distal displacement of the normal anal cushions [1]. The true prevalence of hemorrhoids is difficult to ascertain as patients are reluctant to seek proper medical attention due to various personal, cultural or socio-economic reasons, visit quacks for treatment & also have a tendency to self-medicate.However, it is common in both the sexes. The peak age is 45-65 years & about 50% of people have hemorrhoids by the time they reach 50[1,2]. Risk factors for hemorrhoids are chronic constipation, prolonged sitting or standing, pregnancy, obesity, prolonged sitting on the toilet, heavy lifting, pelvic or abdominal tumors, etc.

The exact pathophysiology of hemorrhoidal development is poorly understood. The age- long theory that hemorrhoids were caused by varicose veins in the anal canal is now obsolete as hemorrhoids & anorectal varices are proven to be distinct entities. Today, the most popular and well accepted theory to explain hemorrrhoidal pathogenesis is the "sliding anal canal lining theory". *Euphorbia Prostrata (EP)* dried extract is being used in the medical management of hemorrhoids for almost a decade. The active principles of this clinically proven drug are chiefly flavonoids, phenolic acid and tannins [3].These active principles are responsible for the multi-modal actions of *Euphorbia Prostrata*. It is a popular treatment for early symptomatic improvement in

bleeding hemorrhoids & has proven its clinical efficacy in various clinical studies [3,4].

Pathogenesis of Hemorrhoids

Multiple factors have been claimed to be responsible for hemorrhoidal development, including constipation & prolonged straining. The pathogenesis of hemorrhoids can be explained on the basis of the "sliding anal canal lining theory". Patients of hemorrhoids generally have high resting anal pressure and this pressure increases further due to constipation & straining at defecation. The high anal pressure impedes venous return & leads to dilatation & distortion of the anorectal venous plexuses & stasis of blood. The stasis leads to activation of the white blood cells followed by release of inflammatory mediators like prostaglandins, TXA_2, TGF-β, interleukins, etc. These inflammatory mediators bring about the disruption of the capillary bed & destructive changes in the supporting connective tissue of the anal cushions. Increased production of reactive oxygen species contribute to the destructive changes in the anal cushions. The high resting anal pressure & dilatation of the vascular channels along with the destructive changes, leads to downward displacement of the anal cushions and formation of hemorrhoids.

The damage caused by the inflammatory mediators leads to increased capillary permeability, fragility & necrosis of the anal cushion. This weak and fragile tissue can easily undergo injury during defecation and leads to bleeding. Per rectal bleeding is the most common complaint for which a hemorrhoidal patient will visit his physician. Edema & swelling due to increased capillary permeability is the basis of heaviness & discomfort that the patient experiences. Some patients also complain of increased mucoid discharge, anal itching & pruritus. Most common complication of hemorrhoids is iron deficiency anemia due to blood loss at every act of defecation. Hemorrhoids also cause severe pain when they undergo strangulation or thrombosis. Other complications of hemorrhoids include ulceration of the hemorrhoidal mass and superimposed infection & suppuration [5, 6].

Hemorrhoidal Management

Therapeutic treatment of hemorrhoids ranges from dietary & lifestyle modifications to medical treatment to radical surgery depending upon the degree & severity of the symptoms. The treatment initially is however aimed at reliving symptoms as quickly as possible. Today, modern as well as traditional drugs are being used increasingly in various grades of hemorrhoids. These drugs (oral, local or many times both) are used as a part of conservative management or as an adjuvant to invasive outpatient or surgical procedures [4]. Patients of advanced grades who are unwilling to undergo surgery, medical management in these patients provide adequate symptomatic relief to improve quality of life.

Flavonoids, Phenolic Compounds, Tannins in *Euphorbia Prostrata*

EP is approved by the Drugs Controller General of India (DCGI) as a 'Drug of Modern Medicine'. *EP* is also Patented in U.S. and European regulated markets for treatment of anorectal diseases including hemorrhoids & colonic diseases. Active principles of *Euphorbia Prostrata* include flavonoids, phenolic compounds & tannins. Flavonoids & Phenolic compounds have been reported to have anti-inflammatory, anti-oxidant, hemostatic, antithrombotic & vasoprotective actions. Tannins are known to possess astringent & hemostatic properties. The chemical analysis of *EP* revealed that it consists of Flavonoids like Apigenin, Apigenin-7-glucoside, Luteolin & Luteolin-7-glucoside; and phenolic compounds like Gallic acid & Ellagic acid [6]. [see **Table 1**]

Table: 1 Active Constituents of *Euphorbia Prostrata* & Their Pharmacological Actions Targeting Hemorrhoidal Pathogenesis.

Sr No.	Composition	Components	Action
1.	Flavonoids	Apigenin, Apigenin-7 Glucoside, Luteolin, Luteolin-7 Glucoside	Anti-inflammatory Anti-oxidant Wound Healing Anti-allergic Analgesic Anti- edema
2.	Phenolic Compounds	Gallic Acid, Ellagic Acid	Anti-inflammatory Anti-oxidant Hemostatic Anti-allergic
3.	Tannins		Astringent Hemostatic Wound Healing

Active Constituents of *Euphorbia Prostrata* Targeting Hemorrhoidal Pathogenesis

Apigenin, Luteolin & Ellagic Acid have been reported to have anti-*inflammatory* activity. Apigenin is a potent inhibitor of transcriptional activation of both cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) enzyme in lipopolysaccharide activated macrophages. In addition, apigenin profoundly reduces the TNF-α stimulated upregulation of VCAM-1, ICAM-1 & E-selectin mRNA [7,8,9]. Luteolin inhibits nuclear factor- κB mediated gene expression and pro-inflammatory cytokine production in murine macrophages. Apart from this, Luteolin also increases expression of anti-inflammatory cytokine IL-10 [10]. Ellagic Acid inhibits IL-1 beta induced adhesion molecule expression [11]. Altogether, they inhibit leucocyte activation, migration & adhesion as well as inhibit the production of various inflammatory mediators & cytokines.

EP possesses anti-oxidant activity as Ellagic Acid & Luteolin inhibit lipid peroxidation, thereby reducing free radical generation. They also increase enzyme glutathione reductase and reduced glutathione which result in increased scavenging activity and reduction of the reactive oxygen species. They also increase levels of other anti-oxidant enzymes like catalase & superoxide dismutase [12,13]. The Tannin component of *EP* has astringent like property. They bring about precipitation of the surface protein and toughen the anal mucosa. This leads to faster wound healing and significant reduction in bleeding, there by validating its hemostatic activity. Ellagic Acidactivates Factor XII (Hageman Factor) thereby activating intrinsic blood coagulation and contributing to the hemostatic activity [6,14]. The combined activity of Tannins & Ellagic Acid leads to early cessation of bleeding in hemorrhoidal patients.

Gallic Acid &Ellagic Acid which are major constituents of *EP* have shown to suppress histamine release in-vivo. Also Flavonoids, inhibit phospholipaseA2, and 5-Lipooxygenase, there by reducing production of leukotrienes (LTs) which are important mediators for an allergic response. Flavonoids also reduce IgE production by inhibiting IL-4, IL-13 & CD40 [15,16]. These actions help in reducing the anal itching & pruritis in hemorrhoidal patients. *EP* has also shown to cause improvement in venous tone, increased lymphatic drainage, protection of capillary bed microcirculation & reduced capillary permeability. Flavonoids have been shown to have edema reducing properties. They bring about regression of the hemorrhoidal mass & decrease the sense of fullness & heaviness experienced by the patient [6,7].

A number of patients experience pain and discomfort due to hemorrhoids. Complications like strangulation & thrombosis cause intense, unbearable pain. Flavonoids & Tannins also have shown to have an analgesic activity. They act by inhibiting phospholipase A2 & COX-2 & thereby inhibit production of prostaglandins, an important pain mediator [17]. **[Figure 1**and**Figure 2]**

Figure 1: Multiple Actions of *Euphorbia Prostrata* (Flavonoids, Phenolic Compounds, Tannins) Targeting Hemorrhoidal Pathogenesis

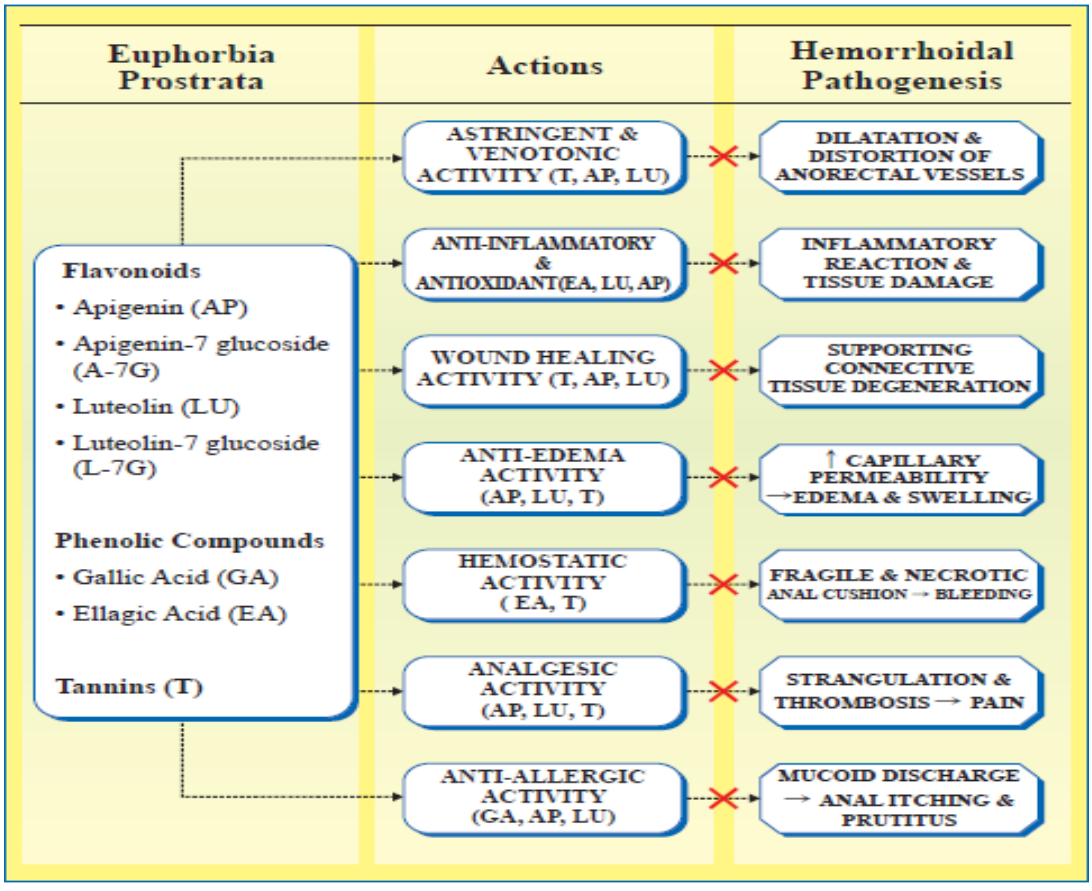
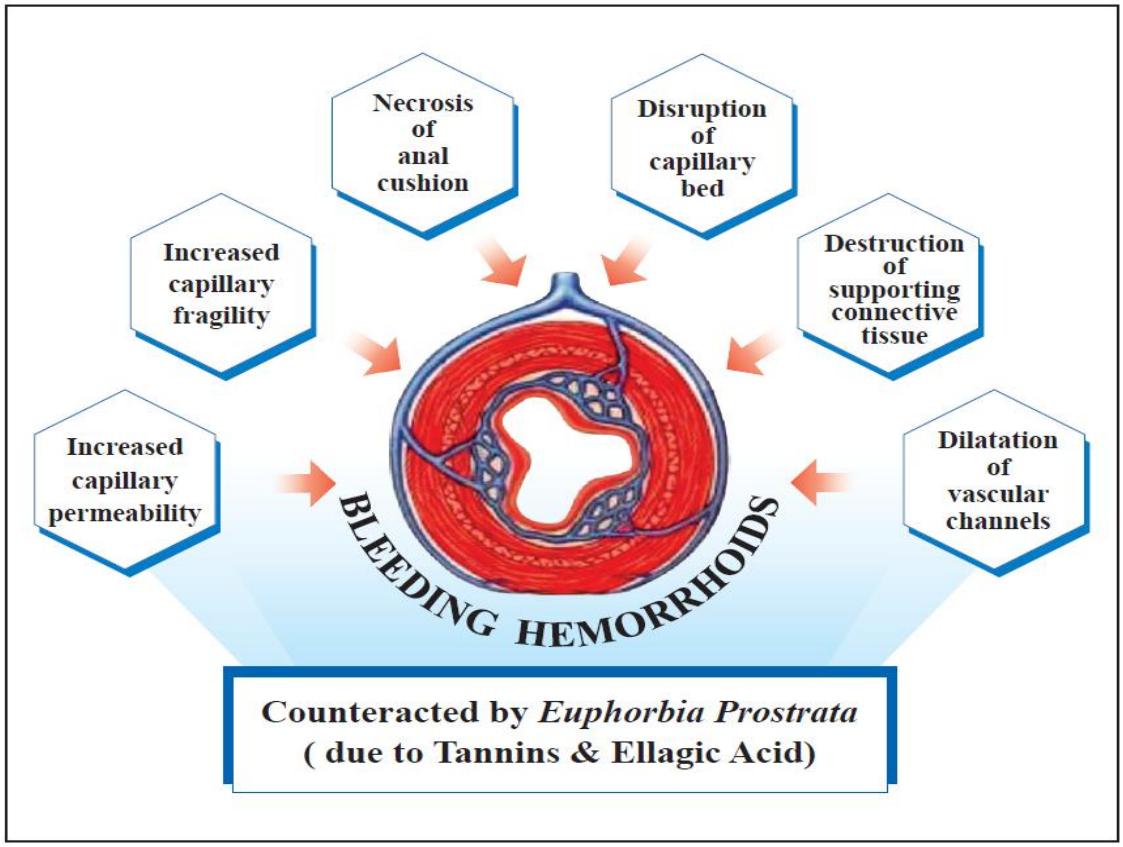


Figure 2: Pathological Processes Causing Hemorrhoidal Bleeding Counteracted Mainly due to Pharmacological Action of Tannins & Ellagic Acid in *Euphorbia Prostrata*



Oral & Topical Use of *Euphorbia Prostrata* in Hemorrhoids

Euphorbia Prostrata is available in India under the brand name *Thank OD* marketed by Panacea Biotec Ltd. since the last 8 years. It is generally prescribed in the dosage of 100 mg once daily for 14 days. In a post marketing surveillance study in 1896 patients, *EP* showed maximum improvement in patients during the first 3 days of therapy. Hence, it shows excellent efficacy early in the course of treatment and provides fast symptomatic relief to the patient. A very small number of adverse events were seen with *EP* which observed are mild and transient in nature [3]. *EP* dry extract is available as an oral (*Thank OD Tablet 100mg*) formulation as well as for topical application *(Thank OD cream 10 mg/g*).

It is also available as a fixed dose combination with Calcium Dobesilate 500 mg (*Thank OD Forte*) for oral use and as a topical combination with Lidocaine 3% w/w (*Thank OD LD*). Calcium Dobesilate acts by decreasing capillary permeability & increasing lymphatic drainage, thereby reducing the edema & discomfort associated with hemorrhoids. Lidocaine is used in the symptomatic treatment of painful hemorrhoids for decades now, but it does not alter the disease progression. The combination of *EP* with Lidocaine provides symptomatic improvement in pain as well as acts on the different pathological processes, thus improving the disease status of the patient. All these drugs are indicated in the treatment of external as well as internal hemorrhoids.

CONCLUSION

Hemorrhoids results from dilatation & distortion of the anorectal venous plexuses in the distal anal canal. The connective tissue supporting this vascular tissue when weakened, leads to descent & prolapse of the hemorrhoids. *Euphorbia Prostrata* is generally recommended in the dose of 100 mg for 14 days. Due to its anti-inflammatory, anti-oxidant, wound healing, hemostatic, anti-allergic, anti-edema & analgesic activities it provides excellent relief in symptoms like bleeding per rectum, pain, itching & pruritus, feeling of heaviness & discomfort etc.

Pharmacological actions of Flavonoids, Phenolic Compounds, Tannins, achieve this by acting at against the hemorrhoidal pathogenesis and brings about significant & early improvement in patients suffering from hemorrhoids. It is indicated in internal as well as external hemorrhoids, as a part of medical management or as an adjuvant to invasive surgical procedures. Due to its wound healing activity and its property to strengthen the anal mucosa, it has been approved by DCGI to use Euphorbia Prostrata (100mg tablets twice a day for 14 days) in 3rd& 4th degree haemorrhoids after hemorrhoidectomy. This approved indication is very significantly important for surgeons to use Euphorbia Prostrata in patients undergoing hemorrhoidectomy.

Declaration of Interest

The all authors declare of not having any conflict of interests or competing interests in preparing this article. Dr

Ashwin Porwal was involved in the concept and preparation of text of the article. Dr Kunal Khobragade and Dr. Sagar Jagtiani were involved in the data collection and providing scientific information.

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