Potential Beneficial Effect of Honey Cocktail Supplement on Improving Dry Eye-Like Parameters Among Postmenopausal Women

Baharuddin Noorlaila1,2, Sivagurunathan Premala-Devi1,2, *Embong Zunaina1,3, Raja-Norliza Raja-Omar2, Nik-Hazlina Nik-Hussain3,4

1Department of Ophthalmology and Visual Science, Universiti Sains Malaysia, Kelantan, Malaysia
2Department of Ophthalmology, Hospital Melaka, Melaka, Malaysia
3Hospital Universiti Sains Malaysia, Kelantan, Malaysia
4Women Health Development Unit, Universiti Sains Malaysia, Kelantan, Malaysia

*Correspondence
Prof. Embong Zunaina
Department of Ophthalmology and Visual Science, Universiti Sains Malaysia, Kelantan, Malaysia
E-mail: zunaina@usm.my

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ABSTRACT

Background/Purpose: Postmenopausal women are prone to develop dry eye due to hormonal imbalance. Antioxidant's properties of honey maybe helpful to improve symptoms and signs of dry eye. The objective of this study was to evaluate the effect of honey cocktail on dry eye-like parameters among postmenopausal women.

Methods: An interventional study was conducted from November 2015 to May 2017. The eligible postmenopausal women were enrolled in this study. Participants for intervention received 20-gram honey cocktail supplement for 3 months (intervention group). Control group were not given any supplement or placebo. All participants were assessed for Ocular Surface Disease Index (OSDI) score using OSDI questionnaire (dry eye symptoms) and evaluated for Schirmer test value and Tear Break-up Time (TBUT) (dry eye signs) at baseline and at 3 months of the study.

Results: A total of 60 postmenopausal women were recruited (30 participants in intervention group and 30 participants in control group). At 3 months, intervention group showed significant reduction of mean OSDI score compared to control group (8.82 SD 8.33 vs 14.17 SD 10.37 scores respectively, p=0.032). There was no significant difference of mean Schirmer test value and TBUT between the two groups.

Conclusion: Short duration of honey cocktail supplementation showed no significant beneficial effect on dry eye-like parameters among postmenopausal women. Longer duration of honey supplementation might provide beneficial effect on dry eye-like parameters as systemic honey supplementation has a slow effect on ocular surface.

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1. INTRODUCTION

Dry eye is a condition of inadequate of tear film that leads to ocular surface disease. Foreign body sensation is the common symptom of dry eye. The incidence of dry eye is higher among female with
Hormonal changes in postmenopausal women also cause systemic symptoms such as hot flashes, insomnia, and fatigue. Hormone replacement therapy (HRT) is the treatment to relief symptoms of menopause. However, there are few harmful effects related to HRT such as heart disease, cancer, and stroke. Due to these harmful effects, dietary supplements such as red clover, black cohosh, honey and evening primrose are the alternative therapy to alleviate the symptoms of menopause.

Honey has been used widely to treat multiple illnesses in view of its anti-oxidant, anti-inflammatory and anti-bacterial effects. Honey is acidic in nature and consist of carbohydrate, flavonoids compounds, vitamins, and enzymes. Mixture of honey with other bee products (such as bee pollen, royal jelly and bee bread) is known as honey cocktail. Previous studies reported that honey supplementation has beneficial effect among postmenopausal women in terms of hormone profiles, cholesterol level and bony density.

The aim of this study was to evaluate the effect of honey cocktail supplementation on dry eye-like parameters among postmenopausal women. Honey cocktail supplementation that consists of multiple nutrients with the effect of antioxidants and anti-inflammatory may help to improve dry eye among postmenopausal women.

2. METHODS

2.1. Study Design and Participants

An interventional study was conducted among postmenopausal women from November 2015 to May 2017. This study received local ethical committee approval [Ref. no: USM/JEPeM/15070257] and was conducted in accordance with Declaration of Helsinki for human research.

Postmenopausal women with systemic comorbidities, ocular infections or inflammations, history of intraocular surgery or ocular trauma, using contact lenses, on tear replacement therapy at least minimum 6 weeks period prior enrollment, taking any oral health products or dietary supplements at least minimum 6 weeks period prior enrollment were excluded from this study. Participants were also excluded if they were on HRT, have history of allergy or sensitivity to study supplement ingredients.

The sample size was calculated using Power and Sample Size Calculation software version 3.1.2. A total of 60 postmenopausal women (30 participants in intervention group and 30 participants in control group) were acquired for this study.

2.2. Sampling and Intervention

All postmenopausal women attending to Ophthalmology clinic and Obstetrics & Gynecology clinic from November 2015 to December 2016 that fulfill the selection criteria were recruited in this study. Written informed consent was obtained from all the participants.

The eligible participants were randomly divided into 2 groups (intervention group and control group) by using opaque envelope technique. A stack of opaque envelope was prepared with 30 envelopes containing a piece of paper with the word ‘Intervention’ and the remaining 30 envelopes stated ‘Control’. The envelope was drawn for each participant by a co-investigator.

The honey cocktail supplement used in this study was Honey Cocktail 124 supplied by Federal Agricultural Marketing Authorities (FAMA), Malaysia. The dosage used in this study was calculated based on the animal study model. In this study, 20 gram of honey cocktail was chosen and was considered as a medium dose to study the effect of honey in human being. Honey Cocktail 124 was packed in 20-gram sachet and consist of 94.3% Acacia honey, 4.7% bee pollen and 1.0% royal jelly.

Intervention group received honey cocktail supplement for a total of 3 months duration. Participants were instructed to ingest one sachet of honey cocktail containing 20 gram per day. They were instructed to take the honey cocktail straight from the sachet without diluting the honey cocktail in water or other liquids, and to take it once a day during morning time before breakfast. Participants in control group were not given any supplements or placebo. Both groups did not receive any artificial tears.

Dry eye parameters that were used in this study include both assessment of dry eye symptoms and dry eye signs. For assessment of dry eye symptoms, Ocular Surface Disease Index (OSDI) questionnaire was used. Whereas for assessment of dry eye signs, Schirmer test value and Tear Break-up Time (TBUT) were used. These dry eye parameters are considered as dry eye-like parameters.

OSDI score, Schirmer test value and TBUT were assessed at baseline and at 3 months post honey cocktail supplementation by primary investigator. The primary investigator that responsible for the operation and data analyses of this study was blinded to the
assumed to be compliant if they take the honey cocktail 75% of the time. Participants who were found to be less than 75% compliant with honey cocktail supplementation were excluded from the data analysis.

2.8. Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 22.0. Paired t-test was used for comparison of data within the group. Whereas independent t-test was used to compare the data between the two groups. The p value of <0.05 was considered as statistically significant. Only right eye was chosen to analyze for standardization.

3. RESULTS

A total of 30 postmenopausal women were enrolled for honey cocktail supplementation and another 30 postmenopausal women were recruited as a control group. Participants in intervention group showed 100% compliance with the honey cocktail supplementation (Figure 1). The mean age of all participants was 60.90 ± 4.84 years old, and all participants were Malay. There was no significant difference of mean age and duration of menopause between the two groups (Table 1).

Baseline mean OSDI score showed there was normal status of the study group.

2.3. Measurement of Ocular Surface Disease Index (OSDI)

A validated OSDI questionnaire in Malay translated version was used in this study. OSDI is a questionnaire consisting of 12 questions. Participants were asked regarding visual function, ocular symptoms, and environmental triggers for the past one week. The OSDI was assessed on a scale of 0 to 100, with higher scores representing greater disability. Based on their OSDI scores, participants were categorized as having a normal ocular surface (0-12 scores) or as having mild (13-22 scores), moderate (23-32 scores), or severe (33-100 scores) ocular surface disease.

2.4. Measurement of Schirmer Test Value

The Schirmer test was performed in a confined room with the fan off and participant seated upright. One drop of topical anesthesia (proparacaine hydrochloride 0.5%) was instilled into conjunctival sac and excess tears were wiped away gently. The Schirmer filter paper was placed in the lateral third of the inferior conjunctival fornix. The Schirmer filter paper was removed after 5 minutes and reading was taken according to the amount of wetting on the calibrated scale printed on the Schirmer paper. The severity of dry eye was divided into mild, moderate, and severe: 10 mm ≤ mild dry eye <15mm; 5 mm ≤ moderate dry eye <10mm; and severe dry eye < 5mm.

2.5. Measurement of TBUT

TBUT was performed by placing moistened fluorescein strips to the conjunctival sac and was assessed using slit lamp bio microscope at 10 times magnification using cobalt blue illumination. The participant was then asked to blink normally and once the last blinking stop, the stopwatch was started. The interval between the last complete blink and the first appearance of a dry spot in the stained tear film was measured. This test was repeated 3 times and the mean was calculated. The severity of dry eye based on TBUT was divided into mild, moderate, and severe: 10 sec ≤ mild dry eye < 15 sec; 5 sec ≤ moderate dry eye < 10 sec; and severe dry eye < 5 sec.

2.6. Adverse Event Monitoring

Any adverse events associated with honey cocktail used in the study were self-reported by the participants and were recorded.

2.7. Compliance

Participants in the intervention group were assessed for the compliance at 3 months follow-up. They were assumed to be compliant if they take the honey cocktail 75% of the time. Participants who were found to be less than 75% compliant with honey cocktail supplementation were excluded from the data analysis.

Figure 1. Study CONSORT diagram

| Table 1. Age and duration of menopause between intervention and control groups |
|-----------------------------|-----------------|-----------------|------|
| Variable                    | Intervention Group | Control Group | p value |
| Age (year) mean (SD)        | 59.90 (4.22)     | 61.90 (5.26)   | 0.110 |
| Age of menopause (years) mean (SD) | 49.63 (3.48)     | 50.23 (4.24)   | 0.551 |
| Duration of menopause (years) mean (SD) | 10.23 (4.93)     | 11.87 (8.31)   | 0.268 |

Independent t test, p value <0.05 significant
dry eye-like symptoms in intervention group (10.07 SD 7.46 scores) and mild dry eye-like symptoms in the control group (14.72 SD 10.62 scores). Both groups of postmenopausal women showed mild dry eye severity level of Schirmer test value (10.40 SD 6.85 mm and 10.23 SD 7.55 mm respectively) and moderate dry eye severity level of TBUT (8.73 SD 2.97 sec and 9.93 SD 3.94 sec respectively). There was no significant difference of mean OSDI score, Schirmer test value and TBUT at baseline between the two groups (Table 2).

At 3 months, the mean OSDI score was significantly reduced in intervention group compared to control group (8.82 SD 8.33 scores vs 14.17 SD 10.37 scores respectively, \( P=0.032 \)) (Table 2). Assessment of dry eye-like parameters within the group showed that there was no significant difference of mean OSDI score, Schirmer test value and TBUT between baseline and at 3 months (Table 3).

### 3.1. Adverse Events

There were no adverse events due to honey cocktail observed or reported in this study among postmenopausal women in the intervention group.

### 4. DISCUSSION

This study was conducted to evaluate the potential effect of honey cocktail supplementation on dry eye-like parameters among postmenopausal women. In our study, their baseline signs of dry eye-like parameters (Schirmer test value and TBUT) was between mild to moderate in severity.

We found that postmenopausal women with honey cocktail supplementation showed significant reduction of mean OSDI score at 3 months compared to control group. OSDI score subjectively evaluates the symptoms of dry eye and the effect of dry eye disease on vision-related functioning. Study done by Tan et al.\(^{24}\) and Imada et al.\(^{25}\) showed that bee products have a role in improving dry eye condition. It is postulated that royal jelly modulates calcium signalling pathway in lacrimal gland and restore the capacity of tear secretion.\(^{25}\)

We observed that there was no significant difference of OSDI score, Schirmer test value and TBUT between baseline and at 3 months among postmenopausal women after completed 3 months honey cocktail supplementation. However, a study done by Inoue et al.\(^{26}\) found that tear volume significantly increased after given 7.2 gram of oral royal jelly honey daily for 8 weeks among Japanese patients. Inoue et al.\(^{26}\) also reported that TBUT was significantly higher at week 4 and 8 than at baseline in the royal jelly groups. The study participants done by Inoue et al.\(^{26}\) involved wide range of age (20-60 years old). In our study, we recruited only postmenopausal women. Furthermore, we used smaller amount of royal jelly (1%) in 20 gram per sachet of honey cocktail compared to study done by Inoue et al.\(^{26}\) (7.2 gram of royal jelly). Probably the hormonal changes in postmenopausal women and smaller amount of royal jelly supplement results in the insignificant findings of OSDI score, Schirmer test and TBUT.

We observed that there was reduction of OSDI score, longer duration of mean Schirmer test value and TBUT at 3 months post honey cocktail supplementation although it was not significant. Anti-inflammatory and anti-microbial properties of honey stabilised the ocular surface by reducing the bacterial overgrowth and inflammation. Overgrowth of bacteria on the ocular surface is one of the factor that associated with tear deficiency.\(^{27-29}\)

Our limitation in this study is the short duration of honey cocktail supplementation. Longer duration of oral supplementation of honey cocktail is recommended to look for the beneficial effect of honey since honey has a slow effect. This study also could be improved by including other ocular surface parameters.
changes tests such as corneal fluorescein staining, measuring inflammatory markers, quantifying goblet cells count and quantitative tests such as tear film osmolarity and impression cytology, measuring antioxidant levels and inflammatory markers in the tears to provide a more global effect of honey on the ocular surface.

5. CONCLUSION

Short duration of honey cocktail supplementation showed no significant beneficial effect on dry eye-like parameters among postmenopausal women. Longer duration of honey supplementation might provide beneficial effect on dry eye-like parameters as systemic honey supplementation has a slow effect on ocular surface.

CONFLICTS OF INTEREST

All authors declare that they have no conflict of interest.

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