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Review

A Systematic Review on Nano Formulations of Natural Products used in Inflammation and Wound Healing

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Abstract

Inflammation and wound healing are complex biological processes essential for tissue repair and defense against injury and infection. Natural products derived from plants, animals, and microorganisms have long been utilized in traditional medicine systems due to their anti-inflammatory, antioxidant, and regenerative properties. However, the therapeutic application of many natural compounds is limited by poor solubility, low bioavailability, instability, and rapid degradation at the site of action. Nanotechnology has emerged as a powerful approach to overcome these limitations by enabling the development of nanoformulations such as nanoparticles, liposomes, nanoemulsions, hydrogels, and polymeric nanocarriers. These systems enhance drug penetration, provide controlled and sustained release, protect bioactive constituents, and improve therapeutic efficacy. This systematic review highlights the historical development, current status, mechanisms, principles, classification, applications, and advantages of nanoformulated natural products in inflammation and wound healing. The integration of nanotechnology with natural therapeutics offers innovative solutions for chronic wounds, burns, diabetic ulcers, and inflammatory disorders, positioning nano-enabled natural products as a promising strategy in modern regenerative medicine.

Keywords: Nanoformulations; Natural products; Inflammation; Wound healing; Nanotechnology; Drug delivery.

INTRODUCTION

Inflammation is a fundamental protective response that helps eliminate harmful stimuli and initiates tissue repair, while wound healing is a coordinated biological process involving inflammation, proliferation, and tissue remodeling [1]. Prolonged or uncontrolled inflammation can disrupt wound healing and lead to chronic inflammatory conditions [2]. For centuries, natural products have been widely used in traditional medical systems such as Ayurveda, Traditional Chinese Medicine, and Unani medicine to manage inflammation and promote wound repair [3]. Medicinal plants including *Curcuma longa*, *Aloe vera*, *Centella asiatica*, and *Azadirachta indica* are well

known for their wound-healing and anti-inflammatory properties[4].

Despite their therapeutic potential, many natural compounds exhibit poor water solubility, limited stability, and low bioavailability, which restrict their clinical application [5]. Recent advances in nanotechnology have provided novel drug delivery platforms that enhance the pharmacokinetic and pharmacodynamic profiles of natural products [6]. Nanoformulations improve tissue penetration, protect active constituents from degradation, and allow sustained drug release at the target site [7]. Consequently, nano-enabled natural therapeutics have gained significant attention for treating inflammatory conditions and accelerating wound healing [8].

HISTORY OF NATURAL PRODUCTS AND NANOFORMULATIONS IN INFLAMMATION AND WOUND HEALING

The therapeutic use of natural products for wound healing and inflammation management can be traced back to ancient civilizations such as Egyptian, Indian, Chinese, and Greek cultures, where plant extracts, oils, gums, and resins were routinely applied to wounds, burns, and inflammatory conditions . Ancient Egyptian papyri describe the use of honey and plant-based poultices for wound cleansing and infection control, while Ayurvedic texts document the application of turmeric, neem, and aloe vera for tissue regeneration and inflammation reduction. Traditional medical systems emphasized holistic healing, relying on natural substances that could simultaneously control infection, reduce inflammation, and promote tissue repair [9].

These traditional systems of medicine highlighted the therapeutic potential of herbal formulations rich in bioactive compounds such as flavonoids, alkaloids, terpenoids, tannins, and phenolic acids, which exhibit antioxidant, antimicrobial, and anti-inflammatory activities. Although the mechanisms were not scientifically understood at the time, empirical observations demonstrated consistent healing outcomes. Over centuries, these remedies were refined and standardized within traditional frameworks, forming the scientific foundation of modern herbal and phytopharmaceutical research [10].

During the 19th and early 20th centuries, advancements in pharmaceutical sciences led to a paradigm shift from whole-plant preparations to the isolation and characterization of individual phytochemicals responsible for therapeutic effects [11]. The identification of compounds such as curcumin, quercetin, resveratrol, and catechins allowed researchers to study their pharmacological actions in a controlled manner. Despite their promising biological activity, many isolated natural compounds exhibited limited clinical success due to poor aqueous solubility, rapid metabolic degradation, chemical instability, and low bioavailability when administered in conventional dosage forms [12].

The emergence of nanotechnology in the late 20th century introduced innovative approaches to overcome these pharmacokinetic limitations by enabling precise control over particle size, surface charge, and drug release characteristics. Nanotechnology-based drug delivery systems provided new opportunities to protect labile natural compounds from degradation, enhance tissue penetration, and achieve sustained therapeutic concentrations at the target site. This technological advancement bridged the gap between traditional natural medicine and modern pharmaceutical delivery strategies [13].

In the early 2000s, the application of nanotechnology to natural products gained significant momentum, with studies demonstrating improved stability, bioavailability, and therapeutic efficacy of herbal compounds when formulated into nano-sized carriers[14]. Polymeric nanoparticles, lipid-based systems, and nanoemulsions were shown to enhance the anti-inflammatory and wound-healing potential of natural bioactives. This development marked a critical transition from conventional herbal formulations to nanoformulated natural therapeutics, establishing a new era in inflammation management and wound healing research [15].

CURRENT STATUS OF NANOFORMULATIONS OF NATURAL PRODUCTS

At present, nanoformulations of natural products

constitute one of the most rapidly advancing research areas in the fields of inflammation management and wound healing therapy. Increasing scientific evidence supports the potential of nanotechnology-based delivery systems to enhance the therapeutic performance of natural bioactive compounds, leading to growing interest from both academic and clinical research communities [16]. A wide range of nanocarriers, including polymeric nanoparticles, solid lipid nanoparticles, liposomes, nanoemulsions, and nanofibrous scaffolds, have been extensively investigated for their ability to improve drug stability, bioavailability, and targeted delivery [17].

Among these systems, curcumin-loaded nanoparticles have received considerable attention due to their enhanced anti-inflammatory efficacy. Nanoencapsulation of curcumin has been shown to significantly suppress pro-inflammatory cytokines and oxidative stress markers when compared to conventional curcumin formulations, resulting in improved therapeutic outcomes [18]. Similarly, nanoformulated aloe vera, honey, and essential oil-based delivery systems have demonstrated superior wound-healing performance by promoting faster wound contraction, increased collagen deposition, and enhanced epithelialization [19].

Biodegradable and biocompatible polymers such as chitosan, alginate, gelatin, and poly(lactic-co-glycolic acid) (PLGA) are widely employed in the development of these nanoformulations due to their favorable biological properties and intrinsic wound-healing potential [20]. Recent advances in nanofabrication techniques have further enabled the design of multifunctional wound dressings that combine antimicrobial, anti-inflammatory, and regenerative properties within a single therapeutic platform [21]. Collectively, these developments underscore the growing potential of nano-enabled natural products as effective and safer alternatives to conventional inflammation and wound-healing therapies [22].

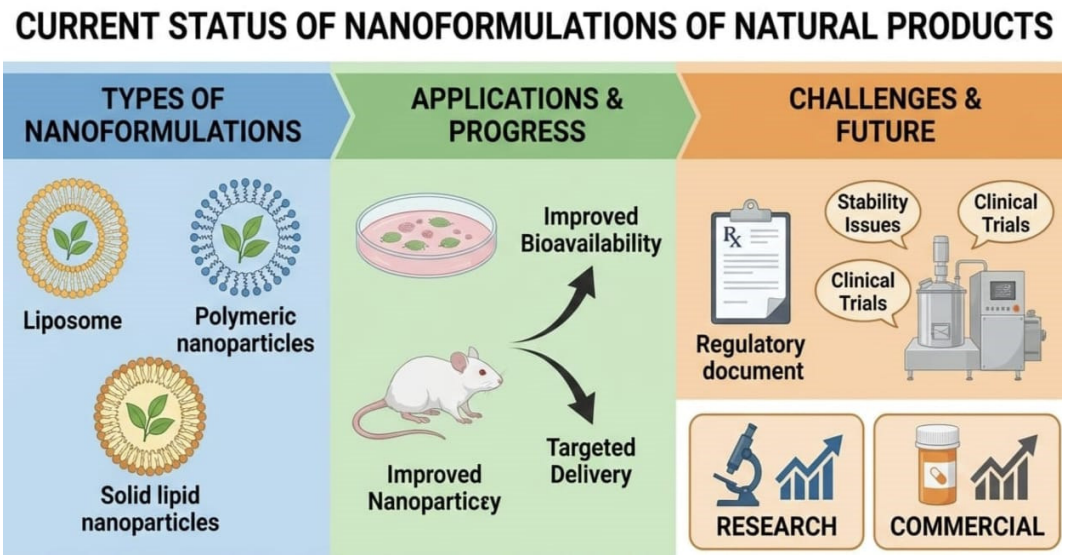


Figure 1: **Current Status Of Nanoformulations Of Natural Products**

MECHANISM OF ACTION OF NANOFORMULATED NATURAL PRODUCTS

Nanoformulated natural products exert their therapeutic effects through multiple interconnected biological mechanisms that collectively enhance anti-inflammatory activity and accelerate wound healing. At the cellular and tissue levels, nano-sized carriers significantly improve the penetration of bioactive compounds across biological barriers such as the stratum corneum, extracellular matrix, and inflamed tissues, allowing greater drug accumulation at the site of injury or inflammation . The small particle size and large surface area of nanoformulations facilitate close interaction with cellular membranes, improving intracellular uptake and retention of phytochemicals. As a result, local bioavailability is increased while systemic exposure and associated adverse effects are minimized [23].

A key mechanism underlying the anti-inflammatory action of nanoformulated natural products involves the modulation of intracellular signaling pathways. Natural compounds such as curcumin, resveratrol, quercetin, and epigallocatechin gallate are known to suppress inflammatory responses by regulating pathways including nuclear factor-κB (NF-κB), mitogen-activated protein kinases (MAPK), and cyclooxygenase-2 (COX-2). Nanoencapsulation protects these compounds from chemical degradation and rapid metabolism, enabling sustained release and prolonged biological activity. This results in effective downregulation of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-1β, and interleukin-6, thereby reducing inflammation intensity and duration [24].

In addition to cytokine modulation, nanoformulated natural products play a critical role in reducing oxidative stress at the wound site. Nanoformulations enhance the antioxidant potential of natural compounds by maintaining stable therapeutic concentrations, enabling efficient scavenging of free radicals. This reduction in oxidative stress protects surrounding tissues, prevents chronic inflammation, and creates a favorable microenvironment for tissue repair and regeneration [25].

During the wound-healing process, nanoformulated natural products actively stimulate cellular events essential for tissue regeneration. These systems promote fibroblast proliferation, collagen synthesis, angiogenesis, and re-epithelialization, all of which are crucial for effective wound closure. Biopolymer-based nanoparticles, particularly those formulated using chitosan and alginate, interact with growth factors and extracellular matrix proteins, enhancing cell adhesion, migration, and differentiation. Such interactions support organized tissue regeneration and improve the structural and functional quality of healed tissue [26]. Collectively, these mechanisms contribute to faster wound closure, reduced scar formation, and improved healing outcomes.

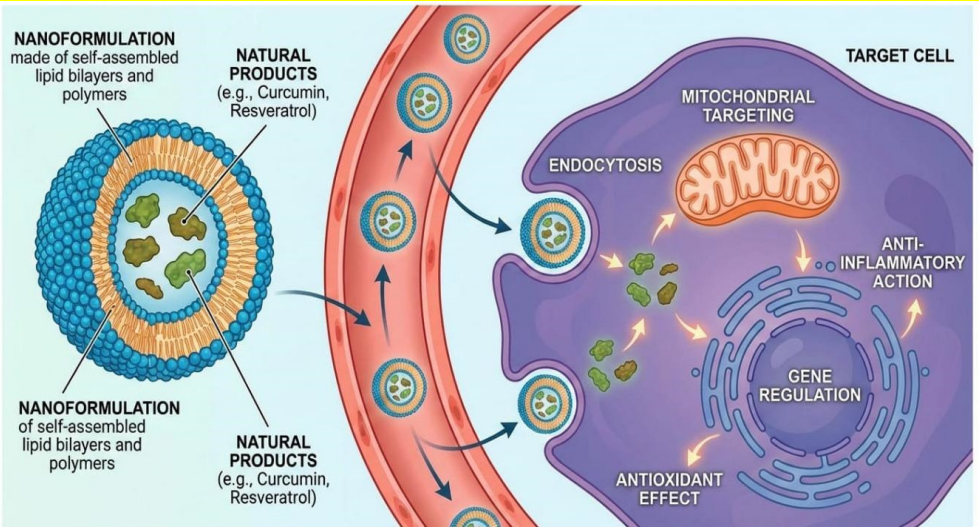


Figure 2: Mechanism Of Action Of Nanoformulated Natural Products

PRINCIPLES OF NANO-FORMULATION FOR NATURAL PRODUCTS

The design of nanoformulations for natural products is based on fundamental principles aimed at improving therapeutic efficiency and safety. One of the primary principles is particle size reduction to the nanometer range, which increases surface area and enhances dissolution rate and bioavailability of poorly soluble phytochemicals [27]. Surface modification of nanoparticles with hydrophilic polymers or ligands further improves stability and targeting efficiency.

Controlled and sustained drug release is another critical principle in nanoformulation development. Encapsulation of natural compounds within polymeric or lipid-based carriers allows gradual release at the wound or inflamed site, maintaining therapeutic concentrations over extended periods [28]. This reduces dosing frequency and improves patient compliance.

Biocompatibility and biodegradability are essential considerations in nanoformulation design. Materials such as chitosan, gelatin, alginate, and PLGA are preferred due to their minimal toxicity and ability to degrade into non-toxic byproducts [29]. The principle of targeted delivery ensures that the therapeutic effect is localized, reducing systemic side effects commonly associated with conventional anti-inflammatory drugs [30].

CLASSIFICATION AND TYPES OF NANOFORMULATIONS USED IN INFLAMMATION AND WOUND HEALING

Table :1 Classification And Types Of Nanoformulations Used In Inflammation And Wound Healing

Type of Nanoformulation	Composition / Structure	Key Characteristics	Role in Inflammation and Wound Healing	Citation
Polymeric nanoparticles	Biodegradable polymers such as chitosan, PLGA, alginate, gelatin	High stability, controlled and sustained drug release, capable of encapsulating hydrophilic and hydrophobic compounds	Provide prolonged anti-inflammatory action, enhance bioavailability of natural compounds, and support tissue regeneration	[31]
Liposomes	Phospholipid bilayer vesicles	High biocompatibility, structural similarity to biological membranes, improved skin penetration	Suitable for topical wound healing, enhance delivery of phytochemicals to inflamed tissues	[32]
Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs)	Solid or mixed solid–liquid lipid matrices	Enhanced stability, controlled release, protection of bioactive compounds	Improve penetration into skin layers and sustain anti-inflammatory and wound-healing activity	[32]
Nanoemulsions	Oil–water or water–oil systems stabilized by surfactants	Thermodynamically stable, improved solubility of lipophilic compounds	Enhance absorption of essential oils and phytochemicals with anti-inflammatory and antimicrobial properties	[33]
Hydrogel-based nanoformulations	Cross-linked polymer networks with high water content	Moist environment, oxygen permeability, biocompatibility	Maintain optimal wound environment, promote epithelialization and tissue regeneration	[34]
Nanofibrous scaffolds	Electrospun polymeric nanofibers	High surface area, porous structure, extracellular matrix mimicry	Support cell adhesion, migration, and proliferation during wound healing	[34]
Metallic nanoparticles	Silver, gold, or zinc nanoparticles synthesized using natural products	Antimicrobial, anti-inflammatory, and antioxidant properties	Prevent wound infection and reduce inflammation, accelerating wound healing	[35]

APPLICATIONS IN INFLAMMATION AND WOUND HEALING

Nanoformulated natural products have demonstrated extensive applications in the management of both acute and chronic inflammatory conditions due to their enhanced bioavailability, targeted delivery, and reduced systemic toxicity. In inflammatory diseases such as rheumatoid arthritis, osteoarthritis, dermatitis, psoriasis, and inflammatory bowel disorders, nano-based delivery systems enable site-specific drug accumulation and sustained release of bioactive

compounds, thereby improving therapeutic efficacy and minimizing adverse effects associated with long-term treatment . Topical nanoformulations containing natural anti-inflammatory agents have shown superior performance in reducing clinical symptoms such as edema, erythema, pain, and swelling, as well as in downregulating inflammatory biomarkers and oxidative stress at affected sites [36].

In the context of wound healing, nano-enabled natural products have been widely applied for the treatment of burns, diabetic ulcers, pressure sores, traumatic injuries, and post-surgical wounds, where conventional therapies often fail to produce satisfactory outcomes [37]. Curcumin-loaded nanoparticles have been reported to accelerate wound contraction, enhance collagen deposition, and regulate inflammatory responses during the early stages of healing. Similarly, nanoformulations incorporating aloe vera, honey, and essential oils promote epithelialization, angiogenesis, and granulation tissue formation, leading to faster and more organized wound repair [38].

Advanced wound care systems incorporating nanofibrous scaffolds loaded with herbal extracts represent a significant innovation in regenerative medicine. These scaffolds mimic the extracellular matrix, provide mechanical support, and facilitate cell adhesion and migration while simultaneously offering antimicrobial protection against wound infections [39]. The integration of nanoformulated natural products into modern wound dressings and therapeutic platforms has significantly improved healing outcomes, particularly in chronic, infected, and non-healing wounds, reducing healing time and improving tissue quality [40].

ADVANTAGES OF NANOFORMULATED NATURAL PRODUCTS

Nanoformulations offer several advantages over conventional formulations of natural products. Enhanced bioavailability and stability are among the most significant benefits, allowing effective therapeutic action at lower doses [41]. Controlled release properties ensure prolonged drug action and reduce the need for frequent application.

Targeted delivery minimizes systemic exposure and associated side effects, making nanoformulated natural products safer for long-term use [42]. Improved penetration through skin and damaged tissues enhances local drug concentration at the wound site. Additionally, the combination of antimicrobial, anti-inflammatory, and antioxidant properties in a single nanoformulation provides multifunctional therapeutic benefits [43].

From a patient perspective, nano-based topical formulations improve ease of application and treatment compliance. These advantages make nanoformulated natural products a promising alternative to synthetic drugs and conventional herbal formulations [44].

COMPARISON WITH EXISTING CONVENTIONAL METHODS

Conventional approaches for managing inflammation and promoting wound healing predominantly involve the use of synthetic pharmacological agents such as corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and antibiotics. These therapies are effective in controlling inflammation and preventing infection; however, prolonged or repeated use is frequently associated with adverse effects including delayed wound healing, skin thinning and atrophy, immunosuppression, gastrointestinal complications, and the development of antimicrobial resistance [45]. Such limitations highlight the need for safer and more sustainable therapeutic alternatives.

Traditional herbal formulations have long been employed as safer alternatives due to their natural origin and lower toxicity. Nevertheless, these formulations often exhibit poor aqueous solubility, limited stability, rapid degradation, and inconsistent therapeutic outcomes, primarily due to low bioavailability and lack of targeted delivery [46]. As a result, their clinical efficacy remains variable and highly dependent on formulation quality and patient-specific factors.

Nanoformulated natural products effectively overcome many of these challenges by enhancing drug stability, improving tissue penetration, and enabling controlled and sustained release of bioactive compounds at the target site [47]. Compared to conventional topical and systemic formulations, nano-based delivery systems provide prolonged therapeutic action with reduced dosing frequency, leading to improved patient compliance. Additionally, the use of biodegradable and biocompatible materials such as chitosan, alginate, and lipid-based carriers minimizes toxicity risks and enhances safety for long-term use [48].

Overall, nano-enabled natural therapeutics represent a significant advancement over existing conventional methods by integrating the inherent safety of natural products with the precision and efficiency of modern drug delivery systems. This synergistic approach offers superior therapeutic outcomes, reduced side

effects, and greater potential for clinical translation in inflammation management and wound healing [49].

PATHOPHYSIOLOGY OF INFLAMMATION AND WOUND HEALING

Inflammation and wound healing are complex, overlapping biological processes that restore tissue integrity following injury. Wound healing involves a highly regulated sequence of cellular and molecular events, including hemostasis, inflammation, proliferation, and remodeling. Inflammation plays a dual role by eliminating pathogens and damaged tissue while initiating repair mechanisms; however, dysregulated or prolonged inflammation impairs healing and contributes to chronic wounds [50]. Understanding the pathophysiology of these phases is critical for designing effective therapeutic strategies, including nanoformulated natural products.

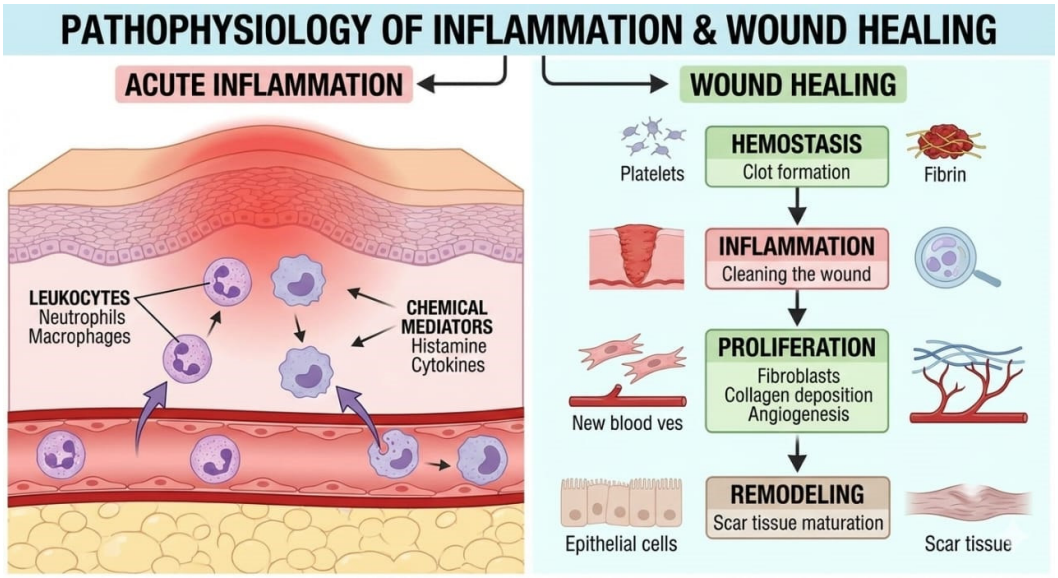


Figure:3 Pathophysiology Of Inflammation And Wound Healing

PHASES OF WOUND HEALING

Haemostasis

Haemostasis is the immediate response to tissue injury and begins within minutes after wound formation. It is characterized by vasoconstriction and platelet aggregation, which prevent excessive blood loss and form a provisional fibrin clot at the wound site. Platelets trapped within the clot release several growth factors, including platelet-derived growth factor (PDGF) and transforming growth factor-β (TGF-β), which act as key signaling molecules to recruit inflammatory cells and stimulate subsequent healing phases [51]. The fibrin matrix also serves as a temporary scaffold for cell migration during later stages of wound repair.

Inflammation

The inflammatory phase begins shortly after haemostasis and typically lasts for several days. During this phase, neutrophils are the first immune cells to migrate to the wound site, where they phagocytose debris and microorganisms. Macrophages subsequently dominate the wound environment and play a central role in coordinating healing by releasing cytokines, chemokines, and growth factors [52]. Pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), along with reactive oxygen species (ROS), are produced to control infection and stimulate cellular responses [53].

While inflammation is essential for wound defense, it must be tightly regulated. Excessive or prolonged inflammation leads to sustained oxidative stress, tissue damage, and delayed progression to the proliferative phase. In chronic wounds, persistent recruitment of inflammatory cells, overproduction of proteolytic enzymes, and continuous ROS generation prevent normal healing and result in non-healing wound states [54].

Proliferation

The proliferative phase is characterized by active tissue formation and typically overlaps with the late inflammatory phase. Fibroblasts proliferate and synthesize extracellular matrix components, particularly collagen, which provides structural support to the newly formed tissue. Angiogenesis occurs through the formation of new blood vessels, ensuring adequate oxygen and nutrient supply to the healing tissue. Growth factors such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) play a crucial role in regulating angiogenesis and fibroblast activity [55].

Simultaneously, keratinocytes migrate from the wound edges to re-epithelialize the wound surface, restoring the epidermal barrier. Granulation tissue formation, composed of new capillaries, fibroblasts, and extracellular matrix, is a hallmark of this phase and is essential for successful wound closure [56].

Remodelling

The remodeling or maturation phase represents the final stage of wound healing and can persist for several months after injury. During this phase, collagen type III deposited during proliferation is gradually replaced by stronger collagen type I. The extracellular matrix undergoes continuous reorganization, resulting in increased tensile strength and improved functionality of the healed tissue [57].

In normal healing, inflammatory activity subsides as remodeling progresses. However, in chronic wounds, failure to transition beyond the inflammatory phase leads to excessive matrix degradation, impaired collagen maturation, and weak tissue repair. Persistent inflammation, elevated protease activity, and ongoing oxidative stress are major pathological features contributing to delayed or incomplete healing [58].

CONCLUSION

Nanoformulations of natural products have emerged as a transformative approach in the management of inflammation and wound healing. Traditional natural therapeutics, although rich in bioactive compounds, are often limited by poor solubility, low bioavailability, instability, and inconsistent therapeutic outcomes. The integration of nanotechnology has successfully addressed these limitations by enhancing stability, improving penetration, enabling controlled release, and increasing therapeutic efficacy. Nano-enabled delivery systems such as polymeric nanoparticles, lipid-based carriers, nanoemulsions, hydrogels, and nanofibrous scaffolds provide multifunctional benefits including anti-inflammatory, antioxidant, antimicrobial, and regenerative effects. These systems not only accelerate wound closure and tissue regeneration but also minimize systemic side effects and dosing frequency. Compared to conventional synthetic drugs and traditional herbal formulations, nanoformulated natural products offer superior safety, efficacy, and patient compliance. Despite promising preclinical and clinical outcomes, further large-scale clinical trials, standardized formulation protocols, and regulatory frameworks are required to facilitate widespread clinical adoption. Overall, nanoformulations of natural products represent a promising and sustainable therapeutic strategy for advancing inflammation control and wound healing in modern medicine.

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