

**UNIVERSITI SAINS MALAYSIA
GERAN PENYELIDIKAN UNIVERSITI PENYELIDIKAN
LAPORAN AKHIR**

**UNDERSTANDING THE MECHANISM OF
ANTICARCINOGENIC EFFECTS OF TUALANG HONEY
(TH) ON DMBA (1, 2-DIMETHYLBENZ ANTHRACENE -
INDUCED BREAST CANCER IN RATS**

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LAPORAN AKHIR GERAN UNIVERSITI PENYELIDIKAN (RUI)

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TAJUK: UNDERSTANDING THE MECHANISM OF ANTI-
CARCINOGENIC EFFECTS OF TUALANG HONEY (TH) ON
DMBA (17,12-DIMETHYLBENZ ANTHRACENE- INDUCED
BREAST CANCER IN RATS

(NO AKAUN:1001/PPSP/813051)

**UNIVERSITY RESEARCH GRANT
FINAL REPORT**
*Geran Penyelidikan Universiti
Laporan Akhir*

Please email a copy of this report to rcmo@usm.my

Emel salinan laporan ini ke rcmo@usm.my

PARTICULARS OF RESEARCH / MAKLUMAT PENYELIDIKAN:	
Title of Research: <i>Tajuk Penyelidikan:</i>	Understanding the mechanism of anti-carcinogenic effects of Tualang honey (TH) on DMBA (7,12-Dimethylbenz[α]anthracene)- induced breast cancer in rats
Account Number: <i>Nombor Akaun:</i>	1001/PPSP/813051
PERSONAL PARTICULARS OF RESEARCHER / MAKLUMAT PENYELIDIK:	
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School/Institute/Centre/Unit: <i>Pusat Pengajian /Institut/Pusat/Unit:</i>	SCHOOL OF MEDICAL SCIENCE (PPSP)
Duration of this research: <i>Tempoh masa penyelidikan ini:</i>	<p>*Duration : 3 years and 7 months <i>Tempoh :</i></p> <p>From : 12/1/2011 To : 30/09/2015 <i>Dari:</i> <i>Ke :</i></p>

UNIVERSITI SAINS MALAYSIA

04 APR 2016

Pusat Penyelidikan dan Inovasi

E. ABSTRACT OF RESEARCH

(An abstract of between 100 and 200 words must be prepared in **Bahasa Malaysia and in English**. This abstract will be included in the Annual Report of the Research and Innovation Section at a later date as a means of presenting the project findings of the researcher/s to the University and the community at large)

Abstrak Penyelidikan

(Perlu disediakan di antara 100 - 200 perkataan di dalam **Bahasa Malaysia dan juga Bahasa Inggeris**.)

Abstrak ini akan dimuatkan dalam Laporan Tahunan Bahagian Penyelidikan & Inovasi sebagai satu cara untuk menyampaikan dapatan projek tuan/puan kepada pihak Universiti & masyarakat luar).

BAHASA MALAYSIA

Memahami mekanisme kesan anti-karsinogen Tualang madu (TH) di DMBA (7,12-Dimethylbenz (□) anthracene) - disebabkan kanser payudara pada tikus

Abstrak

Pengenalan: multifloral Tualang madu (TH) dan monofloral Manuka madu (MH) telah dilaporkan mempunyai antimikrob, anti-radang, antioksidan dan kesan anti-kanser. Tidak seperti MH, TH tidak dikaji secara meluas.

Objektif: Kajian ini dijalankan untuk menilai mekanisme kesan pencegahan dan terapeutik Tualang madu (TH), Manuka madu (MH) dan gula madu analog (HSA) mengenai kanser payudara ujikaji tikus teraruh menggunakan karsinogen 1-metil-1-nitrosourea (mnu).

Metodologi: Seramai 130 wanita tikus Sprague Dawley-digunakan. Enam puluh tikus betina secara rawak dibahagikan kepada 6 kumpulan dengan 10 haiwan setiap kumpulan dalam setiap kajian. Kumpulan '0' (kawalan negatif; tikus biasa); Kumpulan 1 (kawalan positif; induksi tumor tetapi tiada rawatan). Kumpulan 2, 3 dan 4 telah diberi makan secara lisan dengan 0.2, 1.0 dan 2.0 g / kg berat badan TH. Kumpulan 5 diterima 1.0 g / kg MH, dan Kumpulan 6 yang diterima 1.0 g / kg HSA. Bagi "kanser pencegahan" kajian, madu telah diberikan seminggu sebelum mnu-induksi dan untuk "kanser terapeutik" Kajian; rawatan diberikan selepas pembangunan kanser payudara. Rawatan ini diteruskan sehingga hari ke-120 apabila tikus dikorbankan untuk sampel koleksi.

Hasil: Hasil kajian menunjukkan bahawa TH dan MH dirawat tikus dari "kanser pencegahan" kumpulan yang mempunyai insiden tumor yang lebih rendah, dan tempoh kependaman yang lebih lama berbanding dengan kumpulan kawalan yang tidak dirawat. Tumor maju dalam semua kumpulan dirawat langkah-langkah pencegahan dan terapeutik adalah lebih kecil dalam bilangan, saiz dan berat berbanding dengan kawalan yang tidak dirawat. Majoriti tumor dalam kumpulan yang dirawat adalah dari grad yang lebih baik (grad I dan II) berbanding dengan kumpulan kawalan yang tidak dirawat (grad III). Parameter hematologi menunjukkan pelbagai kekuatan TH, MH dan HSA mempunyai kesan potentiating pada hemoglobin, sel-sel darah merah, jumlah sel dibungkus, bermakna jumlah korpuskel, limfosit dan eosinofil dan kesan menurunkan kepada jumlah sel-sel darah putih, sel merah pagedaran lebar, polimorf, monosit dan platelet berbanding dengan kawalan yang tidak dirawat. Rawatan ini tidak menunjukkan sebarang kesan hyperglycemic dan tiada kehilangan berat badan. Pentadbiran sistemik TH, MH dan HSA mengenakan kesan anti-kanser melalui up-regulation ungkapan protein pro-apoptotic seperti caspase 9, Apfa-1 (protease apoptotic mengaktifkan faktor 1), p53, IFN- γ (interferon gamma) dan IFNGR1 (interferon gamma reseptor 1), dan seiring turun-peraturan ungkapan protein anti-apoptotic seperti Bcl-xL (B-sel limfoma-tambahan besar), TNF- α (tumor nekrosis faktor alpha), COX -2 (cyclooxygenase-2), E2 (estradiol) dan ESR1 (estrogen reseptor 1) pada serologi dan atau kanser payudara tisu peringkat.

Perbincangan: Kajian kami menunjukkan bahawa rawatan dengan TH dan MH muncul untuk memberi kesan kanser pencegahan dan atau kanser terapeutik, adalah melalui penggredan tumor modulasi, berat badan, parameter hematologi sambutan peraturan imun, dan modulasi pro dan anti-apoptotic protein daripada laluan apoptotic mitokondria di serum dan kanser payudara tisu tahap. HSA juga bertindak serupa dengan madu.

Kesimpulan: Tualang madu Manuka madu dan gula madu analog boleh digunakan sebagai agen pencegahan kanser dan kanser terapi profilaktik. Mekanisme adalah melalui modulasi penggredan tumor, parameter hematologi, dan modulasi protein pro dan anti-apoptotic di serum dan tisu kanser peringkat.

Bahasa Inggeris

Understanding the mechanism of anti-carcinogenic effects of Tualang honey (TH) on DMBA (7,12-Dimethylbenz[α]anthracene)- induced breast cancer in rats

Abstract

Introduction: The multifloral Tualang honey (TH) and the monofloral Manuka honey (MH) have been reported to have antimicrobial, anti-inflammatory, antioxidant and anticancer effects. Unlike the MH, TH is not extensively studied.

Objectives: This study was conducted to evaluate the mechanisms of the preventive and therapeutic effects of Tualang honey (TH), Manuka honey (MH) and honey sugars analogue (HSA) on experimental breast cancer induced rats using carcinogen 1-methyl-1-nitrosourea (MNU).

Methodology: A total of 130 female Sprague-Dawley rats were used. Sixty female rats were randomly divided into 6 groups with 10 animals per group in each study. Group '0' (negative control; normal rats); Group 1 (positive control; tumour induction but no treatment). Groups 2, 3 and 4 were fed orally with 0.2, 1.0 and 2.0 g/kg body weight of TH. Group 5 received 1.0 g/kg of MH, and Group 6 received 1.0 g/kg HSA. For the "cancer-preventive" study, honey was given one week prior to MNU-induction and for the "cancer-therapeutic" study; treatment was given after breast cancer development. The treatment continued until the 120th day when the rats were sacrificed for samples collections.

Results: Results showed that TH and MH treated rats of "cancer-preventive" groups had a lower tumor incidence, and a longer latency period compared to the non-treated control group. The tumors developed in all treated groups of preventive and therapeutic measures were lesser in number, size and weight compared to the non-treated control. The majority of the tumors in the treated groups were of better grade (grade I and II) compared to the non-treated control group (grade III). The haematological parameters showed that varying strengths of TH, MH and HSA had a potentiating effect on haemoglobin, red blood cells, packed cell volume, mean corpuscular volume, lymphocytes and eosinophils, and a lowering effect on total white blood cells, red cell distribution width, polymorphs, monocytes and platelets compared to the non-treated control. These treatments showed no hyperglycemic effects and no body weight loss. The systemic administration of TH, MH and HSA exerts anti-cancer effects through up-regulation of the expression of pro-apoptotic proteins such as caspase 9, Apfa-1 (apoptotic protease activating factor 1), p53, IFN- γ (interferon gamma) and IFNGR1 (interferon gamma receptor 1), and a concomitant down-regulation of the expression of anti-apoptotic proteins such as Bcl-xL (B-cell lymphoma-extra large), TNF- α (tumor necrosis factor alpha), COX-2 (cyclooxygenase-2), E2 (estradiol) and ESR1 (estrogen receptor 1) at serological and or breast cancer tissues levels.

Discussion: Our study shows that the treatment with TH and MH appears to exert cancer-preventive and or cancer-therapeutic effects, is through the modulation tumour grading, body weight, haematological parameters of immune regulatory response, and modulation of pro and anti-apoptotic proteins of mitochondrial apoptotic pathway at serum and breast cancer tissues level. HSA also acts akin to honey.

Conclusion: Tualang honey, Manuka honey and honey sugars analogue can be used as prophylactic cancer- and cancer-therapeutic agents. The mechanism is through the modulation of tumour grading, haematological and the modulation of pro and anti-apoptotic proteins at serum and cancer tissues level.

F. SUMMARY OF RESEARCH FINDINGS

Ringkasan dapatan Projek Penyelidikan

Our study shows that Tualang and Manuka honeys given one week prior to administration of carcinogen (MNU) (preventive aspect of honey) and after breast cancer development (therapeutic aspect of honey) could alter the progression of breast carcinoma in rats. Tualang and Manuka honeys may not have the capability to completely prevent development of breast cancers. But, it provides evidence that these have positive effect on tumour growth. Thus, Tualang and Manuka honeys have the potential to retard the tumour growth as shown by the reduction in number, weight and size of tumour masses developed. Treatment with Tualang and Manuka honeys has also been seen to modulate the behavior of the tumour as shown by the better tumour grading histologically. Tualang and Manuka honey showed no hyperglycemic effects with good body weight gain.

The mechanism by which Tualang and Manuka honeys exert cancer-preventive and cancer-therapeutic effects is multifold; through modulation of immune response, by ameliorating haematological and serological parameters, and by activation of the intrinsic/ mitochondrial apoptotic pathway. We investigated the level of proteins involved in cellular proliferation and cellular death at serum and tumour tissues levels. Tualang and Manuka honeys ameliorate the intrinsic apoptotic pathway through up-regulation of the expression of pro-apoptotic proteins such as caspase-9, Apfa-1, p53, IFN- γ and IFNGR1. Concomitantly, these honeys down-regulate the expression of anti-apoptotic proteins such as Bcl-xL, TNF- α , COX-2, E2 and ESR1 to favour this apoptotic pathway. The sugars analogue in honey also acts akin to honey in breast cancer therapy. Our research suggests that Tualang honey, Manuka honey and honey sugars analogue can be used as prophylatic cancer-preventive and cancer therapeutic agents.

G. COMPREHENSIVE TECHNICAL REPORT

Laporan Teknikal Lengkap

Applicants are required to prepare a comprehensive technical report explaining the project.

(This report must be attached separately)

Sila sediakan laporan teknikal lengkap yang menerangkan keseluruhan projek ini.

[Laporan ini mesti dikepulkan]

List the key words that reflect our research:

Senaraikan kata kunci yang mencerminkan penyelidikan anda:

English	Bahasa Malaysia
Tualang honey	Madu Tualang
Breast cancer	Kanser Payudara
Anticancer	Antikanser