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Original Article

Effects of honey supplementation on safety profiles among postmenopausal breast cancer patients

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الملخص

أهداف البحث: في هذه الدراسة، استهدفنا تحديد تأثير العسل على ملامح السلامة في المرضى المصابات بسرطان الثدي بعد انقطاع الطمث.

طرق البحث: تمت معالجة ٧٢ امرأة من عيادة الأورام، بمستشفى جامعة سينز ماليزيا مصابة بعد سن اليأس بسرطان الثدي في مراحله الأولى أو الثانية أو الثالثة باستخدام اناستروزول (١ مغم / يوم). وزع المرضى عشوائيا على إحدى المجموعتين (ن=٣٦/ مجموعة): المجموعة الضابطة (بلا عسل) ومجموعة العسل (٢٠ غم / يوم من العسل لمدة ١٢ أسبوعا). أخذت عينات الدم حال الصيام قبل وبعد التدخل للبحث عن الاختلافات في الملامح الدموية والكلوية والكبدية للمرضى في كلتا المجموعتين.

النتائج: كانت مستويات الألانين أميناوترنزفيريز بعد التدخل، أعلى بشكل ملحوظ في المجموعة الضابطة عنها في مجموعة العسل. في مجموعة العسل كانت أعداد خلايا الدم البيضاء وعدد الصفائح الدموية ومستويات الكرياتينين أعلى بكثير بعد أخذ العسل لمدة ١٢ أسبوعا. ومع ذلك، كانت القيم لا تزال ضمن الحدود الطبيعية.

الاستنتاجات: تقترح الدراسة الحالية أن أخذ العسل ٢٠ غ / يوم لمدة ١٢ أسبوعا آمن ومفيد للمصابات بسرطان الثدي بعد انقطاع الطمث.

الكلمات المفتاحية: سرطان الثدي؛ العسل؛ النساء بعد سن اليأس؛ ملامح السلامة

Abstract

Objectives: In this study, we aimed to determine the effect of honey supplementation on the safety profiles of postmenopausal breast cancer patients.

Methods: Seventy-two postmenopausal women with stage I, II, or III breast cancer from the Oncology Clinic, Universiti Sains Malaysia Hospital were treated with anastrozole (1 mg/day). Patients were randomly assigned to one of the two groups (n = 36/group): a control group (no honey) and a honey group (20 g/day of honey for 12 weeks). Fasting blood samples were obtained pre- and post-intervention to investigate differences in the haematological, renal, and liver profiles of patients in both the groups.

Results: Post-intervention, alanine aminotransferase levels were significantly higher in the control group than in the honey group. In the honey group, white blood cell counts, platelet counts, and creatinine levels were significantly higher following honey supplementation for 12 weeks. Nevertheless, the values were still within normal ranges.

Conclusions: The present study suggests that honey supplementation of 20 g/day for 12 weeks is safe and beneficial for postmenopausal breast cancer patients.

Keywords: Breast cancer; Honey; Postmenopausal women; Safety profiles

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Introduction

Breast cancer affects women globally and is the most common type of cancer occurring among women, including women in Malaysia. A recent cancer statistics study conducted by Siegel et al.[1] showed that breast cancer remains the leading cause of estimated new cancer cases and the third leading estimated cause of death among women. In the last 30 years, many products derived from various plant, dietary (such as fruits, vegetables, and spices), marine, and microorganism sources have been found to be beneficial as treatments for various types of human diseases.[2] Conventional therapy used in combination with natural products has been proven to boost the effectiveness of conventional treatment.[3] Honey has been used traditionally for centuries in treating numerous and varied ailments. Honey is also used by breast cancer patients in Malaysia because they believe that it can improve overall health. Honey has been found to have biological characteristics such as antioxidant,[4–6] antibacterial,[7] anticancer,[8] and antiproliferative properties.

A study by Al-Waili[9] on the effect of daily honey consumption (1.2 g/kg body weight) for 4 weeks in normal individuals (men and women) reported no significant changes in haematological and biochemical parameters. Another study investigated the renal, liver, haematological, and lipid profiles of postmenopausal women who were supplemented with 20 g/day of Tualang honey for 4 months. In that study, no significant changes in liver enzyme and haematological profiles were observed; however, total cholesterol, low density lipoprotein, and fasting blood sugar levels were significantly increased.[10] Nevertheless, data on the haematological and biochemical safety profiles of honey supplementation among breast cancer patients has not been previously reported. Therefore, the aim of the present study was to determine the effects of honey supplementation on the safety profiles among postmenopausal breast cancer women.

Materials and Methods

Patients

This was a randomized controlled open-label trial that included 72 postmenopausal breast cancer women who were recruited from the Oncology Clinic at Hospital Universiti Sains Malaysia (USM). Eighty-two patients were initially screened for the study; 12 of these patients were excluded for the following reasons: allergic reaction to honey, noncompliance with the study schedule, and inability to be contacted. The inclusion criteria were postmenopausal women diagnosed with stage I, II, or III breast cancer, who were oestrogen receptor and/or progesterone receptor positive, and who received oral anastrozole at 1 mg/day for at least 2 weeks prior to the study. The exclusion criteria were patients with a history of allergy to honey, current severe infection, and/or undergoing hormone and/or replacement therapies. Randomization into two groups (control and honey groups) was performed by computer-generated random allocation sequence by simple randomization. Women in the honey group were supplemented with 20 g/day of honey for 12 weeks.

Honey

The honey used in this study was pure, local honey known as Tualang honey, which is produced by wild honey bees (*Apis dorsata*). Tualang honey contains considerable amounts of flavonoids, phenolics, and free radical-scavenging activity compared with samples of other Malaysian honey,[11] which may contribute to its high antioxidant activity.[12–14] Tualang honey was prepared and supplied in sachet form (20 g/sachet) by the Federal Agricultural & Agro-Based Industry, Kedah, Malaysia. In a previous study,[6] 30 g of honey dissolved in a glass of water contained considerable antioxidant activity, which was measured *in vitro*. However, the dose of 20 g/day was chosen for this study because the dose is equivalent to 1 tablespoon of honey and is traditionally consumed by local residents.

Experimental design

Patients were screened according to the inclusion and exclusion criteria. They were subsequently briefed regarding the study, and written consent was obtained from all study participants. Pre-intervention (week 0 or visit 1), fasting blood samples were obtained for haematological and biochemical assessments. For the honey group, oral honey supplementation of 20 g/day for 12 weeks was administered to each participant. All patients were followed up by phone to ensure compliance and were advised to report any adverse events. No special diet regimen or change in lifestyle was observed during the study period. Post-intervention (week 12 or visit 2), compliance was assessed by counting the number of remaining honey sachets, and fasting blood samples were again obtained for haematological and biochemical assessments. The participants were informed that the study was completed, and they were advised to continue their normal routine follow-up.

Statistical analyses

All data were analysed using IBM SPSS version 22 (IBM Corp., Armonk, NY, USA). Numerical data were analysed using an independent *t*-test to compare data between the control and honey groups; a paired *t*-test was used to compare pre- and post-intervention data within the groups, and the results are presented as mean (standard error of mean, SEM). Categorical data were analysed using Pearson's chi-square or Fisher's exact tests and presented as percentage. A *p* value of less than 0.05 was considered statistically significant. Analysis of covariance was used to assess differences after adjustment for important confounding factors, such as pre-intervention values, age, and breast cancer stage.

Informed consent was obtained from all participants included in the study.

Results

Patient characteristics

The baseline demographic data for all study participants are presented in Table 1. No significant differences were found between the control and honey groups for age at

Table 1: Baseline demographic data.

Characteristics	Groups	
	Control (n = 36)	Honey (n = 36)
Age (years)[a]	59.6 (1.31)	56.5 (1.00)
Age at diagnosis (years)[a]	55.8 (1.29)	53.3 (0.96)
Level of education[b]		
Primary	4 (11.1%)	2 (5.6%)
Secondary	11 (30.6%)	4 (11.1%)
Tertiary	21 (58.3%)	30 (83.3%)
Ethnicity[b]		
Malay	30 (83.3%)	35 (97.2%)
Non-Malay	6 (16.7%)	1 (2.8%)
Monthly income (RM)[c]		
<1500	31 (86.1%)*	23 (63.9%)
≥1500	5 (13.9%)	13 (36.1%)
Breast cancer stage[c]		
I-IIa	13 (36.1%)	10 (27.8%)
IIb-IIIc	23 (63.9%)	26 (72.2%)

Data are presented as n (%), except for age and age at diagnosis, which are presented as mean (SEM).
*$p < 0.05$ compared with the honey group.
[a] Independent *t*-test.
[b] Fisher's exact test.
[c] Chi-square test.

diagnosis, level of education, ethnicity, monthly income of ≥ RM 1500, and breast cancer stage. The mean age at diagnosis was 55.8 (1.29) years in the control group and 53.3 (0.96) years in the honey group. Most patients were Malay, had a tertiary educational level, and had stage IIb to IIIc breast cancer. Monthly income of <RM 1500 was significantly higher in the control group than in the honey group.

Effects of honey on complete blood count and fasting blood glucose profile

Table 2 shows the results for complete blood count and fasting blood glucose profile in both the groups pre- and

post-intervention and their corresponding normal ranges. At pre-intervention, no significant differences were found in these parameters between the groups, except for haemoglobin level, which was significantly higher in the honey group than in the control group. At post-intervention, there were also no significant differences in these parameters between the groups. In the honey group, post-intervention total white blood cell and platelet counts were significantly higher than pre-intervention counts. However, no significant changes between pre- and post-intervention were found for these parameters in the control group.

Effects of honey on liver and renal function tests

The results of liver and renal function tests are presented in Table 3. At post-intervention, alanine aminotransferase levels were significantly higher in the control group than in the honey group. No significant differences were found for other parameters of liver and renal function pre- and post-intervention between the control and honey groups. However, in the control group, post-intervention albumin, alanine aminotransferase, and creatinine levels were significantly higher than pre-intervention levels. In the honey group, post-intervention creatinine levels were also significantly higher than pre-intervention levels.

Discussion

Most patients receiving cancer therapy are concurrently self-medicating with complementary and alternative medicine[15] in the hope of boosting the effect of conventional treatment.[3,16] However, in contrast to modern or conventional medications, many natural products are not strictly tested for safety profiles in standardized clinical trials.[17] Therefore, problems may arise when natural products are taken together with conventional medications owing to interaction between drugs and natural products.

A previous study on safety profiles among normal postmenopausal women who consumed 20 g/day of honey for 4

Table 2: Complete blood counts and fasting blood glucose profiles, pre- and post-intervention.

Parameters	Pre-intervention mean (SEM)	Post-intervention mean (SEM)	Post-intervention adjusted mean (SEM)[a]
Total WBC ($\times 10^9$/L)			
Control group	6.12 (0.31)	6.44 (0.35)	6.12 (0.22)
Honey group	5.45 (0.23)	5.72 (0.23)[@]	6.05 (0.22)
Hb (g/L)			
Control group	121.94 (1.33)	122.78 (2.04)	125.26 (1.16)
Honey group	126.28 (1.45)*	125.06 (1.67)	122.57 (1.16)
Platelet count ($\times 10^9$/L)			
Control group	235.83 (9.09)	228.56 (7.01)	221.34 (5.60)
Honey group	212.19 (8.10)	229.69 (7.77)[@]	236.91 (5.60)
Total RBC ($\times 10^{12}$/L)			
Control group	4.26 (0.78)	4.26 (0.74)	4.26 (0.04)
Honey group	4.27 (0.06)	4.26 (0.06)	4.26 (0.05)
FBG (mmol/L)			
Control group	6.38 (0.26)	6.07 (0.22)	6.11 (0.19)
Honey group	6.29 (0.41)	6.26 (0.35)	6.24 (0.19)

SEM, standard error mean; WBC, white blood cell; Hb, haemoglobin; RBC, red blood cell; FBG, fasting blood glucose.
*$p < 0.05$ compared with control group pre-intervention (independent *t*-test).
[@]$p < 0.05$ compared with its corresponding level pre-intervention (paired *t*-test).
[a] Analysis of covariance after adjustment for pre-intervention values, age, and breast cancer stage.

Table 3: Liver and renal function tests, pre- and post-intervention.

Characteristics	Pre-intervention mean (SEM)	Post-intervention mean (SEM)	Post-intervention adjusted mean (SEM)[a]
Total protein (g/L)			
Control group	76.44 (0.56)	75.53 (0.80)	75.42 (0.61)
Honey group	76.06 (0.72)	75.50 (0.68)	75.61 (0.61)
Albumin (g/L)			
Control group	40.50 (0.48)	41.58 (0.42)*	41.70 (0.32)
Honey group	40.94 (0.49)	41.67 (0.48)	41.56 (0.32)
Total bilirubin (μmol/L)			
Control group	8.89 (0.83)	8.12 (0.72)	8.25 (0.67)
Honey group	11.32 (1.74)	8.39 (0.62)	8.26 (0.67)
Alkaline phosphatase (U/L)			
Control group	88.25 (4.00)	82.92 (4.09)	80.78 (2.10)
Honey group	76.47 (3.63)	78.97 (3.54)	81.11 (2.10)
Alanine aminotransferase (U/L)			
Control group	25.33 (2.04)	29.00 (3.12)*	31.10 (1.67)[#]
Honey group	29.39 (2.48)	27.50 (2.12)	25.41 (1.67)
Potassium (mmol/L)			
Control group	4.82 (0.07)	4.81 (0.06)	4.84 (0.05)
Honey group	4.89 (0.04)	4.89 (0.05)	4.86 (0.05)
Urea (mmol/L)			
Control group	5.21 (0.73)	5.43 (0.83)	4.92 (0.18)
Honey group	4.26 (0.16)	4.31 (0.17)	4.82 (0.18)
Creatinine (μmol/L)			
Control group	87.63 (16.34)	93.75 (20.11)*	81.20 (1.90)
Honey group	66.91 (1.12)	70.07 (1.32)*	82.64 (1.90)

SEM, standard error of mean.

*$p < 0.05$ compared with its corresponding level pre-intervention (paired t-test).

#$p < 0.05$ compared with honey group post-intervention (analysis of covariance after adjustment for pre-intervention value, age, and breast cancer stage).

[a] Analysis of covariance after adjustment for pre-intervention values, age, and breast cancer stage.

months showed no significant changes in haematological, liver, and renal function test results, although there was a significant increase in fasting blood glucose levels.[10] We report our study findings on the effects of honey supplementation on complete blood count and fasting blood glucose as well as liver and renal function among postmenopausal breast cancer women. Post-intervention fasting blood glucose levels were not significantly different compared with pre-intervention levels in the honey group, which differs from the findings of a previous study.[10] This difference could be due to characteristics of the study participants and duration of honey supplementation. Nevertheless, the present findings suggest that honey supplementation of 20 g/day for 12 weeks is safe for breast cancer patients because it did not increase fasting blood glucose levels. A previous research indicated that hyperglycaemia has an effect on the biological behaviour of cancer cells.[18]

After 3 months of honey supplementation, white blood cell and platelet counts were significantly increased in participants who were supplemented honey. These findings are similar to those of previous studies showing a significant increase in white blood cell and platelet counts in rabbits with lipopolysaccharide-induced organ failure that were administered Gelam honey orally for 14 days[19] and in male Wistar albino rats that were administered honey orally for 7 days.[20] An increase in white blood cell counts in the honey group may corroborate the property of honey as an immune-stimulating agent.[21] A previous study reported the effect of honey supplementation for 7 days on the immune response of cockerel chicks against Newcastle disease. Chicks that received honey before and after vaccination exhibited better haemagglutination inhibition than chicks in the multivitamin and control groups.[22] Other findings indicate that the chemical composition of honey, which consists of a mixture of flavonoids and phenolic acids, is responsible for its action as an antimicrobial agent.[23,24] Improvement in immunity or factors that enhance immunity has also been suggested to have a relationship with the micronutrients zinc, copper, manganese, and selenium,[25,26] which are present in honey.[27,28]

Elevated liver enzyme levels are usually a sign of liver impairment. For example, the liver enzyme alanine aminotransferase levels are normally found elevated with liver damage.[9] The present study showed significantly increased liver albumin and alanine aminotransferase levels in the control group, whereas no significant changes were found in the honey group after 3 months of supplementation. Several cases of anastrozole-induced hepatotoxicity among postmenopausal breast cancer patients with elevated alanine aminotransferase levels in liver function tests following short-term administration of anastrozole for 2 months[29] and 3 weeks have been reported.[30] However, anastrozole treatment for 3 years has been reported to not result in increased alanine aminotransferase levels among breast cancer patients.[31] The present study suggests that elevated levels of this liver enzyme might be due to the progression of disease. However, no significant changes were found for liver function tests in the honey group, which suggests the hepatoprotective effect of honey in breast cancer patients.

Excessive oxidative stress contributes to the advancement and pathological findings of liver disease, and antioxidants may be beneficial in treating liver disease.[32] The ability of honey to reduce oxidative stress and improve antioxidant defence status has been suggested as a hepatoprotective property in liver toxicity.[33,34] Tualang honey, used in the present study, has been reported to contain antioxidants such as phenolic acids (gallic, benzoic, syringic, trans-cinnamic acids) and flavonoids (kaempferol, catechin), which have strong free radical-scavenging activity.[11] In addition, honey may protect against liver damage via its anti-inflammatory properties, thus helping to enhance the host's immune defence.[35−37]

The increased creatinine levels in both the control and honey groups after 3 months of our study were in contrast to findings of a previous study that showed decreased creatinine levels in healthy postmenopausal women following honey treatment for 4 months.[10] The difference in the findings might be due to differences in the study duration and the included participants. Postmenopausal breast cancer women had increased creatinine levels with acute kidney failure after administration of anastrozole for 3 months in one report.[38] Similarly, increased creatinine levels in breast cancer patients were observed after administration of anastrozole for 1 month, indicating the adverse effects of anastrozole.[39] Hence, it is plausible that the increased creatinine levels in both the control and honey groups observed in our study might be due to progressive adverse effects of anastrozole. Furthermore, the present results suggest that honey supplementation for 3 months does not have a protective effect against renal impairment in postmenopausal breast cancer patients.

Conclusions

Tualang honey supplementation for 12 weeks significantly increased white blood cell counts, platelet counts, and creatinine levels in postmenopausal breast cancer women. However, the values were still within the normal range, and monitoring of those parameters is recommended for longer intake of honey. These study findings suggest that Tualang honey supplementation of 20 g/day for 12 weeks is safe among postmenopausal breast cancer patients.

Conflict of interest

On behalf of all authors, the corresponding author states that there are no conflicts of interest to declare.

Ethical approval

The protocol was approved by the Human Ethics Committee, USM (USMKK/PPP/JEPeM [260.3 (21)]), which complies with the Declaration of Helsinki.

Authors' contributions

ZZ, ZFZA, SHG, WZWAH, and MM conceived and designed the study, provided research materials, collected and organized the data, analysed and interpreted the data,

wrote the initial draft and finalized the article, critically reviewed the final draft, and are responsible for the content and originality of the manuscript. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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