TUALANG HONEY IN HEAD AND NECK CANCER PATIENTS: EFFECTS ON CANCER RELATED FATIGUE AND QUALITY OF LIFE

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LIST OF ABBREVIATIONS

ANCOVA: Analysis of covariance

CONSORT: Consolidated Standards of Reporting Trials

CRF: Cancer Related Fatigue

CRP: C- Reactive Protein

FACIT H&N: Functional Assessment of Chronic Illness Therapy, Head and Neck Subset

FACIT: Functional Assessment of Chronic Illness Therapy

FACIT-F: Functional Assessment of Chronic Illness Therapy, Fatigue Subset

FAMA: Federal Agricultural Marketing Authority

HUSM: Hospital Universiti Sains Malaysia

NRDHM: National Committee for Research and Development in Herbal Medicine

QOL: Quality of Life

RCT: Randomized controlled trial

SPSS: Statistical Package for Social Science

UKM: Universiti Kebangsaan Malaysia

VAS: Visual Analogue Scale

WBC: White Blood Cell

WHO: World Health Organisation

ABSTRAK

MADU TUALANG UNTUK PESAKIT KANSER KEPALA DAN LEHER: KESAN KEPADA KELETIHAN BERKAITAN KANSER DAN KUALITI HIDUP

Pengenalan: Keletihan berkaitan kanser adalah masalah yang biasa dialami oleh pesakit kanser kepala dan leher, terutamanya yang menerima rawatan kemo-radioterapi. Keletihan berkaitan kanser mungkin berkekalan untuk beberapa tahun selepas rawatan radioterapi and ini memudaratkan kualiti hidup pesakit tersebut. Madu Tualang amat kaya dengan zat-zat seperti asid amino, vitamin, mineral dan enzim. Oleh itu, madu ini boleh mengurangkan kesan keletihan di kalangan pesakit kanser kepala dan leher. Madu Tualang juga mengandungi unsur anti-radang, anti-oksida dan anti-barah. Keletihan berkaitan kanser adalah berkaitan dengan radang, oleh itu, madu Tulang mungkin boleh mengurangkan keletihan. Tujuan kajian ini adalah untuk menentukan jika madu Tualang boleh mengurangkan kelethan berkaitan kanser and meningkatkan kualiti hidup pesakit kanser kepala dan leher yang telah menjalani rawatan radioterapi dan/atau kemoterapi, dan kesan madu Tualang pada tahap protein C-reaktif dan sel darah putih.

Kaedah: Dalam percubaan klinikal secara rawak ini, 40 peserta berusia antara 18 dan 65 dengan diagnose kanser kepala dan leher yang menyelesaikan kemoterapi atau radioterapi di Hospital USM, Kelantan Malaysia atau Hospital Taiping telah direkrut dan rawak kepada dua kumpulan; kumpulan madu Tualang atau kumpulan Vitamin C. Mereka diberimadu Tualang 20mg atau tablet vitamin C 100mg selama 8 minggu. Tahap keletihan dan kualiti hidup diukur dengan menggunakan soal selidik FACIT-Fatigue dan FACT H & N pada permulaan kajian, minggu keempat dan minggu kelapan. Kiraan sel putih dan tahap protein C-reaktif diukur pada permulaan kajian, minggu keempat dan minggu kelapan.

Keputusan: Selepas rawatan dengan madu Tualang atau Vitamin C, tahap keletihan untuk kumpulan kajian adalah lebih baik dari pada kumpulan kawalan, dan perbezaannya adalah signifikan secara statistik ($p < 0.05$). Peningkatan yang ketara dilihat pada kualiti hidup ($p < 0.05$) bagi kumpulan kajian pada minggu ke-8, walau bagaimanapun, tiada penambah baikan yang ketara dilihat dalam kiraan sel putih dan tahap protein C-reaktif antara kumpulan kawalan dan kajian.

Kesimpulan: Kajian kami menunjukkan penggunaan madu Tualang dapat mengurangkan keletihan dan meningkatkan kualiti hidup pesakit kanser. Keputusan positif kajian ini mengalakan kajian lebih mendalam dalam bidang ini.

ABSTRACT

TUALANG HONEY IN HEAD AND NECK CANCER PATIENTS-EFFECTS ON CANCER RELATED FATIGUE AND QUALITY OF LIFE

Introduction: Cancer related fatigue (CRF) is a problem experienced by head and neck cancer patients, especially those who underwent 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 radiotherapy and/or chemotherapy in Hospital USM, Kelantan Malaysia or Hospital Taiping were recruited and randomized into two groups; experimental group (Tualang honey) or control group (Vitamin C). They were prescribed with either daily oral Tualang honey 20mg or tablet vitamin C 100 mg for 8 weeks.Level of fatigue and quality of life were measured usingFACIT-Fatigue and FACT H&N questionnaires at baseline, 4 weeks and 8 weeks. The white cell countand C-reactive protein level were 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 study 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 study group at week 8, however, no significant

improvements were seen in white cell count and C-reactive protein level between control and study group.

Conclusion: Our study provided support for the use of Tualang honey to improve CRF and QOL. The positive results of this study warrant further studies in this field.

Chapter 1

INTRODUCTION

1.1 INTRODUCTION

Majority of head and neck cancer are squamous cell carcinoma. They include cancer of the oral cavity, salivary gland, oropharynx, hypopharynx, sinonasal, nasopharynx and larynx. It is the seventh commonest malignancy worldwide (1). Generally, the treatment of head and neck cancer is multimodality which includes surgery, radiotherapy and chemotherapy, depending on the staging of the cancer. Palliative therapy and/or systemic therapy are appropriate for patients with metastatic disease. Patients with localized (stage I and II) head and neck carcinomas are generally managed with either surgery or radiation therapy (RT) alone. Patients with more advanced (stage III and IV) disease are typically managed with a multi-modality approach, including both RT and chemotherapy. Regular post treatment follow up is an essential part of the care of patients after potentially curative treatment of head and neck cancer.

Cancer related fatigue (CRF) is usually experienced by head and neck cancer patients who underwent 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 (2). Most of cancer patients will struggle with some amount of fatigue during the course of treatment. About one third will experiencepersistent CRF for few years after completing treatment (3). The prevalence of CRF is about 59–96% in patients receiving chemotherapy, 65–100% in patients havingradiotherapy, and 30% in long term survivors (3, 4). Patients who have completed chemotherapy or radiotherapy should be observedclosely 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, hypothyroidism, menopause, and dehydration (2). Other factors include pre-existing co morbidities, medication side effects, depressed mood and sleep disturbance (2). Low level of haemoglobin (less than 8 g/dL) is known to cause cancer related fatigue symptoms such as tiredness, exercise intolerance, palpitations, dizziness, sleep disturbances and concentration difficulties (3).

Inflammation is also associated with fatigue in head and neck cancer patients (8). Fatigued cancer survivors exhibit higher level of C reactive protein (CRP), an acute phase protein that is the most commonly used biomarker of inflammation compared to non-fatigued survivors (9,10). A study done by Canhuaet. 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 (11). Abnormal production of pro-inflammatory cytokines seen in cancer patients may cause alterations in dopaminergic transmission, which causes CRF (8).

There are many cancer related fatigue assessment tools that have been validated and used to quantify cancer related fatigue (12). The commonly used and best validated tools include the fatigue subscales of the Functional Assessment of Cancer Therapy instrument (FACT-F) (13), Brief Fatigue Inventory (BFI) (14), Multidimensional Fatigue Symptom Inventory Short Form (MFSISF) (15), and the European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC QLQ C30), fatigue subscale (16).

There is no definitive treatment for CRF. Management of CRF involves specific treatment for potentially reversible causes (i.e. treating anaemia or metabolic or

endocrine abnormalities, as well as managing pain, insomnia, depression, or anxiety) and symptomatic measures when no obvious aetiology or reversible cause can be identified.

Nonspecific symptom-based treatment measures include education, counselling, and pharmacologic (e.g., psychostimulants and other wakefulness agents) as well as nonpharmacologic such as exercise, yoga and acupuncture.

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 till date showed that vitamin supplementation was ineffective at improving CRF (8). Some supplement such as L- carnitine, royal jelly and American ginseng has been 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 till date.

Honey has been used to cure many ailments since ancient times. Honey is often named according to the location where it is produced, the floral source of the honey or the trees where the hives are found (17). Tualang honey is a multiflora jungle honey found in Malaysia, and recently attracting attention. Some Malaysian researchers are investigating its effects in clinical trials (18). Tualang honey is produced by the rock bee (*Apisdorsata*). It builds hives high up in the branches of Tualang tree (*Kompassiaexcelsa*) which is found mainly in tropical rainforest (19). Tualang honey is mainly composed of fructose (38%), glucose (31%) and other sugars. It contains more than 180 substances, including amino acids, vitamins, minerals and enzymes. It has dark brown appearance 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, radiotherapy and chemotherapy induced skin reactions and wounds (20). It has been shown to have anti-proliferative effects in bladder cancer (21), colon cancer (22) and squamous cell carcinoma of oral cavity (23). The antitumor and anti-proliferative effect of Tualang Honey is contributed by its high content of phenolic and flavonoid antioxidants, which can suppress oxidative stress (19). It causes apoptosis of cancer cells via depolarisation of the mitochondrial membrane (19).

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 (19). Thus, inhibition of cyclooxygenase-2 will reduce inflammation.

The antimicrobial effects of honey are attributed to the osmotic effect of the substance's sugars, its pH, its peroxidase activity and non-peroxidase substances such as phenolic acids, flavonoids, and lysozymes (19). Tualang Honey also has both bactericidal and bacteriostatic properties against a range of gram positive and negative bacteria (24, 25). At concentrations of 6.25–25%, it inhibits the growth of several bacterial strains, such as Streptococcus pyogenes, Salmonella typhi, Staphylococcus aureus, coagulase-negative Streptococcus spp., and Escherichia coli (19). It is more effective than Manuka Honey against some gram-negative bacteria in burn wounds management, due to high content of phenolics and flavonoids (19).

It also has wound healing properties (25, 26). Honey promotes wound healing by stimulating the growth of epithelial cells and fibroblasts and minimising the oedema, inflammation, and exudation that usually occur in all types of wounds. In studies of

Tualang Honey in full-thickness burn wounds treated with TH and conventional hydro fibre silver-treated wounds, the wounds treated with the TH show a reduction in wound size of 32.26%. The healing efficacy is also superior in TH-treated burn wounds compared with hydro fibre silver and aquacel plain dressings (19).

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 andanti-tumour properties. As CRF is related to inflammatory mediators, the effects of Tualang Honey may improve CRF.

Therefore, we are interested in investigating effect of Tualang honey on cancer related fatigue due to its antioxidant, anti-inflammatory and anti-proliferative effects, and also because it is readily available here.If Tualang honey is proven to improve cancer related fatigue, it can be added as adjunct in managing cancer related fatigue.

Chapter 2

OBJECTIVES OF THE STUDY

2.1: GENERAL OBJECTIVE

1- To evaluate the effectiveness of Tualang Honey on head and neck cancer related fatigue and quality of life.

2.2: SPECIFIC OBJECTIVES

1- To investigate the effects of Tualang Honey on the severity of cancer related fatigue among head and neck cancer patients

2. To investigate the effects of Tualang Honey on the quality of life among head and neck cancer patients.

3. To investigate the effects of Tualang Honey on the blood parameters (white cell count and C Reactive protein) in between experimental group and control group.

Chapter 3

MANUSCRIPT

3.1. TITLE: TUALANG HONEY IN HEAD AND NECK CANCER PATIENTS- EFFECTS ON CANCER RELATED FATIGUE AND QUALITY OF LIFE

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3.2 ABSTRACT

Introduction: Cancer related fatigue (CRF) is a problemexperienced by head and neck cancer patients, especially those who underwent chemoradiation therapy.CRF may persist for years post chemoradiationtherapy and significantly impair their quality of life (QOL).Tualang honeyis 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.

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Conclusion: Our study provided support for the use of Tualang honey to improve CRF and QOL. The positive results of this study warrant further studies in this field.

Keywords: cancer related fatigue; Tualang honey; quality of life;

3.3 INTRODUCTION

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whereas some treatment shows benefit in reducing CRF. The evidence till date shows that vitamin supplementation is ineffective at improving CRF [8]. 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) till date.

Tualang honey is a multi-floral honey found in Malaysian jungle, and recently attracting attention. Tualang honey is produced by the rock bee (*Apisdorsata*), which builds hives in the branches of Tualang tree (*Kompassiaexcelsa*). It is primarilyfound in tropical rainforests [9].The composition of Tualang honey includefructose (38%), glucose (31%) and other sugars. It consists of more than 180 substances, including vitamins, minerals and enzymes. It is dark brown in colour with pH of 3.44 to 4.00.

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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, antioxidantand anti-tumour properties. As CRF is related to inflammatory mediators, the effects of Tualang Honey may improve CRF.

Therefore, we are interested in investigating effect of Tualang honey on cancer related fatigue due to its antioxidant, anti-inflammatory and anti-proliferative effects, and also because it is readily available here.If Tualang honey is proven to improve cancer related fatigue, it can be added as adjunct in managing cancer related fatigue.

3.4 MATERIALS AND METHODS

This was amulticentre, open labelled with equal randomisation (1:1), placebo-controlled, parallel-group clinical trial carried out at HospitalUniversitiSains Malaysia and Hospital Taiping from a period of 12 months from June 2017 to June 2018.This research was reviewed and approved by University Science Malaysia Human Ethical Committee (Approvalnumber: USM/JEPeM/17010068) and Medical Research and Ethics Committee of Ministry of Health, Malaysia (Approvalnumber: 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 histological proven head and neck malignancy, who completed radiotherapy and/or chemotherapy from one month up to two 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 four. 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 randomisation

54 patients were assessed for eligibility for the study. Nine patients were ineligible and five patients declined to participate. 42 participants who were eligible and agreed for the study were recruited and randomized into two groups by computer generated randomisation,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 randomised 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 colour, 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 randomised list. The number and envelope were then discarded and never used again. Subject allocationswere not changed after they were randomised.

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 countand 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 [14]. It has the advantage of having a validated clinically significant score change and is recommended in research setting [15].

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 of 5 domains, which are 9-item head and neck cancer specific quality of life subscale (H&N), Physical (7), Social (7), Emotional (6), and Functional (7).

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[15].

Both FACIT-Fatigue and FACT- FACT-H&N questionnaire had been translated and linguistically validated into local languages, which were Malay, Chinese and Tamil [14]. 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 ShdBhd 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 [16]. 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 [16].

Tablet vitamin C 100mg (MAL19930617XZ) used in this study was provided by Pharmacy Department of Hospital Taiping and UniversitiSains 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. Patient's 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 analysed using SPSS version *22*. Descriptive statistics were used to summarise 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).

3.5 RESULTS

Demographic Characteristics

54 patients were assessed for eligibility for the study. Seven patients were ineligible and five patients declined to participate. 42 participants who were eligible and agreed for the study were recruited and randomized into two groups by computer generated randomisation; Tualang honey (experimental group) or Vitamin C (control group) with 21 participants in each arm. Two 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).

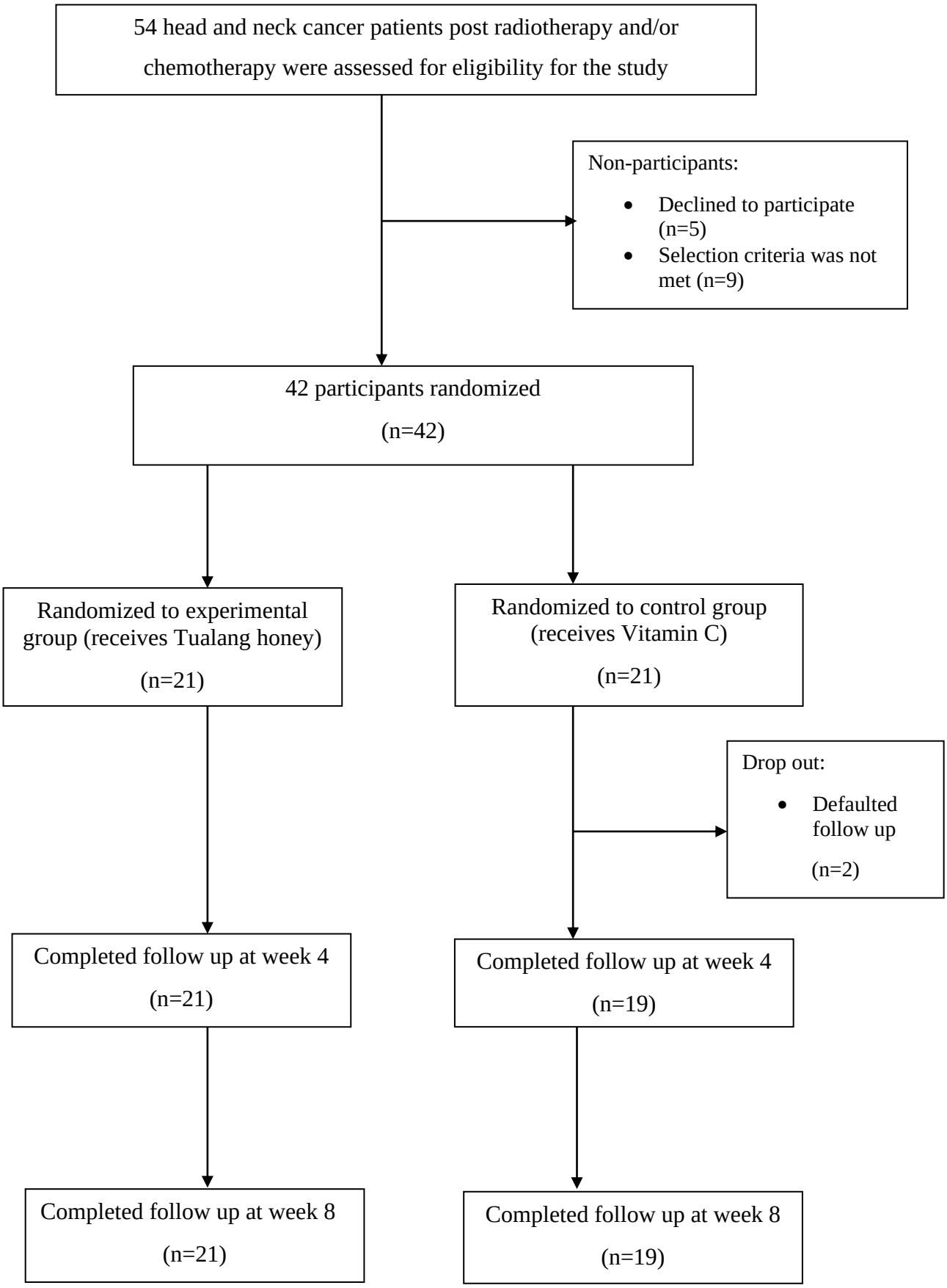

Figure 3.1: Study design flow diagram (CONSORT diagram).

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 3.1).

Table 3.1: Demographic characteristics of participants.

	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)

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 statisically significant improvement in the FACIT-F score at week 4 and week 8 (p-value < 0.05).

Table 3.2shows 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 meanfatigue 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.

Table 3.2:Comparison of fatigue score among two different treatment group based on time (Time-treatment interaction).

Time	**Treatment group**	**Mean[a] (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)	

[a]A higher score reflects a positive effect.

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 3.3shows 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 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.

Table 3.3:Comparison of quality of life score among two different treatment group based on time (Time-treatment interaction).

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

[a]A higher score reflects a positive effect.