ANTI-INFLAMMATORY ACTIVITIES OF *Cleome gynandra* Linn. AND *Melicope ptelefolia* Champ. ex Benth. FOR POSSIBLE USE IN A TOPICAL CREAM FORMULATION

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

December 2021

IB 2021 30

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Chairman : Professor Muhammad Nazrul Hakim Abdullah, PhD
Institute : Bioscience

Herbal formulation is defined as the formulation of one or more than two herbs, with documented efficacies in treating inflammatory diseases, including skin conditions. *Cleome gynandra* (Maman), and *Melicope ptelefolia* (Tenggek Burung) are traditional herb in Malaysia that well-known as a vegetable dish. Both *C. gynandra* and *M. ptelefolia* leaves in methanolic extract have been proven for their anti-inflammatory properties. Previous data on these two herbs were mainly reported their efficacy in the form of standardized extract, while limited data on their anti-inflammatory activity as herbal formulation, particularly as cream-based products. These studies aimed to investigate the anti-inflammatory activities of *C. gynandra*, *M. ptelefolia* and their cream formulation by using *in vitro* and *in vivo* models. The single herb extract of *C. gynandra*, *M. ptelefolia* and their herbal formulation were tested for their toxicity testing using MTT assay and anti-inflammatory activities by nitric oxide inhibition assay. The results indicated that single herb *C. gynandra* exhibited the highest percentage of cell viability (110.59%) at concentration 4 mg/mL on RAW 264.7 cells compared to *M. ptelefolia* (38.01%), suggesting that *C. gynandra* extract is less cytotoxic compared to *M. ptelefolia*. Among the herbal formulations, the highest percentage of cell viability (92.59%) at concentration 4 mg/mL on RAW 264.7 cells were shown in the formulation that contains the highest concentration of *C. gynandra (C. gynandra*: *M. ptelefolia* at ratio 70:30 (w/w)). For nitric oxide inhibition assay, single herb *C. gynandra* exerted comparable (P>0.05) anti-inflammatory activities with diclofenac sodium drug (0.6μM) at 0.5-2 mg/mL. In the meantime, the herbal formulations of *C. gynandra: M. ptelefolia* at ratios 30:70, 50:50, and 70:30, respectively, were insignificant, suggesting that all samples have equal efficacies (P>0.05). From the result *in vitro* assay, extract with best activities overall (single herb *C. gynandra*) were then further developed into topical anti-inflammatory cream. Subsequently, *C. gynandra* in a cream formulation was tested on arachidonic acid-induced ear oedema model of male Sprague-Dawley rats. *C. gynandra* cream treated rats showed significantly (P<0.05) higher percentage recovery (70.21%) than the

negative control (27.43%) and basal cream (55.8%), indicating that this *C. gynandra* cream was effectively reducing inflammation symptoms in the ear oedema model in rats. *C. gynandra* cream also caused no irritation and no changes to the haematological and histopathological parameters in the skin irritation model in rats, suggesting its non-toxic activity for 28 days of exposure. In conclusion, *C. gynandra* could be potential as a herbal formulation in cream-based for treating skin related inflammatory conditions.

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

AKTIVITI ANTI-RADANG *Cleome gynandra* Linn. DAN *Melicope ptelefolia* Champ. ex Benth. YANG BERPOTENSI UNTUK KEGUNAAN FORMULASI KRIM TOPIKAL

Oleh

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Formulasi herba didefinisikan sebagai formulasi satu atau lebih dari dua ramuan herba, dengan khasiat yang didokumentasikan dalam rawatan penyakit radang, termasuk keadaan kulit. *Cleome gynandra* (Maman), dan *Melicope ptelefolia* (Tenggek Burung) adalah herba tradisional di Malaysia yang terkenal sebagai hidangan sayur-sayuran. Kedua-dua daun *C. gynandra* dan *M. ptelefolia* dalam ekstrak metanol telah terbukti sifat anti-radangnya. Data sebelum ini yang ada mengenai kedua herba ini hanya dilaporkan keberkesanannya dalam bentuk ekstrak standard tetapi data amat terhad mengenai aktiviti anti-radang sebagai satu rumusan herba yang digabungkan terutama sebagai produk berasaskan krim. Kajian-kajian ini bertujuan untuk mengkaji aktiviti anti-radang *C. gynandra*, *M. ptelefolia* dan formulasi krim dengan menggunakan model *in vitro* dan *in vivo*. Ekstrak herba tunggal *C. gynandra*, *M. ptelefolia* dan formulasi herba diuji untuk ujian ketoksikan dengan menggunakan kaedah MTT dan aktiviti anti-radang dengan menggunakan kaedah penghambatan nitrik oksida. Hasil kajian menunjukkan bahawa herba tunggal *C. gynandra* menunjukkan kebolehhidupan sel tertinggi (110.59%) pada kepekatan 4 mg / mL pada sel RAW 264.7 berbanding *M. ptelefolia* (38.01%), sekali gus menunjukkan bahawa ekstrak *C. gynandra* kurang sitotoksik berbanding kepada *M. ptelefolia*. Di antara formulasi herba pula, peratusan kebolehhidupan sel tertinggi (92.59%) pada kepekatan 4 mg / mL pada sel RAW 264.7 ditunjukkan dalam formulasi yang mengandungi kepekatan tertinggi *C. gynandra* (*C. gynandra*: *M. ptelefolia* pada nisbah 70 : 30 (b / b)). Untuk kaedah penghambatan nitrik oksida , herba tunggal *C. gynandra* memberikan aktiviti anti-radang yang setanding (P> 0,05) dengan ubat diclofenak sodium (0,6µM) pada 0,5-2 mg / mL. Sementara itu, formulasi herba *C. gynandra*: *M. ptelefolia* masing-masing pada nisbah 30:70, 50:50, dan 70:30, tidak signifikan, menunjukkan bahawa semua sampel mempunyai keberkesanan yang sama (P> 0,05). Dari hasil *in vitro* assay, ekstrak dengan aktiviti terbaik secara keseluruhan (herba tunggal *C. gynandra*) kemudian dikembangkan lagi menjadi krim anti-radang topikal. Untuk menilai keberkesanan krim anti-radang topikal, *C. gynandra* dalam formulasi krim diuji pada

model edema telinga tikus yang dihasilkan oleh asid arakidonik. Tikus yang diberi rawatan krim *C. gynandra* menunjukkan peratusan pemulihan yang lebih tinggi (P <0.05) lebih tinggi (70.21%) daripada kawalan negatif (27.43%) dan krim basal (55.8%), menunjukkan bahawa krim *C. gynandra* ini berkesan mengurangkan gejala keradangan pada model edema telinga pada tikus. Krim *C. gynandra* juga tidak menyebabkan kerengsaan serta tidak ada perubahan pada parameter hematologi dan histopatologi pada model kerengsaan kulit pada tikus, yang menunjukkan aktiviti tidak beracun selama 28 hari. Kesimpulannya, *C. gynandra* berpotensi sebagai formulasi herba dalam bentuk krim untuk merawat keadaan keradangan yang berkaitan dengan kulit.

ACKNOWLEDGEMENTS

In the name of Allah, the Most Gracious and the Most Merciful

Alhamdulillah, all praises to the Almighty ALLAH *Subhanahu Wa Ta'ala*, for giving me strength, patience, and good health condition throughout the research until the completion of this thesis. Selawat and salaam to His righteous messenger, Prophet Muhammad *Sallallaahu' Alaihi Wasallam* (peace be upon Him). This research project would not have been completed without the support of many people.

First and foremost, I would like to express my deepest and sincere gratitude to my beloved supervisor Prof. Dr. Muhammad Nazrul Hakim Abdullah, for her endless encouragement, patience, motivation, and guidance throughout the study and research. Not to forget, my warm and sincere thanks to my co-supervisor, Dr. Koh Soo Peng from Malaysian Agriculture Research Development Institute (MARDI) , Dr. Armania Nurdin, and Dr. Manraj Singh Cheema for their support and encouragement that contribute to the success of this piece of research work.

My deepest gratitude to all staff of the Laboratory of Vaccine and Immunotherapeutics (LiVES) at Insitute of Bioscience, Laboratory of Pharmacology at Faculty of Medicine and Health Sciences, and Laboratory of Metabolomics and Animal House at Malaysian Agriculture Research and Development Institute (MARDI) for their great help and contribution in making this research a success by kindly allowing me to have the access to the facilities.

Last but not least, I personally dedicate this thesis to the following individuals:

Special thanks to my beloved parents, my dad Mr. Ismail Bin Hassan and my mum Mrs. Rohana binti Husain and my dearest family members for their endless love, support, and words of encouragement throughout my life when I need them the most.

Sincere thanks to my colleagues in MARDI, Chandradevan A/L Machap, Muhammad Naim Zakaria, Muhammad Aizuddin, Suhaina Supian, Dr. Sew Yun Shin, and Muhamad Ridzuan Rashid for their helps, advices, supports and importantly for being such a great research team. A special thanks to my boss from MARDI, Dr. Sanimah Simoh for providing me opportunities to use this grant for pursue my studies.

Not to forget, sincere thanks to my postgraduate teammates, Dr. Mohd Rohaizad Roduan, Dr. Joan Anak Blin, Adlina Roslan, Eveiyn Phoon Weng Yan, Diana Suhaiza Said for always supporting me in doing my research, motivate, sharing ideas, and also accompanying me in the laboratory. Last but not least, to those who were directly or indirectly contributing to the completion of the thesis. Your kindness and involvement are highly appreciated.

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment 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

AA	Arachidonic acid
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
ATCC	American type culture collection
CKD	Chronic kidney disease
CO_2	Carbon dioxide
COX-2	Cyclooxygenase-2
DMEM	Dulbecco's modified eagle's medium
DMSO	Dimethyl sulfoxide
EDTA	Ethylene diamine tetra-acetic acid
EPP	Ethylphenyl propiolate
FBS	Fetal bovine serum
FTC	Ferric thiocyanate
g	Gram
GC-MS	Gas chromatography mass spectrometry
HCT	Haematocrit
HDL	High density lipopolysaccharide
Hgb	Haemoglobin
HPLC	High performance liquid chromatography
HRBC	Stabilization of human red blood cell membrane test
IFN	Interferon

IL-1	Interleukin-1
IL-6	Interleukin-6
iNOS	Inducible nitric oxide synthase
kg	Kilogram
LC-MS	Liquid chromatography mass spectrometry
LDL	Low density lipopolysaccharide
LPO	Lipoperoxidation
LPS	Lipopolysaccharides
LTB4	Leukotriene
MARDI	Malaysia Agricultural, Research and Development Insitute
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
mg	Milligram
mL	Mililiter
mm	Milimeter
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
nm	Nanometer
NMR	Nuclear magnetic resonance
NO	Nitric oxide
NSAIDs	Non-steroidal anti-inflammatory drugs
OECD	Organisation for Economic Co-operation and Development
p	Significance difference
PAF	Platelet-activation factor
PGs	Prostaglandin
PLA2	Phospholipase A2

PLT	Platelet
RBC	Red blood cell
rpm	Revolutions per minute
SEM	Standard error mean
SPSS	Statistical package for the social sciences
tHGA	2,4,6-trihydroxy-3-geranyl acetophenone
TNF-α	Tumor necrosis factor alpha
TPA	12-O-tetradecanoyl-13-phorbol acetate
UV	Ultraviolet
v/v	Volume per volume
w/v	Weight per volume
w/w	Weight per weight
WBC	White blood cell
µg	Microgram
µM	Micromolar

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CHAPTER 1

INTRODUCTION

1.1 Background of the study

Inflammation is a process of the body's defence mechanism against harmful agents such as infection or injuries and plays a crucial role in the healing process (Pahwa et al., 2020). This process involves a complex interaction of several inflammatory mediators, such as prostaglandin, nitric oxide, and cytokines, that regulate the inflammatory responses (Abdulkhaleq et al., 2018). It can be divided into acute and chronic inflammation. Acute inflammation is a short-term process response to injury (appear within minutes or hours) and characterized by five cardinal signs, including redness (rubor), swelling (oedema), heat (calor), pain (dolour) and loss of function (function laesa) (Ryan & Majno, 1977). In contrast, chronic inflammation is associated with prolonged inflammation, resulting from various causes of tissue destruction and repair (Chen et al., 2018).

Dermatitis is inflammation specific to the skin, which could be acute, chronic or both (Brar et al., 2021). Acute dermatitis refers to a rapidly evolving red rash that may be blistered and swollen. In contrast, chronic dermatitis refers to a longstanding irritable area. It is often darker than the surrounding skin, thickened (lichenified) and extensively scratched (Tsoi et al., 2020). It is reported that dermatitis affects one in every five people, affecting individuals irrespective of their age, gender, and ethnicity (Owen et al., 2018). The diseases also contribute to the significant economic burden to both Western and Asian countries. Feldman et al. (2019) reviewed that the treatment for dermatitis in the Western region has been reported as high as $1000 per year even after being insured with healthcare insurance. Meanwhile, Asian countries such as Malaysia, Indonesia, and Singapore, have experienced a higher economic burden, with an estimated dermatitis cost per year for children ranging from $2492 to $4473, as reported in 2014 (Bhanegaonkar et al., 2014). This economic burden is even worse in India, where healthcare costs are mainly self-funded (Handa et al., 2015).

Treatment strategies for dermatitis have included a combination of pharmacological and non-pharmacological approaches. Avoiding irritants and allergens, maintaining good skin hydration, and using drugs such as topical corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are among the fundamental approaches in managing dermatitis (Paller et al., 2016). However, frequently used or overdose on drugs will produce an undesirable effect such as organ damage or toxicity, eventually leading to injury or death (Wongrakpanich et al., 2018). Despite the use of drugs as the primary treatment to treat dermatitis, natural products have also commonly been used as alternative treatment (Man et al., 2018).

Natural products contain active compound found in nature with distinctive pharmacological effects and have become a popular demand in health care (Dias et al., 2012). Herbal formulation contains a quantified amount of one or several herbs that

provide nutritional, cosmetic benefits and treatment for human and animal diseases (Kumar et al., 2014). Indeed, several plants such as *Terminalia chebula* (Chebulic myrobalan), *Terminalia belerica* (Belleric myrobalan) and *Embilica officinalis* (Indian gooseberry) are amongst those plant that has been marketed as herbal formulations in Asian regions (Dinesh & Rasool, 2019).

Today, over 1300 medicinal herbs species have grabbed the attention of researchers in Malaysia due to their potent anti-inflammatory activities (Abu Bakar et al., 2018). *Cleome gynandra* and *Melicope ptelefolia* are among the plant species abundantly reported with anti-inflammatory activities (Abu Bakar et al., 2018; Adhikari et al., 2018; Narendhirakannan et al., 2012; Abas et al., 2010; Narendhirakannan et al., 2007; Abas et al., 2006). *Cleome gynandra* (Cleomaceae) is one of the traditional leafy vegetables in Africa and Asia, rich in nutrients such as vitamins and minerals (Shilla et al., 2019). It is locally known as 'Maman' and is usually used as a vegetable dish for daily meals among Malaysians. Studies have reported the ability of *C. gynandra* to treat several diseases such as stomachache, constipation, and epileptic fits (Chandradevan et al., 2020; Adhikari et al., 2018; Narendhirakannan et al., 2005). Bioactive compounds such as flavonoids, quercetin, gallic acid, kaempferol, caffeoylquinic, phenylalanine, choline, mallic acid, citric acid, and dicaffeoylquinic acid have been reported to be responsible for its anti-inflammatory activities (Chandradevan et al., 2020).

Melicope ptelefolia is a well-known traditional herb in most Asian countries. This traditional herb is locally named 'Tenggek Burung' in Malaysia and has become the most favourable vegetable dish in daily meals. The leaf part of *M. ptelefolia* has been reported to have various pharmacological activities, including antioxidant (Kabir et al., 2017), antipyretic (Mahadi et al., 2016) and anti-inflammatory activity (Mustaffa et al., 2011). Alkaloid such as atropine, caffeine and berberine is the most abundant bioactive compound in *M. ptelefolia* and thus contributes to its potent anti-inflammatory activities (Lee et al., 2019). Although both of these traditional herbs have anti-inflammatory actions, there is a dearth of knowledge pertaining to their activities as herbal formulations. Likewise, a considerable number of literatures have reported the potential of herbal formulations and their significance in terms of synergism, and their market demand in treating many diseases, particularly inflammation, as reviewed in detail in Chapter 2, Section 2.5.3.

1.2 Problem statement

To date, topical corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs) are primarily used to treat skin inflammations. Topical corticosteroids are drugs synthesized from the hormone corticosteroid. Examples of such drugs include hydrocortisone, topicort, and betamethasone, among others (Gabros et al., 2020). Undesirable side effects such as burning or stinging sensations, acne, and excessive hair growth on the side of application are amongst the significant flaws of these topical corticosteroids (Coondoo et al., 2014). Besides corticosteroids, NSAIDs are also frequently used to treat skin inflammations. These include diclofenac sodium, aspirin, ibuprofen, and indomethacin (Wongrakpanich et al., 2018). However, long-term use of NSAIDs has been linked to increased unfavourable complications to major organs such as the kidney and liver

(Somchit et al., 2014; Hussein Al Ali et al., 2012; Somchit et al. 2004). A previous study by Dixit et al. (2010) has reported that NSAIDs exhibit a significant risk of kidney damage that potentially lead to acute kidney injury (AKI) or chronic kidney diseases (CKD). Glomerulonephritis, renal papillary necrosis, renal tubular acidosis, and hyponatremia are amongst the diseases that can be developed due to AKI and CKD. It has been reported that 15% of AKI cases are related to the usage of NSAIDs, with about 25% of greater incidence observed in patients older than 65 years (Rahman & Malcoun, 2014). In another study conducted by Sriuttha et al. (2018), the prolonged use of NSAIDs was also associated with hepatic side effects ranging from hepatitis with jaundice to fulminant liver failure and death. In 2008, lumiracoxib, one of the NSAIDs drug, was withdrawn from the market in several countries due to its high potential to cause severe hepatic failure (Bessone, 2010). In addition, the data have shown that NSAIDs have caused approximately 41,000 hospitalizations and 3,300 deaths in older adults each year (Marcum et al., 2010). Prolonged use of NSAIDs therapy for rheumatic patients in Malaysia has increased the risk of upper GI event by 13.2%, with dyspepsia being the most commonly observed complication (Pok et al., 2018). Furthermore, patients with the history of upper GI disease were twice as likely to develop other upper GI events when using NSAIDs. Since the currently available inflammatory drug therapies are always accompanied by their adverse effects, therefore there is a need to find for alternative adjunct(s) to treat inflammation. This could be offered by natural sources, especially herbal medicine (Yuan et al., 2017; Petchi et al., 2014). Thus, it is warranted to shift to natural products as an alternative treatment in curing inflammatory-related diseases, particularly skin inflammatory conditions.

1.3 Justification of the study

There has been emerging attention to the potential use of herbal formulations as anti-inflammatory agents in recent years. A herbal formulation has been proven to have low toxicity and lesser side effects, with comparative efficacy to synthetic drugs (Karimi et al., 2015). In Malaysia, the fundamental data on anti-inflammatory activities of both *C. gynandra* and *M. ptelefolia* are growingly documented; some are in the form of standardized extract (Abu Bakar et al., 2018; Adhikari et al., 2018; Narendhirakannan et al., 2012; Abas et al., 2010; Abas et al., 2006). However, there is scarce data on the anti-inflammatory potential of these herbs as herbal formulations. Considering the advantages of herbal formulation and the potential of *C. gynandra* and *M. ptelefolia* as potent anti-inflammatory agents; therefore, there is a dire need for continuous exploration, particularly to formulate these herbs.

1.4 Objective(s)

1.4.1 General objective

This study investigated the *in vitro* and *in vivo* anti-inflammatory activities of each *C. gynandra*, *M. ptelefolia* and *C. gynandra* cream formulation.

1.4.2 Specific objectives

To determine the cytotoxicity activity of *C. gynandra*, *M. ptelefolia* and their herbal formulation extract in RAW 264.7 cells.

To investigate the anti-inflammatory activities of *C. gynandra*, *M. ptelefolia*, and their herbal formulation extract using nitric oxide inhibition assay.

To assess the topical anti-inflammatory activity of the selected herb in a cream formulation against arachidonic acid-induced ear oedema in the male Sprague Dawley rat model.

To conduct pre-clinical testing of the selected herb in a cream formulation on rat skin using the skin irritation method.

1.5 Hypothesis

Herbal formulations of these two herbs may exhibit low cytotoxicity activities compared to the single herb, *C. gynandra* and *M. ptelefolia*, respectively.

Herbal formulations of these two herbs may exhibit the highest anti-inflammatory activities compared to the single herb, *C. gynandra* and *M. ptelefolia*, respectively.

The selected herb in a cream formulation may possess high topical anti-inflammatory activity against arachidonic acid-induced ear oedema in the rat model.

The selected herb in a cream formulation may produce safe dermatological aspect as tested via *in vivo* skin irritation method.

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