CellMed
Cellmed Orthocellular Medicine and Pharmaceutical Association

Original Article

Efficacy of *Commiphora myrrha* and Honey in Primary Dysmenorrhea: A Randomized Controlled Study

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ABSTRACT

Background: Dysmenorrhea is the most common menstrual complaint in young women with a prevalence as high as 90% and is responsible for substantial repeated short-term absenteeism from school and work in young women. The objective of this study was to compare the efficacy of *Commiphora myrrha* and honey with mefenamic acid in primary dysmenorrhea.

Materials and Methods: This prospective standard controlled trial was conducted at Luqman Unani Medical College Hospital and Research Center Vijayapura, India where 40 diagnosed patients of primary dysmenorrhea were randomly assigned to receive test drug (powdered *Commiphora myrrha* gum resin10g with 30g honey in two divided doses) or active control drug (mefenamic acid 250mg TID) for first 3days of menstruationfor two consecutive cycles. The primary outcome measure was reduction in severity of pain assessed by numerical pain rating scale (NPRS), and secondary outcome measures were improvement in quality of life (QOL) assessed by SF-36 and reduction in perceived stress score (PSS).

Results: During first cycle treatment no significant difference was found in NPRS score ($p=0.085$) between the groups however significant difference in NPRS score ($p<0.001$) was seen during 2nd treatment cycle. Significant reduction ($p=0.022$) in the perceived stress score was noted and overall quality of life was markedly improved after treatment in both the groups.

Conclusion: These data suggest that *Commiphora myrrha* gum resin with honey is an effective herb in reducing symptoms of primary dysmenorrhea. These results need to be confirmed by a properly designed trial with a larger sample size.

Trial registration: Clinical Trial Registry India CTRI/2017/09/009596.

Keywords Primary dysmenorrhea, *Commiphora myrrha,* stress, quality of life

1. INTRODUCTION

Painful menstrual cramps of uterine origin is called as dysmenorrhea. Primary dysmenorrhea is defined as painful menstrual cramps without any organic pathology (Gupta, Kaur & Singh, 2013). Among female adolescents, primary dysmenorrhea is considered as the most common gynecological disorder with a prevalence of 60% to 93%. With increasing age, the prevalence of primary dysmenorrhea decreases. The highest prevalence is seen in 20-24years age group after which it decreases progressively (Dawood, 2006; Mahyash *et al*., 2012). Academic performance, social and sports activities of adolescents are affected highly due to primary dysmenorrhea and it has become a common cause for school absenteeism. Apart from the significant effect on the quality of life and personal health, primary dysmenorrhea also has a global economic impact (Osayande & Mehulic, 2014).

Although the etiology is not well understood, uterine prostaglandins particularly prostaglandin F_2-Alfa is considered responsible behind the origin of primary dysmenorrhea. Increased production of prostaglandins leads to increase uterine contractions which causes uterine ischemia and stimulation of the pain fibers (Jenabi, 2013). To treat primary dysmenorrhea several pharmacological methods like oral contraceptive pills, nonsteroidal anti-inflammatory drugs as well as nonpharmacological treatments including exercise, acupuncture, heat therapy etc. are available. Long term use of synthetic drugs is either associated with side effects (Jaafarpour *et al*., 2015; Armour & Smith, 2016) or they are contraindicated in some women (Younesy *et al*., 2014).

Various parts of the plants are being used as medicine for thousands of years. The utilization of herbal drugs to treat various diseases is getting popularized because of the belief of being comparatively safe with synthetic drugs (Omidvar *et al*., 2012). The medicinal value of the plants are mainly due to the presence of the various phytochemicals which are synthesized

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Received Aug 07, 2021; **Accepted** Nov 05, 2021; **Published** Nov 30, 2021
doi: http://dx.doi.org/10.5667/CellMed.2021.0019

in the different parts of the plant. The phytochemicals produced in the plant are valuable for the maintenance of human health as well as the health of other animals (Ferreira-Valente *et al*., 2011). Several clinical trials have been reported on primary dysmenorrhea evaluating herbs like *Mellisa officinalis, Cinnamomum zeylanicum, Anethum graveolens, Trigonella foenum-graecum, Lavandula angustifolia, Thymus vulgaris, Zingiber officinale, Rosa Damascena* (Jaafarpour *et al*., 2015; Younesy *et al*., 2014; Baani *et al*., 2014; Heidarifar *et al*., 2014; Moghadam & Khosravi, 2012; Rahnama *et al*., 2012; Dehkordi *et al*., 2014). In classical texts of *Unani* medicine, dysmenorrhea has been mentioned as "*dard-e-reham*" (Khan, 2011; Ibn Sina, 2010; Rhazi, 2001) or "*aujae rehm"* (Ibn Sina, 2010) and to treat this condition, several drugs have been mentioned, *mur* (*Commiphora myrrha*) (Rhazi, 2001) is one of them which has antispasmodic (Ibn Baitar, 2003), emmenagogue (Ghani, 2000; Kabeeruddin, 2010; "Standardisation of single drugs of unani medicine," 1992) as well as anti-inflammatory properties (Ghani, 2000; Kabeeruddin, 2010). Myrrh (*Commiphora myrrha*) extract showed antispasmodic effect as it reduced the intestinal muscle tone in experimental studies (Vissiennon *et al*., 2015). It also showed analgesic activity in mice (Su *et al*., 2011). Myrrh inhibited the production of various inflammatory mediators in experimental studies (Su *et al*., 2015; Kim *et al*., 2012). Further honey has been investigated with other herbs to treat primary dysmenorrhea in randomized controlled trial and has been found equally effective with nonsteroidal anti-inflammatory drugs for pain reduction (Shabani *et al*., 2020). Therefore we aimed to investigate the effect of *Commiphora myrrha* and honey in primary dysmenorrhea. The hypothesis of the study was the test drugs have same effect as control drug in the management of primary dysmenorrhea.

2. MATERIAL AND METHODS

2.1 Study design

This was a prospective randomized standard-controlled trial conducted in department of *Ilmul Qabalat wa Amraze Niswan,* Luqman Unani Medical College Hospital and Research Centre Vijaypur. In this trial the effect of *Commiphora myrrha* gum resin were compared with mefenamic acid in diagnosed patients of primary dysmenorrhea. After commencement of the trial no changes was made in the protocol.

2.2 Participants

Patients complaining of pain during menses were interrogated thoroughly for detailed history particularly about onset, duration, character, severity, site, type and nature of pain; physical examination was done and laboratory investigations including complete urine examination, random blood sugar, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, blood urea, serum creatinine and pelvic ultrasonography were performed. Unmarried women in the age group of 18-25 years diagnosed as primary dysmenorrhea were included in this study. Patients having irregular menstrual cycle, organic pelvic pathology and systemic illness were excluded. Patients fulfilling the inclusion criteria were given information sheet having details regarding the nature of study. Patients were given enough time and opportunity to go through the study details mentioned in the information sheet and to ask any question. They were given right to refuse consent or withdraw the treatment during any part of the study without giving any reason. After obtaining the willingness they were asked to participate in the study and sign the informed consent form. Withdrawal criteria was failure to follow protocol therapy and cases in which adverse drug reaction is noticed.

2.3. Intervention

Diagnosed patients of primary dysmenorrhea were randomly allocated to receive either test drug (powdered *Commiphora myrrha* gum resin10g with 30g honey in two divided doses) or active control drug (mefenamic acid 250mg TID) for first 3days of menstruation for two consecutive cycles.

2.4. Preparation of drugs

The gum resins of *Commiphora myrrha* was selected as test drug which was purchased from local crude drug market of Calicut city, Kerala and was identified and authenticated by Professor Sayyed Saleemuddin, department of *Ilmul Advia* (pharmacology), Luqman Unani Medical College Hospital and Research Centre, Vijaypur. In the pharmacy of the institute, drug was cleaned and powdered and honey was mixed in the ratio 1:3 (drug: honey) and 120gm of semi solid mixture was packed in the air tight container. Patients were advised to take 20g of mixture BD for first three days of menses for two consecutive cycles. In control group tablet mefenamic acid each of 250g was removed from the strips and was dispensed in lock bags. Patients were advised to take the tablets TID after meal for first three days of menses for two consecutive cycles. In this study similarity between the interventions was not possible as the test drug was in semisolid form which was dispensed in air tight containers while the control drug was in tablet form which was removed from the strips and dispensed in opaque lock bags. To make the patients of both groups unaware about the treatment provided, the medicine was dispensed to one patient at a time. Compliance was assessed at every follow up by examining the container or packets in which medication was dispensed at previous visit.

2.5 Outcome measures

Primary outcome was reduction in the pain intensity which was assessed by a numeric version of the visual analog scale known as numerical pain rating scale (NPRS) where the patient selects a whole number ranging from 0 to10 to express pain intensity. Score 0 represents the no pain while maximum pain intensity is represented by score 10 (Hawker *et al.,* 2011). Perceived stress score (PSS) and quality of life were secondary outcome parameters. PSS is a self-report questionnaire which is considered as a valid tool to assess an individual's self-perception of stress. There are 14, 10 and 4item versions of PSS. For this study10 item version has been used. It is a measure of the degree to which situations in someone's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable, and overloaded respondents find their lives. The scale also includes a number of direct queries about current levels of experienced stress; and improvement in the overall quality of life assessed through SF-36 questionnaire (Chiu *et al.,* 2016). 36-Item Short questionnaire has been used in several studies to assess the quality of life and it has been found valid and reliable. It has been used in previous studies to assess the quality of life in patients of primary dysmenorrhea showing its suitability for use in primary dysmenorrhea (Armour *et al.,* 2017). It is an instrument consists of 36 items for self-evaluation which provide assessment in eight domains: physical functioning, social functioning, role limitations due to emotional problems, role limitations due to physical problems, bodily pain, vitality, mental health, and general health perception (Unsal *et al.,* 2010).

Patients were followed after menses for three consecutive cycles. At every visit after menstruation NPRS and PSS were

assessed. Overall quality of life was assessed by using SF-36 after two cycles.

2.6. Sample size estimation

From previous literature, the sample size of our study was calculated by taking assumptions, needed to demonstrate a difference by a new treatment in terms of costs and risks: Assumed effect size= 1.99. Assumed standard deviation= 2.12. Based on the above assumptions, a sample size of 36 subjects, 18 in each group was found sufficient to detect a clinically important difference of 1.99 between two groups in reducing menstrual NPRS, assuming a standard deviation of 2.12, using a two tailed t test of difference between means with 80% power and a 5% level of significance. Considering a dropout rate of 10%, the sample size required was exactly 40 (20 per group).

2.7. Safety assessment

Patients were inquired about the development of adverse effects during each follow up visits and were recorded for both groups specifying their characteristics (onset, severity and duration) and possible cause effect relationship with drug administration during the entire trial period. Also SGOT, SGPT, blood urea, serum creatinine were repeated after completion of the therapy to rule out the safety of drugs on kidney and liver.

2.8 Randomization and allocation concealment

Participants were randomly allocated into the test and control group. The intervention was initiated according to simple randomization which was performed by using an open list of random number which was obtained from online randomization list generator (www.randomization.com). The first researcher who was collecting the data was unaware about the sequence as the randomization number was generated by the second researcher and the sequence was concealed from the data collector until the interventions were assigned to each patient.

2.9. Ethical considerations

The trial protocol was approved by the Institutional Ethics Committee under IEC No: LUMC/IEC/2015-16/01/ANQ /03 and was conducted according to the tenets of the Declaration of Helsinki. Also the trial was registered in the Clinical Trial Registry India with registration code CTRI/2017/09/009596.

2.10. Statistical Analysis

Results of continuous variables are presented as Mean ± SD (Min-Max) and results on categorical variables are presented in number (%). Significance is assessed at level of 5 %. To find the significance of study parameters on continuous scale Student t test (two tailed, independent) and Student t test (two tailed, dependent) has been used for inter and intragroup analysis respectively. To find the significance of study parameters on categorical scale between two or more groups, Chi-square/ Fisher Exact test has been used. The statistical software used for the analysis of data are SPSS 18.0 and R environment ver.3.2.2. and to generate graphs and tables Microsoft word and Excel have been used.

3. RESULTS AND DISCUSSION

3.1. Enrollment of patients

For this trial patients were assessed for eligibility from November 2016 to March 2018.A total of 168 patients were screened, 128 patients were excluded from the study and 40 patients were randomly allocated (Fig 1.)

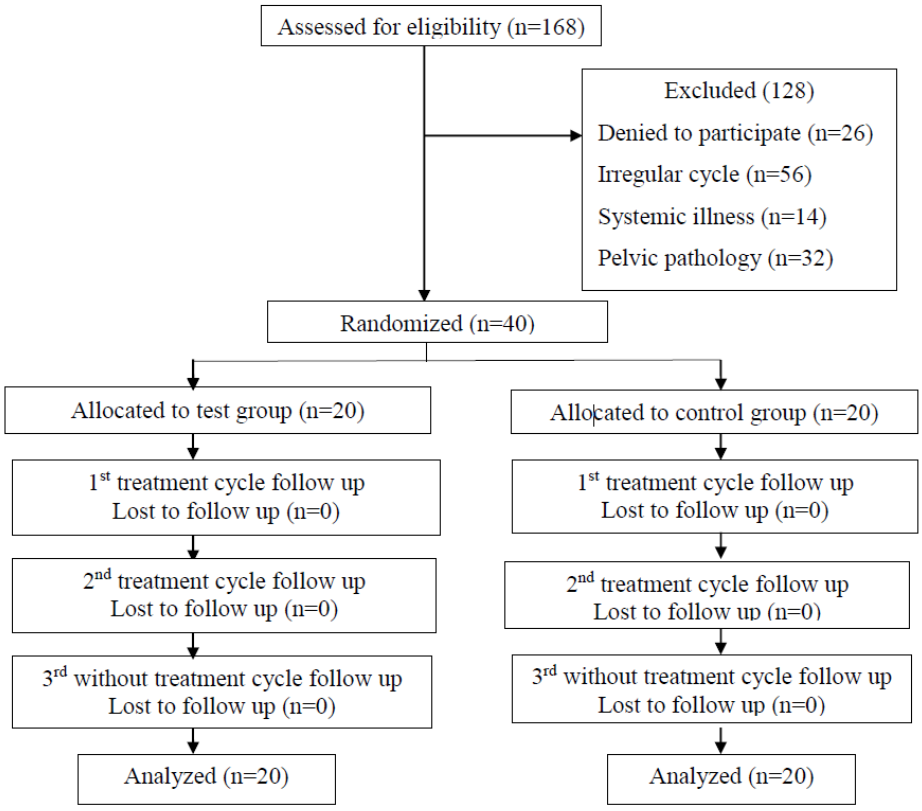

Fig.1 Flow chart as per the CONSORT statement

3.2. Baseline characteristics

At baseline patients were assessed for different variables (age, religion, education, socioeconomic status, occupation, diet, age of menarche, length of the menstrual cycle, duration of flow and amount of flow). Both groups were found statistically similar (Table 1).

3.3. Clinical response

There was no significant difference seen in the pain score at baseline between the groups with p value 0.606. Mild difference was seen in the pain score during first cycle treatment with p-value 0.085 while during second cycle treatment there was difference in the pain score was highly significant with p-value <0.001. There was highly significant difference in the score on third consecutive cycle without treatment (Table 2).

At baseline there was significant difference in the perceived stress score between the groups with p-value 0.034. After first cycle treatment there was no significant difference between the groups with p-value 0.794 while after second cycle treatment there was significant difference between the groups with p-value 0.022. There was highly significant difference in score between the groups on without treatment cycle with p-value <0.001(Table 3). There was no significant difference found between the groups related to change in the quality of life (Table 4).

3.4. Adverse effects

Safety profile measures were found to be within normal limits before and after the treatment. Even the patients did not have any adverse effects which is suggestive of safety of drugs used in study.

Table 1. Baseline characteristics of the patients in test and control group

Variables	Test Group n=20	Control Group n=20	[a]P value
Age in years			
18-20	17(85%)	13(65%)	
21-25	3(15%)	7(35%)	0.277
Mean ± SD	19.15±1.14	19.60±1.43	
Religion			
Hindu	1(5%)	3(15%)	0.605
Muslim	19(95%)	17(85%)	
Education			
Illiterate	1(5%)	1(5%)	
Primary	2(10%)	1(5%)	
Secondary	4(20%)	4(20%)	0.836
Higher secondary	11(55%)	9(45%)	
Graduate	2(10%)	5(25%)	
Socioeconomic status			
Lower middle	4(20%)	7(35%)	
Upper middle	6(30%)	10(50%)	0.061
Upper lower	10(50%)	3(15%)	
Occupation			
Not studying	4(20%)	8(40%)	0.168
Studying	16(80%)	12(60%)	
Diet			
Mixed	19(95%)	12(60%)	0.008
Veg	1(5%)	8(40%)	
BMI (kg/m^2)			
<18.5	0(0%)	0(0%)	
18.5-24.9	19(95%)	20(100%)	
25-30	1(5%)	0(0%)	0.364
>30	0(0%)	0(0%)	
Mean ± SD	22.49±1.97	21.94±1.86	
Habitat			
Rural	10(50%)	10(50%)	1
Urban	10(50%)	10(50%)	
Age of menarche (years)			
12-14	15(75%)	14(70%)	
15-16	5(25%)	6(30%)	0.567
Mean ± SD	13.90±1.21	14.10±0.97	
Menstrual cycle (days)			
25-30	17(85%)	13(65%)	0.144
30-35	3(15%)	7(35%)	

[a]Fisher Exact /Chi-Square test

Table 2. Comparison of numerical pain rating score (NPRS) in two groups of patients studied

NPRS	Test Group (n=20)	Control Group (n=20)	Total (n=40)	[a]P value
Baseline (B)	9.50±1.15	9.65±0.59	9.58±0.90	0.606
First cycle (C1)	2.45±1.43	3.20±1.24	2.83±1.38	0.085
Second cycle (C2)	0.50±0.51	2.05±1.23	1.28±1.22	<0.001**
Post treatment cycle (F)	7.00±1.62	9.50±0.83	8.25±1.79	<0.001**

[a]Analysis is done by Student t test (two tailed, independent)
**Strongly significant (P value: P≤0.01)

Table 3. Comparison of perceived stress score (PSS) in two groups of patients studied

Perceived stress score	Test Group (n=20)	Control Group (n=20)	Total (n=40)	[a]P value
Baseline (B)	34.65±3.30	36.35±1.04	35.50±2.56	0.034*
First cycle (C1)	9.85±5.00	9.45±4.64	9.65±4.76	0.794
Second cycle (C2)	3.60±1.50	5.50±3.24	4.55±2.67	0.022*
Post treatment cycle (F)	25.30±6.34	35.95±1.99	30.63±7.11	<0.001**

[a]Analysis is done by Student t test (two tailed, independent)
* Moderately significant (P value: 0.01<P≤ 0.05)
** Strongly significant (P value: P≤0.01)

Table 4. Comparison of quality of life (SF-36) in two groups of the patients studied

Variables	Test Group	Control Group	Total	[a]P-value
Physical functioning (PF)				
Before Treatment	34.50±2.24	34.75±2.55	34.63±2.37	0.744
After Treatment	96.75±2.45	97.75±2.55	97.25±2.52	0.214
Role limitation due to physical health (RPH)				
Before Treatment	0.00±0.00	0.00±0.00	0.00±0.00	-
After Treatment	95.00±22.36	100.00±0.00	97.50±15.81	0.324
Role limitation due to emotional problem (REP)				
Before Treatment	1.67±7.45	0.00±0.00	0.83±5.27	0.324
After Treatment	93.35±23.18	100.00±0.00	96.68±16.52	0.207
Energy/Fatigue(E/F)				
Before Treatment	34.75±12.92	30.00±12.57	32.38±12.81	0.246
After Treatment	86.25±17.08	86.50±7.27	86.38±12.96	0.952
Emotional wellbeing (EWB)				
Before Treatment	26.20±7.73	23.60±7.88	24.9±7.82	0.299
After Treatment	74.60±13.99	78.80±2.63	76.70±10.16	0.195
Social functioning (SF)				
Before Treatment	9.03±7.30	7.70±8.63	8.36±7.92	0.603
After Treatment	79.05±19.63	80.20±6.53	79.63±14.46	0.805
Pain				
Before Treatment	10.65±2.91	11.30±4.00	10.98±3.47	0.56
After Treatment	70.70±20.88	77.00±3.08	73.85±15.07	0.19
General health (GH)				
Before Treatment	13.50±4.89	18.50±14.15	16.00±10.75	0.144
After Treatment	63.75±18.20	60.00±18.42	61.88±18.18	0.521

[a]Analysis is done by Student t test (two tailed, independent)

4. DISCUSSION

To the best of our knowledge the present study was the first to investigate the effect of *Commyphora myrrha* in primary dysmenorrhea. Until the discovery of the morphine by the European, the myrrh was commonly used as an analgesic and also for cleaning of the wounds and sores (Su *et al*., 2015). The occurrence of sesquiterpenes in the *Commiphora myrrha* are mainly attributed behind the analgesic property (Germano *et al*., 2017). The ethanolic extract of *Commyphora myrrha* showed significant reduction in the acetic acid induced writhing response in mice and the petroleum ether extract of *Commyphora myrrha* showed significant analgesic activity in the mice model (Su *et al*., 2011). Ethanolic extract of *Commyphora myrrha* reduced intestinal muscle tone and acetylcholine-induced contraction of untreated and inflamed ileum/jejunum preparations based on dual calcium antagonism characterized by a right shift of the agonistic dose response curve and a depression of the maximum effect (Vissiennon *et al*., 2015). *Commyphora myrrha* showed anti-inflammatory activity as it inhibited the production of various inflammatory mediators such as nitric oxide, prostaglandin and tumor necrosis factor alpha in experimental study (Kim et al., 2012). Swelling paw of arthritic rats and increased levels of prostaglandinE_2, nitric oxide, tumor necrosis factor alpha, interleukin-2 and malondialdehyde in serum were reduced significantly when the frankincense and myrrh was given as a combined therapy (Su *et al*., 2015). Formalin induced paw swelling development was significantly inhibited by the ethanol and petroleum ether extract of *Commiphora myrrha* also it significantly reduced the levels of inflammatory mediators in paw edema (Su *et al*., 2011). The chloroform extract of *Commiphora myrrha* oleo-gum-resin showed highest anti-inflammatory activity. The ether and petroleum ether extracts and the volatile oil also showed high anti-inflammatory activities (Ammar *et al*., 2013). Further honey with other herbs has been found equally effective with nonsteroidal anti-inflammatory drugs for pain reduction (Shabani *et al*., 2020).
The evidences regarding the association between the stress and menstrual problems are increasing which shows that disturbances in the menstrual cycle may be due to the psychological factors. Also, studies have shown that stress reduction techniques as well as physical activities successfully treated the dysmenorrhea (Mahyash *et al*., 2012). In this study the mean stress score of patients at baseline was found 35.50±2.56 which was not significantly different between groups (Table 3). After first cycle treatment there was no significant difference in the stress score between the groups while after second cycle treatment there was significant difference observed in the stress score between the groups. *Wang et al* also found significant associations between perceived stress in one menstrual cycle with the occurrence of dysmenorrhea in the subsequent cycle (Wang *et al*., 2004). *Bavil et al* also reported that in dysmenorrheic patients, the moderate and high levels of stress was more prevalent when compared with non-dysmenorrheic group (Bavil *et al*., 2016). *Ibrahim et al* also found stress as one of the predictors of dysmenorrhea (Ibrahim *et al.,* 2015). In this study the baseline average scores obtained from all the domains of SF-36 showed decrease indicating that women with dysmenorrhea had lower health related quality of life values (Table 4). *Unsal et al* also observed significantly lower score for many of the SF-36 domains primarily the physical health domain in students with primary dysmenorrhea. With increasing severity of pain in primary dysmenorrhea the other domains like social functioning and mental health are also affected (Anastasakis *et al*., 2008). Dysmenorrhea affects the mood adversely and thereby affects the friendship and family relations. It has been observed by *Mohamed* and *Mansour* that approximately half of the girls with primary dysmenorrhea had family problems and maximum girls were not willing to talk with friends and were not feeling comfortable. They also found relation between pain duration and severity with relations to their friends and family members (Mohamed *et al*., 2013).

5. CONCLUSION

In the present study test drug was found equally effective as control drug in reducing pain due to primary dysmenorrhea. Additionally, test drug was found to have long term effect in pain reduction. Test drug was found equally effective as control drug in reducing stress due to primary dysmenorrhea and also in improving the quality of life due to primary dysmenorrhea. It can therefore be inferred that the research drug controls the primary dysmenorrhea. Thus, it is concluded that *Commiphora myrrha* gum resin with honey can be a safe and effective alternative treatment in the management of primary dysmenorrhea. The limitation of the study was small sample size and loss of long term follow up for efficacy and safety. It is recommended to conduct trial with large sample size to confirm the efficacy and safety of the research drugs.

ACKNOWLEDGEMENT

Authors want to acknowledge the Principal, Vice Principal and Hospital Superintendent for providing all the facilities.

CONFLICT OF INTEREST-

The authors declare that there is no conflict of interest.

FUNDING SOURCE

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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