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Emerging Polymeric Nanogel Systems of Butea Monosperma: Mechanistic Insights and Translational Prospects in Cutaneous Regeneration

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Abstract

Butea monosperma is a medicinal plant everywhere recognized for its conventional use in wound management due to the existence of bioactive phytoconstituents such as flavonoids, tannins and phenolic compounds which exhibit antioxidant, antimicrobial activities and anti-inflammatory. However, the restorative application of these phytoconstituents in topical formulations is limited by poor aqueous solubility, low stability and inadequate penetration at the wound site. The present study was undertaken to design and optimize a polymer-based nanogel delivery system for Butea monosperma phytoconstituents with the aim of improving their wound healing performance. Phytoconstituents extracted from Butea monosperma were encapsulated into polymeric nanoparticles using a suitable formulation technique and subsequently incorporated into a nanogel matrix. Optimization of formulation variables was carried out to obtain a stable system with desirable nanoscale properties. The optimized nanogel was characterized for particle size, polydispersity index, zeta potential, entrapment efficiency, pH, viscosity and spreadability. In vitro drug release studies were performed to evaluate the release behaviour of phytoconstituents from the developed nanogel system. The formulated nanogel exhibited uniformly distributed nanosized particles with high entrapment efficiency, indicating effective federation of phytoconstituents within the polymeric network. Physicochemical evaluation revealed that the nanogel possessed suitable pH, viscosity and spreadability, making it significant for topical wound application. In vitro release studies demonstrated a sustained release profile of phytoconstituents from the nanogel compared to conventional gel formulations, which is advantageous for maintaining prolonged drug availability at the wound site. Additionally, the nanogel system enhanced the stability of the encapsulated phytoconstituents by protecting them from degradation. The observed formulation characteristics propose the potential of the polymer-based nanogel system to improve the topical delivery and therapeutic productiveness of Butea monosperma phytoconstituents in wound healing applications.

Keywords: Polymeric nanogel delivery, Butea monosperma phytoconstituents, Topical wound repair system, Nano-encapsulated bioactive and Controlled phytochemical release

Introduction

Overview of Wound Healing and Its Clinical Significance

Wound healing is a dynamic and multifactorial biological process that restores the integrity and function of damaged skin and tissues. It proceeds through coordinated phases of hemostasis, inflammation, proliferation and remodelling, each regulated by cellular responses, cytokines, growth factors and extracellular matrix remodelling. Proper progression through these stages is essential to prevent infection, limit excessive inflammation and achieve functional tissue regeneration.[1] Clinically, impaired wound healing is a major concern in conditions such as diabetes mellitus, burns, pressure ulcers and chronic venous ulcers, which are associated with delayed recovery, increased risk of infection and substantial healthcare expenditure. [2]

Limitations of Conventional Wound Therapies

Conventional wound treatment strategies typically involve the use of topical antibiotics, antiseptics, anti-inflammatory agents and protective dressings. While these approaches provide symptomatic relief and infection control, they often fail to address the complex biological requirements of wound healing. Poor penetration of drugs into deeper tissue layers, rapid loss of therapeutic activity, frequent dosing and local adverse effects limit their effectiveness. In addition, prolonged use of synthetic antimicrobial agents may contribute to microbial resistance and delayed tissue regeneration, highlighting the need for safer and more effective alternatives. [3]

Role of Herbal Medicines in Wound Management

Herbal medicines have been extensively used in traditional systems of medicine for wound care due to their broad pharmacological activities and natural origin. Medicinal plants are rich sources of bioactive phytoconstituents, including flavonoids, phenolic compounds, tannins and terpenoids, which exhibit anti-inflammatory, antioxidant, antimicrobial and collagen-promoting effects. [1] These compounds can modulate multiple wound healing pathways simultaneously, promoting angiogenesis, epithelialization and extracellular matrix formation. Despite these advantages, the therapeutic use of herbal medicines is often limited by poor solubility, instability and inconsistent bioavailability at the site of injury. [4]

Butea monosperma as a Promising Herbal Agent for Wound Healing

Butea monosperma, commonly known as “Flame of the Forest,” is a medicinal plant widely recognized for its traditional application in wound healing and skin disorders. [2] Various parts of the plant contain bioactive phytoconstituents such as flavonoids, chalcones, tannins and phenolic acids, which contribute to its anti-inflammatory, antioxidant, antimicrobial and tissue regenerative properties. These phytoconstituents have been reported to enhance collagen synthesis, reduce oxidative stress, control microbial growth and accelerate epithelial regeneration, making Butea monosperma a promising candidate for wound healing therapy. [5] However, conventional formulations of Butea monosperma extracts often exhibit limited therapeutic effectiveness due to poor stability and inadequate retention at the wound site. [6]

Rationale for Nanotechnology-Based Topical Delivery Systems

Nanotechnology-based topical delivery systems offer a strategic approach to overcome the limitations associated with conventional and herbal wound therapies. Polymeric nanoparticles and nanogels can improve the solubility, stability and penetration of herbal bioactive while enabling controlled and sustained drug release. Nanogels, in particular, provide a hydrated polymeric network that maintains prolonged contact with the wound surface, protects sensitive phytoconstituents from degradation and enhances local bioavailability. [7] The integration of Butea monosperma phytoconstituents into polymer-based nanogel systems therefore represents a rational and innovative strategy for improving wound healing outcomes. [5]

Pathophysiology of Wound Healing

Wound healing is a highly coordinated biological process involving multiple cell types, signaling molecules and extracellular matrix components. [8] It is traditionally divided into four overlapping but distinct phases: hemostasis, inflammation, proliferation and remodeling. Successful healing depends on the timely progression through these phases. Disruption at any stage can result in delayed healing or chronic wound formation. [9]

Stages of Wound Healing

Hemostasis: Hemostasis is the immediate response following tissue injury and occurs within minutes. The primary objective of this phase is to prevent excessive blood loss. Vasoconstriction occurs at the site of injury, followed by platelet aggregation and clot formation. [10] Platelets release growth factors such as platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β), which initiate subsequent healing events. The fibrin clot not only acts as a temporary barrier against microbial invasion but also serves as a provisional matrix for cell migration. [11]

Inflammation: The inflammatory phase begins shortly after hemostasis and typically lasts for several days. During this phase, neutrophils and macrophages migrate to the wound site to remove debris, pathogens and damaged tissue. [9] These immune cells release cytokines and chemokines that regulate the healing response. Although inflammation is essential for preventing infection, excessive or prolonged inflammation can impair tissue repair and contribute to chronic wound development. [12]

Proliferation: The proliferative phase is characterized by tissue formation and typically occurs from day three to two weeks after injury. Fibroblasts proliferate and synthesize collagen and extracellular matrix components. [13] Angiogenesis promotes the formation of new blood vessels to supply nutrients and oxygen. Keratinocytes migrate across the wound surface to restore the epithelial barrier. The formation of granulation tissue is a hallmark of this phase, indicating active tissue regeneration. [14]

Remodeling: The remodeling or maturation phase may continue for months after injury. During this stage, collagen fibers are reorganized and replaced with stronger type I collagen, enhancing tensile strength. [15] Cellular activity gradually decreases and the scar tissue becomes more organized. Although tissue strength improves over time, it rarely reaches the original pre-injury level. [16,17]

Factors Affecting Delayed or Impaired Wound Healing

Several local and systemic factors can interfere with normal wound healing. Local factors include infection, poor oxygenation, repeated trauma, and excessive exudate. [18] Systemic factors such as diabetes mellitus, malnutrition, aging, vascular insufficiency and immunosuppression significantly impair healing progression. Chronic inflammation, oxidative stress, and reduced collagen synthesis are commonly observed in non-healing wounds. These conditions disrupt cellular communication and prolong the inflammatory phase, preventing transition to effective tissue regeneration. [19,20]

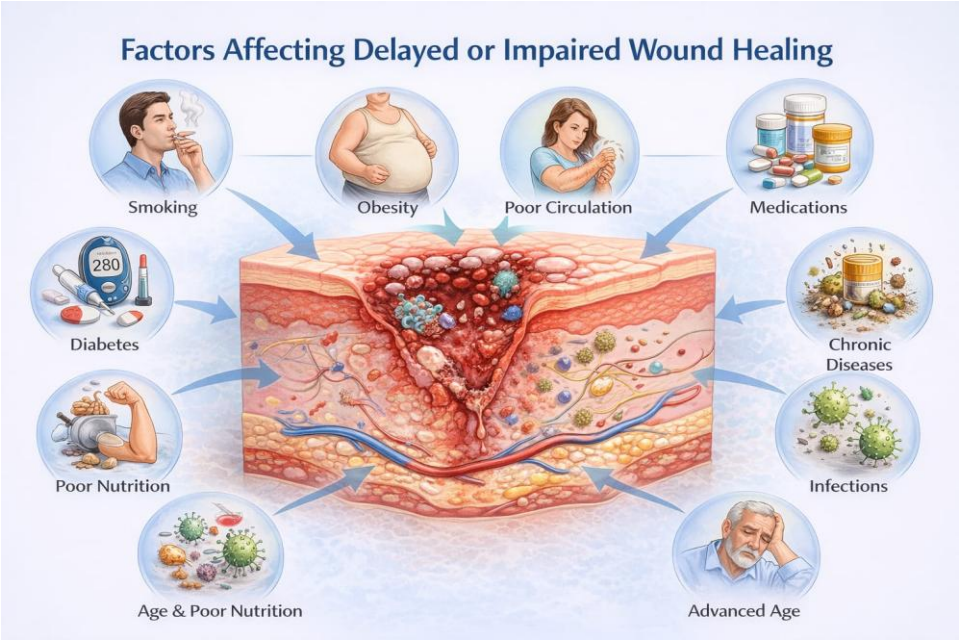

Figure 1: Factors Affecting Delayed or Impaired Wound Healing

Importance of Controlled Drug Delivery at Wound Sites

Effective wound management requires maintaining optimal therapeutic concentrations of bioactive agents at the site of injury. Conventional topical formulations often exhibit rapid drug release and limited retention time, resulting in subtherapeutic levels and frequent reapplication. Controlled drug delivery systems offer sustained release, improved stability and enhanced penetration of therapeutic agents. [21,22] By maintaining consistent drug levels, controlled delivery systems can modulate inflammation, prevent microbial growth, promote collagen synthesis and accelerate tissue regeneration. Advanced nanoscale systems, particularly polymeric nanogels, provide prolonged residence time, enhanced bioavailability and targeted delivery, thereby addressing the multifactorial nature of wound healing and improving overall therapeutic outcomes. [23,24]

Butea monosperma: A Medicinal Plant for Wound Healing

Botanical Description and Traditional Uses

Butea monosperma, commonly known as "Flame of the Forest," is a medium-sized deciduous tree belonging to the family Fabaceae. It is widely distributed across tropical and subtropical regions of South and Southeast Asia. [15] The plant is characterized by its bright orange-red flowers, trifoliate leaves, and rough grayish bark. Various parts of the plant, including flowers, leaves, bark, seeds and gum (commonly known as Bengal kino), have been traditionally used in indigenous systems of medicine. [25]

In traditional Ayurvedic and folk practices, *Butea monosperma* has been employed for the treatment of wounds, ulcers, skin infections, inflammation and burns. Leaf poultices are commonly applied topically to promote wound closure, while bark and gum preparations are used for their astringent and antimicrobial properties. [26] Its traditional reputation as a wound-healing agent has stimulated scientific interest in validating and optimizing its therapeutic applications. [16]

Phytochemical Profile Relevant to Wound Healing

The wound healing potential of *Butea monosperma* is attributed to its diverse phytochemical composition. The plant contains flavonoids (such as butrin, isobutrin and coreopsin), chalcones, phenolic acids, tannins, glycosides and terpenoids. These compounds possess significant antioxidant, anti-inflammatory and antimicrobial properties, which are essential for efficient tissue repair. [27,28]

Flavonoids and phenolic compounds contribute to scavenging reactive oxygen species, thereby reducing oxidative stress at the wound site. Tannins exhibit astringent properties that promote wound contraction and reduce exudation. The presence of bioactive chalcones and glycosides further enhances the therapeutic profile of the plant by supporting cellular regeneration and microbial inhibition. [29,30]

Pharmacological Activities Supporting Wound Repair

Experimental studies have demonstrated that extracts of *Butea monosperma* exhibit multiple pharmacological activities beneficial for wound healing. These include anti-inflammatory effects through modulation of inflammatory mediators, antimicrobial activity against common wound pathogens and antioxidant properties that protect tissues from oxidative damage. Additionally, certain phytoconstituents have been shown to stimulate fibroblast proliferation, enhance collagen deposition and promote granulation tissue formation, which are critical for tissue regeneration. [31] The combined pharmacological actions of these bioactive compounds enable a multifaceted therapeutic approach, addressing infection control, inflammation reduction and tissue remodeling simultaneously. [32]

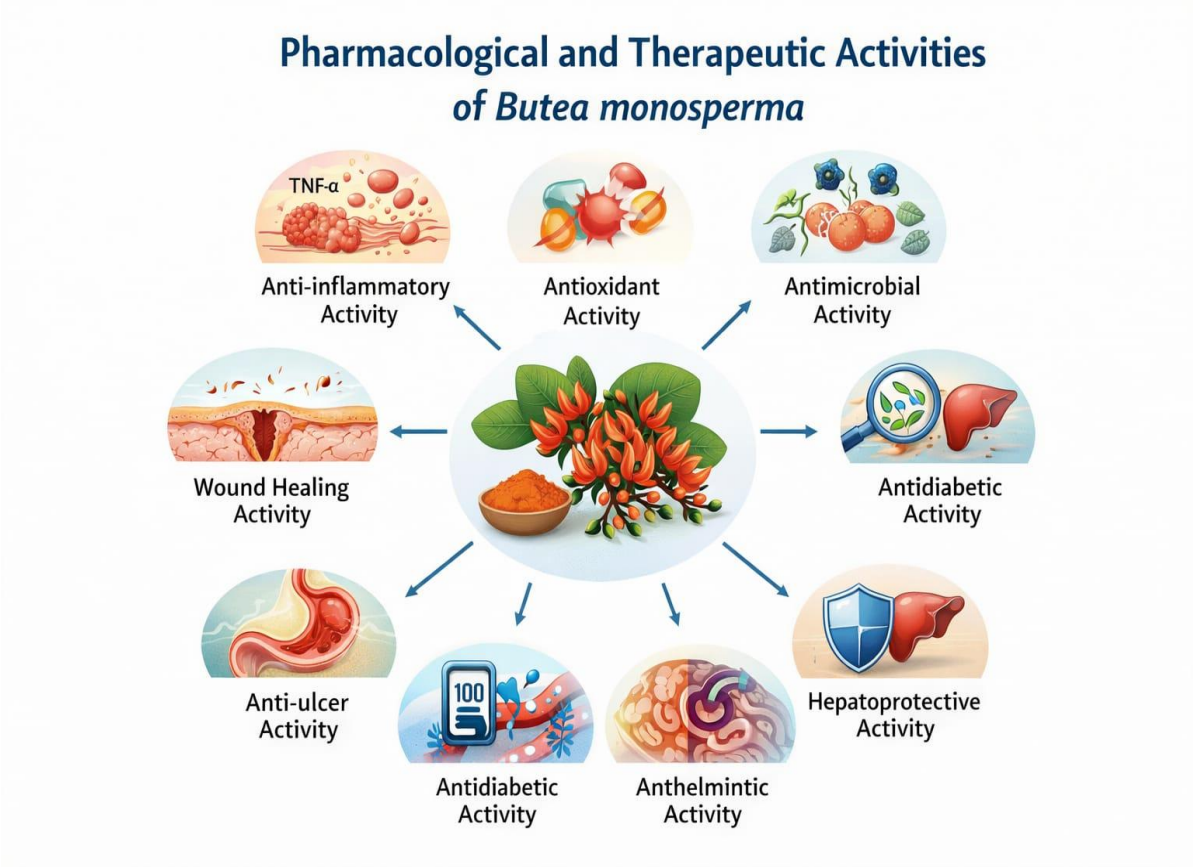

Figure 2: Pharmacological Activities Supporting Wound Repair

Mechanisms of Action of *Butea Monosperma* Phytoconstituents

The wound healing effects of *Butea monosperma* are mediated through several interconnected mechanisms. Antioxidant constituents reduce oxidative stress by neutralizing free radicals, thereby preventing cellular damage. Anti-inflammatory phytochemicals regulate cytokine production and inhibit excessive inflammatory responses, facilitating progression to the proliferative phase. Antimicrobial compounds limit microbial colonization at the wound site, reducing the risk of infection-related complications. [16,33]

Furthermore, certain flavonoids and phenolic compounds enhance collagen synthesis and angiogenesis, promoting faster epithelialization and improved tensile strength of the repaired tissue. The synergistic interaction of these phytoconstituents supports accelerated wound contraction and effective tissue remodeling, making *Butea monosperma* a promising candidate for advanced wound healing formulations. [34]

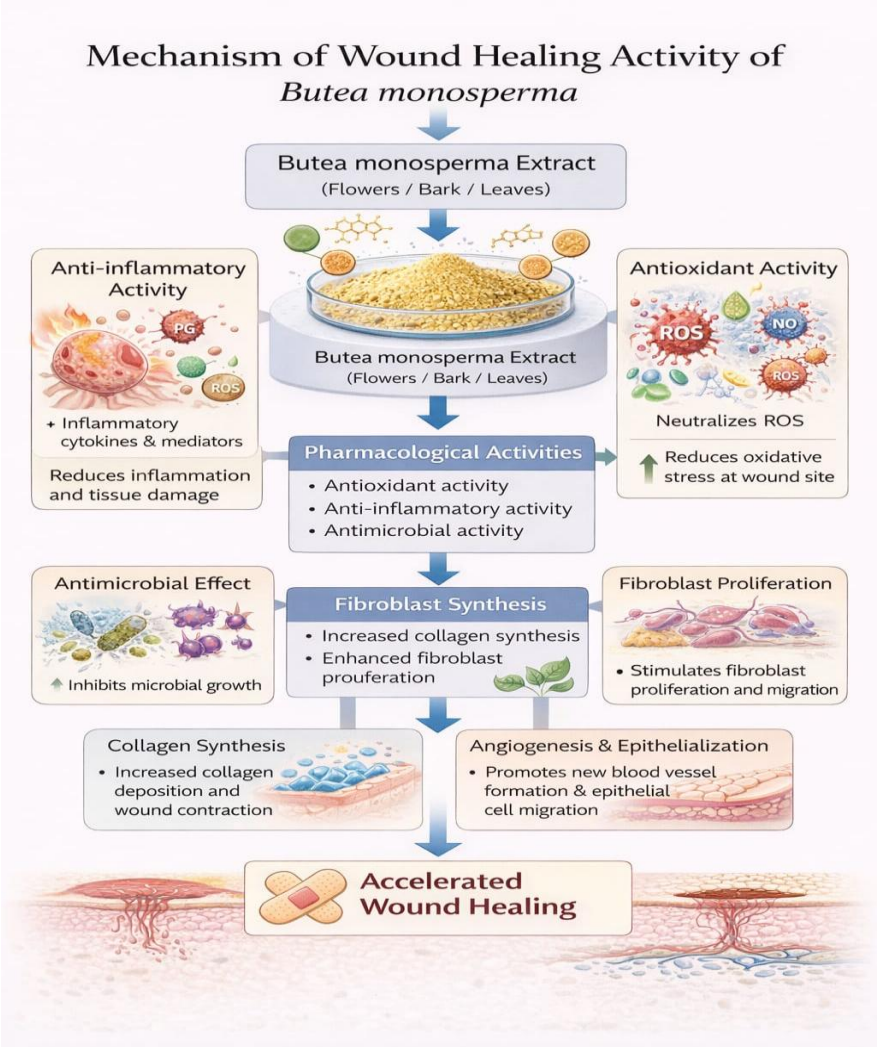

Figure 3: Mechanisms of Action of *Butea Monosperma* Phytoconstituents

Challenges in Topical Delivery of Phytoconstituents

The topical administration of herbal bioactives has gained increasing attention in wound management due to their multifunctional pharmacological properties. However, despite their therapeutic potential, effective delivery of phytoconstituents to the wound site remains a significant challenge. [25] Factors such as poor physicochemical properties, skin barrier resistance and variability in plant-derived compounds often limit their clinical translation and consistent therapeutic performance. [35]

Poor Solubility and Stability of Herbal Bioactives

Many phytoconstituents, including flavonoids, phenolic compounds, and terpenoids, exhibit poor aqueous solubility, which restricts their incorporation into conventional topical formulations. Limited solubility reduces drug diffusion, bioavailability and therapeutic concentration at the wound site. Additionally, several herbal bioactive are chemically unstable and susceptible to degradation when exposed to environmental factors such as light, heat, oxygen and moisture. Oxidation and hydrolysis can lead to loss of biological activity, thereby diminishing therapeutic efficacy. [36] The instability of plant extracts during storage further complicates formulation development and affects shelf life. As a result, achieving optimal solubility and stability remains a major barrier in the development of effective herbal topical systems. [18]

Skin Barrier Limitations and Low Penetration

The skin acts as a protective barrier against external agents, primarily due to the highly organized structure of the stratum corneum. While this barrier function is essential for preventing microbial invasion and water loss, it significantly limits the penetration of active compounds into deeper tissue layers. Most phytoconstituents possess high molecular weight or unfavorable lipophilicity, which restricts their ability to diffuse across the skin barrier. In wound conditions, although the barrier may be partially compromised, effective and controlled penetration is still required to ensure adequate drug concentration at the target site. Conventional topical formulations often fail to enhance permeation sufficiently, resulting in suboptimal therapeutic outcomes. [38,39]

Variability and Degradation of Plant-Derived Compounds

Another important challenge in herbal drug delivery is the inherent variability in plant-derived materials. The concentration of bioactive constituents can vary depending on geographical origin, harvesting season, processing methods and storage conditions. Such variability leads to inconsistencies in therapeutic response and difficulties in dose standardization. Furthermore, plant extracts contain complex mixtures of compounds that may interact with each other, influencing stability and bioavailability. Enzymatic degradation and microbial contamination may also occur if extracts are not properly processed and preserved. These factors collectively complicate formulation design and necessitate advanced delivery systems capable of protecting, stabilizing and standardizing phytoconstituent release at the wound site. [27,40]

Nanotechnology-Based Approaches for Wound Healing

Nanotechnology has emerged as a transformative strategy in wound management by enabling precise delivery of therapeutic agents at the nanoscale. Nanosystems enhance the solubility, stability, permeability and bioavailability of bioactive compounds, particularly those derived from herbal sources. By modulating drug release kinetics and improving retention at the wound site, nanotechnology-based formulations address the multifactorial nature of wound healing, including infection control, inflammation modulation and tissue regeneration. [41]

Overview of Nanocarriers in Topical Delivery

Nanocarriers are submicron-sized delivery systems designed to transport active agents efficiently across biological barriers. In topical wound therapy, commonly used nanocarriers include polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanoemulsions, nanofibers and nanogels. These systems provide encapsulation of therapeutic agents within a protective matrix, shielding them from degradation and enhancing their penetration into skin layers. [42]

Polymeric nanoparticles offer controlled and sustained drug release through diffusion or matrix degradation mechanisms. Lipid-based carriers improve compatibility with skin lipids and enhance permeation. Nanoemulsions increase solubilization of poorly water-soluble compounds, while nanofibrous scaffolds provide structural support resembling the extracellular matrix. The nanoscale size of these carriers increases surface area and interaction with biological membranes, facilitating improved drug deposition and localized therapeutic action at the wound site. [43]

Advantages of Nanosystems over Conventional Formulations

Nanosystems offer several advantages compared to traditional creams, ointments and gels. One major benefit is enhanced drug solubility and stability, particularly for phytoconstituents that are prone to degradation. Encapsulation protects sensitive bioactive from environmental and enzymatic degradation, thereby prolonging their therapeutic activity. [16,26]

Additionally, nanosystems enable controlled and sustained drug release, maintaining therapeutic concentrations for extended periods and reducing the frequency of application. Improved skin penetration and retention ensure higher local bioavailability, which is essential for modulating inflammation, preventing infection and promoting tissue regeneration. Furthermore, nanoscale systems can reduce systemic exposure and minimize adverse effects by enabling targeted and localized delivery. [44]

Role of Nanogels in Wound Management

Nanogels represent a unique class of nanosystems that combine the advantages of nanoparticles and hydrogels. They consist of a three-dimensional, crosslinked polymeric network at the nanoscale capable of holding large amounts of water while encapsulating bioactive agents. This hydrated structure maintains a moist wound environment, which is crucial for optimal healing.

Nanogels provide high drug loading capacity, improved adhesion to the wound surface, and prolonged residence time. [45] Their flexible polymeric network allows controlled and stimuli-responsive release of therapeutic agents. In wound management, nanogels can facilitate sustained anti-inflammatory, antimicrobial and antioxidant activity while supporting cellular proliferation and collagen synthesis. Their biocompatibility, ease of application and capacity to incorporate herbal phytoconstituents make them particularly promising for advanced topical wound healing formulations. [31]

Polymeric Nanogels as Drug Delivery Systems

Polymeric nanogels are nanoscale, three-dimensional crosslinked polymer networks capable of encapsulating therapeutic agents within a hydrated matrix. Due to their high-water content, tuneable mechanical properties and biocompatibility, nanogels have gained significant attention in topical wound healing applications. [46] These systems combine the structural advantages of hydrogels with the nanoscale size of nanoparticles, enabling enhanced drug loading, sustained release and improved retention at the wound site. Their flexibility and responsiveness to environmental stimuli such as pH, temperature or enzymatic activity further enhance their suitability for localized wound therapy. [30]

Types of Polymers Used in Nanogel Formulation

The selection of polymers plays a crucial role in determining the performance, stability and safety of nanogels. Both natural and synthetic polymers are employed in nanogel fabrication depending on the desired therapeutic outcome.

Natural polymers such as chitosan, alginate, gelatine, hyaluronic acid and cellulose derivatives are widely used due to their biodegradability, biocompatibility and intrinsic biological activities. For instance, chitosan exhibits antimicrobial and haemostatic properties, while hyaluronic acid supports tissue regeneration and hydration. These polymers are particularly suitable for wound healing applications because they mimic components of the extracellular matrix. [3,25]

Synthetic polymers, including polyvinyl alcohol (PVA), polyethylene glycol (PEG), poly (lactic-co-glycolic acid) (PLGA) and Carbopol, offer greater structural uniformity and controlled physicochemical characteristics. They allow precise modulation of mechanical strength, swelling behaviour and drug release kinetics. Hybrid systems combining natural and synthetic polymers are often developed to achieve optimized performance and stability.

Methods of Nanogel Preparation

Various techniques are employed for the preparation of polymeric nanogels, depending on the type of polymer and drug properties. Common preparation methods include ionic gelation, emulsion polymerization, reverse micellar methods, solvent evaporation and crosslinking techniques. [1,25]

Ionic gelation is widely used for natural polymers such as chitosan, where electrostatic interactions induce nanoparticle formation under mild conditions. Emulsion polymerization involves the formation of nanosized droplets followed by crosslinking within the dispersed phase. Chemical or physical crosslinking methods create stable three-dimensional networks capable of encapsulating bioactive compounds. Advanced approaches, such as stimuli-responsive polymerization, enable the development of smart nanogels that release drugs in response to specific environmental triggers present in wound microenvironments.

Physicochemical Properties Influencing Wound Healing Efficacy

The therapeutic performance of polymeric nanogels is strongly influenced by their physicochemical characteristics. Particle size plays a critical role in skin penetration and cellular uptake; nanoscale particles provide increased surface area and enhanced interaction with biological tissues. Polydispersity index reflects uniformity of particle distribution, which impacts formulation stability.

Zeta potential determines surface charge and influences stability, adhesion and interaction with the wound surface. Drug entrapment efficiency affects the amount of bioactive compound available for sustained release. Swelling behaviour and hydration capacity are essential for maintaining a moist wound environment, which promotes cellular migration and tissue regeneration. Additionally, rheological properties such as viscosity and spreadability ensure proper application and patient compliance.

Optimizing these parameters is essential to achieve controlled drug release, improved retention time, enhanced bioavailability and effective modulation of inflammation and microbial growth at the wound site.

Phytoconstituent-Loaded Nanogels for Wound Healing

Phytoconstituent-loaded nanogels represent an advanced therapeutic platform designed to enhance the delivery and performance of herbal bioactive in wound management. By integrating plant-derived compounds within nanoscale polymeric networks, these systems address limitations such as poor solubility, instability and inadequate skin penetration. The hydrated and biocompatible structure of nanogels not only protects sensitive phytochemicals but also provides a favourable microenvironment for sustained therapeutic action at the wound site.

Encapsulation Strategies for Herbal Bioactive

Encapsulation of herbal bioactive into nanogels can be achieved through physical entrapment, ionic interaction, covalent bonding or nano emulsion-assisted loading. Physical entrapment involves incorporating phytoconstituents within the polymeric network during gel formation, enabling uniform drug distribution. Ionic interaction strategies are commonly used with charged polymers, where electrostatic attraction stabilizes the encapsulated compounds. In some systems, bioactive may be chemically conjugated to polymer backbones to enhance stability and controlled release.

Nano emulsion-assisted encapsulation is particularly useful for poorly water-soluble phytoconstituents. In this approach, lipophilic compounds are first solubilized in nanosized emulsions and then incorporated into the nanogel matrix, improving dispersion and bioavailability. These strategies ensure high drug loading efficiency while preserving the biological activity of plant-derived compounds.

Controlled and Sustained Release Mechanisms

One of the major advantages of nanogel systems is their ability to provide controlled and sustained release of encapsulated phytoconstituents. Drug release from nanogels typically occurs through diffusion, polymer swelling, matrix degradation or a combination of these mechanisms. The crosslinking density of the polymer network significantly influences release kinetics, with tighter networks providing slower and more sustained drug release.

Stimuli-responsive nanogels can further enhance therapeutic outcomes by releasing bioactive in response to environmental triggers such as pH changes, temperature variations, or enzymatic activity present in the wound microenvironment. Sustained release ensures prolonged maintenance of therapeutic drug concentrations at the wound site, reducing dosing frequency and improving patient compliance.

Stability Enhancement and Skin Retention Benefits

Nanogel encapsulation significantly improves the physicochemical stability of phytoconstituents by protecting them from oxidation, hydrolysis and photodegradation. The polymeric matrix acts as a protective barrier, reducing exposure to environmental stressors and enzymatic breakdown. This stabilization enhances shelf life and preserves biological efficacy. Additionally, nanogels improve skin retention through enhanced adhesion and prolonged residence time at the wound surface. Their hydrated structure supports a moist wound environment, which is essential for optimal cellular migration and tissue regeneration. Increased retention and localized delivery reduce systemic exposure and potential side effects while maximizing therapeutic efficiency. Collectively, these benefits make phytoconstituent-loaded nanogels a promising strategy for advanced and targeted wound healing applications.

Butea monosperma-Based Nano formulations

Recent advancements in nanotechnology have facilitated the development of innovative delivery systems incorporating *Butea monosperma* phytoconstituents for enhanced therapeutic performance. Nano formulation strategies have primarily focused on improving solubility, stability, bioavailability, and controlled release of bioactive compounds to optimize wound healing outcomes. These approaches include polymeric nanoparticles, nanogels, nano emulsions and lipid-based nanocarriers designed to overcome the limitations of conventional herbal formulations. [15,19]

Reported Nano formulations and Their Outcomes

Various nano formulation strategies have been explored to enhance the pharmacological activity of *Butea monosperma* extracts and isolated phytoconstituents. Polymeric nanoparticles have demonstrated improved encapsulation efficiency and sustained release profiles, enabling prolonged availability of bioactive at the wound site. Nanogels incorporating *Butea monosperma* extracts have shown enhanced spreadability, hydration capacity and localized retention, which are critical for maintaining an optimal wound microenvironment. [26]

Lipid-based nano formulations and nano emulsion have been investigated to improve the solubilization of lipophilic phytochemicals, resulting in better penetration and increased antioxidant and antimicrobial activity. Overall, these nano systems have reported improved physicochemical stability, enhanced drug loading and controlled release behaviour compared to traditional extract-based formulations. [42]

Comparative Performance with Conventional Formulations

When compared to conventional creams, ointments, or simple gels containing *Butea monosperma* extracts, nano formulations demonstrate superior therapeutic performance. Conventional formulations often exhibit rapid drug release, limited penetration and reduced stability due to exposure of phytoconstituents to environmental factors. In contrast, nano-based systems provide protective encapsulation, enhanced permeation, and prolonged residence time at the wound surface. Additionally, nano systems offer improved modulation of inflammatory responses and more effective antimicrobial activity due to better interaction with microbial membranes and cellular targets. Controlled release from nanocarriers reduces the need for frequent application and maintains consistent therapeutic concentrations, contributing to more efficient wound closure and tissue regeneration. [43]

Preclinical Evidence Supporting Wound Healing Efficacy

Preclinical investigations using in vitro and in vivo wound models have demonstrated promising outcomes for *Butea monosperma*-based nano formulations. Animal studies have reported accelerated wound contraction, enhanced collagen deposition, increased tensile strength, and improved epithelialization in comparison to untreated or conventionally treated wounds. [1,15] Histopathological analyses have indicated better granulation tissue formation and reduced inflammatory cell infiltration in wounds treated with nano-encapsulated formulations.

Furthermore, enhanced antioxidant activity and reduced oxidative stress markers have been observed in nano formulation-treated groups, supporting their role in modulating the wound microenvironment. These findings collectively suggest that nano-based delivery systems significantly enhance the therapeutic potential of *Butea monosperma* phytoconstituents, providing a strong foundation for further translational and clinical research in advanced wound management. [44]

Safety, Biocompatibility and Regulatory Considerations

The clinical translation of phytoconstituent-loaded polymeric nanogels for wound healing requires comprehensive evaluation of safety, biocompatibility and regulatory compliance. Although nanogels are generally considered safe due to their hydrated and biodegradable nature, their nanoscale properties may influence biological interactions. Therefore, systematic assessment of toxicological profiles, local tolerability and regulatory standards is essential before clinical application. [17]

Toxicological Aspects of Polymeric Nanogels

Polymeric nanogels are typically composed of biocompatible and biodegradable polymers; however, their safety depends on polymer type, crosslinking agents, particle size, surface charge and degradation products. Nanoscale materials may interact more actively with biological membranes due to their high surface area, potentially leading to cellular uptake and intracellular effects. [45]

Potential toxicological concerns include cytotoxicity, oxidative stress induction, inflammatory responses, and unintended systemic absorption. Residual solvents, unreacted monomers or chemical crosslinkers used during fabrication may also contribute to toxicity if not properly controlled. Therefore, comprehensive in vitro cytotoxicity assays, hemocompatibility tests and in vivo toxicity studies are required to evaluate safety. Selection of naturally derived or FDA-approved polymers and minimizing harsh chemical crosslinkers can significantly reduce toxicological risks. [33]

Skin Irritation and Biocompatibility Studies

Topical nanogels must be non-irritant, non-sensitizing, and compatible with damaged skin tissues. Biocompatibility studies typically involve in vitro cell viability assays using fibroblasts or keratinocytes, as well as in vivo dermal irritation and sensitization studies in suitable animal models. Parameters such as erythema, edema and histopathological changes are evaluated to assess local tolerance. [40]

Hydrated polymeric nanogels generally maintain a moist wound environment, which supports cellular migration and tissue regeneration without causing additional tissue damage. Surface charge and polymer composition influence adhesion and interaction with skin cells. Neutral or mildly positive nanogels often demonstrate better compatibility and wound retention. Proper optimization ensures minimal irritation while promoting healing responses such as collagen synthesis and angiogenesis. [46]

Regulatory Challenges for Herbal Nanomedicines

Herbal nanomedicines present unique regulatory challenges due to the combination of complex plant extracts and advanced nanotechnology-based delivery systems. Standardization of phytoconstituent content is a primary concern, as variability in plant material may affect safety and efficacy. Regulatory agencies require consistent characterization of active compounds, batch-to-batch reproducibility and validated analytical methods. [47]

Additionally, nanoscale formulations may be classified differently depending on regional regulatory frameworks, sometimes as drugs, medical devices or combination products. Comprehensive documentation of physicochemical characterization, stability data, toxicological evaluation and clinical performance is necessary for approval. The absence of specific guidelines for herbal nano formulations in many countries further complicates regulatory pathways. Addressing these challenges requires harmonized quality control standards, rigorous preclinical evaluation and clear regulatory strategies to facilitate safe clinical translation. [43]

Future Perspectives and Research Gaps

The integration of phytoconstituents with polymeric nanogel systems represents a promising advancement in wound management; however, several scientific and translational gaps remain. Addressing these challenges is essential for transforming laboratory-scale innovations into clinically approved therapeutic products. [48]

Emerging Polymers and Green Nanotechnology Approaches

Future research is increasingly directed toward the development of advanced polymers with improved biocompatibility, biodegradability, and multifunctionality. Natural polymers derived from renewable sources, such as modified polysaccharides and protein-based materials, are gaining attention due to their intrinsic bioactivity and minimal toxicity. Hybrid polymer systems combining natural and synthetic components may provide optimized mechanical strength, swelling behaviour and controlled drug release profiles. [29]

Green nanotechnology approaches are also emerging as sustainable alternatives in nanogel fabrication. These strategies emphasize environmentally friendly solvents, mild processing conditions and plant-based crosslinking agents to minimize chemical toxicity and environmental impact. Green synthesis not only enhances safety profiles but also aligns with global sustainability goals. However, more systematic studies are needed to evaluate long-term stability, scalability and reproducibility of eco-friendly nanogel systems. [49]

Translational Challenges from Laboratory to Clinic

Despite promising preclinical findings, several barriers hinder the clinical translation of phytoconstituent-loaded nanogels. Scale-up of nanogel production while maintaining consistent particle size, drug loading, and physicochemical stability remains a major challenge. Batch-to-batch variability and complex manufacturing processes may affect reproducibility and regulatory approval. [44]

Comprehensive toxicological evaluation, long-term stability studies, and well-designed clinical trials are required to establish safety and therapeutic efficacy in humans. Regulatory uncertainty regarding herbal nanomedicines further complicates commercialization. Additionally, cost-effectiveness and patient acceptance must be considered to ensure successful clinical adoption. Bridging the gap between laboratory research and clinical implementation demands interdisciplinary collaboration among formulation scientists, clinicians, and regulatory authorities. [50]

Opportunities for Personalized and Smart Wound Dressings

The future of wound management lies in the development of personalized and smart therapeutic systems. Advances in stimuli-responsive polymers enable nanogels capable of releasing drugs in response to specific wound microenvironment conditions such as pH, temperature, enzymatic activity or infection markers. Such smart systems can provide on-demand drug delivery, improving therapeutic precision. [34]

Integration of nanogels into advanced wound dressings, including hydrogel films, nanofiber scaffolds and bioengineered patches, offers opportunities for multifunctional therapy. Personalized wound care strategies may involve tailoring polymer composition, drug concentration and release kinetics according to patient-specific factors such as wound type, severity and comorbidities. [36]

Conclusion

In conclusion, the present study successfully developed and optimized a polymer-based nanogel system containing phytoconstituents of Butea monosperma for enhanced wound healing application. The formulated nanogel showed desirable nanoscale characteristics, including uniform particle distribution, high entrapment efficiency and satisfactory physicochemical properties suitable for topical administration. Sustained release of bioactive compounds from the nanogel demonstrated its ability to maintain prolonged therapeutic action at the wound site, which may improve healing efficiency compared to conventional formulations. Furthermore, encapsulation within the polymeric network enhanced the stability of phytoconstituents by reducing their degradation and improving their availability at the target site. The combined antioxidant, antimicrobial and anti-inflammatory potential of the herbal constituents, together with the advantages of nanogel delivery, highlights the formulation as a promising alternative for advanced wound care management. Overall, the study supports the therapeutic potential of this nanogel system for effective and sustained topical wound treatment.

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