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Original Article

Tualang honey adjunct with anastrozole improve parenchyma enhancement of breast tissue in breast cancer patients: A randomized controlled trial

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ARTICLE INFO

Article history:

Received 18 January 2018

Revised 16 July 2018

Accepted 16 July 2018

Available online 23 July 2018

Keywords:

Anastrozole
Breast cancer
Honey
MRI

ABSTRACT

Background: To investigate whether the combination of anastrozole and Tualang honey (T honey) influences background parenchymal enhancement (BPE) in breast magnetic resonance imaging (MRI) of postmenopausal women with breast cancer.

Methods: A total of 30 patients were recruited and randomly divided into control (anastrozole 1 mg daily) and intervention (anastrozole 1 mg+T honey 20 g daily). The BPE of the contralateral breast before and six months following treatment was compared using the sign test.

Results: There was a decrease in BPE in 10% of the women ($p=0.317$) who received only anastrozole, which resulted in a change of BPE category from moderate to mild. However, the combination of anastrozole and T honey evoked a decrease in BPE in 42% of the patients ($p=0.034$).

Conclusions: The combination of T honey and anastrozole maybe more efficacious than anastrozole alone in decreasing breast BPE in breast cancer patients. These findings support the medicinal value of T honey as an adjuvant treatment to anastrozole.

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1. Introduction

Globally, it is estimated that 1.6 million new cases of breast cancer are diagnosed every year, with 560,000 fatalities.¹ Breast cancer is the leading cause of death among Malaysian

women (National Cancer Registry of Malaysia 2005–2007). Approximately 5000 Malaysian women aged between 30 and 60 years are diagnosed with breast cancer every year, and approximately 50% of these women are relatively young and below 50 years of age.²

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<https://doi.org/10.1016/j.imr.2018.07.002>

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Unlike advanced disease, breast cancer is potentially curable if detected early.³ Treatment of early stage breast cancer following surgery may involve adjuvant therapy consisting of systemic endocrine therapy and/or chemotherapy to prevent or delay tumor recurrence. The ultimate goal of adjuvant endocrine therapy is to treat early breast cancer successfully with minimal adverse effects.

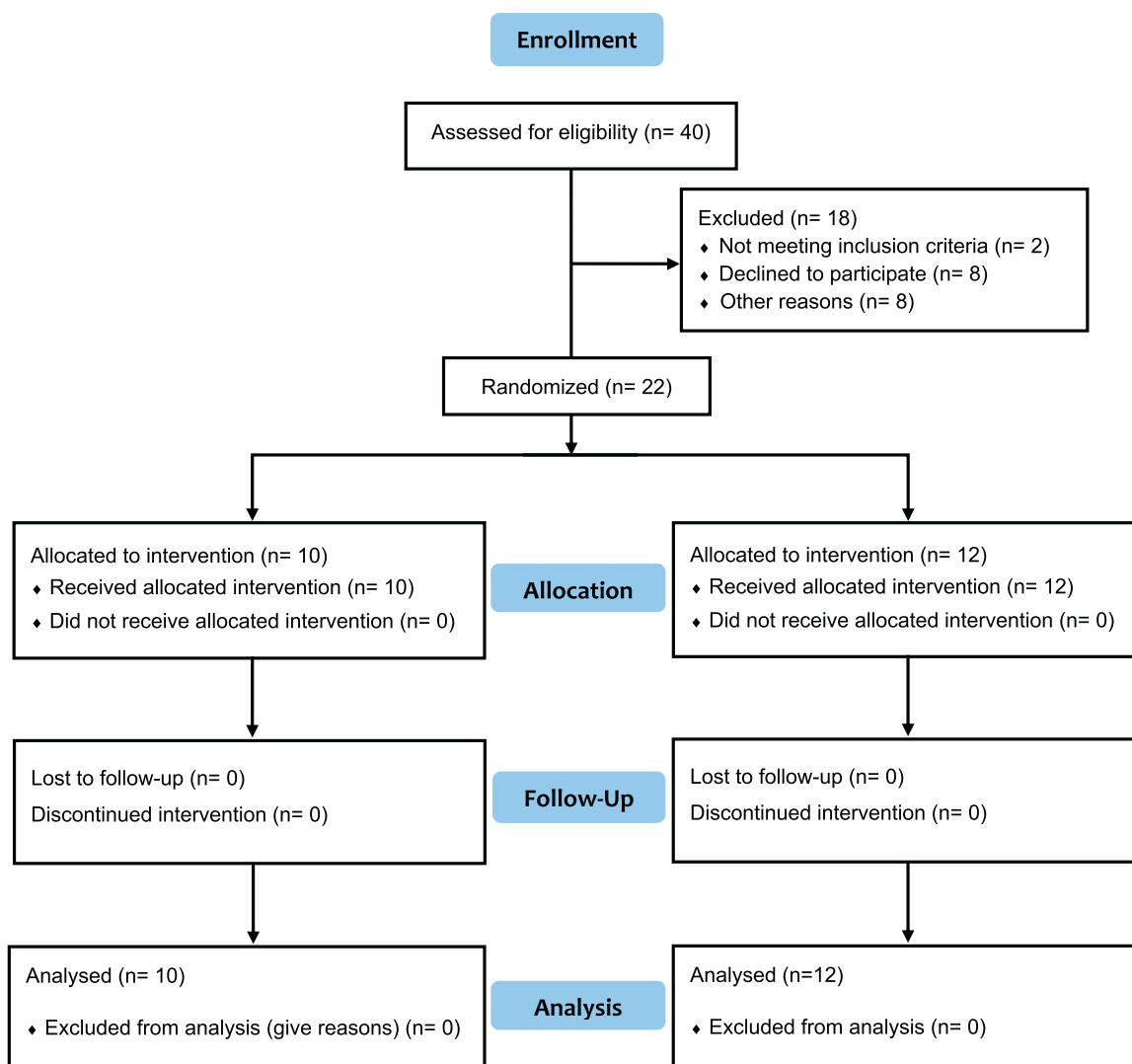
The introduction of aromatase inhibitors (AIs) as an adjuvant treatment for postmenopausal women with estrogen/progesterone receptor-positive breast cancer has significantly changed the management of this disease. Anastrozole is the only third-generation AI with available data as an adjuvant treatment for early breast cancer in postmenopausal women.

Magnetic resonance imaging (MRI) of the breast is often used following breast cancer surgery to monitor disease recurrence.⁴ Recent studies have suggested that background parenchymal enhancement (BPE) of normal breast

parenchyma is useful in breast cancer risk prediction⁵ and in treatment response as well as outcome assessments.⁵ Similar to how breast cancer is associated with breast density on mammography,⁶ it is also suggested to be correlated with BPE on MRI.⁷

Although anastrozole is extensively used for breast cancer treatment, several adverse effects have been reported with its use, including the risk of osteoporosis, falls and fractures.⁸⁻¹¹ Many authors have suggested that honey, which is produced via complex enzymatic processes from nectar and saccharine exudates from various floral sources, has high antioxidant activity¹²⁻¹⁴ with good potential to prevent the development of cancer.¹⁵ However, to the best of our knowledge, its use as an adjuvant to modern therapy has not been investigated.

The aim of this study was to investigate whether Tualang honey (T honey) is a useful adjuvant to anastrozole in postmenopausal women.



2. Methods

2.1. Patients and study design

Ethical approval was obtained from the Human Research Ethics Committee of Universiti Sains Malaysia (USM), USM/KK/PPP/JEPeM/[260.3(21)], which complies with the Declaration of Helsinki. This randomized controlled trial was conducted for 1.5 years (from October 2014 until April 2016) in the Oncology Clinic, Hospital USM, Kubang Kerian, Kelantan, Malaysia. Postmenopausal women with stage I-III unilateral estrogen receptor (ER)- and/or progesterone receptor (PgR)-positive breast cancer who received anastrozole treatment for one year or less were included in the study. Patients with a history of allergy to TH, who took over-the-counter supplements such as honey or herbs, who received hormone replacement therapy or who presented with liver or renal impairments were excluded.

Patients who consented to participate in the study were asked to provide written informed consent. Patients were randomized based on a block size of four using a computer-generated program. The patients were randomly assigned into either the control or intervention group. Patients in the control group received anastrozole (1 mg) daily, while patients in the intervention group received anastrozole (1 mg) and T honey (20 g) daily. The T honey supplements were individually packaged in aluminum foil containing a fixed amount of honey in order to standardize the administered amount. The dose of T honey in this study was based on a previous study conducted by Nik Hazlina et al.¹⁶ In addition, supplement packages were counted at the end of the study to ensure that the patients complied with the treatment regimen. The BPE of the non-affected breast in the control and intervention groups was compared before (at baseline) and after treatment (after six months). Patients were allowed to withdraw from the study at any time.

2.2. Sample size calculation

Sample size calculation was done using a dichotomous variable by utilising G*Power Software Calculation version 3.1.3 (Germany), based on a previous study by King et al.¹⁷

Input

$\alpha = 0.05$

Power = 0.9

Effect size = 0.3 (% of decrease BPE in anastrozole (control group))

Constant proportion = 0.5 (% of expected result decreased BPE in T honey (intervention group)).

The highest calculated sample size was 28. However, after considering a 20% drop-out, the final sample size = 31.

2.3. MRI protocol

Breast MRI with intravenous gadopentetate dimeglumine (Magnevist®) was performed using a Philips Achieva 3.0T X-Series MRI at the Department of Radiology, USM, on the first (0 months) and second visits (six months). All MRI results were

reviewed on a high resolution PACS monitor (Centricity, GE Healthcare).

2.4. MRI interpretation

All images were independently reviewed by a breast imaging radiologist who was blinded to the study group. A combination of pre- and post-contrast T1 fat-saturated images and MIP images was used to determine the BPE. For each MRI examination, BPE was prospectively assigned into one of four categories in accordance with the anticipated BIRAD MRI lexicon classification system: “minimal” (<25% of glandular tissue demonstrating enhancement), “mild” (25–50% enhancement), “moderate” (50–75% enhancement), or “marked” (>75% enhancement). The pre- and post-treatment breast MRI results were compared side-by-side to evaluate the changes in BPE, which increased the sensitivity since images could be compared simultaneously.⁵

2.5. Statistical analysis

Statistical analysis was performed using SPSS (version 18, SPSS Inc., Chicago, IL, USA). The data are presented as the mean \pm S.D. However, if the data were not normally distributed, the median and inter-quartile range were calculated. Data normality was verified using the Shapiro–Wilks test. A side-by-side comparison of BPE before and six months following treatment was utilized to determine the changes in BPE. The sign test was used to identify significant differences in the number of women with BPE changes. Categorical data were compared using chi-square and Fisher’s exact tests. A p value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 40 postmenopausal women with unilateral breast cancer (stages I to III) were assessed for eligibility for this study. Ten subjects have to be excluded [claustrophobia ($n = 7$), having inconsistent history of bilateral breast cancer ($n = 1$), hip implant ($n = 1$) and refused MRI ($n = 1$)]. From the 30 patients recruited, eight dropped out due to refusal of MRI follow up ($n = 4$), non-compliant with the honey regimen ($n = 3$) while a single patient unfortunately passed away due to the disease ($n = 1$). As a result, a total of 22 patients aged 50 to 76 years were enrolled in the study. Among these patients, 10 were randomly allocated to the control group (received anastrozole only), while 12 were placed in the intervention group (received honey supplement and anastrozole). All patients received treatment and were given follow-up for six months. Patient characteristics ($n = 22$) are shown in Table 1. The majority of the patients were Malays (90.9%), which reflects the demography of the local population; the remaining patients were Chinese. The mean patient age was 59 ± 5.9 years at the time the baseline MRI was taken, and the mean menopausal age was 50 ± 3.0 years; all patients experienced natural menopause.

Table 1 – Demographics and clinical characteristics of the study population

Characteristics	Total (N = 22)	Anastrozole (n = 10)	Anastrozole + T honey (n = 12)	p value
Age at menopause (years)	49.8 ± 3.0	49.4 ± 2.6	50.1 ± 3.4	0.448
Age at baseline MRI (years)	58.6 ± 5.9	61.0 ± 7.2	56.6 ± 3.8	0.190
Race				
Malay	20 (90.9)	9 (90.0)	11 (91.7)	0.000
Chinese	2 (9.1)	1 (10.0)	1 (8.3)	0.500
BMI (kg/m ²)	27.3 ± 3.8	27.4 ± 2.7	27.2 ± 4.7	0.947
Breast cancer stage				
I	3 (13.6)	2 (20.0)	1 (8.3)	0.423
II	14 (63.6)	6 (60.0)	8 (66.7)	0.001
III	5 (22.7)	2 (20.0)	3 (25.0)	0.070
Surgery				
Lumpectomy	9 (40.9)	5 (50)	4 (33.3)	0.035
Mastectomy	13 (59.1)	5 (50)	8 (66.7)	0.001
Baseline BPE				
Minimal	3	2 (20.0%)	1 (8.3%)	0.423
Mild	2	1 (10.0%)	1 (8.3%)	0.500
Moderate	11	4 (40.0%)	7 (58.3%)	0.002
Marked	6	3 (30.0%)	3 (25.0%)	0.500

Note: Data are expressed as mean ± S.D. or the number of women with percentages in parentheses. T honey, Tulang honey; BPE, background parenchymal enhancement; BMI, body mass index.

Table 2 – Changes in BPE observed with anastrozole treatment and anastrozole + T Honey

Baseline BPE	Anastrozole + T honey		Anastrozole	
	Number of patients	Decrease in BPE	Number of patients	Decrease in BPE
Minimal	1 (8.3%)	0 (0.0%)	2 (20.0%)	0 (0.0%)
Mild	1 (8.3%)	0 (0.0%)	1 (10.0%)	0 (0.0%)
Moderate	7 (58.3%)	2 (40.0%)	4 (40.0%)	1 (100%)
Marked	3 (25.0%)	3 (60.0%)	3 (30.0%)	0 (0.0%)
Statistical analysis		* $p = 0.034$		** $p = 0.317$

* Data are the number of patients, with percentages in parentheses. p is 0.034 for the number of patients with a decrease in BPE during treatment with anastrozole + T honey (sign test).

** Data are the number of women, with percentages in parentheses. p is 0.317 for the number of patient with a decrease in BPE during treatment with anastrozole (sign test).

Significant at $p < 0.05$. T honey, Tulang honey; BPE, background parenchymal enhancement.

3.2. Background parenchyma enhancement changes

Based on the MRI findings, the patient's BPE was assigned one of several different categories. In the control group, the majority (90.0%) of the women had a stable BPE, but 10% showed a decrease in BPE (Table 2). Approximately 25% of the patients with a moderate BPE at baseline showed a reduction in BPE to mild.

In the intervention group, 41.7% had a decrease in BPE, while 58.3% did not show any change ($p = 0.034$) following treatment. T honey improved BPE by a single category in four women and by two categories in one woman. Among the women who had a moderate BPE prior to treatment, 29% experienced a decrease in BPE to mild following treatment.

4. Discussion

To the best of our knowledge, this is the first clinical trial to provide evidence that adjuvant T honey increases the efficacy

of anastrozole compared to anastrozole alone, as confirmed by the decreased breast BPE in postmenopausal women with ER-positive breast cancer. Therefore, T honey may have the potential to reduce the risk of cancer recurrence. Only 27.3% of postmenopausal breast cancer women had a marked BPE at the baseline MRI; BPE tends to decrease with menopause. These data are similar to those reported by King et al.,¹⁷ who evaluated 28 women who underwent breast MRI before and after menopause and found that a significant number of postmenopausal women showed a demonstrable decrease in BPE and in overall fibroglandular tissue. These authors strongly suggested that menopause tends to decrease BPE findings to a greater degree than age alone. Their study also successfully tested the hypothesis that after menopause, BPE decreases concomitantly with the expected decrease in estrogenic activity.

Our study demonstrated that the combination of anastrozole and T honey resulted in a significant decrease in BPE. There was a higher proportion of patients with a decreased BPE in the intervention group than in the control group, which

received only anastrozole (42% vs. 10%). The observation can be explained by the mechanism by which honey antagonizes estrogen signaling. Estrogen binds to estrogen receptors, which then dimerize and translocate into the nucleus. These estrogen/estrogen receptor complexes then bind to specific DNA sequences called estrogen-response elements, resulting in transcription and translation of estrogen target genes that mediate estrogenic effects in target tissues.¹⁸ The estrogen signaling cascade can be modulated at any stage.¹⁸

Honeys from various floral sources have been reported to mediate estrogenic effects by modulating estrogen receptor activity. Some honey samples from other regions, which are rich in phenolic compounds, have been found to modulate estrogenic activity by exerting agonistic effects when taken at high concentrations (20–100 µg/mL) and antagonistic effects at low concentrations (0.2–5.0 µg/mL).¹⁹ More importantly, the bi-functional activities of honey extracts indicate that they may play an important role in estrogen-dependent diseases, i.e., preventing symptoms associated with estrogen deficiency during menopause or conferring some level of protection against breast cancer by antagonizing estrogen signaling.

Honey has antimutagenic²⁰ and antitumor effects.^{21,22} An in vitro study by Fauzi et al.²³ showed that T honey exerts significant anticancer activity against human breast and cervical cancer cell lines by inducing apoptosis and disrupting the mitochondrial membrane potential.

One limitation of this study was the relatively small sample. Thus, a larger, multicenter randomized controlled trial should be conducted to confirm the benefits of including T honey in treatment regimens for postmenopausal patients with ER-positive breast cancer. Another limitation was the use of qualitative, rather than quantitative, measurements to assess BPE; no validated, reliable quantitative methods are available for measuring BPE. To minimize this limitation, images obtained before and after six months of treatment were compared side-by-side by an investigator who was blinded to the treatment status. The results of this study therefore reflected visible changes in BPE.

In conclusion, our study may show that the combination of T honey and anastrozole maybe more potent than anastrozole alone in decreasing the breast BPE in postmenopausal women with ER-positive breast cancer. Future studies are needed to evaluate the potential benefits of use of T honey as an adjuvant to anastrozole in reducing the risk of breast cancer recurrence in postmenopausal women.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

The authors would like to acknowledge the Research University (Team) Grant (101/PPSP/853005) for funding this research project.

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