

CHARACTERIZATION OF ANTIOXIDANT, ANTIMICROBIAL AND ANTI-  
AGING PROPERTIES OF ALPHA-MANGOSTIN FROM MANGOSTEEN  
PERICARP (*GARCINIA MANGOSTANA* LINN.)

TENG YI SIEW

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**Dedicated to my beloved family and friends.**

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## ABSTRACT

In recent years, public interest on skincare cosmetics has shifted from synthetic to natural product due to adverse reactions of synthetic skincare cosmetics. In present study,  $\alpha$ -mangostin from pericarp extract of *Garcinia Mangostana* Linn was evaluated for its *in vitro* antioxidant, antimicrobial and anti-aging properties. Determination of total antioxidant capacity was carried out by DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging activity and ABTS (2,2-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)) assay. The antimicrobial activity was assessed using Minimum Inhibitory Concentration (MIC) test against: three selected bacteria strains *Staphylococcus aureus* (*S.aureus*), *Propionibacterium acnes* (*P. acnes*) and *Pseudomonas aeruginosa* (*P. aeruginosa*); and two fungi strains *Trichophyton rubrum* (*T. rubrum*) and *Trichophyton mentagrophytes* (*T. mentagrophytes*). Meanwhile, Bromide MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium) assay, collagen estimation assay and anti-collagenase assay were carried out to investigate the *in vitro* anti-aging effect of  $\alpha$ -mangostin on human skin fibroblast cells. The  $\alpha$ -mangostin exhibited high anti-oxidant capacity with IC<sub>50</sub> (Half maximal inhibitory concentration) value of 0.0288 mg and 0.4637 mg, using ABTS assay and DPPH assay, respectively. The MIC values against test bacteria ranged between 0.156 mg/ml and 10 mg/ml whereas against fungi, MIC ranged from 2.5 mg/ml to 10 mg/ml. The following is the order of antimicrobial efficiency of  $\alpha$ -mangostin on selected test microbes: *S. aureus* > *P. acnes* > *T. rubrum* > *P. aeruginosa* > *T. mentagrophytes*. Meanwhile,  $\alpha$ -mangostin significantly restored the synthesis of pro-collagen on UVB (Ultraviolet B) irradiated human skin fibroblast in a dose dependent manner. The collagen content was increased by 3-fold upon treatment of 2  $\mu$ g/ml  $\alpha$ -mangostin. Extract of  $\alpha$ -mangostin also showed good inhibitory effect on collagenase at 89.89  $\pm$ 1.52%. Based on the outcomes, the recommended  $\alpha$ -mangostin concentration to be formulated in cosmetic product is ranged from 1-2  $\mu$ g/ml.

## ABSTRAK

Dalam tahun kebelakangan ini, minat orang awam terhadap kosmetik telah beralih daripada produk sintetik kepada produk semula jadi akibat kesan sampingan produk sintetik. Dalam kajian ini,  $\alpha$ -mangostin daripada ekstrak perikarpa *Garcinia Mangostana* Linn telah dinilai untuk mengkaji sifat-sifat antioksidan, antimikrob dan anti-penuaan in vitro. Penentuan jumlah kapasiti antioksidan telah dijalankan menggunakan DPPH (2,2-Diphenyl-1-picrylhydrazyl) dan ABTS (2,2-azino-bis (asid 3-ethylbenzothiazoline-6-sulphonic)). Aktiviti antimikrob dinilai menggunakan ujian kepekatan perencatan minimum (MIC) terhadap: tiga jenis bakteria terpilih *Staphylococcus aureus* (*S.aureus*), *Propionibacterium acnes* (*P. acnes*) dan *Pseudomonas aeruginosa* (*P. aeruginosa*); dan dua jenis kulat *Trichophyton rubrum* (*T. rubrum*) dan *Trichophyton mentagrophytes* (*T. mentagrophytes*). Sementara itu, ujian Bromide MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium), anggaran kolagen dan anti-kolagenase telah dijalankan untuk menyiasat kesan anti-penuaan daripada  $\alpha$ -mangostin pada sel-sel *fibroblast* kulit manusia. Ekstrak  $\alpha$ -mangostin mencatatkan nilai anti-oksida yang tinggi dengan nilai IC<sub>50</sub> (Half maximal inhibitory concentration) sebanyak 0.0288 mg/ml dan 0.4637 mg/ml, masing-masing menggunakan ujian ABTS dan DPPH. Nilai MIC terhadap bakteria adalah antara 0.156 mg/ml dan 10 mg/ml sebaliknya terhadap kulat, nilai MIC adalah dari 2.5 mg/ml hingga 10 mg/ml. Berikut adalah tertib kecekapan ujian antimikrob oleh  $\alpha$ -mangostin terhadap bahan uji mikrob terpilih: *S. aureus* > *P. acnes* > *T. rubrum* > *P. aeruginosa* > *T. mentagrophytes*. Sementara itu,  $\alpha$ -mangostin dapat memulihkan sintesis pro-kolagen pada radiasi UVB (Ultraviolet B) pada sel *fibroblast* kulit manusia bergantung kepada dos. Kandungan kolagen telah meningkat sebanyak 3 kali ganda melalui dos rawatan 2  $\mu$ g/ml  $\alpha$ -mangostin. Ekstrak  $\alpha$ -mangostin juga menunjukkan kesan perencatan yang baik terhadap kolagenase pada  $89.89 \pm 1.52\%$ . Berdasarkan hasil kajian ini, cadangan kepekatan  $\alpha$ -mangostin untuk digunakan di dalam produk kosmetik anti-penuaan adalah di antara 1-2  $\mu$ g/ml.

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**LIST OF ABBREVIATIONS**

AP-1	Activator Protein 1
ABTS	2,2'-azinobis-(3-ethylbenzothiazoline-6-sulfonic acid)
ATCC	American Type Culture Collection
DPPH	2,2-diphenyl-2-picrylhydrazyl
CAGR	Compound Annual Growth Rate
C <sub>6</sub> -C <sub>3</sub> -C <sub>6</sub>	Tricyclic Aromatic System
CO <sub>2</sub>	Carbon Dioxide
COX-2	Cyclooxygenase-2
DMEM	Dulbecco's Modified Eagle Medium
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic acid
DQ	Dye-quenched
e <sup>-</sup>	electron
EDTA	Ethylenediaminetetraacetic acid
FBS	Fetal Bovine Serum
Fe <sup>2+</sup>	Iron (II) cation
Fe <sup>3+</sup>	Iron (III) cation
GML	<i>Garcinia Mangostana</i> Linn
g	gram
g/L	gram per liter
h	hour
HAT	Hydrogen Atom Transfer
HSF	Human Skin Fibroblast
HPLC	High Performance Liquid Chromatography

HPLC-DAD	High Performance Liquid Chromatography with Diode-Array Detection
IC50	Half Maximal Inhibitory Concentration
IL-1 $\alpha$	Interleukin 1 alpha
IL-6	Interleukin 6
LDL	Low Density Lipoproteins
$\mu\text{g/ml}$	microgram per milliliter
$\mu\text{l}$	microliter
$\mu\text{m}$	micrometre
$\text{cm}^2$	square centimeter
cfu/ml	colony forming units per milliliter
min	minutes
mg	milligram
mg/ml	milligram per milliliter
$\text{MJ/cm}^2$	millijoule per square centimeter
ml	milliliter
mm	millimeters
M	molar
ppm	part per million
v/v	volume per volume
MAP	Mitogen-activated protein
MIC	Minimum Inhibitory Concentration
mRNA	Messenger Ribonucleic acid
MMP	Matrix Metalloproteinase
MMP-1	Collagenases
MMP-2	Gelatinase A
MMP-3	Stromelysin
MMP-9	Gelatinase
MOPS	3-(N-morpholino) propanesulfonic acid
MTT	3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide
nm	nanometer
NCCLS	National Committee for Clinical Laboratory Standards
NF-K $\beta$	Nuclear factor $\beta$

NMR	Nuclear Magnetic Resonance
NO <sup>•</sup>	Nitric Oxide Radicals
O <sub>2</sub>	Oxygen Molecule
O <sub>2</sub> <sup>•-</sup>	Superoxide Anion Radicals
OH <sup>•</sup>	Hydroxyl Radical
H <sup>+</sup>	Hydrogen Atom
H <sub>2</sub> O	Water
H <sub>2</sub> O <sub>2</sub>	Hydrogen Peroxide
pH	Potential of Hydrogen
PDA	Photodiode Array Detector
RMPI	Roswell Park Memorial Institute
ROS	Reactive Oxygen Species
SD	Standard Deviation
SDA	Sabouraud Dextrose Agar
SOD	Superoxide Dismutase
TGF-β	Transforming growth factor beta
TPA	12-O-tetradecanoyl phorbol-13-acetate
UV	Ultraviolet
([Gly-X-Y] <sub>n</sub> )	Repeat Unit of collagen triple helix



**LIST OF SYMBOLS**

*	Asterisk
°C	Degree Celcius
\$	Dollar Sign
=	Equals Sign
$\alpha$	Greek Small Letter Alpha
$\beta$	Greek Small Letter Beta
$\gamma$	Greek Small Letter Gamma
$\kappa$	Greek Small Letter Kappa
<	Less than
$\times$	Multiplication Sign
%	Percent Sign
$\pm$	Plus-Minus Sign
®	Registered Sign
/	Solidus
™	Trade Mark Sign

## **CHAPTER 1**

### **INTRODUCTION**

#### **1.1 Research Background**

In recent years, the global cosmeceutical industry has emerged tremendously owing to the high demand for beauty products that offer a pharmaceutical therapeutic benefit. According to a report from Business Wire (2014), the global cosmeceutical market was estimated at US \$35 Billion and is expected to increase around 7% for the compound annual growth rate (CAGR) during 2013 to 2018. Among it, skin care products own the most important segment along with people of diverse age group. In particular, antibacterial ingredients mostly designated to teenage populations meanwhile antioxidants and anti-aging ingredients formulated products are subjected to people entering the middle stage of life. This report justify that people tend to invest extensively on maintaining youthful and elegance appearance, hence contribute to the massive increment of the cosmeceutical market (William Reed Business Media, 2014).

Nowadays, regardless of the therapeutic advantages of the cosmeceutical product in the market, consumers are more concerned on the safety and hazardous effect. These concerns are due to synthetic cosmetics that have been reported to

cause harmful effect to the skin. For instance, bentonite, parabens, propylene glycol, and ethylene glycol are some common hazardous chemicals used in cosmetics which could cause irritation, photo toxicity, contact allergy, contact dermatitis and serious health conditions if sufficient is absorbed by the body (Chermahini *et al.*, 2011). In turn, public interest has shifted interest from synthetic cosmetics to natural one.

Several medicinal plants are known to be important sources of biologically active chemical substances such as tannins, phenolics, flavonoids, alkaloids, glycosides, saponins, and other chemical compounds which have curative properties (Abalaka and Oyewole, 2011). These biologically active constituents often displayed antioxidant and antimicrobial properties which can help our immune system against both cellular oxidation reactions and pathogens. Over the past decades, mangosteen plant parts have been studied and shown to contain high amount of xanthenes which then learned to have potential biological activities in *in vitro* systems (Obolskiy *et al.*, 2009). Natural antioxidants from plants play significant roles as radical scavengers against oxygen-centered free radicals and other reactive oxygen species (ROS) and hence resist the cellular oxidative damage either in intrinsic or extrinsic way (Ozsoy *et al.*, 2008). As such, it is utmost important to discover safe and potent antioxidants to decrease free radical production in skin as well as to preserve youthful appearance.

Oxidative damage can occur intrinsically and extrinsically which, eventually lead to skin aging. When UV was exposed to skin, superoxide radical is generated and activates a number of phosphorylase mediated kinases, leading to the activation of signal transduction pathways throughout the epidermis. Matrix metalloproteinases (MMP) is a family of zinc-containing proteinases which specifically degrade the extracellular matrix proteins that comprise connective tissue. Among the family of MMPs which initiate the degradation of Type I collagen (90% of its dry weight), MMP-1 play significant role in collagen fragmentation and thus initiate the appearance of aged human skin (Murina *et al.*, 2012). According to Wlaschek *et al.* (2001) and Kang *et al.* (2001), the collagen fragmentation activity is also increases with a positive dose-response relationship with UV radiation. Hereby, the antioxidants which can down regulate the matrix metalloproteinase caused by ROS

will enhance the anti-aging mechanism and promote the restoration of collagen in the epidermis.

Aging occurs across different organs tissues and cells, while the aging signs of internal organs are masked from the ambient “eyes”, the skin provides first obvious marks of the passing time (Ganceviciene *et al.*, 2012). Therefore, skin anti-aging strategies which attempted to reverse the dermal and epidermal signs of photo- and chronological aging have been a subject undergoing intense study. In most of the skin anti-aging therapy, the mainspring is to achieve a healthy, smooth, blemish-free, translucent and resilient skin (Vedamurthy, 2006). In order to diminish presentation of aging, it encounter both intrinsic and extrinsic factors, namely from life to the immune, genetic, emotional and health status in general. The approaches for skin anti-aging can be grouped in few, such as cosmetological care, topical medicine agents or topical agents, invasive procedures, systemic agents, avoiding of exogenous factors of aging, correction of life style and habits, and preventive medicine (Ganceviciene *et al.*, 2012). In this particular study, it focuses on the exploration of antioxidant as the components to control collagen degradation by reducing the concentration of free radicals in the tissues.

Skin infections by bacterial and fungal are sometimes being thought as mild diseases when compared with diseases that cause significant mortality (Hay *et al.*, 2006). However, skin problems often appeared over the body surface, for instance the outer layers of the skin, the nails and hair, affecting the facial appearance and consequently the social relations. Specifically with the advancement of knowledge on cosmetic arena, people tend to seek for cosmeceuticals which can provide safe dermal applications with minimum side effects (Kumari and Khurana, 2013). Therefore, it is a great need to investigate natural component such as  $\alpha$ -mangostin for its antimicrobial activities against bacterial and fungal species to provide new discovery of active ingredients from natural products to be formulated in the cosmetic product.

## 1.2 Problem Statement

Due to the public awareness on the safety of cosmeceutical products, they are keen to shift from synthetic cosmetics to natural ones. This is mainly due to the adverse reactions resulted from the synthetic skincare cosmetics, for instance allergic contact dermatitis, phototoxic and photo-allergic reactions, and irritant contact dermatitis. In the present study, mangosteen pericarp (*Garcinia mangostana* Linn) was chosen to be investigated for its antioxidant, antimicrobial and anti-aging properties. The major component from pericarp of mangosteen,  $\alpha$ -mangostin, was selected as the target compound in order to exploit new natural ingredients in developing safe and potent cosmetic products. Facial appearance is one of the important factors influencing social relations, thus it is important to evaluate the new potent antimicrobial active compound for the use in cosmetic products. Hence, dermatophyte and bacterial pathogen of skin are selected as the test organisms in antimicrobial study. *Garcinia mangostana* Linn. are known to possess a wide spectrum of pharmacologic properties, including antioxidant, anti-tumor, anti-allergic, anti-inflammatory, anti-bacterial, anti-fungal, and anti-viral activities (Shan et al., 2011). There has been no studies reported on anti-aging activities by  $\alpha$ -mangostin of *Garcinia mangostana* Linn., thereby this investigation might be a significant approach to discover a new anti-aging active ingredients that can be utilized in the cosmetic industry.

## 1.3 The Objective of the Research

The aim of the research is to study the antioxidant, antimicrobial and anti-aging properties of  $\alpha$ -mangostin from *Garcinia mangostana* Linn. pericarp extract.

## 1.4 The Scope of the Research

In order to achieve the objective, the scopes of the studies are identified as follow:-

- i) DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical scavenging activity and ABTS (2, 2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)) assay were carried out to measure the antioxidant activity of the  $\alpha$ -mangostin.
- ii) Broth microdilution test was done to screen the antimicrobial activity of  $\alpha$ -mangostin against several selected bacteria and fungi strains.
- iii) To study the anti-aging properties of  $\alpha$ -mangostin, two assays were carried out. Anti-collagenase assay was performed to measure the anti-collagenase properties of  $\alpha$ -mangostin.
- iv) Collagen estimation assay was carried out to investigate the effect of  $\alpha$ -mangostin on collagen synthesis *in vitro* by the fibroblast cells.

## 1.5 Significance of Study

The contributions of this study would be of interest in promoting the new trend that using wellness concept base on natural and plant materials in the skin care product formulation. Besides providing consumers with natural and plant base cosmetics and personal care products, these discoveries could found the concentration range able to apply to product development as cosmetic products. Moreover, the outcomes of the study could facilitate future application of mangosteen waste to be widely and synergistically used, at the same time preserving the environment.

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