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Exploring The Role of Curcumin and Nanoformulations in the Treatment of Wound Healing

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Abstract: Wound healing is a crucial physiological process necessary for restoring skin integrity following trauma. This process involves three essential stages: hemostasis/inflammatory, proliferative, and remodeling. Extensive experimental studies and preclinical models have provided significant insights into the mechanisms underlying wound healing. Curcumin ($C_{21}H_{20}O_6$), the primary curcuminoid derived from *Curcuma longa*, a plant from the *Zingiberaceae* family, has been widely used in traditional Ayurvedic and Chinese medicine. It is a popular herbal supplement, frequently utilized as a dietary ingredient, cosmetic additive, and coloring agent. *Curcuma longa* is rich in curcuminoids, which exhibit notable therapeutic properties. In drug delivery, nano-based carriers such as solid lipid nanoparticles, nano emulsions, and liposomes are preferred due to their high drug-loading capacity, stability, and biocompatibility. This review focuses on understanding the mechanism and types of wounds, the wound healing process, and the significant impact of nanocarriers in wound healing. Additionally, it highlights the accelerated wound healing effects of curcumin at various stages of the natural healing process.

Keywords: Wound Healing, Curcumin, Curcuminoids, Nano Carriers.

1.Introduction

Curcumin ($C_{21}H_{20}O_6$) is a potent polyphenol obtained from the aromatic plant *Curcuma longa*, belonging to the Ginger family. It is one of the most well-known, widely researched, and commonly used spices in Ayurveda as well as Chinese medicine since time immemorial. It is a bright yellow chemical and a natural anti-inflammatory compound widely used for culinary purposes, as an immunity booster, and as a coloring agent. *Curcuma longa* is derived from a group of natural yellow pigments called curcuminoids. The biological activity of turmeric is primarily attributed to curcumin. Curcumin, or diferuloyl methane, has a low molecular weight and is also a lipophilic molecule [1]. Curcumin (chemical formula: $C_{21}H_{20}O_6$; (1E, 6E)-1,7-Bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-Dione) also modulates wound-healing processes [2]. It was first identified in 1815, and its crystalline form was attained in 1910, but its final identification was confirmed in 1913 [1]. Curcumin is recognized as the standard organic healing compound of turmeric, with a multitude of valuable pharmacological properties attributed to it, including anti-inflammatory, anti-cancer, anti-microbial, anti-mutagenic, anticoagulant, anti-infective, and antioxidant activities [3]. Curcumin is insoluble in both water and ether, although it can dissolve in certain organic solvents like ethanol [4]. Curcumin promotes wound healing through various processes, including granulation tissue formation, matrix protein synthesis, re-epithelialization, and collagen deposition in different types of skin wounds. The direct application of curcumin on the skin has been found to promote re-epithelialization and improve neovascularization [1]. Curcumin acts as an anti-tumorigenic agent, and numerous research studies highlight its significant cytotoxic effects on human cancer cell lines [5, 6, 7]. However, its therapeutic effectiveness is limited due to poor bioavailability and rapid elimination [8]. Nano carriers of curcumin enhance its bioavailability and facilitate its delivery to the brain for tumor treatment. To assess its impact on brain targeting and bioavailability, curcumin nano carriers containing tripalmitin, oleic acid, and polysorbate 80 are administered intraperitoneally to null mice bearing A172 xenografts [9]. Curcumin-loaded nano carriers exhibit improved pharmacokinetic properties, with the half-life of the drug increasing from 3.1 to 5.7 hours and the area under the curve (AUC) increasing 6.4-fold in blood drug levels compared to the control group [10].

2. Wounds

A wound can be defined as a disruption in the integrity of the epithelial lining of the skin due to physical

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or thermal damage. Wound healing is an intricate, complex, and dynamic process that restores cellular structures and tissue layers. It is the repair mechanism that follows an injury to the skin and other soft tissues. Following injury, an inflammatory response occurs, and the cells beneath the dermis begin to proliferate, leading to the regeneration of epithelial tissue. Biological and molecular processes involved in wound healing include coagulation, migration-proliferation, inflammation, and remodeling [11]. Depending on the duration and nature of the healing process, wounds can be classified as either acute or chronic [12, 13].

Types of Wounds: Based on healing time and method, wounds are broadly categorized into two types: acute and chronic [11].

2.1. Acute Wounds

Acute wounds result from factors such as radioactivity, corrosive chemicals, mechanical injury, heat, or electrical shock and typically require immediate treatment [11]. Cutaneous injuries do not have any underlying pathophysiological defects, allowing for rapid repair with minimal energy expenditure [14]. Acute wounds can occur due to various reasons, including surgical procedures or tissue loss. These wounds have the ability to heal naturally, following an orderly and timely healing process [15].

2.2. Chronic Wounds

Chronic wounds are often associated with specific conditions such as diabetes mellitus and do not follow the typical wound-healing process. They generally remain in the inflammatory phase for an extended period due to factors such as necrotic tissue, bacterial load, and moisture imbalance in the wound area. Additionally, chronic wounds have a high risk of recurrence unless the underlying illness is properly treated [3]. Some chronic wounds may heal within a short time, while others may take years to fully recover [16]. In chronic wounds with pre-existing physiological abnormalities, developmental variations may not occur, leading to impaired healing [17]. Chronic wounds are more prevalent in the elderly population [18]. Studies show that approximately 3% of individuals over the age of 65 in the United States suffer from open wounds. The U.S. government estimates that by 2060, the elderly population will exceed 77 million, suggesting that chronic wounds will continue to pose a significant healthcare challenge [19]. Currently, around 2% of the total U.S. population is affected by chronic wounds [20]. It is predicted that the impact of chronic wounds will continue to rise globally [21].

Wound Classification Based on Depth: Wounds can also be categorized based on their depth [22]

1. **Superficial wounds** – Do not extend beyond the epidermis.
2. **Partial-thickness wounds** – Affect the epidermis and deeper dermal layers.
3. **Full-thickness wounds** – Extend beyond the subcutaneous fat, severely damaging deeper tissues [22].

3. Wound Healing Process

Wound healing is a vital yet complex process in both humans and animals, involving a series of intricate steps that occur sequentially. This process consists of three primary phases: the hemostasis/inflammation phase, the proliferative phase, and the remodeling phase [23].

3.1. Hemostasis/Inflammation Phase

Immediately after an injury, the process of hemostasis is initiated. The primary goal of this mechanism is to prevent excessive blood loss (exsanguination) [24, 25]. This phase begins instantaneously upon wounding through vascular contraction and fibrin clot formation. Growth factors such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF) are released as a result of clot formation and from various wound tissues [26].

3.2. Proliferative Phase (Wound Damage Repair)

The most prominent cell types involved in dermal repair are fibroblasts and endothelial cells, which promote capillary growth, collagen synthesis, and granulation tissue formation at the site of injury. Fibroblasts, the principal components of the extracellular matrix, produce collagen and proteoglycans at the wound bed. The

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proliferative phase is marked by active cell division, which is essential for tissue regeneration. This phase may continue for an extended period, eventually leading into the final remodeling stage.

3.3. Remodeling Phase

During the remodeling phase, many newly formed capillaries degrade, and the vascular density of the wound returns to normal. A crucial aspect of this phase is the reorganization of the extracellular matrix to resemble the architecture of normal tissue. Throughout the wound healing process, the wound also undergoes physical contraction, which is believed to be facilitated by the appearance of contractile fibroblasts. This is the final phase of wound healing, where granulation tissue gradually diminishes. The dermal vasculature, epidermis, and myofibrils are remodeled, ultimately resulting in the formation of functional tissue [27, 28].

Factors Affecting Wound Healing: Wound healing is influenced by various **local** and **systemic** factors [29].

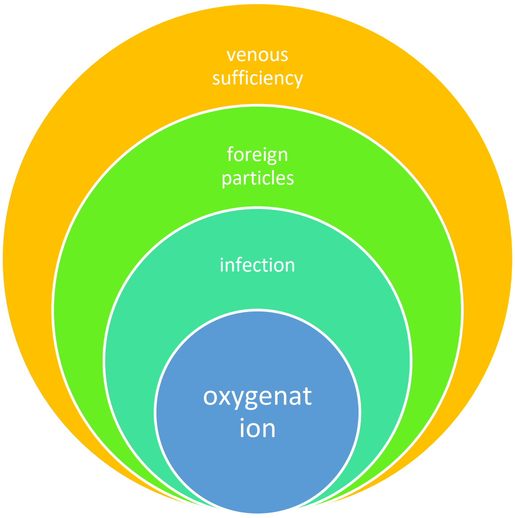

Fig. 1) Systemic factors affecting wound healing

4. Local Factors Affecting Wound Healing

Methods for Preparing Nano Carriers

1. High-pressure homogenization technique
2. Cold homogenization
3. Hot homogenization technique
4. Microemulsion technique
5. Melting dispersion method
6. High-shear homogenization or ultrasonication
7. Solvent emulsification evaporation technique

The smaller size of lipid particles ensures close contact with the upper layer of the skin, thereby enhancing drug penetration into the mucosa or skin.

5. Role of Curcumin in Wound Healing

In line with the ongoing research on “Curcumin in Health and Disease,” it is essential to emphasize the beneficial properties of curcumin, a natural polyphenol obtained from the root of *Curcuma longa*. Curcumin has therapeutic potential due to its antioxidant and anti-inflammatory properties [30]. Although curcumin is effective against various human disorders, its limited bioavailability—caused by poor absorption, rapid metabolism, and quick systemic elimination—hinders its therapeutic efficacy [31]. To address this, various strategies have been developed to enhance curcumin’s bioavailability. One common approach involves using metabolic pathway inhibitors to prevent curcumin’s rapid breakdown. The combined effect of piperine, a known inhibitor of hepatic

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and intestinal glucuronidation, has been studied to assess curcumin's bioavailability in healthy individuals [32].

Aim	Methodology	Result	Reference
1)To study the effect of water solubility as well as stability of curcumin on wound healing	*1)Formation of Nano micelles in aqueous medium 2)Conjugate to hyaluronic acid*	*Curcumin was found more active in wound healing when used by HA acid*	[33]
2To study and demonstrate the effect of antibacterial property of curcumin in wound healing	*Exhaustion method was used for different chemicals derivative so that there is increment in its solubility and cell uptake of curcumin also*	*Curcumin with hydrogel silver nanoparticles when used increase the function of hydrogel silver Nano composite for wound dressing 2)Complex of curcumin with cobalt nanoparticles showed strong antibacterial activity in wound healing against E.coli*	[34]
3)To study the Nano formulated curcumin effect on wound healing	*Spinning solution was made by mixing 1g gelatin and 0.1 g curcumin in 10ml tri fluro ethanol. During electro-spinning process, spinning solution was filled into syringe with help of gauge nozzle away from an aluminum foil wrapped copper plates.*	*Crystalline peaks of curcumin disappear in the range of blended NMs and indicate that curcumin exist in amorphous Nano solid dispersion after electro spinning.*	[35]
4)To study combine effect of curcumin and piperine in wound healing	*Rotatory evaporation technique was used where lipids including tripalmitin ,di palmitoyl phosphatidylcholine and cholesterol together with curcumin or piperine were dissolved in organic solvent and then ultrasonication bath replaced the final extrusion step*	*It was found that in human being taking 2gm of curcumin alone, serum level was signficantly low in them but when given with 20 mg of piperine then its bioavailability in wound healing was found to be increased*	[36]
5) To study the effect of curcumin when applied topically to standardized wounds than diketonic natural curcumin in accelerating reepithelization	*A novel triketonic chemically altered cur cumin was tested for effectiveness in healing*	*It wa found that 1% suspension of chemically modified curcumin was more effective when applied topically to wounds than diketonic natural curcumin*	[37]
6)To study the effect of curcumin when loaded into chitosan and gelatin sponge in wound healing	*Agar diffusion method using Pseudomonas aeruginosa*	*More amount of gelatin in composite sponge was found to exhibit faster release up to 240 minutes in wound healing*	[38]
7) To study the role of curcumin containing ethanolic extract in wound healing using aspirin	*Crystallization ,phytochemical screening*	*Result of aspirin on wound healing obstruction was lessened by using ethanolic extract due to presence of curcumin*	[39]
8)To prepare curcumin Nano emulsion and study its effect in wound healing and inflammation	*Ultrasonication method was used with different oil like almond oil , clove oil*	*Cu NPs play an important role in wound healing and also has anti-inflammatory effects ,demonstrating potential as*	

	and surfactant like tween 80 and PEG 400as co surfactant An aquous micro titration method with high energy ultrasonication was used to prepare cu Ne	*Nano formulation for useful and non-hazardous transdermal delivery*	[40]
9) To study the activity of curcumin loaded Nano films for wound healing	*Nano films of curcumin was prepared by solvent evaporation method using chitosan ,glutaraldehyde ,hydroxyl propyl methylcellulose*	*Better efficacy of prepared Nano films was attributed due to presence of curcumin and chitosan*	[41]
10)To study the effect of silver NPs using curcumin cyclo dextrin's loaded into bacterial cellulose based hydrogel in wound healing	*The method involved bio reduction of AgNo3 with aqueous solution of* CUR:HPβCD *resulting in Nano particle formulation*	It was found that Ag NPs can be successfully synthesized, following the green chemistry approach using CUR:HPβCD and loaded in BC to produce hydrogels with a potential wound-dressing application	[42]

6. Nano Carriers in Wound Healing

Nanoparticles, also known as ultra-microparticles, range in size from 1 to 1000 nm, placing them in the transitional region between atomic clusters and macroscopic objects [43]. Due to their unique properties, nanoparticles can be used to treat various types of wound infections. Consequently, many researchers are exploring better alternative therapeutic methods. Plant-based nanoparticle synthesis is generally stable, fast, and cost-effective. Additionally, nanoparticles can be synthesized with diverse structures [44]. Various structural and chemical compositions of nanoparticles allow for numerous applications [45]. The synthesis of different types of nanoparticles involves several techniques, including **physical methods** (e.g., pulsed wire, ball milling, mechanochemical synthesis), **chemical methods** (e.g., microemulsion, chemical reduction, electrochemical, solvothermal decomposition), and **biological methods** (e.g., plant extracts, bacteria, yeast) [46]. Carbon hydrogels exhibit long-term and broad-spectrum antibacterial activity [47]. Iron oxide nanoparticles are easy to synthesize, biodegradable, and low in toxicity, while also possessing antibacterial properties [48]. Copper nanoparticles (*Cu NPs*) are used in both direct and modified applications. Klinkajon et al. developed a copper alginate hydrogel using alginate, and the results demonstrated that the gel exhibited significant antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus epidermidis*, and *Streptococcus*. This antibacterial effect was proportional to the concentration of Cu^{2+} ions [49]. Chen et al. synthesized silver nanoparticles (*AgNPs*) using a green reducing agent (egg white) and subsequently combined them with konjac glucomannan (KGM) powder to prepare a KGM/AgNPs composite sponge [50]. The combined application of chitosan and AgNPs enhances their individual antibacterial properties, further improving the overall antiseptic effect [51]. Besides ZnO, emerging nanoparticles such as TiO_2, CeO_2, and Fe_2O_3 also play a role in skin wound healing. TiO_2, in particular, exhibits excellent biocompatibility and water retention properties, which can promote wound healing [52, 53].

Due to their chemical properties and resistance to surface modifications, gold nanoparticles (*Au NPs*) are widely used in medical applications, including wound healing. Before use in wound healing applications, AuNPs often require fusion or surface modification with other biomolecules. For instance, the addition of polysaccharide peptides to AuNPs enhances their ability to promote healing [54]. Gold nanoparticles function as antioxidants by inhibiting free radicals such as hydroxyl, nitric oxide, and hydrogen peroxide [55]. When applied to cutaneous wounds, AuNPs increase angiopoietin and collagen expression while decreasing *TGF-β* levels [56]. Beyond wound healing, gold nanoparticles are also used in cancer therapy, biosensing, gene and drug delivery, imaging, and biocompatibility studies [57]. Additionally, an antibiotic-coated gold nanoparticle-doped PCL/gelatin nanofiber mat was tested on infected full-thickness wounds, resulting in reduced bacterial infection and an accelerated healing process [58]. Silver nanoparticles (*AgNPs*) are considered less toxic to mammalian cells compared to other metal nanoparticles. Due to their relatively small size, AgNPs can easily penetrate cells through the cell membrane, making them a potential antimicrobial agent [59]. Ferulic acid, recognized for its numerous pharmacological properties—including antimicrobial, anti-inflammatory, anticancer, anti-arrhythmic, anti-diabetic, and immune-stimulating activities—is a potent antioxidant with low toxicity. It also helps reduce nerve cell damage and may support the healing of injured nerve cells [60, 61]. Specifically, the induction of collagen types I and III, the stimulation of fibroblast proliferation, and wound contraction observed in *in vitro* studies can be attributed to the essential oil's major anti-inflammatory, antibacterial, and antioxidant constituents [62, 63, 64, 65]. Lavandula essential oil is believed to promote better and faster wound healing, most likely due to its ability to enhance granulation tissue formation via platelet-derived growth factors (PDGFs) and stimulate re-epithelialization through epidermal growth factors (EGFs) [66]. Additionally, drug encapsulation in nano carriers can protect drugs from instability, significantly improving their effectiveness [67]. Common nanoparticle preparation methods include **mechanical milling, laser ablation, and ion sputtering** [68, 69, 70].

1) To study how nano collagen containing silver nanoparticles increase regeneration of wound healing as compared to collagen microfibers	*Collagen was extracted from scales of Catla fish and made into nanocollagen with the help of ultrasonication method and nanocollagen with Ag NPs subjected to MTT assay using enhanced concentration*	*Silver nanoparticles possess great medicinal potential, so can be used for both infected diabetic ulcer wound healing Silver Nano particles have antimicrobial resistance and biocompatible wound healing property also*	[71]
2)To evaluate antimicrobial, antioxidant and wound healing properties of photosynthesized NPs	*Au NPs were synthesized through aqueous okra extract with help of citrate synthesis method Different groups such as hydroxyl group,carboxyl groups were used*	*Au NPs act as antioxidant as well as in cancer therapy Okra fruit has chemical like quercetin which has antioxidant and anti I tumor activity*	[72]
3) To study the effect of TiO2 NPs with different activities of wound healing	*Synthesis of TiO2 NPs was done using hydrothermal and solvothermal conditions by microwave assisted green synthesis with the help of growth characterization of multi drug resistance pathogens*	*The synthesized TiO2 NPs shows non genotoxic and have a great alternative to antibiotics in treatment of wound infection Newly formulated TiO2 NPs have superior antibacterial property also*	[73]
4)To evaluate effect of TiO2 NPs on apoptosis and invasion of cancer cells live MKN 45	*MTT assay was performed to assess proliferation of MKN 45 and ethidium bromide was used to visualize cancer cells apoptosis*	*Different forms of TiO2 NPs reduced cell proliferation and induce apoptosis in cancer cells*	[74]
6)To study and evaluate how nitric oxide releasing NPs accelerates wound healing by promoting fibroblast migration and collagen deposition	*Hydrogel glass composite was synthesized by using a mixture of tetra methyl orthosilicate ,polyethylene, chitosan glycol, sodium nitrate in buffer of sodium phosphate*	*NO nanoparticles encourages the retrieval of tissue wound healing via direct re-epithelialization and inspires migration and collagen deposition by fibroblast migration and collagen deposition*	[75]
7)To study how cerium oxide nanoparticle-loaded	*Cotton act as a supporting layer for NP s and well*	*Research propose that Ce-nGel NPs could be a*	

polyvinyl alcohol Nano gels delivery for wound healing care systems on surgery	*dispersed NPs were prepared by stabilizing effect of PVA in the Nano gel medium*	*promising wound care arrangement having effective damage and scar inhibition*	[76]
8) To study the effect of gallum gum when incorporated with titanium dioxide NPs biofilms on wound healing	*The GG +TiO2 NPs biofilms was prepared using evaporative casting method and characterized using FTIR and XRD*	*When GG +TiO2 NPs biofilms contacts wounds, the TiO2 NPs dissociate into titanium ion and released into wound these ions support wound healing process.*	[77]
9) To study the effect of Graphene Oxide/Copper Nano derivatives-Modified Chitosan/Hyaluronic Acid for Wound Healing	GO/Cu-decorated chitosan/hyaluronic acid dressings (C/H/GO/Cu) were prepared using sodium tri meta phosphate (STMP) crosslinking and the vacuum freeze-drying method,	GO/Cu-incorporated chitosan/hyaluronic acid dressing's suggested a synergistic antimicrobial efficacy and acceptable biocompatibility both in vitro and in vivo, as well as a significantly accelerated healing process of bacteria-infected wounds.	[78]
10) To study the effect of Development of Anti biofilm Nanocomposites: Ag/Cu Bimetallic Nanoparticles Synthesized on the Surface of Graphene Oxide Nano sheets in wound healing	Ag and Cu nanoparticles on a GO surface (Ag/Cu/GO) when synthesized using a chemical reduction method, their antimicrobial effects in contradiction of numerous bacterial species were recognized. Ag/Cu/GO nanocomposites were characterized by TEM and energy-dispersive X-ray spectroscopy.	It was found that the wound healing effect could be as effective as that of antibiotics by applying our nanocomposites to animal skin infection models. The Ag/Cu/GO nanocomposites could effectively remove biofilms that formed in the microfluidic channel or in the wounded area of small animals.	[79]

7. Conclusion

Nanotechnology has revolutionized the field of wound healing by introducing nanoparticles as effective therapeutic agents. Various types of nanoparticles, including gold, silver, iron oxide, copper, and titanium dioxide, have demonstrated significant antibacterial, anti-inflammatory, and wound-healing properties. Their ability to enhance angiogenesis, collagen synthesis, and re-epithelialization makes them promising candidates for advanced wound care treatments. Additionally, nano carriers have improved the bioavailability and stability of therapeutic compounds like curcumin, overcoming their limitations in absorption and metabolism. Despite their remarkable potential, challenges such as toxicity, long-term biocompatibility, and large-scale production must be addressed to ensure their safe and effective clinical application. Future research should focus on optimizing nanoparticle formulations, developing targeted drug delivery systems, and conducting extensive clinical trials to validate their efficacy. With continuous advancements in nanotechnology, nanoparticle-based therapies hold great promise in transforming wound management and accelerating the healing process.

List of abbreviations

TGF - Transforming growth factor
PDGF - Platelet-derived growth factor
FGF - Fibroblast growth factor
EGF - Epidermal growth factor
KGM - Konjac glucomannan

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