Review Article

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

Balap A.R*, Gaikwad A.A
PE'S Modern College of Pharmacy, Nigdi, Pune, Maharashtra, India.
***Corresponding author's E-mail:** aishwaryarb@yahoo.co.in

Received: 22-07-2021; **Revised:** 24-10-2021; **Accepted:** 29-10-2021; **Published on:** 15-11-2021.

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.

QUICK RESPONSE CODE →

DOI:
10.47583/ijpsrr.2021.v71i01.015

DOI link: http://dx.doi.org/10.47583/ijpsrr.2021.v71i01.015

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[1].

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[2].

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, Luciliasericata) 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).[4] 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 thrombocytopaenia, 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.[5]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.[6]

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.[7] 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
2. Fillers and Diluents.
3. Lubricants, Glidants, Disintegrants.
4. Plasticizers
5. Preservatives

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.[8]

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 addictive 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.[9]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.

MEDICINAL PLANTS TRADITIONALLY USED IN WOUND HEALING

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 (160-180 gm), Swiss Albino mice (20-25gm), Healthy male Wistar rats weighing (200gm)	Anti-inflammatory, Anti-oxidant, Anti-Proliferative	20-22
Azardirachta 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, Anti-dental, Anti-malarial, Anti-tumour, Anti-fertility. Anti-hypertensive	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, Antioedematous, 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 odarata	Paste, Ointment	Maceration, Soxhlet	Excision	Female Wistar Albino rats weighing (120-80gm), Sprague Dawley rats weighing (180-200gm)	Anti-microbial, Anti-fungal, Anti-inflammatory, Anti-biotic, 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

Hydnocarpus wightiana	Paste, Oil-extracts	Nil	Incision, Dead space, Excision	Male Wistar rats	Antineoplastic, Anti-inflammatory	53-55
Lantana camera	Emulgel, Ointment	Soxhlet, Maceration	Excision	Healthy Inbred male Sprague Dawley rats weighing (200-220gm)	Anthelmintic, Anti-protozoal, Insecticidal, Antiviral, Anti-oxidant, Antibacterial, anti-fungal	56-58
Rosmarinus officinalis	Liquid or Semi-solid dosage forms	Steam distillation	Excision, Cutaneous	Healthy adult male Sprague Dawley rats weighing (160-180gm), Male BALB/Mice 6 weeks age weighing (18-20gm)	Anti-microbial, Anti-inflammatory, Anti-biofilm, Anti-proliferative, Antimutagenic	59-61
Tridax procumbens	Ointment, Leaf juice	Soxhlet, Maceration	Linear and Excision, Dermal	Adult Wistar rats of both sexes weighing (180-200gm), Adult Albino rats of either sex weighing (150-200gm)	Anti-oxidant, Antibacterial	62-68

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 microparticles 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 area[72], 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 medicine[79] 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[84], 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.[85]

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.

REFERENCES

1. Ernst E. Herbal medicines: balancing benefits and risks. In Novartis found symp 2007;282:154-167.
2. SCHILLING JA. Department of Surgery, University of Oklahoma Medical. Physiological Reviews. 1968;48(2-4):374.
3. Cohen IK, Die-gelmann RF, Lindblad WJ, Hugo NE. Wound healing: biochemical and clinical aspects. Plastic and Reconstructive Surgery. 1992 Nov 1;90(5):926.
4. Enoch S, Grey JE, Harding KG. Non-surgical and drug treatments. Bmj. 2006 Apr 13;332(7546):900-3.
5. Tapsell LC, Hemphill I, Cobiac L, Sullivan DR, Fenech M, Patch CS, Roodenrys S, Keogh JB, Clifton PM, Williams PG, Fazio VA. Health benefits of herbs and spices: the past, the present, the future.
6. Huffman MA. Animal self-medication and ethno-medicine: exploration and exploitation of the medicinal properties of plants. Proceedings of the Nutrition Society. 2003 May;62(2):371-81.

7. Dwivedi G, Dwivedi S. History of Medicine: Sushruta–the Clinician–Teacher par Excellence. National Informatics Centre (Government of India). 2007;403.
8. Nagpal N, Kaur P, Kumar R, Rahar S, Dhawan R, Arora M. Pharmaceutical diluents and their unwanted effects: a review. Bull Pharm Res. 2016;6(2):45-9.
9. Karthik V. Excipients used in the formulation of tablets. J Chem. 2016;5(2):143-54.
10. Hemmati AA, Arzi A, Amin M. Effect of Achillea millefolium extract in wound healing of rabbit. Journal of natural remedies. 2002 Jun 1;2(2):164-7.
11. Nirmala S, Karthiyayini T. Wound healing activity on the leaves of Achillea millefolium L. by excision, incision, and dead space model on adult wistar albino rats. Int Res J Pharm. 2011;2(3):240-5.
12. Khosra F, Abrishamchi P, Bahrami AR, Matin MM, Ejtehadi H, Varasteh-Kojourian M. Enhanced cutaneous wound healing by the leaf extract of Achillea eriophora DC using the in vitro scratch assay. Journal of Sciences, Islamic Republic of Iran. 2017 Oct 1;28(4):305-12.
13. Akkol EK, Koca U, Pesin I, Yilmazer D. Evaluation of the wound healing potential of Achillea biebersteiniiAfan.(Asteraceae) by in vivo excision and incision models. Evidence-Based Complementary and Alternative Medicine. 2011 Jan 1;20:11-19.
14. Pirbalouti AG, Koohpayeh A, Karimi I. The wound healing activity of flower extracts of Punica granatum and Achillea kellalensis in Wistar rats. Acta Pol Pharm. 2010 Jan 1;67(1):107-115.
15. Nemeth E, Bernath J. Biological activities of yarrow species (Achillea spp.). Current pharmaceutical design. 2008 Oct 1;14(29):3151-67.
16. Takzare N, Hosseini MJ, Hasanzadeh G, Mortazavi H, Takzare A, Habibi P. Influence of Aloe Vera gel on dermal wound healing process in rat. Toxicology Mechanisms and Methods. 2009 Jan 1;19(1):73-7.
17. Reynolds T, Dweck AC. Aloe vera leaf gel: a review update. Journal of ethnopharmacology. 1999 Dec 15;68(1-3):3-7.
18. Khan AW, Kotta S, Ansari SH, Sharma RK, Kumar A, Ali J. Formulation development, optimization and evaluation of aloe vera gel for wound healing. Pharmacognosy magazine. 2013 Oct;9(Suppl 1):S6.
19. Liu C, Cui Y, Pi F, Cheng Y, Guo Y, Qian H. Extraction, purification, structural characteristics, biological activities and pharmacological applications of acemannan, a polysaccharide from aloe vera: A review. Molecules. 2019 Jan;24(8):1554.
20. Akkol EK, Süntar I, Orhan IE, Keles H, Kan A, Çoksari G. Assessment of dermal wound healing and in vitro antioxidant properties of Avena sativa L. Journal of cereal science. 2011 May 1;53(3):285-90.
21. Veerasubramanian PK, Thangavel P, Kannan R, Chakraborty S, Ramachandran B, Suguna L, Muthuvijayan V. An investigation of konjac glucomannan-keratin hydrogel scaffold loaded with Avena sativa extracts for diabetic wound healing. Colloids and Surfaces B: Biointerfaces. 2018 May 1;165:92-102.
22. Perrelli A, Goitre L, Salzano AM, Moglia A, Scaloni A, Retta SF. Biological activities, health benefits, and therapeutic properties of avenanthramides: from skin protection to prevention and treatment of cerebrovascular diseases. Oxidative medicine and cellular longevity. 2018 Aug 23;2018.
23. Munir M, Shah SN, Almas U, Khan FA, Zaidi A, Bukhari SM, Murtaza G. An assessment of the wound healing potential of a herbal gel containing an *Azadirachta indica* leaf extract. Veterinárnímedicína. 2021 Mar 2;66(3):99-109.
24. Babu KS, Naik VK, Latha J, Prabhakar V. Wound healing activity of ethanolic extract of natural products (*Azadirachta indica* bark) in albino wister rats. World Journal of Pharmacy and Pharmaceutical Sciences. 2016 Apr 5;5(6):1624-32.
25. Nayak BS, Sandiford S, Maxwell A. Evaluation of the wound-healing activity of ethanolic extract of Morindacitrifolia L. leaf. Evidence-based complementary and alternative medicine. 2009 Sep 1;6(3):351-6.
26. Soni A, Dwivedi VK, Chaudharry M, Shrivastava SM, Naithani V. Efficacy of ampucare: A novel herbal formulation for burn wound healing versus other burn medicines. Asian Journal of Biological Sciences. 2010;3(1):18-27.
27. Hashmat I, Azad H, Ahmed A. Neem (*Azadirachta indica* A. Juss)-A nature's drugstore: an overview. Int Res J Biol Sci. 2012 Oct;1(6):76-9.
28. Parente LM, Lino Júnior RD, Tresvenzol LM, Vinaud MC, de Paula JR, Paulo NM. Wound healing and anti-inflammatory effect in animal models of *Calendula officinalis* L. growing in Brazil. Evidence-based complementary and alternative medicine. 2012 Oct;2012.
29. Nicolaus C, Junghanns S, Hartmann A, Murillo R, Ganzera M, Merfort I. In vitro studies to evaluate the wound healing properties of *Calendula officinalis* extracts. Journal of ethnopharmacology. 2017 Jan 20;196:94-103.
30. Preethi KC, Kuttan R. Wound healing activity of flower extract of Calendula offlcinalis. Journal of basic and clinical physiology and pharmacology. 2009 Mar 1;20(1):73-80.
31. Givol O, Kornhaber R, Visentin D, Cleary M, Haik J, Harats M. A systematic review of *Calendula officinalis* extract for wound healing. Wound Repair and Regeneration. 2019 Sep;27(5):548-61.
32. Sengupta R. Combined wound healing activity of *Calendula officinalis* and Basil leaves. Journal of Pharmacognosy and Phytochemistry. 2017;6(1):173-6.
33. Khalid KA, Da Silva JT. Biology of *Calendula officinalis* Linn.: focus on pharmacology, biological activities and agronomic practices. Medicinal and Aromatic Plant Science and Biotechnology. 2012;6(1):12-27.
34. Priya KS, Arumugam G, Rathinam B, Wells A, Babu M. Celosia argentea Linn. leaf extract improves wound healing in a rat burn wound model. Wound repair and regeneration. 2004 Nov;12(6):618-25.
35. Tang Y, Xin HL, Guo ML. Review on research of the phytochemistry and pharmacological activities of Celosia argentea. Revistabrasileira de farmacognosia. 2016 Nov;26:787-96.
36. Somboonwong J, Kankaisre M, Tantisira B, Tantisira MH. Wound healing activities of different extracts of *Centella asiatica* in incision and burn wound models: an experimental

animal study. BMC complementary and alternative medicine. 2012 Dec;12(1):1-7.

37. Shetty BS, Udupa SL, Udupa AL, Somayaji SN. Effect of *Centella asiatica* L (Umbelliferae) on normal and dexamethasone-suppressed wound healing in Wistar Albino rats. The International Journal of Lower Extremity Wounds. 2006 Sep;5(3):137-43.

38. Shukla A, Rasik AM, Jain GK, Shankar R, Kulshrestha DK, Dhawan BN. In vitro and in vivo wound healing activity of asiaticoside isolated from *Centella asiatica*. Journal of ethnopharmacology. 1999 Apr 1;65(1):1-1.

39. Sultan RA, Mahmood SB, Azhar I, Ahmed SW, Mahmood ZA. Biological activities assessment of *Centella asiatica* (Linn.). Journal of Herbs, Spices & Medicinal Plants. 2014 Jul 3;20(3):319-27.

40. Oso B, Abey N, Oyeleke O, Olowookere B. Comparative Study of the in vitro Antioxidant Properties of Methanolic Extracts of *Chromolaena odorata* and Ageratum conyzoides used in Wound Healing. International Annals of Science. 2019;6(1):8-12.

41. Phan TT, Wang L, See P, Grayer RJ, Chan SY, Lee ST. Phenolic compounds of *Chromolaena odorata* protect cultured skin cells from oxidative damage: implication for cutaneous wound healing. Biological and Pharmaceutical Bulletin. 2001;24(12):1373-9.

42. Vijayaraghavan K, Rajkumar J, Seyed MA. Efficacy of *Chromolaena odorata* leaf extracts for the healing of rat excision wounds. Veterinárnímedicína. 2017 Oct 27;62(10):565-78.

43. Mahmood AA, Indran M, Salmah I, Sidix K, Suzainur KA. Evaluation of in vivo wound healing activity of *Chromolaena odorata* leaf extract on excision wounds model in rats. J Food Technol. 2005;3:126-9.

44. Félicien A, Alain AG, Sebastien DT, Fidele T, Boniface Y, Chantal M, Dominique S. Chemical composition and Biological activities of the Essential oil extracted from the Fresh leaves of *Chromolaena odorata* (L. Robinson) growing in Benin. ISCA Journal of Biological Sciences. 2012;1(3):7-13.

45. Thakare VM, Chaudhari RY, Patil VR. Wound healing evaluation of some herbal formulations containing Curcuma longa and Cynodondactylon extract. International Journal of Phytomedicine. 2011 Jul 1;3(3):325-32.

46. Maghimaa M, Alharbi SA. Green synthesis of silver nanoparticles from Curcuma longa L. and coating on the cotton fabrics for antimicrobial applications and wound healing activity. Journal of Photochemistry and Photobiology B: Biology. 2020 Mar 1;204:111806.

47. Pawar RS, Toppo FA, Mandloi AS, Shaikh S. Exploring the role of curcumin containing ethanolic extract obtained from *Curcuma longa* (rhizomes) against retardation of wound healing process by aspirin. Indian journal of pharmacology. 2015 Mar;47(2):160.

48. Araujo CA, Leon LL. Biological activities of Curcuma longa L. Memórias do Instituto Oswaldo Cruz. 2001;96:723-8.

49. Tuhin RH, Begum MM, Rahman MS, Karim R, Begum T, Ahmed SU, Mostofa R, Hossain A, Abdel-Daim M, Begum R. Wound healing effect of *Euphorbia hirtalinn*.(Euphorbiaceae) in alloxan induced diabetic rats. BMC complementary and alternative medicine. 2017 Dec;17(1):1-4.

50. Jaiprakash B, Chandramohan D. Burn wound healing activity of *Euphorbia hirta*. Ancient science of Life. 2006 Jan;25(3-4):16.

51. Bigoniya P, Agrawal S, Verma NK. Potential wound healing activity of *Euphorbia hirta* Linn total flavonoid fraction. Int J Pharm Sci Rev Res. 2013;22(2):149-56.

52. Yang ZN, Su BJ, Wang YQ, Liao HB, Chen ZF, Liang D. Isolation, absolute configuration, and biological activities of chebulic acid and brevifolincarboxylic acid derivatives from *Euphorbia hirta*. Journal of natural products. 2020 Mar 6;83(4):985-95.

53. Sarandy MM, Novaes RD, da Matta SL, Mezencio JM, da Silva MB, Zanuncio JC, Gonçalves RV. Ointment of Brassica oleracea var. capitata matures the extracellular matrix in skin wounds of wistar rats. Evidence-Based Complementary and Alternative Medicine. 2015 Jan 1;2015.

54. Tasleem S, Naqvi SB, Khan SA, Hashmi K. Efficacy of newly formulated ointment containing 20% active antimicrobial honey in treatment of burn wound infections. Journal of Ayub Medical College Abbottabad. 2013 Jun 1;25(1-2):145-8.

55. Díaz-Tielas C, Graña E, Reigosa MJ, Sánchez-Moreiras AM. BIOLOGICAL ACTIVITIES AND NOVEL APPLICATIONS OF CHALCONES1. Planta Daninha. 2016 Jul;34:607-16.

56. Oommen ST, Rao M, Raju CV. Effect of oil of hydnocarpus on wound healing. International journal of leprosy and other mycobacterial diseases. 1999 Jun 1;67:154-8.

57. Oommen ST. The effect of oil of hydnocarpus on excision wounds. International Journal of Leprosy and Other Mycobacterial Diseases. 2000 Mar 1;68(1):69-70.

58. Sharma DK, Hall IH. Hypolipidemic, anti-inflammatory, and antineoplastic activity and cytotoxicity of flavonolignans isolated from *Hydnocarpus wightiana* seeds. Journal of natural products. 1991 Sep;54(5):1298-302.

59. Sultana SS, Swapna G, Lakshmi GS, Swathi S, Jyothi GN, Devi AS. Formulation and evaluation of herbal emulgel of Lantana camara leaves extract for wound healing activity in diabetic rats. Indo American Journal of Pharmaceutical Research. 2016;6(8):6404-17.

60. Nayak BS, Raju SS, Eversley M, Ramsubhag A. Evaluation of wound healing activity of Lantana camara L.–a preclinical study. Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives. 2009 Feb;23(2):241-5.

61. Sousa EO, Costa JG. Genus Lantana: chemical aspects and biological activities. RevistaBrasileira de Farmacognosia. 2012 Oct;22(5):1115-80.

62. Abu-Al-Basal MA. Healing potential of *Rosmarinus officinalis* L. on full-thickness excision cutaneous wounds in alloxan-induced-diabetic BALB/c mice. Journal of ethnopharmacology. 2010 Sep 15;131(2):443-50.

63. Labib RM, Ayoub IM, Michel HE, Mehanny M, Kamil V, Hany M, Magdy M, Moataz A, Maged B, Mohamed A. Appraisal on the wound healing potential of Melaleuca alternifolia and Rosmarinus officinalis L. essential oil-loaded chitosan topical preparations. PloS one. 2019 Sep 16;14(9):e0219561.

64. de Oliveira JR, de Jesus D, Figueira LW, de Oliveira FE, Pacheco Soares C, Camargo SE, Jorge AO, de Oliveira LD. Biological activities of Rosmarinus officinalis L.(rosemary) extract as analyzed in microorganisms and cells. Experimental Biology and Medicine. 2017 Mar;242(6):625-34.

65. Talekar YP, Das B, Paul T, Talekar DY, Apte KG, Parab PB. Evaluation of wound healing potential of aqueous and ethanolic extracts of Tridax procumbens Linn in Wistar Rats. Asian Journal of Pharmaceutical and Clinical Research. 2012;5(4):141-5.

66. Ravindran J, Arumugasamy V, Baskaran A. Wound healing effect of silver nanoparticles from Tridax procumbens leaf extracts on *Pangasius hypophthalmus*. Wound Medicine. 2019 Dec 1;27(1):100170.

67. Yaduvanshi B, Mathur R, Mathur SR, Velpandian T. Evaluation of wound healing potential of topical formulation of leaf juice of Tridax procumbens L. in mice. Indian journal of pharmaceutical sciences. 2011 May;73(3):303.

68. Udupa SL, Udupa AL, Kulkarni DR. Influence of Tridax procumbens on lysyl oxidase activity and wound healing. Planta Medica. 1991 Aug;57(04):325-7.

69. Andriana Y, Xuan TD, Quy TN, Minh TN, Van TM, Viet TD. Antihyperuricemia, antioxidant, and antibacterial activities of Tridax procumbens L. Foods. 2019 Jan;8(1):21.

70. Yadav D, Suri S, Choudhary AA, Sikender M, Hemant BN, Beg NM. Novel approach: Herbal remedies and natural products in pharmaceutical science as nano drug delivery systems. Int J Pharm Tech. 2011 Sep;3(3):3092-116.

71. Bairwa NK, Sethiya NK, Mishra SH. Protective effect of stem bark of Ceiba pentandralinn. against paracetamol-induced hepatotoxicity in rats. Pharmacognosy Research. 2010 Jan;2(1):26.

72. Sahni JK, Baboota S, Ali J. Promising role of nanopharmaceuticals in drug delivery. Pharma Times. 2011;43(10):16-8.

73. Fessi HP, Puisieux F, Devissaguet JP, Ammoury N, Benita S. Nanocapsule formation by interfacial polymer deposition following solvent displacement. International journal of pharmaceutics. 1989 Oct 1;55(1):R1-4.

74. Jung J, Perrut M. Particle design using supercritical fluids: literature and patent survey. The Journal of supercritical fluids. 2001 Aug 1;20(3):179-219.

75. Gunjan M, Naing TW, Saini RS, Ahmad A, Naidu JR, Kumar I. Marketing trends & future prospects of herbal medicine in the treatment of various disease. World Journal of Pharmaceutical Research. 2015 Jun 28;4(9):132-55.

76. Ahmad AS, Sharma R. Comparative Analysis of Herbal and Allopathic Treatment systems. European Journal of Molecular & Clinical Medicine. 2020 Dec 23;7(7):2869-76.

77. Bhargava J, Khan ZY. Comparative Evaluation of the efficacy and side effects of imipramine, sertraline and an ayurvedic formulation in patients of depression. J Clin Diagn Res. 2012 Apr;6(2):220-5.

78. Jawla S, Gupta AK, Singla R, Gupta V. General awareness and relative popularity of allopathic, ayurvedic and homeopathic systems. J Chem Pharm Res. 2009;1(1):105-12.

79. Mahato, R. I., Narang, A. S. Pharmaceutical dosage forms and drug delivery. CRC Press, Oct 25, 2011.

80. Wachtel-Galor S, Benzie IF. An introduction to its history, usage, regulation, current trends, and research needs. Herbal Medicine: Biomolecular and Clinical Aspects, 2nd ed.; Benzie, IFF, Wachtel-Galor, S., Eds.:1-0.

81. Miller LG. Herbal medicinals: selected clinical considerations focusing on known or potential drug-herb interactions. Archives of internal medicine. 1998 Nov 9;158(20):2200-11.

82. Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Brazilian Journal of medical and Biological research. 2000 Feb;33(2):179-89.

83. Gogtay NJ, Bhatt HA, Dalvi SS, Kshirsagar NA. The use and safety of non-allopathic Indian medicines. Drug safety. 2002 Dec;25(14):1005-19.

84. Kumar, K., Rai, A. K. A Review on Conventional and Ayurvedic medicine: Need of Time for their Synergistic Effects. Int. J. Pharm. Life Sci. 2011;18(1):13-21.

85. Pal SK, Shukla Y. Herbal medicine: current status and the future. Asian pacific journal of cancer prevention. 2003 Aug 20;4(4):281-8.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.