Clinical Evaluation of *Commiphora Mukul*, a Botanical resin, in the Management of Hemorrhoids: A randomized controlled trial

Mahdi Yousefi, Mohammad Reza Vaez Mahdavi[1], Seyed Mousalreza Hosseini[2], Abdollah Bahrami[3], Ali Davati[4], Mohammad Kamalinejad[5], Sograt Faghihzadeh[6]

Department of Traditional Iranian Medicine, Faculty of Medicine, Shahed University, Tehran, [1]Department of Physiology, Faculty of Medicine, Research Center for Clinical Trial on Traditional Iranian Medicine (RCCT-TIM), Shahed University, [2]Department of Gastroenterology and Hepatology, Ghaem Hospital, and [3]Department of Internal Medicine, Imam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran, [4]Department of Social Medicine, Faculty of Medicine, Shahed University, [5]Department of Pharmacognosy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, [6]Department of Biostatistics, Zanjan University of Medical Sciences, Zanjan, Iran

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ABSTRACT

Background: Hemorrhoids complaint is one of the most common problems in most society, especially in Asian countries. Current drug treatment protocols cannot cure the disease, and they are palliative. According to Persian traditional medicine, *Commiphora Mukul* (*CM*) resin is a medication choice. **Aim**: This randomized study was undertaken to evaluate the efficacy and safety of crude *CM* resin compared to a combination of *lactolose* and *anti-hemorrhoid* (*LandA*) in patients with uncomplicated hemorrhoids grade 1 and 2. **Materials and Methods**: This trial was carried out on 99 patients with hemorrhoids, in Ghaem and Imam Reaza Hospitals of the Mashhad University of Medical Sciences, Iran. They randomly received *CM* 3 g/d for 4 weeks (as study group) or *LandA* (*Lactolose* syrup in laxative dose for 1 month and *anti-hemorrhoid* suppository daily for 10 days) as control group. Subjective and objectives variables including painful defecation, flatulence, constipation, gastro-esophageal reflux (GER), dyspepsia, proctorrhagia, anal protrusion, and colonoscopic grading were assessed before, immediately after, and 4 weeks after the treatment period. An intent-to-treat analysis was used. Safety was assessed with evaluation of clinical adverse effects by common toxicity criteria version 4.0. Forty-nine patients were assigned randomly to receive *LandA* and 50 to receive *CM*. After 4 weeks, flatulence, dyspepsia, GER, and colonoscopic grading scores significantly decreased in study group, whereas in control group constipation, painful defecation, and proctorrhagia showed better but not significant improvement. After 4-weak follow-up, the rate of constipation, and proctorrhagia also showed significantly improvement in study group. Constipation and proctorrhagia in control group recurred significantly in 4-week follow-up than after the treatment, whereas this recurrence in test group was not seen. **Conclusion**: *CM* was more effective than *LandA* in 4-week treatment of patients with uncomplicated hemorrhoids grade 1 and 2.

Key words: *Anti-hemorrhoid*, *Commiphora Mukul*, *lactolose*, Persian medicine, randomized clinical trial (RCT), uncomplicated hemorrhoids

INTRODUCTION

Hemorrhoid complaints are one of the most common afflictions. The problem can occur at any age and can affect both sexes. It has been estimated that at least 50% of individuals over the age of 50 years have, at sometime experienced symptoms related to hemorrhoids.[1] The prevalence of hemorrhoidal disease ranging from 4.4% in the general population to 36.4% in general practice. It has been reported that 1 in 3 persons with symptomatic hemorrhoids seek medical help. Women have an increased prevalence during pregnancy and in the postpartum period.[2] In both sexes, a peak in prevalence was noted from age 45-65 years, with a subsequent decrease after age 65 years. The development of hemorrhoids before age 20 years was unusual.[3]

Numerous theories concerning the pathogenesis of

Address for correspondence:
Prof. Vaez Mahdavi M.R., Faculty of Medicine, No. 29, Abdollah zadeh St., Keshavarz Ave., Tehran, Iran.
E-mail: vaezmahdavi@shahed.ac.ir

hemorrhoids have been proposed, but the exact mechanism remains elusive. Constipation and straining were once accepted as the major cause of hemorrhoidal disease, but this is considered to be a gross oversimplification.[1] Angiogenesis is evident in hemorrhoid tissue, suggesting the possible mechanism in the pathogenesis of hemorrhoids. The direct degeneration effect of MMP9 (matrix metalloproteinase-9), on supporting structure elastic fibers in anal cushion, is another important mechanism. The high expression of iNOS (nitric- oxide synthase) suggests that the inflammatory factors involved in the pathogenesis of hemorrhoids, and NO may be involve in pathological effect on hemorrhoids.[4]

Hemorrhoidal disease can give rise to varying degree of bleeding, anal swelling, pain, discomfort, discharge, and pruritus. Bleeding is the most common presenting complaint. Hemorrhoidal disease is the most common cause of lower GI (gastrointestinal) bleeding.[5]

Colonoscopy is an accurate and best assessment method for diagnosis and colonoscopy classification of internal hemorrhoids is highly useful in evaluating the effectiveness of the treatment.[6] The use of laxatives including high-fiber diet, bulking agents, stimulants, fecal softeners, osmotic agents, show a consistent beneficial effect for relieving overall symptoms and bleeding in the treatment of symptomatic hemorrhoids.[2] Drugs which improve microcirculation, capillary flow and vascular tone, and strengthen connective tissue of the perivascular amorphous substrate, can relieve capillary impairment and venous insufficiency.[7]

The resin of *Commiphora Mukul,* (bdellium*, C. wightii*, Indian bdellium) Burseraceae, which has exuded from the bark and dried in the air, is the pale yellow granular secretion that is discharged into cavities in the bark when it is wounded. This resin is an astringent antiseptic with anti-inflammatory and demulcent properties.[8] This botanical product is traditionally stated to possess anti-microbial, astringent, carminative, expectorant, anti-catarrhal, antiseptic, and vulnerary properties.[9] Avicenna, the famous physician of Persian medicine, believes that *Commiphora Mukul* (*CM*) is one of the best herbal monotherapy for hemorrhoids, which can be used orally or topically. It is a laxative, hepatoprotective and astringent agent that can metabolize bioactive etiologic component of hemorrhoids which is traditionally called melancholy.[10] Detailed descriptions of the varieties, physical qualities, actions, uses, and indications of *CM* are available in the treatises of Charaka (1000 B.C.). *CM* resin is a complex mixture of various classes of chemical compounds such as lignans and lipids, diterpenoids, and steroids. The nature of these compounds is shown in Figure 1, and the scheme on segregation of *CM* is shown in Figure2. The gum resin of Commiphora proved to be a rich source of steroids. Of the 10 steroids isolated and characterized from the resin [Figure 3], 4 (*viz.* cholesterol and guggulsteroids I, II and Ill) are C_{27} steroids, whereas the others are pregnant derivatives.[11]

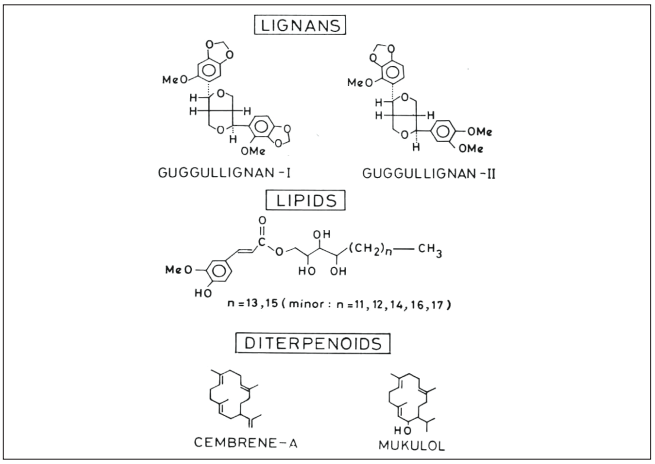

Figure 1: The lignans, lipids, and diterpenoids isolated from *commiphora mukul* gum

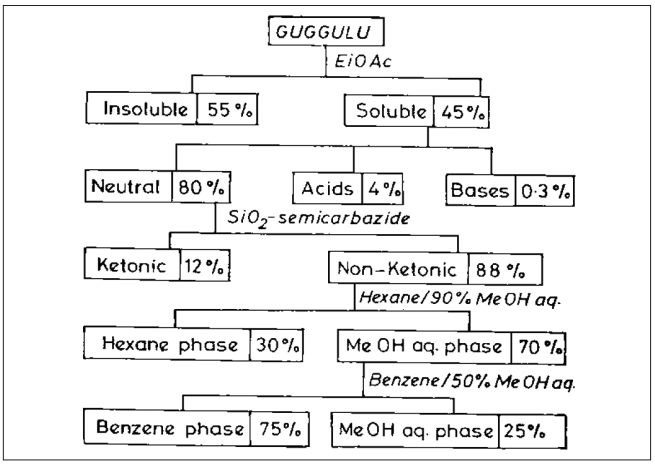

Figure 2: Scheme to show the chemical segregation process of *commiphora mukul* (Guggulu) gum

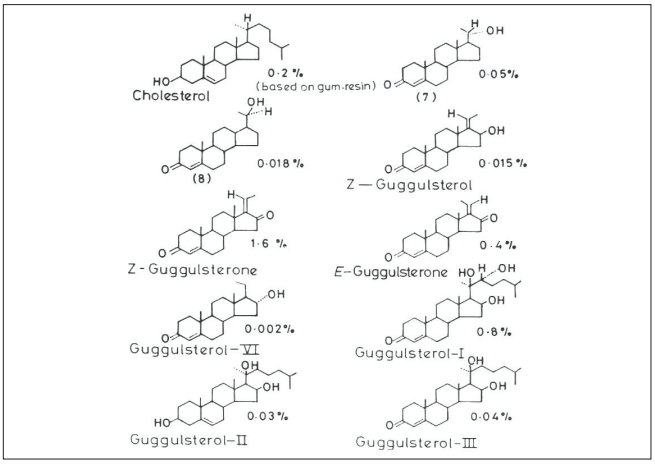

Figure 3: Steroids isolated from *commiphora mukul* gum

Relative high incidence and prevalence of this disease and poor potent effective existing therapeutic drugs, has made the search for new pharmacologically active non surgical remedies unavoidable. The scope of this work is to assess the efficacy of *CM* to treat patients suffering from hemorrhoids.

MATERIALS AND METHODS

Study design

This parallel-group, controlled study was conducted on an out-patient population addressing to the internal and surgery units of the Mashhad University of Medical Sciences (Mashhad, Khorasan, Iran) in Nov. 2010 to May 2012. After receiving informed consent, eligible patients were divided by balanced block randomization method into 2 therapeutic groups: group 1 (*CM*) and group 2 (*lactolose* plus antihemorrhoid). Patients were treated with *CM* as study (test) or combination of *lactolose* and *antihemorrhoid* (*LandA*) as control group. Study group received 3 g *CM* orally in 3 divided doses for 1 month. Control group received combination of *lactolose* syrup in laxative dose for 1 month and *antihemorrhoid* suppository daily for 10 days.

A total of 105 subjects were enrolled at the end of the screening period. Patients were divided into 2 parallel groups of 50 subjects in test and 49 in control, after the randomization procedure [Figure 4].

Eligibility criteria

Patients with uncomplicated internal hemorrhoids grade 1 and 2, who were 20-65 years of age, were eligible if their diagnosis was endoscopically confirmed. All patients who entered the treatment period were required to have developed hemorrhoidal symptoms during the preceding 3 months in the absence of any other medication. Patients with any of the following criteria were ineligible: Advanced hemorrhoids requiring surgery, presence of clinically significant renal, hepatic, or other concurrent severe disease. Concomitant use of medications known to affect pain or other symptoms of hemorrhoids was not allowed. Women who were pregnant or lactating were excluded, as patients with any important complication during the research were dropped out.

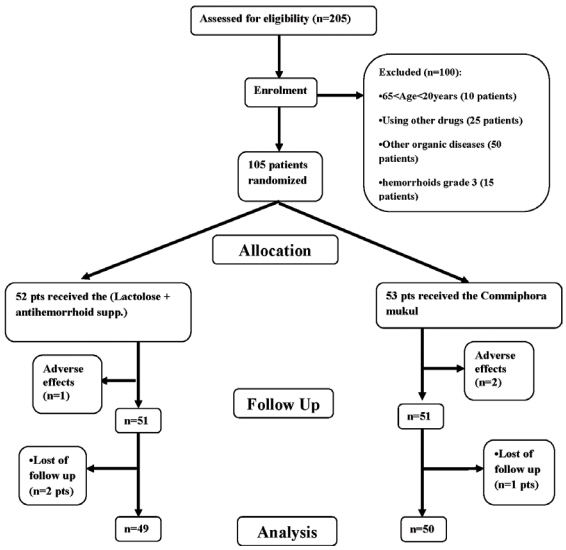

Figure 4: Flow chart summarizing the study process in the two groups

Drug preparation and dosage

Lactolose and *anti-hemorrhoid* suppository were the product of Daroopakhsh pharmaceutical company (Tehran, Iran) according to national formulary of Iran. *Lactolose* was used in syrup (10 g/15 ml) form orally in single dose (10-40 g/d) for 1 month. Patients receiving *lactolose* recommended adjusting dosage according to stool consistency such that not having constipation or diarrhea. *Anti-hemorrhoid* suppository, which is composed from Lidocaine HCL 60 mg, hydrocortisone 5 mg, Aluminium subacetat 50 mg, and Zinc oxide 400 mg, used at bedtime for 10 nights. *CM* resin which is used in this study has been harvested from the state of Gujarat in India in march 2010 and standardized to contain 4 g of (Z) and (E)-guggulstrone per 100 g on the basis of an estimation by means of high performance liquid chromatography (HPLC). Identification was carried out in pharmacy faculty of Shahid Beheshti University of Medical Sciences (Tehran, Iran) and registered by voucher number 1070. Crude purified powdered *CM* was given 3 g/d orally in 3 divided doses for 1 month.

Measurements and statistical analysis

All eligible patients who referred to Ghaem and Imam Reza Hospital of Mashhad University of Medical Sciences (Mashhad, Khorasan, Iran) in Nov. 2010 to Mar. 2012 entered the study. Patients with conventional Goligher's classification of internal hemorrhoids grade 1 and 2, colonoscopically approved and classified by criteria of range, form, and red color signs (RCS).[6] After endoscopic confirmation and grading, detailed history was taken and recorded. Demographic information, duration of hemorrhoid symptoms, and history of previous treatment were asked. Presence of constipation, proctorrhagia, anal protrusion, painful defecation, flatulence, gastro-esophageal reflux, and dyspepsia were questioned and measured on the pattern of visual analog scale (VAS). VAS scores ranged between 0-4, 5-44, 45-74, and 75-100 changed to Likert scales, i.e., 0 = absent, 1 = mild, 2 = moderate, and 3 = severe, respectively.[12]

All patients visited before, and immediately after the treatment period. A 4-week follow-up was carried out after the end of treatment course. Endoscopic scores (0-4) were measured twice, at the beginning and end points of the

treatment period. Drug complications were assessed by common toxicity criteria version 4.0.[13]

Sex and history of previous treatment were considered as nominal, age and duration of symptoms as continuous quantitative and the others as ordinal variables. Sample size was calculated using Sigma stat version 3.5, at the 0.05 significance level with 0.80 power. Randomization was performed using balanced block randomization method. Data were analyzed by SPSS (version 19) with significance accepted at the 5% level. Statistical significance between groups was determined using Chi-square, binominal, and fisher's exact tests for nominal variables and two-tailed Mann-Whitney U test for other ordinal variables because of not passing normality test, and unpaired t-test for quantitative variables if they passed normality test. Results are expressed as mean, SD, median or percentage.

RESULTS

One hundred and five patients were enrolled which include 37.4% males and 62.6% females. 99 patients completed the treatment; remaining 6 patients including 3 males and 3 females did not return for follow-up. Age range was 32 to 56 years with the average of 45.39 (±5.92) years. The most common age range was 40-49 years. 93.9% of participants were married. Forty-seven patients had history of previous treatment. Mean duration of disease was 12.35 months. Data distribution in variables such as age, disease duration, history of previous medication, and clinical grade passed normality test, whereas others were not sampled from Gaussian distribution. The groups of patients randomly allocated to receive study medication (*CM*) or control drug (*LandA*) had similar characteristics in most variables at baseline [Table 1].

The most common referral cause was rectal bleeding while the most common symptom was constipation [Table 2]. For randomization insurance, comparative tests were carried out between control and test group, that none of them was significant [Table 1]. Dependant variables including proctorrhagia, protrusion, constipation, painful defecation, flatulence, GER, and dyspepsia were assessed 3 times; at baseline, immediately after treatment period (1 month), and 4 weeks after the end of treatment course. All patients examined colonoscopically and graded twice; before and after the treatment period.

Flatulence ($P = 0.011$), dyspepsia ($P = 0.018$), GER ($P = 0.002$), and colonoscopic grade ($P = 0.004$) scores significantly decreased in study group after the treatment. After 4-weak follow-up, the rate of constipation ($P = 0.000$),

Table 1: Baseline data of the patients

variable	Control (n = 49)	Test (n = 50)	Comparative test Result (2-tailed sig.)	Normality test result (2-tailed sig.)
Age, years, mean (±SD)	46.12 (±5.4)	44.66 (±6.4)	NS (0.224)[c]	0.349[d]
Sex, n (%)			NS (0.775)[a]	0.015[e]
Male	19 (38.8%)	18 (36%)		
Female	30 (61.2%)	32 (64%)		
Duration of hemorrhoids months, mean (±SD)	12.49 (±7.2)	12.22 (±6.1)	NS (0.842)[c]	0.249[d]
History of previous treatment, n (%)			NS (0.767)[a]	0.688[e]
No	25 (51%)	27 (54%)		
Yes	24 (49%)	23 (46%)		
Clinical grade, n (%)			NS (0.919)[a]	1.000[e]
Grade 1	25 (51%)	25 (50%)		
Grade 2	24 (49%)	25 (50%)		
Marital status (%)				0.000[e]
Married	46 (93.9%)	47 (94%)	NS (0.841)[b]	
Single	3 (6.1%)	3 (6%)		
Referral cause, n(%)				
Bleeding			NS (0.613)[a]	1.000[e]
Protrusion	35 (71.4)	34 (68%)		
Pain	8 (16.3%)	11 (22%)		
Constipation	2 (4.1%)	2 (4%)		
Other GI symptom*	2 (4.1%)	0 (0%)		
	2 (4.1%)	3 (6%)		
Grade in Colonoscopy, n (%)				0.002[e]
One	30 (61.2%)	35 (70%)		
Two	19 (38.8)	15 (30%)	NS (0.402)[b]	

A = Chi-Square test, b = Fisher's Exact test, c = Independent t-test, d = Kolmogorov-Smirnov test, e = Binominal test, NS = not significant, * = including flatulence, reflux and dyspepsia

Table 2: The prevalence of symptoms at baseline

	Bleeding	Constipation	Pain	Reflux	Flatulence	Dyspepsia
Severity, n, (%)						
No						
Mild	8 (8.1%)	4 (4%)	62 (62.6%)	63 (63.6%)	21 (21.2%)	33 (33%)
Moderate	59 (59.6%)	3 (3%)	31 (31.3%)	24 (24.2%)	33 (33.3%)	56 (56.6%)
Severe	26 (26.3%)	46 (46.5%)	5 (5.1%)	7 (7.1%)	38 (38.4%)	7 (7.1%)
	6 (6.1%)	46 (46.5%)	1 (1%)	5 (5.1%)	7 (7.1%)	3 (3%)
Total						
No	8	4	62	63	21	33
Yes*	91	95	35	36	78	66

• = sum of mild, moderate, and severe

Table 3: Outcome data in two groups, immediately and four weeks after the intervention

variable	Baseline			After the intervention			4-week follow-up		
	control	test	Result (2-tailed sig.)*	control	test	Result (2-tailed sig.)*	control	test	Result (2-tailed sig.)*
Constipation Median (min-max)	2 (0-3)	2 (0-3)	NS (0.851)	0 (0-1)	0 (0-2)	NS (0.276)	2 (0-3)	1 (0-2)	S (0.000)
Proctorrhagia Median (min-max)	1 (0-3)	1 (0-3)	NS (0.607)	0 (0-2)	0 (0-3)	NS (0.239)	1 (0-2)	0 (0-3)	S (0.013)
Protrusion median (min-max)	0 (0-1)	0.5 (0-1)	NS (0.920)	0 (0-1)	0 (0-1)	NS (0.619)	0 (0-1)	0 (0-1)	NS (0.487)
Painful defecation Median (min-max)	0 (0-2)	0 (0-2)	NS (0.669)	0 (0-2)	0 (0-2)	NS (0.206)	0 (0-2)	0 (0-3)	NS (0.749)
Flatulence Median (min-max)	1 (0-3)	1 (0-3)	NS (0.994)	1 (0-3)	0 (0-3)	S (0.011)	1 (0-3)	0 (0-1)	S (0.000)
GER Median (min-max)	0 (0-3)	0 (0-3)	NS (0.758)	0 (0-3)	0 (0-2)	S (0.002)	0 (0-2)	0 (0-1)	S (0.005)
Dyspepsia Median (min-max)	1 (0-3)	1 (0-3)	NS (0.452)	1 (0-3)	0 (0-2)	S (0.018)	1 (0-3)	0 (0-3)	S (0.004)
Colonoscopic grade median (min-max)	1 (1-2)	1 (1-2)	NS (0.360)	1 (1-2)	1 (1-2)	S (0.004)			

NS = not significant, S = significant, GER = gastro esophageal reflux • = *P*- value (Mann-Whitney test)

and proctorrhagia ($P = 0.013$) also showed significant improvement in study group. Constipation and proctorrhagia in control group recurred significantly in 4-week follow-up compared with after the treatment, whereas this recurrence in test group was not observed. [Table 3].

Adverse effects

One patient in control and 2 in study group did not complete the treatment period because of allergic reaction and severe GI upset, respectively. The most common adverse effect in control group was diarrhea, whereas abdominal cramp was the most common in study group [Table 4]. Diarrhea managed by decreasing *lactolose* dosage and abdominal cramp decreased in 2nd week of treatment spontaneously.

Table 4: Drug adverse effects in two groups

Group	Side effects, *n* (%)	Sum (%), mean (±SD)	Result (*P* value)
Control	Diarrhea, 4 (8.1%), Flatulence, 3 (6.1%), abdominal cramp, 2 (4.08%), nausea, 2 (4.08%), skin rash, 1 (2.04%)	12 (24.48%), 0.24 (±0.43)	
Test	Abdominal cramp, 5 (10%), Diarrhea, 4 (8%), anorexia, 2 (4%), irregular menstruation, 1 (2%), severe GI irritation, 1 (2%)	13 (26%), 0.26 (± 0.44)	NS (0.8968)

• NS = not significant

DISCUSSION

In this study, more than 50% of patients were in age range 40-49 years, and this may show important effect of life style on hemorrhoids pathogenesis. Over 70% of patients were in age range 30-49 years that is very

important from social and economical viewpoint. More than 93% of participants were married that shows low prevalence in age below 30. Distribution of sex was not normal. This can be interpreted as more common risk factors in women than in men, factors such as low physical activity, obesity, pregnancy, etc. or may be due to more fear of rectal bleeding in women than in men. Almost half of patients experienced previous treatment, and this can show low efficacy of current medical treatment for hemorrhoids grade 1 and 2. Mean duration of disease was about 1 year. Embarrassment in expression of anal discomfort, symptom tolerability, and self-medication by soothing agents may be of delayed reference to the physician and varied prevalence and incidence in different society. Rectal bleeding was the most common referral cause, but among symptoms, constipation was the most. It can probably postulate that people are more sensitive to bleeding than other symptoms or signs. Furthermore bleeding makes patients motivated to seek treatment faster. Constipation was the most common finding and had a significant correlation with main signs of hemorrhoids such as protrusion ($P = 0.000$), rectal bleeding ($P = 0.047$), and colonoscopic grade ($P = 0.018$). This can emphasize on role of constipation as an important etiologic factor. Some theories have mentioned regarding the cause of hemorrhoids. The following factors have been suggested to contribute the development of hemorrhoids: Heredity, anatomic feature, nutrition, occupation, climate, senility, endocrine changes, food and drugs, infection, pregnancy, exercise, coughing, straining, vomiting, constipation, psychological problems, but the actual cause is remaining unclear.[1] Meanwhile there are some evidences suggesting the possible biochemical mechanism in the pathogenesis of hemorrhoids.[4] According to Persian traditional medicine, the main mechanism in majority types of hemorrhoids is accumulation of a biochemically changed blood in anorectal veins, which is called melancholic blood. Based on Persian and Ayurvedic traditional medicine, *CM* is stated to possess astringent, anti thrombotic, laxative, anti-inflammatory, analgesic, hepatoprotective properties and seems to act at a microcirculatory level. These properties cover the main therapeutic goals in hemorrhoids treatment. In this study, the effect of crude purified *CM* resin is evaluated in patients with hemorrhoids grade 1 and 2 in a randomized clinical trial. According to research findings, local symptoms including painful defecation (mean rank= 48.08), constipation (mean rank = 46.96), and bleeding (mean rank = 46.98) were alleviated better in control group (mean rank = 51.89, 52.98, 52.96, respectively). It can be justified by *anti-hemorrhoid* suppository administration in this group. Many studies have been carried out on clinical effects of *CM* resin, in a dose ranging 2-8 g/d for a 3-36 week period. Petroleum ether extract of this resin called Gugulipid is available in form of capsule, as a hypolipidemic agent.[11]

This clinical trial showed significant reduction in symptoms of hemorrhoids like concomitant GI symptoms including flatulence, GE-reflux, colonoscopic stage, and marked improvement in most of hemorrhoids symptoms even after 4-week follow-up. Because of no topical prescription in study (test) group and continuity of some symptom's relief in this group, it can be concluded that *CM* has acted on hemorrhoids by systemic effects. In this study, *CM* is used in low dose and period in comparison whit previous studies. It seems that using upper doses and longer period, in addition to topical formatives, can lead to better results. This should be assessed in more future researches.

CONCLUSION

The efficacy of *CM* in the treatment of uncomplicated hemorrhoids grade 1 and 2 was evidenced in this work. More researches should be done regarding its safety. Comparison with other drug protocols, also upper doses and longer period in addition to local derivatives of *CM*, is recommended.

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