JPharmSci
Journal of Pharmaceutical Sciences
Open access peer-reviewed Journal
www.jpsjournal.com [ISSN: 1520-601x]

A Comprehensive Review On Herbal Nanogel Drug Delivery Systems For Wound Healing: Focus On Biophytum Sensitivum

Tanvir Shaikh[1], Samika Mohod[2], Bharat Jain[3]

Department of Pharmaceutics, MGSM. Smt. Sharadchandrika Suresh Patil College of Pharmacy, Chopda-425107, Dist. - Jalgaon (Maharashtra).

ABSTRACT

Wound healing remains one of the most significant global healthcare challenges, with chronic non-healing wounds affecting more than 6.5 million patients annually in the United States alone, imposing an estimated annual economic burden exceeding $25 billion. Conventional topical formulations including ointments, creams, and traditional gels suffer from critical limitations such as poor skin penetration, inadequate drug retention at the wound site, rapid degradation of bioactive molecules, and inability to provide sustained therapeutic concentrations. Nanotechnology, particularly the application of nanogels, has emerged as a transformative strategy to overcome these barriers. Nanogels — three-dimensional crosslinked polymeric networks in the nanometer range — offer unique advantages including high drug loading capacity, tunable drug release profiles, excellent biocompatibility, and ability to maintain a moist wound microenvironment conducive to cellular regeneration. Biophytum sensitivum (Linn.) DC. (family Oxalidaceae), a traditional medicinal plant widely used in Ayurvedic and Siddha systems, possesses well-documented wound healing, antimicrobial, antioxidant, and anti-inflammatory activities attributed to its rich phytoconstituents including tannins, flavonoids, oxalic acid derivatives, and phytol. The incorporation of Biophytum sensitivum extract into nanogel systems represents a highly promising phyto-nanotechnology approach for advanced topical wound management. This review comprehensively discusses the pathophysiology of wound healing, limitations of conventional topical systems, fundamentals and preparation methods of nanogels, the therapeutic potential of herbal extract-loaded nanogels with emphasis on Biophytum sensitivum, reported preclinical and clinical evidence, regulatory challenges, existing research gaps, and future directions in this rapidly evolving field.

Keywords: Nanogel; Wound healing; Biophytum sensitivum; Topical drug delivery; Chitosan; Phyto-nanotechnology; Controlled release.

INTRODUCTION

A wound is defined as a disruption of the normal anatomical structure and function of the skin and underlying tissues, arising from physical, chemical, thermal, or biological insults. From superficial abrasions to deep chronic ulcers, wounds represent a spectrum of injuries that require coordinated biological responses for restoration of tissue integrity. The global burden of wounds, particularly chronic non-healing wounds, is staggering: diabetic foot ulcers, venous leg ulcers, and pressure sores collectively affect more than 300 million people worldwide and impose enormous financial costs on healthcare systems, estimated at billions of dollars annually [1,2].

Despite decades of clinical advancement, conventional wound care modalities — including topical antibiotics, corticosteroids, hydrocolloid dressings, and wound irrigants — remain fraught with limitations. These include inadequate penetration through the stratum corneum, rapid drug degradation in the wound microenvironment, poor sustained release, systemic absorption leading to side effects, and patient discomfort from frequent dressing changes [3,4]. The challenge is compounded by the increasing prevalence of antibiotic-resistant wound pathogens such as methicillin-resistant

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

Staphylococcus aureus (MRSA), which renders conventional antimicrobial therapy increasingly ineffective [5].

Nanotechnology has emerged as a disruptive paradigm in pharmaceutical science, offering nanocarrier platforms that overcome the inherent limitations of conventional drug delivery. Nanoparticulate systems including liposomes, solid lipid nanoparticles, nanoemulsions, and nanogels have demonstrated superior drug encapsulation, controlled release, enhanced skin penetration via appendageal and transcellular pathways, and the capacity for targeted delivery to wound-associated cells such as fibroblasts and macrophages [6,7].

Among these nanocarriers, nanogels occupy a unique niche. Defined as three-dimensional, hydrophilic polymeric networks swollen with water at the nanoscale, nanogels synergistically combine the advantages of both hydrogels (moisture maintenance, tissue adhesion, drug loading capacity) and nanoparticles (small size, large surface area, cellular uptake, and controlled release kinetics) [8,9]. Their inherent biocompatibility, high water content, and the capacity to respond to physiological stimuli (pH, temperature, redox potential) render them ideally suited for the dynamic wound microenvironment.

Parallel to synthetic pharmaceutical advances, traditional medicine systems such as Ayurveda, Unani, and Chinese herbal medicine have employed plant-derived preparations for wound healing for millennia. Modern phytopharmacology has validated the wound-healing properties of numerous herbal bioactives — curcumin, aloe vera, Centella asiatica, neem, and calendula among others — by elucidating mechanisms including free radical scavenging, inhibition of pro-inflammatory cytokines, stimulation of fibroblast proliferation, and enhancement of collagen deposition [10,11]. However, the clinical translation of herbal wound therapies is hampered by the poor bioavailability, chemical instability, and variable absorption of phytoconstituents. Nanogel-mediated delivery provides a compelling strategy to resolve these limitations.

Biophytum sensitivum (L.) DC, a small, erect annual herb of the family Oxalidaceae, distributed across tropical Asia and Africa, represents one such underexplored medicinal plant with a rich ethnopharmacological heritage. Traditional systems of medicine employ this plant for treating wounds, infections, inflammation, and diabetes. Scientific investigations have confirmed the presence of bioactive flavonoids, saponins, tannins, and polysaccharides with potent antioxidant, anti-inflammatory, antimicrobial, and wound-healing activities [12,13]. Despite this promising pharmacological profile, no published study to date has systematically explored the development of a nanogel formulation incorporating Biophytum sensitivum extract for topical wound healing — constituting a significant and exploitable research gap.

The present review aims to: (i) comprehensively elucidate the biology of wound healing and its phases; (ii) critically analyze conventional and nanotechnology-based wound management strategies; (iii) examine the fundamentals of nanogel design, formulation, and characterization; (iv) survey herbal extracts incorporated into nanogel systems for wound healing; (v) present a detailed phytopharmacological profile of Biophytum sensitivum; and (vi) propose a research framework for the development and evaluation of a Biophytum sensitivum nanogel as a novel wound healing agent.

2. Pathophysiology of Wound Healing

2.1 Phases of Wound Healing

Wound healing is a highly organized, overlapping biological process traditionally divided into four sequential but interdependent phases: hemostasis, inflammation, proliferation, and tissue remodeling [11]. A thorough understanding of these phases is essential for designing targeted nanogel-based drug delivery systems that can intervene at specific stages to optimize healing outcomes.

2.1.1 Hemostasis

Hemostasis is the immediate physiological response to tissue injury, occurring within seconds to minutes. Upon vascular disruption, exposed subendothelial collagen triggers platelet adhesion, activation, and aggregation, leading to formation of the primary platelet plug. Simultaneously, the coagulation cascade

is activated through both intrinsic and extrinsic pathways, culminating in the conversion of fibrinogen to fibrin, which consolidates the clot [11]. Importantly, the fibrin clot serves not merely as a hemostatic barrier but also as a provisional extracellular matrix scaffold for cellular migration and a reservoir for growth factors including platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), which are critical orchestrators of subsequent healing phases [12].

2.1.2 Inflammatory Phase

The inflammatory phase commences within hours of injury and typically lasts 3–5 days in acute wounds. It is characterized by sequential infiltration of neutrophils (predominantly in the first 24–48 hours), followed by monocytes that differentiate into macrophages. Neutrophils perform critical bactericidal functions through phagocytosis, reactive oxygen species (ROS) generation, and release of proteolytic enzymes [12]. Macrophages, the central regulatory cells of inflammation, subsequently perform dual roles — classically activated (M1) macrophages sustain inflammation and antimicrobial defense, while alternatively activated (M2) macrophages shift the wound toward resolution and repair through secretion of anti-inflammatory cytokines including IL-10 and TGF-β, and pro-angiogenic factors such as VEGF [13]. In chronic wounds, persistent macrophage polarization toward the M1 phenotype is a critical pathological feature perpetuating non-healing.

2.1.3 Proliferative Phase

The proliferative phase (days 3–21) is characterized by angiogenesis, granulation tissue formation, re-epithelialization, and wound contraction. Angiogenesis, driven by VEGF and fibroblast growth factor (FGF), restores blood supply to the wound bed. Fibroblasts migrate into the wound, proliferate, and synthesize collagen (predominantly type III), hyaluronic acid, and fibronectin, forming the granulation tissue scaffold. Keratinocytes at the wound margins proliferate and migrate to resurface the wound, a process termed re-epithelialization [14]. Myofibroblasts, derived from fibroblast differentiation, mediate wound contraction, significantly reducing wound surface area. The coordination of these cellular events is orchestrated by a complex network of growth factors, cytokines, and matrix metalloproteinases (MMPs).

2.1.4 Remodeling Phase

The remodeling (maturation) phase is the longest phase of wound healing, lasting from 21 days to over 2 years. During this phase, type III collagen is progressively replaced by stronger type I collagen, organized along lines of mechanical tension. MMPs play a critical role in extracellular matrix remodeling, balanced by tissue inhibitors of metalloproteinases (TIMPs) [15]. The wound acquires progressive tensile strength, eventually reaching approximately 80% of that of normal skin, though never achieving complete restoration of original tissue architecture. Dysregulation at this stage can result in pathological scarring including hypertrophic scars and keloids.

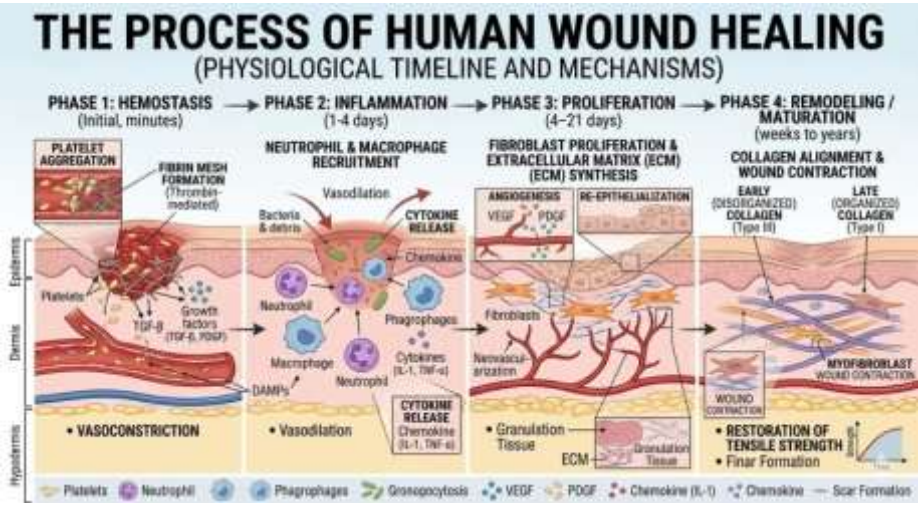


Fig:1 : Process of Wound Healing

2.2 Factors Affecting Wound Healing

Numerous local and systemic factors can impair wound healing progression, converting acute wounds into chronic non-healing wounds. A comprehensive understanding of these factors underpins the rationale for advanced nanogel-based therapeutic interventions. Diabetes Mellitus: Hyperglycemia impairs neutrophil function, reduces growth factor expression, causes advanced glycation end-product (AGE) accumulation, and induces peripheral neuropathy and vasculopathy, collectively creating an environment hostile to tissue repair [16]. Infection and Biofilm Formation: Wound pathogens — particularly Staphylococcus aureus, Pseudomonas aeruginosa, and Escherichia coli — not only delay healing through direct tissue destruction but also form antibiotic-resistant biofilms that are remarkably refractory to conventional topical antimicrobials [17]. Oxidative Stress: Excessive generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) causes cellular and DNA damage, lipid peroxidation, and protease dysregulation, perpetuating the inflammatory state and impeding matrix formation [18].

Impaired Angiogenesis and Poor Vascularization: Inadequate neovascularization, commonly seen in peripheral arterial disease and diabetic wounds, results in tissue hypoxia and nutrient deprivation that are incompatible with cellular proliferation and matrix synthesis [16]. Age-Related Changes: Elderly patients exhibit diminished growth factor production, reduced collagen synthesis, impaired keratinocyte migration, and altered immune responses, all contributing to delay wound healing [19]. Nutritional Deficiencies: Protein malnutrition and deficiencies of vitamins A, C, zinc, and copper are well-recognized impediments to collagen synthesis, immune function, and antioxidant defence [19].

3.CONVENTIONAL APPROACHES FOR WOUND HEALING

3.1 Topical Formulations

Conventional topical wound treatments encompass a diverse range of pharmaceutical forms including ointments, creams, gels, lotions, and powders. Ointments, typically oil-based (petrolatum, lanolin), provide an occlusive barrier that reduces transepidermal water loss (TEWL) and maintains wound moisture, but their inherently low water content limits the dissolution and release of hydrophilic drugs. Creams are oil-in-water or water-in-oil emulsions that are cosmetically acceptable and easily spreadable but may contain preservatives causing contact sensitization. Conventional gels, while water-based and easily applied, suffer from poor drug penetration through the intact stratum corneum and rapid washout from the wound surface [24].

3.2 Wound Dressings

Advanced wound dressings have evolved considerably beyond simple gauze. Modern dressing categories include hydrocolloids (gelatin, pectin, carboxymethylcellulose — maintain moist environment, autolytic debridement), hydrogels (high water content — cool wound, manage exudate, suitable for dry/necrotic wounds), alginate dressings (highly absorbent — manage heavy exudate), foam dressings (polyurethane foam — cushioning, moderate exudate management), transparent films (semi-permeable polyurethane — waterproof, allow wound visualization), and silver-impregnated dressings (broad-spectrum antimicrobial). Despite this diversity, dressings primarily function as passive barriers or exudate managers; they do not deliver bioactive therapeutic agents in a controlled and sustained manner, represent a significant unmet clinical need [25,26].

3.3 Limitations of Conventional Wound Therapies

The fundamental limitations of conventional wound care formulations include: (i) Poor drug penetration — the stratum corneum acts as a formidable barrier (10–20 μm thick) with highly ordered lipid lamellae, preventing adequate permeation of most therapeutics; (ii) Low bioavailability — significant first-pass metabolism for systemically applied drugs and rapid enzymatic degradation in the wound microenvironment reduce efficacy; (iii) Short residence time — conventional gels and creams are quickly removed by wound exudate, mechanical wiping, or body movement; (iv) Lack of controlled release — most formulations deliver drug in an initial burst followed by rapid depletion; (v) Increased risk

of systemic toxicity — large topical doses required to achieve therapeutic wound concentrations; (vi) Frequency of application — necessitates multiple daily applications, reducing patient compliance and increasing nursing burden; and (vii) Inability to target specific cell populations in the wound [27,28].

4. Nanotechnology in Wound Healing

4.1 Overview of Nanocarrier Systems

Nanotechnology-based drug delivery systems are defined as carriers with at least one dimension in the nanometer range (typically 1–1000 nm) designed to optimize the pharmacokinetic and pharmacodynamic profile of therapeutic agents. In the context of wound healing, nanocarrier systems offer transformative advantages including enhanced tissue penetration, sustained drug release, protection of sensitive bioactive molecules, targeted delivery to specific cellular compartments, and multi-functional therapeutic action [6, 21]. Nanoparticles (polymeric, lipid, or inorganic) are solid colloidal particles in the size range of 10–1000 nm. Polymeric nanoparticles composed of biodegradable polymers such as PLGA, PLA, and chitosan are particularly well-studied for wound healing applications. Their solid matrix confers excellent protection to encapsulated drugs and enables sustained zero-order or first-order release kinetics [22].

Liposomes are concentric phospholipid bilayer vesicles that closely mimic cell membrane composition, conferring excellent biocompatibility and enabling both hydrophilic (aqueous core) and lipophilic (bilayer) drug encapsulation. Liposomal formulations have been shown to enhance drug penetration into deeper skin layers and exhibit natural fusogenic interactions with cell membranes [22]. Niosomes are non-ionic surfactant vesicles that offer advantages over liposomes including greater chemical stability, lower cost, and easier large-scale manufacture. Their amphiphilic structure enables encapsulation of diverse drug molecules for topical wound applications [22]. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are composed of physiologically acceptable solid lipids and provide excellent occlusive properties on skin surfaces, enhancing drug bioavailability through improved follicular penetration and formation of a stable drug depot [22]. Among these diverse nanotechnology platforms, nanogels have emerged as a particularly versatile and clinically promising system for topical wound healing applications, combining the advantageous properties of nanoparticles (small size, large surface area) with those of hydrogels (high water content, flexibility, wound-compatible environment).

5. Nanogels: Concept and Fundamentals

5.1 Definition and Structure

Nanogels are defined as three-dimensional, internally crosslinked, hydrophilic polymer networks that are swollen with aqueous solvents, possessing particle sizes typically in the range of 10–500 nm [6, 7]. They represent a unique nanotechnology platform that synergistically integrates the advantageous properties of nanomaterials (nanoscale dimensions, large surface-to-volume ratio, superior tissue penetration) with those of hydrogels (high water content, biocompatibility, swellability, and viscoelasticity). Structurally, nanogels are composed of a polymer backbone forming a three-dimensional mesh network stabilized by physical or chemical crosslinks. The polymer network is highly solvated, enabling efficient encapsulation of hydrophilic and hydrophobic drug molecules within the aqueous compartments or polymer domains of the matrix [7].

The nanogel network structure is characterized by: (i) a crosslinked polymer backbone that provides structural integrity; (ii) mesh-like pores that can accommodate drug molecules and control their release; (iii) hydrophilic surface functional groups (–OH, –COOH, –NH2) that impart colloidal stability and enable surface functionalization; and (iv) high internal water content (typically 70–98%) that maintains a moist wound environment and imparts tissue-like mechanical compliance [6].

5.2 Types of Nanogels

Nanogels may be classified based on the nature of their polymeric constituents, the cross-linking mechanism, or their responsive behavior. Based on polymer origin, nanogels are categorized as synthetic polymer-based (polyacrylic acid, poly-N-isopropylacrylamide [PNIPAM], polyethylene glycol

[PEG]), natural polymer-based (chitosan, hyaluronic acid, gelatin, alginate, dextran, pullulan), or hybrid systems combining synthetic and natural polymers. Based on stimuli responsiveness, nanogels are classified as pH-responsive (incorporating ionizable groups that expand or contract with pH change), thermo-responsive (exhibiting lower critical solution temperature [LCST] behavior — PNIPAM systems), redox-responsive (disulfide cross-links that cleave in the presence of glutathione), light-responsive, and magnetic-responsive nanogels [34,35]. Stimuli-responsive nanogels hold particular promise for wound healing, where the acidic pH, elevated temperature, and high ROS levels of the wound microenvironment can serve as endogenous triggers for on-demand drug release.

5.3 Key Properties of Nanogels for Wound Healing

The physicochemical and biological properties that make nanogels uniquely suited for topical wound healing applications include: high water content (70–99%), which maintains wound moisture essential for healing and prevents scar formation; biocompatibility of natural polymer-based systems with wound tissue; large surface area enabling high drug loading and efficient drug-tissue contact; nanoscale dimensions facilitating penetration into the wound bed and uptake by wound-associated cells; high versatility in drug loading (small molecules, proteins, growth factors, nucleic acids); mechanical deformability enabling passage through wound exudate; tunable drug release from hours to weeks by adjusting cross-link density and polymer composition; and the capacity to incorporate multiple bioactive agents for combinatorial wound therapy [36,37].

6. PREPARATION METHODS OF NANOGELS

The preparation of nanogels employs several physicochemical strategies, each with distinct mechanistic principles, suitable polymer-solvent systems, and practical considerations for herbal drug incorporation. The selection of the appropriate method is governed by the physicochemical properties of the polymer and drug, desired particle size, required drug loading efficiency, scale-up feasibility, and regulatory acceptability.

Emulsion polymerization is among the most widely used industrial methods, where water-soluble monomers are polymerized within micellar or emulsion droplets in the presence of a surfactant and initiator. This yields nanogels with a narrow particle size distribution but may introduce residual surfactant and organic solvents, which require removal for pharmaceutical applications. Free radical polymerization in homogeneous solution offers excellent control over cross-link density and molecular weight. Ionic gelation exploits electrostatic interactions between a polyelectrolyte polymer (e.g., chitosan, a cationic polymer at acidic pH) and a multivalent ionic cross-linker (e.g., sodium tripolyphosphate for chitosan), forming nanogels under mild aqueous conditions without organic solvents or harsh chemicals — making it highly suitable for thermolabile herbal extracts [38]. Chemical cross-linking using bifunctional cross-linkers (glutaraldehyde, genipin, EDC/NHS) forms permanent covalent bonds between polymer chains, yielding mechanically robust nanogels; genipin, derived from gardenia fruits, is preferred for natural polymer nanogels due to its low cytotoxicity relative to glutaraldehyde [39].

Table 1: Comparative Overview of Nanogel Preparation Methods

Preparation Method	Principle	Polymers Used	Advantages	Limitations
Emulsion Polymerization	Monomer polymerized in emulsion droplets	PNIPAM, poly(acrylic acid)	Narrow size distribution, scalable	Residual surfactant, organic solvent use
Free Radical Polymerization	Chain-growth via radical intermediates	PEG, PHEMA	Versatile, tunable cross-link density	Requires initiators; possible toxicity

Ionic Gelation	Electrostatic interaction between polymer and cross-linker	Chitosan, alginate	Mild conditions, no organic solvents	pH-sensitive; may have poor mechanical strength
Chemical Cross-linking	Covalent bond formation between polymer chains	Hyaluronic acid, gelatin	Stable network, controlled porosity	Cross-linking agents may be toxic
Physical Cross-linking	Non-covalent interactions (H-bond, hydrophobic)	Pluronic, PVA	Reversible, stimulus-responsive	Weaker mechanical strength
Photo-polymerization	UV/visible light-initiated polymerization	Poly(ethylene glycol) diacrylate	Spatiotemporal control	Requires photoinitiator; UV exposure risks

7. CHARACTERIZATION OF NANOGELS

Comprehensive physicochemical and biopharmaceutical characterization of nanogel formulations is indispensable to ensure quality, safety, stability, and performance. International guidelines (ICH Q8, Q9, Q10) and regulatory expectations from the USFDA, EMA, and CDSCO necessitate a systematic characterization approach encompassing particle characteristics, drug-polymer interactions, release kinetics, and biological safety.

Particle size and polydispersity index (PDI), measured by dynamic light scattering (DLS), are the most fundamental characterization parameters. The PDI (0 to 1.0 scale) reflects the homogeneity of size distribution; PDI < 0.3 indicates acceptably monodisperse formulations. Zeta potential quantifies the electrical charge on the nanogel surface in dispersion; values of ± 30 mV or greater indicate sufficient electrostatic repulsion to maintain colloidal stability over extended storage periods [40]. Transmission electron microscopy (TEM) or atomic force microscopy (AFM) provides morphological information, complementing DLS data with direct visualization of nanogel shape, surface texture, and internal structure. Drug entrapment efficiency (EE%) and loading capacity (LC%) are determined by separating free drug from the nanogel (via centrifugation or dialysis) and quantifying drug content by validated spectrophotometric or HPLC methods. Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC) characterize drug-polymer interactions, confirming successful entrapment and the absence of drug-polymer incompatibilities. In-vitro drug release studies using Franz diffusion cells with a suitable semi-permeable membrane simulate transdermal permeation; release profiles are fitted to mathematical models (zero order, first order, Higuchi, Korsmeyer-Peppas) to elucidate the release mechanism [41,42].

Table 2: Characterization Parameters, Methods, and Significance for Nanogels

Parameter	Method/Technique	Significance	Acceptable Range
Particle Size	Dynamic Light Scattering (DLS)	Influences penetration depth and drug release	100–500 nm
Zeta Potential	Laser Doppler Velocimetry	Indicates colloidal stability	< -30 mV or > +30 mV
Entrapment Efficiency	UV-Visible Spectrophotometry	% drug retained in nanogel matrix	> 70%
Drug Loading	HPLC / UV-Vis	Amount of drug per unit weight of nanogel	Variable by formulation

Swelling Index	Gravimetric method	Governs water uptake and drug release	pH-dependent
Rheology/Viscosity	Brookfield Viscometer / Rheometer	Spreadability and skin residence time	Formulation-specific
In-vitro Drug Release	Franz Diffusion Cell	Release kinetics (zero-order, first-order, Higuchi)	Sustained over 6–24 h
pH	pH Meter	Compatibility with skin (pH 4.5–6.5)	5.0–6.5
Sterility/Microbial limit	Agar plate method	Safety of topical application	Must be sterile/within limits

8. HERBAL EXTRACTS IN WOUND HEALING

8.1 Importance of Herbal Medicine in Wound Care

Plants have served as humanity's primary therapeutic armamentarium for millennia, and an estimated 80% of the world's population relies on herbal medicines as their primary healthcare resource (WHO, 2019). In wound care, traditional herbal remedies predate modern pharmaceuticals by thousands of years, with documented use of honey, aloe vera, turmeric, neem, and calendula in wound management spanning ancient Egyptian, Ayurvedic, Chinese, and Greco-Roman traditions. The renewed scientific interest in medicinal plants for wound healing is driven by multiple factors: the natural, multitarget pharmacological profiles of plant-derived bioactives; favorable safety profiles relative to synthetic drugs; cost-effectiveness critical for low-income healthcare settings; and the growing prevalence of antibiotic resistance that necessitates novel antimicrobial wound agents [43,44].

8.2 Mechanisms of Herbal Extracts in Wound Healing

The wound-healing activities of herbal phytoconstituents operate through four principal pharmacological mechanisms, often acting synergistically. Anti-inflammatory activity is mediated through inhibition of the cyclooxygenase (COX) and lipoxygenase (LOX) enzymes, suppression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), inhibition of NF-κB signaling, and reduction of inflammatory cell infiltration — thereby preventing the chronic inflammation that impairs wound healing. Antioxidant activity involves scavenging of reactive oxygen species (ROS) and reactive nitrogen species (RNS) through direct radical neutralization (flavonoids, tannins, phenolic acids) and upregulation of endogenous antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase), protecting wound tissue from oxidative damage and lipid peroxidation. Antimicrobial activity against wound pathogens (Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Candida albicans) is conferred by saponins (membrane disruption), tannins (protein precipitation), alkaloids (intercalation with bacterial DNA), and essential oil components. Collagen synthesis stimulation by flavonoids, saponins, and polysaccharides promotes fibroblast proliferation, upregulates procollagen type I expression, and activates TGF-β signaling pathways, all critical for the proliferative phase of healing [45,46].

9.NANOGEL FORMULATIONS INCORPORATING HERBAL EXTRACTS

9.1 Rationale for Herbal-Loaded Nanogels

The integration of herbal phytoconstituents into nanogel delivery systems addresses a critical gap between the rich pharmacological potential of herbal medicines and their limitations in clinical application. Many bioactive phytoconstituents suffer from: poor aqueous solubility (curcumin, quercetin — BCS Class II/IV compounds); chemical instability (oxidation of polyphenols, photodegradation of flavonoids); short biological half-life due to rapid enzymatic metabolism; poor skin permeability due to molecular size, hydrophilicity, or charge; and erratic and variable bioavailability from crude plant extracts

[47,48]. Nanogel encapsulation addresses these limitations by providing a protective aqueous microenvironment that shields phytoconstituents from chemical degradation; enhancing solubilization of poorly water-soluble compounds through micellar dissolution or cosolvency within the polymer matrix; reducing particle size to the nanoscale range, dramatically improving skin penetration and cellular uptake; providing controlled, sustained release that maintains therapeutic phytoconstituent concentrations at the wound site over extended periods; and enabling precise dosage control, reducing intra- and inter-subject variability associated with crude herbal applications [49,50].

10. BIOPHYTUM SENSITIVUM: A PHYTOPHARMACOLOGICAL PROFILE

10.1 Botanical Description and Taxonomy

Biophytum sensitivum (Linn.) DC. is a small, erect, annual herb belonging to the family Oxalidaceae. The genus Biophytum, comprising approximately 50 species distributed across tropical and subtropical regions of Asia, Africa, and the Americas, derives its name from the Greek words bios (life) and phyton (plant), a reference to the remarkable nyctinastic (sleep) movements of its leaflets in response to touch and light — a phenotypic similarity to Mimosa pudica that has earned it the vernacular name 'little tree plant' or 'sensitive plant' in various cultures.

Taxonomically classified as: Kingdom: Plantae; Division: Magnoliophyta; Class: Magnoliopsida; Order: Geraniales; Family: Oxalidaceae; Genus: Biophytum; Species: B. sensitivum (Linn.) DC. The plant is a small herb, 5–30 cm tall, with a simple, erect, and somewhat succulent stem, often unbranched, bearing a tuft of pinnately compound leaves at the apex in a rosette-like arrangement. Each leaf bears 7–12 pairs of oblong, sensitive leaflets, 0.5–1.5 cm long, sensitive to touch, which fold downward upon stimulation — a response mediated by turgor changes in the pulvinus at the leaflet base. Small, bright yellow flowers (5–10 mm in diameter) borne in umbellate clusters at the leaf apex give rise to cylindrical capsule fruits containing numerous seeds [55,56].

The plant is distributed throughout tropical Asia (India, Sri Lanka, Thailand, China, Indonesia), tropical Africa, and Central and South America. In India, it is found widely in moist, shaded localities, roadsides, cultivated fields, and forest margins across the

Western Ghats, Eastern Ghats, Assam, and coastal Karnataka and Tamil Nadu. It is known by numerous vernacular names: Mukkutti (Malayalam), Lajjavati (Sanskrit), Attukkali (Tamil), Lajavanti (Hindi), and Jhanjhaniya (Bengali) [57].

10.2 Ethnopharmacological Uses

The ethnopharmacological repertoire of Biophytum sensitivum is remarkably broad, testifying to its long and culturally validated use across multiple traditional medicine systems. In Ayurveda, the whole plant is classified as a Rasayana (rejuvenating tonic) and is prescribed for conditions including asthma, diabetes, leucorrhoea, dysmenorrhoea, and as a vulnerary (wound healing) agent. Tribal healers in the Tirunelveli and Nilgiris hills of Tamil Nadu apply fresh leaf paste directly to wounds, cuts, and inflammatory swellings. In Kerala, the plant decoction is administered orally for diabetes and urinary disorders, while leaf paste mixed with sesame oil is applied topically for skin infections and wound healing. In Sri Lanka, the leaf paste is used to treat fresh wounds and contusions. In West Africa, related Biophytum species are employed as astringents, antidiarrheals, and wound healers [58,59].

10.3 Phytochemical Constituents

Comprehensive phytochemical investigations have revealed that Biophytum sensitivum is a rich source of bioactive secondary metabolites across multiple chemical classes. Table 4 provides a detailed enumeration of phytoconstituent classes, their key compounds, and their pharmacological roles in wound healing.

Table 3. Phytochemical Constituents of Biophytum sensitivum and Their Roles in Wound Healing

Phytoconstituent Class	Key Compounds	Pharmacological Role in Wound Healing
Flavonoids	Kaempferol, Quercetin, Vitexin	Free radical scavenging; inhibition of inflammatory cytokines (TNF-α, IL-6); promotion of fibroblast proliferation
Saponins	Triterpenoid saponins	Enhanced collagen synthesis; antimicrobial activity; membrane permeabilization of pathogens
Polysaccharides	Mucilaginous polysaccharides	Moisture retention; stimulation of macrophage activity; scaffold for tissue repair
Tannins	Ellagitannins, condensed tannins	Hemostasis; astringent action; protein precipitation on wound surface forming protective layer
Alkaloids	Harmine derivatives (trace)	Antimicrobial; modulation of inflammatory response
Phenolic acids	Caffeic acid, ferulic acid	Antioxidant; inhibition of lipid peroxidation in wound tissue
Amino acids / Proteins	Proline, hydroxyproline precursors	Structural support for collagen formation and tissue remodeling

10.4 Documented Pharmacological Activities Relevant to Wound Healing

10.4.1 Wound Healing Activity

Govindarajan et al. (2007) conducted one of the earliest systematic evaluations of the wound healing potential of Biophytum sensitivum, demonstrating that the methanolic leaf extract applied topically in an excision wound model in Wistar rats produced a significant reduction in wound area (78.3% wound contraction vs. 62.1% in control on day 10), increased tissue hydroxyproline content (indicative of collagen synthesis), and accelerated epithelialization compared to the untreated control. Histopathological examination revealed organized collagen deposition, increased fibroblast density, neovascularization, and complete re-epithelialization in the extract-treated group. A subsequent incision wound model demonstrated significantly higher wound breaking strength in the extract-treated group, confirming superior tensile strength restoration of healed tissue [32].

10.4.2 Anti-inflammatory Activity

Multiple in vivo studies have substantiated the anti-inflammatory activity of Biophytum sensitivum using standard animal models. Sridhar and Subramanian (2021) evaluated ethanol extract of B. sensitivum in carrageenan-induced paw edema model in Wistar rats, demonstrating dose-dependent inhibition of paw edema at 200 mg/kg and 400 mg/kg oral doses (55.8% and 72.3% inhibition at 3 hours, respectively), comparable to the standard anti-inflammatory drug indomethacin (74.1% inhibition). In the cotton pellet granuloma model, the extract significantly reduced granuloma weight, reflecting inhibition of the proliferative phase of inflammation. Mechanistically, the anti-inflammatory effects are attributed to inhibition of COX-2 and 5-LOX enzymes by flavonoids (kaempferol, quercetin), suppression of NF-κB activation, and inhibition of pro-inflammatory cytokine production [35].

10.4.3 Antioxidant Activity

The antioxidant potential of Biophytum sensitivum has been demonstrated across multiple in vitro assays. Chellaram et al. (2014) reported potent free radical scavenging activity of the aqueous leaf extract with IC50 values of 38.2 µg/mL (DPPH), 41.7 µg/mL (ABTS), and significant reducing power in the FRAP assay. The total phenolic content (TPC) was determined as 124.3 mg gallic acid equivalents/g dry extract. Babu et al. (2019) confirmed the presence of kaempferol, quercetin, and caffeic acid as principal antioxidant phytoconstituents through GC-MS and HPLC profiling of the leaf extract [37,38]. In in vivo

models of oxidative stress, B. sensitivum extract significantly restored reduced glutathione (GSH) levels and superoxide dismutase (SOD) and catalase (CAT) activities while reducing malondialdehyde (MDA) levels in wound tissue — collectively reducing oxidative damage and supporting the healing microenvironment.

10.4.4 Antimicrobial Activity

Ranjith (2020) evaluated the antimicrobial activity of ethanol extract of Biophytum sensitivum against common wound pathogens using the agar disc diffusion method, reporting zones of inhibition of 16.3 mm, 14.8 mm, 13.5 mm, and 18.2 mm against Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, and Candida albicans, respectively, at 500 µg/mL concentration. The minimum inhibitory concentration (MIC) against S. aureus (13.9 µg/mL) was particularly noteworthy given the clinical relevance of staphylococcal wound infections. Saponins in the extract likely contribute to antimicrobial activity through amphiphilic membrane disruption, while tannins act through protein precipitation and inhibition of bacterial adhesion to host tissues [36].

11.BIOPHYTUM SENSITIVUM-BASED NANOGEL: RATIONALE AND CONCEPTUAL FRAMEWORK

11.1 Rationale for Selection

The selection of Biophytum sensitivum as the herbal substrate for a nanogel-based topical wound healing system is supported by a convergence of phytopharmacological, pharmaceutical, and clinical rationales. Pharmacologically, B. sensitivum addresses the four pillars of wound healing pathophysiology: its antioxidant constituents mitigate ROS-mediated tissue damage; its anti-inflammatory flavonoids resolve chronic wound inflammation; its antimicrobial saponins and tannins combat wound infection; and its polysaccharides and saponins stimulate collagen synthesis and fibroblast proliferation — constituting a comprehensive, multitarget wound healing agent unmatched by single-component synthetic drugs. From a pharmaceutical perspective, the plant's phytoconstituents include both flavonoids (kaempferol: LogP = 1.90, molecular weight = 286.24 g/mol; quercetin: LogP = 1.48, MW = 302.24 g/mol) with modest lipophilicity suitable for nanogel encapsulation and polysaccharides with mucoadhesive properties that would enhance wound bed residence time. The documented safety, traditional use, and absence of cytotoxicity reports further support its suitability for topical pharmaceutical development [62,63].

11.2 Proposed Mechanism of Action of Biophytum sensitivum Nanogel

The proposed mechanism of action of a Biophytum sensitivum-loaded nanogel on wound tissue involves a multi-step sequence. Following topical application to the wound, the nanogel matrix adheres to the wound bed through mucoadhesive interactions between the polymer (chitosan or carbopol) and wound exudate proteins. The nanoscale particles (target: 150–300 nm) penetrate into the wound margins through impaired stratum corneum, follicular orifices, and wound-associated gaps in the epithelial barrier. In the acidic wound microenvironment (pH 5.5–6.5 in chronic wounds), pH-responsive swelling of the chitosan nanogel matrix triggers accelerated release of the encapsulated phytoconstituents. Released flavonoids (kaempferol, quercetin) are taken up by wound-associated macrophages and fibroblasts, inhibiting NF-κB and MAPK inflammatory signaling pathways. Simultaneously, antioxidant phytoconstituents quench superoxide radicals and hydrogen peroxide in the wound bed, protecting newly migrating keratinocytes and fibroblasts from oxidative damage. Released saponins exert antimicrobial activity at the wound surface, reducing bacterial bioload. Polysaccharide components from the plant extract, combined with the hydrogel matrix, maintain optimal wound moisture [64,65].

11.3 Proposed Formulation Strategy

Based on the phytochemical profile of Biophytum sensitivum and the requirements for an optimal topical wound nanogel, the following formulation approach is proposed as a framework for future studies. Standardized hydroalcoholic extract (60% ethanol:water) of B. sensitivum aerial parts, standardized to total flavonoid content (mg quercetin equivalents/g extract) and antioxidant activity (IC50

by DPPH assay), would serve as the drug substrate. Chitosan (MW: 100–300 kDa, deacetylation degree > 85%) is proposed as the primary polymer, chosen for its mucoadhesive, antimicrobial, and wound-healing properties, its biocompatibility, biodegradability, and established use in wound care products. Sodium tripolyphosphate (TPP) would serve as the ionic cross-linker for preparation via ionic gelation — a method that avoids organic solvents or high temperatures that could degrade thermolabile phytoconstituents. For improved dermal retention and gel consistency, the nanogel particles would be dispersed in a secondary Carbopol 940 hydrogel base, forming a composite 'nanogel-in-gel' system optimized for spreadability and wound adhesion.

11.4 Advantages Over Conventional Biophytum sensitivum Preparations

The proposed nanogel formulation of Biophytum sensitivum offers substantial theoretical advantages over the conventional aqueous or hydroalcoholic extract preparations currently available: significantly enhanced skin penetration through the nanoscale particle-mediated transcutaneous route versus passive diffusion of free extract; protection of labile flavonoids and polyphenols from air oxidation and UV degradation within the polymeric matrix, dramatically improving shelf life; controlled and sustained phytoconstituent release over 12–24 hours, enabling once-daily application versus the multiple daily applications required for conventional preparations; precise standardization and dose reproducibility versus the inherent variability of crude plant extract preparations; additional antimicrobial contribution from the chitosan polymer itself; enhanced wound bed retention through mucoadhesion; and the potential for co-loading complementary wound healing agents (e.g., silver nanoparticles, zinc oxide, vitamin E) within the same nanogel system for synergistic therapy.

12. EVALUATION OF NANOGELS FOR WOUND HEALING

12.1 In-vitro Evaluation

In vitro evaluation of wound-healing nanogels encompasses pharmaceutical quality assessments and cell-based biological studies. Pharmaceutical assessments include the complete characterization parameters described in Section 7. In vitro cell-based studies utilize scratch assay (wound scratch assay) on cultured keratinocyte (HaCaT) or fibroblast (L929, NIH 3T3) monolayers to quantify the rate of in vitro 'wound' closure as an indicator of cell migration, proliferative, and wound healing potential. Cell viability assays (MTT, Resazurin) on keratinocytes and fibroblasts at relevant concentrations establish the safety profile of the formulation. Antimicrobial efficacy against S. aureus, P. aeruginosa, and C. albicans by broth microdilution assays establishes the minimum biofilm inhibitory concentration (MBIC) — particularly relevant for wound infection management [40,41].

12.2 Ex-vivo Skin Permeation Studies

Ex vivo skin permeation studies using Franz diffusion cells and human cadaver skin, porcine skin (structurally most similar to human skin), or rat abdominal skin provide critical data on the penetration characteristics of the nanogel and its drug cargo through biological skin barriers under controlled conditions. The receiver compartment contains phosphate-buffered saline (pH 7.4) or isotonic buffer maintained at 37°C. Receptor fluid samples are collected at predetermined time points, and drug concentrations are determined by validated HPLC or UV-visible spectrophotometry. Parameters derived include permeability coefficient (Kp), flux (Jss), lag time (tlag), and skin deposition (tape stripping analysis) — collectively characterizing the rate, extent, and depth of nanogel penetration into wound tissue [42].

12.3 In-vivo Wound Healing Models

In vivo preclinical evaluation employs standardized animal wound models to assess the therapeutic wound healing potential of the nanogel formulation under regulatory guideline compliance. The excision wound model (created using circular biopsy punch — 400 mm2, full-thickness wound — in dorsal skin of Wistar rats) allows quantitative assessment of wound area reduction over time, expressed as percentage wound contraction. The incision wound model (2.5 cm linear incision sutured with nylon sutures, sutures removed on day 10) measures wound breaking strength using tensiometer, reflecting tensile strength restoration.

The dead space wound model (subcutaneous implantation of cotton pellets) assesses granuloma formation and collagen induction. Parameters measured include: wound closure rate (digital planimetry), epithelialization period (days to complete re-epithelialization), tissue hydroxyproline content (colorimetric assay — collagen synthesis index), wound tensile strength, and inflammatory cell infiltration by histopathology [43,44].

12.4 Histopathological Evaluation

Histopathological examination of wound tissue biopsies (stained with hematoxylin and eosin [H&E] and Masson's trichrome) provides definitive evidence of the cellular and extracellular matrix changes underlying wound healing activity. Key histopathological parameters assessed include: inflammatory cell infiltration (neutrophils, macrophages — indicator of inflammatory phase resolution); fibroblast density and orientation; neovascularization (capillary density); collagen deposition pattern, density, and maturity (Masson's trichrome staining: mature collagen — blue; immature/nascent collagen — green); epidermal thickness and continuity; and the presence of skin appendages (hair follicles, sebaceous glands) as indicators of complete tissue regeneration. Immunohistochemistry (IHC) with antibodies against TGF-β1, collagen type I, α-SMA (myofibroblast marker), and VEGF provides molecular-level evidence of formulation mechanisms [45].

13. ADVANTAGES OF HERBAL NANOGELS FOR WOUND HEALING

Herbal nanogels for wound healing present an integrated set of advantages that collectively position them as superior alternatives to both conventional herbal preparations and synthetic drug-loaded nanocarriers. From the perspective of therapeutic efficacy, the nanoscale size of the delivery system dramatically enhances penetration into the wound bed and cellular uptake by key wound healing cell populations — macrophages, fibroblasts, keratinocytes, and endothelial cells — ensuring drug concentrations at target sites exceed therapeutic thresholds. The controlled and sustained release profile of nanogels maintains therapeutic phytoconstituent concentrations at the wound site over 12–24 hours, addressing all four phases of healing with appropriately timed drug exposure.

From a safety perspective, herbal-loaded nanogels demonstrate substantially reduced systemic exposure and associated toxicity compared to both systemic drug administration and conventional topical formulations that can be absorbed through ulcerated skin. The natural polymer matrices (chitosan, hyaluronic acid, alginate) used in herbal nanogels are biodegradable and biocompatible, undergoing enzymatic degradation to non-toxic metabolites without the tissue accumulation concerns associated with non-degradable synthetic polymers. The use of herbal bioactives rather than synthetic antibiotics or anti-inflammatory drugs reduces the risk of antibiotic resistance development, adverse drug reactions, and drug-drug interactions.

Patient compliance and healthcare economics are significantly improved: once-daily application of a herbal nanogel versus multiple daily conventional dressing changes reduces nursing burden and direct healthcare costs, particularly relevant for the management of chronic wounds in resource-limited settings. The synergistic antimicrobial, anti-inflammatory, antioxidant, and collagen-stimulating activities of herbal phytoconstituents within the same delivery system address multiple pathological mechanisms simultaneously — a multitarget therapeutic approach increasingly recognized as superior for complex conditions like chronic wound healing. Finally, the eco-friendly, plant-derived nature of both the drug (herbal extract) and commonly used polymers (chitosan from marine waste, alginate from seaweed) supports sustainable pharmaceutical manufacturing.

14. LIMITATIONS AND CHALLENGES

Despite their substantial promise, herbal nanogel systems for wound healing face significant scientific, technical, regulatory, and economic challenges that must be systematically addressed to translate these formulations from laboratory to clinical and commercial reality. Stability of herbal nanogels represents a foremost challenge: polyphenolic and flavonoid phytoconstituents are inherently susceptible to oxidative degradation, hydrolysis, and photodegradation, which can substantially reduce

potency during storage and under wound-site conditions. Optimization of antioxidant excipients (e.g., ascorbic acid, butylated hydroxytoluene, vitamin E), packaging (opaque containers, nitrogen flushing), and storage conditions is required to achieve the ≥ 24-month shelf life demanded by regulatory agencies.

Standardization of herbal extracts poses a fundamental challenge: natural plant materials exhibit inherent variability in phytoconstituent composition due to factors including geographic origin, seasonal variation, agricultural practices, plant part used, and extraction conditions. Without robust, validated standardization methods (HPLC fingerprinting, standardization to marker compounds, total phenolic content assays), batch-to-batch consistency of the nanogel cannot be assured — a critical quality requirement for pharmaceutical products. Regulatory pathways for herbal nanogel combinations are ambiguous and complex: regulatory agencies classify such products differently (as drugs, cosmetics, or medical devices depending on jurisdiction and therapeutic claims), creating uncertainty for developers. Harmonized international regulatory guidance specifically addressing nanomedicine-herbal combinations is urgently needed.

Scale-up from laboratory batch sizes (milligrams) to pharmaceutical manufacturing volumes (kilograms) introduces formidable engineering and process challenges: maintaining nanoscale particle size distribution, ensuring homogeneous drug loading, preserving stimuli-responsiveness, and achieving sterility across large batches of inherently complex polymeric systems require sophisticated manufacturing infrastructure (high-shear homogenizers, microfluidics, spray drying) not universally available. The absence of clinical trial data for herbal nanogel wound treatments — with virtually all published studies limited to in vitro and preclinical animal experiments — represents a critical gap in the translational evidence base. Well-designed, adequately powered Phase II/III randomized controlled trials are needed before herbal nanogels can achieve clinical adoption. Economic challenges, including the cost of nanoformulation manufacturing relative to conventional wound dressings, may limit accessibility in low-income settings where chronic wounds are most prevalent.

15. RESEARCH GAP

A systematic analysis of the existing literature reveals a number of critical research gaps that circumscribe the current state of knowledge in this field and that must be addressed to realize the clinical potential of herbal nanogels for wound healing. Most fundamentally and specifically, despite the well-documented multi-mechanistic wound healing, anti-inflammatory, antioxidant, and antimicrobial activities of Biophytum sensitivum and its pharmacologically appropriate phytoconstituent profile, no published study to date has reported the systematic development, optimization, characterization, or preclinical evaluation of a nanogel-based topical formulation incorporating B. sensitivum extract for wound healing applications. This constitutes a significant and readily exploitable research opportunity at the intersection of ethnopharmacology, nanotechnology, and wound care.

Beyond this primary gap, broader deficiencies include: a near-complete absence of clinical trial data for any herbal nanogel wound treatment — translational studies progressing from in vitro and animal models to human clinical trials are urgently needed; lack of standardized, internationally harmonized characterization protocols specific to herbal nanogels that account for the chemical complexity of plant extracts; limited comparative studies rigorously benchmarking herbal nanogel formulations against established clinical standard-of-care wound treatments (e.g., Inadine, Mepilex, Aquacel Ag) under identical experimental conditions; insufficient investigation into the long-term stability of phytoconstituent-loaded nanogels under ICH Q1A-defined real-time and accelerated stability conditions; inadequate mechanistic studies at the molecular and cellular level elucidating the precise pharmacodynamic interactions between herbal phytoconstituents, polymeric nanogel matrices, and wound healing cell populations; and very limited studies on nanogel performance in wound models relevant to specific chronic wound etiologies (diabetic foot ulcer models, venous insufficiency models,

pressure ulcer models) that more accurately reflect clinical chronic wound physiology.

16. CONCLUSION

This comprehensive review has critically examined the landscape of nanogel-based topical drug delivery systems for wound healing, with a focused exploration of herbal extract incorporation and special reference to Biophytum sensitivum. The following principal conclusions emerge from this analysis. Wound healing is a complex, multi-phase biological process — hemostasis, inflammation, proliferation, and remodeling — that is disrupted in chronic wounds affecting hundreds of millions globally, representing a significant unmet clinical and scientific challenge. Conventional topical wound therapies are fundamentally limited by poor skin penetration, rapid drug degradation, lack of controlled release, and inadequate antibiofilm activity, necessitating the development of advanced drug delivery platforms.

Nanogels represent an exceptionally promising nanocarrier platform for topical wound healing by uniquely combining the advantages of hydrogels and nanoparticles: nanoscale size for enhanced skin penetration and cellular uptake, high water content for wound moisture maintenance, tunable drug release kinetics, biocompatibility, mucoadhesion to the wound bed, and stimuli-responsiveness for on-demand therapeutic delivery. The incorporation of herbal phytoconstituents into nanogel systems provides multitarget pharmacological wound coverage — anti-inflammatory, antioxidant, antimicrobial, and pro-collagenic activities — within a single biocompatible delivery vehicle, addressing multiple simultaneous pathological mechanisms of impaired wound healing.

Biophytum sensitivum (L.) DC. emerges as a particularly compelling candidate for nanogel-based wound formulation development. Its well-documented phytochemical profile — including flavonoids (kaempferol, quercetin), saponins, tannins, polysaccharides, and phenolic acids — corresponds directly to the four mechanistic pillars of wound healing pharmacology. Preclinical evidence substantiates its wound healing, anti-inflammatory, antioxidant, and antimicrobial activities in validated experimental models. The complete absence of reported nanogel formulations incorporating B. sensitivum constitutes a significant and immediately actionable research gap. The development, optimization, and rigorous preclinical evaluation of a chitosan-Carbopol 940-based nanogel incorporating standardized B. sensitivum extract represents a scientifically compelling and commercially relevant research objective with genuine potential to contribute a novel, cost-effective, multitarget topical wound healing agent to the clinical armamentarium. The realization of this potential requires systematic research across extract standardization, nanogel formulation optimization, comprehensive characterization, and structured preclinical-to-clinical translational studies.

REFERENCES

1. Sen CK, Gordillo GM, Roy S, Kirsner R, Lambert L, Hunt TK, et al. Human skin wounds: a major and snowballing threat to public health and the economy. Wound Repair Regen. 2009;17(6):763–71. doi:10.1111/j.1524-475X.2009.00543.x
2. Järbrink K, Ni G, Sönnergren H, Schmidtchen A, Pang C, Bajpai R, et al. The humanistic and economic burden of chronic wounds: a protocol for a systematic review. Syst Rev. 2017;6(1):15. doi:10.1186/s13643-016-0400-8
3. Nussbaum SR, Carter MJ, Fife CE, DaVanzo J, Haught R, Nusgart M, et al. An economic evaluation of the impact, cost, and Medicare policy implications of chronic nonhealing wounds. Value Health. 2018;21(1):27–32. doi:10.1016/j.jval.2017.07.007
4. Boateng JS, Matthews KH, Stevens HN, Eccleston GM. Wound healing dressings and drug delivery systems: a review. J Pharm Sci. 2008;97(8):2892–923. doi:10.1002/jps.21210
5. Vloemans AF, Hermans MH, van der Wal MB, Liebregts R, Middelkoop E. Optimal treatment of partial thickness burns in children: a systematic review. Burns. 2014;40(2):177–90.
6. Jiang Y, Chen J, Deng C, Suuronen EJ, Zhong Z. Click hydrogels, microgels and nanogels: emerging platforms for drug delivery and tissue engineering. Biomaterials. 2014;35(18):4969–85. doi:10.1016/j.biomaterials.2014.03.001

7. Kabanov AV, Vinogradov SV. Nanogels as pharmaceutical carriers: finite networks of infinite capabilities. Angew Chem Int Ed Engl. 2009;48(30):5418–29. doi:10.1002/anie.200900441
8. Krishnakumar S, Augustin MA. Biophytum sensitivum (L.) DC — an overview. Int J Pharm Res. 2010;2(4):11–18.
9. Nair AGR, Ramesh P, Subramanian SS. Bioflavonoids of Biophytum sensitivum. Curr Sci. 1977;46(11):392–3.
10. Kumari S, Singh SK, Jaiswal M. Phytochemistry and pharmacological activities of Biophytum sensitivum: a review. Int J Phytomed. 2020;12(3):451–62.
11. Peppas NA, Hilt JZ, Khademhosseini A, Langer R. Hydrogels in biology and medicine: from molecular principles to bionanotechnology. Adv Mater. 2006;18(11):1345–1360.
12. Hamidi M, Azadi A, Rafiei P. Hydrogel nanoparticles in drug delivery. Adv Drug Deliv Rev. 2008;60(15):1638–1649.
13. Kabanov AV, Vinogradov SV. Nanogels as pharmaceutical carriers: finite networks of infinite capabilities. Angew Chem Int Ed. 2009;48(30):5418–5429.
14. Vinogradov SV. Nanogels in the race for drug delivery. Nanomedicine. 2010;5(2):165–168.
15. Maya S, Sarmento B, Nair A, Rejinold NS, Nair SV, Jayakumar R. Smart stimuli sensitive nanogels in cancer drug delivery and imaging: a review. Curr Pharm Des. 2013;19(41):7203–7218.
16. Merino S, Martin C, Kostarelos K, Prato M, Vazquez E. Nanocomposite hydrogels: 3D polymer–nanoparticle synergies for on-demand drug delivery. ACS Nano. 2015;9(5):4686–4697.
17. Rao NV, Ko H, Lee J, Park JH. Recent progress and advances in stimuli-responsive polymers for cancer therapy. Front Bioeng Biotechnol. 2018;6:110.
18. Vashist A, Vashist A, Gupta YK, Ahmad S. Recent advances in hydrogel based drug delivery systems for the human body. J Mater Chem B. 2014;2(2):147–166.
19. Onaizi SA, Leong SS. Tethering antimicrobial peptides: current status and potential challenges. Biotechnol Adv. 2011;29(1):67–74.
20. Tran NQ, Joung YK, Lih E, Park KD. In situ forming and rutin-releasing chitosan hydrogels as injectable dressings for dermal wound healing. Biomacromolecules. 2011;12(8):2872–2880.
21. Amin MA, Bhatt S, Patel BD. Nanotechnology in wound healing: current approach. Int J Pharm Sci Rev Res. 2020;61(1):174–181.
22. Gaikwad VL, Bhatia MS. Polymers influencing transportability profile of drug. Artif Cells Nanomed Biotechnol. 2013;41(5):326–333.
23. Patel A, Bhatt N. Nanogels as a novel approach for drug delivery systems. Int J Pharm Chem Sci. 2012;1(4):1490–1497.
24. Soni G, Yadav KS. Nanogels as potential nanomedicine carrier for treatment of cancer: a mini review of the state of the art. Saudi Pharm J. 2016;24(2):133–139.
25. Oh JK, Drumright R, Siegwart DJ, Matyjaszewski K. The development of microgels/nanogels for drug delivery applications. Prog Polym Sci. 2008;33(4):448–477.
26. Hoare TR, Kohane DS. Hydrogels in drug delivery: progress and challenges. Polymer. 2008;49(8):1993–2007.
27. Siddiqui MH, Al-Whaibi MH, Mohammad F, editors. Nanotechnology and Plant Sciences: Nanoparticles and Their Impact on Plants. Springer; 2015.
28. Cavalcanti IM, Mendonça EA, Lira MC, Lira MC. Nanoemulsions containing plant extracts. Int J Pharm. 2021;606:120854.
29. Bilia AR, Bergonzi MC, Isacchi B, Antiga E, Caproni M. Curcumin nanoparticles potentiate therapeutic effectiveness of acitrein in moderate-to-severe psoriasis patients and control serum cholesterol levels. J Pharm Pharmacol. 2018;70(8):1000–1013.
30. Sumanth T, Prathap B, Deepthi P. Biophytum sensitivum (Linn.) DC: an overview. Asian J Pharm Clin Res. 2018;11(1):45–49.
31. Srinivasan K, Muruganandan S, Lal J, Chandra S, Tandan SK, Ravi Prakash V. Evaluation of anti-inflammatory activity of Pongamia pinnata leaves in rats. J Ethnopharmacol. 2001;78(2–3):151–157.
32. Govindarajan R, Vijayakumar M, Rao CV. Antioxidant and wound healing properties of

Biophytum sensitivum DC. J Complement Integr Med. 2007;4(1):1–10.
33. Ayyanar M, Ignacimuthu S. Traditional knowledge of Kani tribals in Kouthalai of Tirunelveli hills, Tamil Nadu, India. J Ethnopharmacol. 2005;102(2):246–255.
34. Murali R, Saravanan R. Antidiabetic effect of d-pinitol, a low molecular weight inositol of Terminalia catappa L. on streptozotocin-induced diabetic rats. J Biochem Mol Toxicol. 2012;26(1):44–54.
35. Sridhar C, Subramanian S. Anti-inflammatory activity of Biophytum sensitivum in carrageenan-induced paw edema model in Wistar albino rats. Indian J Pharm Sci. 2021;83(2):258–264.
36. Ranjith MS. Antimicrobial activity of ethanol extract of Biophytum sensitivum against pathogenic bacteria. J Med Plants Stud. 2020;8(4):210–214.
37. Chellaram C, Murugaboopathi G, John AA. Antioxidant activity of aqueous extract of Biophytum sensitivum. IOSR J Pharm Biol Sci. 2014;9(1):12–15.
38. Babu S, Krishnan M, Rajagopal P, Venugopal B, Bhaskaran A. Phytochemical screening and GC-MS analysis of Biophytum sensitivum leaf extract. J Drug Deliv Ther. 2019;9(4-s):716–720.
39. Anitha T. Biophytum sensitivum (Linn.) DC – a miracle herbal medicine. Global J Res Med Plants Indig Med. 2012;1(8):353–360.
40. Alam MS, Ali MS, Alam N, Shamim S, Yusuf M, Mushir M. Formulation and in vivo evaluation of clotrimazole nanogel using Carbopol-940 for topical fungal diseases. Int J Pharm Sci. 2012;3(8):5612–5623.
41. Nutan MT, Reddy IK. General Principles of Suspensions. In: Kulshreshtha AK, Singh ON, Wall GM, editors. Pharmaceutical Suspensions: From Formulation Development to Manufacturing. Springer; 2010. p. 39–65.
42. Arunachalam K, Parimelazhagan T. Antidiabetic activity of the methanol extract of Biophytum sensitivum in streptozotocin-induced diabetic rats. J Pharm Pharmacol. 2011;63(12):1498–1505.
43. Rajeh MA, Zuraini Z, Sasidharan S, Latha LY, Amutha S. Assessment of Euphorbia hirta L. leaf, flower, stem and root extracts for their antibacterial and antifungal activity and brine shrimp lethality. Molecules. 2010;15(9):6008–6018.
44. Nair R, Varghese SH, Nair BG, Maekawa T, Yoshida Y, Kumar DS. Nanoparticulate material delivery to plants. Plant Sci. 2010;179(3):154–163.
45. Garg A, Aggarwal D, Garg S, Singla AK. Spreading of semisolid formulations: an update. Pharm Technol. 2002;26(9):84–105.
46. Bhattacharyya SS, Paul S, Khuda-Bukhsh AR. Encapsulated plant extract (Gelsemium sempervirens) poly (lactide-co-glycolide) nanoparticles enhance cellular uptake and increase bioavailability in vivo. Exp Biol Med. 2010;235(6):678–688.
47. Desai NP, Hubbell JA. Solution technique to incorporate polyethylene oxide and other water-soluble polymers into surfaces of polymeric biomaterials. Biomaterials. 1991;12(2):144–153.
48. Swain S, Beg S, Singh A, Patro CN, Bhattacharya S. Advanced techniques for penetration enhancement in transdermal drug delivery system. Curr Drug Deliv. 2011;8(5):456–473.
49. Khandare J, Minko T. Polymer-drug conjugates: progress in polymeric prodrugs. Prog Polym Sci. 2006;31(4):359–397.
50. Alvarez-Lorenzo C, Concheiro A. Smart drug delivery systems: from fundamentals to the clinic. Chem Commun. 2014;50(48):6316–6338.
51. Bhowmik D, Chiranjib B, Krishnakanth, Pankaj, Chandira RM. Fast dissolving tablet: an overview. J Chem Pharm Res. 2009;1(1):163–177.
52. Blagoeva RK, Erceg AN, Miteva MJ, Tchervenkov CI. Antimicrobial activity of plant extracts against multiresistant bacteria: an in vitro study. Biotechnol Biotechnol Equip. 2009;23(4):1526–1529.
53. Mehnert W, Mader K. Solid lipid nanoparticles: production, characterization and applications. Adv Drug Deliv Rev. 2001;47(2–3):165–196.
54. Park K. Controlled drug delivery systems: past forward and future back. J Control Release. 2014;190:3–8.
55. Naves LB, Dhand C, Almeida L, Rajamani L, Ramakrishna S, Soares GC. Poly (lactic-co-glycolic) acid/titanium dioxide nanocomposite microspheres for controlled and extended drug

delivery. J Biomed Mater Res B Appl Biomater. 2017;105(6):1601–1608.
56. Langer R, Peppas NA. Advances in biomaterials, drug delivery, and bionanotechnology. AIChE J. 2003;49(12):2990–3006.
57. Drury JL, Mooney DJ. Hydrogels for tissue engineering: scaffold design variables and applications. Biomaterials. 2003;24(24):4337–4351.
58. Kim JO, Ngo HV, Vu TT, Lee BJ, Park C, Yong CS, et al. In situ topical gel system for bleomycin delivery to the superficial tumor. Int J Pharm. 2016;513(1–2):267–275.
59. Ali A, Ahmad U, Akhtar J, Badruddeen, Khan MM. Engineered nano scale formulation strategies to augment efficiency of nutraceuticals: a comprehensive review. J Funct Foods. 2019;62:103554.
60. Sultana Y, Maurya DP, Iqbal Z, Aqil M. Nanotechnology in ocular delivery: current and future directions. Drugs Today (Barc). 2011;47(6):441–455.
61. Tiwari G, Tiwari R, Sriwastawa B, Bhati L, Pandey S, Pandey P, et al. Drug delivery systems: an updated review. Int J Pharm Investig. 2012;2(1):2–11.
62. Garg T, Rath G, Goyal AK. Comprehensive review on additives of topical dosage forms for drug delivery. Drug Deliv. 2015;22(8):969–987.
63. Rai M, Yadav A, Gade A. Silver nanoparticles as a new generation of antimicrobials. Biotechnol Adv. 2009;27(1):76–83.
64. Vashisth P, Nikhil K, Roy P, Pruthi PA, Singh RP, Pruthi V. A novel gellan-PVA nanofibrous scaffold for skin tissue engineering: fabrication and characterization. Eur Polym J. 2016;86:107–122.
65. Malam Y, Loizidou M, Seifalian AM. Liposomes and nanoparticles: nanosized vehicles for drug delivery in cancer. Trends Pharmacol Sci. 2009;30(11):592–599.

HOW TO CITE: Tanvir Shaikh, Samika Mohod, Bharat Jain, A Comprehensive Review On Herbal Nanogel Drug Delivery Systems For Wound Healing: Focus On Biophytum Sensitivum, J. Pharm. Sci., 2026, 2 (5), 691-708. https://doi.org/10.5281/zenodo.20473570