A DISSERTATION ON

DERMAL PATCH DEVELOPMENT WITH UV- PROTECTIVE AND WOUND-HEALING ACTIVITIES

SUBMITTED TO THE
DEPARTMENT OF BIOENGINEERING
FACULTY OF ENGINEERING
INTEGRAL UNIVERSITY, LUCKNOW

IN PARTIAL FULFILMENT
FOR THE
DEGREE OF MASTER OF TECHNOLOGY
IN
BIOTECHNOLOGY
BY

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(M.Tech Biotechnology) (IV Semester),
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UNDER THE SUPERVISION OF

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DECLARATION FORM

I, **Upasana Rawat**, a student of **(M. Tech Biotechnology)** (2^{nd} year / IV Semester), Integral University have completed my six months dissertation work entitled **"Dermal patch development with UV protective and wound healing activities"** successfully from **Place of work** under the able guidance of **Dr. Iffat Zareen Ahmad.**

I, hereby, affirm that the work has been done by me in all aspects. I have sincerely prepared this project report and the results reported in this study are genuine and authentic.

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CERTIFICATE BY SUPERVISOR

This is to certify that Ms. **Upasana Rawat** (Enrollment Number 2100101620) has carried out the research work presented in this thesis entitled **"Dermal patch development with UV protective and wound healing activities"** for the award of **(M. Tech Biotechnology)** from Integral University, Lucknow under my/our supervision. The thesis embodies results of original work and studies carried out by the student herself and the contents of the thesis do not form the basis for the award of any other degree to the candidate or to anybody else from this or any other University. The dissertation was a compulsory part of her **(M. Tech Biotechnology)**.

I wish her good luck and bright future.

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TO WHOM IT MAY CONCERN

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I wish her good luck and bright future.

Dr. Alvina Farooqui
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ACKNOWLEDGEMENT

First of all, I bow in reverence to the Almighty for blessing me with strong will power, patience and confidence, which helped me in completing the present work.

At the very outset I pay my warm thanks to our Honorable **Chancellor and Founder, Integral University, Lucknow. Prof. S.W Akhtar** for providing excellent infrastructure and Lab facilities at IIRC-7 Integral University, Lucknow. I am also grateful to Honorable **Vice Chancellor Integral University, Lucknow. Prof. Javed Musarrat** for his continuous motivation and a Special vote of thanks to **Pro chancellor, Dr. Nadeem Akhtar** for his encouragement and support.

I would like to express my special thanks to **Dr. (Er.) Alvina Farooqui (Head, Department of Bioengineering)** for given me an opportunity to join the department laboratory and providing all the necessary facilities ever since I started my work.

I would I like to express my deep sense of gratitude to my **Supervisor Dr. Iffat Zareen Ahmad (Professor), Internal advisor, and Course coordinator Dr. Salman Akhtar (Associate Professor)** for their invaluable guidance throughout the course of my dissertation work and academic session. It would have been impossible to complete this work in so short a time without her constant guidance.

I would like to thank respected dissertation coordinator **Dr. Roohi** for their continuous support and help.

My acknowledgement will be incomplete if I do not mention my parents and my friends with whose blessing; I was able to achieve my goal successfully. There are no words to express my feelings toward them. I silently acknowledge my debt to them.

Upasana Rawat

TABLE OF CONTENTS

LIST OF ABBREVATIONS

Abbrevation	Full form
COM	*Cydonia oblonga*Miller
UV	Ultravoilet
MAA	Mycosporine-like amino acids
SOS	Save our souls
ROS	Reactive oxygen species
SOD	Superoxide dismutase
ZnO	Zinc oxide
EDTA	Ethylenediamine tetraacetic acid
PEO	Plasma electrolyte oxidation
FBS	Fetal bovine serum
GPS	Gastroesophageal reflux
ME	Microemulsion
NE	Nanoemulsion
LPL	Lipoprotein lipase
UV	Ulcer index value
UC	Ulcerative colitis
RBC	Red blood cells
C6H18O9	Chlorogenic acid
VH	Vascular hypertrophy
NO	Nitrogen monooxide
XO	Xanthine oxidase
IgE	Immunoglobulin E
RBL	Rat basophilic leukaemia
HexB	Hexosaminidase B
HW	Hot water
QMC	Quince seed mucilage
HaCaTs	Cultured human keratinocyte (cells)
DMEM	Dulbecco’s modified eagle medium
PDI	Poly dispersity index

1. INTRODUCTION

The goal of this research is to development of dermal patch with UV- protective and wound healing activities. Formulation of dermal patch by using cynobacteria which have UV protection properties and also it includes in vivo study which was carried on rat by using the drug loaded and unloaded composite transdermal patch. In order to restore the skin's barrier function, wound healing is essential. There are four steps to this intricate process: hemostasis, inflammation, proliferation, and tissue healing. During the healing process, the cells in the wound bed must multiply and move. This migration phase is the rate-limiting event in wound healing (Gefen *et al*., 2019).

The skin is the largest organ in the body in terms of surface area. It is an essential component that shields inside organs from mechanical damage, UV radiation, microbial infection, and heat shock. Normal living entities are incapable of regenerating new tissue. Although there are many wound healing treatments available, most are only partially effective (Eming *et al.,* 2014). Consequently, there is a need for stronger wound healing therapies. To repair a skin wound, various cell types within these three layers must work together at particular phases. As a result, repair of damaged organs necessitates a multi-step procedure that involves migration of collagen and inflammatory cells, cytokine activity, the deposition of extracellular matrix, and scar remodeling (Gilbert ME *et al*., 2004). To facilitate and speed up wound healing, a number of intricate and redundant systems cooperate (Singer *et al*., 1999). When the skin's regenerating capacities are impaired and wounds cannot heal physiologically, the healthcare system may be severely burdened in some cases.

Wounds that take longer than 90 days to heal are referred to as chronic wounds (Vasconcelos *et al*., 2011). Large burns and diabetic wounds are two examples of chronic wounds; they require many surgical procedures since they are expensive, difficult to heal, and more likely to become infected. The cost of treating chronic wounds on healthcare systems is rising each and every day due to the rising rates of diabetes and obesity (Sen *et al*., 2009). The United States Food and Drug Administration approved the first prescription patch that was commercially accessible in December 1979 and delivered scopolamine to treat motion sickness. A dermal patch, also known as a skin patch, is an adhesive patch used to apply medications to the skin. They deliver a precise, preset amount of medication that is absorbed into the bloodstream through the skin. It works fairly simple; a medicine is administered within a patch that is worn on the skin for a long period of time

in a pretty high dosage. The medicine directly enters the bloodstream through the skin through a diffusion process. The medication will continue to diffuse into the blood for a considerable amount of time, maintaining the consistent concentration of drug in blood flow, due to the high concentration on the patch and low concentration in the blood.

Parts of dermal patch includes:

a) Matrix: The drug layer in the semisolid matrix system of the matrix system contains a drug solution or suspension. This patch's sticky layer partially covers and encircles the medication layer. Likewise called a monolithic device (Michinaka and Y, 2017).

b) Reservoir: A distinct drug layer exists in the reservoir transdermal system. The adhesive layer serves as a physical barrier between the drug layer and a liquid compartment holding a drug solution or suspension. The drug reservoir is completely enclosed in a shallow compartment manufactured from a laminate of metallic plastic that is impermeable to drugs and has a membrane for rate control composed of a polymer similar to vinyl acetate on one surface.

c) Single-Layer Drug-in-Adhesive: The entire patch is made up of a single layer of adhesive that also contains the medicine dosage. This is known as a single-layer drug-in-adhesive. This layer adheres to the skin and concurrently releases the medication when applied (Hanbali *et al*., 2018).

d) Drug-in-Adhesive with Multiple Layers: This type of drug-in-adhesive is similar to one with only one layer. used most frequently for longer-term patches. As the layers closest to the skin finish delivering the medicine, diffusion will begin via the subsequent layer (Hanbali *et al*., 2018).

e) Vapour Patch: A vapour patch's adhesive layer also acts as a conduit for vapour release. The most popular uses for vapour patches, which can last up to six hours, are decongestants and sleep aids. (G. Ravi and N. Vishal Gupta, 2015).

The active or passive delivery systems are used by all five of these techniques. Passive systems are renowned for being reliable. In order to get the medication from the patch through the skin and

into the circulation, they rely on natural membrane diffusion. Active systems transfer the medicine with the help of an enhancer or additional aid. These can contain different transdermal drugs in addition to enhancers in patches (Tewabe *et al*., 2021). This part includes backing, drug, membrane, adhesive, overlaminate tape and release liner. Mary's Nutritionals Transdermal Patch, Social CBD Infused Patch, The Good Patch Hemp Queen, Dutch Natural, Healing CBD Patches for Sleep, CBD Living Patch, MUV Transdermal Patch these are some examples of the marketed transdermal patches (Lodzki *et al*., 2003).

Dermal patch benefits and drawbacks includes-Merits:1) Offers steady, long-lasting plasma drug concentrations without variations. 2) Skin drug application prevents the pH changes associated with gastrointestinal transit. 3) The drug bypasses first-pass hepatic metabolism, even though the skin is a metabolically active organ. 4) It is possible to administer oneself. 5) The transdermal patch can be removed at any time to end drug use. 6) The streamlined drug schedule results in increased patient compliance, fewer side effects, and less variation between and among patients. 7)Transdermal patches prevent the difficulty of parenteral therapy because they are noninvasive. 8) Compared to the dose of the same medicine when administered orally, an equivalent therapeutic effect can be evoked with a lower dose when delivered as a transdermal patch. 9) Similarities to intravenous infusion in terms of features. 10) Patients who feel nauseous or unconscious may choose this mode of medicine administration (Vishwakarma *et al*., 2017).

Almost always, a scar appears after a wound has healed. According to (Walmsley *et al*. 2015), excessive scarring tips the balance of hypertrophic scarring and keloid formation in favour of fibrotic states. Scarring in the healing skin may result from many cellular responses to mechanical stress, according to mounting evidence (Duscher *et al*., 2014). The type of injury has little effect on this process, which varies little from tissue to tissue. Traditional remedies with a natural origin, such as plant extracts, honey, and larvae, are fascinating options. These therapies open up new treatment options for skin conditions while enhancing patient access to healthcare and removing some of the disadvantages of modern products and therapies, such as their high costs, drawn-out manufacturing processes, and rise in bacterial resistance (Souto *et al*., 2011). Different plant components, including roots, flowers, fruits, leaves, and seeds, have historically been used regularly to treat a variety of difficulties because of the secondary metabolites contained in plants, such as tannins, terpenoids, alkaloids, and other chemicals (Harborne *et al*., 1999). In the past,

people have utilized quince extracts as nutritional supplements as a kind of treatment for inflammatory and infectious disorders (Church *et al*., 2013). According to Sadeghi Mahoonak *et al*. (2017), mucilage from quince seeds has long been utilized as a home treatment for wound healing.

Cyanobacteria that produce oxygen belong to the genus *Scytonema*. Dark mats are formed as it grows in filaments. A promising UV-screen and antioxidant small molecule is *Scytonemin*. The second main family of UV-absorbing chemicals in cyanobacteria, *Scytonemin* is a lipid-soluble, yellow-brown pigment that is only present in some cyanobacteria (Vega *et al*., 2021). It offers protection against UV radiation due to its potential to absorb considerably at 384, 300, 278 and 252 nm. In certain but not all cyanobacteria, *Scytonemin*, a lipid-soluble, extremely stable, yellow-brown secondary metabolite, accumulates in the extracellular polysaccharide sheath and functions as a photoprotectant in response to UV-A radiation stress (UV-A; 315-400nm). A potential natural UV sunscreen and antioxidant for skin protection, *Scytonemin* demonstrates acceptable levels of radical scavenging activity (Gao *et al*., 2011).

Dermatologists are highly interested in this because, unlike synthetic sunscreen chemicals, it has evolved via a selection process that makes it appropriate for human usage. MAAs and *Scytonemin*, which are produced by cyanobacteria and have the ability to reduce toxicity, are UV-protecting compounds. With the use of photo, excision, recombination, and repair processes, cyanobacteria are able to fix UV-induced DNA damages (Pathak *et al*., 2019). Cell death and the SOS response both affect cyanobacteria's ability to withstand stress. *P. Murrayi* (*Pericallis murrayi* plant) was found to grow linearly as UV-A levels rose when grown under white light and both UV-A and UV-B radiation (Quesada *et al*., 1995). The UV-B inhibition was also found to be at balancing the processes of damage and repair.

It appears that cyanobacteria have a stress tolerance mechanism because they are the most environmentally successful prokaryotes on Earth. Cyanobacteria are able to produce secondary metabolites with substantial bioactivity in addition to being UV protective, cytotoxic, antibacterial, anticancer, antiviral, antifungal, antimalarial, anti-inflammatory, antiprotozoal, and antituberculosis (Rosic *et al*., 2021).

Cyanobacteria were present on Earth during the absence of oxygen billions of years ago. Cyanobacteria have developed a range of defensive mechanisms, including the creation of proteins, antioxidants, and UV-protective chemicals, to shield themselves from the impacts of UV radiation (Baracaldo *et al*., 2022). Cyanobacterial metabolites are utilized in a number of ways by the pharmaceutical and biotechnology industries. In the creation of nanoparticles, proteins, pigments, flavonoids, and plant extracts are frequently employed (Khalifa *et al*., 2021). Long-term UV exposure damages the skin in a number of ways, including by causing sunburn, wrinkles, skin ageing, hyperpigmentation, and even skin cancer. The good news is that UV rays can be reduced by following a few simple safety measures. Blue-green algae contains some of the chemicals used in cosmetic products. Because cyanobacteria can hold onto water and create UV protecting chemicals, they can be used to make natural UV filters and moisturizers (Derikvand *et al*., 2017). Additionally, they contain a lot of antioxidants, which aid in scavenging free radicals (Singh *et al*., 2004).

A medicinal plant from the Rosaceae family called *Cydonia oblonga* Mill. is used to cure a number of diseases like cancer, diabetes, hepatitis, ulcers, lung and urinary infections, among others. Secondary metabolites include phenolics, steroids, flavonoids, terpenoids, tannins, sugars, organic acids, and glycosides are abundant in quince (García and Barrachina, 2020). The pharmacological effects of various portions of *C. oblonga* (CO) include antioxidant, antibacterial, antifungal, anti-inflammatory, hepatoprotective, cardiovascular, antidepressant, antidiarrheal, hypolipidemic, diuretic, and hypoglycemic properties. In order to speed up the healing process in dermal patches, glucuronoxylan, a polysaccharide mucilage extruded from quince seeds, is utilized (Karimi *et al*., 2017). The quince tree, or *Cydonia oblonga* Miller, is a little deciduous tree. In 2000 and 2006, respectively, studies on the healing properties of quince seed mucilage on skin wounds in animal models and humans with untreated wounds were conducted. The findings showed that quince seed mucilage cured the wounds more quickly than phenytoin cream (Hemmati *et al*., 2000).

2. OBJECTIVES

1. Extraction of *Scytonemin* from *Scytonema javanicum* and *Cydonia oblonga* Mill. Extract.

2. Preparation and characterization of nano emulsion of *Scytonemin* and *Cydonia* extract.

3. Development of dermal patch prototype for clinical applications.

4. To study the weight, thickness and folding endurance properties of dermal patch.

3. REVIEW OF LITERATURE

Injuries such as abrasions, lacerations, contusions, and hematomas can disrupt the normal structure and function of tissues when the skin's epithelial integrity is compromised due to cuts or incisions caused by physical trauma (Erickson and Echeverri, 2018). The process of wound healing begins immediately after the injury occurs, and the speed of progress towards complete healing is determined by the severity of the injury, influencing the quality and appearance of the healed tissue. The stages of wound healing—hemostasis, inflammation, proliferation, and tissue remodeling or resolution—are interconnected and overlap significantly (Wilkinson and Hardman, 2020). Metabolic irregularities and underlying health conditions can impede the regeneration process, resulting in delayed recovery. This not only poses a considerable economic burden on both developed and developing economies but also drives the exploration of cost-effective alternative therapies based on native plant remedies (Tottoli *et al*., 2020). China and India, as the two largest countries in Asia, possess a wide array of recognized and significant medicinal plants. India, in particular, stands out due to its rich array of codified and indigenous knowledge about medicinal plants, as well as the substantial variations in climate, rainfall, and topography that contribute to its wealth of herbal medicines. Preserving these traditional values is essential in light of contemporary trends in therapeutic medical knowledge (Kala *et al*., 2006).

Traditional Indian medicine, especially Ayurveda, is deeply entrenched in a folk medical system that has garnered widespread acceptance. According to the World Health Organization (WHO), approximately 80% of the global population relies on natural remedies for primary healthcare. Despite this, only a fraction—around 15%—of the world's 300,000 plant species have been studied for their potential therapeutic applications (De Luca *et al*., 2012). However, India's government-established ministry for environment and forests has documented over 9500 plant species relevant to the pharmaceutical industry. The healing properties of *Cydonia oblonga*, commonly known as quince, have been recognized for wound healing since ancient times (Derakhshanfar *et al*., 2019). Additionally, cyanobacteria produce secondary metabolites with strong bioactivity, including antibacterial, antiviral, anticancer, antifungal, antituberculosis, antiprotozoal, anti-inflammatory, and antimalarial properties. Cyanobacteria were able to survive on Earth in an oxygen-free atmosphere billions of years ago (Srivastava *et al*., 2022).

3.1. Cyanobacteria

3.1.1. Description

Cyanobacteria, also known as Cyanophyta, make up a bacterial phylum that derives energy through photosynthesis. The term "cyanobacteria" is derived from their characteristic color (Greek = blue). While they are commonly referred to as blue-green algae, some experts consider this name misleading since cyanobacteria are prokaryotic, whereas algae are generally considered eukaryotic; however, alternative definitions of algae include prokaryotic organisms as well. Cyanobacteria played a significant role in altering Earth's atmosphere by generating oxygen as a byproduct of photosynthesis. This oxygen production transformed the early reducing atmosphere into an oxidizing one, resulting in profound changes to the diversity of life forms on Earth and the near-extinction of oxygen-intolerant organisms. Based on the endosymbiotic theory, chloroplasts found in plants and eukaryotic algae are believed to have evolved from ancestral cyanobacteria through endosymbiosis. Cyanobacteria represent a group of photosynthetic organisms capable of fixing nitrogen, and they thrive in diverse habitats, including soil and water. Within this group, the photosynthetic pigments include cyanophycin, allophycocyanin, and erythro-phycocyanin.

Scientific Classification

- Domain: Bacteria
- Kingdom: Eubacteria
- Phylum: Cyanobacteria

Orders:

- Unicellular forms, Chroococcales.
- Filamentous (colonial) forms, Nostocales.
- True branching (budding over multiple axes), Stigonematale.

3.1.2. UV protecting compounds of Cyanobacteria

UV-B exposure has been observed to cause significant harm to cyanobacteria and various other organisms. While cyanobacteria typically produce a small amount of oxygen forms that might be toxic, excessive levels of UV light can lead to an increased production of reactive oxygen species (ROS) due to excited photosynthetic pigments. These ROS can result in damage to the cellular membrane's polyunsaturated fatty acids and breaks in DNA strands, as seen in Anabaena sp. (Sinha and Häder, 2002). UV-B radiation can affect proteins and DNA, making them susceptible to damage. The D1 reaction center protein of PS II, Rubisco, phycobiliproteins (such as phycocyanin), and nitrogenase are frequently impacted by UV-B wavelengths.

When DNA absorbs UV-B photons, various types of damage occur, including double-stranded breaks, single-stranded breaks, DNA-protein cross-links, cyclobutane dimers, and pyrimidine-(6,4)-pyrimidone photoproducts. The energy required to counteract and repair this damage affects the cells' energy resources. Organisms exposed to UV-B tend to grow slower and reproduce less frequently than those subjected to lower UV-B levels. Cyanobacteria often avoid the detrimental effects of UV-B radiation by moving. Some species form mat communities in soil by relocating to a level where they can absorb the most light while facing minimal UV threat. Due to variations in sensitivity to UV light even among closely related cyanobacteria species (Suresh, 2017), mat communities display distinct cyanobacterial layers. Cyanobacteria defend against UV-B radiation that reaches the cells by intercepting harmful rays before they cause damage. UV-absorbing molecules are one way cyanobacteria shield themselves against UV-B photons.

Radiation involves the release of energy from a source. Ultraviolet (UV) radiation constitutes a form of electromagnetic radiation. The sun is the primary source of UV radiation, although artificial sources like tanning beds and welding torches also emit UV rays. Radiation spans a spectrum from high-energy (high-frequency) radiation like x-rays and gamma rays to low-energy (low-frequency) radiation like radio waves. In terms of energy, UV rays possess more energy than visible light but less than x-rays. While numerous researchers have reported the presence of sheath pigments in cyanobacterial species, the characteristics, physiological role, and prevalence of *Scytonemin* remain to be fully understood**.**

3.1.3. Deleterious or Harmful Effects of Ultraviolet Radiation

The harmful effects from exposure to ultraviolet (UV) radiation can be classified as acute or chronic. The acute effects of UV-A and UV-B exposure are both short-lived and reversible. These effects include mainly sunburn (or erythema) and tanning (or pigment darkening). The chronic effects of UV exposure can be much more serious, even life threatening, and include premature aging of the skin, suppression of the immune system, damage to the eyes, and skin cancer

3.2. *Cydonia oblonga*

Cydonia oblonga Mill., a member of the Rosaceae family, stands as a sole species within the monotypic genus Cydonia. The term "Cydonia" is derived from "κυδονία," originating from the ancient city "Kydo" on the Greek island of Crete, and is also associated with Dioscorides. The descriptive term "oblong" comes from the Latin word "oblongus," reflecting the shape of the quince fruit (Rather *et al*., 2020). This plant has been cultivated as a native species across the Mediterranean region for an extensive period. While commercial cultivation is primarily observed in eastern Europe and Asia Minor, it has now spread worldwide, particularly in countries like Iraq, Iran, Afghanistan, Syria, Algeria, Tunisia, as well as various nations in southern Europe, France, and Portugal (Ashraf *et al*., 2016). In India, quince is predominantly grown in regions such as Jammu and Kashmir, along with certain parts of Himachal Pradesh, often found in backyard gardens and along fence lines.

3.2.1. Bioactive Compounds of *Cydonia oblonga*

Quince is recognized as a nutraceutical fruit due to its abundance of health-promoting phytochemicals. It contains various polyphenols and polysaccharide fractions such as flavanols, tannins, ionone glycosides, and tetracyclic sesterterpenes (Pirvu *et al*., 2018). The antioxidant activity of ascorbic acid found in quince fruit has been documented by Rasheed *et al.* (2018). Chemical profiling has identified thirteen major phenolic compounds in quince fruits, including derivatives of caffeoylquinic acid (such as 5-O-caffeoylquinic, 4-O-caffeoylquinic, 3-O-caffeoylquinic, and 3,5-dicaffeoylquinic), rutin, quercetin-3-galactoside, p-coumaric acid, acetylated quercetin glycosides, and acetylated glycosides of kaempferol (Rasheed *et al.*, 2018).

HPLC analysis of fruit jams made from both peeled and unpeeled quince fruits revealed that jams from unpeeled quince contain higher flavonoid concentrations (19%) compared to those from peeled quince (3%) (Silva *et al*., 2002). Another HPAEC study identified various sugar derivatives like ribose, maltose, fructose, rhamnose, isomaltose, sucrose, D-glucose, D-trehalose, D-galactitol, and D-sorbitol, as well as a similar percentage of amino acids. The high pectin content in C. oblonga fruit is why it's predominantly used for treating irritable bowel syndrome (IBD) (Silva *et al.*, 2004).

Carotenoid pigments such as zeaxanthin, lycopene, β-cryptoxanthin, β-carotene, and lutein, found in the epidermal cells of C. oblonga fruit, exhibit potent antioxidant activity. Mass spectrometric techniques, including gas chromatography (GC) and nuclear magnetic resonance (NMR), have been utilized to identify diverse carotenoid derivatives (Lopes *et al*., 2018).

Sut *et al*. (2019) employed LC-MS with diode array detection to analyze secondary metabolites in quince pulp and peel, comparing them with a few apple cultivars. They found significant amounts of quinic acid, shikimic acid derivatives, procyanidins, and flavonoids. In pulp, 3-O-caffeoylquinic acid was the most abundant component according to their profiling. Organic acids reported through chemical profiling include malic, oxalic, quinic, ascorbic, shikimic, fumaric, and citric acids (Silva *et al*., 2004). The metabolite 5-p-coumaroylquinic acid exhibited notable antioxidant properties (Baroni *et al*., 2018). Four hydroxycinnamic acids and quinic acid were discovered during sample analysis. The presence of flavanols like kaempferol and glycosylated quercetin and aglycone combinations contributes to the antioxidant effect. Quercetin-3-O-rutinoside was also detected in significant amounts. Flavanols, including catechins and procyanidins, were commonly found, with epicatechin being the most abundant in all samples (Baroni *et al*., 2018). Quince leaves were found to contain 36.2% of 5-O-caffeoylquinic acid, along with quercetin-3-O-rutinoside and kaempferol-3-O-rutinoside (Tsuneya *et al*., 1983). Fatty and organic acid composition analysis by Dzhan (2016) identified quinic acid as the most prevalent organic acid (72.7%), alongside oxalic acid, citric acid, shikimic acid, fumaric acid, and malic acid (Dzhan, 2016). Quince leaves contain essential oils, fatty acids, oxygenated monoterpene, aromatic aldehydes, and sequesterpene hydrocarbons (such as (E)-ionone, benzaldehyde, linalool, hexadecanoic acid, and germacrene D). Extracted essential oils feature components like (Z)-3-hexenal, (Z)-benzaldehyde, germacrene D,

farnesene, and (E) phytol (Winterhalter and Schreier, 1988). 2-methylbutanoate is a significant component in quince leaves (Velikovi *et al*., 2016).

Flavones constitute the majority of phytochemical constituents in quince seeds (63–66%), accompanied by caffeoylquinic acids and their derivatives, and isoschaftoside. Organic acids like fumaric, malic, ascorbic, D (-)-quinic, citric, and L-shikimic acids have been identified in seed profiles, with the absence of oxalic acid. Additionally, carotenoid pigments such as zeaxanthin, lycopene, β-cryptoxanthin, β-carotene, and lutein have been found in the epidermal cells of C. oblonga fruit, displaying strong antioxidant activity. Mass spectrometric techniques like gas chromatography (GC) and nuclear magnetic resonance (NMR) coupled with mass analyzers have been used to identify various carotenoid derivatives (Lopes *et al*., 2018).

Quince finds its use in various culinary applications, producing beverages, jellies, marmalades, and jams. It's also employed in canning and distillation for aromatic products. Traditional medicine, particularly Iranian traditional medicine, has extensively utilized C. oblonga due to its nutritional and therapeutic properties. In Roman weddings, newlyweds used to consume quince as a symbol of fertility. Quince leaves have historical usage as an antiseptic and astringent. Quince root was used against Scrofula, and leaves were made into decoctions to treat conditions like hypertension, stomach pains, diarrhea, and hyperglycemia. Quince is also used for various ailments like liver conditions, uterine hemorrhages, leucorrhea, haemoptysis, dysentery, and diarrhea due to its antiseptic, liver-protective, anti-inflammatory, and astringent properties. The seeds have a long history of use in treating gastrointestinal issues, respiratory problems, and oral health concerns. Gencydo®, a mixture of quince extract and lemon juice, is a remedy for asthma and rhinitis (Gründemann *et al*., 2011).

3.2.2. Therapeutical applications of *Cydonia oblonga*

Quince extracts from various parts of the plant, including flowers, fruit (seeds, pulp, and peel), and vegetative leaves, have demonstrated resistance against the development and proliferation of human colon and kidney cancer cells. Polyphenols found in quince fruit extracts were reported to synergistically inhibit the growth of human adenocarcinoma cells by stimulating the apoptotic signaling pathway. These polyphenols also exhibited anti-inflammatory effects against human-derived macrophages stimulated by LPS (Riahi-Chebbi *et al.*, 2016). Neochlorogenic acid,

identified through LC-MS analysis of an extract, was found to inhibit basophil degranulation and significantly reduce the production of tumor necrosis factor (TNF) and interleukin IL-8 by mast cells (Huber et al., 2012). The presence of polyphenols in quince, which possess hypoglycemic effects, may contribute to the prevention and mitigation of diabetes-related consequences (*Tang et al*., 2016).

Catechins and flavones, prominent compounds in quince, are believed to be effective defenders against reactive oxygen species (ROS). They suppress lipid peroxidation and subsequent cellular membrane damage, which leads to cell death. Phenolics, including caffeoylquinic derivatives, quercetin, flavonoids, astragalin, and kaempferol derivatives in quince leaves, have potential cardioprotective properties due to their ability to trap and quench ROS (Pirvu *et al*., 2018). Extracts rich in caffeoylquinic acid, kaempferol glycosides, and quercetin from leaves and fruits have shown efficacy in reducing lipid levels and alleviating symptoms of progressive atherosclerotic disorders (Khademi *et al*., 2013). The antioxidant behavior of polyphenols, coupled with their interaction with mucilage fractions, may contribute to the wound-healing and antiallergic properties of quince-based products (Shinomiya *et al*., 2009).

Quince seed, a biological macromolecule with therapeutic potential, has been extensively used in ancient Iranian medicine for inflammation and pain relief, wound healing, and skin re-epithelialization (Ghafourian et al., 2015). Quince seed has gained research attention due to its health-related benefits, attributed to its phenolic composition, anti-infective properties, antioxidant potential, anti-inflammatory and antibacterial capabilities of seed mucilage (Hussain *et al*., 2019). Quince seed mucilage (QSM) extracted from the seeds, which consists of glucuronoxylan and glucuronic acid-based biomaterials, has been used for wound healing studies. QSM is water-soluble, biocompatible, and inflates in water due to hydrophilic functional groups, making it suitable for various biomedical applications (Szymaska and Winnicka, 2015).

3.3. Nanotechnology in wound healing

Nano emulsions are lipid-containing emulsions that are mostly created through high- or low-energy emulsification. Due to the development of droplets in the submicron range, NEs are sometimes referred to as ultrafine emulsions. The range for the average droplet size of nano emulsions has been established as 50–500 nm, with a typical value of 200–300 nm. This is less

than the average range of macroemulsion droplet sizes of 1-100 mm. Because they are so small, droplets are vulnerable to physical damage via gravitational separation, flocculation, or coalescence. According to Patel *et al*. (2012), nanometer-size/diameter and polydispersity index have an impact on emulsion qualities like particle stability, rheology, image, color, texture, and shelf life as well as increasing medication pharmacological effects.

The four phases of typical wound healing are hemostasis, inflammation, proliferation, and maturation. Because they phagocytose pathogenic organisms, breakdown debris, and promote the creation of granulation tissue, macrophages are the most significant inflammatory cells in wound healing (Schultz GS *et al*.,2011). For proliferating and producing structural proteins including collagen, elastin, and extracellular matrix proteins, fibroblasts are necessary. During the remodeling process, which can take weeks to years, type III collagen is changed into type I collagen. The strength of mature scars is roughly 80% that of healthy skin. Numerous variables, including wound size, depth, location, patient age, and local and systemic disease, have an impact on how quickly a wound heals. Acute wounds go through the stages of healing regularly and fast (Sen C. K, 2019). Chronic wounds either do not heal normally, orderly, or promptly, or they do not do so without regaining normal anatomy and function (Bowers *et al*., 2020).

3.4. Importance of UV protectant in cosmetics and nano formulation

UV Filters are substances used to either absorb or reflect the ultraviolet (UV) rays present in sunlight or artificial light. They serve to protect the skin, products, and their ingredients from the harmful effects of UV radiation. UV Filters can be found in various skincare and cosmetic products, offering both cosmetic and functional benefits. These filters come in different forms, including molecules that absorb UV light, such as cinoxate or octocrylene, and opaque powders like zinc oxide or titanium dioxide that are used in creams. Their primary purpose is to counteract the detrimental effects of UV light, which include skin damage, premature aging, and increased risk of skin cancer.

UV Filters play a crucial role in safeguarding the skin by either absorbing or scattering UV radiation. UV-absorbing ingredients take in the UV rays and then release the energy as heat or transform it into less harmful wavelengths of light. On the other hand, UV-scattering components reflect the UV light in various directions, preventing it from penetrating the skin. Not only do UV

Filters shield the skin from the potential dangers of UV radiation, but they also help maintain the quality of products by preventing color fading, scent degradation, and other damage caused by UV exposure. This makes them valuable additives in sunscreens, moisturizers, and other personal care items.

The UV spectrum comprises ultraviolet A (UVA) and ultraviolet B (UV-B) rays, with UVA having wavelengths of 320 to 400 nanometers (nm) and UV-B having wavelengths of 280 to 320 nm. UV Filters are designed to combat both UVA and UV-B rays, given their potentially harmful effects on the skin. In addition to protecting the skin from UV rays, UV Filters can also serve as a safeguard for products and their packaging, ensuring that their quality and efficacy are preserved. They are even employed to shield hair color, particularly for dyed hair, from fading when exposed to sunlight.

In summary, UV Filters are essential components in many skincare and cosmetic products, acting as a defense against the damaging effects of UV radiation on the skin and the deterioration of products and packaging.

3.5. *Cydonia oblonga* in dermal treatment

An investigation was conducted to assess the effectiveness of Quince Seed Mucilage (QSM) in promoting wound healing. Cream formulations containing 5%, 10%, and 20% QSM in an Eucerin base were evaluated. Statistical analysis indicated a notable difference in wound contraction between creams containing 10% and 20% QSM and the control groups ($P<0.05$). Further examination showed that the cream with 20% QSM exhibited the highest efficacy, with improved tissue resistance, elevated growth factors in wound fluids, and increased hydroxyproline content. This led to complete healing within thirteen days (Tamri *et al*., 2014).

A double-blind clinical trial involving 34 patients with benign lesions for excisional biopsy revealed that a 10% quince mucilage ointment contributed to wound healing in approximately 10.72 days. This outcome was significantly better compared to groups using Eucerin ointment or receiving no treatment. These findings underscored the potential of quince mucilage for chronic ulcer treatment (Moosavi et al., 2006). Chemical analysis of quince mucilage indicated a dry

weight of 95.62%, moisture content of 4.38%, and ash content of around 8.24%, resulting in a yield of 10.9% (Fekri *et al*., 2008).

In a study focused on treating second-degree burns, an ethanolic extract derived from *Cydonia oblonga* seeds was evaluated for its antioxidant potential and wound healing effects. Treatment with a one-percent concentration of the seed extract demonstrated significant wound healing capabilities, achieving about 99.50% recovery. This result surpassed the recovery rate of control groups treated with sulfadiazine (92.97%), and the healing time was relatively shorter with the seed extract treatment (Tajoddini *et al*., 2013).

3.6. Quince incorporation with nanotechnology for wound healing

Recent advancements have enabled the development of wound dressings designed to deliver active substances or medications directly to wound sites (Negut *et al*., 2018). Biocompatible silver nanoparticles have gained significant attention as a nanostructured material, supported by substantial scientific evidence (Burdușel *et al*., 2018). In an in vivo investigation, Mohseni *et al*. (2019) explored antimicrobial dressings for chronic wound healing that incorporated silver nanoparticles (AgNPs) and silver sulfadiazine (SSD). While both AgNPs and SSD exhibited potent antimicrobial effects against S. aureus at comparable concentrations, AgNPs demonstrated superior biocompatibility and accelerated healing, epithelization, and skin regeneration. In terms of wound healing, nano-silver was found to be more effective than silver sulfadiazine (Mohseni *et al*., 2019).

The antimicrobial properties of a leaf extract from C. oblonga, both methanolic and acetonic, and AgNPs derived from quince seed mucilage (QSM) were assessed against Staphylococcus aureus-infected wounds. Another study indicated that quince leaf extracts and silver nanoparticles have potential inhibitory effects against Aspergillus niger, with a synergistic outcome observed between an ethanolic quince leaf extract and AgNPs. This combination demonstrated significant antifungal activity against A. niger, suggesting its potential utility in managing this pathogen (Alizadeh *et al*., 2014).

A study reported the creation of nano-bandages through an eco-friendly approach involving the use of quince seed mucilage (QSM) as a biopolymer and walnut leaf extract to prepare zinc oxide

nanoparticles. These nano-bandages were tested against severe burns and bacterial infections. The nano-bandages containing nanoparticles exhibited notable wound healing effects and prevented infections. An animal study showed complete wound healing within 21 days, with no signs of burns on the skin. The proposed nano-bandage demonstrated substantially better wound healing outcomes compared to control groups or those without nanoparticles (Darvishi *et al*., 2021).

4. MATERIALS AND METHODS

4.1 Culturing of *Scytonema javanicum* and extraction of Scytonemin

Scytonema javanicum axenic cultures will be acquired from the University of Allahabad's Algal Research Laboratory. Cells were buffered to pH 7.5 and allowed to develop in the BG-11 medium (Rippka *et al*., 1979). In order to keep the test algae in the exponential phase, sub-culturing was carried out every 28 days by moving them to new media under the same conditions. Solid agar slants were used to maintain stock cultures. After the cells were taken, centrifuged, washed with nitrogen-free solution, and re-suspended in the same new medium, the cultures were grown in bulk. Inoculum for all the experiments was this. The following are the parts of BG-11 medium:

Table 1. Macro elements components used for BG-11 medium.

Macro elements	gm/l
MgSO4.7H2O	0.075
CaCl2.2H2O	0.036
Na2CO3	0.020
EDTA (pH 8)	0.001
Citric Acid	0.006
Ferric Citrate	0.006
K2HPO4	0.004

Table 2. Microelements Components used for BG-11 medium.

Microelements	Mg/l
H2BO4	2.860

MnCl2.H2O	1.810
NaMO4.2H2O	0.391
ZnSO4.7H2O	0.222
CuSO4.5H2O	0.079
Co (NO3)2.6H2O	0.049

4.2 Collection of *Cydonia oblonga* Mill. Seeds

The *C. oblonga* seeds were purchased from the authentic seed supplier, Yuvika, having a registered FSSAI license number 13317002000140, in Lucknow, Uttar Pradesh, India.

4.3 Preparation of extract of *Cydonia oblonga* Mill. seeds

For extraction, the seeds were finely powdered. The solvent for the extraction of *Cydonia oblonga* Mill was methanol. Quince seed extract was isolated using the Soxhlet method for 24 hours at temperatures below the boiling point of the solvent. Following filtering, the solvent was evaporated at room temperature, and the resulting residue was used for future analysis. For further analysis, the finished extract was preserved (Babashpour and Piryaei, 2021).

4.2 Preparation of combined extract

The final combined extract of *Cydonia oblonga* and *Scytonemin* were prepared in an equal ratio (1:1) for further studies.

4.2 Preparation of Nanoemulsion from the combined extract

4.2.1 Solubility studies

The solubility of poorly soluble pharmaceuticals in oils, surfactants, and cosurfactants is the most crucial component of screening criterion (Akhter *et al*., 2008). Solubilities of the *Scytonemin-Cydonia oblonga* extract in oleic acid, olive oil, and Sefsol 218 were investigated. Small vials containing an excess of medication were filled with 2 ml of various oils. The vials were firmly

sealed and centrifuged for 10 minutes at 10,000 rpm after being shaken for 72 hours at 37°C. After filtering the suspension with a 0.45 µm membrane filter and diluting it with ethanol, the solubility was assessed using UV spectroscopy.

4.2.2 Pseudo Ternary Phase Diagram

In a titration tube, the medication was combined with a binary mixture of surfactant and co-surfactant. The ratio of oil to binary mixture was adjusted using the titration table. The titration tube was placed in a vortex for a short while, and different concentrations were assessed. The concentration at which nanoemulsion synthesis took place at that specific oil and symmetric combination concentration was marked as the concentration at which a bluish hue occurs. For stability and dispersibility, several formulations were investigated (Gurpreet & Singh, 2018).

Oil, water, and cosurfactant/surfactant mixture pseudo-ternary phase diagrams were produced at predetermined cosurfactant/surfactant weight ratios. To make the phase diagrams, the components were combined, weighed beforehand into glass vials, titrated with water, and carefully agitated. Visual evidence supports the monophasic/biphasic system's genesis. Biphasic samples are those that first show turbidity before going into phase separation. Monophasic, transparent, and clear mixtures should be evaluated after stirring, and the samples should be noted as points on the phase diagram. Pseudo ternary phase diagrams were produced using the aqueous titration method using oil, Smix (surfactant-cosurfactant combination), and double-distilled water. As cosurfactant concentration grew in relation to surfactant and vice versa, surfactant and cosurfactant were mixed in a variety of volume ratios (1:0, 1:1, 1:2, and 2:1). According to Jhawat et al. (2021) each phase diagram has its own oil and phase diagram.

Thirteen different oil and Smix mixtures (1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:9, 2:1, 3:1, 4:1, 5:1, 6:1, and 7:1) were titrated with aqueous phase and evaluated visually for transparency and flowability. Three phases - the aqueous phase, the oil phase, and the Smix phase—were employed to represent the physical condition of the nano emulsion in phase diagrams. The nano emulsion area was plotted for each phase diagram, and the greater the region, the better the outcomes.

4.2.3 Preparation of *Cydonia* and *Scytonemin* loaded nano emulsion (COSNE)

10 ml of the nano emulsion were prepared with 95.04% of water, Smix 4.13% and sefsol 218 0.83%. The extract of about 10% w/v was added to the nano emulsion. Following the nano emulsion mixture were sonicated for two hours. Following sonification, the material was filtered at kept at 4℃ for further analysis.

4.3 Physicochemical characteristics and Characterization of COSNE

4.3.1 Visual inspection

The main technique for evaluating self-nano emulsification is visual inspection. The efficiency of self-emulsification could be estimated using the rate of emulsification and droplet size distribution. Turbidity measurements can be used to assess the process's repeatability and the dispersion's quick equilibrium.

4.3.2 Thermodynamic Stability Studies

With no phase separation, creaming, or cracking, nano emulsions are thermodynamically stable systems that form at a given oil concentration, surfactant-co-surfactant ratio, and water concentration. In comparison to regular emulsions, the nano emulsion has a longer shelf life due to its thermodynamic stability. They are set apart from emulsions with kinetic stability, which will eventually phase-separate. To evaluate the physical stability of chosen formulations, various thermodynamic stability tests were performed. To ascertain whether drug-loaded nano-emulsions were thermodynamically stable, the following tests were performed:

a) **Heating-cooling cycle:** Six cycles between 4 °C and 45 °C in the refrigerator were done, with storage at each temperature lasting at least 48 hours. The formulations' stability at these temperatures was assessed.

b) **Centrifugation test:** We looked for phase separation after centrifuging the formulations at 5000 rpm for 30 min.

c) **Freeze-thaw cycle:** The formulation was stored at each temperature for a minimum of 24 hours through three separate freeze-thaw cycles between 20 °C and +20 °C.

4.3.3 Measurement of Particle Size, PDI and Zeta Potential

Malvern Zetasizer (Nano ZS, Malvern Instruments, UK) was used to measure the average particle size (Z-average) and polydispersity index (PDI) of the produced nanoparticles using laser Dynamic Light Scattering. By evaluating the autocorrelation function at 90 in triplicate, the PDI value reveals the nanoparticle particle size distribution in a given sample (Gurpreet & Singh, 2018).

4.3.4 Scanning electron microscopy (SEM):

Scanning electron microscopy (SEM) was employed to investigate the physical attributes of the nanoformulation incorporating the combined extract. The specimens were made conductive through the application of a thin layer of platinum coating. Following that, the aforementioned samples underwent analysis utilising a Scanning Electron Microscope (SEM) with an acceleration voltage of 20 kilovolts (KV).

4.3.5 Fourier-transform infrared spectroscopy (FTIR) analysis

The FTIR study determines the COE entrapment capacity inside the surfactant layer and its interaction with lipids in the nanoformulation. The Japanese 8400S type FTIR spectrophotometer is supplied with a wide range of attenuated formulations and extracts at room temperature. To reduce the impact of moisture residues during scanning, the materials were vacuum dried after being ground into a fine powder with IR grade KBr. The KBr pressing unit was filled with the KBr mixture and the samples. The sample was softly pulverized in the press unit for around 60 seconds at a rate of 2000 kg/cm^2 of pressure. Scanning was performed between 400 and 4000 cm^1 with a 4 cm1 resolution on the produced disc.

4.4 Preparation of dermal patch

The patch was created using a technique called solvent evaporation. In the beginning, a 4% solution of a 1:1 mixture of water and ethanol was made. The previously prepared solution was then used to create a 4% lactic acid solution. Then, 5mL of this solution was taken, and its temperature was kept at 37 °C with the aid of a hot plate. Later, using a magnetic stirrer, 125 mg of chitosan was gently and gradually added to it and dissolved. 1mL of PEG-400

(Polyethyleneglycol) was added once the chitosan had completely dissolved, and then 1 mL of distilled water. To produce a thick, homogenous solution, the mixture was thoroughly agitated. After that, 1mL of the previously improved emulsion was added dropwise and thoroughly mixed. The solution was then added to the mould, which had a surface area of 4 by 2×2 cm2, and allowed to dry at room temperature overnight. Two patches of 2×2 cm2 each were produced after drying.

4.5 Characterization of dermal patch

4.5.1 Uniformity of weight

This was accomplished by weighing five distinct patches from each batch, selecting a random uniform size, and averaging the three weights. The patch was used for the experiments after being dried at 60 °C for four hours**.**

4.5.2. Folding Endurance property

The patch was repeatedly folded at the same spot until it broke. The quantity of folds a patch could withstand before cracking was recorded.

4.5.3. Thickness of the Patch

At various locations on the patch, the thickness was measured using a digital vernier caliper. Three patches were chosen at random from each formulation. The thickness of a single patch was calculated on average.

4.6. In- vitro wound healing assay

Briefly, HaCaT cells (5×10^4) were seeded into six-well cell culture plates and allowed to grow to 70–80% confluence as a monolayer. The monolayer was gently scratched across the center of the well with a sterile one-mL pipette tip. After scratching, the medium was removed, and the wells were washed twice in PBS (Sigma-Aldrich, Milan, Italy) solution. Fresh medium containing 5% V/V of heat-inactivated FBS were added and cells treated with Scytonemin-*Cydonia oblonga* extract and its encapsulated nanoemulsion was added to each well, and cells were grown for 24 hours and 48 hrs. Images were obtained from the same fields immediately after scratching (t_0) and

after 24 hours using Olympus microscope and images was analyzed using ImageJ software by manually selecting the wound region and recording the total area.

The experiments were conducted in triplicate, and two fields were analyzed for each replicate (n =6). Untreated scratched cells represented the control. The percentage of wound closure was calculated using the following formula:

$$[(\text{Wound area } t_0 - \text{Wound area } t)/\text{Wound area } t_0] \times 100$$

5. RESULTS AND DISCUSSIONS

5.1. Maintenance of cyanobacterial strain, *Scytonema javanicum* and evaluation of *scytonemin* pigment

Cultures were maintained at 25°C ± 1°C under a white fluorescent tube of intensity 30-40μEm^2 s^1 and light and dark cycle with a ratio of 14:10. *Scytonemin* is the main sunscreen pigment which plays an important role in UV protection. The heterocystous strains *Scytonema javanicum* used for the evaluation of *scytonemin* pigment. In *S. javanicum* (720μg/gm fresh weight) were found (Figure 1(a) and (b)).

Figure 1. (a) Maintenance of cyanobacterial cultures and **(b)** *Scytonemin* extract.

5.2. Preparation of *Cydonia oblonga* Mill. Extract:

The seeds were ground into a fine powder before extraction. The seeds were extracted with 100% methanol after being ground to a fine powder in a grinder. Using the Soxhlet equipment, quince seed extract was refluxed for 24 hours at temperatures below the solvent's boiling point. Utilizing the Whatman filter No. 1, *Scytonemin* was extracted with 100% acetone. Following filtration, the solvent was allowed to evaporate at ambient temperature, and the leftover material was put to use in other studies (Figure 2). After filtration, the *Scytonemin-Cydonia oblonga* extract was prepared

at the proper ratio. The last *Scytonemin-Cydonia oblonga* extract was kept for additional examination.

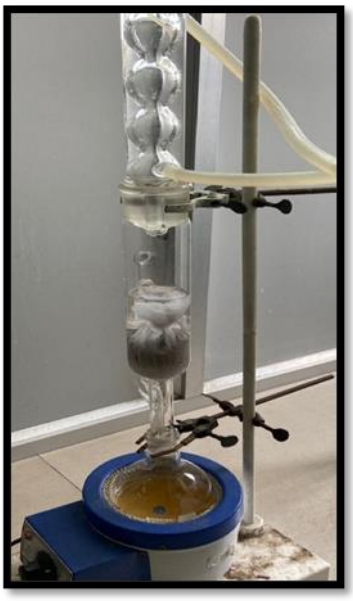


Figure 2. Preparation of *Cydonia oblonga* Mill. extract using Soxhlet apparatus.

5.3. Preparation of NE

The ratio 2:1 provided the best nano emulsion among all those made with various surfactant compositions, concentrations, co-surfactants, and water percentages with medication (Figure. 3), according to the screening of Smix ratios with a pseudo phase diagram.

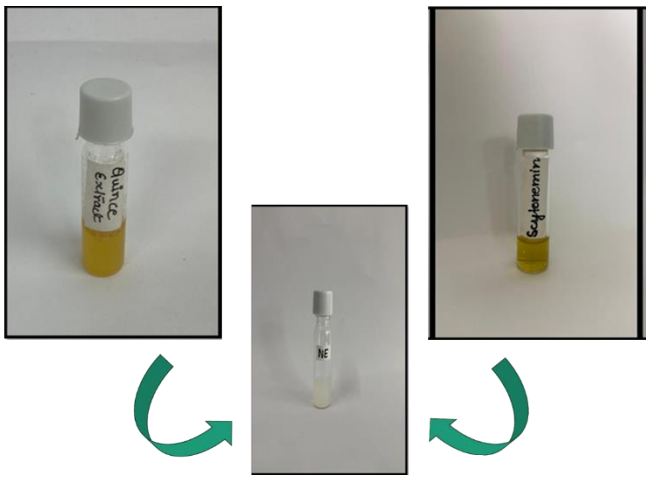


Figure 3. Nanoemulsion preparation using aqueous titration method.

5.3.1. Solubility studies

The purpose of conducting solubility tests was to identify a suitable oil phase for developing a COE-based nanoemulsion with the objective of achieving the maximum feasible drug loading. The improved solubility of the extract in the oil phase is essential for the nanoemulsion to maintain the drug in its solubilized phase. Sefsol 228 had the best solubility of the extract, of about 120.05 ± 0.815 mg/ml, trailed by olive oil (67.578 ± 0.829 mg/ml). With an extract solubility of only about 37.31 ± 1.33 mg/ml, triacetin has the least solubility for the extract (Figure 4). Subsequently, Sefsol 228 was adopted as the oil phase in the formulation of COSNE.

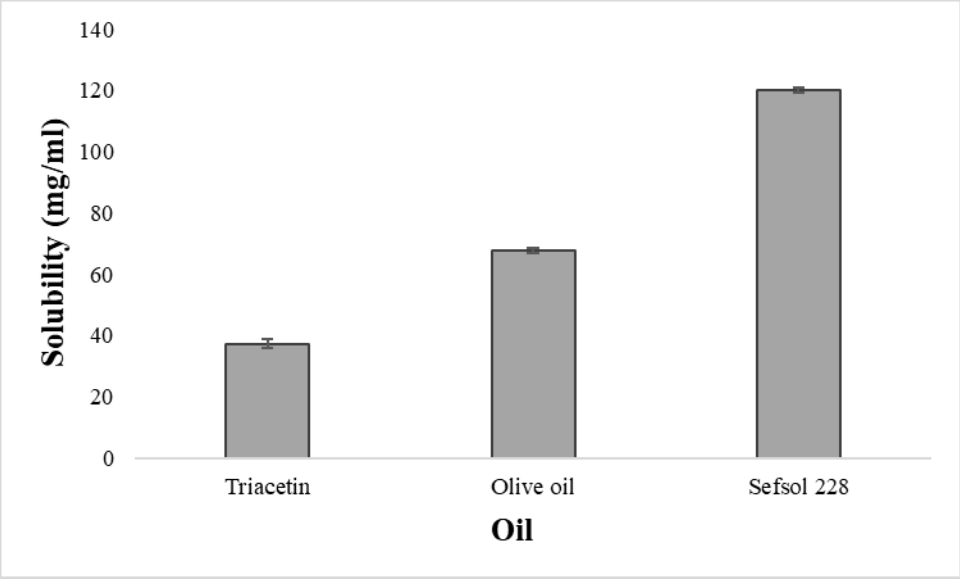


Figure 4. Sefsol 228 exhibits the highest solubility of the C. oblonga seed extract

5.4. Characterization of nanoemulsion

5.4.1. Pseudo ternary phase diagram

Based on the screening of Smix ratios using a pseudo phase diagram, the ratio 2:1 is the best nanoemulsion among all the others that were made with various surfactant compositions, concentrations, co-surfactant, and water percentages with medication (Figure 5).

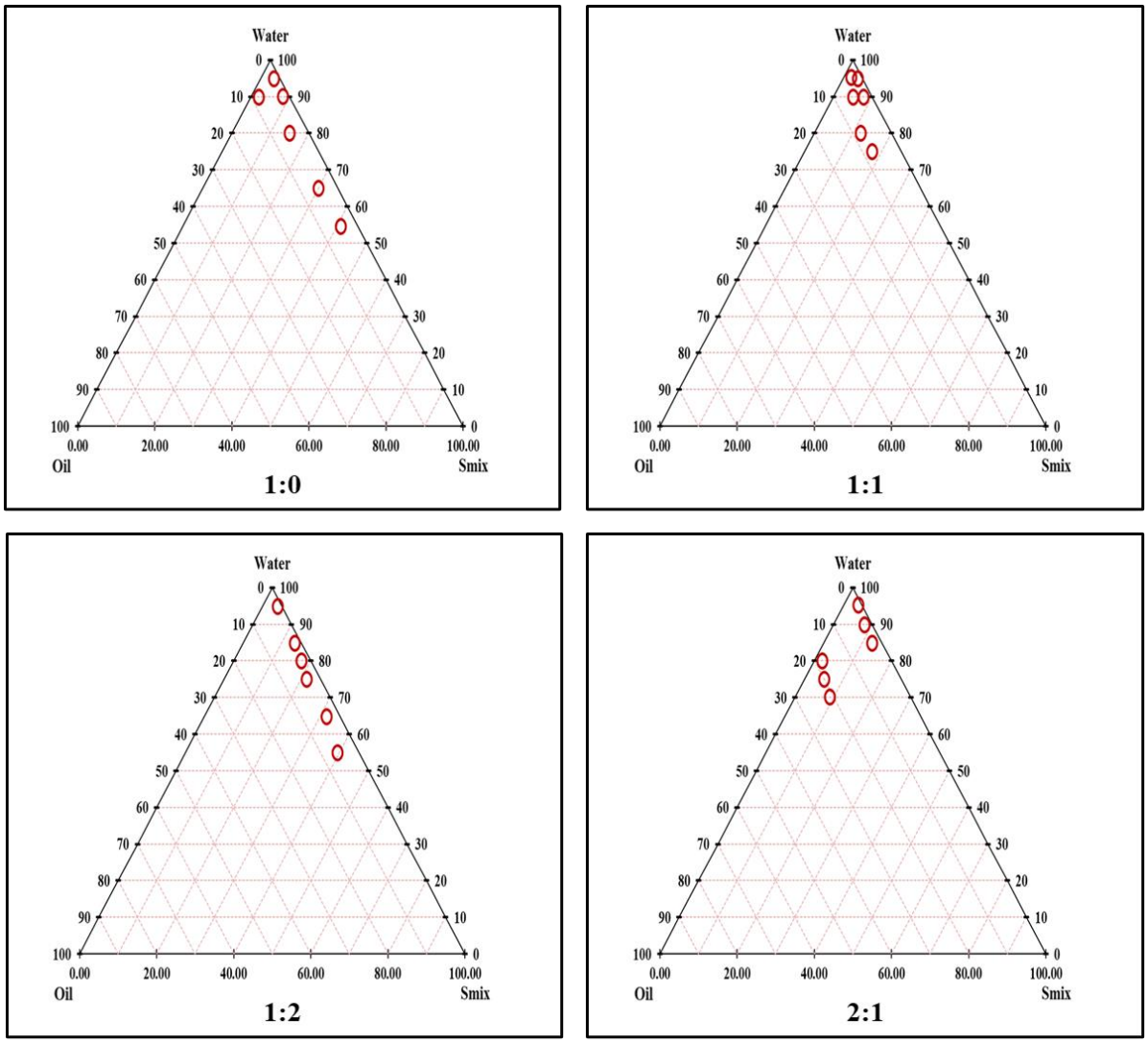


Figure 5. Pseudoternary phase diagrams of Smix ratios (a) 1:0, (b) 1:1, (c) 1:2 and (d) 2:1.

5.4.2. Thermostability analysis

Once the ternary phase diagram area was optimized, the generated nanoemulsions underwent assessment for their thermal stability. The stability of each formulation was examined at various Smix ratios, and the findings were recorded in Table 3. This evaluation was carried out by subjecting the samples to the stress cycle detailed in the methodology section. After each cycle, visual inspections were performed to monitor turbidity and phase separation. The primary factor contributing to the instability of the formulations is known as Ostwald ripening. This phenomenon involves the stabilized monomer components in circulation causing the

smaller particles to aggregate and form larger droplets. The centrifugation tests revealed the separation of layers due to the increased particle sizes. Furthermore, fluctuations in temperature during the heating and cooling cycle also contribute to the instability of the nanoemulsion.

Table 3. Thermostability test of each region of the formulated nanoemulsion of four Smix combinations.

Formulations	**S_{mix} ratio**	**%Oil**	**%S_{mix}**	**%Water**	**Thermostability studies tests**			**Dispersibility Tests**		**Results**
					Heating/ Cooling	**Centrifugation**	**Heat/ thaw**	**0.1 N**	**H_2O**	
NE_1	1:0	1.67	3.33	95.00	X	-	-	B	B	Failed
NE_2		1.64	8.20	90.16	✓	✓	✓	A	A	Passed
NE_3		5.00	15.00	80.00	✓	✓	x	B	C	Failed
NE_4		8.00	2.00	90.00	✓	✓	✓	C	D	Failed
NE_5		4.55	40.91	54.55	X	-	-	C	C	Failed
NE_6		5.00	30.00	65.00	✓	✓	x	B	C	Failed
NE_7		20.90	8.96	70.15	✓	✓	-	C	B	Failed
NE_8		3.33	11.67	85.00	X	-	-	D	C	Failed
NE_9	1:1	2.86	1.90	95.24	✓	X	-	B	C	Failed

NE_{10}		5.00	5.00	90.00	X	-	-	D	A	Failed
NE_{11}		8.00	12.00	80.00	X	-	-	C	A	Failed
NE_{12}		7.50	17.50	75.00	✓	✓	✓	A	A	Passed
NE_{13}		1.25	3.75	95.00	✓	✓	-	C	C	Failed
NE_{14}		2.22	7.78	90.00	✓	-	-	C	C	Failed
NE_{15}		2.50	12.50	85.00	✓	✓	✓	D	C	Failed
NE_{16}		3.57	21.43	75.00	✓	X	-	B	D	Failed

NE_{17}	1:2	1.11	3.89	95.00	✓	X	-	B	C	Failed
NE_{18}		1.67	13.33	85.00	✓	✓	x	C	C	Failed
NE_{19}		2.50	17.50	80.00	✓	✓	✓	A	A	Passed
NE_{20}		3.57	21.43	75.00	✓	✓	x	A	C	Failed
NE_{21}		3.51	31.58	64.91	X	-	-	B	D	Failed
NE_{22}		5.62	39.33	55.06	✓	✓	✓	D	C	Failed
NE_{23}		16.67	33.33	50.00	✓	X	-	C	D	Failed
NE_{24}		3.33	26.67	70.00	X	-	-	C	B	Failed
NE_{25}		5.00	25.00	75.00	✓	X	-	D	B	Failed
NE_{26}		13.70	41.10	45.21	X	-	-	C	A	Failed

NE_{27}	2:1	3.00	8.00	90.00	✓	✓	✓	D	C	Failed
NE_{28}		0.95	3.81	95.24	✓	X	-	C	A	Failed
NE_{29}		2.50	12.50	85.00	✓	✓	✓	C	D	Failed
NE_{30}		20.90	8.96	70.15	X	-	-	A	B	Failed
NE_{31}		18.00	2.00	80.00	X	-	-	A	C	Failed
NE_{32}		20.00	5.00	75.00	✓	✓	x	B	C	Failed
NE_{33}		0.83	4.13	95.04	✓	✓	✓	A	A	Passed

5.4.3. Analysis of particle size and morphology

The stable nano emulsion was optimized using various emulsifier and co-surfactant concentrations at various mass ratios. After optimizing the parameters for nano emulsion preparation, 15 minutes of sonification produced a stable nano emulsion. The *Scytonemin-Cydonia oblonga* loaded nano emulsion's mean particle size was about 216.3 nm with a PDI (Poly dispersity index) of 0.245. The potential of the COSNE was also determined by the zeta sizer. The prepared formulation is within the neutral potential range i.e., within +10 to -10. Our formulation has a potential value of about -14.1 mV (Figure 6). SEM analysis also showed a round shape structure of nanoemulsion within a desirable range (Figure 6).

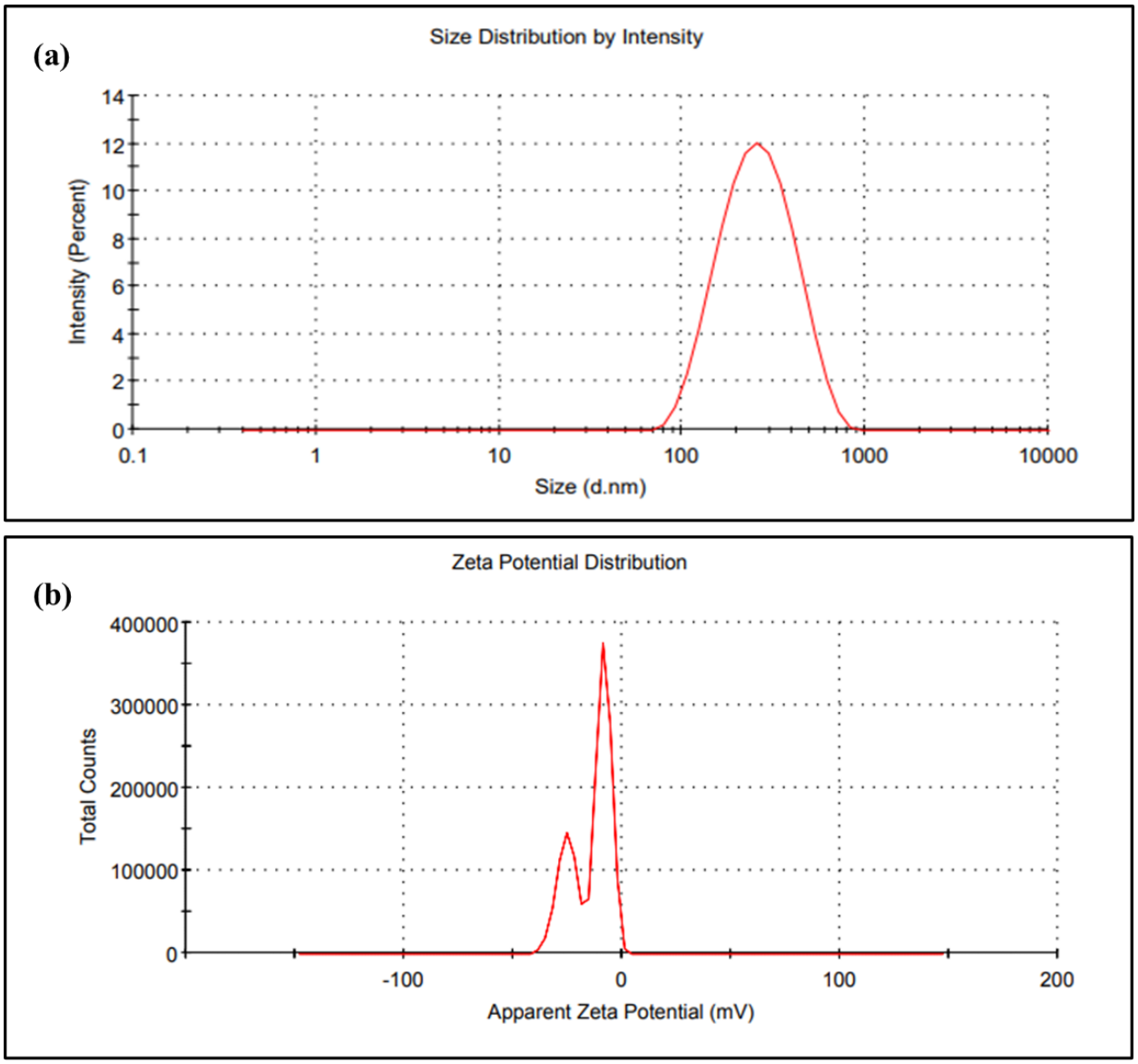


Figure 5. Zeta size and potential of the COSNE.

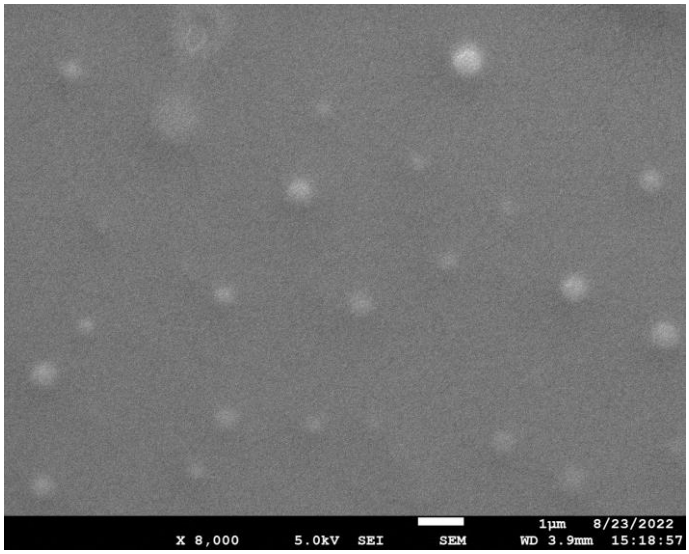


Figure 6. SEM image of COSNE

5.4.4. Entrapment of drug study by FTIR Spectroscopy

The *Scytonemin-Cydonia oblonga* extract's FTIR spectra (Figs. 6(a) and 6(b)) showed a strong absorption at 3418 cm1, which is associated with the phenol group. Alkanes' characteristic C-H stretching vibrations exhibit absorbance at 2923 cm1. At 1083 cm1, C-O stretching was often noticed. As seen in the picture, nano formulations displayed the characteristic peaks of the excipients they used, but sharp peaks of the *C. oblonga* and scytonemin extract were present. This may be because the extract was completely entrapped inside the system, as shown in Figures 7(a) and (b).

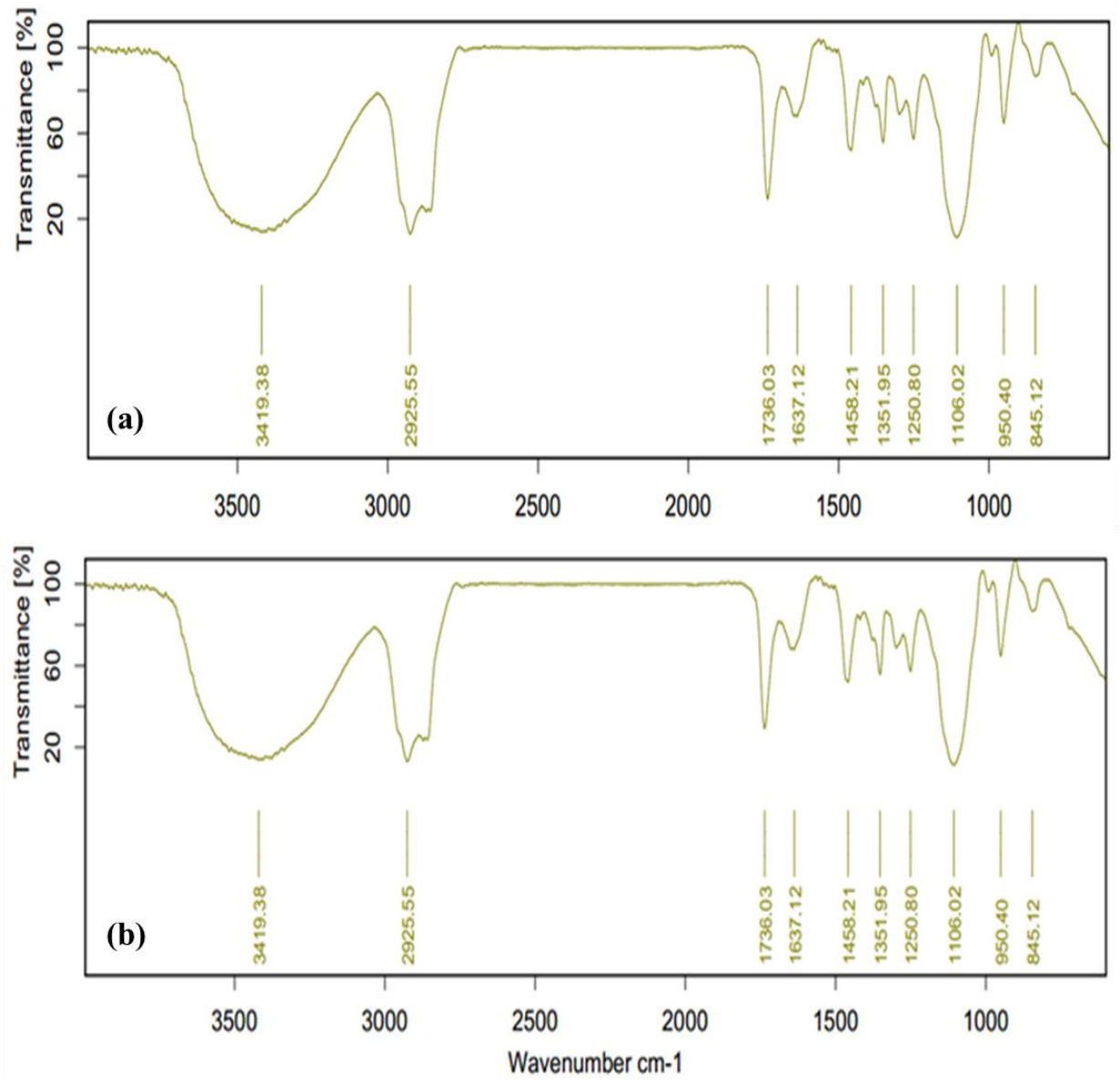


Figure 7. FTIR analysis of (a) *C. oblonga* and scytonemin extract and (b) *C. oblonga* and scytonemin extract loaded nanoemulsion (COSNE).

5.5. Preparation of Dermal patch:

Figure 8. Sample of Prepared Dermal patch.

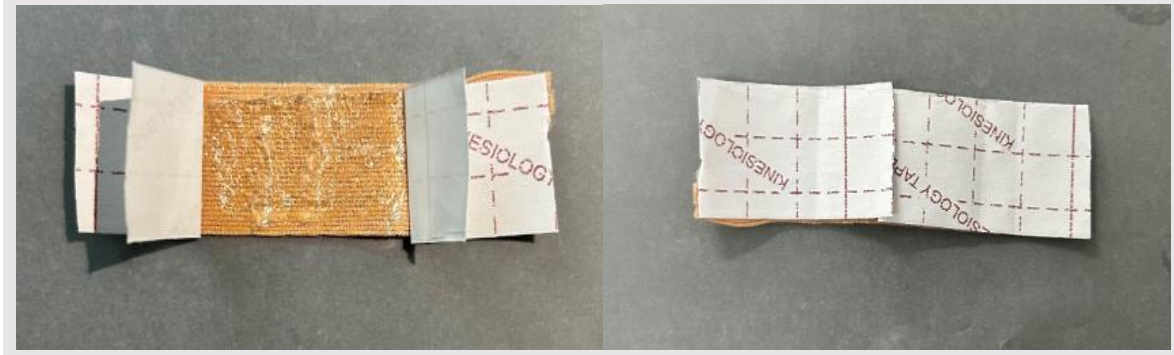


Figure 9. Prepared Dermal patch using COSNE

The patches that were created exhibited a somewhat translucent appearance, having a light hue. These gel-like preparations displayed commendable flexibility and smoothness. An example of one of these prepared patches is depicted in Figure 9.

5.6. Characterization of dermal patch

5.6.1. Weight of dermal patch

Dermal patches are specialized forms of medical or cosmetic products that are affixed to the skin's surface to deliver the medication (COSNE). The weight of a dermal patch plays a crucial role in its functionality and effectiveness. The prepared patch showed uniformity in weight and has easily adhere to the base matrix.

Table 4. The mean weight of prepared patches was 0.2485 ± 0.0007 gm.

Serial no.	Weight (gm)
1.	0.257
2.	0.249
3.	0.248

5.6.2. Folding endurance property

The folding endurance property is important because it directly influences the quality, durability, and usability of various materials and products across different industries. Materials with good folding endurance offer enhanced performance, reduced maintenance costs, and improved user satisfaction. Our prepared patch has shown a significant folding property (Table 5).

Table 5. The mean folding endurance of prepared patches was 42.67 ± 2.081

Serial no.	Folding endurance
1.	42
2.	45
3.	41

5.6.3. Thickness of the Patch

The thickness of a patch is a critical design parameter that affects its performance, comfort, functionality, and overall user experience. Balancing these factors is essential to create patches that effectively fulfill their intended purpose while meeting user expectations. The prepared patch has an average thickness of 0.367 mm (Table 6), which easily sealed into the prepared bandage.

Table 6. The thickness of prepared patches was 0.3667 ± 0.0321 mm.

Serial no.	Thickness (mm)
1.	0.33
2.	0.38
3.	0.39

5.7. Evaluation the effects of Scytonemin-*Cydonia oblonga* extract and its nanoemulsion on wound healing assay

Results of the scratch assays are given in Figure 10(a) and 10 (b). In general, when using Human Keratinocytes cells (HaCaT), NEs with incorporated active ingredients led to significantly smaller cell free gaps after 24h and 48 h in most cases (Figure 10). An example of an *in vitro* scratch assay after treatment with the loaded and unloaded NE containing Sefsol oil as the oil phase. Surprisingly, NEs incorporated with the well-established wound healing drug Scytonemin-*Cydonia oblonga* extract did not show superior wound healing properties when compared to NEs with Scytonemin-*Cydonia oblonga* nanoemulsion as the active ingredient. NE loaded with Scytonemin-*Cydonia oblonga* extract was able to close the artificial wound significantly better than the NE loaded with Scytonemin-*Cydonia oblonga* extract. In the case of the NEs with sefsol oil, NE with an extract showed significantly smaller cell free gaps than the alone Scytonemin-*Cydonia oblonga* extract. Scytonemin-*Cydonia oblonga* extract showed wound closure: 74 and 79 % at 24 and 48 h respectively while Scytonemin-*Cydonia oblonga* extract loaded nanoemulsion showed wound closure 85 and 90 % respectively which was significantly higher than the wound closures obtained with the extract (Figure 11). It is found that some oils may significantly influence

wound healing as vehicle compounds themselves. Additionally, the release of the extract from the vehicle oil can either enhance or impair wound healing and a complex triangular interaction between wound, vehicle is assumed. However, most wound healing experiments have been carried out with immortalised HaCaT cell lines. Due to substantial interaction and cooperation between the two cell types during the wound healing process, it is conceivable that the following reported responses from keratinocytes may be mirrored or supported in our scratch assays. This finding could explain in part the observed wound healing effects of Quince. It presumably stimulates fibroblasts of the tissue around the wound to proliferate, expresses appropriate integrin receptors and migrates into the wound space. In fact, the appearance of fibronectin and appropriate integrin receptors that bind fibronectin, fibrin, or both on fibroblasts appears to be the rate-limiting step in the formation of granulation tissue. Enhancement of fibroblasts proliferation indicates that Quince may contain growth promoting factor(s). These components are likely to candidates for the effects of quince on proliferation of fibroblasts in the present study. Quince seed presents a phenolic profile composed of 3-O-caffeoylquinic, 4-O-caffeoylquinic, 5-O-caffeoylquinic and 3, 5-dicaffeoylquinic acids, lucenin-2, vicenin-2, stellarin-2, isoschaftoside, schaftoside, 6-C-pentosyl-8-C-glucosyl chrysoeriol and 6-C-glucosyl-8-C-pentosyl chrysoeriol. The caffeoylquinic acid is a potent antioxidant. Radical scavenging and antioxidant activity of quince seed may explain the accelerative effect of quince on fibroblast proliferation. Skin provides a mechanical and immunological barrier between the body and the environment, and dysregulated inflammatory reactions in the skin can cause a variety of skin diseases. Exacerbated inflammation is a hallmark of a variety of inflammatory skin diseases, including dermatitis, psoriasis, and rosacea. Skin inflammation is also known as a key process involved in tumorigenesis and wound healing in the skin. Therefore, it is required to down-regulate exacerbated or persistent inflammation of the skin to prevent these pathological conditions. In this study, we investigated the anti-inflammatory effect of scytonemin in a mouse model of skin inflammation. Still, further research on the exact mode of action, especially in the later phases of the wound healing process, is of eminent interest and might provide important insight into the wound healing activity of Scytonemin-*Cydonia oblonga* nanoemulsion (Vater *et al*., 2022).

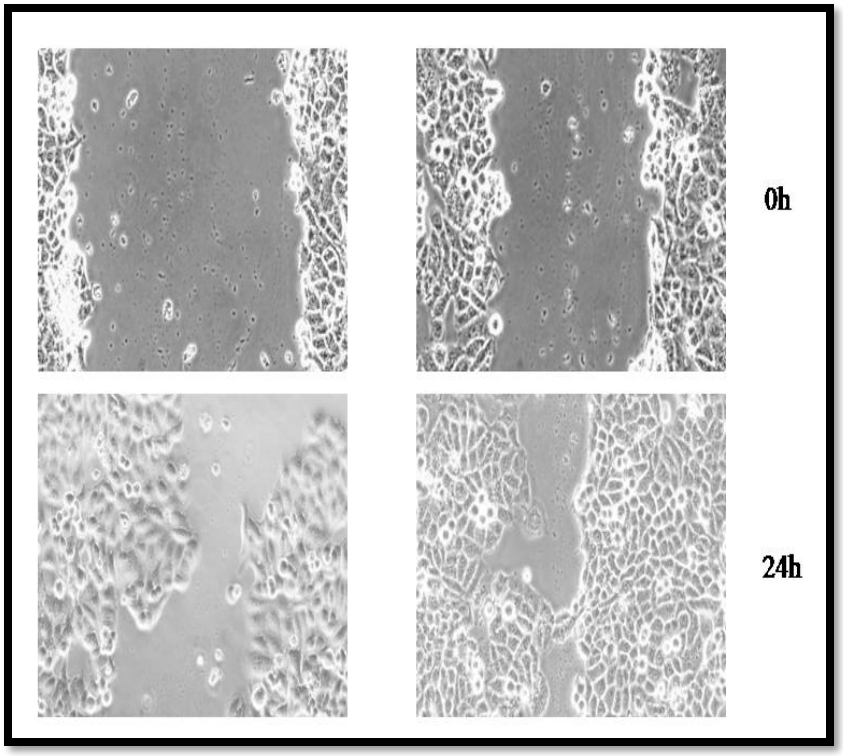


Figure 10. (a) In vitro scratch assay of HaCaT cells with unloaded and Scytonemin-*Cydonia oblonga* extract and Scytonemin-*Cydonia oblonga* nanoemulsion loaded containing jojoba oil as the oil phase for 0h and 24h.

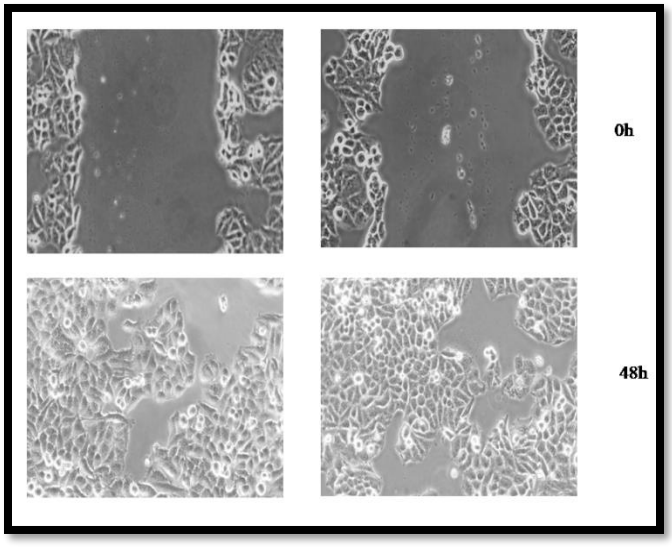
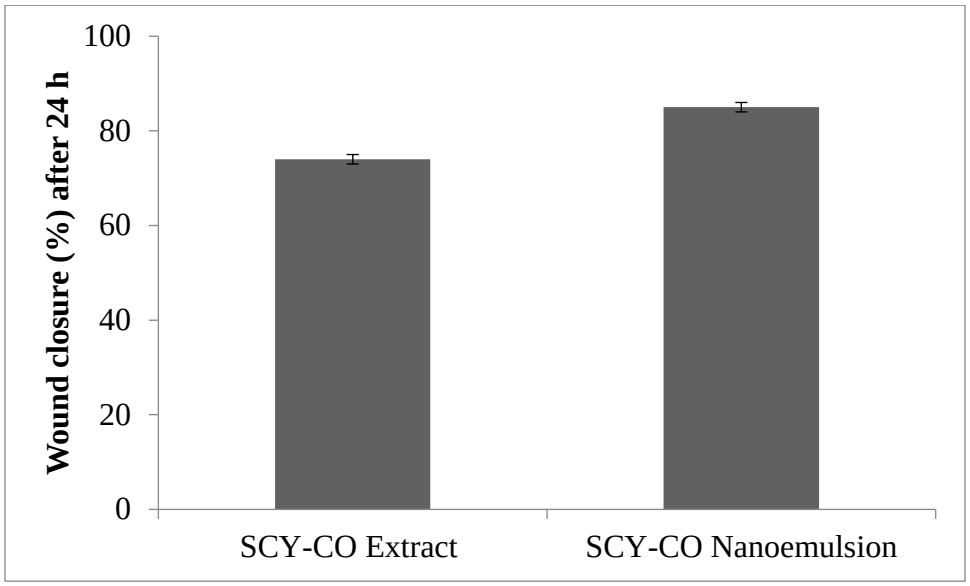


Figure 10. (b) *In vitro* scratch assay of HaCaT cells with unloaded and cytonemin-*Cydonia oblonga* extract and Scytonemin-*Cydonia oblonga* nanoemulsion loaded containing sefsol oil as the oil phase for 0h and 48h.



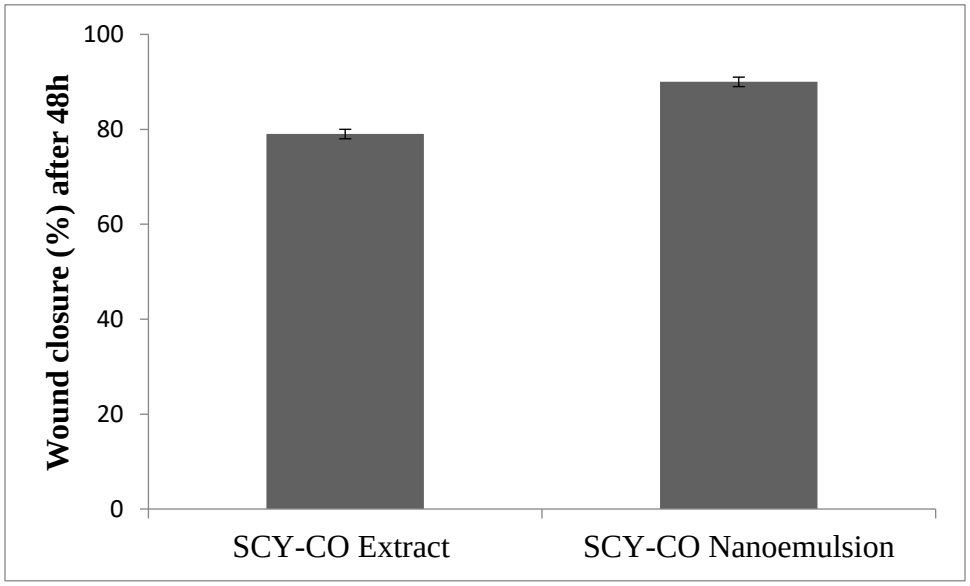


Figure 11. Wound closures of HaCaT free gaps after 24h and 48h (a and b) treatment with scytonemin –*Cydonia oblonga* extract and its loaded nanoemulsion. Data are expressed as % wound closure, ±SD, n = 6.

6. CONCLUSION

Cydonia oblonga and *scytonema javanicum* extracts screened in this study exhibited good wound healing activity, a promising prospect for the development of wound healing agents. Coupled with the excellent antioxidant activities displayed by some of the extracts in this study using different mechanistic models, the good wound healing activities makes excellent combination that assist in various processes of inflammation. The extracts screened in this study are utilised by traditional healers as management recipes or natural resource for healing wounds and skin disorders. The mode of action for the dermatological use of medicinal plants is sometimes determined by their phenolic content, positive anti-inflammatory, antioxidant activity and protein interaction properties. Nanoemulsion was developed comprising the extracts of the medicinal plants including *Cydonia oblonga* and *Scytonema javanicum.* Anti-cancer, anti-inflammatory, anti-microbial, anti-hypertensive, and other properties have been documented for the medicinal plants listed above. The seeds of each plant were extracted in their individual solvents, and the extracts were then blended in an optimum ratio to create a scytonemin-*Cydonia oblonga* mixture. Scytonemin-*Cydonia oblonga* extracts was incorporated into a nanoemulsion (NE) by using the titration method to determine the percentage of Smix (surfactant and co-surfactant) and oil (Sefsol 218). The three phases of the NE were optimized using the pseudo ternary phase diagram (water, Smix and oil). The filtered ratios' thermodynamic stability was explored further. The size, shape, and stability of the selected ratios were evaluated further. The seeds of *Cydonia oblonga* were extracted in their individual solvents, and the extracts were then blended in an optimum ratio to create a combined mixture. The combined extract was incorporated into a nanoemulsion (NE) by using the titration method to determine the percentage of Smix (surfactant and co-surfactant) and oil (Sefsol 218). The three phases of the NE were optimised using the pseudo-ternary phase diagram (water, Smix, and oil). The filtered ratios' thermodynamic stability was explored further. The size, shape, and stability of the selected ratios were evaluated further. The results showed that the nanoemulsion has an optimum size within 200 nm with neutral potential. Furthermore, the prepared combined extract and nanoemulsion also showed a significant wound healing potential in the HaCAT cell line. The present work has achieved the objectives of the formulation of a transdermal patch of Aqueous extract of *Cydonia oblonga* seed extract and Scytonemin by using solvent evaporation. The patch containing loaded extracts was prepared in a laminar hood to maintain its sterility. These data, taken together, suggest that a future medication delivery method

of scytonemin-*Cydonia oblonga* nanoemulsion extract loaded NE have the valuable capacity and potential to be used in wound healing and skin care management. Our findings show that understanding of existing medicinal systems can be utilised to bio prospect, select, develop, and market novel sources of medicines that are safe, cost-effective, and highly efficient, with superior targeted drug delivery capabilities. Through evaluations involving thickness, weight consistency, folding durability and *in vitro* wound healing potential, the formulations were chosen for future *in vivo* investigations.

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