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Review Article

Advances In Herbal Drugs for Wound Healing: A Review

Megha V. S.*, Arun Kumar, Anagha Mohan, M. Roshni, Sandhra S., Haritha K. And Sindhu V.

Department of Pharmaceutics, Rajiv Gandhi Institute of Pharmaceutical Sciences and Research, Trikaripur-671 310

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ABSTRACT

A wound can be caused by physical, chemical, thermal, microbial, or immunological insults and is defined as a disruption of the cellular, anatomical, and functional continuity of a living tissue. Wound healing is the process of repairing damaged tissue to its original structure and functions. To bring back the structure of the injured tissue, a complex process involving migration, proliferation, interaction and differentiation of multiple cell types, biomolecular interactions, synthesis of matrix components and a complex signaling network must occur. Plants have the immense potential for the management and treatment of wounds. The wound healing process is an orderly sequence of overlapping, interacting processes commonly categorized into four distinct phases such as coagulation, inflammation, proliferation /migration/re-epithelialization/granulation, and re-modelling/maturation. Based on the underlying cause of the wound's creation, wounds are classified as either open or closed, and based on the physiology of the wound's healing, they are classified as either acute or chronic. Dressings are classified in a number of ways depending on their function in the wound such as debridement, antibacterial, occlusive, absorbent, adherence, type of material employed to produce the dressing such as hydrocolloid, alginate, collagen and the physical form of the dressing which includes ointment, film, foam, gel. The use of phytochemicals and naturally derived substances in wound healing is a promising development. There are different emerging novel strategies and approaches for the cure of wounds such as nanotherapeutics, stem cells therapy, 3D bio printed skin, extracellular matrix-based approaches, platelet-rich plasma-based approaches, and cold plasma treatment therapy. Vesicular nano systems exhibit beneficial properties, such as biocompatibility, targeted and sustained delivery capacity, and increased phytocompounds bioavailability and protection, conferring them a great potential for future applications in wound care.

***Corresponding Author:** MEGHA V. S.
Address: *Rajiv Gandhi Institute of Pharmaceutical Sciences and Research, Trikaripur-671 310*
Email : meghavidhyadharan921@gmail.com
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INTRODUCTION

In comparison to other synthetic products made of chemicals, the demand for herbal nano-formulations has increased significantly in the recent population, offering a safer product with fewer side effects and improving overall efficacy and drug safety[1]. Herbs (including leaves, seeds, roots, bark, etc.), herbal materials (fresh juices, essential oils, etc.), herbal preparations (extracts, tinctures, and fatty oils), and completed herbal products are all considered herbal medicines, also known as phytomedicine. It is a composite mixture of substances from different chemical classes, and the combined actions of the individual components produce the effect due to their combined bioactivity[2]. Herbal remedies have the ability to treat and cure conditions like scabies, leprosy, ulcers, wound healing, inflammation, and venereal disease. Herbal remedies for wound care involve debridement, disinfection, and creating a moist environment to promote the formation of a suitable natural healing climate. Many plants are used in folklore cultures as burn, wound, and cut remedies[3]. A wound can be caused by physical, chemical, thermal, microbial, or immunological insults and is defined as a disruption of the cellular, anatomical, and functional continuity of a living tissue4.

WOUND HEALING

The process of repairing damaged tissue to its original structure and functions is known as wound healing. Interactions between cytokines, growth factors, blood and cellular components, and the extracellular matrix led to wound healing. By promoting the synthesis of basement membrane constituents, averting dehydration, escalating inflammation, and fostering the development of granulation tissue, among other mechanisms, the cytokines aid in the healing process. Depending on their cause, wounds can be broadly divided into acute and chronic wounds. Accidents like burns or trauma are the main cause of acute wounds. Acute wounds should typically heal quickly if the proper care is received. Since the resulting scar tissue will be more satisfactory, it is always pertinent to achieve rapid and complete wound healing. Hence, achieving early wound healing should be the aim of any medical professional treating wounds. Chronic wounds require more time to heal and may even reopen as a result of underlying pathology. Therefore, it is important to first identify the underlying issue and address it appropriately[5]. The wound healing process consists of four phases: haemostasis, inflammation, proliferation and remodelling.

COAGULATION AND HEMOSTASIS

In order to preserve the organ's functionality, the first step helps to protect the vascular system. The coagulation-induced clot serves as a matrix for the cells involved in the inflammation and haemostasis processes that follow. The wound tissue and clot release a range of growth factors and pro-inflammatory cytokines. The inflammatory phase is then aided by the migration of inflammatory cells to the wound site through the process of chemotaxis.

INFLAMMATION

Fighting potential bacterial contamination of the wound and inducing cytokine secretion are the objectives of the inflammatory phase. The early migratory effect can be destroyed by unchecked inflammation, which will stop the healing process.

PROLIFERATION

The proliferation phase overlaps with the preceding inflammatory phase. It denotes an increase in both dermal and epithelial elements, leading to the primary extracellular matrix being laid down and the wound being re-epithelialized. During this stage, bone marrow-derived stem cells and epidermal stem cells are also involved. Hematopoietic stem cell-derived endothelial progenitor cells are the secondary cause of angiogenesis.

WOUND REMODELING LEADING TO SCAR FORMATION[6]

The skin recovers and its aesthetic restoration occurs at this phase, which is the last in the process of tissue remodelling and differentiation. Collagen matrix reorganization leads to
dermal reconstruction. The differentiation of fibroblasts into myofibroblasts results in the contraction and closure of wounds.

CLASSIFICATION OF WOUND

A wound's aetiology, location, kind of injury or presenting symptoms, depth and tissue loss, or clinical appearance can all be used to classify a wound. Based on the underlying cause of the wound's creation, wounds are classified as either open or closed, and based on the physiology of the wound's healing, they are classified as either acute or chronic.

Open Wound: In this instance, bleeding is obviously visible and blood escapes the body. It can also be further classified as a laceration, tear, or incised wound. Gunshot wounds, penetration wounds, abrasions or superficial wounds, and punctures.

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

Acute Wound: An acute wound is a tissue damage that often results from a prompt, systematic healing process that restores the damaged area's anatomical and functional integrity over time. Cuts or surgical incisions are typically the source of acute wounds, which heal within the anticipated time frame.

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[7].

MECHANISM OF WOUND HEALING

The skin heals itself through a process called cutaneous wound healing. It is widely acknowledged that there are four stages to the healing of cutaneous wounds: haemostasis, inflammation, proliferation, and remodelling. Re-epithelialization, or the fast formation of a functional epidermis by keratinocytes, closes wounds and restores tissue homeostasis in humans. After migrating into the wound bed, dermal fibroblasts multiply and produce "granulation tissue," which is rich in extracellular matrix proteins and helps to promote the formation of new blood vessels. In the end, this is remodelled over a long time to restore the damaged tissue to its pre-injury state. Any stage of the wound healing cascade that is dysregulated impairs healing and increases the risk of developing chronic ulcers or other skin diseases[8].

FACTORS AFFECTING WOUND HEALING 3.9

Oxygenation

Oxygen is necessary for nearly all wound healing processes as well as for the metabolism of cells, especially for the synthesis of energy through ATP. It promotes angiogenesis, enhances keratinocyte differentiation, migration, and re-epithelialization, enhances fibroblast proliferation and collagen synthesis, and helps wounds contract. It also prevents infections from spreading to wounds.

Infections

Invasive infection is the presence of replicating organisms within a wound that causes harm to the host. Naturally occurring during the healing process of wounds, inflammation is essential for the removal of infected microorganisms. However, because microbial clearance is insufficient in the absence of successful decontamination, inflammation may persist longer.

Age

Over 60-year-olds make up the largest age group in the population, and their elevated age and the World Health Organization are major risk factors for delayed wound healing. Age-related changes and wound healing delays have been studied in a number of clinical, animal, and cellular/molecular level investigations. It is generally acknowledged that aging causes a brief stoppage in the healing process of wounds in healthy older individuals, but not a true impairment in terms of healing consistency.

Stress

Stressors can exacerbate detrimental mental illnesses like anxiety and depression, which can then change physiological processes and/or behavioural patterns that influence health outcomes. In addition to the direct effects of anxiety and depression on endocrine and immune function, stressed individuals are more likely to engage in risky behaviours, such as irregular sleep schedules, inadequate diets, less exercise, and a higher risk of consuming alcohol, nicotine, and other medication.

Body Type

Wound healing can also be influenced by one's body form. For example, a low blood supply to adipose tissue can impede wound healing in an obese patient.

Furthermore, some obese patients have protein malnutrition, which makes recovery even more difficult. On the other hand, when a patient is malnourished, the lack of oxygen and nutrition stores can impede the healing of wounds.

Chronic Diseases

Peripheral vascular disease, diabetes mellitus, coronary heart disease, and stroke are a few chronic illnesses that can hinder the healing of wounds. Patients with chronic illnesses need to be closely monitored throughout their course of care in order to have an appropriate plan.

Vascular Insufficiency

The lower extremities can be affected by a variety of wounds or ulcers, including venous, diabetic, arterial, and pressure ulcers. One common cause of these ulcers is a decrease in blood supply. To ensure that topical and supportive therapies are appropriate, the clinician must determine the type of ulcer.

Nutrition

For over a century, food has been acknowledged as a critical factor influencing the healing of wounds. What is most obvious is that wound healing can be significantly impacted by malnutrition or specific nutritional deficiencies that arise after trauma and surgery. Patients with nutritional deficiencies as well as those with chronic or non-healing wounds require specific nutrients. The healing process is influenced by the metabolism of energy, proteins, fats, carbohydrates, vitamins, and minerals.

CONVENSIONAL APPROACHES IN WOUND HEALING[10]

The main goal of conventional wound care is to locate and eliminate any aggravating or precipitating factors before letting the healing cascade take its course. The cornerstones of wound management are infection control, wound bed preparation, dressings, and surgery. These can be used singly or in combination to promote wound healing, either directly (by closing the wound and allowing primary healing) or indirectly (by optimizing the wound to allow healing by secondary intention).

BASIC WOUND CARE

Acute wound: Topical antibiotic, Antiseptic

Chronic wound: Topical antibiotic, Topical anti-fungal

Burns: Topical silver nitrate, Antimicrobials

ADVANCED WOUND CARE

Acute wound: Foam dressing, Hydrogel dressing, Film dressing, Alginate dressing, Hydrocolloid dressing.

Chronic wound: Foam dressing, Hydrogel dressing, Film dressing, Alginate dressing, Hydrocolloid dressing.

Burns: Foam dressing, Hydrogel dressing.

ACTIVE WOUND CARE

Acute wound: Cell based therapy, Growth factors

Chronic wound: Cell based therapy, Growth factors

Burns: Skin replacement11.

TOPICAL PHARMACEUTICAL FORMULATIONS[12]

These formulations, which are widely used, are made as semi-solid (ointments and creams) and liquid (solutions, suspensions, and emulsions) preparations. Povidone iodine and other similar solutions work best in the early phases of wound healing to reduce the bacterial load and act as debriding and desloughing (removing slough from wound) agents to keep healthy tissue from being macerated by removing necrotic tissue from the fresh wound. Dressings can occasionally contain antimicrobial agents like poly hexamethylene biguanide, silver, and povidone-iodine to reduce or prevent infection. Physiological saline solution is used to cleanse wounds to get rid of dead tissue and any remaining polymer dressings that have dissolved. In order to facilitate dressing removal with little to no pain, saline solution is also used to irrigate dry wounds during dressing changes. However, the main issue with liquid dosage forms is their brief residence times on the wound site, particularly in cases where there is a discernible level of wound fluid suppuration (exudation). When treating bacterial infections, semi-solid preparations like silver sulphadiazine cream and silver nitrate ointment stay on the wound's surface longer than solutions do. Semi-solid dressings are not very effective at staying on heavily exuding wounds because they absorb fluid quickly, change from their original rheological characteristics, and become mobile. Cotton wool, natural or synthetic bandages, and gauzes are examples of traditional dressings. In contrast to topical pharmaceutical formulations, these dressings don't create a moist wound environment because they are dry. They can be applied as primary or secondary dressings, or they can be a component of a composite dressing, each of which serves a particular purpose. To prevent cellulose fibres from contaminating the wound, Gamgee tissue, which consists of a tubular cotton gauze wrap encircling a layer of absorbent cotton wool, is used to absorb exudate and is applied over a primary wound dressing. Different materials, such as cotton wool and cellulose, as well as synthetic materials like polyamide, are used to make bandages. The materials used to make gauze dressings can be rayon polyester, cotton, or a combination of the two. When packing open wounds, sterile gauze pads are used to absorb fluid and exudates. The dressing's fibres function as a filter to remove fluid from the wound. In comparison to more modern dressings, gauze dressings have been reported to be less cost-effective and require frequent replacement in order to prevent maceration of the healthy underlying tissue.

MODERN WOUND DRESSINGS

Modern dressings are an advancement over the conventional wound-healing substances mentioned earlier. Their primary function is to keep the area surrounding the wound moist in order to promote healing. Modern dressings are primarily categorized based on the materials used to make them, such as hydrocolloids, alginates, and hydrogels. These materials are typically found in the form of gels, thin films, and foam sheets.

HYDROCOLLOID DRESSINGS

The family of wound care products known as "hydrocolloids" is made up of colloidal (gel-forming agent) materials mixed with other materials like adhesives and elastomers. Pectin, gelatin, and carboxymethyllcellulose (CMC) are common gel-forming agents. Examples of hydrocolloid dressings include GranuflexTM and

Aquacel TM (Conva Tec, Hounslow, UK), ComfeelTM (Coloplast, Peterborough, UK) and TegasorbTM (3M Healthcare, Loughborough, UK).

ALGINATE DRESSINGS

The calcium and sodium salts of alginic acid, a polysaccharide made up of mannuronic and guluronic acid units, are used to make alginate dressings. Alginate dressings can be found as flexible fibres, which are recommended for packing cavities in wounds, or as freeze-dried porous sheets (foams). The main reason alginates are used as dressings is because of their high absorbency, which allows them to gel when in contact with wound exudates.

Strong hydrophilic gel formation enables the high absorption while reducing bacterial contamination and wound secretions. Comfeel PlusTM is a hydrocolloid/ alginate combination dressing.

HYDROGEL DRESSINGS

Hydrogels are synthetic polymers like poly(methacrylates) and poly vinylpyrrolidine that are swellable, hydrophilic, and insoluble. Certain dressings, like PurilonTM (Coloplast) and Nu-gelTM (Johnson & Johnson, Ascot, UK), are blends of alginate and hydrogel.

FOAM DRESSINGS

These dressings are made of polyurethane foam that is porous or film that is porous, occasionally with adhesive edges. Certain foam dressings, like TielleTM, have an occlusive polymeric backing layer to stop excess fluid loss and bacterial contamination, and extra wound. contact layers to prevent adherence when the wound is dry. Foam dressings are easy to use, offer thermal insulation, and keep the area surrounding the wound moist.

Examples of foam dressing include: Lyofoam (Conva Tec) and Allevyn (Smith and Nephew).

HERBAL DRUGS IN WOUND HEALING[13]

The medicinal plants contain a wide range of active and effective components, including flavonoids, essential oils, alkaloids, phenolic compounds, terpenoids, fatty acids, and others, they can be considered as potent and promising therapeutics for improving wound healing processes. Traditional medicines have low cost, minimal side effects, bioavailability, and effectiveness, hence they may be preferred over modern therapy. Beside the advantages of medicinal plants for wound management, one of the promising ways to promote their efficacy is to subject them to nanosizing process or incorporate them into nanostructures. Because of their nanoscale size and high surface area to volume ratio, nanomaterials have special properties. Nano-sizing medicinal plants can also result in changes to their chemical and physical properties.

SOME MEDICINAL PLANTS HAVING WOUND HEALING ACTIVITIES

1. Aloe barbadensis14
2. Azadirachta indica 15
3. Curcuma longa L. 16
4. Cacrica papaya L. 17
5. Catheranthus roseus 18
6. Calendula officinalis 19
7. Cassia alata L. 20
8. Euphorbia hirta L. 21
9. Grewia tiliiaefolia 22
10. Jatropha curcas L. 23
11. Moringa oleifera 24
12. Pongamia pinnata L. 25

Presently, the development of vesicular systems with improved delivery performances is the main focus of wound healing research. In recent times, there has been a notable focus on the advancement of novel, secure, eco-friendly, expandable, and reasonably priced delivery methods that have the potential to convert conventional herbal remedies into products that effectively promote health.

TOPICAL DELIVERY SYSTEMS CONTAINING HERBAL EXTRACTS[26]

Adding phytocompounds to nanocarriers is a contemporary method of enhancing their effectiveness at the skin's surface. Owing to their

structure, biocompatibility, and resemblance to skin components, phospholipid vesicles stand out among the many nanocarriers as one of the most useful and adaptable systems, particularly for skin delivery. Furthermore, Vesicular nano system improve the stability of loaded substances, inhibit physical and chemical degradation brought on by light, air, acid, and alkali, raise Phytocompounds bioavailability, and facilitate better skin penetration. These benefits are attributed to their lipid content, elasticity, and size, which promote interaction with the layers of skin. Phospholipid vesicles can also incorporate and deliver Phytocompound molecules at the intended site of action, making them non-toxic and biocompatible nano systems. Numerous studies show that molecules trapped in phospholipid vesicles and accumulating in deep layers of the skin are more effective when applied topically. More than 3000 wound dressings are available as of right now for wound treatment. There are many alternatives available, ranging from classic dressings like gauze to film, hydrogel, hydrocolloid, foam, hydro fibre, alginate, biological, and composite dressings. Modern methods like drug delivery devices and dosage forms printed in three dimensions have recently been developed. Insufficient blood supply, inflammation, and microbial infection are the main problems with traditional wound care. Advanced techniques like oxygen therapy, negative-pressure wound therapy, and gene therapy have been developed in recent decades, but their clinical applicability is restricted due to their high cost or requirement for specialized technologies. Numerous classifications based on various factors, including clinical performance, physical form, or the material's source, have been proposed due to the great diversity of wound care products. Wound care products are categorized as drugs, medical devices, biological products, or combination products by the FDA. Liquid (solutions, suspensions, or emulsions) and semisolid (creams or ointments) pharmaceutical formulations are used in traditional wound healing procedures. Wound care devices can be classified as Class I, II, III, or unclassified. To make wound application easier, lipid nanovesicles can be incorporated into a variety of topical systems, including powders, gels, solutions, creams, ointments, and dressings. The formulation's targeted action and the active ingredients' prolonged release are thought to be the main prerequisites for chronic wound healing. When the right formulations are used, the lipid vesicles can effectively meet these requirements. Liposomes, Ethosomes, Niosomes, and Transferosomes are among the various types of vesicular nano systems. In novel drug delivery technology; control of the distribution of drug is achieved by incorporating the drug in carrier system or in changing the structure of the drug at molecular level. When it comes to delivering herbal medications, novel drug delivery methods have a number of advantages over conventional formulations.

It consists of:

- Enhancement of solubility.
- Increased bioavailability.
- Protection from toxicity.
- Enhancement of pharmacological activity.
- Enhancement of stability.
- Improved tissue macrophages distribution.
- Sustained delivery.
- Protection from physical and chemical degradation [27].

TYPES OF NOVEL HERBAL DRUG DELIVERY SYSTEMS[28-31]

1. **LIPOSOMES**

   Liposomes are spherical particles that encapsulate a fraction of the solvent, in which they freely diffuse or float into their interior. These are micro-particulate, or colloidal, carriers that typically have a diameter of 0.05–5.0 μm and form spontaneously when specific

lipids are hydrated in aqueous media. Their concentric membrane count can range from one to several. Polar lipids, the building blocks of liposomes, are distinguished by the presence of both hydrophilic and lipophilic groups on the same molecules.

The primary advantages of using liposomes include:

- High biocompatibility
- Easiness of preparation
- Chemical versatility that allows the loading of hydrophilic, amphiphilic, and lipophilic compounds
- Simple modulation of their pharmacokinetic properties by varying the chemical composition of the player components.

2. PHYTOSOME

Herbal formulations called phytosomes, which are more readily absorbed than extracts, were recently introduced. The term "phyto" means plant, while "some" means cell-like.

Throughout the last hundred years, the fields of phytochemical and phytopharmacological sciences have determined the chemical compositions, biological functions, and health-promoting advantages of various botanical products. Molecules that are polar or water soluble make up the majority of the biologically active components of plants. Water-soluble phytoconstituents, such as flavonoids, tannins, and glycosidic aglycones, are not well absorbed because of their large molecular size, which prevents passive diffusion, or because of their poor lipid solubility, which severely restricts their ability to cross biological membranes rich in lipids, leading to poor bioavailability.

Advantages

- Phytosomes enhances the absorption of lipid insoluble polar phytoconstituents through oral as well as topical route showing better bioavailability, hence significantly greater therapeutic benefit.
- As the absorption of active constituent(s) is increased, so its dose requirement is reduced.
- Phosphatidylcholine used in preparation of phytosomes, besides acting as a carrier also acts as a hepatoprotective.
- In case of phytosomes. Chemical bonds are formed between phosphatidylcholine molecule and phytoconstituent, so they show better stability profile than liposome. Application of phytoconstituents in form of phytosome improve their percutaneous absorption and act as functional cosmetics.

3. NIOSOME

They have lamellar (bilayer) structures composed of amphiphilic molecules surrounded by an aqueous compartment. These amphiphilic molecules, known as surfactants, contain both hydrophobic groups (tails) and hydrophilic groups (heads) and show self-assembling properties, aggregating into a variety of shapes like micelles or into a planar lamellar bilayer.

Advantages

- Niosomal dispersion in an aqueous phase can be emulsified in a non-aqueous phase to control drug delivery rate and deliver normal vesicle in external nonaqueous phase.
- The suspension system of the vehicle is water-based. Compared to oily dosage forms, this provides a higher level of patient compliance.
- They enhance the penetration of drugs into the skin and increase the oral bioavailability of poorly absorbed medications.
- There are no particular requirements for the handling or storage of surfactants.
- The drug may be released from the vesicles in a regulated manner, serving as a depot.

- By delaying the drug's clearance from the bloodstream, protecting it from the biological environment, and limiting its effects to the targeted cells, they enhance the therapeutic efficacy of the drug molecules.

INNOVATIVE STRATEGIES FOR WOUND HEALING32

NANOTHERAPEUTICS-BASED STRATEGIES

Different types of nanomaterials (nanoparticles, nanofibers, nanogels, and nano emulsions) loaded with growth factors, interferons, antimicrobial peptides, and other agents and delivered at the wound site have been used in the nanotherapeutics approach to treat various types of wounds. Furthermore, approaches based on nanotechnology have shown promise in overcoming the different challenges related to traditional wound healing modalities, including delayed wound healing, suboptimal penetration to deeper skin tissues, and sepsis.

STEM CELL THERAPY-BASED STRATEGIES

The use of stem cells in regenerative medicine to treat wounds and regenerate skin has attracted a lot of attention because of its ability to self-renew over the long term and to differentiate into different cell types. In order to speed up the vascularization and re-epithelialization of chronic wounds, stem cell-based therapy makes use of a number of mechanisms, including the interactions and actions of growth factors, the regulation of inflammatory processes, and the stimulation of immune processes.

3. D BIOPRINTING-BASED STRATEGIES

A promising method for creating biocompatible artificial skins is three-dimensional (3D) bioprinting, an additive manufacturing technique that involves precisely depositing growth factors, biomaterials, living cells, and biomolecules layer by layer. In terms of accuracy and functionality, this automated technology is a versatile tool that is better suited for clinical applications. In order to promote innervation, pigmentation, and vascularization, 3D bio printed skin constructs offer the following benefits: (1) automation and faster fabrication at a lower cost and time; (2) flexibility to introduce different cells and biomolecules during the process; (3) the ability to precisely deposit multiple biomaterials and cells in different positions; and (4) large-scale fabrication with good plasticity and extensibility. The precise deposition of multiple cells and biomaterials results in bio printed skin equivalents that closely resemble the native skin architecture and heterogenicity. Cold Atmospheric Plasma Therapy-Based Strategies, Extracellular Matrix (ECM)-Based Strategies and MicroRNA (miR)-Based Strategy for Wound Healing are the other innovative strategies.

CONCLUSION

This review concludes that the development of vesicular systems with improved delivery performances is the main focus of wound healing research. In recent times, there has been a notable focus on the advancement of novel, secure, eco-friendly, expandable, and reasonably priced delivery methods that have the potential to convert conventional herbal remedies into products that effectively promote health. In novel drug delivery technology, control of the distribution of drug is achieved by incorporating the drug in carrier system or in changing the structure of the drug at molecular level. When it comes to delivering herbal medications, novel drug delivery methods have a number of advantages over conventional formulations. It consists of enhancement of solubility, increased bioavailability, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophages distribution, sustained delivery and protection from physical and chemical degradation.

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