EVALUATION OF *Mitragyna speciosa* (Korth.) Havil EXTRACT-BASED NANOSTRUCTURED LIPID CARRIERS INCORPORATED INTO HYDROGEL FILM FOR WOUND HEALING

By

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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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The evaluation of *Mitragyna speciosa* (Korth.) Havil (MS) extract as an active ingredient in nanostructured lipid carriers incorporated into hydrogel film (MS-NLC hydrogel) for wound healing were reported herein. MS extract demonstrated advantageous characteristics such as low toxicity, anti-inflammation, antioxidant, and antibacterial that may facilitate the mechanisms of the wound healing process but low biocompatibility and bioavailability. Overcoming the skin's robust barrier function to transport the active ingredients to the target site in an adequate and optimal concentration is the challenging element. Hence, a nanohybrid system, MS-NLC hydrogel was used because of its nanosized, stability and low toxicity that will improve the effectiveness of skin absorption and encapsulation for transdermal drug delivery. In this study, MS extract yielded (19.92%) using maceration method. The extract contained phytochemicals such as alkaloids (mitragynine, 7-hydroxymitragynine, speciogynine), flavonoids (quercetin, apigenin, kaempferol), saponins (daucosterol, quinovic acid 3-o-beta-d-quinovopyranoside, 1-o-feruloyl-beta-d-glucose) and other bioactive phytochemicals (chlorogenic acid, umbelliferone, ursolic acid). The quantitative analysis showed that 52.8% of mitragynine compound was obtained from the MS extract. The flavonoid, phenolic content and DPPH assay of MS extract were 50.43 ± 0.47 mg GAE/g, 90.88 ± 0.30mg QE/g and IC_{50} at 0.0397±0.0035 mg/mL, respectively. Based on the screening assessment of MS-NLC, the maximum solubility in liquid lipid was 2.859 ±0.010 mg/mL whereas drug entrapped efficiency (%) in solid lipid was 53.02 ±0.39% and Tween 80 (51.53 %) was selected as the main surfactant. The optimum formulation using response surface methodology (RSM) of MS-NLC was 5.0 % (w/w) of MS extract, 3.0 % (w/w) of oleic acid: compritol 888 ATO, 60 min of reaction time and 9400 rpm of homogenizer stirring rate.

The particle size, PDI and zeta potential of MS-NLC hydrogel was 130.00 ± 0.18 nm, 0.25 PDI and -33.0mV, respectively. MS-NLC hydrogel showed highest swelling ratio (349%), gel fraction (28.89%) and shear thinning behaviour which appropriate design for wound healing. The best temperature for storing with maintained nanoparticle size of MS-NLC hydrogel was at 25 ^{o}C (132.55 ± 1.6 nm). In antimicrobial study, MS-NLC hydrogel showed the strongest inhibitory activity level against *S. aureus* (19.20 ± 0.2 mm) whereas low inhibition towards hyaluronidase activity (2.33 1.07%). After 24h scratch assay treatment using 3T3 fibroblast cells, MS-NLC hydrogel (64.21%) demonstrated improvement in the cell migration with non-toxic effect (IC_{50} > 500 µg/mL. The *in vivo* nanotoxicity test revealed that MS-NLC hydrogel were non-toxic towards zebrafish embryo with LC_{50} > 500 µg/mL. Besides, the *in vitro* permeation study of MS-NLC hydrogel (90.40 %) showed improvement of permeation and able to sustained the release of MS extract over 24 h.

Keywords: *Mitragyna speciosa*, nanostructured lipid carriers, transdermal drug delivery, wound, hydrogel

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

PENILAIAN EKSTRAK *Mitragyna speciosa* (Korth.) Havil -PEMBAWA LIPID NANOSTRUKTUR YANG DIMASUKKAN KE DALAM FILEM HIDROGEL UNTUK PENYEMBUHAN LUKA

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Penilaian ekstrak *Mitragyna speciosa* (Korth.) Havil (MS) sebagai bahan aktif dalam pembawa lipid berstruktur nano yang dimasukkan ke dalam filem hidrogel (MS-NLC hidrogel) untuk penyembuhan luka telah dilaporkan di sini. Ekstrak MS menunjukkan ciri-ciri berfaedah seperti ketoksikan rendah, anti-keradangan, antioksidan, dan antibakteria yang boleh memudahkan mekanisme proses penyembuhan luka tetapi sifat biokompatibiliti dan bioavailabiliti yang daripada ekstrak MS akan menyukarkan penyerapan ubat ke dalam kulit. Mengatasi fungsi penghalang teguh kulit untuk mengangkut bahan aktif ke tapak sasaran dalam kepekatan yang mencukupi dan optimum adalah elemen yang mencabar. Oleh itu, sistem nanohibrid MS-NLC hidrogel digunakan kerana saiz nano, kestabilan dan ketoksikannya yang rendah akan meningkatkan keberkesanan penyerapan dan enkapsulasi kulit untuk penghantaran ubat transdermal. Dalam kajian ini, ekstrak MS menghasilkan (19.92%) menggunakan kaedah maserasi. Ekstrak tersebut mengandungi fitokimia seperti alkaloid (*mitragynine, 7-hydroxymitragynine, speciogynine*), flavonoid (*quercetin, apigenin, kaempferol*), saponin (*daucosterol, asid quinovic 3-o-beta-d-quinovopyranoside, 1-o-feruloyl-beta- d-glukosa*) dan fitokimia bioaktif lain (asid klorogenik*, umbelliferone,* asid ursolik*).* Analisis kuantitatif menunjukkan bahawa 52.8% sebatian *mitragynine* diperoleh daripada ekstrak *MS*. Ujian flavonoid, kandungan fenolik dan ujian DPPH ekstrak MS ialah 50.43 ± 0.47 mg *GAE*/g, 90.88 ± 0.30mg *QE*/g dan IC_{50} pada 0.0397±0.0035 mg/mL, masing-masing. Berdasarkan penilaian saringan MS-NLC, keterlarutan maksimum dalam lipid cecair ialah 2.859 ±0.010 mg/mL manakala kecekapan terperangkap dadah (%) dalam lipid pepejal ialah 53.02 ±0.39 % dan Tween 80 (51.53 %) telah dipilih sebagai surfaktan utama untuk penyediaan NLC.

Rumusan optimum MS-NLC menggunakan metodologi permukaan tindak balas (RSM) ialah 5.0 % (b/b) ekstrak MS, 3.0 % (b/b) asid oleik: compritol 888 ATO, 60 minit masa tindak balas dan 9400 rpm kadar kacau *homogenizer*. Saiz zarah, PDI dan potensi zeta oleh MS-NLC hidrogel masing-masing ialah 130.00 ± 0.18 nm, 0.25 PDI dan -33 mV. Dalam kajian tingkah laku, hidrogel MS-NLC menunjukkan nisbah bengkak tertinggi (349%), pecahan gel (28.89%) dan tingkah laku penipisan ricih yang sesuai dengan reka bentuk untuk penyembuhan luka. Suhu terbaik untuk menyimpan dengan saiz nanopartikel oleh MS-NLC hidrogel adalah pada 25 °C (132.55 ± 1.6 nm). Dalam kajian antimikrobial, MS-NLC hidrogel menunjukkan tahap aktiviti perencatan terkuat terhadap *S. Aureus* (19.20 ± 0.2 mm) manakala rendah pada aktiviti perencatan *hyaluronidase* (2.33 1.07 %). Selepas rawatan ujian calar 24 jam menggunakan sel fibroblas 3T3, MS-NLC hidrogel (64.21%) menunjukkan peningkatan dalam penghijrahan sel dan menunjukkan kesan bukan toksik (IC_{50} > 500 µg/mL). Ujian nanotoksisiti *in vivo* mendedahkan bahawa MS-NLC hidrogel adalah tidak toksik terhadap embrio ikan zebra dengan LC_{50} > 500 µg/mL. Selain itu, kajian resapan *in vitro* MS-NLC hidrogel (90.40 %) menunjukkan peningkatan resapan dan mampu mengekalkan pembebasan ekstrak MS selama 24 jam.

Kata kunci: *Mitragyna speciosa*, pembawa lipid nanostruktur, penghantaran ubat *transdermal*, luka, hidrogel

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LIST OF ABBREVIATIONS

µg	Microgram
µL	Microlitre
µm	Micrometer
3,6-AG	3,6-Anhydrogalactose
AAC	Acrylic Acid
Bp	Boiling Point
CAE	Catechin Equivalents
CCRD	Central Composite Rotatable Design
COM	Compritol 888 ATO
DETC	Dendritic Epidermal T-Cells
DMSO	Dimethyl Sulfoxide
DP	Degree Of Polymerization
DPPH	2,2-Diphenyl-1-Picrylhydrazyl
ECM	Extracellular Matrix
ED_{50}	Effective Dose
EG	Ethylene Glycol
EGF	Epidermal Growth Factor
FGF	Fibroblast Growth Factor
FGF-7	Fibroblast Growth Factor 7
FTIR	Fourier-Transform Infrared
g	Gram
GE	Quercetin Equivalent
h	Hour

HA	Hyaluronic Acid
HACC	2-Hydroxypropyl Trimethylammonium Chloride Chitosan
HEK-293	Human Embryonic Kidney
HeLa	Hela Chang Liver
HLB	Hydrophilic–Lipophilic Balance
hpf	Post-Fertilization
HPH	High-Pressure Homogenization
HRP	Horseradish Peroxidase
IC_{50}	Half-Maximal Inhibitory Concentration
IPN	Interpenetrating Polymer Network
kg	Kilogram
L	Litre
LC_{50}	Lethal Concentration 50
LD_{50}	Median Lethal Dose
M-CMCS	Modified Carboxymethyl Chitosan
mg	Milligram
MIC	Minimum Inhibitory Concentrations
min	Minutes
mL	Millilitre
mm	Millimeter
MS	*Mitragyna Speciosa*
MS-NLC hydrogel	*Mitragyna Speciosa* Extract-Based Nanostructured Lipid Carriers Incorporated Hydrogel Film
N-CMC	N-Carboxymethylchitosan
NLC	Nanostructured Lipid Carriers

NMP	N-Methyl Pyrrolidone
NPC	Nasopharyngeal Carcinoma
OA	Oleic Acid
O-HES	Oxidized Hydroxyethyl Starch
PAA	Polyacrylic Acid
PAM	Polyacrylamide
PAMPA	Parallel Artificial Membrane Permeability Assay
PAM-SA	Polyacrylamide/Sodium Alginate
PDGF	Platelet-Derived Growth Factor
PDI	Polydispersity Index
PE	Pericardial Edema
PEG	Poly (Ethylene Glycol)
PVA	Polyvinyl Alcohol
PVAc	Polyvinyl Acetate
QAE	Gallic Acid Equivalents
ROS	Reactive Oxygen Species
rpm	Revolution Per Minute
RSM	Response Surface Methodology
S	Saturated Fat
SA	Sodium Alginate
SBL	Short Body Length
SLB	Solid-Liquid Binary Lipids
SLN	Solid Lipid Nanoparticles
TDD	Transdermal Drug Delivery

TFC	Total Flavanoid Contents
TGF	Transforming Growth Factor
TPC5	Total Phenolic Content
UAE	Ultrasound Assisted Extraction
UV	Ultraviolet
UV-Vis	Ultraviolet-Visible
US	Unsaturated Fat
WHO	World Health Organization
WVTR	Water Vapor Transmission Rate
YE	Yolk Edema

CHAPTER 1

INTRODUCTION

1.1 Background Study

In recent years, there has been growing interest in alternative therapies and the therapeutic use of natural products, especially those derived from plants. This interest in drugs of plant origin is due to several reasons, namely, conventional medicine can be inefficient in terms of their side effects and toleration. Therefore, the modern social context and economic view of health services, the needs of the pharmaceutical market and the recognition that research on medicinal plants represents a suitable approach for the development of new drugs (Guzeldag, 2013). Based on several studies, medicinal plants contain compounds like peptides, unsaturated long chain fatty acids, aldehydes, alkaloids, essential oils, phenols and water or ethanol soluble compounds. These compounds are significant in therapeutic application against human and animal pathogens, including bacteria, fungi and viruses. Numerous drug resistances in human pathogenic microorganisms have developed due to the indiscriminate use of commercial antimicrobial drugs commonly used in the treatment of infectious diseases. On the other hand, free radicals are known to be the major cause of various chronic and degenerative diseases. Oxidation is a natural process in organisms for the production of energy to fuel biological cycles. Conversely, the uninhibited production of oxygen-derived free radicals is involved in the onset of many diseases such as arthritis, atherosclerosis, rheumatoid and cancer as well as in many degenerative diseases related with aging. This situation has prompted the continuous search for various plant sources with these medicinal values (Parthasarathy et al., 2010).

Natural products, such as plant extract, either as pure compounds or as standardized extracts, provide unlimited opportunities for new drug discoveries because of the unmatched chemical diversity the can provide. According to the World Health Organization (WHO), more than 80% of the world's population relies on traditional medicine for their primary healthcare needs. This has captured the interest of many researchers to explore local medicinal plants for valuable medicinal traits (Parthasarathy et al., 2009). Currently, the use of medicinal plants as an alternative medicine for various treatment has increased tremendously due to their positive effects. This include a potential plant-based source, *mitragyna speciosa* (MS) leaf or also known as kratom leaf which has been traditionally used for fever, diarrhoea, hypertension and for wound therapy (Ramanathan et al., 2015). MS demonstrated beneficial medicinal properties such as antioxidant, anti-inflmmatory and antimicrobial. It contained various phytochemicals, including alkaloids, flavonoids, and polyphenols, which are known to possess antioxidant properties (Parthasarathy et al., 2009; Limcharoen et al., 2022). These compounds scavenge free radicals and inhibit oxidative damage to biomolecules. These compounds help in neutralize the harmful free

radicals in the body, reducing oxidative stress and protecting cells from damage. MS alkaloids such as mitragynine and 7-hydroxymitragynine, are believed to contribute to its pharmacological effects. Some research suggests that these alkaloids may possess anti-inflammatory properties by modulating immune responses and inflammatory pathways (Tohar et al., 2019). Apart from that, study reported that MS extract may exhibit antibacterial effects against a range of bacterial strains, including both Gram-positive and Gram-negative bacteria mediated by the presence of bioactive compounds such as alkaloids (Suhaimi et al., 2019; Rahman et al., 2022). The major alkaloid of MS, mitragynine is a weak base with poor solubility in water (hydrophobic) and basic media, and conversely in acidic environments (Ramanathan et al., 2015). In addition, MS showed low biocompatibility and bioavaibility (large molecule, poor absorption, low aqueous solubility) that may hinder their effective delivery to the intended site of action into the skin. MS extract showed extremely low permeability indicated that they were poorly absorbed through semi-permeable membrane due to its ionized state (Wai et al., 2017). Therefore, a proper mechanism vehicle should be applied so that the MS extract could benefits fully in the treatment of wound healing.

Nanodelivery systems are a class of drug delivery platforms that utilize nanotechnology to improve the delivery, targeting, and release of therapeutic agents (Mirza et al., 2014). These systems employ nano-sized carriers or nanoparticles to encapsulate drugs, vaccines, genes, or diagnostic agents, offering several advantages over traditional delivery methods. These systems encompass a wide range of platforms, including liposomes, polymeric nanoparticles, micelles, dendrimers, and nanostructured lipid carriers (NLC). These platforms can be tailored in terms of size, shape, surface properties, and payload to optimize drug delivery for specific applications. Furthermore, the system offers solutions to challenges such as drug resistance, limited bioavailability, and off-target effects (Jahangirian et al., 2017), thus holding great promise for advancing the treatment of various diseases. Nanotechnology plays a signifcant role in advanced medicine and drug formulations, targeting arena and their controlled drug release and delivery with immense success. However, it is difficult to precisely tailor the properties of these carrier systems. The solution may however, lies in the protocol followed for the selection of the formulation components as well as optimization. Among the different nanoparticulate systems, lipid nanocarriers hold the distinct position in drug delivery. Lipid nanocarriers include a number of different formulations such as nanoemulsions (Rajpoot et al., 2011), microemulsions (Mehta and Kaur, 2010), micro emulsifying system (Patel and Sawant, 2009), solid lipid nanoparticles (Müller et al., 2000) and nanostructured lipid carriers (Fang et al., 2013). Such particles offer many advantages over other nanoparticles with wide range of materials to be selected as per requirement. Most of the lipids used for the manufacture of these particles are of GRAS category and have low toxicity concerns.

An advanced carrier system technology such as nanostructured lipid carriers (NLC) are suitable candidate. Nanostructured lipid carriers (NLC) contain both solid liquid and liquid lipids in defined proportion. NLC demonstrated good biocompatibility, small particle size, high drug entrapment efficiency and low toxicity helps better skin penetration (Grag et al., 2022). However, the

development of NLC system may include screening of various components like type of solid lipid, type liquid lipid, ratios of solid to liquid lipid, type of surfactant due to the availability of a wide range of lipids, oils and surfactant, screening of these components is a cumbersome process. Apart from development, lipid nanoparticles are also associated with some serious quality issues such as polymorphic changes in lipids, gelation, presence of supercooled melts, presence of different colloidal species and sterilization stability (Mehnert and Mäder, 2001). The lipids which are used in the nano lipid formulations have different polymorphs. During the formulation the lipid crystallizes into imperfect but unstable polymorph, which in due course of time during storage get converted to more stable and finally to polymorphs. These stable polymorphs are more perfect in structure as compared to unstable polymorphs. Hence, such polymorphic changes may lead to the expulsion of the drug incorporated in lipid imperfections. Gelation is a common problem with lipid formulations, which leads to the formation of high viscosity gel from non-viscous particle suspension. Such physical changes may lead to the loss of whole purpose of development of nanoparticles. Furthermore, it could prove fatal if develop during the intravenous administration. Besides, supercooled melts may be described as the phenomenon in which the lipid may fail to crystallize even when stored at the temperature below its melting point. Such formulations are not solid nanoparticles but nanoemulsions and hence loose the potential advantages associated with the solid lipid (Mehnert and Mäder, 2001). To maximize the sustained released into the skin, NLC was incorporated into hydrogel film system.

Moreover, the transdermal delivery system seems like the most sensible approach to minimize adverse effects and improve patient compliance. The unique feature of hydrogel makes them soft and wet materials with both solids and liquids characteristics, such as a large amount of free water and potentially soluble molecules that can diffuse in and out of the hydrogels (Francesko et al., 2018). Hydrogels can encapsulate and release therapeutic agents, including drugs, proteins, and growth factors, in a controlled and sustained manner. The porous structure of hydrogels facilitates drug diffusion, while their biocompatibility and ability to protect drugs from degradation make them ideal for drug delivery applications. Hydrogels are mainly composed of water-swollen polymer networks, mimicking the natural environment of living tissues. They are biocompatible and exhibit low cytotoxicity, making them suitable for use in biological systems without causing significant adverse effects. Plus, the higher water content similar to natural tissues of the hydrogel, demonstrated good hydration and supportive environment for cells (Broussard et al., 2013). This water retention property promotes cell proliferation, migration, and tissue regeneration, making hydrogels valuable for wound healing and tissue engineering applications. In addition, hydrogel's wide variety of biocompatible matrices and biologically active materials such as chitosan, cellulose, starch, alginate, and neutralized polyacrylic acid (PAA), hydrogel-based wound dressings are currently of great interest to scientists all over the world (Zhang and Zhao, 2020). These natural polymer has attracted many researchers because of their unique properties such as low toxicity, biocompatibility, and biodegradability. The hybrid system of the nanotechnology used, nanostructured

lipid carriers and hydrogel film would suggest to give an excellent penetration and desirable results for future transdermal drug delivery. For best of our knowledge, there are limited studies on the evaluation of *mitragyna speciosa* extract-based nanostructured lipid carriers incorporated hydrogel film (MS-NLC hydrogel) for wound healing. The research includes a hybrid system, nanotechnology from nanostructured lipid carriers and hydrogel film for sustained release application. Therefore, the investigation mechanism of MS-NLC hydrogel for wound healing may be advantages for future research. In this research, the formulation and optimization of MS-NLC was carried out using Response Surface Methodology (RSM) to study the interaction between parameters effected towards particle size. The small particle size, large surface area, and high drug loading capacity (Stoica et al., 2020) of NLC make it crucial component in drug delivery for wound healing. These characteristics allow NLC to effectively encapsulate and deliver the healing agent to the wounded skin. Besides, the small particle size of NLC accelerates and enhances the healing effect, and can be engineered to deliver the wound healing agent in a controlled manner, thereby reducing side effects and optimizing therapeutic advantages (Wang et al., 2018). The design of hydrogel film was carried out to maximize the delivery of the drugs into skin and was further characterized for its physicochemical properties. Pharmacology and toxiclogy studies of MS-NLC hydrogel was evaluated for its suitability in wound healing. The highlighted of this study is expected to provide a new discovery in the drug delivery system involving the narcotic species, *mitragyna speciosa* (MS) extract using a hybrid system of nanostructured lipid carriers and hydrogel film system for further application in wound healing. The advent of nanotechnology has provided the useful tools to develop superior drug delivery systems for catering the needs of modern era. It has always been an area of fascination among the formulators to develop the carrier systems with precise control over their characteristics.

1.2 Problem Statements

The development of *mitragyna speciosa* (MS) as the active ingredient in nanostructured lipid carriers system incorporated into hydrogel film for wound healing is the subject of considerable research. MS showed good properties of antioxidant, anti-inflammation, antimicrobial and low toxicity (Sabetghadam et al., 2013; Parthasarathy et al., 2009) that could facilitate on the mechanism and mediators of the wound healing process. However, MS has its limitation to deliver the active ingredients into skin. MS showed low biocompatibility and bioavaibility (large molecule, poor absorption, low aqueous solubility) that may hinder their effective delivery to the intended site of action into the skin. Previous study from Wai et al., 2017 suggested that from PAMPA assay (parallel artificial membrane permeability assay), mitragynine (main compound in mitragyna speciosa) and mitragyna speciosa alkaloid extract showed extremely low permeability indicated that they were poorly absorbed through semi-permeable membrane due to its ionized state. Therefore, formulation containing the biological active ingredient of MS must be stable and suitable for consumers use. The challenging part of transdermal drug delivery is to overcome the strong barrier function of the skin to deliver the active ingredients to the target site with sufficient and optimum concentration. Thus, appropriate formulation, characteristic and behaviour of the transdermal drug delivery must be studied.

Transdermal delivery system using hydrogel seems like the most sensible approach to minimize adverse effects, improve patient compliance and maximize the sustained released into the skin. However, MS is hydrophobic drug and has low aqueous solubility (Ramanathan et al., 2015) so it could not directly formulate into MS hydrogel. Thus, combination with a lipid nanocarrier such as NLC is preferred for maximum benefits. Nanohybrid system of nanostructured lipid carriers (NLC) and hydrogel system is chosen to encapsulated MS because the nanosized particle will give effective delivery for skin absorption (less than 200 nm), better encapsulation, stable in size and stability towards recrystallization and low toxicity (Schwarz et al. 2012) whereas the large spaces in the hydrogel film networks not only provide homes for a huge number of nanoparticles but also work as nanoreactors for their synthesis (Wahid et al., 2017). The polymeric hydrogels act like a “host” that can accommodate NLC as a “guest” to form hybrid system efficiently (Bhattacharya et al., 2016). In addition, factor affecting interaction between each component of the MS-NLC incorporated into hydrogel film has been individually determined thus, time consuming, and the approach of well-designed data collection process would benefit the experiments to achieve high desirable results. To date, there are limited report on the development of MS-NLC using statistical approach for optimization such as response surface methodology (RSM) experimental design. Therefore, this approach is suitable to be used for MS-NLC where it enables to predict more accurate value to the actual response plus the number of experimental run can be reduce (Taib et al., 2015).

1.3 Research Objectives

The purpose of this research was to evaluate the *mitragyna speciosa* extract-based nanostructured lipid carriers incorporated into hydrogel film for wound healing. Therefore, the following specific objectives were pursued:

1) To prepare and optimize *mitragyna speciosa* extract-based nanostructured lipid carriers

2) To examine the swelling and rheology behaviour of *mitragyna speciosa* extract-based nanostructured lipid carriers incorporated into hydrogel film

3) To characterize the physicochemical properties of the optimized *mitragyna speciosa* extract-based nanoparticles incorporated into hydrogel film

4) To evaluate the wound healing properties of the *mitragyna speciosa* extract-based nanostructured lipid carriers incorporated into hydrogel film

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