Challenges, Advances and Opportunities of Herbal Medicines in Wound Healing: A Review

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ABSTRACT
A large portion of the world’s population relies on herbs for medical purposes today. About 25-30% of modern drugs are chemical intermediates derived from plant constituents. Traditional medicinal plant preparations are frequently utilised for wound healing, encompassing a wide range of skin-related disorders. In wound management, herbal medicine entails cleaning, debridement, and the creation of an environment that promotes natural healing. This review discusses wound, healing of the wound, allopathic treatment in wound healing, types of herbal medicines used in the treatment of wound healing and common excipients used in topical herbal formulations. In this article, we look at 15 plants that have been utilised as wound healers in traditional medicine around the world. This study is an attempt to search the difficulties and challenges of herbal formulations need for novel drug delivery system nanocarriers for herbal remedies with other nanotechnology strategies and techniques as a new drug delivery system and its future prospective. The purpose of this review is to examine the most common excipients used in herbal formulations, as well as various medicinal plants traditionally used in wound healing, wound healing difficulties and challenges, the use of nanotechnology in herbal formulation, the future scope of herbal medicines in wound healing, and a comparison of allopathy and herbal formulations.

Keywords: Herbal medicine; Traditional medicine; Skin; Wound; Wound healing; Herbal medicine in wound healing.

INTRODUCTION
Skin is the largest organ of the body. Skin performs some major functions like protection from external harm or physical injury, regulation of body temperature and sensation to stimuli. It performs several roles, and any damage or injury increases the organism's sensitivity to additional biological and physical risks, resulting in the wound. The wound is an injury to the body that necessitates the cracking of the skin and thereby harms the underlying tissue.

HEALING OF WOUND
Healing is a complicated and time-consuming process of restoring cell structure and tissue layers that can take place in two ways:

a) Regeneration – It is a process of renewal of the extinct tissue by a like tissue.

b) Repair – It’s the process of replacing the lost/damaged tissue with new granulation tissue. This granulation tissue fully develops to form the scar tissue. Healing of the wound includes the following phases: Haemostasis, Inflammatory Phase, Proliferation or Granulation, Remodelling and Scar Formation.

1) Haemostasis
Haemostasis is the first phase of wound healing, which involves the sealing of ruptured blood vessels with the help of platelets to heal the wound. Platelets secrete vasoconstrictor chemicals to aid in the sealing process by producing a stable clot that seals off the injured blood vessels. In the presence of Adenosine Di Phosphate (ADP), platelets clump together and attach to the exposed collagen. Thrombin initiates the synthesis of fibrin from fibrinogen. Platelet-derived growth factor (PDGF), which is secreted by platelets, initiates the following steps. Except in the case of any clotting disorders, hemostasis occurs immediately after the initial injury.

2) Inflammation Phase
The inflammatory phase is the second phase in wound healing. It is the body’s physiological response to prevent or stop the bleeding to heal a wound. Following the initial wounding, the blood vessel in the wound area contracts and a thick clot forms. After hemostasis, blood arteries dilate, allowing antibodies, growth factors, vital cells, and WBC to reach the damaged area thus, exudate levels rise. Hence the neighboring skin should be examined for the signs of softening and breaking down. During this phase, the typical signs of inflammation such as aberrant redness of the skin, heat, swelling, pain, and functional dysfunction might be visible. Neutrophils and Macrophages are two types of phagocytic cells that play an important part in necrotic tissue autolysis. The secretion of growth factors like FGF, EGF and IL-1 also occur during this stage.
3) Proliferative Phase

The proliferative phase is 3rd phase of wound healing. During this stage, repair of the wound tissue occurs with the formation of granulation tissue, which primarily consists of collagen and extracellular matrix. The new granulation tissue develops a new network of blood vessels. This process is known as angiogenesis. The blood vessels supply sufficient oxygen and nutrients to the fibroblast, which in turn results in the proliferation of granulation tissue. Healthy granulation tissue appears granular and uneven, and is pink in colour, indicating that the wound is healing. If the granulation tissue is black or dark, it means there is a problem with perfusion and the presence of infection. Epithelialization refers to the process of epithelial cells reappearing over the wound surface.

4) Remodelling or Maturation Phase

The remodeling or Maturation Phase is 4th phase of wound healing. During this phase fibroblast play a major role in the remodeling of the dermal tissues occurs once the wound has closed. Collagen type I get remodeled from type III and decreased blood vessels minimize the cellular activity.

5) Scar formation

It is 5th and final phase of wound healing. The healing process leaves a scar. Atypical scars might emerge as a result of inconsistencies in the healing process.³

TREATMENTS AND DRUGS (ALLOPATHIC) FOR WOUND HEALING

I) Non-Surgical Treatments

Vacuum-assisted closure

Vacuum-assisted closure is a non-invasive and negative pressure wound healing treatment for a variety of chronic, non-healing wounds. The vacuum-assisted closure device removes surplus wound fluid from the extravascular space using controlled subatmospheric pressure, resulting in better local oxygenation and peripheral blood flow. This encourages angiogenesis and the production of granulation tissue, both of which are beneficial in deep cavitating wounds because they speed up the “filling” of the wound space. Patients with thin, easily bruised or abraded skin, as well as those with neoplasms on the wound floor, should avoid vacuum-assisted closure. In some circumstances, cost and patient adherence may be a source of concern.

Hyperbaric oxygen

The use of hyperbaric oxygen as an additional therapy to treat a variety of non-healing wounds has been advised (as many non-healing tissues are hypoxic). Increased atmospheric pressure in a chamber while breathing 100% oxygen is used to treat the patient. Hyperbaric oxygen has been linked to side effects such as convulsions and pneumothorax. However, a systematic analysis of the Cochrane database revealed insufficient evidence for its usefulness in healing chronic wounds, though it could play a role in lowering the risk of severe amputation in diabetic foot ulcer patients.

Biosurgery (myiasis)

Sterile maggots (typically of the green bottle fly, Lucillia sericata) are used in biosurgery to decompose sloughy and necrotic debris from wounds without harming normal tissue nearby. They’ve been demonstrated to be effective in treating venous, arterial, and pressure ulcers in small-scale studies. Some patients report increased wound pain, while psychological discomfort and aesthetics may be concerns for others.

Other approaches

Radiant heat dressing, ultrasound therapy, laser treatment, hydrotherapy, electrotherapy, electromagnetic therapy, and PUVA therapy are some other non-surgical techniques that have been supported in the treatment of chronic wounds (psoralen plus ultraviolet A irradiation).³ However, the effectiveness of these treatments has only been investigated in a few randomized controlled trials.

II) Drugs

Effect of some commonly used drugs on wound healing

| Class and name of the drug | Effects |
|---------------------------|---------|
| NSAIDs Ibuprofen          | Inhibits cyclo-oxygenase production, which affects the inflammatory phase and lowers the wound’s tensile strength. |
| Colchicine                | Affects inflammatory phase; affects proliferative phase by inhibiting fibroblast growth; affects remodeling phase by destroying the freshly produced extracellular matrix |
| Corticosteroids (prednisolone) | Affects the hemostatic phase by reducing platelet adhesion; affects the inflammatory phase by influencing phagocytosis; affects the remodeling phase by suppressing collagen production and reducing fibroblast activity. |
| Antiplatelets (aspirin)    | Reduces platelet aggregation, which affects the hemostatic phase; also inhibits arachidonic acid metabolites-mediated inflammation. |
| Anticoagulants Heparin     | By affecting fibrin formation, it affects the hemostatic phase; by producing thrombocytopenia, it might contribute to thrombus formation (white clot syndrome). |
| Warfarin                  | Causes tissue necrosis and gangrene by releasing atheromatous plaque emboli in the form of micro cholesterol crystals; affects hemostatic phase by affecting fibrin production. |
| Vasoconstrictors (nicotine, cocaine, adrenaline) | Inhibits neovascularization and decreases granulation tissue production during the proliferative phase; Increases graft rejection and ulcer necrosis by affecting microcirculation. |
HERBAL MEDICINE

Herbal medicines or Phytomedicine refers to herbs (including leaves, seeds, roots, bark, etc.), herbal materials (fresh juices, essential oils, etc.), herbal preparations (extracts, tinctures and fatty oils) and finished herbal products. It is a composite blend of ingredients from various chemical classes, whose bioactivity combines to produce an effect resulting from the independent components’ combined actions. Other inactive substances act as ballast or fillers in addition to these. As a result, the medicine under consideration is a complicated mixture, both chemically and in terms of various bioactivities combining to generate a specific effect. Modern synthetic medications are potentially hazardous, have recurrence symptoms after withdrawal, and are extremely costly. But herbs are generally asserted to be nontoxic, as they are from a natural source and are being used since the emergence of civilization.

**Types of Herbal Medicine Systems:**

Herbal medicines have been produced in a variety of cultures and can be divided into three groups.

- Western herbal medicine
- Chinese herbal medicine
- Traditional Indian medicine (Ayurveda, Siddha, Unani).

1. **Western herbal medicine:**

Western herbal medicine was the primary kind of medicine available before the twentieth century, but it has since been eclipsed by orthodox or inorganic medicine based on scientific medicinal models. However, there has been a shift in public perception away from traditional medicine in recent years. Until the seventeenth century, European herbalism was based on Hippocrates' touches of humour; the sanguine, choleric, bilious, and melancholic temperaments, which describe the patient’s constitution; and the quantity of heat, cold, wet, or dry applied to illness states and herbs.

2. **Chinese herbal medicine:**

The yellow emperor Huang-ti (2697-2597 BC), who is credited with systematizing and arranging Chinese herbal medicine, wrote the earliest known classical book on the subject. Most Chinese herbalists utilize one main herb in combination with the diet because both are beneficial to the body. Herbalism is performed in the same way across the Indian subcontinent. There are four different ways to make herbal combinations in Chinese medicine. Complementary herbs are utilized when two or more herbs with similar properties or effects are used on the body to complement one another. Assisting herbs offer a variety of functions and effects. One herb takes the lead, while the other serves as catalytic support. Fright herbs reduce the chance of injury by lowering the power and fierceness of companion plants in a mixture. Canceling herbs such as the combination of a laxative and astringent herbs to minimize constipation produced by the latter is used to eliminate undesired side effects.

3. **Traditional Indian medicine:**

Ayurvedic medicine is a traditional Indian system of public health that focuses on concerns such as medicine, as well as general health care programs, dietary advice, and health education. By 1400 BC, Ayurveda, or the science of life, had evolved into a healthcare system based on teaching and health promotion. This medical method is based on the three biological humors of Vata (air), Pitta (fire), and Kapha (water). These tridoshas exist in every person, but one element reigns dominant constitutionally. The constitutional strength and weaknesses are defined by the primary element. Vata is characterized by a lack of strength and endurance, as well as shortness of breath, poor digestion, flatulence, and circulatory issues. Pitta tends to be a hot constitution that is prone to rage and has crimson skin. They have decent digestion and circulatory health, but they are prone to inflammatory and viral disorders. Kapha has white, moist skin and is sensitive and romantic. It moves slowly and is prone to situations such as excess phlegm, cold, dampness, and carries extra fat or water. Food activity is classified in Ayurveda into different categories. Food that is greasy, sticky, and sweet is said to have a tamasic nature i.e heavy and dulling to the system. Foods associated with Rajas, such as cayenne and black pepper, are fiery, spicy, and salty, imitating or obstructing inequality. Sattvic foods are mildly flavoured, organic foods including vegetables, fruits, nuts, and everyday items that are calming and nourishing to the body. Ayurvedic practitioners analyze each patient's eating habits for signs of an excess of one quality over another, and any changes are weighed against the prevailing sickness.

**COMMON EXCIPIENTS USED IN HERBAL FORMULATION**

A herbal formulation is a dosage form that contains one or more herbs or processed herb(s) in specific amounts to provide specific nutritional, cosmetic, and/or other benefits for use in diagnosing, treating, or mitigating diseases in humans or animals, as well as to change the structure or physiology of humans or animals. Herbal compositions such as Gels, Ointments, dried comminuted fruits, Creams, Pastes, Powder, Emulsion, and others were utilized.

Herbal or natural excipients offer a significant benefit over their synthetic counterparts in that they are non-toxic, inexpensive, and readily available. The pharmaceutical industry is becoming increasingly open to using herbal excipients, which are mainly polymers of natural origin, in formulation development as awareness about them grows. Binders, fillers, and diluents, lubricants, glidants, disintegrants, plasticizers, and preservatives, are all used in herbal formulations.
Common excipients used in the herbal formulation are:

1. **Binders**
   Binders are the excipients that are utilized to bind or hold all of the ingredients in the dosage formulation together. Binders are added to the mixture to exhibit plasticity or to boost the possibility of particle binding. Binding capabilities and other features are found in natural binders such as starch gum and dried fruit mucilage. Fillers and disintegrants, for example. Natural polymers are more environmentally friendly and cost less than synthetic polymers.

   **Examples** - Tamarind seed, Fenugreek mucilage, Mangifera indica gum, Gum acacia.

2. **Fillers and Diluents**
   Diluents or fillers are medicinal ingredients that have no pharmacological activity yet are required in the production of pharmaceuticals. Diluents are chemically ineffective excipients that are utilized up to 80% of the time in the formulation to provide bulk to the dosage form.

   **Examples** - Microcrystalline cellulose, lactose, sucrose, Glucose.

3. **Lubricants, Glidants and Disintegrants**

   3.1 **Lubricants**
   Lubricants prevent components from clumping together and stick to the filling tablet or capsule machine. Lubricants reduce friction between the solid and the die, allowing the tablet to be formed and ejected with ease. Lubricants reduce inter-particle friction, which improves product flow. Lubricants are usually divided into two categories: hydrophilic and non-hydrophilic. Hydrophilic lubricants, in general, have limited lubricating properties and do not have anti-adherent properties. The second is hydrophobic. The pharmaceutical industry is the most common user of hydrophobic lubricants. They have a good lubricating property and are used in tiny amounts as anti-adhesives and gliders.

   **Examples** - Stearic acid, Sodium Stearyl Fumarate, Castor oils, Sodium chloride, Paraffin oil.

3.2 **Glidants**
   Glidants are additive compounds that are used to improve a powder's flowability by lowering interparticle friction, surface charge, and cohesiveness, lowering the angle of repose. They're usually added as a dry powder right before direct compression. Due to their inability to reduce die wall friction, glidants are usually used in conjunction with lubricants. Excessive levels of glidant can have a negative impact on the flow qualities of the powder combination by impeding its flowability.

   **Examples** - Ascorbyl palmitate, Calcium Palmitate, Magnesium stearate, Fumed silica (colloidal silicon dioxide), Starch, and Talc are some of the ingredients in this product.

3.3 **Disintegrants**
   Disintegrating agents are compounds found in tablets and certain stiff capsule formulations that help the dissolving fluid penetrate moisture and disseminate the dosage form. The core particles from which an oral solid form of dosage was created should preferably be disseminated into the core particles.

   **Examples** - Gum Karaya, Guar gum, Plantago ovata seed mucilage, Chitin and chitosan.

4. **Plasticizers**
   A plasticizer is a substance that is added to a material during the production process to make it softer and more flexible, improve plasticity, reduce viscosity, or minimize friction.

   **Examples** - Propylene glycol, Glycerol, Diethyl phthalate, Acetylated monoglycerides

5. **Preservatives**
   Preservatives are commonly used to extend the shelf life of a variety of food and pharmaceutical items. Preservatives are necessary to prevent microorganisms from changing and degrading during storage, especially in products with high water content.

   **Examples** - Clove oil, Neem oil, Cumin seeds, Turmeric, Cinnamon.
The following list of medicinal plants and their qualities with a known or proven effect on wound healing is provided.

| Name              | Formulations Type | Extraction Methods | Wound Model Used     | Animal Used                                  | Other Biological Activities                                                                 | Reference |
|------------------|-------------------|--------------------|----------------------|---------------------------------------------|------------------------------------------------------------------------------------------------|-----------|
| Achillea         | Liquid dosage forms | Maceration Soxhlet | Excision, Incision, Dead space, Cutaneous | Male Sprague Dawley rats weighing (160-180gm), Male Wistar rats weighing (180-200gm) | Antioxidant, Anti-inflammatory, Anti-microbial, Antinociceptive, Spasmolytic, Anti-diabetic and Anti-tumor | 10-15     |
| Aloe vera        | Gel, Ointment     | Incision Slice     | Incision, Burn        | 2-3 months old healthy Sprague Dawley rats weighing (300+20gm) | Anti-cancer, Antioxidant, Immunomodulation are gastric and intestinal, Neuroprotective, Hepatoprotective | 16-19     |
| Avena sativa     | Dried comminuted fruits, Liquid extracts | Maceration | Circular excision, Linear excision | Male Sprague Dawley rats weighing (160-180gm), Swiss Albino mice (20-25gm), Healthy male Wistar rats weighing (200gm) | Anti-inflammatory, Antioxidant, Anti-Proliferative | 20-22     |
| Azadirachta Indica | Gel, Ointment | Maceration | Excision, Incision, Burn | Albino &Wistar rats of either sex weighing (170-210gm), Healthy Sprague Dawley male rats weighing between (180-200gm), male albino mice weighing (18-22gm) | Larvicidal activity, Antibacterial, Antidiabetic, Anti-oxidant, Anti-ulcer, Antinatal, Anti-malarial, Antitumour, Anti-fertility, Antihypertensive | 23-27     |
| Calendula officinalis | Liquid extracts, Ointments | Maceration, Soxhlet | Excision, Cutaneous, Acute, chronic, Burn | Female Wistar rats weighing (150-200gm), Wistar albino rats of either sex weighing (120-200gm) | Anti-inflammatory, Antiedematous, Antioxidant, Immunostimulant, Anticancer, Antibacterial, Antifungal, Hepatoprotective, Anti-HIV | 28-30     |
| Celosia argentea | Ointment | Soxhlet | Burn | Male albino rats weighing (100-125gm) | Hepatoprotection, Tumour treatment, Anti-diarrhoea, Anti-diabetes, Anti-oxidant, Anti-hypertension | 31,32     |
| Centella asiatica | Ointment, Cream | Maceration, Soxhlet | Excision, Burn | Male Sprague Dawley rats weighing (250-300gm), Wistar albino rats of either sex weighing (150-250gm) | Cytotoxic, Insecticidal, Phytotoxicity, Anti-microbial, Analgesic, Anti-inflammatory, Anti-oxidant | 33-36     |
| Chromolaena odorata | Paste, Ointment | Maceration, Soxhlet | Incision | Female Wistar Albino rats weighing (120-80gm), Sprague Dawley rats weighing (180-200gm) | Anti-microbial, Anti-fungal, Anti-inflammatory, Antibiotic, Antibacterial | 37-41     |
| Curcuma longa    | Paste, Ointment, Powder | Soxhlet, Maceration | Excision, Incision, Dead space | Healthy Swiss Wrister rats, Albino Wistar rats weighing (150-200gm) | Anti-parasitic, Antispasmodic, Anti-oxidant, Antiprotozoal, Antibacterial, Anti-inflammation, Gastrointestinal, Anti-HIV, Nematocidal | 42-45     |
| Euphorbia hirta  | Ointment | Maceration, Soxhlet | Excision, Burn, Incision, Dead space | Female Swiss Albino rats weighing (180-200gm), Male Wistar Albino rats weighing (175+10gm) | Anti-inflammatory, Anti-oxidant, Hepatoprotective, Anti-hyperglycemic, Anti-diabetic | 46-49     |
| Helianthus annus | Ointment, Emulsion | Maceration | Incision, Burn | Male Wistar rats (302.23±26.23gm) | Antitumor, Anti-inflammatory, Anti-diabetic, Anti-bacterial, Anti-fungal | 50-52     |
Difficulties and Challenges of Herbal Formulations:

There are many challenges with herbal drugs which need to be overcome like the difficulty of:

1) During the entire extraction process, herbal substances require specific attention and protection. Proper drying conditions should be followed. Inadequate drying can result in unintended adulteration. Decomposition of glycosides through enzymatic hydrolysis, for example, if digitalis leaves are dried above 65°.

2) There is no single standard that will apply to herbal formulations, thus there is no good way to determine whether substances can be utilized, to what extent, and to what standards.

3) In the development of herbal formulations, only a few natural substances can be employed. The problem of formulating with fewer ingredients may result in the formation of a product that does not work as well with synthetic chemical-based products.

4) In herbal formulations, difficulties may occur during Conducting clinical research.

5) In herbal formulations difficulties in Pharmacological and toxicological evaluation occurs.

6) Difficulties in developing methods, investigating absorption sites, discovering numerous animal models for toxicity and safety evaluation, and legal and regulatory problems of herbal medications, among other things.

Need for Novel Drug Delivery System “Nanocarriers” for “Herbal Remedies”:

Many ingredients of herbal medications will be destroyed in the very acidic pH of the stomach before reaching the bloodstream, while others may be metabolized by the liver. As a result, the optimal amount of herbal medications may not enter the bloodstream.69 There will be no way to demonstrate the drug's therapeutic impact if it does not reach the ideal amount to the affected region at the “minimum effective level.” Due to their small size, nanocarriers applied to herbal medicines will convey the maximum amount of the drug to its site of action, avoiding all barriers such as acidic pH of the stomach, liver processing, and increasing the drug's prolonged circulation into the blood.70

Because of the following features, herbal treatments were chosen as viable drug candidates for distribution using a nano delivery system:

1. There are effective chloroform, petrol, acetone, and methanolic extracts available that may or may not be acceptable for delivery.

2. Because they are bulk medications, dosage minimization is the goal.

3. Currently, commercial formulations for numerous chronic illnesses lack target specificity.

4. There are a few other negative effects linked with currently available formulations.

5. Patient non-compliance due to high doses and ineffectiveness of currently available formulations.

NANOTECHNOLOGY STRATEGIES AS A NEW DRUG DELIVERY SYSTEM

The drug delivery system received an NDDS, which is a groundbreaking method of overcoming the limitations of traditional drug delivery systems.

For the following reasons, a nano-sized delivery mechanism was chosen:

- Because of their unusual size and large loading capacity, they appear to be able to deliver significant concentrations of medications to disease locations.

- Use a small particle size to deliver the drug, which improves the total surface area of the drug and allows for faster blood solubility.
• The concentration appears to last longer at the sites.
• Exhibits the EPR (enhanced permeation and retention) effect, i.e., enhanced penetration through the barriers due to the tumor’s small size and retention due to poor lymphatic drainage.
• It has passive targeting to the disease site of action without requiring the use of a specific ligand moiety.
• Decrease in the side effects.
• A reduction in the medicinal formulation’s dose.

Techniques

The following are some of the most prevalent formulation techniques:

1) High-pressure homogenization method

The lipid is driven under high shear stress with high pressure (100 to 2000 bar), resulting in particle breakup down to the submicrometer or nanometer range. For the large-scale synthesis of nanostructured lipid carriers, lipid drug conjugates, SLNs, and parenteral emulsions, the high-pressure homogenization process is a very dependable and powerful technology.71 Because the exposure to a higher temperature is brief, the hot homogenization process is also ideal for medications that are temperature sensitive. The cold homogenization process can be used with particularly temperature-sensitive substances. This step is also essential when making hydrophilic formulations since they will partition between the melted lipid and the water phase during the heat homogenization process. The drug-containing lipid melt is cooled, the solid lipid is ground into lipid microparticles (approximately 50-100 mm), and the lipid micro particles are dispersed in a cold surfactant solution, resulting in a pre-suspension, according to the cold homogenization process. The cavitation forces are strong enough to fracture the lipid microparticles directly into solid lipid nanoparticles after homogenizing the pre-suspension at or below room temperature. The melting of the lipid is avoided or minimized in this method, reducing the loss of hydrophilic medicines to the aqueous phase. Of course, the temperature difference between the lipid’s melting point and the homogenization temperature must be significant enough to prevent the lipid from melting in the homogenizer. The homogenization procedure raises the temperature of the product (e.g., 10±20°C per homogenization cycle).

2) Complex coacervation method

In colloidal systems, the spontaneous phase separation of two liquid phases is caused by the interaction of two oppositely charged polyelectrolytes in an aqueous solution. When a solution of two hydrophilic colloids is combined under adequate conditions, coacervation means the separation of a liquid or phase. The three immiscible phases of core material, solvent, and coating material are created in this process, and the coating material is then deposited on the core. The core material is uniformly disseminated in the coating material solution, which is dissolved in a suitable solvent. The coating material is then phased out of its solution and begins to deposit on the core material’s particles.

3) Co-precipitation method

This method is a modification of the complicated coacervation process for the creation of nanoscale core-shell particles. Poorly water-soluble medicines have been observed to have good dispersion stability using this approach. The three basic processes of coprecipitation are inclusion, occlusion, and adsorption. When an impurity occupies a lattice site in the crystal structure of the carrier, a crystallographic effect develops; this can happen when the impurity’s ionic radius and charge are similar to those of the carrier. An adsorbate is an impurity that is weakly or strongly attached to the precipitate’s surface (adsorbed). When an adsorbed impurity becomes physically stuck inside the crystal as it grows, occlusion occurs.

4) Salting-out method

This approach is based on the fact that when an electrolyte is added to a non-electrolyte, its solubility in water decreases. The salting-out of a protein solution to generate protein coacervates is a straightforward method for making protein-based nanoparticles. Hydrophilic and hydrophobic regions of proteins exist. Hydrophobic components can interact with water molecules, allowing proteins to create hydrogen bonds with the water molecules in the surrounding environment.

5) Nanoprecipitation method or solvent displacement method

This method relies on the interfacial deposition of a polymer following the displacement of a semipolar solvent miscible with water from a lipophilic solution, resulting in a decrease in interfacial tension between the two phases, increased surface area72, and the formation of small droplets of organic solvent even without mechanical stirring.

6) Solvent emulsification–diffusion method

In a high shear mixer, an o/w emulsion including polymer and oil in an organic solvent is emulsified with an aqueous phase containing stabilizer, and then water is added to induce organic solvent diffusion, resulting in the formation of nanoparticles.

7) Supercritical fluid methods

This method can be used to create submicrometer and nanometer-sized formulations. A supercritical fluid (SCF) is a liquid or gas used at temperatures and pressures higher than its thermodynamic critical point.73 The most often utilized SCFs are carbon dioxide and water.
8) Self-assembly methods

Self-assembly is a physical process in which pre-existing disordered components, atoms, or molecules self-organize into controlled nanoscale structures via physical or chemical processes without the need for an external source.

FUTURE PROSPECTIVE

Natural products and herbal remedies have been investigated all over the world. At the fundamental and clinical trial levels, several institutes are focusing on the development of herbal medicines in the drug delivery system. The only requirement is to develop more effective methods for delivering such pharmaceuticals to specific locations and throughout the body in doses that do not interfere with present treatment. Something that not only reduces toxicity and hypersensitive reactions but also improves the patient's internal strength is highly desirable. The idea of using herbal nanoparticles to deliver cancer treatments may pique the interest of certain future research organizations, leading to potentially eye-catching results.

As a result, incorporating "herbal remedies" into nanocarriers will improve their ability to treat a wide range of chronic diseases and provide health benefits. There are countless successful examples of nanotechnology with verifiable evidence. Herbal medications also have a lot of good stuff in them, such as antioxidants and ingredients that can be used in functional foods.74 This type of collaborative research combining traditional "Herbal treatments" and newer techniques to current medication delivery systems, such as "Nanotechnology," has established attractive therapies for the pharmaceutical business that will enhance people's health soon. The efficacy and value of natural commodities and herbal treatments combined with the nanocarrier are projected to increase the value of existing drug delivery systems.

COMPARISON BETWEEN ALLOPATHY AND HERBAL FORMULATION

Treatment Perspectives:

Allopathic Medicinal System

Allopathy is derived from two Greek terms: allos, which means "opposite," and pathos, which means "suffering," and was coined by a German physician called Samuel Hahnemann. The administration of a medical medication that has the exact opposite effect as the disease is the basis of allopathic treatment.75 Scientific tests, equipment, and treatments that have been proven to be effective underpin the allopathic medical system. It uses synthetic, semi-synthetic, and improved pharmaceuticals with proven efficacy, safety, and quality in the treatment of diseases and diseased states.76 It emphasizes the specific illness that affects the body and defines good health as a condition of being disease-free. In terms of approval, use, and commercialization, the medicinal system makes use of pharmaceuticals that are suitably governed by numerous international and local regulatory authorities. It can be thought of as an asymptomatic therapy system.77

Herbal Medicinal System

Herbal medicine gets its name from the word herb, which historically meant dried and fresh flowering or leafy green parts of plants. However, the phrase is now often used to refer to any plant part that can be utilized as medicine, such as the leaf, root, bark, flower seed, resin, and so on.78 As a result, a completely new discipline of medicinal chemistry has emerged, which comprises all systems that utilize plant parts for disease treatment, diagnosis, cure, mitigation, or prevention. Ayurveda, Homeopathy, Western medicine, and Chinese medicine are only a few examples of well-known medical systems. Herbal medicine, which is a supplement or alternative to allopathy, is now referred to as complementary, alternative, non-conventional, non-allopathic, and occasionally traditional medicine79 because it is a compliment or alternative to allopathy. Because of the system's origin, it is based mostly on the experiences, beliefs, and theories of indigenous peoples from various civilizations. It is also known as botanical and phytomedicine about the plant that is its primary source. Herbal medications, botanicals, nutraceuticals, dietary supplements, and phytopharmaceuticals are examples of herbal medicine formulations that can be categorized depending on their class, usage, or function.80 Herbal medicine is used to treat a holistic approach to life rather than a specific disease or ailment. It focuses on the body's, mind's, and surrounding environment's state of equilibrium or balance. According to the findings, herbal medicines are widely used to cure a variety of disorders all over the world. According to surveys, about 85% of the population in Africa, 75% in India, and a significant number of the population in the United States, Europe, and other parts of the world use herbal medicine.81 The concept and practice of herbal medicine are influenced by the environment, current conditions, and geographical location.82 One of the system's significant flaws is the lack of systematic techniques to assessing and demonstrating the usefulness, effectiveness, safety, and quality of herbal medicine.83

Concept and Approaches towards Disease Management

Herbal medicine looks at the body as a whole and aims to boost the body's ability to repair itself by boosting the immune system. In terms of treatment and prescription, it strikes a balance between methodical, natural, and unique techniques. Herbal treatments are provided as personalized medications, which means that the remedies are adapted to the specific needs of the patient. It explores how each person differs from others in particular areas, such as his appearance, speech, decisions, conduct, or susceptibility to diseases. As a result, it has a high level of individuality.

The Allopathic medicinal approach, on the other hand, believes in treating a disease or problem by focusing on its symptoms. As a result, each sickness or collection of disorders, as well as its side effects, has a specific medicine that is thought to be the sole way to cure the disease or
disorder. Because the cure concentrates on the disease, there is little or no individualization for the patients in allopathy. For example, two persons who are both sick with the flu will most likely take the same medicine.

**Dosage Forms and Mode of Administration**

The herbal method has been widely adopted in daily life, from herbal bitters to herbal soap, toothpaste, cream, and even tea. It also encompasses a variety of folk, unconventional, and indeed any type of treatment practice that has been passed down via a community or ethnic group's tradition. Herbal medications are sold in a variety of forms, including solid, semisolid, and liquid extracts, as well as fresh or dried herbs. They're used to treat chronic ailments including back pain and stress-related conditions that can be tough to manage. Herbs have also been used as health supplements to address sexual problems, in addition to treating diseases.

Allopathic drugs come in a variety of dose forms, including solid, semi-solid, liquid, and even gaseous. After thorough research of the most effective form of medicine, the allopathic medicinal system formulates and produces pharmaceuticals as tablets, capsules, granules, powders, solutions, suspensions, emulsions, sprays, injections, and other forms. They are given orally, subcutaneously, intramuscularly, inhaled, and in a variety of other ways.

**The Impact and Choice of Medicinal System Globally regarding Wound healing**

Although allopathy has long been the most widely accepted school of medicine, people are increasingly turning to herbal therapy. This is due to the following shortcomings of allopathic medicine:

- The allopathic system has serious and frustrating side effects
- Allopathic medicines are very costly

In these situations, herbal treatments such as Ayurveda and homeopathy are favoured due to the following characteristics:

- The concept of moist wound healing has acquired a lot of traction, and it's now being used in traditional medicine to speed up the healing process.
- In wound care management, several investigations using herbal and traditional medicine from several continents have been published.
- Honey has been utilized in wound care for many years with great success. Recent scientific findings and clinical trials in wound care that included traditional and alternative medicine show promise for the future.
- Herbal medicines are less expensive and more reasonable
- Herbal medicines directly correspond to the patient's beliefs
- Herbal medicines are more accessible, have a longer shelf life, are natural, and safer, and have fewer or no adverse effects.

**OPPORTUNITIES AND CONCLUSION**

Many medicinal plants help the skin's natural repair mechanisms, and so have a lot of therapeutic promise in wound care. Wound healing can be treated using a variety of treatments, including allopathic and herbal. Wound healing is treated with a variety of herbal formulations such as gels, ointments, creams, pastes, and so on. There are many challenges and difficulties with herbal drugs that must be overcome, such as the difficulty of herbal ingredients requiring special care and precautions throughout the entire extraction process, proper drying conditions must be adhered to, no specific standardization, and only a few natural ingredients can be used in the formulation during clinical research. The use of nanotechnology in herbal formulations is an innovative way to get around the limitations of existing medication delivery systems. Various techniques for herbal formulations include a high-pressure homogenized method, complex coacervation method, co-precipitation method, salting out method, and so on. Both allopathic and herbal medicines are used to treat wound healing, but allopathic medicines have some drawbacks, such as serious and frustrating side effects, and are very expensive, whereas herbal medicines are preferred because they have fewer side effects, are more accessible, have been time tested, and are considered natural and safer. The purpose of this review is to examine the most common excipients used in herbal formulations, as well as various medicinal plants traditionally used in wound healing, wound healing difficulties and challenges, the use of nanotechnology in herbal formulation, the future scope of herbal medicines in wound healing, and a comparison of allopathy and herbal formulations. Novel medications for wound healing can be created using a blend of traditional and current expertise, with much fewer undesired side effects.

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