OPTIMIZATION OF ANTIOXIDANT ACTIVITIES, BIOACTIVE COMPOUND PROFILES AND IN-VITRO EFFICACY OF *Barleria lupulina* LIND FOR COSMECEUTICAL TOPICAL APPLICATION

By

NOOR WAHIDA BINTI ISMAIL SUHAIMY

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Barleria lupulina Lindl., colloquially referred to as "Penawar Seribu Bisa," is a member of the Acanthaceae family. It has been a traditional remedy among indigenous communities in northern Malaysia, revered for its efficacy in treating various ailments owing to its rich medicinal properties and plethora of bioactive compounds. The objective of this study is to assess the antioxidant properties of *B. lupulina* leaves, elucidate the presence of bioactive compounds, and explore their potential application in cosmeceutical formulations. The assessment of antioxidant activities involved a combination of conventional and modern extraction techniques, including Soxhlet Extraction (SE), Ultrasound-Assisted Extraction (UAE), and Microwave-Assisted Extraction (MAE). Statistical analysis utilized both the One Variable At Time (OVAT) approach and Response Surface Methodology (RSM) to obtain the optimal conditions for extracting the highest levels of antioxidant bioactive compounds. Various antioxidant assay methods were employed, encompassing Total Phenolic Content (TPC), Total Flavonoid Content (TFC), as well as 1,1-diphenyl-2-

picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) assays. The findings revealed Microwave-Assisted Extraction (MAE) as notably an efficient technique, with optimal extraction conditions identified as 80% ethanol at 600 W for 30 seconds. A comprehensive analysis utilizing Ultra-High-Performance Liquid Chromatography-Quadrupole Time-of-Flight Mass Spectrometry (UHPLC-QTOF/MS), Gas Chromatography-Mass Spectrometry (GCMS), and Fourier-Transform Infrared Spectroscopy (FTIR) successfully identified 26 compounds with both cosmetic and medicinal properties. The toxicity evaluation utilizing Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) revealed that the concentration of metals remains within acceptable limits. Additionally, the Brine Shrimp Lethality Assay (BSLA) demonstrated no mortality effects from the extracts on brine shrimp. Thus, these findings affirm the non-toxicity of the *B. lupulina* leaf extracts. A functional cosmetic analysis using *in vitro* method demonstrated that the extracts may serve as natural photoprotective agents and natural inhibitors of tyrosinase, collagenase and elastase. In therapeutic assessment, the extracts demonstrated anti-inflammatory activities by increasing of interleukin-10 and decreasing of interleukin-6 and interleukin-8. The extracts may facilitate wound healing by showing cell migration as early 4 hours after injury and fully close after 24 hours treatment. The comprehensive development and characterization of the cosmeceutical formulation demonstrated that the facial serum had favorable textural qualities and desirable rheological properties, making it a promising potential in enhancing skin conditions. This innovative approach to formulating cosmeceuticals, particularly through the incorporation of active ingredient sourced from *B. lupulina* leaf extracts, has led to the creation of highly effective products with significant

benefits for skin health. These advancements hold great promise for the cosmeceutical industry, offering valuable ingredients derived from plant-based materials.

Keywords: *Barleria lupulina* Lindl. One Variable At Time (OVAT), Response Surface Methodology (RSM), Microwave-Assisted Extraction (MAE), cosmeceutical

SDG: GOAL 3: Good Health and Well-being

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

PENGOPTIMUMAN AKTIVITI ANTIOKSIDAN, PROFIL SEBATIAN BIOAKTIF DAN EFIKASI IN-VITRO *Barleria lupulina* LIND BAGI PENGGUNAAN TOPIKAL KOSMESUTIKAL

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Barleria lupulina Lindl., secara santai dirujuk sebagai "Penawar Seribu Bisa," merupakan ahli keluarga Acanthaceae. Ia telah diguna secara tradisional di kalangan komuniti asli di utara Malaysia kerana keberkesanannya dalam merawat pelbagai penyakit dan sifat perubatannya yang kaya dengan pelbagai sebatian bioaktif. Matlamat kajian ini adalah untuk menilai sifat antioksidan daun *B. lupulina*, mengenalpasti sebatian bioaktif yang hadir, dan meneroka aplikasi potensinya dalam formulasi kosmeutikal. Penilaian aktiviti antioksidan melibatkan gabungan teknik pengekstrakan konvensional dan moden, termasuk Pengekstrakan Soxhlet (SE), Pengekstrakan Bantuan Gelombang Bunyi (UAE), dan Pengekstrakan Bantuan Gelombang Mikro (MAE). Analisis statistik menggunakan pendekatan Satu Pembolehubah Pada Satu Masa (OVAT) dan Metodologi Permukaan Tindak Balas (RSM) untuk mendapatkan keadaan optimum dalam mengekstrak sebatian bioaktif antioksidan tertinggi. Pelbagai kaedah ujian antioksidan digunakan, termasuk

Kandungan Fenolik Total (TPC), Kandungan Flavonoid Total (TFC), serta ujian 1,1-difenil-2-pikrilhidrazil (DPPH) dan 2,2'-azino-bis(3-etilbenzotiazolin-6-sulfonat) (ABTS). Penemuan menunjukkan Pengekstrakan Bantuan Gelombang Mikro (MAE) teknik yang sangat berkesan, dengan keadaan pengekstrakan optimum dikenalpasti sebagai 80% etanol pada 600 watt selama 30 saat. Analisis menyeluruh menggunakan Kromatografi Cecair Prestasi Ultra-Tinggi-Kuadrupel Masa Penerbangan/ Spektrometri Jisim (UHPLC-QTOF/MS), Kromatografi Gas-Massa Spektrometri (GCMS), dan Spektroskopi Infra Merah Transformasi Fourier (FTIR) berjaya mengenal pasti 26 sebatian dengan sifat kosmetik dan perubatan. Penilaian toksisiti menggunakan Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) menunjukkan kepekatan logam berada dalam had yang diterima. Tambahan pula, Bioasai Kemautan Udang Brin (BSLA) menunjukkan tiada kesan kematian daripada ekstrak ke atas udang air garam. Oleh itu, penemuan ini mengesahkan bahawa ekstrak daun *B. lupulina* adalah tidak toksik. Analisis kosmetik menggunakan kaedah dalam vitro menunjukkan ekstrak boleh berfungsi sebagai agen semulajadi fotoprotektif dan perencat tirosinase, kolagenase, dan elastase. Dalam penilaian terapeutik, ekstrak menunjukkan aktiviti anti-radang dengan peningkatan interleukin-10 dan penurunan interleukin-6 dan interleukin-8. Ekstrak tersebut boleh memudahkan penyembuhan luka dengan menunjukkan migrasi sel seawal 4 jam selepas kecederaan dan penutupan penuh selepas rawatan 24 jam. Pembangunan dan pencirian komprehensif formulasi kosmeutikal menunjukkan serum muka mempunyai tekstur yang baik dan sifat rheologikal yang diingini, menjadikannya berpotensi dalam meningkatkan keadaan kulit. Pendekatan inovatif untuk membentuk kosmeutikal, terutamanya dalam penggunaan bahan aktif yang diperoleh dari ekstrak daun *B. lupulina*, telah menghasilkan produk yang sangat berkesan dengan manfaat yang ketara untuk

kesihatan kulit. Kemajuan ini menjanjikan untuk industri kosmeutikal, menawarkan bahan berharga yang berasal dari bahan tumbuhan.

Kata Kunci: *Barleria lupulina* Lindl. Satu Pembolehubah Pada Satu Masa (OVAT), Metodologi Permukaan Tindak Balas (RSM), Pengekstrakan Bantuan Gelombang Mikro (MAE), kosmeutikal

SDG: GOAL 3: Good Health and Well-being

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LIST OF ABBREVIATIONS

Abs	Absorption of sunscreen product
ABTS	2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid)
a.k.a	Also known as
AOAC	Association Official Analytical Chemists
BBD	Box-Behnken Design
BHA	Butylated Hydroxyanisole
BHT	Butylated Hydroxytoluene
BLLE	*Barleria lupulina* Lindl. Leaves Extract
CAB	Collagenase Assay Buffer
CF	Correction Factor
CID	Collision-Induced-Dissociation
COL	Collagenase
DMSO	Dimethyl Sulfoxide
DNA	Deoxyribonucleic Acid
DOE	Design Of Experiment
DPPH	1,1-diphenyl-2-picrylhydrazyl
ECM	Extracellular Matrix
EE	Erythermal Effect Spectrum
ESI	Electrospray Ionization
FALGPA	Synthetic substrate N-[3-(2-furyl) acryloyl]-Leu-Gly-Pro-Ala
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FTIR	Fourier-Transform Infrared Spectroscopy
GAE	Gallic Acid Equivalents

GC	Gas Chromatography
GCMS	Gas Chromatography-Mass Spectrometer
HCl	Hydrochloric acid
HPLC	High-Performance Liquid Chromatography
I	Solar intensity spectrum
IBS	Institute of Bioscience
ICP-MS	Inductively coupled plasma mass spectrometry
IL	Interleukin
KA	Kojic acid
LC	Liquid Chromatography
LE	Leukocyte Elastase
L-DOPA	Levodopa or L-3,4-dihydroxyphenylalanine
MAE	Microwave-Assisted Extraction
MMPs	Matrix Metalloproteinases
MS	Mass Spectrometry
OFAT	One-Factor-At-a-Time
OVAT	One-Variable-At-a-Time
PBS	Phosphate Buffer Solution
PhGs	Phenylethanoid Glycosides
PLE	Pressurised Liquid Extractor
PMNs	Polymorphonuclear Neutrophils
QE	Quercetin Equivalents
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
RSM	Response Surface Methodology
SE	Soxhlet Extraction

SPF	Sun Protective Factor
TFC	Total Flavonoid Content
TPC	Total Phenolic Content
UAE	Ultrasound Assisted Extraction
UHPLC-QTOF/MS	Ultra-High-Performance Liquid Chromatography Quadrupole Time-of-Flight Mass Spectrometry
USA	United State America
UV	Ultraviolet
UV-VIS	Ultraviolet-Visible Spectroscopy
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Background of Study

Plants have been used for millennia for their extraordinary potential in treating and preventing oxidative stress-related disorders. Plants are rich in a broad range of naturally occurring antioxidants, distinct in their composition, physicochemical properties, sites of occurrence, and mechanisms of action (Salehi et al., 2020). Plant compositions may vary according to geography, climate (Jargalsaikhan et al., 2021; Li et al., 2019), and the processing technique used in the extraction (Gopalasatheeskumar et al., 2022; Azwanida, 2015).

Phytochemicals, the bioactive compounds derived from plants, exhibit potent antioxidant properties, along with other beneficial effects such as antibacterial, anti-inflammatory, and other biological properties (Phan et al., 2018; Karaś et al., 2017). They are commonly categorized into primary and secondary metabolites based on their respective roles in metabolic processes. Primary metabolites are integral to fundamental functions like respiration, growth, cell division, photosynthesis, and food storage. Secondary metabolites, on the other hand, are produced in limited quantities and often at specific growth stages. They are primarily involved in plant defense against various stresses, including biotic and abiotic factors such as light intensity, temperature, water availability, and soil composition. These factors collectively impact the productivity and quality of plants (Ramphinwa et al., 2023; Oulahal & Degraeve, 2022). The effectiveness of phytochemicals in promoting health hinges on their purity and structural stability. The extraction process of phytochemicals can be

influenced by factors such as the matrix containing the phytochemical, extraction method, solvent choice, temperature, and duration, which, in turn, can significantly impact the yield, purity, and structural integrity of the extracted compounds (Kumar et al., 2023).

Naturally derived ingredient-based products have garnered global popularity owing to their safety, compatibility with all skin types, minimal side effects, and widespread availability that synthetic ingredients often lack (Goyal et al., 2022). This shift can be attributed to consumers' increasing awareness of the adverse health and environmental impacts associated with synthetic chemicals. Plants, a longstanding natural resource, have been utilized for centuries, and their positive effects on human skin are well-acknowledged. Traditional plant-based skincare remedies, ranging from teas and infusions to ointments and lotions, have historically been employed to address various skin concerns, including discolorations and changes in elasticity, as well as certain medical conditions (Tabassum & Hamdani, 2014). Cosmetic formulations enriched with bioactive compounds not only meet diverse skincare needs effectively but also boast greater eco-friendliness compared to conventional cosmetics. Plant extracts incorporated into cosmetic products serve as reservoirs of biologically active substances that exert significant effects on human skin. These extracts exhibit a broad spectrum of properties, offering therapeutic benefits for conditions like acne, psoriasis, or atopic dermatitis while also contributing to skincare through attributes such as antioxidant, antibacterial, astringent, moisturizing, regenerating, cleansing, smoothing, or lightening effects (Michalak, 2023).

Barleria lupulina Lindl., a member of the Acanthaceae family, is indigenous to East Africa (Mauritius), Eastern India, and Bangladesh (Banerjee et al., 2021). The hophead philippine violet is its common name and goes by several regional names. These include Penawar seribu bisa (Malaysia), Landik (Indonesia), Sa-let-pangpon, Chong-ra-ar (Thailand), Kanta vishalyakarni (India), and Neel saireyak (Sanskrit) (Ismail-Suhaimy et al., 2021). In Malaysia, it is extensively cultivated in the north and is used as an alternative medicine by indigenous people (Samuel et al., 2010). Traditionally, the plant leaves have been employed for medicinal purposes, addressing a range of conditions such as snakebites, swelling, body aches, cough, fever, eczema, itches, bleeding wounds, and rheumatism (Banerjee et al., 2021; Kumari & Dubey, 2016; Moin et al., 2012). These leaves possess a range of pharmacological properties, such as antibacterial, anti-inflammatory, antidiabetic, antiulcer, antimitotic, diuretic, saluretic, kaliuretic, antiarthritic, antiviral, psychopharmacological, anticancer, analgesic, antioxidant, and immunomodulatory activities (Sawarkar et al., 2023; Banerjee et al., 2021; Gangaram et al., 2021). Over time, researchers have identified and elucidated various phytoconstituents, with saponins, glycosides, resins, steroids, phenolic compounds, alkaloids, tannins, and flavonoids emerging as predominant components (Sawarkar et al.,2023). This knowledge positions the herb as a promising candidate for the isolation of biomarkers, potentially paving the way for the development of novel drugs.

Cosmetics can improve an individual's appearance and personality, making them a daily necessity. Cosmetics can be segmented into the following categories: skin care (cream, toner, moisturizer, serum, face mask, and others), makeup (foundation, lipsticks, eyebrows, and others), hair care (shampoo, conditioner, along with others),

and fragrances (perfumes). Cosmeceuticals are cosmetic products that contain active ingredients, such as vitamins, minerals, antioxidants, and peptides, that provide therapeutic or medicinal benefits to the skin. They are designed to improve the health and appearance of the skin by delivering targeted and scientifically validated active ingredients that can improve the texture, tone, and overall quality of the skin. (Nguyen et al., 2020; Pandey et al., 2019; Milam & Rieder, 2016). Over the years, a growing fascination with medicinal and cosmetic products derived from plant materials has been noted in highly developed nations. Numerous studies have highlighted the positive impacts of various plants and their constituents on skin health, encompassing moisturizing effects (e.g., *Hydrangea serrata*), anti-aging properties (e.g., *Euphorbia characias*), antimicrobial attributes (e.g., *Betula pendula*), antioxidant qualities (e.g., *Rosmarinus officinalis*), anti-inflammatory features (e.g., *Helianthus annuus*), regenerative capabilities (e.g., *Aloe vera*), wound healing potential (e.g., *Agrimonia eupatoria*), photoprotective activities (e.g., *Calea fruticose*), anti-tyrosinase activity (e.g., *Schisandra chinensis*), serving as coloring agents (e.g., *Hibiscus sabdariffa*) and providing protective and aromatic elements (e.g., *Verbena officinalis*) (Michalak, 2023).

The term “Reactive Oxygen Species” (ROS) refers to a wide variety of oxidant molecules with vastly diverse properties and biological functions, ranging from cell signaling to cell damage (Sies et al., 2022). ROS is a by-product of cellular metabolism produced by all living things. Organisms have antioxidant defenses, such as enzymes, proteins, and micronutrients; however, an overproduction or failure in the antioxidant system may allow ROS to accumulate, triggering “oxidative stress” (Sies et al., 2017). An increase in oxidative stress can have severe repercussions on biological systems,

including the deterioration of molecules such as nucleic acids, lipids, and proteins, which can significantly harm health (Carocho & Ferreira, 2013). Exogenous sources of ROS may include nutrients, alcohol, medications, industrial solvents, heavy metals, transition metals, air pollution, physical stressors (UV, X-rays, and others), and lifestyle (Jimenez et al., 2022).

Antioxidants are defined broadly as any substance that delays, prevents, or eliminates oxidative damage to a target molecule (Gutteridge & Halliwell, 2000). Studies have shown that antioxidants are implicated in various human health-related processes, including illness treatment, prevention, and general health maintenance, due to their capacity to lower oxidative stress (Neha et al., 2019). Antioxidant compounds inhibit the chain reaction of oxidation by a variety of mechanisms. The natural antioxidant defense consists of endogenous antioxidants generated by the body and exogenous antioxidants taken from external sources (Mut-Salud et al., 2016).

The skin is a dynamic organ comprising various cell types and structures synergistically working to maintain the integrity of the cutaneous barrier and combat external stressors. In addition to averting desiccation, shielding against chemical damage, and preventing hypothermia, this protective barrier defends the body from potential pathogens through employing a sophisticated innate immune response and a co-adapted community of commensal microorganisms (Smythe & Wilkinson, 2023). Skin reflects culture, lifestyle, age, and general health. Skin with even color, tone, and pigmentation, as well as a smooth surface, is frequently regarded as an indication of health and beauty (Cavinato, 2019). Every day the skin is constantly exposed to various harmful factors that induce oxidative stress. This is why the skin, among all

organs, is the most prominent in revealing indications of aging or dermal transformations. Aging and environmental pollution, especially ultraviolet (UV) radiation, are two of the most significant physiological changes that can adversely affect the skin's appearance (Krutmann et al., 2017; Rodan et al., 2016).

The global cosmetic market is booming, with its size reaching USD 277.67 billion in 2020, and is expected to reach a valuation of more than USD 400 billion by 2028 (Fortune Business Insights, 2021). The growth is fueled by a couple of trends; one is the rising demand for anti-aging products, with the market expected to increase at a compound annual growth rate (CAGR) of about 8% from 2022 to 2030, from an estimated USD 60 billion in 2021 to USD 120 billion by 2030 (Custom Market Insights). Two is the significant use of skin-whitening products, with 15% of the global population using them, particularly in Asia (Pillaiyar et al., 2017). Recognizing this market potential, The Malaysian External Trade Development Corporation (MATRADE) identifies the opportunities for Malaysia's beauty industry to capitalize on export growth and solidify the country's position within the global beauty market. As a result of this expanding market, research efforts are intensifying to enhance consumer contentment by incorporating natural ingredients and innovating the most efficient delivery mechanisms.

Thus, this study sought to develop a cosmeceutical product incorporating *Barleria lupulina* Lindl. leaf extracts. Emphasis was placed on determining an efficient extraction method to yield optimal antioxidant components and evaluating the functional cosmetic attributes and medicinal properties inherent in the plant to meet

the specified objective. Following the formulation, the cosmeceutical product was subjected to *in vitro* evaluation to validate its efficacy and safety.

1.2 Problem Statement

Cosmetic products are widely utilized globally, and their efficacy in enhancing physical appearance and personal hygiene is undeniable. Furthermore, the utilization of these cosmetic items has experienced a surge in popularity due to technological advancements, evolving fashion trends, and the allure of a luxurious lifestyle. Cosmetics contain a number of different components. However, certain components incorporated in cosmetics, such as heavy metals, hydroquinone, and microorganisms, have the potential to cause a range of health issues, including neurotoxicity, carcinogenic health effects, oxidative stress, skin allergies, and skin ulcers (Li et al., 2021; Ghaderpoori et al., 2020). In addition, excessive amounts of certain components can be toxic and lead to major health concerns. Metals like lead carbonate and mercury chloride are utilized in cosmetic products due to their cleansing and skin-whitening properties (Ababneh & Al-Momani, 2018). However, they may result in allergic responses and can permeate the skin's appendages or traverse the intercellular and intracellular routes, ultimately entering the human circulatory system (Arshad et al., 2020). Hydroquinone is commonly found in fairness creams since it inhibits the production of melanin and treats melasma. Regardless, the prolonged utilization of these products has been documented to result in unfavorable outcomes such as inflammation, skin inflammation, degradation of melanin, and ochronosis (Chisvert et al., 2010; Moldovan et al., 2017). Although they are necessary components of cosmetics, many components, such as flavors and preservatives, are known to cause allergic reactions upon application or consumption (Sharmeen et al., 2021).

Considering the demand for cosmeceutical products, significant efforts were made to develop a safer formulation for consumers. In this perspective, the present study aimed to develop cosmeceutical formulations using natural sources of plant-based active components in formulations for topical applications that are potentially safer and more effective. Furthermore, research suggests that natural ingredients are more readily assimilated by the superficial layers of the skin, which can reduce skin allergy issues (Lin et al., 2017).

Throughout history, *Barleria lupulina* Lindl. leaves have been utilized topically in traditional medicine to address a wide array of ailments, ranging from snakebites and dog bites to swelling, boils (painful, pus-filled bumps that develop under the skin caused by a bacterial infection), and rheumatism. Remarkably, this plant boasts an extensive array of pharmacological properties, including antibacterial, anti-inflammatory, antidiabetic, and antiviral activities, among others. Researchers have meticulously examined various phytoconstituents over time, identifying prevalent components such as saponins, glycosides, resins, steroids, phenolic compounds, alkaloids, tannins, and flavonoids. This knowledge positions the plant as a promising resource for pharmaceuticals and potentially the development of innovative cosmetics.

Plant constituents exhibit significant variation depending on geographical origin, climatic conditions (Jargalsaikhan et al., 2021), and extraction methods (Abubakar & Haque, 2020). This variability necessitates a comprehensive approach to natural product evaluation. Therefore, the present study was undertaken to screen the chemical constituents using several methods, evaluate their antioxidant capacity, and determine their functional cosmetic and therapeutic properties. The challenges of this

study were optimizing the extraction conditions to obtain optimal antioxidant activity using efficient methods and developing a suitable formulation to ensure the stability and efficacy of active ingredients and product safety.

1.3 Objectives

The general objective of the study was to optimize the conditions for extracting antioxidants from *Barleria lupulina* Lindl. leaves, evaluate their antioxidant capacity, functional cosmeceutical activities, therapeutic properties, and efficacy as a cosmeceutical product for topical application.

The following are the specific objectives:

i. To optimize the extraction conditions of *B. lupulina* Lindl. leaf extracts for maximum antioxidant activity.

ii. To identify the bioactive compounds of *B. lupulina* Lindl. leaf extracts using Gas Chromatography–Mass Spectrometer (GC–MS), Ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC-QTOF/MS), and Fourier-transform infrared spectroscopy (FTIR).

iii. To evaluate the safety of *B. lupulina* Lindl. leaf extracts using Inductively Coupled Plasma-Mass Spectrometry (ICP-MS) and Brine Shrimp Lethality Assay.

iv. To determine the functional cosmeceutical properties and therapeutic properties of *B. lupulina* Lindl. leaf extracts.

v. To develop a cosmeceutical formulation containing *B. lupulina* Lindl. leaf extracts and to evaluate the *in vitro* efficacy and safety of formulation.

1.4 Scope of Study

In this study, the exploration of *B. lupulina* Lindl. as an alternative active ingredient in cosmeceutical formulations is divided into six stages. The first stage is the optimization of extraction conditions for maximum antioxidant activities using One-Variable-At-Time (OVAT) and Response Surface Methodology (RSM). The second stage is the identification of compounds *via* GC-MS, UHPLC-QTOF/MS, and FTIR. The third stage is the determination of the toxicity level by using ICP-MS and Brine Shrimp Lethality Assay, followed by the evaluation of the functional cosmeceutical properties. These include photoprotective activity, anti-tyrosinase activity, anti-elastase activity, and anti-collagenase activity. The evaluation of the therapeutic properties of the extract, such as cytotoxicity, anti-inflammatory activity, and wound healing properties, are performed in *in vitro* studies. The final stage is the development of the cosmeceutical formulation, i.e., facial serum containing *B. lupulina* Lindl. leaf extracts (BLLE) and the evaluation of their stability, physiochemical properties, efficacy, and safety.

1.5 Significance of Study

The objective of this research is to investigate the most effective extraction methods for obtaining the greatest level of antioxidant activity of *B. lupulina* Lindl. The identification of compounds and their associated functional cosmeceutical and therapeutic properties may provide valuable insights for the cosmetic and pharmaceutical sectors.

REFERENCES

Ababneh, F. A., & Al-Momani, I. F. (2018). Assessments of toxic heavy metals contamination in cosmetic products. *Environmental Forensics*. 19(2): 134-142.

Abdul-Aziz, Z., Wahid, Z., and Metcalfe, A. V. (2002). Using "Design of Experiments" to overcome limitation of "one-variable-at-a-time" approach to experimentation; the case of a rubber glove manufacturing facility in Malaysia. Robotics, Automation, Control and Manufacturing: Trends, Principles and Applications - Proceedings of the 5th Biannual World Automation Congress, WAC 2002, ISORA 2002, ISIAC 2002 and ISOMA 2002, 14, 487–493. https://doi.org/10.1109/wac.2002.1049485.

Abubakar, A. R., and Haque, M. (2020). Preparation of medicinal plants: Basic extraction and fractionation procedures for experimental purposes. In *Journal of Pharmacy and Bioallied Sciences*. *Wolters Kluwer Medknow Publications*. 12(1): 1–10. https://doi.org/10.4103/jpbs.JPBS_175_19.

Ågren, M. S., Chvapil, M., and Franzén, L. (1991). Enhancement of re-epithelialization with topical zinc oxide in porcine partial-thickness wounds. *Journal of Surgical Research*. 50(2): 101-105.

Aguilar, N. O. (2001). *Barleria lupulina* Lindley. *In*: van Valkenburg JLCH, Bunyapraphatsara N, editors. Plant Resources of South-East Asia No. 12(2): Medicinal and poisonous plants 2. Leiden, Netherlands: Backhuys Publisher: 527.

Aguilar, T. A. F., Navarro, B. C. H., and Pérez, J. A. M. (2016). Endogenous antioxidants: a review of their role in oxidative stress. A master regulator of oxidative stress-the transcription factor nrf2. 3-20.

Ajeet Singh, Navneet (2017). Antibacterial potential and phytochemical analysis of *Barleria lupulina* Lindl. (aerial parts) extracts against respiratory tract pathogens. I*nternational Journal of Pharmaceutical and Clinical Research*. 9(7): 534-538. doi: 10.25258/ijpcr.v9i7.8787

Al-Rubaye, A. F., Hameed, I. H., and Kadhim, M. J. (2017). A Review: Uses of gas chromatography-mass spectrometry (GC-MS) technique for analysis of bioactive natural compounds of some plants. *International Journal of Toxicological and Pharmacological Research*. 9(01): 81–85. https://doi.org/10.25258/ijtpr.v9i01.9042.

Alara, O. R., Abdurahman, N. H., and Ukaegbu, C. I. (2021). Extraction of phenolic compounds: A review. *Current Research in Food Science*. 4: 200–214. https://doi.org/10.1016/j.crfs.2021.03.011.

Ali, A. A. H. (2023). Overview of the vital roles of macro minerals in the human body. *Journal of Trace Elements and Minerals*. 100076 (4): 1-11. https://doi.org/10.1016/j.jtemin.2023.100076

Altemimi, A., Lakhssassi, N., Baharlouei, A., Watson, D. G., and Lightfoot, D. A. (2017). Phytochemicals: Extraction, isolation, and identification of bioactive compounds from plant extracts. *Plants*. 6(4): 1-23. https://doi.org/10.3390/plants6040042.

Amaral, L. F. B., Moriel, P., Foglio, M. A., and Mazzola, P. G. (2014). *Caryocar brasiliense* supercritical CO2 extract possesses antimicrobial and antioxidant properties useful for personal care products. *BMC Complementary and Alternative Medicine*. 14: 1-7. https://doi.org/10.1186/1472-6882-14-73.

Ambedkar, G., Pragalathan, S., Sabaridasan, A., Gandhimaniyan, K., Dineshkumar, S., and Balamurugan, V. (2019). *FTIR Spectrum Analysis and Antibacterial Activity of Tribulus terrestris Leaves Extract*. December: 25–30. www.stmjournals.com.

Anchisi, C., Maccioni, A. M., Sinico, C., & Valenti, D. (2001). Stability studies of new cosmetic formulations with vegetable extracts as functional agents. *Il Farmaco*. 56(5-7): 427-431.

Andreini, C., Bertini, I., Cavallaro, G., Holliday, G. L., and Thornton, J. M. (2008). Metal ions in biological catalysis: From enzyme databases to general principles. *Journal of Biological Inorganic Chemistry*. 13(8): 1205–1218. https://doi.org/10.1007/s00775-008-0404-5.

Anjum, N. A., Singh, H. P., Khan, M. I. R., Masood, A., Per, T. S., Negi, A., ... & Ahmad, I. (2015). Too much is bad—an appraisal of phytotoxicity of elevated plant-beneficial heavy metal ions. *Environmental Science and Pollution Research*. 22: 3361-3382.

Angerhofer, C. K., Maes, D., and Giacomoni, P. U. (2008). The use of natural compounds and botanicals in the development of anti-aging skin care products. *Skin Aging Handbook: An Integrated Approach to Biochemistry and Product Development*. 205–263. https://doi.org/10.1016/B978-0-8155-1584-5.50014-4.

Arshad, H., Mehmood, M. Z., Shah, M. H., & Abbasi, A. M. (2020). Evaluation of heavy metals in cosmetic products and their health risk assessment. *Saudi Pharmaceutical Journal*. 28(7): 779-790.

Asgari Lajayer, B., Ghorbanpour, M., and Nikabadi, S. (2017). Heavy metals in contaminated environment: Destiny of secondary metabolite biosynthesis, oxidative status and phytoextraction in medicinal plants. *Ecotoxicology and Environmental Safety*. July (145): 377–390. https://doi.org/10.1016/j.ecoenv.2017.07.035.

Attard, T., and Attard, E. (2022). Heavy metals in cosmetics. In *Heavy metals - new insights*. 1-21. https://doi.org/10.5772/intechopen.102406.

Attia, E. A., Belal, D. M., El Samahy, M. H., and El Hamamsy, M. H. (2014). A pilot trial using topical regular crystalline insulin vs. aqueous zinc solution for uncomplicated cutaneous wound healing: Impact on quality of life. *Wound*

Repair and Regeneration. 22(1): 52-57.

Aydar, A. Y. (2018). Utilization of response surface methodology in optimization of extraction of plant materials. In *Statistical Approaches With Emphasis on Design of Experiments Applied to Chemical Processes*. InTech. 11 (13): 157-169. https://doi.org/10.5772/intechopen.73690.

Azahar, N. F., Gani, S. S. A., Zaidan, U. H., Bawon, P., and Halmi, M. I. E. (2020). Optimization of the antioxidant activities of mixtures of Melastomataceae leaves species (*M. Malabathricum* Linn Smith, *M. Decemfidum*, and *M. Hirta*) using a simplex centroid design and their anti-collagenase and elastase properties. *Applied Sciences (Switzerland)*. 10(19): 1–18. https://doi.org/10.3390/app10197002.

Azahar, N. F., Salwa, S., Gani, A., Zaidan, U. H., Bawon, P., and Effendi, M. I. (2019). *In vitro* whitening properties and antioxidative potentials of the extracts of three Melastoma leaves species (*M. malabathricum*, *M. hirta* and *M. decemfidum*). *Journal of Applied Sciences Research*. 15(3): 6–11. https://doi.org/10.22587/jasr.2019.15.3.2.

Azwanida, N. N. (2015). A review on the extraction methods use in medicinal plants, principle, strength and limitation. *Medicinal & Aromatic Plants*. 4(3): 3–8. https://doi.org/10.4172/2167-0412.1000196.

Bainbridge, P. (2013). Wound healing and the role of fibroblasts. *Journal of Wound Care*. 22(8): 407-412.

Balasundram, N., Sundram, K., and Samman, S. (2006). Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses. *Food Chemistry*. 99(1): 191-203.

Balkwill, M. J., & Balkwill, K. (1998). A preliminary analysis of distribution patterns in a large, pantropical genus, Barleria L.(Acanthaceae). *Journal of Biogeography*, 25(1): 95-110.

Ballard, T. S., Mallikarjunan, P., Zhou, K., and O'Keefe, S. (2010). Microwave-assisted extraction of phenolic antioxidant compounds from peanut skins. *Food chemistry*, 120(4): 1185-1192. https://doi.org/10.1016/j.foodchem.2009.11.063.

Banerjee, S., Banerjee, S., Jha, G. K. and Bose, S. (2021). Conspectus of phytoconstituents and pharmacological activities of *Barleria lupulina* Lindl.: A Review. *Curr. Tradit. Med*. 7:325–334. doi: 10.2174/2215083806666200312150825.

Banu, K. S., and Cathrine, L. (2015). General techniques involved in phytochemical analysis. *International Journal of Advanced Research in Chemical Science*. 2(4): 25–32. www.arcjournals.org.

Barreca, D., Gattuso, G., Bellocco, E., Calderaro, A., Trombetta, D., Smeriglio, A., ... and Nabavi, S. M. (2017). Flavanones: Citrus phytochemical with health-

promoting properties. *BioFactors*. 43(4): 495-506.

Bay, E. Y. (2022). Review article aging skin and anti-aging strategies. *Exploratory Research and Hypothesis in Medicine*. *8*(3): 269-279. https://doi.org/10.14218/ERHM.2022.00030.

Beard, J. (2003). Iron deficiency alters brain development and functioning. *The Journal of nutrition*. 133(5): 1468-1472.

Benali, T., Bakrim, S., Ghchime, R., Benkhaira, N., El Omari, N., Balahbib, A., ... and Bouyahya, A. (2022). Pharmacological insights into the multifaceted biological properties of quinic acid. *Biotechnology and Genetic Engineering Reviews.*1-30.

Bibi Nitzan, Y., and Cohen, A. D. (2006). Zinc in skin pathology and care. *Journal of Dermatological Treatment*. 17(4): 205–210. https://doi.org/10.1080/09546630600791434.

Bjørklund, G., Shanaida, M., Lysiuk, R., Antonyak, H., Klishch, I., Shanaida, V., and Peana, M. (2022). Selenium: An antioxidant with a critical role in anti-aging. *Molecules*. 27(19): 6613.

Blois, M. S. (1958). Antioxidant determinations by the use of a stable free radical. In *Nature*. 181: 1199-1200. https://doi.org/10.1038/1811199a0.

Boisseau, A. M., Donatien, P., Surlève-Bazeille, J. E., Amédée, J., Harmand, M. F., Bézian, J. H., Maleville, J., and Taieb, A. (1992). Production of epidermal sheets in a serum free culture system: A further appraisal of the role of extracellular calcium. *Journal of Dermatological Science*. 3(2): 111–120. https://doi.org/10.1016/0923-1811(92)90044-C.

Borkow, G. (2015). Using copper to improve the well-being of the skin. *Current Chemical Biology*. 8(2): 89–102. https://doi.org/10.2174/2212796809666150227223857.

Bose, B., Choudhury, H., Tandon, P., and Kumaria, S. (2017). Studies on secondary metabolite profiling, anti-inflammatory potential, *in vitro* photoprotective and skin-aging related enzyme inhibitory activities of *Malaxis acuminata*, a threatened orchid of nutraceutical importance. *Journal of Photochemistry and Photobiology B: Biology*. 173(July): 686–695. https://doi.org/10.1016/j.jphotobiol.2017.07.010.

Bouras, M., Chadni, M., Barba, F. J., Grimi, N., Bals, O., and Vorobiev, E. (2015). Optimization of microwave-assisted extraction of polyphenols from Quercus bark. *Industrial Crops and Products.* 77: 590–601. https://doi.org/10.1016/j.indcrop.2015.09.018.

Bouzroud, S., El Maaiden, E., Sobeh, M., Merghoub, N., Boukcim, H., Kouisni, L., and El Kharrassi, Y. (2023). Biotechnological approaches to producing natural antioxidants: Anti-ageing and skin longevity prospects. *International Journal of Molecular Sciences*. 24(2): 1397. https://doi.org/10.3390/ijms24021397.

Brás, N. F., Gonçalves, R., Mateus, N., Fernandes, P. A., Ramos, M. J., and De Freitas, V. (2010). Inhibition of pancreatic elastase by polyphenolic compounds. *Journal of Agricultural and Food Chemistry*. 58(19): 10668–10676. https://doi.org/10.1021/jf1017934.

Briffa, J., Sinagra, E., and Blundell, R. (2020). Heavy metal pollution in the environment and their toxicological effects on humans. *Heliyon*. 6(9): 1-26. https://doi.org/10.1016/j.heliyon.2020.e04691.

Buddeen, M. B. M. S. S. (2018). *Optimization, stability and characterization of face serum formulation* (Doctoral Dissertation, Universiti Teknologi Malaysia).

Burk, D. R., Cichacz, Z. A., and Daskalova, S. M. (2010). Aqueous extract of *Achillea millefolium* L.(Asteraceae) inflorescences suppresses lipopolysaccharide-induced inflammatory responses in RAW 264.7 murine macrophages. *J Med Plants Res.* 4(3): 225-234.

Burman, S., Bhattacharya, K., Mukherjee, D., and Chandra, G. (2018). Antibacterial efficacy of leaf extracts of *Combretum album* Pers. against some pathogenic bacteria. *BMC Complementary and Alternative Medicine*. 18(1): 1–8. https://doi.org/10.1186/s12906-018-2271-0.

Cai, Z., Zhang, J., and Li, H. (2019). Selenium, aging and aging-related diseases. *Aging Clinical and Experimental Research*. 31: 1035-1047. https://doi.org/10.1007/s40520-018-1086-7.

Carocho, M., and Ferreira, I. C. F. R. (2013). A review on antioxidants, prooxidants and related controversy: Natural and synthetic compounds, screening and analysis methodologies and future perspectives. *Food and Chemical Toxicology*. 51: 15–25. https://doi.org/10.1016/j.fct.2012.09.021.

Carvalho, A. M. S., Heimfarth, L., Pereira, E. W. M., Oliveira, F. S., Menezes, I. R. A., Coutinho, H. D. M., Picot, L., Antoniolli, A. R., Quintans, J. S. S., and Quintans-Júnior, L. J. (2020). Phytol, a chlorophyll component, produces antihyperalgesic, anti-inflammatory, and antiarthritic effects: Possible NFκB pathway involvement and reduced levels of the proinflammatory cytokines TNF-α and IL-6. *Journal of Natural Products*. 83(4): 1107–1117. https://doi.org/10.1021/acs.jnatprod.9b01116.

Cavinato, M. (2019). Cosmetics and cosmeceuticals. *Encyclopedia of Biomedical Gerontology*. 446–461. https://doi.org/10.1016/B978-0-12-801238-3.62150-5.

Cefali, L. C., Ataide, J. A., Fernandes, A. R., Sanchez-Lopez, E., de Oliveira Sousa, I. M., Figueiredo, M. C., Ruiz, A. L. T. G., Foglio, M. A., Mazzola, P. G., and Souto, E. B. (2019). Evaluation of *in vitro* solar protection factor (SPF), antioxidant activity, and cell viability of mixed vegetable extracts from *Dirmophandra mollis* Benth, *Ginkgo biloba* L., *Ruta graveolens* L., and *Vitis vinífera* L. *Plants.* 8(11): 1–13. https://doi.org/10.3390/plants8110453.

Celli, A., Tu, C. L., Lee, E., Bikle, D. D., and Mauro, T. M. (2021). Decreased calcium-sensing receptor expression controls calcium signaling and cell-to-cell adhesion defects in aged skin. *Journal of Investigative Dermatology*. 141(11): 2577–2586. https://doi.org/10.1016/j.jid.2021.03.025.

Chamratpan, S., and Homchuen, S. A. (2003). Ethnobotany in upper northeastern Thailand. In III WOCMAP Congress on Medicinal and Aromatic Plants-Volume 1: Bioprospecting and Ethnopharmacology. 675: 67-74.

Chasapis, C. T., Ntoupa, P.-S. A., Spiliopoulou, C. A., and Stefanidou, M. E. (2020). Recent aspects of the effects of zinc on human health. *Archives of Toxicology*. 94(5): 1443–1460. https://doi.org/10.1007/s00204-020-02702-9.

Chatatikun, M., and Chiabchalard, A. (2017). Thai plants with high antioxidant levels, free radical scavenging activity, anti-tyrosinase and anti-collagenase activity. *BMC Complementary and Alternative Medicine*. 17(1): 1–9. https://doi.org/10.1186/s12906-017-1994-7.

Chedea, V., Vicaș, S., and Socaciu, C. (2005). Lipoxygenases from soybean: Reaction kinetics and inhibition factors. 201-205.

Chemat, F., Vian, M. A., and Cravotto, G. (2012). Green extraction of natural products: Concept and principles. *International Journal of Molecular Sciences*. 13(7): 8615–8627. https://doi.org/10.3390/ijms13078615.

Chen, S. (2011). Natural products triggering biological targets-a review of the anti-inflammatory phytochemicals targeting the arachidonic acid pathway in allergy asthma and rheumatoid arthritis. *Current Drug Targets*. 12(3): 288-301.

Chen, L., Hu, J. Y., and Wang, S. Q. (2012). The role of antioxidants in photoprotection: A critical review. *Journal of the American Academy of Dermatology*. 67(5): 1013–1024. https://doi.org/10.1016/j.jaad.2012.02.009.

Chen, P., Bornhorst, J., and Aschner, M. (2018). Manganese metabolism in humans. *Frontiers in Bioscience - Landmark*. 23(9): 1655–1679. https://doi.org/10.2741/4665.

Chew, K. K., Khoo, M. Z., Ng, S. Y., Thoo, Y. Y., Aida, W. M. W., and Ho, C. W. (2011). Effect of ethanol concentration, extraction time and extraction temperature on the recovery of phenolic compounds and antioxidant capacity of *Orthosiphon stamineus* extracts. *International Food Research Journal*.

Chirinos, R., Rogez, H., Campos, D., Pedreschi, R., and Larondelle, Y. (2007). Optimization of extraction conditions of antioxidant phenolic compounds from mashua (*Tropaeolum tuberosum* Ruíz & Pavón) tubers. *Separation and Purification Technology*. 55 (2): 217–225. https://doi.org/10.1016/j.seppur.2006.12.005.

Chisvert, A., Sisternes, J., Balaguer, Á., & Salvador, A. (2010). A gas chromatography–mass spectrometric method to determine skin-whitening

agents in cosmetic products. *Talanta*. 81(1-2): 530-536.

Chiwapreecha, B., Janprasert, K., and Kongpakdee, C. (2011). Comparative anatomy of three medicinal plants in Acanthaceae. In I*nternational Symposium on Medicinal and Aromatic Plants*. 1023: 229-232.

Chomnawang, M. T., Surassmo, S., Nukoolkarn, V. S., and Gritsanapan, W. (2005). Antimicrobial effects of Thai medicinal plants against acne-inducing bacteria. *Journal of Ethnopharmacology*. 101(1-3): 330-333. https://doi.org/10.1016/j.jep.2005.04.038.

Chopra, R. N., Nayar, S. L., and Chopra, I. C. (1968). Glossary of Indian Medicinal Plants. *Academic Publishers, New Delhi, India*. p. 20.

Chuarienthong, P., Lourith, N., and Leelapornpisid, P. (2010). Clinical efficacy comparison of anti-wrinkle cosmetics containing herbal flavonoids. *International Journal of Cosmetic Science*. 32(2): 99–106. https://doi.org/10.1111/j.1468-2494.2010.00522.x.

Cialdai, F., Risaliti, C., and Monici, M. (2022). Role of fibroblasts in wound healing and tissue remodeling on earth and in space. *Frontiers in bioengineering and biotechnology*. 10 (958381): 1-18.

Coates, J. (2000). Interpretation of infrared spectra, a practical approach. *Encyclopedia of Analytical Chemistry*. 12: 10815-10837. https://doi.org/10.1002/9780470027318.a5606.

Coetzee, P. P., Steffens, F. E., Eiselen, R. J., Augustyn, O. P., Balcaen, L., and Vanhaecke, F. (2005). Multi-element analysis of South African wines by ICP–MS and their classification according to geographical origin. *Journal of Agricultural and Food Chemistry*. 53(13): 5060-5066.

Collin, M. S., Venkatraman, S. K., Vijayakumar, N., Kanimozhi, V., Arbaaz, S. M., Stacey, R. S., ... and Swamiappan, S. (2022). Bioaccumulation of lead (Pb) and its effects on human: A review. *Journal of Hazardous Materials Advances*. 7: 100094.

Cosmetics Europe. (2004). Guidelines on stability testing of cosmetic products. *Cosmetic Toiletry and Fragrance Association and The European Cosmetic Toiletry and Perfumery Association*. March: 1–8.

Cramer, J., Sager, C. P., and Ernst, B. (2019). Hydroxyl groups in synthetic and natural-product-derived therapeutics: A perspective on a common functional group. *Journal of Medicinal Chemistry*. 62(20): 8915–8930. https://doi.org/10.1021/acs.jmedchem.9b00179.

Dahmoune, F., Nayak, B., Moussi, K., Remini, H., and Madani, K. (2015). Optimization of microwave-assisted extraction of polyphenols from *Myrtus communis* L. leaves. *Food Chemistry*. 166: 585-595. https://doi.org/10.1016/j.foodchem.2014.06.066.

Dahmoune, F., Spigno, G., Moussi, K., Remini, H., Cherbal, A., and Madani, K. (2014). *Pistacia lentiscus* leaves as a source of phenolic compounds: Microwave-assisted extraction optimized and compared with ultrasound-assisted and conventional solvent extraction. *Industrial Crops and Products*. 61: 31-40. https://doi.org/10.1016/j.indcrop.2014.06.035.

Darbyshire, I., Fisher, A. E., Kiel, C. A., & McDade, L. A. (2019). Phylogenetic relationships among species of Barleria (Acanthaceae, Lamiales): Molecular data reveal complex patterns of morphological evolution and support a revised classification. *Taxon*. 68(1): 92-111.

de Lima Cherubim, D. J., Buzanello Martins, C. V., Oliveira Fariña, L., and da Silva de Lucca, R. A. (2020). Polyphenols as natural antioxidants in cosmetics applications. *Journal of Cosmetic Dermatology*. 19(1): 33–37. https://doi.org/10.1111/jocd.13093.

de Moura Sperotto, N. D., Steffens, L., Veríssimo, R. M., Henn, J. G., Péres, V. F., Vianna, P., Chies, J. A. B., Roehe, A., Saffi, J., and Moura, D. J. (2018). Wound healing and anti-inflammatory activities induced by a *Plantago australis* hydroethanolic extract standardized in verbascoside. *Journal of Ethnopharmacology*. 225: 178–188. https://doi.org/10.1016/j.jep.2018.07.012.

Defoirdt, T., Bossier, P., Sorgeloos, P., and Verstraete, W. (2005). The impact of mutations in the quorum sensing systems of *Aeromonas hydrophila*, *Vibrio anguillarum* and *Vibrio harveyi* on their virulence towards gnotobiotically cultured Artemia franciscana. *Environmental microbiology*. 7(8): 1239-1247.

Denda, M. (2009). Methodology to improve epidermal barrier homeostasis: How to accelerate the barrier recovery? *International Journal of Cosmetic Science*. 31(2): 79–86. https://doi.org/10.1111/j.1468-2494.2008.00487.x.

Denda, M., Hosoi, J., and Asida, Y. (2000). Visual imaging of ion distribution in human epidermis. *Biochemical and Biophysical Research Communications*. 272(1): 134–137. https://doi.org/10.1006/bbrc.2000.2739.

Denda, M., Katagiri, C., Hirao, T., Maruyama, N., and Takahashi, M. (1999). Some magnesium salts and a mixture of magnesium and calcium salts accelerate skin barrier recovery. *Archives of Dermatological Research.* 291(10): 560–563. https://doi.org/10.1007/s004030050454.

Deniz, F. S. S., Orhan, I. E., and Duman, H. (2021). Profiling cosmeceutical effects of various herbal extracts through elastase, collagenase, tyrosinase inhibitory and antioxidant assays. *Phytochemistry Letters*. 45: 171-183. https://doi.org/10.1016/j.phytol.2021.08.019.

Destandau, E., Michel, T., and Elfakir, C. (2013). Microwave-assisted extraction. *RSC Green Chemistry*. In book: Natural Product Extraction: Principles and Application. 113-156. https://doi.org/10.1039/9781849737579-00113.

Dini, I., and Grumetto, L. (2022). Recent advances in natural polyphenol research. *Molecules*. 27(24): 8777.

Duan, S., Qi, W., Zhang, S., Huang, K., and Yuan, D. (2017). Ultra high performance liquid chromatography coupled with electrospray ionization/quadrupole time-of-flight mass spectrometry for the rapid analysis of constituents in the traditional Chinese medicine formula Wu Ji Bai Feng Pill. *Journal of Separation Science*. 40(20): 3977–3986. https://doi.org/10.1002/jssc.201700438.

Duruibe, J. O., Ogwuegbu, M. O. C., and Egwurugwu, J. N. (2007). Heavy metal pollution and human biotoxic effects. *International Journal of Physical Sciences*. 2(5): 112-118.

Dutra, E. A., Da Costa E Oliveira, D. A. G., Kedor-Hackmann, E. R. M., and Miritello Santoro, M. I. R. (2004). Determination of sun protection factor (SPF) of sunscreens by ultraviolet spectrophotometry. *Revista Brasileira de Ciencias Farmaceuticas/Brazilian Journal of Pharmaceutical Sciences*. 40(3): 381–385. https://doi.org/10.1590/S1516-93322004000300014.

Ebrahimzadeh, M. A., Enayatifard, R., Khalili, M., Ghaffarloo, M., Saeedi, M., and Charati, J. Y. (2014). Correlation between sun protection factor and antioxidant activity, phenol and flavonoid contents of some medicinal plants. *Iranian Journal of Pharmaceutical Research*. 13(3): 1041–1048.

El-Domyati, M., Attia, S., Saleh, F., Brown, D., Birk, D. E., Gasparro, F., ... and Uitto, J. (2002). Intrinsic aging vs. photoaging: A comparative histopathological, immunohistochemical, and ultrastructural study of skin. *Experimental dermatology*. 11(5): 398-405.

Engwa, G. A., Ferdinand, P. U., Nwalo, F. N., and Unachukwu, M. N. (2019). Mechanism and health effects of heavy metal toxicity in humans. In book: *Poisoning in the modern world-new tricks for an old dog*. 77-99.

Eradati, N., Tajabadi, F., Ahmadi-Ashtiani, H. R., Rezazadeh, S., Taherian, M., and Rastegar, H. (2021). Optimization of cleaning and analytical method for determination of arbutin, hydroquinone and kojic acid in cosmetic products. *Journal of Medicinal Plants*. 20(77): 50–59. https://doi.org/10.29252/jmp.20.77.50.

Erb, M., and Kliebenstein, D. J. (2020). Plant secondary metabolites as defenses, regulators, and primary metabolites: The Blurred Functional Trichotomy. *Plant Physiology*. 184(1): 39–52. https://doi.org/10.1104/PP.20.00433.

Fairweather-Tait, S. J., Bao, Y., Broadley, M. R., Collings, R., Ford, D., Hesketh, J. E., and Hurst, R. (2011). Selenium in human health and disease. *Antioxidants & Redox Signaling*. 14(7): 1337–1383. https://doi.org/10.1089/ars.2010.3275.

Fan, M., Ding, H., Zhang, G., Hu, X., and Gong, D. (2019). *LWT - Food Science and Technology Relationships of dietary flavonoid structure with its tyrosinase inhibitory activity and affinity*. 107(July): 25–34.

Farag, M. A., Abib, B., Qin, Z., Ze, X., and Ali, S. E. (2023). Dietary macrominerals: Updated review of their role and orchestration in human nutrition throughout the life cycle with sex differences. *Current Research in Food Science.* 6: 100450.

Farahbakhsh, S., Arbabian, S., Emami, F., Moghadam, B. R., Ghoshooni, H., Noroozzadeh, A., Sahraei, H., Golmanesh, L., Jalili, C., and Zrdooz, H. (2011). Inhibition of cyclooxygenase type 1 and 2 enzyme by aqueous extract of *Elaeagnus angustifolia* in mice. *Basic and Clinical Neuroscience*. 2(2): 31–37.

Ferreira, M. S., Magalhães, M. C., Oliveira, R., Sousa-Lobo, J. M., and Almeida, I. F. (2021). Trends in the use of botanicals in anti-aging cosmetics. *Molecules*. 26(12): 1–18. https://doi.org/10.3390/molecules26123584.

Flórez, N., Conde, E., and Domínguez, H. (2015). Microwave assisted water extraction of plant compounds. *Journal of Chemical Technology & Biotechnology.* 90(4): 590-607.

Forman, H. J., and Zhang, H. (2021). Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy. *Nature Reviews Drug Discovery*. 20(9): 689-709.

Fu, G., Pang, H., and Wong, Y. H. (2008). Naturally occurring phenylethanoid glycosides: Potential leads for new therapeutics. *Current Medicinal Chemistry*. 15(25): 2592-2613.

Fujimura, T., Haketa, K., Hotta, M., and Kitahara, T. (2007). Loss of skin elasticity precedes to rapid increase of wrinkle levels. *Journal of Dermatological Science.* 47(3): 233-239.

Ganceviciene, R., Liakou, A. I., Theodoridis, A., Makrantonaki, E., and Zouboulis, C. C. (2012). Skin anti-aging strategies. *Dermato-endocrinology*. 4(3): 308-319.

Gangaram, S., Naidoo, Y., Dewir, Y. H., and El-Hendawy, S. (2021). Phytochemicals and biological activities of Barleria (Acanthaceae). *Plants.* 11(1): 82. https://doi.org/10.3390/plants11010082.

Garg, C., Khurana, P., and Garg, M. (2017). Molecular mechanisms of skin photoaging and plant inhibitors. *International Journal of Green Pharmacy*. 11(2): S217–S232.

Ghaderpoori, M., Kamarehie, B., Jafari, A., Alinejad, A. A., Hashempour, Y., Saghi, M. H., ... and Ferrante, M. (2020). Health risk assessment of heavy metals in cosmetic products sold in Iran: The Monte Carlo simulation. *Environmental Science and Pollution Research*. 27: 7588-7595.

Ghahremanfard, F., Semnani, M. R., Mirmohammadkhani, M., Mansori, K., and Pahlevan, D. (2023). The relationship between iron deficiency anemia with restless leg syndrome and sleep quality in workers working in a textile factory

in Iran: A cross-sectional study. *Middle East Current Psychiatry*. 30(1): 23.

Ghasemzadeh, A., Jaafar, H. Z. E., Rahmat, A., and Swamy, M. K. (2017). Optimization of microwave-assisted extraction of zerumbone from *Zingiber zerumbet* L. rhizome and evaluation of antiproliferative activity of optimized extracts. *Chemistry Central Journal*. 11(1): 1–10. https://doi.org/10.1186/s13065-016-0235-3.

Ghosh, P. K., and Gaba, A. (2013). Phyto-extracts in wound healing. *Journal of Pharmacy and Pharmaceutical Sciences*. 16(5): 760–820. https://doi.org/10.18433/j3831v.

Ghule, B. V., Kotagale, N. R., and Patil, K. S. (2020). Inhibition of the pro-inflammatory mediators in rat neutrophils by shanzhiside methyl ester and its acetyl derivative isolated from *Barleria prionitis*. *Journal of Ethnopharmacology*. 249 (September 2019): 112374. https://doi.org/10.1016/j.jep.2019.112374.

Gochfeld, M. (2003). Cases of mercury exposure, bioavailability, and absorption. *Ecotoxicology and Environmental Safety*. 56(1): 174-179.

Godlewska-żyłkiewicz, B., Świsłocka, R., Kalinowska, M., Golonko, A., Świderski, G., Arciszewska, Ż., Nalewajko-Sieliwoniuk, E., Naumowicz, M., and Lewandowski, W. (2020). Biologically active compounds of plants: Structure-related antioxidant, microbiological and cytotoxic activity of selected carboxylic acids. *Materials.* 13(19): 1–37. https://doi.org/10.3390/ma13194454.

Gopalasatheeskumar, K., Kalaichelvan, V. K., Kannappan, N. and Mullai, P. (2022). Different extraction methods for the extraction of phenolics, flavonoids, antioxidant and antidiabetic phytochemicals from *Momordica cymbalaria* leaves. *Indian Journal of Natural Sciences*. 12(70): 0976-0997.

Gosain, A., and DiPietro, L. A. (2004). Aging and wound healing. *World Journal Of Surgery*. 28: 321-326.

Goyal, A., Sharma, A., Kaur, J., Kumari, S., Garg, M., Sindhu, R.K., Rahman, M.H., Akhtar, M.F., Tagde, P., Najda, A. and Banach-Albińska, B. (2022). Bioactive-based cosmeceuticals: An update on emerging trends. *Molecules.* 27(3): 828. https://doi.org/10.3390/molecules27030828.

Gupta, M., Mahajan, V. K., Mehta, K. S., and Chauhan, P. S. (2014). Zinc therapy in dermatology: A Review. *Dermatology Research and Practice.* 2014: 1–11. https://doi.org/10.1155/2014/709152.

Gutteridge, J. M., and Halliwell, B. (2000). Free radicals and antioxidants in the year 2000: A historical look to the future. A*nnals of The New York Academy of Sciences*. 899(1): 136-147.

Haftek, M., Abdayem, R., and Guyonnet-Debersac, P. (2022). Skin minerals: Key roles of inorganic elements in skin physiological functions. *International*

Journal of Molecular Sciences. 23(11): 6267. https://doi.org/10.3390/ijms23116267.

Hamidi, M. R., Jovanova, B., and Panovska, T. K. (2014). Toxicological evaluation of the plant products using Brine Shrimp (*Artemia salina* L.) model. *Macedonian Pharmaceutical Bulletin*. 60(1): 9-18. https://doi.org/10.33320/maced.pharm.bull.2014.60.01.002.

Han, X., Shen, T., and Lou, H. (2007). Dietary polyphenols and their biological significance. *International Journal of Molecular Sciences*. 8(9): 950–988. https://doi.org/10.3390/i8090950.

Hariana, H. A. (2008). Tumbuhan obat dan khasiatnya. Seri Kedua. Jakarta: Niaga Swadaya: 81-82.

Hashim, P., and Mat Hashim, D. (2013). A review of cosmetic and personal care products: Halal perspective and detection of ingredient. *Pertanika Journal of Science and Technology*. 21(2): 281–292.

Hasnain, A., Naqvi, S.A.H., Ayesha, S.I., Khalid, F., Ellahi, M., Iqbal, S., Hassan, M.Z., Abbas, A., Adamski, R., Markowska, D. and Baazeem, A. (2022). Plants *in vitro* propagation with its applications in food, pharmaceuticals and cosmetic industries; current scenario and future approaches. *Frontiers in Plant Science.* 13: 1009395. https://doi.org/10.3389/fpls.2022.1009395.

Hassan, M., Shahzadi, S., and Kloczkowski, A. (2023). Tyrosinase inhibitors naturally present in plants and synthetic modifications of these natural products as anti-melanogenic agents: A review. *Molecules*. 28(1): 378.

Heinrich, U., Tronnier, H., De Spirt, S., and Stahl, W. (2011). Green tea polyphenols: Provide photoprotection and improve physiological parameters of human skin. *Agro Food Industry Hi-Tech*. 22(6): 38–39. https://doi.org/10.3945/jn.110.136465.green.

Herbal Medicine Research Centre, Institute for Medical Research. (2002). *Compendium of medicinal plants used in Malaysia. Volume 2*. Kuala Lumpur: HMRC IMR, 2002: 101.

Hering, A., Stefanowicz-Hajduk, J., Gucwa, M., Wielgomas, B., and Ochocka, J. R. (2023). Photoprotection and antiaging activity of extracts from honeybush (*Cyclopia sp.*)—*In vitro* wound healing and inhibition of the skin extracellular matrix enzymes: Tyrosinase, collagenase, elastase and hyaluronidase. *Pharmaceutics*. 15(5): 1542. https://doi.org/10.3390/pharmaceutics15051542.

Hill, H. R., and Martins, T. B. (2006). The flow cytometric analysis of cytokines using multi-analyte fluorescence microarray technology. *Methods*. 38(4): 312–316. https://doi.org/10.1016/j.ymeth.2005.11.014.

Hoang, H. T., Moon, J. Y., and Lee, Y. C. (2021). Natural antioxidants from plant extracts in skincare cosmetics: Recent applications, challenges and

perspectives. *Cosmetics*. 8(4): 1–24. https://doi.org/10.3390/cosmetics8040106.

Hostynek, J. J., Dreher, F., and Maibach, H. I. (2010). Human skin retention and penetration of a copper tripeptide in vitro as function of skin layer towards anti-inflammatory therapy. *Inflammation Research*. 59: 983-988.

Hruza, L. L., and Pentland, A. P. (1993). Mechanisms of UV-induced inflammation. *Journal of Investigative Dermatology*. 100(1): 35–41.

Hu, Z., Cai, M., and Liang, H. H. (2008). Desirability function approach for the optimization of microwave-assisted extraction of saikosaponins from *Radix Bupleuri*. *Separation and Purification Technology*. 61(3): 266-275. https://doi.org/10.1016/j.seppur.2007.10.016.

Ibrahim, H. M., and Elkhidir, E. E. (2011). Response surface method as an efficient tool for medium optimisation. *Trends in Applied Sciences Research*. 6(2): 121–129. https://doi.org/10.3923/tasr.2011.121.129.

Islam, M. T., Ali, E. S., Uddin, S. J., Shaw, S., Islam, M. A., Ahmed, M. I., Chandra Shill, M., Karmakar, U. K., Yarla, N. S., Khan, I. N., Billah, M. M., Pieczynska, M. D., Zengin, G., Malainer, C., Nicoletti, F., Gulei, D., Berindan-Neagoe, I., Apostolov, A., Banach, M., Yeung, A. W. K., … Atanasov, A. G. (2018). Phytol: A review of biomedical activities. *Food and Chemical Toxicology*, 121: 82–94. https://doi.org/10.1016/j.fct.2018.08.032

Ismail-Suhaimy, N. W., Gani, S. S. A., Zaidan, U. H., Halmi, M. I. E., & Bawon, P. (2021). Optimizing conditions for microwave-assisted extraction of polyphenolic content and antioxidant activity of *Barleria lupulina* Lindl. *Plants*. 10(4): 682.

Jargalsaikhan, G., Wu, J. Y., Chen, Y. C., Yang, L. L., and Wu, M. S. (2021). Comparison of the phytochemical properties, antioxidant activity and cytotoxic effect on HepG2 cells in Mongolian and Taiwanese rhubarb species. *Molecules*. 26(5): 1217. https://doi.org/10.3390/molecules26051217.

Järup, L. (2003). Hazards of heavy metal contamination. *British Medical Bulletin.* 68: 167–182. https://doi.org/10.1093/bmb/ldg032.

Jennifer, C., Stephie, C. M., Abhishri, S. B., and Shalini, B. U. (2012). A review on skin whitening property of plant extracts. *International Journal of Pharma and Bio Sciences*. 3(4): 332–347.

Jha, A. K., and Sit, N. (2022). Extraction of bioactive compounds from plant materials using combination of various novel methods: A review. *Trends in Food Science & Technology*. 119: 579–591. https://doi.org/10.1016/j.tifs.2021.11.019.

Jimenez, M. T. B., Hahad, O., Kuntic, M., Daiber, A., and Münzel, T. (2023). Noise, air, and heavy metal pollution as risk factors for endothelial dysfunction. *European Cardiology Review*. 18: 1-10.

Jyothi, V. G. S., Bulusu, R., Rao, B. V. K., Pranothi, M., Banda, S., Bolla, P. K., and Kommineni, N. (2022). Stability characterization for pharmaceutical liposome product development with focus on regulatory considerations: An update. *International Journal of Pharmaceutics*. 624: 122022.

Ju, Z., Su, M., Hong, J., La Kim, E., Moon, H. R., Chung, H. Y., ... and Jung, J. H. (2019). Design of balanced COX inhibitors based on anti-inflammatory and/or COX-2 inhibitory ascidian metabolites. *European Journal of Medicinal Chemistry*. 180: 86-98.

Juee, L. Y. M. (2022). Phytochemical characterization and mushroom tyrosinase inhibition of different extracts from *Salvia officinalis* L. leaves. *Journal of Pharmacy and Pharmacognosy Research*. 10(4): 605–615. https://doi.org/10.56499/jppres22.1343.10.4.605.

Kageyama, H., and Waditee-Sirisattha, R. (2019). Antioxidative, anti-inflammatory, and anti-aging properties of mycosporine-like amino acids: Molecular and cellular mechanisms in the protection of skin-aging. *Marine Drugs*. 17(4): 222. https://doi.org/10.3390/md17040222.

Kanchanapoom. T., Kasai, R., Yamasaki, K. (2001). Iridoid glucosides from *Barleria lupulina*. *Phytochemistry*. 58(2): 337-341.

Karahan, F., Ozyigit, I. I., Saracoglu, I. A., Yalcin, I. E., Ozyigit, A. H., and Ilcim, A. (2020). Heavy metal levels and mineral nutrient status in different parts of various medicinal plants collected from eastern mediterranean region of Turkey. *Biological Trace Element Research*. 197(1): 316–329. https://doi.org/10.1007/s12011-019-01974-2.

Karaś, M., Jakubczyk, A., Szymanowska, U., Złotek, U., and Zielińska, E. (2017). Digestion and bioavailability of bioactive phytochemicals. *International Journal of Food Science & Technology*. 52(2): 291-305.

Karim, A. A., Azlan, A., Ismail, A., Hashim, P., Abd Gani, S. S., Zainudin, B. H., and Abdullah, N. A. (2014). Tyrosinase inhibitory activities of cocoa pod extract. *BMC Complementary and Alternative Medicine*. 14(381): 1–13.

Karioti, A., Protopappa, A., Megoulas, N., and Skaltsa, H. (2007). Identification of tyrosinase inhibitors from *Marrubium velutinum* and *Marrubium cylleneum*. *Bioorganic and Medicinal Chemistry*. 15(7): 2708–2714. https://doi.org/10.1016/j.bmc.2007.01.035.

Kast, R. E. (2001). Borage oil reduction of rheumatoid arthritis activity may be mediated by increased cAMP that suppresses tumor necrosis factor-alpha. *International Immunopharmacology*. 1(12): 2197-2199.

Kaur, I. P., Kapila, M., and Agrawal, R. (2007). Role of novel delivery systems in developing topical antioxidants as therapeutics to combat photoageing. *Ageing Research Reviews*. 6(4): 271–288. https://doi.org/10.1016/j.arr.2007.08.006.

Kaurinovic, B., and Vastag, D. (2019). Flavonoids and phenolic acids as potential natural antioxidants. *London, UK: IntechOpen*. pp 1-20. doi:10.5772/intechopen.88731.

Keen, M. A., and Hassan, I. (2016). Vitamin E in dermatology. *Indian Dermatology Online Journal*. 7(4): 311-315.

Khushnood, M., Hafeez, F., Suleman, M., Noor, T., Siddique, S., Bakar, A., and Bano, R (2024). Formulation and Evaluation of Strawberry Extract/Oil infused anti-aging and anti-pigmenting Face serum. *Journal of Xi'an Shiyou University, Natural Science Edition*. 20 (2): 914-924.

Kim, G. H., Kim, J. E., Rhie, S. J., and Yoon, S. (2015). The role of oxidative stress in neurodegenerative diseases. *Experimental Neurobiology*. 24 (4): 325–340. https://doi.org/10.5607/en.2015.24.4.325.

Kim, H. Do, Choi, H., Abekura, F., Park, J. Y., Yang, W. S., Yang, S. H., and Kim, C. H. (2023). Naturally-occurring tyrosinase inhibitors classified by enzyme kinetics and copper chelation. *International Journal of Molecular Sciences.* 24(9): 8226. https://doi.org/10.3390/ijms24098226.

Kim, K. H., Park, Y. J., Chung, K. H., Yip, M. R., Clardy, J., Senger, D., and Cao, S. (2015). Iridoid glycosides from *Barleria lupulina*. *Journal of Natural Products*. 78(2): 320-324.

Kim, Y. M., Jung, H. J., Choi, J. S., and Nam, T. J. (2016). Anti-wrinkle effects of a tuna heart H_2O fraction on Hs27 human fibroblasts. *International Journal of Molecular Medicine.* 37(1): 92-98.

Korkmaz, B., Attucci, S., Jourdan, M. L., Juliano, L., and Gauthier, F. (2005). Inhibition of neutrophil elastase by α1-protease inhibitor at the surface of human polymorphonuclear neutrophils. *The Journal of Immunology*. 175(5): 3329-3338.

Knaggs, H., and Lephart, E. D. (2023). Enhancing skin anti-aging through healthy lifestyle factors. *Cosmetics*. 10(5): 142.

Krishnaswamy, K., Orsat, V., Gariépy, Y., and Thangavel, K. (2013). Optimization of microwave-assisted extraction of phenolic antioxidants from grape seeds (*Vitis vinifera*). *Food and Bioprocess Technology*. 6(2): 441-455. https://doi.org/10.1007/s11947-012-0800-2.

Krutmann, J., Bouloc, A., Sore, G., Bernard, B. A., and Passeron, T. (2017). The skin aging exposome. *Journal of Dermatological Science*. 85(3): 152–161. https://doi.org/10.1016/j.jdermsci.2016.09.015.

Kumar, A., P, N., Kumar, M., Jose, A., Tomer, V., Oz, E., Proestos, C., Zeng, M., Elobeid, T., K, S. and Oz, F. (2023). Major phytochemicals: Recent advances in health benefits and extraction method. *Molecules*. 28(2): 887. https://doi.org/10.3390/molecules28020887.

Kumar, V., Kumar, N., and Singh, G. (2024). Natural products and derivatives applied for skin care: An updated review. *Current Traditional Medicine*. 10(1): 18-30.

Kumari, R., and Dubey, R. C. (2016). Phytochemical analysis and antibacterial and cytotoxic properties of *Barleria lupulina* Lindl. Extracts. *Journal of Plant Pathology Microbiology:* 7(380): 2. doi: 10.4172/2157-7471.1000380.

Kumari, R., Kumar, S., Kumar, A., Goel, K. K., and Dubey, R. C. (2017). Antibacterial, antioxidant and Immuno-modulatory properties in extracts of *Barleria lupulina* Lindl. *BMC Complementary and Alternative Medicine*. 17(484): 1-11. https://doi.org/10.1186/s12906-017-1989-4.

Leccia, M. T., Richard, M. J., Bean, J. C., Faure, H., Monjo, A. M., Cadet, J., ... and Favier, A. (1993). Protective effect of selenium and zinc on UV-A damage in human skin fibroblasts. *Photochemistry and Photobiology*. 58(4): 548-553.

Lee, S. R., Clardy, J., Senger, D. R., Cao, S., and Kim, K. H. (2016). Iridoid and phenylethanoid glycosides from the aerial part of *Barleria lupulina*. *Revista Brasileira de Farmacognosia*. 26: 281-284.

Li, L., and Yang, X. (2018). The essential element manganese, oxidative stress, and metabolic diseases: Links and interactions. *Oxidative Medicine and Cellular Longevity*. 2018: 1-11. https://doi.org/10.1155/2018/7580707.

Li, Y., Li, S., Lin, S. J., Zhang, J. J., Zhao, C. N., and Li, H. Bin. (2017). Microwave-assisted extraction of natural antioxidants from the exotic *Gordonia axillaris* fruit: Optimization and identification of phenolic compounds. *Molecules*. 22(9): 1481. https://doi.org/10.3390/molecules22091481.

Li, Y., Liu, Z., Zhang, Y., Jiang, L., Cai, Y., Chen, X., ... and Liu, C. (2021). Investigation and probabilistic health risk assessment of trace elements in good sale lip cosmetics crawled by Python from Chinese e-commerce market. *Journal of Hazardous Materials*. 405: 124279.

Lin, T. K., Zhong, L., and Santiago, J. L. (2017). Anti-inflammatory and skin barrier repair effects of topical application of some plant oils. *International Journal of Molecular Sciences*. 19(1): 70.

Lin, Z., Wang, X., Liu, J., Tian, Z., Dai, L., He, B., ... and Hu, Z. (2015). On the role of localized surface plasmon resonance in UV-Vis light irradiated Au/TiO 2 photocatalysis systems: Pros and cons. *Nanoscale*. 7(9): 4114-4123.

Liu, J., Han, X., Zhang, T., Tian, K., Li, Z., and Luo, F. (2023). Reactive oxygen species (ROS) scavenging biomaterials for anti-inflammatory diseases: From mechanism to therapy. *Journal of Hematology & Oncology*. 16(1): 116.

Liu, R., Xing, L., Fu, Q., Zhou, G. H., and Zhang, W. G. (2016). A review of antioxidant peptides derived from meat muscle and by-products. *Antioxidants*. *5*(3): 32. https://doi.org/10.3390/antiox5030032.

Lochhead, R. (2017). Basic physical sciences for the formulation of cosmetic products. *Cosmetic Science and Technology: Theoretical Principles and Applications*. 39-76.

Luca, S. V., Miron, A., Ignatova, S., and Skalicka-Woźniak, K. (2019). An overview of the two-phase solvent systems used in the countercurrent separation of phenylethanoid glycosides and iridoids and their biological relevance. *Phytochemistry Reviews*. 18(2): 377–403. https://doi.org/10.1007/s11101-019-09599-y.

Ma, W., Lu, Y., Dai, X., Liu, R., Hu, R., and Pan, Y. (2009). Determination of anti-tumor constitute mollugin from traditional Chinese medicine *Rubia cordifolia*: Comparative study of classical and microwave extraction techniques. *Separation Science and Technology*. 44(4): 995-1006. https://doi.org/10.1080/01496390802691265.

Madan, K., and Nanda, S. (2018). *In-vitro* evaluation of antioxidant, anti-elastase, anti-collagenase, anti-hyaluronidase activities of safranal and determination of its sun protection factor in skin photoaging. *Bioorganic Chemistry*. 77: 159–167. https://doi.org/10.1016/j.bioorg.2017.12.030.

Malich, G., Markovic, B., and Winder, C. (1997). The sensitivity and specificity of the MTS tetrazolium assay for detecting the in vitro cytotoxicity of 20 chemicals using human cell lines. *Toxicology*. 124(3): 179-192.

Mandal, S. M., Dias, R. O., & Franco, O. L. (2017). Phenolic compounds in antimicrobial therapy. *Journal of Medicinal Food*. 20(10): 1031–1038. https://doi.org/10.1089/jmf.2017.0017.

Mapoung, S., Semmarath, W., Arjsri, P., Umsumarng, S., Srisawad, K., Thippraphan, P., Yodkeeree, S., and Limtrakul, P. (2021). Determination of phenolic content, antioxidant activity, and tyrosinase inhibitory effects of functional cosmetic creams available on the Thailand market. *Plants*. 10(7): 1383. https://doi.org/10.3390/plants10071383.

María Teresa, R.-C., Rosaura, V.-G., Elda, C.-M., and Ernesto, G.-P. (2014). The avocado defense compound phenol-2,4-bis (1,1-dimethylethyl) is induced by arachidonic acid and acts *via* the inhibition of hydrogen peroxide production by pathogens. *Physiological and Molecular Plant Pathology*. 87: 32–41. https://doi.org/10.1016/j.pmpp.2014.05.003.

Marini, M., Angouria-Tsorochidou, E., Caro, D., and Thomsen, M. (2021). Daily intake of heavy metals and minerals in food – A case study of four Danish dietary profiles. *Journal of Cleaner Production*. 280: 124279. https://doi.org/10.1016/j.jclepro.2020.124279.

Marinovich, M., Boraso, M. S., Testai, E., and Galli, C. L. (2014). Metals in cosmetics: An a posteriori safety evaluation. *Regulatory Toxicology and Pharmacology*. 69(3): 416-424.

Matos, M. S., Romero-Díez, R., Álvarez, A., Bronze, M. R., Rodríguez-Rojo, S., Mato, R. B., Cocero, M. J., and Matias, A. A. (2019). Polyphenol-rich extracts obtained from winemakingwaste streams as natural ingredients with cosmeceutical potential. *Antioxidants*. 8(9): 355. https://doi.org/10.3390/antiox8090355.

Mauro, T., Bench, G., Sidderas-Haddad, E., Feingold, K., Elias, P., and Cullander, C. (1998). Acute barrier perturbation abolishes the Ca^{2+} and K^{+} gradients in murine epidermis: Quantitative measurement using PIXE. *Journal of Investigative Dermatology*. 111(6): 1198–1201. https://doi.org/10.1046/j.1523-1747.1998.00421.x.

Mazumder, P. M., Mondal, A., Sasmal, D., Arulmozhi, S., and Rathinavelusamy, P. (2012). Evaluation of antiarthritic and immunomodulatory activity of *Barleria lupulina*. *Asian Pacific Journal of Tropical Biomedicine*. 2(3): 1400-1406.

Mazumder, P. M., Paramaguru, R., Mohanty, A., and Sasmal, D. (2014). Evaluation of *in vitro* anticataract activity and aldose reductase potential of *Barleria lupulina* Lindl. *Pharmacologia*. 5(5): 172-176. https://doi.org/10.5567/pharmacologia.2014.172.176.

Mechqoq, H., Hourfane, S., El Yaagoubi, M., El Hamdaoui, A., da Silva Almeida, J.R.G., Rocha, J.M. and El Aouad, N., 2022. Molecular docking, tyrosinase, collagenase, and elastase inhibition activities of argan by-products. *Cosmetics*. 9(1): 24.

Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature.* 454(7203): 428–435. https://doi.org/10.1038/nature07201.

Mesa-Arango, A., Flórez-Muñoz, S., and Sanclemente, G. (2017). Mechanisms of skin aging. *IATREIA*. 30(2): 160–170. https://doi.org/10.17533/udea.iatreia.v30n2a05.

Michalak, M. (2023). Plant extracts as skin care and therapeutic agents. *International Journal of Molecular Sciences*. 24(20): 15444. https://doi.org/10.3390/ijms242015444.

Michalak, M. (2022). Plant-derived antioxidants: significance in skin health and the ageing process. *International Journal of Molecular Sciences.* 23(2): 8–12. https://doi.org/10.3390/ijms23020585.

Michalak, M., Pierzak, M., Kręcisz, B., and Suliga, E. (2021). Bioactive compounds for skin health: A review. *Nutrients*. 13(1): 1–31. https://doi.org/10.3390/nu13010203.

Milam, E. C., and Rieder, E. A. (2016). An approach to cosmeceuticals. *Journal of Drugs in Dermatology*. 15(4): 452–456. https://doi.org/10.1002/9781119680116.ch4.

Mohamed Mahzir, K. A., Abd Gani, S. S., Hasanah Zaidan, U., and Halmi, M. I. E. (2018). Development of *Phaleria macrocarpa* (Scheff.) boerl fruits using

response surface methodology focused on phenolics, flavonoids and antioxidant properties. *Molecules*. 23(4): 724. https://doi.org/10.3390/molecules23040724.

Moin, S., Babu, S. S., and Mahalakshmipriya, A. (2012). *In vitro* callus production and antibacterial activity of *Barleria lupulina* Lindl. *Asia-Pacific Journal of Molecular Biology and Biotechnology*. 20(2): 59-64.

Moldovan, Z., Popa, D. E., David, I. G., Buleandra, M., & Badea, I. A. (2017). A derivative spectrometric method for hydroquinone determination in the presence of kojic acid, glycolic acid, and ascorbic acid. *Journal of Spectroscopy*. 2017 (6929520): 1-9. https://doi.org/10.1155/2017/6929520.

Monika, P., Waiker, P. V., Chandraprabha, M. N., Rangarajan, A., and Murthy, K. N. C. (2021). Myofibroblast progeny in wound biology and wound healing studies. *Wound Repair and Regeneration*. 29(4): 531-547.

Montserrat-De La Paz, S., Fernández-Arche, M. A., Ángel-Martín, M., and García-Giménez, M. D. (2014). Phytochemical characterization of potential nutraceutical ingredients from evening primrose oil (*Oenothera biennis* L.). *Phytochemistry Letters*. 8(1): 158–162. https://doi.org/10.1016/j.phytol.2013.08.008.

Moon, S., Kim, D. H., and Shin, J. U. (2021). *In vitro* models mimicking immune response in the skin. *Yonsei Medical Journal*. 62(11): 969.

Mosić, M., Dramićanin, A., Ristivojević, P., and Milojković-Opsenica, D. (2021). Extraction as a critical step in phytochemical analysis. *Journal of AOAC International*. 103(2): 365–372. https://doi.org/10.5740/jaoacint.19-0251.

Mukherjee, P. K., Biswas, R., Sharma, A., Banerjee, S., Biswas, S., and Katiyar, C. K. (2018). Validation of medicinal herbs for anti-tyrosinase potential. *Journal of Herbal Medicine*. 14: 1–16. https://doi.org/10.1016/j.hermed.2018.09.002.

Murphy, B., Hoptroff, M., Arnold, D., Eccles, R., and Campbell-Lee, S. (2021). *In-vivo* impact of common cosmetic preservative systems in full formulation on the skin microbiome. *PLoS One*.16(7): 1-13.

Mut-Salud, N., Álvarez, P. J., Garrido, J. M., Carrasco, E., Aránega, A., and Rodríguez-Serrano, F. (2016). Antioxidant intake and antitumor therapy: Toward nutritional recommendations for optimal results. *Oxidative Medicine and Cellular Longevity*. 2016 (6719534): 1-19. https://doi.org/10.1155/2016/6719534.

Nandiyanto, A. B. D., Oktiani, R., and Ragadhita, R. (2019). How to read and interpret FTIR spectroscope of organic material. *Indonesian Journal of Science and Technology*. 4(1): 97-118.

Napagoda, M. T., Malkanthi, B. M. A. S., Abayawardana, S. A. K., Qader, M. M., and Jayasinghe, L. (2016). Photoprotective potential in some medicinal plants used to treat skin diseases in Sri Lanka. *BMC Complementary and Alternative*

Medicine. 16(1): 1–6. https://doi.org/10.1186/s12906-016-1455-8.

National Center for Biotechnology Information (2024). PubChem Compound Summary for CID 332, 2-Methoxy-4-vinylphenol. Retrieved April 25, 2024 from https://pubchem.ncbi.nlm.nih.gov/compound/2-Methoxy-4-vinylphenol.

Neha, K., Haider, M. R., Pathak, A., and Yar, M. S. (2019). Medicinal prospects of antioxidants: A review. *European Journal of Medicinal Chemistry*. 178(7): 687–704. https://doi.org/10.1016/j.ejmech.2019.06.010.

Newton, K., and Dixit, V. M. (2012). Signaling in innate immunity and inflammation. *Cold Spring Harbor Perspectives in Biology*. 4(3): 1-19. https://doi.org/10.1101/cshperspect.a006049.

Nguyen, J. K., Masub, N., and Jagdeo, J. (2020). Bioactive ingredients in Korean cosmeceuticals: Trends and research evidence. *Journal of Cosmetic Dermatology*. 19(7): 1555–1569. https://doi.org/10.1111/jocd.13344.

Nguyen, T., Sherratt, P. J., and Pickett, C. B. (2003). Regulatory mechanisms controlling gene expression mediated by the antioxidant response element. *Annual Review of Pharmacology and Toxicology*. 43(2): 233–260. https://doi.org/10.1146/annurev.pharmtox.43.100901.140229.

Nichols, J. A., and Katiyar, S. K. (2010). Skin photoprotection by natural polyphenols: Anti-inflammatory, antioxidant and DNA repair mechanisms. *Archives of Dermatological Research.* 302(2): 71–83. https://doi.org/10.1007/s00403-009-1001-3.

Nordberg, G. F., Costa, M., and Fowler, B. A. (2022). Risk assessment for metal exposures. In *Handbook on the Toxicology of Metals* (pp. 629-661). Academic Press.

Nortjie, E., Basitere, M., Moyo, D., and Nyamukamba, P. (2022). Extraction methods, quantitative and qualitative phytochemical screening of medicinal plants for antimicrobial textiles: A review. *Plants*. 11(15): 2011.

Ntungwe N, E., Domínguez-Martín, E. M., Roberto, A., Tavares, J., Isca, V., Pereira, P., ... and Rijo, P. (2020). Artemia species: An important tool to screen general toxicity samples. *Current Pharmaceutical Design*. 26(24): 2892-2908.

Obaid, R. J., Mughal, E. U., Naeem, N., Sadiq, A., Alsantali, R. I., Jassas, R. S., Moussa, Z., and Ahmed, S. A. (2021). Natural and synthetic flavonoid derivatives as new potential tyrosinase inhibitors: A systematic review. *RSC Advances*. 11(36): 22159–22198. https://doi.org/10.1039/d1ra03196a.

Ogawa, Y., Kinoshita, M., Shimada, S., and Kawamura, T. (2018). Zinc and skin disorders. *Nutrients*. 10(2): 199. https://doi.org/10.3390/nu10020199.

Okur, M. E., Karadağ, A. E., Özhan, Y., Sipahi, H., Ayla, Ş., Daylan, B., Kültür, Ş., Demirci, B., and Demirci, F. (2021). Anti-inflammatory, analgesic and *in vivo-in vitro* wound healing potential of the *Phlomis rigida* Labill. extract. *Journal*

of Ethnopharmacology. 266 (February 2020): 113408. https://doi.org/10.1016/j.jep.2020.113408.

Oshadie, G., Silva, D., Abeysundara, A. T., Minoli, M., and Aponso, W. (2017). Extraction methods, qualitative and quantitative techniques for screening of phytochemicals from plants. *American Journal of Essential Oils and Natural Products*. 5(2): 29–32.

Oton, L. B., de Azevedo, M. G. B., and Falcão, J. de S. A. (2018). Preliminary stability study of dry and glycolic extract of *Ginkgo biloba* L. incorporated in phytocosmetic formulations. *International Journal of Phytocosmetics and Natural Ingredients. 5*(1): 1-6. https://doi.org/10.15171/ijpni.2018.08.

Oulahal, N., and Degraeve, P. (2022). Phenolic-rich plant extracts with antimicrobial activity: An alternative to food preservatives and biocides. *Frontiers in Microbiology*. 12(753518): 1-31. https://doi.org/10.3389/fmicb.2021.753518.

Ozyigit, I. I., Yalcin, B., Turan, S., Saracoglu, I. A., Karadeniz, S., Yalcin, I. E., and Demir, G. (2018). Investigation of heavy metal level and mineral nutrient status in widely used medicinal plants' leaves in Turkey: Insights into health implications. *Biological Trace Element Research*. 182(2): 387–406. https://doi.org/10.1007/s12011-017-1070-7.

Paixão, N., Perestrelo, R., Marques, J. C., and Câmara, J. S. (2007). Relationship between antioxidant capacity and total phenolic content of red, rosé and white wines. *Food Chemistry*. 105(1): 204-214. https://doi.org/10.1016/j.foodchem.2007.04.017.

Pan, S. Y., Zhou, S. F., Gao, S. H., Yu, Z. L., Zhang, S. F., Tang, M. K., ... and Ko, K. M. (2013). New perspectives on how to discover drugs from herbal medicines: CAM's outstanding contribution to modern therapeutics. E*vidence-Based Complementary and Alternative Medicine*. 2013 (627375): 1-25.

Pandey, A., Jatana, G. K., and Sonthalia, S. (2019). *Cosmeceuticals*. StatPearls. 1–21.

Pandur, E., Micalizzi, G., Mondello, L., Horváth, A., Sipos, K., and Horváth, G. (2022). Antioxidant and anti-inflammatory effects of thyme (*Thymus vulgaris* L.) essential oils prepared at different plant phenophases on *Pseudomonas aeruginosa* LPS-activated THP-1 macrophages. *Antioxidants*. 11(7): 1330. https://doi.org/10.3390/antiox11071330.

Panzella, L., and Napolitano, A. (2019). Natural and bioinspired phenolic compounds as tyrosinase inhibitors for the treatment of skin hyperpigmentation: Recent advances. *Cosmetics*. 6(4): 57. https://doi.org/10.3390/cosmetics6040057.

Park, K. (2015). Role of micronutrients in skin health and function. *Biomolecules and Therapeutics*.23(3): 207–217. https://doi.org/10.4062/biomolther.2015.003.

Patel, I., and Mashru, R. (2020). Development of herbal SPF formulation. *Journal of Pharmacognosy and Phytochemistry*. 9(1): 40–44. https://doi.org/10.22271/

phyto.2020.v9.i1a.10469.

Pham, T. H., Kim, M. S., Le, M. Q., Song, Y. S., Bak, Y., Ryu, H. W., ... and Yoon, D. Y. (2017). Fargesin exerts anti-inflammatory effects in THP-1 monocytes by suppressing PKC-dependent AP-1 and NF-κB signaling. *Phytomedicine*. 24: 96-103.

Phan, M. A. T., Paterson, J., Bucknall, M., and Arcot, J. (2018). Interactions between phytochemicals from fruits and vegetables: Effects on bioactivities and bioavailability. *Critical reviews in food science and nutrition*. 58(8): 1310-1329.

Philips, N., Hwang, H., Chauhan, S., Leonardi, D., and Gonzalez, S. (2010). Stimulation of cell proliferation and expression of Matrixmetalloproteinase-1 and Interluekin-8 genes in dermal fibroblasts by copper. *Connective Tissue Research*. 51(3): 224–229. https://doi.org/10.3109/03008200903288431.

Pillaiyar, T., Manickam, M., and Namasivayam, V. (2017). Skin whitening agents: Medicinal chemistry perspective of tyrosinase inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 32(1): 403–425. https://doi.org/10.1080/14756366.2016.1256882.

Pisoschi, A. M., and Pop, A. (2015). The role of antioxidants in the chemistry of oxidative stress: A review. *European Journal of Medicinal Chemistry*. 97: 55-74.

Pittayapruek, P., Meephansan, J., Prapapan, O., Komine, M., and Ohtsuki, M. (2016). Role of matrix metalloproteinases in photoaging and photocarcinogenesis. *International Journal of Molecular Sciences*. 17(6): 868. https://doi.org/10.3390/ijms17060868.

Polefka, T. G., Bianchini, R. J., and Shapiro, S. (2012). Interaction of mineral salts with the skin: A literature survey. *International Journal of Cosmetic Science*. 34(5): 416–423. https://doi.org/10.1111/j.1468-2494.2012.00731.x.

Polverino, E., Rosales-Mayor, E., Dale, G. E., Dembowsky, K., and Torres, A. (2017). The role of neutrophil elastase inhibitors in lung diseases. *Chest*. 152(2): 249-262.

Ponec, M., Weerheim, A., Kempenaar, J., Mulder, A., Gooris, G. S., Bouwstra, J., and Mommaas, A. M. (1997). The formation of competent barrier lipids in reconstructed human epidermis requires the presence of vitamin C. *Journal of investigative dermatology*. 109(3): 348-355.

Ponnusamy, Y., Chear, N. J. Y., Ramanathan, S., and Lai, C. S. (2015). Polyphenols rich fraction of *Dicranopteris linearis* promotes fibroblast cell migration and proliferation *in vitro*. *Journal of Ethnopharmacology*. 168: 305–314. https://doi.org/10.1016/j.jep.2015.03.062.

Ponphaiboon, J., Krongrawa, W., Aung, W. W., Chinatangkul, N., Limmatvapirat, S., and Limmatvapirat, C. (2023). Advances in natural product extraction

techniques, electrospun fiber fabrication, and the integration of experimental design: A comprehensive review. *Molecules*. 28(13): 5163. https://doi.org/10.3390/molecules28135163.

Prajapati, V., Tripathi, A. K., Khanuja, S. P. S., and Kumar, S. (2003). Anti-insect screening of medicinal plants from Kukrail Forest, Lucknow, India. *Pharmaceutical Biology*. 41(3): 166-170.

Pröfrock, D., and Prange, A. (2012). Inductively coupled plasma-mass spectrometry (ICP-MS) for quantitative analysis in environmental and life sciences: A review of challenges, solutions, and trends. *Applied Spectroscopy*. 66(8): 843–868. https://doi.org/10.1366/12-06681.

Puértolas, E., Saldaña, G., Álvarez, I., and Raso, J. (2011). Experimental design approach for the evaluation of anthocyanin content of rosé wines obtained by pulsed electric fields: Influence of temperature and time of maceration. *Food Chemistry*. 126(3): 1482-1487. https://doi.org/10.1016/j.foodchem. 2010.11.164.

Qadir, A., Jahan, S., Aqil, M., Warsi, M. H., Alhakamy, N. A., Alfaleh, M. A., Khan, N., and Ali, A. (2021). Phytochemical-based nano-pharmacotherapeutics for management of burn wound healing. *Gels*. 7(4): 1–19. https://doi.org/10.3390/gels7040209.

Quattrocchi, U. (2012). CRC world dictionary of medicinal and poisonous plants: common names, scientific names, eponyms, synonyms, and etymology (5 Volume Set). *CRC Press*. 537-538.

Radice, M., Manfredini, S., Ziosi, P., Dissette, V., Buso, P., Fallacara, A., and Vertuani, S. (2016). Herbal extracts, lichens and biomolecules as natural photo-protection alternatives to synthetic UV filters. A systematic review. *Fitoterapia*. 114: 144–162. https://doi.org/10.1016/j.fitote.2016.09.003.

Rajam, R. P., Kannan, S., and Kajendran, D. (2019). Cosmeceuticals an emerging technology—A review. *World J. Pharma. Res.* 8(12): 664-685.

Ramphinwa, M. L., Mchau, G. R. A., Mashau, M. E., Madala, N. E., Chimonyo, V. G. P., Modi, T. A., and Mudau, F. N. (2023). Eco-physiological response of secondary metabolites of teas: Review of quality attributes of herbal tea. *Frontiers in Sustainable Food Systems*. 7: 990334. https://doi.org/10.3389/fsufs.2023.990334

Rauf, I. A. (2015). Applied statistical design of experiments: Applications in natural sciences. *Journal of Physical Chemistry & Biophysics*. 5(5): 129-130. https://doi.org/10.4172/2161-0398.1000e129.

Rayman, M. P. (2008). Food-chain selenium and human health: Emphasis on intake. *British Journal of Nutrition*. 100(2): 254–268. https://doi.org/10.1017/ S0007114508939830.

Re, R., Pellegrini, N., Proteggente, A., Pannala, A., Yang, M., and Rice-Evans, C. (1999). Antioxidant activity applying an improved ABTS radical cation decolorization assay. *Free Radical Biology and Medicine*. 26(9-10): 1231-1237. https://doi.org/10.1016/S0891-5849(98)00315-3.

Reinke, J. M., and Sorg, H. (2012). Wound repair and regeneration. *European Surgical Research*. 49(1): 35-43.

Ribeiro, A. S., Estanqueiro, M., Oliveira, M. B., and Lobo, J. M. S. (2015). Main benefits and applicability of plant extracts in skin care products. *Cosmetics*. 2(2): 48–65. https://doi.org/10.3390/cosmetics2020048.

Rodan, K., Fields, K., Majewski, G., and Falla, T. (2016). Skincare bootcamp: The evolving role of skincare. *Plastic and Reconstructive Surgery - Global Open*. 4(July): 1152. https://doi.org/10.1097/GOX.0000000000001152.

Roohani, N., Hurrell, R., Kelishadi, R., & Schulin, R. (2013). Zinc and its importance for human health: An integrative review. *Journal of research in medical sciences: The official journal of Isfahan University of Medical Sciences*. 18(2): 144.

Routray, W., and Orsat, V. (2012). Microwave-assisted extraction of flavonoids: A review. *Food and Bioprocess Technology*. 5: 409-424.

Rybczyńska-Tkaczyk, K., Grenda, A., Jakubczyk, A., Kiersnowska, K., and Bik-Małodzińska, M. (2023). Natural compounds with antimicrobial properties in cosmetics. *Pathogens*. 12(2): 320.

Sadick, N. S. (2010). Futuristic approaches to skin care. In *Cosmeceutical Science in Clinical Practice*. CRC Press. 97-107.

Saidalavi, R., Hashim, A., Kishor, K. B., Leena, P. K., and Adake, P. (2017). Analysis of lead and arsenic in cosmetics and assessment of students awareness about cosmetic toxicity. *Int. J. Basic Clin. Pharmacol*. 6: 1426-1430.

Salehi, B., Azzini, E., Zucca, P., Maria Varoni, E., V. Anil Kumar, N., Dini, L., ... and Sharifi-Rad, J. (2020). Plant-derived bioactives and oxidative stress-related disorders: A key trend towards healthy aging and longevity promotion. *Applied Sciences*. 10(3): 947.

Salvemini, D., Kim, S. F., and Mollace, V. (2013). Reciprocal regulation of the nitric oxide and cyclooxygenase pathway in pathophysiology: Relevance and clinical implications. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*. 304(7): 473-487.

Samuel, A. J. S. J., Kalusalingam, A., Chellappan, D. K., Gopinath, R., Radhamani, S., Husain, H. A., Muruganandham, V. and Promwichit, P. (2010). Ethnomedical survey of plants used by the Orang Asli in Kampung Bawong, Perak, West Malaysia. *Journal of Ethnobiology and Ethnomedicine*. 5(6): 1-6.

Santhanam, R. kumar, Akhtar, M. T., Ahmad, S., Abas, F., Ismail, I. S., Rukayadi, Y., and Shaari, K. (2017). Utilization of the ethyl acetate fraction of *Zanthoxylum rhetsa* bark extract as an active ingredient in natural sunscreen formulations. *Industrial Crops and Products*. 96: 165–172. https://doi.org/10.1016/j.indcrop.2016.11.058.

Santo, C. E., Quaranta, D., and Grass, G. (2012). Antimicrobial metallic copper surfaces kill S*taphylococcus haemolyticus via* membrane damage. *Microbiology Open*. 1(1): 46–52. https://doi.org/10.1002/mbo3.2.

Sarkar, R., Arora, P., and Garg, Kv. (2013). Cosmeceuticals for hyperpigmentation: What is available? *Journal of Cutaneous and Aesthetic Surgery*. 6(1): 4. https://doi.org/10.4103/0974-2077.110089.

Sartor, L., Pezzato, E., Dell'aica, I., Caniato, R., Biggin, S., and Garbisa, S. (2002). Inhibition of matrix-proteases by polyphenols: Chemical insights for anti-inflammatory and anti-invasion drug design. *Biochemical Pharmacology*. 64(2): 229–237. https://doi.org/10.1016/S0006-2952(02)01069-9.

Sasidharan, S., Chen, Y., Saravanan, D., Sundram, K. M., and Latha, L. Y. (2011). Extraction, isolation and characterization of bioactive compounds from plants' extracts. *African journal of traditional, complementary and alternative medicines*. 8(1): 1–10. https://www.phytojournal.com/archives/2014/vol2issue5/PartB/11.1.

Sawangjaroen, N., Phongpaichit, S., Subhadhirasakul, S., Visutthi, M., Srisuwan, N. and Thammapalerd, N. (2006). The anti-amoebic activity of some medicinal plants used by AIDS patients in southern Thailand. *Parasitol Res*. 98(6): 588-592.

Sawarkar, H. A., Pandey, A. K., and Biyani, K. R. (2023). Phytochemicals and therapeutic potentials of *Barleria lupulina. Bangladesh Journal of Pharmacology*. 18(4): 119-129.

Sayre R. M., Agin P. P., LeVee, G. J. and Marlowe E (1979). A comparison of *in vivo* and *in vitro* testing of sunscreening formulas. *Photochem Photobiol*. 29(3): 559-566. doi:10.1111/j.1751-1097.1979.tb07090.x

Schempp, C. M., Dittmar, H. C., Hummler, D., Simon-Haarhaus, B., Schulte-Mönting, jürgen, Schöpf, E., and Simon, J. C. (2000). Magnesium ions inhibit the antigen-presenting function of human epidermal Langerhans cells *in vivo* and *in vitro*. Involvement of ATPase, HLA-DR, B7 molecules, and cytokines. *Journal of Investigative Dermatology*. 115(4): 680–686. https://doi.org/10.1046/j.1523-1747.2000.00090.x.

Senger, D. R., and Cao, S. (2016). Diabetic wound healing and activation of Nrf2 by herbal medicine. *Journal of Nature and Science*. 2(11): 1-13.

Shaaban, M. T., Ghaly, M. F., and Fahmi, S. M. (2021). Antibacterial activities of hexadecanoic acid methyl ester and green-synthesized silver nanoparticles against multidrug-resistant bacteria. *Journal of Basic Microbiology*. 61(6):

557–568. https://doi.org/10.1002/jobm.202100061.

Shahid, M., Dumat, C., Khalid, S., Schreck, E., Xiong, T., and Niazi, N. K. (2017). Foliar heavy metal uptake, toxicity and detoxification in plants: A comparison of foliar and root metal uptake. *Journal of Hazardous Materials*. 325: 36–58. https://doi.org/10.1016/j.jhazmat.2016.11.063.

Shahidi, F., and Ambigaipalan, P. (2015). Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects - A review. In *Journal of Functional Foods*. 18 (2015): 820-897. https://doi.org/10.1016/j.jff. 2015.06.018.

Shahidi, F., and Zhong, Y. (2015). Measurement of antioxidant activity. *Journal of Functional Foods*. 18: 757–781. https://doi.org/10.1016/j.jff.2015.01.047.

Shaikh, J. R., and Patil, M. (2020). Qualitative tests for preliminary phytochemical screening: An overview. *International Journal of Chemical Studies*. 8(2): 603-608.

Shang, A., Luo, M., Gan, R. Y., Xu, X. Y., Xia, Y., Guo, H., Liu, Y., and Li, H. Bin. (2020). Effects of microwave-assisted extraction conditions on antioxidant capacity of sweet tea (*Lithocarpus polystachyus* rehd.). *Antioxidants*. 9(8): 1–17. https://doi.org/10.3390/antiox9080678.

Sharma, A., Khanna, S., Kaur, G., and Singh, I. (2021). Medicinal plants and their components for wound healing applications. *Future Journal of Pharmaceutical Sciences*. 7(1): 1-13. https://doi.org/10.1186/s43094-021-00202-w.

Sharmeen, J. B., Mahomoodally, F. M., Zengin, G., and Maggi, F. (2021). Essential oils as natural sources of fragrance compounds for cosmetics and cosmeceuticals. *Molecules*. 26(3): 666.

Shu, P., Yu, M., Zhu, H., Luo, Y., Li, Y., Li, N., Zhang, H., Zhang, J., Liu, G., Wei, X., and Yi, W. (2021). Two new iridoid glycosides from *Gardeniae fructus*. *Carbohydrate Research*. 501(February):1-6. https://doi.org/10.1016/j.carres.2021.108259.

Sies, H., Berndt, C., and Jones, D. P. (2017). Oxidative Stress. *Annual Review of Biochemistry*. 86(1): 715–748. https://doi.org/10.1146/annurev-biochem-061516-045037.

Singh, P. K., Singh, J., Medhi, T., and Kumar, A. (2022). Phytochemical screening, quantification, FT-IR analysis, and *in silico* characterization of potential bioactive compounds identified in HR-LC/MS analysis of the polyherbal formulation from Northeast India. *ACS omega*. 7(37): 33067-33078.

Singh, R. P., and Agarwal, R. (2009). Cosmeceuticals and silibinin. *Clinics in Dermatology*. 27(5): 479–484. https://doi.org/10.1016/j.clindermatol.2009. 05.012.

Singh, R., Gautam, N., Mishra, A., and Gupta, R. (2011). Heavy metals and living systems: An overview. *Indian Journal of Pharmacology*. 43(3): 246-253.

Singleton, V. L., and Jr., R. J. A. (1965). Colorimetry of total phenolics with phosphomolybdic-phosphotungstic acid reagents. *American Journal of Enology and Viticulture.* 16:144–158. https://doi.org/10.12691/ijebb-2-1-5id Rea.

Sirisidthi, N. K., Chabra, S., Jiraungkoorskul, K., and Jiraungkoorskul, W. (2016). Evaluation of total essential oil and cytotoxic activity of *Barleria lupulina* Lindl. *Asia-Pacific Journal of Molecular Biology and Biotechnology*. 24: 1-6. https://repository.li.mahidol.ac.th/handle/123456789/43146.

Smythe, P., and Wilkinson, H. N. (2023). The skin microbiome: current landscape and future opportunities. *International Journal of Molecular Sciences*. 24(4): 3950.

Sobhon, P., Savedvanich, G., and Weerakiet, S. (2023). Oxidative stress and inflammation: the root causes of aging. *Exploration of Medicine*. 4(2), 127-156.

Soetan, K. O., Olaiya, C. O., and Oyewole, O. E. (2010). The importance of mineral elements for humans, domestic animals and plants: A review. *African Journal of Food Science*. 4(May): 1–23.

Solano, F. (2020). Photoprotection and skin pigmentation: Melanin-related molecules and some other new agents obtained from natural sources. *Molecules*. 25(7): 1–18. https://doi.org/10.3390/molecules25071537.

Stanković, M. (2011). Total phenolic content, flavonoid concentration and antioxidant activity of *Marrubium peregrinum* L. extracts. *Kragujevac Journal of Science*. 33(2011): 63-72.

Suba, V., Murugesan, T., Rao, R. B., Pal, M., Mandal, S. C., Saha, B. P. (2002). Neuropharmacological profile of *Barleria lupulina* Lindl. extract in animal models. *J Ethnopharmacol*. 81(2):251-255.

Suba. V., Murugesan, T., Pal, M., Mandal, S. C., Saha, B. P. (2004). Antiulcer activity of methanol fraction of *Barleria lupulina* Lindl. in animal models. *Phytother Res*. 18(11): 925-929.

Suba, V., Murugesan, T., Bhaskara Rao, R., Ghosh, L., Pal, M., Mandal, S. C., and Saha, B. P. (2004). Antidiabetic potential of *Barleria lupulina* extract in rats. *Fitoterapia*. 75(1): 1-4.

Suba, V., Murugesan, T., Arunachalam, G., Mandal, S. C., Saha, B. P. (2004). Anti-diabetic potential of *Barleria lupulina* extract in rats. *Phytomedicine*. 11(2-3): 202-205.

Suba, V., Murugesan, T., Arunachalam, G., Mandal, S. C., Saha, B. P. (2005). Antiinflammatory, analgesic and antiperoxidative efficacy of *Barleria*

lupulina Lindl. extract. *Phytother Res*. 19(8): 695-699.

Subramanian, R., Gayathri, S., Rathnavel, C., and Raj, V. (2012). Analysis of mineral and heavy metals in some medicinal plants collected from local market. *Asian Pacific Journal of Tropical Biomedicine*. 2(1): 74-78.

Suksamrarn, S., Wongkrajang, K., Kirtikara, K., Suksamrarn, A. (2003). Iridoid glucosides from the flowers of *Barleria lupulina*. *Planta Med.* 69(9): 877-879.

Sun, W., and Shahrajabian, M. H. (2023). Therapeutic potential of phenolic compounds in medicinal plants—Natural health products for human health. *Molecules*. 28(4): 1845.

Süntar, I., Akkol, E. K., Nahar, L., and Sarker, S. D. (2012). Wound healing and antioxidant properties: Do they coexist in plants? *Free Radicals and Antioxidants*. 2(2): 1–7. https://doi.org/10.5530/ax.2012.2.2.1.

Surber, C., and Kottner, J. (2017). Skin care products: What do they promise, what do they deliver. *Journal of Tissue Viability*. 26(1): 29–36. https://doi.org/10.1016/j.jtv.2016.03.006.

Tabaraki, R., and Nateghi, A. (2011). Optimization of ultrasonic-assisted extraction of natural antioxidants from rice bran using response surface methodology. *Ultrasonics Sonochemistry*. 18(6): 1279-1286. https://doi.org/10.1016/j.ultsonch.2011.05.004.

Tabassum, N., and Hamdani, M. (2014). Plants used to treat skin diseases. *Pharmacognosy reviews*. 8(15): 52-60. http://doi: 10.4103/0973-7847.125531.

Tamura, T., Zhai, R., Takemura, T., Ouhara, K., Taniguchi, Y., Hamamoto, Y., Fujimori, R., Kajiya, M., Matsuda, S., Munenaga, S., Fujita, T., and Mizuno, N. (2022). Anti-inflammatory effects of geniposidic acid on porphyromonas gingivalis-induced periodontitis in mice. *Biomedicines*. 10(12): 3096. https://doi.org/10.3390/biomedicines10123096.

Tarnowska, M. (2019). *Evaluation of skin absorption of inorganic ions with regard to their physicochemical properties* (Doctoral dissertation, Université de Lyon).

Tchounwou, P. B., Yedjou, C. G., Patlolla, A. K., and Sutton, D. J. (2012). Environmental toxicology. *Molecular, Clinical and Environmental Toxicology, Experientia Supplementum*. 3: 133-164. https://doi.org/10.1007/978-3-7643-8340-4.

Tenaud, I., Sainte-Marie, I., Jumbou, O., Litoux, P., and Dreno, B. (1999). *In vitro* modulation of keratinocyte wound healing integrins by zinc, copper and manganese. *British Journal of Dermatology*. 140(1): 26-34.

Thorat, P. S., Bhadane, H. B., Wagh, S. S., Gaikwad, M. S., and Chhajed, S. S. (2023). General review on face serum. *World Journal of Pharmaceutical Research.* 12 (6): 445-462. https://doi.org/10.20959/wjpr20236-27839.

Thring, T. S. A., Hili, P., and Naughton, D. P. (2009). Anti-collagenase, anti-elastase and anti-oxidant activities of extracts from 21 plants. *BMC Complementary and Alternative Medicine*. 9: 1–11. https://doi.org/10.1186/1472-6882-9-27.

Tian, X.-Y., Li, M.-X., Lin, T., Qiu, Y., Zhu, Y.-T., Li, X.-L., Tao, W.-D., Wang, P., Ren, X.-X., and Chen, L.-P. (2021). A review on the structure and pharmacological activity of phenylethanoid glycosides. *European Journal of Medicinal Chemistry*. 209: 112563. https://doi.org/10.1016/j.ejmech. 2020.112563.

Torres-Contreras, A. M., Garcia-Baeza, A., Vidal-Limon, H. R., Balderas-Renteria, I., Ramírez-Cabrera, M. A., and Ramirez-Estrada, K. (2022). Plant secondary metabolites against skin photodamage: Mexican plants, a potential source of UV-radiation protectant molecules. *Plants*. 11(2): 220. https://doi.org/10. 3390/plants11020220.

Tsala, D. E., Amadou, D., and Habtemariam, S. (2013). Natural wound healing and bioactive natural products. *Phytopharmacology*. 4(3): 532–560.

Tsatsou, F., Trakatelli, M., Patsatsi, A., Kalokasidis, K., and Sotiriadis, D. (2012). Extrinsic aging: UV-mediated skin carcinogenesis. *Dermato-Endocrinology*. 4(3): 285-297. https://doi.org/10.4161/derm.22519.

Tundis, R., Loizzo, M. R., Menichini, F., Statti, G. A., and Menichini, F. (2008). Biological and pharmacological activities of iridoids: Recent developments. *Mini Reviews in Medicinal Chemistry*. 8(4): 399-420.

Uauy, R., Olivares, M., & Gonzalez, M. (1998). Essentiality of copper in humans. *The American Journal of Clinical Nutrition*. 67(5): 952S-959S.

Varani, J., Warner, R. L., Gharaee-Kermani, M., Phan, S. H., Kang, S., Chung, J., ... and Voorhees, J. J. (2000). Vitamin A antagonizes decreased cell growth and elevated collagen-degrading matrix metalloproteinases and stimulates collagen accumulation in naturally aged human skin1. *Journal of Investigative Dermatology*. 114(3): 480-486.

Varesi, A., Chirumbolo, S., Campagnoli, L. I. M., Pierella, E., Piccini, G. B., Carrara, A., Ricevuti, G., Scassellati, C., Bonvicini, C., and Pascale, A. (2022). The role of antioxidants in the interplay between oxidative stress and senescence. *Antioxidants*, 11(7): 1–42. https://doi.org/10.3390/antiox11071224.

Vertuani, S., Beghelli, E., Scalambra, E., Malisardi, G., Copetti, S., Toso, R. D., Baldisserotto, A., and Manfredini, S. (2011). Activity and stability studies of verbascoside, a novel antioxidant, in dermo-cosmetic and pharmaceutical topical formulations. *Molecules*. 16(8): 7068–7080. https://doi.org/10.3390/molecules16087068.

Viljoen, A., Mncwangi, N., and Vermaak, I. (2012). Anti-inflammatory iridoids of botanical origin. *Current Medicinal Chemistry*. 19(14): 2104-2127.

Volpe, M. G., Nazzaro, M., Coppola, R., Rapuano, F., and Aquino, R. P. (2012). Determination and assessments of selected heavy metals in eye shadow cosmetics from China, Italy, and USA. *Microchemical Journal*. 101: 65-69.

Wallace, L. A., Gwynne, L., and Jenkins, T. (2019). Challenges and opportunities of pH in chronic wounds. *Therapeutic Delivery*. 10(11): 719-735.

Wanakhachornkrai, O., Banglao, W., Thongmee, A., and Sukplang, P. (2020). Determination of antioxidant, anti-aging and cytotoxicity activity of the essential oils from *Cinnamomum zeylanicum*. *Journal of Microbiology, Biotechnology and Food Sciences*. 10(3): 436-440.

Wang, C., Gong, X., Bo, A., Zhang, L., Zhang, M., Zang, E., Zhang, C., and Li, M. (2020). Iridoids: Research advances in their phytochemistry, biological activities, and pharmacokinetics. *Molecules*. 25(2): 287. https://doi.org/10.3390/molecules25020287.

Wang, L., and Weller, C. L. (2006). Recent advances in extraction of nutraceuticals from plants. *Trends in Food Science and Technology*. 17(6): 300-312. https://doi.org/10.1016/j.tifs.2005.12.004.

Wanikiat, P., Panthong, A., Sujayanon, P., Yoosook, C., Rossi, A. G., and Reutrakul, V. (2008). The anti-inflammatory effects and the inhibition of neutrophil responsiveness by *Barleria lupulina* and *Clinacanthus nutans* extracts. *Journal of Ethnopharmacology*. 116(2): 234–244. https://doi.org/10.1016/j.jep.2007.11.035.

Waters, D. J., Shen, S., Cooley, D. M., Bostwick, D. G., Qian, J., Combs, G. F., Glickman, L. T., Oteham, C., Schlittler, D., and Morris, J. S. (2003). Effects of dietary selenium supplementation on DNA damage and apoptosis in canine prostate. *Journal of The National Cancer Institute*. 95(3): 237–241. https://doi.org/10.1093/jnci/95.3.237.

Widyowati, R., Tezuka, Y., Miyahara, T., Awale, S. and Kadota, S. (2010). Alkaline phosphatase (ALP) enhancing iridoid glucosides from the Indonesian medicinal plant *Barleria lupulina*. *Nat Prod Commun*. 5(11):1711-1716.

Wilgus, T. A., Roy, S., and McDaniel, J. C. (2013). Neutrophils and wound repair: positive actions and negative reactions. *Advances in Wound Care*. 2(7): 379-388.

Wilkinson, H. N., and Hardman, M. J. (2020). Wound healing: cellular mechanisms and pathological outcomes. *Open Biology*. 10(9): 1-14. https://doi.org/10.1098/rsob.200223.

Witkowska, D., Słowik, J., and Chilicka, K. (2021). Review heavy metals and human health: Possible exposure pathways and the competition for protein binding sites. *Molecules*. 26(19): 6060. https://doi.org/10.3390/molecules26196060.

Wittenauer, J., MäcKle, S., Sußmann, D., Schweiggert-Weisz, U., and Carle, R. (2015). Inhibitory effects of polyphenols from grape pomace extract on

collagenase and elastase activity. *Fitoterapia*. 101: 179–187. https://doi.org/10.1016/j.fitote.2015.01.005.

World Health Organisation (WHO). Guidelines for Drinking-Water Quality: Fourth Edition, Incorporating the First Addendum, 1-631, 2017.

Xiao, Y., Qian, J., Deng, X., Zhang, H., Wang, J., Luo, Z., and Zhu, L. (2024). Macrophages regulate healing-associated fibroblasts in diabetic wound. *Molecular Biology Reports*. 51(1): 203.

Xue, Z., and Yang, B. (2016). Phenylethanoid glycosides: Research advances in their phytochemistry, pharmacological activity and pharmacokinetics. *Molecules*. 21(8): 991.

Yang, J.-W., Fan, G.-B., Tan, F., Kong, H.-M., Liu, Q., Zou, Y., and Tan, Y.-M. (2023). The role and safety of UVA and UVB in UV-induced skin erythema. *Frontiers in Medicine*. 10: 1163697. https://doi.org/10.3389/fmed.2023. 1163697.

Yolci Omeroglu, P., Acoglu, B., Özdal, T., Tamer, C. E., and Çopur, Ö. U. (2019). Extraction techniques for plant-based bio-active compounds. *Natural Bio-active Compounds: Volume 2: Chemistry, Pharmacology and Health Care Practices*. 465-492.

Yoosook, C., Panpisutchaia, Y., Chaichanab, Y., Santisukc, T. and Reutrakulb, V. (1999) Evaluation of anti-HSV-2 activities of *Barleria lupulina* and *Clinacanthus nutans. J Ethnopharmacol*. 67(2):179-187.

Yousef, H., Alhajj, M., and Sharma, S. (2022). Anatomy, skin (integument), epidermis. StatPearls. Preprint. Available at: https://www. ncbi. nlm. nih. gov/books/NBK470464/(Accessed: 21 June 2023).

Yuan, Y., Gao, Y., Mao, L., and Zhao, J. (2008). Optimisation of conditions for the preparation of β-carotene nanoemulsions using response surface methodology. *Food Chemistry*. 107(3): 1300-1306. https://doi.org/10.1016/j.foodchem. 2007.09.015.

Yusof, A. H. M., Abd Gani, S. S., Zaidan, U. H., and Halmi, I. E. (2019). Central composite design as a tools for optimization of antioxidant activity on cocoa shell extract. *International Journal of Engineering and Advanced Technology*. 8(6S3): 169-173.

Yusuf, E., and Yajid, M. S. A. (2016). Halal pharmaceuticals and cosmeceuticals from the perspective of higher education. *Asian Journal of Pharmaceutical Sciences.* 11(1): 18–19. https://doi.org/10.1016/j.ajps.2015.10.013.

Zailan, N. F. Z., Jaganathan, N., Sandramuti, T., Sarchio, S. N. E., and Hassan, M. (2020). Inhibition of GSK-3 by tideglusib suppresses activated macrophages and inflammatory responses in lipopolysaccharide-stimulated RAW 264.7 cell line. *Malaysian Journal of Medicine and Health Sciences*. 16(7): 2–8.

Zhang, Q., Fong, C. C., Yu, W. K., Chen, Y., Wei, F., Koon, C. M., Lau, K. M., Leung, P. C., Lau, C. B. S., Fung, K. P., and Yang, M. (2012). Herbal formula Astragali Radix and Rehmanniae Radix exerted wound healing effect on human skin fibroblast cell line Hs27 *via* the activation of transformation growth factor (TGF-β) pathway and promoting extracellular matrix (ECM) deposition. *Phytomedicine*. 20(1): 9–16. https://doi.org/10.1016/j.phymed.2012.09.006.

Zhang, Q. W., Lin, L. G., and Ye, W. C. (2018). Techniques for extraction and isolation of natural products: A comprehensive review. *Chinese Medicine (United Kingdom)*. 13(1): 1–26. https://doi.org/10.1186/s13020-018-0177-x.

Zhang, S., and Duan, E. (2018). Fighting against Skin Aging: The Way from bench to bedside. *Cell Transplantation*. 27(5): 729–738. https://doi.org/10.1177/0963689717725755.

Zhang, Z. S., Li, D., Wang, L. J., Ozkan, N., Chen, X. D., Mao, Z. H., and Yang, H. Z. (2007). Optimization of ethanol-water extraction of lignans from flaxseed. *Separation and Purification Technology*. 57(1): 17-24. https://doi.org/10.1016/j.seppur.2007.03.006.

Zheng, Y. J., and Loh, X. J. (2016). Natural rheological modifiers for personal care. *Polymers for Advanced Technologies*. 27(12): 1664–1679. https://doi.org/10.1002/pat.3822.

Zillich, O. V., Schweiggert-Weisz, U., Eisner, P., and Kerscher, M. (2015). Polyphenols as active ingredients for cosmetic products. *International Journal of Cosmetic Science*. 37(5): 455–464. https://doi.org/10.1111/ics.12218.

Zolghadri, S., Bahrami, A., Hassan Khan, M. T., Munoz-Munoz, J., Garcia-Molina, F., Garcia-Canovas, F., and Saboury, A. A. (2019). A comprehensive review on tyrosinase inhibitors. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 34(1): 279–309. https://doi.org/10.1080/14756366.2018.1545767.