IN VITRO PERMEATION AND SKIN RETENTION OF ALPHA-MANGOSTIN PRONIOSOME

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To my beloved mother and father

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ABSTRACT

Alpha-mangostin has been identified as a potent anti-melanogenesis compound *in vitro* on B16F1 melanoma cells. A concentration of 5 μg/mL demonstrated promising anti-melanogenesis effect without compromising the cell viability. However, due to its high lipophilic nature, the cosmeceutical application of α-mangostin in topical formulation is restricted. The current investigation aimed to evaluate the potential of proniosome as a carrier to enhance skin permeation and skin retention of α-mangostin. Alpha-mangostin proniosomal formulations were prepared using coacervation phase separation method. Upon hydration, α-mangostin-loaded niosomes were characterized for size, polydispersity index, entrapment efficiency, zeta potential and morphology. Using different surfactants, preliminary study to evaluate skin concentration suggested that Spans significantly ($p < 0.05$) enhanced deposition of α-mangostin in the viable epidermis/dermis layer (VED) as compared to Tween 60. Incorporation of soya lecithin in the proniosomal formulation also significantly enhanced the VED concentration of α-mangostin. The *in vitro* permeation experiments using dermis-split Yucatan Micropig skin revealed that proniosomes composed of Spans, soya lecithin and cholesterol were able to enhance the skin permeation of α-mangostin with a factor range from 1.8 to 8.0-fold as compared to the control suspension. All the proniosomal formulations (except for S20L) had significantly ($p < 0.05$) enhanced the deposition of α-mangostin in the VED layer with a factor range from 2.5 to 2.9-fold as compared to the control suspension. Proniosome S85L showed the highest permeation profile (8.0-fold) and the highest enhancement of VED concentration of α-mangostin (2.9-fold). Collectively, these results suggested that proniosomes can be utilized as a promising carrier for a highly lipophilic compound like α-mangostin.

ABSTRAK

Alfa-mangostin telah dikenalpasti sebagai kompaun anti-melanogenesis yang kuat pada sel melanoma B16F1 *in vitro*. Kepekatan optimum 5 μg/ml menunjukkan kesan anti-melanogenesis tanpa menjejaskan kebolehidupan sel. Walau bagaimanapun, sifat α-mangostin yang sangat lipofilik telah mengehadkan aplikasinya dalam formulasi sediaan topikal kosmetik. Kajian ini bertujuan untuk menilai potensi proniosom sebagai sistem pembawa α-mangostin untuk meningkatkan kadar penyerapan dan kesampaiannya ke kulit. Formulasi proniosom α-mangostin telah disediakan dengan menggunakan kaedah pemisahan fasa koaservatan. Selepas proses penghidratan, niosom α-mangostin dicirikan menerusi saiz, indeks kepoliserakan, kecekapan perangkap, potensi zeta dan morfologi. Kajian awal menujukkan bahawa proniosom yang disediakan daripada surfaktan Span dapat menyampaikan α-mangostin ke lapisan epidermis/dermis yang hidrofilik (VED) dengan lebih berkesan berbanding dengan surfaktan Tween 60 ($p < 0.05$). Di samping itu, lesitin soya juga didapati meningkatkan prestasi pembawaan α-mangostin ke lapisan VED ($p < 0.05$). Eksperimen penyerapan *in vitro* yang dijalankan dengan menggunakan kulit *Yucatan Micropig* yang terpisah lapisan dermisnya mendapati bahawa proniosom yang dihasilkan daripada Span, lesitin soya dan kolesterol dapat meningkatkan penyerapan α-mangostin di kulit ($p < 0.05$) lebih berkesan berbanding dengan kumpulan kawalan. Semua formulasi proniosom (kecuali S20L) menunjukkan keupayaan untuk meningkatkan kesampaian α-mangostin ke lapisan VED sebanyak 2.5 – 2.9 kali ganda dengan perbezaan yang signifikan ($p < 0.05$) berbanding dengan kumpulan kawalan. Formulasi proniosom S85L menunjukkan penyerapan (8.0 kali ganda) dan pembawaan α-mangostin di lapisan VED (2.9 kali ganda) yang paling tinggi. Secara keseluruhannya, keputusan menunjukkan bahawa proniosom boleh digunakan sebagai pembawa bagi kompaun yang sangat lipofilik seperti α-mangostin.

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LIST OF ABBREVIATIONS

CCL	-	Chemokines
CPP	-	Critical packing parameter
DCP	-	Dicetyl phosphate
ECM	-	Extracellular matrix
EE	-	Entrapment efficiency
FDA	-	U.S. Food and Drug Administration
GRAS	-	Generally Recognized as Safe
HPLC	-	High performance liquid chromatography
IL.	-	Interleukin
LC/MS/MS	-	Liquid chromatography/mass spectrometry/ mass spectrometry
MSH	-	Melanocyte stimulating factor
NO	-	Nitric oxide
PDI	-	Polydispersity index
SA	-	Stearylamine
SC	-	Stratum corneum
TGF	-	Transforming growth factor
TNF	-	Tumor necrosis factor
U.S.	-	United State
VED	-	Viable epidermis/dermis
w/o	-	Water in oil
YMP	-	Yucatan Micropig
α-mangostin	-	Alpha-mangostin

LIST OF SYMBOLS

A	-	Skin surface area
C	-	Concentration
C_{ss}	-	Steady state skin concentration
D	-	Diffusion coefficient
h	-	Diffusional path length
J	-	Flux
k	-	Boltzmann constant
T	-	Absolute temperature
η	-	Viscosity
d_H	-	Hydrodynamic diameter
K_p	-	Permeability coefficient
K_s	-	Partition coefficient
ΔCv	-	Concentration gradient of drug

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CHAPTER 1

INTRODUCTION

1.1 Research Background

To date, due to the increased awareness of consumer and the advancement of research and development (R&D), the cosmeceutical industries have switched their focus from the use of chemical derivatives to the use of natural products as cosmeceutical ingredient. However, there are several common problems associated with the development of cosmeceutical products using natural products, one being the poor permeation of the natural derivatives through the skin. It is a clear fact that no matter how powerful a natural compound is, it is useless unless the compound is effectively delivered to its targeted site for action.

Mangosteen (*Garcinia mangostana* Linn.) which is native to Malaysia has been valued for a variety of bioactive compounds isolated from its edible plant parts, namely xanthones and phenolics (Karim and Azlan, 2012). Xanthones are of great interest to researchers as they exerted a wide range of remarkable bioactivities such as antioxidant, antimicrobial, antiviral, anti-cancer, and anti-inflammatory activities (Abdalrahim *et al.,* 2012; Yoswathana, 2013). More than 50 xanthones have been isolated and α-mangostin is the major xanthone identified from the pericarp of mangosteen (Abdalrahim *et al.,* 2012). A previous work (Mariani *et al.,* 2014) reported that α-mangostin is a potent depigmenting agent due to its strong anti-melanogenic activity, capable of inhibiting activity of tyrosinase enzyme and down-regulating genes expression involved in the melanogenesis pathways. The study

suggested the potential of α-mangostin in the development of whitening range cosmeceutical products.

Despite its strong biological activities, α-mangostin is a highly lipophilic compound, with an estimate log *P* value of 4.64 (ChemDraw Professional 15.0, Cambridge Soft, Perkin Elmer). Due to its poor water solubility, the permeation of α-mangostin through the skin layers is very challenging. In order to overcome the skin permeation limitation by α-mangostin, proniosome, which is a potent colloidal type delivery system was chosen as a carrier vesicle to transport the α-mangostin to its skin targeted site. The melanocytes are located at the basal epidermis layer for anti-melanogenesis activity.

Coacervation phase separation method, a method for proniosomes preparation was employed in this study. This method works under simple idea that the mixture of surfactant: alcohol: aqueous phase can be used to form the concentrated proniosomal formulation, which upon dilution with excess aqueous phase will convert spontaneously to a stable niosomal dispersion (Vora *et al.,* 1998). This method allows easy future scale up of production as it is simple and practical for routine, does not involved lengthy procedures, does not required expensive instrumentations, and does not involved the unnecessary use of organic solvent and unacceptable additives (Vora *et al.,* 1998; Fang *et al.,* 2001). The main ingredient of proniosome was non-ionic surfactant while others ingredients (*i.e.* cholesterol and soya lecithin) were added to enhance the vesicle stability and skin permeability.

1.2 Problem Statement

Alpha-mangostin has been identified as a potent depigmenting compound that suitable to be incorporated in whitening range cosmeceutical products. Despite its potent anti-melanogenic activity, application of α-mangostin in topical cosmeceutical is restricted due to its high lipophilicity and poor water solubility.

Lipophilicity is one of the important descriptor governing drug permeation across a biological membrane (Malkia *et al.,* 2004). Lipophilicity is generally expressed quantitatively as the $\log_{10}$ of the partitioning of a neutral drug species between n-octanol and water ($\log K_{o/w}$ or $\log P$). Skin permeation of compounds was reported to be increased with lipophilicity. However, a further increase in $\log P$ to more than 4.1 was reported to decrease the skin permeability. Alpha-mangostin is highly lipophilic ($\log P = 4.64$), therefore the permeation of α-mangostin through the rate-limiting skin membrane is very challenging and thus needs to be overcome.

This study was proposed to develop a convenient and low-cost transdermal drug delivery for α-mangostin using proniosome as a novel carrier. Several non-irritant, non-toxic, and relatively cheap non-ionic surfactants were screened for α-mangostin proniosome preparations. Since the development of proniosome still in its infancy, therefore further exploration is required to study the factors that could influence the characteristics and performance of proniosome. The influence of formulation components on the characteristics of α-mangostin proniosome such as vesicle size, polydispersity index (PDI), encapsulation efficiency (EE), zeta potential and morphology were investigated. Furthermore, the *in vitro* permeation and skin retention of α-mangostin proniosome were also studied using dermis-split Yucatan Micropig (YMP) skin.

To date, no report was found on the development of α-mangostin proniosome using coacervation phase separation method (a recently developed method). Also, no report was found reporting the *in vitro* permeation and skin retention of α-mangostin through the non-viable skin, hence the novelty of this study.

1.3 Hypothesis

Due to the highly lipophilic nature of α-mangostin, the compound might tend to accumulate in the outermost layer of skin (hydrophobic stratum corneum) and has limited permeation across the lower layers (the hydrophilic viable epidermis/dermis

or VED), thereby results in reduced bioavailability and therapeutic effect of the compounds. In this study, the α-mangostin proniosomes were developed to enhance topical delivery. Proniosomes improved permeation flux of α-mangostin across the skin and increased the skin retention of α-mangostin in the viable epidermis /dermis (VED) layer where the melanocytes (pigment forming cells) are located. Furthermore, the formulation aspects of proniosome play a major role in determining the characteristics and performance of α-mangostin proniosomes.

1.4 Research Objectives

1.4.1 To develop and characterize the α-mangostin proniosome.

1.4.2 To determine the *in vitro* permeation and skin retention of α-mangostin proniosome.

1.5 Scopes of Study

In order to achieve the objectives, scopes of the study had been identified and narrowed down. This research covered the scopes of study as listed as following:

1.5.1 Screening of formulation ingredients of α-mangostin proniosome based on solubility and preliminary skin retention study. Development of α-mangostin proniosome by using coacervation phase separation method. Formulation ingredients including the non-ionic surfactants (Spans and Tweens), cholesterol and soya lecithin. Characterization of the α-mangostin proniosome in term of size, polydispersity index (PDI), entrapment efficiency (EE), zeta potential and morphology.

1.5.2 *In vitro* permeation study and skin retention study of α-mangostin proniosome through dermis-split Yucatan Micropig (YMP) skin (48h).

Determine the concentration of α-mangostin retained in the stratum corneum and the viable epidermis-dermis layer (VED) (refers to as the 'total concentration') and the concentration of α-mangostin retained in the tap-stripped skin (refers to as the 'VED concentration').

1.5.3 Determine the effect of formulation ingredients on the characteristics and performance (*in vitro* permeation and skin retention) of α-mangostin proniosome.

1.6 Significances of Study

This study developed a novel topical delivery system (proniosome) of α-mangostin with enhanced *in vitro* skin permeation and skin retention in the viable epidermis/dermis (VED) layer (which is the targeting site for anti-melanogenesis activity), critical for cosmeceutical application. The developed α-mangostin proniosomal formulations provide a good ingredient for whitening cosmeceuticals (e.g. whitening serum, cream *etc.*), thus promoting the use of local herbs as an ingredient for cosmeceutical application. Besides, data concerning the development, characterization, *in vitro* permeation and skin retention of α-mangostin through the non-viable skin could provide useful literature for researchers working in cosmeceutical and pharmaceutical areas, as α-mangostin was also reported to exhibit a variety of bioactivities. The data regarding the effect of formulation ingredients on the characteristics and performance of vesicles could also provide useful references for formulation development, optimization, and scaling up in future.

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