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The effect of frankincense (*Boswellia serrata,* oleoresin) and ginger (*Zingiber officinale*, rhizoma) on heavy menstrual bleeding: A randomized, placebo-controlled, clinical trial

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ABSTRACT

Objectives: To evaluate the effect of frankincense (*Boswellia serrata,* oleoresin) and ginger (*Zingiber officinale,* rhizoma) as complementary treatments for heavy menstrual bleeding (HMB) among women of reproductive age.
Design: Randomized, placebo-controlled, clinical trial.
Setting: Gynecology outpatient clinics.
Interventions: Patients with HMB (n = 102) were randomly assigned to three groups. All patients received ibuprofen (200 mg) and either frankincense (300 mg), ginger (300 mg), or a placebo, which contains 200 mg anhydrous lactose as the filling agent and was similar in appearance to the two other drugs. Patients received the medications three times a day for seven days of the menstrual cycle, starting from the first bleeding day and this was repeated for two consecutive menstrual cycles.
Main outcome measures: Amount and duration of menstrual bleeding and quality of life (QOL).
Results: Duration of menstrual bleeding was decreased in the frankincense (-1.77 ± 2.47 days, $P = 0.003$) and ginger (-1.8 ± 1.79 days, $P = 0.001$) groups, but not in the placebo group (-0.52 ± 1.86 days, $P = 0.42$). Amount of menstrual bleeding was decreased in all ($P < 0.05$), with no difference among the study groups ($P > 0.05$). More improvement in QOL was observed in the frankincense (-25.7 ± 3.1; $P < 0.001$) and ginger (-29.2 ± 3.7: $P < 0.001$) groups compared to the placebo group (-15.07 ± 3.52; $P < 0.001$) and between the groups, differences were statistically significant ($P = 0.02$).
Conclusions: Ginger and frankincense seem to be effective complementary treatments for HMB. Further studies with a larger sample size and longer follow-up are warranted in this regard.

1. Introduction

Heavy menstrual bleeding (HMB) is defined as menstrual blood loss greater than 80 mL during each menstrual cycle and/or a menstrual duration longer than seven days.[1] The pathophysiology of HMB is not completely understood. However, besides uterine pathological conditions (e.g. polyps, fibroids, and adenomyosis) and bleeding disorders, increased synthesis of prostaglandin E2 (PGE2) and PGE-binding sites in the uterine tissue are suggested as possible mechanisms for HMB.[2] The estimated prevalence of HMB in the general population ranges between 11 and 13%,[1] causing complications including anemia [3] and negatively impacting women's quality of life (QOL).[4]

Current medical treatments recommended for HMB include hormone therapy (e.g., oral contraceptives and progestin) and non-hormonal medications (e.g., non-steroid anti-inflammatory drugs (NSAIDs) and tranexamic acid).[5] The main shortcom of these medications is their unwanted side effects when used long term. Hormone therapy might increase the risk of myocardial infarction, stroke, breast cancer, and

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thrombosis in susceptible patients.[6] Patients taking NSAIDs are also susceptible to gastric bleeding.[7]

A few number of controlled clinical trials have evaluated the effect of herbal therapies including *Zingiber officinale* rhizoma, *Myrtus communis* leaves, and *Punica granatum* flowers as an alternative or complementary to recommended medications for HMB.[8] These trials have found a reduction in the amount and/or duration of menstrual bleeding.[8] The therapeutic effects of these herbs seem to be attributed to their anti-inflammatory properties.[9–11] Frankincense is another herb which is recommended for the treatment of HMB in Persian medicine,[12] and has been shown to have anti-inflammatory properties.[13] However, there has been no reported controlled clinical trial to evaluate the effect of this herb on HMB.

According to the available evidence and the studies done on traditional (Persian) medicine in Iran, as well as the anti-inflammatory mechanisms of the mentioned herbs, we selected frankincense and ginger in combination with ibuprofen for the treatment of HMB. Similar to the previous studies, herbal medicines in the current study have been investigated as complementary to NSAID. We hypothesized that complementary therapy with these herbal medicines is more effective than ibuprofen alone in the treatment of HMB.

2. Patients and methods

2.1. Study design and setting

This randomized, double-blind, placebo-controlled clinical trial was conducted in two gynecology outpatient clinics in Isfahan city (Iran) from August 2016 to January 2018. Patients with complaints of menorrhagia in several consecutive menstrual cycles were evaluated according to the study criteria. Inclusion criteria were as follows: a) age from 18 to 45 years; b) menstrual bleeding more than 80 mL per cycle and/or more than seven days based on the pictorial blood loss assessment chart [14]; c) regular menstrual cycles from 22 to 35 days; d) normal gynecological examinations (no infection or mass); and e) normal Pap smear test during the past year. Patients with any of the following characteristics were excluded from the study: a) pregnancy or breastfeeding; b) abnormal endometrial thickness or uterine morphology according to a transvaginal sonography; c) uterine fibroids > 3 cm; d) ovarian cysts; e) hemoglobin < 10.5 mg/dL; f) history of an allergic reaction to ginger, frankincense, or ibuprofen; and g) receiving hormone therapy (e.g., contraceptives) or other medications affecting menstrual bleeding (e.g., aspirin). The Ethics Committee of the Isfahan University of Medical Sciences approved the study protocol (IR.MUI.REC.1395.30414). Written informed consent was obtained from all participants before enrollment. Also, the trial was registered at the Iranian Registry of Clinical Trials (registration code: IRCT2016062228579N1). This report is prepared based on the CONSORT extension for reporting herbal medicines.[15]

2.2. Intervention

Eligible patients were invited to participate in the study and were interviewed by the researcher, who then randomized patients into three groups (frankincense, ginger, and placebo). Randomization was done using random digit numbers generated by SPSS software (SPSS, Inc., Chicago, IL, USA). The gynecologist who evaluated the study eligibility criteria was not involved in the randomization process.

All patients received 200 mg of ibuprofen tablets (Razi Co., Tehran, Iran) as recommended by the evidence.[5] Patients in the frankincense group received capsules containing 300 mg of frankincense powder and 200 mg of anhydrous lactose as bulking excipient. Patients in the ginger group received capsules containing 300 mg of ginger powder as well as 200 mg of anhydrous lactose. Patients in the placebo group received capsules containing 200 mg of lactose that were similar in appearance to the two other drugs.

For preparation of the herbs, Indian frankincense (*Boswellia serrata* oleoresin) and fresh rhizomes of *Zingiber officinale* (80 kg) were purchased from the Isfahan Traditional Medicine Center and identified by a pharmacologist specializing in pharmacognosy. Next, the rhizomes were flaked and dried overnight. Then the dried plant material (15 kg) was powdered and extracted in a maceration tank using ethanol: water (70:30) for three days in triplicate. Afterward, the extract was filtered and concentrated using a vacuum rotary evaporator at 40 °C. Lastly, the concentrated extract was mixed with lactose in a ratio of 3:2 (dry weight) as a drying bulking excipient using the wet granulation method and was dried at 40 °C.

All the above mentioned procedures for drug preparation were done by an independent pharmacologist in the Faculty of Pharmacy, Isfahan University of Medical Sciences. To maintain blinding of the study participants, all the drugs were prepared and placed in capsules of the same shape, color and opacity. Patients, gynecologists, and the researcher who interviewed the patients were all blinded to the treatment allocation and capsule packages, which were coded by the pharmacologist and statistical advisor.

All the patients were treated for two continuous menstrual cycles. All medications were consumed three times a day starting from the first bleeding day and continued for seven days. Patients were treated for two consecutive menstrual cycles and were asked not to take other medications for HMB during the study period.

2.3. Assessments

Demographic data including age, height, weight, menarche age, parity, and birth control method were gathered using a questionnaire. Study outcomes included duration of menstrual bleeding, amount of bleeding, and QOL.

Duration of menstrual bleeding was assessed at baseline, and then after the first and second cycles after medication by a single question asking the number of days with bleeding. The amounts of menstrual bleeding were measured at baseline, and then after the first and second cycles after medication using the pictorial blood assessment chart (PBAC). The PBAC measures the amount of menstrual blood loss based on the visual appearance of stained towels, tampons, and the presence of clots.[14] In this chart, patients indicate the number of pads or tampons used each day and the degree they are soiled with blood. The number of pads and tampons is then multiplied by a factor of 1 for lightly soiled, 5 for medium soiled, 10 for totally soaked for tampons, and 20 for totally soaked for pads. For blood clots on the pad, an additional score of 1 (for small clots) or 5 (for large clots) are added. Also, clots passed and episodes of flooding have additional scores of 5 points. A PBAC score of $\geq$100 has a specificity and sensitivity of above 80% for indicating menstrual blood loss greater than 80 mL during each menstrual cycle.[14] To ensure the homogeneity of the measurements, all women were given the same kind of sanitary pads.

The QOL of patients was evaluated by the Menorrhagia Questionnaire.[16] The questionnaire evaluates bleeding-specific symptoms and QOL with 13 items, covering pain, problems with bleeding through clothes, work life, leisure activities, and sexual activity. The final transformed score ranges from 1 to 100 with lower scores indicating better QOL.[16] A validated translation of the questionnaire was used in this study.[17]

2.4. Statistical analyses

The sample size was calculated as 19 in each group considering type one error (α) = 0.05 and statistical power = 0.90 for detecting the standardized effect size (Δ) = 0.7.[18] We included 34 women in each group to cover possible attrition during the study period.

Continuous and categorical data were presented as Mean ± SD and frequency (percentage), respectively. Normality of continuous data was evaluated using the Kolmogorov-Smirnov test and Q-Q plot. Non-

normal data were subjected to logarithmic transformation. The repeated measures ANOVA was used for comparing the mean score of PBAC and bleeding duration over time in each group and between groups. The analysis of variance (ANOVA) was used for comparing the mean changes from baseline between the three study groups. Within and between group analyses of QOL were done by the paired samples *t*-test and ANOVA, respectively. Data analysis was conducted in the per-protocol framework. We also followed the intention to treat analysis through applying the linear mixed effects model. All statistical analyses were done using SPSS software (SPSS, Inc., Chicago, IL, USA, version 23).

3. Results

3.1. Baseline characteristics

During the study period a total number of 136 patients with HMB were evaluated from which 26 were not eligible according to the study criteria. Eight eligible patients were not willing to participate. One hundred and two patients were randomized into the study groups, 34 in each treatment group. During the first month of the study, 23 patients were lost to follow-up or discontinued the treatment. During the second month of intervention, 13 patients were lost to follow-up or discontinued the study (Fig. 1). Baseline characteristics of the patients are summarized in Table 1. There was no difference among the study groups regarding baseline characteristics ($P > 0.05$).

Table 1
Baseline characteristics of studied groups.

	Frankincense	Ginger	Placebo	P
Age, year	37.8 ± 6.5	37.1 ± 5.8	37.1 ± 7.2	0.88*
Body mass index, kg/m^2	27.2 ± 4.4	27.3 ± 4.8	27.7 ± 6.0	0.95*
Contraception method				
Withdrawal	29.6%	45.8%	40.0%	0.42†
Condom	18.5%	20.8%	24.0%	
Vasectomy	14.8%	20.8%	24.0%	
Tubal ligation	18.5%	0	4.0%	
None	14.8%	12.5%	8.0%	
Menarche age, year	13.5 ± 1.3	13.4 ± 1.1	13.1 ± 1.2	0.49*
Parity, n	1.9 ± 1.2	1.8 ± 1.0	2.0 ± 1.1	0.49*

P-values calculated using *One way ANOVA or †Chi square test.

3.2. Comparisons of the study outcomes among the treatment groups

Table 2 summarizes the within and between groups comparisons for duration of menstrual bleeding, PBAC score, and QOL during the study period. The mean duration of menstrual bleeding was significantly reduced in the frankincense($P = 0.003$) and ginger ($P = 0.001$) groups during the study, but not in the placebo group ($P = 0.42$). Between group analyses showed that the mean reduction in duration of bleeding was not significantly different between groups at the end of the first month ($P = 0.37$), while it was different at the end of the second month of follow up (0.045). The observed overall changes during the study period were significantly different between the three study groups ($P = 0.04$), as shown in Fig. 2.

Significant decrease in the PBAC score was observed in all three groups from baseline to the end of the intervention period (Fig. 3). Although frankincense and ginger showed more notable clinical reduction, the observed changes did not show a statistically significant difference between groups ($P = 0.35$). On the other hand, no statistically significant differences were observed between groups in terms of change in the PBAC score at the end of the first ($P = 0.74$) or second month of follow up ($P = 0.46$).

Significant improvement was observed in QOL in all study groups ($P < 0.001$, all groups, Fig. 4). However, more notable changes were observed in the frankincense(-25.65 ± 15.09) and ginger groups (-29.17 ± 17.12) compared with the placebo group (-15.07 ± 16.14) ($P = 0.02$).

A sensitivity analysis was done for evaluating the results in the framework of intention to treat analysis using the linear mixed effects model. The results were similar as with the per-protocol approach.

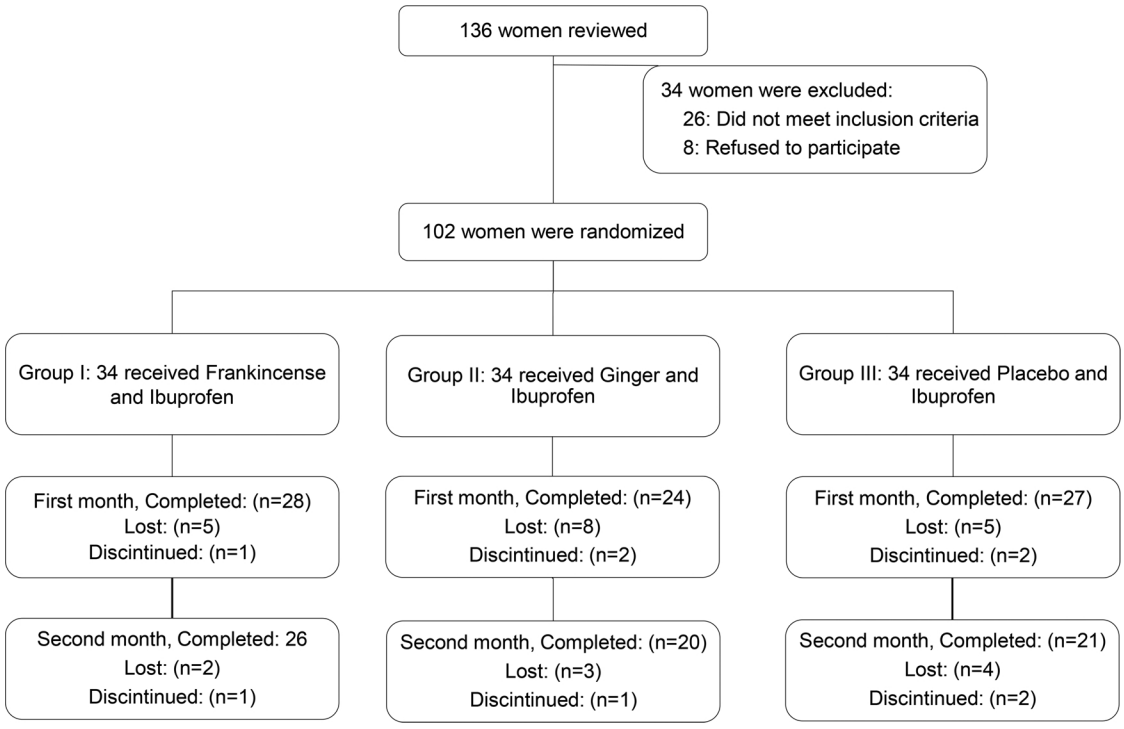

Fig. 1. Study flow diagram.

Table 2
Comparison of changes in amount and duration of menstrual bleeding and quality of life among the study groups.

	Frankincense	Ginger	Placebo	P[2]	P[3]
PBAC score					
Baseline	274.5 ± 139.9	277.7 ± 9.3	311.0 ± 143.1	0.74[§]	
First month	172.3 ± 137.4	182.6 ± 86.0	209.6 ± 136.2	0.46[§]	
Changes from baseline	(-97.8 ± 15.5)	(-87.5 ± 16.2)	(-113.1 ± 21)		
Second month	147.5 ± 130.1	152.8 ± 95.3	215.3 ± 143.4		
Changes from baseline	(-127 ± 18.4)	(-125 ± 17.5)	(-113 ± 31)		
P[1]	< 0.001	< 0.001	0.01	0.49	0.35
Duration of menstrual bleeding, day					
Baseline	9.1 ± 2.7	8.8 ± 2.3	8.7 ± 2.5	0.37[§]	
First month	7.6 ± 1.9	7.6 ± 1.9	8.4 ± 3.5	0.045[§]	
Changes from baseline	(-1.46 ± 1.97)	(-1.33 ± 1.74)	(-0.67 ± 2.78)		
Second month	7.4 ± 1.6	7.0 ± 2.1	8.1 ± 2.8		
Changes from baseline	(-1.77 ± 2.47)	(-1.80 ± 1.79)	(-1.46 ± 1.97)		
P[1]	0.003	0.001	0.42	0.66	0.04
Quality of life score					
Baseline	57.6 ± 15	58.8 ± 15.6	54.3 ± 16.6	0.02[§]	
End of intervention	32.0 ± 15.4	29.7 ± 16	39.2 ± 16.7		
Changes from baseline	(-25.7 ± 3.1)	(-29.2 ± 3.7)	(-15.07 ± 3.52)		
P (paired sample t test)	< 0.001	< 0.001	< 0.001		

PBAC pictorial blood assessment chart.
P[1], assessed trend of variables during study period within groups using repeated measurements ANOVA. (Time effect).
P[2], assessed interaction of time and intervention resulted from repeated measures ANOVA.
P[3], assessed the between groups changes resulted from repeated measurers ANOVA.
[§] Resulted from analysis of variance (ANOVA).

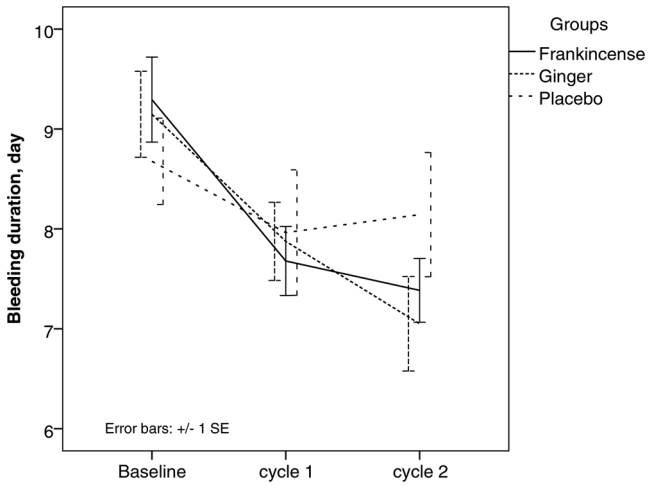

Fig. 2. Trend of changes in duration of menstrual bleeding in the study groups during the study period.

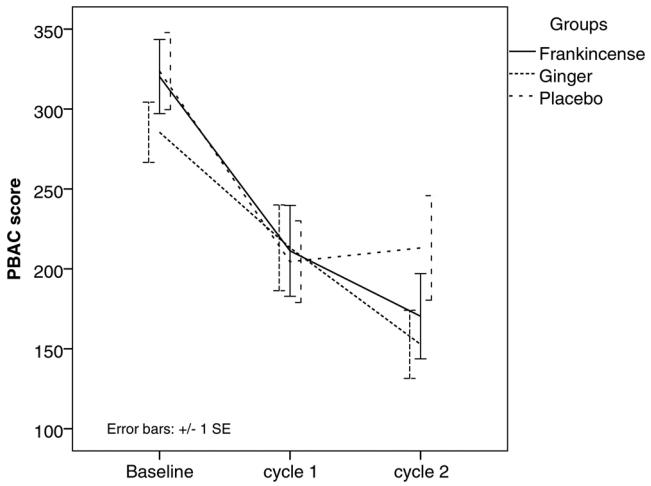

Fig. 3. Trend of changes in PBAC score in the study groups during the study period. *PBAC* pictorial blood assessment chart.

3.3. Side effects

Side effects with frankincense were constipation (5.8%), abdominal pain, dyspepsia, and headache (2.9%). Side effects with ginger were constipation, abdominal pain, dyspepsia, and headache (2.9%). One patient (2.9%) also had an allergic reaction to ginger. In the placebo group, side effects were diarrhea, abdominal pain, dyspepsia (2.9%), and headache (5.8%). Frequency of side effects was not different among the study groups ($P > 0.05$).

4. Discussion

This study evaluated the effects of frankincense and ginger as complementary to NSAID therapy in the treatment of HMB. Frankincense and ginger enhanced the therapeutic effects with regards to duration of menstrual bleeding and QOL. However, these herbal medicines had no further benefits for the amount of menstrual bleeding. A few controlled clinical trials have assessed the effect of herbal remedies on HMB. The effectiveness of *Punica granatum* flowers,[19] *Myrtus communis*,[20] and *Zingiber officinale* (ginger) [18] in the treatment of HMB has been evaluated by randomized controlled trials. *Zingiber officinale* and *Myrtus communis* were found more effective than the placebo in reducing menstrual duration as well as amount of blood loss.[18,20] *Punica granatum* flower was as effective as tranexamic acid in reducing blood loss.[19] While previous studies have used herbal medicines as alternatives to conventional methods, we assessed the effect of ginger and frankincense complementary to NSAID and found that these complementary treatments can enhance the therapeutic effects in patients with HMB.

Proposed mechanisms in HMB include an increase in total endometrial prostaglandins and prostacyclin, a shift of endometrial prostaglandins (PGF2α) to vasodilatory prostaglandins (PGE2 and PGI2), and an increase in the rate of PGE2 receptors and in fibrinolysis.[2,21,22] Studies have shown an increase in the synthesis of PGE2 and PGE-binding sites in the tissue of women with menorrhagia. A higher level of PGE2 and prostacyclin results in vasodilatation and

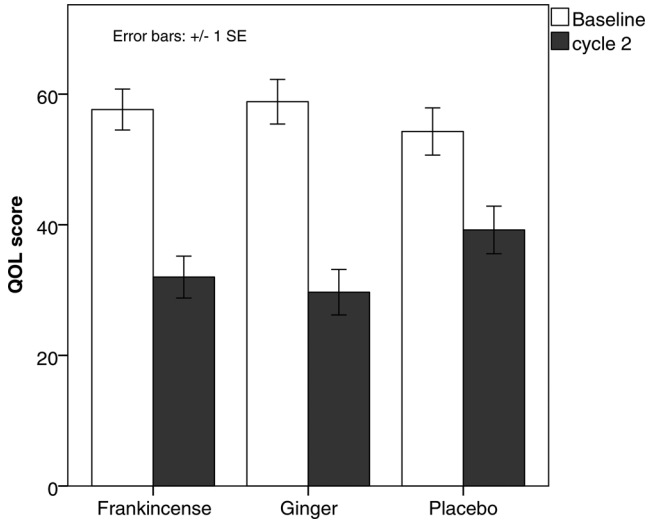

Fig. 4. Quality of life before and after treatment in the study groups.

local accumulation of platelets.[22] Also, a lower level of PGF2α, which has vasoconstriction properties, increases menstrual blood loss.[22] Prolonged vasodilation causes poor platelet aggregation and plaque formation.[2,21,22] Therefore, prostaglandin synthesis inhibitors can improve HMB through reducing vasodilatory prostaglandins and improve hemostatic actions.[23]

Ginger rhizome contains gingerols as its main constituent as well as gingerdiones, beta carotene, caffeic acid, and curcumin.[24] These components, especially gingerol, have immuno-modulatory and anti-inflammatory properties.[25,26] The anti-inflammatory activities of ginger are through inhibiting cyclooxigenesae-2 (COX-2), lipoxygenase (LOX), and leukotriene biosynthesis pathways,[27] which affect the synthesis of prostaglandins especially PGE2. The broad anti-inflammatory properties of ginger support our observation that complementary therapy with ginger and NSAID, probably with a synergic effect, can enhance treatment response in HMB patients.

Frankincense contains boswellic acid derivatives. Anti-inflammatory effects of boswellic acid and its derivatives are through the inhibition of LOX, nitric oxide synthase, COX-2, and prostaglandins.[28–30] Unlike NSAIDs, long-term use of frankincense has not been shown to increase gastrointestinal problems.[31] Studies suggested the efficacy of frankincense for the management of other inflammatory disorders like inflammatory bowel disease, rheumatoid arthritis, and osteoarthritis.[31] Our findings indicate that frankincense can be considered as an adjuvant therapy for the management of HMB.

This study is the first reported investigation of the complementary effects of herbal medicines to test whether they have any additional effects over the standard treatment. Ginger was previously evaluated in HMB in high school girls [18] and for the first time we evaluated ginger in women at reproductive age. Also, this is the first controlled clinical trial evaluating the effect of frankincense in the treatment of HMB. However, our study had some limitations. The sample size was limited and we followed patients for only two menstrual cycles. Also, the hematological indexes of the patients were not assessed after treatment, which could have provided additional information on the improvement of HMB. Such assessments are of importance particularly considering some concerns with the potential effects of ginger on platelet function.[32]

5. Conclusion

Ginger and frankincense seem to be effective as a complement to NSAID in the treatment of HMB in women of reproductive age. Further studies with a larger sample size and longer duration of treatment, and evaluating other valuable treatment outcomes including hematological indexes are warranted in this regard.

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Conflict of interest

None

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