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Clinical trial

Effects of *Terminalia chebula* Retz. in treatment of hemorrhoids: A double – blind randomized placebo – controlled clinical trial

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ABSTRACT

Introduction: Hemorrhoids are one of the most common complaints affecting the gastrointestinal tract. The treatment of hemorrhoids in modern medicine causes many side effects. In Persian Medicine (PM), *Terminalia. chebula* Retz. is one of the best choices for the treatment of hemorrhoids. The aim of this study was to evaluate the efficacy and safety of *T. chebula* on hemorrhoids.

Materials and methods: Microbial tests and standardization of *T. chebula* were conducted prior to the preparation of the capsules. Patients (n = 104) meeting the inclusion criteria were randomly assigned to either the herbal intervention (*T. chebula)* or placebo capsules, four times daily on an empty stomach for four weeks. Outcomes included pain, constipation, hemorrhoids mass size, and bleeding.

Results: There was a significant difference between the two groups in terms of pain in the first and fourth weeks ($p = 0.003$, $p = 0.025$ respectively). Also, constipation and reduction of hemorrhoids mass size were significantly different between the intervention and placebo groups ($p = 0.001$, $p < 0.001$, respectively). However, there were no differences between the two groups in bleeding days ($p = 0.123$) during the four weeks. All variables (pain, constipation, haemorrhoids mass size, and hemorrhoids hemorrhage) had significant differences ($p < 0.001$, $p = 0.002$, $p < 0.001$, $p = 0.003$) between the two groups two months after the end of the treatment, respectively.

Conclusion: This study suggests that *T. chebula* may be effective on hemorrhoids and potentially supplement for the treatment -of hemorrhoids.

1. Introduction

Hemorrhoids are abnormal dilated vascular channels which are dislocated by changes in the supporting tissue of anal cushions [1]. Internal hemorrhoids are categorized into four grades: grade I hemorrhoids are prominent blood vessels without prolapse; grade II hemorrhoids are prominent blood vessels with prolapse, but spontaneous reduction; grade III hemorrhoids refer to prominent blood vessels with prolapse requiring manual reduction; and grade IV hemorrhoids are prominent blood vessels with prolapse and inability to be manually reduced [2]. The true prevalence and incidence of hemorrhoids is unknown [3]; however, some epidemiological studies have indicated that prevalence ranges from around 4.4% to 38% in the general population in the United States and according to a colorectal cancer screening in Austria, respectively [4,5]. In UK, the incidence is reported as 40% according to a screening colonoscopy [6]. Because of the high prevalence and incidence of this disease, it is considered as one of the socioeconomic and medical problems worldwide [1].

The most common symptoms and signs that patients with hemorrhoids present include bleeding, prolapsing masses, and itching [7]. The treatment method will be decided depending on grading of hemorrhoids. The preferred treatment in the first and second-degree hemorrhoids is medical therapy which involves local hygiene, addition of dietary fiber, increased water intake, stool softeners, avoidance of straining, and cortisone suppository [7–9]. Most patients with conservative treatment will need a definitive treatment later [5]. In patients with grade I, II, III hemorrhoids who have not been treated by medical treatment, some office-based procedures should be applied

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such as rubber banding, sclerotherapy, and infrared photocoagulation [7,9]. Surgical hemorrhoidectomy should be reserved for patients with grade IV hemorrhoids and some patients with grade III hemorrhoids who have not responded to office procedures or cannot tolerate them [7,9]. There are many complications following office-based procedures and operations such as stenosis, infection, fibrosis, fecal incontinence, urinary retention, and ectropion [8,9].

Given the importance of the disease and its treatment complications, new approaches should be found for prevention and treatment of hemorrhoids. Application of medicinal plants and complementary therapies is usually considered as a novel source in finding new remedies [10]. Persian Medicine (PM) is one of the main traditional systems of medicine which was the main medical paradigm in the Europe and western Asia until the 17th century AD [11]. Persian practitioners have used natural remedies for preventing and treating different diseases [12].

Terminalia. chebula Retz. is one of the main medicinal plants which was used for hemorrhoids in PM for centuries [12,13]. *T. chebula* has been mentioned as a purgative agent of Black bile (*suada*) and Phlegm (*balgham*) (two important causes of hemorrhoids in humoral theory of PM) in *Al Qanun fi al-Tibb* (*Canon of Medicine)* written by Avicenna and *Al Hawi (Liber Continens)* written by Rhazes in 10th and 11th century AD, respectively [14,15]. Since it is astringent, the sugar derived from sugarcane is added to it for preventing its harmful effects (as a *mosleh*) [16]. In addition to PM, this herb was mentioned to shrink the hemorrhoid mass size and stop the bleeding in other traditional systems of medicines like Ayurveda [17].

There are many poly herbal formulations containing *T. chebula* whose efficacy against bleeding and hemorrhoid mass size has been shown in both animal [18] and human studies [19–23].

Meanwhile, current findings suggest that *T. chebula* contains various compounds including tannins, polyphenols, terpenes, glycosides [10,24], flavonoids [24,25], alkaloids, anthocyanins [10] which possess anti-inflammatory, antimicrobial [10,26], mild laxative, analgesic, astringent, antifungal [10], wound healing [10,27], and anti-ulcerogenic [28] effects.

Although there is some experimental research evidence as well as evidence from traditional use on the efficacy of *T. chebula* for hemorrhoids, there have been no clinical evaluations on its use. Therefore, in this paper we aimed to consider *T. chebula's* efficacy on hemorrhoids in a clinical trial.

2. Materials and methods

2.1. Study design

This randomized, double-blind placebo-controlled trial had two-parallel arms which was conducted in Taleqani Hospital, Tehran, Iran between September 2016 and October 2018.

2.2. Compliance with ethical standards

The trial was approved by Local Medical Ethics Committee of Shahid Beheshti University of Medical Sciences (approval code: IR.sbmu.retech.rec.1395.424). It was also registered in the Iranian Registry of Clinical Trials (registration ID: IRCT2016101830372N1). The patients were enrolled after signing date-specified, informed, and colonoscopy consent forms.

2.3. Preparation of the materials

2.3.1. Supplying raw materials

Three Kg of *T. chebula* was purchased for the study from one of the medicinal plant markets (*Attari*) in Tehran. Sugar was purchased from AmirKabir Sugarcane Agro-Industry Co. of Ahvaz in Tehran. *T. chebula* was identified in the herbarium center of Pharmacy School, Shahid Beheshti University of Medical Sciences (Tehran, Iran) and registered by voucher NO. SBMU-8070.

2.3.2. Microbial tests

The Total Viable Aerobic Count (TVAC) of the organisms was determined by most probable number (MPN) method. Briefly, the *T. chebula* powder was prepared in 10-fold dilution series by sterile normal saline, after which 1 ml sample of each dilution was inoculated in triplicate into three broth culture tubes containing 9 ml of Soy Casein Digest Broth (SCDB) for incubation at 35 °C for 5 days. TVAC was determined based on comparing the number of tubes with growth against the USP tables [29].

The sample were tested for 5 microorganisms including *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella spp*, and *Candida albicans* according to WHO method [30].

2.3.3. Determination of gallic acid as a marker by HPTLC method

Recent findings suggest that gallic acid is the main constituent of *T. chebula*. It was determined for standardization of the product produced in this study. For preparation and standardization of the sample, 0.5 g of dried fruit powder with 10 ml ethanol in a flask was placed in an ultrasonic chamber at 50°C for 30 min. The amount of gallic acid was determined on HPTLC plates (10 × 10) pre-coated with silica gel 60F-254 as the stationary phase by CAMAG automatic TLC sampler 4. The linear ascending development was carried out in a CAMAG automatic developing chamber (ADC2) with mobile phase consisting of toluene: ethyl acetate: formic acid 5:4:1 (v/v/v). After development, the plate was air dried for 5 min and scanned immediately at 272 nm using TLC scanner III (CAMAG scanner-III). A TLC visualizer was employed for the photo documentation of the plates [31].

2.3.4. Preparing the drug and placebo

In order to provide *T. chebula* capsules, each capsule was filled with 250 mg of *T. chebula* powder (without seeds) and 250 mg of sugar which were ground and passed through a sieve with mesh size 40. Further, the capsules were filled with 250 mg starch for preparing placebo capsules. Both *T. chebula* and placebo capsules were prepared in the Sanabol Daru Co. (a pharmaceutical company), with the same shape, size, and color to be blinded.

Lactulose syrups and anti-hemorrhoid suppositories were purchased from Soha and Aboureihan Pharmaceutical Companies in Tehran, Iran, respectively.

2.4. Inclusion and exclusion criteria

Patients referred to the gastrointestinal clinic in Taleqani Hospital from September 2016 to October 2018 who had grade II and grade I hemorrhoids, were identified by a physician according to the study's inclusion and exclusion criteria (based on history, physical examination, and colonoscopy). The inclusion criteria for participants in this study were being 18 to 65 years of age with bleeding hemorrhoids or prolapse of hemorrhoids, or pain or both, or all of them. In this study, the exclusion criteria included the patients with anorectal diseases such as rectal prolapse, fissure, fistula, perianal abscess, thrombosed, strangulated or gangrenous hemorrhoids, cancer in any part of the body, advanced infectious, cardiovascular, liver and kidney diseases, advanced mentally retarded patients, patients with inflammatory bowel disease (IBD), diabetes and hypertension, pregnant and lactating women, patients who had consumed anticoagulant and antiplatelet (within less than the previous month), analgesic (less than a week ago) and steroidal or flavonoid (less than one month ago) medicines. The patients with severe complications during the research, those showing severe allergy to the medicine, and the individuals who preferred to be excluded from the study, were also excluded.

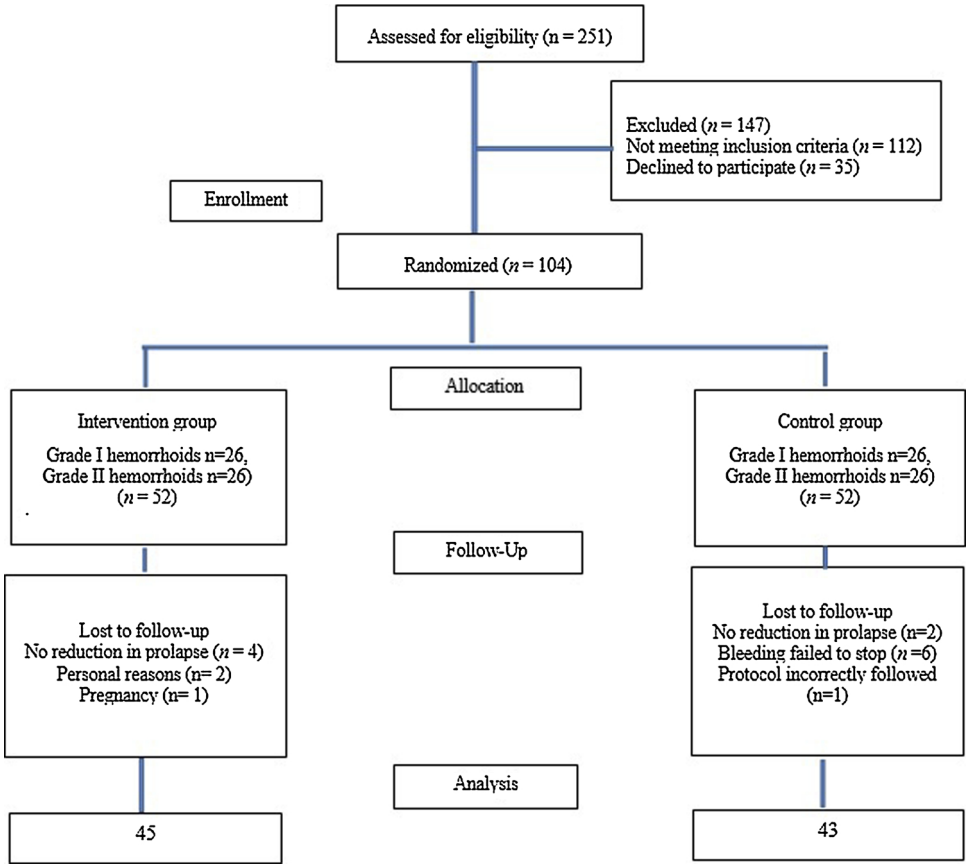

Fig. 1. Consort chart of the clinical trial.

2.5. Intervention

2.5.1. Randomization, blinding, and concealment of allocation

The sample size was estimated by considering two-sided significance level of 0.95 and 0.80 power. Eventually, having considered a probable 15% drop-out rate, the eligible patients were randomly assigned to parallel groups of placebo (n = 52) and drug (n = 52) via simple random sampling (simple randomization with random digit table) [32]. During the investigation, the physician and patients were blind to the drug allocation.

2.5.2. Placebo and test drug

The patients were prescribed *T. Chebula* or placebo capsules and asked to take these capsules 4 times a day on an empty stomach for 4 weeks. If any patient had pain, constipation, and bleeding after using the capsules for about one week in either arm of the study, they were given lactulose syrup to use 5–10 cc (laxative dose). The aim was to ensure defecation at least once a day easily, and after defecation they were advised to use one anti-hemorrhoid suppository.

2.6. Outcome measures

The primary outcome included pain (burning) was measured weekly using a Visual Analogue Scale (VAS). Secondary outcomes were constipation as defined by Rome IV criteria [33] and the hemorrhoids mass size captured with patients' history and physical examination on a weekly basis. Finally, self reported bleeding was measured based on the number of days with bleeding every week for 4 weeks. Meanwhile, use of lactulose syrup and anti-hemorrhoid suppositories was measured based on milliliter and number respectively.

The considered possible side effects were headache, dizziness [34], skin dryness [35], diarrhea [9] and constipation based on Rome IV criteria [33].

Outcome data were collected using a researcher-made checklist and completed by the physician weekly for 4 weeks by phone. The hemorrhoid mass size was evaluated at the beginning and at the end of every week up to 4 weeks with a physical examination by the physician.

2.7. Statistical analysis

Demographic (including age, sex, pain, constipation, hemorrhoids mass size and rectorrhagia, gathered by the physician in the first patients visit) and clinical data of the enrolled patients were presented as mean ± standard deviation (SD). Chi-Square, Fisher's Exact, Repeated Measure ANOVA Tests, and Independent *t*-test were used in the statistical analysis. *P*-value < 0.05 was considered as significant. All of the statistical analyses were performed using Statistical Package for the Social Sciences, version 16.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Microbial control test and standardization of the T. chebula capsules

Microbial test consideration of the *T. chebula* sample indicated that there were no microorganisms in Total Aerobic Microbial Count (TAMC), no *Pseudomonas aeruginosa, Salmonella typhimurium, Escherichia coli,* and *Staphylococcus aureus*, and no molds [30].

According to the results, the *T. chebula* powder sample had a good quality. Also, standardized *T. chebula* powder by HPTLC method [31] revealed that the sample had 0.48% (W/W) gallic acid.

3.2. RCT results and outcomes

From September 2016 to October 2018, 251 patients were assessed

Table 1
Demographic data in experimental and control groups.

Variable	Experimental group	Control group	*P* value
age	45.76 ± 13.03 (the mean of age)	44.77 ± 12.61 (the mean of age)	0.719
sex	Male = 29 Female = 16 (the number of patients)	Male = 25 Female = 18 (the number of patients)	0.662
pain	23 (the number of patients)	18 (the number of patients)	0.402
constipation	14 (the number of patients)	20 (the number of patients)	0.189
hemorrhoids mass size	22 (the number of patients)	21 (the number of patients)	0.990
rectorrhagia	2.91 ± 1.84 (the mean of bleeding days)	2.49 ± 1.88 (the mean of bleeding days)	0.290

for eligibility. From this number, 104 patients met the inclusion criteria. Of 52 patients in the control group, 9 patients and from 52 patients in the intervention group 7 patients discontinued the intervention. Finally, 45 and 43 patients remained in the intervention and control groups, respectively (Fig. 1). Demographic information on the two groups is summarized in Table 1 and shows that there were no significant differences between the two groups. Specifically, there were 22 and 23 patients in the intervention group with grade II and grade I hemorrhoids respectively. On the other hand, the placebo group consisted of 21 and 22 patients with grade II and grade I hemorrhoids respectively. So, there was no significant difference between the two groups in terms of grading ($p = 1.000$).

Data show that there were significant differences between the experimental and control groups for pain in the first week, fourth week and two months after the end of the treatment ($p = 0.003$, $p = 0.025$, $p < 0.000$ respectively), constipation in the first week and two months after the end of the treatment ($p = 0.001$, $p = 0.002$ respectively), hemorrhoid mass size in the fourth week and two months after the end of the treatment ($p < 0.001$, $p < 0.001$ respectively), and also hemorrhage two months after the end of the treatment ($p = 0.003$) (Tables 2–4). Also, the significant differences in the number of patients (percentage) suffering from pain, constipation, enlarged hemorrhoid mass, and no significant difference in the bleeding days were showed in the first visit and within four weeks of treatment in the two groups in Figs. 2 and 3. During the study, no side effects were reported by the patients in either groups.

4. Discussion

There were significant differences between intervention and placebo groups in terms of pain (burning), constipation, size of hemorrhoid mass, hemorrhoid hemorrhage, and use of lactulose syrup. However, there was no significant difference between the two groups in applying anti-hemorrhoid suppositories.

Possibly, the efficacy of *T. chebula* against pain could be attributed to its central analgesic effects and triterpenoids saponin which blocks the cholecystokinin (CCK) receptors [36]. This in turn may be due to anti-inflammatory and analgesic characters of tannins (gallic acid, ellagic acid, chebulinic acid, and corilagin) via reducing the serum levels of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β or inhibiting enzyme cyclooxygenase and prostaglandin synthesis [37–40]. Also, gallic acid and its metabolites control the pain in another way while acting as a glucocorticoid receptor agonist [41]. Chebulagic acid relieves the pain, with inhibition of cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) [42] plus flavonoids (quercetin and kaempferol) [43,44] in *T. chebula*.

The efficacy of *T. chebula* against constipation might be due to the tannin's astringent characteristics (gallic acid, ellagic acid) [39] and anthraquinones [12] in *T. chebula*. They increase the volume of stool and cause complete defecation of the bowel. In this way, the gastrointestinal tract empties for a long time, whereby gastrointestinal tract especially its glands (Brunner's glands) will function well and constipation will relieve [10].

The efficacy of *T. chebula* against hemorrhoid mass size can be owing to its venotonic characteristic (chebulinic acid and terflavin B) [10,39] as well as venoprotective (via cytoprotective characteristics with inhibiting oxidative stress) features [10,45].

Although there was no significant difference in hemorrhoid hemorrhage between the two groups during four weeks, two months after the end of the treatment, a significant difference was found between them. Expectedly, the significant difference in hemorrhoid hemorrhage between the two groups could be attributed to *T. chebula's* wound healing properties via antifungal, antiviral, antibacterial, and anti-inflammation [10,39] tannins (gallic acid, ellagic acid, anthraquinones) [46,47], flavonoids (catechin, quercetin) [46,47] and terpenoids [46] acting as an antibacterial agent. For instance, tannins such chebulagic and chebulinic acids have anti-HSV-2 activity through inhibiting virus attachment and penetrating to the host cells [48]. Further, ellagic acid inhibits polyphosphate kinase (IPK1) and makes *Pseudomonas aeruginosa* stress sensitive [49]. Another mechanism that gallic acid stops bleeding is its function as a strong coagulation factor [50].

The patients had been allowed to use lactulose syrup and anti-hemorrhoid suppositories if their signs and symptoms did not resolve. The patients did not use lactulose syrup in the intervention group but in the placebo group, many patients consumed it after about one week. So, we did not expect significant differences in variables during the treatment period except for the first week. As mentioned earlier, there was a significant difference between the two groups in use of lactulose syrup explaining lack of significant differences in the last three weeks of treatment in terms of constipation and pain. Meanwhile, the patients did not desire to use anti-hemorrhoid suppositories for a long time, so there was a significant difference between the two groups in terms of pain in the fourth week again. Finally, there was no significant difference between the two groups in applying anti-hemorrhoid suppositories.

In previous studies, *T. chebula* has been used with other drug

Table 2
Comparison of pain, constipation and rectorrhagia between experimental and control groups.

Group / Follow up time	Experimental group (Number of patients who had variables)			Control group (Number of patients who had variables)			*P* value		
Variables	Pain	Constipation	Rectorrhagia (days)	Pain	Constipation	Rectorrhagia (days)	Pain	Constipation	Rectorrhagia
First visit	23	14	2.91 ± 1.84	18	20	2.49 ± 1.88	0.402	0.189	0.290
First week	2	2	0.42 ± 0.86	12	14	0.58 ± 1.15	0.003	0.001	0.466
Second week	3	1	0.20 ± 0.54	8	2	0.30 ± 0.93	0.114	0.612	0.532
Third week	4	1	0.40 ± 0.80	8	1	0.28 ± 0.88	0.224	1.000	0.504
Fourth week	2	2	0.22 ± 0.73	9	3	0.65 ± 1.58	0.025	0.673	0.105

Table 3
Comparison of hemorrhoids mass size, use of lactulose syrups and use of anti-hemorrhoids suppositories between experimental and control groups at 4 weeks.

Group Follow up time	Experimental group (patients with grade II hemorrhoids) (n = 22)	Experimental group)		Control group (patients with grade II hemorrhoids) (n = 21)	Control group (Whole number of patients)		*P* value		
Variable	Hemorrhoids mass size	Use of the lactulose syrup (cc)	Use of the anti-hemorrhoid suppository	Hemorrhoids mass size	Use of the lactulose syrup (cc)	Use of the anti-hemorrhoid suppository	Hemorrhoids mass size	Use of the lactulose syrup	Use of the anti-hemorrhoid suppository
Four weeks	22	0	0	5	47.47 ± 76.9	1.6 ± 5.16	0.000	0.001	0.081

Table 4
Comparison of pain, constipation, rectorrhagia and hemorrhoids mass size between experimental and control groups, over 4 weeks.

Group Follow up time	Experimental group (Number of patients who had not variables)			Experimental group (patients with grade II hemorrhoids) (n = 22)	Control group (Number of patients who had variables)			Control group (patients with grade II hemorrhoids) (n = 21)	*P* value			
Variable	Pain	Constipation	Rectorrhagia	Hemorrhoids mass size	Pain	Constipation	Rectorrhagia	Hemorrhoids mass size	Pain	Constipation	Rectorrhagia	Hemorrhoids mass size
Four weeks	17	11	30	22	4	3	19	5	0.000	0.002	0.003	0.000

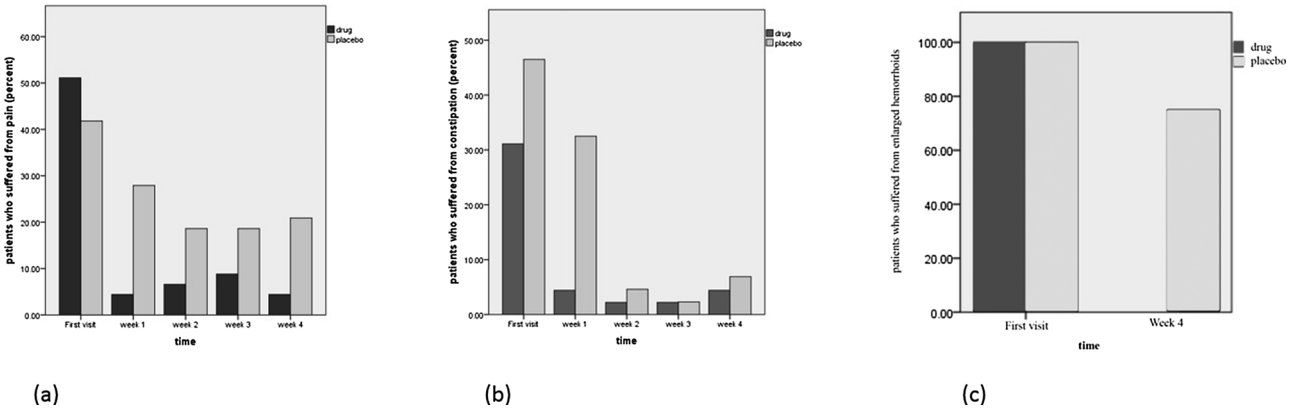

Fig. 2. Comparison of the number of patients (percent) with pain (a), constipation (b) and the enlarged hemorrhoids mass (c) in the first visit and within four weeks of treatment in the experimental and control groups.

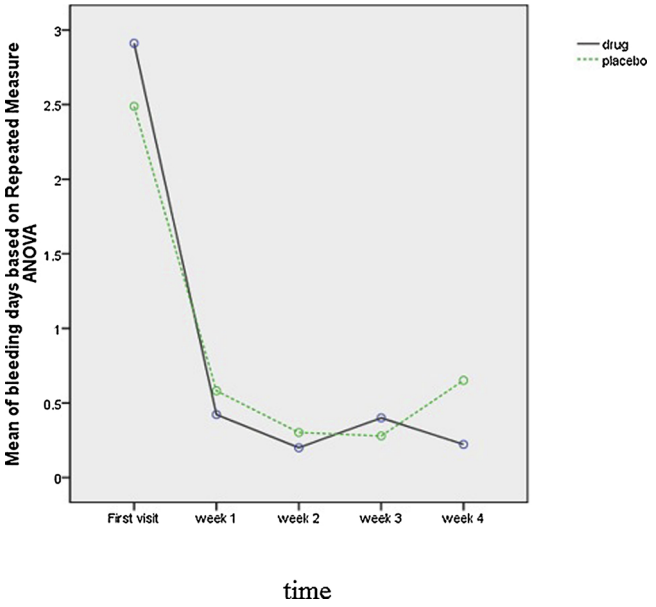

Fig. 3. Comparison of the bleeding days in the first visit and within four weeks of treatment in the experimental and control groups.

combinations. Other other studies have indicated the effects of only one plant on symptomatic hemorrhoids. This study has compared methods for treatment of grade I and II hemorrhoids in modern medicine.

In many studies [19–23] where *T. chebula* was used in their drug combinations, the results suggested the effect of the drug on grade I, II plus some grade III hemorrhoids. Nevertheless, there have been some weak points when compared with the present study such as use of many ingredients in drug combinations, lack of control group, co-administration of oral and topical medications, insufficient number of patients, short follow up, and expression of the results in general terms such as good and very good. The most important problem in these studies is use of many ingredients of drug combinations; one cannot recognize which ingredient or compound of the drug has affected the hemorrhoids [19–23]. Note that in some of the mentioned studies, the number of patients and the follow-up duration were greater than in our study [19,21,23]23].

In the Mosavat et al.'s study working on leek cream locally, only termination of bleeding had a significant difference with the other groups. Note that the number of patients in each group was less than that in the present study; the drug was used locally so its effect would be short; and the follow up was shorter than in our study [51].

In the Yosefi et al.'s study using oral *Mukul*, no significant difference was observed in terms of pain, constipation, protrusion of hemorrhoids, and proctorrhagia after the four-week follow-up. Only rectorrhagia variable had a statistically significant difference in the second week. Note that pain (burning), which is an annoying symptom in hemorrhoid disease as with any other illness, did not improve by *Mukul* after 4 weeks [52]. However, in the present study, there were significant differences between the two the groups in terms of pain and constipation in the first week. On the other hand, *T. chebula* improved pain and constipation with a lower dose in comparison to *Mukul*. Also, there were significant differences on the size of hemorrhoids (protrusion of hemorrhoids) in the end of four weeks and termination of bleeding after three-month follow-up.

Although in studies only one plant (*Aesculus hippoc astanum, Cissus quadrangularis, Euphorbia prostrata, Ginkgo biloba*, and *plantago ovat*) has proved beneficial against hemorrhoids, there are many problems in these studies. Most of them did not have any control group; they had a short follow-up period; and the number of patients was low. Further, in their preparation of medicines, they should have had a pharmaceutical process [50,53–56]. Additionally, one of them had side effects such gastritis, headache, and drowsiness [54]. Nevertheless, the important point in our study is that *T. chebula* is a fruit which can be used as powder without any pharmaceutical process. Further, the active ingredients for the treatment of hemorrhoids in each mentioned plant may include flavonoids, terpenoids, and tannins, but all of them are not active for the treatment of hemorrhoids. However, all of them are active in *T. chebula* for the treatment of hemorrhoids. Possibly, tannins, flavonoids, and terpenoids are in a balanced ratio with each other in *T. chebula* whose synergistic effect causes its faster and better treatment for hemorrhoids.

Comparing our study with the modern ways of hemorrhoids treatment, the following can be mentioned. Firstly, use of fiber supplements as well as local medicines such as ointments, suppositories, and laxatives only relieve symptoms of hemorrhoids for a short time [8,9,56]. Therefore, after frequent recurrence, invasive procedures are used for the treatment of grade I and grade II hemorrhoids, the most important and common of which are infrared coagulation, rubber band ligation, and sclerotherapy. They have many side effects such as recurrence, pain, bleeding, rectovaginal fistula, liver abscess, tetanus, urinary retention, retroperitoneal sepsis, necrotizing fasciitis, stenosis, sepsis, and even death [8,57,58].

In all of these procedures, in addition to recurrence, normal hemorrhoid tissues are also necrosed [8,57,58]. On the other hand, through *T. chebula*, the main cause of hemorrhoids (Black bile & Phlegm) is discharged from the whole body and pile masses, while the hemorrhoid damaged tissues are also repaired [10].

This study had some limitations. Firstly, there was no objective measurement for hemorrhoid mass size. On the other hand, there was

no significant difference between the two groups during the four weeks in hemorrhoid hemorrhage. Therefore, further studies should be performed by an instrument for measuring the mass of hemorrhoids. The number of patients involved in the study and duration of follow up were other limitations; if studies are done with more patients or a longer follow up, there may also be a significant difference in termination of bleeding between the two groups during four weeks.

The reasons patients dropped out in this study included failure in complete recovery of hemorrhoid prolapse, failure to halt bleeding, not doing the protocol correctly, personal reasons, and pregnancy.

5. Conclusion

The present study suggested that *T. chebula* may be effective for haemorrhoids and could be used to supplement the treatment of this condition.

Authors

All research done by the authors.

Declaration of Competing Interest

None.

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