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Bahrain Association of Plastic Surgery  
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جمعية البحرين لمكافحة السرطان  
BAHRAIN CANCER SOCIETY

## The Third Combined Gulf Cancer Conference

Quality Care: New Horizons  
Kingdom of Bahrain  
7-9 December 2019

### GFFCC-ESTRO COOPERATION

A grid of eight circular portraits of individuals, likely speakers or organizers, arranged in two rows of four. The top row features three men and one woman, while the bottom row features two women and two men.

Kingdom of Morocco, February 2019

## The Management of Breast and Colorectal Cancer

Kuwait Conference: Recent Updates  
16-18 November 2019

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## Original Article

# Effects of Tualang Honey on Cancer Related Fatigue: A Multicenter Open–label Trial of H&N Cancer Patients

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## Abstract

**Introduction:** Cancer related fatigue (CRF) is a problem experienced by head and neck cancer patients, especially those who undergo chemoradiation therapy. CRF may persist for years post chemoradiation therapy and significantly impair their quality of life (QOL). Tualang honey is rich in amino acids, vitamins, minerals and enzymes. It is proven to have anti-inflammatory, antioxidant and anti-tumour properties. As CRF is related to inflammatory mediators, the effects of Tualang Honey may improve CRF. The aim of this study is to determine if Tualang honey has a role in improving CRF and quality of life among head and neck cancer patients post chemoradiation.

**Methodology:** In this open labelled randomized clinical trial, 40 participants aged between 18 and 65 with head and neck cancer who completed chemotherapy and/or radiotherapy in Hospital USM, Kelantan Malaysia or Hospital Taiping were recruited and randomized into two groups: Tualang honey (experimental) group or Vitamin C (control) group. They were prescribed with either daily

oral Tualang honey 20mg or vitamin C tablet 100 mg for 8 weeks. Level of fatigue and quality of life were measured using FACIT–Fatigue and FACT H&N questionnaires at baseline, 4 weeks and 8 weeks. The white cell count and C–reactive protein level were also measured at baseline, 4 weeks and 8 weeks.

**Results:** After four and eight weeks of treatment with Tualang honey or Vitamin C, the fatigue level for experimental group was better than in the control group, and the differences were statistically significant ( $p < 0.05$ ). Statistically significant improvements were seen on quality of life ( $p < 0.05$ ) for the experimental group at week 8, however, no significant improvements were seen in white cell count and C–reactive protein level between control and experimental group.

**Conclusion:** Our research provided support for the use of Tualang honey to improve CRF and QOL in head and neck cancer patients post chemotherapy or radiotherapy.

**Keywords:** cancer related fatigue; Tualang honey; quality of life; QOL, C– reactive protein

## Introduction

Majority of head and neck cancers are squamous cell carcinoma. They include cancer of the oral cavity, salivary gland, oropharynx, hypopharynx, sinonasal, nasopharynx and larynx. It is the seventh most common malignancy worldwide. <sup>(1)</sup> Generally, the treatment of head and neck cancer is multimodality which includes surgery, radiotherapy and chemotherapy, depending on the staging of the cancer.

Cancer related fatigue (CRF) is usually experienced by head and neck cancer patients who undergo chemotherapy or radiotherapy. CRF is defined as a persistent subjective sense of physical, emotional, and/or cognitive tiredness related to cancer or its treatment that is not due to recent activity and significantly interferes with

normal functioning and causing distress <sup>(2)</sup>. Most cancer patients will struggle with some amount of fatigue during the course of treatment. About one third will experience persistent CRF for few years after completing treatment. <sup>(3)</sup> The prevalence of CRF is about 59–96% in patients receiving chemotherapy, 65–100% in patients having radiotherapy, and 30% in long term survivors. <sup>(3,4)</sup> Patients who have completed chemotherapy or radiotherapy

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should be observed closely because fatigue may remain beyond the time of active treatment.

The contributing factors to CRF include cancer therapy such as cytotoxic agents and radiotherapy, progressive tumour growth, unrelieved pain, anaemia, poor nutrition, electrolytes imbalance, menopause, hypothyroidism and dehydration.<sup>(2)</sup> Other factors include pre-existing co-morbidities, medication side effects, depressed mood and sleep disturbance.<sup>(2)</sup> Low level of haemoglobin (less than 8 g/dL) is known to cause CRF symptoms such as tiredness, lethargy, palpitations, dizziness, sleep disturbances and concentration difficulties.<sup>(5)</sup>

Inflammation is also associated with fatigue in head and neck cancer patients.<sup>(6)</sup> Fatigued cancer survivors exhibit higher level of C–reactive protein (CRP), an acute phase protein that is the most commonly used as a biomarker of inflammation compared to non-fatigued survivors.<sup>(6,7)</sup> A study done by Canhua et al showed that inflammatory markers such as IL–6 and CRP was associated with fatigue both before and after intensity modulated radiation therapy in head and neck cancer patients.<sup>(7)</sup> Abnormal production of pro-inflammatory cytokines seen in cancer patients may cause alterations in dopaminergic transmission, which causes CRF.<sup>(6)</sup>

There is no definitive treatment for CRF. Management of CRF involves specific treatment for potentially reversible causes (i.e. treating anaemia or metabolic abnormalities, as well as treatment of pain, depression, or anxiety) and symptomatic measures when no reversible cause can be identified.<sup>(5)</sup>

Non-specific symptom-based treatment measures include education, counselling, and pharmacologic such as psychostimulants, as well as nonpharmacologic such as exercise and acupuncture.<sup>(5)</sup>

Many adjuvant medicines have been experimented for treatment for CRF, such as multivitamins, ginseng, coenzyme–Q, royal jelly and others. Some are ineffective whereas some treatment shows benefit in reducing CRF. The evidence to date shows that vitamin supplementation is ineffective at improving CRF.<sup>(8)</sup> Some supplement such as L–carnitine, royal jelly and American ginseng has proven to improve CRF. However, there was no published data or study looking into the effect on Tualang honey in head and neck CRF and quality of life (QOL) to date.

Tualang honey is a multi-floral honey found in Malaysian jungle, and recently attracting attention. Tualang honey is produced by the rock bee (*Apis dorsata*), which builds hives in the branches of Tualang tree (*Kompassiaexcelsa*). It is primarily found in tropical rainforests.<sup>(9)</sup> The composition of Tualang honey include fructose (38%), glucose (31%) and other sugars. It consists of more than 180 substances,

including vitamins, minerals and enzymes. It is dark brown in color with pH of 3.44 to 4.00.

Many researches have investigated the role of Tualang honey as an adjunct in cancer treatment. It has been used in palliative care as adjunct to treat radiation induced mucositis and chemoradiotherapy induced skin reactions.<sup>(10)</sup> Tualang honey has been demonstrated to have anti-proliferative effects in bladder cancer<sup>(11)</sup>, colon cancer<sup>(12)</sup> and squamous cell carcinoma of oral cavity.<sup>(13)</sup> The antiproliferative effect of Tualang Honey is contributed by its high concentration of phenolic and flavonoid antioxidants, which may suppress oxidative stress<sup>(9)</sup>. It causes depolarization of the mitochondrial membrane in cancer cells, leading to apoptosis<sup>(9)</sup>.

Tualang honey also has anti-inflammatory properties. The flavonoid content inhibits cyclooxygenase–2, an enzyme that forms prostanoids, including thromboxane and prostaglandins which are inflammatory mediators.<sup>(9)</sup> Thus, inhibition of cyclooxygenase–2 will reduce inflammation.

Tualang honey, in its natural form is rich in amino acids, vitamins, minerals and enzymes; therefore, it may reduce CRF in head and neck cancer patients. It is also proven to have anti-inflammatory, antioxidant and anti-tumour properties. As CRF is related to inflammatory mediators, the effects of Tualang Honey may improve CRF.

We were therefore interested in investigating the effects of Tualang honey on cancer related fatigue due to its antioxidant, anti-inflammatory and anti-proliferative effects, and also because it is readily available in Malaysia. If Tualang honey is proven to improve cancer related fatigue, it can be added as adjunct in managing cancer related fatigue.

## Materials and Methods

This was a multicenter, open labelled with equal randomization (1:1), placebo–controlled, parallel–group clinical trial carried out at Hospital Universiti Sains Malaysia and Hospital Taiping, Malaysia for a period of 12 months from June 2017 to June 2018. This research was reviewed and approved by University Science Malaysia Human Ethical Committee (Approval number: USM/JEPeM/17010068) and Medical Research and Ethics Committee of Ministry of Health, Malaysia (Approval number: NMRR–16–2772–33760). The study was done in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines.

## Study Subjects

Eligible patients were those ages 18 to 65 years, with histologically–proven head and neck malignancy,

who completed radiotherapy and/or chemotherapy from 1 month up to 2 years after the last dose of chemo/radiotherapy. Additional inclusion criteria were haemoglobin level more than 8g/dL and normal thyroid function test with fatigue visual analogue scale more than 4. Patients who were hypersensitive to honey or other honey products, regular consumers of honey, diabetic patients or patients with serious medical condition, liver or renal impairment, patients with major depressive disorder, or patients taking medication with potential side effects on fatigue, were excluded from the study.

### Study design and randomization

54 patients were assessed for eligibility for the study. 9 patients were ineligible and 5 patients declined to participate. 42 participants who were eligible and agreed for the study were recruited and randomized into two groups by computer generated randomization, either Tualang honey (experimental) group or Vitamin C (control) group. Prior to their participation in the trial, the written informed consent form was signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

By using randomization software, a list of numbers from 1 to 42 were randomized into two groups (control and experimental group). The list was printed and kept for future reference.

42 identical envelopes measuring 175mm x 122mm, brown in color, each containing a small white paper with a number printed on it was prepared. The number ranged from 1 to 42 without repetition. The envelopes were sealed and number it contained was concealed. An envelope was chosen by the patient once he/she agrees to join the study. The number in the envelope was revealed and the patient was subjected into experimental or control group based on that number corresponding to the randomized list. The number and envelope were then discarded and never used again. Subject allocations were not changed after they were randomized.

### Study Intervention

Subjects were prescribed with either daily oral Tualang honey 20mg if they were in experimental group or tablet vitamin C 100 mg if they were in control group for 8 weeks. Level of fatigue and QOL were measured using FACIT–Fatigue and FACT H&N questionnaires respectively at baseline, 4 weeks and 8 weeks. The white cell count and C–reactive protein level were measured at baseline, 4 weeks and 8 weeks.

CRF was quantified with Functional Assessment of Chronic Illness Therapy: fatigue subscale (FACIT–Fatigue)

questionnaire, version 4. It is a validated 13 item stand-alone scales questionnaires<sup>(14)</sup>. It has the advantage of having a validated clinically significant score change and is recommended in research setting.<sup>(15)</sup>

Quality of life (QOL) was measured using the Functional Assessment of Cancer Therapy Head and Neck (FACT–H&N) questionnaire version 4. The 38–item FACT–H&N consists 5 domains, which are 9–item head and neck cancer specific quality of life subscale (H&N), Physical<sup>(7)</sup>, Social<sup>(7)</sup>, Emotional<sup>(6)</sup>, and Functional<sup>(7)</sup>.

Each response was rated by the patient from 0 to 4 on a Likert scale, with 0 described as “not at all” and 4 as “very much.” Scores were calculated separately for each domain, and a summary score was calculated for FACT–H&N. The maximum score of 144 reflects the best possible QOL. The maximal score for each domain was as follows: Physical 28, Social 28, Emotional 24, Functional 28, HN 36. FACT–H&N had demonstrated reliability and validity, and was chosen following a structured review of the literature because it was commonly used, short, and provides a summary score for ease of analysis.<sup>(15)</sup>

Both FACIT–Fatigue and FACT–FACT–H&N questionnaire had been translated and linguistically validated into local languages, which were Malay, Chinese and Tamil<sup>(14)</sup>. The appropriate language of questionnaire was used for each subject. Licensing agreement was obtained from FACIT.org to use the questionnaire for this study.

The blood investigations that were done during first visit include Full Blood Count (FBC), renal function test, liver function test, thyroid function test, and C Reactive Protein level.

On subsequent visits, full blood count and C–Reactive Protein level were taken. About 10ml of the subject's blood was taken from antecubital fossa and sent either to Laboratory in Taiping Hospital or Universiti Sains Malaysia Hospital for analysis. The blood was discarded after analysis.

### Intervention product

Tualang honey used in this study was provided by Department of Pharmacology, Hospital Universiti Sains Malaysia. The honey was provided to Hospital University Sains Malaysia by Federal Agricultural Marketing Authority (FAMA) Kelantan. The honey was natural and did not contain added preservatives or contaminant, as evidenced by the honey analysis. It was sterilised by gamma irradiation before packed in sachet form. Each sachet contained 20 grams of Tualang Honey in liquid form. This product was registered for use as a natural health product in Malaysia.

The honey sample was sent to UNIPEQ Shd Bhd for analysis. It had pH of 3.53 and moisture of 26.87g/100g.

The result of analysis showed that it is safe for consumption. The honey content analysis result was reviewed by National Committee for Research and Development in Herbal Medicine (NRDHM) and declared fit to be used in this study.

The participants in Tualang Honey group were given honey in a form of sachet. Each sachet contained 20 grams of Tualang honey, equivalent to two tablespoons, to be taken orally once daily in the morning after meal. The dosage was determined based on traditional local human consumption of honey and previous clinical trials done using Tualang Honey.<sup>(16)</sup> The dose of 20 grams of Tualang honey is derived from previous study done by Ismail et al, where the use of 20 grams of honey yielded statistically significant result without any adverse effects.<sup>(16)</sup>

Tablet vitamin C 100mg (MAL19930617XZ) used in this study was provided by Pharmacy Department of Hospital Taiping and Universiti Sains Malaysia. It was consumed orally once daily every morning after meal.

To ensure compliance, patients were given clear instruction and information sheet on when and how to take the honey or vitamin C. 30 sachets of honey or 30 tablets of vitamin C were given during first and second visit. Patients diary sheet was provided to ensure compliance. Patients were instructed to tick appropriate box on the sheet as soon as they consume honey or vitamin C.

## Outcome Measurement

The primary objective of this study was to assess the effect of Tualang honey on head and neck cancer related fatigue post radiotherapy and/or chemotherapy. The secondary objectives were to assess effects of Tualang honey on quality of life, white cell count and C–reactive protein level of head and neck cancer patients post radiotherapy and/or chemotherapy.

Data were entered and analyzed using SPSS version 22. Descriptive statistics were used to summarize the socio–demographic characteristics of subjects. Numerical data were presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data were presented as frequency (percentage).

Repeated measure ANOVA was applied in order to fulfill the objectives of the study. There were three RM ANOVA model fitted; RM ANOVA within group analysis (Time effect), RM ANOVA between group analysis (Treatment effect) and RM ANOVA between group based on time (Time–treatment interaction).

## Results

### Demographic Characteristics

54 patients were assessed for eligibility for the study. 7 patients were ineligible and 5 patients declined to participate. 42 participants who were eligible and agreed for the study were recruited and randomized into two groups by computer generated randomization; Tualang honey (experimental group) or Vitamin C (control group) with 21 participants in each arm. 2 participants from vitamin C group defaulted follow up and was excluded from the study. Therefore, 21 participants from experimental group and 19 participants from control group were included in data analysis (Figure 1).

Mean (SD) of age (years) of vitamin C group was 54.37 (11.73) while Tualang honey was 54.57 (10.96). There were 13 male patients in vitamin C group (68.4%) and 17 male patients in Tualang honey group (80.9%). The most common head and neck cancer among participants was nasopharyngeal cancer (62.5%), followed by laryngeal cancer (12.5%) and sinonasal cancer (7.5%) (Table 1).

### Fatigue

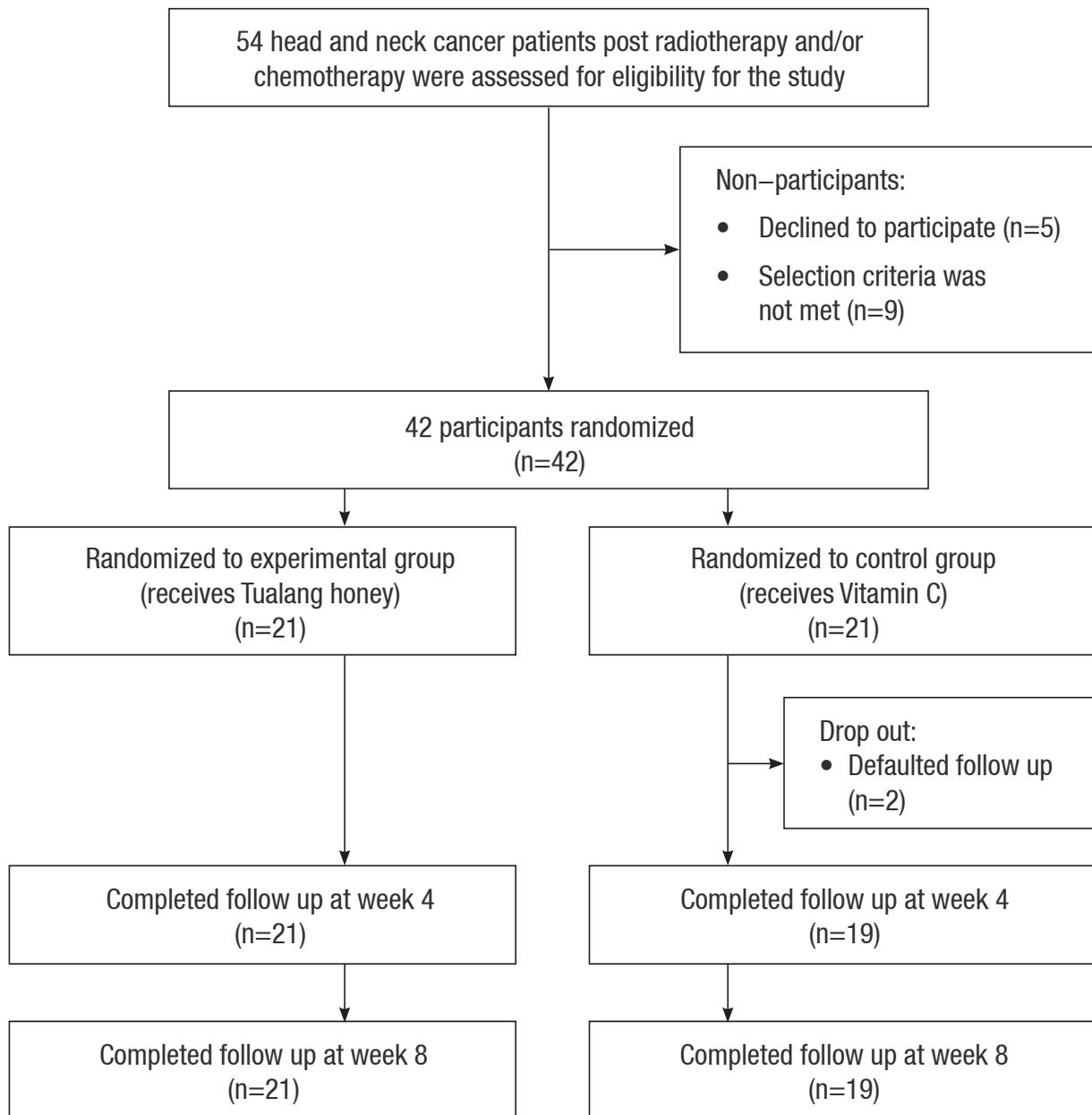
Repeated measure ANOVA was used to measure cancer related fatigue (CRF) score between each group using FACIT–F questionnaire at baseline, week 4 and week 8. The experimental group had statistically significant improvement in the FACIT–F score at week 4 and week 8 ( $p$ -value  $< 0.05$ ).

Table 2 shows the results of repeated measure ANOVA between two treatment group based on time analysis (time–treatment interaction) for fatigue score. It was found that the mean fatigue score between experimental group and control group were significantly different at week 4 and week 8, with better fatigue score for experimental group.  $p$ -value for week 4 was 0.029, while in week 8  $p < 0.001$ . At baseline, mean fatigue score between experimental and control group was not significantly different with  $p = 0.951$ .

### Quality of Life

The experimental group also had statistically significant improvement in quality of life (QOL) at 8 weeks, measured with FACIT H&N questionnaire using repeated measure ANOVA ( $p$ -value  $< 0.05$ ).

Table 3 shows the results of comparison of QOL among two different treatment group based on time (time–treatment interaction). It was found that only one comparison was significantly different in week 8 with  $p = 0.002$ . At week 8, mean QOL score were significantly better in experimental group compared to control group. In



**Figure 1: Study design flow diagram (CONSORT diagram).**

baseline and week 4, there were no significant difference of mean quality of life between Vitamin C and Tualang honey group with  $p = 0.361$  and  $p = 0.165$ , respectively.

### CRP and white blood cell count level

There were no significant difference in CRP level and white blood cell count in both experimental and control group ( $p$ -value  $> 0.05$ ).

Table 4 shows the result of Mann–Whitney test on the comparison of C–reaction protein level among two different treatment groups based on time. From the results, it was found that there was no significant difference of CRP level between Vitamin C and Tualang honey group at all three–assessment time. The  $p$ -value

were 0.691, 0.752 and 0.560 at baseline, week 4 and week 8, respectively.

Table 5 below shows the results of repeated measure ANOVA for white blood cell count between two treatment group based on time analysis (time–treatment interaction). However, this analysis found that the mean white cell count was not significantly different at all assessment time (baseline, week 4 and week 8).  $P$ -value for baseline, week 4 and week 8 were 0.679, 0.724 and 0.525, respectively.

### Safety and Toxicity

No serious adverse effect occurred throughout the study.

	Intervention group (n=21)	Control group (n=19)
Mean age (SD)	54.57 (10.96)	54.37 (11.73)
Gender, n (%)		
Female	4 (19.1)	6 (31.6)
Male	17 (80.9)	13 (68.4)
Site of head and neck cancer, n (%)		
Nasopharynx	12 (57.1)	13 (68.4)
Larynx	3 (14.4)	4 (21.1)
Sinonasal	3 (14.4)	2 (10.5)
Major salivary gland	1 (4.8)	1 (5.3)
Oral cavity	1 (4.8)	1 (5.3)
Oropharynx	1 (4.8)	1 (5.3)
Hypopharynx	0 (0)	1 (5.3)

**Table 1: Demographic characteristics of participants.**

Time	Treatment group	Mean <sup>a</sup> (SD)	p-value
Baseline	Vitamin C	24.53 (6.48)	0.951
	Tualang honey	24.67 (7.52)	
Week 4	Vitamin C	26.00 (5.64)	0.029
	Tualang honey	31.10 (7.92)	
Week 8	Vitamin C	28.21 (5.44)	<0.001
	Tualang honey	39.52 (6.91)	

**Table 2: Comparison of fatigue score among two different treatment group based on time (Time-treatment interaction).**

<sup>a</sup> A higher score reflects a positive effect.

## Discussion

The results of our study showed that Tualang Honey has favorable effect on cancer related fatigue (CRF) without significant adverse effects. This is attributed to anti-oxidant and anti-inflammatory properties of Tualang honey. The analysis of Tualang honey has showed that it has high content of phenolic and flavonoid antioxidants, which can suppress oxidative stress and reduce inflammation.<sup>(9)</sup> Tualang honey had higher content of phenolics and flavonoids compared to other local honey found in Malaysia and Manuka honey.<sup>(9)</sup> The health benefit of Manuka honey, which is a monofloral honey from New Zealand/Australia is much researched and internationally recognized. However, the benefit of Tualang honey is only recently gaining attention.

Flavonoid content in Tualang honey inhibits cyclooxygenase-2, an enzyme that form prostanoids,

Time	Treatment group	Median <sup>a</sup> (IQR)	Mean difference (95% CI)	p-value
Baseline	Vitamin C	88.95 (13.43)	3.61 (-4.30, 11.52)	0.361
	Tualang honey	85.33 (10.60)		
Week 4	Vitamin C	94.21 (12.94)	-5.31 (-12.91, 2.28)	0.165
	Tualang honey	99.52 (10.14)		
Week 8	Vitamin C	98.90 (11.30)	-11.82 (-18.87, -4.77)	0.002
	Tualang honey	110.71 (10.18)		

**Table 3: Comparison of quality of life score among two different treatment group based on time (Time-treatment interaction).**

<sup>a</sup> A higher score reflects a positive effect.

Time	Treatment group	Median <sup>a</sup> (IQR)	z-statistic	p-value <sup>b</sup>
Baseline	Vitamin C	10.00 (7.00)	-0.40	0.691
	Tualang honey	11.00 (19.00)		
Week 4	Vitamin C	0.00 (9.00)	-0.32	0.752
	Tualang honey	5.00 (10.00)		
Week 8	Vitamin C	5.00 (9.00)	-0.58	0.560
	Tualang honey	0.00 (8.00)		

**Table 4: Comparison of C-reaction protein level among two different treatment group based on time.**

<sup>a</sup> A lower score reflects a positive effect.

<sup>b</sup> Mann-Whitney test was applied; significance level set at 0.05

Time	Treatment group	Mean <sup>a</sup> (SD)	p-value
Baseline	Vitamin C	8.57 (3.08)	0.679
	Tualang honey	9.03 (3.59)	
Week 4	Vitamin C	8.44 (3.31)	0.724
	Tualang honey	8.11 (2.50)	
Week 8	Vitamin C	8.49 (3.11)	0.525
	Tualang honey	7.88 (2.75)	

**Table 5: Comparison of white blood count among two different treatment group based on time (Time-treatment interaction).**

<sup>a</sup> A lower score reflects a positive effect.

including thromboxane and prostaglandins which are inflammatory mediators. Inflammation is associated with CRF, as evidenced by elevations in circulating markers of inflammation such as interleukin as well as increase in tumour necrosis factor (TNF) receptors in patients post chemoradiation with fatigue.<sup>(6)</sup> Therefore, CRF can be

improved by reducing the inflammation process post chemoradiation.

The result of our study is consistent with another research done using processed honey and royal jelly for CRF by Bahram et al. in 2013<sup>(17)</sup>. In the study, 52 cancer patients were divided into 2 groups. The study group was given royal jelly and processed honey whereas the control group received pure honey. CRF score were assessed at the beginning of the study, after 2 weeks, and then at the end of 4 weeks of treatment. The study showed that the use of processed honey and royal jelly able to significantly improve CRF<sup>(17)</sup>.

Apart from honey, many herbal medicines were studied to determine their effect on CRF. Some of the studies had shown promising results. A study was done by Giulia et al in 2004 in Italy to determine efficacy of L-carnitine administration on fatigue and quality of life of cancer patients undergoing anticancer therapy. The study showed that fatigue decreased significantly and quality of life improved significantly after L-carnitine consumption.<sup>(18)</sup> Another study done by Jeong et al in Republic of Korea showed that consumption of Bojungikki-tang, a widely used herbal prescription in traditional medicine in China, Japan, and Korea, have beneficial effects on CRF in cancer patients.<sup>(19)</sup> In these studies, the improvement in CRF post radiotherapy was attributed to antioxidant and anti-inflammatory properties of the study materials, i.e. processed honey and royal jelly, L-carnitine and Bojungikki-tang.<sup>(17,18,19)</sup>

Quality of life (QOL) of head and neck cancer patients improved at 4 and 8 weeks after given Tualang honey. However, Tualang honey significantly improves QOL compared to placebo after 8 weeks. The gain in QOL can be attributed to improvement in CRF by Tualang honey. As CRF and related symptoms such as pain and sleep disorder are strongly associated with decline in QOL, improvement in CRF will improve QOL of head and neck cancer patients.<sup>(21,22)</sup> Another factor that causes improvement in QOL is reduction of pain by Tualang honey. A study done by Aziz et. al. in 2014 found that Tualang honey has analgesic properties. This is attributed to gallic acid, which is one of the components of Tualang honey. Gallic acid was reported to inhibit synthesis of nitric oxide, cyclooxygenase-2, histamine release and production of cytokines in macrophages. The mechanism of antinociceptive effect by Tualang honey could be due to suppression of nitric oxide and prostaglandin release into inflamed tissues or inhibition of nociceptive pain transmission by the nervous system.<sup>(23)</sup>

Similar study on QOL was done in 2010 by Jeong et al in Republic of Korea with Bojungikki-tang, which is a traditional medicine consumed in China, Japan, and

Korea<sup>(19)</sup>. Similar to Tualang honey, Bojungikki-tang has anti-inflammatory and anti-oxidant properties as well. In the study, a total of 40 cancer patients with fatigue were randomized into an experimental or control group. The experimental group showed statistically significant improvements in fatigue level and QOL after treated with Bojungikki-tang compared to control group.<sup>(19)</sup>

Our study found out that there is no significant difference in C-reactive protein (CRP) level and white blood cell count (WBC) between Tualang honey group and control group in 8 weeks duration. Even though level of inflammatory markers such as CRP is associated with CRF<sup>(11)</sup>, there are many factors that affect the level of CRP and WBC, such as intercurrent infection, trauma or any inflammation.<sup>(24)</sup> These are confounding factors that can cause changes in level of WBC or CRP. Other inflammatory markers that are more specific to CRF such as interleukin-6 should be measured in future to minimize these confounding factors.<sup>(7)</sup> However, our findings were consistent with a study done by Giulia et al in 2004 to determine efficacy of L-carnitine administration on fatigue and quality of life of advanced cancer patients undergoing anticancer therapy. In this study, fatigue and quality of life were evaluated in relation to oxidative stress and laboratory parameters, mainly levels of reactive oxygen species, glutathione peroxidases, and proinflammatory cytokines, such as CRP. The study showed that fatigue decreased significantly and quality of life improved significantly after L-carnitine consumption. Levels of reactive oxygen species also decreased and glutathione peroxidase increased but not significantly. CRP level did not change significantly after L-carnitine consumption.<sup>(18)</sup> These findings were similar to the result of our study.

There are few limitations in the study. Even though the subjects are randomized and vitamin C is given as placebo, they are not blinded. Therefore, subjects receiving Tualang honey are aware of it and this may lead to bias in the study. Other limitations are short duration of intervention and low number of patients. The study was conducted only for eight weeks with 40 subjects. A longer duration and larger participant in the study will determine the effects of Tualang honey in long term. Since there are no significant adverse effects to Tualang honey and the results of the study look encouraging, larger double blinded randomized trial are warranted in future to confirm the result of this study.

## Conclusion

We conclude that Tualang honey is tolerable and safe and improves cancer related fatigue in head and neck cancer patients post chemoradiation. Double blinded placebo controlled randomized trials are warranted in future.

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