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Original article

Clinical Efficacy of Concurrent Therapy with Oral FDC Tablet of *Euphorbia Prostrata* plus Calcium Dobesilate and Topical FDC Cream of *Euphorbia Prostrata* plus Lidocaine in the Management of Haemorrhoids: A Prospective, Open-Labeled Multicentric Study

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ABSTRACT

Objective: Haemorrhoids are associated with bleeding, pain, itching, exudation and swelling. So there is an unmet need for effective treatment by both oral and topical drugs. Hence this study was designed to evaluate the efficacy of oral *Euphorbia Prostrata* fortified with Calcium Dobesilate and topical cream of *Euphorbia Prostrata* with Lidocaine. **Methods:** The study was a prospective, open label, single arm, multicentric study, in 30 patients with hemorrhoids treated with oral FDC *Euphorbia Prostrata* extract 100 mg plus Calcium Dobesilate 500 mg and topical FDC cream of *Euphorbia Prostrata* extract 1% w/w plus Lidocaine 3% w/w for 14 days.Symptoms like bleeding, pain, itching, exudation and swelling were assessed and scored during and at the end of the study. **Results:** There was decline from the baseline value scores right from day 4 i.e. bleeding (0.97±0.15), pain (0.60±0.13), itching (0.47±0.13), exudation (0.13±0.06) and swelling (0.43±0.09); after 7 days bleeding (0.15±0.07), pain (0.12±0.06), itching (0.15±0.07), exudation (0.15±0.07) and swelling (0.19±0.08) and after day 14 the symptoms of bleeding (0.09±0.06), pain (0.08±0.06) and swelling (0.08±0.06) were almost cured while symptoms like itching (0.00±0.00), exudation (0.00±0.00) disappeared completely. There was reduction in the number of patient's population with symptoms towards the end of the study. **Conclusion:** Oral *Euphorbia Prostrata* extract 100 mg fortified with Calcium Dobesilate 500 mg and topical cream of *Euphorbia Prostrata*extract 1% w/w with Lidocaine 3% w/w showed maximum improvement during first 4 days of therapy and achieved total improvement till the end of therapy thus providing multimodal targeted approach to treat a multimodal haemorrhoidal disease.

KEYWORDS: Calcium Dobesilate, *Euphorbia Prostrata*, Haemorrhoids, Lidocaine, Multimodal actions.

INTRODUCTION

The occurrence of haemorrhoids is extremely high across the countries and industrialized societies, with millions affected worldwide [1, 2]. The true prevalence of haemorrhoids is still unknown, but it is postulated that 50% of the population will experience hemorrhoids at some or other point in their life by the age of 50 and approximately 5% people suffer from haemorrhoids, having high prevalence in Indian population[3].

Haemorrhoids have a higher impact on quality of life and are one of the leading causes of lower gastrointestinal bleeding [4]. Normal cushioning of vascular blood flow is supported by tissues in the anal canal [5, 6]. Haemorrhoidal pathophysiology which is still poorly understood, but is thought to be multifactorial including; sliding anal cushion; hyperperfusion of haemorrhoid plexus; vascular abnormality; tissue inflammation; and internal rectal prolapse [7, 8, 9]. Possible factors that may lead to enlargement of haemorrhoids are sedentary lifestyle, straining during defecation, constipation, diarrhoea, pregnancy and are common in both men and women with increasing age [10]. The exact cause of enlarged and symptomatic hemorrhoids is debated, and numerous etiologies have been suggested.

Previously haemorrhoids were considered as anorectal varices [11] but now it is postulated that it is due to sliding of anal canal lining which is widely accepted theory for haemorrhoids. Typically, there are three major anal cushions, located in the right

anterior, right posterior and left lateral aspect of the anal canal [12] Haemorrhoids enlarge when the supporting tissue of anal cushions disintegrate, deteriorate and displace downward causing venous dilation [13].

Management of haemorrhoids is initially aimed at reducing the symptoms of haemorrhoids i.e. bleeding, pain, itching and anal discomfort [14]. First and second grade haemorrhoids can usually be treated conservatively as long as symptoms are minor. If symptoms are severe, especially bleeding and pain then referral are required. Third and fourth grade haemorrhoids usually require surgery. Treatment options may include conservative procedures (high fiber diet, antimotility agents, topical analgesics and corticosteroid creams, oral flavonoids, etc.); or non-operative procedures (cryotherapy, sclerotherapy, rubber band ligation, etc.); or surgical procedures (open, closed or stapled haemorrhoidectomy and haemorrhoidectomy, etc.) [15, 16].

Various botanicals containing flavonoids like diosmin, hesperidine, apigenin, luteolinetc are used internally and topically in treatment of early grades of hemorrhoids and as adjuncts in higher grades of hemorrhoids, where surgical treatment is necessary [17]. Oral combination with topical local treatments containing both traditional and modern drugs have been effective and targeting causative pathophysiological factors that lead to haemorrhoids. The extensive collaborative research work in-between Panjab University, Pharmacy Department and Panacea Biotec Ltd. R&D introduced *Euphorbia Prostrata*(EP) to the world, pharmacological ingredients approved by DCGI- The Regulatory Authority of India in 2008 as a prescription drug.

Multiple and complex process are involved to obtain drug extracts from EP containing flavonoids (apigenin and luteolin), phenolic compounds (ellagic and gallic acids) and tannins [18]. Oral flavonoids like apigenin and luteolin have anti-inflammatory actions in bowel disease [19]. Flavonoids and phenolic acids have anti-inflammatory, analgesic, antioxidant, haemostatic, antithrombotic and vasoprotective actions [20] while tannins are known to possess astringent and haemostatic actions [21]. Importantly add on therapy of Calcium Dobesilate (CaDb) as venotonic agent decreases capillary permeability, inhibit platelet aggregation and improves blood viscosity thereby correcting underlying defects in haemorrhoids [22]. Whereas it is very much rational to use drugs specifically targeting haemorrhoidal responsible factors via external route of administration, hence cream containing EP extracts provides local relief by reducing inflammation, swelling, bleeding with highly potent local anesthetic like lidocaine to ease pain burning and itching that occurs around the hemorrhoids [23].

Haemorrhoids exhibits a multiple pathology showing symptoms like bleeding, pain, itching, exudation and swelling, hence it is essential to address all these pathological symptoms which can be achieved by targeting haemorrhoids via internal (oral) and external (topical) administration of drugs. Thus oral FDC (Fixed dose Combination) of *Euphorbia Prostrata* 100 mg plus Calcium Dobesilate 500 mg (Sitcom Forte) and topical FDC of *Euphorbia Prostrata* extract 1% w/w plus Lidocaine 3% w/w (Sitcom LD cream) have been proven to be effectiveand beneficial in treatment of the overall symptoms of haemorrhoids. Hence, the present study was aimed to evaluate the efficacy of oral Sitcom Forte and local Sitcom LD cream in patients with hemorrhoids.

MATERIALS AND METHODS

Study Design

The present study was designed as an open label, single arm and multicentric. Thirty patients with hemorrhoids were enrolled from three different clinics in Midnapore district, West Bengal, India from August 2017 to January 2018. Inform consent for participation in the study was obtained from all the patients prior to enrolment. The study was performed according to the Declaration of Helsinki.

Patients Enrollment and Follow-ups

Patients of either sex, with an average age of 38 years, who were diagnosed with hemorrhoids, and had no abnormalities on physical examination and with vital parameters, were included in the study. Pregnant and lactating women were excluded and females of child bearing potential who consented to use reliable measures of birth control were included. Patients who were using other drugs or any surgical procedure for haemorrhoids were excluded. Patients who had given the history of or suggested the presence of any significant cardiac, gastrointestinal, endocrine, neurological, liver, kidney or psychological disease were also excluded. Patients who were on drug or alcohol dependent or having any clinically significant illness four weeks prior to the screening were excluded.

On the first visit (V0 visit: Screening and enrolment), patients with hemorrhoids who were willing to participate in the study were enrolled. Medical history was recorded for each patient and full physical examination including height, weight; vital signs (blood pressure, pulse rate, temperature, and respiratory rate) were recorded. Patients were prescribed with Sitcom Forte Tablets orally (*Euphorbia Prostrata*100 mg fortified with Calcium Dobesilate 500 mg) daily on empty stomach for 14 days along with Sitcom LD cream (*Euphorbia Prostrata*Extract 1% w/w and Lidocaine 3% w/w) twice daily or after each act of defecation for 14 days. Patients were advised to return on day 4 (visit V1), day 7 (visit V2) and day 14 (visit V3); and also, can visit on any day if they had any problem or their condition deteriorated.

Investigator assessed during each visit, the local symptoms in anal region like per-rectal bleeding, pain at defecation, itching, exudation and swelling in patients. The symptoms were evaluated as mild, moderate and severe depending upon the nature of the disease and scored as 0 for no, 1 for mild, 2 for moderate and 3 for severe symptoms.

Statistical Analysis

Statistical analysis was performed using GraphPad Prism 8 software. Data were expressed as average, standard error of mean (SEM) and numbers. Patient's average scores for parameters viz. pain at defecation, itching, exudation and swelling were analyzed by using one-way ANNOVA followed by Dunnett's test. Chi-Square test was applied for number of patients showing presence or absence of symptoms. $P \leq 0.05$ were considered to be statistically significant.

RESULTS

A total of 30 patients (15 male and 15 female) of haemorrhoids were enrolled in the trial at three different clinics. There were four drop-outs at day 7 and two drop-outs at day 14. Patients enrolled in the study were with internal haemorrhoids 24, internal and external haemorrhoids 05 and external haemorrhoids 01. Patients with degree 1 or 2 were 21, degree 3 were 07 and degree 4 were 01 (Table 1).

Table 1: Demographics and Distribution of Patients (n=30)

Demography		**n (%)**
Age (Mean ± SD)	37.87±10.49	
Sex	Male	15 (50.0)
	Female	15 (50.0)
Haemorrhoids Type	Internal	24 (80.0)
	Internal & External	05 (16.6)
	External	01 (3.3)
Degree of Haemorrhoids	Degree 1 or Degree 2	21 (70.0)
	Degree 3	07 (23.33)
	Degree 4	01 (3.3)
Relapse	First Time Visit	09 (30.0)
	Relapse 2 or less than 2	05 (16.6)
	Relapse more than 2 but less than 5	05 (16.6)
	Relapse more than 5	11 (36.6)

The parameters were evaluated from mild to moderate to severe and scored (Table 2 and Graph 1) based on the patients responses on the day of visit. The baseline (V0 visit) scores showed significant improvements on day 4 (V1 visit); after 7 days (V2 visit) of treatment, the symptoms in patients were further improved and after day 14 (V3 visit) the symptoms were almost cured while symptoms like itching, exudation disappeared completely.

Table 2: Comparison of the mean scores for each symptom among the patients during the follow-up period.

Symptoms	**Bleeding**	**Pain at Defecation**	**Itching**	**Exudation**	**Swelling**
Day 0	1.97 ±0.12	1.93±0.14	1.53±0.13	0.80±0.15	0.83±0.17
Day 4	0.97±0.15****	0.60±0.13****	0.47±0.13****	0.13±0.06****	0.43±0.09*
Day 7	0.15±0.07****	0.12±0.06****	0.15±0.07****	0.15±0.07****	0.19±0.08***
Day 14	0.09±0.06****	0.08±0.06****	0.00±0.00****	0.00±0.00****	0.08±0.06****

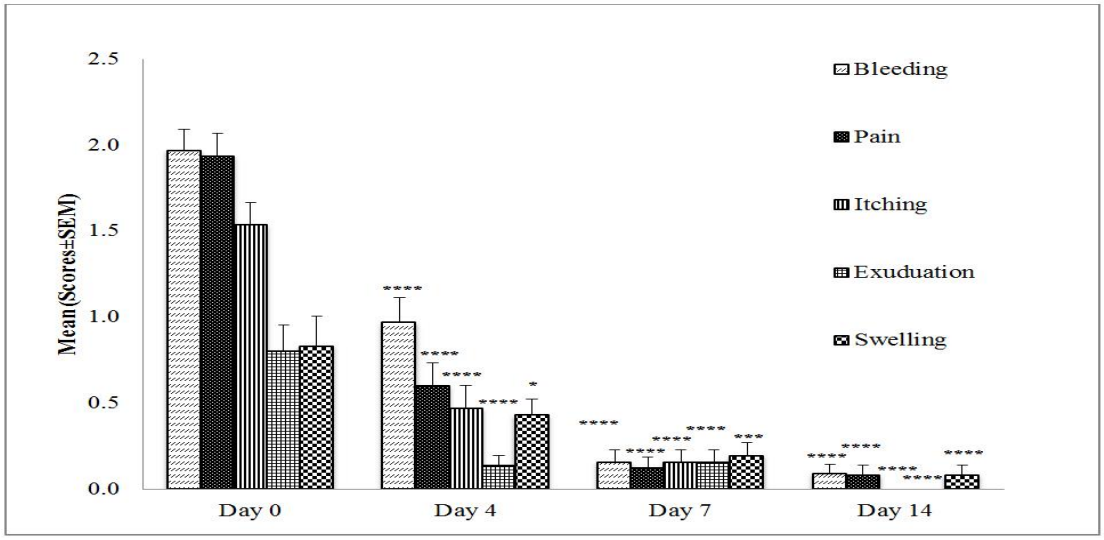
Scores (mean ± SEM) for bleeding, pain, itching, exudation and swelling before and at various days after administration of oral Sitcom Forte tablets and Sitcom LD cream for 14 days; *P<.05, ***P<.0005, ****P<.0001 in comparison to Day 0 scores respectively.

Improvement in symptoms was calculated (Graph 2) which showed decrease in all the symptoms towards the improvement in haemorrhoidal conditions from day 4, Day 7 to Day 14. The results demonstrated that co-administration of oral Sitcom Forte Tablet with topical Sitcom LD cream, in haemorrhoids showed maximum improvement during first 4 days of therapy and nearly achieved total improvement at the end of the therapy thus showing the necessity of systemic and topical drug actions which are very much required in anti-haemorrhoidal therapy.

When looking at the number of patients and percentages with different symptoms before and at subsequent visits (Table 3), majority of the patients observed absence of symptoms on day 4, day 7 and on day 14 achieving nearly an asymptomatic state.

These results indicate that both systemic and local effects are must essential in rapid and complete cure proving therapeutic efficacy of oral Sitcom Forte and topical Sitcom LD cream in haemorrhoidal patients.

Graph 1: Scores for each symptoms among the patients during the follow-up period.



Scores (mean ± SEM) for bleeding, pain, itching, exudation and swelling before and at various days after administration of oral Sitcom Forte tablets and Sitcom LD cream for 14 days; *P<.05, ***P< .0005, ****P<.0001 in comparison to Day 0 scores respectively.

Table 3: Number of Patients with presence and absence of symptoms before and after treatment with oral Sitcom Forte tablets (EP + CaDb) and topical Sitcom LD cream (EP + Lidocaine) for 14 days

Symptom	Day 0		Day 4			Day 7			Day 14		
	Present	Absent	Present	Absent	*P*	Present	Absent	*P*	Present	Absent	*P*
Bleeding	30 (100%)	0 (0%)	20 (66.66%)	10 (3%)	***	4 (15.38%)	22 (84.61%)	****	2 (8.33%)	22 (91.66%)	****
Pain	30 (100%)	0 (0%)	14 (46.66%)	16 (53.33%)	****	3 (11.53%)	23 (88.46%)	****	2 (8.33%)	22 (91.66%)	****
Itching	29 (96.66%)	1 (3.33%)	10 (33.33%)	20 (66.66%)	****	4 (15.38%)	22 (84.62%)	****	0 (0%)	24 (100%)	****
Exudation	18 (60%)	12 (40%)	4 (13.33%)	26 (86.66%)	***	4 (15.38%)	22 (84.62%)	***	0 (0%)	24 (100%)	****
Swelling	16 (53.33%)	14 (46.66%)	13 (43.33%)	17 (56.66%)	-	5 (19.23%)	21 (80.77%)	**	2 (8.33%)	22 (91.66%)	***

Number of Patients (%) with and without symptoms of bleeding, pain, itching, exudation and swelling before and at various days after administration of oral Sitcom Forte tablets and Sitcom LD cream for 14 days; **P< .005 ***P< .001 and ****P< .0001.

Graph 2: Improvement in Symptoms (percentage change):

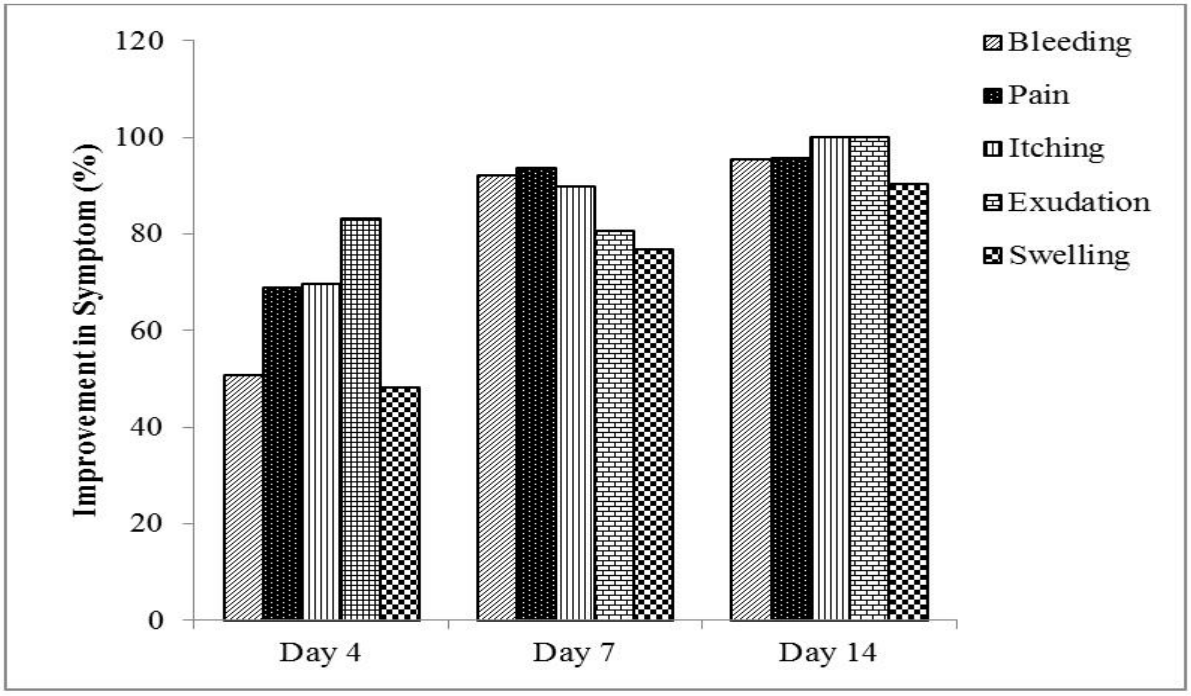
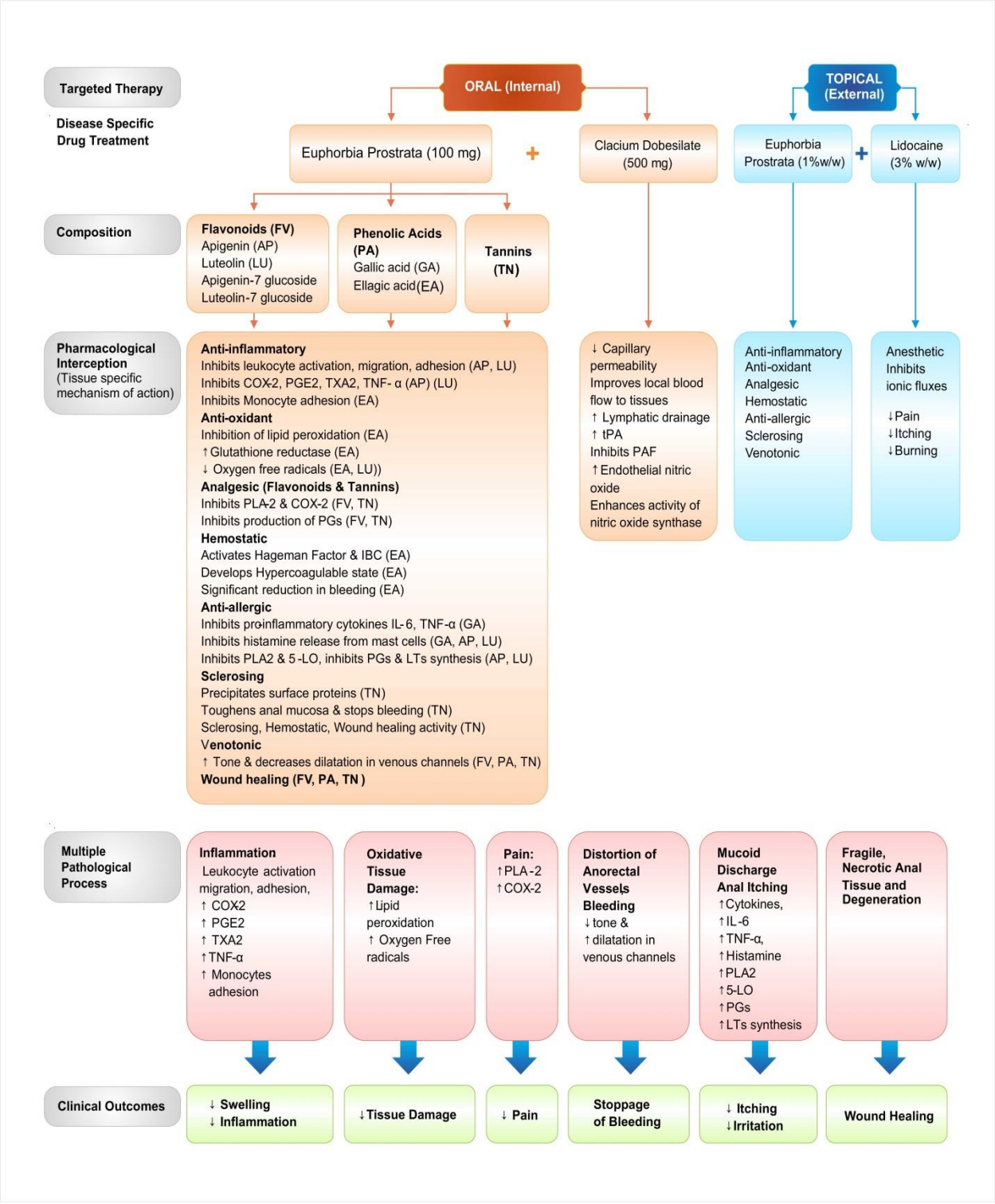


Figure 1: Targeting multiple Pathological Processes withoral Sitcom Forte tablets (EP + CaDb) (internally) and with Sitcom LD cream (EP + Lidocaine) (externally) in the management of Haemorrhoids.



Source; Strategic Medical Affairs, Panacea Biotec Ltd.

PAF: platelet activation factor, tPA tissue plasminogen activator, COX-2 Cyclooxygenase enzyme, PLA-2Phospholipases A2, PGs Prostaglandins, IL-6 Interleukin 6, TNF-α Tumor necrotic factor, PGE2Prostaglandin E2, TXA2Thromboxane A2, 5 LO 5-lipoxygenase, ↑ Increase/Stimulation, ↓ Decrease/Inhibition.

DISCUSSION

Euphorbia Prostrata [EP] extract is used in the treatment of haemorrhoids [24] and is available as prescription drug approved by DCGI in 2008 after submission of multicentric phase III clinical trials conducted at Department of Surgery in various hospitals across India. EP is available in the form of tablet and cream either as a single component or in combination with CaDb (oral) and Lidocaine (cream). Our study demonstrated that the oral Sitcom Forte and topical Sitcom LD cream were clinically efficacious in treatment of overall symptoms of haemorrhoids.

Haemorrhoidal patients show a multiple pathological changes like vasodilation, thrombosis, degenerative collagen fibers, fibro-elastic tissues with rupture and distortion of anal muscle accompanied by inflammation around the vessel wall and surrounding tissues [25]. High anal pressure impedes venous return leading to dilatation and distortion of the anorectal venous plexuses with stasis of blood. This stasis leads to activation of the white blood cells followed by release of inflammatory mediators like prostaglandins, TXA2, TGF-β, interleukins, etc. causing disruption of the capillary bed and aggravate destructive changes in the supporting connective tissues [18]. Various mediators have been reported to cause damage to the supporting anal cushioning tissues; mast cells cause several changes at the tissue by releasing histamine and leukotrienes which induce vasoconstriction and vascular permeability, while platelet activation factor, increase thrombolytic aggregation and vasodilation. Enzymes, like tryptase and chymase, promote vascular breakdown [26], while matrix metalloproteinase (MMP-9) causes degradation of proteins like elastin, fibronectin and collagen. Transforming growth factor-β (TGF-β) promotes anigoproliferation activity and neovascularization. Vascular endothelial growth factors (VEGF) expression is also increased in haemorrhoidal tissues [27]. Itching and irritation are caused due to mucus discharge at prolapse [10].

There is increase in production of reactive oxygen species which further contributes to the destructive changes in the anal cushions. A number of noxious free radicals are formed in the anal tissues due to injury, further this damaged tissue causes bleeding resulting in degradation of hemoglobin due to exposure to hydrogen peroxidase generated by neutrophils and xanthine oxide, which consequently releases catalytic iron ions and toxic free haem that are capable of initiating or aggravating lipid peroxidation [28].

Thus, all the above factors aggravate and results in bleeding, swelling, pain, exudation and irritation in patients suffering from haemorrhoids. Figure 1 shows various pathological changes in haemorrhoids v/s multimodal actions of the Sitcom Forte and Sitcom LD cream treatment.

The earlier clinical trials conducted across the country on oral EP dry extract have shown reduction in the symptoms of bleeding, pain, itching and prolapse in patients with first and second degree haemorrhoids. [7, 29, 30] The current study was hence undertaken to analyze the efficacy of combination treatment with oral Sitcom Forte tablet and topical application of Sitcom LD cream in patients suffering from haemorrhoids. *Euphorbia Prostrata*contains flavonoids like apegenin, leutolin, apigenin-7 glucoside, luteolin-7 glucoside, phenolic compounds like gallic and ellagic acids and tannins produce multimodal actions like anti-inflammatory, analgesic, antioxidant, haemostatic, antithrombotic and vasoprotection which effectively treat sign and symptoms specific for haemorrhoids [21].

Various studies have proven the effectiveness of flavonoids in treatment of haemorrhoids. Flavonoids like apegenin and leutolin are reported to produce inhibition of leukocytes, COX-2, PGE2, TXA2, TNF-α, adhesion molecules (VCAM, ICAM, Selectins) and transcription of inflammatory mediators while phenolic compound like ellagic acid inhibits monocyte adhesion, thus these flavonoids produce an overall anti-inflammatory effect for EP [31,32,33]. Ellagic acid also causes inhibition of lipid peroxidation with increased glutathione reductase while leutolin activates superoxide dismutase (SOD) and catalase enzymes which results in reduction of free radical formation thus providing an anti-oxidant effect [34, 35, 36]. Thus results obtained in our study showed reduction in swelling from day 4 to day 14 which is attributed to the anti-inflammatory effects of EP.

Further ellagic acid activates Hageman Factor and intrinsic blood coagulation (IBC) developing a hypercoagulable state producing significant reduction in bleeding [37] EP did not produce any clot formation and it should be used with caution when co-administered with anti-coagulating agents. Gallic acid and flavonoids inhibits cytokines, prostaglandins, phospholipase A2 resulting in inhibition of histamine release from mast cells thus reducing anal itching and pruritis, attributing to the anti-allergic property of EP, which reflected in this study, which showed reduction in itching and exudation from day 4 which disappeared by day 14 indicating the role of EP in improvement in quality of life of the patients [38, 39], while tannins provide astringent action by protein precipitation, strengthening the anal mucosa, providing sclerosing, hemostatic and wound healing effects [40]. EP overall has a venotonic action by increasing tone and decreases dilatation in venous channels. Flavonoids and tannins present in EP produce analgesic action by inhibiting prostaglandin formation [21].

The reduction in pain was observed from day 4 and complete pain free defecation was seen in this study by day 14. CaDb is been used in treatment of haemorrhoids but it controls bleeding and edema, CaDb per se fails to act on the multi-pathological processes of haemorrhoids; hence there is a need to use oral EP in combination with CaDb. CaDb is a venotonic drug, having important actions in haemorrhoids by inhibiting capillary permeability induced by histamine, serotonin, bradykinin, also having antioxidant properties and causes release of nitric oxide [41]. A dose dependent inhibition of 6-oxy-PG, F1α, PGF2α, PGF2 and thromboxane B2 resulted in reduction of platelet aggregation. Reduction in capillary hyperpermeability by inhibiting thrombus formation and platelet deposition was observed [42]. CaDb reduced intra-lymphatic pressure and encouraged fluid entry [43]. Thus, CaDb possesses haemorheological effects by regulating microvascular permeability and reduces oedema by activating lymphatic drainage. The combinational effect of EP with CaDb was evident in this current study which showed almost complete stoppage of bleeding by day 14.

On topical application of EP in combination with Lidocaine provides relief from pain and itching and relives different pathological processes of haemorrhoids. EP produces its local anti-inflammatory, analgesic, antioxidant, haemostatic, antithrombotic and vasoprotective effects while Lidocaine reduces pain, burning sensation and itching providing fast and rapid relief [23].

The combined treatment with oral EP fortified with CaDb and topical EP with Lidocaine provides an overall symptomatic improvement in relatively all pathological processes, thus improving the disease status of the patients.Overall the present study demonstrated that the patients treated with oral Sitcom Forte and topical Sitcom LD cream for 14 days resulted in decrease of haemorrhoidal parameters like bleeding, pain, itching, exudation and swelling from day 4 (48% to 83% rsp.) and almost achieved complete relief by day 14 (90% to 100% rsp.).

CONCLUSION

In conclusion, the combination treatment of oral Sitcom Forte tablet, along with topical Sitcom LD cream targeted the multiple pathological processes of haemorrhoids, thus providing superior clinical efficacy. Although the limitation of this study was small number of patients, the results obtained in this study were similar to the earlier studies. However further trials need to be conducted in comparison to the standard anti-haemorrhoidal therapy.

Competing interest: The authors declare that they have no competing interests.

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