The Effects of Tualang Honey versus Honey Cocktail (HC124) on Physiological Changes and Hormonal Profiles among Postmenopausal Women: A Preliminary Study

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Abstract

Introduction: Honey and other bee hive products have been reported to contain many highly nutritious substances in various medical fields. A combination of bee hives products known as Honey Cocktail 124 may provide additional values to Tualang Honey.

Objectives: The objective of this study was to investigate the effects of of Tualang Honey versus Honey Cocktail (HC124) on physiological changes (cardiovascular parameters) and hormonal profile among post-menopausal women.

Designs: A randomized, double blinded, prospective, preliminary clinical study was conducted involving post-menopausal women aged 45 to 65 years.

Materials and Methodology: Hundreds healthy post-menopausal women were given 20 g/day of Tualang Honey or Honey Cocktail and followed up for 6 months. ANCOVA was performed for statistical analysis.

Results: There were significant changes in the diastolic blood pressure, serum total cholesterol and LDL levels between the two groups after 6 months. Other clinical findings and laboratory investigations were not significant.

Conclusion: Honey Cocktail has slightly better effects than Tualang Honey in improving the physiological profile of post-menopausal women.

Key words: Tualang Honey, Honey Cocktail, post-menopause, cardiovascular parameters, female hormonal profiles and biochemical parameters

Introduction

Menopause is a natural progression of women's physiology.[1] Menopause is known to cause cardiovascular complications, osteoporosis, physical and psychological changes for women.[1] Hormone replacement therapy (HRT) has been the basis of the treatment of menopausal state.[2] However, many studies have shown that HRT with unopposed oestrogen increases risks for breast and endometrium cancer.[2]

Honey and other bee hive products such as royal jelly, propolis, bee pollens, bee bread and bee venom have been reported to contain several highly nutritious and valuable substances that have many therapeutic effects.[3] 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.[4] Royal jelly on the other hand contains 21 essential amino acids and the most important being aspartic acid and glutamic acid.[4]

An animal study revealed that administration of Tualang honey to ovariectomised rats improves the endometrial and vaginal epithelium.[4] There was also increase in the serum testosterone and progesterone level in the honey treated rats.[4] On top of that, there was a study demonstrated significant lowering of systolic blood pressure among postmenopausal women administered with Tualang honey as compared to the control group treated by hormone replacement therapy.[1] This generates a possibility on whether honey can be used as an agent to replace HRT among postmenopausal women. Another pilot study comparing Tualang honey with Hormonal Replacement Therapy (HRT) for four months among postmenopausal women showed significant hormonal changes in both groups with no adverse effects documented.[5] Other bee hive products such as bee bread and royal jelly contain higher minerals, vitamins, free fatty acid, protein and essential amino acids compared to honey.[3] Hence a combination of bee hive products known as Honey Cocktail 124 may provide additional or added values to Tualang Honey. Combining two or more bee hive products in treating various kinds of diseases is a common practice in Apitherapy to achieve their maximum desired effects.[6]

Objective

This study was aimed to compare the effects of Tualang Honey versus Honey Cocktail (HC124) on the physiological changes and hormonal profiles among post-menopausal women.

Methodology

This was a randomized, prospective, double blinded, preliminary clinical study to determine the effects of Tualang Honey versus Honey Cocktail (HC124) on the physiological and hormonal changes among post-menopausal women. Subjects were healthy post-menopausal women who were either artificially or naturally menopause for more than five years. The study period was six months.

Group 1: Subjects received 20 g/day of **Tualang Honey**. The honey was from a single batch honey supply by Federal Agricultural Marketing Authorities (FAMA),

Malaysia, evaporated by FAMA to achieve a water content of about 20%, and was then submitted to Sterile Gamma company at Shah Alam, Selangor, Malaysia for sterilization at 25 kGy and packed in 20 g sachet in collaboration with School of Pharmaceutical Sciences laboratory.

Group 2: Subjects received 20 g/day of **Honey Cocktail (HC124)**. The honey Cocktail (HC124) was from a single batch supplied by Federal Agricultural Marketing Authorities (FAMA), Malaysia, evaporated by FAMA to achieve a water content of about 20%, and was then submitted to Sterile Gamma Company at Shah Alam, Selangor, Malaysia for sterilization at 25 kGy and packed in 20 g sachet in collaboration with School of Pharmaceutical Sciences laboratory.

The choice of the dose used in the study was based on the animal study using the ovariectomised rat.[4] The optimal dose shown to increase the testosterone level was 200 mg/kg/day in the animal model. After taking the average human weight as 60 kg, the dose calculated for human was 12 gram (200 mg/kg x 60 kg (average human weight) = 12g). 20 gram was considered as medium dose to study the effect of honey in human being. The participants were given either the Tualang Honey or Honey Cocktail. Later, the participants were advised to take the honey products once in every morning. They were advised to not to overtake or take other over the counter drug. The study duration was six months.

There were four visits throughout the study period. First visit was the screening and selection programme of the subjects. During the second visit, eligible subjects were given the honey products for consumption. At the same time, the subjects were examined clinically and had their blood taken to measure the relevant baseline laboratory results. Third visit was the third month after they consumed the product. They were interviewed to know the products compliancy and to get further products supply. Compliance was assumed if they consumed the honey products 75% of the time. Subjects who failed to do so were withdrawn from the study by the investigators. Last visit was the sixth month after the subjects had consumed the honey products. Post-interventional assessments were done at this point.

Research tools

Physical measurements including blood pressure (BP), weight and height measurements, body mass index (BMI) and waist circumference (WC) were recorded at the beginning and end of the study.

10mls of venous blood were withdrawn at the beginning and end of the study to study the following profiles;

a) Hormonal profile - Serum estradiol, testosterone and other related hormones

b) Liver function (LFT) and renal function tests (RFT)

c) Serum glucose level: Serum fasting plasma glucose

d) Serum lipids levels like LDL, HDL, VLDL and chylomicron level.

Sample size calculation

$\alpha = 0.05$

power = 0.9

σ = standard deviation of uterus weight in Tualang Honey group in rats was 16.0

δ = Detectable difference in population mean was 11.5

m = ratio of control to intervention group was 1

Sample size was calculated based on animal study[4] using Power and Sample Size Calculation software by PS software for comparing two means. Taking the alpha of 0.05, power of 90%, detectable difference of 11.5, standard deviation of 16.0[4] and non-response rate of 20%, the sample size calculated was 50 per group.

Total subjects that recruited for the study were 50 X 2 groups = 100 subjects.

Inclusion Criteria:

1. Healthy post-menopausal women, age ≥ 45 -65 years old either surgically or naturally menopause for more than five years.
2. Healthy physically and mentally as determined by laboratory results, medical history and physical examination.
3. Has given written and informed consent to participate in the study.

Exclusion Criteria:

1. Condition(s) which opposes inclusion criteria;
2. Any other condition which in the Investigator's opinion may adversely affect the subject's ability to complete the study or its measures or which may pose significant risk to the subject.

Patient withdrawal

The investigators could withdraw the subject(s) or the subject(s) could withdraw herself from participation at any time. The withdrawal reason(s) was recorded.

Withdrawal reasons included:

1. The need to take medication, which interfered with study measurements
2. An occurred intolerable or unacceptable adverse events
3. Non compliance with the protocol
4. Development of any illnesses which has interfered with the study outcome.

Data Handling and Record Keeping

Data recording and collection including the informed consent, medical history, physical examination, vital signs, adverse events, conformation of medication dispensation and quality of life were recorded on the documents prepared for the study. Data entry and analysis were done at Clinical Triad Unit, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia.

Statistical analysis

The association of the sociodemographic data between the two groups was tested using the independent-t test. Association of the categorical information of the sociodemographic data like number of parity, race, occupation and so on between the two groups were tested using either Chi-Square test or Fisher-Exact test. P-value of less than 0.05 was considered as significant.

ANOVA and ANCOVA were used to compare the changes between the cardiovascular parameters (systolic and diastolic blood pressure, body mass index and waist circumference), biochemistry profile (lipid profile and fasting blood glucose), hormone profile (FSH, LH and estradiol) studied at pre and post intervention in both different groups. P-value of less than 0.05 was taken as significant.

Ethics

The study commenced after approval by the Human Research and Ethics Committee for Clinical Studies of Universiti Sains Malaysia. Ethics Reference Number: USMKK/PPP/JEPeM [243.3(3)]. The grant obtained was Universiti Sains Malaysia's Research University Grant for Individual (RUI). Grant Ref. No: 1001/PPSP/812098.

Results

Hundred subjects were recruited for this six month study. Fifty subjects were given Tualang Honey and another fifty subjects were given Honey Cocktail. One subject was withdrawn from the Tualang Honey group and no subject was withdrawn from the Honey Cocktail group.

The mean age of the subjects in the study was 58.1 years old. The average age of the subjects in Tualang Honey group and Honey Cocktail group was 57.76 and 58.40 years old respectively. There was no significant difference (p=0.383) in the mean age between the 2 groups.

The average age of the subjects at menarche was 13.2 years old. The average monarchial age for subjects in Tualang Honey and Honey Cocktail was both 13.2 years old. There was no significant difference (p=0.503) in the mean age for both groups.

The mean age of menopause for the Tualang Honey group and Honey Cocktail group was 48.94 years and 50.34 years respectively. There was no significant difference (p=0.946) between the two groups. The mean duration of menopause for Tualang Honey group was 8.82 years, while for the Honey Cocktail group was 8.08 years. Both groups had insignificant difference (p=0.113) in their mean duration of menopause.

Approximately half of all subjects (49%) have more than 5 children. Subjects having more than 5 children for Tualang Honey and Honey Cocktail group are 44% and 54% respectively. There was no significant difference between these two groups (p=0.424).

Majority of the participants (63%) are not working. Most of them had a mean household income of more than RM 3000 (45%) and 23% of them with a mean household income of less than RM 1000. The socioeconomic status of the participants was also reflected in their educational level, whereby majority (43%), continued their education until tertiary level and only 2% of the subjects were non-schooling. There were no significant differences for mean household incomes and education level in both study groups.

For clinical findings, there was a significant difference in diastolic blood pressure (DBP) between Tualang Honey and Honey Cocktail groups at the end of the study period after analysing with ANCOVA test and controlling the baseline values. The adjusted mean DBP for Tualang Honey and Honey Cocktail were 76.87 and 73.61 respectively with (p= 0.048). However, other parameters such as systolic blood pressure, waist circumference and BMI showed no significant differences.

For the biochemical profile between the two groups, there were significant changes in the serum total cholesterol level (p=0.003) and LDL level (p=0.001) among the postmenopausal subjects at the end of the study after analysing with ANCOVA test and controlling the baseline values, age and age of menopause. The adjusted mean total cholesterol for Tualang Honey and Honey Cocktail was 5.87mmol/L and 5.40mmol/L respectively. The adjusted mean LDL-C for Tualang Honey and Honey Cocktail was 3.60mmol/L and 3.19mmol/L respectively. There were no significant changes in the TG, HDL-C and FBS among the subjects of the two groups at the end of the study.

There were no significant differences in the hormonal profile (FSH, LH, estradiol and testosterone) between the two groups at the end of the study period after analysing with ANCOVA test and controlling the baseline values, age and age of menopause (P>0.05).

Discussion

Royal jelly, a component of Honey Cocktail has shown to contain peptides that inhibit angiotensin I-converting enzyme (ACE) activity and have antihypertensive effect in repeated oral administration for 28 days on spontaneously hypertensive rats.[7] This is consistent with our study which showed significant reduction of DBP by Honey Cocktail. However, the insignificant difference in systolic blood pressure remained unexplained.

In another study involving fifty female volunteers aged 30-65 with Type II diabetes mellitus assigned into a daily dose of 1000 mg royal jelly soft gel or placebo, royal jelly showed significant decrease in mean body weight in 3 months' time.[8] However this study cannot be compared directly with our study because the age of subjects differs and their subjects have underlying medical condition. In another study, different doses (500 mg or 1 or 2 g) of royal jelly supplementation in male swimmers, 5 days a week for 4 weeks did not decrease body weight, BMI and body fat mass.[9] This result is consistent with our findings in which Honey Cocktail does not show significant reduction in BMI and waist circumference when compared to Tualang Honey. However their results cannot be compared directly with our study because the gender, age and physical activities differ.

A Japanese study which lasted for 4 weeks showed that serum TC and LDL-C in the royal jelly group decreased significantly compared to the control group, whereas the HDL and TG level had no significant difference between both groups.[10] These results are consistent with our study. Another study of 6 months duration showed no significant difference in improvement of the serum lipids between the royal jelly group and control group.[11] The reasons are probably due to different dosages used in each study, for example: the subjects in study done by in Japan took 6 g of Royal Jelly a day for 4 weeks[10]; subjects in the second study[11] took 3000 mg a day for 6 months whereas for our study, 20g per day for 6 months. Sample size and gender distribution are other factors that would possibly affect the outcome.

It is postulated that large number of proteins in royal jelly causes lowering of plasma cholesterol and LDL.[12] Dietary protein has been shown to affect plasma cholesterol concentration.[12] Another study found that dietary soybean protein lowers plasma TG concentration and plasma ApoB level and increases VLDL uptakes by hepatocytes.[13]

A study done in United States showed that aqueous extract of royal jelly from *Apis mellifera* produced hypoglycemia when injected into larvae of *Manduca sexta*.[14] The study found out insulin-like peptides in the Royal Jelly.[14] However from our study, the insignificance of Honey Cocktail compared to Tualang Honey in controlling blood sugar may be due to postmenopausal insulin resistance. Although Honey Cocktail contains insulin-like substance, it cannot be used by the body tissues to lower blood glucose.

The results of this study showed that Tualang Honey and Honey Cocktail did not cause any significant changes in the female hormonal profiles of the participants which were almost similar to the results of another study.[1] However, the study showed that Tualang Honey caused significant increase in the serum LH among the subjects. Another study showed that royal jelly caused significant increase in the serum testosterone which was not seen in this study.[11] The study duration for both studies were the same, that was 6 months.

Besides, both products did not show any significant increase in the serum estradiol level for both groups. Royal jelly is a known product that has estrogenic effect.[15] Honey Cocktail which is a combination of Tualang Honey, royal jelly and bee bread was expected to able to increase the serum estradiol level. Several reasons could explain this phenomenon. The study duration of this study was not enough to allow royal jelly to have significant effect on the serum estradiol level. Possible underlying substance-substance interaction between the royal jelly and Tualang Honey could cause the royal jelly to lose its estrogenic effect. Therefore, a thorough molecular study can be done in the future to investigate the possible interaction.

Conclusion

Honey Cocktail compared with Tualang Honey, consumed for 6 months by postmenopausal women showed significant reduction of diastolic blood pressure, however no demonstrable effects on other physical parameters. Besides, there was a significant difference in lowering total cholesterol and LDL level. No significant changes were noted for other biochemistry and hormonal profile at 6 months of treatment.

Limitation of study

1. The study recruited mostly Malay postmenopausal women which result in sampling bias.

2. Duration of the study of 6 months might not be enough to assess the full effect of Tualang Honey and Honey Cocktail on post-menopausal women.

Recommendations

1. The study should include multi-racial subjects to reduce the subject bias.

2. A longer period of study is recommended to boost the reliability of the results.

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Conflict of Interest: The authors declare that there are no conflicts of interest.

Authors' contributions

Conception and design: Nik Hazlina Nik Hussain, Norhayati Mohd Noor, Azidah Abdul Kadir, Siti Amrah Sulaiman, Intan Idiana Hassan, Siti Zubaidah Abdul Wahab

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Table 1: Social-demographic data

Sociodemographic Data	All[a]	Groups[a]		*p*-value[b]
		Honey Tualang (n=50)	Honey Cocktail (n-50)	
Age (years)	58.08(3.67)	57.76(3.48)	58.40(3.87)	0.383
Age of menarche (years)	13.21(1.34)	13.20(1.41)	13.22(1.27)	0.503
Mean age at menopause (years)	49.64(3.56)	48.94(3.67)	50.34(3.45)	0.946
Duration of menopause (years)	8.45(3.53)	8.82(4.20)	8.08(2.85)	0.113
Number of parity* <5 ≥5	 51(51) 49(49)	 28(56) 22(44)	 23(46) 27(54)	0.424[c]
Race* -Malay -Chinese -Others	 95(95) 3(3) 2(2)	 48(96) 1(2) 1(2)	 47(94) 2(4) 1(2)	1.000[d]
Occupation* -Working -Non-working	 38(38) 62(62)	 23(46) 27(54)	 15(30) 35(70)	0.149[c]
Income* <RM1000 RM1000-RM3000 >RM3000	 23(23) 32(32) 45(45)	 10(20) 15(30) 25(50)	 13(26) 17(34) 20(40)	0.585[c]
Marital Status* -Married -Unmarried -Widowed	 86(86) 1(1) 13(13)	 44(88) 0(0) 6(12)	 42(84) 1(2) 7(14)	0.774[d]
Education Level* -Non-schooling -Primary school -Secondary school -Tertiary institution	 2(2) 13(13) 42(42) 43(43)	 0(0) 6(12) 23(46) 21(42)	 2(4) 7(14) 19(38) 22(44)	0.612[d]

[a] Values expressed in mean (standard deviation, SD) unless otherwise specified

*Values expressed in frequency (percentage)

[b] Independent t test, [c] Chi-squared test, [d] Fisher Exact test

Table 2: Comparison of cardiovascular outcome in term of clinical findings between Tualang Honey and Honey Cocktail group at 6 months of intervention

Characteristics	Mean (SD)		P value[a]	Mean (95% CI)		F statistics	P value[b]
	Tualang Honey	Honey Cocktail		Tualang Honey	Honey Cocktail		
SBP (mmHg)	131.45 (16.95)	130.58 (14.94)	0.787	132.60 (128.82, 136.38)	129.45 (125.71, 133.20)	1.340	0.250
DBP (mmHg)	75.76 (8.88)	74.70 (10.64)	0.594	76.87 (74.61, 79.12)	73.61 (71.38, 75.84)	4.012	**0.048**
BMI (kg/m^2)	27.87 (4.12)	27.35 (4.34)	0.549	27.81 (27.35, 28.27)	27.41 (26.96, 27.86)	1.523	0.220
WC (cm)	85.18 (8.32)	86.15 (8.94)	0.578	85.64 (83.80, 87.48)	85.71 (83.89, 87.52)	0.002	0.961

[a] ANOVA
[b] ANCOVA

Table 3: Comparison of cardiovascular outcome in tern of biochemical profiles between Tualang Honey and Honey Cocktail group at 6 months of intervention

Characteristics	Mean (SD)		P value[a]	Mean (95% CI)		F statistics	P value[b]
	Tualang Honey	Honey Cocktail		Tualang Honey	Honey Cocktail		
TC (mmol/L)	5.91 (0.92)	5.36 (0.80)	**0.002**	5.87 (5.65, 6.08)	5.40 (5.19, 5.61)	9.349	**0.003**
TG (mmol/L)	1.56 (0.69)	1.50 (0.67)	0.623	1.58 (1.44, 1.72)	1.48 (1.34, 1.62)	1.012	0.317
LDL-C (mmol/L)	3.64 (0.84)	3.15 (0.65)	**0.002**	3.60 (3.42, 3.77)	3.19 (3.02, 3.36)	10.721	**0.001**
HDL-C (mmol/L)	1.55 (0.30)	1.51 (0.29)	0.540	1.52 (1.47, 1.58)	1.54 (1.49, 1.60)	0.346	0.558
Fasting Blood Glucose (mmol/L)	6.05 (1.28)	6.14 (1.11)	0.699	5.93 (5.65, 6.21)	6.26 (5.98, 6.54)	2.650	0.107

[a] ANOVA
[b] ANCOVA

Table 4: Comparison of hormonal profiles between Tualang Honey and Honey Cocktail group at 6 months of intervention

Characteristics	Mean (SD)		P value[a]	Mean (95% CI)		F statistics	P value[b]
	Tualang Honey	Honey Cocktail		Tualang Honey	Honey Cocktail		
FSH (μIU/ml)	64.81 (22.95)	61.94 (22.65)	0.532	62.49 (59.99, 65.00)	64.21 (61.73, 66.69)	0.911	0.342
LH (μIU/ml)	25.68 (8.63)	25.15 (9.74)	0.778	26.30 (24.64. 27.97)	24.54 (22.89, 26.19)	2.196	0.142
Estradiol (pmol/L)	38.65 (6.83)	39.27 (11.21)	0.741	38.98 (36.33, 41.64)	38.95 (36.32, 41.58)	<0.001	0.987
Testosterone (nmol/L)	1.44 (0.68)	1.10 (1.54)	0.159	1.31 (0.98, 1.63)	1.24 (0.92, 1.56)	0.084	0.772

[a] ANOVA
[b] ANCOVA