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NUTRIENT ENRICHMENT OF FERMENTED SOYBEAN TEMPEH VIA ANAEROBIC FERMENTATION WITH VARIOUS BIOLOGICAL ACTIVITIES

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Master of Science

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Chairman : Assoc. Prof. Noorjahan Banu Alitheen, PhD

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Fermented soybean is found to contain increased level of bioactive contents such as proteins, polyphenolics, vitamins and minerals as a result of its microbial activity. Tempeh is an example of fermented soybean that has been recognized to have various health benefits contributed by the increased level of amino acids and antioxidants. Further enhancement of the bioactive properties of tempeh can be achieved *via* combination of anaerobic fermentation with selected strain of *Rhizopus* sp. as an innoculant. The purpose of this study is to determine and compare the cytotoxic, immunomodulatory, anti-inflammatory, liver ameliorative activities as well as acute toxicity of aqueous extract of nutrient enriched of soybean tempeh (NESTE) with non-fermented soybean (SBE). The production of NESTE involved by normal aerobic fermentation of tempeh followed by anaerobic fermentation using *Rhizopus oligosporus* (*R. oligosporus*) 5351 strain that was obtained from the culture collection of Malaysian Agricultural Research and Development Institute (MARDI). NESTE was produced by soaking soybeans for 18 h, steaming for 40 min, mixing with *R. oligosporus* 5351 strain starter culture prior to packaging with perforated plastic, incubating in aerobic condition for 30 h at 30 ˚C and continue incubating in anaerobic condition for 20 h at room temperature. Results have demonstrated that anaerobic fermentation on soybean had successfully produced NESTE, which contains 3210 ± 0.01 mg/ 100 g DW (dried weight) total free amino acids, 1100 ± 0.01 mg/ 100 g DW (dried weight) total essential amino acids and 338 ± 0.025 mg/ 100 g DW (dried weight) gamma-aminobutyric acid (GABA). Besides, NESTE also contains 42.64 ± 1.59 µg/ g extract of soluble phenolic acids and 22.56 ± 0.31 mg GAE/ g extract of total phenolic acids. These results indicated that the level of amino acids, GABA and antioxidants had significantly increased ($p < 0.05$). In addition, NESTE also inhibited the growth of MCF 7 cells in MTT assay with IC_{50} 3.6 ± 0.22 mg/ mL after 72 h incubation while no cytotoxicity was detected in MCF 10A normal breast cell line. Cell cycle with flow cytometry analysis illustrated that NESTE arrested MCF 7 cells at G_0/G_1 phase. Furthermore, increment of the cell population in sub G_0/G_1 has shown that IC_{50} of NESTE at 72 h was able to

induce the best apoptotic effect towards MCF 7 cells. Annexin V-FITC/PI assay has further confirmed the apoptotic effect induced by NESTE on MCF 7 cells where substantial amount of early apoptotic cells were detected. On the other hand, the immunomodulatory study of NESTE has shown that NESTE stimulated splenic cells proliferation in time and dosage dependent manner which can be observed through MTT and BrdU assays. Additionally, NESTE was also able to stimulate and enhance cytokine secretion (IL-2 and IFN-gamma) in time and dosage dependent manner. Anti-inflammatory study has shown that NESTE exhibited no sign of cytotoxicity towards RAW 264.7 cells (macrophage cells) and was able to suppress the level of nitric oxide, which is an inflammatory indicator. *In vivo* tests on mice ear edema and analgesic demonstrated that the best effect was achieved when treated with 1000 mg/ kg of NESTE suggesting that NESTE was able to suppress the edematous effect of mice ear and produce better and lasting analgesic effect. The evaluation of *in vivo* liver ameliorative activity of NESTE indicated that NESTE could revert the effect of steatosis in hepatocytes to normal condition, increase the antioxidant level and reduce the inflammation of the ethanol treated mice. Moreover, NESTE exhibited no sign of toxicity towards mice up to 5000 mg/ kg. Overall, anaerobic fermentation of soybean using *R. oligosporus* sp. 5351 strain has successfully produced NESTE with higher bioactive contents such as GABA, amino acid and antioxidants. This finding suggested that NESTE could be formulated as a healthy food supplements that possessed the anticancer, immunomodulatory, anti-inflammatory and liver ameliorative effect.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Sarjana Sains

PENINGKATAN NUTRIEN DALAM TEMPEH KACANG SOYA MELALUI KAEDAH PENAPAIAN SECARA ANAEROBIK SERTA KEPELBAGAIAN AKTIVITI BIOLOGI

Oleh

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Penapaian kacang soya didapati mengandungi peningkatan terhadap tahap kandungan bioaktif seperti protin, polifenolik, vitamin dan mineral akibat daripada aktiviti mikrobnya. Tempeh adalah contoh penapaian soya yang telah diketahui mempunyai pelbagai manfaat kesihatan yang disumbangkan oleh tahap peningkatan asid amino dan antioksidan. Peningkatan kandungan bioaktif tempeh boleh dilakukan melalui gabungan penapaian secara anaerobik dengan menggunakan jenis *Rhizopus sp.* yang terpilih sebagai inokulan. Tujuan kajian ini dilakukan adalah untuk menentukan dan membandingkan tahap sitotoksik, imunomodulatori, anti-inflamasi, aktiviti memperbaiki hati serta pengesanan toksik melalui kajian ketoksikan akut terhadap ekstrak akues mentah tempeh kacang soya yang diperkaya dengan nutrisi (NESTE) dan ekstrak akues mentah kacang soya tanpa penapaian (SBE). Penghasilan NESTE adalah melibatkan penapaian secara aerobik biasa diikuti dengan penapaian secara anaerobik dengan menggunakan *Rhizopus oligosporus* (*R. oligosporus*). jenis 5351 yang diperolehi daripada koleksi kultur Institut Penyelidikan dan Kemajuan Pertanian Malaysia (MARDI). NESTE dihasilkan melalui merendam kacang soya selama 18 jam, mengukus selama 40 minit, mencampurkan dengan kultur pemula *R. oligosporus* jenis 5351 sebelum pembungkusan dengan menggunakan plastik yang berlubang, diinkubasi secara aerobik selama 30 jam pada 30 ˚C dan menyambung proses inkubasi secara anaerobik selama 20 jam pada suhu bilik. Keputusan telah menunjukkan bahawa penapaian anaerobik pada kacang soya telah berjaya menghasilkan NESTE yang mengandungi 3210 ± 0.01 mg/ 100 g DW (berat kering) jumlah keseluruhan asid amino bebas, 1100 ± 0.01 mg/ 100 g DW (berat kering) jumlah asid amino perlu dan 338 ± 0.025 mg/ 100 g DW (berat kering) asid gamma-aminobutyric (GABA). Selain itu, NESTE juga menghasilkan asid fenolik larut yang berjumlah 42.64 ± 1.59 μg/ g ekstrak dan asid fenolik total berjumlah 22.56 ± 0.31 mg GAE/ g ekstrak. Kesemua keputusan data nutrient NESTE menunjukkan bahawa tahap asid amino, GABA dan antioksidan telah meningkat secara signifikan ($p < 0.05$). Di samping itu, NESTE juga menunjukkan

rencatan pertumbuhan sel-sel MCF 7 pada esei MTT dengan menghasilkan IC_{50} 3.6 ± 0.22 mg/ mL ekstrak selepas inkubasi selama 72 jam. Di samping itu, tiada sitotoksik yang dikesan pada sel payudara normal, MCF 10A. Ujian kitaran sel dengan menggunakan analisis sitometri aliran menunjukkan bahawa NESTE telah menghalang kitaran sel MCF 7 pada fasa G_0/G_1. Tambahan pula, peningkatan populasi sel pada sub G_0/G_1 telah menunjukkan bahawa IC_{50} daripada NESTE pada 72 jam dapat memberi kesan apoptosis terbaik terhadap sel-sel MCF 7. Ujian Annexin V-FITC/PI telah menambahkan lagi bukti bahawa kesan apoptosis pada sel MCF 7 adalah disebabkan oleh NESTE di mana sel-sel apoptotik fasa awal dikesan pada jumlah yang tinggi. Sebaliknya, kajian imunomodulatori pada NESTE melalui ujian MTT dan ujian BrdU telah menunjukkan bahawa NESTE mampu menambahbaik pertumbuhan sel-sel limpa mengikut penambahan masa dan dos ekstrak. Selain itu, NESTE juga mampu untuk merangsang dan meningkatkan rembesan sitokin (IL-2 dan IFN-gamma) mengikut penambahan masa dan dos ekstrak. Kajian antiinflamasi pula telah menunjukkan bahawa NESTE tidak menunjukkan sebarang kesan sitotoksik terhadap sel-sel RAW 264.7 (sel makrofaj) dan ia juga menunjukkan kemampuan untuk menyekat peningkatan nitrik oksida yang diketahui sebagai penunjuk kesan inflamasi. Ujian *in vivo* terhadap kesan edema telinga tikus dan analgesik telah menunjukkan kesan pemulihan terbaik apabila dirawat dengan 1000 mg NESTE/ kg berat tikus dan ini menunjukkan bahawa NESTE mampu menyekat kesan edema pada telinga tikus dan menghasilkan kesan analgesik yang lebih baik dan berkekalan. Penilaian aktiviti memperbaiki hati secara *in vivo* terhadap NESTE menunjukkan bahawa kesan steatosis pada sel hati telah kembali kepada keadaan normal, peningkatan terhadap tahap antioksidan dan pengurangan keradangan etanol pada tikus. Selain itu, NESTE tidak mempamerkan sebarang tanda-tanda keracunan terhadap tikus sehingga pada tahap 5000 mg/ kg. Secara keseluruhan, penapaian secara anaerobik terhadap kacang soya dengan menggunakan *R. oligosporus* sp. jenis 5351 telah berjaya menghasilkan NESTE dengan menghasilkan kandungan bioaktif seperti GABA, asid amino dan antioksidan yang lebih tinggi. Penemuan ini menunjukkan bahawa NESTE berpotensi untuk dirumuskan sebagai makanan tambahan kesihatan yang mempunyai kesan antikanser, imunomodulatori, anti-inflamasi dan memperbaiki hati.

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I certify that a Thesis Examination Committee has met on 17 December 2013 to conduct the final examination of Hamidah binti Mohd. Yusof on her thesis entitled "Nutrient Enrichment of Fermented Soybean *Tempeh* via Anaerobic Fermentation with Various Biological Activities" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

%	Percentage
γ	Gamma
μ	Micro
m	Mili
AAE	Ascorbic acid equivalent
ALD	Alcoholic liver disease
ALT	Alanine aminotransferase
ANOVA	One-way analysis of variance
AO	Acridine orange
ASA	Acetyl Salicylic Acid
AST	Aspartate aminotransferase
ATCC	American Type Culture Collection
Balb/c	Albino, laboratory-bred strain mice
BHT	Butylatedhydroxytoulene
BrdU	Bromo-deoxyuridine
Con A	Concanavalin A
CO_2	Carbon dioxide
DMEM	Dulbecco's modified eagle media
DMSO	Dimethysulphoxide
DNA	Deoxyribonucleic acid
DPPH	1,1-diphenyl-2-picryl-hydrazil
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme Link Immunosorbent assay
FACS	Fluorescene Activated Cell Sorter
FBS	Fetal bovine serum
FITC	Fluorescein isothiocynate
FRAP	Ferric reducing antioxidant power
g	gram

G	Gap
GABA	γ-amino butyric acid
GAE	Gallic acid equivalents
h	hour
HBBS	Hank's Balance Salt Solution
HCL	Hydrochloric acid
HDL	High-density lipoprotein
IC_{50}	Inhibition concentration that reduces 50% of cells viability
IFN	Interferon
IL	Interleukin
LD_{50}	Lethal dose that cause 50% of death in animal
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LPS	Lipopolisaccharide
MARDI	Malaysian Agriculture Research Development Institute
MCF 10A	Human mammary epithelial cells
MCF-7	Human mammary gland adenocarcinoma cells
MDA	Malondialdehyde
min	Minutes
mL	Mililiter
mm	Millimeter
mM	Milimolar
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
Na_2HPO_4	Disodium hydrogen phosphate anhydrous
NaCL	Sodium chloride
NBT	Nitro blue tetrazolium
NESTE	Nutrient enriched soybean tempeh
nm	Nanometer
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
PBS	Phosphate buffer saline

PI	Propidium Iodide
RAW264.7	Murine macrophage cell line
RPMI	Roswell Park Memorial Institute
SBE	Non-fermented soybean extract
sec	Second
SEM	Standard Error Mean
SOD	Superoxide dismutase
TG	Triglycerides
TMB	Peroxidase substrate 3,3',5,5"-tetramethylbenzidine
TPC	Total phenolic content
TPTZ	2, 4, 6-tripyridyl-s-triazine
TypLE	Express-Trypsin replacement enzyme for cells dissociation
UPM	Universiti Putra Malaysia
UV	Ultraviolet
x g	times gravity

CHAPTER 1

INTRODUCTION

Fermented foods have contributed to one third of food intake all around the world and are one of the oldest forms of biotechnology product that converts complex food substrate into simpler and digestible food with the help of enzymes that are produced from microbial activity (Blandino *et al*., 2002). According to Steinkraus (1995), food fermentation process could serve five main purposes which are to develop various aromas, flavours and textures; produce proteins, essential amino acids and vitamins; save time and fuel; preserve the food through lactic acid, alcohol, acetic acid and alkaline fermentation and remove the antinutrient substance. Furthermore, production of the end-products of food fermentation such as acids, alcohol and carbon dioxide has the ability to control the growth of spoilage microbe (Paul Ross *et al*., 2002). Due to these reasons, many researchers are attracted to investigate the process and health benefits of fermented food products for the development of functional foods (Stanton *et al*., 2005).

For many years, functional food is one of the important food ingredients for people in Asia as they believe that food and medicine are derived from the same source, hence exhibit similar effect (Verschuren, 2002; Siro *et al*., 2008). Great emphasis has been put on functional foods as they can act as medicine with less side effects (Shah, 2007). Fermentation has been used to produce functional foods since enhanced nutrient content is always observed in fermented foods (Verschuren, 2002). Several fermented foods have been developed into functional foods such as tempeh, fermented rice and prebiotic product such as fermented milk (Aoki *et al*., 2003a; Su *et al*., 2003; Park and Oh, 2007; Granato *et al*., 2010).

Numerous legumes have been consumed in daily dietary either as a staple or nutrient added foods. Among vegetarians, legumes are their protein substitute and through the consumption of legumes, it could help to reduce the risks of multiple diseases (Dunham and Kollar, 2006). *Glycine max* or generally known as soybean has been extensively consumed all over the world (Cherng *et al*., 2007; Hartman *et al*., 2011). Soybean contains several phytochemicals and phytonutrients which are stipulated to possess many potential health benefits (Omoni and Aluko, 2005; Mateos-Aparicio, 2008). Numerous soybean products are available and the most widely consumed products in Asian region are in fermented form. Several studies have revealed that fermented soybeans could potentially enhance the immune system and alleviate several diseases including cancer, cardiovascular, osteoporosis and obesity (Messina, 2003; Villares *et al*., 2011).

Tempeh is one of fermented soybean that is widely known among vegetarians and also a traditional food for many people in Indonesia and Malaysia. Tempeh has been consumed extensively by people around Europe, United States and Japan due to its high level of nutritional contents (Nout and Kiers, 2005). As one of nutritious

soybean fermented food, tempeh has been claimed to possess many health benefits including lowering the risks of heart disease, stroke, osteoporosis, cancer, digestive disorder and to reduce weight and symptoms of menopause (Astuti *et al*., 2000; Babu *et al*., 2009). The elevated nutritious substances in tempeh such as amino acid and antioxidant have attracted many investigators to study the properties of tempeh. Study towards its nutrient quality had brought Aoki *et al*. (2003a) to develop a method to increase its nutrient content including GABA, amino acids and antioxidants of tempeh via anaerobic fermentation (Aoki *et al*., 2003a; Watanabe *et al*., 2007). *R. oligosporus* 5351 strain from MARDI was chosen in this study as a starter culture of tempeh fermentation since it was observed to generate the highest content of amino acids and GABA during aerobically fermentation of tempeh as compared to other *R.* oligosporus strain (Koh *et al*., 2012). In this study, Nutrient Enriched Soybean Tempeh (NESTE) was produced by combination process of aerobic and anaerobic fermentation as well as using *R. oligosporus* 5351 strain as a starter culture. In addition, bioactivities including cytotoxicity, immunomodulatory, anti-inflammatory and hepatoprotective activities of its nutritional contents were also evaluated.

Therefore, the objectives of this study were :

(1) to establish an improved technique in order to enrich the nutrient component in tempeh *via* anaerobic incubation.

(2) to determine the amino acid, GABA and antioxidant content in the fermented tempeh produced *via* anaerobic incubation.

(3) to evaluate the crude sample of anaerobic tempeh for its cytotoxic effect towards breast cancer cell line, immunomodulator, anti-inflammation, alcoholic liver damage ameliorator as well as to determine the acute toxicity level.

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