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Effect of royal jelly on menopausal symptoms: A randomized placebo-controlled clinical trial☆

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ABSTRACT

Background: and Purpose: Menopause is associated with physical and emotional discomfort for women and has major negative effects on their quality of life. The purpose of this study was to determine the effects of royal jelly on menopausal symptoms.

Materials and methods: This double-blind randomized clinical trial was carried out in Bandar Abbas, Iran, from June to November 2018. The study population consisted of 200 postmenopausal women (45–60 years). Each participant received either 1000 mg of royal jelly capsules or placebo daily for eight weeks.

Results: The mean baseline menopausal score did not differ between groups. The menopausal score reduced significantly after eight weeks of intervention in experimental group whereas reduction was not significant in control group.

Conclusion: The findings showed that daily consumption of oral royal jelly (1000 mg) for eight weeks was effective in alleviating the menopausal symptoms. However, further research is necessary to confirm the effects.

1. Introduction

Menopause is a stage in a woman's life that marks the end of the reproductive age. As a physiological process, it is associated with both physical and emotional discomfort and has negative effects on quality of life [1]. In the postmenopausal stage, several somatic, urogenital, and psychological changes occur, which are attributed to reduced estrogen levels. Generally, menopausal symptoms may range from mild to severe. It has been evidenced that 80–85% of women experience some of these symptoms during the menopausal period [2].

To relieve menopausal symptoms, hormone replacement therapy (HRT) has been suggested for women [3]. Despite the confirmed advantages of HRT [4], there have been some concerns about the safety of this therapeutic method after the publication of Million Women Study and Women's Health Initiative [5], which encouraged the application of alternative approaches [6]. In complementary and alternative medicine, a wide range of compounds have been applied to alleviate the menopausal symptoms, such as isoflavones, lignin, St John's wort, black cohosh, ginseng, evening primrose oil, and royal jelly [7].

Royal jelly, a viscous jelly-like substance, is produced by the mandibular and hypopharyngeal glands of honeybees (*Apis mellifera*). It consists of water (50–60%), proteins (18%), carbohydrates (15%), lipids (3–6%), mineral salts (1.5%), and vitamins [8]. Royal jelly is widely used as a dietary nutritional substance to combat various chronic conditions [9]. Different pharmacological effects, such as antitumor, anti-allergy, antibacterial, anti-inflammatory, and immunomodulatory effects, have been attributed to royal jelly [10].

Some studies have evaluated the effect of royal jelly as a nutritional supplement on women's health, and several clinical trials have confirmed its safety [11,12]. Traditionally, royal jelly has been used to improve menopausal symptoms [13]. In this regard, a case report revealed that menopausal symptoms improved with royal jelly supplementation in menopausal women [14]. The first published clinical trial by Asama et al. (2018) showed that royal jelly supplementation (800 mg/day) is effective in relieving menopausal symptoms, such as anxiety, backache, and low back pain in Japanese postmenopausal women [15]. To the best of our knowledge, the present study is the second trial evaluating the effects of oral royal jelly on the menopausal symptoms of postmenopausal women.

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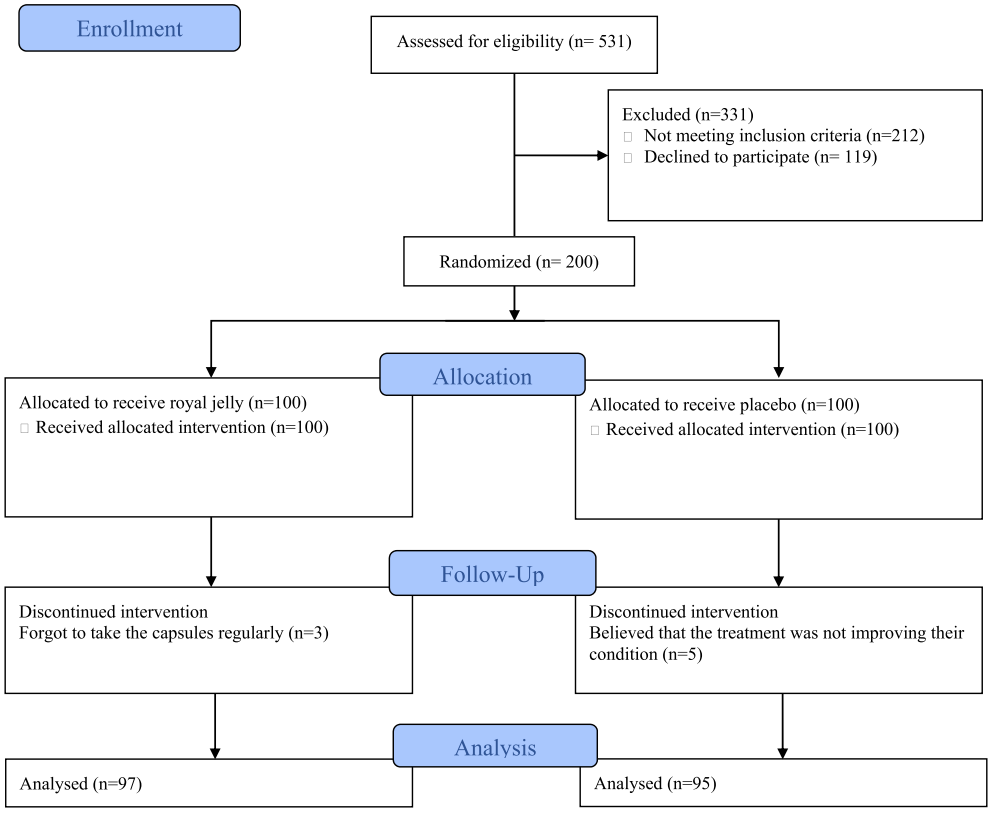

Fig. 1. CONSORT flow diagram of the groups' enrollment, allocation, intervention, follow up, and analysis.

2. Materials and Methods

2.1. Study design

This double-blind randomized placebo-controlled trial was carried out according to the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. It aimed to investigate the effects of royal jelly on the menopausal symptoms of postmenopausal women, referred to the menopausal clinic of a major teaching hospital in Bandar Abbas, Iran, from June to November 2018. The study protocol was approved by the Ethics Committee of Hormozgan University of Medical Sciences. Also, the study was registered in the Iranian Registry of Clinical Trials (1RCT20181107041585N1).

2.2. Study sample

The study population comprised of 200 postmenopausal women, aged 45–60 years, who showed symptoms of menopause, based on the Menopause Rating Scale (MRS). The inclusion criteria were as follows: 1) amenorrhea for at least one year; 2) being married; 3) normal Papanicolaou test results in the last year; 4) no history of malignancy or chronic medical disease; and 5) no allergy to honey products. On the other hand, the exclusion criteria were: 1) use of other treatments during the study (e.g., hormone therapy); and 2) any kind of crisis involving participants or their family. A sample size of 200 women was selected at type I error of 5% and power of 80% to detect 5.5 differences in menopausal symptoms (MRS scores) from the baseline to the end of the intervention between the two groups [16–18]. The participants were divided randomly into the experimental (n = 100) and control (n = 100) groups.

2.3. Intervention

Eligible women randomly received either royal jelly capsules (1000 mg) or placebo (1000 mg lactose sugar) daily for eight weeks. The placebo capsules (Alzahravi Pharma Co., Iran) and royal jelly capsules (Nature Life Co., Canada) were similar in size, shape, and color, and their packages were coded as A or B. Every participant was assigned randomly to group A or B, based on the randomization codes, which were selected by a computer using dynamic allocation (with a balanced marginal distribution algorithm). The participants were randomized on a 1:1 ratio of drug to placebo and assigned sequentially to the next treatment code. The subjects, researchers, and outcome assessors remained blinded to the group assignments. The codes emerged once the primary data processing was performed.

2.4. Primary outcome measures

The outcomes evaluated in this study included menopausal symptoms based on MRS. In order to evaluate the occurrence and severity of symptoms, MRS was standardized [16]. This scale consists of 11 items on menopausal symptoms, including depressive mood, irritability, heart palpitations, hot flashes, anxiety, sexual problems, sleep disorders, bladder problems, muscle dysfunction, and vaginal dryness. In this scale, each symptom is scored from 0 (no symptoms) to 4 (severe symptoms), depending on severity. The sum of scores for every symptom represents the total MRS score [17].

A reliable and valid version of this scale in Persian [18] was used in the present study. Sociodemographic characteristics, including age, age at menopause and menarche, body mass index, parity, and number of children, were assessed in a questionnaire, which was completed before the intervention for every participant. Considering the illiteracy of some respondents, face-to-face interviews were conducted rather than administering self-report questionnaires. For every participant, two menopausal scores were calculated; one before and one immediately after the end of the intervention. Participants were asked to report any adverse drug effects in the follow-up visit.

2.5. Statistical analysis

SPSS version 19 (SPSS Inc., USA) was used for all statistical analyses. Descriptive data were expressed as mean ± SD. The distribution of data was evaluated using Kolmogorov-Smirnov test. Also, independent sample *t*-test was used for inter-group comparisons and paired sample *t*-test for comparisons between pre- and post-treatment stages. P–value ≤ 0.05 was considered statistically significant.

3. Results

Of 531 women referred to the menopausal clinic, 200 eligible women were randomly selected. The eight-week intervention was completed for 192 women, including 97 women in the experimental group and 95 women in the placebo group. Three participants who forgot to take the capsules regularly were eliminated from the experimental group. Also, five women from the control group dropped out of the study, as they believed that the treatment was not improving their condition (Fig. 1).

The groups were not significantly different in terms of demographic characteristics, such as body mass index, age, age at menopause and menarche, duration of menstrual cessation, parity, and number of children (Table 1). The frequency of menopausal symptoms according to MRS is demonstrated in Table 2.

The mean baseline menopausal score did not differ between the two groups. However, the MRS scores were significantly lower in the experimental group, compared with the control group after eight weeks of intervention (Table 3).

To distinguish the effect of royal jelly, we compared the reduction in the menopausal score in each group. In the experimental group, pre-treatment and post-treatment MRS scores were significantly different ($P < 0.001$), unlike the control group (Table 4).

4. Discussion

Multiple studies have examined the effectiveness of non-pharmacological and pharmacological treatments for menopausal symptoms [14,15,18,19]. In the present study, the effect of royal jelly was assessed in postmenopausal women. A randomized clinical study reported that royal jelly is effective in reducing premenstrual syndrome [11]. Another randomized placebo-controlled double-blind trial reported that daily consumption of 3000 mg of royal jelly for six months improved the mental health of 30 individuals, aged 42–83 years [20].

In the present study, women described serious menopausal symptoms at baseline, such as hot flashes, sleep problems, depressive mood, anxiety, physical and mental exhaustion, and muscle and joint pain. The symptoms significantly alleviated in the experimental group after eight weeks of intervention, compared with the control group. These findings are in line with an earlier study, examining the effects of royal jelly supplementation on menopausal symptoms [15]. Also, in another randomized clinical trial, the effectiveness of royal jelly in the treatment of urinary problems and quality of life was reported in postmenopausal women [21].

Although it is not exactly clear how royal jelly improves menopausal symptoms, we assume that its estrogenic activity may play an important role in the modulation of selective estrogen receptors [9]. Various studies have been conducted on the potential estrogenic activities of royal jelly [9,22,23]. This substance may modulate estrogen signaling through various mechanisms, such as binding to the ligand binding pocket of receptors, activating estrogen receptors, and affecting the distribution of estrogen subtypes. It may also trigger proteins, which can disrupt estradiol dimerization and result in the increased transcription of reporter genes by an estrogen-responsive element [22,23]. It has been also reported that royal jelly contributes to hormonal balance and improves hormone levels by stimulating the production of testosterone, which in turn helps synthesize estrogen [24].

Several studies detected some estrogenic compounds in royal jelly, including 10-hydroxy-trans-2-decenoic acid, 10-hydroxydecanoic acid, and trans-2-decenoic acid. The major active component of royal jelly is 10-hydroxy-2-decenoic acid, which enhances the synthesis of ovulation hormones; it can also prevent the follicle pool depletion and enhance hormonal regulation [25]. Moreover, royal jelly has been shown to possess versatile bioactive properties, such as antibacterial, immunemodulatory, wound-healing, antioxidant, nephron-protective, and anti-inflammatory activities [10–12]. Consequently, royal jelly can be considered a “weak estrogenic compound”, leading to the alleviation of menopausal symptoms [26]. In the literature, some side effects of royal jelly have been described [27,28]. However, in the present study, we did not observe any serious adverse effects.

Limitations of our study should be considered for achieving a reliable and comprehensive understanding about our results. Data from the subjects’ final assessments were collected immediately after the final treatment to evaluate the short-term benefits of treatment. Further research is necessary on the long-term effects of treatment, weeks or months after treatment. Also, long-term treatments should be designed to evaluate the effect of time on the efficacy of treatment.

5. Conclusion

The findings showed that daily consumption of oral royal jelly (1000 mg) for eight weeks was effective in alleviating the menopausal symptoms. It can be concluded that royal jelly might be considered as a complementary treatment for menopausal symptoms. However, further research is necessary to examine and confirm the effects of royal jelly on somatic, psychological and urogenital symptoms of menopause.

Table 1
Demographic characteristics of all participants (N = 192).

Characteristics [a]	Experimental group	Control group	P-Value [b]
Age (Year)	52.15 ± 3.47	51.92 ± 4.21	0.548
Duration of menstrual ceasing (Month)	26.02 ± 7.19	24.99 ± 8.34	0.134
Age at menopause (Year)	50.87 ± 1.42	50.43 ± 3.22	0.467
Age at menarche (Year)	13.88 ± 1.97	13.01 ± 1.56	0.612
Number of children	3.82 ± 0.97	4.01 ± 1.02	0.112
Number of pregnancy	5.12 ± 1.03	5.09 ± 0.08	0.701
Number of parity	3.99 ± 1.01	4.12 ± 0.93	0.103
Body mass index	27.01 ± 2.91	28.12 ± 2.33	0.420

[a] Data are presented as mean ± SD.
[b] Based on independent sample *t*-test.

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Disclosure

The authors report no conflicts of interest in this study.

Author contribution

S.N.Sh had a role in preparing the protocol of study. F.D had a role in monitoring the study, data analyzing of study and editing the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.08.006.

Table 2
Frequency of menopausal symptoms in participants at baseline.

Severity of symptoms	None, N (%)	Mild, N (%)	Moderate, N (%)	Severe, N (%)	Very severe, N (%)
Depressive mood	11 (5.7%)	60 (31.2%)	53 (27.6%)	44 (22.9%)	24 (12.6%)
Irritability	17 (8.9%)	76 (39.6%)	42 (21.9%)	36 (18.7%)	21 (10.9%)
Anxiety	9 (4.9%)	72 (37.4%)	54 (28.1%)	22 (11.54%)	35 (18.2%)
Mental exhaustion	43 (22.4%)	34 (17.7%)	53 (27.6%)	39 (20.3%)	23 (12%)
Hot flushes	8 (4.2%)	15 (7.8%)	45 (23.4%)	78 (40.6%)	46 (24%)
Heart discomfort	51 (26.6%)	71 (37%)	33 (17.2%)	22 (11.4%)	15 (7.8%)
Sleeping problems	5 (2.6%)	11 (5.7%)	76 (39.6%)	72 (37.5%)	28 (14.6%)
Muscle problems	20 (10.4%)	31 (16.1%)	49 (25.5%)	53 (27.6%)	39 (20.4%)
Sexual problems	35 (18.2%)	49 (25.5%)	47 (24.5%)	47 (24.5%)	14 (7.3%)
Bladder problems	50 (26%)	63 (32.8%)	43 (22.4%)	32 (16.7%)	4 (2.1%)
Vaginal dryness	38 (19.8%)	40 (20.8%)	35 (18.2%)	42 (21.9%)	37 (19.3%)

Table 3
Comparison of menopausal symptoms within groups (Mean ± SD).

	Before	After	Mean difference	95% CIs [a] Lower value	Higher value	P-Value [b]
Experimental	32.14 ± 4.65	19.03 ± 4.13	−13.11	−10.01	−16.21	0.001
Control	31.65 ± 5.01	28.11 ± 3.09	−3.54	−1.95	−5.13	0.203

[a] CIs: Confident Intervals.
[b] Based on paired sample *t*-test.

Table 4
Comparison of the paired differences of menopausal score (before—after treatment change) between groups.

	Experimental group	Control group	Mean difference	95% CIs [a] Lower value	Higher value	P-Value [b]
Paired differences	13.11 ± 4.65	3.54 ± 1.13	−9.57	−11.01	−3.21	0.001

[a] CIs: Confident Intervals.
[b] Based on independent sample *t*-test.

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