COMPARISON OF DRY EYES PARAMETERS IN POSTMENOPAUSAL WOMEN WITH AND WITHOUT HONEY SUPPLEMENT

By

DR. NOORLAILA BAHARUDDIN

MBBS (MMMC)

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE (OPHTHALMOLOGY)

SCHOOL OF MEDICAL SCIENCES

UNIVERSITI SAINS MALAYSIA

2017

DISCLAIMER

I hereby certify that the work in this dissertation is my own except for the quotations and summaries which have been duly acknowledged.

Date: 20th November 2017 ……..

Noorlaila Baharuddin

P-UM0149/12

ACKNOWLEDGEMENTS

Foremost I would like to express my sincere gratitude to my supervisor, Associate Professor Datin Dr Zunaina Embong, Consultant Ophthalmologist and senior lecturer in Hospital Universiti Sains Malaysia for her undivided guidance and direction throughout this entire dissertation. She has been continually supporting all through my journey as a master candidate. I'm truly grateful to have her as my supervisor. Without her supervision and constant help this dissertation would not have been possible. I would also like to thank my co-supervisor, Prof Dr Nik Hazlina Nik Hussain from Women's Health Development Unit, University Sains Malaysia for her reviews in this study and Dr Raja Norliza Raja Omar for her encouragement and teaching.

I am also grateful to all the lecturers in the Department of Ophthalmology, consultants and specialists, supporting staffs in Ophthalmology Clinic, Hospital Universiti Sains Malaysia for their support and cooperation in this undertaking.

Last but not least, I would like to thank my family for this journey would not have been possible without the support from them. Thank you to my late loving mother, Mdm Hamidah Kathershah and beloved father, Mr Baharuddin Mohd Ali for all the support and sacrifices they had made.

TABLE OF CONTENTS

ABSTRACT

Background

Dry eyes is one of the most common ocular surface problems among elderly particularly among postmenopausal women due to hormonal imbalance. Ocular surface inflammation and tears hyperosmolarity are known pathogenesis of dry eyes.

Objective

The objective of this study is to compare the mean change (baseline and three months post treatment) in symptom [base on Ocular Surface Disease Index (OSDI) score] and signs (Schirmer test value and TBUT) between oral supplementation of honey cocktail and non-honey groups among postmenopausal women.

Methods

A randomised interventional study was conducted from November 2015 to May 2017, at Hospital Universiti Sains Malaysia, Kelantan, Malaysia. The eligible postmenopausal women were randomised into 2 groups (honey cocktail group and non-honey group) by using random sampling envelope technique. Participants were assessed for OSDI score using OSDI questionnaire and evaluated for Schirmer test value and TBUT at baseline and at 3 months after daily oral supplementation of 20g honey cocktail. Statistical analyses were performed using SPSS version 22.0. Only right eye was chosen to analyse for standardization.

Results

A total of 60 postmenopausal women were recruited (30 participants in honey cocktail group and 30 participants in non-honey group). Honey cocktail group showed reduction of disability of OSDI score and improvement in Schirmer test value at 3 months post honey supplementation compared to non-honey group. There was no significant difference in mean change of OSDI score (p=0.644), Schirmer test value (p=0.372) and TBUT (p=0.471) between honey cocktail and non-honey groups.

Conclusion

Postmenopausal women with honey cocktail supplements shows better clinical response compared to non-honey group. However, there was no significant difference between the two groups. Further studies with longer duration of honey supplementation is recommended as honey have a slow effect. Oxidative stress and inflammatory markers are essential to establish the effect of honey supplements in postmenopausal women.

ABSTRAK

Latarbelakang

Mata kering adalah masalah permukaan okular yang sering di alami oleh masyarakat terutamanya golongan tua khususnya di kalangan wanita yang sudah menopaus disebabkan oleh ketidakseimbangan hormon. Keradangan permukaan okular dan hyperosmolarity air mata dikenalpasti dalam patogenesis mata kering.

Objektif

Objektif kajian ini adalah untuk membandingkan perubahan min (asas dan tiga bulan selepas rawatan) dalam gejala [berdasarkan skor Indeks Penyakit Permukaan Okular (OSDI)] dan tanda-tanda (ujian nilai Schirmer dan TBUT) di antara kumpulan yang mengambil madu koktel secara oral dan tidak mengambil madu di kalangan wanita menopaus.

Kaedah kajian

Kajian ini merupakan kajian terkawal secara rawak yang dijalankan di Hospital Universiti Sains Malaysia bermula dari Nov 2015 hingga May 2017. Wanita yang sudah menopaus telah dipilih dan dibahagikan secara rawak kepada 2 kumpulan (kumpulan yang mengambil madu koktel 20g setiap hari secara oral dan kumpulan tidak diberi madu koktel) dengan menggunakan kaedah pensampelan rawak sampul surat. Perubahan permukaan okular dinilai melalui ujian Schirmer, masa pemecahan filem air mata (TBUT) dan skor OSDI sebelum dan 3 bulan selepas rawatan. Analisis data dilaksanakan dengan menggunakan SPSS versi 22.0.

Keputusan

Sebanyak 60 pesakit dinilai (kumpulan madu koktel: 30 pesakit dan kumpulan tanpa madu koktel: 30 pesakit) telah dipilih untuk kajian ini. Didapati tiada perbezaan signifikan dalam perubahan purata skor OSDI (p=0.644), ujian Schirmer (p=0.372) dan ujian TBUT (p=0.471) selepas 3 bulan antara kedua-dua kumpulan. Terdapat lebih penurunan perubahan purata skor OSDI dan peningkatan dalam purata asas ujian Schirmer selepas 3 bulan pengambilan madu koktel berbanding kumpulan tanpa madu koktel.

Kesimpulan

Kedua dua kumpulan tidak menunjukan perbezaan statistic yang signifikan, walaubagaimanapun wanita menopaus yang mengambil madu koktel menunjukan respon klinikal yang lebih baik daripada kumpulan wanita menopaus tanpa madu koktel. Tempoh kajian yang lebih lama diperlukan kerana madu memberi keberkesanan yang lambat. Penanda oksidatif dan inflamasi adalah penting untuk mengukuhkan kesan suplemen madu pada wanita menopause.

CHAPTER 1:

INTRODUCTION

Dry eye is one of the most frequently encountered ocular morbidities, a growing public health problem and one of the most common conditions seen by eye care practitioners (O'Brien PD et al., 2004). Dry eye is defined as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tears film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface (International Dry Eye Workshop Subcommittee., 2007a). The tear secretion is controlled by the lacrimal functional unit which consists of the ocular surface, the main lacrimal gland and as well as the interconnecting nerve innervations. Disturbance of these components will compromise the tear film and ocular surface.

The ocular surface is enclosed by precorneal tear film. Tear film is an essential component of the ocular surface. It can be subdivided into an anterior lipid layer produced by meibomian glands, a middle aqueous layer by lacrimal gland and an innermost mucin layer by goblet cells of the conjunctiva [Lemp MA et al., 1997]. Dry eye is a multifactorial disorder due to inflammation of the ocular surface and lacrimal gland, neurotrophic deficiency and meibomian gland dysfunction.

Changes in tear hyperosmolarity and tear instability lead to dry eye symptoms. The common manifestations of dry eyes are foreign body sensation, redness in the eyes, blurred vision, watery eyes, eye irritation when reading or driving, ocular pain upon waking, photophobia, sensitivity against air conditioner or windy conditions [Sriprasert I et al., 2016] and potentially blinding infections, such as bacterial keratitis [Lemp MA et al., 1997].

The risk of dry eyes increases with age in both sexes, while its incidence is higher among females (International Dry Eye Workshop Subcommittee., 2007b). A study done by Rahul Agarwal et al [2016], they found that there is 32% prevalence of dry eye among postmenopausal women. The prevalence of symptomatic dry eye in the United States from a large epidemiological study is about 7% in women and 4% in men over the age of 50 years [Schaumberg DA et al., 2009]. The first report of population-based data of dry eye that includes symptoms and signs in elderly Asians showed dry eyes is significantly higher in women compared to men in Taiwan [Lin PY et al., 2003].

Sex hormones have roles in ocular surface physiology and they impact differently on ocular surface tissues. It is hypothesised that hormonal changes alter the homeostasis of the ocular surface and contribute to dry eye. Androgens exert a protective function on the ocular surface (Versura P et al., 2014). Oestrogen may modulate a cascade of inflammatory events, which is an underlying pathogenesis of dry eye [Susan Truong et al., 2014]. In menopause, there will be structural and functional weakening of lacrimal and meibomian glands resulting in hyposecretion causing significant thinning of the tears lipid and aqueous layers. This will cause higher rates of tear evaporation, thus leading to increased tear film osmolarity which will activates inflammatory cascades in the cornea and conjunctiva, leading to the activation of nociceptor signals by inflammatory mediators and thus resulting in subjective symptoms of dry eye [Sriprasert I et al., 2016].

The severity of dry eye can be subjectively diagnosed based on symptoms and objectively using corneal fluorescein staining in the majority of dry eye patients. A validated questionnaire Ocular Surface Disease Index (OSDI) developed by the Outcomes Research

Group at Allergan Inc (Irvine, Calif) has a good to excellent reliability, validity and sensitivity used to assess ocular symptoms and effectively discriminating between normal, mild to moderate, and severe dry eye disease [Schiffman *et al.*, 2000].

Objective clinical measures are conjunctival and corneal staining, tear break-up time (TBUT) as well as Schirmer score. However, there has been no generally agreed gold standard in the diagnosis of dry eyes [Christophe Baudouin et al., 2014].

There are several modalities of treatments for dry eyes. In mild to moderate dry eye, artificial tears, gels and ointments are used to replenish deficient tears [Javadi MA et al., 2011]. Topical steroids, immunomodulating drugs, antibiotics, bandage contact lenses, autologous serum and amniotic membrane transplantation may be used in more severe cases [Javadi MA et al., 2011]. Surgical intervention such as punctal occlusion can be employed to minimize tear drainage in severely dry eyes [Javadi MA et al., 2011].

Artificial tears have become one of the most widely used modalities for the relief of discomfort from dryness of the eyes and for conservative treatment of ocular surface diseases. Long-term use of topical artificial tears with preservatives such as benzalkonium chloride (BAK) can alter the ocular surface which can lead to foreign body sensation and deterioration of vision. Artificial tears with preservative free is the alternative but it is costly [International Dry Eye Workshop Subcommittee., 2007c]. Hence, studies to find other alternative for this common ailments without harmful effects are essential.

Many postmenopausal women uses hormone replacement therapy (HRT), estrogen with or without progestin, to treat symptoms of menopause including dry eye disease. Although treatment of symptoms of menopause, such as hot flashes and urogenital atrophy, among others, is a common indication for short-term use, potential preventive effects of HRT on long-term health outcomes have become an increasingly important consideration. The Women's Health Initiative (WHI) Study have shown that although HRT is beneficial in preventing osteoporotic fractures and colorectal cancer, it also harbours harmful effects such as coronary heart disease, stroke, thromboembolic events, breast cancer with 5 or more years of use and cholecyctitis (Heidi DN et al, 2002). In view of this problem, more women nowadays are turning towards botanical and dietary supplements such as evening primrose (*Oenothera biennis*), Ginkgo (*Ginkgo biloba*), ginseng (*Panax ginseng*) and others for relief of menopausal symptoms.

The use of bee products in treating illness is known as apitherapy [Majtánová N et al., 2015]. Honey contains about 200 substances such as mixture of sugars (fructose, glucose, maltose and sucrose), small amounts of other constituents such as minerals, proteins, vitamins, organic acids, flavonoids, phenolic acids, enzymes and other phytochemicals [Zaid SSM et al., 2010]. Honey cocktail is a combination of honey with other bee products such as royal jelly, bee pollen, propolis, royal jelly, bee venom, bee bread and bee wax. Royal jelly contains essential amino acids, aspartic acid and glutamic acid [Zaid SSM et al., 2010]. Combination of honey with bee products provides additional values to honey alone [Viuda-Martos M et al., 2008].

Several studies had been done to establish the effect of honey in postmenopausal women. Antioxidant effect of Tualang honey reduced the blood oxidative stress level to combat stress induced neurodegenerative disease [Shafin N et al., 2014]. An animal study revealed administration of honey to ovariectomised rats improves the endometrial and vaginal thickness [Siti Sarah M et al., 2010]. A pilot study measuring cardiovascular parameters, hormonal profiles and bone density among postmenopausal women given Tualang honey compared to women given HRT showed that there is no difference in the parameters between two groups [Hazlina NHN et al., 2012]. Honey cocktail has better effects than Tualang honey in improving physiological profile (blood pressure, cholesterol level) in postmenopausal women [Zhi XC et al., 2015]. In terms of safety, daily intake of honey 20 g/day showed no significant changes in biochemical parameters such as renal, liver and haematological profile [Lili Husniati Y et al., 2013].

Honey is known to have anti-oxidant, anti-inflammatory and anti-bacterial effects. Based on previous studies, bee products have a role in improving dry eyes condition [Tan JJ et al., 2014; Toshihiro I et al., 2014]. Tualang honey possesses antioxidant properties and can improve cell migration and cellular resistance to oxidative stress in human corneal epithelial progenitor (HCEP) cells in vitro [Tan JJ et al., 2014]. Consumption of royal jelly restored the tear secretion capacity by decrease in lacrimal gland adenosine tri phosphate content and mitochondrial levels to the largest extent in rat [Toshihiro I et al., 2014]. Royal jelly can be used as a preventative intervention for dry eye by managing tear secretion capacity in the lacrimal gland [Toshihiro I et al., 2014]. Acacia honey accelerates wound closure of cultured corneal epithelial cells of the in vitro corneal abrasion wound healing model [Choy KW et al., 2015].

Anti-bacterial effect of honey with topical honey administration significantly reduced total colony forming units for the eyelids and conjunctiva of dry eye [Albietz JM et al., 2006]. Bacteria could not grow in concentrated honey solutions due to its acidity and high glucose concentration which created an unfavourable environment for bacteria to survive. In an animal study done by Gakhramanov [2015], the study groups that were treated with oral antioxidants and topical anti-inflammatory drugs showed higher total antioxidant activity in the aqueous humour, vitreous humour and retina compared to the control group where only topical anti-inflammatory drugs were given. This study demonstrated that oral supplement of honey can increase the antioxidant capacity in eye tissues of rabbits [Gakhramanov FS., 2015]. In another animal study done by Bashkaran et al [2011], they found that rabbits with ocular chemical injury that were treated with oral and topical honey showed higher level of antioxidant level in aqueous humour compared to conventionally treated groups.

The objective of this study is to evaluate the effect of honey cocktail on dry eye parameters (OSDI score, Schirmer test value and TBUT) among postmenopausal women. Using honey is a novel approach because honey is a natural nutritional material. A combination of bee products which includes honey, propolis and bee bread in honey cocktail maybe helpful as supplements as it is packed with nutrients, antioxidants and anti-inflammatory which may help to improve dry eyes.

REFERENCES:

Albietz JM & Lenton LM (2006). Effect of antibacterial honey on the ocular flora in tear deficiency and meibomian gland disease. *Cornea.* Oct; 25(9):1012-9.

Bashkaran K, Zunaina E, Bakiah S et al (2011). Anti-inflammatory and antioxidant effects of Tualang honey in alkali injury on the eyes of rabbits: experimental animal study. *BMC Complement. Altern. Med.,* 9; 11:90. doi: 10.1186/1472-6882-11-90.

Choy KW, Norzana Abd Ghafar, Chua Kien Hui et al (2015). The effects of acacia honey on in vitro corneal abrasion wound healing model. *BMC Cell Biol*, 16: (2) 18. doi:10.1186/s12860-015-0053-9.

Christophe Baudouin, Pasquale Aragona, Gysbert Van Setten et al (2014). Diagnosing the severity of dry eye: a clear and practical algorithm. *Br J Ophthalmol*, 98(9): 1168–1176. doi:10.1136/bjophthalmol-2013-304619.

Gakhramanov FS: Effect of natural antioxidants on antioxidant activity and lipid peroxidation in eye tissue of rabbits with chemical burns (2005). *Bull Exp Biol Med*, 140 (3): 289-291.

Hazlina NHN, Amrah SS, Azidah AK et al (2012). The effects of tualang honey and HRT on cardiovascular, hormonal profiles and bone density among postmenopausal women. *J Food Res*, 1(2):171.

Heidi DN, Linda LH, Peggy N et al (2002). Postmenopausal hormone replacement therapy scientific review. *JAMA*, 288(7):872-881.

International Dry Eye Workshop Subcommittee (2007a). The definition and classification of dry eye disease: report of the definition and classification subcommittee of the International Dry Eye Work Shop (DEWS). *Ocul Surf,* 5:75-92.

International Dry Eye Workshop Subcommittee (2007b). The epidemiology of dry eye disease: report of the epidemiology subcommittee of the International Dry Eye Work Shop (DEWS). *Ocu Surf,* 5(2):93-107.

International Dry Eye Workshop Subcommittee (2007c). Management and therapy of the dry eye disease: report of the management and therapy subcommittee of the International Dry Eye Work Shop (DEWS). *Ocu Surf,* 5(2):163-174.

Javadi MA, Feizi S (2011). Dry Eye Syndrome. *J Ophthalmic Vis Res*, 6(3): 192–198.

Lemp MA, Chacko B (1997). Diagnosis and treatment of tear deficiencies. *Duane's Clinical Ophthalmology.*

Lili Husniati Y, Nik Hazlina NH, Azidah AK et al (2013). Safety of honey in postmenopausal women. *Int Med J,* 20 (1) p 25 - 28.

Lin PY, Tsai SY, Cheng CY et al (2003). Prevalence of dry eye among an elderly Chinese population in Taiwan: the Shihpai Eye Study. 10(6):1096-101.

Majtánová N, Vodrazkova E, Kurilova V et al (2015). Complementary treatment of contact lens induced corneal ulcer using honey. *Cont Lens Anterior Eye,* 38(1):61-3.

O'Brien PD & Collum LM (2004). Dry Eye: Diagnosis and current treatment strategies. *Curr Allergy Asthma Rep,* 4:314-9.

Rahul Agarwal, Priti Singh, Tanya Rajpal et al (2016). Hospital based study of prevalence of dry eye in post-menopausal women. *Indian J Clin Exp Ophthalmol*, 2(1): 57-62.

Schaumberg D A, Dana R, Buring J E, and Sullivan D A (2009). Prevalence of Dry Eye Disease among US Men: Estimates from the Physicians' Health Studies. *Arch Ophthalmol.* 127(6):763–768.

Schiffman, R. M., Christianson, M. D., Jacobsen, G., Hirsch, J. D. & Reis, B. L. (2000). Reliability and validity of the ocular surface disease index. *Arch Ophthalmol.* 118(5), 615-21.

Shafin N, Zakaria R, Nik Hussain N. H et al (2014). Tualang honey supplementation reduces blood oxidative stress levels/activities in postmenopausal women. *ISRN Oxidative Medicine*. 4. doi: 10.1155/2014/364836.364836.

Siti Sarah M, Siti Amrah S, Kuttulebbai NM et al (2010). Effect of Tualang honey on female reproductive organs, tibia bone and hormonal profile in ovariectomised rats- animal model for menopause, *BMC Complement Altern Med,* 10:82.

Sriprasert I, Warren DW, Mircheff AK et al (2016). Dry eye in postmenopausal women: a hormonal disorder. *Menopause.* 23(3):343-51.

Susan Truong, Nerida Cole, Fiona Stapleton et al (2014). Sex hormones and the dry eye. *Clin Exp Optom*. 97: 324–336. doi:10.1111/cxo.12147.

Tan JJ, Azmi SM, Yong YK et al (2014). Tualang honey improves human corneal epithelial progenitor cell migration and cellular resistance to oxidative stress in vitro. *PLoS One,* 9(5):e96800.

Toshihiro I, Shigeru N, Noaki K et al (2014). Oral administration of royal jelly restores tear secretion capacity in rat blink suppressed dry eye model by modulating lacrimal gland function. *PLoS oNE,* 9(9):e106338.

Versura P, Giannaccare G, Campos EC (2014). Sex-Steroid Imbalance in Females and Dry Eye. *Curr Eye Res*. Oct 7:1-14.

Viuda-Martos M, Ruiz-Navajas Y, Fern'andez-Lopez J et al (2008). Functional properties of honey, propolis, and royal jelly. *J Food Science,* 73(9):117-124.

Zaid SS, Sulaiman SA, Sirajudeen KN et al (2010). The effects of Tualang honey on female reproductive organs, tibia bone and hormonal profile in ovariectomised ratsanimal model for menopause. *BMC Complement Altern Med*, 10:82.

Zhi XC, Jia HH, Nik Hussain N.H et al (2015).The Effects of Tualang Honey versus Honey Cocktail (HC124) on Physiological Changes and Hormonal Profiles among Postmenopausal Women: A Preliminary Study. *Int J Collab Res Intern Med Public Health*, Vol. 7 No. 4 page 40-51.

CHAPTER 2:

OBJECTIVES

2.1: General Objective

To evaluate the clinical symptoms and signs of dry eyes in postmenopausal women with and without honey cocktail supplement.

2.2: Specific Objectives

2.2.1: To compare the mean change (baseline and three months post treatment) in OSDI score in postmenopausal women with and without honey cocktail supplement.

2.2.2: To compare the mean change (baseline and three months post treatment) in Schirmer test value in postmenopausal women with and without honey cocktail supplement.

2.2.3: To compare the mean change (baseline and three months post treatment) in TBUT in postmenopausal women with and without honey cocktail supplement.

CHAPTER 3:

MANUSCRIPT

3.1: THE EFFECT OF BEE PRODUCT SUPPLEMENT ON DRY EYES PARAMETERS AMONG POSTMENOPAUSAL WOMEN: A RANDOMIZED INTERVENTIONAL STUDY

Baharuddin Noorlaila[1,2,3], Embong Zunaina[1,3], Raja-Norliza Raja-Omar[2], Nik-Hazlina Nik-Hussain[3,4]

[1]Department of Ophthalmology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.

[2]Department of Ophthalmology, Hospital Melaka, Melaka, Malaysia.

[3]Hospital Universiti Sains Malaysia, Jalan Raja Perempuan Zainab II, 16150 Kubang Kerian, Kelantan, Malaysia.

[4]Women'S Health Development Unit, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.

Baharuddin Noorlaila: lailabaha157@gmail.com

Raja Norliza Raja Omar: norliza_eye@yahoo.com

Nik-Hazlina Nik-Hussain: hazlinakck@usm.my

Embong Zunaina: zunaina@usm.my

Correspondence should be addressed to: Embong Zunaina

Department of Ophthalmology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, 16150 Kubang Kerian, Kelantan, Malaysia.

Email: zunaina@usm.my

Phone: 609 767 6362 Fax: 609 765 3370

3.2: ABSTRACT

Background

Dry eyes is one of the most common ocular surface problems among elderly particularly among postmenopausal women due to hormonal imbalance. Ocular surface inflammation and tears hyperosmolarity are the known pathogenesis of dry eyes. The objective of this study is to evaluate the effect of honey cocktail on dry eye parameters [based on Ocular Surface Disease Index (OSDI) score, Schirmer test value and Tear Break-up Time (TBUT)] among postmenopausal women.

Methods

A randomized interventional study was conducted from November 2015 to May 2017, at Hospital Universiti Sains Malaysia, Kelantan, Malaysia. The eligible postmenopausal women were randomised into 2 groups (honey cocktail group and non-honey group) by using random sampling envelope technique. Participants were assessed for OSDI score using OSDI questionnaire and evaluated for Schirmer test value and TBUT at baseline and at 3 months post honey cocktail supplementation. Statistical analyses were performed using SPSS version 22.0. Only right eye was chosen to be analyzed for standardisation.

Results

A total of 60 postmenopausal women were recruited (30 participants in honey cocktail group and 30 participants in non-honey group). Honey cocktail group showed trend of reduction disability of OSDI score and improvement in Schirmer test value at 3 months post honey cocktail supplementation compared to non-honey group. However, there was no significant

difference in mean change of OSDI score (p=0.644), Schirmer test value (p=0.372) and TBUT (p=0.471) between honey cocktail and non-honey groups.

Conclusion

Postmenopausal women with honey cocktail supplements shows better clinical response compared to non-honey group on dry eye parameters. However, there was no statistically significant difference between the two groups. Further studies with longer duration of honey supplementation is recommended as honey have a slow effect. Oxidative stress and inflammatory markers are essential to establish the effect of honey supplements in postmenopausal women.

Keywords: Honey, dry eyes, postmenopause.

3.3: BACKGROUND

Dry eye is one of the most frequently encountered ocular morbidities, a growing public health problem and one of the most common conditions seen by eye care practitioners [1]. Dry eye is defined as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tears film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface [2]. The tear secretion is controlled by the lacrimal functional unit which consists of the ocular surface, the main lacrimal gland and as well as the interconnecting nerve innervations. Disturbance of these components will compromise the tear film and ocular surface.

The ocular surface is enclosed by precorneal tear film. Tear film is an essential component of the ocular surface. It can be subdivided into an anterior lipid layer produced by meibomian glands, a middle aqueous layer by lacrimal gland and an innermost mucin layer by goblet cells of the conjunctiva [3]. Dry eye is a multifactorial disorder due to inflammation of the ocular surface and lacrimal gland, neurotrophic deficiency and meibomian gland dysfunction.

Changes in tear hyperosmolarity and tear instability lead to dry eye symptoms. The common manifestations of dry eyes are foreign body sensation, redness in the eyes, blurred vision, watery eyes, eye irritation when reading or driving, ocular pain upon waking, photophobia, sensitivity against air conditioner or windy conditions [4] and potentially blinding infections, such as bacterial keratitis [3].

The risk of dry eyes increases with age in both sexes, while its incidence is higher among females [5]. A study done by [6], they found that there is 32% prevalence of dry eye among postmenopausal women. The prevalence of symptomatic dry eye in the United States from a large epidemiological study is about 7% in women and 4% in men over the age of 50 years [7]. The first report of population-based data of dry eye that includes symptoms and signs in elderly Asians showed dry eyes is significantly higher in women compared to men in Taiwan [8].

Sex hormones have roles in ocular surface physiology and they impact differently on ocular surface tissues. It is hypothesised that hormonal changes alter the homeostasis of the ocular surface and contribute to dry eye. Androgens exert a protective function on the ocular surface [9]. Oestrogen may modulate a cascade of inflammatory events, which is an underlying pathogenesis of dry eye [10]. In menopause, there will be structural and functional weakening of lacrimal and meibomian glands resulting in hyposecretion causing significant thinning of the tears lipid and aqueous layers. This will cause higher rates of tear evaporation, thus leading to increased tear film osmolarity which will activates inflammatory cascades in the cornea and conjunctiva, leading to the activation of nociceptor signals by inflammatory mediators and thus resulting in subjective symptoms of dry eye [4].

The severity of dry eye can be subjectively diagnosed based on symptoms and objectively using corneal fluorescein staining in the majority of dry eye patients. A validated questionnaire Ocular Surface Disease Index (OSDI) developed by the Outcomes Research Group at Allergan Inc (Irvine, Calif) has a good to excellent reliability, validity and

sensitivity used to assess ocular symptoms and effectively discriminating between normal, mild to moderate, and severe dry eye disease [11].

Objective clinical measures are conjunctival and corneal staining, tear break-up time (TBUT) as well as Schirmer score. However, there has been no generally agreed gold standard in the diagnosis of dry eyes [12].

There are several modalities of treatments for dry eyes. In mild to moderate dry eye, artificial tears, gels and ointments are used to replenish deficient tears [13]. Topical steroids, immunomodulating drugs, antibiotics, bandage contact lenses, autologous serum and amniotic membrane transplantation may be used in more severe cases [13]. Surgical intervention such as punctal occlusion can be employed to minimize tear drainage in severely dry eyes [13].

Artificial tears have become one of the most widely used modalities for the relief of discomfort from dryness of the eyes and for conservative treatment of ocular surface diseases. Long-term use of topical artificial tears with preservatives such as benzalkonium chloride (BAK) can alter the ocular surface which can lead to foreign body sensation and deterioration of vision. Artificial tears with preservative free is the alternative but it is costly [14]. Hence, studies to find other alternative for this common ailments without harmful effects are essential.

Many postmenopausal women uses hormone replacement therapy (HRT), estrogen with or without progestin, to treat symptoms of menopause including dry eye disease. Although treatment of symptoms of menopause, such as hot flashes and urogenital atrophy, among others, is a common indication for short-term use, potential preventive effects of HRT on long-term health outcomes have become an increasingly important consideration. The Women's Health Initiative (WHI) Study have shown that although HRT is beneficial in preventing osteoporotic fractures and colorectal cancer, it also harbours harmful effects such as coronary heart disease, stroke, thromboembolic events, breast cancer with 5 or more years of use and cholecyctitis [15]. In view of this problem, more women nowadays are turning towards botanical and dietary supplements such as evening primrose (*Oenothera biennis*), Ginkgo (*Ginkgo biloba*), ginseng (*Panax ginseng*) and others for relief of menopausal symptoms.

The use of bee products in treating illness is known as apitherapy [16]. Honey contains about 200 substances such as mixture of sugars (fructose, glucose, maltose and sucrose), small amounts of other constituents such as minerals, proteins, vitamins, organic acids, flavonoids, phenolic acids, enzymes and other phytochemicals [17]. Honey cocktail is a combination of honey with other bee products such as royal jelly, bee pollen, propolis, royal jelly, bee venom, bee bread and bee wax. Royal jelly contains essential amino acids, aspartic acid and glutamic acid [Zaid SSM et al., 2010]. Combination of honey with bee products provides additional values to honey alone [18].

Several studies had been done to establish the effect of honey in postmenopausal women. Antioxidant effect of Tualang honey reduced the blood oxidative stress level to combat stress induced neurodegenerative disease [19]. An animal study revealed administration of honey to ovariectomised rats improves the endometrial and vaginal thickness [20]. A pilot study measuring cardiovascular parameters, hormonal profiles and bone density among postmenopausal women given Tualang honey compared to women given HRT showed that there is no difference in the parameters between two groups [21]. Honey cocktail has better effects than Tualang honey in improving physiological profile (blood pressure, cholesterol level) in postmenopausal women [22]. In terms of safety, daily intake of honey 20 g/day showed no significant changes in biochemical parameters such as renal, liver and haematological profile [23].

Honey is known to have anti-oxidant, anti-inflammatory and anti-bacterial effects. Based on previous studies, bee products have a role in improving dry eyes condition [24, 25]. Tualang honey possesses antioxidant properties and can improve cell migration and cellular resistance to oxidative stress in human corneal epithelial progenitor (HCEP) cells in vitro [24]. Consumption of royal jelly restored the tear secretion capacity by decrease in lacrimal gland adenosine tri phosphate content and mitochondrial levels to the largest extent [25]. Royal jelly can be used as a preventative intervention for dry eye by managing tear secretion capacity in the lacrimal gland [25]. Acacia honey accelerates wound closure of cultured corneal epithelial cells of the in vitro corneal abrasion wound healing model [26].

Anti-bacterial effect of honey with topical honey administration significantly reduced total colony forming units for the eyelids and conjunctiva of dry eye [27]. Bacteria could not grow in concentrated honey solutions due to its acidity and high glucose concentration which created an unfavourable environment for bacteria to survive. In an animal study done by Gakhramanov [28], the study groups that were treated with oral antioxidants and topical anti-inflammatory drugs showed higher total antioxidant activity in the aqueous humour, vitreous humour and retina compared to the control group where only topical anti-inflammatory drugs were given. This study demonstrated that oral supplement of honey can increase the antioxidant capacity in eye tissues of rabbits [28]. In another animal study done by Bashkaran et al [29], they found that rabbits with ocular chemical injury that were treated with oral and topical honey showed higher level of antioxidant level in aqueous humour compared to conventionally treated groups.

The objective of this study is to evaluate the effect of honey cocktail on dry eye parameters (OSDI score, Schirmer test value and TBUT) among postmenopausal women. Using honey is a novel approach because honey is a natural nutritional material. A combination of bee products which includes honey, propolis and bee bread in honey cocktail maybe helpful as supplements as it is packed with nutrients, antioxidants and anti-inflammatory which may help to improve dry eyes.