UNIVERSITI PUTRA MALAYSIA

ANALYSIS OF SELECTED BIOACTIVE COMPOUNDS AND BIOLOGICAL ACTIVITIES OF UNTREATED, GERMINATED AND FERMENTED MUNG BEAN AQUEOUS EXTRACTS

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By

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Chair: Assoc. Prof Noorjahan Banu Alitheen, PhD

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Mung bean (*Vigna radiata*), a legume plant with seed that is frequently consumed in Asia is gaining its popularity worldwide. Germination and fermentation processes are well documented to increase the concentration of various bioactive compounds as well as to enhance the organoleptic characteristics and nutritional values of various foods. The use of common treatments such as chemotherapy drugs, radiotherapy and surgery to treat various diseases have been reported to cause adverse side effects, induce drugs resistancy, which reduced their effectiveness and initiation of other diseases. Therefore, alternative therapy using natural active compounds from mung bean plant was employed. Although mung bean plant has been consumed traditionally, very limited scientific reviews have been reported regarding its benefits and efficacy. The purpose of this study was to examine the bioactive compounds and biological activities of mung bean (MB), germinated mung bean (GMB) and fermented mung bean (FMB) aqueous extracts. More specifically, the content of amino acids, γ-aminobutyric acid (GABA)

and total phenolic compound (TPC) were evaluated along with their effects as immumodulator, cytotoxic, hepatoprotectant, anti-inflammatory and anti-nociceptive. Results showed that the content of total free amino acid and essential amino acids increased by 12-fold and 17-fold in GMB and 13-fold and 26-fold in FMB. On contrary, only fermentation was able to accumulate TPC with increment by 4-fold compared to untreated mung bean. To demonstrate the multiple biological properties of extracts, various Reactive Oxygen Species (ROS)-related diseases were employed throughout the study for instance immune system dysfunction, cancer, alcoholic liver disease (ALD), inflammatory and pain-related inflammatory. In immunomodulatory study, immune cells (mice splenocytes) treated with FMB aqueous extract resulted in stimulation of cell proliferation and cytokines expression. Cytotoxicity study revealed that FMB was selective against breast cancer cells (MCF-7) with IC_{50} 2.3 mg/mL and decreased cell viability by 50% after 72 h of incubation. Meanwhile, increased detection of phosphatidylserine (PS) and Sub-G_0/G_1 cells population with Sub-G_0/G_1 population increased significantly from 1.08 ± 0.06% to 21.5 ± 0.23% indicating the increase of cancer cell death *via* apoptosis. Hepatoprotective effect of GMB and FMB on alcohol-induced liver injury in mice was found to be higher than MB where the elevated level of liver function biomarkers (alanine aminotransferase (ALT), aspartate aminotransferase (AST), cholesterol, triglycerides (TG)) and antioxidant liver homogenate (Malondialdehyde (MDA), superoxide dismutase (SOD), Ferric Reducing Antioxidant Power (FRAP)) reverted close to normal. Treatment with FMB at high dose (1000 mg/kg) displayed the highest suppression percentage of all serum markers, 63.73% (ALT), 69.84% (AST) 38.4% (TG) and 23.42% (cholesterol). Also, FMB was able to

reduce the level of MDA by 3.6 fold, nitric oxide (NO) by 1.6 fold, SOD by 2.3 fold and FRAP activity by 2.2 fold. Similarly, histopathological evaluation of extracts particularly GMB and FMB on alcohol treated liver tissues resulted in the reduction of sinusoidal and central vein dilations, ballooning and hepatocytes necrosis. In anti-inflammation and anti-nociceptive study, all extracts showed no sign of toxicity on normal murine macrophages (RAW 264.7) cells meanwhile, merely GMB and FMB were able to inhibit the stimulation of pro-inflammatory mediator NO. Study on mice showed that both GMB and FMB exerted significant anti-inflammatory effect with ear-oedema inhibition by 18% and 35% respectively. Apart from that, in heat-induced central pain study, all extracts at certain interval time showed anti-nociceptive effect against pain stimulus. Germination and fermentation successfully enhanced the nutritional values of mung bean in term of bioactive compounds and biological properties. These findings indicated the novel approach of anaerobic germination and fermentation using *Rhizopus sp.* 5351 on mung bean and the potential of FMB and GMB extracts to improve the clinical symptoms of immune, cancer, liver and inflammation associated diseases.

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SEBATIAN BIOAKTIF DAN AKTIVITI BIOLOGI DARI EKSTRAK AKUEUS KACANG HIJAU, KACANG HIJAU BERCAMBAH DAN TAPAI KACANG HIJAU

Oleh

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Pengerusi: Prof. Madya Noorjahan Banu Alitheen, PhD

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Kacang hijau (*Vigna radiata*) adalah tumbuhan benih kekacang yang sering diambil dalam pemakanan oleh penduduk di Asia serta semakin dikenali di seluruh dunia. Proses percambahan dan penapaian telah didokumentasi dapat meningkatkan kandungan pelbagai sebatian bioaktif, ciri-ciri organolepsis dan nilai nutrisi pelbagai makanan. Penggunaan rawatan biasa seperti ubat kemoterapi, radioterapi dan pembedahan untuk merawat pelbagai penyakit boleh menyebabkan kesan-kesan sampingan yang buruk dan daya rintangan terhadap ubat kemoterapi yang mengurangkan keberkesanan dan boleh menyumbang kepada risiko terjadinya penyakit lain. Oleh itu, terapi secara alternatif menggunakan bahan aktif semula jadi daripada ekstrak tumbuhan kacang hijau telah dikaji. Walaupun tumbuhan kacang hijau telah digunakan secara tradisi, laporan mengenai manfaat dan keberkesanannya dari segi saintifik adalah terhad. Tujuan kajian ini dijalankan adalah untuk mengkaji kandungan sebatian bioaktif dan aktiviti biologi dari ekstrak akueus kacang hijau (MB), kacang

hijau bercambah (GMB) dan tapai kacang hijau (FMB). Lebih khusus lagi, kandungan asid amino, asid γ-aminobutyric (GABA) dan jumlah kandungan fenolik (TPC) telah dinilai bersama-sama dengan kesannya sebagai immumodulator, sitotoksik, hepatoprotektif, anti-radang dan anti-kesakitan. Hasil kajian menunjukkan bahawa kandungan asid amino bebas (FAA) dan asid amino penting (EAA) telah meningkat dengan ketara sebanyak 12 dan 17 kali ganda selepas proses percambahan secara anaerobik dan sebanyak 13 dan 26 kali ganda selepas proses penapaian kacang hijau. Sebaliknya, peningkatan jumlah kandungan fenolik (TPC) hanya dapat dapat dilihat selepas proses penapaian iaitu sebanyak 4 kali ganda. Untuk membuktikan keberkesanan ekstrak, kajian telah dijalankan ke atas penyakit-penyakit yang berkaitan dengan spesies oksigen reaktif (ROS) seperti sistem imunisasi yang tidak seimbang, kanser, penyakit hati yang berpunca daripada pengambilan alkohol (ALD), keradangan dan kesakitan. Dalam kajian immunomodulatori, sel-sel imun (sel limpa tikus) telah dirawat dengan ekstrak akueus FMB yang mengakibatkan pertambahan rangsangan terhadap proliferasi sel dan ekspresi sitokin. Kajian sitotoksik mendapati ekstrak akueus FMB adalah selektif terhadap sel kanser payudara (MCF-7) dengan IC_{50} sebanyak 2.3 mg/mL, iaitu penurunan aktiviti sel sebanyak 50% selepas 72 jam. Selain itu, peningkatan jumlah fosfatidilserin (PS) dan populasi sel di Sub-G_0/G_1 yang ketara dari 1.08 ± 0.06% kepada 21.5 ± 0.23% membuktikan kematian sel kanser secara apoptosis. Kesan hepatoprotektif GMB dan FMB pada kecederaan hati tikus yang diakibatkan oleh pendedahan kepada alkohol telah didapati kesannya lebih baik daripada MB di mana tahap tinggi biomarker fungsi hati (alanin aminotransferase (ALT), aspartat aminotransferase (AST), kolesterol, trigliserida (TG)) dan antioksidan homogenasi hati

(malondialdehida (MDA), superoksida dismutase (SOD), ferric reducing antioksidan power (FRAP)) telah dikembalikan kepada paras normal. Penggunaan ekstrak FMB pada dos 1000 mg/kg menunjukkan peratusan penurunan yang tinggi keatas biomarker serum, 63.73% (ALT), 69.84% (AST) 38.4% (TG) dan 23.42% (kolesterol). Selain itu juga, ekstrak FMB dapat mengurangkan kadar MDA sebanyak 3.6, nitrik oksida (NO) sebanyak 1.6, SOD sebanyak 2.3 dan aktiviti FRAP sebanyak 2.2 kali ganda. Penilaian histopatologi ekstrak terutamanya GMB dan FMB pada tisu hati yang terdedah kepada alkohol menunjukkan pengurangan pengembangan urat sinusoidal dan urat pusat, pembelonan dan nekrosis hepatosit. Dalam kajian anti-radang dan anti-kesakitan, semua ekstrak menunjukkan tiada tanda toksik pada sel-sel normal makrofaj tikus (RAW 264.7), manakala hanya ekstrak GMB dan FMB mampu untuk menghalang rangsangan pro-radang NO. Kajian ke atas haiwan menunjukkan kedua-dua ekstrak GMB dan FMB telah mengurangkan kesan keradangan edema telinga sebanyak 18% dan 35%. Kajian tahap keberkesanan ekstrak dalam mengurangkan kadar kesakitan menunjukkan semua ekstrak pada selang masa tertentu mempunyai kesan anti-kesakitan terhadap rangsangan haba. Secara rumusnya, proses percambahan dan penapaian telah berjaya meningkatkan nilai pemakanan kacang hijau dari segi sebatian bioaktif dan aktiviti biologi. Penemuan ini menunjukkan pendekatan proses percambahan anaerobik dan penapaian menggunakan *Rhizopus sp.* 5351 pada kacang hijau dan potensi ekstrak terutamanya GMB dan FMB untuk memperbaiki simptom-simptom klinikal penyakit imun, kanser, hati dan keradangan.

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LIST OF ABBREVIATIONS

%	Percentage
γ	Gamma
μ	Micro
m	Milli
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	Butylated hydroxytoulene
BrdU	Bromo-deoxyuridine
Con A	Concanavalin A
COXs	Cyclooxygenases
CO_2	Carbon dioxide
DMEM	Dulbecco's modified eagle media
DMSO	Dimethysulphoxide

DNA	Deoxyribonucleic acid
DPPH	1,1-diphenyl-2-picryl-hydrazil
DOPA	3,4-dihydroxyphenylalanine
EAA	Essential amino acids
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme Link Immunosorbent assay
FAA	Free amino acids
FACS	Fluorescene Activated Cell Sorter
FBS	Fetal bovine serum
FITC	Fluorescein isothiocynate
FMB	Fermented mung bean
FRAP	Ferric reducing antioxidant power
g	gram
g	Gravity
G	Gap
GABA	γ-amino butyric acid
GAE	Gallic acid equivalents
GMB	Germinated mung bean (anaerobic)
h	hour
HBBS	Hank's Balance Salt Solution
HCl	Hydrochloric acid
HDL	High-density lipoprotein
hEGF	Human epidermal growth factor

K562	Human chronic myeloid leukemia cells
IC_{50}	Inhibition concentration that reduces 50% of cells viability
IFN	Interferon
IL	Interleukin
L	Liter
LD_{50}	Lethal dose that cause 50% of death in animal
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LPS	Lipopolisaccharide
M	Mitosis
MAPK	Mitogen activated protein kinase
MARDI	Malaysian Agriculture Research Development Institute
MB	Mung bean
MCF 10A	Human mammary epithelial cells
MCF-7	Human mammary gland adenocarcinoma cells
MDA	Malondialdehyde
min	Minutes
mL	Milliliter
mm	Millimeter
mM	Millimolar
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
nm	Nanometer
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
PBS	Phosphate buffer saline
PI	Propidium Iodide
p.o.	Pre-treated orally
PS	Phosphatidyl Serine
RAW264.7	Murine macrophage cell line
ROS	Reactive oxygen species
Rpm	Revolutions per minute
RPMI	Roswell Park Memorial Institute
SEM	Standard Error Mean
SD	Standard Deviation
SOD	Superoxide dismutase
SSF	Solid-state fermentation
TBA	Thiobarbituric acid
TBARS	Thiobarbituric acid-reactive substance
TCA	Trichloroaceticacid
TG	Triglycerides
TMB	Peroxidase substrate 3,3',5,5"-tetramethylbenzidine
TNF	Tumor necrosis factor
TPC	Total phenolic content

TPTZ	2, 4, 6-tripyridyl-*s*-triazine
TypLE	Express-Trypsin replacement enzyme for cells dissociation
UV	Ultraviolet
v	Volume
w	Weight

CHAPTER 1

INTRODUCTION

Mung bean is a legume traditionally consumed for its medicinal properties in treating heat and fever. It is normally consumed as raw, sprouted, cooked as soup or made into flour worldwide (Zhu et al., 2012). It has been broadly advertised that mung bean is rich in polyphenols, amino acids and other secondary metabolites yet its contribution to the biological activities as a potential antioxidant (Kim et al., 2012), anti-tumor (Soucek et al., 2006), liver protection (Wu et al., 2001), tyrosinase inhibitor (Yao et al., 2012), anti-hyperglycemic (Yeap et al., 2012) and anti-diabetic (Yao et al., 2008) are overlooked until recently.

The use of sprout from other legumes such as soybean as salad and fermented soybean as tofu, tempe and miso has been widely commercialized (Frias et al., 2005). The high polyphenol and active compounds in mung bean can be an alternative to the soybean product (Yao et al., 2011). In addition, germination and fermentation are processing methods to increase the nutritional values and qualities of raw food. Sprouting of seeds and incorporation of microbes to help modify the condition of raw seed are employed in germination and fermentation, respectively (Ali et al., 2013).

Reactive oxygen species (ROS) is a result of oxidative stress that occurs in the subcellular events during cells metabolism. Oxidative stress can be generated internally (mitochondria respiratory chain) and externally (stress, exercise, alcohol, smoking, environmental pollutant and UV radiation) (Sosa et al., 2013). Imbalance of ROS production can stimulate the accumulation of ROS, which can be toxic to the cells and lead to cell damage and generation of many diseases such as cancer (Sosa et al., 2013), inflammation (Cipollone et al., 2007), liver injury (Duzguner & Erdogan, 2012), immune system dysfunction (Leonard & Maes, 2012), diabetes (Muhammad et al., 2009), cardiovascular disease (Cipollone et al., 2007) and a lot more.

Excessive level of ROS can induce the initiation of cancer by increasing DNA mutations resulting in DNA damage and genetic alteration (Reuter et al., 2010). Furthermore, it can promote the growth of tumor by evading the apoptosis mechanism and increasing the cell proliferation. Genetic alteration in cancer can affect the expression of genes responsible for cellular regulation. In hereditary breast cancer, 40-50% of tumor suppressor breast cancer gene 1 (BRCA 1) is mutated resulting in low regulation of antioxidant enzymes (Sosa et al., 2013). Moreover, point mutation involved in Ras activation, over expression of oncogene proteins and silencing of tumor suppressor genes such as p53 have been reported to be related to oxidative stress (Reuter et al., 2010; Sosa et al., 2013). Meanwhile, suppression of desired immunomodulators and overexpression of undesired immunomodulators have led to the development of immune system dysfunction (Asad & Srivathsa, 2012). Involvement of

ROS and aging has also been reported to contribute to the decline of immunity which associate with the initiation and development of many chronic diseases (Gupta, 2004).

Hypothesis for this study is that germination and fermentation will increase the bioactive compounds and antioxidant properties of mung bean and subsequently contribute to other biological benefits for disease treatment. The general objective of the study was to evaluate the effects of anaerobic germination and fermentation on bioactive compounds and biological activities of mung beans.

The specific objectives of this study were:

1) To analyze the amino acids, Gamma-aminobutyric acid (GABA) and total phenolic content (TPC) profile of untreated mung bean (MB), anaerobic germinated mung bean (GMB) and fermented mung bean (FMB) aqueous extracts

2) To evaluate and compare the effects of untreated mung bean (MB), anaerobic germinated mung bean (GMB) and fermented mung bean (FMB) aqueous extracts as immunomodulator, cytotoxic, hepatoprotectant, anti-inflammatory and anti-nociceptive agents.

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PUBLICATIONS

1. Ali, N. M., Yusof, H. M., Long, K., Yeap, S. K., Ho, W. Y., Beh, B. K., Koh, S. P., Abdullah, M. P., Alitheen, N. B. (2013). Antioxidant and hepatoprotective effect of aqueous extract of germinated and fermented mung bean on ethanol-mediated liver damage. *BioMed Research International*, vol. 2013, pp. 1-9, 2013.