

## The Biological Effects of *Teucrium polium* on the Severity of Primary Dysmenorrhea

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### Abstract

Primary dysmenorrhea is a prevalent issue and it can reduce the quality of life in many females worldwide. Based on the properties of *Teucrium polium* as a herbal medicine with analgesic and inflammatory properties, this triple-blind, randomized, placebo controlled trial was performed. The study aimed to evaluate the effects of *Teucrium polium* on the severity of primary dysmenorrhea in students. In this study, single students were categorized in two groups who received *Teucrium Polium* (n=35) or placebo (n=35). For the first 3 days of menstruation, subjects were asked to take some capsules containing powder *Teucrium polium* (250 mg) four times daily for two consecutive menstrual cycles. Pain severity was examined using a visual analog scale. According to the results, there was no significant difference in the pain severity at the baseline between two groups. Pain severity was significantly decreased in both groups after the intervention; however, larger pain reduction was significantly seen in the group which had received *Teucrium Polium* (p< 0.001). No side effect was observed in the *Teucrium Polium*-received group. In conclusion feature of *Teucrium polium* during menstruation led to decrease in the severity of dysmenorrhea.

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### Introduction

Dysmenorrhea is a painful uterine contractions during menstruation [1], which is related to spasmodic pains in the abdomen during menstrual bleeding [2]. Primary dysmenorrhea is the main reason of work absenteeism and reduction in life quality [3, 4]. Pelvic disorder is not along with the pain in primary dysmenorrhea. In addition, it greatly takes place in younger women but may last until the fifth decade of life [5]. Dysmenorrhea results from uterine contractions associated with ischemia and increases sensitivity in uterine nerves [5]. Increased prostaglandins, vasopressin and leukotrienes in the endometrium results in dysmenorrhea [2].

It is stated that the prevalence of primary dysmenorrhea is between 16% to 90% in reproductive ages [6]. Various solutions are recommended to cure the primary dysmenorrhea, such as yoga, massage, transcutaneous electrical nerve stimulation, vitamins, nutritional supplements and herbal medicine. Prescribed medications include prostaglandin synthesis inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs) to decrease the pain. Non-pharmaceutical treatments include acupuncture and surgery. Some of them may contain side effects or be contraindicated in certain groups of women [2, 5, 7-9].

In recent years, there has been a growing interest in using herbal medication in order to prevent and treat illnesses across the world particularly in Iran, because of the lack of

satisfactory in many diseases and undesirable side effects of chemical medications [10]. Traditional medicines such as herbal medicine are taken for dysmenorrhea treatment across the world, such as *Fenugreek*, *Valeriana offic*, *Thymus vulgaris*, etc. [8, 9, 11].

*Teucrium polium* belonged to the family of *Lamiaceae* is a perennial plant. It is covered with dense, long, and soft hairs with the height of 30-50 cm in its rather woody bushes and a dwarf, pubescent, aromatic shrub, posing oval leaves with enrolled margins and dense head of white flowers. Its color varies from white and off white to yellow and pink. The regions where this plant grows are arid and rocky areas of Europe, Mediterranean Basin, North Africa and South West Asia including Iran [10].

*Teucrium polium* (locally called as *chez* or *kalporeh* in Khuzestan Province, Iran) is traditionally employed as a way to treat headache, convulsion, dysmenorrhea; and moreover, its hypoglycemic, hypolipidemic, and antibacterial effects have been reported in recent studies. In addition, it is also used traditionally in gastrointestinal disorders [12]. Many other characteristics are also cited to this herb in new researches including anticonvulsant, anti-inflammatory, analgesic, antipyretic, wound healing, anti-microbial activity, antioxidant, anti-ulcer, and lowering blood pressure properties [13]. Its main remedial structure contains tannins, terpenoids, saponins, sterols, and eucoanthocyanin [10].



The well-documented therapeutic uses of *Teucrium polium* include its activity against antispasmodic in smooth muscle [12]. The present study evaluated the effect of oral administration of *Teucrium polium* on primary dysmenorrhea severity in students. This research also examined the other studies performed in the field of traditional medicine and abundance of some plants with analgesic and anti-inflammatory effects among Iranian traditional medicines.

## Materials and Methods

### Participants

This was a triple-blind, randomized, placebo controlled trial research on single students living in a dormitory at Shahid Beheshti University (Tehran, Iran) from October 2014 to February 2014 with moderate-to-severe dysmenorrhea experiences. The study protocol was confirmed by the Research and Ethics Committee of International Branch, Shahid Beheshti University of Medical Sciences and registered in the Iranian Registry of Clinical Trials (Number IRCT2014120917501N1). Students were informed on the aim and methods of the study and provided by written consent forms before participation.

It was estimated that 70 subjects were needed to reach statistical significance at 95% confidence interval. We advertised on the bulletin board and people who tended were wanted to register. According to the book of applied lineal statistical models the effect size was (1.0),  $\alpha=0.05$  and  $1-\beta = 0.9$ . Randomly computer-generated numbers were used to separate participants in two main groups for taking *Teucrium polium* or placebo. Participants, researchers and statistic advisor were kept blinded during the study. Variables related to dysmenorrhea including age, menarche age, dysmenorrhea age and BMI were matched in two groups. Other variables such as underlying diseases (Diabete, Chronic hypertension, Infectious diseases) which may be affected by *Teucrium polium* such people were excluded in order to control the study. Students with irregular menstrual cycles, history of medication usage, endometriosis, vaginal symptoms, and/or experienced acute stress (burning, irritation, itching, or discharge), as well as people with allergy to *Teucrium Polium* or other plants or those who had used herbal drugs during the previous 3 months or had not used it properly were excluded. Although no case with allergy to *Teucrium polium* was found.

### Procedures

*Teucrium polium* (from one geographical region) was bought from Barij Esans Pharmaceuticals (Kashan, Iran). After verification and identification of *Teucrium polium* samples in Pharmacogenosy Laboratory at the Faculty of Pharmacology of Shahid Beheshti University of Medical Sciences, samples were extracted and their powder was prepared and packed in capsules (250 mg) by an automated machine. The safety dose, based on the PDR (Herbal Medicine) book [14], was 250 mg for *Teucrium Polium*. Also the toxicity dose of plant on kidney and liver [15, 16] is caused by permanent usage therefore it does not happen to alternative use of the plant 3 days monthly in dysmenorrhea [12]. Because we used the safe dosage of

plant, we did not need to test for liver or kidney toxicity. The placebo capsules included of potato starch. The capsules were the same in shape, color, and packaging. *Teucrium polium* and placebo capsules were taken four times a day during menstruation in first 3 days. The intervention went on for two consecutive menstrual cycles. We made a pharmaceutical form of capsules of plant (*Teucrium polium*) and starch powder that did not smell any of the flavorful taste. Capsules were quite similar appearance; so, none of the samples from the two groups could not guess the nature of the drugs.

In our study, only the pharmacist knew what the code is related to *Teucrium Polium*, and what the code is related to placebo, researchers and statisticians and samples did not know it (triple blind). After the ending of intervention, and after the ending of analysis by the statisticians, that it was became clear for the researchers that the Code (A), could reduce pain, and the code (B) could not, then pharmacists revealed the code (A) related to the *Teucrium Polium* and code (B) related to placebo.

The subjects were permitted to use NSAIDs such as ibuprofen and mefenamic acid  $\geq 1$  hour after taking the given capsules by researcher, if required. In spite of being excluded from the study, they were asked to write down pain severity before consuming the sedative.

Content and test-retest methods were used to evaluate the validity and reliability before the intervention and during each treatment cycle ( $r = 0.85$ ). Collected demographic data were: age, body mass index (BMI), educational level, occupation of the parents, exercise program, and stressful factors in the past 6 months. A self-reported checklist was performed to collect data on the amount of sedative drugs taken for dysmenorrhea and pain severity. During the first three days of menstruation, the pain severity was scored in each sample three times a day on a 10 cm visual analog scale (VAS) at hours 8 to 13, 13 to 18, and 18 to 24 (per 8 hour) with scores 1-3, 4-7, and 8-10 for "mild", "moderate", and "severe" pain, respectively [14].

VAS validity is confirmed in many studies with a wide range of applications and considered as one of the most useful and reliable measures for pain [15, 16]. The imprint codes were registered on a separate sheet for the capsules. Drug intervention was performed in the second and third menstruations. In this study, 13 students left the trial (5 samples from *Teucrium polium* group and 8 samples from placebo group); some of samples received another medication, and the other were reluctant to continue cooperation.

### Statistical analyses

SPSS Ver 20 (SPSS, Chicago, IL, USA) was used for statistical analysis. Descriptive data are frequencies, mean values and standard deviations and t-test was used to compare the age, age menarche and other variables between two groups.

The Repeated Measure test and Mann-Whitney test were used in the comparison of pain severity among three menstrual cycles and satisfactions in both groups, respectively. Significance level was considered 0.05.

### Ethical considerations

The study protocol was approved by the Research and Ethics Committee of International Branch, Shahid Behesh-

ti University of Medical Sciences. Students were aware of the purpose and methods of the study and provided with written consent forms for participation.

**Results**

Primary dysmenorrhea reported was by 123 of 204 single female students, and after exclusions, 70 subjects were enrolled in the study. The final analysis included 57 students with 30 subjects controlled by *Teucrium polium* and 27 subjects by placebo. No significant difference was seen between the groups with respect to age, menarche age, onset of dysmenorrhea, BMI, duration between menstrual, duration of menstrual and duration of dysmenorrhea (Table 1).

**Table 1.** Demographic characteristics of the participants.

Variation	Mean values (SD) <sup>a</sup> ( <i>Teucrium Polium</i> )	Mean values (SD) (Placebo)	P* (Independent t-test)
Age (year)	21(1.91)	21(1.73)	0.236
BMI (Kg/m <sup>2</sup> )	20 (2.87)	21(3.25)	0.896
Age at menarche (year)	13 (1.39)	12 (1.34)	0.477
Duration between menstrual (day)	26 (3.15)	25 (3.52)	0.605
Duration of menstrual (day)	6 (1.12)	6 (1.34)	0.630
Age at onset of dysmenorrhea (year)	15 (2.30)	14 (2.21)	0.388
Duration of dysmenorrhea	2 (1.02)	2 (1.03)	0.664

<sup>a</sup>: standard deviations

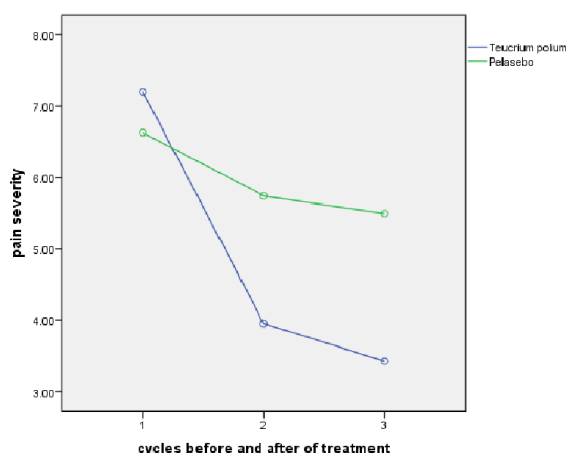
There was no significant difference in pain severity at baseline between the groups. In the *Teucrium polium* group, pain severity decreased from 7.20 (2.1) at baseline to 3.34 (2.3) in the second cycle (Table 2), whereas it decreased from 6.62 (1.73) to 5.50 (2.05) in the placebo group (Table 2). Pain severity was observed in both groups in each intervention cycle with more reduction in the *Teucrium polium* group (Table 3). An obvious difference was seen in pain severity between two groups (Fig. 1). No side effect was reported in both groups of *Teucrium Polium* and placebo.

**Table 2.** Comparison of the mean values and the standard deviations of Pain severity in before and after the treatment in *Teucrium polium* and Placebo groups.

Pain severity	SD (T. polium)	SD (Placebo)
First cycle	7.20(2.1)	6.62(1.73)
Second cycle	3.95(2.3)	5.74(1.93)
Third cycle	3.43(2.3)	5.50(2.05)
Test consequent of independent samples	P = 0.001	P = 0.001

**Table 3.** Comparison of the mean values and the standard deviations of pain severity before and after the treatment in both groups.

Pain severity	Mean values and standard deviations
First cycle	<i>Teucrium Polium</i> 7.2 (2.1)
	Placebo 6.62 (1.73)
Second cycle	<i>Teucrium Polium</i> 3.95 (2.3)
	Placebo 5.74 (1/93)
Third cycle	<i>Teucrium Polium</i> 3.43 (2.3)
	Placebo 5.50 (2.05)
Test consequent of repeated measure	P = 0.025



**Figure 1.** The difference in severity pain in between groups.

**Discussion**

It was the first report on the effects of *Teucrium polium* in pain alleviation in Primary Dysmenorrhea in women. The problem of females with dysmenorrhea is the excessive production of endometrial prostaglandins [3]. It is seen that *Teucrium polium* (locally called 'kalporeh') possess therapeutic effects against diabetes, fungal infections, with analgesic and anti-inflammatory and it is used traditionally as a way to treat headache, dysmenorrhea and convulsion and moreover, its hypoglycemic, hypolipidemic and anti-bacterial effects are reported in recent studies. Additionally, it is also taken traditionally to treat gastrointestinal disorders [12].

Some antispasmodic effects are seen on gastrointestinal system by *Teucrium polium* and it is declared that the plant has also some antispasmodic effects on smooth muscle [12]. In other study it is stated that hydro-alcoholic extract of *Teucrium Polium* has reductive effect on castor oil-induced diarrhea in male rat [13]. Antispasmodic effects of *Teucrium polium* are also observed in animal models (rat) [13]. Phytochemical studies revealed that flavons and flavonoids are two major components in *Teucrium polium* extracts which are causes of antispasmodic effect in *Teucrium Polium* [12]. It is also stated that

the analgesic effects of *Teucrium polium* and morphine is similar [17], and it may justify its effectiveness on pain reduction in dysmenorrhea. A survey on another plant, (*Echinophora platyloba*) represented that the plant had some reductive effects on dysmenorrhea severity [1]. Another study concluded that Fenugreek seed can reduce the severity of dysmenorrhea [9]. A similar study indicated that *Valeriana Officinalis*, like the present study, had reductive effect on the severity of dysmenorrhea [8]. In the research, Jenabi and Fereidoony were showed that a *millefolium* is effective in minimizing the pain severity in primary dysmenorrhea [18]. In a systematic review and meta-analysis study about ginger it was indicated that these RCTs provide suggestive evidence for the effectiveness of 750-2000 mg ginger powder during the first 3-4 days of menstrual cycle for primary dysmenorrhea [19]. Omidvar *et al.*, stated in their study, fennel is an effective herbal drug for menstrual pain [20]. Nahid *et al.*, pointed that herbal drugs (500 mg of highly purified saffron, celery seed, and anise) relieved menstrual pain as compared with the placebo effectively [21].

All studies show that natural remedies are as effectiveness as synthetic remedies without important side effects [1, 9]. Also Mirabi *et al.*, showed promising evidence supporting the use of herbal medicine for primary dysmenorrhea [22]. In present study, pain severity reduction in *Teucrium polium* group was more than the reduction observed in placebo group. Therefore, *Teucrium polium* can greatly reduce the severity of dysmenorrhea.

The effectiveness of *Teucrium polium* on dysmenorrhea and its harmlessness have been observed in the study. Based on present results, further studies are recommended to compare *Teucrium polium* with anti-inflammatory medications. *Teucrium Polium* should be compared with a variety of effective drugs for dysmenorrhea like (NSADS). According to plant characteristics, it can be effective against menstrual bleeding and duration of pain. Then, we recommend that a study be carried out on these cases.

### Conclusion

Our study indicated that *Teucrium Polium* can be used to decrease the severity of primary dysmenorrhea. Adverse effects were not reported for *Teucrium Polium*; therefore, the herb can be taken safely to manage the condition.

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