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CURRENT ADVANCES IN THE USE OF *OCIMUM BASILICUM* FOR CYCLOPHOSPHAMIDE-INDUCED DELAYED WOUND HEALING

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ABSTRACT

Cyclophosphamide (CPA) is a widely used chemotherapeutic and immunosuppressive agent that often delays wound healing by inducing oxidative stress, inflammation, immunosuppression, impaired angiogenesis, and reduced collagen synthesis. These effects prolong tissue repair and increase the risk of wound complications. *Ocimum basilicum* (sweet basil) is a medicinal herb rich in bioactive compounds such as rosmarinic acid, eugenol, linalool, flavonoids, and phenolic acids, which possess antioxidant, anti-inflammatory, antimicrobial, angiogenic, and collagen-promoting properties. Recent advances in nanotechnology, including nanoemulsions, liposomes, phytosomes, hydrogels, and polymeric nanoparticles, have improved the stability, bioavailability, and therapeutic efficacy of basil phytochemicals. This review highlights the current advances in the use of *Ocimum basilicum* for cyclophosphamide-induced delayed wound healing, emphasizing its pharmacological mechanisms, molecular targets, and novel drug delivery systems. Overall, *O. basilicum* shows considerable promise as a natural therapeutic agent; however, further preclinical and clinical studies are needed to confirm its safety and efficacy.

KEYWORDS: *Ocimum basilicum*, Cyclophosphamide, Delayed wound healing, Antioxidant, Inflammation, Nanotechnology.

1. INTRODUCTION

Globally, it is estimated that approximately six million individuals are affected by chronic wounds. A wound is defined as a physical disruption of tissue integrity due to mechanical, chemical, or thermal insults. Effective wound management is essential to re-establish the anatomical and functional integrity of the skin. The acute wound healing process is a complex cascade of tightly regulated cellular and biochemical events, modulated by endocrine and paracrine factors. This process can be divided into three or four temporally overlapping but distinct stages: the hemostasis phase, the inflammatory phase, the proliferative phase (characterized by granulation tissue formation and collagen synthesis), and the remodeling phase, which determines the mechanical strength and appearance of the healed tissue **(Yang *et al.*, 2021).**

Wound healing is a natural physiological reaction to tissue injury. However, wound healing is not a simple phenomenon but involves a complex interplay between numerous cell types, cytokines, mediators, and the vascular system. The cascade of initial vasoconstriction of blood vessels and platelet aggregation is designed to stop bleeding. This is followed by an influx of a variety of inflammatory cells, starting with the neutrophil. These inflammatory cells, in turn, release a variety of mediators and cytokines to promote angiogenesis, thrombosis, and reepithelialization. The fibroblasts, in turn, lay down extracellular components which will serve as scaffolding **(Sharma *et al.*, 2021).**

The inflammatory phase is characterized by hemostasis, chemotaxis, and increased vascular permeability, limiting further damage, closing the wound, removing

cellular debris and bacteria, and fostering cellular migration. The duration of the inflammatory stage usually lasts several days **(Coger *et al.*, 2019).**

1.1 Physiology of Wound Healing

Wound healing is a dynamic and highly orchestrated biological process aimed at restoring the structural and functional integrity of damaged skin. This process involves the interaction of various cellular populations and molecular mediators across four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. The correct initiation, sequence, timing, and duration of each phase are essential for successful healing. Disruption in any phase may lead to impaired healing or chronic wound formation. These phases are interdependent and continuous, with each stage influencing the progression and efficacy of the next. In acute wounds, this process typically proceeds without complications; however, chronic wounds often experience a prolonged inflammatory phase, delaying progression to later stages **(Tottoli *et al.*, 2020).**

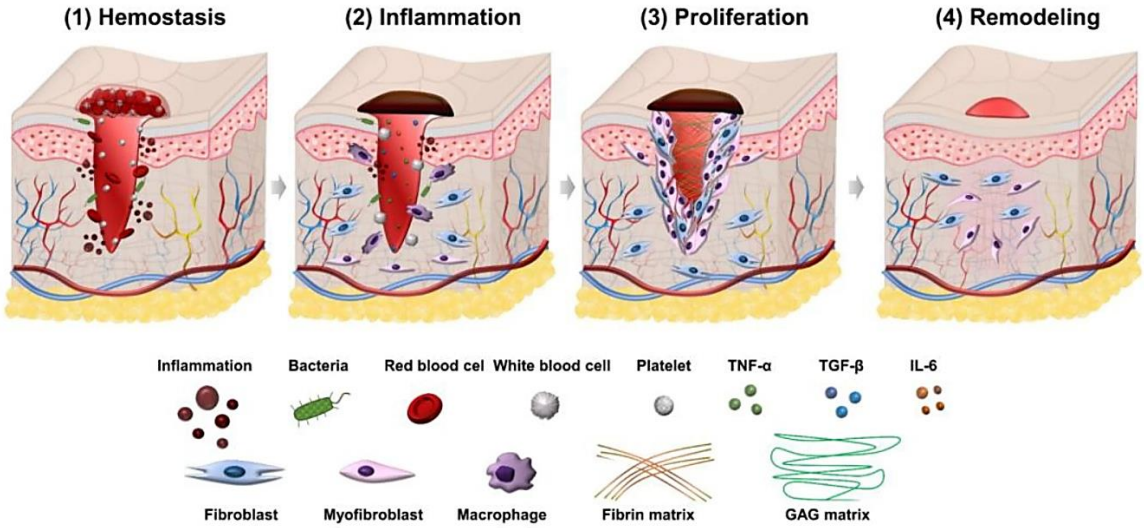

Figure 1: Illustration of four phases in the wound healing process.

1.1.1 Hemostasis Phase

Wound healing first begins with hemostasis. The lymphatic vessels are injured in this phase, and blood flows out to remove microorganisms and antigens. The body will activate different clotting cascades and thrombocytes to agglomerate by exposed collagen. At the same time, platelets activate vasoconstriction to reduce blood loss and fill tissue gaps in injured vessels with blood clots containing cytokines and growth factors. The clot contains the molecules fibrin, fibronectin, vitronectin, and thrombospondin, which form a temporary matrix as a scaffolding structure for the migration of leukocytes, keratinocytes, fibroblasts, and endothelial cells, and it is a reservoir of growth factors that stabilize blood clots and avoid bleeding **(Trinh *et al.*, 2022).**

1.1.2 Inflammation Phase

The second phase of wound healing is inflammation which focuses on cleaning the wound and preparing for new tissue formation in the wound. This stage has the appearance of neutrophils and lasts about 2–5 days from when the wound becomes infected. Neutrophils can phagocytize and secrete proteases (elastase, cathepsin G, proteinase 3) that help destroy bacteria in the wound and deco remove debris. Neutrophils also release mediators (TNF-α, IL-1 and IL-6) to amplify the inflammatory response, stimulating VEGF and IL-8 to respond to repair during wound healing **(Landén and Ståhle, 2016).** The macrophage process then supports the ongoing process by phagocytosis of the debris and secretion of growth factors, chemokines, and cytokines. Macrophages promote and address inflammation, eliminate apoptotic, and support cell proliferation and tissue recovery after injury. In the inflammatory phase, there are often symptoms of edema, erythema and pain **(Oishi and Manabe, 2018).**

1.1.3 Proliferation Phase

The proliferation phase is the most important phase of the wound healing process and lasts from 6 to 21 days. During the proliferation phase of wound healing, the wound is healed with fresh collagen and extracellular matrix tissue. After that, the wound shrinks as new tissues develop. A new network of blood vessels must be created for granulation tissues to remain healthy and receive an adequate supply of nutrients and oxygen. The modulation of fibroblasts toward myofibroblasts promotes the formation of granulation tissue. The myofibroblasts are characterized by the capacity to produce force and synthesize extracellular matrix components that allow the contraction of granulation tissue **(Krzyszczyk *et al.*, 2018).** By gripping the wound boundaries and pulling them together, myofibroblasts use a technique akin to that of smooth muscle cells to close the wound. In the initial stages of wound healing, granulation tissue appears pink or red and has an uneven texture. Furthermore, healthy granulation tissue is clot-

resistant. Dark granulation tissue may be brought on by an infection, ischemia, or insufficient perfusion. Near the conclusion of the proliferation phase, epithelial cells resurface the wound. Keeping wounds moist accelerates epithelialization. Epithelialization occurs when occlusive or semi-occlusive dressings are applied within 48 h after the injury. This is because adequate tissue humidity is maintained. One accomplishment of the proliferation phase is replacing the temporary fibrin matrix with a new matrix made of collagen fibers, proteoglycans, and fibronectin to restore the structure and function of tissues. Another crucial stage of healing is angiogenesis, or the ingrowth of new capillaries to replace previously damaged vessels and restore circulation. The creation of granulation tissue and epithelialization are other important phenomena in this healing period. In the proliferation phase of healing, fibroblasts are the most important cells **(Miricescu *et al.*, 2021).** For fibroblasts to migrate in the extracellular matrix, they must first recognize and interact with particular matrix components. Fibroblasts in the normal dermis are usually dormant and sparsely scattered, but they are active and plentiful in the provisional matrix wound site and granulation tissue. Their migration and aggregation in the wound site necessitate morphological changes and the production and secretion of proteases to clear a passage from the ECM into the wound site. The chemotactic growth factors, cytokines, and chemokines concentration gradient, as well as the alignment of the fibrils in the ECM and provisional matrix, control the direction of fibroblast migration. Rather than crossing these fibrils, fibroblasts prefer to move along them **(Chen *et al.*, 2021).** To help them move through the matrix, fibroblasts produce proteolytic enzymes on a local level. Collagenase (MMP-1), gelatinases (MMP-2 and MMP-9) that destroy gelatin substrates, and stromelysin (MMP-3), which has various protein substrates in the ECM, are three kinds of MMPs released by fibroblasts. After migrating into the matrix, fibroblasts change shape, settle down, and begin to proliferate and generate granulation tissue components such as collagen, elastin, and proteoglycans. Fibroblasts connect to the provisional fibrin matrix cables and begin producing collagen. Type III collagen, like other extracellular matrix proteins and proteoglycans, is generated in high amounts at first. Collagen mRNA is connected to polyribosomes on the endoplasmic reticulum, where new collagen chains are formed after transcription and processing. A crucial stage in this process involves proline and lysine residue hydroxylation **(Wang *et al.*, 2020).**

1.1.4 Remodeling Phase

Closure of acute and chronic wounds is regarded as the wound healing endpoint in most clinical settings, yet wounds can continue to undergo remodeling or tissue maturation for months or even years. This final stage of wound healing decides whether scarring will occur and whether the wound will reoccur. Regression of the neo vasculature, a periodic deposition to the ECM, and subsequent reconstruction of granulation tissue to scar tissue are all part of the remodeling phase **(Xue *et al.*, 2015).** Collagen III makes up the majority of granulation tissue, which is gradually replaced by the stronger collagen I as the wound heals. This occurs due to simultaneous collagen I production and collagen III lysis, followed by ECM remodeling. In the remodeling phase, scar tissues are created, and it might take several months or years to complete, depending on the severity and location of the wound, and used therapeutic procedures. During this time, the new tissue gradually gets stronger and more flexible. Elasticity and tensile strength of the skin are both getting stronger because of collagen synthesis. After re-epithelialization, macrophages regain their phagocytic phenotype. Excessed cells and matrix no longer required for wound healing are phagocytosed by Mreg or M2c-like macrophages **(Rodrigues *et al.*, 2018).**

1.2 Factors Contributing to Delayed Wound Healing

Wound healing may be impeded by a range of local and systemic factors.

Local Factors

- **Oxygenation:** Adequate oxygen supply is essential for angiogenesis, collagen synthesis, epithelialization, and overall wound contraction. Hypoxia, commonly associated with ischemic conditions, disrupts these processes and contributes to the development of chronic or ulcerated wounds.
- **Infection:** Infection prolongs the inflammatory phase and increases the production of pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). Elevated levels of matrix metalloproteinases (MMPs) degrade ECM components, while their natural inhibitors are reduced, further impairing tissue repair **(Slaats *et al.*, 2016).**

Systemic Factors

- **Age:** Aging leads to epidermal thinning and systemic metabolic changes. The inflammatory response in elderly individuals is compromised, with reduced leukocyte chemotaxis, impaired macrophage phagocytosis, and diminished cytokine/growth factor secretion. Consequently, fibroblast activity, angiogenesis, re-epithelialization, and collagen remodeling are significantly delayed. **(Beyene *et al.*, 2020).**
- **Sex Hormones:** Estrogens exhibit anti-inflammatory properties by reducing leukocyte infiltration and cytokine production. They also promote endothelial and keratinocyte proliferation, thus enhancing re-epithelialization and angiogenesis. Conversely, androgens such as testosterone and 5αdihydrotestosterone exert pro-inflammatory effects, prolonging inflammation and impairing healing. **(Horng *et al.*, 2017).**
- **Diabetes Mellitus:** Hyperglycemia impairs neutrophil function, cytokine signaling, collagen synthesis, and angiogenesis. Maintaining blood glucose levels close to normal significantly

improves healing outcomes. Patients with HbA1c levels below 7.1% exhibit faster wound closure rates **(Lee *et al.*, 2024).**

- **Venous Insufficiency:** Chronic edema due to venous hypertension results in capillary leakage of fibrinogen into the dermis, forming fibrin cuffs that impede oxygen and nutrient diffusion. This induces tissue hypoxia, suppresses fibroblast and epithelial cell activity, and promotes anaerobic infections **(Zhou *et al.*, 2022).**
- **Smoking:** Cigarette smoke contains over 4,000 harmful chemicals. Nicotine induces vasoconstriction and platelet aggregation; carbon monoxide binds to hemoglobin, reducing oxygen delivery; and hydrogen cyanide interferes with oxidative metabolism. These effects collectively impair oxygenation and delay wound repair **(Bonilla, 2025).**

2. Cyclophosphamide

Cyclophosphamide is a medication primarily used in the management and treatment of neoplasms, including multiple myeloma, sarcoma, and breast cancer. Cyclophosphamide is a nitrogen mustard that exerts its anti-neoplastic effects through alkylation. This activity reviews the indications, contraindications, mechanism of action, and other key factors of cyclophosphamide as a valuable agent in the treatment and management of neoplastic diseases by an interprofessional team. There is also a discussion of cyclophosphamide use in the management of severe multiple sclerosis.

2.1 Mechanism of action

Cyclophosphamide is a type of nitrogen mustard drug which exerts its effects through the alkylation of DNA. The drug is not cell-cycle phase-specific and metabolizes to an active form capable of inhibiting protein synthesis through DNA and RNA crosslinking. The majority of the antineoplastic effects of cyclophosphamide are due to the phosphoramide mustard formed from the metabolism of the drug by liver enzymes like cytochrome P-450. Hepatic enzymes first convert cyclophosphamide to hydroxycyclophosphamide and then subsequently metabolized to aldophosphamide. Aldophosphamide is cleaved to the active alkylating agent phosphoramide mustard and acrolein. The phosphoramide metabolite forms cross-linkages within and between adjacent DNA strands at the guanine N-7 position. These modifications are permanent and eventually lead to programmed cell death. Acrolein has no antitumor activity but is the principal-agent responsible for the manifestation of hemorrhagic cystitis **(Mills *et al.*, 2019).**

In addition to antimitotic and antineoplastic effects, cyclophosphamide has immunosuppressive effects and selectivity for T cells. High-dose cyclophosphamide is used in eradication therapy of malignant hematopoietic cells, while lower dosages have shown merit for use in selective immunomodulation of regulatory T cells. The drug decreases the secretion of interferon-gamma and IL-12 while increasing the secretion of Th2 cytokines like IL-4 and IL-10 in the CSF and peripheral blood **(Ahlmann *et al.*, 2016).** Due to these effects, cyclophosphamide is considered as a valuable addition to tumor vaccination protocols, post-transplant alloreactivity management, and the treatment of immune-mediated conditions and some forms of vasculitis. While the precise mechanism with which cyclophosphamide exerts its immunomodulatory effects are not completely clear, several studies have suggested a few probable modes of action. These include the elimination of regulatory T cells in naïve or malignant host cells, the induction of T cell growth factors like type I interferons, and preconditioning host cells for donor T cells, thus reducing alloreactivity **(Chatelanat *et al.*, 2018).**

3. Ocimum basilicum

Ocimum basilicum is an erect, much-branched, perennial, aromatic plant growing 20 - 80cm tall. The plant is often grown as an annual, especially in cooler climates.

A very commonly used herb with a range of culinary and medicinal applications. The plant also yields an essential oil and has insect repellent properties. It is often grown in gardens and commercially.

Figure 2: *Ocimum basilicum.*

3.1 Morphology

Sweet basil is an annual herb with dense foliage and a variety of aromatic components. This plant thrives in an agroclimatic environment, with temperatures ranging from 7 to 27 °C, annual precipitation from 0.6 to 4.3 m, and soil pH from 4.3 to 8.2. This plant requires low maintenance, and it is easy to grow in indoor and outdoor settings. Although it can be damaged by frost and temperatures below freezing, this species flourishes under conditions of long daylight with full sun and well-drained soil **(Lal *et al.*, 2018).**

The plant can grow up to 0.6 m in height, with lateral branches creating an angle of more than 30° with the main branch. The stem is round–quadrangular, glabrous (smooth, hairless), or puberulent (fine short hairs), concentrated on the two opposing faces of the stem. Inflorescence is dense, arranged around a point on an axis up to 12 mm apart; the axis is pubescent and with a

total of six flowers surrounding the apex. The leaves are green, the apex mostly acute or acuminate; the shape is ovate or elliptic ovate; the size is about 15–50 × 5–25 mm; the leaf margin is entirely or sparsely serrate and with a glandular–punctate shape. The petiole is about 20 mm long and pubescent (covered with soft short hair). The corolla with a white or pinkish color tube—about 7–8 mm long—is funnel-shaped. The calyx pilose (covered with soft long hair or pubescent) has a dense ring of hairs at the throat, and a fruiting calyx is about 6 mm long. The stamen has tufted hairs near the base. The nutlets are dark brown in color, with an elliptic shape, and they produce mucilage upon interaction with water **(Shasany and Kole, 2018).**

3.2 Basil nutritional composition and chemical constituents

It has been reported that important essential oil components are terpnes, phenylpropanoids, alcohols and aldehydes, and essential oil composition influenced by location, growing conditions, cultivars, different agronomic management, seasonal variation, harvesting, drying and processing methods. Both productivity and quality of essential oils of basil plants also change on the basis of field conditions. Phenolic acids and flavonol-glycosides are the main phenolic components in basil. The main fatty acid composition of basil species are Stearic acid, Oleic acid, Palmitic acid, Linoleic acid, Myristic acid, α-Linolenic acid, Carpic acid, Lauric acid and Arachidonic acid. Higher light and temperature conditions have influence on antioxidant capacity. The most important antioxidant compounds of basil are caffeic, vanillic, rosmarinic acids, quercetin, rutin, apigenin, chlorogenic and *p*-hydroxybenzoic. Essential oils of basil are α-Pinene, β-Pinene, Methyl chavicol, 1,8 cineole, Llinalool, Ocimene, Borneol, Geraneol, B-Caryphyllone, n-Cinnamate and Eugenol **(Bozyel *et al.*, 2024).**

3.3 Pharmacological Activities

Medicinal plants contain rich, yet underexploited, bioactive compounds, with a limited amount of their potential qualities having been thoroughly examined. The exploration of a medicinal plant with high chemical constituents holds promise in the pursuit of developing therapeutic treatments in the future. Each part of the plant offers potentially valuable biomedical knowledge, which remains uncovered. As one of the medicinal plants, *O. basilicum* L. possesses considerable undiscovered potential in the field of antimicrobial and biomedical research. The goal of biomedical therapy through the utilization of medicinal plants requires continuous exploration and development **(Li and Weng, 2017).**

3.3.1 Antioxidant Activity

One of the most significant pharmacological properties of *Ocimum basilicum* is its potent antioxidant activity, which plays a crucial role in protecting tissues from oxidative damage during wound healing. Cyclophosphamide metabolism generates excessive reactive oxygen species (ROS), including superoxide radicals, hydroxyl radicals, and hydrogen peroxide, leading to lipid peroxidation, DNA damage, protein oxidation, and cellular apoptosis. The leaves and essential oil of *O. basilicum* are rich in flavonoids, phenolic acids, rosmarinic acid, caffeic acid, eugenol, linalool, and other bioactive compounds that effectively scavenge free radicals and inhibit oxidative stress **(Shahrajabian *et al.*, 2020).** Experimental studies have demonstrated that basil extract significantly enhances the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), while simultaneously increasing intracellular glutathione (GSH) levels and reducing malondialdehyde (MDA), a major marker of lipid peroxidation. By restoring the oxidant-antioxidant balance, *Ocimum basilicum* protects fibroblasts, keratinocytes, and endothelial cells from oxidative injury, thereby facilitating cell survival, proliferation, and tissue regeneration. These antioxidant properties make basil particularly beneficial in counteracting cyclophosphamide-induced oxidative stress and promoting faster wound healing **(Zhakipbekov *et al.*, 2024).**

3.3.2 Anti-inflammatory Activity

Ocimum basilicum exhibits remarkable anti-inflammatory activity by modulating multiple inflammatory signaling pathways involved in tissue injury and repair. During cyclophosphamide-induced delayed wound healing, prolonged inflammation results in excessive production of pro-inflammatory cytokines and inflammatory mediators, which impair fibroblast function, collagen synthesis, and epithelial regeneration. Basil extract suppresses these detrimental responses by inhibiting the activation of nuclear factor-kappa B (NF-κB), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) **(Raina *et al.*, 2016).** It also reduces the secretion of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), thereby limiting leukocyte infiltration and oxidative tissue damage. Additionally, basil regulates inflammatory cell activity and promotes a timely transition from the inflammatory phase to the proliferative phase of wound healing. Through these mechanisms, *Ocimum basilicum* minimizes chronic inflammation, reduces tissue destruction, and creates a favorable environment for wound repair and regeneration **(Soliman and Barreda, 2022).**

3.3.3 Antimicrobial Activity

The antimicrobial activity of *Ocimum basilicum* is another important factor contributing to its wound-healing potential. Wounds are highly susceptible to bacterial and fungal infections, particularly in immunocompromised individuals receiving cyclophosphamide therapy. The essential oil of basil contains bioactive constituents such as linalool, eugenol,

methyl chavicol (estragole), and β-caryophyllene, which possess strong antimicrobial properties. These compounds disrupt microbial cell membranes, inhibit enzyme activity, interfere with microbial metabolism, and suppress biofilm formation **(Stanojevic *et al.*, 2017).** Numerous studies have demonstrated that *Ocimum basilicum* exhibits broad-spectrum antimicrobial activity against pathogenic microorganisms including *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*, all of which are commonly associated with wound infections. By preventing microbial colonization and reducing the risk of infection, basil helps maintain a sterile wound environment, decreases inflammatory complications, and promotes rapid tissue repair, making it particularly valuable for managing cyclophosphamide-induced delayed wound healing **(Dhama *et al.*, 2023).**

3.3.4 Promotion of Collagen Synthesis

Collagen synthesis is a critical event during the proliferative phase of wound healing, as collagen provides structural support and mechanical strength to newly formed tissue. Experimental investigations have shown that *Ocimum basilicum* stimulates fibroblast proliferation and enhances the synthesis and deposition of collagen within the wound matrix. Treatment with basil extract significantly increases hydroxyproline content, a biochemical marker of collagen formation, indicating enhanced extracellular matrix production. Basil also promotes fibronectin synthesis, accelerates extracellular matrix remodeling, and improves the organization of collagen fibers. Furthermore, enhanced collagen deposition contributes to increased wound tensile strength, faster wound contraction, and improved quality of regenerated tissue. These effects are primarily attributed to the antioxidant and anti-inflammatory properties of basil, which preserve fibroblast viability and support optimal cellular function during tissue repair. Consequently, *Ocimum basilicum* plays an important role in restoring skin integrity and promoting efficient wound healing in cyclophosphamide-treated conditions **(Zangeneh *et al.*, 2019).**

3.3.5 Angiogenic Activity

Angiogenesis, the formation of new blood vessels from existing vasculature, is essential for successful wound healing because it ensures adequate oxygen and nutrient supply to regenerating tissues. Cyclophosphamide impairs angiogenesis by suppressing endothelial cell proliferation and reducing the expression of several pro-angiogenic growth factors, thereby delaying granulation tissue formation and wound closure **(Dudley and Griffioen, 2023).** Studies have demonstrated that *Ocimum basilicum* enhances angiogenesis by upregulating the expression of vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), and fibroblast growth factor (FGF), all of which are key regulators of new blood vessel formation. Increased angiogenesis improves local blood circulation, facilitates oxygen and nutrient delivery, enhances fibroblast migration, and supports collagen synthesis and extracellular matrix deposition. The improved vascular network also accelerates granulation tissue development, epithelialization, and overall wound contraction. Through its angiogenic properties, *Ocimum basilicum* effectively promotes tissue regeneration and helps overcome the vascular deficiencies associated with cyclophosphamide-induced delayed wound healing **(Thulasingam *et al.*, 2026).**

3.4 Nanoformulations of *Ocimum basilicum* for Wound Healing

Nanotechnology has emerged as one of the most promising strategies for enhancing the therapeutic performance of medicinal plant extracts. Nano-based delivery systems increase the solubility, stability, skin penetration, and sustained release of bioactive compounds, thereby improving wound healing outcomes. Various nanoformulations of *Ocimum basilicum* have been developed and evaluated for their wound-healing potential.

3.4.1 Nanoemulsions

Nanoemulsions are thermodynamically stable colloidal systems with droplet sizes generally ranging between 20 and 200 nm. They are composed of oil, water, surfactants, and co-surfactants, which encapsulate basil essential oil or extract within nanosized droplets. Nanoemulsions enhance the topical delivery of basil phytochemicals by increasing their solubility and facilitating deeper penetration into the epidermal and dermal layers of the skin. The small droplet size provides a larger surface area, allowing rapid interaction with damaged tissues and improving drug absorption. Nanoemulsion-based formulations also protect volatile compounds such as linalool and eugenol from oxidation and evaporation, thereby preserving their biological activity. Studies have demonstrated that basil nanoemulsions exhibit superior antioxidant, antimicrobial, and anti-inflammatory activities compared to conventional extracts, leading to accelerated wound contraction, enhanced collagen synthesis, and faster epithelialization **(McClements *et al.*, 2021).**

3.4.2 Polymeric Nanoparticles

Polymeric nanoparticles are biodegradable carriers prepared from natural or synthetic polymers such as chitosan, poly(lactic-co-glycolic acid) (PLGA), alginate, and gelatin. These nanoparticles encapsulate basil phytochemicals and provide sustained and controlled drug release. The encapsulation of *Ocimum basilicum* extract within polymeric nanoparticles protects sensitive bioactive compounds from enzymatic degradation and environmental oxidation. Their nanoscale size enhances cellular uptake by fibroblasts and keratinocytes, resulting in improved intracellular delivery of antioxidant and anti-inflammatory molecules. Controlled drug release maintains therapeutic concentrations at the wound site for prolonged periods, reducing the frequency of application and improving patient compliance.

Furthermore, polymeric nanoparticles enhance fibroblast proliferation, collagen deposition, angiogenesis, and extracellular matrix remodeling, thereby accelerating tissue regeneration **(Đorđević *et al.*, 2025).**

3.4.3 Liposomes

Liposomes are phospholipid-based vesicular systems consisting of one or more lipid bilayers surrounding an aqueous core. Due to their structural similarity to biological membranes, liposomes exhibit excellent biocompatibility and skin permeability. Liposomal formulations effectively encapsulate both hydrophilic and lipophilic phytochemicals present in *Ocimum basilicum*. These vesicles improve drug penetration through the stratum corneum and facilitate targeted delivery to deeper skin layers. Liposomes also provide sustained release of basil constituents while minimizing systemic absorption and reducing the risk of adverse effects. Enhanced skin hydration produced by phospholipid vesicles further supports epithelial regeneration and wound closure. Liposomal basil formulations have shown improved antimicrobial activity, reduced oxidative stress, and enhanced collagen synthesis compared to conventional topical preparations **(Kyriakoudi *et al.*, 2021).**

3.4.4 Phytosomes

Phytosomes are advanced lipid-based delivery systems in which phytoconstituents form molecular complexes with phospholipids, resulting in improved membrane permeability and bioavailability. Many flavonoids and phenolic compounds present in *Ocimum basilicum* exhibit poor oral and topical bioavailability due to limited lipid solubility. Phytosome technology significantly enhances the absorption and stability of these compounds by improving their compatibility with biological membranes. Basil phytosomes exhibit prolonged retention at the wound site and increased penetration into damaged tissues. Consequently, they provide sustained antioxidant protection, suppress inflammatory responses, stimulate fibroblast activity, and promote collagen maturation. Phytosomal formulations therefore represent an effective strategy for maximizing the therapeutic benefits of basil phytochemicals **(Barani *et al.*, 2021).**

3.4.5 Hydrogels

Hydrogels are three-dimensional polymeric networks capable of absorbing large quantities of water while maintaining structural integrity. Their high moisture-retention capacity makes them ideal wound dressing materials. Hydrogels containing *Ocimum basilicum* extract provide a moist wound environment that promotes cell migration, granulation tissue formation, and epithelialization. They also protect the wound from external contamination while allowing adequate oxygen exchange. Controlled release of basil phytochemicals from hydrogels ensures prolonged antioxidant, antimicrobial, and anti-inflammatory activity at the wound site. In addition, hydrogels reduce pain, minimize dehydration, and facilitate autolytic debridement, thereby creating optimal conditions for tissue repair. Several studies have demonstrated enhanced wound contraction, increased collagen deposition, and improved tissue organization following treatment with basil-loaded hydrogels **(Roșca *et al.*, 2025).**

3.5 Potential Role of *Ocimum basilicum* in Cyclophosphamide-Induced Delayed Wound Healing

Ocimum basilicum contains numerous bioactive phytochemicals, including rosmarinic acid, eugenol, linalool, ursolic acid, caffeic acid, flavonoids, and phenolic compounds, which exhibit potent antioxidant, anti-inflammatory, antimicrobial, angiogenic, immunomodulatory, and collagen-promoting activities. These multitarget therapeutic effects suggest that basil may serve as an effective natural adjunctive therapy for accelerating wound healing in patients receiving cyclophosphamide treatment. The potential mechanisms through which *Ocimum basilicum* may improve cyclophosphamide-induced delayed wound healing are discussed below.

3.5.1 Reduction of Oxidative Stress

Oxidative stress is considered one of the principal mechanisms underlying cyclophosphamide-induced tissue injury. During hepatic metabolism, cyclophosphamide generates toxic metabolites such as acrolein and phosphoramide mustard, which stimulate excessive production of reactive oxygen species (ROS). These free radicals initiate lipid peroxidation, DNA damage, protein oxidation, mitochondrial dysfunction, and apoptosis of fibroblasts, keratinocytes, and endothelial cells, ultimately delaying wound repair **(Srirangan and Sabina, 2025).**

3.5.2 Suppression of Chronic Inflammation

Persistent inflammation significantly contributes to delayed wound healing following cyclophosphamide administration. Increased production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) prolongs the inflammatory phase and delays progression to tissue regeneration **(Kany *et al.*, 2019).**

3.5.3 Prevention of Wound Infection

Cyclophosphamide- induced immunosuppression increases susceptibility to bacterial and fungal infections, making wound contamination one of the major causes of delayed healing. Infection prolongs inflammation, increases tissue necrosis, and interferes with collagen synthesis and epithelial regeneration **(Aswathanarayan *et al.*, 2022).**

3.5.4 Enhancement of Fibroblast Proliferation

Fibroblasts play a central role in wound healing by synthesizing collagen, fibronectin, proteoglycans, and other extracellular matrix components.

Cyclophosphamide suppresses fibroblast proliferation by inhibiting DNA synthesis and cellular replication, resulting in delayed granulation tissue formation.

3.5.5 Promotion of Angiogenesis

Adequate angiogenesis is necessary for supplying oxygen, nutrients, and growth factors to regenerating tissues. Cyclophosphamide impairs angiogenesis by reducing endothelial cell proliferation and suppressing vascular endothelial growth factor (VEGF) expression. *Ocimum basilicum* promotes angiogenesis by increasing the expression of VEGF, fibroblast growth factor (FGF), and transforming growth factor-beta (TGF-β). Enhanced blood vessel formation improves tissue oxygenation, nutrient delivery, and waste removal while supporting fibroblast migration and collagen synthesis. Increased angiogenesis also facilitates granulation tissue formation and accelerates wound healing **(Malviya and Malviya, 2023).**

4. Future Perspectives

Future research should focus on the standardization of *Ocimum basilicum* extracts, identification of key bioactive compounds, and development of advanced nanoformulations to improve drug delivery and therapeutic efficacy. Further mechanistic studies and well-designed preclinical and clinical trials are required to establish its safety, optimal dosage, and clinical effectiveness in cyclophosphamide-induced delayed wound healing. The integration of basil with nanotechnology and regenerative medicine may provide more effective and targeted wound-healing therapies.

5. CONCLUSION

Ocimum basilicum is a promising medicinal plant with significant potential for managing cyclophosphamide-induced delayed wound healing due to its antioxidant, anti-inflammatory, antimicrobial, angiogenic, and collagen-promoting activities. Advances in nanotechnology-based delivery systems have further enhanced its therapeutic potential. Although current findings are encouraging, additional standardized experimental studies and clinical trials are necessary to validate its efficacy and facilitate its translation into clinical wound care.

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