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UNDERSTANDING OF PHYTO-NANOMEDICINE FOR THE MANAGEMENT OF INFLAMMATION AND WOUND HEALING: AN OUTLOOK

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ABSTRACT: Nanoparticles are the modern-day drug delivery system for biocompatible drugs. Numerous products have developed from nanotechnology to develop effective wound healing and inflammatory treatments. Plant extracts (phytoconstituents) have a lot of therapeutically potential because of their distinctive properties, including anti-inflammatory, antioxidant and insulin-sensitizing properties etc. Furthermore, the nanostructure of herbal extracts and phytoconstituents could enhance the bioavailability, influence relieves of the manner of drug carrier systems to the wounded area, and increase permeation ability to the underlying layers of the skin, all of which are essential for the recovery process and treating inflammation. This review emphasizes nano-formulations of plant extracts. Many approaches have already been published for the preparation of metal nanoparticles, including laser ablation, evaporation-condensation, thermal-decomposition, chemical reduction, photochemical processes, and biological methods (Green synthesis of metal nanoparticles utilizing diverse herbal extracts). Some herbal extracts and their phytochemicals are classified as a potential substitute for wound healing and treating inflammation intermediates due to the presence of various bioactive ingredients, the ease of access, and the reduction of adverse effects. Overall, when employed in nano-formulations, various herbal extracts and related phytoconstituents have shown excellent effectiveness in treating wounds and inflammation and could be considered as possible pharmaceutical medications in the future. This review provides a conceptual information of various herbal based nanoparticles for the management of inflammation and wound healing.

INTRODUCTION: Nanoparticles have been derived from the Greek term "Nanos," which means "little," "tiny," "dwarf," or "extremely small." Their particle sizes range from 1 to 100 nm [1]. Since, antiquity, herbal treatments have been utilized to cure a wide range of ailments.

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Herbal medications became more popular due to their ability to cure many conditions with fewer complications and side effects.

Phytoconstituents derived from traditional plants are now widely accepted as pilot molecules in modern medications [2]. Plants contain phytoconstituents, which are part of the physiological functions of living plants. As a result, they are expected to be more compatible with the human body. The poor oral bioavailability of phytoconstituents, however, concerns researchers. These are being formed into various novel delivery methods, such as phytosomes, liposomes, and nanoparticles, to overcome these impediments and increase the effectiveness of herbal medicines [3]. Herbal nanotechnology is classified among the most promising new drug delivery systems with nano-formulations thought to have many advantages over conventional phytoconstituents formulations, including enhanced permeability, dissolution, bioavailability, pharmacological activity, stabilization, enhanced biodistribution, and prolonged administration [4]. In nanotechnology, metal nanoparticles appear to have an improved surface-to-volume ratio and antibacterial properties due to their capacity to interact with biological membranes [5].

Noble metal nanoparticles, including platinum, gold, silver, iron, titanium, zinc, and palladium have sparked much interest because of their many biological and physiochemical uses. To date, many ways for producing silver nanoparticles (Ag-NPs) have been published, including chemical, physical and biological methods [6] **Fig. 1**. Sharma *et al.* [7] prepared triptolide silver nanoparticles for anti-inflammatory activity from plant extract of *Tripterygium wilfordii*. They found that enhancement of the permeation of drugs via the stratum corneum by improved hydration and showed anti-inflammatory action on skin. Manikandan *et al.* [8] biosynthesized silver nanoparticles (Ag-NPs) from rose petals (*Rosa indica*) and tested their *in-vitro* Antibacterial activities against pathogenic human pathogens, Anti-cancer activity against the human colon adenocarcinoma cancer-cell line (HCT 15), and Anti-inflammatory activity against rat peritoneal macrophages. Wounds and inflammation are serious illnesses that have an impact on people's quality of life across the world. Fortunately, the body's natural healing process depends on inflammation, which keeps cells functioning normally. However, acute and chronic inflammation is recognized as troublesome types of inflammation. People are familiar with the symptoms of acute inflammation, which include redness, swelling, and pain around tissues and joints. Numerous things, including microbial diseases, environmental risks, and chemical agents, can induce inflammation [9]. Despite current advancements in wound treatment and inflammation, traditional approaches based on natural and herbal medicines are now seen as potential substitute medications due to the diversity of phytoconstituents, easy accessibility, restricted adverse effects, and reduced costs. The following overview covers a thorough investigation on the herbal nanoformulations both for wound-healing and inflammation treatment, **Table 1** and **Table 2** summarised the herbal extracts and phytoconstituents that aid in anti-inflammatory and wound healing successfully. Nanostructures and nanoformulations have shown success in recent years in conquering the limitations of common medications, providing an intelligent healing process, regulating therapeutic release, reducing healing doses, and developing a unique possibility to assist healing events for chronic wounds [10].

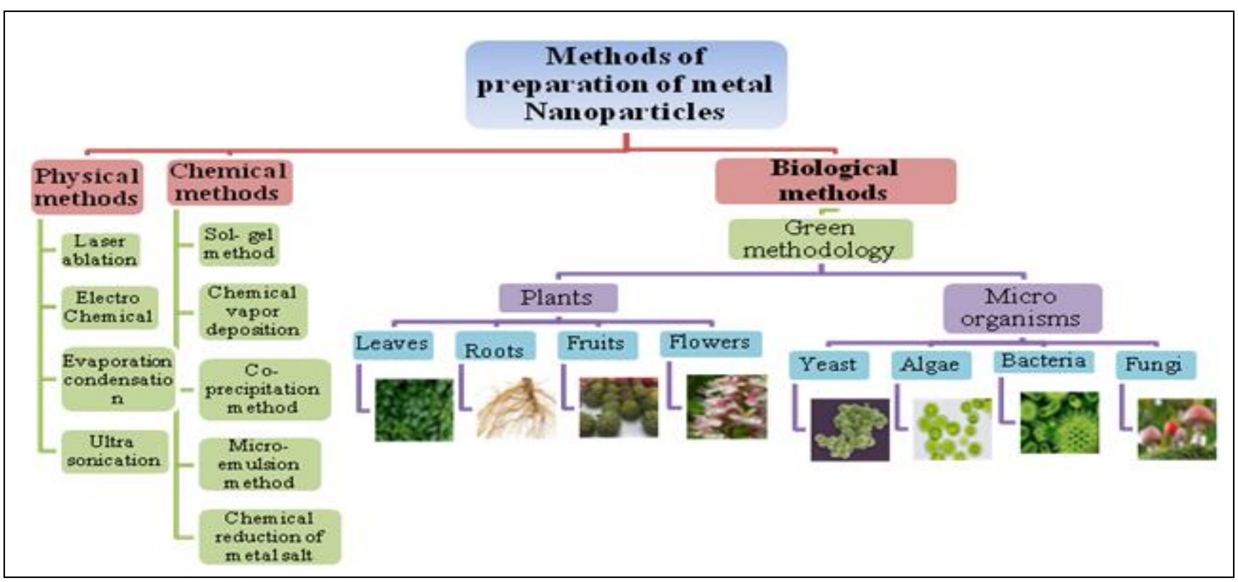

FIG. 1: DIFFERENT APPROACHES FOR PRODUCTION OF METAL NANOPARTICLE

Production of Metal Nanoparticles: The following methods for producing metal nanoparticles are discussed:

Chemical Methods: Chemical vapour deposition, Sol-gel process, Chemical reduction of metal salt, Co-precipitation method, Micro-emulsion method.

Physical Methods: Evaporation-condensation, laser ablation and thermal-decomposition.

Biological Methods: From plants and microorganisms like bacteria, fungi, yeast, and algae.

Chemical Methods: General synthesis of NPs by chemical methods may be influenced by several components like Metallic precursor(s), Silver citrate, Silver nitrate ($AgNO_3$) or Silver acetate, Tetrachloroauric acid ($HAuCl_4$), Reducing agents (solvent) like Sodium borohydride ($NaBH_4$), Ascorbate, N, N- Dimethyl Formamide (DMF) and Stabilizing agents like trisodium citrate, Polyethylene glycol (PEG), Polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), or sodium oleate. The speed of these processes, which is regulated by factors like concentration, temperature, pH and reducing capacity at critical points in the synthesis, determines the diameter and morphology of particles. On the other hand, the stabilizing agent is crucial in biosynthesis because it protects the nanoparticles from undesired aggregation while they are shaped and sized [11].

Although chemical production methods require less time to produce vast quantities of nanoparticles, they also require capping entities to sustain the size of the nanoparticles (NPs). The chemicals used to manufacture and produce stable nanoparticles are toxic and produce unfriendly byproducts. On the other hand, Chemical techniques are generally costly and include poisonous compounds that might cause several biological problems [12].

As a result, the 'Green procedure,' which is less damaging, more eco-friendly, and less expensive, is being searched. Herbal Nanoparticles (NPs) formation is quick and a one-step biosynthesis technique that is biocompatible, simple and safe for human medicinal usage [13]. Seo *et al*. [14] produced Ag-NPs using a chemical reduction approach, evaluated them physicochemically and examined their influence on wound-healing activities in Zebrafish.

Physical Methods: The primarily physical methods used for metallic NPs are evaporation-condensation, laser ablation and thermal decomposition. In evaporation-condensation, a typical tube furnace at atmospheric pressure is required, which demands several kilowatts of energy, ample space, and lots of preheating time to reach thermal stability. Unlike tubular furnaces, the temperature difference at the outer surface is relatively sharp, allowing the water vapors to cool rapidly [15].

Ag-NPs may be generated *via* the laser ablation approach, which involves ionizing a metal or metal source in the presence of a liquid medium. After ionizing radiation upon a pulsed laser, the liquid medium surroundings contain Ag-NPs solely from the start of the metals, which have been cleaned of extraneous ions, chemicals, or reducing agents [16].

In the thermal-decomposition method, the powder form of Ag-NPs is formed by the decomposition of metal complex. Physical processes have several advantages over chemical approaches, including removing solvent impurities from thin films and the homogeneity of nanoparticle distribution. However, aggregation is often challenging due to the lack of capping agents [17].

Dadashi *et al*. [18] utilized laser ablation in acetone to produce stable and pure iron NPs with great dispersibility and single-phase purity. The generation of stable iron NPs was validated by a compositional and structural examination utilizing FE-SEM, XRD and UV-Visible light spectroscopy. The average particle size of iron NPs synthesized in acetone is 30 nm, whereas iron and iron oxide NPs synthesized in water have an average particle size of 27 nm. Niasari *et al.* [19] effectively generated copper and copper oxide nanoparticles size ranging from 8 to 10 nm by thermal degradation of precursor complexes; [bis (salicylaldiminato) copper (II)] complex. This method employed a low-cost, reproducible process for the large-scale production of copper nanoparticles. Jung *et al*.[20] manufactured metallic nanoparticles by evaporation/ condensation using a smaller ceramic furnace with a limited heating zone where these source metals (silver) could be vaporized.

Biological Methods (Green Approach): Many studies on the biosynthesis of metal-NPs have been published by utilizing different sources like bacteria [21], fungus [22], algae [23], yeast [24] and plants [25], due to their anti-oxidant or reductive powers required for metal component reduction processes in their respective NPs. Green approach is a biocompatible and eco-friendly process involving a reducing agent/stabilizing agent (to manage the size and avoid aggregation [7]. The reducing and stabilizing agents are exchanged by constituents produced by living microorganisms like bacteria, yeasts, fungus, algae and plants in the biosynthesis of NPs, resulting in prominent-scale manufacture with lesser contamination. Because harmful chemicals are not being utilised in the biosynthesis algorithm, using eco-friendly materials to prepare silver nanoparticles has several advantages and biomedical applications [26].

Plants are the superior framework for manufacturing NPs since they are devoid of hazardous substances and include naturally capping agents, a single-step method for large-scale manufacturing of NPs. Furthermore, using herbal drugs minimises the demand for microbial isolation and culture medium, increasing the cost-effectiveness of microbial NPs [27]. Due to the need for exceptionally sterile conditions and maintenance, microbe-mediated manufacturing is unsuitable for industrial applications. Plant extracts are thus chosen over microorganisms because of their ease of preparation, reduced biohazard, and more complicated cell culture maintenance process [28]. This review has compiled various herbal extracts derived from metal nanoparticles beneficial for multiple pharmacological activities. Wen *et al.* [29] revealed a straightforward green one-pot biosynthesis of stable AgNPs at ambient temperature using the adaptive strain of fungus *Penicillium spinulosum*. They proved that the endophytic fungus's proteins coated the AgNPs, kept them from aggregating, enhanced their inhibitory effects, and increased the AgNPs' ability to be recognized as antibacterial and significantly accelerated wound healing. Younis *et al* [30] produced biogenic AgNPs by *cyanobacteria Phormidium* sp. shown antibacterial and wound healing properties. Researchers reported several papers on metallic nanoparticles that were made from green plants' leaves and stemmed, including *Azadirachta indica* [31], *Erythrina suberosa* [32], *Ammania baccifera* [33], *Aloe barbadensis* (Aloe vera plant) [34], *Ocimum sanctum* [35], *Acalypha indica* [36], *Curcuma longa* [37], *Meliaazedarach* [38], *Moringa oleifera* seeds extract [39] having wound healing activities. A few examples of plants with Anti-inflammatory properties are as follows: aqueous leaf extract *Brachychiton populneus* [40], *Azadirachta indica* kernel aqueous extract [41], *Madhuca longifolia* leaf extract [42], aqueous leaves extract *Sterculia diversifolia* [43], aqueous leaves extract *Rhizophora apiculata* [44], methanolic leaves extract of *Solanum khasianum* [45], methanolic seeds extract of *Phoenix dactylifera* [46].

Benefits of Herbal Methods:

Herbal Preparation Methods and their Benefits Over Physical/ Chemical Methods: The biosynthesis of metal NPs mediated by plant extracts, such as Ag-NPs, has gained popularity due to its ease and effectiveness in manufacturing NPs with a consistent size and shape distribution. The plants are readily available, easy to handle well, and can conveniently expand to colossal scale production. Moreover, unlike physical procedures, no high-pressure, temperature, energy, or toxic compounds are required. Aggregation due to a lack of capping agents and nanoparticles distribution homogeneity are another complex approach in physical processes. To the initial solution, a stabiliser (surfactant) is added to the original solution in chemical synthesis methods to prevent the agglomeration of Ag-NPs. In contrast, no stabilizer is required in biological synthesis [47, 48]. Gudikandula K. and Charya Maringanti S. produced Ag-NPs both chemically and biologically utilizing the *Pycnoporus sp.*, awhite rot fungi. They also discovered that silver nanoparticles synthesized biologically had superior antibacterial efficacy against pathogens than chemically synthesized silver nanoparticles [49].

Several Preparative Approaches of Phyto-medicine: According to Vaculikova *et al*. [50] the observed solvent evaporation process can be used for a viable and cost-effective methodology for manufacturing NPs. This process may be scaled up after selecting a handy non-toxic organic solvent.

Candesartan cilexetil or Atorvastatin NPs produced in this technique would then be employed in nanotechnology with improved bioavailability. Gardouh *et al.* [51] successfully produced lipophilic model medications (Dibenzoyl peroxide, Erythromycin base, and Triamcinolone acetonide) to access the efficacy of Solid-Lipid Nanoparticles (SLNs). By utilising the high shear hot homogenization process, the drug molecules were effectively integrated into SLNs. The influence of formulation factors such as viscosity, surfactant types, particle size, concentrations on encapsulation efficiency, and physiochemical characteristics of developed SLNs was examined. *In-vitro* drug release studies revealed that drug released from created SLNs formulas was greater than that from commercially available formulae. Aside from glycerol, as a viscosity enhancer, the type and concentration of surfactant had substantially influenced the physicochemical characterization of SLNs and *in-vitro* drug release.

Protocol for Producing Nanoparticles from Plant Extract: A broad range of plants has been documented to contribute to generating Ag-NPs. The step for selecting and procuring plant parts from available sources on the internet is considered a general protocol for synthesizing NPs with a green approach **Fig. 2** [52]. To eliminate any dirt or debris from the plant parts, they were carefully cleansed with fresh and distilled water. After being shade dried for 15-20 days, the clean sources were pulverized using a high-speed mixer and passed from a stainless sieve. Then, a plant extract was obtained using a suitable method (usually continuous hot percolation extraction) and a suitable solvent. After that, the infusion was filtered.

The herbal extract was then mixed with a few millilitres of metal salt solution (e.g., silver nitrate solution), resulting in the bio-reduction of A^+ to A^o, and visual color shifts have identified from bright to dark. The UV-visible spectrophotometer was employed to determine the wavelength at different time intervals to confirm nanoparticles [6]. The produced NPs were then separated and analyzed using a UV-Vis spectrophotometer, Fourier-Transform Infrared Spectroscopy (FTIR), X-Ray Diffraction (XRD), Transmission Electron Microscopy (TEM), and Scanning Electron Microscopy (SEM) [53].

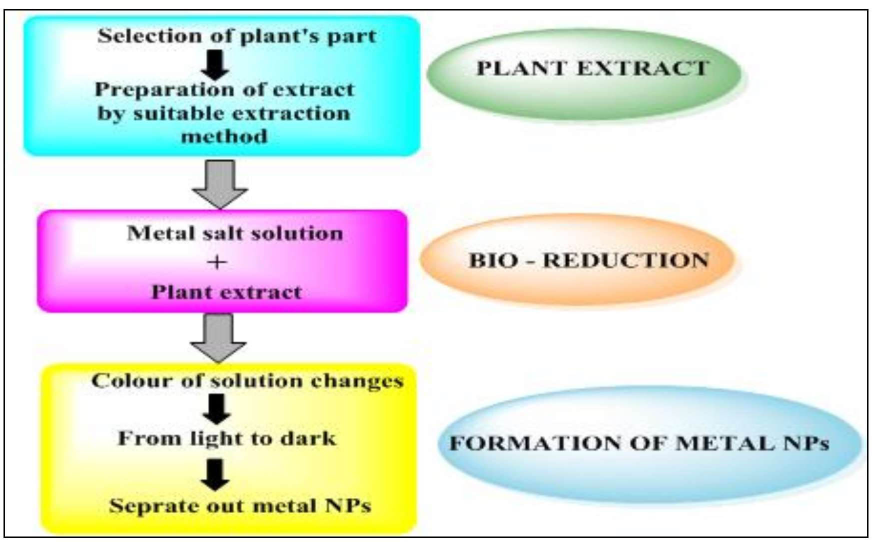

FIG. 2: BIOLOGICAL METHOD (PROTOCOL FOR PRODUCTION OF NPS USING PLANT EXTRACT)

Wound healing is a complicated set of well co-ordinated biochemical and molecular processes that regenerate skin integrity and adjacent subcutaneous tissues. Several plant extracts and phytoconstituents have been found as viable wound healing agents since they include a variety of active components, are easy to get, and have fewer adverse effects. The advancement of nano-technological approaches can aid in the improvement of medicinal effectiveness and also herbal-related materials. The study findings are given, and a discussion of the usefulness of herbal metal NPs in wound healing therapy using an experimental paradigm [54] **Table 1**. In the present review, herbal nanoparticles (particularly Ag-NPs) have the potential therapeutic objectives in wound healing and anti-inflammatory characteristics and thus demonstrate the best therapeutic results among the various methods utilized to produce phytochemical nanoformulations [55].

TABLE 1: LIST OF PLANTS FOR HERBAL METAL NANOPARTICLES (NPs) INVESTIGATED FOR WOUND HEALING ACTIVITY

Sr. no.	Family	Botanical name	Part used	Metal NPs	Experimental design (*In-vitro/in-vivo*)	Findings/Results
1.	Euphorbiaceae	*Acalypha indica*	L	Au-NPs	BALB/c mice model with diabetic wound infection (*in-vivo*)	On the 15th day, the wound area got completely re-epithelialized[36]
2.	Fabaceae	*Erythrina suberosa*	L	Ag-NPs	Normal fibroblast cell lines Cell scratch assay (*in-vitro*)	Positive effect[32]
3.	Lythraceae	*Ammania baccifera*	Wh	Ag-NPs	Burn wound infection and inflammation	Infections in burns were treated by promoting cellular proliferation and reducing inflammation[33].
4.	Lamiaceae	*Ocimum sanctum*	L	Ag-NPs TiO_2-NPs	Burn wound healing model (*in-vivo*)	Nanogel showed 96.20% wound healing activity on burn wounds[35,56–57]
5.	Lauraceae	*Lindera strychnifolia*	R	Ag-NPs	Cell scratch method (*in-vitro*)	Wound closure activity: 64%[58].
6.	Meliaceae	*Azadirachta indica*	L	Ag-NPs ZnO-NPs	Excision wound model (*in-vivo*) Incision wound model (*in-vivo*)	Wound contraction rate: 94.54% on 10th day [59 - 61]
7.	Moringaceae	*Moringa oleifera*	L	TiO_2-NPs	Excision wound model (*in-vivo*)	Treated animals showed 92.36 ± 0.5% wound healing activity on the 12th day[62, 63].
8.	Zingiberaceae	*Curcuma longa*	Rh, L	Curcumin-Si-NPs	Scratch-wound healing assay *(in-vitro)*	On HDF cells, Curcumin-Si-NPs showed complete wound closure after 24 hours[64, 37]

L: Leaves, *R*: Roots, *Rh:* Rhizome, *Wh:* Whole plant, *BALB/c*: Bagg Albino, *HDF:* Human Dermal Fibroblasts, *Si-NPs*: Silica nanoparticles, *TiO_2-NPs*: Titamium dioxide nanoparticles, *Ag-NPs*: Silver nanoparticles, *Au-NPs*: Gold Nanoparticles, *ZnO-NPs*: Zinc oxide nanoparticles.

This review substantially demonstrates the experimental design focused on the anti-inflammatory properties of NPs **Table 2.** The anti-inflammatory properties of Ag-NPs play a crucial role in wound healing by reducing inflammatory events during the early stages of wound healing in both *in-vivo* and *in-vitro* models [65].

TABLE 2: LIST OF PLANTS FOR HERBAL METAL NANOPARTICLES (NPs) INVESTIGATED FOR ANTI-INFLAMMATORY ACTIVITY

S. no.	Family	Botanical name	Part used	Metal NPs	Experimental model (*In-vitro/in-vivo*)	Findings/ Results
1.	Acanthaceae	*Andrographis paniculata*	L	Zno-NPs	Protein denaturation assay (*in-vitro*)	IC_{50} value 66.78 µg/mL[66-72].
2.	Combretaceae	*Terminalia catappa*	L	Ag-NPs	Carrageenan-induced hind paw oedema in rats (*in-vivo*)	% inhibition of oedema, at dose 50 mg/kg, 95.7% [73-75].
		T. bellerica	L	Ag-NPs	Same as above	92.13%
		T. bentazoe	L	Ag-NPs	Same as above	95.6%
		T. mellueri	L	Ag-NPs	Same as above	93%
3.	Piperaceae	*Piper nigrum*	Un F	Ag-NPs	LPS- induced expression of cytokines TNFα, IL-1β and IL-6. *(in-vitro)*	At concentrations, 10 to 20 µg/ml, cytokines were inhibited [76-79].
4.	Polygalaceae	*Polygala tenuifolia*	R	ZnO-NPs	LPS-induced expression of COX-2, iNOS and cytokines (*in-vitro*)	Suppresses the LPS-induced protein expressions of TNF-α at 1mg/ml [80-81].

5.	Rosaceae	*Prunus serrulata*	F	Ag-NPs Ag-NPs	LPS-induced inflammatory response on RAW cell line *(in-vitro)*	Effectively reduced inflammatory mediators NO, PEG_2, and COX-2 [82-84].
6.	Solanaceae	*Atropa acuminate*	L	Ag-NPs	Albumin denaturation assay	IC_{50} (µg/ml) 12.98 [85].
					Antiproteinase activity (*in-vitro*)	18.401
7.	Ulmaceae	*Holoptelea integrifolia*	L	Ag-NPs	Denaturation assay and BSA proteins binding (*in-vitro*)	K value (Binding constant) [86-87] $2.60 \pm 0.05 \times 10^{-4}$
8.	Verbenas/ Acanthaceae	*Avicennia marina*	L	Ag-NPs	Protein denaturation inhibition	72.1 %[88-94]
					Antiproteinase activity (*in-vitro*)	72.9% [95]

Al pt.: Aerial plant, *B:* Bark, *F:* Fruit, *L:* Leaves, *UnF:* Unripe Fruits, *R:* Roots, *Rh:* Rhizome, *Wh:* Whole plant, *BSA:* Bovine Serum Albumin, *COX-2:* Cyclooxygenase-2, *iNOS:* Inducible Nitric Oxide Synthase, *IL-1β*: Interleukins-1β, *LPS:* Lipopolysaccharide, *MPO:* Myeloperoxidase *NO:* Nitric Oxide, *PEG2:* Prostaglandin E2, *PVP:* Poly Vinyl Pyrrolidone, *PEG:* Polyethylene Glycol, *PVA:* Poly(Vinyl Alcohol), *TNF-α:* Tumor Necrosis Factor-α, *IC_{50}:* Half-maximal inhibitory concentration.

CONCLUSION: The outcomes of the present review primarily emphasized the importance of bioactive components as another option for healing the various types of wounds and inflammation through a successful need for nanotechnology. The influence of nanoparticles has gained interest due to bio-availability, targeted therapy and stability. Moreover, experimental biological studies are imperative to assess the intracellular goals associated with wound healing and the anti-inflammatory impacts of herbal nanomedicine; implementing well-refined clinical trials would be essential to ascertain the effectiveness and safety of natural herbal product-based nano-formulations for treatment. Phytosomes are plant-derived compounds comprising a phospholipid layer surrounding a molecule or group of molecules.

This unique combination of phospholipids and molecules provides several advantages in therapeutic delivery. First, since a phospholipid layer surrounds the molecules, they can move more rapidly across the cell membrane and efficiently than if not encapsulated. This leads to faster uptake of the therapeutic agents into the cell, which can result in a more rapid therapeutic effect. Second, because of the lipophilic nature of phytosomes, they can penetrate the cell membrane more easily than many other molecules, resulting in greater drug delivery. Finally, because of their non-toxic nature, phytosomes are safer for therapeutic delivery than many other compounds. This makes them an attractive option for patients sensitive to certain pharmaceuticals. Phytomedicines have also been proven beneficial in treating inflammation and wound healing by reducing inflammation, stimulating the development of new cells, and promoting the regeneration of healthy tissue. For example, as ginger, turmeric, and garlic has been shhave

Additionally, Aloe vera gel, honey, and essential oils have been found to be beneficial in treating wounds and promoting healing. In addition to their anti-inflammatory and wound-healing properties, phytomedicines could be intended to assess underlying conditions contributing to the inflammation and wound-healing response. For example, some herbal extracts have been found to have anti-bacterial, anti-viral, and anti-fungal properties, which can help to reduce the underlying cause of the inflammation and promote faster healing. Overall, using phytomedicines to prevent inflammation and wound-healing has a long history and is an effective treatment option. By reducing inflammation, promoting cell and tissue growth, and treating underlying causes of inflammation, phytomedicines can help to promote faster and more effective healing.

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