INHIBITION OF CYCLOOXYGENASE AND LIPOXYGENASE ACTIVITIES OF *Momordica charantia*

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DEDICATION

This thesis is dedicated to the 23 years old me.
Who knew that someday you will be choosing this path?

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ABSTRACT

Momordica charantia (MC) or bitter gourd is a climber belongs to the family of cucurbitaceae. There are numbers of evidences showing anti-diabetic, anti-oxidant, anti-inflammatory and anti-cancer activities of MC, however the effects of fractionation and processing of MC on its anti-inflammatory activity have not been fully elucidated. Therefore, the objectives of this study are to investigate the anti-inflammatory effects of MC raw juice and fractions and to evaluate the effect of processing methods on its anti-inflammatory activity. First, MC juice was obtained using a conventional juicer and fractionated into five fractions, namely strong acid, weak acid, neutral, weak base, and strong base fractions using solid phase extraction method. The raw juice and its fractions were then tested for their anti-inflammatory activities which included cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX), and 15-lipoxygenase (15-LOX) inhibition assays. The current results showed that the COX-1 inhibition activity of MC can be attributed to the neutral fraction metabolites (52.60% inhibition), and no significant difference in COX-1 inhibition activity was found between the neutral fraction and the raw juice. In contrast, the anti-COX-2 activity of MC was found exerted collectively by metabolites in multiple fractions (including strong base, neutral, and strong acid fractions). On the other hands, all five fractions contributed to the inhibition activities of MC juice on 5-LOX (55.51% inhibition for raw juice) and 15-LOX (55.3% inhibition for raw juice). In addition, the current findings showed that the juice processing method using conventional juicer or slow juicer influenced the bioactivity of the plant, where fruit juice obtained from a slow juicer showed consistently higher anti-inflammatory activities than juice from a conventional juicer. The MC juice has a bitter taste and may be unfavorable to some people. Results from a descriptive sensory analysis showed that a mixture of 50% MC + 50% green apple juice able to improve palatability of MC juice. The mixture also gave better inhibition effects on COX-1, COX-2 and 15-LOX activities, even when compared with the 100% MC raw juice. This study reported on the anti-inflammatory activities of MC and its fractions, which may contribute towards an effective processing and fractionation strategy for MC.

ABSTRAK

Momordica charantia (MC) atau peria katak adalah sejenis tumbuhan menjalar daripada keluarga cucurbitaceae. Terdapat banyak bukti menunjukkan aktiviti anti-diabetik, anti-oksida, anti-radang dan anti-kanser oleh MC, namun kesan kaedah pemisahan dan pemprosesan kepada aktiviti anti-radang MC masih belum dijelaskan sepenuhnya. Justeru, objektif kajian ini adalah untuk mengkaji kesan anti radang jus mentah dan pecahan MC serta menilai kesan kaedah pemprosesan kepada aktiviti anti-radang tumbuhan ini. Pertamanya, jus MC telah diperolehi menggunakan alat pemerah jus konvensional dan dipecahkan kepada lima pecahan iaitu pecahan asid kuat, asid lemah, neutral, alkali lemah dan alkali kuat menggunakan kaedah pengekstrakan fasa pepejal. Jus mentah dan pecahan-pecahannya kemudian diuji dengan aktiviti anti-radang yang merangkumi ujian penyekatan cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX) dan 15-lipoxygenase (15-LOX). Keputusan terkini menunjukkan bahawa aktiviti sekatan COX-1 MC adalah disebabkan oleh metabolit dalam pecahan neutral (52.60% sekatan), dan tiada perbezaan ketara dalam aktiviti penyekatan COX-1 ditunjukkan antara pecahan neutral dan jus mentah. Sebaliknya, aktiviti anti-COX-2 MC telah dijumpai secara kolektif oleh metabolit dalam pelbagai pecahan (termasuklah pecahan alkali kuat, neutral dan asid kuat). Selain itu, kelima-lima pecahan jus MC telah menyumbang kepada aktiviti penyekatan 5-LOX (55.51% sekatan bagi jus mentah) dan 15-LOX (55.3% sekatan bagi jus mentah). Sebagai tambahan, penemuan terkini menunjukkan bahawa kaedah pemprosesan jus menggunakan alat pemerah jus konvensional atau alat pemerah jus perlahan mempengaruhi aktiviti bio tumbuhan ini, yang mana jus buah yang diperolehi daripada alat pemerah jus perlahan menunjukkan aktiviti anti-radang yang lebih tinggi berbanding jus daripada alat pemerah jus konvensional secara konsisten. Jus MC mempunyai rasa yang pahit dan mungkin kurang digemari oleh sesetengah orang. Keputusan daripada analisis deskriptif sensori menunjukkan bahawa campuran 50% MC + 50% jus epal hijau berupaya menambahbaik rasa jus MC. Campuran tersebut juga memberikan kesan penyekatan yang lebih baik terhadap aktiviti COX-1, COX-2 dan 15-LOX, walaupun dibandingkan dengan jus mentah MC 100%. Kajian ini telah melaporkan aktiviti anti-radang MC dan pecahannya, yang mana dapat menyumbang kepada kaedah pemprosesan serta strategi pemisahan MC yang lebih efektif.

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LIST OF ABBREVIATIONS

ANOVA	-	Analysis of variance
CO_2	-	Carbon dioxide
COX	-	Cyclooxygenase
COX-1	-	Cyclooxygenase-1
COX-2	-	Cyclooxygenase-2
DMSO	-	Dimethyl sulfoxide
DNA	-	Deoxyribonucleic acid
EAAS	-	Atomic-absorption spectrophotometry
FLAP	-	5-lipoxygenase-activating protein
GC/O-MS	-	Gas chromatography-olfactometry mass spectrometer
HETE	-	Hydroxy-eicosatetraenoic acids
HPETE	-	Hydroperoxyl-eicosatetraenoic acid
HSMM	-	Human skeletal muscle myoblasts
HYA	-	Hyaluronidase
GLUT4	-	Glucose transporter type 4
IC_{50}	-	Inhibitor Concentration where the response is reduced by 50%
ICP-MS	-	Inductively coupled plasma mass spectrometry
IL-1β	-	Interleukin-1β
IL-6	-	Interleukin-6
iNOS	-	Inducible nitric oxide synthase
LPS	-	Lipopolysaccharide
LTs	-	Leukotrienes
LTA_4	-	Leukotrienes A_4
LTB_4	-	Leukotrienes B_4
LTC_4	-	Leukotrienes C_4
LTD_4	-	Leukotrienes D_4
LTE_4	-	Leukotrienes E_4
LOX	-	Lipoxygenase
MAPK	-	Mitogen-activated protein kinases (MAPK)
MC	-	*! "# "$%&( )' *($(+, &)*

mRNA	-	Messenger ribonucleic acid
NDGA	-	Nordihydroguaiaretic acid
NSAIDs	-	Nonsteroidal Anti-inflammatory Drugs
NF-κB	-	Nuclear factor kappa B
NO	-	Nitric oxide
PGs	-	Prostaglandins
PGE_2	-	Prostaglandin E_2
PGG_2	-	Prostaglandin G_2
PGH_2	-	Prostaglandin H
$PGF_{2\alpha}$	-	Prostaglandin $F_{2\alpha}$
PGD_2	-	Prostaglandin D_2
RA	-	Rheumatoid arthritis
ROS	-	Reactive oxygen species
SD	-	Standard deviation
SPE	-	Solid phase extraction
SPSS	-	Statistical Package for the Social Sciences
TNF-α	-	Tumor necrosis factor- α
TXA_2	-	Thromboxane A_2
XO	-	Xanthine oxidase
5-LOX	-	5-Lipoxygenase
12-LOX	-	12-Lipoxygenase
15-LOX	-	15-Lipoxygenase

LIST OF SYMBOLS

CO_2	-	carbon dioxide
et al.	-	and others
g	-	gram
kg	-	kilogram
mg	-	miligram
ml	-	milimeter
µM	-	micromolar
RPM	-	revolution per minutes
Mg	-	microgram
MPa	-	megapascal pressure unit
µL	-	microlitre
µm	-	micrometre
µM	-	micromolar
°C	-	degree celsius
%	-	percent
nm	-	nanometer

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CHAPTER 1

INTRODUCTION

1.1 Background

Inflammation is a condition derived from tissue response to biological, physical and chemical stimulations to eliminate injuring stimuli such as pathogens, irritant and damaged cells (Hadagali and Chua, 2014; Verdam *et al.*, 2015). Although inflammation response is important in physiological condition, there are accumulating evidences associating inflammation with diseases including asthma, psoriasis, inflammatory bowel disease, atherosclerosis, insulin resistance, rheumatoid arthritis and cancer (Libby, 2006; Solinas *et al.*, 2010; Li *et al.*, 2015).

To date, inflammation is typically treated with a number of anti-inflammatory drugs, which include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, immunosuppressant drugs. However, many of the drugs are found to be insufficiently effective and may cause side effects (Fürst and Zündorf, 2014) especially gastrointestinal complications such as intestinal bleeding, peptic ulceration, and chronic gastritis (Langman, 1997). There is an increasing interest to search for plant-derived anti-inflammatory compounds which may have less toxicity, more accessibility and less expensive than synthetic compounds (Iftikhar and Rashid, 2014).

Momordica charantia Linn. (MC) or peria katak is a member of Cucurbitaceae family. The seeds, fruit and leaves of MC had shown a wide range of pharmacological activities, and MC has been traditionally used for its therapeutic activities including anti-diabetic, anti-inflammatory, anti-ulcer, anti-leukemic, anti-HIV, anti-tumor, and

anti-microbial effects (Grover and Yadav, 2004). Notably, MC is particularly known for its hypoglycemic activity which will lead to reduction in blood glucose level in Type 2 diabetic patients (Fuangchan *et al.*, 2011; Hasan and Khatoon, 2012) and rodents (Perumal *et al.*, 2015; Xu *et al.*, 2015).

In addition to its anti-diabetic activity, MC is also recognized as an anti-inflammatory agent. Several reports had consistently shown its anti-inflammatory activities; Chao *et al.* (2014) reported that adding MC to diets of sepsis-induced mice inhibited the NF-κB, iNOS and COX-2 expressions, leading to improvement of the inflammation responses. A study by Bao *et al.* (2013) showed that MC freeze-dried fruit reduced the adipose tissue inflammation in diet-induced obese mice where the pro-inflammatory cytokine MCP-1 expression was depressed in epicardial adipose tissue and brown adipose tissue. Furthermore, the IL-6 and TNF-α expression in epicardial adipose tissue were also reduced. In addition, a previous study that involved MC-treated rat model showed that the levels of pro-inflammatory cytokines in the liver, muscle and epididymal fats were significantly down-regulated. Moreover, the activation of NF-κB in the liver and muscle was decreased in MC -treated rat group compared to the non-treated group (Yang *et al.*, 2015). These accumulating evidences support MC as a potent anti-inflammatory agent.

1.2 Problem Statements

In daily life, consumers usually obtain fruit juice by using common home appliances such as conventional juicer or slow juicer. A conventional juicer works using centrifugal forces and cuts fruit with a flat cutting blade and then spins the produce at high speed rotation to separate the juice from the pulp (Lee *et al.*, 2013). While a slow juicer works by pressing the fruit through a rotating juicing screw at low rotation to obtain the juice from the pulp (Lee *et al.*, 2013). Van Der Sluis *et al.* (2004) in their previous study showed that, though the processing of fruit and vegetables may result in polyphenols and flavonoids losses, however, there are possibilities occur

within the juice production chain to enhance the flavonoid content in fruit and vegetables juices. As a result, different processing method to obtain juice from fruit and vegetable may have its own impact on the bioactive compounds concentration and juice quality (Nogata *et al.*, 2003).

Previously, a number of studies had been carried out on solvent fractionation of MC (Chuang *et al.*, 2006; Kobori *et al.*, 2008; Sin *et al.*, 2012). However, fractionation of MC based on ionic exchange for the recovery of acidic, neutral and basic components from MC has yet to be established, and anti-inflammatory effects of the resulting fractions have yet to be fully elucidated. It is known that natural products consist of acid-base character which enables compounds to be selectively isolated based on the functional groups through pH manipulation in the fractions protocol (Araya *et al.*, 2010).

The bitter taste of MC juice is unfavorable to some people. A previous study suggested that combination of MC juice with sour-flavored fruit was able to improve the palatability of MC juice (Snee *et al.*, 2011). However, the addition of sour-flavored fruit to MC juice may alter its bioactivity and its effect on anti-inflammatory properties of MC is currently unknown.

The MC sample used in anti-inflammatory studies is commonly undergone freeze-drying process before extraction (Kobori *et al.*, 2008; Sin *et al.*, 2012). To date, there is still lack of data to examine the anti-inflammatory activities of freeze-dried MC particularly on inhibition of cyclooxygenase (COX-1, COX-2) and lipoxygenase (5-LOX, 15-LOX). Taken together, a study on fractionation, MC processing methods may provide a novel understanding of their effects on anti-inflammatory activities of MC.

1.3 Hypothesis

The hypotheses of the current study include:

1) The MC raw juice obtained from a conventional juicer may exhibit anti-inflammatory activity potential.
2) The raw juice from conventional juicer can be fractionated and each fraction may have different anti-inflammatory activities.
3) MC juice obtained from a slow juicer may have higher anti-inflammatory activity compared to conventional juicer due to a lower heat generated during the juicing process of a slow juicer.
4) The bitter taste of MC juice can be improved by mixing with green apple juice. The additional green apple juice also may show different inhibition effect on cyclooxygenase (COX-1, COX-2) and lipoxygenase (5-LOX, 15-LOX) activities.
5) The freeze-dried MC fruit may exhibit inhibition activities on cyclooxygenase (COX-1, COX-2) and lipoxygenase (5-LOX, 15-LOX).

1.4 Objectives

The objectives of this study include:

1) To screen anti-inflammatory activities of MC juice and to determine the anti-inflammatory effects of MC juice processed using a conventional juicer and its fractions obtained using a solid phase extraction method.
2) To compare the anti-inflammatory activities of juice produced obtained from a conventional juicer and a slow juicer
3) To improve palatability of MC juice by mixing MC juice with green apple juice
4) To determine the anti-inflammatory activities of freeze-dried MC.

1.5 Research Scopes

The research scopes for this study include:

1) To conduct screening for anti-inflammatory activities (including lipoxygenase, xanthine oxidase and hyaluronidase) of MC juice obtained from a conventional juicer.
2) To fractionate the MC juice produced by a conventional juicer using solid phase extraction into strong acid, weak acid, neutral, weak base and strong base fractions.
3) To conduct anti-inflammatory assays (including cyclooxygenase and lipoxygenase) for juice and fractions of MC.
4) To produce MC juice by a slow juicer and compare its anti-inflammatory activities with juice produced from a conventional juicer.
5) To improve the palatability of MC by formulating different ratio of MC juice and green apple juice (both produced by slow juicer) and examine the acceptance among consumers through sensory testing.
6) To conduct anti-inflammatory assays on mixed MC-green apple juice based on the selected ratio obtained from sensory testing.
7) To produce freeze-dried MC and examine its anti-inflammatory activities.

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2. Au, A., Abdul Rahim, N. D., **Yunos, A.R.M.Y**, Cheng, K. K. (2016). "Therapeutic Effects of Malaysian Herbs on Diabetes Mellitus." *Recent Trends in Malaysian Medicinal Plants Research*, UTM Press.

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1. **Yunos, A.R.M.Y**, Nadri, M.H., Sarmidi, M.R., Cheng, K.K (2018). Inhibition of lipoxygenases and cyclooxygenases by *Momordica charantia* extract. *7th International Conference on Biotechnology for the Wellness Industry*, 27-28 August 2018, Universiti Teknologi Malaysia Kuala Lumpur, Malaysia.

2. **Yunos, A.R.M.Y**, Zainol, N., Ab Karim, R., Abdul Rahim, N., & Cheng, K. K. (2017). Effect of *Momordica charantia* Linn. on Human Skeletal Muscle Cell. *International Postgraduate Symposium in Biotechnology (IPSB) 2017*, 21 August 2017, Institute of Bioproduct Development, Universiti Teknologi Malaysia Johor Bahru, Johor, Malaysia.