PRELIMINARY INVESTIGATION OF *Mitragyna speciosa* (KORTH.) HAVIL LEAVES METHANOL CRUDE EXTRACT AND FORMULATION TOWARDS WOUND HEALING PROPERTY

By

FAZILA BINTI ZAKARIA

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

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December 2023

Chair : Siti Efliza binti Ashari, PhD
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The demand for natural-based remedies is rising due to their safety and efficiency compared to synthetic-based medicine. In view of this, the unique bioactive properties of *Mitragyna speciosa* (Korth.) Havil (MS) have attracted high interest for its potential application in the pharmacological industry. This study aimed to determine *in vitro* the wound healing capacities of methanol crude extract (MCE) and fractions of MS leaves in promoting proliferation, monolayer migration, and angiogenesis activities. The ultrasound-assisted extraction (UAE) method using response surface methodology (RSM) was used to optimised the production of MCE. The optimised extraction conditions were then used to obtain the MCE and the corresponding fractions (hexane, dichloromethane, ethyl acetate, and butanol) using the liquid-liquid extraction (LLE). The developed quadratic polynomial model correlated with the experimental data is based on the coefficient of determination (R^2) of the extraction yield (0.9972, $p < 0.0001$) and the total phenolic content (TPC) (0.9553, $p < 0.0001$). At 25 ˚C, 15 min sonication time, and 10 mL/g of solvent to solid ratio, the optimal conditions recorded an extraction yield and TPC of 21.99 % and 144.70 (mgGAE)/g, respectively. The wound healing screening of the MCE and fractions revealed that the semi polar solvent of the ethyl acetate fraction (EAF) exhibited highest TPC (277.55 ± 4.89 mg GAE/g) and total flavonoid content (TFC) (90.72 ± 8.96 mg RE/g), a strong antioxidant of DPPH IC_{50} (25.24 ± 30.56 µg/mL), strong antibacterial activity against *Staphylococcus aureus* (17.89 ± 0.68 mm), and moderate anti-inflammatory inhibition (42.36 ± 1.53 %). The EAF showed the highest migration rate and branching length at a lower concentration (3.13 µg/mL) of 70.85 % and 9014.33 pixels, respectively. EAF was selected to encapsulated into the newly developed cubosomes formulations using a single stabiliser of F127 (F) and a combined stabiliser of F127 and Tween 80 (Mix F-T). The optimal composition of formulation F consisted of 0.5 % F127 as it exhibited the lowest particle size (PS) of 177.93 ± 0.65 nm. Meanwhile the formulation Mix F-T consists of 0.25 % F127 and 0.25 % Tween 80 as it

demonstrated lowest PS (141.53 ± 0.21 nm). The measured PDI was 0.17 ± 0.01(F) and 0.23 ± 0.01 (Mix F-T), zeta potential was - 26.40 ± 0.10 (F) and – 28.07 ± 2.40 mV (Mix F-T), and the pH was 4.17 (F) ± 0.02 and 4.18 ± 0.03 (Mix F-T). Furthermore, % entrapment efficiency was 95.63 ± 1.54 % (F) and 90.09 ± 1.89 % (Mix F-T). Both formulations showed no toxic effect on the 3T3 fibroblast cells, with cell viability values of higher than 80 % (up to 500 µg/mL). The mortality rate of zebrafish embryos was unaffected when exposed to all formulations of less than 500 µg/mL. Normal morphological features were observed when zebrafish embryos were exposed to unencapsulated EAF at concentrations less than 200 µg/mL, except that they exhibited hatching inhibition compared to the control group. This study suggests the potential of MS as wound healing and thus supporting its traditional claim.

Keywords: Cubosomes, methanolic crude extract, *Mitragyna speciosa*, wound healing

SDG: GOAL 3: Good Health

Abstrak thesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

SIASATAN AWAL TERHADAP *Mitragyna speciosa* (KORTH.) HAVIL DAUN EKSTRAK MENTAH METANOL DAN RUMUSAN KE ARAH PENYEMBUHAN LUKA

Oleh

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Permintaan untuk ubat berasaskan semula jadi semakin meningkat kerana keselamatan dan kecekapannya berbanding dengan ubat berasaskan sintetik. Memandangkan perkara ini, sifat bioaktif yang unik oleh *Mitragyna speciosa* (Korth.) Havil (MS) telah menarik minat yang tinggi untuk potensi aplikasinya dalam industri farmakologi. Kajian ini bertujuan untuk menentukan kapasiti penyembuhan luka secara *in vitro* bagi ekstrak mentah metanol (MCE) dan pecahan daun MS dalam menggalakkan percambahan, migrasi lapisan mono, dan aktiviti angiogenesis. Kaedah pengekstrakan berbantukan ultrasound (UAE) menggunakan metodologi permukaan tindak balas (RSM) digunakan untuk mengoptimumkan pengeluaran MCE. Keadaan pengekstrakan yang dioptimumkan kemudiannya digunakan untuk mendapatkan MCE dan pecahan sepadan (heksana, diklorometana, etil asetat, dan butanol) menggunakan kaedah pengekstrakan cecair-cecair (LLE). Model polinomial kuadratik yang dibangunkan berkorelasi dengan data eksperimen adalah berdasarkan pekali penentuan (R^2) hasil pengekstrakan (0.9972, $p < 0.0001$) dan TPC (0.9553, $p < 0.0001$). Pada 25 ˚C, masa sonikasi 15 minit, dan 10 mL/g nisbah pelarut kepada pepejal, merupakan keadaan optimum mencatatkan hasil pengekstrakan dan TPC sebanyak 22.69 % dan 143.51 mg bersamaan asid gallik (GAE)/g. Saringan penyembuhan luka MCE dan pecahan mendedahkan pelarut separa polar bagi pecahan etil asetat (EAF) menunjukkan TPC tertinggi (277.55 ± 4.89 mg GAE/g) dan TFC (90.72 ± 8.96 mg RE/g), antioksidan yang tinggi dengan IC_{50} DPPH (25.24 ± 30.56 µg/mL), aktiviti antibakteria yang tinggi terhadap *Staphylococcus aureus* (17.89 ± 0.68 mm), dan sederhana perencatan keradangan (42.36 ± 1.53 %). EAF menunjukkan kadar migrasi tertinggi dan panjang cabang (potensi tinggi untuk angiogenesis) pada kepekatan yang lebih rendah (3.13 µg/mL) masing-masing sebanyak 70.85 % dan 10986 piksel. EAF telah dipilih untuk dikapsulkan ke dalam formulasi kubosom yang dibangunkan menggunakan penstabil tunggal F127 (F) dan penstabil gabungan F127 dan Tween 80 (Mix F-T). Komposisi optimum rumusan F terdiri daripada 0.5 % F127 kerana ia

mempamerkan saiz zarah (PS) terendah iaitu 177.93 ± 0.65 nm. Sementara itu, rumusan Mix F-T terdiri daripada 0.25 % F127 dan 0.25 % Tween 80 kerana ia menunjukkan PS terendah (141.53 ± ± 1 nm). PDI yang diukur ialah 0.17 ± 0.01(F) dan 0.23 ± 0.01 (Mix F-T), potensi zeta ialah - 26.40 ± 0.10 (F) dan – 28.07 ± 2.40 mV (Mix F-T), dan pH ialah 4.17 (F) dan pH 2.17 (Mix F) dan 4.18 ± 0.03 (Mix F-T). Tambahan lagi, peratus kecekapan perangkap ialah 95.63 ± 1.54 % (F) dan 90.09 ± 1.89 % (Mix F-T). Kedua-dua formulasi tidak menunjukkan kesan ketoksikan pada sel fibroblas 3T3, dengan nilai sel lebih tinggi daripada 80 % (sehingga 500 µg/mL). Kadar kematian embrio ikan zebra tidak terjejas apabila terdedah kepada semua formulasi kurang daripada 500 µg/mL. Ciri morfologi normal diperhatikan apabila embrio ikan zebra terdedah kepada EAF yang tidak berkapsul pada kepekatan kurang daripada 200 µg/mL, kecuali ia menunjukkan perencatan penetasan berbanding kumpulan kawalan. Kajian ini mencadangkan potensi MS sebagai penyembuhan luka dan dengan itu menyokong tuntutan tradisionalnya.

Kata Kunci: Ekstrak mentah metanol**,** kubosom, *Mitragyna speciosa*, penyembuhan luka

SDG: *GOAL 3: Good Health*

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2-D	Two-dimensional
3-D	Three-dimensional
ANOVA	Analysis of variance
API	Active Pharmaceutical Ingredient
BF	Butanol fraction
bpm	Beats per min
CCRD	Central Composite Rotatable Design
CFU	Colony-forming unit
CV	Coefficients of Variation
DCMF	Dichloromethane fraction
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DPPH	2,2-diphenyl-1-picrylhydrazyl
E3M	Embryo medium
EAF	Ethyl acetate fraction
ECM	Extracellular matrix
EE	Entrapment Efficiency
F127	Poloxamer 407
FDA	Food and Drug Administration
GMO	Glyceryl monooleate
GRAS	Generally Recognised as Safe
HF	Hexane fraction
hpf	Hour of post fertilization

HUVECs	Human umbilical vein endothelial cells
IC_{50}	Inhibition Concentration of 50%
IR	Industrial revolution
kV	Kilovolt
LC	Liquid chromatography
LC/MS-MS	Tandem Liquid chromatography–Mass spectrometry
LC_{50}	Concentration that cause 50% mortality
LCNPs	Liquid crystalline nanoparticles
LLE	Liquid-liquid extraction
MCE	Methanol crude extract
MG	Mitragynine
mg GAE/g	Milligram gallic acid equivalent per gram
mg RE/g	Milligram of rutin equivalent per gram
mM	Millimolar
MO	Monoolein
MS	*Mitragyna speciosa*
MS/MS	Mass spectrometry
MTT	3-[4,5-dimethyl1thiazol-2yl]-2,5-diphenyltetrazolium bromide
mV	Millivolt
NADH	Nicotinamide adenine dinucleotide (NAD) + hydrogen (H)
NCI	American National Cancer Institute
NIH	National Institute of Health
NIST	National Institute Standard
nm	Nanometer
NPs	Nanoparticles

O^{2-}	Superoxide radical
OECD	Organisation for Economic Co-operation and Development
OH^{-}	Hydroxyl radicals
PBS	Phosphate Buffer Saline
PDI	Polydispersity Index
PEO	Polyethylene Oxide
pH	Power of hydrogen
PPO	Polypropylene
PS	Particle size
PT	Phytantriol
ROS	Reactive oxygen species
rpm	Revolutions per minutes
RSE	Residual standard error
RSM	Response surface methodology
R^2	Coefficient of determination
RT	Retention time
SD	Standard deviation
TEM	Transmission electron microscopy
TFC	Total Flavanoid Content
TPC	Total Phenolic Content
UAE	Ultrasound-assisted extraction
UHPLC	Ultra-High Performance Liquid Chromatography
UV-Vis	Ultraviolet Visible
ZP	Zeta potential

CHAPTER 1

INTRODUCTION

1.1 Background Study

Wounds are referred to as an unnatural break, defect, or tear in the skin as a result of thermal/physical injury or an underlying pathological condition. Depending on the restoration process, wounds can be categorised into acute or chronic. Tissue injuries from acute wounds mostly tend to be completely restored with minimal scarring around 8 - 12 weeks. In contrast, chronic wounds have an extended healing time of more than 12 weeks and tend to reoccur. Underlying physiological conditions may delay the wound healing process or lead to completely unsuccessful restoration (Mir *et al*., 2018).

Non-healing wounds pose a heavy financial burden to healthcare organisations, causing significantly reduced quality of life of affected individuals and usually antecede severe health-related events, such as premature deaths and amputations (Järbrink *et al*., 2017). The Medicare beneficiaries retrospective analysis 2018 reported that around 8.2 million people had been injured with and without infections (Sen, 2019). In addition, the global advanced wound management market was projected to rise at a Compound Annual Growth Rate (CAGR) of 6.6% from 2020 to 2027 and reach $18.7 billion by 2027 (Sen, 2021). The search for ideal plant-based medicine as a wound healing agent has begun since early human civilisation (Fazil & Nikhat, 2020). The prevalence and effectiveness of plant-derived products, including in crude preparations, have made them a primary option as potential wound healing agents (Sasidharan *et al*., 2010). Although plants' secondary metabolites, such as flavonoids, phenols, alkaloids, and saponin, may not be helpful for their growth or reproduction, they have been scientifically proven to provide selective advantages in terms of natural therapeutic effects (Pai *et al*., 2022). In fact, numerous conventional drugs are plant-based, some with outstanding treatment efficiency. These phytomedicines, including digoxin (from foxglove), aspirin (from willow bark), morphine (from the opium poppy) (Vickers *et al*., 2001), and quinine (from cinchona bark), are very cheap, affordable, and safe. Hence, the discovery of various life-sustaining bioactive constituents in plant-based medicine has prompted the scientific community to explore these plants and determine the extent of their potential wound healing properties (Thakur *et al*., 2011).

Despite that, various studies have specifically investigated the efficacy of natural plant metabolites in cell culture and preclinical animal model systems for human consumption, their *in vitro* and *in vivo* effects have yet been implemented for clinical practice due to many factors, such as the poor systemic delivery outcome and inadequate bioavailability of the promising agents. In this respect, the development of novel carriers and drug delivery systems for herbal drugs should preferably achieve certain objectives, such as proper rate of drug delivery

according to the body's needs over the treatment period, and the herbal drug should reach the target site and carry out its role as expected (Rahman *et al*., 2020).

Over the years, the emergence of nanopharmaceuticals as a branch of pharmaceutics has attracted considerable attention owing to its effective topical delivery of drug molecules. The human skin is regarded as the most accessible organ for topical drug delivery due to its exceptionally high surface area. Concurrently, the advancement of nanosized particulate systems highlights the beneficial applications of nanocarriers, such as the varying levels of membrane stress, large membrane surface area-to-volume ratio, and hydrophobic and membrane proteins with elevated loading capacities. Nano-self-assembling lipid-based systems represent one such nanocarrier system, in which the liquid crystalline phase has received a growing research interest and has been broadly studied for drug delivery applications (Rapalli *et al*., 2020).

One of the various lipid-based carriers that have gained massive attention from the pharmaceutical industry is the liquid crystalline nanoparticles (LCNPs) not only because of their ability to boost the bioavailability and improve the absorbency of active ingredients (Elnaggar *et al*., 2015; Liu & Feng, 2015) but also because LCNPs offers such improvements with no visible skin irritation (Freag *et al*., 2019). Most of the LCNPs currently applied are thermodynamically stable in excess water and categorised into four types of mesophase: three-dimensional (3-D) inverse bicontinuous and discontinuous cubic phases and two-dimensional (2-D) and 3-D inverse hexagonal phases. The ability of each phase to disperse into LCNPs results in a different formation. As such, the inverse bicontinuous cubic phase forms cubosomes, the discontinuous cubic phase forms micellar cubosomes while the inversed hexagonal phase forms hexosomes (Lancelot *et al*., 2014). The formation of a highly organised internal structure in cubosomes enables the slow-release matrix of active pharmaceutical ingredient (API) of different sizes and polarities. In addition, they possess unique physicochemical properties, including the high compatibility to encapsulate various active molecules ranging from hydrophilic, hydrophobic, and amphiphilic classes (Singhvi *et al*., 2018). Such potential use of cubosomes and their unique features have received wide interest from the scientific community.

Mitragyna speciosa (Korth.) Havil., (MS) locally known in Malaysia as *'ketum'* or *'biak-biak*' and in Thailand as '*kratom,'* is a popular contentious herbal plant with various remedy values. Since ancient times, it has been applied as a traditional herbal remedy to heal wounds through decoction and poultices of its leaves. Previous literature stated that various compounds in MS, such as alkaloids, flavonoids, saponins, sterols, and tannins, offer a wide range of pharmacological activities, such as antimicrobial, antioxidant (Parthasarathy *et al*., 2009) and antinociceptive and anti-inflammation (Mossadeq *et al*., 2009) that are vital in treating wounds.

In line with the global shift towards the fast-paced Industrial Revolution 4.0 (IR 4.0), each stakeholder must adapt swiftly to the rapid development of technological products. Researchers within academic circles also have a crucial role in contributing to the development of high-quality products, and the extent of commercialisation will significantly impact the industry, community, and country. Therefore, efforts have been focused on emphasising design and innovation to drive IR 4.0 by producing output-based natural resources using native plants in Malaysia, such as MS, which was listed in the 2015 Malaysian Herbal Monograph.

1.2 Problems Statement

Extraction of plant components via the conventional approach such as maceration, decoction, soxhlet extraction is restricted due to various drawbacks and challenges, such as time consumption, huge solvent usage, multiple experimental runs, and low crude yield percentage (Krakowska *et al*., 2017; Tzanova *et al*., 2020). Antioxidant bioactive substances in plant extracts are also naturally unstable, easily oxidised, and degrade upon exposure to light (Hoang *et al*., 2021).Therefore, there is a need to develop a reliable model to optimise the independent variables, including the sonication time, the concentration and volume of solvent, extraction temperature, and solvent to solid ratio, to achieve a sufficient amount of extract yield and phenolic recovery from plant samples (Arteaga-Crespo *et al*., 2020).

Both the empirical and statistical approaches can be used to study the optimisation process (Ameena Ali *et al*., 2017; Ilghami *et al*., 2015). In view of this, the response surface methodology (RSM) is a useful technique that involves mathematical and statistical analysis, which is acquired from the fit of empirical models to the obtained data from experiments. Generally, the linear or square polynomial functions are utilised to describe the studied system. Therefore, an optimisation study can be performed to investigate the experimental conditions (Zainol *et al*., 2012). Since the RSM reduces the total amount of experimental trials, operational cost, and time compared to other techniques, thus, it is widely employed in the optimisation of extraction of several compounds, such as polysaccharides, phenolic compounds, and carotenoids from different plant materials (Ghasemzadeh *et al*., 2014; Shirzad *et al*., 2017).

Throughout modern history, numerous infectious pathogens or inflammatory conditions have contributed to unhealed of wounds and posing significant challenges (Pereira & Bártolo, 2016). The role of dermatologists in the ever-expanding field of global health (Seth *et al*., 2017) is becoming more crucial as the global burden of wound cases (Yao *et al*., 2020). Therefore, it is essential to develop safer and more efficient compounds to cure wounds so that the healing process may be improved, and treatment expenses can be decreased. Furthermore, plant-based products possess significant properties and effects on immunity, which are advantageous in treating wounds (Liu *et al*., 2019). Production cost is also generally low due to the abundance of natural plants.

Furthermore, plant extracts might reduce the risks of adaptive resistance commonly reported in single-agent therapies (Ng *et al*., 2018).
Formulating plant extract products containing beneficial bioactive ingredients has also encountered challenging obstacles due to various factors, including poor solubility and low bioavailability, which may affect topical drug delivery (Mohapatra *et al*., 2021). A practical topical application requires the target product to permeate through the skin's inner layer successfully (Casanova & Santos, 2016). Although penetration enhancers are typically added to promote drug delivery across the stratum corneum, some of them, such as dimethyl sulfoxide (DMSO) and propylene glycol, trigger undesirable side effects such as skin irritation, systemic drug absorption, and skin damage (Rapalli *et al*., 2020).

In addition, the utmost challenge in lipid-based development systems is maintaining the nanometre particle size range while remaining physically stable for a certain period (Mishra *et al*., 2018). Despite intense research on using drug or plant extract formulation for the encapsulation of bioactive ingredients, the interaction between the components in the formulation may directly or indirectly affect the stability of the formulation, making them inaccessible for absorption (Rahman *et al*., 2020). Therefore, it is crucial to investigate the encapsulation process of bioactive compounds into plant extract-based formulations with stable, compatible physicochemical characteristics and safe for optimal topical drug delivery.

1.3 Scope of Study

The current study was conducted in four major stages. The first stage involved ultrasound-assisted extraction (UAE) using RSM to optimise the process parameters, including sonication time, extraction temperature, solvent to solid ratio in response to the percentage yield, and total phenolic content (TPC), to produce methanol crude extract (MCE) of MS. The optimised crude extract was then fractionated using liquid-liquid extraction to obtain hexane (HF), dicholoromethane (DCMF), ethyl acetate (EAF), and butanol (BF) fractions.

In the second part, the wound healing effects of the MCE and its fractions were evaluated, which includes TPC, total flavonoid content (TFC), antioxidant, antibacterial, anti-inflammatory, cytotoxicity assay (proliferation), scratch assay, and tube formation assay.

In the third stage of the study, the selected MCE or fractions was encapsulated in a lipid-based lyotropic (cubosomes) formulations. This was followed by physicochemical characterisation of the developed formulations, such as the particle size, zeta potential, polydispersity index, pH measurement, morphological observation, entrapment efficiency, stability study, and permeation release using Franz diffusion cell.

In the final stage, the toxicity of the cubosomes formulations was determined *in vitro* using fibroblast cells and *in vivo* using zebrafish embryos. Figure 1.1 illustrates the overall schematic methodological flow of the present research.

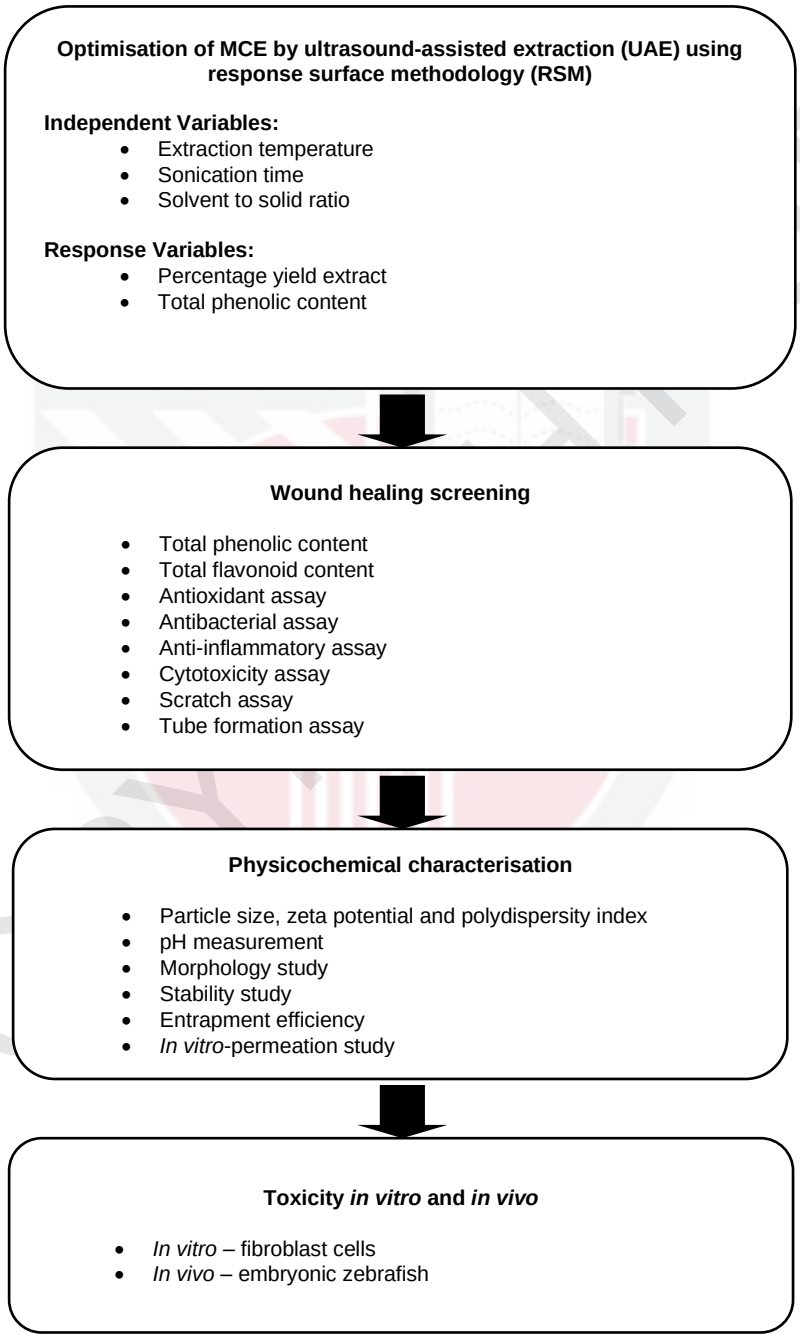

Figure 1.1: Schematic diagram of research study

1.4 Research Objectives

The objectives of the research are as follows:

1. To optimise the extraction method of MS leaves by UAE using central composite rotatable design (CCRD) of RSM.

2. To determine biological activities (total phenolic content, total flavonoid content, antioxidant, antibacterial, and anti-inflammatory), *in vitro* wound healing cell-based assays (cytotoxicity, migration assay, and tube formation assay), and identify the phytocompounds using tandem Liquid chromatography–Mass spectrometry (LC/MS-MS).

3. To encapsulate the MCE/fraction of MS loaded with a lipid-based lyotropic liquid crystal (cubosomes) formulations and characterise the physicochemical properties.

4. To evaluate *in vitro* cytotoxicity (3T3 fibroblast cells) and *in vivo* toxicity (embryonic zebrafish) of the lipid-based-lyotropic liquid crystal (cubosomes) formulations containing MS MCE/fraction.

REFERENCES

Abarca-Vargas, R., Peña Malacara, C. F., & Petricevich, V. L. (2016). Characterization of chemical compounds with antioxidant and cytotoxic activities in bougainvillea x buttiana holttum and standl, (Var. rose) extracts. *Antioxidants*, *5*(4). https://doi.org/10.3390/antiox5040045

Abd Razak, D. L., Jamaluddin, A., Abd Rashid, N. Y., Sani, N. A., & Abdul Manan, M. (2020). Assessment of Cosmeceutical Potentials of Selected Mushroom Fruitbody Extracts Through Evaluation of Antioxidant, Anti-Hyaluronidase and Anti-Tyrosinase Activity. *J—Multidisciplinary Scientific Journal*, *3*(3), 329–342. https://doi.org/10.3390/j3030026

Akbar, A., Soekamto, N. H., Firdaus, & Bahrun. (2021). Antioxidant of n-hexane, ethyl acetate and methanol extracts of Padina sp with DPPH method. *IOP Conference Series: Earth and Environmental Science*, *800*(1). https://doi.org/10.1088/1755-1315/800/1/012019

Akbik, D., Ghadiri, M., Chrzanowski, W., & Rohanizadeh, R. (2014). Curcumin as a wound healing agent. *Life Sciences*, *116*(1), 1–7. https://doi.org/10.1016/j.lfs.2014.08.016

Al-Rifai, A., Aqel, A., Al-Warhi, T., Wabaidur, S. M., Al-Othman, Z. A., & Badjah-Hadj-Ahmed, A. Y. (2017). Antibacterial, Antioxidant Activity of Ethanolic Plant Extracts of Some Convolvulus Species and Their DART-ToF-MS Profiling. *Evidence-Based Complementary and Alternative Medicine*, *2017*. https://doi.org/10.1155/2017/5694305

Ali, Ameena, Lim, X. Y., Chong, C. H., Mah, S. H., & Chua, B. L. (2017). Optimization of ultrasound-assisted extraction of natural antioxidants from Piper betle using response surface methodology. *LWT - Food Science and Technology*. https://doi.org/10.1016/j.lwt.2017.11.033

Ali, Ayesha, Aslam, M., & Chaudhary, S. S. (2020). A Review A Review on Pharmacognostic and Therapeutic Uses of Rubia cordifolia. *Journal of Drug Delivery and Therapeutics*, *10*(6), 195–202. https://doi.org/10.22270/jddt.v10i6.4514

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

Anaya-Esparza, L. M., Ramos-Aguirre, D., Zamora-Gasga, V. M., Yahia, E., & Montalvo-González, E. (2018). Optimization of ultrasonic-assisted extraction of phenolic compounds from Justicia spicigera leaves. *Food Science and Biotechnology*, *27*(4), 1093–1102. https://doi.org/10.1007/s10068-018-0350-0

Araya-Sibaja, A. M., Salazar-López, N. J., Romero, K. W., Vega-Baudrit, J. R., Domínguez-Avila, J. A., Contreras, C. A. V., Robles-Zepeda, R. E., Navarro-Hoyos, M., & González-Aguilar, G. A. (2021). Use of nanosystems to improve the anticancer effects of curcumin. *Beilstein Journal of Nanotechnology*, *12*, 1047–1062. https://doi.org/10.3762/BJNANO.12.78

Archana, A., Sri, K. V., Madhuri, M., & Kumar, C. H. A. (2015). Curcumin Loaded Nano Cubosomal Hydrogel: Preparation, In Vitro Characterization and Antibacterial Activity. *Chemical Science Transactions*, *4*(1), 75–80. https://doi.org/10.7598/cst2015.913

Arifullah, Nazahatul, A. A., Klaiklay, S., Chumkaew, P., Norhazlini, M. Z., Abdulhafiz, F., & Zulhazman, H. (2021). Elucidation of total phenolic content and antioxidant activity in medicinal Aroid, Alocasia longiloba Miq. *IOP Conference Series: Earth and Environmental Science*, *756*(1). https://doi.org/10.1088/1755-1315/756/1/012043

Arteaga-Crespo, Y., Radice, M., Bravo-Sanchez, L. R., García-Quintana, Y., & Scalvenzi, L. (2020). Optimisation of ultrasound-assisted extraction of phenolic antioxidants from Ilex guayusa Loes. leaves using response surface methodology. *Heliyon*, *6*(1), 0–7. https://doi.org/10.1016/j.heliyon.2019.e03043

Asati, S., Sahu, A., & Jain, A. (2020). Nanotoxicity: The Dark Side of Nanoformulations. *Current Nanotoxicity and Prevention*, *1*(1), 6–25. https://doi.org/10.2174/2665980801999201230095324

Aslantürk, Ö. S. (2018). In Vitro Cytotoxicity and Cell Viability Assays: Principles, Advantages, and Disadvantages. *Genotoxicity - A Predictable Risk to Our Actual World*, 1–18. https://doi.org/10.5772/intechopen.71923

Aziddin R.E, R., M.R, M., Z, M., & M.A, M. (2005). Anti-inflammatory Properties of Mitragyna Speciosa Extract. *Malaysian Journal of Science*, *24*(1 SE-Original Articles), 191–194. https://mjs.um.edu.my/index.php/MJS/article/view/8971

Azizi, J., Ismail, S., Mordi, M. N., Ramanathan, S., Said, M. I. M., & Mansor, S. M. (2010). In vitro and in vivo effects of three different mitragyna speciosa korth leaf extracts on phase II drug metabolizing enzymes-glutathione transferases (GSTs). *Molecules*, *15*(1), 432–441. https://doi.org/10.3390/molecules15010432

Bainbridge, P., Healing, W., & Repair, T. (2013). *Wound Fibro*.

Barriga, H. M. G., Holme, M. N., & Stevens, M. M. (2019). Cubosomes: The Next Generation of Smart Lipid Nanoparticles? *Angewandte Chemie - International Edition*, *58*(10), 2958–2978. https://doi.org/10.1002/anie.201804067

Bimakr, M., Ganjloo, A., Zarringhalami, S., & Ansarian, E. (2017). Ultrasound-assisted extraction of bioactive compounds from Malva sylvestris leaves and its comparison with agitated bed extraction technique. *Food Science and Biotechnology*, *26*(6), 1481–1490. https://doi.org/10.1007/s10068-017-0229-5

Boffa, L., Ghè, C., Barge, A., Muccioli, G., & Cravotto, G. (2018). Alkaloid profiles and activity in different Mitragyna speciosa strains. *Natural Product Communications*, *13*(9), 1111–1116. https://doi.org/10.1177/1934578x1801300904

Bolla, S. R., Mohammed Al-Subaie, A., Yousuf Al-Jindan, R., Papayya Balakrishna, J., Kanchi Ravi, P., Veeraraghavan, V. P., Arumugam Pillai, A., Gollapalli, S. S. R., Palpath Joseph, J., & Surapaneni, K. M. (2019). In vitro wound healing potency of methanolic leaf extract of Aristolochia saccata is possibly mediated by its stimulatory effect on collagen-1 expression. *Heliyon*, *5*(5), e01648. https://doi.org/10.1016/j.heliyon.2019.e01648

Cardona, A. F., & Wilson, S. E. (2015). Skin and Soft-Tissue Infections: A Critical Review and the Role of Telavancin in Their Treatment. *Clinical Infectious Diseases*, *61*(Suppl 2), S69–S78. https://doi.org/10.1093/cid/civ528

Casanova, F., & Santos, L. (2016). Encapsulation of cosmetic active ingredients for topical application-a review. *Journal of Microencapsulation*, *33*(1), 1–17. https://doi.org/10.3109/02652048.2015.1115900

Caselli, A., Cirri, P., Santi, A., & Paoli, P. (2016). Morin: A Promising Natural Drug. *Current Medicinal Chemistry*, *23*(8), 774–791. https://doi.org/10.2174/0929867323666160106150821

Cassar, S., Adatto, I., Freeman, J. L., Gamse, J. T., Iturria, I., Lawrence, C., Muriana, A., Peterson, R. T., Van Cruchten, S., & Zon, L. I. (2020). Use of Zebrafish in Drug Discovery Toxicology. *Chemical Research in Toxicology*, *33*(1), 95–118. https://doi.org/10.1021/acs.chemrestox.9b00335

Chahardehi, A. M., Arsad, H., & Lim, V. (2020). Zebrafish as a successful animal model for screening toxicity of medicinal plants. *Plants*, *9*(10), 1–35. https://doi.org/10.3390/plants9101345

Che Sulaiman, I. S., Basri, M., Fard Masoumi, H. R., Chee, W. J., Ashari, S. E., & Ismail, M. (2017). Effects of temperature, time, and solvent ratio on the extraction of phenolic compounds and the anti-radical activity of Clinacanthus nutans Lindau leaves by response surface methodology. *Chemistry Central Journal*. https://doi.org/10.1186/s13065-017-0285-1

Chebil, L., Humeau, C., Anthony, J., Dehez, F., Engasser, J. M., & Ghoul, M. (2007). Solubility of flavonoids in organic solvents. *Journal of Chemical and Engineering Data*, *52*(5), 1552–1556. https://doi.org/10.1021/je7001094

Chen, Xing, Liang, L., & Han, C. (2020). Borate suppresses the scavenging activity of gallic acid and plant polyphenol extracts on DPPH radical: A potential interference to DPPH assay. *Lwt*, *131*, 109769. https://doi.org/10.1016/j.lwt.2020.109769

Chen, Xuan, Deng, Z., Zheng, L., Zhang, B., Luo, T., & Li, H. (2021). Interaction between flavonoids and carotenoids on ameliorating oxidative stress and cellular uptake in different cells. *Foods*, *10*(12). https://doi.org/10.3390/foods10123096

Chhabra, S., Chhabra, N., Kaur, A., & Gupta, N. (2017). Wound Healing Concepts in Clinical Practice of OMFS. *Journal of Maxillofacial and Oral Surgery*, *16*(4), 403–423. https://doi.org/10.1007/s12663-016-0880-z

Chong, J. Y. T., Mulet, X., Boyd, B. J., & Drummond, C. J. (2015). Steric Stabilizers for Cubic Phase Lyotropic Liquid Crystal Nanodispersions (Cubosomes). In *Advances in Planar Lipid Bilayers and Liposomes* (1st ed., Vol. 21). Elsevier Inc. https://doi.org/10.1016/bs.adplan.2014.11.001

Cucci, L. M., Satriano, C., Marzo, T., & La Mendola, D. (2021). Angiogenin and copper crossing in wound healing. *International Journal of Molecular Sciences*, *22*(19), 1–14. https://doi.org/10.3390/ijms221910704

Cytryniak, A., Nazaruk, E., Bilewicz, R., Górzyńska, E., Żelechowska-Matysiak, K., Walczak, R., Mames, A., Bilewicz, A., & Majkowska-Pilip, A. (2020). Lipidic cubic-phase nanoparticles (Cubosomes) loaded with doxorubicin and labeled with177 lu as a potential tool for combined chemo and internal radiotherapy for cancers. *Nanomaterials*, *10*(11), 1–14. https://doi.org/10.3390/nano10112272

Dai, J., & Mumper, R. J. (2010). Plant phenolics: Extraction, analysis and their antioxidant and anticancer properties. *Molecules*, *15*(10), 7313–7352. https://doi.org/10.3390/molecules15107313

Damodaran, T., Chear, N. J. Y., Murugaiyah, V., Mordi, M. N., & Ramanathan, S. (2021). Comparative Toxicity Assessment of Kratom Decoction, Mitragynine and Speciociliatine Versus Morphine on Zebrafish (Danio rerio) Embryos. *Frontiers in Pharmacology*, *12*(August), 1–9. https://doi.org/10.3389/fphar.2021.714918

Danaei, M., Dehghankhold, M., Ataei, S., Hasanzadeh Davarani, F., Javanmard, R., Dokhani, A., Khorasani, S., & Mozafari, M. R. (2018). Impact of particle size and polydispersity index on the clinical applications of lipidic nanocarrier systems. *Pharmaceutics*, *10*(2), 1–17. https://doi.org/10.3390/pharmaceutics10020057

Das, N., Islam, M. E., Jahan, N., Islam, M. S., Khan, A., Islam, M. R., & Parvin, M. S. (2014). Antioxidant activities of ethanol extracts and fractions of Crescentia cujete leaves and stem bark and the involvement of phenolic compounds. *BMC Complementary and Alternative Medicine*, *14*(1), 1–9. https://doi.org/10.1186/1472-6882-14-45

De Oliveira Rodrigues, R., Yaochite, J. N. U., Sasahara, G. L., Albuquerque, A. A., da Cruz Fonseca, S. G., de Vasconcelos Araújo, T. D., Santiago, G. M. P., de Sousa, L. M., de Carvalho, J. L., Alves, A. P. N. N., de Carvalho, P. G., & Nagao-Dias, A. T. (2020). Antioxidant, anti-inflammatory and healing potential of ethyl acetate fraction of Bauhinia ungulata L. (Fabaceae) on in vitro and in vivo wound model. *Molecular Biology Reports*, *47*(4), 2845–2859. https://doi.org/10.1007/s11033-020-05332-7

Diller, R. B., & Tabor, A. J. (2022). The Role of the Extracellular Matrix (ECM) in Wound Healing: A Review. *Biomimetics*, *7*(3), 14–16. https://doi.org/10.3390/biomimetics7030087

Dobrinčić, A., Repajic, M., Elez Garofulić, I., Tuđen, L., Dragović-Uzelac, V., & Levaj, B. (2020). Comparison of Di ff erent Extraction Methods for the. *Processes*, *8*(9), 1008.

Doke, S. K., & Dhawale, S. C. (2015). Alternatives to animal testing: A review. *Saudi Pharmaceutical Journal*, *23*(3), 223–229. https://doi.org/10.1016/j.jsps.2013.11.002

Dos Santos, V. L. P., Ribas, J. L. C., de Lima, C. P., Campos, R., Garcia, A. C., Budel, J. M., & Messias-Reason, I. J. (2020). The wound healing effect of aqueous extract from Piper amalago L. in diabetic patient. *Explore*. https://doi.org/10.1016/j.explore.2019.12.001

Eastlack, S. C., Cornett, E. M., & Kaye, A. D. (2020). Kratom—Pharmacology, Clinical Implications, and Outlook: A Comprehensive Review. *Pain and Therapy*, *9*(1), 55–69. https://doi.org/10.1007/s40122-020-00151-x

El-Enin, H. A., & AL-Shanbari, A. H. (2018). Nanostructured liquid crystalline formulation as a remarkable new drug delivery system of anti-epileptic drugs for treating children patients. *Saudi Pharmaceutical Journal*, *26*(6), 790–800. https://doi.org/10.1016/j.jsps.2018.04.004

El Atki, Y., Aouam, I., El kamari, F., Taroq, A., Lyoussi, B., Taleb, M., & Abdellaoui, A. (2019). Total phenolic and flavonoid contents and antioxidant activities of extracts from Teucrium polium growing wild in Morocco. *Materials Today: Proceedings*, *13*, 777–783. https://doi.org/10.1016/j.matpr.2019.04.040

Ellis, S., Lin, E. J., & Tartar, D. (2018). Immunology of Wound Healing. *Current Dermatology Reports*, *7*(4), 350–358. https://doi.org/10.1007/s13671-018-0234-9

Elnaggar, Y. S. R., Etman, S. M., Abdelmonsif, D. A., & Abdallah, O. Y. (2015). Novel piperine-loaded Tween-integrated monoolein cubosomes as brain-targeted oral nanomedicine in Alzheimer's disease: Pharmaceutical, biological, and toxicological studies. *International Journal of Nanomedicine*, *10*, 5459–5473. https://doi.org/10.2147/IJN.S87336

Fadilah, N. I. M., Ahmad, H., Abdul Rahman, M. B., Chia, S. L., Ng, S. F., & Leong, S. W. (2020). Synthesis and in vitro biological evaluations of novel tetrapeptide as therapeutic agent for wound treatment. *Journal of Saudi Chemical Society*, *24*(8), 606–619. https://doi.org/10.1016/j.jscs.2020.06.003

Falcão, M. A. P., de Souza, L. S., Dolabella, S. S., Guimarães, A. G., & Walker, C. I. B. (2018). Zebrafish as an alternative method for determining the embryo toxicity of plant products: a systematic review. *Environmental Science and Pollution Research*, *25*(35), 35015–35026. https://doi.org/10.1007/s11356-018-3399-7

Favre, L. C., dos Santos, C., López-Fernández, M. P., Mazzobre, M. F., & Buera, M. del P. (2018). Optimization of β-cyclodextrin-based extraction of antioxidant and anti-browning activities from thyme leaves by response surface methodology. *Food Chemistry*, *265*, 86–95. https://doi.org/10.1016/j.foodchem.2018.05.078

Fazil, M., & Nikhat, S. (2020). Topical medicines for wound healing: A systematic review of Unani literature with recent advances. *Journal of Ethnopharmacology*, *257*(April), 112878. https://doi.org/10.1016/j.jep.2020.112878

Freag, M. S., Torky, A. S., Nasra, M. M., Abdelmonsif, D. A., & Abdallah, O. Y. (2019). Liquid crystalline nanoreservoir releasing a highly skin-penetrating berberine oleate complex for psoriasis management. *Nanomedicine*, *14*(8), 931–954. https://doi.org/10.2217/nnm-2018-0345

Fronza, M., Caetano, G. F., Leite, M. N., Bitencourt, C. S., Paula-Silva, F. W. G., Andrade, T. A. M., Frade, M. A. C., Merfort, I., & Faccioli, L. H. (2014). Hyaluronidase modulates inflammatory response and accelerates the cutaneous wound healing. *PLoS ONE*, *9*(11), 1–12. https://doi.org/10.1371/journal.pone.0112297

Fuchs, E. (2016). Epithelial Skin Biology. Three Decades of Developmental Biology, a Hundred Questions Answered and a Thousand New Ones to Address. In *Current Topics in Developmental Biology* (1st ed., Vol. 116). Elsevier Inc. https://doi.org/10.1016/bs.ctdb.2015.11.033

Gaballa, S., El Garhy, O., & Abdelkader, H. (2019). Cubosomes: composition, preparation, and drug delivery applications. *Journal of Advanced Biomedical and Pharmaceutical Sciences*, *0*(0), 0–0. https://doi.org/10.21608/jabps.2019.16887.1057

Gazi, U., Taylan-Ozkan, A., & Mumcuoglu, K. Y. (2021). The effect of Lucilia sericata larval excretion/secretion (ES) products on cellular responses in wound healing. *Medical and Veterinary Entomology*, *35*(3), 257–266. https://doi.org/10.1111/mve.12497

George, B. P., Parimelazhagan, T., & Chandran, R. (2014). Anti-inflammatory and wound healing properties of Rubus fairholmianus Gard. root-An in vivo study. *Industrial Crops and Products*, *54*, 216–225. https://doi.org/10.1016/j.indcrop.2014.01.037

Ghafoor, K., Choi, Y. H., Jeon, J. Y., & Jo, I. H. (2009). Optimization of ultrasound-assisted extraction of phenolic compounds, antioxidants, and anthocyanins from grape (Vitis vinifera) seeds. *Journal of Agricultural and Food Chemistry*, *57*(11), 4988–4994. https://doi.org/10.1021/jf9001439

Gharbia, F. Z., Abouhashem, A. S., Moqidem, Y. A., Elbaz, A. A., Abdellatif, A., Singh, K., Sen, C. K., & Azzazy, H. M. E. (2023). Adult skin fibroblast state change in murine wound healing. *Scientific Reports*, *13*(1), 1–13. https://doi.org/10.1038/s41598-022-27152-4

Ghasemzadeh, A., Jaafar, H. Z. E., Karimi, E., & Rahmat, A. (2014). Optimization of ultrasound-assisted extraction of flavonoid compounds and their pharmaceutical activity from curry leaf (Murraya koenigii L .) using response surface methodology. *BMC Complementary and Alternative Medicine*, *14*(318).

Ghitescu, R. E., Volf, I., Carausu, C., Bühlmann, A. M., Gilca, I. A., & Popa, V. I. (2015). Optimization of ultrasound-assisted extraction of polyphenols from spruce wood bark. *Ultrasonics Sonochemistry*, *22*, 535–541. https://doi.org/10.1016/j.ultsonch.2014.07.013

Ghosh, P. K., & Gaba, A. (2013). *Phyto-Extracts in Wound Healing*. *16*(5), 760–820.

Gil-Martín, E., Forbes-Hernández, T., Romero, A., Cianciosi, D., Giampieri, F., & Battino, M. (2022). Influence of the extraction method on the recovery of bioactive phenolic compounds from food industry by-products. *Food Chemistry*, *378*. https://doi.org/10.1016/j.foodchem.2021.131918

Ginovyan, M., Petrosyan, M., & Trchounian, A. (2017). Antimicrobial activity of some plant materials used in Armenian traditional medicine. *BMC Complementary and Alternative Medicine*, *17*(1), 1–9. https://doi.org/10.1186/s12906-017-1573-y

Gogineni, V., Leon, F., Avery, B. A., Mccurdy, C., & Cutler, S. J. (2014). Psychopharmacological Indole Alkaloids from Terrestrial Plants. *Kratom and Other Mitragynines*, *October*, 40–55. https://doi.org/10.1201/b17666-7

Goh, T. B., Yian, K. R., Mordi, M. N., & Mansor, S. M. (2014). Antioxidant value and antiproliferative efficacy of mitragynine and a silane reduced analogue. *Asian Pacific Journal of Cancer Prevention*, *15*(14), 5659–5665. https://doi.org/10.7314/APJCP.2014.15.14.5659

Goh, Y. S., Karunakaran, T., Murugaiyah, V., Santhanam, R., Abu Bakar, M. H., & Ramanathan, S. (2021). Accelerated solvent extractions (Ase) of mitragyna speciosa korth. (kratom) leaves: Evaluation of its cytotoxicity and antinociceptive activity. *Molecules*, *26*(12). https://doi.org/10.3390/molecules26123704

Gothai, S., Arulselvan, P., Tan, W. S., & Fakurazi, S. (2016). Wound healing properties of ethyl acetate fraction of Moringa oleifera in normal human dermal fibroblasts. *Journal of Intercultural Ethnopharmacology*, *5*(1), 1–6. https://doi.org/10.5455/jice.20160201055629

Graham, H. K., Eckersley, A., Ozols, M., Mellody, K. T., & Sherratt, M. J. (2019). Human Skin: Composition, Structure and Visualisation Methods. *Studies in Mechanobiology, Tissue Engineering and Biomaterials*, *22*, 1–18. https://doi.org/10.1007/978-3-030-13279-8_1

Guerra, A., Belinha, J., & Jorge, R. N. (2018). Modelling skin wound healing angiogenesis: A review. *Journal of Theoretical Biology*, *459*, 1–17. https://doi.org/10.1016/j.jtbi.2018.09.020

Guo, C., Wang, J., Cao, F., Lee, R. J., & Zhai, G. (2010). Lyotropic liquid crystal systems in drug delivery. *Drug Discovery Today*, *15*(23–24), 1032–1040. https://doi.org/10.1016/j.drudis.2010.09.006

Gushiken, L. F. S., Beserra, F. P., Bastos, J. K., Jackson, C. J., & Pellizzon, C. H. (2021). Cutaneous wound healing: An update from physiopathology to current therapies. *Life*, *11*(7), 1–15. https://doi.org/10.3390/life11070665

Gut, P., Reischauer, S., Stainier, D. Y. R., & Arnaout, R. (2017). Little fish, big data: Zebrafish as a model for cardiovascular and metabolic disease. *Physiological Reviews*, *97*(3), 889–938. https://doi.org/10.1152/physrev.00038.2016

Haddadi, R., Tamri, P., & Javani Jooni, F. (2019). In vitro wound healing activity of Scrophularia striata hydroalcoholic extract. *South African Journal of Botany*, *121*, 505–509. https://doi.org/10.1016/j.sajb.2019.01.002

Hadidi, M., Ibarz, A., & Pagan, J. (2020). Optimisation and kinetic study of the ultrasonic-assisted extraction of total saponins from alfalfa (Medicago sativa) and its bioaccessibility using the response surface methodology. *Food Chemistry*, *309*(April), 125786. https://doi.org/10.1016/j.foodchem.2019.125786

Harikarnpakdee, S., & Chowjarean, V. (2018). Grammatophyllum speciosum Ethanolic Extract Promotes Wound Healing in Human Primary Fibroblast Cells. *International Journal of Cell Biology*, *2018*. https://doi.org/10.1155/2018/7836869

Hartnett, T. E., Ladewig, K., O'Connor, A. J., Hartley, P. G., & McLean, K. M. (2015). Physicochemical and cytotoxicity analysis of glycerol monoolein-based nanoparticles. *RSC Advances*, *5*(34), 26543–26549. https://doi.org/10.1039/c4ra13890b

Hoang, H. T., Moon, J. Y., & 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

Hong, S. K., Ma, J. Y., & Kim, J. C. (2012). In Vitro Skin Permeation Enhancement of KIOM-MA-128 by Monoolein Cubosomes. *Journal of Dispersion Science and Technology*, *33*(10), 1503–1508. https://doi.org/10.1080/01932691.2011.620863

Huynh Mai, C., Thanh Diep, T., Le, T. T. T., & Nguyen, V. (2020). Advances in colloidal dispersions: A review. *Journal of Dispersion Science and Technology*, *41*(4), 479–494. https://doi.org/10.1080/01932691.2019.1591970

Ibrahim, N. 'Izzah, Wong, S. K., Mohamed, I. N., Mohamed, N., Chin, K. Y., Ima-Nirwana, S., & Shuid, A. N. (2018). Wound healing properties of selected natural products. *International Journal of Environmental Research and Public Health*, *15*(11). https://doi.org/10.3390/ijerph15112360

Ilghami, A., Ghanbarzadeh, S., & Hamishehkar, H. (2015). *Optimization of the Ultrasonic-Assisted Extraction of Phenolic Compounds , Ferric Reducing Activity and Antioxidant Activity of the Beta vulgaris Using Response Surface Methodology*. *june*, 46–50. https://doi.org/10.15171/PS.2015.16

Im, T. J., Kang, M. J., Seo, D. W., & Lee, J. (2008). Effect of cubic liquid crystalline systems on skin localization of oregonin and hirsutanonol. *Biomolecules and Therapeutics*, *16*(3), 226–230. https://doi.org/10.4062/biomolther.2008.16.3.226

Ivanova, A., Gerasimova, E., & Gazizullina, E. (2020). Study of Antioxidant Properties of Agents from the Perspective of Their Action Mechanisms. *Molecules*, *25*(18). https://doi.org/10.3390/molecules25184251

Jain, S., Patel, N., Shah, M. K., Khatri, P., & Vora, N. (2017). Recent Advances in Lipid-Based Vesicles and Particulate Carriers for Topical and Transdermal Application. *Journal of Pharmaceutical Sciences*, *106*(2), 423–445. https://doi.org/10.1016/j.xphs.2016.10.001

Järbrink, K., Ni, G., Sönnergren, H., Schmidtchen, A., Pang, C., Bajpai, R., & Car, J. (2017). The humanistic and economic burden of chronic wounds: A protocol for a systematic review. *Systematic Reviews*, *6*(1), 1–7. https://doi.org/10.1186/s13643-016-0400-8

Jarque, S., Rubio-Brotons, M., Ibarra, J., Ordoñez, V., Dyballa, S., Miñana, R., & Terriente, J. (2020). Morphometric analysis of developing zebrafish embryos allows predicting teratogenicity modes of action in higher vertebrates. *Reproductive Toxicology*, *96*, 337–348. https://doi.org/10.1016/j.reprotox.2020.08.004

Jayasinghe, C. D., & Jayawardena, U. A. (2019). Toxicity Assessment of Herbal Medicine Using Zebrafish Embryos: A Systematic Review. *Evidence-Based Complementary and Alternative Medicine*, *2019*. https://doi.org/10.1155/2019/7272808

Jia, B., Li, G., Cao, E., Luo, J., Zhao, X., & Huang, H. (2023). Recent progress of antibacterial hydrogels in wound dressings. *Materials Today Bio*, *19*(January), 100582. https://doi.org/10.1016/j.mtbio.2023.100582

Jia, H. R., Zhu, Y. X., Duan, Q. Y., Chen, Z., & Wu, F. G. (2019). Nanomaterials meet zebrafish: Toxicity evaluation and drug delivery applications. *Journal of Controlled Release*, *311–312*(July), 301–318. https://doi.org/10.1016/j.jconrel.2019.08.022

Juncos Bombin, A. D., Dunne, N. J., & McCarthy, H. O. (2020). Electrospinning of natural polymers for the production of nanofibres for wound healing applications. *Materials Science and Engineering C*, *114*(February). https://doi.org/10.1016/j.msec.2020.110994

Karodi, R., Jadhav, M., Rub, R., & Bafna, A. (2009). Evaluation of the wound healing activity of a crude extract of Rubia cordifolia L. (Indian madder) in mice. *International Journal of Applied Research in Natural Products*, *2*(2), 12–18.

Kasote, D., Ahmad, A., & Viljoen, A. (2015). Proangiogenic Potential of Medicinal Plants in Wound Healing. In *Evidence-Based Validation of Herbal Medicine*. Elsevier Inc. https://doi.org/10.1016/B978-0-12-800874-4.00006-4

Kebede, B., & Shibeshi, W. (2022). In vitro antibacterial and antifungal activities of extracts and fractions of leaves of Ricinus communis Linn against selected pathogens. *Veterinary Medicine and Science*, *8*(4), 1802–1815. https://doi.org/10.1002/vms3.772

Khoddami, A., Wilkes, M. A., & Roberts, T. H. (2013). Techniques for analysis of plant phenolic compounds. *Molecules*, *18*(2), 2328–2375. https://doi.org/10.3390/molecules18022328

Kõljalg, U., Nilsson, R. H., Abarenkov, K., Tedersoo, L., Taylor, A. F. S., Bahram, M., Bates, S. T., Bruns, T. D., Bengtsson-Palme, J., Callaghan, T. M., Douglas, B., Drenkhan, T., Eberhardt, U., Dueñas, M., Grebenc, T., Griffith, G. W., Hartmann, M., Kirk, P. M., Kohout, P., … Larsson, K.-H. (2013). Towards a Unified Paradigm on Fungal Identification. *Molecular Ecology*, *January*, 5271–5277. https://doi.org/10.1007/978-1-4939-1417-3

Koulis, G. A., Tsagkaris, A. S., Aalizadeh, R., Dasenaki, M. E., Panagopoulou, E. I., Drivelos, S., Halagarda, M., Georgiou, C. A., Proestos, C., & Thomaidis, N. S. (2021). Honey phenolic compound profiling and authenticity assessment using hrms targeted and untargeted metabolomics. *Molecules*, *26*(9), 1–21. https://doi.org/10.3390/molecules26092769

Krakowska, A., Rafińska, K., Walczak, J., Kowalkowski, T., & Buszewski, B. (2017). Comparison of Various Extraction Techniques of Medicago sativa: Yield, Antioxidant Activity, and Content of Phytochemical Constituents. *Journal of AOAC International*, *100*(6), 1681–1693. https://doi.org/10.5740/jaoacint.17-0234

Kumah, E. A., Fopa, R. D., Harati, S., Boadu, P., Zohoori, F. V., & Pak, T. (2023). Human and environmental impacts of nanoparticles: a scoping review of the current literature. *BMC Public Health*, *23*(1). https://doi.org/10.1186/s12889-023-15958-4

Kumar, S., Sandhir, R., & Ojha, S. (2014). Evaluation of antioxidant activity and total phenol in different varieties of Lantana camara leaves. *BMC Research Notes*, *7*(1), 1–9. https://doi.org/10.1186/1756-0500-7-560

Kumar Scholar, M. K., Sujatha, K., & Kumar, M. K. (2019). Non-enzymatic antioxidant defense system in plants. *~ 929 ~ Journal of Pharmacognosy and Phytochemistry*, *2*, 929–932.

Kumar, V., Sharma, N., & Maitra, S. S. (2017). In vitro and in vivo toxicity assessment of nanoparticles. *International Nano Letters*, *7*(4), 243–256. https://doi.org/10.1007/s40089-017-0221-3

Kumari, M., & Nanda, D. K. (2023). Potential of Curcumin nanoemulsion as antimicrobial and wound healing agent in burn wound infection. *Burns*, *49*(5), 1003–1016. https://doi.org/https://doi.org/10.1016/j.burns.2022.10.008

Kuo, S. H., Shen, C. J., Shen, C. F., & Cheng, C. M. (2020). Role of pH value in clinically relevant diagnosis. *Diagnostics*, *10*(2), 1–17. https://doi.org/10.3390/diagnostics10020107

Lai, K. P., Gong, Z., & Tse, W. K. F. (2021). Zebrafish as the toxicant screening model: Transgenic and omics approaches. *Aquatic Toxicology*, *234*(March), 105813. https://doi.org/10.1016/j.aquatox.2021.105813

Lancelot, A., Sierra, T., & Serrano, J. L. (2014). Nanostructured liquid-crystalline particles for drug delivery. *Expert Opinion on Drug Delivery*, *11*(4), 547–564. https://doi.org/10.1517/17425247.2014.884556

Lee, S. Y., Mediani, A., Nur Ashikin, A. H., Azliana, A. B. S., & Abas, F. (2014). Antioxidant and α-glucosidase inhibitory activities of the leaf and stem of selected traditional medicinal plants. *International Food Research Journal*, *21*(1), 165–172.

Leksungnoen, N., Andriyas, T., Ngernsaengsaruay, C., Uthairatsamee, S., Racharak, P., Sonjaroon, W., Kjelgren, R., Pearson, B. J., McCurdy, C. R., & Sharma, A. (2022). Variations in mitragynine content in the naturally growing Kratom (Mitragyna speciosa) population of Thailand. *Frontiers in Plant Science*, *13*(October), 1–15. https://doi.org/10.3389/fpls.2022.1028547

Limcharoen, T., Pouyfung, P., Ngamdokmai, N., Prasopthum, A., Ahmad, A. R., Wisdawati, W., Prugsakij, W., & Warinhomhoun, S. (2022). Inhibition of α-Glucosidase and Pancreatic Lipase Properties of Mitragyna speciosa (Korth.) Havil. (Kratom) Leaves. *Nutrients*, *14*(19), 1–15. https://doi.org/10.3390/nu14193909

Ling, S. K., Tanaka, T., & Kouno, I. (2003). Effects of iridoids on lipoxygenase and hyaluronidase activities and their activation by β-glucosidase in the presence of amino acids. *Biological and Pharmaceutical Bulletin*, *26*(3), 352–356. https://doi.org/10.1248/bpb.26.352

Liu, Y., & Feng, N. (2015). Nanocarriers for the delivery of active ingredients and fractions extracted from natural products used in traditional Chinese medicine (TCM). *Advances in Colloid and Interface Science*, *221*, 60–76. https://doi.org/10.1016/j.cis.2015.04.006

Lu, J., Li, J., Jin, R., Li, S., Yi, J., & Huang, J. (2019). Extraction and characterization of pectin from Premna microphylla Turcz leaves. *International Journal of Biological Macromolecules*, *131*, 323–328. https://doi.org/10.1016/j.ijbiomac.2019.03.056

Ly, H. T., Pham Nguyen, M. T., Nguyen, T. K. O., Bui, T. P. Q., Ke, X., & Le, V. M. (2020). Phytochemical Analysis and Wound-Healing Activity of Noni (Morinda Citrifolia) Leaf Extract. *Journal of Herbs, Spices and Medicinal Plants*, *26*(4), 379–393. https://doi.org/10.1080/10496475.2020.1748159

Macáková, K., Afonso, R., Saso, L., & Mladěnka, P. (2019). The influence of alkaloids on oxidative stress and related signaling pathways. *Free Radical Biology and Medicine*, *134*(January), 429–444. https://doi.org/10.1016/j.freeradbiomed.2019.01.026

Maes, J., Verlooy, L., Buenafe, O. E., de Witte, P. A. M., Esguerra, C. V., & Crawford, A. D. (2012). Evaluation of 14 Organic Solvents and Carriers for Screening Applications in Zebrafish Embryos and Larvae. *PLoS ONE*, *7*(10), 1–9. https://doi.org/10.1371/journal.pone.0043850

Majeed, M., Hussain, A. I., Chatha, S. A. S., Khosa, M. K. K., Kamal, G. M., Kamal, M. A., Zhang, X., & Liu, M. (2016). Optimization protocol for the extraction of antioxidant components from Origanum vulgare leaves using response surface methodology. *Saudi Journal of Biological Sciences*, *23*(3), 389–396. https://doi.org/10.1016/j.sjbs.2015.04.010

Maran, J. P. (2017). Ultrasound assisted extraction of bioactive compounds from Nephelium lappaceum L . fruit peel using central composite face centered response surface design. *Arabian Journal of Chemistry*, *10*, S1145–S1157. https://doi.org/10.1016/j.arabjc.2013.02.007

Mariadoss, A. V. A., Park, S., Saravanakumar, K., Sathiyaseelan, A., & Wang, M. H. (2021). Ethyl acetate fraction of helianthus tuberosus l. Induces anti-diabetic, and wound-healing activities in insulin-resistant human liver cancer and mouse fibroblast cells. *Antioxidants*, *10*(1), 1–22. https://doi.org/10.3390/antiox10010099

Martin, A. (1996). The use of antioxidants in healing. In *Dermatologic Surgery* (Vol. 22, Issue 2, pp. 156–160). https://doi.org/10.1111/j.1524-4725.1996.tb00499.x

Matloub, A. A., AbouSamra, M. M., Salama, A. H., Rizk, M. Z., Aly, H. F., & Fouad, G. I. (2018). Cubic liquid crystalline nanoparticles containing a polysaccharide from Ulva fasciata with potent antihyperlipidaemic activity. *Saudi Pharmaceutical Journal*, *26*(2), 224–231. https://doi.org/10.1016/j.jsps.2017.12.007

Meda, A., Lamien, C. E., Romito, M., Millogo, J., & Nacoulma, O. G. (2005). Determination of the total phenolic, flavonoid and proline contents in Burkina Fasan honey, as well as their radical scavenging activity. *Food Chemistry*, *91*(3), 571–577. https://doi.org/10.1016/j.foodchem.2004.10.006

Meikle, T. G., Dyett, B. P., Strachan, J. B., White, J., Drummond, C. J., & Conn, C. E. (2020). Preparation, Characterization, and Antimicrobial Activity of Cubosome Encapsulated Metal Nanocrystals. *ACS Applied Materials and Interfaces*, *12*(6), 6944–6954. https://doi.org/10.1021/acsami.9b21783

Meireles, V., Rosado, T., Barroso, M., Soares, S., Gonçalves, J., Luís, Â., Caramelo, D., Simão, A., Fernández, N., Duarte, A., & Gallardo, E. (2019). Mitragyna speciosa: Clinical, Toxicological Aspects and Analysis in Biological and Non-Biological Samples. *Medicines*, *6*(1), 35. https://doi.org/10.3390/medicines6010035

Melgar, B., Dias, M. I., Barros, L., Ferreira, I. C. F. R., Rodriguez-Lopez, A. D., & Garcia-Castello, E. M. (2019). Ultrasound and microwave assisted extraction of Opuntia fruit peels biocompounds: Optimization and comparison using RSM-CCD. *Molecules*, *24*(19), 1–16. https://doi.org/10.3390/molecules24193618

Milak, S., & Zimmer, A. (2015). Glycerol monooleate liquid crystalline phases used in drug delivery systems. *International Journal of Pharmaceutics*, *478*(2), 569–587. https://doi.org/10.1016/j.ijpharm.2014.11.072

Mir, M., Ali, M. N., Barakullah, A., Gulzar, A., Arshad, M., Fatima, S., & Asad, M. (2018). Synthetic polymeric biomaterials for wound healing: a review. *Progress in Biomaterials*, *7*(1), 1–21. https://doi.org/10.1007/s40204-018-0083-4

Mishra, D. K., Shandilya, R., & Mishra, P. K. (2018). Lipid based nanocarriers: a translational perspective. *Nanomedicine: Nanotechnology, Biology, and Medicine*, *14*(7), 2023–2050. https://doi.org/10.1016/j.nano.2018.05.021

Moazzen, A., Öztinen, N., Ak-Sakalli, E., & Koşar, M. (2022). Structure-antiradical activity relationships of 25 natural antioxidant phenolic compounds from different classes. *Heliyon*, *8*(9). https://doi.org/10.1016/j.heliyon.2022.e10467

Moeini, A., Pedram, P., Makvandi, P., Malinconico, M., & Gomez d'Ayala, G. (2020). Wound healing and antimicrobial effect of active secondary metabolites in chitosan-based wound dressings: A review. *Carbohydrate Polymers*, *233*(January), 115839. https://doi.org/10.1016/j.carbpol.2020.115839

Mohapatra, D., Agrawal, A. K., & Sahu, A. N. (2021). Exploring the potential of solid dispersion for improving solubility, dissolution & bioavailability of herbal extracts, enriched fractions, and bioactives. *Journal of Microencapsulation*, *38*(7–8), 594–612. https://doi.org/10.1080/02652048.2021.1963342

Mohd Fahmi, M. S. A., Swain, P., Ramli, A. H., Wan Ibrahim, W. N., Saleh Hodin, N. A., Abu Bakar, N., Tan, Y. S., Mohd Faudzi, S. M., & Kim, C. H. (2023). In silico studies, X-ray diffraction analysis and biological investigation of fluorinated pyrrolylated-chalcones in zebrafish epilepsy models. *Heliyon*, *9*(2), e13685. https://doi.org/10.1016/j.heliyon.2023.e13685

Mossadeq, W. M., Sulaiman, M. R., Tengku Mohamad, T. A., Chiong, H. S., Zakaria, Z. A., Jabit, M. L., Baharuldin, M. T. H., & Israf, D. A. (2009). Anti-inflammatory and antinociceptive effects of Mitragyna speciosa Korth methanolic extract. *Medical Principles and Practice*, *18*(5), 378–384. https://doi.org/10.1159/000226292

Muheem, A., Shakeel, F., Warsi, M. H., Jain, G. K., & Ahmad, F. J. (2017). A Combinatorial Statistical Design Approach to Optimize the Nanostructured Cubosomal Carrier System for Oral Delivery of Ubidecarenone for Management of Doxorubicin-Induced Cardiotoxicity: In Vitro–In Vivo Investigations. *Journal of Pharmaceutical Sciences*, *106*(10), 3050–3065. https://doi.org/10.1016/j.xphs.2017.05.026

Mulet, X., Boyd, B. J., & Drummond, C. J. (2013). Advances in drug delivery and medical imaging using colloidal lyotropic liquid crystalline dispersions. *Journal of Colloid and Interface Science*, *393*(1), 1–20. https://doi.org/10.1016/j.jcis.2012.10.014

Muniandy, K., Gothai, S., Tan, W. S., Kumar, S. S., Mohd Esa, N., Chandramohan, G., Al-Numair, K. S., & Arulselvan, P. (2018). In Vitro Wound Healing Potential of Stem Extract of Alternanthera sessilis. *Evidence-Based Complementary and Alternative Medicine*, *2018*(2011). https://doi.org/10.1155/2018/3142073

Muñiz-Márquez, D. B., Martínez-Ávila, G. C., Wong-Paz, J. E., Belmares-Cerda, R., Rodríguez-Herrera, R., & Aguilar, C. N. (2013). Ultrasound-assisted extraction of phenolic compounds from Laurus nobilis L. and their antioxidant activity. *Ultrasonics Sonochemistry*, *20*(5), 1149–1154. https://doi.org/10.1016/j.ultsonch.2013.02.008

Munteanu, I. G., & Apetrei, C. (2021). Analytical methods used in determining antioxidant activity: A review. *International Journal of Molecular Sciences*, *22*(7). https://doi.org/10.3390/ijms22073380

Murugesu, S., Khatib, A., Ahmed, Q. U., Ibrahim, Z., Uzir, B. F., Benchoula, K., Yusoff, N. I. N., Perumal, V., Alajmi, M. F., Salamah, S., & El-Seedi, H. R. (2019). Toxicity study on Clinacanthus nutans leaf hexane fraction using Danio rerio embryos. *Toxicology Reports*, *6*(February), 1148–1154. https://doi.org/10.1016/j.toxrep.2019.10.020

N-E, T., Das, R., Lami, M. S., Chakraborty, A. J., Mitra, S., Tallei, T. E., Idroes, R., Mohamed, A. A. R., Hossain, M. J., Dhama, K., Mostafa-Hedeab, G., & Emran, T. Bin. (2022). Ginkgo biloba: A Treasure of Functional Phytochemicals with Multimedicinal Applications. *Evidence-Based Complementary and Alternative Medicine*, *2022*. https://doi.org/10.1155/2022/8288818

Naini, M. A., Zargari-Samadnejad, A., Mehrvarz, S., Tanideh, R., Ghorbani, M., Dehghanian, A., Hasanzarrini, M., Banaee, F., Koohi-Hosseinabadi, O., Tanideh, N., & Iraji, A. (2021). Anti-Inflammatory, Antioxidant, and Healing-Promoting Effects of Aloe vera Extract in the Experimental Colitis in Rats. *Evidence-Based Complementary and Alternative Medicine*, *2021*. https://doi.org/10.1155/2021/9945244

Nasr, M., Ghorab, M. K., & Abdelazem, A. (2015). In vitro and in vivo evaluation of cubosomes containing 5-fluorouracil for liver targeting. *Acta Pharmaceutica Sinica B*, *5*(1), 79–88. https://doi.org/10.1016/j.apsb.2014.12.001

Nasr, M., Younes, H., & Abdel-Rashid, R. S. (2020). Formulation and evaluation of cubosomes containing colchicine for transdermal delivery. *Drug Delivery and Translational Research*, *10*(5), 1302–1313. https://doi.org/10.1007/s13346-020-00785-6

Negi, A., Dobhal, K., Ghildiyal, P., & Semwal, A. (2022). *Antioxidant Potential and Effect of Extraction Solvent on Total Phenol Content, Flavonoids*. *September*.

Niu, Y., Sun, Y., Liu, Y., Du, K., Xu, X., & Ding, Y. (2023). Using Zebrafish Animal Model to Study the Genetic Underpinning and Mechanism of Arrhythmogenic Cardiomyopathy. *International Journal of Molecular Sciences*, *24*(4). https://doi.org/10.3390/ijms24044106

Noroozi, R., Sadeghi, E., Yousefi, H., Taheri, M., Sarabi, P., Dowati, A., Ayatallahi, S. A., Noroozi, R., & Ghafouri-Fard, S. (2019). Wound healing features of Prosopis farcta: in vitro evaluation of antibacterial, antioxidant, proliferative and angiogenic properties. *Gene Reports*, *17*(August). https://doi.org/10.1016/j.genrep.2019.100482

Nourian Dehkordi, A., Mirahmadi Babaheydari, F., Chehelgerdi, M., & Raeisi Dehkordi, S. (2019). Skin tissue engineering: Wound healing based on stem-cell-based therapeutic strategies. *Stem Cell Research and Therapy*, *10*(1), 1–20. https://doi.org/10.1186/s13287-019-1212-2

Ojha, K. S., Aznar, R., O'Donnell, C., & Tiwari, B. K. (2020). Ultrasound technology for the extraction of biologically active molecules from plant, animal and marine sources. *TrAC - Trends in Analytical Chemistry*, *122*. https://doi.org/10.1016/j.trac.2019.115663

Olatunde, O. O., Benjakul, S., & Vongkamjan, K. (2018). Antioxidant and antibacterial properties of guava leaf extracts as affected by solvents used for prior dechlorophyllization. *Journal of Food Biochemistry*, *42*(5), 1–11. https://doi.org/10.1111/jfbc.12600

Osman, M. A., Mahmoud, G. I., & Shoman, S. S. (2020). Correlation between total phenols content, antioxidant power and cytotoxicity. *Biointerface Research in Applied Chemistry*, *11*(3), 10640–10653. https://doi.org/10.33263/BRIAC113.1064010653

Othman, A. R., Abdullah, N., Ahmad, S., Ismail, I. S., & Zakaria, M. P. (2015). Elucidation of in-vitro anti-inflammatory bioactive compounds isolated from Jatropha curcas L. plant root. *BMC Complementary and Alternative Medicine*, *15*(1), 1–10. https://doi.org/10.1186/s12906-015-0528-4

Othman, L., Sleiman, A., & Abdel-Massih, R. M. (2019). Antimicrobial activity of polyphenols and alkaloids in middle eastern plants. *Frontiers in Microbiology*, *10*(MAY). https://doi.org/10.3389/fmicb.2019.00911

Otsuka, H. (2006). Purification by Solvent Extraction Using Partition Coefficient. *Natural Products Isolation*, *20*, 269–273. https://doi.org/10.1385/1-59259-955-9:269

Ouchari, L., Boukeskasse, A., Bouizgarne, B., & Ouhdouch, Y. (2019). Antimicrobial potential of actinomycetes isolated from the unexplored hot Merzouga desert and their taxonomic diversity. *Biology Open*, *8*(2). https://doi.org/10.1242/bio.035410

Ozturk Sarikaya, S. B. (2015). Acethylcholinesterase inhibitory potential and antioxidant properties of pyrogallol. *Journal of Enzyme Inhibition and Medicinal Chemistry*, *30*(5), 761–766. https://doi.org/10.3109/14756366.2014.965700

Pai, S., Hebbar, A., & Selvaraj, S. (2022). A critical look at challenges and future scopes of bioactive compounds and their incorporations in the food, energy, and pharmaceutical sector. *Environmental Science and Pollution Research*, *29*(24), 35518–35541. https://doi.org/10.1007/s11356-022-19423-4

Pan, G., Yu, G., Zhu, C., & Qiao, J. (2012). Optimization of ultrasound-assisted extraction (UAE) of flavonoids compounds (FC) from hawthorn seed (HS). *Ultrasonics Sonochemistry*, *19*(3), 486–490. https://doi.org/10.1016/j.ultsonch.2011.11.006

Papaccio, F., D'arino, A., Caputo, S., & Bellei, B. (2022). Focus on the Contribution of Oxidative Stress in Skin Aging. *Antioxidants*, *11*(6). https://doi.org/10.3390/antiox11061121

Parthasarathy, S., Azizi, J. Bin, Ramanathan, S., Ismail, S., Sasidharan, S., Mohd, M. I., & Mansor, S. M. (2009). Evaluation of antioxidant and antibacterial activities of aqueous, methanolic and alkaloid extracts from Mitragyna speciosa (rubiaceae family) leaves. *Molecules*, *14*(10), 3964–3974. https://doi.org/10.3390/molecules14103964

Patil, D. M., & Akamanchi, K. G. (2017). Ultrasound-assisted rapid extraction and kinetic modelling of influential factors: Extraction of camptothecin from Nothapodytes nimmoniana plant. *Ultrasonics Sonochemistry*, *37*, 582–591. https://doi.org/10.1016/j.ultsonch.2017.02.015

Penduka, D., Buwa, L., Mayekiso, B., Basson, A. K., & Okoh, A. I. (2014). Identification of the anti listerial constituents in partially purified column chromatography fractions of garcinia kola seeds and their interactions with standard antibiotics. *Evidence-Based Complementary and Alternative Medicine*, *2014*. https://doi.org/10.1155/2014/850347

Peng, X., Zhou, Y., Han, K., Qin, L., Dian, L., Li, G., Pan, X., & Wu, C. (2015). Characterization of cubosomes as a targeted and sustained transdermal delivery system for capsaicin. *Drug Design, Development and Therapy*, *9*, 4209–4218. https://doi.org/10.2147/DDDT.S86370

Pereira, R. F., & Bártolo, P. J. (2016). Traditional Therapies for Skin Wound Healing. *Advances in Wound Care*, *5*(5), 208–229. https://doi.org/10.1089/wound.2013.0506

Pham, H. N. T., Vuong, Q. Van, Bowyer, M. C., & Scarlett, C. J. (2017). Optimization of ultrasound-assisted extraction of Helicteres hirsuta Lour. for enhanced total phenolic compound and antioxidant yield. *Journal of Applied Research on Medicinal and Aromatic Plants*, *7*(August 2016), 113–123. https://doi.org/10.1016/j.jarmap.2017.07.002

Ping, Z., Chen, X., Fang, L., Wu, K., Liu, C., Chen, H., Jiang, X., Ma, J., & Yu, W. (2023). Effect of Angelica Sinensis extract on the angiogenesis of preovulatory follicles (F1–F3) in late-phase laying hens. *Poultry Science*, *102*(2), 1–14. https://doi.org/10.1016/j.psj.2022.102415

Pitz, H. D. S., Pereira, A., Blasius, M. B., Voytena, A. P. L., Affonso, R. C. L., Fanan, S., Trevisan, A. C. D., Ribeiro-Do-Valle, R. M., & Maraschin, M. (2016). In Vitro Evaluation of the Antioxidant Activity and Wound Healing Properties of Jaboticaba (Plinia peruviana) Fruit Peel Hydroalcoholic Extract. *Oxidative Medicine and Cellular Longevity*, *2016*. https://doi.org/10.1155/2016/3403586

Ponnampalam, E. N., Kiani, A., Santhiravel, S., Holman, B. W. B., Lauridsen, C., & Dunshea, F. R. (2022). The Importance of Dietary Antioxidants on Oxidative Stress, Meat and Milk Production, and Their Preservative Aspects in Farm Animals: Antioxidant Action, Animal Health, and Product Quality—Invited Review. *Animals*, *12*(23). https://doi.org/10.3390/ani12233279

Pradal, D., Vauchel, P., Decossin, S., Dhulster, P., & Dimitrov, K. (2016). Kinetics of ultrasound-assisted extraction of antioxidant polyphenols from food by-products: Extraction and energy consumption optimization. *Ultrasonics Sonochemistry*, *32*, 137–146. https://doi.org/10.1016/j.ultsonch.2016.03.001

Prasad, K. N., Hassan, F. A., Yang, B., Kong, K. W., Ramanan, R. N., Azlan, A., & Ismail, A. (2011). Response surface optimisation for the extraction of phenolic compounds and antioxidant capacities of underutilised Mangifera pajang Kosterm. peels. *Food Chemistry*, *128*(4), 1121–1127. https://doi.org/10.1016/j.foodchem.2011.03.105

Prasad, K. N., Kong, K. W., Ramanan, R. N., Azlan, A., & Ismail, A. (2012). Determination and Optimization of Flavonoid and Extract Yield from Brown Mango using Response Surface Methodology. *Separation Science and Technology*, *47*(1), 73–80.

Priya, K. S., Arumugam, G., Rathinam, B., Wells, A., & Babu, M. (2004). Celosia argentea Linn. leaf extract improves wound healing in a rat burn wound model. *Wound Repair and Regeneration*, *12*(6), 618–625. https://doi.org/10.1111/j.1067-1927.2004.12603.x

Rahman, H. S., Othman, H. H., Hammadi, N. I., Yeap, S. K., Amin, K. M., Samad, N. A., & Alitheen, N. B. (2020). Novel drug delivery systems for loading of natural plant extracts and their biomedical applications. *International Journal of Nanomedicine*, *15*, 2439–2483. https://doi.org/10.2147/IJN.S227805

Ramanathan, S., Parthasarathy, S., Murugaiyah, V., Magosso, E., Tan, S. C., & Mansor, S. M. (2015). Understanding the physicochemical properties of mitragynine, a principal alkaloid of Mitragyna speciosa, for preclinical evaluation. *Molecules*, *20*(3), 4915–4927. https://doi.org/10.3390/molecules20034915

Rapalli, V. K., Waghule, T., Hans, N., Mahmood, A., Gorantla, S., Dubey, S. K., & Singhvi, G. (2020). Insights of lyotropic liquid crystals in topical drug delivery for targeting various skin disorders. *Journal of Molecular Liquids*, *315*, 113771. https://doi.org/10.1016/j.molliq.2020.113771

Razavi, B. M., Ghasemzadeh Rahbardar, M., & Hosseinzadeh, H. (2021). A review of therapeutic potentials of turmeric (Curcuma longa) and its active constituent, curcumin, on inflammatory disorders, pain, and their related patents. *Phytotherapy Research*, *35*(12), 6489–6513. https://doi.org/10.1002/ptr.7224

Rente, D., Paiva, A., & Duarte, A. R. (2021). The role of hydrogen bond donor on the extraction of phenolic compounds from natural matrices using deep eutectic systems. *Molecules*, *26*(8). https://doi.org/10.3390/molecules26082336

Rescober, A. A. S., Blanco, I. F. M., Janio, J. A. T., Custodio, S. E. A., Daguman, F. L. D., Viray, J. M. D., & Dollesin, J. H. (2022). Antimicrobial and Wound Healing Activity of Ixora coccinea Leaf Extract in Hydrogel Formulation. *Acta Medica Philippina*, *56*(7), 12–17. https://doi.org/10.47895/amp.vi0.1975

Rex Jeya Rajkumar, S., Gnanavel, G., Muthukumar Nadar, M. S. A., & Sankaranarayanan, R. (2018). wound healing activity of Morinda tinctoria Roxb aqueous leaf extract. *3 Biotech*, *8*(8), 0. https://doi.org/10.1007/s13205-018-1361-5

Riaz, A., Rasul, A., Hussain, G., Zahoor, M. K., Jabeen, F., Subhani, Z., Younis, T., Ali, M., Sarfraz, I., & Selamoglu, Z. (2018). Astragalin: A Bioactive Phytochemical with Potential Therapeutic Activities. *Advances in Pharmacological Sciences*, *2018*. https://doi.org/10.1155/2018/9794625

Rizwan, S. B., Dong, Y. D., Boyd, B. J., Rades, T., & Hook, S. (2007). Characterisation of bicontinuous cubic liquid crystalline systems of phytantriol and water using cryo field emission scanning electron microscopy (cryo FESEM). *Micron*, *38*(5), 478–485. https://doi.org/10.1016/j.micron.2006.08.003

Rodríguez De Luna, S. L., Ramírez-Garza, R. E., & Serna Saldívar, S. O. (2020). Environmentally Friendly Methods for Flavonoid Extraction from Plant Material: Impact of Their Operating Conditions on Yield and Antioxidant Properties. *Scientific World Journal*, *2020*. https://doi.org/10.1155/2020/6792069

Ryan M. Brown, Christopher J., MeahVictoria L., H. B. S. B. (2016). Tube-Forming Assays. In *Angiogenesis* (In: Martin, Vol. 1430). Humana Press, New York, NY. https://doi.org/10.1007/978-1-4939-3628-1

Safavi, F., Farimani, M. M., Golalipour, M., Leung, P. C., Lau, K. M., Kwok, H. F., Wong, C. W., Bayat, H., & Lau, C. B. S. (2019). Investigations on the wound healing properties of Onosma dichroantha Boiss root extracts. *South African Journal of Botany*, *125*, 344–352. https://doi.org/10.1016/j.sajb.2019.08.005

Saghazadeh, S., Rinoldi, C., Schot, M., Kashaf, S. S., Sharifi, F., Jalilian, E., Nuutila, K., Giatsidis, G., Mostafalu, P., Derakhshandeh, H., Yue, K., Swieszkowski, W., Memic, A., Tamayol, A., & Khademhosseini, A. (2018). Drug delivery systems and materials for wound healing applications. *Advanced Drug Delivery Reviews*, *127*, 138–166. https://doi.org/10.1016/j.addr.2018.04.008

Şahin, S., & Şamli, R. (2013). Optimization of olive leaf extract obtained by ultrasound-assisted extraction with response surface methodology. *Ultrasonics Sonochemistry*, *20*(1), 595–602. https://doi.org/10.1016/j.ultsonch.2012.07.029

Said, M., Aboelwafa, A. A., Elshafeey, A. H., & Elsayed, I. (2020). Central composite optimization of ocular mucoadhesive cubosomes for enhanced bioavailability and controlled delivery of voriconazole. *Journal of Drug Delivery Science and Technology*, *August*, 102075. https://doi.org/10.1016/j.jddst.2020.102075

Samimi, S., Maghsoudnia, N., Eftekhari, R. B., & Dorkoosh, F. (2018). Lipid-Based Nanoparticles for Drug Delivery Systems. In *Characterization and Biology of Nanomaterials for Drug Delivery: Nanoscience and Nanotechnology in Drug Delivery*. Elsevier Inc. https://doi.org/10.1016/B978-0-12-814031-4.00003-9

Sampurna, B. P., Audira, G., Juniardi, S., & Lai, Y. (2018). *A Simple ImageJ-Based Method to Measure Cardiac Rhythm in Zebrafish Embryos*. *1*, 1–11. https://doi.org/10.3390/inventions3020021

Sannigrahi, S., Mazuder, U. K., Pal, D. K., Parida, S., & Jain, S. (2010). Antioxidant potential of crude extract and different fractions of Enhydra fluctuans Lour. *Iranian Journal of Pharmaceutical Research*, *9*(1), 75–82.

Santos, D. S., Barreto, R. de S. S., Serafini, M. R., Gouveia, D. N., Marques, R. S., Nascimento, L. de C., Nascimento, J. de C., & Guimarães, A. G. (2019). Phytomedicines containing Matricaria species for the treatment of skin diseases: A biotechnological approach. *Fitoterapia*, *138*, 104267. https://doi.org/10.1016/j.fitote.2019.104267

Sasidharan, S., Nilawatyi, R., Xavier, R., Latha, L. Y., & Amala, R. (2010). Wound healing potential of Elaeis guineensis Jacq leaves in an infected albino rat model. *Molecules*, *15*(5), 3186–3199. https://doi.org/10.3390/molecules15053186

Scudiero, O., Brancaccio, M., Mennitti, C., Laneri, S., Lombardo, B., De Biasi, M. G., De Gregorio, E., Pagliuca, C., Colicchio, R., Salvatore, P., & Pero, R. (2020). Human defensins: A novel approach in the fight against skin colonizing staphylococcus aureus. In *Antibiotics* (Vol. 9, Issue 4, pp. 1–16). https://doi.org/10.3390/antibiotics9040198

Selvakumar, P. M., Rajkumar S, R. J., & MSA, M. N. (2018). Phytochemicals as a potential source for anti-microbial, anti-oxidant and wound healing - a review. *MOJ Bioorganic & Organic Chemistry*, *2*(2), 61–70. https://doi.org/10.15406/mojboc.2018.02.0058

Sen. (2019). Human Wounds and Its Burden: An Updated Compendium of Estimates. *Advances in Wound Care*, *8*(2), 39–48. https://doi.org/10.1089/wound.2019.0946

Sen. (2021). Human Wound and Its Burden: Updated 2020 Compendium of Estimates. In *Advances in wound care* (Vol. 10, Issue 5, pp. 281–292). https://doi.org/10.1089/wound.2021.0026

Sen, P. K., & Garg, S. (2019). Wound repair and regenerating effect of ethyl acetate soluble fraction of ethanolic extract of Cinnamomum camphora leaves in wistar albino rats. *Journal of Drug Delivery & Therapeutics*, *9*(4-S), 1173–1176.

Seth, D., Cheldize, K., Brown, D., & Freeman, E. E. (2017). Global Burden of Skin Disease: Inequities and Innovations. *Current Dermatology Reports*, *6*(3), 204–210. https://doi.org/10.1007/s13671-017-0192-7

Shanmugam, T., & Banerjee, R. (2011). Nanostructured self assembled lipid materials for drug delivery and tissue engineering. *Therapeutic Delivery*, *2*(11), 1485–1516. https://doi.org/10.4155/tde.11.105

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

Shirzad, H., Niknam, V., Taheri, M., & Ebrahimzadeh, H. (2017). Ultrasound-assisted extraction process of phenolic antioxidants from Olive leaves : a nutraceutical study using RSM and LC – ESI – DAD – MS. *Journal of Food Science and Technology*, *54*(8), 2361–2371. https://doi.org/10.1007/s13197-017-2676-7

Singh, D., Narayanan, S., Vicknasingam, B., Corazza, O., Santacroce, R., & Roman-Urrestarazu, A. (2017). Changing trends in the use of kratom (Mitragyna speciosa) in Southeast Asia. *Human Psychopharmacology*, *32*(3), 1–6. https://doi.org/10.1002/hup.2582

Singhvi, G., Banerjee, S., & Khosa, A. (2018). Lyotropic liquid crystal nanoparticles. In *Organic Materials as Smart Nanocarriers for Drug Delivery*. Elsevier Inc. https://doi.org/10.1016/B978-0-12-813663-8.00011-7

Sivadasan, D., Sultan, M. H., Alqahtani, S. S., & Javed, S. (2023). Cubosomes in Drug Delivery—A Comprehensive Review on Its Structural Components, Preparation Techniques and Therapeutic Applications. *Biomedicines*, *11*(4). https://doi.org/10.3390/biomedicines11041114

Smith, M. J. E., Ci, K. C., & Indira, G. (2016). Wound healing activity of ethanolic extract of roots of Morinda pubescens J.E. Smith. *Journal of Pharmacognosy and Phytochemistry*, *5*(3), 43–46.

Soib, H. H., Ismail, H. F., Husin, F., Abu Bakar, M. H., Yaakob, H., & Sarmidi, M. R. (2020). Bioassay-guided different extraction techniques of Carica papaya (Linn.) leaves on in vitro wound-healing activities. *Molecules*, *25*(3), 1–13. https://doi.org/10.3390/molecules25030517

Soraya, I., Sulaiman, C., Basri, M., Chan, K. W., Ashari, S. E., Reza, H., Masoumi, F., & Ismail, M. (2015). *African Journal of Pharmacy and Pharmacology In vitro antioxidant, cytotoxic and phytochemical studies of Clinacanthus nutans Lindau leaf extracts*. *9*(34), 861–874. https://doi.org/10.5897/AJPP2015

Sorg, H., Tilkorn, D. J., Hager, S., Hauser, J., & Mirastschijski, U. (2017). Skin Wound Healing: An Update on the Current Knowledge and Concepts. *European Surgical Research*, *58*(1–2), 81–94. https://doi.org/10.1159/000454919

Souders, C. L., Perez-Rodriguez, V., El Ahmadie, N., Zhang, X., Tischuk, C., & Martyniuk, C. J. (2020). Investigation into the sub-lethal effects of the triazole fungicide triticonazole in zebrafish (Danio rerio) embryos/larvae. *Environmental Toxicology*, *35*(2), 254–267.

Souto, E. B., Fernandes, A. R., Martins-gomes, C., Coutinho, T. E., Durazzo, A., Lucarini, M., Souto, S. B., Silva, M., & Santini, A. (2020). *applied sciences Nanomaterials for Skin Delivery of Cosmeceuticals and Pharmaceuticals*.

Spielman, A. F., Griffin, M. F., Parker, J., Cotterell, A. C., Wan, D. C., & Longaker, M. T. (2022). Beyond the Scar: A Basic Science Review of Wound Remodeling. *Advances in Wound Care*, *12*(2), 57–67. https://doi.org/10.1089/wound.2022.0049

Srichana, K., Janchawee, B., Prutipanlai, S., Raungrut, P., & Keawpradub, N. (2015). Effects of mitragynine and a crude alkaloid extract derived from Mitragyna speciosa korth. On permethrin elimination in rats. *Pharmaceutics*, *7*(2), 10–26. https://doi.org/10.3390/pharmaceutics7020010

Strong, A. L., Neumeister, M. W., & Levi, B. (2017). Stem Cells and Tissue Engineering: Regeneration of the Skin and Its Contents. *Clinics in Plastic Surgery*, *44*(3), 635–650. https://doi.org/10.1016/j.cps.2017.02.020

Suhaimi, S. H., Hasham, R., Khairul, M., & Idris, H. (2019). *Optimization of Ultrasound-Assisted Extraction Fractionation from Orthosiphon stamineus Benth*.

Sun, W., & Shahrajabian, M. H. (2023). Therapeutic Potential of Phenolic Compounds in Medicinal Plants—Natural Health Products for Human Health. *Molecules*, *28*(4).

Temviriyanukul, P., Sritalahareuthai, V., Jom, K. N., Jongruaysup, B., Tabtimsri, S., Pruesapan, K., Thangsiri, S., Inthachat, W., Siriwan, D., Charoenkiatkul, S., & Suttisansanee, U. (2020). Comparison of phytochemicals, antioxidant, and in vitro anti-alzheimer properties of twenty-seven morus spp. cultivated in Thailand. *Molecules*, *25*(11), 1–15. https://doi.org/10.3390/molecules25112600

Thakur, R., Jain, N., Pathak, R., & Sandhu, S. S. (2011). Practices in wound healing studies of plants. *Evidence-Based Complementary and Alternative Medicine*, *2011*(May 2014). https://doi.org/10.1155/2011/438056

Ticar, B. F., Rohmah, Z., Mussatto, S. I., Lim, J. M., Park, S., & Choi, B. D. (2017). Hyaluronidase-inhibitory activities of glycosaminoglycans from Liparis tessellatus eggs. *Carbohydrate Polymers*, *161*(16), 16–20. https://doi.org/10.1016/j.carbpol.2016.12.065

Tohar, N., Shilpi, J. A., Sivasothy, Y., Ahmad, S., & Awang, K. (2019). Chemical constituents and nitric oxide inhibitory activity of supercritical carbon dioxide extracts from Mitragyna speciosa leaves. *Arabian Journal of Chemistry*, *12*(3), 350–359. https://doi.org/10.1016/j.arabjc.2016.09.005

Toma, M., Vinatoru, M., Paniwnyk, L., & Mason, T. J. (2001). Investigation of the effects of ultrasound on vegetal tissues during solvent extraction. *Ultrasonics Sonochemistry*, *8*(2), 137–142. https://doi.org/10.1016/S1350-4177(00)00033-X

Tomsone, L., & Kruma, Z. (2013). Comparison of different solvents for isolation of phenolic compounds from horseradish (Armoracia Rusticana L.) leaves. *Research for Rural Development*, *1*(August 2016), 104–110.

Tracy, L. E., Minasian, R. A., & Caterson, E. J. (2016). Extracellular Matrix and Dermal Fibroblast Function in the Healing Wound. *Advances in Wound Care*, *5*(3), 119–136. https://doi.org/10.1089/wound.2014.0561

Truong, D. H., Nguyen, D. H., Ta, N. T. A., Bui, A. V., Do, T. H., & Nguyen, H. C. (2019). Evaluation of the use of different solvents for phytochemical constituents, antioxidants, and in vitro anti-inflammatory activities of severinia buxifolia. *Journal of Food Quality*, *2019*. https://doi.org/10.1155/2019/8178294

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

Tzanova, M., Atanasov, V., Yaneva, Z., Ivanova, D., & Dinev, T. (2020). Selectivity of current extraction techniques for flavonoids from plant materials. *Processes*, *8*(10), 1–30. https://doi.org/10.3390/pr8101222

Van Gennip, J. L. M., Boswell, C. W., & Ciruna, B. (2018). Neuroinflammatory signals drive spinal curve formation in zebrafish models of idiopathic scoliosis. *Science Advances*, *4*(12), 1–11. https://doi.org/10.1126/sciadv.aav1781

Venmathi Maran, B. A., Josmeh, D., Tan, J. K., Yong, Y. S., & Shah, M. D. (2021). Efficacy of the aqueous extract of Azadirachta indica against the marine parasitic leech and its phytochemical profiling. *Molecules*, *26*(7), 1–10. https://doi.org/10.3390/molecules26071908

Verma, S. K., Nandi, A., Sinha, A., Patel, P., Jha, E., Mohanty, S., Panda, P. K., Ahuja, R., Mishra, Y. K., & Suar, M. (2021). Zebrafish (Danio rerio) as an ecotoxicological model for nanomaterial induced toxicity profiling. *Precision Nanomedicine*, *4*(1), 750–781. https://doi.org/10.33218/001c.21978

Vickers, A., Zollman, C., & Lee, R. (2001). Herbal medicine. *The Western Journal of Medicine*, *175*(2), 125–128. https://doi.org/10.1136/ewjm.175.2.125

Vitale, S., Colanero, S., Placidi, M., Emidio, G. Di, Tatone, C., Amicarelli, F., & Alessandro, A. M. D. (2022). Phytochemistry and Biological Activity of Medicinal Plants in Wound. *Molecules*, *27*(11), 1–30.

Wang, B., Qu, J., Luo, S., Feng, S., Li, T., Yuan, M., Huang, Y., Liao, J., Yang, R., & Ding, C. (2018). Optimization of ultrasound-assisted extraction of flavonoids from olive (olea europaea) leaves, and evaluation of their antioxidant and anticancer activities. *Molecules*, *23*(10). https://doi.org/10.3390/molecules23102513

Widodo, H., Sismindari, Asmara, W., & Rohman, A. (2020). Antioxidant activities of methanolic extract and its fractions of Baccaurea racemosa and Macaranga subpeltata leaves. *Food Research*, *4*(1), 127–134. https://doi.org/10.26656/fr.2017.4(1).144

Woo, W. M. (2019). Skin structure and biology. *Augmented Customer Strategy: CRM in the Digital Age*, 1–14.

Yaliwal, R. G., Biradar, A. M., Kori, S. S., Mudanur, S. R., Pujeri, S. U., & Shannawaz, M. (2020). Menstrual Morbidities, Menstrual Hygiene, Cultural Practices during Menstruation, and WASH Practices at Schools in Adolescent Girls of North Karnataka, India: A Cross-Sectional Prospective Study. *International Journal of Microbiology*, *2020*. https://doi.org/10.1155/2020/8897338

Yamashita, K., Tagawa, R., Higami, Y., & Tokunaga, E. (2020). Noninvasive and safe cell viability assay for breast cancer MCF-7 cells using natural food pigment. *Biology*, *9*(8), 1–14. https://doi.org/10.3390/biology9080227

Yang, L., Wen, K. S., Ruan, X., Zhao, Y. X., Wei, F., & Wang, Q. (2018). Response of plant secondary metabolites to environmental factors. *Molecules*, *23*(4), 1–26. https://doi.org/10.3390/molecules23040762

Yao, Z., Niu, J., & Cheng, B. (2020). Prevalence of Chronic Skin Wounds and Their Risk Factors in an Inpatient Hospital Setting in Northern China. *Advances in Skin and Wound Care*, *33*(9), 1–10. https://doi.org/10.1097/01.ASW.0000694164.34068.82

You, L., Bin, P., Yan, L., Yanan, W., & Zhenqiang, W. (2018). SC. *Process Biochemistry*. https://doi.org/10.1016/j.procbio.2018.08.003

Zain, M. S. C., Lee, S. Y., Sarian, M. N., Fakurazi, S., & Shaari, K. (2020). In vitro wound healing potential of flavonoid c-glycosides from oil palm (Elaeis guineensis jacq.) leaves on 3t3 fibroblast cells. *Antioxidants*, *9*(4). https://doi.org/10.3390/antiox9040326

Zainol, S., Basri, M., Basri, H. Bin, Shamsuddin, A. F., Abdul-Gani, S. S., Karjiban, R. A., & Abdul-Malek, E. (2012). Formulation optimization of a palm-based nanoemulsion system containing levodopa. *International Journal of Molecular Sciences*, *13*(10), 13049–13064. https://doi.org/10.3390/ijms131013049

Zewail, M., E. Gaafar, P. M., Ali, M. M., & Abbas, H. (2022). Lipidic cubic-phase leflunomide nanoparticles (cubosomes) as a potential tool for breast cancer management. *Drug Delivery*, *29*(1), 1663–1674. https://doi.org/10.1080/10717544.2022.2079770

Zhang, L., Li, J., Tian, D., Sun, L., Wang, X., & Tian, M. (2020). Theranostic combinatorial drug-loaded coated cubosomes for enhanced targeting and efficacy against cancer cells. *Cell Death and Disease*, *11*(1), 1–12. https://doi.org/10.1038/s41419-019-2182-0

Zheng, D., Huang, C., Huang, H., Zhao, Y., Khan, M. R. U., Zhao, H., & Huang, L. (2020). Antibacterial Mechanism of Curcumin: A Review. *Chemistry and Biodiversity*, *17*(8). https://doi.org/10.1002/cbdv.202000171

Zhou, T., Xu, D. P., Lin, S. J., Li, Y., Zheng, J., Zhou, Y., Zhang, J. J., Li, H. Bin, & Chatel, G. (2017). Ultrasound-assisted extraction and identification of natural antioxidants from the fruit of Melastoma sanguineum Sims. *Molecules*, *22*(2), 1–15. https://doi.org/10.3390/molecules22020306