UNIVERSITI PUTRA MALAYSIA

GASTROPROTECTIVE ACTIVITY OF SEMI-PURIFIED (PARTITIONS) METHANOLIC LEAF EXTRACT OF MELASTOMA MALABATHRICUM L. (SENDUDUK

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By

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

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

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Chairman : Associate Professor Zainul Amiruddin Zakaria, PhD
Faculty : Medicine and Health Science

Melastoma malabathricum L. (Melastomaceae) is traditionally used by the Malays to treat gastric ulcer and this claim was supported by the gastroprotective activity observed with methanolic extract of *M. malabtahricum* leaves (MEMM). The present study aimed to determine the gastroprotective activity of the methanolic crude extract of *Melastoma malabathricum* (MEMM) by semi-purified extract (partitions) using solvents of different polarities. The study began with screening the potential acute toxicity of MEMM before it was partitioned using different solvents. The petroleum ether partition (PEMM) was non-polar, ethyl acetate partition (EAMM) was intermediate polar and aqueous extract (AQMM) was polar. Next, we screened their phytochemical compounds followed by evaluation of their *in vitro* antioxidant activities using total phenolic content (TPC), 2,2-diphenyl-1-picrylhydrazyl (DPPH), superoxide dismutase (SOD) and oxygen radical absorbance capacity (ORAC) assays and screened their *in vitro* anti-inflammatory activities using xanthine oxidase (XO) and lipoxygenase (LOX) assays. All partitions were investigated for possible gastroprotective activity against ethanol-induced gastric ulcer. Rats (n = 6) received 10% dimethyl sulfoxide (DMSO, negative control), 100 mg ranitidine (positive control) or semi-purified extract (50, 250, 500 mg/kg) orally once daily for 7 days followed by ulcer induction using absolute ethanol (1 mL/200 gm). The gastric tissues were collected for macroscopic and microscopic examination to determine the most effective partition. The most effective partition was selected for studied their anti-secretory activity by using a pylorus ligation model to determine the gastric juice volume, pH, free and total acidity, and mucus content. The selected partition progressed to the next stage of the study, to determine the antioxidant enzyme activity (SOD, catalase [CAT], glutathione [GSH], thiobarbituric acid–reactive substances [TBARS]) and cytoprotective activity (prostaglandin E_2 [PGE_2]) in gastric tissues. The effective dose of the partition was investigated to determine the possible involvement of endogenous nitric oxide (NO) and sulfhydryl (SH) compounds in the gastroprotective effects. Finally, the compounds responsible for gastroprotection in the effective partition were identified. Result showed phytochemical screening of PEMM,

EAMM and AQMM revealed the presence of saponins, flavonoids, triterpenes, tannins and polyphenolic, but not alkaloids. In the *in vitro* antioxidant assay, i) EAMM showed high TPC content compared to PEMM and AQMM, ii) all partitions showed high scavenging activity in the SOD assay; EAMM and AQMM showed better results as compared to PEMM in the iii) DPPH and iv) ORAC assays. In the *in vitro* anti-inflammatory assay, the partitions had low activity in the XO assay while EAMM and AQMM had moderate and low activity, respectively, in the LOX assay. All partitions exerted significant ($p < 0.05$) gastroprotection against ethanol-induced gastric ulcer in the following order: EAMM > AQMM > PEMM. EAMM was the most effective partition as proven via its mechanisms of action: i) anti-secretory activity as shown by the reduction of gastric juice volume, free and total acidity as well as increased pH and gastric wall mucus, ii) antioxidant enzyme activity as shown by the increased SOD, CAT, GSH and decreased malondialdehyde (MDA) in gastric tissues, iii) cytoprotective activity as shown by the increased PGE_2 levels in gastric tissue. The gastroprotective activity involved NO and SH compounds, as shown by the partition being ineffective in iv) assay when N-omega-nitro-L-arginine methyl ester (L-NAME; a NO blocker) and v) N-ethylmaleimide (NEM; a SH blocker) were used. In conclusion, EAMM showed better *in vitro* antioxidant and antiinflammatory activity partly attributed to its gastroprotective activity demonstrated via the mechanisms of action of its anti-secretory, antioxidant and cytoprotective activity that depend on the presence of NO and SH. The presence of flavonoids-based compounds and hydrocinnamic acid compounds which might act synergistically was believed to contribute to this gastroprotective activity.

Abstrak tesis yang dikemukan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

AKTIVITI GASTROPROTEKTIF OLEH SEMI-ASLI (PECAHAN) EKSTREK METANOL DARI DAUN *MELASTOMA MALABATHRICUM* L. (SENDUDUK)

Oleh

NOOR WAHIDA BT ISMAIL SUHAIMY

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Pengerusi : Profesor Madya Zainul Amiruddin Zakaria, PhD
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Melastoma malabathricum L. (Melastomaceae) secara tradisional digunakan oleh orang Melayu dalam merawat gastrik ulser dan ini disokong dengan aktiviti gastroprotektif yang diperhatikan dari daun-daun *Melastoma malabathricum* (MEMM) ekstrek methanol. Kajian ini bertujuan untuk menentukan aktiviti gastroprotektif daun-daun *Melastoma malabathricum* (MEMM) ekstrak metanol untuk disemi-pecahankan menggunakan pelarut yang berbeza polariti. Kajian bermula dengan pemeriksaan potensi toksisiti akut pada MEMM sebelum dipecahkan menggunakan pelarut berbeza. Pecahan dari ekstrak petroleum eter (PEMM) ialah tidak-polar, pecahan dari ekstrak etil asetat (EAMM) ialah pertengahan polar dan ekstrak dari akueus (AQMM) ialah polar. Berikutnya, kami memeriksa kompaun fitokimia diikuti penilaian beberapa aktiviti *in vitro* antioksidan diantaranya bagi menentukan kandungan jumlah fenol (TPC), cerakin 2,2-diphenyl-1-picrylhydrazyl radikal (DPPH), penguji perangkap aktiviti superoxide dismutase (SOD) dan cerakin penyerapan oksigen radikal kapasiti (ORAC) dan pemeriksaan aktiviti *in vitro* anti-radang menggunakan analisis aktiviti xanthine oxidase (XO) and lipoxygenase (LOX). Semua ekstrak semi-pecahan telah diuji aktiviti gastroprotektif dengan memberi rangsangan etanol penyebab gastrik ulser. Tikus (n = 6) menerima 10% dimethyl sulfoxide (DMSO, kawalan negatif), 100 mg ranitidine (kawalan positif) atau ekstrak semi-pecahan (50, 250, 500 mg/kg) secara oral sekali setiap hari untuk 7 hari diikuti dengan rangsangan ulser menggunakan etanol (1 mL/200 gm). Tisu gastrik telah diambil untuk penilaian makroskopik dan mikroskopik bagi menentukan ekstrak semi-pecahan paling berkesan. Ekstrak semi-pecahan paling berkesan telah dipilih untuk mengkaji aktiviti anti-sekresi dengan menggunakan model pilorus ligation untuk menentukan jumlah jus gastrik, pH, jumlah asiditi dan tanpa asiditi dan kandungan mucus. Ekstrak semi-pecahan yang terpilih dilanjutkan dengan kajian berikutnya, menentukan aktiviti enzim antioksida (SOD, catalase [CAT], glutathione [GSH], thiobarbituric acid–reactive substances [TBARS]) dan aktiviti sitoprotektif (prostaglandin E_2 [PGE_2]) dalam tisu gastrik. Dos ekstrak semi-pecahan paling berkesan akan dikaji bagi menentukan kemungkinan penglibatan kompaun nitrik oksid (NO) dan sulfidril (SH) dalam keberkesanan gastroprotektif. Akhirnya kompaun yang bertanggungjawab untuk gastroprotektif dari ekstrak semi-pecahan yang berkesan

telah dikenalpasti. Keputusan menunjukkan pemeriksaan fitokimia ke atas PEMM, EAMM dan AQMM mendedahkan kewujudan saponin, flavonoid, triterpene, tannin dan polifinolik, tetapi tidak alkaloid. Dalam asai *in vitro* antioksidan , i) EAMM menunjukkan tinggi jumlah TPC dibandingkan PEMM dan AQMM., ii) semua ekstrak semi-pecahan menunjukan tinggi aktiviti memerangkap dalam asai SOD; EAMM dan AQMM menunjukkan keputusan yang bagus berbanding PEMM dalam asai iii) DPPH dan iv) ORAC. Dalam asai *in vitro* anti-radang, semua ekstrak semi-pecahan menunjukkan aktiviti rendah dalam asai XO manakala EAMM dan AQMM menunjukkan aktiviti sederhana dan rendah dalam asai LOX. Semua ekstrak semi-pecahan menunjukkan signifikan gastroprotektif ($p < 0.05$) menentang etanol merangsang gastrik ulser dalam susunan berikut: EAMM > AQMM > PEMM. EAMM adalah ekstrak semi-pecahan paling berkesan dan terbukti melalui tindakan mekanisma: i) aktiviti anti-sekresi yang menunjukkan pengurangan jumlah jus gastrik, jumlah asiditi dan tanpa asiditi begitu juga peningkatan pH dan mukus dinding gastrik, ii) aktiviti enzim antioksida menunjukkan peningkatan SOD, CAT, GSH dan pengurangan malondialdehyde (MDA) dalam tisu gastrik, iii) aktiviti sitoprotektif menunjukkan peningkatan tahap PGE_2 dalam tisu gastrik. Aktiviti gastroprotektif melibatkan kompaun NO dan SH yang menunjukkan ekstrak semi-pecahan kurang berkesan dalam asai iv) omega-nitro-L-arginine methyl ester (L-NAME; pemblok NO) dan v) N-ethylmaleimide (NEM; pemblok SH). Kesimpulan, EAMM menunjukkan bagus dalam aktiviti *in vitro* antioksidan dan anti-radang dimana menyumbang kepada aktiviti gastroprotektif yang telah dipamerkan melalui tindakan mekanisma aktiviti anti-sekresi, antioksida dan sitoprotektif dengan bergantung pada kewujudan kompaun NO dan SH. Kewujudan kompaun asas flavonoid dan acid hidrosinamik yang mungkin bertindak secara sinergistik dipercayai menyumbang kepada aktiviti gastroprotektif ini.

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I certify that a Thesis Examination Committee has met on 6 September 2016 to conduct the final examination of Noor Wahida binti Ismail Suhaimy on her thesis entitled "Gastroprotective Activity of Semi-Purified (Partitions) Methanolic Leaf Extract of *Melastoma malabathricum* L. (Senduduk)" 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.

Members of the Thesis Examination Committee were as follows:

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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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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AAPH	2,2'-azobis (2-amidinopropane) dihydrochloride
Ach	Acetylcholine
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANOVA	One-way analysis of variance
AQMM	Aqueous
AST	Aspartate aminotransferase
AUC	Area under the curve
BPLC	High-performance liquid chromatography
CAT	Catalase
CBX	Carbenoxolone
CCK	Cholecystokinin
dH_2O	Distilled water
DMSO	Dimethyl sulfoxide
DPPH	2,2-diphenyl-1-picrylhydrazyl
EAMM	Ethyl acetate
ECL	Enterochromaffin-like
FRAP	Ferric reducing/antioxidant power
G-6-PDH	Glucose-6-phosphate dehydrogenase
GIP	Gastric inhibitory polypeptide
GPX	Glutathione peroxidase
GR	Glutathione reductase
GSH	Glutathione
H. pylori	*Helicobacter pylori*
H_2O_2	Hydrogen peroxide
HCl	Hydrochloric acid
IF	Intrinsic factor
L-NAME	N^G-nitro-L-arginine methyl ester
LOO•	Lipid peroxyl
LOX	Lipoxygenase
MEMM	Methanol extract of *M. malabathricum*
NADPH	Nicotinamide adenine dinucleotide phosphate
NaOH	Sodium hydroxide
NBT	Nitroblue tetrazolium
NDGA	Nordihydroguaiaretic acid
NEM	N-ethylmaleimide
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
O^-_2	Superoxide
OH•	Hydroxyl
ORAC	Oxygen radical absorbance capacity
PEMM	Petroleum ether
PGs	Prostaglandins
PMS-NADH	Phenazine methosulfate–nicotinamide adenine dinucleotide
PPI	Proton pump inhibitors
p.o	Oral administration
ROO•	Peroxyl
ROS	Reactive oxygen species

ROW	Relative organ weight
R_T	Retention time
SEM	Standard error of the mean
SH	Sulfhydryl
SOD	Superoxide dismutase
UA	Ulcer area
UV-vis	Ultraviolet/visible
XO	Xanthine oxidase

CHAPTER 1

INTRODUCTION

1.1 Introduction

The stomach is part of the gastrointestinal system and is where food or any substance received from the oesophagus will be digested before it is released to the small intestine. However, the constant exposure of the stomach to a variety of substances has a tendency to cause injury (Saladin, 2012).

The stomach injury associated with gastric ulcer, described as erosions of the stomach wall or deep lesions penetrating the mucosa and muscularis mucosa and cause persistent damage (Vimala and Shoba, 2014; Kaur et al., 2012; Marieb and Hoehn, 2007). This disease is widely experienced by most people worldwide, where prevalence is 10% in the Western countries (Barkun and Leontiadis, 2010) and 11.5% in the Asian and South Pacific countries (Scott et al., 2013).

There are various factors for gastric ulcer occurrence, including disproportion between the protective factors (e.g. mucus, prostaglandins [PGs], mucosal blood flow and mucosal epithelial regeneration) and aggressive factors (gastric acid and pepsin) in the stomach (Nugroho et al., 2016; Srikanth and Muralidharan, 2009; Lima et al., 2006). Furthermore, the unlimited consumption of non-steroidal anti-inflammatory drugs (NSAIDs), *Helicobacter pylori* infection, inappropriate habits or lifestyle such as smoking, stress, poor diet and alcohol are among the factors that increase the risk of ulcers (Nugroho et al., 2016; Konturek et al., 2005).

Currently, there are two main approaches for treating gastric ulcer: the inhibition of gastric acid production, and increasing gastric mucosa protection (McQuaid, 2012; Valle 2005). The current medications available for treating gastric ulcers are commonly referred to as H_2 receptor antagonists, proton pump inhibitors (PPI) and antacids. Unfortunately, they have several adverse effects after long-term use or high-dose intake. The common side effects are constipation, diarrhoea and hypophosphatemia, thrombocytopenia (34%), distruption of central nervous system such as confusion, restlessness, somnolence, agitation, headaches and dizziness (~80%), 170 cases of hepatotoxicity, 16 cases and 25 published reports of acute interstitial nephritis (AIN), dyspepsia, heartburn, or regurgitation (22%), nausea (3.2%), flatulence (2.9%), dyspepsia (2.0%), vomiting (1.3%), gynaecological disorder such as spotting (0.7%), cramps (0.6%), hypermenorrhea (0.5%), menstrual disorder (0.3%) and dysmenorrhea (0.1%) (Neena, 1991; Lam et al., 2013; McQuaid, 2012; Reimer et al. 2009; Ecker et al., 2004; Fisher and Le Couteur, 2001; Cantu and Korek, 1991; Berardi et al., 2008; Shields, 1978; https//www.drugs.com/pro/misoprostol.html).

In this context, there is a strong need for extensive research to discover new treatments for gastric ulcer. Plant natural products have been proven centuries ago as alternative medicine, including for gastric ulcer, and the pharmacological activity of some of these products has been well established (Wasman et al., 2011; Stege et al., 2006). In addition, there are many reports on the various bioactive compounds in plant products (Yadav et al., 2011; Alama et al 2009).

Melastoma malabathricum, commonly known as *senduduk* in Malaysia, is used as folk medicine (Joffry et al., 2012). The crude extract of this plant has effective gastroprotective activity (Zainulddin et al., 2016; Zakaria et al., 2015; Balamurugan et al., 2013; Zabidi et al., 2012; Hussain et al., 2008; Nazlina et al., 2008). The present study used semi-purified extracts (partitions) from the methanol crude extract of *M. malabathricum* (MEMM) to investigate their mechanisms of action and to identify the compound responsible.

1.2 Problem statement

Gastric ulcers are peptic ulcers which are a serious gastrointestinal disorder. Gastric ulcer occurs when there is an imbalance between the protective and aggressive factors of the stomach and can also be due to lifestyle habits that lead to perforations of the stomach lining and cause bleeding in the stomach wall. Many commercially drugs are available for treating this, but are accompanied by unpleasant side effects following long-term use or high-dose intake. The use of natural plant-based products as alternative medicine is believed to be safer and cheaper. Accordingly, *M. malabathricum* leaves were selected based on the traditional belief for treating gastric ulcers. However, there is still a lack of scientific proof, thus this plant was chosen to prove its ethnomedicinal benefits in gastroprotection.

1.3 General objective

To study the gastroprotective activity and mechanism of action of the effective partition of MEMM.

1.4 Specific objectives

- To assess the toxicity of MEMM prior to semi-purifying the extract.
- To analyse the *in vitro* antioxidant and anti-inflammatory activities, and gastroprotective activity of each partition against ethanol-induced gastric ulcer model in rats.
- To determine the involvement of anti-secretory, endogenous antioxidant enzymes and cytoprotective activities, as well as the role of nitric oxide (NO) and sulfhydryl (SH) compounds in the modulation of gastroprotection exerted by the most effective partition.

- To identify the compounds present in the effective partition using high-performance liquid chromatography (HPLC).

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Noor Wahida Bt Ismail Suhaimy was born in Kuala Lumpur, Malaysia on October 5th, 1986. She received her early primary education at Sekolah Kebangsaan Manjoi Satu, Ipoh. Then she continued her secondary education at Sekolah Menengah Kebangsaan Dr. Megat Khas, Ipoh and Sekolah Menengah Kebangsaan Bandar Utama, Petaling Jaya, Selangor.

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Under supervision of Assoc. Prof. Dr Zainul Amiruddin Zakaria and co-supervisors, Dr Norhafizah Mokhtaruddin and Dr Manraj Singh, she carried out the present Master research entitled "Gastroprotective activity of semi-purified (partitions) methanolic leaves extract of *Melastoma malabathricum* L. (Senduduk)".

LIST OF PUBLICATIONS

Journal

Noor Wahida Ismail Suhaimy, Ahmad Khusairi Noor Azmi, Norhafizah Mohtarrudin, Maizatul Hasyima Omar, Siti Farah Md. Tohid, Manraj Singh Cheema, Teh Ley Kek, Mohd. Zaki Salleh And Zainul Amiruddin Zakaria. 2016. Semi-Purified Ethyl Acetate Partition Of Methanolic Extract Of *Melastoma Malabathricum* Leaves Exerts Gastroprotective Activity Partly Via Its Antioxidant-Antisecretory-Anti-Inflammatory Action And Synergistic Action Of Several Flavonoid-Based Compounds. *Oxidative Medicine And Cellular Longevity*. (Research Article 6542631: Impact Factor 4.492).

Proceeding

Noor Wahida Ismail Suhaimy, Noorsyaza Eddrina Kamsani, Norhafizah Mohtaruddin, Manraj Singh Cheema, Zainul Amiruddin Zakaria. 2015. Gastroprotective Activity Of Various Methanolic Extract Partitions Of *Melastoma Malabathricum* Against Ethanol-Induced Gastric Ulcer In Rats: The Role Of Antioxidant And Cytoprotective. Poster Presented At The *29th Scientific Meeting Of Malaysian Society Of Pharmacology And Physiology*, 24th – 25th August 2015, Setia City Convention Centre, Selangor, Malaysia.

N. E. Kamsani, **N. W. Ismail Suhaimy**, M. K. Hussain, S. F. Md Tohid, Z. A. Zakaria. 2014. Melatea – Antioxidant Activity And Total Phenolic Content From Methanol Extract Of *Melastoma Malabathricum* Leaves. Poster Presented At *The 2nd International Innovation Design And Articulation*, 16th – 19th September 2014, Universiti Teknologi Mara (Uitm) Perlis, Malaysia.

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