



Bee Products for Relieving Menopausal Symptoms

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Abstract

BACKGROUND: An overview of honey and other bee products and their health and biological health potentials was highlighted.

AIM: The aim of the study was to help females alleviate their menopausal symptoms, when estrogen hormone levels decrease at the end of their fertility phase of life using natural bee products.

SUBJECTS AND METHODS: Two groups of Egyptian women in the menopausal stage, suffering from different symptoms of menopause, participated as volunteers. Full clinical examination, Menopause Rating Scale, Beck anxiety score, and Beck depression score evaluations were recorded. Blood sampling and biochemical analysis were done including female sex hormones, and anti-inflammatory, and antioxidant markers. Participants consumed two tablespoon of the honey (32 ml) diluted in 250 ml of water once daily in the morning for 2 months. Control group received conventional clover honey while the other group consumed a calculated ratio of clover honey enriched with bee pollen, royal jelly, and bee gum.

RESULTS: Subjects with a mean age of 49.51 ± 0.82 years who consumed enriched clover honey had significant improvement in somatic, psychological, urogenital, and anxiety score assessment and depression score evaluation. Data from this study group showed that the women experienced the disappearance of hot flashes, night sweats, generalized body pain, and psychological symptoms such as irritability, anxiety, depression, and disturbed sleeping. As for biochemical parameters, estradiol, free testosterone, the antioxidant marker malondialdehyde (MDA), and the anti-inflammatory marker interleukin-6 (IL-6) significantly improved at the end of the study. While the control group had mean age of 48.24 ± 0.74 years, they experienced significant improvement of the somatic subscale, depression score, and MDA, and there was no significant effect on urogenital symptoms, anxiety score, IL-6, or any of the female sex hormones.

CONCLUSION: Adding Bee pollen, propolis, and royal jelly to the clover honey are more effective in slowing down menopausal symptoms.

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Introduction

Menopause is a natural physiological phenomenon through which women, between ages 45 and 52 years, cease to be fertile or menstruate. A reduction in female sex hormone estrogen levels can lead to the symptoms of menopause. More than 85% of these women will complain of symptoms disturbing their quality of life. Symptoms may appear before menopause and last for years after menstrual cessations, including hot flashes, night sweats, sleep problems, mood disorders, anxiety, depression, musculoskeletal pain, and sexual and urinary symptoms [1].

Nowadays, the demands for complementary therapy such as therapeutic nutrition, homeopathy, acupuncture, and reflexology have increased due to their impressive effects on relieving annoying symptoms [2]. Functional food and beverages demonstrated health benefits in reducing the symptoms of several diseases [3], [4].

Bee products such as honey, beeswax, royal jelly, propolis, and bee pollen are common substances available in Egyptian markets. Honey is a sweet viscous liquid processed by the honeybee (*Apis mellifera*) with highly nutritive components that are beneficial for human health; it is used internationally as a functional food to provide energy and nourishment [5], [6]. It has also been used as a complementary antibacterial agent against various pathogenic bacteria strains to inhibit their growth [7], [8].

Bee pollen has gained health traction in the past few years, because it is loaded with amino acids, healthy fats, vitamins, and minerals. Bee pollen is a mixture of bee secretions, flower pollen, nectar, wax, and enzymes. The German Federal Ministry of Health considers bee pollen a medicine [9].

Royal jelly is a dietary nutritional complex that is used to combat different health conditions, due to its various pharmacological activities. Royal jelly is rich in polyphenols, minerals, and vitamins. It contains a mix

of vitamins, minerals, proteins, and fatty acids, along with acid glycosides and sterols [10].

Bee venom (BV) has been used for the control of pain and inflammation in various chronic inflammatory diseases [11], [12], [13]. BV activates cellular and humoral immune systems and can be used for the management of SARS-CoV-2 infections [14]. BV attenuates lipopolysaccharides of *Porphyromonas gingivalis*, which induced inflammatory responses, by activation of related transcription factors as activator protein-1 and nuclear factor kappa-light-chain-enhancer of activated B cells [15].

Propolis is composed of phenolic compounds, flavonoids, beta-steroids, vitamins, minerals, and adenosine triphosphatase [16]. The chemical composition of the Egyptian propolis sample was investigated by GC/MS and High Performance Liquid Chromatography (HPLC). More than 300 compounds have been identified, 26 of which are new to propolis [17], [18].

The objective of this study was to evaluate the effectiveness of bee products in relieving various menopausal symptoms (psychological, somatic, and urogenital symptoms) in peri-menopausal Egyptian females.

Materials and Methods

Subjects

Sixty-three women suffering from symptoms of menopause were recruited from the attendants at outpatient NRC clinic of obstetrics and gynecology department. Participants had history of menstruation cessation since 1 year at least, with symptoms of menopause (hot flushes, night sweats, vaginal symptoms, urological problems, and other different symptoms as evaluated by menopause rating scale) and serum Follicle Stimulating Hormone (FSH) level ≥ 30 mIU/mL. Ethical approval from the Ethical Committee of NRC (Registration Number 16/110) and written informed consent from each of the participating women was obtained. Participants were randomly divided into two groups; control group received conventional clover honey while the other group consumed a calculated ratio of a mixture of clover honey enriched with bee pollen, royal jelly, and bee gum as described in (Table 1). Females consumed two tablespoons (32 ml) of the honey per day dissolved in 250 ml of water each the morning for 2 months.

Table 1: Enriched clover honey

Amount	Ingredients
1 kg	Clover honey
400 g	Bee pollen
40 g	Royal jelly
100g	Propolis

Exclusion criteria included: Diabetes mellitus, thyroid disorders, iron deficiency anemia, metabolic diseases, and liver or kidney diseases.

1-Chemical properties determination

1.i. The sugar content and pH measurement

Quantities of sugars were determined in accordance with (Bogdanov *et al.*, 1988) [19] using HPLC to measure the concentration of fructose and glucose. The pH was measured in honey samples in accordance with AOAC (2016) [20] methods using a pH meter (Hanna pH-meter Z741791 Sigma - Germany).

1.ii. Determination of total phenolic content, total flavonoid content, and antioxidant activity

The total phenolic content was assessed in accordance with Singleton *et al.*, 1999 [21]. The result was presented as (μg of Gallic acid equivalent per g of sample). The total flavonoid ABTS radical scavenging content was evaluated in accordance with (Barros *et al.*, 2007) [22] and the result was expressed as mg Catechin equivalent/kg of honey. The antioxidant activity of the two samples was evaluated as ascorbic acid equivalent antioxidant content (AEAC) using assay in accordance with Meda *et al.* (2005) [23], the result was expressed as mg of (AEAC)/100 g of sample.

2- Full clinical examinations and weekly follow-ups of the sample of peri-menopausal women during the study period (8 weeks) were carried out. All participants were subjected to the following:

- Full medical history was taken.
- Full clinical examinations and weekly follow-ups of the sample of perimenopausal women during the 8-week study period.
- Evaluation of menopausal symptoms using the Menopause Rating Scale (Schneider *et al.*) [24]. The scale included 11 items reflecting the different symptoms. Each item had a value corresponding to the degree of symptom severity (0 points for none and 5 points for severe). The "total score" is the sum of the = scores of the three subscales (psychological, somatic, and urogenital).

Somatic symptoms: Hot flashes, episodes of night sweats, awareness of heart beat, heart tightness, and sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, and waking up early), as well as joint and muscular discomfort.

Psychological symptoms: Depressive mood (feeling down, sad, on the verge of tears, lack of

drive, and mood swings), irritability (feeling nervous, inner tension, and feeling aggressive), anxiety (inner restlessness and feeling panicky), and physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, and forgetfulness).

Urogenital symptoms: Sexual problems (change in sexual desire, sexual activity, and satisfaction) and bladder problems (difficulty in urination, increased need to urinate, bladder incontinence, and/or vaginal dryness).

- Assessment of hot flashes using the hot flashes score: Mild = sensation of hotness without sweating; moderate = sensation of hotness with sweating, but allows for continuation of current activity; and severe = sensation of intense hotness with sweating that interferes with continuation of activity [25].
- Assessment of the presence of anxiety and its grade using the Beck Anxiety Inventory (BAI) [26]. Reliability of the BAI: Internal consistency for the BAI = (Cronbach's $\alpha = 0.92$) and test-retest reliability (1 week) for the BAI = 0.75.

Scoring: The total score is calculated by finding the sum of the 21 items.

Score of 0–21 = Low anxiety

Score of 22–35 = Moderate anxiety

Score of 36 and above = Severe anxiety

- Assessment of the presence of depression and its grade using the Beck Depression Inventory (BDI) [27], [28]: Each of the 21 items corresponding to a symptom of depression is summed to give a single score for the BDI. There is a 4-point scale for each item ranging from 0 to 3. Items 16 and 18 included seven options to indicate either an increase or decrease of appetite and sleep.

Total Score _____ Levels of Depression

1–10 _____ These ups and downs are considered normal

11–16 _____ Mild mood disturbance

17–20 _____ Borderline clinical depression

21–30 _____ Moderate depression

31–40 _____ Severe depression

Over 40 _____ Extreme depression

3- Blood sampling

Five ml of blood were withdrawn from each patient twice per study. Test strip electrochemical technology was used to determine fasting blood

glucose in fresh samples using Bayer's CONTOUR® PLUS Glucometer [29]. The rest of the blood samples were left to clot and cool-centrifuged at 3000 rpm for 15 min; then the sera were separated, divided into aliquots, and stored at -80°C until the determination of the FSH, testosterone, progesterone, estradiol (E2), lipid peroxide malondialdehyde (MDA), and interleukins 6 was carried out.

Serum level of FSH was measured using the human ELISA reagent kit purchased from abia, AB Diagnostic Systems GmbH Sport fliegerstraße, Berlin, Germany [30]. Serum level of estradiol was measured using the human ELISA reagent kit purchased from Bio Check, Inc, 425 Eccles Avenue, South San Francisco, CA, USA [31]. Serum level of progesterone hormone was measured using the human ELISA reagent kit purchased from abia, AB Diagnostic Systems GmbH Sport fliegerstraße, Berlin, Germany [32]. Serum level of testosterone hormone was measured using the human ELISA reagent kit purchased from DiaMetra, S.r.l. Headquarter: Through Garibaldi, SEGRATE (MI), Italy [33]. Serum interleukin-6 (IL-6) level was determined using the human ELISA reagent kits purchased from Sino Gene Clon Biotech Co., Ltd, Cangxin Road, Yu Hang District, Hang Zhou, China [34]. Serum lipid peroxide MDA was estimated colorimetrically using the thiobarbituric acid reaction method [35].

Statistical analysis

The data collected from the two groups before and after the interventions were calculated, compared, and analyzed. Descriptive results for different variables are expressed as mean \pm SD and/or percentage. Independent-samples t-tests or Mann-Whitney U tests were used as appropriate for comparison between the two groups as well as to compare data from each group before and after the intervention. Significance was defined at $p < 0.05$. Analysis was performed using SPSS version 16 (SPSS Inc. Chicago, IL).

Results

Thirty-two non-diabetic women suffering from symptoms of menopause participated as volunteers in the enriched honey group, with a mean age of 49.51 ± 0.82 years. Twenty-six non-diabetic women of the 31 volunteers' subjects suffering from symptoms of menopause completed the study in the control group with a mean age of 48.24 ± 0.74 years. Chemical analysis of clover honey revealed that it contained 42.1% reducing sugars, mainly fructose and glucose. The pH value of clover honey was 4.1 while the enriched honey pH value was 3.9. Enriched honey was richer in total phenolic compounds, total flavonoid content,

Table 2: Chemical composition of studied honey

	pH	K mg/kg	Ca mg/kg	Fe mg/kg	Mg mg/kg	P mg/kg	Zn mg/kg	Total phenolic contents (mg GAE/100 g)	Total Flavonoids contents (mg Catechin/kg)	AEAC (mg/100 g)
Clover honey	4.1	437.4	311.5	40.6	88.2	127.4	46.1	17.7	40.1	12.0
Mixture Enriched honey	3.9	978.6	932.4	597.8	261.7	203.0	189.8	54.4	119.8	29.3

K: Potassium; Ca: Calcium, Fe: Iron, Mg: Magnesium, P: Phosphorus, Zn: Zinc, GAE: Gallic acid equivalent, AEAC: Ascorbic acid equivalent antioxidant content.

antioxidant activity, calcium, phosphorus, magnesium, potassium, iron, and zinc than the conventional clover honey (Table 2).

Subjects consumed clover honey enriched with bee pollen, royal jelly, and propolis (Group A) had highly significant improvement of somatic, psychological, urogenital, and anxiety score assessments and depression score evaluations. Concerning biochemical parameters; estradiol, testosterone, the antioxidant (MDA), and the anti-inflammatory marker (IL-6) serum levels significantly improved by the end of the study. Pure clover honey consumption (group B) had significantly improved somatic and psychological symptoms, depression score, MDA, and no significant effect on urogenital symptoms, anxiety score, IL-6, or other female sex hormones (Table 3).

Table 4 demonstrated the percentage of reduction in the menopausal symptoms among the studied groups. Females who consumed the enriched honey reported better improvement in all menopausal symptoms (somatic, psychological, and urogenital symptoms), as well as the hot flashes frequency, night sweats, palpitations, sleep disturbances, joint and muscle pain, mood swings, anxiety, depression, irritability, impaired memory and concentration, sexual problems, bladder symptoms, and vaginal dryness problems.

Discussion

Bee products were consumed for nutrition and as folk remedies. Honey, bee pollen, propolis, and royal jelly have multiple health benefits [36].

Honey, in addition to being a food, is known to have anti-bacterial, antiviral, antifungal, and wound healing property. The active components of honey such as glucose, fructose, flavonoid, polyphenols, and organic acids play an important role in its quality [7]. Propolis has been reported to have health benefits related to oral diseases, gastrointestinal disorders, allergies, and dermatological problems. Royal jelly is well known for its protective effects on aging, reproductive health, and neurodegenerative diseases [37].

The Federal Ministry of Health in Germany considers bee pollen a medicine due to its positive impact on health [38]. Chemical analysis of clover honey revealed that its pH value was 4.1 while the enriched honey pH was 3.9. The change in pH values is affected by the mineral contents in the honey [39]. These values coincided with those established by Ikegbunam and Okwu (2021) who confirmed that honey pH ranges between 3.8 and 4.1 [40]. All of the honey samples analyzed were found to be acidic in character. The low honey pH value indicates its capability to slow down the growth of microorganisms [41].

The enriched honey was richer in total phenolic compounds, total flavonoid content, antioxidant activity, calcium, phosphorus, magnesium, potassium, iron, and zinc than conventional clover honey. The effect of different preparations of honey on human health depends on the bioavailability of the active compounds. The total phenolic contents and the phenolic compounds are considered crucial components in honey due to their influence on the honey's functional properties [42]. The honeys revealed varying amounts of antioxidant ability [43]. High antioxidant activity in the enriched honey could be due to its high total phenolic, flavonoid, minerals, and antioxidants contents [44], [45].

Table 3: Mean ± SD of clinical scores and biochemical parameters before and after honey supplements consumption

Parameters	Group A: Enriched honey supplement group (n = 32)			Group B: Control group (n = 26)		
	Mean ± SD	% Change		Mean ± SD	% Change	
	Before	After		Before	After	
Age (years)	53.8 ± 5.53			51.3 ± 4.99		
FSH (mIU/ml)	40.83 ± 11.09			31.30 ± 8.28		
BMI	30.67 ± 4.55			30.01 ± 8.42		
Waist circ. (cm)	94.7 ± 11.9			93.0 ± 15.27		
MRS	19.9 ± 5.7	8.0 ± 4.5 ^a	-59.8	24.6 ± 6.23	12.8 ± 4.49 ^c	-47.9
Somatic subscale	9.1 ± 4.0	4.1 ± 3.5 ^a	-54.9	10.0 ± 2.58	5.10 ± 2.2 ^{bc}	-49.0
Psychological subscale	7.6 ± 3.2	2.6 ± 1.9 ^a	-65.8	10.2 ± 2.20	5.20 ± 2.78 ^{bc}	-49.0
Urogenital subscale	2.8 ± 1.39	1.3 ± 1.25	-53.6	4.4 ± 2.58	2.5 ± 2.01	-43.2
Beck Anxiety score	19.9 ± 5.7	8.0 ± 4.5 ^a	-59.8	27.5 ± 11.3	18.6 ± 11.3 ^c	-32.4
Beck Depression score	17.9 ± 6.2	8.2 ± 3.5 ^a	-54.2	17.8 ± 12.9	14.20 ± 8.0 ^{bc}	-20.2
Free Testosterone (pg/mL)	25.07 ± 10.74	14.65 ± 10.31 ^{ab}	-41.56	25.11 ± 16.42	16.43 ± 10.81	-34.57
Progesterone (ng/ml)	10.75 ± 5.11	6.71 ± 3.31	-37.58	10.10 ± 4.78	9.86 ± 3.91 ^c	-2.4
Estradiol (pg/mL)	96.8 ± 78.28	141.7 ± 84.23 ^{abc}	+46.38	84.76 ± 9.45	75.74 ± 13.90 ^{abc}	-10.64
FBS	88.76 ± 12.31	88.74 ± 12.21	-0.02	91.01 ± 12.92	90.97 ± 11.89	-0.04
IL-6 (ng/L)	11.28 ± 5.44	3.46 ± 4.07 ^{abc}	-69.33	10.03 ± 4.18	8.23 ± 3.98 ^{abc}	-17.95
MDA (nmol/mL)	6.79 ± 0.28	3.21 ± 0.31 ^{abc}	-52.72	6.94 ± 0.31	4.81 ± 0.28 ^{abc}	-30.69

FSH: Follicle stimulating hormone, FBS: Fasting blood sugar, MDA: Malondialdehyde. ^aSignificant at p < 0.05 ^{bc}highly Significant at p < 0.01. a and b: Before versus after of Group A and Group B, respectively. c: % changes in Group A versus Group B.

Menopause usually occurs in females due to the cessation of secretion of ovarian sex hormones; the associated symptoms may persist for more than 15 years in 12% of women [46]. The effects witnessed in this study of honey, bee pollen, propolis, and royal jelly on menopausal symptoms were impressive. About 75% of menopausal women complained of hot flashes, the sudden feeling of intense heat not caused by external surrounding sources. Their faces and chests turn red or flush with an increased awareness of heart beats. Hot flashes accompanied by sweating during sleeping hours are called night sweats. A hot flash usually lasts for 5 min, followed by heart palpitations and sweating, then chilling and anxiety. The frequency of hot flashes may range from one or two flashes per day to one every hour. Research shows that hot flashes and night sweating were often linked to poor quality of life. They affect sleep patterns resulting in sleep time and quality disturbance, fatigue, anxiety, irritability, depression, and reduced cognitive functions [47].

Table 4: % reduction of the menopausal symptoms among the studied groups

Menopause symptoms	Menopausal evaluation questionnaires	Group I (no. = 32)	Group II (no. = 26)
		enriched honey %reduction	control group % reduction
Somatic symptoms	Hot flashes	-87.23	-
	Night sweats	-53.36	-
	Palpitations	-59.51	-19.01
	Sleep problems	-27.27	-9.90
	Joint discomfort	-66.67	-39.18
Psychological symptoms	Muscle discomfort	-75.21	-37.81
	Mood swing	-79.65	-37.55
	Anxiety	-69.74	-16.85
	Irritability	-50.31	-17.46
	Depression	-56.98	-31.61
	impaired memory	-49.69	-34.67
Urogenital symptoms	Impaired concentration	-74.93	-39.73
	Sexual problems	-45.95	-
	Bladder problems	-14.61	-
	Vaginal dryness	-59.85	-

In a previous study, 46 menopausal women consumed a daily amount of pure honey or honey and pollen to alleviate hot flashes; 71% of females receiving the mixture reported an improvement in their symptoms [48]. Our results agreed with Bălan *et al.* (2020) [49] that verified the efficiency of royal jelly in the easing of female postmenopausal complaints. Furthermore, recent studies demonstrated that royal jelly possesses a heightened ability to modulate natural aging. Hence, royal jelly could be profitably consumed by postmenopausal females as a dietary supplement for the handling of aging-related pathologies. Unfortunately, there is a limited amount of scientific research studying the effects of royal jelly on postmenopausal humans, as the majority of related research was conducted on animal models.

During the menopause phase of women's lives, the decrease of the follicular size affects the regular secretion of the female sex hormone estrogen, leading to an increase in the secretion of FSH in the premenopausal phase. Royal jelly supplementation was reported to be very helpful in enhancing hormonal regulation due to its content of 10-hydroxyl-2-decenoic fatty acid which maintains low levels of FSH in the serum and helps the synthesis of estrogens [49].

The deficiency of estrogen in postmenopausal women develops oxidative stress, due to release of free radicals or reactive oxygen species and becomes the cause of various pathologies like the development of hypertension. Estrogen is a powerful antioxidant, which prevents lipid peroxidation [50]. Bee pollen can regulate progesterone and estradiol sex steroidogenesis, hormonal balance is important for adjusting the mechanisms of proapoptotic (caspase) pathway and anti-apoptotic (Bcl-2) pathway [51].

Although honey possesses several physiological and biological activities in humans, Münstedt *et al.* (2015) draw attention to the fact that the increase in the E2 serum levels with honey consumption raises some queries about the safety versus the risk of honey ingestion in female patients with breast cancer receiving drugs that suppress estrogen production (aromatase inhibitors/inactivators) [48]. This query is of clinical importance as honey is considered by people worldwide to be a healthy food particularly women who may consume honey regularly without being aware of this potential risk. Thus, the use of honey and bee products for menopausal complaints in women with breast cancer should be addressed in the future studies, especially since the previous studies were conducted on animal models.

Conclusion

This study discovers the positive impressive effect of bee pollen, propolis, and royal jelly combination informing a natural honey product mixture with a beneficial effect for alleviating the somatic, urogenital, and psychological menopausal symptoms.

Declarations

Ethics approval

The research was given ethical approval from Ethical Committee of the National Research Centre with (Registration Number is 16/110); signed written informed consent forms were required to participate in the research project after the participants had been given a full explanation of the study.

Author contribution

Suzanne Fouad designed this research project. Aliaa El Gendy and Rasha Monir were responsible for the clinical examination and weekly follow-up; Ahmed G. Hegazi was responsible for the preparation and analysis

of mixture honey; Khaled Gamal Abdel-Wahhab was responsible for the biochemical analysis; Khaled Gamal Abdel-Wahhab and Suzanne Fouad were responsible for the statistical analysis of the data; Suzanne Fouad wrote the manuscript; Heba F. Shafei and Ahmed G. Hegazi revised the manuscript; All authors read and approved the final manuscript.

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