



Formulation and Finger Printing of a Poly Herbal Film-Coated Tablet for Treatment of Hemorrhoids

Sahar Dehdari¹, Homa Hajimehdipoor^{2*}, Somayeh Esmaeili², Seyed Alireza Mortazavi³, Rasool Choopani⁴

¹Department of Traditional Pharmacy, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

²Traditional Medicine and Materia Medica Research Center and Department of Traditional Pharmacy, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

³Department of Pharmaceutics, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

⁴Department of Traditional Medicine, School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Background and objectives: Hemorrhoids is the most prevalent rectal disease. Despite different medical efforts, its complications are not managed well. In the present research, a popular prescription for treatment of hemorrhoids was formulated as tablet dosage form and, its HPTLC fingerprint prepared. **Methods:** *Commiphora mukul* was dissolved in *Allium ampeloprasum* juice (1:3). Then, this solution was blended with *Terminalia chebula*, *Phyllanthus emblica* and *Terminalia bellirica* (1:1:1) powder. Different formulations were prepared from the mixture and the best one was selected for tablet preparation. Subsequently, the tablets were coated and their physicochemical characteristics and fingerprint pattern were obtained using silica gel plate, NP/PEG reagent and toluene: ethyl acetate: formic acid (70:15:15) as mobile phase. Laboratory stability studies were carried out as well. **Results:** Formulation C revealed excellent results in flowability studies (angle of repose: 26, carr's index: 6, hausner ratio: 1.00). It was also demonstrated acceptable results in different tests including weight variation (500 mg), hardness (8.04 kg/cm²), disintegration time (28.50 min), friability (0.6%), dissolution (97.6% phenolics and 96.1% tannins, respectively) and the coating process. Total phenolics and tannins contents were determined as 125.8 mg/tab and 89.2 mg/tab, respectively. In fingerprinting study, characteristic spots of each species were distinguished. The film-coated tablets were stable in laboratory stability test. **Conclusion:** With reference to anti-inflammatory, astringent and wound healing roles of phenolics and tannins in hemorrhoids, the present tablets could be an appropriate candidate for hemorrhoids regarding its historical backgrounds.

Keywords: *Allium ampeloprasum*, *Commiphora mukul*; hemorrhoids; *Phyllanthus emblica*; *Terminalia*

Citation: Dehdari S, Hajimehdipoor H, Esmaeili S, Mortazavi SA, Choopani R. Formulation and finger printing of a poly herbal film-coated tablet for treatment of hemorrhoids. Res J Pharmacogn. 2020; 7(4): 39-47.

Introduction

Hemorrhoids is the most prevalent rectal complication which is defined as enlargement and dislocation of normal rectal cushions [1,2]. Intensified pressure on rectal vascular plexus,

mainly due to straining and pregnancy, seems playing the chief role in the development of hemorrhoids [3,4]. The prevalence of 39% has been reported for this disease [5]. Symptoms of

* Corresponding author: hajimehd@smbu.ac.ir

hemorrhoids may include bleeding, inflammation, anal discharge and pain. Treatments for grades I and II can include increasing water intake, high fiber diet and topical therapies like steroids. Treatment for grades III and IV may be non-surgical or surgical intervention [1,6,7]. In spite of current medical efforts, many complications of the disease are not managed well [8]. Medicinal herbs are the valuable sources for preparing new drugs. Consumption of herbal preparations is preferred by more than 79% of the global population [9]. The usage of traditional herbal prescriptions is a robust way to prepare cheaper and more efficient herbal drugs. One of the most prescribed formulations by “Avicenna” and “Rhazes”, famous Persian physicians [10,11], is “Itrifal-e moql” which consists of the dried fruits of *Terminalia chebula*, *Phyllanthus emblica* and *Terminalia bellirica*, oleo-gum resin of *Commiphora mukul* and leaf juice of *Allium ampeloprasum* in proportion of 1:1:1:3:9 [12-14]. Nowadays, anti-inflammatory properties of all mentioned herbs [15-21], analgesic effect of *T. chebula* and *T. bellirica* [17,22-25], wound healing effect of *T. chebula* and *Ph. emblica* [26,27] and anti-bleeding property of *A. ampeloprasum* have been confirmed [28]. These pharmacological effects are very important for the management of hemorrhoids discomforts [1,29]; therefore, the described formulation seems to be a good candidate for hemorrhoids. According to Iranian traditional medicine (ITM) prescriptions, *C. mukul* should be soaked and heated in the juice of *A. ampeloprasum* until it is dissolved. Afterwards, this solution is blended with fruit powders of *T. chebula*, *Ph. emblica* and *T. bellirica*. Then, resultant paste should be cut into small rounded pieces by hand that is traditionally named “Hab” [12-14]. Indeed, “Hab” is a traditional dosage form that is similar to pills. Since, traditional dosage forms should be converted to modern dosage forms for better acceptance by patients and more stability and possibility of production in industrial scale, in the present investigation, coated tablets were prepared and related quality control tests were performed.

Material and Methods

Ethical considerations

The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran with the code No. IR.SBMU.RETECH.REC.1395.376.

Chemicals

Hide powder was obtained from Sigma-Aldrich, UK. Folin-Ciocalteu, all reagents, solvents and HPTLC silica gel 60 F₂₅₄ plates (20×20 cm) were purchased from Merck, Germany.

Plant material

The fruits of *Ph. emblica* L., *T. chebula* Retz., and *T. bellirica* Retz., the oleo-gum resin of *C. mukul* (Hook. ex Stocks) Engl. and fresh leaves of *A. ampeloprasum* were purchased from herbal market, Tehran, Iran in September 2015. All samples were authenticated at the Herbarium of Traditional Medicine and Materia Medica Research Center (TMRC), Shahid Beheshti University of Medical Sciences, Tehran, Iran. Samples of *Ph. emblica* (382 HMS), *C. mukul* (379 HMS), *T. chebula* (380 HMS) and *T. bellirica* (381 HMS) were kept at the Herbarium of TMRC. The juices of fresh leaves of *A. ampeloprasum* were extracted through crushing vegetable machine and then, dried using freeze drying method.

Plant material analysis

Different physiochemical tests such as loss on drying, total ash, matter insoluble in ethanol, foreign matter, alcohol-soluble extractive, water-soluble extractive and total phenolics and tannins contents were performed based on the plants monographs [30,31]. Considering that there was no monograph for *A. ampeloprasum*, its tannins content was determined.

Pre-formulation studies

Dried juice of *A. ampeloprasum* was dissolved in water to make similar concentration to primary juice. Then different formulations were made using plant powders and juice of *A. ampeloprasum*.

Formulation A

In this formulation, equal quantities of fruits powders from *T. chebula*, *Ph. emblica* and *T. bellirica* were blended and passed through sieve no. 20. *Commiphora mukul* was weighted equal to sum of fruits and added to *A. ampeloprasum* juice (1:3). The mixture was heated in water-bath for 2 hours. Then, the solution was filtered and the filtrate was added to the blended powder of fruits. Because of high volume of filtrate in comparison to fruit powders, this formulation looked like a paste and needed long time for drying.

Formulation B

The process was similar to formulation A, but the filtrate was heated till the volume was reduced to one-fifth of its initial volume. Next, the filtrate was added to the powders. The mixture was passed through sieve no. 18. Subsequently, it was placed in oven at 40 °C and passed through sieve no. 20 after drying.

Formulation C

This formulation was same as formulation B, but the filtrate was heated till the volume was reduced to one-fourth of its first volume. Next, the filtrate was added to powders. The granules were passed via sieve no. 12. Afterwards, the water was evaporated in oven at 40 °C. After drying, it was passed through sieve no. 14. The granule size was larger than of formulation B.

Formulation D

To achieve optimum disintegration time, cross carmellose sodium (super disintegrant agent) was added to the ingredients of formulation C in different percentages (1, 3, 5, 7 and 10%). Avicel 102 was added as filler to obtain constant tablet weight in all formulations of D series.

The described formulations have been displayed in table 1.

Flowability properties

The resultant powders from three series of formulations (B, C and D) were evaluated for flowability properties including angle of repose, Carr's index, and Hausner ratio. According to the results of flowability properties of powders, best formulations were selected for tablet preparation. The resulting herbal powders were compressed via 12 mm concave punch using a single stroke punching machine.

Evaluation of tablet properties

Different tests including weight variation,

friability, hardness, disintegration time, thickness, diameter, dissolution test and assay of total phenolics and tannins were performed on the tablets [30,31].

Determination of total phenolics and tannins contents

For determination of total phenolics and tannins contents, 10 tablets were powdered and the weight of one tablet was dissolved in 1 litre of distilled water (stock solution). Two mL of stock solution was mixed with 1mL of folin-Ciocalteu reagent and 10 mL distilled water and diluted to 25 mL with sodium bicarbonate 29%. The samples were kept in a dark place for 30 min. Then, their absorbances at 760 nm were measured. Pyrogallol (0.125, 0.0625 and 0.0312 mg/mL) was used as the standard.

For determination of total tannins contents, 10 mL of the stock solution was added to 100 mg hide powder and shaken for 60 min. Next, the mixture was filtered and the above mentioned process was performed for the solution [30].

In vitro dissolution studies

Dissolution study was performed on 6 herbal tablets of formulation C using apparatus 2 (paddle method). The dissolution test was done with 900 mL of water, at 37 °C, 75 rpm for 60 min. Sampling was carried out after 30, 45 and 60 min intervals and the percentage of released total phenolics and tannins compounds were determined.

Film-coating process

According to the results of physicochemical tests, the best formulations (B and C) were selected for the coating process. Both the aqueous and alcohol soluble coating methods were performed. First, aqueous film-coating process was done using pink powder of Opadry II, Colorcon®.

Table 1. Ingredients of different tablet formulations

Ingredients	Formulation codes								
	A	B	C	D ₁	D ₂	D ₃	D ₄	D ₅	
<i>Terminalia chebula</i> (mg)	100	100	100	100	100	100	100	100	
<i>Terminalia bellirica</i> (mg)	100	100	100	100	100	100	100	100	
<i>Phyllanthus emblica</i> (mg)	100	100	100	100	100	100	100	100	
<i>Commiphora mukul</i> (mg)	300	300	300	300	300	300	300	300	
<i>Allium ampeloprasum</i> juice (mL)	900	180	225	225	225	225	225	225	
Cross carmellose sodium (mg)	-	-	-	5.6	16.8	28	39.2	56	
Avicell 102 (mg)	-	-	-	54.4	43.2	32	20.8	4	
Mesh size	-	18,20	12,14	12,14	12,14	12,14	12,14	12,14	

This powder was mixed and stirred with water for 30 min in different percentages (15, 20 and 25%). The alcohol soluble coating included HPMC K4M (4%), ethanol 96° (80.81%), TiO₂ (1.78%), PG (1.42%), water (11.94%) and FC4W, FC4S color (0.047%).

All physicochemical tests were performed on coated tablets as well.

HPTLC finger printing of film-coated tablets

One gram of film-coated tablets of formulation C was extracted with 5 mL ethyl acetate. Ethyl acetate extracts of *T. chebula*, *Ph. emblica*, *T. bellirica* and mixture of *C. mukul* in *A. ampeloperasum* were used as control materials. Forty µL of each extracts were spotted on pre-coated silica gel plate through Linomat V (Camag, Switzerland) using 100 µL Hamilton syringe. The plate was developed to 90 mm through a mobile phase of toluene: ethyl acetate: formic acid (70:15:15). Dried plates were sprayed using natural product/polyethylene glycol (NP/PEG) reagent. Developed plates were photographed in ultraviolet light at 366 nm via Camag Reprostar 3, Camag, Switzerland.

Laboratory stability studies

Tablets were packed in poly ethylene containers (40 tablets in each bottle) and kept at 40 °C ± 2 and 75% ± 5 humidity for 3 months. Samplings were performed at first and at the end of 3rd month and physicochemical examinations were carried out.

Statistical analysis

The means of the releases of total tannins and phenolics from core and film-coated tablets were compared statistically according to paired-samples *t*-test. Besides, the means of physical tests of different formulations were analyzed using one way ANOVA post hoc Tukey test via SPSS 23.

Results and Discussion

In this study, a poly herbal film-coated tablet was formulated for the treatment of hemorrhoids according to the selected traditional prescription. This formulation is named "Itrifal-e moql" in Iranian traditional manuscripts. Ancient physicians have ascribed different curing effects to this drug such as hemorrhoids treatment, purgation the body from black bile, detoxifying property and as a suitable laxative in chronic constipation [32,33]. The results of plant materials analysis have been demonstrated in table 2. The results were in agreement with acceptable criteria [30,31]. Among different formulations (table 1), formulation A did not matched to pharmaceutical's criteria. So, it was put aside. Formulation C contained granules with greater size compared to formulation B. Excipients was used only in formulations series D. Formulations D₄ and D₅ showed lower hardness compared to other formulations (< 6 kg/cm²), thus D₄ and D₅ were excluded. Flowability properties of the three formulations series including angle of repose, Carr's index and Hausner ratio have been illustrated in table 3.

Table 2. Plant material analysis of poly herbal tablet

Ingredients	Total phenolics content %	Total tannins content %	Foreign matter %	Total ash %	Alcohol-insoluble extractive %	Alcohol-soluble extractive %	Water-soluble extractive %	Loss on drying %
<i>Terminalia chebula</i>	30.69±0.04	21.65±0.09 (NLT 20)*	-	3.00±0.76 (NMT 5)*	-	-	79.08±0.16 (NLT 50)*	6.19±0.60 (NMT 10)*
<i>Terminalia bellirica</i>	27.10±0.57	18.43±0.08 (NLT 10)*	-	3.56±0.90 (NMT 7)*	-	-	76.15±0.73 (NLT 45)*	2.51±0.10 (NMT 5)*
<i>Phyllanthus emblica</i>	24.01±0.14	16.20±0.52 (NLT 6)*	0.99±0.04 (NMT 5)*	2.46±0.28 (NMT 7)*	-	29.11±0.98 (NLT 15)*	65.01±0.32 (NLT 50)*	2.92±0.67 (NMT 10)*
<i>Commiphora mukul</i>	-	-	-	3.53±0.09 (NMT 7)*	56.69±0.24 (NMT 70)*	-	-	8.73±0.01 (NMT 15)*
<i>Allium ampeloperasum</i>	28.11±0.02	18.55±0.13	-	-	-	-	-	-

*Acceptable range according to pharmacopeia [30,31]

Table 3. Flowability studies of different formulations

Flowability characteristics	Formulation code				
	B	C	D ₁	D ₂	D ₃
Angle of repose (°)	27	26	27	29	29
Carr's index (%)	6	6	7	8	8
Hausner ratio	1.02	1.00	1.10	1.10	1.11

They were in excellent range according to USP [31]. The outcomes of physical tests for formulations B, C and D₁₋₃ have been displayed in table 4. As shown in table 4, formulations B and C revealed acceptable friability and disintegration time with no usage of excipients. Hence, these formulations were considered for the film-coating process. In statistical analysis, there was no significant change ($p < 0.05$) among formulations B, C and D₁₋₃ in diameter and disintegration times. About thickness, formulations B and C revealed no significant difference, but they showed significant changes with formulations D series. Based on hardness, significant changes were observed in formulations B, C and D₁. But, formulations D₂ and D₃ displayed no significant differences. Albeit formulations D₁ and D₂ demonstrated no significant changes about friability, others showed significant changes.

Commiphora mukul is introduced as tablet binder in Ayurvedic formulations [34,35]. The volume of solvent (*A. ampelopsium* juice) that was used to dissolve *C. mukul* and its contact time with “Triphala” (which means three fruits; *T. chebula*, *Ph. emblica* and *T. bellirica*) powders are involving factors in both hardness and disintegration times of tablets. Indeed, higher volume of solvent and more contact time make prolong disintegration time and hardness of tablets [36]. Hence, formulation B that had fewer volume of solvent revealed lower hardness than formulation C. Although disintegration time for herbal tablets is acceptable up to 60 min [30], in formulation series D an attempt was done to

reduce this time using crosscarmellose sodium (a super disintegrant agent) but, no significant time reduction was observed. In addition, our goal was to formulate a completely natural tablet without any excipient. So, formulation series D were discarded.

Film-coating process was carried out to cover the unpleasant taste of tablets that resulting from presence of tannins. During this process, an attempt was made to coat formulation B with aqueous film-coating solution. But, this formulation was chipped and cracked during test. So, this formulation was excluded for coating purpose. Afterwards, formulation C was coated. This process lasted 4 hours and a 25% solution made the smoothest film-coated tablets. In lower concentrations, tablets were clung to pan. So, formulation C was coated with alcohol soluble coating solution. This step lasted for just 20 min and got smoother film-coated tablets in comparison to that of aqueous film-coating solution. *Commiphora mukul* is a water soluble oleo gum-resin. So, it is the probable cause of occurred problems during film-coating process with the water soluble coating materials. Indeed, *C. mukul* absorbed the water of coating solution and make laminated appearance on tablets, thus selected method for this tablet is alcohol soluble coating solution. The results of evaluations of physical tests of formulations C film-coated tablets have been demonstrated in table 4.

Table 4. Results of physical tests of different formulations

Tests	Formulation codes					
	B	C	D ₁	D ₂	D ₃	C-coated
Description	green with yellow spots, rough and biconvex	green with yellow spots, rough and biconvex	green with yellow and white spots, rough and biconvex	green with yellow and white spots, rough and biconvex	green with yellow and white spots, rough and biconvex	Rounded, coated, biconvex, opaque purple
Friability (%)	0.71±0.05	0.60±0.01	0.79±0.03	0.80±0.06	0.83±0.08	-
Diameter (mm)	12.20 ± 0.01	12.21 ± 0.01	12.20 ± 0.03	12.22 ± 0.02	12.20 ± 0.01	12.21 ± 0.01
Thickness (mm)	3.42 ± 0.03	3.41 ± 0.02	3.71 ± 0.05	3.70 ± 0.05	3.70 ± 0.02	3.52 ± 0.20
Weight variation (mg)	500.10 ± 0.98	500.30 ± 0.71	560.30 ± 0.25	558.30 ± 0.95	560.30± 0.54	515.10 ± 3.60
Hardness (kg/cm ²)	6.50 ± 0.90	8.04 ± 0.12	6.35 ± 0.60	6.05 ± 0.25	6.03 ± 1.03	10.00±0.38
Disintegration Time (min)	28.41±0.13	28.50±0.11	28.23±0.12	27.38±0.09	26.43±0.12	41.57±0.96

Total phenolics and tannins contents of core and film-coated tablets were found 125.8, 89.2, 125.2 and 89.0 mg/ tab, respectively.

In dissolution studies, both core and film-coated tablets of formulation C were evaluated. The outcomes of total phenolics and tannins releases during 30, 45 and 60 minutes have been shown in table 5. Due to undetectable release of tannins in 30 minutes, their releases were reported at 45 and 60 minutes. The percentage of total phenolics and tannins releases from both core and film-coated tablets of formulation C were statistically analyzed. There were significant difference between total phenolics and tannins contents releases from core and film-coated tablets in all sampling times. The results of phenolics and tannins releases in 60 min were in agreement

with pharmacopoeia requirements (>80%, Q: 75%) [31].

The detection of tablet phytoconstituents with different polarities was done via ethyl acetate extract of the tablet. For spotting tablet extract and controls, various volumes (from 10-50 μL) were evaluated. Finally, volume of 40 μL was selected for all plant materials. Among some tested solvent systems, toluene: ethyl acetate: formic acid (70:15:15) exhibited most selective and repeatable properties for the detection of plant constituents with low and high polarity. NP/PEG reagent was the most selective reagent by which phenolics contents were appeared in various colored spots. Chromatograph of tablets and controls has been presented in figure 1.

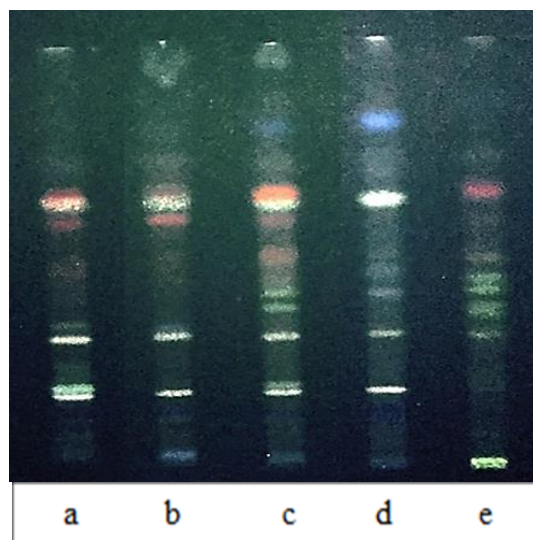


Figure 1. HPTLC fingerprint profile of (a) *Terminalia chebula* (b) *Terminalia bellirica* (c) tablet (d) *Phyllanthus emblica* (e) dissolved *Commiphora mukul* in *Allium ampeloprasum*

Table 5. Total phenolics and tannins releases from core and coated tablets

	Time (min)	Core							Coated-tablets						
		1	2	3	4	5	6	Mean \pm SD	1	2	3	4	5	6	Mean \pm SD
Total phenolics release	30	30.5	29.6	30.0	29.7	30.9	30.1	30.2 \pm 0.4	27.0	27.1	29.0	28.6	28.0	28.0	28.0 \pm 0.7
	45	63.9	62.6	62.1	65.1	62.2	63.0	63.2 \pm 1.0	56.3	55.2	56.7	57.0	56.1	55.3	56.1 \pm 0.8
	60	97.1	97.6	97.2	97.6	98.0	98.0	97.6 \pm 0.4	84.7	85.9	84.8	84.5	85.6	84.1	84.9 \pm 1.1
Total tannins release	45	61.8	62.5	61.1	62.2	61.3	61.2	61.9 \pm 1.4	52.7	51.7	52.0	51.6	51.6	52.8	52.0 \pm 0.9
	60	96.2	95.5	96.2	95.9	96.4	96.4	96.1 \pm 0.6	83.3	83.8	82.4	83.1	83.9	82.0	83.1 \pm 0.7

The existed spots in both tablet and controls with proper concentration were considered as characteristic spots for the detection of each tablet contents. The chromatogram exhibited the characteristic colored spots of herb extracts at Rf values of 0.14 (doubled yellow), 0.37-0.47 (green) and 0.82 (blue) related to *T. chebula*, dissolved *C. mukul* in *A. ampeloprasum* and *Ph. emblica* extracts. In addition, *T. chebula* and *T. bellirica* had demonstrated some similar spots at Rf values of 0.35 (yellow), 0.55 (red) and 0.58 (yellowish red). So, HPTLC fingerprint could be considered as a reliable method for quality control assessment of the prepared tablets. Through stability studies, no change in appearance and smell of tablets were found. Phenolics and tannins were reduced less than 5% during 3 months. However, real stability should be performed on the final package of tablets in industrial scales.

There were clinical trials with good results for some of used herbs in this tablet as well. Topical application of *A. ampeloprasum* cream twice daily for 3 weeks, improved bleeding in patients with grade I and II of hemorrhoids [28]. In addition, oral consumption of crude resin of *C. mukul* 3g/day for 4 weeks decreased some of symptoms of patients such as painful defecation and constipation [37]. Besides, pain reliever effect of *T. chebula* at the dose of 500 mg twice daily was confirmed through a randomized double blind clinical trial through hot air pain model on 12 healthy humans [23]. Hence, present tablet is a good offer for patients with symptomatic hemorrhoids due to probable synergistic effects of its ingredients. Herbal medicines have great abilities for the management of hemorrhoids and post hemorrhoidectomy complications [38]. Presence of tannins and phenolics phytochemicals in the present poly herbal tablet was confirmed through qualitative and quantitative assays. Antioxidant and anti-inflammatory effects of phenolics and tannins have been confirmed [39-43]. In addition, wound healing, astringent and antibacterial properties have been ascribed to tannins [27,44-46]. Mentioned pharmacological effects are necessary for the management of hemorrhoids [47]. Regarding the anti-inflammatory, antioxidant, antibacterial, wound healing and astringent properties of the mentioned herbs,

the tablets could be good choice for clinical purpose.

Acknowledgments

This article was a part of Ph.D. thesis (Sahar Dehdari, No. 171), Traditional Pharmacy which was granted by School of Traditional Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran (No. 160).

Author contributions

Homa Hajimehdipoor and Somayeh Esmaeili designed and supervised the study. Seyed Alireza Mortazavi coordinated formulation part and Rasool Choopani contributed in traditional information extraction. Sahar Dehdari performed the experimental part and prepared the manuscript. All the authors contributed in revising the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

References

- [1] Moulton HP, Aubert M, Parades VD. Classical treatment of hemorrhoids. *J Visc Surg.* 2014; 7(2): 1-7.
- [2] Lohsiriwat V. Approach to hemorrhoids. *Curr Gastroenterol Rep.* 2013; 15(3): 13-16.
- [3] Abramowitz L, Godeberge P, Staumont G, Soudan D. Clinical practice guidelines for the treatment of hemorrhoid diseases. *Gastroen Clin Biol.* 2001; 25(6-7): 674-702.
- [4] Lohsiriwat V. Hemorrhoids: from basic pathophysiology to clinical management. *World J Gastroenterol.* 2012; 18(17): 2009-2017.
- [5] Riss S, Weiser FA, Schwameis K, Riss T, Mittlböck M, Steiner G, Stift A. The prevalence of hemorrhoids in adults. *Int J Colorectal Dis.* 2012; 27(2): 215-220.
- [6] Jeffrey L, Barnett MD, Peter C, Gary R, Lichtenstein H. Technical review on the diagnosis and treatment of hemorrhoids. *Gastroenterology.* 2004; 5085(04): 1463-1473.
- [7] Lohsiriwat V. Treatment of hemorrhoids : a coloproctologist's view. *World J*

- gastroenterol.* 2015; 21(31): 9245-9252.
- [8] Rahimi R, Abdollahi M. Evidence-based review of medicinal plants used for the treatment of hemorrhoids. *Int J Pharmacol.* 2013; 9(1): 1-11.
- [9] van Andel T, Carvalheiro LG. Why urban citizens in developing countries use traditional medicines: the case of suriname. *Evid Based Complement Altern Med.* 2013; Article ID: 687197.
- [10] Zargarani A, Mehdizadeh A. Avicenna (980–1037 AD). *J Neurol.* 2012; 259(2): 389-390.
- [11] Zarshenas MM, Mehdizadeh A, Zargarani A, Mohagheghzadeh A. Rhazes (865-925 AD). *J Neurol.* 2012; 259(5): 1001-1002.
- [12] Nazem Jahan MA. Qarabadin-e Azam. Tehran: Iran University of Medical Sciences, 2004.
- [13] Shafae Esfehiani MM. Qarabadin-e Shafaie. Tehran: Iran University of Medical Sciences, Research Institute for Islamic and Complementary Medicine, 2004.
- [14] Aghili Khorasani MH. Qarabadin-e kabir. Tehran: Ostad Allah Qoli Khan Qajar publisher, 1855.
- [15] Bag A, Kumar Bhattacharyya S, Kumar Pal N, Ranjan Chattopadhyay R. Anti-inflammatory, anti-lipid peroxidative, antioxidant and membrane stabilizing activities of hydroalcoholic extract of *Terminalia chebula* fruits. *Pharm Biol.* 2013; 51(12): 1515-1520.
- [16] Evangeline S, Sundaram V, Manian RP, Kulanthaivelu K, Balasundaram S. Antioxidant, antibacterial and anti-inflammatory activity of *Acalypha indica* and *Terminalia chebula*: an in-vitro analysis. *Res J Pharm Biol Chem Sci.* 2015; 6(3): 388-396.
- [17] Jami SI, Sultana Z, Ali E, Begum MM, Haque M. Evaluation of analgesic and anti-inflammatory activities on ethanolic extract of *Terminalia chebula* fruits in experimental animal models. *Am J Plant Sci.* 2014; 5(1): 63-69.
- [18] Reddy TC, Aparoy P, Babu NK, Kumar KA, Kalangi SK. Kinetics and docking studies of a COX-2 inhibitor isolated from *Terminalia bellerica* fruits. *Protein Peptide Lett.* 2010; 17(10): 1251-1257.
- [19] Ihantola-Vormisto A, Summanen J, Kankaanranta H, Vuorela H, Asmawi ZM, Moilanen E. Anti-inflammatory activity of extracts from leaves of *Phyllanthus emblica*. *Planta Med.* 1997; 63(6): 518-524.
- [20] Francis JA, Raja SN, Nair MG. Bioactive terpenoids and guggulosteroids from *Commiphora mukul* gum resin of potential anti-inflammatory interest. *Chem Biodivers.* 2004; 1(11): 1842-1853.
- [21] Adao CR, Da Silva BP, Parente JP. A new steroidal saponin with antiinflammatory and antiulcerogenic properties from the bulbs of *Allium ampeloprasum* var *porrum*. *Fitoterapia.* 2011; 82(8): 1175-1180.
- [22] Kumar CU. Evaluation of the analgesic activity of standardized aqueous extract of *Terminalia chebula* in healthy human participants using hot air pain model. *J Clin Diagn Res.* 2015; 9(5): 1-4.
- [23] Jong BS, Jae YJ, Jae YP, Eun MJ, Sang IL, Sung SC, Do YP, Eun WC, Dong SS, Jong SL, Tae GLee. Anti-arthritis and analgesic effect of NDI10218, a standardized extract of *Terminalia chebula*, on arthritis and pain model. *Biomol Ther.* 2012; 20(1): 104-112.
- [24] Sireeratawong S, Jaijoy K, Khonsung P, Soonthornchareonnon N. Analgesic and anti-inflammatory activities of the water extract from *Terminalia chebula* Rezt. *Afr J Trad Complement Altern Med.* 2015; 11(6): 77-82.
- [25] Khan AU, Gilani AH. Antisecretory and analgesic activities of *Terminalia bellerica*. *Afr J Biotechnol.* 2010; 9(18): 2717-2719.
- [26] Suguna L, Singh S, Sivakumar P, Sampath P, Chandrakasan G. Influence of *Terminalia chebula* on dermal wound healing in rats. *Phytother Res.* 2002; 16(3): 227-231.
- [27] Chularojmontri L, Suwatronnakorn M, Wattanapitayakul SK. *Phyllanthus emblica* L. enhances human umbilical vein endothelial wound healing and sprouting. *Evid Based Complement Altern Med.* 2013. Article ID 720728.
- [28] Mosavat SH, Ghahramani L, Sobhani Z, Haghghi ER, Heydari M. Topical *Allium ampeloprasum* subsp *iranicum* (leek) extract cream in patients with symptomatic hemorrhoids: a pilot randomized and controlled clinical trial. *J Evid Based Complement Altern Med.* 2015; 20(2): 132-136.
- [29] Altomare DF, Giannini I. Pharmacological treatment of hemorrhoids : a narrative review.

- Expert Opin Pharmacother.* 2013; 14(17): 1-7.
- [30] Editorial Board. British Pharmacopoeia. London: The Stationary Office, 2015.
- [31] Editorial Board. United States Pharmacopeia 39, National Formulary 34. Rockville: USP Convention, 2016.
- [32] Ibn Sina HAA. Al Qanun Fi al-Tibb (Canon of medicine). Beirut: Alamy Le- Al-Matboat Institute, 2005.
- [33] Rhazes. Al Havi (Liber Continent). Tehran: Academy of Medical Sciences, 2005.
- [34] Patel S, Jayvadan K, Patel RK. To study proximate analysis & biological evaluation of *Triphala guggulu* formulation. *Int J PharmTech Res.* 2012; 4(4): 1520-1526.
- [35] Savarikar SS, Barbhind MM, Halde UK, Kulkarni AP. Pharmaceutical and analytical evaluation of triphalaguggulkalpa tablets. *J Ayurveda Integr Med.* 2011; 2(1): 21-25.
- [36] Kulkarni A, Chimangude P, Wagh V, Kolatkar A. Formulation and evaluation of triphalaguggulkalpa tablets for optimum disintegration time. *Int J Pharm Sci Rev Res.* 2015; 34(1): 270-275.
- [37] Yousefi M, Mahdavi MRV, Hosseini SM, Bahrami A, Davati A, Kamalinejad M, Faghihzadeh S. Clinical evaluation of *Commiphora mukul*, a botanical resin, in the management of hemorrhoids: a randomized controlled trial. *Pharmacogn Mag.* 2013; 9(36): 350-356.
- [38] Dehdari S, Hajimehdipoor H, Esmaili S, Choopani R. Scientific Evaluation of the prescribed herbs by Avicenna for the management of post hemorrhoidectomy complications. *Galen Med J.* 2017; 6(3): 166-184.
- [39] Zhong X, Shi Y, Chen J, Xu J, Wang L, Beier RC, Hou X, Liu F. Polyphenol extracts from *Punica granatum* and *Terminalia chebula* are anti-inflammatory and increase the survival rate of chickens challenged with *Escherichia coli*. *Biol Pharm Bull.* 2014; 37(10): 1575-1582.
- [40] Lee HH, Paudel KR, Kim DW. *Terminalia chebula* fructus inhibits migration and proliferation of vascular smooth muscle cells and production of inflammatory mediators in RAW 264.7. *Evid Based Complement Altern Med.* 2015; Article ID 502182.
- [41] Bandyopadhyay SK, Chatterjee A, Chattopadhyay S. Biphasic effect of *Phyllanthus emblica* L. extract on NSAID-induced ulcer: an antioxidative trail weaved with immunomodulatory effect. *Evid Based Complement Altern Med.* 2011; Article ID 146808.
- [42] Hossen SMM, Sarkar R, Mahmud S, Aziz NMA. Medicinal potential of *Phyllanthus emblica* (Linn.) fruits extracts: biological and pharmacological activities. *J Pharm Res Int.* 2014; 4(12): 1486-1499.
- [43] Nampoothiri SV, Prathapan A, Cherian OL, Raghu KG, Venugopalan VV, Sundaresan A. In vitro antioxidant and inhibitory potential of *Terminalia bellerica* and *Emblica officinalis* fruits against LDL oxidation and key enzymes linked to type 2 diabetes. *Food Chem Toxicol.* 2011; 49(1): 125-131.
- [44] Li K, Diao Y, Zhang H, Wang S, Zhang Z, Yu B, Huang S, Yang H. Tannin extracts from immature fruits of *Terminalia chebula* Fructus Retz. promote cutaneous wound healing in rats. *BMC complement Altern Med.* 2011; 11(1): 86-90.
- [45] Palit M, Hegde SK, Bhat Sh. Effectiveness of mouthrinse formulated from aqueous extract of *Terminalia chebula* on salivary *Streptococcus mutans* count and pH among 8- to 12-year-old school children of karnataka : a randomized clinical trial. *Int J Clin Pediatr Dent.* 2016; 9(4): 349-354.
- [46] Andarkhor P, Sadeghi A, Khodadoost M, Kamalinejad M, Gachkar L, Abdi S, Zargar A. Effects of *Terminalia chebula* Retz. in treatment of hemorrhoids: a double – blind randomized placebo – controlled clinical trial. *Eur J Integr Med.* 2019; 30: 100935.
- [47] Andarkhor P, Khodadoost M, Kamalinejad M, Talaie R, Gachkar L, Zargar A. Twelve vegetables used for prevention and treatment of hemorrhoids in Persian Medicine. *J Tradit Chin Med.* 2019; 39(4): 466-473.

Abbreviations

ITM: Iranian traditional medicine; NP: Natural product; PEG: polyethylene glycol