NATURAL AND SEMI SYNTHETIC ANTI-TYROSINASE AGENT FROM *PHALERIA MACROCARPA* (SCHEFF.) BOERL USING ULTRASONIC-ASSISTED EXTRACTION

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ABSTRACT

Hyperpigmentation disorders cause several aesthetic issues such as melasma, lentigo and sunburn. Tyrosinase enzyme is described as the key limiting enzyme responsible in regulating melanin production. Hence, to prevent hyperpigmentation disorders, the key approach is to control tyrosinase activity. However, several natural whitening agents such as hydroquinone and kojic acid are toxic. Therefore, much effort has been devoted to develop safe and efficient anti-tyrosinase agents. Phytochemical investigation of *Phaleria macrocarpa* (Scheff.) Boerl led to the isolation of three compounds identified as stigmasterol, mangiferin, and phalerin. Phalerin was identified as the major component and a benzophenone derivative which has been speculated to possess anti-tyrosinase activity. Herein, phalerin was structurally modified by removing methoxyl and glucose moiety to yield (2, 6-dihydroxy-4-methoxyphenyl) (4-hydroxyphenyl) methanone (DHM) and (2, 4, 6-trihydroxyphenyl) (4-hydroxyphenyl) methanone (THM), respectively. The compounds were identified using modern spectroscopic method and evaluated in terms of their antioxidant and tyrosinase inhibitory activities. 2,2-diphenyl-1-picrylhydrazyl assay reveals that THM was the most potent pro-antioxidant followed by mangiferin and DHM with IC_{50} values of 7.02, 11.30 and 11.50 μM, respectively. Similarly, melanogenesis inhibition assays using 3-isobutyl-1-methylxanthine-stimulated B16F1 melanoma cells shows that THM markedly inhibited tyrosinase activity in dose dependent manner and even stronger than kojic acid which acts as the positive control. In contrast, mangiferin moderately inhibited mushroom tyrosinase in cell free system as well as intracellular tyrosinase activity in B16F1 cells. Collectively, the results indicate that removal of glucose and methoxyl moiety from benzophenone aglycone could enhance tyrosinase inhibition which is in agreement with structure activity relationship that has been reported previously. Evidently, THM is a stronger indirect tyrosinase inhibitor than its aglycone and kojic acid as the positive control while mangiferin displayed moderate inhibitory activity. Both compounds show neutral toxicity against B16F1 melanoma cells. Optimization of phalerin extraction using ultrasonic assisted extraction (250 W with a frequency of 40 kHz) revealed that solvent ratio of 71 % of methanol:water, extraction temperature of 50 ºC and solid to solvent ratio of 1:45 g/mL are the optimum condition to extract phalerin (4.26 mg/g). The results in this study were supported by scanning electron microscope analysis insinuated that the proposed condition is cost effective and a green technique to intensify phalerin yield as compared to the conventional methods of hot and cold maceration. These data are valuable and could be useful to extract phalerin in industrial scale. In addition, the findings also show that the artificial neural network exhibited better predictive capability than response surface methodology.

ABSTRAK

Hiperpigmentasi menyebabkan beberapa masalah estetik seperti melasma, lentigo dan selaran matahari. Enzim tirosinase digambarkan sebagai enzim pembatas utama yang bertanggungjawab dalam mengatur penghasilan melanin. Oleh itu, untuk mengelakkan masalah hiperpigmentasi, pendekatan yang terbaik adalah dengan mengawal aktiviti tirosinase. Walau bagaimanapun, beberapa agen pemutihan semula jadi seperti hidrokuinon dan asid kojik dianggap beracun. Oleh itu, banyak usaha telah dilakukan untuk memperluaskan kajian keatas agen anti-tirosinase yang selamat dan berkesan. Penyelidikan fitokimia *Phaleria macrocarpa* (Scheff.) Boerl membawa kepada pengasingan tiga sebatian yang dikenali sebagai stigmasterol, mangiferin, dan phalerin. Phalerin dikenal pasti sebagai komponen utama dan sejenis benzofenon yang telah diduga mempunyai aktiviti anti-tirosinase. Di sini, struktur phalerin telah diubah dengan membuang bahagian metoksil dan glukosa untuk menghasilkan (2, 6-dihidroksi-4-methoksifenil) (4-hidroksifenil) metanon (DHM) dan (2, 4, 6-trihidroksifenil) (4-hidroksifenil) metanon (THM). Semua sebatian tersebut dikenalpasti menggunakan kaedah spektroskopi moden dan dinilai dari segi antioksidan dan perencatan tirosinase. Ujian 2,2-difenil-1-pikrilhidrazil menunjukkan bahawa THM didapati sebagai pro-antioksidan paling kuat diikuti oleh mangiferin dan DHM dengan nilai IC_{50} masing-masing 7.02, 11.30 dan 11.50 μM. Begitu juga, ujian perencatan melanogenesis menggunakan sel melanoma B16F1 yang dirangsang oleh 3-isobutil-1-metilxantina menunjukkan bahawa THM dengan ketara menghalang aktiviti tirosinase bergantung kepada dos bahkan lebih kuat daripada asid kojik sebagai kawalan positif. Sebaliknya, mangiferin secara sederhana menghalang tirosinase dalam sistem bebas sel serta aktiviti tirosinase intraselular dalam sel B16F1. Secara kolektif, hasil kajian ini menunjukkan bahawa penyingkiran glukosa dan metoksil dari aglikon benzofenon dapat meningkatkan perencatan tirosinase yang sesuai dengan hubungan aktiviti struktur yang telah dilaporkan sebelumnya. THM adalah perencat tirosinase tidak langsung yang lebih kuat daripada aglikon phalerin dan asid kojik sebagai kawalan positif sementara mangiferin mengurangkan aktiviti perencatan secara sederhana. Kedua-dua sebatian tersebut menunjukkan ketoksikan neutral terhadap sel melanoma B16F1. Pengoptimuman pengekstrakan phalerin menggunakan pengekstrakan berbantu ultrasonik (250 W dengan frekuensi 40 kHz) menunjukkan bahawa nisbah pelarut 71 % methanol:air, suhu pengekstrakan 50 ºC dan nisbah pepejal ke pelarut 1:45 g / mL adalah keadaan optimum untuk mengekstrak phalerin (4.26 mg/g). Hasil dalam kajian ini disokong oleh analisis mikroskop electron imbasan yang disiratkan bahawa keadaan yang dicadangkan adalah efektif dari segi kos dan merupakan teknik hijau untuk meningkatkan hasil pengekstrakan phalerin berbanding dengan kaedah konvensional pemanasan panas dan sejuk. Data-data ini berharga dan berguna untuk pengekstrakan phalerin pada skala industri. Di samping itu, penemuan kajian ini juga menunjukkan bahawa rangkaian saraf tiruan mempunyai kemampuan ramalan yang lebih baik berbanding kaedah gerak balas permukaan.

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LIST OF ABBREVATIONS

AAD	-	Average absolute deviation
ANN	-	Artificial neural network
ANOVA	-	Analysis of Variance
BBD	-	Box Behnken Design
COSY	-	Correlated spectroscopy
DHM	-	(2,6-dihydroxy-4-methoxyphenyl) (4-hydroxyphenyl) methanone
DOE	-	Data of experiment
EIMS	-	Electrom Impact Mass Spectroscopy
GC-MS	-	Gas Chromatography-Mass Spectroscopy
HMBC	-	Heteronucluear Multiple Bond Connectivity
HMQC	-	Heteronucluear Multiple Quantum Coherence
IBMX	-	3-isobutyl-1-methylxanthine
IC_{50}	-	Inhibition concentration at 50 percent
IR	-	Infrared
IR	-	Infrared
m/z	-	Mass per charge
m/z	-	Mass per charge
MSE	-	Mean square error
RSM	-	Response Surface Methodology
SAR	-	Structural activity relationship
SEM	-	Scanning Electron Microscopy
THM	-	(2,4,6'-trihydroxyphenyl) (4-hydroxyphenyl) methanone
UAE	-	Ultrasonic Assisted Extraction
UV	-	ultraviolet
^{13}C	-	Carbon-13
^{1}H	-	proton

LIST OF SYMBOLS

δ	-	Chemical shift in ppm
λ_{max}	-	Maximum wavelength in mm
µM	-	micromolar
µg/ml	-	Microgram per millilitre

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

Melanin is a mixture of heterogenoues pigmented biopolymers that is mainly manufactured by melanosomes, a specialised pigment organalles distributed mainly in basal layer of human skin. The major role of melanin is to protect the skin from UV radiations as ultraviolet light is known to cause premature aging to the skins and could lead to several health issues. Though melanin production plays vital role to photoprotect human skin from UV radiation and to prevent sun-induced diseases that may contribute to changes of skin and hair color, however, excessive melanin production caused by hyper activity of melanocytes may also cause hyperpigmentation and accumulation of melanin diseases such as wrinkling, melasma, freckles and skin cancer (Kim et al., 2013; D'Mello et al., 2016a). In addition, it is also reported, melanin accumulations were also believed to be linked to Parkinson's and other neurodegenerative diseases (Liu et al., 2012).

The production of melanin is rather complicated and controlled by several proteins for instance tyrosinase enzyme, tyrosinase related protein-1 (TRP-1), tyrosinase related protein-2 (TRP-2), protein kinase A(PKA) and microphalmia-associated transcription factor (MITF) (D'Mello et al., 2016b). Among these proteins, tyrosinase is known to be the key enzyme in regulating melanin synthesis. The copper-containing enzyme catalyzes two different reactions in melanogenesis: monophenolase and diphenolase activity. The end product of the reactions is DOPA quinone which has been known to be the substrate for the synthesis of eumelanin and pheomelanin, a red and brown pigment responsible for skin, hair and eye color. Owing to its pivotal role in regulating melanogenesis, modulation of tyrosinase activity has become major concern worldwide to treat hyperpigmentation disorders (Masum, Yamauchi and Mitsunaga, 2019).

Majority anti tyrosinase agents acts by direct or indirectly interfering with tyrosinase production and activity (Han et al., 2018). Over the years, various anti tyrosinase agent have been evaluated. Generally, anti-tyrosinase can be categorized into natural, semi synthetic and synthetic inhibitors. It is a well-known fact that natural product has been the major source in drug industry especially for cancer treatment, infectious diseases, neurodegenerative disorders and several other diseases. However, there are over 10% of drugs in the world that comes from natural origin while 60% were semi-synthesized and inspired from natural chemical structures (Bade, Chan and Reynisson, 2010; Gurnani et al., 2014). The modified semi-synthetic drugs such as aspirin, penicillin and paclitaxel are said to be more efficient, selective and better patient tolerance as compared to their original components (Mathur and Hoskins, 2017). Semi-synthetic drugs are literally the hybrid version of synthetic and natural chemical groups. They are structurally modified from starting materials of natural sources to produce better and stronger drugs (M. B. Mapunya et al., 2011; Mathur and Hoskins, 2017). That said, the ethnopharmacology knowledge highlighting on both traditional and scientific knowledge of selected potential medicinal plants are important in drug discovery industry and commercialized worldwide.

Due to increase awareness and demand for tyrosinase inhibitors, a number of studies have been dedicated to evaluate and established the structural activity relationship (SAR) pattern towards tyrosinase inhibition (Arquitectura et al., 2015; Jeong et al., 2015; Pillaiyar et al., 2018). To date, polyphenols are the largest anti tyrosinase agent as a result of their unique physicochemical properties that mimic tyrosinase substrate; L-tyrosine and L-DOPA. Previous study revealed that polyphenols from various class of compound have been reported to exhibit strong anti-tyrosinase activity whereas the number and position of hydroxyl moiety remains as an important factor to regulate tyrosinase activity (Chang, 2009; Zolghadri et al., 2019). Additionally, benzophenone which comes from biphenyl class of compound exhibited great structural diversity and broad spectrum of biological activities. Owing to their great photoinitiator properties, benzophenone derivatives have been widely commercialized in sunscreen and UV-filters in United States, Australia, Europe and China (Thia, Chou and Chen, 2020). Their potent ability as UV blockers and increased demand in sunscreen formulation has garnered attention among

researchers to develop polyhydroxyl benzophenone as tyrosinase inhibitors (Wu, Hu and Ma, 2011). To date, there were 300 of benzophenone derivatives that have been isolated and identified from several plant families including Thymelaceae, Clusiaciae, Moraceae, and Polygalaceae.

Phaleria macrocarpa is a tall tree belonging to Thymelaeaceae family which is widely distributed in Indonesia and Malaysia. The species is commonly known as crown of god or 'mahkota dewa' usually grows in tropical area. *P. macrocarpa* (Scheff.) Boerl has been used extensively as traditional medicines to control cancer, impotency, haemorrhoids, diabetes mellitus, allergies, liver and heart disease, kidney disorders, blood disease, acne, stroke, migrane, high blood pressure and various skin diseases (Mae Sri Hartati et al., 2005; Hendra et al., 2011; Azmir, I.S.M. Zaidul, et al., 2014). Previous studies show that benzophenone, flavonoids, fatty acids, alkaloids, megastigmane as well as saponins were isolated from several parts the plant (Azmir et al., 2014; Hendra et al., 2011; Winarno et al, 2009; Abe et al., 1993). However, it is important to note that phalerin, a benzophenone derivative compound was reported to be the major component to the leaves of *P. macrocarpa* (Hendra et al., 2011; Nor Fariza et al., 2012). Previous studies show that the compound demonstrated remarkable biological activities such as anti inflammation, anti cancer, and antioxidant (Oshimi et al., 2008a).

Over the years, medicinal plants and herbs provide an exceptional source of bioactive components. Due to the growing need of natural remedies, active components have provided the primary source in drug development industry. In general, herbal extract could be defined as mixtures of active constituents obtained by various extraction procedures (Vinatoru, 2001). However, extraction method is a limiting process to separate desired phyto-pharmaceutical agents from the raw materials. There are several factors that can affect efficiency of phytochemical extraction from plant source. Medium extraction properties such as particle size, extraction solvent, temperature and duration plays critical role to facilitate mass transfer of bioactive components from the vegetal materials (Zhang, Lin and Ye, 2018). For this reason, to ensure optimum extraction of desired constituents, various statistical tool such as response surface methodology (RSM), artificial neural

network (ANN) and partial least square (PLS) often used to aid in determining the optimum extraction conditions (Astray et al., 2016; Jibril et al., 2018).

The world has witnessed development of extraction method such as microwave assisted extraction (MAE), ultrasonic assisted extraction (UAE) and supercritical fluid extraction to enhance extraction of phytochemicals from vegetal material (Vinatoru, 2001). Among these extraction techniques, ultrasonic assisted extraction is said to be economical, efficient, and can be easily scaled up to industrial level. UAE also has been applied to extract bioactive compounds from different materials owing to its high reproducibility at shorter time, simplified manipulation, significant reduction in solvent consumption and temperature (Liu, Wei and Liao, 2013). It is important to highlight that efficiency of UAE to extract phytochemicals from different sources is not only influenced by operating variables such as ultrasonic power, ultrasonic frequency, but also highly dependent on the medium variables such as extraction temperature and solvent to solid interaction, solvent concentration, particle size and extraction time.

1.2 Problem Statement

Demand for natural ingredients which are reported to be safe and health-promoting property is increasing due to the awareness of consumers on health diet. Considering the fact that tyrosinase is a very important enzyme in regulating melangenesis, it is crucial to search and develop for a promising and good anti tyrosinase with minimal adverse effects (Manse et al., 2016). However, despite the advance research on melanogenic activity, many naturally occurring tyrosinase inhibitors have been reported to suffer from poor skin penetration, insufficient activity or low stability (Jeong et al., 2015; Lee et al., 2016). Furthermore, commercialized anti tyrosinase agents such as hydroquinone and kojic acid have been banned from Japan due to the toxicity caused by the product. There have been a lot of research conducted on melanogenesis to treat hyperpigmentation however; none of them are of complete satisfactory. In view of the above, it is known that natural bioactive chemicals such as benzophenones, xanthones, lactam, diterpenoids, nitrogen-containing compounds and chalcones and flavonoids are not only stable but

they also provide a strategic site for organic reactions which makes these types of compound are favorable as the precursor of semi-synthetic drugs (Nerya et al., 2004; Zhang et al., 2012; Li et al., 2014).

Phalerin is a benzophenone derivative that has been reported to be the major component of leaves of *P. macrocarpa* (Pin KY, 2014). The pharmacology properties of the compound have been widely documented (Ramli *et al.*, 2020). In addition, polyphenols benzophenone has been speculated to inhibit melanogenesis since it has been commercially formulated as sunscreen protector (Wu, Hu and Ma, 2011). According to structural activity relationship (SAR), number hydroxyl moiety and position plays crucial role in modulating melanogenesis. It has been reported that resorcinol moiety in ring A of flavonoids could inhibit tyrosinase inhibition. Similarly, 4-hydroxyl position on ring B of polyphenols could mimic tyrosinase substrate and enhance activity of tyrosinase binding site (Akhtar et al., 2015). However, the reports focusing on hypopigmentation activity of on either phalerin or polyphenol benzophenone derivatives are very limited.

Taking this information into account, phalerin could be a great source of benzophenone with great potential to be developed as anti tyrosinase agent. Hence, the recent challenge is to identify and develop efficient and economical semi synthetic drug originated from the major component of *P. macrocarpa*, phalerin. However, it is important to first optimize the extraction of phalerin prior to isolation and structure modification of the compound to ensure a more promising outcomes. Furthermore, optimization is crucial as baseline studies in industrial approach. Ultrasonic assisted extraction (UAE) is known to be a robust, environmental friendly and simple modern technique that has been used to extract phytochemicals from plant source. Handayani et al (2019) optimized the total phenolic content (TPC) of fruit from *P. macrocarpa* using ultrasonic assisted extraction. In this study, extraction of phalerin from leaves of *P. macrocarpa* based on three parameters namely solvent ratio, extraction temperature and solid-to-solvent ratio by ultrasonic assisted extraction were optimized using RSM and simultaneously compared with ANN.

1.3 Objectives of Study

1. To determine the optimum medium extraction parameters using ultrasonic-assisted extraction (UAE) and compare its predictive capability between response surface methodology (RSM) and artificial neural network (ANN).
2. To characterize the isolated compound and develop a hypopigmentation semi-synthetic agent from natural sources.
3. To evaluate the significant of hydroxyl position towards the mechanism of underlying anti-tyrosinase activity of the pure compounds through in vitro biological assays.

1.4 Scope of Study

This study was proposed to determine the potential of bioactive constituents from *Phaleria macrocarpa* as anti-tyrosinase and antioxidant agent. The scope of this study includes:

1. Extraction and optimization of phalerin from *P. macrocarpa* by using ultrasonic assisted extraction (UAE) operating at 250 W and a frequency of 40 kHz. Ultrasonic assisted extraction was compared with two conventional methods namely water bath assisted extraction and cold maceration. In this study, three relevant medium extraction parameters; solvent concentration (60, 70, 80%), extraction temperature (40, 50, 60°C), solid to solvent ratio (1/30, 1/40, 1/50 g/mL) were examined, for the response of the highest extraction of phalerin. The same DOE of RSM was used to compare with that of ANN.
2. Characterization and structural modifications of phalerin from *Phaleria macrocarpa* by using various chromatography and spectroscopy techniques such as column chromatography, thin layer chromatography, High Performance Liquid Chromatography (HPLC), Nuclear Magnetic Resonance (NMR) and Liquid Chromatography Mass Spectroscopy (LCMS).

3. Identifications and investigation of antioxidant and anti-melanogenic activity of the compounds were evaluated through several cell-free and cell-based assays such as DPPH, mushroom tyrosinase, MTT assay, secreted melanin, melanin content, intracellular tyrosinase and zymography assay.

1.5 Limitation of Study

There are two types of techniques to apply ultrasound in extraction namely ultrasonic bath and probe-type ultrasonic. However, due to limited operability of our laboratory ultrasonic cleaning bath, the ultrasonic power and sonication was fixed at 250 W at a frequency of 40 kHz. Ultrasonic bath is said to be less intrusive and reduce degradation of valuable components (Vinatoru, 2001). In order to ensure constant acoustic field throughout the extraction system, the level and size of extraction vessel were maintained at a specified position. Similarly, the water inside the tank was maintained at three-fourth of tank capacity.

1.6 Significance of Study

The great demand for a safe and economic anti tyrosinase agent justifies the need for a better understanding of tyrosinase activity. Structure activity relationship (SAR) offers a great deal in drug discovery providing vital information for scientist to predict the bioactivities of new molecule and provide useful data for structural modifications. Hence, scientific approached derived from this study provide a clear view of chemical properties particularly the effect of certain functional group (ie: hydroxyl, methoxyl and glucoside moiety) in benzophenone derivatives towards modulating tyrosinase activity. These findings could provide a platform in drug design predominantly to personalized and developing benzophenone derivatives as anti-tyrosinase agents. Most importantly, the mechanism and path of actions of benzophenone derivatives towards modulating tyrosinase activity derived from this study provide further insight on melanogenesis and its potential anti-tyrosinase agents.

Furthermore, this study provides sufficient data to determine the optimum medium UAE parameters (extraction time, methanol concentration, solid to solvent ratio and extraction temperature) to intensify phalerin extraction, a major benzophenone component isolated from leaves of *P. macrocarpa* which could be useful in scale up industry applications.

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LIST OF PUBLICATIONS

Journal with Impact Factor

1. **Ramli, F.,** Hamid, M. A., Wahab, R. A., Ismail, I. S. and Karunakaran, T. (2020) 'Ultrasonic-Assisted Extraction of Phalerin from *Phaleria macrocarpa*: Response Surface Methodology and Artificial Neural Network Modelling', *Arabian Journal for Science and Engineering*, 45, 7635–7644. https://doi.org/10.1007/s13369-020-04639-8. **(Q3, IF: 1.711)**

Indexed Journal

1. Hamid, M.A., Bakar, N.A., Park, C.S., **Ramli, F.,** Wan, W.R.: Optimisation of alpha mangostin extraction using supercritical CO2 from *Garcinia mangostana*. Chem. Eng. Trans. 63, 577–582 (2018)
2. Mariani Abdul Hamid, **Faiqah Ramli** and Rabe'ah Adam. 2016. 'Malaysian Tropical Plants: Source of Skin Lightening' in Rosnani Hasham (ed.). Recent Trends in Malaysian Medicinal Plants Research. Skudai: UTM Press.