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Original Research

Effect of *Commiphora mukul* (Hook. ex Stocks) Engl.-Based Herbal Product on Menorrhagia:A Pilot Randomized Triple-Blind Clinical Trial

Asma Ahmadzadeh Heshmati[1,2], Tayebeh Naderi[3], Maryam Rameshk[1], Tania Dehesh[4], Haleh Tajadini[2,5], Pegah Arfae Fathollahkhani[6], Mohadese Kamali[1,2]*

[1]*Herbal and Traditional Medicines Research Center, Kerman University of Medical Sciences, Kerman, Iran*
[2]*Department of Traditional Medicine, Faculty of Persian Medicine, Kerman University of Medical Sciences, Kerman, Iran*
[3]*Obstetrics and Gynecology Center, Afzalipour School of Medicine, Kerman University of Medical Sciences, Kerman, Iran*
[4]*Department of Biostatistics and Epidemiology, School of Public Health, Kerman University of Medical Sciences, Kerman, Iran*
[5]*Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran*
[6]*Valie-Asr Hospital, Rafsanjan University of Medical Sciences, Anar, Iran*

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Abstract

Use of traditional medicinal plants offers an effective non-surgical treatment for menorrhagia with a prevalence of 19.2% in Iran. Thus, *Commiphora mukul* (Hook. ex Stocks) Engl. (guggul) was investigated in this study. This was a randomized, triple-blind clinical trial. The participants were 24 patients suffering from menorrhagia. Group A received 250 mg of mefenamic acid; while group B received 250 mg of guggul capsules, both administered three times a day for three cycles. The primary outcomes were the pictorial blood loss assessment chart (PBAC) score and menstrual duration, which assessed the volume of bleeding. The secondary outcome was the safety of the drug. Demographically, there was no significant difference between the guggul and mefenamic acid groups. In both groups, the number of days of bleeding decreased, but there was no significant difference between the two groups ($p = 0.353$). Similarly, there was no significant difference in PBAC scores between the groups ($p = 0.604$), although the guggul group showed a significant decrease over time ($p < 0.001$). The results indicate that guggul may be as effective as mefenamic acid in reducing the volume and duration of menstrual bleeding in women with menorrhagia. No side effects were observed during the treatment period. Therefore, the herbal product guggul could be considered a safe and effective remedy for decreasing the volume and duration of menstrual bleeding in patients with menorrhagia. It is recommended that these findings be confirmed through multicenter clinical trials with higher precision.

Keywords: Menorrhagia; Uterine hemorrhage; Persian medicine; Complementary therapies, *Commiphora mukul*; Guggul

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*Corresponding Author: Mohadese Kamali
Department of Traditional Medicine, Faculty of Persian Medicine, Kerman University of Medical Sciences, Kerman, Iran
Email: mohadesekamali0912@gmail.com

Introduction

Menorrhagia, characterized by heavy menstrual bleeding, is one of the most common forms of abnormal uterine bleeding (AUB) [1]. The prevalence of menorrhagia in the general population is estimated to be 10–20% [2], affecting 30% of women of reproductive age [3-5]. Menorrhagia is the leading cause of anemia in women and accounts for approximately one-third of all outpatient visits to gynecologic clinics [6]. In Iran, its prevalence is reported to be 19.2% [7]. This condition causes significant emotional distress and limits social and professional activities, particularly in women experiencing heavy menstrual bleeding (HMB). Compared to those with normal bleeding, women with HMB report a markedly reduced quality of life [8]. Menorrhagia also significantly impacts healthcare utilization among women [1]. Consequently, it is a serious issue for many, peaking in severity around the menopausal transition [9]. Currently, medical, surgical, and herbal treatments are used to manage menorrhagia. Medical treatments include combined hormonal drugs (estrogen and progesterone), such as oral contraceptive pills (OCPs), oral progestins, levonorgestrel intrauterine devices (IUDs), gonadotropin-releasing hormone (Gn-RH) agonists, and non-hormonal drugs like nonsteroidal anti-inflammatory drugs (NSAIDs) and tranexamic acid. Surgical options include various methods of endometrial destruction, laser procedures, and, ultimately, hysterectomy [10,11]. However, each of these treatments comes with its own side effects and may not always be effective [12]. For example, the use of NSAIDs carries risks such as heart attacks, stomach ulcers, bleeding, and allergic reactions. Additionally, side effects like abdominal pain, diarrhea, constipation, heartburn, dizziness, nausea, and vomiting have been reported [13]. Surgical procedures, on the other hand, are invasive, expensive, and may require repetition. They also carry risks of complications, including amenorrhea, increased morbidity, and even mortality.

The World Health Organization advocates for integrating traditional and complementary medicine with modern medicine [14], as is the case with many other diseases [15-17]. As a result, exploring additional resources to find effective treatments for menorrhagia is reasonable [18]. Guggul, scientifically known as *Commiphora mukul* (Hook. ex Stocks) Engl., has been used for centuries in traditional medicine systems in China, India [19], Iran, and other countries. In the United States and other Western nations, *C. mukul* is available as an over-the-counter nutritional supplement. Some studies suggest it may be effective in alleviating painful and heavy menstruation [20]. The primary active component of guggul is its oleo-gum resin, extracted by tapping the stem and branches of *Commiphora wightii* (Arnott) Bhandari [syn. *Commiphora mukul* (Hook. ex Stocks) Engl.; *Balsamodendron mukul* (Hook. ex Stocks); Family: *Burseraceae*]. This plant is also known by various names, including gugar, Indian bdellium, guggula, guggal, and gugara [21]. Naturopathic practitioners value guggul for its medicinal properties [22]. Preliminary studies highlight the anti-inflammatory and antioxidant properties of guggul, although more robust evidence is needed to support its efficacy for these and other conditions [23]. As a commercially and medicinally valuable plant, *C. mukul* requires further investigation [19]. Future research should focus on patient-centered outcomes to gain holistic insights into the use of guggul. Addressing current knowledge gaps will enhance the development of evidence-based guidelines for incorporating herbal remedies into menorrhagia management. Although *C. mukul* has not been specifically tested for treating menorrhagia, its demonstrated anti-inflammatory and antioxidant properties may help control abnormal bleeding. Given these properties, the current study aimed to evaluate the efficacy of guggul compared to mefenamic acid, a commonly used NSAID, in patients with menorrhagia. High-quality studies are still needed to confirm these findings and elucidate the plant's mechanisms of action. Healthcare providers should consider these herbal options when discussing treatment plans with patients experiencing heavy menstrual bleeding [24,25-28].

Materials and Methods

Study Design

This prospective, randomized, triple-blind, parallel, experimental clinical trial was conducted at Afzalipur Hospital, affiliated with Kerman University of Medical Sciences (KUMS), Kerman, from October 2nd, 2022, to February 6th, 2023. The study adhered to the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) 2010. Patients were initially examined by a gynecologist, and their diagnoses were confirmed using a pictorial blood loss assessment chart (PBAC) based on their previous menstrual period. After providing informed consent, patients were randomly assigned to two groups. Each participant received one 250 mg capsule three times daily after meals for three menstrual cycles, spanning from the first to the fifth day of each cycle. Participants were permitted to discontinue therapy if they experienced significant adverse effects and could contact the therapist if necessary.

Ethical Issues

The trial followed the principles outlined in the Declaration of Helsinki. It was evaluated and approved by the Ethics Committee of KUMS, Kerman, Iran (approval code: IR.KMU.REC.1400.666) and was regis-

tered in the Iranian Clinical Trials Registration Center (IRCT) under the code IRCT20211125053177N1 (registered on May 5, 2022). All participants, or their legal guardians, signed a written informed consent form after a thorough discussion of the potential benefits and risks. Confidentiality of patient information was strictly maintained throughout the study. Participants or their guardians retained the right to withdraw from the trial at any point without affecting their ongoing medical care. Face-to-face consultations and phone support were provided to address any questions or concerns from participants.

Eligibility Criteria

Patients with AUB, regular menstruation cycles, and ages 15 to 55 years old were included in two parallel study groups. Exclusion criteria were: pregnancy or decision to become pregnant within the next three months, breastfeeding, concomitant use of any type of medication for AUB, history of any type of side effect related to the use of any type of medication in the past, suffering from systemic diseases (thyroid, pituitary gland, liver, coagulation disorders, diabetes, or cardiovascular disease, etc.), problematic physical examination, Pap smear, or sonography, drug abuse, severe mental retardation, abnormal BMI, use of hormonal contraceptives during the last three months, having an IUD, fallopian tube closure, the presence of any other warning signs (severe weight loss, anemia (Hb<10)), not following the study protocol and not signing the consent form.

Randomization and blinding

This trial was conducted as a triple-blind study, ensuring that patients, physicians, and data assessors were unaware of group assignments. Randomization was performed using a randomized permutation block design with a block size of four. The 24 participants were evenly distributed among the blocks. Upon referral to the clinic, patients were assigned a code (A or B) by a research assistant based on the block schedule. After diagnosis by the physician, patients received the treatment corresponding to their assigned code. The drugs, packaged identically, were prepared by the Faculty of Persian Medicine at Kerman University of Medical Sciences. Physicians recorded only the patient's name and code to maintain blinding. To preserve blinding, the randomization codes were disclosed only after the study's completion. Even during data analysis, researchers were unaware of the group assignments or the nature of the treatments. A diagram illustrating the sampling and allocation process is provided in figure 1. The reduced sample size and participant flow disruptions were primarily due to participant withdrawal and non-compliance with the study protocol. Specifically, two participants in the guggul group and four in the mefenamic acid group were excluded.

Chemicals and reagents

Mefenamic acid powder was obtained from Razak Pharmaceutical Company (Iran) and encapsulated into 250 mg hard gelatin capsules. All other chemicals and solvents used were of analytical grade and purchased from Merck (Germany).

Preparation of Guggul

Guggul was procured from a local market in Kerman, Iran, and its identity was confirmed by a botanist at

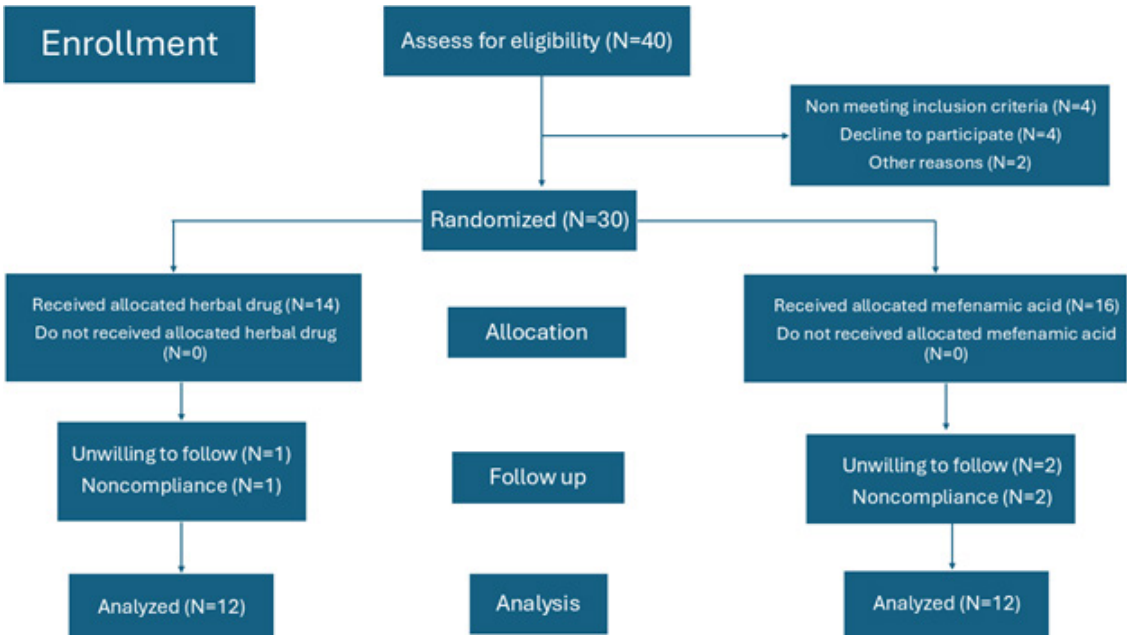

Figure 1. CONSORT flowchart

Kerman University of Medical Sciences (KUMS). The guggul was first washed and dried in a shaded area, then ground into a fine powder. The dried oleo-gum resin was milled, passed through a 60-mesh sieve, and encapsulated into 250 mg hard gelatin capsules.

Phytochemical Screening

Phytochemical screening of guggul confirmed the presence of tannins, alkaloids, saponins, cardiac glycosides, steroids, anthraquinones, terpenoids, and flavonoids in the crude extract of the oleo-gum resin [29,30].

Standardization of Guggul

Standardization was performed by determining the total phenolic content using the Folin-Ciocalteu reagent method, measured with a molecular spectrophotometer at 765 nm using an ELISA reader (Biotek, USA). Gallic acid was used as the standard for the calibration curve, and the total polyphenol content was expressed in terms of gallic acid equivalents [31]. All quantitative experiments were conducted in triplicate, with results reported as the mean ± standard deviation (SD).

Outcome measures

The primary outcome measure of the study was the PBAC score, complemented by a diary for recording the duration of menstruation. Secondary outcomes focused on the safety of the treatment, which was assessed using a diary in which participants recorded daily side effects and medication usage. At the conclusion of the study, these diaries were collected for analysis. The PBAC is a validated tool for evaluating the extent of menstrual bleeding. Patients completed the PBAC over three menstrual cycles, with the assessment consisting of eight questions, yielding scores ranging from 8 to 32. The PBAC includes a table showing the number of menstrual days (horizontal row) and the number of blood-stained pads (vertical row) in three categories: mild, moderate, and severe. For mild staining, a factor of 1 is used; for moderate staining, a factor of 5; and for heavily blood-soaked pads, a factor of 20 is applied. Additional factors include a score of 1 for small clots (dime-sized), 5 for large clots (quarter-sized or larger), and 5 for menstrual accidents such as flooding. After each pad change, participants marked the extent of blood staining at home. At the end of menstruation, each mark was multiplied by the corresponding factor, and the total PBAC score was calculated. A score of 100 or higher indicates menorrhagia; while a score below 100 represents normal menstruation. This method demonstrates high sensitivity (86%) and specificity (98%) for distinguishing menorrhagia from normal menstruation [32]. Participants were instructed to use medium-sized winged pads (Panbehriz brand) with an average blood absorption capacity of 96 mL, produced in 2023. These pads were comparable in absorbency to Kotex regular napkins and Stayfree Maxi Pads, which have average absorption ranges of 11.06–45.93 mL and 24.86–94.94 mL, respectively [33]. In this study, a per-protocol (PP) analysis was used, as only data from participants who completed all three cycles and adhered to the study protocol were included in the analysis.

Safety Assessments

Participants were instructed to report any potential side effects during the study period and to contact the researchers promptly if they experienced adverse events.

Sample Size

As this was a pilot study, a total of 30 participants were randomly assigned to two groups, with 12 patients remaining in each group at the end of the trial.

Statistical Analysis

Descriptive statistics were expressed as mean ± standard deviation (SD) for quantitative variables and as frequencies (numbers and percentages) for qualitative variables. To compare demographic variables between the two groups, the independent t-test, Mann-Whitney U test, chi-square test, and Fisher's exact test were applied as appropriate. A repeated measures analysis was performed to compare outcomes between the two groups over time.

The level of statistical significance was set at 0.05 for all tests. Effect sizes were calculated using Cohen's for independent samples t-tests, Cramér's for chi-square tests, and partial eta-squared for repeated measures analyses. In this study, data were analyzed using both descriptive and inferential statistical methods. For quantitative variables, the mean and standard deviation (SD) were reported; while for categorical variables, frequencies and percentages were presented. To assess differences in baseline demographic and clinical characteristics between the two groups, independent t-tests were used for continuous variables, and chi-square or Fisher's exact tests were applied for categorical variables. For the repeated measures data, a mixed-effects linear model was used to analyze changes in PBAC scores and the number of bleeding days over time. This approach was chosen to account for the correlation between repeated measurements within individuals and to handle any missing data under the assumption of missing at random (MAR). The fixed effects included group (guggul vs. mefenamic acid), time (month 1, month 2, and month 3), and the group × time interaction; while the random effect accounted for inter-individual variability. Effect sizes were calculated to interpret the magnitude

of differences, with Cohen's d used for between-group comparisons at individual time points, and partial eta-squared (η^2) reported for the overall effects of time and the group × time interaction. Statistical significance was set at $p < 0.05$. All analyses were performed using SPSS version 25. As this study was designed as a pilot, a formal power analysis was not conducted prior to recruitment. However, a post hoc power analysis was performed based on the observed effect sizes for the primary outcome (PBAC score). The analysis indicates that the current sample size provides preliminary evidence, but is underpowered to detect smaller effect sizes with high confidence.

Results

Standardization of guggul results

The total phenolic compound content of guggul was 53.27 ± 2.79 mg of gallic acid equivalents (GAE) per kg of dried Guggul.

Intervention results

After screening 40 patients, 30 were selected and randomly assigned to two groups, as shown in figure 1. In the guggul group, 2 patients withdrew from the study early due to their unwillingness to adhere to the protocol; while 4 patients from the mefenamic acid group were excluded because they did not follow the study guidelines and had insufficient data. Ultimately, the data from 24 patients were statistically analyzed, with 12 patients in each group. Demographic information, including age, number of children, marital status, and history of uterine surgery, is presented in table 1. Table 2 displays the comparison of the number of bleeding days between the guggul and mefenamic acid groups over time: at the end of the first, second, and

Table 1. Comparison of age, marital status, number of children and surgery in two guggul and mefenamic acid groups

Variable		Mefenamic acid group	Guggul group	*p* value	Effect size
Age (Mean ± SD)		39.25±7.18	41.33±6.98	0.479	0.74
Number of children (Mean ± SD)		0.95± 2	0.98± 2.33	0.385	0.72
Marriage	Yes, N (%)	11 (91.7)	11 (91.7)	0.999 <	0.46
	No; N (%)	1 (8.3)	1 (8.3)		
Uterus surgery	Yes, N (%)	5 (41.7)	6 (50)	0.682	0.42
	No; N (%)	7 (58.3)	6 (50)		

The demographic and clinical characteristics of the participants were comparable between the two groups at baseline. No significant differences were observed in age, number of children, marital status, or history of uterine surgery ($p > 0.05$ for all comparisons).

Table 2. Comparison of the number of bleeding days in two guggul and mefenamic acid groups over time

Time	Variable	Mefenamic acid group(Mean ± SD)	Guggul group (Mean ± SD)	*p* value (Between Groups)	*p* value (Time Effect)	*p* value (Time × Group Interaction)	Effect size
Month 1	Number of bleeding days	7.83±2.08	8.08±1.97	0.353	0.003	0.084	0.07
Month 2	Number of bleeding days	7.41±1.51	6.75±1.35				
Month 3	Number of bleeding days	7.25±1.60	5.91±1.97				

Table 3. Comparison of PBAC score in two intervention and control groups over time

Time	Variable	Mefenamic acid group (Mean ± SD)	Guggul group (Mean ± SD)	*p* value (Between Groups)	*p* value (Time Effect)	*p* value (Time × Group Interaction)	Effect size
Month 1	PBAC Score	138.08±97.3	210.75±114.9	0.604	0.001>	0.001>	0.11
Month 2	PBAC Score	122.83±96.3	129.25±66.33				
Month 3	PBAC Score	110±83.5	83.92±48.57				

third months. Table 3 shows the comparison of PBAC scores in the two groups over time: at the end of the first, second, and third months. Figures 2 and 3 illustrate the changes in the number of menstrual days and PBAC scores during three menstrual cycles for both groups.

The repeated measurement analysis showed a significant main effect of time ($p < 0.001$), indicating that PBAC scores decreased across the study period for both groups. The group × time interaction was also significant ($p = 0.02$), suggesting that the rate of reduction differed between the groups. Post-hoc comparisons revealed that the guggul group experienced a significantly greater decrease in PBAC scores from baseline to month 3 compared to the mefenamic acid group (mean difference: -20.5, p = 0.01, Cohen's d = 0.75). For the number of bleeding days, a significant main effect of time was observed ($p = 0.003$), but the group effect was not significant ($p = 0.35$). The group × time interaction was not statistically significant ($p = 0.084$), indicating that the decrease in bleeding days over time was similar in both groups. However, within-group comparisons showed a significant reduction in bleeding days from baseline to month 3 in both groups (guggul: -2.17 days, $p = 0.01$; mefenamic acid: -1.58 days, $p = 0.03$). Effect sizes for the main outcomes indicate moderate to large effects for PBAC score changes in the guggul group ($\eta 2 = 0.11$) and smaller effects for the number of bleeding days ($\eta 2 = 0.07$). These findings suggest that guggul may be particularly effective in reducing the volume of menstrual bleeding over time. No adverse events were reported during the study, confirming the safety of both interventions.

There are not any sides effects during the treatment period.

Discussion

This study examined the effectiveness of the gum of *C. mukul* and compared it with mefenamic acid in patients with menorrhagia, providing valuable insights into the potential of herbal medicines as an option for non-surgical management and fertility retention in these patients. The present study is the first randomized clinical trial to evaluate the effect of *C. mukul* as a treatment, compared with mefenamic acid, for heavy menstrual bleeding.

The results demonstrated that taking 750 mg of *C. mukul* for five days starting from the first day of menstruation significantly reduced the amount of menstrual bleeding. The findings also showed that *C. mukul* is a safe and effective treatment compared to mefenamic acid, with no specific side effects reported. In Traditional Persian Medicine, the therapeutic effects of herbal drugs cannot be definitively attributed to a single factor. This study provides a foundation for further research. Scientific studies have demonstrated that medicinal plants control AUB through four mechanisms including inhibition of the inflammatory process, inhibition of prostaglandin production, antiproliferative activity on HeLa cells, and estrogenic activity [34]. In the luteal phase of the menstrual cycle in idiopathic menorrhagia, some inflammatory factors lead to endometrial edema. For example, leukocyte migration causes micro-erosion in the endometrial epithelium. This inflammation is one of the causes of abnormal uterine bleeding. Furthermore, inflammatory macrophages and natural killer (NK) cells produce inflammatory vasculature that damages the capillary epithelium, leading to increased bleeding. Previous research indicates that *C. mukul* contains a mixture of plant elements, including volatile oils such as terpenoids (monoterpenoids, sesquiterpenoids, diterpenoids, and triterpenoids), as well as steroids, flavonoids, guggulsterones, lignans, amino acids, dimersin, alpha-camphorene, lin-

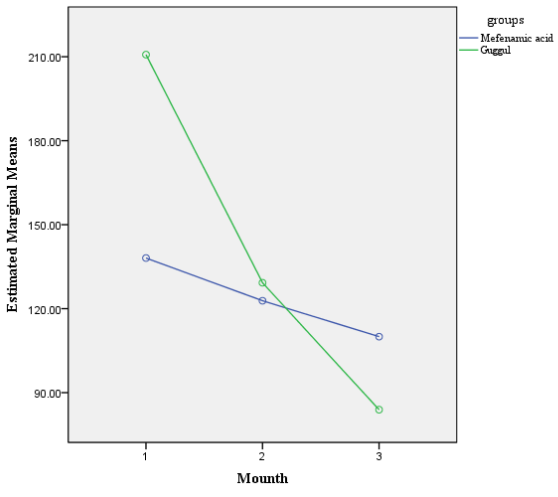

Figure 2. Menstrual duration changes

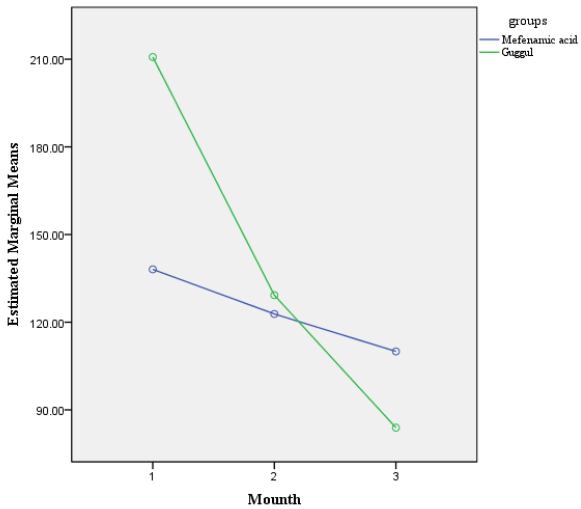

Figure 3. PBAC score changes

oleic acid, oleic acid, stearic acid, palmitic acid, and sitosterol [35]. Like other oleo-gum resins, *C. mukul* increases leukocytes and stimulates phagocytes in the blood. It is a complex mixture of secondary metabolites, including steroids, diterpenoids, aliphatic esters, carbohydrates, volatile oils, amino acids, and triglycerides, which can have both medicinal and toxic effects depending on the dosage and type of consumption. *C. mukul* has anti-inflammatory, antifungal, antibacterial, antispasmodic, anti-infective, liver-tonic, and thyroid-stimulating properties. It is effective in treating neurological diseases, heart diseases, skin conditions, anthelmintic issues, muscle spasms, blood pressure regulation, and urinary tract diseases. It also acts as a strong antioxidant and reduces platelet adhesion. Additionally, *C. mukul* can lower cholesterol and triglycerides, making it potentially beneficial in treating atherosclerosis. According to an animal study, it may also aid in the treatment of type 2 diabetes due to its blood sugar and lipid-lowering effects [36]. Since Guggul suppresses the activation of the proinflammatory transcription factor nuclear factor-κB (NF-κB), it can be used to treat chronic inflammatory diseases. A study showed that its steroid fraction significantly impacted primary and secondary inflammation in rat pyrexia induced by Freund's adjuvant. *C. mukul* is also beneficial in treating inflammatory bowel disease (IBD) due to its immunomodulatory, antioxidant, and antibacterial properties. It reduces NF-κB, nitric oxide, and COX-2, and exhibits significant anti-inflammatory effects without side effects in diseases such as arthritis, rheumatoid arthritis, gout, and osteoarthritis [37]. The elements found in *C. mukul* have numerous therapeutic effects, including anti-inflammatory effects and strong antagonistic activity against the mineralocorticoid receptor, glucocorticoid receptor, and androgen receptor, leading to antiestrogenic and antiandrogenic effects [38]. Some of these elements are effective in controlling menstrual bleeding. The most important active ingredient in *C. mukul* is guggulsterone, a phytosterol used to treat inflammatory diseases [39,40]. Guggulsterone belongs to the steroid class and has two isomers: E-guggulsterone and Z-guggulsterone [41,42]. It exhibits strong anti-inflammatory effects by inhibiting TNF-α, IL-1β, and IL-6, as well as reducing macrophage and neutrophil infiltration and lowering pro-inflammatory cytokines. Terpenoid compounds also contribute to the significant anti-inflammatory effects of *C. mukul* resin. *In vitro* and *in vivo* studies on the resin of *Commiphora* species have demonstrated its anti-inflammatory properties, which are linked to the terpenoid and steroid compounds present. These compounds primarily exert their anti-inflammatory effects by inhibiting cyclooxygenase (COX), NO (nitric oxide) formation, ROS (reactive oxygen species), TNF-α, PGE2, NF-κB, and mitogen-activated protein kinase (MAPK) [42-45]. Guggulsterones regulate gene expression by controlling molecular targets such as transcription factors (NF-κB, STAT), and steroid receptors [46]. Additionally, they play a role in regulating growth and inflammatory factors through the modulation of anti-apoptotic and anti-inflammatory genes [47]. Guggulsterone also has antioxidant properties by inhibiting the production of free radicals [48]. *C. mukul* also contains α-pinene, a terpenoid with antimicrobial and anti-inflammatory properties. It increases basic fibroblast growth factor (BFGF) and platelet-derived growth factor [49-58], and is considered an effective substance in wound healing [51]. Quercetin in *C. mukul* has strong coagulation activity, and β-sitosterol can shorten bleeding time, clotting time, and reduce uterine bleeding [59]. Methyl chavicol, a terpenoid oxide, also has anti-inflammatory properties [49]. The octanodammarane triterpenes, mansumbinoic acid, and mansumbinone in *C. mukul* have also shown significant anti-inflammatory activity [49,60]. Phytochemical screening of *C. mukul* revealed various bioactive compounds, which may contribute to its therapeutic effects in controlling menorrhagia. Discovering the exact mechanism of action of the resin compounds requires further study.

The limitations of this study include the small sample size and the lack of long-term follow-up to evaluate the sustained effects of this herbal treatment on menorrhagia. The strengths of the study lie in its careful triple-blind randomization design, adherence to CONSORT guidelines, and the use of standardized tools, such as the PBAC score, to assess treatment effectiveness. Future research should address these limitations and focus on investigating the long-term effects and safety of *C. mukul* in the management of menorrhagia. In this study, a per-protocol analysis was used, as only data from participants who completed all three cycles and adhered to the study protocol were included in the analysis. An intention-to-treat analysis might provide additional insights, and this was another limitation of current study.

Conclusion

The findings of this study support the beneficial effect of the oleo-gum resin of the *C. mukul* as a suitable option for reducing both the intensity and duration of menstrual bleeding in women with menorrhagia.

Conflict of Interests

The authors declare no conflicts of interest.

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