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Review Paper

Natural Bioactive Compound Loaded Nanomaterials for Wound Healing

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ABSTRACT

Wound healing is a complex biological process involving haemostasis, inflammation, proliferation and remodelling. Conventional wound treatments, including topical antibiotics and dressings, often fail to provide sustained therapeutic effects, leading to poor patient compliance and increased risk of antimicrobial resistance. Recent advancements have highlighted the potential of natural bioactive compounds, derived from plants, marine organisms, and animals, for wound management due to their antioxidant, anti-inflammatory, antimicrobial, and angiogenic properties. However, the therapeutic application of these bioactive agents is limited by their poor solubility, stability, and bioavailability. Nanotechnology offers a promising solution by enhancing the delivery, retention, and efficacy of these natural compounds through various nanocarriers, including polymeric nanoparticles, liposomes, nanofibers, and hydrogels. This review critically explores the role of natural bioactive compound-loaded nanomaterials in wound healing, focusing on their mechanisms of action, types of bioactive compounds, and their Nano formulation strategies. The review also addresses the challenges associated with the clinical translation of these nanotherapeutics and highlights future perspectives for their application in advanced wound care.

INTRODUCTION

Tissue integrity restoration occurs through a highly organized biological process which heals wounds after damage. The process develops through four successive yet detached stages: hemostasis, inflammation, proliferation, and remodeling. A fibrin clot develops from platelet aggregation during the initial phase of hemostasis as neutrophils and macrophages activate inflammatory responses to clean pathogens and debris. Granulation tissue formation occurs due to proliferative activity followed by angiogenesis then re-epithelialization which finally ends in extracellular matrix strengthening through tissue contraction and collagen maturation (Gurtner et

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al., 2008). The complicated wound healing process requires perfect health conditions since small environmental changes can result in non-healing wounds. Wound management poses a considerable clinical challenge to healthcare providers when treating chronic conditions like diabetic ulcers, pressure sores and venous leg ulcers. The integrated healing process of wounds gets insufficient address by standard treatment strategies that incorporate topical antibiotics together with dressings and systemic therapies. These treatments fail to create prolonged therapeutic effects on wounds which leads to numerous medication applications together with reduced patient compliance and greater antimicrobial resistance risk (Boateng & Catanzano, 2015). Standard therapeutic formulations suffer from limited exposure of essential drugs to the wound site due to degradation and insolubility and environment instability. Scientific interest in natural bioactive compounds increases steadily for their use as therapeutic agents to treat wound injuries. Wound healing properties of natural substances like curcumin and aloe vera, chitosan and honey originate from plant and marine or animal origins (Puppi et al., 2010).

These bioactive compounds exhibit antimicrobial properties alongside antioxidant benefits, anti-inflammatory functions, and angiogenic effects. These therapeutic agents demonstrate superior therapeutic effectiveness within traditional pharmaceutical practice as well as modern healthcare practices. The clinical effectiveness of these agents diminishes because they have poor water solubility and quick degradation and poor permeability through the skin (Bhowmik et al., 2018). A suitable delivery platform remains essential because it enables maximum utilization of therapeutic compounds.

Pharmaceutical sciences adopt nanotechnology as a transformative delivery system because it provides new solutions for drug delivery. Utilization of nanomaterials allows medical practitioners to manage the release kinetics of therapeutic agents for better pharmacokinetic and pharmacodynamic profiles. Due to their protective nature liposomes along with polymeric nanoparticles and solid lipid nanoparticles and nanofibers create stable protected spaces for bioactives because they improve both solubility and delivery accuracy to the wound (Makadia & Siegel, 2011). The successful delivery of therapeutic agents requires these benefits especially within moist enzymatically active wound healing environments because conventional drugs fail prematurely under such conditions.

The combination between nanotechnology and natural bioactive compounds creates an effective dual-approach for wound therapy in medical practice. Bioactive compounds enclosed inside nanocarriers manage both stability and solubility problems as well as enable targeted delivery to particular sites while maintaining extended drug action which enhances therapeutic outcomes and reduces overall side effects (Liakos et al., 2015). A new line of advanced wound care products emerged possible through this combined interaction enabling safer and more effective as well as user-friendly solutions.

The main goal of this critical evaluation is to assess in depth the advancing utilization of natural bioactive compound-loaded nanomaterials within wound healing applications. The present study establishes its objective to deliver pharmacy students and researchers with comprehensive knowledge about wound repair biology as well as natural compounds' healing potential along with nanomaterial functions and translation obstacles. The research dives into a single aspect of this interdisciplinary domain through a sequential presentation that joins natural pharmacology with modern nanotechnology within wound care beds.

Natural Bioactive Compounds in Wound Healing

Traditional healing practices consist of natural bioactive compounds which scientists now apply to consolidate their therapeutic merits for promoting wound healing processes. Compounds derived from plants and marine organisms and animals accumulate various activities which enhance tissue regeneration by accelerating its multi-phase sequence. Because they affect oxidative stress and anti-inflammation processes as well as control both microbial infections and new blood vessel formation these compounds are excellent choices for creating wound care treatments (Bhowmik et al., 2018).

Plant-Derived Bioactives

Research on curcumin has revealed extensive knowledge of this plant compound because it demonstrates anti-inflammatory and antioxidant effects and antimicrobial properties. The compound restrains TNF-α, IL-1β and inhibits NF-κB nuclear movement while simultaneously reducing inflammation and stimulating fibroblast cell growth (Akbik et al., 2014). Acemannan along with glucomannan contained in aloe vera stimulates collagen synthesis and reinforces fibroblast activity and promotes re-epithelialization (Surjushe et al., 2008). Strong antimicrobial and antioxidant properties exist in neem (Azadirachta indica) which effectively promotes wound margin contraction and speeds up epithelial cell migration (Subapriya & Nagini, 2005). The botanical Centella asiatica performs multiple functions due to its triterpenoids which include asiaticoside and madecassoside and raises collagen synthesis levels and stimulates VEGF-mediated angiogenesis but also reduces inflammation by lowering COX-2 and pro-inflammatory cytokines (Brinkhaus et al., 2000).

Marine-Derived Bioactives

Marine-derived substances function as effective bioactive agents. Chitosan which emerges from chitin deacetylation functions as a polysaccharide to maintain wound dampness while demonstrating antimicrobial properties and enables tissue healing through process of hemostasis and cellular regenerative activity (Rinaudo, 2006). The application of TGF-β enhancing bioactive properties contributes to the remodeling stage in the process of wound healing. The substituted sugar compound known as Fucoidan which originates from brown seaweed functions as both an anti-inflammatory substance and an activator of angiogenesis. The substance has been proven to boost fibroblast duplication and increase the production of VEGF and bFGF proteins which drive new blood vessel growth in wound tissue (Fitton, 2011).

Animal-Derived Bioactives

Honey represents one of the oldest animal-derived remedies which the human species has used for centuries to treat wounds. The combination of high osmolarity and hydrogen peroxide content and phenolic compounds in Fucoidan produces anti-inflammatory and anti-angiogenic effects (Molan, 2001). The application of honey leads to both enhanced granulation tissue development and improved epithelial skin growth. Structural protein collagen serves as a cell-adhesion scaffold originating from bovine, porcine and marine sources. When used topically collagen activates fibroblasts for correct wound matrix formation while changing the expression patterns of TGF-β1 and other remodeling proteins (Chattopadhyay et al., 2014).

Pharmacological Activities and Mechanistic Pathways

The pharmacological effects of these bioactives match up with different stages of wound healing.

Cells need antioxidant protection throughout the inflammatory phase and proliferative phase because tissue regeneration and proper fibroblast functionality become dysfunctional with excessive oxidative stress. Cells remain intact through neutralizing ROS with compounds including curcumin along with honey and Centella asiatica (Moustafa et al., 2014). Antimicrobial functions of neem and chitosan and honey actively reduce microbial counts and cut down the resulting inflammatory response primarily in chronic wound settings. Three ingredients in this analysis namely curcumin, fucoidan and aloe vera demonstrate anti-inflammatory properties by blocking NF-κB signaling and reducing COX-2 activity while decreasing inflammatory cytokine expression.

Several compounds stimulate angiogenesis through activation of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) toward promoting tissue repair. The compounds curcumin and fucoidan and Centella asiatica activate VEGF to improve blood vessel development along with nutrient transport to healing tissues according to Gupta et al. (2013). Chitosan and collagen bioactives modify the TGF-beta signaling signals which enhances extracellular matrix rearrangement as well as scar tissue development.

Limitations in Direct Application

Traditional medical systems utilize natural bioactive compounds for therapeutic purposes since modern pharmacological studies confirm these compounds can heal wounds effectively. Wound healing facilitation occurs through these compounds which come from plant and animal and marine biological sources and provide multiple therapeutic activities during tissue regeneration. The therapeutic properties of these compounds extend to their regulation of oxidative stress alongside inflammation and microbial infections and angiogenesis qualify them for use in wound treatment formulations (Bhowmik et al., 2018).

Plant-Derived Bioactives

The anti-inflammatory and antioxidant properties along with antimicrobial activities of curcumin from Curcuma longa have been extensively studied among plant-derived chemicals. The compound controls inflammatory mediator activity including TNF-α, IL-1β and blocks NF-κB nuclear migration to decrease tissue inflammation and boost fibroblast cell growth (Akbik et al., 2014). Aloe vera possesses two bioactive substances named acemannan and glucomannan that initiate collagen synthesis processes and boost fibroblast functions and support epithelial reattachment (Surjushe et al., 2008). Studies show Azadirachta indica neem works as an antimicrobial with its antioxidant properties while assisting wound margin contraction while speeding epithelial cell movement (Subapriya & Nagini, 2005). The botanical substance Centella asiatica delivers two triterpenoids called asiaticoside and madecassoside that strengthen collagen synthesis and stimulate angiogenesis through VEGF pathways while undermining COX-2 cells and inflammatory factors such as pro-inflammatory cytokines (Brinkhaus et al., 2000).

Marine-Derived Bioactives

Modern studies demonstrate how substances from marine environments have proven themselves effective bioactive compounds. Chitosan represents a polysaccharide made from chitin deacetylation which establishes a moist wound bed while showing intrinsic antiseptic properties and promoting bleeding cessation and facilitating cell regeneration and movement throughout the wound space (Rinaudo, 2006). Wound healing experts confirm that TGF-β expression increases through

its application which plays an essential role in the remodeling phase of tissue repair. Fucoidan acts as an inflammatory controlling and blood vessel evolution promoting sulfated polysaccharide that originates from brown seaweed. Fibroblast stimulation and the simultaneous increase of VEGF and bFGF are well-documented functions of this substance which help neovascularization in wound beds (Fitton, 2011).

Animal-Derived Bioactives

The ancient and universal remedy for wound treatment called honey has originated from animals and represents one of the oldest medicinal natural remedies derived from animal sources. The multiple mechanisms of action for this substance include its high osmolarity coupled with hydrogen peroxide content that slows microbial growth along with phenolic compounds which provide antioxidant protection according to Molan (2001). The tissue forming process known as granulation advances more rapidly when using honey while its action also speeds up epithelial tissue development. The structural protein collagen functions as a cell attachment and migration platform since it comes from bovine, porcine, and marine sources. When applied topically collagen plays a dual role by activating fibroblasts while helping matrix formation and modifying the expression of TGF-β1 as well as other remodeling proteins (Chattopadhyay et al., 2014).

Pharmacological Activities and Mechanistic Pathways

The bioactive substances display multiple pharmacological effects which correspond to the healing phases of wounds. The wound's inflammatory along with proliferative stages require antioxidant properties because oxidative stress affects both fibroblast functions and tissue restorative activities. The compounds curcumin and honey and Centella asiatica protect cell structures by eliminating reactive oxygen species (Moustafa et al., 2014). The antimicrobial compounds in neem and chitosan and honey effectively decrease microbial amounts and minimize inflammatory responses in chronic wounds. Multiple inflammation-reducing activities exist in curcumin and fucoidan together with aloe vera which suppress inflammatory cytokines by inhibiting NF-κB and suppressing COX-2 activity.

Several compounds encourage angiogenesis in tissue repair through activation of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). Medical research has proven that curcumin along with fucoidan and Centella asiatica work to increase VEGF levels which results in better blood vessel development and improved tissue nutrient supply (Gupta et al., 2013). Two bioactive compounds specifically chitosan and collagen alter TGF-β signaling to influence extracellular matrix remodeling and create scar formation.

Nanomaterials for Targeted Wound Therapy

The use of nanotechnology for wound treatment advancements constitutes an essential development in contemporary pharmaceutical research. Therapeutic agents delivered through nanomaterials reach wounds effectively due to precise controlled methods while improving upon problems of fast degradation and poor drug stability and low permeability and systemic adverse effects. Nanocarriers improve tissue regeneration and control inflammation and fight microbial infections because they directly engage with cellular substances and molecular components present within wounds (Shoeib et al., 2022).

Types of Nanomaterials in Drug Delivery

Nanotechnology research has established new types of nanocarriers which effectively address diverse problems that occur during wound healing processes. Researchers extensively study polymeric nanoparticles along with lipid-based nanoparticles and metallic nanoparticles and hydrogels and nanofibers as they represent the most examined nanocarriers. All four categories of nanocarriers possess different strengths for wound treatment because they optimize bioactivity levels and control drug release mechanisms while ensuring targeted delivery to specific sites.

Polymeric Nanoparticles

Wounds benefit from polymeric nanoparticles built using poly (lactic-co-glycolic acid) (PLGA) and chitosan because these materials possess all three properties: biocompatibility and biodegradability and versatility. PLGA nanoparticles have useful properties which enable them to biodegrade and maintain and control the gradual release of bioactive compounds to support extended therapeutic treatment. Surface modifications perform two functions on these particles to improve penetration through tissues while guiding their interaction with particular receptors or cells in the healing environment. Research has proven that PLGA nanoparticles function effectively for drug delivery systems and simultaneously reduce side effects through careful agent release management throughout therapeutic periods. Wound healing needs can be addressed through PLGA systems by adjusting three main attributes including particle size specifications alongside drug encapsulation parameters and surface modifications.

Scientists have identified several positive aspects of chitosan nanoparticles due to the distinctive features of chitosan as a biopolymer obtained from chitin materials. Natural antimicrobial properties found in these nanoparticles serve well for treating infections within wounds. The cationic property of chitosan enables strong electrostatic interactions that improve its adhesion to wound tissues and therefore enhance healing capabilities. The environment within wounds remains moist because chitosan nanoparticles create this supportive condition that enables re-epithelialization and speeds up healing time. The suitable characteristics of chitosan nanoparticles enable their incorporation into advanced wound dressings which support healing processes together with infection control mechanisms.

Lipid-Based Nanocarriers

The wound healing field benefits greatly from lipid-based nanoparticles as their three main forms include liposomes along with solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). Spherical nanostructures named liposomes use phospholipid bilayers to encase medication compounds that include hydrophilic and lipophilic therapeutic agents. These nanocarriers possess a membrane composition similar to cells which grants them excellent compatibility and increases drug absorption for diverse therapeutic agents. The attachment of ligands targeting specific receptors and cells to liposomes improves their propagation efficiency to desired receptors like fibroblasts and macrophages.

This solid particulate drug carrier system made from lipids provides outstanding stability to enclosed substances through protection against degradation effects such as light exposure and temperature changes combined with oxidative stress. The therapeutic outcomes in wound care improve when using SLNs because these carriers deliver hydrophobic drugs while sustaining controlled drug release doses. The combination of solid and liquid lipids within NLCs grants them beneficial attributes from SLNs while allowing more drug content to be stored and improving kinetics for drug release. There are two advantages

which come from adding liquid lipids to solid lipid matrices in NLCs: these enhances solid lipid stability and enables customized release control thus allowing sustained delivery of active compounds for prolonged durations.

Metallic Nanoparticles

Silver (AgNPs) along with zinc oxide (ZnO) nanoparticles stand out as the most researched metallic nanoparticles for wound healing because they demonstrate strong antimicrobial and anti-inflammatory properties together with antioxidant function. AgNPs demonstrate proven capability to break bacterial cell membranes and stop bacterial growth while interfering with biofilm creation. These nanoparticles demonstrate extraordinary effective treatments for wounds that are both infected and chronic in nature. The use of AgNPs enhances patients' wound healing process because they fight inflammatory responses while promoting tissue recovery and reducing microbial numbers. Higher concentrations of silver nanoparticles have shown potential toxicity to cells which requires precise control over formulation controls including particle size and concentration and release speed in order to achieve both safety and lower the occurrence of adverse effects.

ZnO nanoparticles function through two independent mechanisms during their action. The combined action of zinc oxide nanoparticles protects against multiple microorganisms and helps wound healing through proper management of inflammatory response mechanisms. The wound closure processes which depend on collagen synthesis and epithelial proliferation and new vessel formation known as angiogenesis require zinc as a vital element. The wound healing process receives acceleration through ZnO nanoparticles because they both speed up vital processes while shielding wounds against potential oxidation damage. The clinical reliability of ZnO nanoparticles depends on specific formulation approaches which establish effective drug release mechanisms alongside maintaining patient safety.

Hydrogels and Nanofibers

The functionality of hydrogels in wound care derives from their distinctive characteristic to preserve moist conditions at the wound site thus optimizing healing outcomes. Wounds receive sustained release of therapeutic compounds and nanoparticles along with bioactive agents from these polymeric or natural material networks which exist as three-dimensional structures. Hydrogels serve two important functions during autolytic debridement because they assist in tissue necrosis clearance alongside the promotion of cellular mobility and collagen synthesis and new blood vessel creation. Nanoparticles inside hydrogels transform these substances into storage containers that deliver therapeutic agents and bioactives with prolonged time release for better therapeutic results. Hydrogels demonstrate exceptional value for treating chronic wounds and diabetic ulcers and burns and offer controlled moisture and antimicrobial properties alongside damage repair stimulation.

Scientists have developed nanofibers using electrospinning methods as a new technology for wound dressing applications. These fibers replicate the extracellular matrix structure to provide a suitable foundation for cells that promote attachment and active growth and natural migration. Their open structure provides large surface contact area for effective medication loading which includes nanoparticles with proteins and growth factors. Nanofiber structures are designed to display particular mechanical attributes including elasticity and tensile strength this enables their use as support systems for wound recovery. Electrospun nanofibers function as tissue regeneration scaffolds for wound dressings

applied in the treatment of burns alongside diabetic ulcers and surgical wounds (Cheng et al., 2017).

The development of innovative wound care solutions has resulted from nanotechnology integration in wound treatment processes. Each wound healing stage benefits from different features provided by polymeric nanoparticles and lipid-based nanocarriers and metallic nanoparticles and hydrogels and nanofibers which enables purpose-specific healings for both acute wounds and chronic wounds. Drug delivery systems achieve enhanced stability through these systems while simultaneously improving bioavailability and controlled drug release capabilities and they enable precise delivery to the healing wound site permitting better medicinal effects. Research advancement will drive the ongoing development of technologies that create more efficient wound healing treatments which blend biocompatibility and friendliness to patients.

Key Physicochemical Properties

The efficiency of nanocarriers to support wound healing depends on their physics chemical traits including size, surface attributes along with zeta potential measurement and characteristics. Nanoparticles smaller than 200 nm and larger than 10 nm show improved ability to penetrate skin tissue and enter cells as well as remain present at wound sites. Nanoparticles bearing positive surface charges show better adherence towards biofilms and microbial cell surfaces that maintain negative charges. By integrating surface modification through hyaluronic acid ligands combined with peptides and PEGylation the delivery becomes targeted and systemic circulation stays prolonged while immunological recognition decreases (Danhier et al., 2012).

Synthesis and Characterization Techniques

Research groups develop nanocarriers synthetically before characterizing them for expanding pharmaceutical wound therapy treatments and ensuring their safety. To meet the performance requirements of targeted delivery, controlled release and biocompatibility nanostructure synthesis needs perfect method control and robust physicochemical nanostructure assessment.

The selection of synthesis methods depends on the nanocarrier type together with the therapeutic objectives. Polymeric nanoparticles receive synthesis through three main approaches: nanoprecipitation and emulsion-solvent evaporation and ionic gelation. The preparation of liposomes requires a thin-film hydration process that leads to extrusion steps and solid lipid nanoparticles and nanostructured lipid carriers need hot or cold homogenization steps to develop. Selection of each technique proceeds with consideration of its encapsulation abilities regarding desired bioactive compound and stability requirements and release kinetics needs. The synthesis of silver nanoparticles as inorganic nanocarriers happens through chemical reduction methods and plant extract-based green synthesis processes. The assessment of nanoparticle properties becomes essential after their production to check if they comply with pharmaceutical industry requirements. The Dynamic Light Scattering (DLS) method is used primarily for determining particle size measurements alongside size distribution and Polydispersity Index (PDI). Uniform particles with a narrow PDI value below 0.2 are fundamental for predictable biological effects as well as product stability during shelf life. The surface charge information obtained through Zeta potential analysis determines how stable the formulated colloids will be. A zeta potential reading above ±30 mV indicates enough electrostatic repulsion between particles to maintain stability while stowing and during in vivo activities.

The microscopic analysis using SEM and TEM generates detailed images to verify both the structural appearance and topographical details and diameter consistency of nanoparticles. The internal structure of liposomes or nanocomposites alongside the observation of core-shell architectures becomes possible with TEM due to its exceptional value.

The verification of drug incorporation and chemical composition uses FTIR technology which functions as an important spectroscopic technique. FTIR shows both the specific functional groups present and possible bonding connections between drugs and carrier elements. The X-ray Diffraction (XRD) technique determines whether nanoparticles possess crystalline formations or remain amorphous in nature. Drug encapsulation success leads to an amorphous state transformation thus improving bioavailability because of enhanced solubility.

The thermal characteristics of nanocarriers become clear through Thermal analysis because it measures their thermal stability while detecting glass transition temperature as well as degradation responses through Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA). The identified parameters serve as vital indicators for deciding storage methods and determining formulation longevity under physiological temperature conditions.

These techniques contribute to both demonstration of reproducible stable nanocarrier formulations as well as adherence to pharmaceutical product regulatory requirements. The deep knowledge of synthesis methods and characterization techniques enables pharmacy experts to develop better pharmaceutical formulations whereas enhancing stability capabilities along with clinical outcomes projection which leads to effective nanomedicine wound healing therapies (Kumari et al., 2010).

Biocompatibility and Release Kinetics

The clinical achievement of nanotechnology-based wound healing systems depends fundamentally on biocompatibility along with release kinetic properties. When applied directly onto healing tissues the compatibility of these formulations must remain optimal for human tissue cells as well as support tissue processes without leading to any harm to healing. Selection of the materials used for wound healing formulations including chitosan and alginate biopolymers and PLGA and PEG synthetic polymers and lipid-based and metallic nanoparticles requires two-stage evaluation for biological safety and functional properties.

Biocompatibility levels of polymeric and lipid-based nanocarriers remain high because these systems break down into physiological products that resemble native human components. The carriers break down into non-toxic end products while the body removes them as waste or uses them in metabolic functions. Optimization procedures for inorganic or metallic systems like silver, gold and zinc oxide nanoparticles need to be handled with additional caution. Antimicrobial potency of such agents comes at a cost since their mechanisms can produce reactive oxygen species (ROS) or emit toxic ions which endangers local cell homeostasis through oxidative stress generation. Scientists must implement three fundamental approaches including surface functionalization of the nanoparticles along with particle size control and biopolymer matrix integration to lower these unwanted effects.

The preclinical phase requires multiple in vitro and ex vivo tests to determine cytocompatibility and safety levels. When used for cell viability assessments the MTT assay measures mitochondrial activity to determine cytological risks quickly. The lactate dehydrogenase (LDH) release assay tests cell membrane damage by monitoring the amount of enzyme which escapes cells through disruption. Topical nanocarrier

formulations require hemolysis testing to understand how much red blood cells can suffer damage during exposure. This evaluation is crucial because blood vessels may encounter the nanocarrier formulation when it is applied topically. Multiple test methods provide complete safety information about biological effects that enables formulation advancement in the trial process.

The drug release kinetics from the nanocarrier system need proper optimization for effective results. The wound healing journey consists of four sequential stages starting from hemostasis and inflammation until it advances to proliferation and finishes with tissue remodeling. Drug release mechanisms need to be controlled according to each biological healing phase. Acute wounds benefit from rapid therapeutic release of anti-inflammatory or antimicrobial products at the start to achieve effective both infection prevention and inflammation suppression. Long-lasting drug delivery systems are necessary for treating diabetic ulcers or pressure sores because they need sustained therapy to activate angiogenesis and cellular development and matrix repair in addition to stopping secondary infections. Different drug release durations can be achieved by modifying the carrier's ingredients or crosslinking qualities together with selecting particle dimensions or implementing response-triggered delivery methods that activate the medicine release based on wound site pH variation and biological processes or environmental temperature.

The therapeutic success of nanomedicine-based wound therapy relies on strike the perfect equilibrium between safe material properties and controlled substance discharge profiles. The range of values influences both therapeutic response outcomes in addition to determining the results of regulatory product certifications and clinical decisions.

Penetration Enhancement

Nanocarrier-based wound therapies help patients by breaking through skin barriers which have their primary defense in the stratum corneum. This outer layer combines tightly fused corneocytes with lipid bilayers. The penetration ability of traditional topical ointments or creams reaches only skin depth hence they lack sufficient effectiveness on deep wounds or persistent wounds which require agent delivery through the dermis and hypodermis tissue.

Research shows that transdermal and intradermal delivery can be successfully enhanced through the application of nanocarriers such as liposomes and niosomes and solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) and nanoemulsions. Because nanocarriers measure between 10–200 nm they can easily attach to skin surfaces to facilitate passive diffusion or promote active transport through the intercellular or transappendageal (hair follicles and sweat glands) routes. The drug permeation enhancement mechanism of lipid-based systems works effectively because they contain materials that morph into skin lipids thus allowing them to structure with stratum corneum layers.

Several nanocarriers possess the ability to temporarily change the tight junctions and lipid bilayers in the epidermis. Therapeutic molecules including hydrophilic substances and ones with large sizes can penetrate barriers that usually resist permeation because of this temporary weakening effect. Biological factors including peptides and growth factors and other bioactives contribute to wound healing and tissue regenerative processes thus benefit strongly from this delivery mechanism.

The penetration techniques of nanocarriers receive additional support from recent developments in surface engineering technologies. The addition of cell-penetrating peptides (CPPs) including TAT

and penetratin to nanoparticles produces carriers that actively transport through fibroblast and keratinocyte and immune cell membranes. Therapeutic agents accumulate more inside cells after their uptake by energy-independent mechanisms which include direct membrane translocation and endocytosis due to the presence of these peptides. The strategic application of targeting ligands like hyaluronic acid and folic acid and specific antibody receptors assists nanocarriers to locate and attach to tissue receptors during inflammation which helps decrease untoward side effects.

The development of stimuli-responsive systems incorporates additional sophisticated features to nanocarrier systems. Nanocarriers employ engineered systems that execute cargo release in response to both wound environment pH changes and increases in ROS levels and enzymatic activities in specific target regions. Through targeted delivery systems the drugs penetrate better while providing greater therapeutic accuracy to decrease their impact on systemic elements and side effects.

The application of nanocarrier systems defines new possibilities for drug delivery through skin and beneath skin layers during wound management. The adjustable structure together with their size and design properties enable nanocarriers to penetrate biological barriers so they can carry bioactives to exact locations inside the skin's layers targeting individual cell types. The skin architecture becomes accessible to nanocarriers because of their superior navigation capabilities thus making them essential tools in contemporary wound care practices. We will examine natural bioactives—albeit herbal extracts among others—as well as essential oils and plant derivatives in the upcoming chapter alongside nanocarriers since they generate effective yet biocompatible therapies that merge both nanoscience precision with native wisdom for enhanced clinical results within patient healthcare experiences (Prow et al., 2011).

Bioactive Compound-Loaded Nanomaterials – Case Studies & Applications

Wound therapy has entered a new age because bioactive natural compounds introduced to nanocarriers create a powerful synthesis of traditional pharmacology and nanoscience. The combination of both plant-derived ingredients with nanotechnology advances the solubility profiles and enhances stability features and targeted distribution of phytochemical compounds whose pharmacokinetic limitations existed before these hybrid formulations. The research examines bioactive-loaded nanomaterials which demonstrate promising results during preclinical and clinical studies to outline their educational potential and therapeutic application scope.

1. Curcumin-Loaded Nanoparticles

Scientist recognize curcumin which comes from the Curcuma longa rhizome roots as an important natural compound because it presents strong anti-inflammatory capabilities and powerful antioxidant effects and antimicrobial activity. The therapeutic usage of curcumin in wound healing remains limited due to its inadequate water solubility together with its swift elimination from the body system and its minimal absorbability through oral administration (Yallapu et al., 2012). The issue of suboptimal curcumin delivery has motivated researchers to focus on nanoformulation development through curcumin-loaded polymeric nanoparticles. Research indicates that reliable methods for PLGA nanoparticle production include both nanoprecipitation and emulsion-solvent evaporation. The formulation's retention at wound sites becomes more effective because of surface modifier agents that include polyethylene

glycol (PEG) and chitosan which enhance tissue penetration and mucoadhesion properties.

The application of curcumin in PLGA nanoparticles for murine excision wounds has been proven to enhance wound closure speed alongside better skin renewal. Curcumin-based formulations exceed unencapsulated curcumin by producing superior results regarding granulation tissue generation as well as collagen production and tissue angiogenesis (Banik et al., 2016). Medical tests from wound tissue analysis reveal diminished inflammatory cell entry together with elevated fibroblast activity which together signify proper wound healing. The nanoparticles maintain their medicines over an extended period because of their controlled release system which reduces the number of required applications.

The nanoformulation develops pharmaceutical treatment methods by combining both traditional herbal medicine and contemporary drug delivery systems through its manufacturing scalability and biomedical compatibility and therapeutic usefulness for wound care applications. The main hurdles for curcumin stability during biological conditions also encompass industry-scale expenses related to nanoparticle fabrication. Curcumin-loaded nanoparticles serve as a demonstration of how nanotechnology revives natural bioactive compounds for medical use in multipurpose wound healing management. Phytopharmacological research with nanomedicine applications demonstrates how pharmacies work to reform traditional medicines into advanced effective clinical solutions.

2. Aloe Vera Nanogels

The therapeutic plant aloe vera possesses various active constituents including polysaccharides and glycoproteins with vitamins and enzymes which enhance its ability to heal wounds. The application of raw aloe vera gel causes difficulties because it rapidly breaks down in the body while penetrating poorly and showing inconsistent levels of availability. The synthesis of aloe vera-loaded nanogels depends on polymeric matrices which combine their hydrophilic properties with mucoadhesive and film-forming abilities of carbopol and chitosan. Collaborating ionic gelation with crosslinking methods produces semi-solid, translucent nanogels that conduct moist wound healing environment effectively (Nema et al., 2011).

Various preclinical studies have shown extensive evidence supporting the pharmacological effects of aloe vera nanogels. The application of aloe-based nanogels to rat burn models resulted in shortened wound contraction durations along with improved skin renewal and quicker recovery of the skin surface. Nanogels stimulated fibroblast multiplication and angiogenic tissue growth based on histopathological examination results (Pal et al., 2019). The immunohistochemical findings indicated elevated VEGF vascular endothelial growth factor levels (Pal et al., 2019). The study demonstrates that aloe exerts diverse actions throughout the different phases of wound healing including inflammation as well as proliferation and remodeling.

Aloe vera nanogels demonstrate beneficial properties that strengthen their application in pharmacy and formulation science. The combination of non-irritating material characteristics with ease of use and excellent biocompatibility gives aloe vera nanogels the potential to be used as over-the-counter (OTC) wound dressings and offers both pharmaceutical-level antibacterial actions and anti-inflammatory characteristics. Sustained release combined with increased penetration depth of active agents is possible through nanogels because of their hydrophilic properties.

The formulation produces variations in pharmacological outcomes because natural aloe vera extract yields inconsistent results between

batches which creates obstacles in achieving standardized manufacturing methods. The pharmacy innovation process requires the implementation of formal quality control measures and the evaluation of standardized aloe vera fractional materials. The combination of traditional botanical wisdom with advanced pharmaceutical technology allows aloe vera nanogels to develop into a promising natural patient-acceptable approach for modern wound treatment.

3. Neem-Loaded Nanofibers

The traditional use medicines have recognized the medicinal potential of Neem (Azadirachta indica) in its ability to fight bacteria while controlling inflammation and enhancing immunity thus developing it as a treatment option for wound healing needs. Formulating neem extracts into products becomes difficult because they show poor solution stability and react poorly to environmental changes and produce inconsistent drug concentrations. The development of neem-loaded nanofibrous mats exists through researcher application of electrospinning technology to resolve existing issues with these materials. The combination of neem extracts with biocompatible polymers PCL or gelatin develops ultrafine fibrous scaffolds that have high surface-area-to-volume ratios along with an open structure. Effective wound healing requires features which improve both cell adhesion and bioactive substance distribution and moisture retention according to Ghosh et al. (2014).

Proof of neem-loaded nanofibers' pharmaceutical power comes from their effective treatment results in test models of infected wounds. Making wounds infected by Staphylococcus aureus or Pseudomonas aeruginosa more susceptible to antimicrobial activity was possible by using these nanofiber structures which effectively decreased bacterial presence. Experimental findings showed that these dressings enabled a 40–50% reduction in wound surface area during day 7 testing results which surpassed the performance of routine wound treatments according to Patel et al. (2018). The histological analyses results demonstrated that neem reduced wound inflammation simultaneously with an improvement in new tissue development which highlights its multiple therapeutic qualities.

The pharmaceutical use of nanofiber dressings containing neem meets the market requirement for eco-friendly and dissolvable wound management products. The incorporation of PCL or gelatin provides both extended degradation properties and supports the active properties of neem to boost the overall performance of the wound dressing. The scaffolds prove valuable in healing chronically infected wounds because standard topical antimicrobials demonstrate reduced effectiveness and cause systemic issues.

The formulation challenges occur even though the products have beneficial aspects. Patients may hesitate to use commercial dressing products because the bitter odor and green coloration of Neem can affect their willingness to wear these products. Formulation attractiveness can be improved by introducing odor-masking agents or purified bioactive fractions to resolve these current problems.

Nanofiber-based neem delivery systems create a valuable union of ethnopharmacology and nanotechnology since they prove how plants operate effectively with modern drug delivery platforms. Sustainable release properties along with antimicrobial strength combined with natural degradability establish neem as the perfect ingredient for pharmacy-based advanced wound care products.

4. Honey-Incorporated Liposomes

Medical personnel employ innovative formulations of liposomal honey which unite

nanopharmaceutical methods with traditional medical practices for managing diabetic and chronic wounds. The thin-film hydration method produces liposomes with medical-grade honey inside them which primarily consists of phosphatidylcholine and shows antimicrobial along with antioxidant and anti-inflammatory action. Through encapsulation honey bioactive elements remain stable alongside glucose oxidase and hydrogen peroxide and phenolic acids because liposomes establish better phospholipid interactions and barrier penetration across the epidermis (Erejuwa et al., 2014). Through processing raw honey into nano-carrier systems formulators manage solidity problems along with creating uniform delivery systems and enhance the clinical utility of the product.

The pharmacological assessments of liposomal honey gels show better performance in treating diabetic wounds because these wounds heal poorly due to delayed vascular development and extended inflammatory states. The study showed that liposomal honey increased wound healing through contraction while simultaneously encouraging tissue development and inhibiting matrix metalloproteinases (MMPs) activities that typically cause extracellular matrix breakdown in chronic wounds (Moghbel et al., 2018). Tests utilizing histopathological methods demonstrated that wounds treated with unencapsulated honey showed decreased neovascularization in combination with lower fibroblast cell population. The sterility and bioactivity and homogeneity of liposomal formulations endured throughout long-term storage periods as pharmaceutical manufacturers require these features to scale their production for effective shelf life duration.

A honey-liposome system delivers various significant benefits. The combinations of honey and liposomes improve both antimicrobial and antioxidant properties because they localize and distribute active compounds while permitting deep skin penetration without harming tissue structure. Honey-liposome systems can benefit wounds specifically when medical agents need to reach sub-epidermal depths for treatment such as pressure ulcers or diabetic foot ulcers. The formulation comes with certain performance restrictions that need to be noted. The mechanism that causes liposomes to deteriorate through oxidation makes their shelf-life vulnerable requiring antioxidants alongside cold storage conditions for extended stability. The formulation needs special consideration for allergic reactions triggered by honey or phospholipid components while being developed for clinical purposes.

Honey-liposome gels allow patients to benefit from the established natural remedy while receiving modernized sophisticated incornfoient topical treatment at the pharmacy level. Traditional substances can fulfill pharmaceutical requirements through reprogramming with advanced drug delivery methods that improve their pharmacokinetic profile. Modern wound care shows promise due to the existence of non-invasive systems which combine compatibility with personal medicine while implementing evidence-based natural medicine strategies for healing purposes.

5. Chitosan–Silver Nanocomposite

Wound treatment through chitosan–silver nanocomposites brings together the antimicrobial power of silver nanotechnology with the natural properties of chitosan which makes them an advanced method to fight infections in wounds. Wound-healing properties of cationic polysaccharide chitosan include effective hemostasis promotion together with biocompatibility and weak antimicrobial activity because it stems from chitin. This nanocomposite product combines the properties of chitosan as a stabilizing agent and delivery matrix for silver nanoparticles (AgNPs) to tackle essential wound

care issues of infection prevention and tissue healing. The chemical reduction of silver nitrate under chitosan conditions results in uniformly distributed AgNPs throughout the polymeric matrix during nanocomposite synthesis. Research shows the nanocomposite product enables flexible film and hydrogel and sprayable formulation production which makes it suitable for topical application (Rabea et al., 2009).

Researchers have documented extensive pharmacological findings regarding chitosan–silver nanocomposites through studies of in vitro models and in vivo models. These formulations maintain strong antibacterial effectiveness by demonstrating complete protection against various wound-related microbial pathogens that include both Gram-positive and Gram-negative bacteria. The nanocomposites applied to rodent surgical and thermal wounds resulted in minimized bacterial counts as well as faster skin healing along with strengthened collagen levels. The formulation shows promising results through histological tests because it generated minimal inflammation response together with enhanced tissue repair properties (Jung et al., 2010). The chitosan matrix controls silver ion release kinetics which both reduces toxicity effects and maintains strong antimicrobial properties throughout the duration.

This pharmaceutical nanocomposite maintains dual-action functionality which makes it appropriate for treating infected wounds in high-risk conditions such as burns, diabetic ulcers and post-operative sites. Chitosan controls tissue hydration levels and encourages cellular growth as well as creating effective film structures while silver performs prompt antimicrobial functions by causing oxidative tissue damage and cell wall destruction. When silver interaction occurs with the chitosan elements it creates a highly effective treatment for wounds that take long to heal or become infected.

To avoid possible toxic effects from silver exposure health professionals must maintain strict control over silver ion concentration specifically when long-term treatment is needed. Risk reduction in therapeutic safety can be achieved through optimized dosing along withmutations in the release control mechanism or multiple-layer film compositions.

The combination of chitosan–silver nanocomposites exists as a technological merger between pharmacological use of natural products and nanotechnology-based innovation. Pharmacy-based wound dressing development embraces their combination as a high-potential patient-friendly answer which implements antimicrobial defense mechanisms together with regenerative support needed for modern wound management.

6. Centella Asiatica–Based Hydrogel Dressing

The incorporation of Centella asiatica extract into hydrogel dressings achieves a strong union between contemporary topical delivery systems and herbal pharmacology to promote tissue regeneration and reduce post-wound scarring outcomes. The mixture of biologically active triterpenoids which includes asiaticoside madecassoside and asiatic acid from medicinal herb Centella asiatica resides within hydrogels made from polymeric carbopol or sodium alginate matrices. The hydrogel allows for a sustained wet healing environment through which nanoemulsion and vesicular systems of ethosomes or niosomes give better penetration depth and phytocompound release control (Hashim et al., 2019). Nanocarriers inserted into these systems help bypass skin penetration restrictions while sustaining triterpenoids availability at the affected area for better therapeutic results.

Laboratory tests show continual validation of wound-healing effectiveness by these hydrogel systems through pharmacological results. When applied to porcine skin wounds that mimic human

physiology Centella asiatica–loaded hydrogels showed enhanced results by improving tissue tensile strength and presenting substantial anti-scarring effects. The research showed that these biological effects corresponded to elevated fibroblast growth combined with improved collagen synthesis and heightened expression of transforming growth factor-beta (TGF-beta) through histological and molecular testing (Shukla et al., 2007). Researchers documented two beneficial effects which combined to accelerate the healing process by reducing inflammation signs together with better blood vessel growth.

The hydrogels provide optimal skin adhesion in formulation while giving easy application characteristics alongside cooling properties that deliver prompt comfort benefits to patients. The anti-scar properties of these products create advantages to become suitable for various medical settings including post-operative wound management and cosmetic procedures and burn treatment. The main constraint regarding phytochemical variability exists due to inconsistent plant source selection and different harvesting practices and extraction protocols. Standardized protocols must be developed to deliver repeatable treatment effects combined with pharmaceutical quality requirements because of these differences.

The application of Centella asiatica–based hydrogels appears to link modern pharmaceutical standards and traditional herbal practices to evidence-based cosmeceuticals according to pharmacy practitioners and researchers. The developed formulations bridge clinical opportunities for wound treatment with aesthetic requirements together with current preferences for plant-based cosmetic wound care products. The integration of nanotechnology with phytochemical standardization practice will make hydrogel dressings essential for both personalized wound care management and dermaceutical development in pharmacies.

Translational Insights for Pharmacy Practice

Nanotechnology expands the clinical worth and delivery effectiveness of plant-based therapies along with natural medicines in medical settings. Pharmacology students find the medicines recreate actual drug development scenarios in formulation science, pharmacognosy and translational research. Pharmacists now play an expanded role which goes beyond medication dispensing to include formulation development together with quality control investigation and innovation especially for wound care treatment where these advanced materials bring forth first-line treatment transformation and better patient adherence rates.

The future of individualized evidence-based wound therapy demonstrates itself in nano-bioactive formulations that include controlled delivery systems and hydrogels which provide favorable experiences for patients. Educational institutions should include these therapeutic developments in both pharmacy undergraduate and continuing education programs to train healthcare professionals about next-generation treatments.

Regulatory, Safety & Translational Barriers

Despite the therapeutic promise of nanomaterials in wound healing, their real-world translation is fraught with significant safety, regulatory, and developmental challenges. A critical concern is the safety assessment of these nanosystems, which involves understanding their biodegradability, cytotoxicity, and potential to provoke immune responses. Nanomaterials may penetrate biological barriers and accumulate in tissues, raising long-term safety concerns that remain insufficiently explored in both preclinical and clinical contexts (Fadeel et al., 2018). For instance,

while silver nanoparticles exhibit broad-spectrum antimicrobial activity, their uncontrolled release can lead to oxidative stress, cellular apoptosis, and delayed wound healing (Manke et al., 2013). Similarly, lipid-based nanocarriers and polymeric systems, although generally recognized as safe, require detailed toxicity profiling because their physicochemical properties can significantly alter biological interactions (Mukherjee et al., 2019).

Regulatory frameworks for nanopharmaceuticals remain ambiguous. Agencies such as the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have acknowledged the unique complexities posed by nanoscale products, yet specific guidance remains limited. The FDA, for instance, evaluates nanomedicines under existing drug and device regulations, without a dedicated nanotech pathway, thereby leading to uncertainties for developers regarding approval criteria and testing standards (Chaudhry et al., 2020). This lack of clarity often stalls the progression from laboratory research to clinical application. Moreover, manufacturing consistency, scalability, and quality control of nanomaterials represent significant hurdles. Batch-to-batch reproducibility, stability, and the ability to scale up production while preserving bioactivity are essential for successful commercialization—yet notoriously difficult to achieve in nanoparticle fabrication (Ventola, 2017).

Although a few commercial wound care products utilizing nanotechnology have reached the market—such as Acticoat™, which incorporates nanocrystalline silver—most products suffer from high costs, limited shelf life, and insufficient clinical validation (Monteiro et al., 2012). These limitations underscore the pressing need for large-scale, pharmacy-led clinical trials to establish efficacy and safety under real-world conditions. Pharmacists and clinical scientists play a pivotal role here, as their understanding of formulation science and therapeutic evaluation positions them at the forefront of translational research. Bridging the gap between benchtop innovation and bedside application demands not only regulatory harmonization but also interdisciplinary collaboration, particularly between pharmaceutical scientists, clinicians, and toxicologists (Dobrovolskaia & McNeil, 2015). A robust pipeline of evidence-based, reproducible, and safe nanotherapeutics can only be realized through such coordinated efforts.

CONCLUSION AND FUTURE SCOPE

The convergence of natural bioactive compounds and nanotechnology in wound healing represents a paradigm shift in pharmaceutical science, offering a multifaceted, precise, and biologically attuned approach to tissue regeneration. This review has highlighted how plant-derived agents like curcumin and Centella asiatica, marine compounds such as chitosan and fucoidan, and animal-based actives like honey and collagen, each possess intrinsic pharmacological effects—ranging from antimicrobial and antioxidant to angiogenic and anti-inflammatory—that align with the complex physiological needs of wound repair (Pereira & Bartolo, 2016; Thangapazham et al., 2016). Yet, their limitations in bioavailability, solubility, and stability pose significant barriers to clinical application when used in unmodified forms. The integration of these bioactives into nanocarriers—such as polymeric nanoparticles, liposomes, and nanofibrous hydrogels—not only enhances their delivery and retention at wound sites but also ensures controlled release and improved therapeutic efficacy (Mourdikoudis et al., 2018). This synergy redefines wound management by aligning pharmacodynamics with material science innovation.

For pharmacy, this intersectional field opens vast opportunities, both in terms of research and translational medicine. Personalized wound care

solutions, guided by nanocarrier customization and patient-specific responses, could mark the next frontier in therapeutics. However, there remain critical roadblocks. The current lack of standardization in nanoparticle synthesis protocols and inconsistency in animal models used for efficacy testing weaken the reproducibility of findings and delay clinical translation (Fadeel et al., 2018). Furthermore, clearer regulatory frameworks—specific to nanoformulations and bioactive-loaded devices—are urgently needed to guide pharmaceutical innovation safely and effectively into market pipelines (Chaudhry et al., 2020). Going forward, pharmacy research must embrace interdisciplinary collaboration, integrating insights from nanotechnology, pharmacology, biomaterials, and clinical science. There is a pressing need for large-scale, controlled clinical studies to evaluate long-term outcomes and safety profiles. As pharmacists and formulation scientists, our role extends beyond benchwork—we must actively contribute to setting new standards for dosage forms, advocating regulatory advancements, and designing patient-centric therapeutics. In doing so, pharmacy will not merely participate in the evolution of wound care; it will lead it.

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