INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA): IJPS00]
Journal Homepage: https://www.ijpsjournal.com

Review Article

Herbal Niosomes- Nature's Secret For Accelerated Wound Healing: A Review

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ARTICLE INFO

Received: 26 July 2024
Accepted: 30 July 2024
Published: 31 July 2024

Keywords:
Transdermal drug delivery, Nanocarriers, Skin Barriers, Drug Penetration

DOI:
10.5281/zenodo.13137702

ABSTRACT

The use of herbal medicines in the healthcare system is essential. Herbalism, botanical medicine, and herbology are other terms used to describe herbal medicine. It is the use of plants in a variety of forms for their therapeutic qualities. Because they produce and contain a variety of chemical compounds that act upon the body, there by promoting health and well-being. herbal plants can be used to treat or prevent disease. People are becoming more interested in using natural remedies because synthetic drugs are costly and can have negative effects.

Non-ionic surfactant vesicles known as niosomes are produced by hydrating synthetic nonionic surfactants, either with or without the addition of lipids such as cholesterol. These are vesicular systems that resemble liposomes and can be employed to transport both lipophilic and amphiphilic medications. Being non-ionic, niosomes are a promising drug delivery vehicle. They are also biodegradable, biocompatible, non-immunogenic, and have flexible structural characterization. Both hydrophilic and lipophilic drugs can be entrapped by niosomes, which also extends the drug's time in the body's circulation.

A wound can be characterized as a disruption of a tissue's cellular and anatomic continuity, whether or not there is a microbial infection present. This could be explained as numerous ways, such as cuts, scrapes, scratches, or accidental punctures to the skin. Although minor wounds are not dangerous, they do require the right care and attention to be viable and heal. Owing to a breakdown in skin function and wounds resulting in damage to the epithelium, underlying tissues and organs may sustain injuries. Wounds heal either by closing the wounds with sutures or by healing naturally, in which case damaged tissue is repaired and eventually forms a connective tissue that allows for the growth of new epithelium.

INTRODUCTION

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

For primary healthcare, between 75 and 80 percent of the world's population still turns to herbal medicine, mostly in developing nations. This is mostly due to the believe that herbal medications are safe and readily available in the area in addition to having no negative effects. The World Health Organization (WHO) reports that the use of herbal remedies is two to three times greater globally than that of conventional drugs. Much of modern medicine has its roots in the ancient practice of using plants for medicinal purposes, which predates human history. Plants are the source of many conventional medications; just a century ago, the majority of the few effective medications came from plants. Aspirin (found in willow bark), digoxin (found in foxglove), quinine (found in cinchona bark), and morphine (found in opium poppy) are a few examples.

The combination of generations of indigenous medical practitioners' therapeutic experiences spanning over hundreds of years results in herbal medicines. Not only are herbal medicines more widely used in developing countries for primary healthcare needs, but they are also more widely accepted culturally, have fewer negative effects on the body, and are less likely to cause side effects. Recent research, however, suggests that not all herbal medications are safe, as some have been linked to serious side effects. The majority of herbal products available today have not undergone testing to confirm their safety and efficacy through the drug approval process. The selection, preparation, and application of herbal formulations can be guided by invaluable guidelines gleaned from thousands of years of traditional use. The same rigorous process of scientific and clinical validation must be used to demonstrate the safety and efficacy of a therapeutical product before it can be recognized as a competitive alternative to modern medicine1.

Advantages of herbal drugs

The following benefits apply to herbal medications.

- Low risk of side effects
  Compared to traditional medications, herbal medications are generally safer to use, have fewer side effects, and are well-tolerated by the patient.
- Effectiveness
  Herbal remedies are a better option for treating chronic health conditions that don't improve with conventional medicine. One example is the use of complementary therapies and herbs to treat arthritis. Popular prescription drug Vioxx, which is used to treat arthritis and raise the risk of cardiovascular issues, was recalled. Herbal treatments for arthritis, however, are less likely to cause side effects. These therapies entail dietary changes such as adding common herbs, steering clear of nightshade vegetables, and cutting back on white sugar.
- Lower cost
  Herbal remedies are significantly less expensive than prescription medications. Research, testing, and marketing all contribute significantly to the high cost of prescription drugs. Generally speaking, herbs are less expensive than pharmaceuticals.
- Accessible to all
  You can buy herbs over-the-counter. You can grow easy herbs at home, like peppermint and chamomile.

Limitation of herbal drugs

- Unsuitable for a variety of illnesses
  When it comes to treating unanticipated, serious illnesses and accidents, herbal or alternative remedies are far less effective. More people could be successfully treated for appendicitis or a heart attack by a traditional doctor using modern diagnostic techniques, surgery, and medication than by herbalist for serious injuries like a broken leg.

Additionally, he wouldn't be able to treat appendicitis or heart attacks as effectively as a conventional doctor using the most recent diagnostic techniques, processes, and drugs.

- Insufficient dosage guidance
  There may be a variety of risk factors for using herbal remedies for self-treatment. Overdosing is another possible outcome of incorrect dosage guidance.
- Wild herbs pose a poisoning risk
  Using the incorrect plant part or taking herbal remedies without properly identifying the plant can both lead to poisoning.
- Absence of rules
  Because there are no strict laws governing herbal products, consumers might buy inferior herbs. The quality of herbal products can vary amongst batches, brands, or manufacturers. As a result, it could be much harder to recommend the right dosage of an herb. Not all herbal medicines are safe; some have the potential to be fatal or cause allergic reactions. New drug delivery systems are being developed to address the shortcomings of traditional medication administration. Among the cutting-edge drug carriers that are currently available on the market are noisome, phytosome, liposome, and nanoparticle. Combining herbal medicines with cutting-edge carriers can enhance their solubility and stability, pharmacological action, toxicity protection, prolonged delivery, and other qualities. Here we are going to discuss about niosome.

NIOSOME

Microscopic non-ionic surfactant vesicles known as niosomes are produced by hydrating synthetic non-ionic surfactant, either with or without cholesterol2.These resemble liposomes. Amphiphilic and lipophilic drugs are actively transported by both niosomes and liposomes. The phospholipids that make up the liposomal bilayer are formed by liposomal systems, whereas non-ionic surfactants form the niosomal bilayer. Niosomes are created when non-ionic surfactants self-assemble in aqueous media. Depending on the preparation technique, they can take on spherical, unilamellar, bilayered, multilamellar, or polyhedral structures, or they can take on an inverse structure when the solvent is non-aqueous. The surfactant's orientation in the niosome is such that its hydrophilic ends face outward and its hydrophobic ends face each other, forming a surfactant bilayer.

The niosomes vary in size from 10 to 1000 nm. The stabilization of niosomal vesicles formed by the non-ionic surfactant is achieved through the addition of cholesterol and a small amount of anionic surfactant, such as dicetyl phosphate3. Since phospholipids are more readily hydrolyzed due to the ester bond and are less expensive than niosomes, it is suggested that niosomes are superior to liposomes due to the greater chemical stability of surfactants. A promising drug delivery method is demonstrated by niosomes. Niosomal formulation can be administered subcutaneously, intramuscularly, intravenously, or orally 4.

ADVANTAGES OF NIOSOME

- The suspension system of the vehicle is water-based. Compared to greasy dosage forms, this has a higher rate of patient compliance and an infrastructure made up of hydrophilic, amphiphilic, and lipophilic moieties all at once.
- The vesicle formulation's properties are malleable and manageable. The drug may be released from the vesicles in a regulated manner, serving as a depot.
- They enhance the stability of entrapped drugs, increase the oral bioavailability of poorly absorbed drugs, and improve the therapeutic performance of the drug molecules. They are also osmotically active and stable 5.

COMPOSITIONS OF NIOSOMES

Niosome preparation involves the use of two primary ingredients or components:

1. Cholesterol: - It gives the niosome preparations their proper rigidity and shape.
2. Nonionic surfactants: - surfactants play an important role in the preparation of niosomes.

The following non-ionic surfactants are generally used for the preparation of niosomes.

E.g. 1. Spans (span 60, 40, 20, 85, 80)
2. Tweens (tween 20, 40, 60, 80) and
3. Brijs (brij 30, 35, 52, 58, 72, 76).

The nonionic surfactants possess a hydrophilic head and a hydrophobic tail6.

METHOD OF PREPARATION

Some important methods that are used to formulate niosomes are as follows

1. **Ether injection method**
   Using a specific ratio and a slow ether mixing process, cholesterol and surfactant are combined to create niosomes in a heated aqueous solution. The medications kept at 60° C using the designated gauze needle and the surfactant unilameller vesicles, which include the medication created when ether vaporizes, the method yields niosomes that vary in size from 50 to 1000 μm, primarily due to preparation techniques, experimental setup, and environmental factors 7.
2. **Hand Shaking Method**
   Using this method, solid surfactant and cholesterols are dissolved in an organic solvent (such as ether, chloroform, benzene, etc.) and the solvent evaporates under low pressure, helping to remove the mixture of the two solutions from the wall of the round-bottom flask. After rehydrating with a drug-loaded aqueous solution while being continuously shaken, the resulting layer—which is made up of cholesterol and solid surfactant,swells and eventually folds into vesicles that contain the drugs. It was discovered that the liquid volume trapped in vesicles was only 5–10%.
3. **Sonication**
   The third method is the sonication method, which involves first allowing the mixture of surfactant and cholesterol solution to disperse in the aqueous phase at 60°C for 10 minutes. This leads to the formulation of multilameller vesicles (MLV), which are then further ultrasonicated using a probe sonicator or bath sonicator, which forms unilameller vesicles.
4. **Reverse phase evaporation method**
   cholesterol and surfactant are dissolved in a mixture of ether and chloroform (1:1), and the drug-containing aqueous solution is added. The mixture is then allowed to sit at 45°C. The resulting solution is then sonicated with the addition of phosphate buffer saline (PBS), which forms gel. This gel formation enables the addition of PBS and heating on a water bath for 10 minutes at 60°C to produce niosomes8.
5. **Remote loading, or trans membrane pH gradient drug uptake**
   This method increases the entrapment efficiency of such drugs because it operates on the principle that the interior of a niosome has a lower pH (acidic pH) than the outer side. The added unionized basic drug crosses the membrane, but once inside the niosome, it becomes ionized in an acidic medium and cannot exit. The drugs are trapped inside the arteries by the acidic pH of the niosomes.
6. **Micro fluidization method**
   This method uses the submerged jet principle, which states that energy supplied

to the system stays in the region of niosome formations, to react ultrafast in precisely defined micro channels within the interaction chamber between two fluidized streams solution (one containing drug and the other surfactant). It leads to improved niosome formulation in terms of reproducibility, size reduction, and uniformity9.

7. **Multiple membrane extrusion method**
   Using a membrane filter, the niosomes are passed through to reduce in size. It is a useful technique for regulating niosomal size and can be used to produce both big unilamellar vesicles and multi-lamellar vesicles.
8. **Ethanol injection technique**
   Using a fine needle to quickly inject an alcoholic (ethanol) solution of surfactant into an excess of saline or another aqueous medium, vesicles are formed as a result of the ethanol's vaporization. It has been documented as one of the substitute methods utilized for sonication-free small unilamellar vesicles (SUVs) preparation.

Applications of niosomes

The application of niosomal technology is widely varied and can be used to treat a number of diseases

1. **Niosome as drug carriers**
   Niosomes have also been employed as delivery systems for the diagnostic drug iobitridol, which is used in X-ray imaging. Topical niosomes can act as a solubilization matrix, a local site for the sustained release of chemicals that are dermally active, penetration enhancers, or a membrane barrier that limits the rate at which drugs are absorbed systemically.
2. **Drug Targeting**
   Niosomes' capacity to target medications is one of their most advantageous features. Drugs can be targeted to the reticuloendothelial system using niosomes. Niosome vesicles are preferentially taken up by the reticulo-endothelial system (RES). Opsonin are circulating serum factors that regulate niosome uptake. The opsonin indicate the niosome for removal. Drugs that localize this way are used to treat tumors in animals that have a history of metastasizing to the spleen and liver. Drugs localized in this way can also be used to treat liver parasite infections. Drugs can also be targeted with niosomes to organs other than the RES. Since immunoglobulins bind to the lipid surface of niosomes easily, a carrier system (such as antibodies) can be attached to niosomes to target.
3. **Anti-neoplastic Treatment**
   The majority of antitumor drugs have serious adverse effects. Niosomes have the ability to modify drug metabolism, extending the drug's half-life and circulation, and reducing its adverse effects.
4. **Leishmaniasis**
   A parasite belonging to the genus Leishmania that infects the liver and spleen cells, causing leishmaniasis. Tests involving the use of niosomes demonstrated that higher dosages of the medication could be given without causing side effects, which increased treatment efficacy10.
5. **Delivery of Peptide Drugs**
   For a long time, oral peptide drug delivery has struggled to avoid enzymes that would break down the peptide. Research is being done on the effective use of niosomes to shield peptides from gastrointestinal peptide breakdown. The stability of the peptide was found to be significantly

increased by the entrapment of a vasopressin derivative in niosomes, as demonstrated by an oral delivery method used in an in vitro study.

6. **Use in Studying Immune Response**
   The nature of the immune response triggered by antigens is being studied using niosomes because of their immunological selectivity, low toxicity, and increased stability. When a variety of antigens and peptides are administered parenterally, non-ionic surfactant vesicles have amply demonstrated their capacity to act as an adjuvant.
7. **Niosomes as Carriers for Haemoglobin**
   Niosomes have the potential to function as bloodborne hemoglobin carriers. Because the niosomal vesicle can pass oxygen, it can carry hemoglobin in anemic individuals11.

Other Applications

- Sustained release

Since niosomal encapsulation keeps drugs with low therapeutic index and low water solubility in the bloodstream, sustained release niosomes can be used to improve their effects.

- Particular Drug Action

Because of their small size and poor ability to pass through connective tissue and epithelium, niosomes are one method of delivering drugs that have a localized effect at the site of administration12.

WOUND

A wound is caused by an accident or a cut made with a sharp object and is defined as a disruption of the cellular and anatomic continuity of a tissue, with or without microbial infection. It could result from the tissues being abused physically, chemically, thermally, microbiologically, or immunologically. The process of repairing damaged tissue to its original structure and functions is known as wound healing. The body naturally heals itself when damaged tissue is restored, but the process is extremely sluggish and there is a high risk of microbial infection. This increases the need for a drug that quickens the healing process. One of the most important ingredients in a soldier's basic supply of medications is wound healers, which can hasten the return of wounded soldiers to combat zones. By using them, wound healers also reduce the need for additional medications like antibiotics and the likelihood of their negative side effects13. There is a long history of plant-based medical knowledge in India. In India, tribal people and folklore traditions use a wide variety of plants, plant extracts, decoctions, and pastes to treat burns, wounds, and cuts.

Classification of Wound

Wounds may be classified by several methods; their location, type of injury or presenting symptoms, wound depth and tissue loss or clinical appearance of the wound. Wounds are classified as open and closed wound on the underlying cause of wound creation and acute and chronic wounds on the basis of physiology of wound healing.

Open wound

In this instance, bleeding is obviously visible and blood escapes the body. It is additionally categorized as: cut wound, Tear wound or laceration, cuts or gouges in the skin, wounds from punctures, Gunshot and penetration wounds.

Closed wounds

Blood in closed wounds leaves the body but escapes the circulatory system. It includes crush injuries, haematomas or blood tumors, contusions or bruises, etc.

Acute wounds

An acute wound is a tissue damage that typically results from a prompt, systematic healing process that preserves the anatomical and functional integrity of the injured area. Cuts or surgical incisions are typically the source of acute wounds, which heal within the anticipated time frame14.

Chronic wounds

Chronic wounds are those that have not healed through the regular phases and have instead entered a state of pathologic inflammation. As a result, they either take a long time to heal or heal again on a regular basis.

Steps Associated with Healing Wounds

The steps in the healing process depend on the wound's characteristics; there are two types of wounds based on these characteristics.

Primary union of wound

This occurs when a wound exhibits a small, clean, uninfected state with minimal cell loss. Primary union involves the following steps:

(a) Bleeding

(b) Inflammation

(c) Proliferation and migration of the epidermis's basal cells toward the incision

(d) Invasion by fibroblasts and new collagen fibers.

Secondary union of wound

Phase 1 of this category deals with coagulation; the Secondary union characteristics include an open wound with a significant tissue defect and significant tissue and cell loss. The primary union's first three steps are also followed in the secondary union. The next step is visible after that. The majority of secondary healing occurs in the fourth step, where granulation and granulation tissue are created by fibroblast and angiogenesis proliferation. Myofibroblasts act to cause wound contraction in the last stage. Sutures can be used for the first type of wound, but not for the second. The only choice is to use wound healers15.

Wound Healing Phases

Numerous complex and remarkable steps are involved in wound healing, and they are also susceptible to disruption due to both local and systemic factors such as age, nutritional status, moisture, maceration, and contagion (systemic). The four sequential ways that the entire process is traditionally divided into are shown below16.

1. Phase 1: Hemostasis
2. Phase 2: Inflammation
3. Phase 3: Proliferation
4. Phase 4: Remodeling/Maturation

Hemostasis phase

During this phase, the sympathetic nervous system induces vasoconstriction, which limits the draining and eventually causes clotting. The goal of hemostasis, the first stage of healing, which began with an injury, is to stop bleeding. The body starts the blood coagulation system, the crisis fix system, and builds a dam to contain waste during this phase. A safe cell collection occurs at the injury site when cells of injured tissue release warning signs, chemokines, and development factors that separate vulnerable cells from blood flow and stimulate the proliferation of tissue-inhabitant populaces17.

Inflammation phase

defensive/inflammatory phase that follows aims to eradicate waste and kill bacteria in order to prepare the wound bed for the growth of the most recent tissue. In Phase 2, neutrophils—a type of white blood cell enter the wound to destroy microorganisms and remove any leftover debris. As long as white blood cells leave behind macrophages, they can keep clearing debris. These cells gravitate toward the systemic cell, which is in charge of growth and protein supplements, to facilitate the healing of wound tissue. This phase, which lasts for four to six days and is associated with erythema, heat, edema, and pain, is regarded as chronic inflammation.

Proliferation Phase

After the injury is completely healed, it enters the third phase, during which filling and the canopy are thought to be the primary targets for the wound. The arrangement of granulation, which includes newly formed veins, safe cells, and fibroblasts, represents the proliferation stage. It allows skin cells to move on top of this tissue during the re epithelization process18.

(1) Wound filling; (2) shrinking the wound area; and (3) forming a thin layer on the wound (epithelialization) are the three distinct proliferative stages. Different species have different skin structural arrangements, which promote rapid healing. Most of the Proliferative stage lasts between 4 and 24 days.

Remodeling/ Maturation Phase

During the maturation stage, newly formed tissue progressively becomes more flexible and stronger. Collagen fibers now reorganize the tissue as it develops and rebuilds, giving it a generally longer lifespan (though the maximum strength is only 80% of its pre-injury strength). The maturation period, which varies greatly amongst wounds, lasts anywhere from 21 days to 2 years19.

COMMONLY USED MEDICINAL PLANT AS WOUND HEALERS

Aloe vera

The perennial herb Aloe Vera, sometimes referred to as Kumari, is a member of the Liliacee family. With large, fleshy, sessile leaves arranged in rosettes, it has a shallow root system and a short stem. In arid regions of India, it is regarded as a wild herb. Aloe vera gel is now a common ingredient in hundreds of cosmetics, sun blocks, and skin lotions. Aloe Vera works wonders for minor cuts, burns, and sunburns. The leaves' juice and aqueous extract exhibit notable therapeutic qualities. Additionally, it is said to hasten healing and keep the surface of an injury from becoming infected20.

Gingko

As a member of the Gingkoaceae family, it is frequently referred to as the Kew tree. It is extensively grown in China and Korea. Vegetative methods and seeds are two types of propagation. They help the wound area heal by supplying vital nutrients. It is used as an anti-inflammatory and anti-allergic agent in addition to healing wounds.

Nelumba nucifera

Nelumba nucifera, a member of the Nymphacaceae family, is referred to as Lotus in English and Kamal in Hindi. It's a large flowering perineal aquatic herb embedded in mud. It is frequently grown in ponds and wetlands with rhizomes used for propagation. Natural and conventional healers frequently use Nelumba nucifera. They gather rhizomes and leaves, dry them, and burn them to make ash that can be used to treat wounds.

Tulsi

This extract is made from the Ocimum sanctum plant, which is a member of the Labiatae family. It is frequently grown in gardens and is grown all over the world. Ocimum sanctum has historically been used to treat hepatic infections, stomach problems, and malarial fevers. The leaves of Ocimum sanctum are also used to treat earaches, ringworm, bronchitis, and other cutaneous conditions. The leaves are used to improve memory and as a nerve tonic. Along with the volatile oil, Ocimum sanctum leaves also contain alkaloids, glycosides, and saponins, in addition to an abundance of tannins such as gallic acid and chlorogenic acid. The primary active ingredient found in holy basil leaves is urosolic acid. Carvenol, eugenol, and eugenol-methyl ether make up 70% of its contents21.

Neem

Neem alcoholic extract helps with eczema and scabies. Seed oil and extracts from neem leaves have been shown to have antimicrobial properties. This prevents microbes from causing secondary infections to any wounds or lesions. Additionally, neem inhibits inflammation just as well as cortisone acetate, according to clinical studies, which speeds up the healing of wounds. Margosic acid, butyric acid, glycerides of fatty acids, and trace amounts of valeric acid are all present in neem oil.

Eucalyptus

Another name for it is Dinkum Oil. The process of steam distilling fresh Eucalyptus globules leaves, which belong to the Myrtaceae family, yields this oil. It is native to Tasmania and Australia. It is grown in India, Portugal, Spain, and the United States. It has cineole, sometimes referred to as eucalyptol. Additionally, it contains geranyl acetate, citronellal, phellandrene, and pinene. Burns, blisters, herpes, cuts, wounds, skin infections, and insect bites can all be treated with it in terms of skin care. Additionally, it can strengthen the immune system and help with measles, colds, chicken pox, and the flu. Oil has antiseptic, expectorant, and counterirritating properties22.

Bael

Bael Another name for it is an Indian bael fruit. It is composed of ripe or unripe fruits from the Rutaceae family plant known as Aegel marmelos. It comes from India originally and can be found in Sri Lanka and Myanmar. The pulp tastes astringent and mucilaginous, and it has a red color. Furocoumarin marmelosin is the main ingredient in the medication. Tanines, protein, carbohydrates, and volatile oil are also present in the medication. Vitamins C and A are also present in the pulp. From fruits, two alkaloids—O methylhalfordional and isopentylhalfordinol—have been identified. In addition to being an appetizer and digestive aid, it also treats dysentery and diarrhea. It has the ability to heal wounds and is a tonic as well23.

Turmeric

It is also called Indian saffron, curcuma. It consists of dried as well as fresh rhizomes of the plant known as curcuma longa belonging to family zingiberaceae. It contains about 5% of volatile oil, resin. Starch grains and curcuminoids which is the chief constitutes of curcumin, Volatile oil, content sesquiterpenes such as α and β pinene, α-phellandrene, camphor, zingiberene. It is used as a condiment or spices, and colouring agent, especially for ointments and creams.

CONCLUSION

Research into herbal niosomes for wound healing is a potential area of the pharmaceutical industry. Researchers hope to improve the bioavailability and therapeutic efficiency of these natural chemicals by encasing herbal extract in niosomal structure. Because herbal noisomes can better penetrate the skin, allow for regulated release, and lessen side effects as compared to standard formulations. Further research and clinical trials are necessary to validate their safety and efficacy. Overall herbal niosomes hold a great promise as innovative therapeutic agent for accelerating wound healing process.

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HOW TO CITE: Haritha K.*, Arun Kumar K.v., Anagha Mohan, M. Roshni, Sandhra S., Sindhu V. And Megha V. S., Herbal Niosomes- Nature's Secret For Accelerated Wound Healing: A Review, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 7, 2256-2265. https://doi.org/10.5281/zenodo.13137702