ANTIOXIDANT AND ANTI-AGEING ACTIVITIES OF COCOA BEAN EXTRACT FOR COSMECEUTICAL USE

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By

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Chairman : Professor Russly Abdul Rahman, PhD
Faculty : Halal Products Research Institute

Theobroma cacao which is best-known as 'Food of the God' by an ancient Greek, belongs to *Sterculiaceae* family. It is an indigenous plant from the tropical region of America which culture was further extended to equatorial areas of Africa and Asia. The goodness of *T.cacao* bean against cancer, cardiovascular-related diseases, certain neurodegenerative disorders and premature ageing have been often reported. However, information pertaining to antioxidant capacity and anti-ageing activity of potential Malaysian cocoa bean extract (CBE) for cosmeceutical use is limited.

Therefore, the main objective was to determine the antioxidant capacity and anti-ageing activity of two types of cocoa beans' clones, known as PBC140 and PBC123. Response surface methodology employing a central composite design throughout twenty experiments was conducted for the optimization of extraction condition, focusing on ethanol (30-80%, v/v), temperature (30-60°C) and extraction time (60-240 min). Optimal ethanol concentration (70% [v/v]) and extraction temperature (50°C) have resulted in the highest total phenolic (377 and 231 mg GAE/g DW, respectively) and total flavonoid content (73 and 63 mg RE/g DW, respectively). For antioxidant capacity, PBC140 was significantly higher (p>0.05) than PBC123 in term of 2,2-Diphenyl-1-picrylhydrazyl scavenging whereas ferric reducing antioxidant power and β-carotene leanoleate bleaching assays showed no significant different (p>0.05). PBC140 was higher than PBC123 but with no significant different (p>0.05) in both anti-collagenase and anti-elastase when conducted on Ac-PLG-[2-mercapto-4-methyl-pentanoyl]-LG-OC_2H_5 and MeOSuc-Ala-Ala-Pro-Val-pNA substrates, respectively. PBC140 was cytotoxic at IC_{50}=1100 µg/mL on $1x10^5$ human dermal fibroblast (HDFa) cells/well at sixth passage or the highest average HDFa cell viability level. The extracted ribonucleic acid of HDFa treated with $1x10^3$ µg/mL CBE significantly (p<0.05) downregulated the

ultraviolet-induced matrix metalloproteinase-1 by 25-fold relative to calibrator. Ultraviolet A ratio for *in vitro* photoprotective effect of 0.1% (w/v) CBE formulation indicated 0.553 from the Boots Star Rating (Good). Intervention of approximately 500 mg 0.1% (w/v) CBE formulation on 20 human subjects aged between 30 to 46 years for 2 months duration in the *in vivo* skin efficacy studies recorded significant (p<0.05) percent changes of skin texture parameters, namely volume (-40%), energy (46%), contrast (-18%) and variance (-21%). The skin elasticity parameter for CBE formulation recorded significant (p<0.05) increment of ten times compared to placebo group. To conclude, Malaysian CBE is a potential active material due to the encouraging results of antioxidant capacity, *in vitro* anti-ageing, safety, and *in vivo* skin efficacy that meet the primary objective of producing harmless yet natural cosmeceutical with significant skin improvement.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

ANTIOKSIDAN DAN AKTIVITI ANTI-PENUAAN EKSTRAK BIJI KOKO UNTUK KEGUNAAN KOSMESEUTIKAL

Oleh

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Theobroma cacao tergolong dalam keluarga *Sterculiaceae* dan dikenali sebagai *'Food of the God'* oleh Yunani kuno. Ia adalah tumbuhan asli dari rantau tropika Amerika dan penanamannya telah diperluaskan ke kawasan khatulistiwa benua Afrika dan Asia. Kebaikan *T.cacao* dalam pencegahan penyakit kanser, kardiovaskular, gangguan *neurodegenerative*, dan penuaan pramatang telah sering dilaporkan. Walau bagaimanapun, maklumat berkaitan dengan kapasiti antioksidan dan aktiviti anti-penuaan ekstrak biji koko klon terpilih Malaysia (CBE) untuk kegunaan kosmeseutikal adalah terhad.

Oleh itu, objektif utama penyelidikan ialah bagi menentukan kapasiti antioksidan dan aktiviti anti-penuaan bagi dua jenis klon koko iaitu PBC140 dan PBC123. Kaedah *response surface methodology* menggunakan *central composite design* yang melibatkan dua puluh eksperimen telah dijalankan bagi mengoptimumkan keadaan pengekstrakan iaitu peratusan etanol (30-80 %, i/i), suhu (30-60°C) dan masa (60-240 min). Kandungan fenolik yang tertinggi bagi PBC140 dan PBC123 masing-masing sebanyak 377 dan 231 mg GAE/g DW manakala kandungan flavonoid iaitu 73 dan 63 mg RE/g DW telah dihasilkan daripada peratusan etanol (70% [i/i]) dan suhu pengekstrakan (50°C) yang optimum. Bagi kapasiti antioksidan, PBC140 lebih tinggi daripada PBC123 untuk ujian *2,2-Diphenyl-1-picrylhydrazyl* manakala masing-masing klon tidak menunjukkan perbezaan signifikan (p>0.05) untuk ujian *ferric reducing antioxidant power* serta *β-carotene leanoleate bleaching*. PBC140 lebih tinggi daripada PBC123 namun tiada perbezaan signifikan (p>0.05) bagi kedua-dua ujian anti-kolagenase ke atas substrat *Ac-PLG-[2-mercapto-4-methyl-pentanoyl]-LG-*OC_2H_5 dan anti-elastase ke atas substrat *MeOSuc-Ala-Ala-Pro-Val-pNA*. PBC140 bersifat sitotoksik pada IC_{50}=1100 µg/mL ke atas $1x10^5$ sel *human dermal fibroblast* (HDFa)/*well* iaitu pada transaksi sel yang keenam di mana sel HDFa berada pada tahap yang paling progresif. Ekstrak asid

ribonukleik daripada HDFa pada dos $1x10^3$ µg/mL CBE telah menunjukkan rencatan ekspresi ke atas gen *matrix metalloproteinase 1* daripada rangsangan sinar ultraungu, yang signifikan (p<0.05) iaitu 25 kali ganda relatif kepada calibrator. Penarafan *Boots Star* formulasi 0.1% (b/i) CBE bagi kesan fotoprotektif daripada sinar ultraungu A ialah 0.553 (Baik). Sejumlah 500 mg 0.1% (b/i) formulasi CBE yang diaplikasikan ke atas 20 subjek manusia antara 30 hingga 46 tahun selama 2 bulan bagi ujian *in vivo,* telah merekodkan peratus perubahan tekstur kulit yang signifikan (p<0.05) dari segi *volume* (-40%), *energy* (46%), *contrast* (-18%) dan *variance* (-21%) serta purata kenaikan yang signifikan (p<0.05) bagi parameter keanjalan kulit iaitu sepuluh kali ganda berbanding kumpulan plasebo. Kesimpulannya, hasil ujian keupayaan antioksidan, anti-penuaan secara *in vitro*, aspek keselamatan, dan keberkesanan kulit secara *in vivo* memenuhi objektif utama kajian iaitu potensi CBE klon Malaysia untuk dibangunkan sebagai bahan aktif semulajadi di dalam penghasilan kosmeseutikal yang selamat serta berkebolehan membaiki tekstur kulit dengan berkesan.

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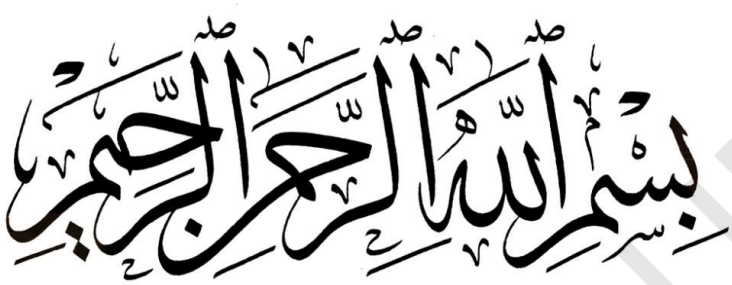

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

A	Water to Skin Ratio Coefficient
Ac	Mean OD of Control
At	Mean OD of Tested Extract
ACD	ASEAN Cosmetic Directive
AOC	Antioxidant Capacity
APC	Aerobic Plate Count
AR	Allergic Reactions
b	Estimated Regression Coefficient
BHA	tert-butyl-4-hydroxy anisole
BHT	2,6-di-tert-butyl-p-hydroxy-toluene
Brij™ 35	Nonionic Polyoxyethylene Surfactant
CAGR	Compound Annual Growth Rate
CBE	Cocoa Bean Extract
CCD	Central Composite Design
CPB	Cocoa Pod Borer
d0	Variation in Concentration
d1	Space Travelled
DPPH	2,2-Diphenyl-1-picrylhydrazyl
E	PCR Efficiency
FD&C	Food, Drugs, and Cosmetic Act
FRAP	Ferric Reducing Antioxidant Power
GAE	Gallic Acid Equivalents
HD	High Dose of CBE Sample
HDFa	Human Dermal Fibroblasts, adult
JAKIM	Jabatan Kemajuan Islam Malaysia

JKEUPM Malaysia	Jawatankuasa Etika Universiti Putra
l	Path Length of Light Through the Sample in cm
MCB	Malaysian Cocoa Board
MMP	Matrix Metalloproteinase
MMPLO	Ac-PLG-[2-Mercapto-4-Methyl-Pentanoyl]-LG-OC_2H_5
MMP-1	Matrix Metalloproteinase-1
MMP-12	Matrix Metalloproteinase-12
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazoliumbromide MTT
MYR	Malaysian Ringgit
M/V	Solid to Liquid Ratio
NDGA	Nordihydroguaiaretic acid
NPRA	National Pharmaceutical Regulatory Agency
PIF	Product Information File
R	Residual Deformation at the End of Measuring Cycle
RE	Rutin Equivalents
RSM	Response Surface Methodology
SC	Stratum Corneum
SELS	Surface Evaluation of Living Skin
SEr	Skin Roughness
SEsc	Skin Scaliness
SEsm	Skin Smoothness
SEw	Skin Wrinkles
T.cacao	*Theobroma cacao*
TBHQ	Tertiary Butylhydroquinone

TPC	Total Phenolic Content
TFC	Total Flavonoid Content
TEWL	Transepidermal Water Loss
UV	Ultraviolet
VSD	Vascular-streak Dieback
YMC	Yeast and Mould Count
β-CB	β-carotene-linoleate bleaching
IIR	Immediate Irritation Reactions
IR	Irritation Reactions
3D	Three Dimensional

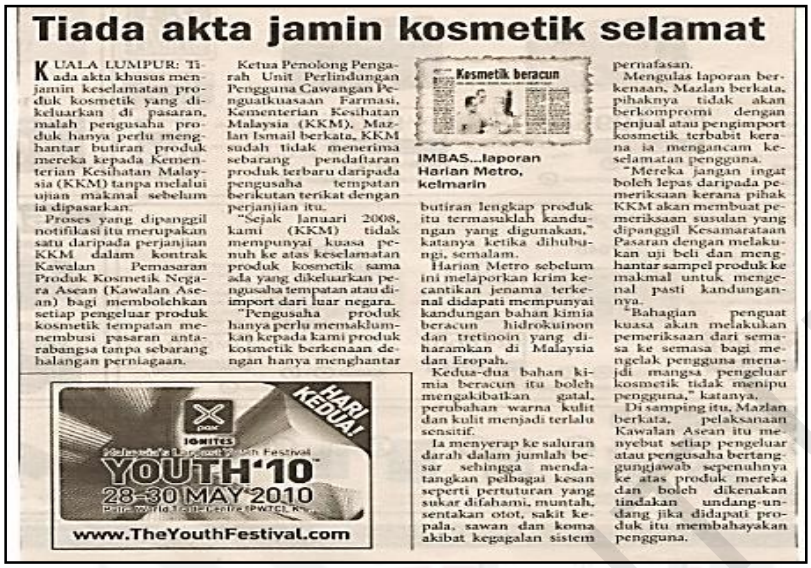
CHAPTER 1

GENERAL INTRODUCTION

1.1 Background of the Study

Cosmeceuticals are topical cosmetic-pharmaceutical hybrids mainly to promote the beauty through permeation of active ingredients into the dermis skin layer. Cosmeceuticals constitute of materials that have significant effect on skin's biological function. The global cosmeceuticals market which was estimated at USD46.93 billion in 2017 has been forecasted to reach USD80.36 billion by 2023 at 9.83% compound annual growth rate (CAGR) within the predicted period (2018 – 2023). Incorporation of polyphenol antioxidants has boosted the sales of anti-ageing cosmeceuticals in the overall cosmetic product market. Moreover, emergence of organic and halal ingredients has significantly affected the demand for cosmeceutical products. This is to indicate the huge margin of sales, thus offering endless opportunity in the exploration of natural-based cosmeceutical.

In Malaysia, assurance of cosmetic/cosmeceutical product's safety and non-hazardous to consumers as required by the Act 368 (Sales of Drug Act, 1952), are subjected to the regulations of National Pharmaceutical Regulatory Agency (NPRA) which is indispensable in the application of Malaysian Standard MS 2200-1:2008-Islamic Consumer Goods Part 1: Cosmetic and Personal Care-General Guidelines (MS 2200-1:2008, 2008). However, despite of the rule, occurrences of adulteration in cosmetics due to utilization of toxic synthetic chemicals, i.e., mercury, hydroquinone, tretinoin, methylene chloride and synthetic antioxidants such as 2,6-di-tert-butyl-p-hydroxy-toluene (BHT) and tert-butyl-4-hydroxy anisole (BHA), among others, have been relentlessly reported as the main cause of adverse health risks and severe skin injuries (Atta et al., 2017; Moein et al., 2008; Utusan Malaysia, 25th March 2017; News Straits Times, 25th Disember 2016; Harian Metro, 29th May 2010). The danger lurked due to various hazardous cosmetic products which were freely marketed in Malaysia is shown in Figure 1.1. In addition, a recent report entitled *NPRA senaraikan 14 produk kosmetik beracun* which was published in Berita Harian dated on 9th October 2018, indicating serious deficiency with regard to safety enforcement of cosmetic products in Malaysia.



Tiada akta jamin kosmetik selamat

KUALA LUMPUR: Tiada akta khusus menjamin keselamatan produk kosmetik yang dikeluarkan di pasaran, malah pengusaha produk hanya perlu menghantar butiran produk mereka kepada Kementerian Kesihatan Malaysia (KKM) tanpa melalui ujian makmal sebelum ia dipasarkan.

Proses yang dipanggil notifikasi itu merupakan satu daripada perjanjian KKM dalam kontrak Kawalan Pemasaran Produk Kosmetik Negara Asean (Kawalan Asean) bagi membolehkan setiap pengeluar produk kosmetik tempatan menembusi pasaran antarabangsa tanpa sebarang halangan perniagaan.

Ketua Penolong Pengarah Unit Perlindungan Pengguna Cawangan Penguatkuasaan Farmasi, Kementerian Kesihatan Malaysia (KKM), Mazlan Ismail berkata, KKM sudah tidak menerima sebarang pendaftaran produk terbaru daripada pengusaha tempatan berikutan terikat dengan perjanjian itu.

"Sejak Januari 2008, kami (KKM) tidak mempunyai kuasa penuh ke atas keselamatan produk kosmetik sama ada yang dikeluarkan pengusaha tempatan atau diimport dari luar negara.

"Pengusaha produk hanya perlu memaklumkan kepada kami produk kosmetik berkenaan dengan hanya menghantar butiran lengkap produk itu termasuklah kandungan yang digunakan," katanya ketika dihubungi, semalam.

Harian Metro sebelum ini melaporkan krim kecantikan jenama terkenal didapati mempunyai kandungan bahan kimia beracun hidrokuinon dan tretinoin yang diharamkan di Malaysia dan Eropah.

Kedua-dua bahan kimia beracun itu boleh mengakibatkan gatal, perubahan warna kulit dan kulit menjadi terlalu sensitif.

Ia menyerap ke saluran darah dalam jumlah besar sehingga mendatangkan pelbagai kesan seperti pertuturan yang sukar difahami, muntah, sentakan otot, sakit kepala, sawan dan koma akibat kegagalan sistem pernafasan.

Mengulas laporan berkenaan, Mazlan berkata, pihaknya tidak akan berkompromi dengan penjual atau pengimport kosmetik terbabit kerana ia mengancam keselamatan pengguna.

"Mereka jangan ingat boleh lepas daripada pemeriksaan kerana pihak KKM akan membuat pemeriksaan susulan yang dipanggil Kesamarataan Pasaran dengan melakukan uji beli dan menghantar sampel produk ke makmal untuk mengenal pasti kandungannya.

"Bahagian penguat kuasa akan melakukan pemeriksaan dari semasa ke semasa bagi mengelak pengguna menjadi mangsa pengeluar kosmetik tidak beniptu pengguna," katanya.

Di samping itu, Mazlan berkata, pelaksanaan Kawalan Asean itu menyebut setiap pengeluar atau pengusaha bertanggungjawab sepenuhnya ke atas produk mereka dan boleh dikenakan tindakan undang-undang jika didapati produk itu membahayakan pengguna.

Kosmetik beracun

IMBAS...laporan Harian Metro, kelmarin

Figure 1.1: Inadequate enforcement pertaining to the cosmetics safety regulation in Malaysia (Source: *Harian Metro*, 29th May 2010)

Nowadays, incorporation of plant materials in a cosmetic formulation is considerably desirable due to public fears over various hazardous synthetic chemicals present in anti-ageing cosmeceuticals. There have been several reports concerning application of natural phenolics for anti-ageing effects as an alternative antioxidant against oxidative damages. In doing so, recoveries of bioactives at the highest yield and quality have been regularly conducted in the optimization on extraction conditions of plant materials. Many studies showed that response surface methodology (RSM) which design of experiment accounts for possible interaction effects between variables, have significantly maximized the extraction yield with targeted components and antioxidant power at optimized variables condition (Spigno et al., 2007; Tan et al., 2014). Moreover, for this tool, the mathematical model helps in providing an apparent visual regarding the effects of various extraction factors and also to view the region wherein the extraction is optimized (Bezerra et al., 2008).

Due to chronic UV exposure, denaturation of collagen and elastin have often attributed to excessive formation of collagenase and elastase in the dermis skin layer. This has given rise to the formation of wrinkles whereas severe hyperpigmentation which is another type of skin photoageing due to over production of melanin in animal tissues, can be effectively prevented through anti-tyrosinase catalytic treatment. Significant correlations between antioxidant capacity and anti-ageing properties in terms of anti-collagenase, anti-elastase and anti-tyrosinase activities, have been found in many phytochemical studies that reflected the reactive responses of antioxidant phenolics (Dudonné et al., 2009). Overall, collagenase, elastase and tyrosinase activities can be

suppressed through preventive action against oxidative damages, which are driven by antioxidant capacity property of the extract material. It helps by preventing the initiation and extension of oxidizing chain reaction metabolic processes disorder (Chanda and Nagani, 2010).

Phenolic compounds demonstrate diverse range of medicinal and pharmacological benefits particularly on antioxidant, anti-microbial, anti-inflammatory, anti-cancer and cardioprotective effects. It is thus suggested that these constituents can eliminate the shelf life of cancer cells as well as healthy cells due to cytotoxicity effect of many phenolic compounds (Balasundram et al., 2006). Fibroblast cell lines have been regularly conducted in the *in vitro* cytotoxicity test due to their presences which can be found mainly in the dermis skin layer. Lower doses of phenolic compounds are sufficient for the antioxidant attribute whereas increasing doses may cause pro-oxidant effects (Amudha et al., 2011). For this reason, cytotoxicity assessment in a healthy fibroblast cell has been conducted particularly to avoid toxicological risks that were often caused by the plant concentrates (Dufrane et al., 2001). Moreover, *in vitro* inhibition of matrix metalloproteinase-1 (MMP-1) expression in UV-irradiated fibroblast cell portrays the substantial function of phenolic components for the prevention of accelerated ageing due to external insults in the dermis skin layer.

Potential results of antioxidant compounds showed from photoprotective and inhibition of destructive tyrosinase, collagenase and elastase of plant materials including beans/seeds, are the desirable anti-ageing property own by cosmeceutical products. Plant material of *Theobroma cacao* bean which is classified under the genus *Theobroma* and belongs to the *Sterculiaceae* family, has been blessed with major bioactive components such as epicatechin, catechin, and methylxanthines (Scapagnini et al., 2014). In Malaysia, potential cocoa clones with premium quality, namely MCBC1, MCBC4, MCBC5, MCBC6, KKM1, KKM5, KKM22, PBC140, PBC123 and QH1003, have been developed in Malaysian Cocoa Board research and development stations at Jengka, Pahang and Bagan Datoh, Perak. Antioxidant benefits of cocoa bean have been considerably reported in consumable products, however, data on polyphenolic components of the Malaysian potential clone extracts for cosmeceutical use have not been thoroughly investigated. Furthermore, development of phenolics-rich cocoa extract cosmeceutical may contribute to the merit in assessing the product's feasibility study.

1.2 Problem Statement

According to Jahanban-Esfahlan et al. (2019), Truong et al. (2019), Plaza et al. (2017) and Altemimi et al. (2017), solvents for phenolic compounds extractions from plant materials are mainly ethanol, water, acetone, methanol, and their water mixtures, either with or without acid. With regard to safety concern, water and ethanol are more desirable due to their non-toxic property compared to other diluents (Liyana-Pathirana and Shahidi, 2005). However, extraction

efficiency informations of water and ethanol mediums on recoveries of total phenolic content (TPC) and total flavonoid content (TFC) of the ten (10) potential Malaysian clones are limited. In addition, it is questionable whether the amount of phenolic compounds extracted could be also affected by the different type of clones. Having said that, according to the Two-way ANOVA, it is hypothesized that; H_0 = Extraction medium and cocoa clone do not affect the total phenolic (TPC) and total flavonoid content (TFC) in mg GAE/g DW and mg RE/g DW, respectively (p>0.05), whereas H_1 = At least one of the factors gives significant amount of the TPC and TFC (p<0.05).

Experimental design suggested by Response Surface Methodology (RSM) in many researches has been proven as an effective appliance in providing the highest yield of bioactive compounds in diverse plant extracts (Raissi, 2009; Tan et al., 2014). Many types of extraction solvents with several concentrations were proposed to obtain the required bioactives. However, informations pertaining to optimization of extraction conditions by using RSM on *Theobroma cacao* bean extracts of Malaysian potential clones are still limited. Moreover, subsequent analyses involving characterization of their cosmeceutical properties, namely antioxidant capacity such as DPPH radical scavenging, ferric reducing power, and β-carotene-linoleate bleaching along with anti-ageing activity in terms of tyrosinase, collagenase, and elastase inhibition, leads to this investigation since no wide research has ever been done on the optimized cocoa bean crude extracts of Malaysian potential clones.

There were several reports regarding natural products to play as a substantial character on the downregulation of MMPs in UV-irradiated cells (Chae et al., 2011; Zhang et al., 2009; Mohan et al., 2016). Since focus of Malaysian potential clones have been on the development of food-based products, thus cocoa-based cosmeceutical-related study in terms of evaluation of their harmful effects or cytotoxicity degree as well as photoprotective property against MMP-1 production on UV-irradiated human dermal fibroblasts cells for anti-ageing property, are yet to discover. Even though many researchers have worked on antioxidants and anti-ageing of *Theobroma cacao*, very few researches were conducted on skin benefits pertaining to intervention of a cosmeceutical product formulated from bean extract of potential Malaysian cocoa clone that reflects the limitation data of natural cosmeceutical product development incorporated with such extract. In term of novelty, though there are similar works, but the present bean extracts are specifically derived from potential Malaysian cocoa clones with superior quality that has never been before assessed for their antioxidant and anti-ageing activities for cosmeceutical use. This study aims to investigate overall potential of Malaysian cocoa bean extracts for their antioxidant capacity and anti-ageing activities in term of photoprotective effect against matrix metalloproteinase-1 (MMP-1) gene expression of human dermal fibroblast cells *in vitro*. Furthermore, *in vivo* application of cocoa bean extract formulation involving twenty (20) human volunteers between 30 to 46 years of age for 2 months of assessment period, are expected to gain skin benefits particularly in a prevention of destructive ultraviolet (UV) light over skin's connective tissues such as collagen and elastin fibres which lie in the deeper layer of skin dermis.

1.3 Objectives

The objectives of this research are:

1. To determine the extraction conditions of optimized ethanol concentrations, extraction time and temperature on total phenolic content (TPC) and total flavonoid content (TFC) of CBEs.

2. To determine antioxidant capacity of CBEs, namely radical scavenging ability, ferric reducing power, and neutralization of linoleate-free radical, whereas *in vitro* anti-ageing activity include anti-collagenase, anti-elastase and anti-tyrosinase activities.

3. To determine the cytotoxicity of CBE towards human dermal fibroblast cell (HDF) and its protective effect on the expression of MMP-1.

4. To develop a stable, safe and efficient CBE formulation with functional *in vitro* photoprotective and non-invasive *in vivo* assessment of skin structure for anti-ageing.

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