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Research article

Royal jelly for genitourinary syndrome of menopause: A randomized controlled trial☆

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ABSTRACT

Objective: Genitourinary syndrome of menopause is a progressive condition characterized by a decrease in estrogen, which causes bothersome genital symptoms. The purpose of the study was to determine the effect of royal jelly on the genitourinary syndrome of menopause.

Materials and methods: A randomized controlled trial was carried out from November 2018 to June 2019 in Bandar Abbas, Iran. The trial was registered in the Iranian Registry of Clinical Trials (1RCT20181107041585N1) with the main objective of determining if royal jelly could reduce the genitourinary syndrome of menopausal women. Eligible women were randomly assigned to receive either daily 1g of oral royal jelly or placebo for 8 weeks. The urogenital subscale of the Menopausal Rating Scale was used to determine genitourinary syndrome. Independent samples *t*-test was used for inter-group comparisons and paired samples *t*-test for pre-and post-treatment comparisons.

Results: There were no differences in the severity of sexual problems, bladder complications, or vaginal dryness between groups before intervention. Although the intervention group's bladder complications improved slightly after eight weeks of royal jelly treatment compared to the control group ($p = 0.04$), there were no significant changes in vaginal dryness, sexual problems, or total urogenital score. The within-group changes (before and after treatment) also showed no differences in urogenital symptoms.

Conclusions: A daily dose of 1g royal jelly taken orally for 8 weeks did not alleviate menopausal genitourinary syndrome. No serious side effects were observed. To make more reliable decisions about the use and safety of royal jelly in the future, different doses of royal jelly and longer trials are required.

1. Introduction

Genitourinary syndrome of menopause is a chronic and progressive condition characterized by a decrease in estrogen, which causes bothersome genital symptoms (dryness, vaginal bleeding and discharge, burning, and irritation), sexual symptoms (pain and discomfort), and urinary symptoms (dysuria, frequency, urgency, nocturia, and recurrent urinary tract infections), with vaginal dryness and dyspareunia being the most bothersome complications.[1] Women may present with some or all of the signs and symptoms listed above, which do not go away without treatment and can have a negative impact on their quality of life.[2] The goal of treatment for genitourinary syndrome is to alleviate symptoms. It has been reported that only 7% of symptomatic women seek treatment.[3] Many women are unaware that there are treatments available.[4] Hormonal therapy is the gold standard treatment,[5] but the risk of unwanted adverse events including breast cancer and abnormal uterine bleeding raises concerns about its safety,[6,7] which is why more natural alternatives are used.[8]

Natural alternatives refer to the use of non-hormonal methods to alleviate menopausal symptoms.[9] Apitherapy, a branch of complementary therapy that uses natural honeybee products such as royal jelly,[10] has recently been used to treat menopausal symptoms.[11]

Royal jelly is a creamy substance secreted by the worker honeybee's mandibular and hypopharyngeal glands that are composed of water (60–70%), proteins (9–18%), sugars (7.5–15%), lipids (7–18%), and minor components such as minerals, amino acids, vitamins, enzymes,

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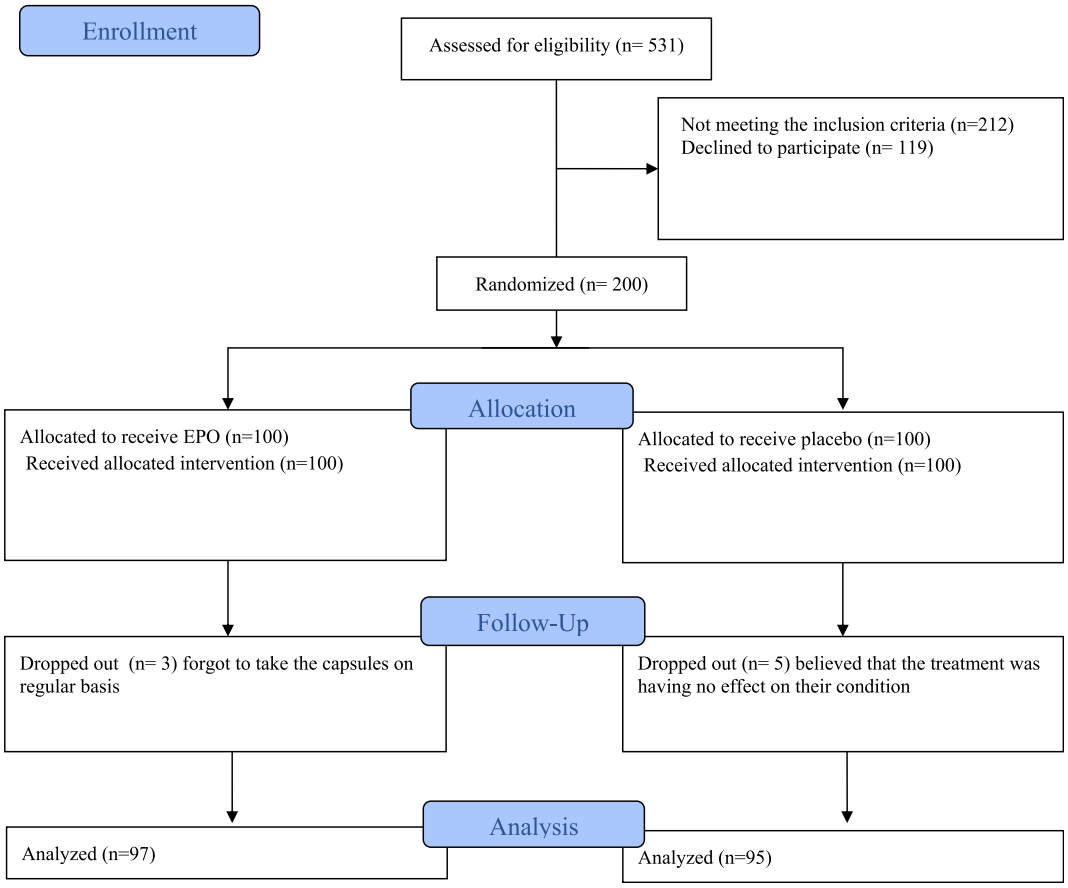

Fig. 1. Flow diagram of the study.

hormones, polyphenols, nucleotides, and minor heterocyclic compounds.[12] According to recent reports, royal jelly is a valuable product with a variety of components, such as anti-inflammatory, antibacterial, antitumor, antioxidant, estrogen-like effects, that potentially can improve women's health.[13,14] Given the estrogenic effect of royal jelly, we sought to see how it affects the genitourinary syndrome of menopause.

2. Materials and methods

This was a sub-study of a randomized controlled trial carried out from November 2018 to June 2019 in Bandar Abbas, Iran. The trial was registered in Iranian Registry of Clinical Trials (1RCT20181107041585N1) with the main objectives of determining if royal jelly could reduce the symptoms of menopause.[15] This is a subgroup trial investigating the impact of royal jelly on the genitourinary syndrome of menopause. The research protocol was approved by the Hormozgan University of Medical Sciences Ethics Committee (Ethics Number: 970,149). All participants provided written informed consent.

The study population comprised of menopausal women who visited the Khaleej-e-Fars hospital clinic in Bandar Abbas, Iran. Participants ranged in age from 45 to 60 years old, had at least one year of amenorrhea, had recent normal Papanicolaou test results, had no history of cancer or medical comorbidities, and had no allergy to honey products. Those who used other treatments (such as hormone therapy or lubricants) during the study were excluded.

The sample size was determined by comparing the urogenital symptoms (urogenital scores) between the intervention and control groups from baseline to the end of the intervention. A difference of 1.5 in the mean urogenital score was considered clinically significant in a previous study.[16,17] As a result a sample size of 200 women was chosen with a type I error of 5% and power of 80% to detect such differences. Every participant was randomly assigned to either group A (n = 100) or B (n = 100) based on randomization codes, which were generated by a computer using Microsoft Excel®[18] using dynamic allocation with a balanced marginal distribution algorithm. The participants were randomized to the control or intervention group in a 1:1 ratio and were assigned sequentially to the next treatment code. The group assignments were kept a secret from the participants, and researchers. The codes were revealed once the primary data processing was completed.

For 8 weeks, eligible women were given either 1g of oral lyophilized royal jelly or a placebo (lactose sugar made by Pharma Co., Iran). The placebo and royal jelly capsules were prepared by a pharmacist that was not involved in the study and they were identical in size, shape, and color, and their packages were labeled A or B.

The urogenital subscale of the Menopausal Rating Scale (MRS) was used to determine genitourinary syndrome as the primary outcome measure in this study. This subscale includes sexual issues (changes in sexual desire, sexual activity, and satisfaction), bladder complications (difficulty urinating, increased need to urinate, and urinary incontinence), and vaginal dryness (sensation of dryness and burning in the vagina, difficulty with sexual intercourse). Each symptom is scored on a five-point Likert scale, ranging from 0 (no symptoms) to 4 (extremely severe symptoms). The total urogenital score is the sum of the scores for each symptom. The final urogenital score ranges from 0-12.[16] A Persian version of this scale was used in this study. This scale's reliability and validity have previously been investigated.[19] A questionnaire was completed by each participant prior to the intervention to assess sociodemographic characteristics. Because some respondents were illiterate, a face-to-face interview was conducted rather than a self-report

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

Characteristics [a]	Intervention 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.

questionnaire. Two urogenital scores were calculated for each participant: one before the intervention and one immediately after it ended. The researcher contacted participants once a week to confirm medication compliance and to record side effects. They were also asked to refer for outpatient checkups on a regular basis. Participants were asked if they had experienced any side effects at each study visit.

SPSS software version 21 (SPSS Inc., Illinois, USA) was used for statistical analysis. The descriptive data was presented as a mean, standard deviation, and percentage (%). The Kolmogorov-Smirnov test was used to determine the normal distribution of data. The Kolmogorov-Smirnov test was used to assess data distribution. The Chi-square test was used to determine the differences in severity of genitourinary syndrome between the intervention and control groups. The paired samples *t*-test and independent sample *t*-test were used to examine continuous variables. P-value <0.05 was considered as statistically significant. Per-protocol analyses were performed: participants who completed follow-up were included.

3. Results

There were 200 eligible women among the 531 women referred to the menopausal clinic. The intervention was completed for 192 women, 97 of whom were in the intervention group and 95 of whom were in the control group. It is worth mentioning that no negative drug side effects were reported in groups. Fig. 1 depicts the processes of enrollment, allocation, intervention, follow-up, and analysis. The demographic characteristics of participants in both groups did not differ significantly (Table 1).

Fig. 2 depicts the prevalence of genitourinary syndrome in menopausal participants based on MRS. According to the findings, a significant proportion of participants suffer from severe and very severe vaginal dryness in both groups even after the intervention. The severity of other symptoms including bladder complications and sexual problems also were considerable.

The independent sample *t*-test was used to compare each symptom of the genitourinary syndrome of menopause at baseline and after intervention. There was no significant difference in the mean baseline urogenital symptoms score between groups. Although the intervention group's bladder complications score decreased slightly (MD: 0.37, 95% Confidence Interval of Difference: 0.06 to 0.68) ($p < 0.045$), there were no significant changes in vaginal dryness, sexual problems, and total urogenital score (Table 2). We used the paired *t*-test to assess changes within groups. The severity of urogenital symptoms did not differ significantly across groups. In other words, there was no improvement in the intervention group's outcome measure when it came to within-group changes (Table 3).

4. Discussion

Several studies on women's health have found royal jelly to be beneficial. Clinical studies have shown that oral administration of royal jelly can reduce the severity of menopausal symptoms and improve

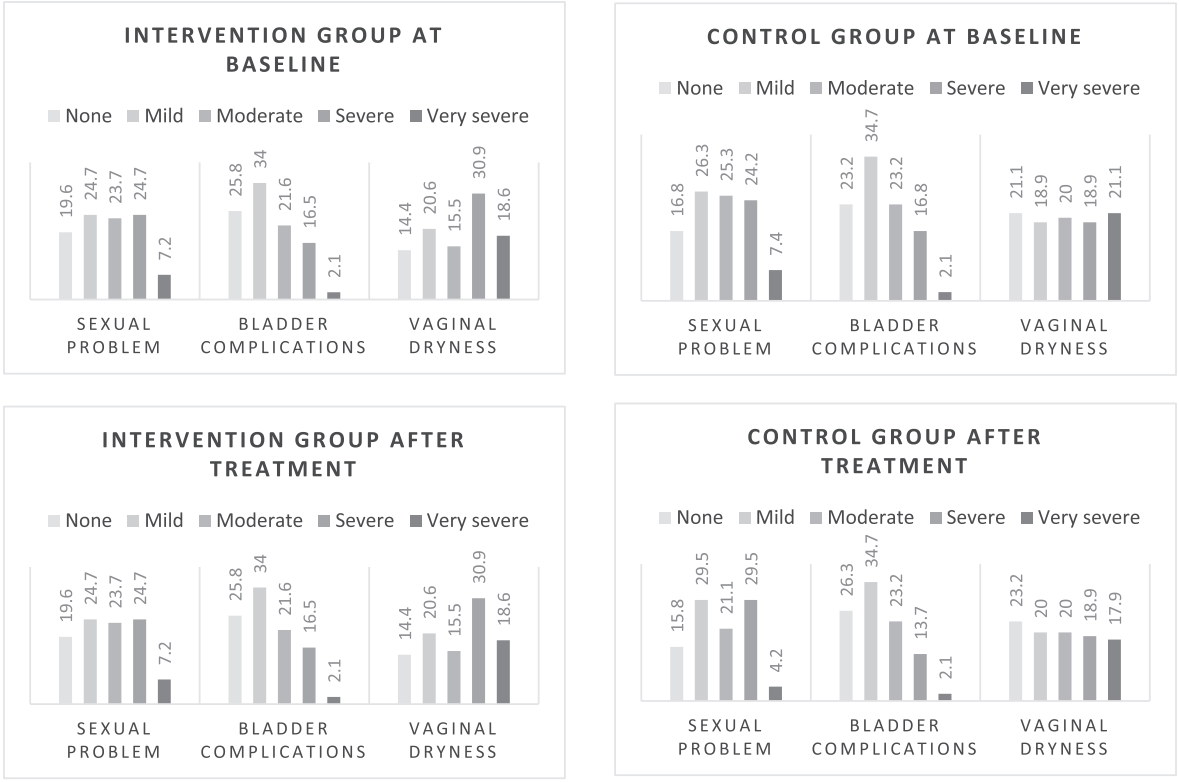

Fig. 2. Frequency of genitourinary syndrome in participants (%).

Table 2
Comparison of urogenital symptoms of menopausal women between groups (Mean ± SD).

	Intervention	Control	*P*-Value
Baseline			
Sexual problem	1.79 ± 1.20	1.75 ± 1.23	0.834
Bladder complications	1.30 ± 1.00	1.35 ± 1.10	0.754
Vaginal dryness	2.00 ± 1.44	2.19 ± 1.34	0.359
Urogenital score	5.08 ± 3.65	5.28 ± 3.49	0.861
End of study			
Sexual problem	1.77 ± 1.16	1.66 ± 1.22	0.529
Bladder complications	1.03 ± 0.98	1.40 ± 1.17	0.045
Vaginal dryness	1.86 ± 1.42	2.14 ± 1.33	0.161
Urogenital score	4.95 ± 3.33	5.20 ± 3.48	0.504

Based on Independent sample *t*-test.
SD: Standard Deviation.

Table 3
Changes in urogenital symptoms of menopausal women before and after treatment in each group (Mean ± SD).

	Before treatment	After treatment	*P*-Value
Intervention			
Sexual problem	1.79 ± 1.20	1.77 ± 1.16	0.923
Bladder complications	1.30 ± 1.00	1.03 ± 0.98	0.098
Vaginal dryness	2.00 ± 1.44	1.86 ± 1.42	0.522
Urogenital score	5.08 ± 3.65	4.95 ± 3.33	0.230
Control group			
Sexual problem	1.75 ± 1.23	1.66 ± 1.22	0.711
Bladder complications	1.35 ± 1.10	1.40 ± 1.17	0.801
Vaginal dryness	2.19 ± 1.34	2.14 ± 1.33	0.736
Urogenital score	5.28 ± 3.49	5.20 ± 3.48	0.612

Based on paired sample *t*-test.
SD: Standard Deviation.

quality of life.[15,20] However, in contrast to our previous study, which found royal jelly to be effective in alleviating the full spectrum of menopausal symptoms,[15] the current sub-study found that oral consumption of royal jelly did not reduce the severity of menopausal genitourinary symptoms such as sexual problems, bladder complications, and vaginal dryness. Another study on 90 married postmenopausal women aged 50 to 65, which found that vaginal royal jelly was significantly more effective than conjugated estrogens and lubricant in improving sexual and urinary function in postmenopausal women.[21] This disparity could be explained by the fact that using royal jelly as a lubricant may have a more topical effect on urogenital symptoms. Because the amount of royal jelly absorbed orally is unknown, a higher dose of royal jelly may produce different results.

Royal jelly has been shown to have estrogenic properties both in vitro and in vivo. The interaction with estrogenic receptors mediates this effect.[22] The result of one animal study showed that royal jelly boosted ovarian hormones and follicular development while improving fertility parameters in rats.[23] Furthermore, a recent study found that combining royal jelly with exogenous progesterone increased the rate of pregnancy and estrogenic response in Awassi ewes.[24]

Royal jelly has been reported to be extremely effective at preventing aging-related follicular depletion and improving hormonal regulation by boosting estrogen synthesis due to its high concentration of fatty acids, particularly 10-hydroxyl-2-decanoic acid.[11] Royal jelly aids in the maintenance of hormonal balance and the enhancement of hormone levels by stimulating testosterone production, which in turn aids in the synthesis of estrogen.[25]

Royal jelly has been shown to modulate estrogen signaling via a variety of mechanisms, including binding to receptor ligand-binding pockets, activating estrogen receptors, and influencing the distribution of estrogen subtypes. It may also activate proteins that disrupt estradiol dimerization and cause an estrogen-responsive element to increase transcription of reporter genes.[22] As a result, royal jelly can be considered a "weak estrogenic compound," alleviating menopausal symptoms. Royal jelly is a natural product that is popular all over the world. However, some negative adverse events such as haemorrhagic colitis and a case of anaphylaxis have been reported as a result of its use.[26,27]

As with any natural product, the effective dose, length of treatment, follow-up period, and long-term side effects have not been thoroughly investigated. Data from the participants' final assessment was collected immediately after the end of intervention which means that the study assessed only short-term effects; long-term effects were not evaluated in this study; therefore these limitations should be taken into consideration in future researches.

5. Conclusion

A daily dose of 1g royal jelly taken orally for 8 weeks did not alleviate menopausal genitourinary syndrome such as sexual problems, bladder complications, and vaginal dryness during menopause. In the current study, fortunately, no serious side effects were observed. To make more reliable decisions about the use and safety of royal jelly in the future, different doses of royal jelly and longer trials are required.

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Contribution

F.D. conceived of the presented idea and developed the protocol. F.D. and V.M. conducted the study and verified the analytical methods. Both authors discussed the results and contributed to the final manuscript. F.D. revised the manuscript.

Disclosure

The authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gocm.2021.10.001.

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