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Review

Phytochemical-Loaded Nanotherapeutics in Cosmetic Surgery Wound Healing: A Narrative Review

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Abstract

Wound healing in cosmetological and aesthetic surgery extends beyond tissue closure to achieving rapid regeneration, minimal scarring, and restoration of functional skin architecture. However, conventional wound care strategies inadequately regulate the complex wound microenvironment required for optimal cosmetic outcomes, leading to prolonged healing times and suboptimal aesthetic results, which can negatively impact patient satisfaction and increase the risk of complications. Phytochemicals exhibit multifunctional bioactivities, such as antioxidant, anti-inflammatory, antimicrobial, and pro-regenerative effects, but their clinical translation faces obstacles due to poor solubility, stability, and bioavailability. Nanotechnology-based delivery systems have emerged as a critical enabling strategy to overcome these limitations. This narrative review provides an updated, mechanistically integrated synthesis of phytochemical-loaded nanotherapeutics, including polymeric nanoparticles, nanohydrogels, nanofibers, and lipid- and vesicle-based systems, with a specific focus on their roles in modulating key wound-healing pathways, such as inflammation resolution, angiogenesis, collagen remodelling, and re-epithelialization. Evidence from preclinical studies consistently demonstrates that nano-enabled phytochemicals enhance therapeutic efficacy, improve skin penetration, and contribute to superior cosmetic outcomes, particularly by reducing fibrosis and scar formation. However, critical gaps remain, including limited high-quality clinical evidence, a lack of standardized formulation design, variability in reported outcomes, and unresolved concerns regarding long-term safety and regulatory translation. Taken together, the key insight of this review is that phytochemical-loaded nanotherapeutics represent a promising but still transitional strategy, biologically compelling at the preclinical level yet clinically under-validated. Bridging this gap requires rigorously designed clinical trials, quantitative outcome reporting, and balanced regulatory frameworks. Advancing these areas will be essential to translate nano-enabled phytochemicals from experimental systems into reliable, evidence-based solutions for cosmetological wound management.

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1. Introduction

1.1. Skin and Its Anatomy: A Brief

Human skin, the body's largest organ, covers approximately 1.5 to 2 m^2 and accounts for 12 to 15% of body weight. It functions as a multifunctional interface between the internal and external environments, serving protective, sensory, thermoregulatory, and metabolic roles [1,2]. Beyond acting as a passive barrier, the skin is a metabolically active organ integrating immune, neuroendocrine, and endocrine functions [1,3]. Key cellular components, including keratinocytes, fibroblasts, melanocytes, and resident immune cells (e.g., Langerhans cells, dermal dendritic cells, and resident memory T cells), engage in dynamic crosstalk through the secretion of cytokines, chemokines, neuropeptides, and antimicrobial peptides such as defensins and cathelicidin, thereby regulating local inflammation and infection [4,5].

The skin also possesses a functional neuroendocrine axis, with epidermal and dermal cells capable of synthesizing and responding to corticotropin-releasing hormone, adrenocorticotropic hormone, glucocorticoids, and various neuropeptides, contributing to barrier homeostasis and stress-related immune modulation [6]. In addition, the epidermis is the primary site of vitamin D synthesis, where active vitamin D regulates keratinocyte differentiation, tight junction integrity, antimicrobial peptide expression, and immune responses via vitamin D receptors [7]. These characteristics collectively designate the skin as a neuro-immuno-endocrine interface that converts environmental stimuli (e.g., UV radiation, microbes, stress) into molecular signals that affect both local and systemic physiology [4,8]. Structurally, the skin consists of three interdependent layers (epidermis, dermis, and hypodermis) that maintain overall homeostasis [9,10].

The epidermis is a keratinized stratified squamous epithelium, primarily composed of keratinocytes undergoing continuous differentiation over approximately 28 to 40 days to form a "brick-and-mortar" barrier essential for mechanical protection and water retention [2,9–11]. Additional specialized cells include melanocytes (pigmentation and UV protection), Langerhans cells (immune surveillance), and Merkel cells (mechanoreception), collectively reinforcing its neuro-immuno-sensory role [11–13]. The epidermis is anchored to the dermis via a basement membrane zone composed of structural proteins such as type IV collagen and laminins, which are critical for tissue integrity and wound healing [10].

The dermis provides structural strength and elasticity through a collagen- and elastin-rich extracellular matrix synthesized by fibroblasts, with hydration maintained by glycosaminoglycans such as hyaluronic acid [1,9,10]. It also contains vascular, neural, and lymphatic networks, along with appendages including hair follicles, sebaceous glands, and sweat glands that support thermoregulation and sensory functions [1,2]. The hypodermis, composed mainly of adipose tissue, serves roles in cushioning, insulation, and energy storage, while also acting as an endocrine and immunomodulatory organ through adipokine signaling, influencing inflammation, angiogenesis, and wound healing [11,14–17].

Together, these layers and associated appendages form an integrated system that maintains skin homeostasis, mediates environmental interactions, and supports regenerative processes [1,2,10]. Figure 1 illustrates the structural organization of the skin and the general mechanism of nano-delivery of active compounds.

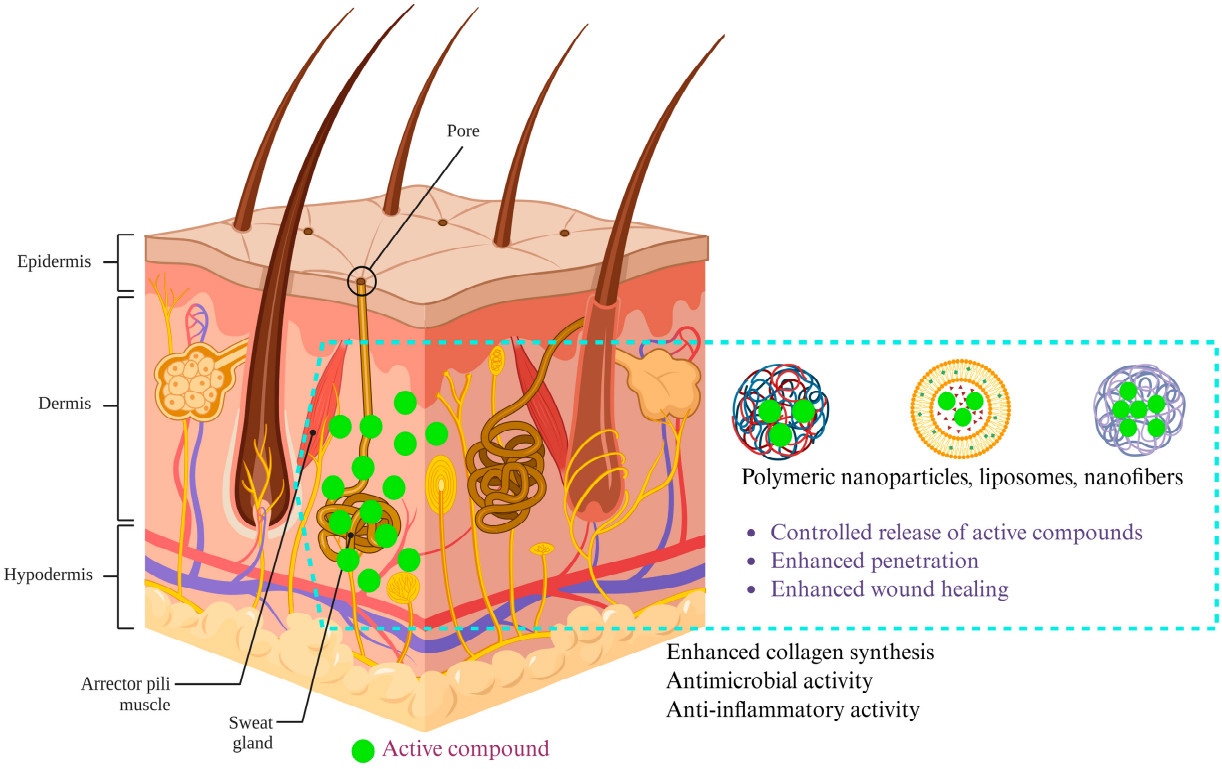


Figure 1. Anatomy of skin illustrating the structure of epidermis, dermis, and hypodermis and the general action of nano-delivery of active compounds (Created in BioRender.com).

1.2. Types of Cosmetic Surgery

Cosmetic surgery is a specialized discipline of plastic surgery that encompasses both surgical and non-surgical procedures aimed at improving or enhancing the aesthetic appearance of the face and body by modifying normal anatomical structures, generally for cosmetic rather than medical reasons [18]. The most common types of cosmetic surgery include the following:

- Breast Augmentation—Surgical treatment that entails the insertion of breast implants to enhance the volume and contour of the breasts.
- Liposuction—Surgical technique that eliminates surplus adipose tissue from targeted regions of the body, such as the belly, hips, thighs, or buttocks.
- Rhinoplasty—commonly referred to as a nose job—is a surgical operation that alters the shape of the nose to enhance its aesthetic appeal and functionality.
- Facelift—Surgical operation that elevates and firms the skin of the face and neck to diminish the visibility of wrinkles and lax skin.
- Stomach Tuck—Abdominoplasty is a surgical operation that excises surplus skin and adipose tissue from the abdomen to achieve a more streamlined and contoured appearance.
- Blepharoplasty—An eyelid surgery procedure that excises surplus skin and adipose tissue from the upper and lower eyelids to achieve a more youthful and refreshed appearance.
- Breast Reduction—This treatment involves the excision of surplus breast tissue and skin to diminish breast size and enhance shape.
- Botox—Non-invasive therapy that entails the injection of a neurotoxin to temporarily immobilize the muscles responsible for wrinkles and creases on the face.

1.3. Challenges in Cosmetological Wound Healing

Quality requirements beyond wound closure: In aesthetic and cosmetic contexts (such as resurfacing, facelifts, donor sites, and body contouring), simply achieving epithelial closure is insufficient. The ideal outcome demands that the regenerated skin have minimal visible scarring, normal texture and pigmentation, appropriate elasticity, satisfactory functional integration, and rapid return to baseline appearance. Yet even when closure is achieved, the quality of regenerated tissue frequently falls short: collagen may be disorganized, elastin networks may be incomplete, microvascular density may be suboptimal, and pigmentation irregularities or surface irregularities may persist [19].

Variability and Risk of Aberrant Healing: The cutaneous wound healing response exhibits significant heterogeneity beyond the normal healing process. Clinical outcomes are modulated by a complex interaction between intrinsic variables (e.g., cellular senescence, immunocompetence, metabolic comorbidities such as diabetes mellitus, and vascular insufficiency) and extrinsic determinants (e.g., actinic damage and surgical trauma). Furthermore, local mechanotransduction pathways, specifically vector tension and anatomic location, critically influence scar formation. Dysregulation of healing processes leads to either chronic non-healing wounds or excessive scarring (hypertrophic scars or keloids) [20,21]. In aesthetic settings, even a modest scar or pigmentation change may be unacceptable to patients, making these variabilities a major challenge.

Procedural complexity and limitations of standard care: In modern cosmetological practice, wounds may result from various procedures, including laser resurfacing, injectables, microneedling, surgical excisions, body contouring, donor sites, and resurfacing. The interplay of these factors generates heterogeneous injury patterns, ranging from superficial partial-thickness erosions to complex full-thickness defects. These injuries are graded by their histological depth, microvascular perfusion status, mechanical tension vectors, and anatomical characteristics. Moreover, aesthetic patients have high expectations, like minimal downtime, minimal visible evidence of the procedure, and an optimal cosmetic finish. These demands elevate the standards significantly beyond those of typical wound care contexts. Nevertheless, the standard wound care procedures (gauze, simple dressings, standard closing) are often inadequate for delivering scar-minimal results [22–25]. Many dressings, suturing techniques, and protocols do not actively modulate the wound microenvironment (e.g., inflammation, angiogenesis, excessive extracellular matrix (ECM) alignment, and pigmentation) required for high-quality cosmetic outcomes [26]. This gap between what standard care offers and what optimal cosmetic healing demands creates the need for advanced therapeutics.

The key challenges in cosmetological wound healing are associated with the inherent biological complexity of skin and its repair process, the elevated aesthetic demands of cosmetic patients, the heterogeneity and unpredictability of healing responses, and the mismatch between traditional wound-care modalities and the need for reconstructive quality (Figure 2). These factors show that consumers need therapeutics that go beyond closure, and they have to actively support regeneration and achieve high-quality aesthetic results. Among the emerging trends, phyto-nanotechnology, which integrates plant-derived bioactive compounds with nanotechnology-based delivery systems, offers a promising strategy for enhancing wound healing by improving the bioavailability of therapeutic agents and promoting faster tissue regeneration.

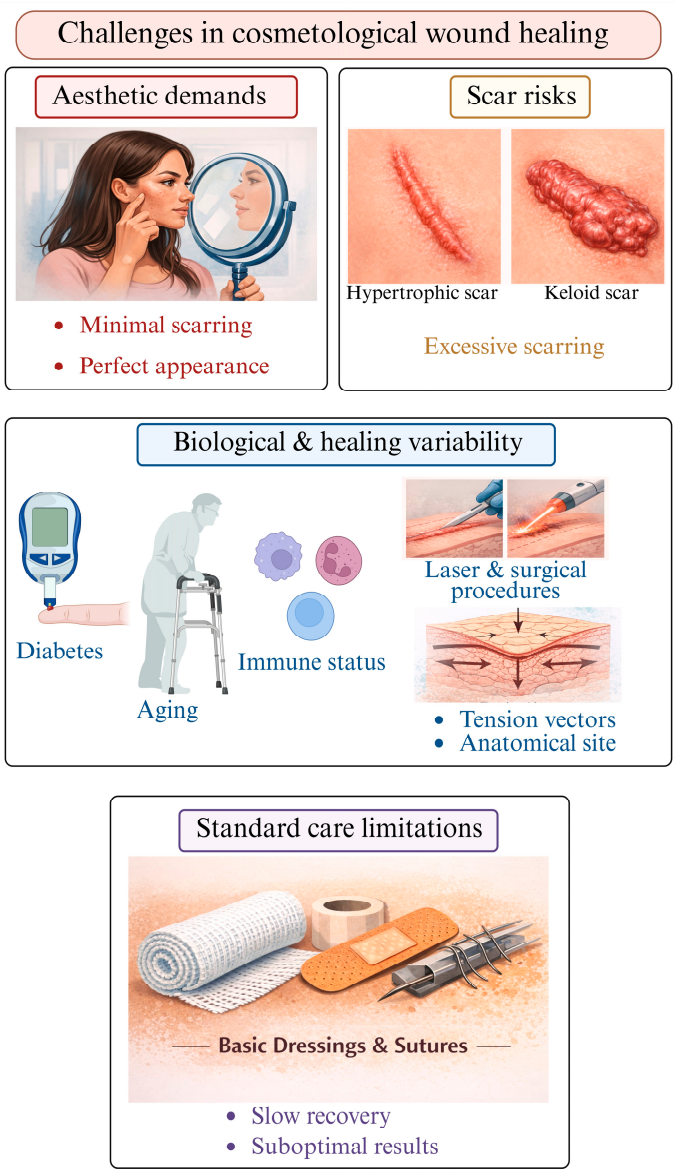


Figure 2. Challenges in Cosmetological Wound Healing. Schematic overview highlighting key factors (aesthetic demands, risk of aberrant scar formation, procedural complexity, and limitations of standard wound care approaches) influencing outcomes in cosmetological wound healing (created in BioRender.com).

1.4. Need for Advanced Therapeutics in Cosmetological Wound Healing

Acute wound repair begins immediately upon tissue injury. It proceeds through overlapping, highly orchestrated phases such as initial hemostasis and inflammation, followed by proliferation (including granulation tissue formation, re-epithelialization, and angiogenesis), and finally remodeling or maturation of the extracellular matrix and scar [27,28]. During the hemostasis phase, platelets aggregate, fibrin clots form, and vasoconstriction transitions to vasodilation to recruit inflammatory cells [29]. The inflammatory phase clears debris and pathogens and secretes growth factors, and then the proliferative phase features fibroblast migration, endothelial growth, and keratinocyte migration to recover the surface [27,30]. Ultimately, in the remodelling phase, collagen III is replaced by collagen I, matrix metalloproteinases remodel the extracellular matrix, and wound tensile strength gradually increases [27,30]. When any of these phases is dysregulated, particularly prolonged inflammation, excessive fibroblast or myofibroblast activation, mechanical tension at the wound margin, or inadequate vascular supply, pathological scarring (hypertrophic

or keloid scars) may occur. For example, persistent inflammatory signalling (e.g., elevated transforming growth factor-β (TGF-β) and macrophage infiltration) causes excessive collagen deposition and myofibroblast persistence that underlie hypertrophic scars [20,31,32]. Mechanical tension has been shown to enhance myofibroblast differentiation and thus increase fibrotic scarring [33]. Clinically, these mechanistic insights imply that optimizing wound closure by reducing ischemia (ensuing better blood flow), minimizing mechanical tension at the wound edges, controlling infection, and limiting prolonged inflammation are key to reducing pro-fibrotic signaling and improving healing outcomes.

However, any minor disturbances, including infection, ischemia, oxidative stress, or excessive wound tension, may prolong inflammation, impair angiogenesis, and delay fibroblast maturation, resulting in poor wound closure and suboptimal cosmetic outcomes [26,27,30,34].

Even when epithelial closure is achieved, the cosmetic and functional burden of abnormal repair remains important. Hypertrophic scars and keloids arise from dysregulated wound healing marked by excessive fibroblast proliferation, prolonged inflammation, and ECM deposition, particularly of collagen types I and III. This process is primarily driven by persistent activation of the TGF-β/Smad signaling cascade, alongside aberrant activity in the Wnt/β-catenin, integrin-FAK, and YAP/TAZ mechanotransduction pathways, which together maintain a profibrotic microenvironment. The resulting lesions often cause contracture, pruritus, pain, and visible disfigurement, complications that are especially distressing in cosmetological and reconstructive contexts [35,36].

Clinically, hypertrophic scars are firm, raised lesions that remain confined within the wound margins and may gradually regress, whereas keloids extend beyond the original boundaries and rarely resolve spontaneously. Histologically, hypertrophic scars display collagen arranged in parallel bundles with abundant myofibroblast activity, while keloids exhibit dense, haphazard collagen bundles, increased vascularity, and persistent immune-cell infiltration, reflecting chronic inflammation and impaired ECM remodeling [37,38]. Because no single treatment fully reverses the underlying pathophysiology, early, multimodal intervention remains the standard of care. Strategies such as silicone occlusion therapy, intralesional corticosteroids, 5-fluorouracil, and fractional laser resurfacing have demonstrated synergistic effects by modulating fibroblast signaling, promoting collagen realignment, and reducing scar thickness. Integrating such approaches early in the healing process significantly improves aesthetic and functional outcomes while lowering recurrence risk [36,38].

This review distinguishes itself from previous reports by providing an updated mechanistic and cosmetology-oriented synthesis of phytochemical-based nanotherapeutics, with particular emphasis on their role in modulating wound healing pathways and improving aesthetic outcomes.

2. Methodology

This narrative review was conducted following PRISMA-informed reporting principles adapted for non-systematic reviews to enhance transparency and reproducibility.

A structured literature search was performed across three major scientific databases: Scopus, Web of Science, and Google Scholar. The search strategy employed combinations of the following keywords: “nanotechnology,” “skin,” “nanoformulation,” “cosmetics,” “wound healing,” and “phytocompound.” These terms were used individually and in various Boolean combinations to maximize retrieval of relevant studies.

Studies were considered eligible if they met the following criteria: (i) addressed nanoformulations incorporating phytocompounds as active ingredients, (ii) focused on

skin-related applications, including cosmetics or wound healing, and (iii) were published in English.

Exclusion criteria included: (i) studies not related to phytocompound-based nanoformulations, (ii) articles lacking sufficient methodological or experimental detail, and (iii) non-English publications.

No restriction on publication timeframe was applied to capture both foundational and recent advances in the field. Retrieved studies were screened based on title, abstract, and full-text relevance. Priority was given to studies providing mechanistic insights, well-designed experimental data, or significant contributions to the development of nanoformulations for skin applications (Figure 3).

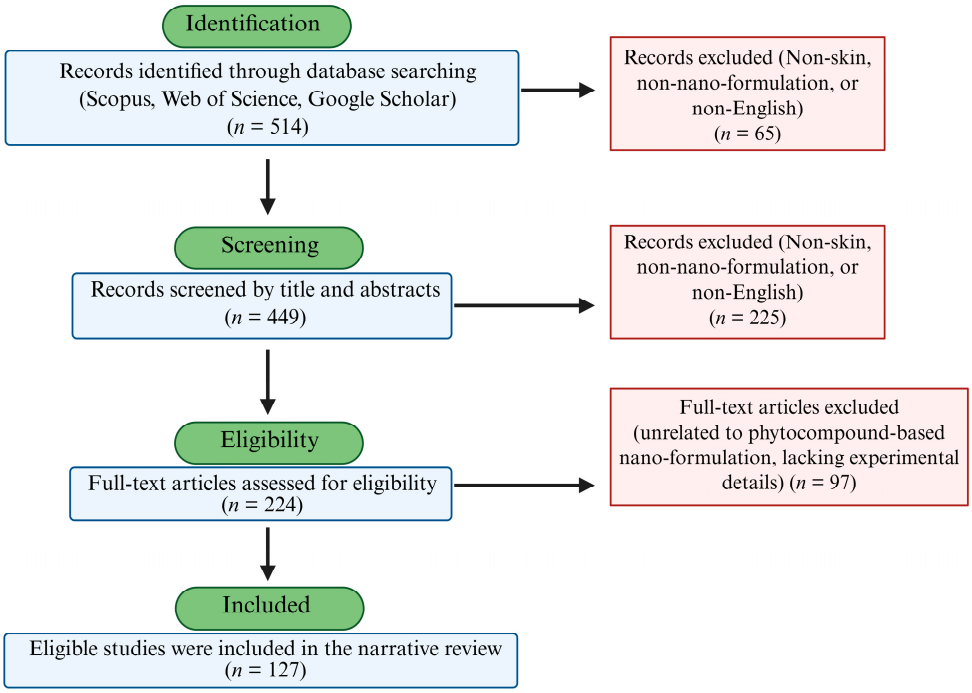


Figure 3. PRISMA flow diagram of literature search and study selection.

3. Phytochemicals with Wound Healing Properties

Traditional medicines have used phytochemicals for wound management, which continue to attract significant attention to this day due to ubiquitous availability, biocompatibility, low cost, and pleiotropic biological activities. Plant secondary metabolites such as flavonoids, tannins, saponins, glycosides, phenolic acids, terpenoids, and alkaloids play a vital role in regulating multiple phases of the wound-healing cascade, including inflammation, infection control, angiogenesis, and tissue remodeling [39].

The multipotent nature of phytochemicals enables modulation of oxidative stress, microbial burden, and cellular regeneration, making them promising candidates for wound-healing applications. Among the phytochemicals, flavonoids have been widely studied due to their strong antioxidant and anti-inflammatory properties. Flavonoids scavenge reactive oxygen species (ROS), inhibit lipid peroxidation, and modulate key signaling pathways involved in inflammatory responses. Excessive ROS production is a hallmark of chronic wounds, leading to cellular damage and ECM degradation [40]. By neutralizing oxidative stress, phytochemicals restore cellular integrity and promote effective tissue repair. Compounds such as curcumin and chlorogenic acid have additionally been shown to enhance angiogenesis by improving fibroblast viability and reducing oxidative damage. Several phytochemicals, including those derived from honey and curcumin, downregulate pro-inflammatory mediators such as tumor necrosis factor-alpha (TNF-α), TGF-β1,

matrix metalloproteinases (MMPs), and inducible nitric oxide synthase, thereby reducing ECM degradation, oxidative stress, and fibroblast hyperproliferation, the key pathological features of chronic wounds and hypertrophic scarring [41].

Phytochemicals also exhibit broad-spectrum antimicrobial activity, which is essential for preventing wound infections. Compounds such as saponins, tannic acid, alkaloids, and berberine disrupt bacterial membranes or inhibit microbial enzymes, showing efficacy against common pathogens associated with wounds, including *Staphylococcus aureus* and *Pseudomonas aeruginosa* [42]. In addition to direct antimicrobial effects, many plant-derived compounds possess antioxidant properties that further accelerate wound healing by mitigating oxidative stress-induced tissue damage [43]. Antioxidants are particularly crucial in chronic wounds, where persistent oxidative stress delays healing and exacerbates tissue injury. Several medicinal plants have been extensively validated in preclinical models for their wound-healing efficacy. For example, *Centella asiatica* enhances antioxidant levels and promotes fibroblast proliferation, primarily due to the presence of the phytochemical asiaticoside, which accelerates both acute and chronic wound repair [44].

Chromolaena odorata leaf extracts rich in flavonoids stimulate fibroblast proliferation, keratinocyte migration, and endothelial cell activity, thereby enhancing re-epithelialization and angiogenesis [45]. Similarly, *Buddleja globosa*, traditionally used for treating burns and ulcers, has demonstrated fibroblast-stimulating and antioxidant activity in vitro, primarily due to its flavonoid and caffeic acid content, which supports early tissue repair and skin regeneration [46]. By influencing key growth factors such as epidermal growth factor (EGF) and fibroblast growth factor (FGF), phytochemicals further regulate cellular migration and proliferation, facilitating effective tissue regeneration [47]. In spite of promising preclinical evidence, translating these bioactivities into clinically effective therapies remains a challenge, owing to their unfavorable taste, poor permeability, low solubility, and poor bioavailability, highlighting the need for advanced delivery strategies to fully harness their therapeutic potential.

Despite extensive preclinical evidence supporting the wound-healing efficacy of phytochemicals, most studies are limited to in vitro systems or small animal models, which may not fully replicate the complexity of human skin physiology and immune responses. Furthermore, variability in extract composition, lack of standardization, and inconsistent dosing across studies introduce challenges in reproducibility and translational reliability.

However, not all studies report uniformly positive outcomes. Some phytochemicals have demonstrated limited or variable efficacy depending on extraction methods, dosage, and model systems. In certain cases, improvements in wound healing parameters were modest or not statistically significant when compared to standard treatments, highlighting the need for cautious interpretation of their therapeutic potential.

4. Current Clinical Strategies for Surgical Wound Management

4.1. Infection Prevention

Institutional and global guidelines support perioperative bundles of care, which aim to reduce the incidence of surgical site infections (SSIs). For example, the Centers for Disease Control and Prevention 2017 guideline recommends the appropriate timing and selection of prophylactic antibiotics, maintenance of perioperative normothermia, perioperative glycemic control, maintaining adequate oxygenation, and use of an alcohol-based skin antiseptic [48]. A meta-analysis of perioperative care bundles found a consistent reduction in SSIs when multiple strategies were implemented [49]. Regarding skin antisepsis choice, a randomized controlled trial (RCT) compared preoperative skin preparation with chlorhexidine–alcohol versus povidone–iodine in clean-contaminated surgeries. The study

found that the chlorhexidine–alcohol reduced SSI rates to 9.5% compared to 16.1% with povidone–iodine, representing an approximate 40% relative reduction [50].

Subsequent meta-analyses by Wade et al. support that alcoholic chlorhexidine was roughly twice as effective as povidone–iodine in preventing SSIs after clean surgery [51]. Thus, choosing the antiseptic agent is vital, and it is a critical component of SSI-prevention strategies. In addition, nasal decolonization of *S. aureus* has been shown in multiple settings to reduce *S. aureus*-associated SSIs. However, rising mupirocin resistance and the investigation of alternatives (e.g., povidone–iodine intranasal, alcohol-based skin antiseptics) are active areas of further research [52].

Despite overall favorable findings, some studies report minimal differences between interventions, particularly in low-risk surgical settings, where baseline infection rates are already low. This suggests that the relative benefit of certain interventions may be context dependent.

4.2. Surgical Closure Materials

Closing the wound with devices and materials that minimize bacterial colonization and micro-environmental risk can further reduce SSI risk. A recent systematic review and meta-analysis revealed that the use of triclosan-coated sutures was associated with a lower risk of SSIs compared with non-triclosan sutures [53]. The abdominal fascial closure showed an approximate 2% lower risk of SSIs when triclosan-coated sutures were used compared with standard sutures. It supports the antimicrobial benefit of triclosan coating in reducing bacterial colonization and postoperative wound complications [54]. While the data are moderately strong, cost-effectiveness and generalizability across surgical specialties, including plastic or reconstructive surgery, remain under assessment [55]. For low-tension linear incisions, tissue adhesives (e.g., cyanoacrylate) have been compared favorably with sutures: similar infection rates and cosmetic outcomes, with shorter closure times and less discomfort. For example, it has been shown that cyanoacrylate adhesives achieved similar SSI and scar outcomes for face/neck scratches vs. sutures [56–58].

4.3. Advanced Wound Devices [Closed-Incision Negative-Pressure Therapy (ciNPT)]

For high-risk closed incisions (e.g., in breast/abdominal surgery, heavy tension, or patient comorbidities), closed-incision negative-pressure therapy (ciNPT) has emerged as an effective adjunct [59,60]. A systematic review and meta-analysis covering 84 studies reported that ciNPT, compared to standard dressings, was associated with significantly lower rates of surgical site complications such as SSIs, seroma, dehiscence, and skin necrosis; reduced readmissions and reoperations; and shortened hospital stay [61]. A recent meta-analysis on free-flap donor sites showed that ciNPT significantly lowered dehiscence compared to conventional dressings. It also reduces the surgical site complications [62]. The studies support ciNPT for selected high-risk incisions, acting through mechanisms such as reduction in lateral wound tension, removal of fluid/seroma potential, and improved microperfusion. Both RCTs and observational studies, including breast, abdominal, and reconstruction cohorts, show ciNPT reduces composite surgical site complications in high-risk incisions [60,61,63–65].

Meta-analytic evidence indicates that ciNPT reduces surgical site complications, with several studies reporting relative risk reductions ranging from approximately 20% to 50%, depending on patient risk profile and surgical context [61].

4.4. Scar Modulation Strategies

Mechanical tension off-loading: The role of mechanical forces in post-surgical scarring has been recognized as necessary for fibrosis modulation. Excessive tension across wound edges promotes fibroblast activation, collagen deposition, and scar widening, whereas tension off-loading improves organized matrix remodeling and cosmesis. The studies

collectively demonstrate that strategies that reduce static or dynamic tension on healing incisions significantly mitigate scar hypertrophy and improve aesthetic outcomes [66,67]. The studies showed the efficacy of elastic polymer tension-offloading devices (Embrace®) in surgical scar prevention [66,67]. Longaker et al. [66] demonstrated that the Embrace device significantly improved 12-month scar appearance compared with standard care, alongside better Patient and Observer Scar Assessment Scale (POSAS) ratings and no serious adverse events [66].

Lim et al. [67] found that using the Embrace dressing on half of an incision, to reduce tension, resulted in a significantly better-looking scar after six months compared to the other half of the incision [67]. These studies disclosed that maintaining a low-strain microenvironment during the remodeling phase directly translates to narrower, flatter scars. Complementing external off-loading, botulinum toxin A (BoNT-A) supports functional immobilization of wounds by rapidly denervating adjacent musculature, thereby diminishing repetitive micro-tension along incision lines. This biochemical approach reproduces the benefits of mechanical unloading within dynamic facial regions. It has been demonstrated that peri-incisional BoNT-A injections improved facial scar adaptability, color and width, visual analysis scores, and patient satisfaction [68,69]. Winayanuwattikun et al. [70] further demonstrated reduced scar severity in post-mastectomy transmen treated with incobotulinumtoxin A with decreased redness values compared to placebo at three and six months [70].

Silicone therapy: Silicone-based interventions are an adjunct in conservative scar management, particularly for hypertrophic scars once epithelialization is complete. The therapeutic principle is primarily hydration and occlusion. Silicone dressings reduce transepidermal water loss, increase stratum corneum hydration, and modulate fibroblast activity, thereby reducing collagen synthesis and improving scar pliability. While the precise mechanism is incompletely defined, silicone therapy may also elevate local temperature, enhancing collagenase activity and promoting balanced extracellular matrix remodeling [71,72].

The Cochrane systematic review compared silicone gel sheeting (SGS) with various comparators, including no treatment, silicone gel, pressure garments, and onion extract. Compared with no silicone sheeting, SGS showed a mean reduction in scar severity assessed by the Vancouver Scar Scale (VSS) and pain reduction. When compared with pressure garments, SGS yielded lower pain scores. Against topical onion extract, SGS slightly improved scar severity [72].

Intralesional therapy: The use of intralesional 5-fluorouracil (5-FU), alone or in combination with triamcinolone acetonide (TAC), is an effective therapy for keloids and hypertrophic scars. TAC (40 mg/mL), 5-FU (50 mg/mL), and the combination (1:9 ratio) significantly improved VSS parameters and pruritus, where the combination treatment exhibited the fastest and most balanced improvement in scar height, pliability, pigmentation, and vascularity with fewer adverse effects. 5-FU monotherapy reduced pruritus most rapidly, whereas TAC monotherapy was associated with more telangiectasia and atrophy [73]. Acharya et al. [74] compared the effectiveness of TAC (20 mg/mL) alone and the TAC + 5-FU (25 mg/mL) combination. After 12 weeks, about 50% of height reduction was observed in more than 96% of the combination group versus TAC alone (about 67%), with a significantly greater decrease in both VSS and POSAS scores and fewer side effects [74]. A review of clinical trials revealed that 5-FU monotherapy yields consistent keloid improvement [75].

Lasers and energy devices: Scientific reports support the early use of fractional CO_2 lasers for optimizing surgical scar outcomes [76,77]. Yenyuwadee et al. reported the effect of early fractional CO_2 laser intervention in thyroidectomy patients. At 12 weeks, laser-treated scars demonstrated significantly lower VSS and POSAS scores, indicating

improvements in height, pigmentation, and pliability, with minimal adverse effects such as transient erythema or edema [76]. A recent meta-analysis confirmed that fractional CO_2 laser treatment significantly reduced the VSS score. Furthermore, it demonstrated that initiating treatment within a month of post-operation yields the greatest benefits, whereas treatments started beyond three months showed no significant improvement [77].

Even though a substantial body of preclinical research supports the efficacy of phytochemical-loaded nanotherapeutics in wound healing, clinical evidence remains limited and fragmented. Overall, most clinical investigations involve conventional therapies or non-nano phytochemical formulations, while well-designed clinical trials specifically evaluating nano-enabled phytotherapeutics are scarce. Existing studies also exhibit heterogeneity in design, patient population, and outcome measures, which complicates direct comparison and limits generalizability.

Despite randomized trials and meta-analyses supporting these findings, heterogeneity in study populations, surgical types, and outcome definitions may limit direct comparability. Additionally, many studies are conducted in controlled settings, which may not fully reflect real-world variability in clinical practice, such as differences in patient demographics, treatment adherence, and healthcare resource availability.

5. Emerging Adjunct Therapies

Platelet-rich plasma (PRP): Evidence in plastic/aesthetic surgery is mixed. Systematic reviews show promise for some indications (chronic wounds, adjunct to dermal matrices), yet RCTs in clean elective incisions (e.g., breast reduction) show no aesthetic advantage. Expect heterogeneity from variable PRP preparation and dose [78–80]. While some studies report modest improvements in healing parameters, others show no statistically significant differences compared to standard care, particularly in clean surgical wounds, indicating effect sizes that are small or clinically negligible in certain contexts.

Biofilm-aware care: Chronic or non-healing wounds often contain bacterial biofilms that delay recovery. The main treatment is sharp debridement combined with suitable antimicrobial therapy. New antibiofilm treatments, including negative pressure wound therapy and sustained-release iodine dressings (Plurogel™, Ioplex™, Iodosorb™, Iodoflex™), are being developed to further improve healing [81–86].

Post-operative water exposure: The early postoperative water exposure is safe and does not increase surgical site infection or wound complications [87,88]. Patients who showered 48 h after surgery had similar infection rates and no higher rates of pain or wound dehiscence (clean or clean-contaminated wounds after thyroid, lung, hernia, or skin surgery) but reported greater comfort and lower wound-care costs than those who kept wounds dry [87]. In dermatologic surgery patients, the effect of early water exposure at 6 h with standard dry care for 48 h has been reported. The results indicated that surgical wounds can be safely exposed to water soon after surgery without increasing the risk of infection or affecting healing or scar appearance [88].

The inconsistency in clinical outcomes is likely attributable to substantial variability in PRP preparation protocols, platelet concentration, and activation methods, which remain poorly standardized across studies. This methodological heterogeneity introduces bias and limits the generalizability of findings.

While some studies report beneficial effects, other well-controlled trials have demonstrated no significant improvement in aesthetic or healing outcomes, particularly in clean surgical wounds. This inconsistency calls into question standardized protocols and more robust clinical validation.

6. Nanotechnology in Wound Healing (Nanotechnology-Based Delivery Systems)

Nanotechnology has emerged as a transformative force in 21st-century biomedicine, offering innovative strategies for advanced wound management. The distinctive features of nanomaterials, such as nanoscale size, high surface-to-volume ratio, tunable surface characteristics, unique optical characteristics, enhanced conductivity, and capacity for surface functionalization, enable precise interactions with biological systems at cellular and molecular levels. These properties make nanomaterials highly adaptable platforms for designing next-generation wound-healing therapies [89]. A wide range of nanoformulations has been investigated to target different phases of wound healing. Broadly, these include:

(i) nanomaterials possessing intrinsic therapeutic properties beneficial for wound treatment, and

(ii) nanomaterials functioning as delivery systems for bioactive agents [90].

Compared with conventional therapeutics, nanoformulations offer several distinct advantages. Their tunable size, often below 200 nm, facilitates deeper skin penetration, enabling bioactive compounds to reach inner dermal layers and enhance tissue repair. The porous architecture of many nanomaterials supports sustained and controlled drug release, reducing systemic exposure, minimizing drug wastage, and improving patient compliance. In addition, engineered nano-based topical systems can be designed as mucoadhesive or stimuli-responsive platforms that respond to local factors such as pH changes or microbial presence, thereby suppressing pathogen growth and promoting faster healing. Importantly, nano-encapsulation can also improve the solubility and bioavailability of poorly water-soluble drugs, further enhancing therapeutic effectiveness [91].

The convergence of nanotechnology with phytocompounds has further expanded therapeutic possibilities. Phytochemical-loaded nanomaterials enhance tissue regeneration, regulate microbial infections, enable targeted drug delivery, and help reduce scar formation. By engineering multifunctional nanostructures, it is possible to simultaneously achieve antimicrobial activity, sustained and controlled drug release, and localized delivery of bioactive molecules that modulate the wound-healing cascade. Certain nanostructured systems also mimic the native extracellular matrix, thereby supporting cell adhesion, proliferation, and migration while influencing key signaling pathways involved in tissue repair and regeneration. A diverse range of nanomaterials has been investigated for wound-healing applications [92]. Metallic and metal oxide nanoparticles such as silver, gold, and zinc oxide have demonstrated broad-spectrum antimicrobial activity against common wound pathogens, contributing to effective infection control and faster wound closure [93]. In parallel, nanotechnology-based drug delivery systems have been extensively explored to enhance therapeutic outcomes in wound infections and other diseases. Topically applied drug-loaded nanoparticles can accumulate within hair follicles, which facilitates drug permeation across the stratum corneum and promotes deeper penetration into skin layers. This property enhances the localized delivery and therapeutic efficacy of bioactive compounds in wound treatment. Among the various nanotechnology-based systems explored for wound healing and infection control, polymeric nanoparticles (PNPs), inorganic nanoparticles, lipid nanoparticles, and nanofibers are the most widely studied. These nanoformulations can also be incorporated into wound dressings to further improve drug stability, controlled release, and overall healing performance. In this context, polymeric and inorganic nanoparticles, along with other nanoformulations loaded with phytochemicals, have gained considerable attention. Additionally, electrospun nanofiber-based wound dressings incorporating phytochemicals are increasingly investigated due to their ability to mimic the extracellular matrix and support effective wound repair. Figure 4 illustrates the role of nanomaterials in wound healing.

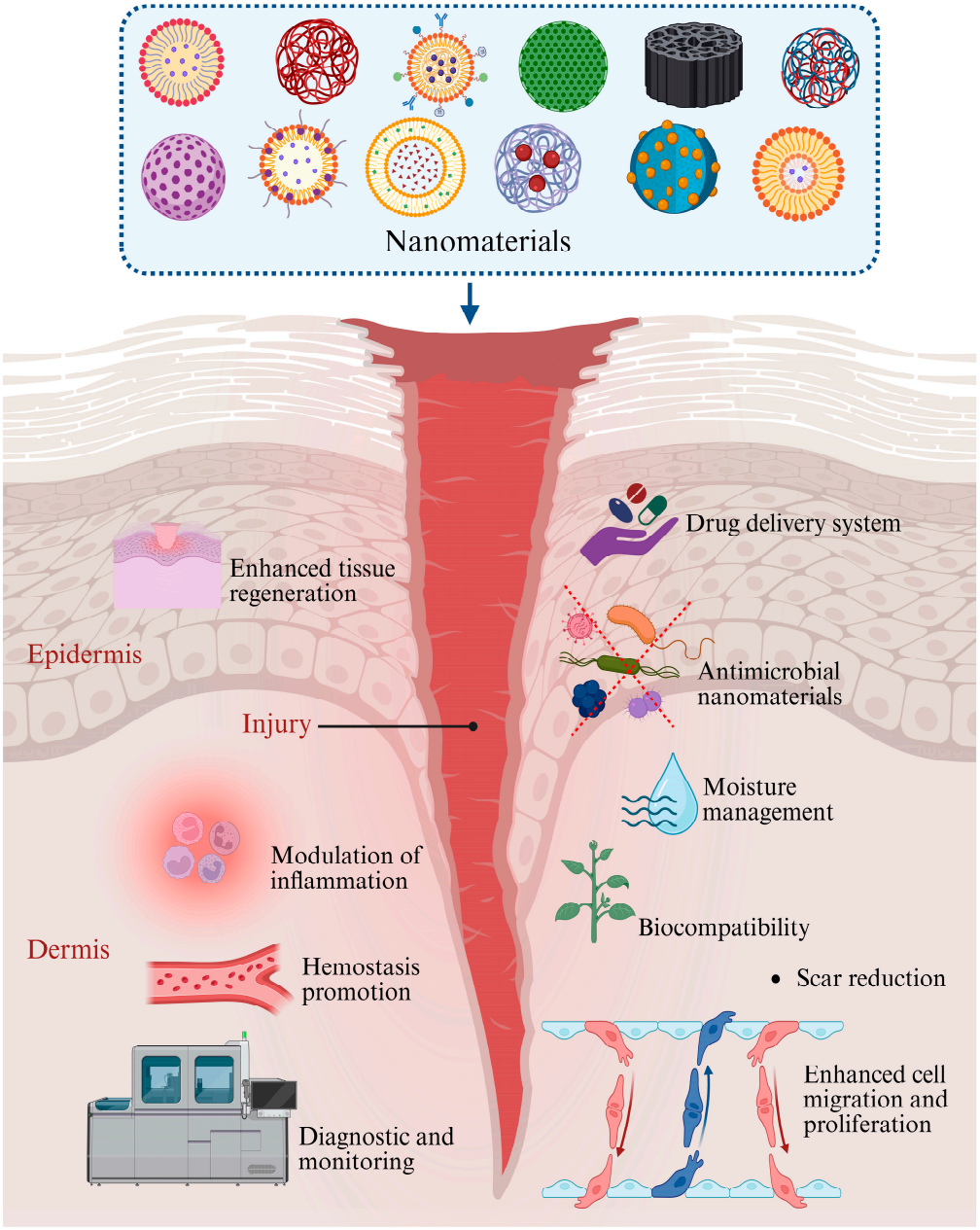


Figure 4. Multifunctional Nanomaterial-Based Strategies for Wound Healing (Modified based on Madaninasab et al. [94] with the copyright license of https://creativecommons.org/licenses/by/4.0/) (accessed on 20 February 2026).

Importantly, not all nanoformulations demonstrate superior performance over conventional therapies. In some studies, improvements in wound closure or antimicrobial activity were comparable rather than significantly enhanced, suggesting that the added complexity of nanocarrier systems does not universally translate into clinically meaningful benefits. Preclinical studies frequently report accelerated wound closure, with a significant level of improvement compared to free compounds or control treatments; however, such results are highly dependent on experimental conditions and may not directly translate to clinical settings, particularly because the effectiveness observed in controlled environments often diminishes when applied to real-world clinical scenarios.

Despite the promising therapeutic advantages demonstrated by nanoformulations, the majority of evidence is derived from preclinical studies, often conducted under controlled laboratory conditions. Differences in nanoparticle size, composition, surface modification,

and dosing regimens across studies create significant heterogeneity, complicating direct comparison and reproducibility. Moreover, long-term safety, systemic absorption, and potential nanotoxicity remain insufficiently characterized, representing critical barriers to clinical translation.

6.1. Polymeric Nanocarriers

Nanocarriers are nanosized cargoes (1–100 nm) designed to transport therapeutic agents to specific target sites within the body. Compared to conventional drug delivery systems, nanocarriers offer several advantages, such as improved efficacy, enhanced stability, increased bioavailability, better target specificity, and the ability to provide controlled and sustained drug release. These properties significantly enhance therapeutic outcomes while minimizing systemic side effects. Furthermore, nanocarriers are capable of encapsulating and delivering a wide range of drugs with diverse biological properties, including hydrophilic, hydrophobic, and biomacromolecular agents. They can also effectively encapsulate natural bioactive compounds such as phytochemicals, protecting them from degradation, improving solubility, and enhancing their therapeutic potential [95].

Several nanocarriers, such as nanoemulsions, polymeric nanocarriers (nanospheres and nanocapsules), and vesicular nanosystems (liposomes, ethosomes, transferosomes, solid lipid nanoparticles, niosomes, and phytosomes), were widely used as drug delivery systems for wound healing. These carriers effectively carry the medication to different layers of skin via various mechanisms depending on their compositions, such as passive diffusion, endocytosis, or enhanced permeability, which facilitate targeted and efficient drug delivery for wound healing [96].

PNPs are nanoscale carriers ranging from 1 to 1000 nm, characterized by diverse structures and morphologies that enable versatile biomedical applications. Biopolymers derived from diverse natural sources such as plants (e.g., starch and cellulose), animals (e.g., collagen, hyaluronic acid, and chitosan), fungi (e.g., chitin), bacteria (e.g., bacterial cellulose and exopolysaccharides), and algae (e.g., alginate). Due to their biocompatibility, biodegradability, low immunogenicity, and renewable nature, biopolymers are often preferred over synthetic materials in biomedical applications. Commonly used biopolymers in wound healing include collagen, cellulose, chitosan, alginate, hyaluronan, fucoidan, and carrageenan, which exhibit antibacterial, anti-inflammatory, and cell-proliferative properties that support tissue repair and sustained release of bioactive compounds involved in wound healing. Synthetic polymers such as poly(lactic acid) (PLA), poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), and poly(amino acids) are widely used for wound repair. Biopolymer-based nanoparticles have shown considerable potential in wound healing because they enable controlled and sustained delivery of therapeutic agents, ensuring localized and prolonged release of drugs, growth factors, or bioactive molecules at the wound site, thereby enhancing therapeutic efficacy [97].

Owing to their diverse origins and physicochemical properties, biopolymer-based nanocarriers can be tailored to meet specific therapeutic requirements, such as enhancing drug solubility, targeting specific tissues, or controlling the release rate of the therapeutic agents. Biopolymer-based polymeric nanocarriers represent a major class of nanocarriers with broad applications in biomedicine, including drug delivery and wound management. Based on their structural characteristics, these nanoparticles are commonly categorized into hydrogel nanoparticles, filled hydrogel nanoparticles, and biopolymeric nanoparticles.

PNPs play a crucial role in the controlled and sustained release of therapeutic agents, including DNA, growth factors (FGF2, EGF), cytokines, and antibiotics, thereby promoting cell proliferation, tissue regeneration, antimicrobial activity, and wound healing [98,99]. Encapsulation protects bioactive compounds from enzymatic degradation (e.g., MMPs)

while enabling targeted delivery and improved bioavailability. PNPs enhance antimicrobial efficacy by penetrating biological barriers such as biofilms and microbial membranes, with physicochemical properties (size, surface area, and charge) influencing their performance. For instance, ZnO nanoparticles stabilized with PVA demonstrated strong antibacterial activity against *Escherichia coli* and *S. aureus* [100]. The surface area and surface charge of nanoparticles also influence their antibacterial performance [101]. The surface modifications, such as DSPE-PEG2000, improve mucus penetration and pathogen elimination [102]. Additionally, cationic systems like chitosan nanoparticles interact with negatively charged microbial membranes, leading to microbial inhibition [103]. PNP-based wound dressings, such as cellulose nanofibers loaded with AgNPs, have shown enhanced antibacterial activity and support tissue regeneration [103–105]. Furthermore, PNPs promote angiogenesis, collagen synthesis, and re-epithelialization, accelerating wound healing, particularly in chronic wounds [106]. Nitric oxide-releasing nanoparticles and PLGA-based systems loaded with growth factors have demonstrated enhanced fibroblast activity, epithelialization, and wound closure in experimental models [107].

In addition to accelerating healing, PNPs contribute to reduced scar formation by regulating inflammation and preventing excessive collagen deposition [108]. For example, asiaticoside-loaded PNPs have shown excellent biocompatibility and improved wound healing outcomes with minimal scarring in both in vitro and in vivo models [109,110]. Although studies on phytochemical-loaded PNPs remain limited, emerging evidence highlights their significant therapeutic potential. Quercetin-loaded hordein/chitosan nanoparticles demonstrated strong antioxidant, anti-inflammatory, and antimicrobial activities, significantly enhancing wound healing in infected animal models compared to free compounds [111]. Similarly, *Moringa oleifera*-loaded zein nanoparticles improved wound healing efficacy relative to crude extracts, indicating enhanced stability and bioactivity through encapsulation [112]. Advanced nanostructures, such as zein-based electrospun dressings incorporating tea carbon dots and calcium peroxide, further demonstrate improved antimicrobial activity and tissue regeneration, supporting their potential application in diabetic wound management [113].

However, many reported outcomes are based on short-term experimental models, with limited assessment of chronic exposure or long-term tissue responses. Additionally, potential publication bias toward positive findings may overestimate therapeutic efficacy, leading to a skewed understanding of the true effectiveness of treatments in real-world, long-term scenarios.

6.2. Hydrogel Nanoparticles

Hydrogel nanoparticles consist of hydrophilic polymer networks capable of absorbing and retaining large amounts of water or biological fluids. Their porous structure and tunable mechanical properties enable efficient loading and controlled release of therapeutic agents, making them suitable for drug delivery, tissue engineering, and wound healing. Filled hydrogel nanoparticles are hydrogel matrices embedded with active agents such as drugs, proteins, or other nanoparticles. These systems enhance therapeutic efficacy by protecting the encapsulated cargo and enabling sustained or stimuli-responsive release at the target site. In addition, nanohydrogels exhibit excellent biocompatibility and therapeutic efficacy, making them widely explored for skin regeneration applications. For example, baicalin-loaded gellan–cholesterol nanohydrogels have been developed to enhance wound healing. In a mouse model of epidermal inflammation, these nanohydrogels demonstrated improved skin regeneration along with significant anti-inflammatory activity [98].

Similarly, nanocrystal bacterial cellulose hydrogels have shown strong adhesion to fibroblasts, preserving the morphology of human dermal fibroblasts, promoting cell pro-

liferation, and regulating multiple gene expressions associated with tissue repair. Shefa et al. [114] reported that cellulose–polyvinyl alcohol hydrogel encapsulating curcumin showed enhanced uptake in L929 cells. In vivo wound healing studies in adult male Sprague Dawley rats showed quick wound closure due to the formation of neo-epidermis, granulation tissue, and collagen fibers. Tissue engineering using polymeric scaffolds such as hydrogels has received considerable attention in wound healing. Natural polymers, including chitosan (CS) and alginate (ALG), are commonly used for hydrogel fabrication due to their biocompatibility, biodegradability, and ability to support cell growth and tissue repair. Incorporation of *Urtica dioica* (nettle) essential oil and extracts in the form of nanoemulsion (Tween 80) in CS-ALG gel hydrogel improved the stability, bioavailability, and controlled release of bioactive compounds within the hydrogel matrix. The bioactive compound-integrated CS-ALG hydrogel showed potent antibacterial activity against pathogenic microbes associated with wounds, a low cytotoxic effect, improved cell adhesion in the L929 mouse fibroblast cell line, high water absorption capacity, and excellent hemocompatibility, highlighting their potential as advanced wound dressings [114].

Similarly, *Perovskia abrotanoides* essential oil nanoemulsions incorporated into chitosan hydrogels have demonstrated promising wound-healing activity. The nanoemulsion, prepared via ultrasonic emulsification and embedded in a 2% chitosan gel, showed favorable physicochemical properties, including a particle size of 13 ± 0.5 nm, quasi-spherical morphology, and good stability. In vivo studies using Wistar rat models confirmed enhanced wound closure, tissue regeneration, and collagen deposition, as demonstrated by histopathological analysis [115].

Another approach involved encapsulating lupeol, a pentacyclic triterpene with wound healing properties but poor water solubility, into silver-modified chitosan nanoparticles, which were then incorporated into a thermosensitive sericin hydrogel. The resulting nanocomposite system exhibited high encapsulation efficiency (62.1%), strong antibacterial activity against Gram-positive and negative bacteria, and minimal hemolytic effects. Application of this hydrogel to infected wounds significantly reduced bacterial growth, accelerated re-epithelialization, reduced inflammation, and enhanced collagen deposition, leading to improved healing outcomes [116]. Evidence revealed that phytochemical-loaded nanocarriers and hydrogel-based systems serve as advanced therapeutic platforms for wound healing and infection control.

6.3. Nanofibers

Nanofibers are formed from continuous polymer chains of natural or synthetic materials and can be assembled into thin fibrous mats for wound treatment. Their structure closely resembles collagen fibrils of the ECM, which supports cellular attachment, proliferation, and tissue regeneration. Due to their porous architecture and interconnected pores, nanofibers allow oxygen exchange and maintain optimal moisture levels at the wound site, both of which are essential for efficient wound healing.

Electrospinning is one of the most widely used methods for producing nanofibrous wound dressings. In this process, a polymer solution composed of natural polymers (such as chitosan, hyaluronic acid, alginate, and gelatin) or synthetic polymers [such as PLA, PLGA, PVP, and poly (vinyl alcohol) PVA] is injected through a syringe under a high-voltage electric field. The droplet at the needle tip forms a cone-shaped structure known as the Taylor cone, and when the electrostatic force exceeds surface tension, a polymer jet is ejected and solidifies into nanofibers. These fibers are collected on a grounded metallic collector, forming randomly oriented or aligned nanofibrous mats. Electrospun nanofibers possess a high surface-to-volume ratio, tunable mechanical properties, and structural similarity to the ECM. These characteristics enhance cell adhesion, proliferation,

and differentiation, while simultaneously enabling efficient drug loading and controlled release. Their porous structure facilitates oxygen diffusion and moisture retention, creating a favorable environment for wound repair [117].

Incorporation of phytochemicals into nanofibrous matrices has shown promising results for wound healing. These bioactive compounds provide antimicrobial, antioxidant, and anti-inflammatory effects that accelerate tissue regeneration. Emodin-loaded nanofibers (e.g., PVP or cellulose acetate) exhibit antimicrobial and anti-inflammatory activity and promote re-epithelialization and collagen synthesis [118]. Table 1 shows phytochemically incorporated nanofibers and their properties, which enhance wound healing activities.

Table 1. Wound healing application of phytochemical-loaded polymeric nanofibers *.

Nanofiber Matrix	Loaded Phytochemical/Extract	Properties	Biological Activities Related to Wound Healing	Reference
Cellulose acetate nanofibers	Asiaticoside (*C. asiatica*)	Porous nanofibrous structure, ECM-like morphology, good drug loading and release	Increased antioxidant activity, stimulated collagen synthesis (types I & III procollagen), and promoting tissue regeneration	[119]
Plant-derived nanofibers	Alfalfa extract (*Medicago sativa*)	Bioactive fibrous matrix with good porosity and cell compatibility	Antibacterial activity and phytoestrogenic effects supporting skin regeneration	[120]
PLGA nanofibers	Propolis	Controlled release, biodegradable	Promoted burn wound healing	[121]
Cellulose nanofibers	Essential oils (cinnamon, lemongrass, peppermint)	High surface area, porous structure, good vapor permeability, non-cytotoxic	Antimicrobial activity against *E. coli*	[122]
CS/PVA active layer + PCL backing (bilayer)	Pomegranate flower extract	Liquid absorption capacity, diameter ~400 nm	Antimicrobial activity against *S. aureus* and *P. aeruginosa*; ~88% wound healing within 2 weeks	[123]
PLA/PVA/Chitosan nanofibers	*Hypericum perforatum* extract	Extracellular matrix-like characteristics—porous morphology, good swelling, wettability, and WVTR	Cytocompatibility and antibacterial activity against *S. aureus*	[124]
PCL/collagen multilayer nanofibers	*Malva sylvestris* extract	Fiber diameter 120–140 nm, good WVTR similar to commercial dressings	Improved water uptake, blood clotting, and tissue regeneration	[125]
PCL nanofibers	Curcumin + berberine	Improved mechanical strength, swelling ability, thermal stability	Strong antibacterial activity against MRSA; rapid wound closure in the zebrafish model	[126]
PVA/CS nanofibers	*Thymus vulgaris* and *Zingiber officinale* extracts	Porous structure, enhanced wettability, high liquid absorption, diameter ~380 nm	Antioxidant and antibacterial activity; improved healing in infected rat wounds	[127]

Table 1. *Cont.*

Nanofiber Matrix	Loaded Phytochemical/Extract	Properties	Biological Activities Related to Wound Healing	Reference
Cellulose microfiber layer + pectin/soy protein/pomegranate peel layer	Pomegranate peel extract	Bilayer structure mimicking skin and improved mechanical strength	Promoted angiogenesis, cell adhesion, and rapid wound healing in vivo	[128]
PVA/alginate nanofibers	*Lawsonia inermis* and *Scrophularia striata* extracts	Biocompatible matrices with improved physico-mechanical properties	Antimicrobial activity and enhanced tissue regeneration in vivo	[129]
PCL/cellulose acetate nanofibers	*Rhamnus prinoides* leaf extract	Smooth morphology, fiber diameter 330–380 nm	Antibacterial activity; enhanced cell migration and hydrophilicity	[130]
Pectin–CS–PVA nanofibers	Dihydromyricetin–cyclodextrin complex	Hydrophilic, interconnected ECM-like structure, fiber diameter 200–400 nm	Antioxidant and antibacterial activity; improved wound healing in vitro and in vivo	[131]
PVA nanofibers with dopamine-functionalized alginate	Chlorogenic acid	Improved water absorption, hydrophilicity, desirable WVTR, porous structure	Antioxidant and antibacterial activity; protection against oxidative stress and improved wound healing	[132]
PCL/PVA-CS nanofibers	*Tridax procumbens* leaf extract	Good mechanical properties and biocompatibility	Greater inhibition of *E. coli* than *S. aureus*; enhanced tissue regeneration in wounds	[133]
PCL–silk sericin nanofiber layer + CS–alginate hydrogel layer	10-hydroxydecanoic acid (10-HDA)	Controlled swelling, multilayered structure	Improved cell proliferation, antimicrobial activity, and accelerated wound healing in rats	[134]
PCL-CS nanofibers	Oryzanol–β-cyclodextrin complex	Improved wettability and antibacterial activity	Reduced inflammation and enhanced re-epithelialization	[135]
PLGA/PMMA/collagen/glycine nanofibers	*Syzygium cumini* leaf extract	Biocompatible electrospun scaffold	Antimicrobial activity against multiple bacteria and fungi; improved healing In vivo	[136]
PVA/CS nanofibers	Royal jelly	Hydrophilic, good vapor permeability, fiber diameter ~200–300 nm	Infection control—Antibacterial activity against *S. aureus* and *E. coli*	[137]
Chitosan/Poly(ethylene oxide) nanofibers	Rosmarinic acid	Uniform electrospun fibers with good wettability and controlled release capability	Increased α-smooth muscle actin and elastin expression, accelerating wound contraction and tissue regeneration	[138]

Table 1. *Cont.*

Nanofiber Matrix	Loaded Phytochemical/Extract	Properties	Biological Activities Related to Wound Healing	Reference
PVA nanofibers	Flaxseed extract (*Linum usitatissimum*)	Hydrophilic nanofibers with high surface area and good mechanical stability	Rapid wound closure with antimicrobial activity against Gram-positive and Gram-negative bacteria	[139]

Abbreviations: ECM: Excessive extracellular matrix; PLA: Poly(lactic acid); PVA: Poly(vinyl alcohol); CS: Chitosan; PCL: Poly(ε-caprolactone); PLGA: Poly(lactic-co-glycolic acid); WVTR: Water vapor transmission rate; PMMA: Poly(methyl methacrylate); MRSA: methicillin-resistant *Staphylococcus aureus*. * Many studies summarized in this table lack standardized outcome metrics and are predominantly based on in vitro or small animal models, which may limit direct clinical extrapolation.

6.4. Nanocapsules/Nanospheres

Nanocapsules/nanospheres are biocompatible colloidal carriers with a size ranging from 1 to 1000 nm and have gained considerable attention in biomedical and bioengineering applications, particularly in wound healing. These nanoparticles are usually made from charged polymers that interact with each other through cationic and anionic groups. This makes it possible to encapsulate therapeutic agents. Incorporation of drugs into polymeric nanocarriers protects them from enzymatic degradation at the wound site and enables sustained, controlled release, thereby reducing the need for frequent administration. Due to their antibacterial properties and ability to promote tissue regeneration, polymeric nanomaterials are widely explored for wound management. Growth factors, such as keratinocyte growth factor (KGF), play a critical role in skin regeneration. Nanovesicles containing KGF have been shown to enhance epithelialization and skin remodeling, while EGF-loaded nanoparticles promote fibroblast proliferation and accelerate healing in full-thickness wounds by facilitating keratinocyte differentiation and restoration of the epithelial barrier [96].

However, several studies report only incremental improvements over free compounds, and in some cases, the benefits of polymeric nanocarriers were limited or dependent on specific formulation parameters, indicating that therapeutic outcomes are highly formulation-sensitive.

7. Lipid Nanocarriers

Lipid-based nanoparticles (LBNs) have emerged as multifunctional nanocarriers in biomedical and cosmetic applications owing to their biocompatibility, biodegradability, and capacity to enhance drug delivery. These nanosystems, typically consisting of a lipid matrix stabilized by surfactants, range in size from 1 to 100 nm and serve as effective platforms for sustained and targeted drug delivery. Their amphiphilic characteristics enable encapsulation of both hydrophilic and hydrophobic drugs, frequently utilizing oil-in-water nanoemulsion systems, thus enhancing medication solubility, stability, and therapeutic efficacy while reducing potential adverse effects. In wound management, LBNs play a crucial role in enhancing healing outcomes. They facilitate the preservation of an ideal moisture environment, improve drug retention at the wound location, and promote the function of growth factors essential for tissue regeneration. Supplementary benefits include thermal stability, sterilizing convenience, production scalability, and prolonged drug release characteristics, diminishing dose frequency and enhancing patient adherence. These characteristics render LBNs intriguing options for the treatment of diverse wound types, including diabetic ulcers, cutaneous wounds, and burn injuries [140].

Furthermore, LBN-based formulations that include bioactive molecules such as growth factors or natural compounds like essential oils with antimicrobial, anti-inflammatory, and

regenerative properties have shown improved skin regeneration and expedited healing in first- and second-degree burns. LBNs are commonly incorporated into both natural and synthetic wound dressings, promoting cell proliferation, regulating moisture balance, enhancing oxygen and water vapor exchange, and diminishing the risk of microbial infection. A variety of lipid-based nanocarriers have been engineered for wound healing applications, encompassing solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), lipid–polymer nanoparticles (LPNs), nanoemulsions, polymeric phospholipid micelles (PPMs), and vesicular nanosystems. These nanocarriers augment therapeutic efficacy by enhancing drug solubility, safeguarding bioactive compounds from degradation, and facilitating prolonged and targeted drug release [141].

7.1. Solid Lipid Nanoparticles (SLNs)

SLNs are lipid-based nanocarriers consisting of a solid lipid matrix supported by surfactants, generally maintaining a solid state at ambient and physiological temperatures. These nanoparticles are synthesized utilizing nontoxic and biodegradable lipids, frequently without the necessity for organic solvents. Over the past two decades, SLNs have emerged as promising alternatives to conventional colloidal carriers such as liposomes, emulsions, and polymeric microparticles due to their improved stability, controlled drug release, and low toxicity [142]. In wound healing applications, SLNs improve the delivery of therapeutic drugs and growth factors to the target region while safeguarding them from degradation. Their lipid makeup enhances contact with damaged or inflamed tissues, thereby accelerating tissue regeneration. Principal advantages encompass elevated drug encapsulation efficiency, sustained drug release, improved skin penetration, and extended retention at the wound site, which combined expedite wound closure and boost healing quality. Recent studies illustrate the efficacy of SLN-based formulations in administering antioxidants, anti-inflammatory medicines, antibiotics, and growth-factor-modulating pharmaceuticals. These formulations enhance wound healing by regulating inflammatory cytokines, promoting collagen deposition, facilitating angiogenesis, and diminishing microbial infection, rendering SLNs effective carriers for the treatment of diabetic wounds, skin injuries, burns, and oral mucosal wounds [142].

Several studies have demonstrated the potential of SLNs to enhance wound healing through improved drug delivery and sustained therapeutic effects. Nasiri et al. [143] developed α-tocopherol acetate-loaded SLNs using stearic acid as the lipid matrix and chitosan coating, achieving a particle size of about 175 nm and high entrapment efficiency (90.58%) with prolonged stability and controlled drug release. Gad et al. [144] reported that chamomile-loaded SLNs significantly accelerated wound healing, achieving nearly 96% wound closure after 16 days by reducing inflammatory cytokine IL-1β and increasing TGF-β1 during the proliferative phase. Bogadi et al. [145] reported silk fibroin-coated resveratrol solid lipid nanoparticles, which exhibited high entrapment efficiency with sustained release of resveratrol; enhanced stability; and biological activity, including strong antioxidant, antibacterial, and fibroblast migration under in vitro conditions, highlighting their promise as a multifunctional nanocarrier for diabetic wound healing. Sandhu et al. [146] developed curcumin solid lipid nanoparticles using solvent-free high-pressure homogenization, which exhibited strong antimicrobial activity against *S. aureus* and effectively disrupted mature biofilms, along with enhanced antioxidant properties. In vivo studies demonstrated accelerated wound closure, reduced oxidative stress and inflammatory cytokines, increased vascular endothelial growth factor (VEGF) expression, and improved re-epithelialization within 11 days.

7.2. Nanostructured Lipid Carriers (NLCs)

NLCs are advanced lipid-based nanocarriers with a typical size of 100–500 nm. They are composed of a mixture of solid and liquid lipids stabilized by surfactants, forming an imperfect crystalline matrix that accommodates higher amounts of bioactive molecules compared with conventional SLNs. Solid lipids, such as glyceryl monostearate, stearic acid, and beeswax, are essential in NLC formulations for imparting structural stability and modulating the release of the encapsulated medication. Conversely, liquid lipids such as oleic acid, medium-chain triglycerides, and diverse natural oils are integrated to introduce structural irregularities within the solid lipid matrix. These defects enhance the system's capability to accommodate drug molecules and facilitate the regulation of lipid polymorphic transitions, thereby improving the drug loading capacity. The amalgamation of solid lipids with oils like argan oil, oleic acid, or medium-chain triglycerides is frequently utilized to enhance the encapsulation efficiency of lipophilic bioactive substances. The selection of surfactants is a crucial determinant in the effective formulation of NLCs, as it directly affects particle size, colloidal stability, and biocompatibility for topical applications, generally within the range of 150–300 nm. Surfactants and co-surfactants, including Tween 80, Poloxamer 188, and lecithin, are extensively employed to stabilize lipid dispersions and regulate characteristics such as droplet size and zeta potential. Moreover, alternative stabilizing agents, including polysorbates and biodegradable non-ionic surfactants such as sucrose esters (sucrose monostearate and sucrose monopalmitate), are frequently favored for their reduced irritation potential and enhanced skin compatibility. Supplementary components like α-tocopheryl acetate are occasionally used to augment lipid stability, while pentylene glycol functions as a preservative to ensure antibacterial stability and boost the overall tolerance of NLC formulations. Structurally, NLCs are categorized into three types: imperfect crystals, multiple (oil-in-fat-in-water), and amorphous lipid matrices, each designed to minimize drug leakage and enhance drug loading [147].

For topical applications, NLCs are frequently incorporated into hydrogel matrices (NLC-gels), which improve wound adhesion, hydration, and local drug retention, thereby maintaining a moist microenvironment conducive to tissue repair [148]. NLC-based formulations promote wound healing through multiple mechanisms, including sustained drug release, enhanced skin permeation, antimicrobial activity, and modulation of inflammatory and oxidative pathways. Experimental studies demonstrate that NLC-gel systems stimulate fibroblast and keratinocyte proliferation, collagen deposition, and angiogenesis, resulting in accelerated wound closure in both in vitro and in vivo models (Table 2). Various phytocompounds, including curcumin, propolis, resveratrol, and astaxanthin, have been successfully incorporated into NLC systems to improve therapeutic outcomes in chronic and infected wounds [149].

Table 2. Phytocompound-loaded NLC for wound healing applications *.

Phytocompound	Source	NLC Composition (Solid/Liquid Lipid/Surfactant)	Mode of Action in Wound Healing	Experimental Model System	Reference
Hyperforin	*H. perforatum*	Compritol 888 ATO/Almond/Borage oil; Polysorbate 80	Anti-inflammatory activity; stimulates keratinocyte proliferation and tissue regeneration	HaCaT keratinocyte scratch assay; Streptozotocin-induced diabetic mouse excisional wound model	[150]

Table 2. *Cont.*

Phytocompound	Source	NLC Composition (Solid/Liquid Lipid/Surfactant)	Mode of Action in Wound Healing	Experimental Model System	Reference
Rutin	*Ruta graveolens*	Beeswax/sesame oil; Tween 80	Antioxidant activity enhances collagen deposition and angiogenesis.	Full-thickness excisional wound model in Wistar rats	[151]
Aloe-emodin	*Aloe vera*	Stearic acid/oleic acid; Tween 80	Antibacterial and anti-inflammatory; promotes epithelialization	Fibroblast proliferation assay (NIH-3T3 cells); rat excisional wound model	[152]
Astaxanthin	*Haematococcus pluvialis*	Glyceryl monostearate/oleic acid; Span 60/Tween 60	Potent antioxidant; enhances fibroblast migration and collagen synthesis	Human dermal fibroblast assay; mouse excisional wound model	[153]
Propolis	Bee product	Glyceryl monostearate/capric acid; lecithin/Tween 80	Antimicrobial and anti-inflammatory; promotes granulation tissue formation	Rat-burn wound model	[154]
Zerumbone	*Zingiber zerumbet*	Hydrogenated palm oil/olive oil; Tween 80	Suppresses TNF-α and IL-6 and increases IL-10; enhances wound contraction	Sprague-Dawley rat excisional wound model	[155]
Quercetin-Resveratrol	Fruits and vegetables *Vitis vinifera*	Labrafil lipids; Cremophor RH40S.	Antioxidant activity promotes fibroblast proliferation and angiogenesis, anti-inflammatory; improves tissue remodeling.	L929 fibroblast cell proliferation assay, human dermal fibroblast migration assay	[156]
Mentha pulegium essential oil	*M. pulegium*	Precirol ATO5/Miglyol 812; Poloxamer 407	Antibacterial; increases IL-10 and TGF-β and suppresses NF-κB.	Rat-infected excisional wound model	[157]
Rosemary essential oil	*Rosmarinus officinalis*	Precirol ATO5/Miglyol 812; Poloxamer 407	Antimicrobial and antioxidant; enhances angiogenesis	Rat excisional wound healing model	[158]
Thymol	*T. vulgaris*	Illipe butter/Calendula oil; Pluronic F68	Anti-inflammatory and antimicrobial; accelerates wound closure	Rat full-thickness wound model	[159]
20(S)-Protopanaxadiol	*Panax ginseng*	Glyceryl monostearate/MCT; Tween 80/Pluronic F68	Stimulates fibroblast proliferation and collagen deposition	NIH-3T3 fibroblast assay; mouse excisional wound model	[160]
Thymoquinone	*Nigella sativa*	Compritol 888 ATO, Miglyol 812, and Poloxamer 188	Promotes fibroblast proliferation and migration, attenuates ROS levels, enhances fibroblast proliferation and migration, and decreases apoptosis.	3T3-L1 cells, streptozotocin-induced diabetic mouse wound	[161]

Table 2. *Cont.*

Phytocompound	Source	NLC Composition (Solid/Liquid Lipid/Surfactant)	Mode of Action in Wound Healing	Experimental Model System	Reference
Caraway essential oil	*Carum carvi*	Precirol ATO5 + Miglyol 812, Poloxamer 407	Antibacterial activity. Suppresses TNF-α and IL-1β, enhances granulation tissue formation	Rat excisional wound model	[162]

Abbreviations: NLC: Nanostructured lipid carrier; TNF: Tumor necrosis factor; IL: Interleukin; TGF: Transforming growth factor; NF-κB: Nuclear factor-kappa B; MCT: Medium-chain triglycerides; ROS: Reactive oxygen species. * Many studies summarized in this table lack standardized outcome metrics and are predominantly based on in vitro or small animal models, which may limit direct clinical extrapolation.

8. Vesicular Nanosystems

A modern strategy to improve the therapeutic efficacy of phytochemicals at the skin level involves their incorporation into phospholipid-based vesicles, which are highly valued for topical delivery due to their biocompatibility, structural similarity to skin lipids, and ability to enhance drug penetration. Vesicular nanocarriers improve the stability, bioavailability, and skin permeation of phytochemicals by protecting them from degradation caused by light, oxygen, and pH changes. Their small size, elasticity, and lipid composition facilitate interactions with skin layers, enabling efficient delivery of active compounds to the target site. Skin absorption of phytochemicals generally occurs through transepidermal, intercellular, or transfollicular pathways. However, many plant-derived compounds have high molecular weight, polar functional groups, and low membrane permeability, which limit their bioavailability. Encapsulation within vesicular nanocarriers helps overcome these barriers by enhancing membrane permeability and maintaining therapeutic concentrations in skin tissues [163]. Liposomes, transferosomes, and ethosomes are among the most widely used vesicular systems. Liposomes mainly deposit drugs within the stratum corneum, whereas transferosomes and ethosomes improve deeper penetration into the dermis due to their deformability and ethanol-mediated membrane fluidization. Table 3 summarizes phytochemical-loaded vesicular nanocarriers for wound healing.

Table 3. Herbal extract and phytocompound-based vesicular nanocarriers for wound healing *.

Vesicular Nano System	Principal Constituents of Vesicles	Encapsulated Herbal Extract/ Phytocompound	Bioactive Compounds	Wound Healing Affect	Quantitative Wound-Healing Improvement	References
Liposomes	Soy lecithin	*A. vera* gel extract	Glycoproteins, Aloesin	Tissue regeneration	Increased the human epidermal keratinocytes' proliferation by 77% at the concentration of 4 µg/mL of *A. vera* gel extract.	[164]
	Phosphatidylcholine	Usnic acid	Lichen metabolite	Antibacterial, wound healing	Exact % epithelialization not reported.	[165]
	Egg lecithin	Madecassoside	Triterpenoid	Wound healing, collagen synthesis	Not reported	[166]
	Phosphatidylcholine	Quercetin	Flavonoid	Antioxidant	Not reported	[167]
	Lecithin, cholesterol	Curcumin	Polyphenol	Anti-inflammatory, antioxidant	After 8 days, significant recovery of wound-repair effects was observed; after 18 days, wound contraction was significantly greater than in other groups, but the exact % wound-closure values were not reported.	[168]
	Dipalmitoylpho-sphatidylcholine, cholesterol	*Salvia aramiensis* extract	Phenolics	Antioxidant	Not reported	[169]
	Hydrogenated phosphatidylcholine, cholesterol	*Carpobrotus edulis* extract	Flavonoids	Antioxidant and wound healing	Wound healing and contraction, cell migration and invasion, and angiogenesis were significantly improved compared to the control.	[170]
Liposomes/ Hyalurosomes	Phosphatidyl choline, hyaluronate	*Glycyrrhiza glabra* extract	Glycyrrhizin, Polyphenols	Anti-inflammatory	Not reported	[171]
	Soy lecithin, sodium hyaluronate	Neem oil (*Azadirachta indica*)	Flavonoids, Fatty acids	Antimicrobial, healing	The wound closure effect of neem oil-loaded liposomes, argan liposomes, and argan-hyalurosomes was 85% within 24 h and reached ~100% by 48 h.	[172]

Table 3. *Cont.*

Vesicular Nano System	Principal Constituents of Vesicles	Encapsulated Herbal Extract/ Phytocompound	Bioactive Compounds	Wound Healing Affect	Quantitative Wound-Healing Improvement	References
Hyalurosomes	Phosphatidylcholine	Curcumin	Polyphenol	Antioxidant, healing	0.5 hyalurosomes showed ~100% wound closure at 48 h, demonstrating superior efficacy compared to other formulations (liposomes and 0.1 hyalurosomes).	[173]
Niosomes	Tween 60, cholesterol	*Calendula officinalis* extract	Flavonoids, Terpenoids	Anti-inflammatory, healing	Exact % wound-closure values were not reported.	[174]
	Span surfactants, cholesterol	*H.perforatum* extract	Hyperforin, Hypericin	Antibacterial, wound repair	The niosomal gel significantly reduced inflammatory cell count (18.4 ± 5.3) by day 7 and accelerated the transition to the proliferative phase of healing. By day 21, it achieved complete re-epithelialization and a marked wound size reduction compared to the control.	[175]
Transferosomes	Lipoid S75, Tween 80	*Myrciaria jaboticaba* extract	Flavonoids, Anthocyanins	Antioxidant, skin repair.	The nanoformulations achieved ~90–100% wound closure at 48 h, compared to 40% in untreated cells and 50% with free extract, indicating an approximate 4–60% improvement in wound healing.	[176]
Phytosomes	Lecithin, cholesterol	*M. oleifera* extract	Quercetin, chlorogenic acid	Anti-inflammatory, healing	Not reported	[177]
	Soy lecithin	*A. vera* extract	Acemannan, β-sitosterol	Anti-inflammatory, ↑ VEGF expression	At 500 µg/mL, nanophytosomes improved: wound scratch healing rate (4.92 ± 0.3 mm/h vs. 3.07 ± 0.3 mm/h), tube formation (15 ± 3 vs. 2 ± 0.3), transwell migration (586 ± 32 vs. 394 ± 18), invasion (172 ± 9 vs. 115 ± 5), and nitric oxide synthesis (26.11 ± 0.19 vs. 5.1 ± 0.33).	[178]

Table 3. *Cont.*

Vesicular Nano System	Principal Constituents of Vesicles	Encapsulated Herbal Extract/ Phytocompound	Bioactive Compounds	Wound Healing Affect	Quantitative Wound-Healing Improvement	References
AuNP-Phytosomes/ Liposomes	Egg phosphatidylcholine	*C. officinalis* extract	Chlorogenic acid, quercetin	Antioxidant, wound healing	Antioxidant protection: 81% cell viability for AuNP-phytosomes vs. 74% for free AuNP and 48.8% for free *Calendula* extract under H_2O_2 stress. In the scratch assay, plain liposomes gave 23.5% gap closure at 8 h, while free *Calendula* gave 27.42% at 8 h; results showed stronger wound healing, but the exact percentage for AuNP-phytosomes was not reported.	[179]
Ethosomes	Egg lecithin	Curcumin	Polyphenol	Anti-inflammatory	Burn bacterial flora reduction was ~11% better than free curcumin; complete wound contraction occurred by day 16, with a significant $p < 0.001$.	[180]
Ethosomes/PEVs	Phospholipon®, fatty acids	*Fraxinus angustifolia* extract	Polyphenols	Antioxidant and antimicrobial	Not reported	[181]
Glycerosomes	Phosphatidylcholine, glycerol	*R. officinalis* extract	Polyphenols	Antioxidant, antimicrobial	Not reported	[182]
Liposomes/ Glycerosomes/PEVs	Soy lecithin	*Thymus capitatus* oil	Carvacrol	Antimicrobial	~100% wound closure was observed after 48 h of the *Thymus* essential oil extract-containing nanovesicle.	[183]
Glycerosomes/ Hyalurosomes	Lipoid S75, hyaluronate	*Citrus limon* extract	Flavonoids	Anti-inflammatory, antioxidant	Not reported	[184]

Abbreviations: VEGF: Vascular Endothelial Growth Factor; AuNP: Gold nano-particle; H_2O_2: Hydrogen peroxide; PEV: Penetration enhancer vesicles. * Many studies summarized in this table lack standardized outcome metrics and are predominantly based on in vitro or small animal models, which may limit direct clinical extrapolation. ↑: Increased.

8.1. Liposomes

Liposomes are self-assembled phospholipid vesicles formed in aqueous environments, consisting of one or more lipid bilayers surrounding an aqueous core. Because phospholipids are amphipathic, containing both hydrophilic heads and hydrophobic tails, they spontaneously organize into stable bilayer structures through hydrophobic interactions, van der Waals forces, and hydrogen bonding. Liposomes are versatile drug carriers capable of encapsulating hydrophilic, hydrophobic, and amphiphilic molecules. Hydrophilic drugs are trapped within the aqueous core, hydrophobic drugs are incorporated into the lipid bilayer, and amphiphilic compounds align at the membrane interface [184]. This structural organization allows liposomes to protect encapsulated drugs from degradation caused by light, oxygen, or moisture, while also enabling controlled and site-specific drug releases. Biocompatible, biodegradable, non-immunogenic, and non-toxic systems are recognized as safe nanosystems for topical application in human patients due to their membrane composition, phospholipids, and cholesterol, which are identical to cells' components. Lecithin-based liposomes have attracted attention in wound healing due to their antioxidant and immunomodulatory properties, which support tissue regeneration and improve dermal drug delivery.

Nasab et al. compared liposomes prepared from egg lecithin and soy lecithin and reported enhanced radical-scavenging activity in both formulations. Topical application of lecithin liposomes significantly improved wound healing, with egg-lecithin liposomes showing superior results in an excision wound model compared with 1% phenytoin cream [185]. Jangde and Singh [167] developed liposomes encapsulated with quercetin using the thin film hydration method for wound healing applications, which showed sustained release of quercetin in wound areas, enhancing the healing effect. Cui et al. [186] developed Buxue-loaded liposomes using a thin-film dispersion ultrasonic method and incorporated them into a thermosensitive gel for topical delivery. Liposomes showed sustained release of *Danggui Buxue* decoction in the excision wound model system, accelerating wound closure by stimulating angiogenesis and collagen synthesis via upregulation of VEGF/PI3K/Akt and TGF-β/Smads signaling pathways. Castangia et al. [187] developed biocompatible quercetin- and curcumin-loaded nanovesicles (liposomes and PEG-PEVs) for the treatment of chronic skin damage. The vesicles were spherical, multilamellar, and nanosized (112–220 nm), indicating good stability and suitability for topical delivery. In vitro and in vivo studies showed significant anti-inflammatory effects, with strong inhibition of myeloperoxidase activity and reduced lesion formation. PEG-PEVs notably enhanced re-epithelialization, demonstrating that nano-encapsulated polyphenols effectively protect and restore damaged skin tissue. Curcumin-loaded liposomes showed enhanced scar treatment and accelerated wound healing more effectively than curcumin nanoplexes in vivo [187,188].

Despite several advantages, conventional liposomes have certain limitations, such as an inability to incorporate poorly water-soluble drugs and quick release of hydrophobic compounds from the lipid bilayer, which reduces their therapeutic efficiency [189]. In addition, traditional liposomes exhibit limited skin penetration, as they mainly deposit drugs on the skin surface and cannot effectively cross the stratum corneum due to the rigidity of their lipid bilayer. To overcome these limitations, advanced vesicular systems such as ethosomes and transferosomes have been developed. These systems possess greater deformability, enabling better interaction with skin structures and improved penetration through the stratum corneum [190].

8.2. Transferosomes

Transferosomes are ultra-deformable phospholipid vesicles that exhibit greater flexibility than conventional liposomes. Deformable liposomal vesicles, commonly used in topical drug delivery for skin regeneration and wound healing, achieve this enhanced elasticity. Due to their flexible structure and high elasticity, transfersomes can easily pass through the skin barrier and

deliver therapeutic agents, including drugs and herbal extracts, into deeper skin layers. Their unique composition enhances skin permeability and drug absorption, allowing a greater amount of the active compound to accumulate at the target site. As a result, topical vesicular formulations can improve therapeutic effectiveness while minimizing systemic side effects. The incorporation of elasticity-enhancing components in the vesicle membrane further increases their deformability, enabling efficient penetration through the skin and promoting faster wound healing [191]. For example, Manconi and colleagues investigated the application of baicalin-loaded transfersomes for wound treatment. Their study demonstrated that baicalin, a bioactive compound with anti-inflammatory and skin-regenerative properties, showed improved therapeutic performance when delivered through a nanohydrogel-based transfersome system. The core–shell gellan transfersomes enhanced baicalin deposition in deeper skin layers, increasing its accumulation in the dermis by approximately 8%. This improved penetration was associated with a reduction in inflammation and enhanced repair of damaged skin tissue in experimental models, indicating the potential of baicalin-loaded transfersomes as an effective strategy for wound healing [192].

8.3. Herbosomes

Herbosomes, also known as phytosomes, are advanced drug delivery systems composed of phospholipids (such as lecithin or phosphatidylcholine) complexed with plant-derived bioactive compounds. In these systems, phospholipids form hydrogen-bond interactions with herbal constituents, creating stable complexes that enhance the bioavailability and stability of phytochemicals. Unlike conventional liposomes, in which the active compound is enclosed within the aqueous core or lipid bilayer, phytosomes integrate the plant-derived active molecules directly into the phospholipid membrane, forming stable phyto-phospholipid complexes. This interaction typically occurs between phosphatidylcholine and polyphenolic compounds such as flavonoids, tannins, terpenoids, or xanthones that contain active hydrogen groups (e.g., –OH, –COOH, $–NH_2$). Compared with conventional herbal formulations, phytosomes show improved absorption and skin permeability, particularly in topical applications. This enhanced delivery increases the therapeutic effectiveness of plant extracts while allowing the use of lower doses due to improved bioavailability [193].

Mazumder et al. [194] developed sinigrin–phytosome complexes, which demonstrated enhanced wound healing activity compared with free sinigrin or blank phytosomes. The formulation achieved about 50% wound closure at a lower concentration (0.07 mg/mL) and complete wound closure at a higher concentration (0.14 mg/mL), indicating improved therapeutic efficacy. This enhanced activity was attributed to the increased permeability of sinigrin across the stratum corneum, which facilitated better delivery of the bioactive compound to the wound site. Darvishi et al. [178] developed a phytosome containing *A. vera* and L-carnosine extracts, which showed promising wound healing effects in conditions associated with impaired angiogenesis in type II diabetes. Similarly, gold nanoparticle phytosomes loaded with *C. officinalis* extract exhibited antioxidant and wound-healing properties [179]. Another study reported enhanced wound repair using a phytosomal formulation of *M. oleifera* extract, indicating the potential of phytosomes as effective carriers for plant-derived bioactives in wound healing applications [177].

Liposomes containing glycerol as a penetration enhancer are termed glycerosomes, which were prepared by replacing glycerol with water in a conventional liposome formulation. Glycerol in the formulations improves skin hydration and alters the structure of the stratum corneum, allowing better penetration and accumulation of active compounds in different skin layers. Studies have indicated that glycerosomes loaded with herbal extracts such as *Hypericum scruglii*, *C. limon* var. *pompia*, *T. capitatus* oil, and *R. officinalis* extract improved stability, antioxidant activity, and delivery of bioactive compounds to wound sites [182–184,195].

Glycethosomes are another modified phytosome that combines glycerol and ethanol to improve skin hydration and penetration. For example, mangiferin-loaded glycethosomes have demonstrated improved wound healing in experimental skin inflammation models [196].

Similarly, hyalurosomes, containing sodium hyaluronate, provide greater mechanical stability and prolonged residence time on the skin, improving drug retention and preventing leakage. These systems have been successfully used to deliver plant extracts such as *G. glabra*, and curcumin for wound healing applications [171,173]. Penetration enhancer vesicles (PEVs) are another vesicular system that incorporates compounds such as polyethylene glycol, ethanol, or propylene glycol to improve skin penetration of essential oils.

Marinosomes, composed of marine lipids rich in omega-3 and omega-6 fatty acids, help reduce inflammation, oxidative stress, and abnormal cell proliferation [197]. Sphingosomes, formed from sphingomyelin lipids, enhance skin hydration by increasing ceramide levels, thereby supporting skin barrier repair and regeneration [198].

8.4. Ethosomes

Ethosomes are multilamellar lipid vesicles considered the third generation of elastic lipid carriers, widely used for topical drug delivery, and composed of phospholipids (e.g., phosphatidylcholine), high concentrations of ethanol (20–50%); small amounts of alcohols such as propylene glycol or isopropyl alcohol; cholesterol; and water. Ethanol acts as a strong permeation enhancer, increasing the flexibility, softness, and deformability of the vesicles while also giving them a negative surface charge that reduces aggregation and improves stability. As a result, ethosomes often have smaller particle sizes, higher drug entrapment efficiency, and better stability than conventional liposomes [190].

Ethosomes enhance skin delivery through two mechanisms, such as the "ethanol effect," which disrupts the tightly packed lipid structure of the stratum corneum, increasing membrane fluidity, and the "ethosome effect," which allows the flexible vesicles to fuse with skin lipids and penetrate deeper layers of the skin. This combined action makes ethosomes very promising for wound healing because they can efficiently deposit and control the release of phytochemicals and drugs into the dermis. Studies have explored ethosomes for wound care, including formulations containing Fraxinus angustifolia extract, curcumin, and piroxicam, which demonstrated improved topical delivery and therapeutic effects. Currently, ethosomes are widely investigated for local and systemic transdermal drug delivery [199]. A related system, transethosomes, is formed by adding surfactants to ethosomes, which act as edge activators, increasing vesicle deformability and transdermal penetration. However, some studies report that surfactant-based nanocarriers may cause skin irritation or inflammation, highlighting the need for careful formulation design.

8.5. Niosomes

Niosomes are novel vesicular drug delivery systems, also known as non-ionic surfactant vesicles, composed of surfactant (e.g., Span™ 60) and cholesterol, which self-assemble to form stable vesicles. They are capable of encapsulating both lipophilic and hydrophilic phytochemicals. Lipophilic compounds are incorporated within the vesicular bilayer membrane, while hydrophilic compounds are enclosed in the aqueous core. This dual loading capability makes niosomes versatile carriers for various bioactive molecules. Unlike liposomes that rely on phospholipids, niosomes are considered more cost-effective and chemically stable, with improved storage stability and longer shelf life. In addition, these vesicles protect the encapsulated therapeutic agents and enable controlled drug release and improved skin penetration, enhancing the effectiveness of topical treatments [200]. Several studies have demonstrated the potential of niosomes in wound healing applications. For example, a niosomal gel containing anthocyanin extract showed enhanced topical delivery, anti-inflammatory effects, and accelerated oral wound

healing in rat models. Similarly, niosomal formulations loaded with herbal extracts such as *H. perforatum*, *C. officinalis*, and propolis have shown promising therapeutic outcomes, highlighting their potential as effective nanocarriers for wound-healing therapies [201].

8.6. Cubosomes

Cubosomes, the cubic phase particles, are advanced lipid-based nanocarriers that serve as promising alternatives to conventional vesicular systems such as liposomes. These nanoparticles are formed from self-assembled liquid crystalline structures, typically composed of water and glyceryl monooleate, which create a bicontinuous cubic phase. Cubosomes maintain the structural advantages of cubic liquid crystals while exhibiting lower viscosity, making them suitable for pharmaceutical formulations. Because glyceryl monooleate can undergo lipolysis, cubosomal systems are biodegradable and biocompatible. Cubosomes possess a unique three-dimensional nanostructure with interconnected hydrophilic and hydrophobic domains, a large surface area, and strong bioadhesive properties. These features enable them to encapsulate hydrophilic, lipophilic, and amphiphilic drugs, making them versatile carriers for topical drug delivery. Their structure also allows sustained drug release and improved interaction with biological tissues [202], which enhances the efficacy of the drug delivery system and minimizes side effects associated with rapid drug release.

Thakkar et al. [203] reported that cubosomal hydrogel containing silver sulfadiazine and *A. vera* showed significantly improved healing of infected burn wounds compared with formulations containing silver sulfadiazine alone. Rehman et al. [204] fabricated a hesperidin-loaded cubogel, which showed superior wound contraction ability within 14 days under in vivo conditions compared to hesperidin alone. These findings demonstrate the potential of cubosomal nanosystems as effective carriers for wound healing applications.

9. Inorganic Nanocarriers

Green synthesis has emerged as an innovative approach for nanoparticle synthesis in the biomedical field owing to its affordability, scalability, biocompatibility, eco-friendly nature, cost-effectiveness, and simplicity. Phyto-mediated synthesis utilizes aqueous extracts of various parts of plants such as leaves, roots, fruits, and seeds rich in phytochemicals, including flavonoids, phenolics, alkaloids, and terpenoids, which act as reducing and stabilizing agents, facilitating the conversion of metal ions into nanoparticles and attenuating aggregation [205].

The size, shape, morphology, and function of the nanoparticles are influenced by the choice of the plant species, the extraction technique, and the concentration of bioactive molecules. Plant-mediated synthesis is compatible with a broad spectrum of metal precursors, such as noble metals, other metal oxides, etc. Synthesis is based on the redox properties of the bioactive metabolites in which the reducing agent donates electrons to the metal ion, reducing it to a zerovalent nanoparticle size, while the other metabolites, such as proteins and polysaccharides, act as capping agents stabilizing the synthesized nanoparticles. Green-synthesized metal nanoparticles (G-MNPs; MNPs) have received considerable attention in wound healing due to their strong antimicrobial, anti-inflammatory, and regenerative properties. Their antibacterial activity can be tailored by modifying physicochemical characteristics such as particle size, surface coating, and chemical composition. Compared with conventional antibiotics, metal nanoparticles are less likely to induce bacterial resistance and can also function as drug delivery systems, where therapeutic agents are encapsulated or attached to the nanoparticle surface. However, careful evaluation of their cytotoxicity is necessary, as their small size allows them to cross cellular membranes and accumulate in subcellular structures, potentially leading to genotoxic or immunotoxic effects. G-MNPs, such as silver (AgNPs), gold (AuNPs), and zinc oxide

(ZnONPs), have shown significant potential in enhancing wound healing due to their antibacterial, anti-inflammatory, pro-angiogenic, and collagen-stimulating properties [206].

9.1. Representative Inorganic Nanoparticles in Wound Healing

9.1.1. Silver Nanoparticles (Ag NPs)

Among metallic nanomaterials, AgNPs have received much attention due to their broad-spectrum antibacterial activity against both Gram-positive and Gram-negative bacteria, as well as antifungal and antiviral effects. AgNPs can be easily incorporated into wound dressings to enhance antimicrobial protection and accelerate healing. AgNPs exhibit broad-spectrum antimicrobial activity against Gram-positive and Gram-negative bacteria, antifungal effects against *Aspergillus niger* and *Candida albicans*, and antiviral activity against viruses such as human immunodeficiency viruses, hepatitis B virus, and herpes simplex virus [207].

AgNPs have limited penetration into bacterial biofilms and tend to accumulate on the biofilm surface, which may reduce their diffusion and antibacterial efficiency [208]. AgNPs possess several advantages for wound care, including ease of large-scale synthesis, high surface reactivity allowing surface modification, compatibility with various wound dressing materials, and anti-inflammatory effects [209]. Green-synthesized AgNPs derived from *Catharanthus roseus* and *A. indica* have been reported to enhance collagen deposition and antioxidant activity in mouse models, resulting in accelerated wound closure and improved re-epithelialization [210].

AgNPs have also been successfully incorporated into advanced wound dressing materials. For example, collagen-coated nanofiber membranes functionalized with AgNPs demonstrated strong antimicrobial protection against antibiotic-resistant pathogens such as *P. aeruginosa* and vancomycin-resistant *Enterococcus* [211]. Similarly, AgNPs synthesized from matcha green tea and embedded in chitosan-alginate hydrogels significantly enhanced antibacterial activity against multiple bacterial and fungal strains, highlighting their potential for improving wound dressing performance [212].

9.1.2. Copper Nanoparticles (CuNPs)

Copper plays an important role in all stages of wound healing by stimulating the release of key growth factors, such as platelet-derived growth factor, fibroblast growth factor, TGF-β, and nerve growth factor, which support tissue regeneration. It also promotes the expression of structural proteins, such as collagen and elastin, which contribute to tissue remodeling. In addition to their regenerative properties, CuNPs and copper oxide nanoparticles exhibit strong antibacterial activity, making them promising materials for wound care applications [213,214]. Several studies have explored the incorporation of CuNPs into wound dressing materials. For instance, hydrogels loaded with ultra-small CuNPs were shown to accelerate diabetic wound closure in rat models by promoting angiogenesis through stimulation of VEGF and activation of the copper transporter [215]. Similarly, cotton fabrics coated with CuNPs and reduced graphene oxide demonstrated strong antibacterial activity against multiple pathogens, including *E. coli* and *Corynebacterium xerosis*, and effectively inhibited biofilm formation [216]. In another study, nanofibrous wound dressings composed of polylactic acid, chitosan, and CuNPs exhibited enhanced antibacterial activity against both Gram-positive and Gram-negative bacteria. However, careful control of CuNP concentration is essential, as excessive levels may lead to cytotoxic effects [217], which can compromise the effectiveness of the wound dressings and pose risks to patient safety.

9.1.3. Gold Nanoparticles (AuNPs)

AuNPs, despite their high cost, possess multifaceted beneficial properties such as antioxidant, antimicrobial, and anti-inflammatory activities, which contribute to improved wound repair. Additionally, AuNPs can stimulate the secretion of growth factors and

cytokines such as VEGF, Interleukin-12 (IL-12), Interleukin-8 (IL-8), and TNF-α, promoting angiogenesis and tissue regeneration [218]. Surface modification of AuNPs has been widely explored to enhance their biological activity and cellular uptake. For instance, collagen-I-coated AuNPs demonstrated accelerated wound closure and increased expression of VEGF and basic FGF in vitro, indicating enhanced tissue regeneration due to improved cellular interaction [219]. Meng et al. [220] developed chitosan-modified AuNPs incorporated into gelatin–sodium alginate hydrogels, which showed strong antibacterial activity against MRSA, *E. coli*, and *S. aureus*, along with anti-inflammatory effects in vivo. AuNPs have also been incorporated into advanced wound dressings, such as chitosan methacryloyl hydrogels loaded with AuNPs and soy isoflavones, which demonstrated enhanced antibacterial activity and promoted angiogenesis, suggesting their potential as multifunctional wound dressing materials [221].

9.1.4. Zinc Oxide Nanoparticles (ZnO NPs)

ZnONPs have attracted considerable attention due to their biocompatibility, stability, and cost-effectiveness. Zinc also shows minimal interaction with most pharmaceutical compounds, allowing ZnONPs to be combined with other wound-healing agents [222]. ZnONPs exhibit strong antimicrobial activity against both Gram-positive and Gram-negative bacteria, including multidrug-resistant strains, as well as antifungal and antiviral effects. In addition, their anti-inflammatory properties make them promising candidates for wound healing therapies [223]. For example, ZnONPs have shown effective antibacterial activity against MRSA and significantly improved the healing of MRSA-infected wounds in rabbit models [224]. ZnONPs have also been incorporated into advanced wound dressings to enhance therapeutic performance. A multifunctional hydrogel composed of gelatin, tannic acid, oxidized sodium alginate, and ZnONPs demonstrated strong antibacterial activity and improved wound healing. In addition, the presence of ZnONPs promoted fibroblast attachment and proliferation, further supporting tissue regeneration in experimental models [225]. Although metal and metal oxide nanoparticles represent promising nanomaterials for advanced wound dressings and therapeutic systems due to their combined antimicrobial, anti-inflammatory, and tissue-regenerative properties, studies regarding safety, dosage, and long-term clinical applicability are necessary. Table 4 summarizes an overview of green-synthesized metal- and metal oxide-based nanoparticles for wound healing applications.

Table 4. Plant-mediated synthesis of metal and metal oxide nanoparticles for wound healing applications.

Metal Nanoparticle	Plant Source	Phytochemical	Biological Functions	Wound-Healing Property	Reference
Silver nanoparticles (AgNPs)	*C. roseus*	Alkaloids, flavonoids, phenolics	Antibacterial, antioxidant	Increased collagen deposition and accelerated wound closure	[210]
	A. indica	Terpenoids, flavonoids, phenolics	Antimicrobial, anti-inflammatory	Promotes re-epithelialization and tissue regeneration	[210]
	Ocimum sanctum	Flavonoids, polyphenols	Antibacterial, antioxidant	Enhances fibroblast proliferation and wound contraction	[226]
	M. oleifera	Polyphenols, proteins	Antioxidant, antimicrobial	Improves tissue repair and cellular regeneration	[227]

Table 4. *Cont.*

Metal Nanoparticle	Plant Source	Phytochemical	Biological Functions	Wound-Healing Property	Reference
Gold nanoparticles (AuNPs)	*A. vera*	Polysaccharides, phenolics	Anti-inflammatory, antioxidant	Promotes angiogenesis and fibroblast migration	[228]
	Camellia sinensis	Catechins, flavonoids	Antioxidant, antimicrobial	Supports wound contraction and collagen formation	[229]
	Brassica oleracea	Flavonoids and isothiocyanides	Antioxidant, Antimicrobial	Enhanced collagen deposition and complete epithelialization.	[230]
Zinc oxide nanoparticles (ZnONPs)	*Gliricidia sepium*	Apigenin-7-O-glucoside, kaempferol, protocatechuic acid	Anti-inflammatory, antibacterial	Accelerates diabetic wound healing and reduces inflammation	[231]
	Ficus religiosa	Phenolics, tannins	Antimicrobial, antioxidant	Enhances collagen synthesis and tissue remodeling	[232]
Copper oxide nanoparticles (CuONPs)	*M. oleifera*	Polyphenols, flavonoids	Antibacterial, pro-angiogenic	Stimulates growth factor release and wound closure	[233]
Titanium dioxide nanoparticles (TiO_2 NPs)	*A. indica*	Phenolic compounds	Antimicrobial	Prevents infection and supports wound healing	[234]

Despite the promising therapeutic potential of inorganic nanoparticles such as AgNPs, AuNPs, and ZnONPs, their safety profile remains a critical concern that may limit clinical translation. Nanoparticle-induced toxicity is strongly influenced by physicochemical properties, including particle size, morphology, surface charge, concentration, and surface functionalization [206]. Smaller nanoparticles exhibit higher cellular uptake and surface reactivity, which may lead to increased cytotoxicity through the generation of ROS, mitochondrial dysfunction, and potential DNA damage. For instance, AgNPs, while demonstrating broad-spectrum antimicrobial activity, have been reported to accumulate at biological interfaces and may induce oxidative stress and inflammatory responses at elevated concentrations [207,208].

Similarly, ZnONPs can release Zn^{2+} ions, contributing to cytotoxic effects through oxidative stress mechanisms and disruption of cellular homeostasis [206]. Although AuNPs are generally regarded as more biocompatible, concerns remain regarding their long-term accumulation, cellular internalization, and potential interference with intracellular signaling pathways [206]. In addition, the ability of nanoparticles to interact with and penetrate biological barriers raises important considerations regarding biodistribution, persistence, and possible systemic toxicity, particularly in relation to their long-term effects on human health and the environment.

To address these challenges, recent approaches emphasize the development of safer nanomaterials through green synthesis and surface modification strategies using plant-derived phytochemicals, which act as reducing and stabilizing agents and may improve biocompatibility [205,206]. Furthermore, optimizing nanoparticle dose, controlling physicochemical characteristics, and integrating nanoparticles into biocompatible matrices such as hydrogels or nanofibers can reduce toxicity while preserving therapeutic efficacy [209–212]. Overall, while inorganic nanoparticles offer significant advantages in wound healing applications, careful evaluation of their safety profile is essential to ensure successful clinical translation.

10. Major Possible Mechanisms

The mechanism behind the wound-healing ability of nanoparticles involves the following major activities (Figure 5).

Bactericidal activity: Microbial infection is the major barrier to wound healing, which complicates and delays the healing process. Green-synthesized MNPs attenuate bacterial infection through various mechanisms, including (a) disruption of the bacterial cell membrane, which leads to a loss of structural integrity and ultimately cell death; (b) triggering the generation of ROS, resulting in oxidative stress-mediated damage to biomolecules such as lipid peroxidation, protein degradation, and DNA fragmentation that lead to apoptosis; and (c) interference with DNA replication and protein synthesis by MNPs, which prevents microbial proliferation. Green-synthesized MNP attenuates bacterial growth at the wound site, reducing complication risk and promoting faster healing [235,236].

Anti-inflammatory activity: Inflammation is a double-edged sword that plays a vital role in the wound-healing process; however, an excessive inflammatory process hinders the tissue repair, leading to chronic wounds. MNPs regulate the inflammatory process by suppressing pro-inflammatory cytokines associated with prolonged inflammation, such as TNF-α, IL-6, and IL-1β, and also by enhancing the expression of anti-inflammatory cytokines like IL-10, ensuring a balanced immune response. In addition, some nanoparticles, like CuO NPs, ZnO NPs, and Se NPs, combat oxidative stress by neutralizing free radicals, thereby minimizing cellular damage at the wound site. MNPs create a favorable environment for tissue regeneration by regulating the inflammatory process, leading to quicker and more efficient wound closure [237,238].

Angiogenesis: Angiogenesis is a key process in wound healing, which provides oxygen and essential nutrients for the tissue regeneration process. Certain G-MNPs, particularly AUNPs and ZnO NPs, stimulate angiogenesis by upregulating VEGF expression and improve endothelial cell proliferation and migration, thereby enhancing blood vessel development. Enhanced angiogenesis ensures an adequate supply of oxygen and nutrients for the regeneration of tissue, thereby accelerating wound closure, especially in chronic or non-healing wounds [239,240].

Collagen is a fundamental component of the ECM, providing structural integrity and tensile strength to healed tissues. MNPs promote collagen synthesis by stimulating the expression of collagen-producing genes (COL1 and COL3), enhancing fibroblast proliferation and migration, and triggering TGF-β activity leading to ECM remodeling and fibrosis. Enhanced collagen deposition by MNPs improves tissue tensile strength and structural integrity, supporting effective remodeling of the extracellular matrix, which not only accelerates healing but also contributes to reduced scar formation [240,241].

Organic nanoparticles, particularly polymeric nanoparticles (PNPs), accelerate wound healing through multiple coordinated biological mechanisms. These systems enable the controlled and sustained release of therapeutic agents, which enhance fibroblast proliferation, cell migration, and tissue regeneration [98,99]. By protecting encapsulated bioactives from enzymatic degradation (e.g., matrix metalloproteinases), PNPs maintain therapeutic efficacy at the wound site and create a favorable microenvironment for repair. In addition, their nanoscale size and high surface area facilitate enhanced penetration into biological barriers, including biofilms and damaged tissue, thereby improving antimicrobial action and reducing infection risk [100,101]. Surface functionalization, such as PEGylation or the use of cationic polymers (e.g., chitosan), further promotes interaction with microbial membranes and enhances cellular uptake, contributing to more effective pathogen elimination and tissue response [102,103].

Furthermore, organic nanoparticles actively promote key regenerative processes, including angiogenesis, collagen synthesis, and re-epithelialization, which are critical for wound closure and tissue remodeling [106]. For example, nanoparticle-mediated delivery of nitric oxide or growth factors has been shown to stimulate fibroblast proliferation, increase cytokine production

(e.g., TGF-β), and accelerate epithelial regeneration [107]. These systems also modulate the inflammatory response, preventing excessive collagen deposition and thereby reducing scar formation [108]. Phytochemical-loaded nanoparticles further enhance healing by providing antioxidant and anti-inflammatory effects, as demonstrated in systems containing asiaticoside, quercetin, or plant extracts, which improve collagen organization, reduce oxidative stress, and accelerate wound contraction in in vivo models [109–112]. Collectively, these multifunctional mechanisms position organic nanocarriers as highly effective platforms for improving wound healing outcomes (Figure 5).

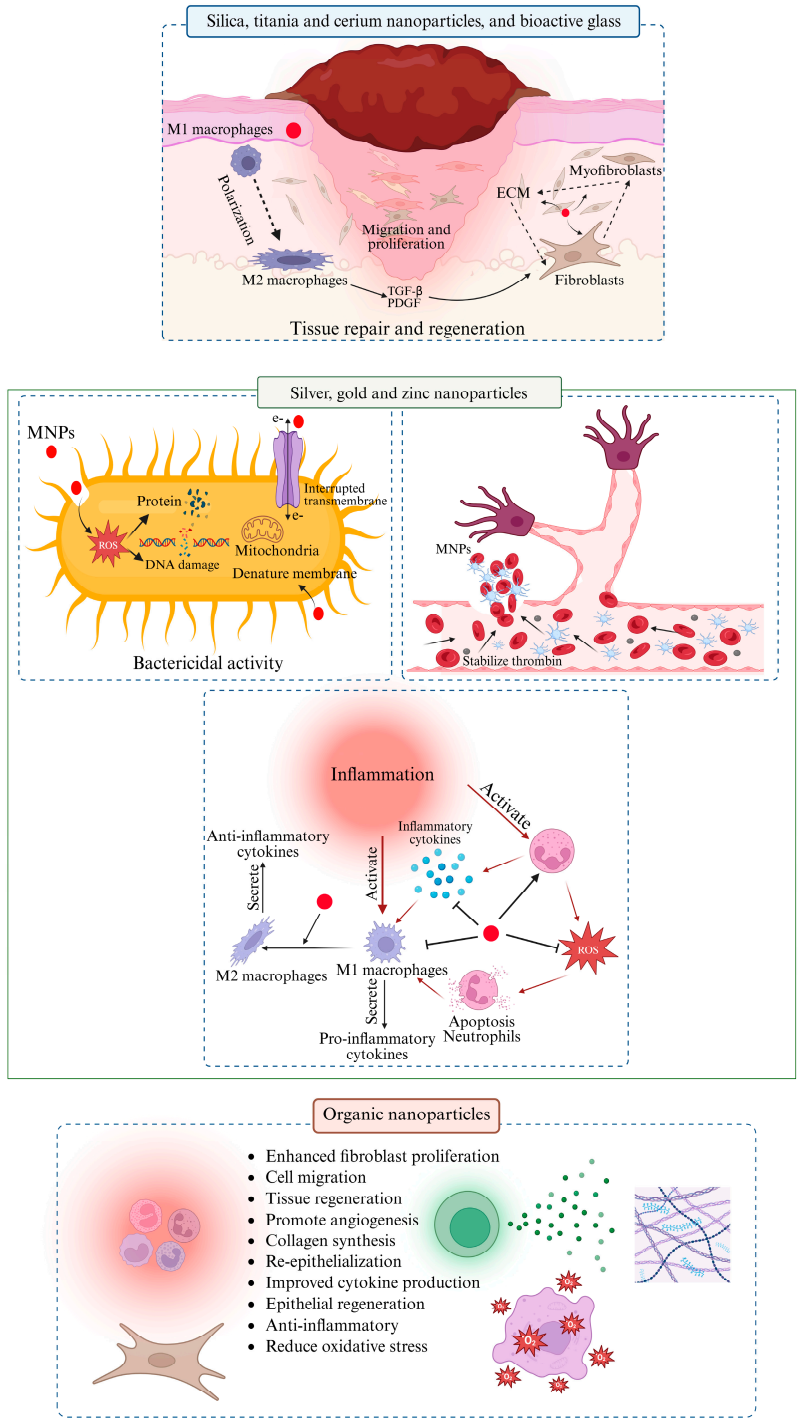


Figure 5. Possible wound healing mechanism of nanoparticles. (Recreated based on Wang et al. [242] with the Creative Commons Attribution-NonCommercial (unported, v3.0) License).

11. Phytochemical-Based Nanocarriers for Cosmetic Surgery

Phytocompounds have been employed in cosmeceuticals for decades, exhibiting potential in cosmetic applications, including sunscreen, moisturizing, anti-aging, and dermatological treatment. The principal challenges associated with phyto-based cosmeceuticals are insufficient penetration and considerable compound instability among diverse cosmetic items, which impede consistent and enhanced compound administration for dermatological treatment. Nanosized delivery technologies are currently utilized to address these limitations, enabling extended and enhanced administration of plant-derived bioactive compounds in the cosmeceutical sector and products. Nanosized phytocompounds enhance the aseptic experience in various cosmeceutical formulations, facilitating sustained administration and improved skin protection effects. To date, there is no direct clinical evidence regarding the use of phytochemical-loaded nanocarriers in cosmetic surgery. However, in vitro and in vivo experimental studies illustrate that phytochemical nanoformulations possess improved antioxidant, anti-inflammatory, and wound-healing properties, suggesting their potential as adjunctive therapeutic systems for enhancing post-cosmetic surgery outcomes, such as tissue regeneration, scar reduction, and skin rejuvenation, which are essential for treatment of breast augmentation, liposuction, facelifts, and laser resurfacing [243].

Table 5 illustrates phytochemical-loaded nanocarriers that may serve as potential adjuvants in cosmetic surgery applications. Table 6 lists commercially available nanotechnology-based products for post-surgery skin care.

Table 5. Phytochemical-loaded nanocarriers that may serve as potent adjuvants in cosmetic surgery.

Cosmetic Procedure	Phytochemical	Nanocarrier System	Role in Cosmetic Surgery/Dermatology	Reference
Breast augmentation (post-surgical healing and scar reduction)	Curcumin	Chitosan nanoparticles/SLNs	Anti-inflammatory, antimicrobial, promotes wound healing, and reduces scar formation.	[244]
Breast augmentation (skin regeneration)	Resveratrol	SLNs, nanocapsules	Antioxidant protection; stimulates collagen synthesis and tissue repair	[245]
Breast augmentation recovery	Quercetin	NLCs	Anti-oxidative and anti-inflammatory effects that reduce post-surgical inflammation	[246]
Liposuction/body contouring	*A. vera* extract	Liposomes/nanoemulsions	Enhances wound healing, improves skin hydration and regeneration	[164]
Facial cosmetic surgery (facelift, rhinoplasty healing)	Green tea catechins	Liposomes/nanoemulsions	Antioxidant activity and protection against oxidative stress in damaged skin	[247]
Scar reduction after cosmetic procedures	Genistein	Nanoemulsions	Stimulates collagen production and improves skin elasticity	[248]
Skin resurfacing/laser cosmetic procedures	Lycopene	Transfersomes/ethosomes	Photoprotection and reduction in oxidative damage	[249]
Post-surgical skin rejuvenation	Vitamin C	Liposomes/SLNs	Promotes collagen synthesis and improves wound healing	[250]

Abbreviations: SLNs: Solid lipid nanoparticles; NLCs: Nanostructured lipid carriers.

Table 6. Commercially available nanotechnology-based products used in post-cosmetic surgery skin care.

Product Name	Company/Brand	Nanotechnology System	Key Active Ingredient	Cosmetic/Post-Procedure Use	Reference
Capture Le Sérum	Dior	Nanoliposomes	Anti-aging peptides and antioxidants	Skin rejuvenation and wrinkle reduction after facial cosmetic treatments	[251]
Plénitude Revitalift	L'Oréal Paris	Polymeric nanocapsules	Retinol	Anti-aging therapy and collagen stimulation after aesthetic procedures	[252,253]
Cutanova Cream Nanorepair Q10	Dr. Rimpler	Nanostructured lipid carriers (NLCs)	Coenzyme Q10	Skin repair and anti-wrinkle care after dermatological procedures	[254]
LR Nano Gold Day Cream	LR Zeitgard	Gold nanoparticles	Nano-gold	Antioxidant protection and skin regeneration after cosmetic treatments	[253]
Nano Gold BB Cream SPF 50	Tony Moly	Gold nanoparticles	Nano-gold	Skin protection and cosmetic coverage after aesthetic skin procedures	[253]
Soleil Soft-Touch Anti-Wrinkle Sun Cream SPF 15	Lancôme	Nanocapsules	Vitamin-based antioxidants	UV protection and prevention of photodamage after laser or peeling treatments	[255]
PhytoRx UV Defense Sunblock SPF 100	Lotus Professionals	ZnO/TiO_2 nanoparticles	Mineral UV filters	Sun protectio n for sensitive skin following cosmetic dermatology procedures	[256]

Abbreviations: NLCs: Nanostructured lipid carriers; BB: Blemish Balm; SPF: Sun Protection Factor; UV: Ultraviolet radiation; ZnO: Zinc oxide; TiO_2: Titanium di-oxide.

Numerous commercial nano-cosmeceutical products employ nanoliposomes, nanocapsules, nanoemulsions, and metallic nanoparticles to improve the penetration and stability of active substances. These solutions are extensively utilized for anti-aging, photoprotection, skin hydration, and collagen stimulation, which are crucial for post-cosmetic surgery skin healing and maintenance.

12. Limitations

Despite the generally positive outcomes reported for phytochemical-based nanotherapeutics, conflicting evidence and limitations must be carefully considered. The therapeutic efficacy of nanoformulations can vary significantly depending on physicochemical properties such as particle size, surface charge, and composition, leading to inconsistent biological responses across models. In some cases, improvements in wound healing parameters are modest or not statistically significant when compared to optimized conventional treatments [91,257,258].

Moreover, while many nanoformulations enhance antimicrobial and regenerative effects, dose-dependent cytotoxicity has been reported, particularly for inorganic nanoparticles, where excessive concentrations may induce oxidative stress, inflammation, or cellular damage. Additionally, discrepancies between in vitro, in vivo, and clinical findings highlight the limitations of current experimental models, which may not fully replicate the

complexity of human wound environments [257], leading to challenges in accurately predicting the efficacy and safety of these nanoformulations in real-world applications.

Another important consideration is the lack of standardization in experimental design, including differences in wound models, evaluation methods, and outcome measures, which complicates direct comparison across studies. These inconsistencies may contribute to publication bias toward positive findings and limit the reproducibility of reported results.

Therefore, while phytochemical-based nanocarriers show considerable promise, a more critical interpretation of existing evidence is necessary, and future research should prioritize standardized methodologies, dose optimization, and rigorous validation in clinically relevant settings.

13. Future Perspectives

The integration of phytochemicals with nanotechnology represents a promising direction for next-generation wound management; however, several critical challenges must be addressed to enable successful clinical translation. One of the primary concerns is the lack of standardized regulatory frameworks for nanomaterials in dermatological and cosmetological applications. Variability in nanoparticle composition, size, surface characteristics, and synthesis methods can significantly influence safety, efficacy, and reproducibility, highlighting the need for standardized guidelines and quality control standards.

In addition, scalability and manufacturing consistency remain major barriers. While many nanoformulations demonstrate promising results at the laboratory scale, translating these systems into cost-effective, large-scale production suitable for clinical use is still challenging. The long-term safety and toxicity profiles of both polymeric and inorganic nanoparticles must also be thoroughly evaluated through well-designed preclinical and clinical studies, particularly considering their potential for bioaccumulation and systemic exposure.

Future research should focus on the development of biocompatible and biodegradable nanomaterials, moving beyond conventional polymers such as PCL, PVA, chitosan, sodium alginate, and PLGA. Emerging systems, including stimuli-responsive nanocarriers (e.g., pH-responsive and enzyme-responsive systems), offer significant potential for site-specific and controlled drug delivery, particularly in dynamic wound environments. Furthermore, lipid-based nanocarriers may enhance the penetration and retention of phytochemicals within skin layers, thereby improving the therapeutic efficacy of these compounds in treating skin conditions.

Advanced technologies such as artificial intelligence-assisted material design, predictive modeling, and smart wound dressings capable of real-time monitoring and adaptive drug release are expected to further revolutionize this field. Collectively, addressing these regulatory, technological, and translational challenges will be essential to fully realize the clinical potential of phyto-nanotechnology-based wound therapies.

14. Conclusions

Phytochemical-loaded nanotherapeutics represent a promising convergence of natural bioactives and advanced delivery technologies for improving cosmetological wound healing outcomes. By enhancing the stability, bioavailability, and targeted delivery of phytochemicals, these systems demonstrate clear advantages in modulating key healing processes, including inflammation control, angiogenesis, collagen remodeling, and re-epithelialization. Preclinical evidence consistently supports their potential to accelerate wound closure and reduce scar formation, aligning with the high aesthetic demands of cosmetic procedures.

However, despite strong mechanistic rationale and experimental support, clinical translation remains limited and uneven. The most critical challenges can be prioritized in three key areas:

(i) lack of standardized and comparable efficacy metrics, which restricts quantitative evaluation across studies;

(ii) insufficient clinical validation, with a clear gap between preclinical success and human application; and

(iii) uncertainties in long-term safety and regulatory pathways, particularly concerning nanomaterial-related toxicity and scalability.

To advance the field, future research should focus on actionable priorities: (1) establishing standardized experimental and clinical endpoints for wound healing and cosmetic outcomes; (2) conducting well-designed, adequately powered clinical trials to validate efficacy and safety; and (3) developing scalable, reproducible, and regulatory-compliant manufacturing strategies. In parallel, integrating multidisciplinary approaches such as combining nanotechnology, dermatology, and cosmetology will be essential to bridge current translational gaps, such as those between laboratory research and clinical application, ensuring that innovative treatments are effectively translated into practice.

Where available, quantitative comparisons indicate that nano-enabled systems can improve wound healing outcomes significantly over controls in preclinical models; however, variability across studies and limited clinical validation necessitate cautious interpretation of these effect sizes.

In summary, while phytochemical-based nanotherapeutics are biologically compelling and technologically advanced, their transition into routine clinical practice will depend on rigorous validation, standardization, and regulatory alignment. Addressing these priorities will be critical to transforming these systems from promising experimental platforms into reliable, evidence-based solutions for cosmetological wound management.

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