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# Healing Beyond the Wound: A Whole-Person Integrative Approach to a Chronic Non-Healing Post-Mastectomy Wound in a Breast Cancer Survivor

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## Abstract

**Background:** Chronic nonhealing wounds following mastectomy in breast cancer survivors represent a significant therapeutic challenge, often driven by persistent inflammation, impaired angiogenesis, immune dysregulation, oxidative stress, and tissue hypometabolism. These wounds frequently resist standard care approaches, leading to delayed healing, recurrent infection, and compromised quality of life.

**Objective:** This case report describes the therapeutic impact of an integrative medicine protocol as an adjunct to conventional wound management in a breast cancer survivor with a chronic nonhealing post-mastectomy wound.

**Methods:** A multimodal integrative intervention was administered alongside standard oncologic and surgical wound care. The protocol included oral administration of freshly prepared *Curcuma longa* (turmeric), *Zingiber officinale* (ginger), and *Piper nigrum* (black pepper) juice; sublingual delivery of cannabidiol (CBD) and tetrahydrocannabinol (THC); and topical application of *Piper nigrum* essential oil diluted in a cold-pressed almond oil carrier, supplemented with one drop each of fresh turmeric and ginger juice as a wound dressing. The therapeutic rationale was grounded in the known synergistic anti-inflammatory, antioxidant, angiogenic, and antimicrobial properties of these phytochemicals. The patient also continued conventional treatments, including antibiotics, surgical debridement, and oncologic therapies as indicated.

**Results:** The patient demonstrated clinically significant improvements in wound healing, including reduced wound size, exudate, and pain, with accelerated granulation tissue formation and re-epithelialization. The botanical constituents modulated key molecular targets implicated in chronic wound pathophysiology, including NF-κB, Nrf2, TRPV1, and CB1/CB2 receptors. Cannabinoids contributed to immunomodulation, reduction of neurogenic inflammation, and enhanced mesenchymal stem cell recruitment via p42/44 MAPK activation. The oral and topical phytochemicals exhibited synergistic effects, with black pepper enhancing the bioavailability of curcumin and gingerol and potentiating their anti-infective action at the wound site. Adjunctive micronutrients (zinc, vitamin C, omega-3 fatty acids) and psychosocial interventions (yoga, meditation, acupressure) further supported systemic healing and reduced psychological stress, known to impair cutaneous repair via hypothalamic-pituitary-adrenal (HPA) axis dysregulation.

**Conclusion:** This integrative regimen, combining targeted phytotherapeutics and cannabinoid-based interventions with conventional care, resulted in favorable clinical outcomes in a breast cancer survivor with a chronic nonhealing post-mastectomy wound. This case highlights the therapeutic potential of a system-based, phytomedicine-supported approach in resolving complex wound pathologies. Further studies are warranted to validate these outcomes, clarify mechanisms, and inform standardized treatment protocols.

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## Introduction

Chronic nonhealing wounds present a substantial clinical burden in breast cancer survivors, particularly following mastectomy and oncologic therapies. Clinically, a chronic wound is defined as one that fails to proceed through an orderly and timely reparative process to restore functional integrity within approximately 4 to 6 weeks, or one that shows no significant signs of healing over a 30-day period [1]. These wounds are characterized by persistent inflammation, impaired angiogenesis, and dysregulated extracellular matrix remodeling [2,3]. In post-mastectomy cases, the risk of impaired wound healing is compounded by immunosuppression from systemic chemotherapy, radiotherapy, hormonal therapy, or targeted biologics, all of which compromise tissue regenerative capacity and immune competence [4,5].

The pathophysiology of chronic post-surgical wounds is multifactorial. Oncologic treatments frequently induce leukopenia, oxidative stress, and mitochondrial dysfunction, while impairing the function of macrophages, fibroblasts, and keratinocytes—cellular actors central to the repair cascade [6,7]. Estrogen deprivation from hormone-blocking therapies further contributes to dermal thinning, delayed re-epithelialization, and reduced collagen synthesis [3,8]. Inflammatory cytokine overexpression (e.g., TNF-α, IL-6) and persistent NF-κB activation perpetuate wound chronicity [9,10]. Neuroimmune dysregulation and microbial colonization, particularly by resistant organisms such as *Staphylococcus aureus*, exacerbate tissue damage and heighten infection risk [11,12].

In individuals with impaired immunity, diminished angiogenic signaling and mesenchymal stem cell (MSC) recruitment limit granulation tissue formation and vascular remodeling—processes essential for wound closure [13,14]. Concomitant metabolic comorbidities such as diabetes mellitus or prolonged corticosteroid exposure may further delay healing [15]. Consequently, conventional strategies—including systemic antibiotics, surgical debridement, and standard dressings—are often insufficient for durable resolution.

There is growing interest in adjunctive and integrative approaches that address the complex biological deficits underlying chronic wounds. Interventions that simultaneously target inflammation, oxidative stress, immune dysfunction, and tissue hypoxia may offer synergistic benefits. Natural compounds with multimodal bioactivity—particularly phytocannabinoids and plant-derived polyphenols—have shown promise in preclinical and early clinical research [16,17]. Their potential to modulate signaling pathways central to wound repair, including the endocannabinoid system (ECS), Nrf2 antioxidant response, TRPV1 ion channels, and MAPK cascades, supports their integration into comprehensive wound care strategies [6,7,10].

This case report describes the clinical application of such an integrative approach in a breast cancer survivor with a chronic nonhealing post-mastectomy wound. The protocol combined sublingual cannabidiol (CBD) and tetrahydrocannabinol (THC), oral *Curcuma longa* (turmeric), *Zingiber officinale* (ginger), and *Piper nigrum* (black pepper), along with a phytotherapeutic topical dressing, in conjunction with conventional oncologic and surgical care. The aim is to illustrate how these interventions collectively supported wound resolution and to highlight mechanistic pathways relevant to tissue regeneration in a compromised systemic environment.

## Methods

### Patient Selection and Clinical Background

A breast cancer survivor with a chronic nonhealing wound following mastectomy was enrolled in this case-based observational report. She had been receiving conventional medical and surgical management but was referred for adjunctive integrative therapy due to persistent wound dehiscence and delayed healing despite standard care.

The patient had stage I estrogen receptor–positive breast cancer and underwent bilateral total mastectomy with expander placement in anticipation of DIEP flap reconstruction. She was prescribed anastrozole as part of adjuvant endocrine therapy. Postoperative infection of the expander led to hospitalization, explanation, and extended wound care. Due to persistent nonhealing at the surgical site, she was referred to as complementary wound management prior to reconstructive surgery.

### Wound Healing Assessment

Wound healing was monitored through serial clinical examinations and patient-reported outcomes. Photographic documentation was not obtained, as the patient declined imaging due to severe psychological distress and a request for complete privacy. Accordingly, all clinical information was collected and reported in fully de-identified form, with written consent provided for the publication of anonymized findings.

### Integrative Adjunctive Protocol for Nutritional and Topical Support

The patient was placed on a structured integrative protocol designed to promote tissue regeneration, modulate systemic and local inflammation, and enhance immune competence in the setting of chronic post-mastectomy wound healing. This multimodal strategy combined nutritional interventions, phytotherapeutic agents, cannabinoid therapy, and topical botanical preparations with conventional oncologic and surgical care. Biophysical modalities targeting psychoneuroimmune pathways were also included to optimize the wound microenvironment and support whole-person recovery.

### Nutritional Intervention

The patient adhered to a high-protein, low-glycemic diet with increased fluid intake and daily consumption of green leafy vegetables, aligned with both Traditional Chinese Medicine (TCM) and Ayurvedic principles. Emphasis was placed on warm-natured, digestion-supportive, and detoxifying foods to fortify spleen and kidney Qi, reduce systemic inflammation, and promote metabolic resilience [4,5].

### Mind–Body and Biophysical Modulation

The patient engaged in mindfulness-based stress reduction (MBSR) following the Kabat-Zinn protocol, including guided meditation and daily mindful walking in forested environments to promote parasympathetic activation through phytoncide exposure and Schumann frequency entrainment. Neurophysiological coherence was supported with neurofeedback and biofeedback technologies (biosensing headbands, Brain Tap systems), with heart rate variability (HRV) tracked as a surrogate marker for autonomic balance [15].

Adjunctive biophysical support included daily 30-minute sessions with a pulsed electromagnetic field (PEMF) therapy mat

incorporating infrared photon–emitting elements and therapeutic gemstones, aimed at enhancing mitochondrial bioenergetics, microcirculation, and redox homeostasis [6,7].

### Oral Phytotherapeutic Regimen

The patient received a freshly prepared, cold-pressed oral juice formulation consisting of *Curcuma longa* (turmeric) rhizome and *Zingiber officinale* (ginger) rhizome, with freshly ground *Piper nigrum* (black pepper) added immediately before consumption. The preparation was administered once daily in the morning and consumed within 30 minutes to preserve phytochemical integrity.

- **Turmeric:** Each serving contained 2–3 g of fresh turmeric rhizome, yielding ~150–200 mg of curcumin daily. This dosage was selected to remain within recognized safety thresholds for fresh turmeric and avoid hepatotoxicity associated with high-dose extracts. Baseline and biweekly liver function panels (ALT, AST, ALP, total bilirubin) were monitored.

- **Ginger:** Each dose included 2–3 g of fresh-pressed ginger rhizome juice, providing physiologically relevant levels of gingerols and shogaols. These doses fall within common dietary ranges and have demonstrated anti-inflammatory, antioxidant, gastrointestinal, and circulatory benefits.

- **Black pepper:** To enhance curcumin bioavailability, 100–200 mg of freshly ground black pepper was added, delivering an estimated 3–5 mg of piperine daily. Piperine inhibits hepatic and intestinal glucuronidation, thereby increasing systemic curcuminoid concentrations [5,18,19].

No adverse effects were observed, and no elevations in hepatic enzymes occurred during the treatment period. The intervention was well tolerated and complemented conventional wound care protocols [20-22].

### Topical botanical therapy

A custom-compounded botanical formulation was prepared using *Piper nigrum* essential oil blended into a sweet almond oil carrier, supplemented with two drops each of freshly expressed *Curcuma longa* (turmeric) and *Zingiber officinale* (ginger) juice. The formulation was applied topically to the wound site once daily under sterile dressing conditions. Prior to initiation, dermal patch testing was performed to assess hypersensitivity.

The botanicals were selected for their antimicrobial, anti-inflammatory, and collagen-stimulating properties relevant to chronic wound resolution and tissue regeneration [9,17,23].

### Cannabinoid-based adjunctive therapy

A sublingual formulation containing cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) was administered nightly. Dosing commenced with one drop and was gradually titrated up to a maximum of four drops, depending on tolerability and therapeutic response. The cannabinoid regimen was intended to modulate systemic inflammation, alleviate anxiety, improve sleep quality, and support immune homeostasis through activation of the endocannabinoid system [4,6,15].

### Safety monitoring

All phytotherapeutic interventions were reviewed and approved by the patient's primary oncology and surgical teams. Herb–drug and essential oil–drug interactions were assessed prior to initiation and throughout the course of therapy to ensure pharmacological compatibility and patient safety.

## Results

Following initiation of the integrative therapeutic protocol, the patient demonstrated progressive clinical improvement in wound healing parameters. Notable reductions were observed in wound surface area, peri-wound erythema, and local cellulitis, accompanied by decreased exudative output and gradual re-approximation of wound margins. No adverse events or hypersensitivity reactions were reported in association with the oral or topical interventions.

By the conclusion of the four-week intervention period, the patient achieved complete epithelial closure. Clinical examination confirmed restoration of structurally intact epithelial surfaces, with no evidence of residual infection, inflammation, or wound dehiscence.

The patient was advised to continue the nutritional regimen—including daily oral administration of turmeric and ginger juice with black pepper—and the sublingual cannabinoid formulation (CBD/THC) as a maintenance strategy to support ongoing tissue integrity and systemic resilience.

She was subsequently transitioned back to the care of her oncology and surgical teams. Intermittent follow-up assessments conducted by the integrative medicine team confirmed sustained wound closure, absence of recurrence, and satisfactory long-term healing outcomes.

## Discussion

The present case demonstrates successful healing of a chronic, nonhealing post-mastectomy wound in a breast cancer survivor through the application of a structured integrative therapeutic protocol alongside conventional medical care. Despite persistent wound dehiscence and delayed healing under standard treatments—including antibiotics, repeated surgical debridement, and hormonal therapy—the patient achieved complete wound closure within four weeks of initiating the integrative intervention. The absence of adverse effects and the sustained resolution of wound pathology at follow-up further underscore the potential clinical value of this approach.

These findings support the role of integrative medicine as an adjunct in managing complex, treatment-resistant wounds in oncology patients. The protocol combined phytotherapeutic agents, cannabinoid-based therapies, targeted nutritional strategies, topical botanical dressings, and mind–body techniques, addressing both biological and systemic barriers to healing. This multimodal approach was designed to counteract key pathophysiological mechanisms implicated in chronic wound persistence, including excessive inflammation, oxidative stress, impaired angiogenesis, microbial colonization, and psychoneuroimmune dysregulation.

In the following sections, each therapeutic modality is examined in detail, with emphasis on its proposed mechanisms of action and supporting evidence from scientific literature.

## Turmeric (*Curcuma longa L.*)

Turmeric, derived from the rhizome of *Curcuma longa L.*, contains the polyphenol curcumin, which exerts potent antioxidant, anti-inflammatory, antimicrobial, angiogenic, and epigenetic activities relevant to chronic wound repair, including non-healing post-mastectomy wounds [9]. Curcumin supports all phases of healing by enhancing epithelial regeneration, fibroblast proliferation, neovascularization, collagen synthesis, and extracellular matrix remodeling [5,23]. Mechanistically, it modulates NF-κB, AP-1,

**Table 1:** Mechanisms of Action of Turmeric (Curcumin) in Wound Healing

| Mechanism of Action | Description | References |
|---|---|---|
| Antioxidant Activity | Scavenges reactive oxygen species (ROS) via phenolic hydroxyl and methoxy groups; activates Nrf2/HO-1 pathway, upregulating antioxidant enzymes (SOD, catalase, GSH) to reduce oxidative stress and promote tissue repair. | 2,3,6,7,33 |
| Antimicrobial Activity | It exhibits broad-spectrum antibacterial, antiviral, and antifungal effects, preventing secondary infections in wounds, thus maintaining sterility and enhancing healing. | 9,34 |
| Epigenetic Modulation | Inhibits DNA methyltransferases; regulates histone acetylation/deacetylation; modulates microRNAs (miR-21, miR-146a) to promote fibroblast proliferation, ECM remodeling, and inflammation resolution. | 35, 36, 37, 19 |
| Transcription Factor Regulation | It modulates NF-κB, AP-1, and PPAR-γ to control inflammation, cell proliferation, and ECM remodeling; it also enhances the expression of growth factors (TGF-β, VEGF) critical for repair and angiogenesis. | 6, 10, 4,16 |
| Growth Factor Modulation | Upregulates TGF-β and VEGF, promoting fibrosis, ECM synthesis, angiogenesis, and vascularization essential for tissue repair. | 4,16 |
| Cell Proliferation & Migration | Enhances keratinocyte proliferation and migration through EGFR signaling; promotes fibroblast migration critical for granulation tissue formation and re-epithelialization. | 41,13, 23,5 |
| Angiogenesis & Neovascularization | Stimulates VEGF expression, promotes endothelial nitric oxide synthase (eNOS) activity, and increases NO production for vasodilation and vascular perfusion. It also regulates caveolin-1, enhancing capillary density and stem cell function. | 5, 13, 61 |
| Extracellular Matrix Remodeling | Balances MMP-9 downregulation and TIMP upregulation to preserve ECM integrity; stimulates collagen synthesis, maturation, and granulation tissue formation; enhances collagen fiber alignment for tensile strength. | 13,3,2,7,13 |
| Autophagy Induction | Activates FOXO1, RAB7, BECN1; inhibits PI3K-AKT-mTOR pathway to promote autophagy, aiding cellular homeostasis, debris clearance, and survival of fibroblasts and keratinocytes. | 42,12,55 |
| Inflammation Resolution | Suppresses JAK2/STAT3 pathway and NF-κB signaling, reducing pro-inflammatory cytokines; promotes apoptosis of excess inflammatory cells via caspase-3 activation; modulates oxidative stress pathways to minimize scar formation. | 19,2, 51 |
| Regulation of Fibrosis and Scarring | Inhibits myofibroblast differentiation via NF-κB suppression; limits Egr-1 expression; balances TGF-β/Smad pathway to prevent excessive fibrosis while supporting repair. | 51,45,50 |
| Molecular Signaling Pathway Modulation | Modulates HIF-1α, Shh, JAK/STAT, Wnt/β-catenin, MAPK pathways to promote angiogenesis, apoptosis, cell proliferation, differentiation, and tissue remodeling. | 38, 39,40, 33, 3,47, 32 |
| Enhancement of DNA/Protein Synthesis | Increases DNA and protein synthesis; promotes type III collagen deposition essential for epithelial regeneration and wound closure. | 56 |
| Nitric Oxide Production Enhancement | Upregulates eNOS, boosting nitric oxide levels that improve vascular perfusion and antimicrobial activity within the wound bed. | 15 |
| Dose-Dependent Pro-oxidant Effects | At high concentrations, curcumin may increase ROS production, causing oxidative stress, impairing healing, and inducing apoptosis; this necessitates careful dose optimization. | 9, 17 |

cytokine profiles, and growth factor signaling pathways critical to tissue repair [4,16]. These actions promote fibroblast migration, granulation tissue formation, and sustained tissue regeneration, highlighting curcumin's therapeutic value in refractory oncologic wound management [5,9,23].

## Mechanisms of Action of Curcumin in Inflammatory Regulation

Curcumin exerts anti-inflammatory and pro-regenerative effects essential for wound healing by abbreviating the inflammatory phase and preventing chronicity. It suppresses pro-inflammatory cytokines such as TNF-α, IL-1β, and PGE2, reducing tissue damage and promoting transition to the proliferative phase [23-25], while enhancing anti-inflammatory mediators and inducing M2 macrophage polarization to support resolution and remodeling [2]. Curcumin's biphasic regulation of TNF-α—early enhancement for host defense and later suppression to prevent chronic damage—further optimizes healing dynamics [26]. Mechanistically, it inhibits NF-κB signaling by targeting upstream kinases AKT, PI3K, and IKK, downregulating transcription of pro-inflammatory genes [2,27], and blocks TLR4 activation by interfering with MD2–LPS binding [28,29]. Curcumin also suppresses COX-2, thereby limiting prostaglandin and thromboxane synthesis [16], and inhibits NLRP3 inflammasome activation to reduce IL-1β and IL-18 release, enhancing granulation, collagen deposition, and epithelial closure [30,31]. Additionally, it downregulates the JAK2/STAT3 axis, mitigating fibrosis and chronic inflammation while promoting fibroblast-driven repair [19], and modulates TGF-β and MAPK pathways to support ECM remodeling and wound maturation [32].

## Antioxidant and Antimicrobial Activities of Curcumin in Wound Healing

Curcumin exerts critical antioxidant and antimicrobial effects that support wound healing by limiting oxidative stress, preventing infection, and enhancing tissue regeneration. Its phenolic structure enables direct scavenging of reactive oxygen species (ROS), reducing oxidative damage, DNA injury, and cellular dysfunction associated with chronic wounds [2,3,17,32]. Dose-dependent effects are notable; while low to moderate doses are cytoprotective, higher concentrations may induce pro-oxidant activity and impair healing, necessitating therapeutic optimization [9,17]. Curcumin enhances endothelial nitric oxide synthase (eNOS) activity and nitric oxide (NO) bioavailability, improving tissue perfusion and antimicrobial defense [15]. Additionally, it activates the Nrf2 signaling pathway, upregulating antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione (GSH), and heme oxygenase-1 (HO-1), which together reduce malondialdehyde (MDA), restore redox homeostasis, promote collagen deposition, and facilitate extracellular matrix remodeling [6,7,33]. Curcumin's broad-spectrum antimicrobial, antiviral, and antifungal actions further prevent secondary wound infections and maintain a sterile environment conducive to regeneration [9,34].

## Epigenetic and Molecular Regulatory Mechanisms of Curcumin

Curcumin exerts potent epigenetic and molecular regulatory effects that accelerate wound healing by modulating gene expression through DNA demethylation, histone modification, microRNA regulation, and transcription factor activity. It inhibits DNA methyltransferases, reversing pathological gene silencing and promoting re-expression of pro-regenerative genes [35,36], while altering chromatin accessibility via histone acetylation to upregulate genes involved in repair and suppress fibrotic or inflammatory transcription [35,37]. Curcumin

also regulates microRNAs such as miR-21 and miR-146a, enhancing fibroblast activation, ECM remodeling, and inflammation resolution [19]. At the transcriptional level, it modulates NF-κB, AP-1, and PPAR-γ to control inflammation, cellular proliferation, and ECM dynamics [6,4,10,16]. Additionally, curcumin increases transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF), supporting ECM synthesis and neovascularization necessary for tissue regeneration [4,16]. These integrated epigenetic and molecular mechanisms underscore curcumin's therapeutic potential in chronic and non-healing wound environments.

## Specific Molecular Pathways Influenced by Curcumin in Wound Healing

Curcumin regulates multiple signaling pathways involved in wound repair, including inflammation resolution, angiogenesis, ECM remodeling, and fibrosis control. Under hypoxic conditions, it enhances angiogenesis by upregulating HIF-1α and VEGF [38-40], and activates EGFR to support keratinocyte migration and re-epithelialization [13,41]. It modulates autophagy via FOXO1, RAB7, and BECN1 while inhibiting PI3K–AKT–mTOR signaling [12,42], and suppresses JAK2/STAT3 to reduce inflammatory cytokines and activate fibroblasts [19,43]. Curcumin induces antioxidant defenses through Nrf2/HO-1 activation, increasing SOD, GSH, and HO-1 while lowering ROS and MDA [7,10,33]. It improves perfusion via eNOS-induced nitric oxide [15], attenuates inflammation through Shh pathway suppression [44], and preserves ECM by reducing MMP-9 and upregulating TIMPs [13]. Activation of PPAR-γ [28] and modulation of TGF-β/Smad [45] reduces fibrosis, while Wnt/β-catenin signaling enhances cell migration, angiogenesis, and re-epithelialization [3,46,47]. MAPK activation promotes tissue repair and detoxification [32], while upregulation of MMP-2, MT1-MMP, VEGF, and TGF-β drives neovascularization [48,49]. Downregulation of Egr-1 reduces fibrosis [50], and biphasic TNF-α regulation balances immune defense and chronic inflammation [51]. Curcumin also upregulates Caveolin-1, supporting endothelial repair and angiogenesis [52], and inhibits NF-κB to limit myofibroblast differentiation and α-SMA expression [51]. Finally, Nrf2 activation promotes aligned collagen deposition, enhancing tissue strength [2,7]. Collectively, these actions position curcumin as a pleiotropic modulator with therapeutic relevance in chronic and non-healing wounds.

## Effects of Curcumin on the Proliferative Phase of Wound Healing

Curcumin enhances the proliferative phase of wound healing by stimulating fibroblast proliferation, angiogenesis, ECM remodeling, and epithelial regeneration. It promotes fibroblast migration and granulation tissue formation, driving collagen synthesis and wound closure [23,53], while upregulating VEGF to support neovascularization [5,13]. Curcumin induces TGF-β and VEGF expression, facilitating angiogenesis, granulation, and epithelialization [5,8,13], and enhances DNA and protein synthesis, type III collagen deposition, and epithelial regeneration [54]. By activating autophagy in fibroblasts and keratinocytes, it promotes cell survival, matrix turnover, and tissue remodeling [55]. Curcumin also modulates MMP-9 and upregulates α-SMA to support fibroblast differentiation and ECM restructuring [8], and increases MMP-2, MT1-MMP, VEGF, and TGF-β to enhance vascular sprouting and collagen deposition [48]. Both *in vitro* and *in vivo* studies confirm accelerated epithelialization and wound closure [14,56], with pre-radiation curcumin pretreatment enhancing collagen synthesis, hexosamine and DNA content, nitrate levels, and neovascularization, improving healing in irradiated tissues [57].

## Remodeling and Tissue Contraction

Curcumin facilitates the remodeling phase of wound healing by promoting collagen maturation, ECM reorganization, and wound contraction [9,58]. It induces fibroblast-to-myofibroblast differentiation through α-smooth muscle actin (α-SMA) upregulation, enhancing tissue contraction [59]. Curcumin modulates matrix homeostasis by balancing MMPs and TIMPs, preventing excessive ECM degradation and supporting structural remodeling [3,13,60]. It also promotes resolution of inflammation by inducing apoptosis of residual inflammatory cells and fibroblasts via caspase-3 activation and oxidative stress modulation [2]. Additionally, curcumin enhances neovascularization and mechanical strength of regenerated tissue, contributing to stable wound closure and reduced fibrosis [57].

## Neovascularization and Epithelialization

Curcumin promotes neovascularization and epithelial regeneration by enhancing angiogenesis and keratinocyte migration, thereby supporting oxygen delivery and re-epithelialization [5,9,13,14]. It activates EGFR signaling and upregulates caveolin-1 in epidermal stem cells, increasing capillary density and tissue renewal [61]. Despite its therapeutic potential, curcumin's clinical utility is limited by poor systemic bioavailability due to low solubility and first-pass metabolism [5,18]. Topical formulations—such as 5% turmeric gels or hyaluronic acid–curcumin conjugates—enhance local delivery, stability, and efficacy in wound healing [18,17].

## Formulations and Bioavailability Challenges

Curcumin's therapeutic potential in wound healing is constrained by poor systemic bioavailability due to its hydrophobicity, low aqueous solubility, and extensive first-pass metabolism, making topical delivery the preferred route for achieving effective local concentrations [2,4]. Advanced formulations such as hyaluronic acid–curcumin conjugates improve solubility and enhance bioactivity by promoting keratinocyte proliferation and migration [5,18], while nanoparticle encapsulation increases curcumin's stability, cellular uptake, and sustained release, augmenting antibacterial efficacy and accelerating wound closure [5,18,62]. Topical application of 5% turmeric extract gels further reduces inflammation and enhances re-epithelialization [17]. However, curcumin exhibits dose-dependent duality, where high concentrations may induce pro-oxidant effects, elevate intracellular reactive oxygen species, and impair tissue repair [9,17]. Given the difficulty in achieving therapeutic plasma levels via oral administration, optimized topical systems—including gels, nanoparticles, and HA conjugates—offer a promising approach to maximize curcumin's wound-healing efficacy while minimizing systemic limitations [2].

## Pharmacological Considerations

Curcumin's clinical application is limited by poor systemic bioavailability, due to low aqueous solubility and extensive first-pass hepatic metabolism [2,4]. Topical delivery remains preferred, achieving effective local concentrations at the wound site. Advanced formulations—including hyaluronic acid–curcumin conjugates—enhance solubility, stability, and bioactivity, promoting keratinocyte proliferation and migration [5,18]. Nanoformulations further improve curcumin's pharmacokinetics by increasing solubility,

protecting against degradation, enabling sustained release, and enhancing antimicrobial efficacy [5,18,62]. Topical 5% turmeric gels accelerate wound closure and attenuate inflammation in preclinical models [17]. However, supratherapeutic concentrations may induce pro-oxidant effects, elevating intracellular ROS and impairing repair mechanisms, necessitating careful dose optimization [9,17]. Beyond pharmacokinetics, curcumin modulates key transcription factors (NF-κB, AP-1), cytokines, and growth factors (VEGF, TGF-β), regulating angiogenesis, ECM remodeling, and inflammatory resolution [4,16]. It activates multiple signaling pathways—including HIF-1α, EGFR, Shh, JAK/STAT, and Wnt/β-catenin—supporting cellular proliferation, migration, and differentiation [4,5,23]. These molecular effects underpin curcumin's ability to enhance fibroblast migration, granulation, collagen deposition, epithelial regeneration, and neovascularization [5,23], supporting its use as an adjunct in chronic wound management, particularly in post-mastectomy settings. Future studies should optimize delivery platforms and dosing to fully harness curcumin's therapeutic potential.

## Ginger in the Treatment of Nonhealing Post-Mastectomy Wounds

*Zingiber officinale* (ginger) has traditional use and growing scientific support for treating complex nonhealing wounds post-mastectomy, which are complicated by surgical trauma, radiation damage, immunosuppression, and microbial colonization. Its bioactive compounds—gingerols, shogaols, paradols, and zingerone—exert potent antioxidant and anti-inflammatory effects critical for restoring tissue repair by modulating chronic inflammation, oxidative stress, and immune dysregulation [63,64]. Ginger reduces persistent inflammation that delays healing phases, promoting angiogenesis, fibroblast proliferation, and epithelial regeneration [65-67]. Additionally, it regulates immune responses by modulating macrophage polarization, neutrophil infiltration, and T-cell and dendritic cell activity, supporting balanced immunity essential for wound resolution in immunocompromised patients [68].

## Anti-Inflammatory Mechanisms of Ginger

Ginger's bioactives—[6]-gingerol, [6]-shogaol, zingerone, and paradol—modulate key inflammatory and oxidative pathways. It inhibits nuclear factor kappa B (NF-κB), reducing TNF-α, IL-1β, and IL-6 [63,64,69], and selectively suppresses cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX) while sparing COX-1, minimizing prostaglandin and leukotriene synthesis without typical NSAID side effects [70-72]. Ginger upregulates IL-10 [73,74], activates AMP-activated protein kinase (AMPK), and inhibits mechanistic target of rapamycin (mTOR), shifting immune responses toward resolution [75]. It also activates nuclear factor erythroid 2–related factor 2 (NRF2), enhancing HO-1, NQO1, and GPx expression to counter oxidative inflammation [75]. Ginger suppresses mitogen-activated protein kinase (MAPK), toll-like receptor (TLR), signal transducer and activator of transcription (STAT), nucleotide-binding oligomerization domain-like receptor (NLRP), and myeloperoxidase (MPO) signaling, attenuating innate immune activation [76]. Its compounds inhibit protein kinase C-alpha (PKCα) and Akt phosphorylation, reducing cytokine and inducible nitric oxide synthase (iNOS) expression [64,77]. Notably, 6-gingerol and 6-shogaol inhibit NLRP3 inflammasome activation, lowering IL-1β/IL-18 release and pyroptosis [78], while 6-shogaol disrupts TLR4/MD2 complex and MyD88-dependent NF-κB signaling [79]. Ginger downregulates Janus kinase (JAK)/STAT and hypoxia-inducible factor-1α (HIF-1α) pathways, rebalancing cytokine and angiogenic signaling [80,81], and inhibits high-mobility group box 1 (HMGB1) release, mitigating receptor for advanced glycation end products (RAGE)- and TLR-mediated inflammation [82]. It also inhibits microsomal prostaglandin E synthase-1 (mPGES-1), reducing prostaglandin E2 (PGE2) while preserving COX-1–derived prostaglandins [83].

Ginger alleviates neurogenic inflammation and pain via COX-2 and PGE2 suppression [84,85], with *in vivo* studies demonstrating reduced macrophage infiltration and enhanced wound healing [73,85]. It synergizes with curcumin to enhance anti-inflammatory and reparative effects [66,67]. Antioxidant mechanisms include increased superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) activity [86], decreased malondialdehyde (MDA) and nitric oxide (NO) levels [87,88], and iNOS suppression [89], collectively preserving cellular integrity and redox balance in chronic wounds.

## Antioxidant Mechanisms of *Zingiber officinale* (Ginger) in Wound Healing

*Zingiber officinale* exhibits robust antioxidant activity that mitigates oxidative stress–induced tissue damage in chronic wounds, including post-mastectomy breast cancer wounds. Oxidative stress impairs fibroblast function, collagen synthesis, and re-epithelialization. Ginger's bioactives—gingerols, shogaols, zingerone, and paradols—directly scavenge reactive oxygen and nitrogen species (ROS/RNS), reducing oxidative burden locally [63,90]. It upregulates endogenous antioxidants—superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione redox balance—while activating the Nrf2/ARE pathway to induce genes such as HO-1, GCLC, GPx, and NQO1 [63,86,91-93]. These actions decrease lipid and protein oxidation markers including malondialdehyde (MDA), nitrite/nitrate, and myeloperoxidase (MPO) [86,92,94). Ginger suppresses inducible nitric oxide synthase (iNOS) and nitric oxide (NO), reducing nitrosative stress [92,93], and downregulates pro-inflammatory cytokines TNF-α, IL-12, and IFN-γ, attenuating oxidative-inflammatory crosstalk [92,93]. It promotes cell survival by inhibiting apoptosis via Bax and caspase-3 downregulation and activating PI3K/Akt signaling [92]. Mitochondrial integrity and ATP production are preserved, sustaining energy metabolism essential for repair [95]. Ginger also induces HO-1, degrading pro-oxidant heme to cytoprotective metabolites [96], inhibits NADPH oxidase to reduce immune cell ROS [97], and chelates transition metals to limit hydroxyl radical formation [69]. *In vitro*, ginger demonstrates potent antioxidant capacity ($IC_{50}$ = 4.25 μg/mL) [63], and *in vivo* studies confirm reductions in oxidative DNA damage and apoptosis, preserving tissue integrity [91,94].

## Antimicrobial Mechanisms of *Zingiber officinale* (Ginger) in Wound Healing

*Zingiber officinale* exhibits broad-spectrum antimicrobial activity critical for managing chronic and post-mastectomy wounds. Ginger essential oil (GEO) and bioactives such as [6]-gingerol, shogaol, zingiberene, and α-cumene exert bactericidal effects via multiple mechanisms. GEO shows potent *in vitro* efficacy against wound pathogens including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli* [98-101]. Hydrophobic GEO constituents integrate into bacterial membranes, disrupting phospholipid bilayers, increasing permeability, causing

**Table 2:** Mechanisms of Action of Ginger (*Zingiber officinale*) in Wound Healing

| Mechanism of Action | Description | Key References |
|---|---|---|
| Anti-inflammatory Activity | Inhibits NF-κB signaling and downregulates pro-inflammatory cytokines (TNF-α, IL-6, IL-1β, COX-2), reducing chronic inflammation and immune overactivation that impair healing. | 77, 148 |
| Immunomodulation | Promotes M2 macrophage polarization, enhancing tissue repair by shifting macrophages from pro-inflammatory (M1) to anti-inflammatory (M2) phenotypes. | 144, 146, 145 |
| Epigenetic Regulation | Modulates DNA methyltransferases (DNMTs), histone deacetylases (HDACs), histone methyltransferases (HMTs), and miRNAs (e.g., suppresses miR-155; upregulates miR-146a, miR-15a), restoring gene expression crucial for proliferation, migration, and ECM remodeling. | 277, 188, 135, 67, 172 |
| Modulation of MicroRNAs (miRNAs) | Regulates miRNAs involved in inflammation and tissue repair, including downregulation of pro-inflammatory miR-155 and miR-20a, and upregulation of miR-146a and miR-15a, which enhances collagen synthesis and re-epithelialization. | 67, 108, 172 |
| Gut–Skin Axis Regulation | Restores beneficial gut microbiota (*Lactobacillus*, *Bifidobacterium*), reducing systemic inflammation and promoting epithelial regeneration, critical for skin barrier and wound repair, especially post-chemotherapy/radiotherapy. | 152,153,151, 95,154 |
| Antioxidant Activity | Enhances endogenous antioxidant defenses, reduces reactive oxygen species (ROS), and mitigates oxidative stress, thus protecting cells from injury and promoting tissue regeneration. | 1,47,155 |
| Modulation of Cellular Energy Metabolism (AMPK Pathway) | Activates AMPK–PGC-1α signaling axis, promoting mitochondrial biogenesis, ATP production, and metabolic homeostasis, essential for energy-demanding processes such as cell proliferation and ECM remodeling in wound healing. | 160, 162,75,161 |
| Inhibition of Matrix Metalloproteinases (MMPs) | Downregulates overexpressed MMPs (MMP-2, MMP-9) and upregulates tissue inhibitors of metalloproteinases (TIMPs), balancing ECM degradation and synthesis to prevent chronic matrix breakdown and support tissue remodeling. | 125,126, 127, 14,74 |
| Promotion of Fibroblast and Keratinocyte Activity | Stimulates proliferation, migration, and differentiation of fibroblasts and keratinocytes via activation of Akt/mTOR and MAPK signaling pathways, enhancing granulation tissue formation and re-epithelialization. | 66,178, 122, 20, 44 |
| Neuroimmune Modulation | Suppresses neurogenic inflammation by downregulating neuropeptides (substance P, CGRP) and modulating macrophage polarization, reducing pain and neuroinflammatory signaling that impair healing. | 143,144,145,149, 150 |
| Modulation of Stress Hormones via HPA Axis | Reduces hyperactivity of the hypothalamic–pituitary–adrenal axis, lowering cortisol and corticosterone levels, which mitigates stress-induced immune suppression and collagen synthesis inhibition. | 1,55,156 |
| Anti-fibrotic Effects | Inhibits TGF-β/Smad signaling and α-SMA expression, reducing myofibroblast activation and excessive ECM deposition, thereby preventing hypertrophic scarring and keloid formation. | 163,164,159,165, 167 |
| Promotion of Collagen Crosslinking and ECM Maturation | Upregulates lysyl oxidase, facilitating collagen and elastin crosslinking for ECM stabilization, and fine-tunes TGF-β1 signaling for organized collagen fibrillogenesis and functionally competent scar tissue formation. | 157, 158,159 |
| Antimicrobial Activity (Topical) | It exhibits broad-spectrum antimicrobial effects against pathogens, including *Staphylococcus aureus* and *Pseudomonas aeruginosa*, reducing infection risk and supporting wound sterility. | 98, 99, 100, 101 |

cytoplasmic leakage, membrane depolarization, and cell lysis [100-104). GEO also impairs bacterial mitochondria by disrupting electron transport and ATP synthesis; zingiberene binds bacterial DNA, inhibiting replication and transcription [103,105]. Additionally, GEO downregulates genes governing the tricarboxylic acid cycle, membrane biosynthesis, and nucleic acid metabolism, suppressing bacterial growth and energy metabolism [100]. Anti-biofilm effects arise from inhibition of quorum sensing and extracellular polymeric substance synthesis, preventing biofilm formation [99,106]. Phenolic components promote leakage of bacterial enzymes and structural proteins, intensifying microbial death [100,106]. These synergistic antimicrobial actions underpin ginger's integrative potential in chronic wound management.

Post-mastectomy wounds are susceptible to bacterial colonization due to ischemia, lymphatic disruption, and immunosuppression from oncologic therapies. Opportunistic infections by *S. aureus*, *P. aeruginosa*, and *E. coli* exacerbate wound chronicity by impairing re-epithelialization. Ginger's antimicrobial, anti-inflammatory, and antioxidant effects collectively reduce microbial load and facilitate healing. *In vitro* and *in vivo* data affirm GEO's bactericidal efficacy against these pathogens, with Singh (2008), Lei (2017), and Zhang (2023) demonstrating membrane disruption and cytoplasmic leakage as primary mechanisms. Furthermore, ginger-derived hydrogels and bioactive dressings maintain bactericidal activity while promoting tissue regeneration and re-epithelialization [107].

## Promotion of Angiogenesis by *Zingiber officinale* in Wound Healing

Angiogenesis is critical for wound repair, particularly in ischemic or radiotherapy-compromised tissues such as post-mastectomy wounds. *Zingiber officinale* promotes neovascularization primarily through upregulation of vascular endothelial growth factor (VEGF), enhancing endothelial proliferation, migration, and tissue oxygenation (108, 109). Its angiogenic effects are dose- and context-dependent, with higher concentrations or pro-inflammatory environments potentially suppressing angiogenesis via inhibition of COX-2, p38 MAPK, and NF-κB [109]. 6-Gingerol indirectly supports angiogenesis by modulating platelet release of VEGF, PDGF, bFGF, EGF, and matrix metalloproteinases [110-114]. Studies show that 6-gingerol with microneedling enhances angiogenesis and collagen deposition [115], while gingerol plus vitamin D increases vascularization, fibrin matrix formation, and myofibroblast recruitment [67,116]. The derivative 10-shogaol further activates TGF-β signaling and stimulates PDGF-αβ release from fibroblasts, keratinocytes, macrophages, and endothelial cells, supporting vascular remodeling [117-119]. Additionally, 6-gingerol activates the PI3K/Akt pathway, promoting eNOS phosphorylation and nitric oxide (NO) production, which facilitate vasodilation and endothelial migration [120]. These effects are supported by ginger's antioxidant and anti-inflammatory properties, which preserve endothelial integrity and promote regenerative signaling [69]. Given angiogenesis's central role in granulation and tissue repair, ginger represents a promising adjunct in treating chronic post-mastectomy wounds [121].

## Modulation of Fibroblast and Keratinocyte Activity by Ginger

Ginger promotes wound repair by enhancing fibroblast

proliferation, myofibroblast differentiation, and keratinocyte migration—processes critical for granulation tissue formation and re-epithelialization, particularly in chronic wounds. The bioactive compound 10-shogaol upregulates key growth factors including TGF-β, PDGF-αβ, and VEGF, facilitating fibroblast activation, angiogenesis, and epithelial migration [66]. Chen (2012) showed that 10-shogaol stimulates fibroblast and keratinocyte proliferation and migration, accelerating wound closure. Ginger powder extract activates PI3K/Akt/mTOR signaling, promoting actin polymerization and cytoskeletal remodeling essential for cell motility [122], while also modulating the MAPK pathway, with ERK driving proliferation and p38 MAPK inducing heat shock proteins via HSF-1 to improve survival under stress [44]. These coordinated effects underscore ginger's therapeutic potential to restore epithelial integrity and ECM remodeling nonhealing wounds.

## Inhibition of Matrix Metalloproteinases (MMPs) by Ginger

Chronic Wounds exhibit pathological overexpression of matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, leading to extracellular matrix (ECM) degradation, impaired growth factor signaling, and disrupted fibroblast and keratinocyte function [123,124]. 6-gingerol and 6-shogaol, downregulate MMPs by inhibiting NF-κB signaling, a central transcriptional regulator of proteolytic and inflammatory mediators [125-127]. Ginger concurrently upregulates tissue inhibitors of metalloproteinases (TIMPs), particularly TIMP-1, restoring MMP/TIMP balance essential for regulated ECM turnover and re-epithelialization [128,129]. Al Shibani (2022) demonstrated that ginger extract suppresses MMP-1, -2, -8, -9 and IL-8, indicating anti-inflammatory control of proteolysis. MMP modulation is a validated therapeutic target in chronic wound care [130,131]; however, complete inhibition disrupts physiological remodeling, while excessive expression impairs closure [132]. Ginger's context-specific regulation of MMP/TIMP dynamics preserves ECM integrity and supports tissue repair, highlighting its clinical potential in chronic wound management.

## Epigenetic Modulation by *Zingiber officinale* in Wound Healing

Epigenetic mechanisms—including DNA methylation, histone modification, and non-coding RNA regulation—govern gene expression in wound repair, with aberrations contributing to chronic and cancer-related wound pathologies [133]. Phytochemicals in *Zingiber officinale*, including [6]-gingerol, [6]-shogaol, paradol, quercetin, kaempferol, rutin, catechin, and naringenin, modulate epigenetic enzymes such as DNA methyltransferases (DNMTs), histone deacetylases (HDACs), histone methyltransferases (HMTs), and histone acetyltransferases (HATs), and regulate microRNAs critical for proliferation, inflammation resolution, and ECM remodeling [134-137]. Quercetin inhibits EP300/CBP, alters histone H3 acetylation and phosphorylation, and promotes chromatin remodeling [138], while gingerols and shogaols modulate DNA methylation, histone acetylation, and non-coding RNA profiles to reprogram gene expression [139]. These compounds may reverse pathological silencing by targeting epigenetic enzymes now recognized as therapeutic targets in wound healing [140,141]. Additionally, they enhance DNA repair and regulate apoptosis through histone acetylation and promoter demethylation [142], positioning ginger as a natural epigenetic modulator with therapeutic relevance in chronic, nonhealing wounds.

## Modulation of Neuroimmune Crosstalk by *Zingiber officinale* in Wound Healing

Chronic post-mastectomy wounds involve neurogenic inflammation and immune dysregulation that impede resolution and regeneration. *Zingiber officinale* modulates neuroimmune crosstalk by suppressing neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), thereby reducing nociception, mast cell degranulation, and vasodilation [143]. Ginger promotes macrophage polarization toward the M2 reparative phenotype, resolving inflammation and supporting tissue repair [144-146]. Flavonoids such as quercetin enhance the M2/M1 ratio and downregulate TNF-α, IL-6, IL-8, IL-1β, IP-10, COX-2, and NF-κB components JNK, c-Jun, and IκBα [147,148]. At the neuronal level, [6]-gingerol reduces CGRP secretion via calcium channel inhibition in CA77 neuroendocrine cells [149,150]. This integrated neuroimmune modulation enables inflammation resolution, analgesia, and regeneration in nonhealing wounds.

## Regulation of the Gut–Skin Axis via Microbiome Modulation by *Zingiber officinale*

The gut–skin axis integrates immune, metabolic, and neuroendocrine pathways, which are often disrupted by chemotherapy- and radiotherapy-induced dysbiosis in breast cancer patients, impairing mucosal immunity and wound repair [151]. *Zingiber officinale* restores gut microbiota by increasing beneficial taxa such as *Lactobacillus* and *Bifidobacterium*, enhancing epithelial barrier function and immune homeostasis [152,153]. 6-gingerol boosts microbial diversity, suppresses pathogens, and downregulates IL-6 and iNOS, thereby attenuating systemic inflammation [152]. This microbial modulation reduces peripheral inflammatory signaling, promotes epithelial regeneration, and supports cutaneous wound healing [95,154]. By influencing T-cell differentiation, cytokine profiles, and epithelial turnover, ginger reestablishes gut–skin immune balance and accelerates tissue repair in cancer-related chronic wounds [153,154].

## Modulation of Stress Hormones *via* HPA Axis Regulation

Chronic stress impairs wound healing by elevating glucocorticoids—cortisol and corticosterone—that suppress immune function, inhibit collagen synthesis, and delay tissue regeneration through dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. This neuroendocrine imbalance is exacerbated in cancer patients undergoing intensive therapy, where normalization of HPA activity may improve wound repair. *Zingiber officinale* exhibits adaptogenic effects modulating HPA axis function and mitigating stress-induced endocrine and oxidative disturbances. Bioactives such as geraniol and 1,8-cineole decrease corticosterone and cortisol levels, reversing immunosuppression and oxidative damage. Geraniol attenuates neuroinflammation and oxidative stress, key mediators of stress-related tissue injury [155]. Similarly, 1,8-cineole reduces cortisol and enhances systemic antioxidant capacity, lowering reactive oxygen species and fostering tissue repair [156]. These actions support ginger's adjunctive potential to restore a reparative milieu in stress-compromised wound healing, notably in breast cancer patients [155,156].

## Promotion of Collagen Crosslinking and ECM Maturation

Chronic wounds frequently display impaired extracellular matrix (ECM) remodeling characterized by disorganized collagen deposition and weak scar tissue. Ginger demonstrates a capacity to enhance collagen crosslinking and ECM maturation, thereby improving tissue tensile strength and structural integrity. Mechanistically, ginger polyphenols upregulate lysyl oxidase, the critical enzyme catalyzing covalent crosslinking of collagen and elastin fibers essential for ECM stabilization and remodeling [157]. Furthermore, ginger modulates transforming growth factor-beta 1 (TGF-β1) signaling, a key regulator of fibroblast activation, ECM synthesis, and collagen organization. While TGF-β1 governs proliferation, differentiation, immune responses, and matrix production during healing, its dysregulation contributes to chronic wound pathology and fibrosis (158, 159). Ginger's modulation of TGF-β1 signaling promotes organized collagen fibrillogenesis and optimal ECM assembly, facilitating functionally competent scar formation. These effects highlight ginger's therapeutic potential as a natural adjunct in chronic and post-surgical wound healing where ECM disarray and compromised tissue strength are prominent challenges.

## Regulation of Cellular Energy Metabolism via AMPK Pathway

Mitochondrial dysfunction and ATP depletion under hypoxia, oxidative stress, or radiation impair cellular proliferation, migration, and extracellular matrix remodeling in chronic wounds. *Zingiber officinale* activates AMP-activated protein kinase (AMPK), a master regulator of energy homeostasis, enhancing mitochondrial biogenesis and ATP synthesis critical for tissue repair. The bioactive compound 6-gingerol upregulates the AMPK–PGC-1α axis, increasing mitochondrial content, mtDNA replication, ATP production, and respiratory chain efficiency [160]. AMPK activation concurrently inhibits mTORC1, suppressing energy-demanding anabolic processes linked to chronic inflammation [161]. Additionally, ginger modulates AMPK–NF-κB signaling to reduce pro-inflammatory cytokine expression and inflammatory stress [75,162]. These combined effects restore mitochondrial function, optimize energy metabolism, and attenuate inflammation, thereby enhancing cellular resilience in ischemic, radiotherapy-exposed, and oxidative stress–compromised wound environments.

## Anti-Fibrotic Effects of Ginger in Post-Mastectomy Wound Healing

Hypertrophic scars and keloids in post-mastectomy wounds arise from dysregulated fibroblast activity and excessive extracellular matrix deposition. Ginger inhibits fibrosis by suppressing the TGF-β/Smad pathway, downregulating α-smooth muscle actin, and reducing myofibroblast differentiation. TGF-β1 overexpression and persistent Smad activation drive hypertrophic scar formation by promoting collagen types I and III synthesis and inhibiting ECM degradation via tissue inhibitors of metalloproteinases [159,163-167]. Distinct TGF-β isoforms regulate wound repair phases: TGF-β1 mediates inflammation and VEGF-dependent angiogenesis [168]; TGF-β2 promotes ECM production and cell migration [169]; TGF-β3 facilitates scarless healing through organized collagen alignment [45,168,170]. Ginger's modulation of these isoform-specific pathways supports antifibrotic remodeling and may mitigate pathological scarring in oncology patients.

## Regulation of MicroRNAs by Ginger in Wound Healing

MicroRNAs (miRNAs) are key post-transcriptional regulators of inflammation, angiogenesis, extracellular matrix remodeling, and epithelial regeneration. Gingerol modulates miRNA profiles critical to tissue repair. In diabetic wound models, combined gingerol and vitamin D upregulated reparative miR-146a and miR-15a while suppressing pro-inflammatory miR-155, enhancing fibrin deposition, collagen synthesis, and re-epithelialization, implicating a miRNA-dependent mechanism [68]. Chronic wounds often overexpress miR-20a, which impairs healing by downregulating TGF-β receptor II in keratinocytes, disrupting TGF-β–mediated regeneration [45,171,172]. Dysregulated miRNAs further perturb growth factor signaling, perpetuating wound chronicity [172,173]. Circulating miRNAs are emerging as dynamic biomarkers of healing progression [68]. Vitamin D complements these effects by alleviating endoplasmic reticulum stress [174,175], enhancing macrophage bactericidal activity [176], suppressing inflammatory cytokines [68,177], and modulating insulin receptor expression to maintain metabolic homeostasis during repair. These data highlight ginger as a natural epigenetic modulator that facilitates wound healing via targeted miRNA regulation, especially synergistically with vitamin D.

## Oral *Zingiber officinale* as a Systemic Adjunct in Wound Healing

Oral *Zingiber officinale* provides a multifaceted adjunct for impaired wound healing in cancer patients by modulating inflammatory, oxidative, neuroendocrine, immune, microbial, and epigenetic pathways crucial to tissue repair. Ginger inhibits NF-κB activation, reducing pro-inflammatory cytokines TNF-α, IL-6, and IL-1β, thus attenuating chronic inflammation [147,148]. Its antioxidant constituents enhance resilience against reactive oxygen species and promote macrophage polarization toward the reparative M2 phenotype [144-146]. Gingerol-rich fractions regulate microRNAs governing angiogenesis, extracellular matrix remodeling, and epithelial regeneration [67,172]. Through gut–skin axis modulation, ginger restores microbial homeostasis by increasing Lactobacillus and Bifidobacterium populations and suppresses systemic inflammation [95,152-154]. Additionally, 6-gingerol and 1,8-cineole normalize hypothalamic–pituitary–adrenal axis activity, lowering cortisol and corticosterone levels that impair immune function, collagen synthesis, and angiogenesis [155,156]. Ginger enhances mitochondrial function via AMPK–PGC-1α activation, increasing biogenesis and ATP production in metabolically compromised wounds [160], relevant in radiotherapy- or ischemia-affected tissues. Oral forms include capsules, extracts (500–2000 mg/day), powders, and infusions; however, its antiplatelet effects warrant caution in patients on anticoagulants or chemotherapy [128]. Randomized controlled trials are needed to optimize dosing and validate clinical efficacy for oncology wound

## Topical Application of *Zingiber officinale* in Wound Healing

Topical *Zingiber officinale* delivers targeted anti-inflammatory, antimicrobial, analgesic, and regenerative effects critical to wound management. It inhibits cyclooxygenase-2 (COX-2) and prostaglandin synthesis, reducing local inflammation and nociception [143]. Its essential oil components—6-gingerol, 10-shogaol, zingiberene, and α-cumene—exert broad-spectrum antibacterial activity against

Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, and Klebsiella pneumoniae [98-101]. Ginger promotes fibroblast proliferation, keratinocyte migration, angiogenesis, and granulation tissue formation [66,109,178]. It modulates matrix metalloproteinases MMP-2 and MMP-9 while upregulating tissue inhibitors of metalloproteinases (TIMPs), restoring ECM balance via NF-κB suppression [74,125,126,128]. Common topical formulations include creams, hydrogels, and ointments containing ginger essential oil diluted in carriers such as coconut oil or combined with synergistic agents like curcumin or honey [107]. These are effective for superficial, colonized, or inflamed wounds, providing an alternative for patient's intolerant to oral ginger. Topical use minimizes systemic exposure but may cause irritation or hypersensitivity, especially on irradiated skin; patch testing is recommended. Rigorous clinical trials are warranted to establish optimal dosing, efficacy, and integration into standard wound care.

## Combined Oral and Topical *Zingiber officinale* Therapy in Wound Healing

Combined oral and topical administration of *Zingiber officinale* (ginger) offers a synergistic approach addressing systemic and local factors impeding wound healing. Orally, ginger inhibits NF-κB signaling, activates AMP-activated protein kinase (AMPK), promotes M2 macrophage polarization, and restores gut microbiota by increasing Lactobacillus and Bifidobacterium, supporting the gut–skin axis [152,153,162]. Topically, ginger enhances fibroblast and keratinocyte proliferation, angiogenesis, extracellular matrix remodeling, and exerts antimicrobial effects against Staphylococcus aureus, Pseudomonas aeruginosa, and *Escherichia coli* [107,178,179]. This dual modality is particularly suitable for chronic post-mastectomy wounds in breast cancer patients not on chemotherapy and without contraindications such as anticoagulants or hypersensitivity. Recommended regimens include oral standardized ginger extract (~1 g/day) with topical application of diluted essential oil or ginger-infused gel once or twice daily. When combined administration is not possible, oral ginger targets systemic dysregulation, whereas topical therapy addresses local inflammation, infection, and impaired tissue regeneration.

## *Piper nigrum* in the Management of Chronic Post-Mastectomy Wounds in Breast Cancer

Chronic non-healing post-mastectomy wounds, often exacerbated by radiotherapy-induced fibrosis, lymphatic disruption, and systemic immunosuppression, are characterized by persistent inflammation, microbial biofilm formation, oxidative stress, impaired angiogenesis, and dysregulated extracellular matrix (ECM) remodeling. Conventional treatments frequently fail to resolve these multifactorial pathologies. *Piper nigrum*, through its bioactive alkaloid piperine, exerts anti-inflammatory, antioxidant, antimicrobial, angiogenic, and immunomodulatory effects relevant to wound repair. Piperine downregulates NF-κB and COX-2, suppressing pro-inflammatory cytokines and promoting inflammation resolution [147,148]. It inhibits quorum sensing and biofilm formation in key pathogens including *Staphylococcus aureus* and *Pseudomonas aeruginosa* [98-100]. Piperine enhances VEGF-mediated angiogenesis [8], restores redox balance, and promotes fibroblast proliferation and epithelial regeneration [66,178]. Additionally, it inhibits cytochrome P450 isoenzymes and P-glycoprotein, enhancing the systemic bioavailability of co-administered agents [14]. These multifaceted actions support *Piper nigrum* as a phytotherapeutic adjunct capable of addressing both molecular and clinical barriers to wound resolution in breast cancer patients.

## Anti-Inflammatory Mechanisms of *Piper nigrum*

Piperine exerts potent anti-inflammatory effects essential for resolving chronic wounds sustained by persistent immune activation. It inhibits the NF-κB signaling cascade, suppressing transcription of TNF-α, IL-1β, and IL-6—central mediators in chronic wound inflammation [180]—and downregulates MAPK pathways (ERK, JNK, p38), reducing cytokine output [181]. Piperine also suppresses COX-2 and iNOS expression, lowering PGE2 and nitric oxide levels, which otherwise exacerbate vascular permeability, oxidative stress, and ECM degradation [182]. Furthermore, it modulates macrophage polarization by activating the PI3K/Akt/mTOR axis, promoting a shift from M1 to reparative M2 phenotypes—key for angiogenesis and matrix remodeling [183]. *In vivo*, piperine reduces neutrophil and macrophage infiltration at wound sites, mitigating chronic inflammation and supporting orderly healing progression [184].

## Antimicrobial and Antibiofilm Activities of *Piper nigrum*

Chronic post-mastectomy wounds are frequently colonized by multidrug-resistant pathogens such as *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Escherichia coli*, often residing in biofilms that impair immune clearance and antibiotic efficacy. Piperine has broad-spectrum antimicrobial activity against these organisms by disrupting bacterial membrane integrity, increasing permeability, and impairing respiration, resulting in cell death [185]. It inhibits quorum sensing, suppressing virulence factor expression and biofilm formation, and blocks efflux pump activity, enhancing intracellular antibiotic accumulation and reversing drug resistance [185,186]. These combined mechanisms support the use of *Piper nigrum* as an adjunctive therapy in biofilm-associated chronic wound management.

## Angiogenic and Vasculogenic Effects of *Piper nigrum*

Effective wound healing requires neovascularization to restore oxygenation, nutrient delivery, and immune function—processes often impaired in post-mastectomy wounds due to radiotherapy-induced fibrosis. Hypoxia-induced expression of vascular endothelial growth factor (VEGF) initiates angiogenesis, with optimal tissue oxygen tension (~30–40 mmHg) essential for fibroblast activation, collagen synthesis, and epithelial proliferation [187,188]. Piperine upregulates VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF), enhancing endothelial proliferation, migration, and capillary formation [189]. *In vivo* evidence confirms increased capillary density in piperine-treated wounds, supporting *Piper nigrum*'s role in vascular regeneration, improved oxygenation, and accelerated healing in ischemic or irradiated post-mastectomy tissue.

## Fibroblast Activation and ECM Remodeling by *Piper nigrum*

Post-mastectomy wounds often exhibit fibroblast dysfunction and disordered extracellular matrix (ECM) turnover due to inflammation, ischemia, and radiation injury. Piperine promotes fibroblast proliferation and upregulates collagen types I and III, enhancing ECM scaffolding and dermal regeneration [189]. It suppresses

**Table 3:** Mechanisms of Action of *Piper nigrum* in Wound Healing

| Mechanism of Action | Description | References |
|---|---|---|
| Anti-inflammatory Activity | Inhibition of NF-κB, MAPK (ERK, JNK, p38) pathways; downregulation of TNF-α, IL-1β, IL-6; suppression of COX-2 and iNOS enzymes; macrophage polarization from M1 to M2 via PI3K/Akt/mTOR; reduction of leukocyte infiltration | 180, 181,182, 183, 184 |
| Antimicrobial and Antibiofilm Effects | Broad-spectrum antimicrobial activity against S. aureus, P. aeruginosa, E. coli; disruption of bacterial membrane integrity; inhibition of quorum sensing and biofilm formation; efflux pump inhibition | 1,85,186 |
| Angiogenesis and Vasculogenesis | Upregulation of VEGF, FGF, PDGF; promotion of endothelial proliferation, migration, and capillary formation; improved vascular repair in ischemic/irradiated wounds | 188, 189, 187 |
| Fibroblast Activation and ECM Remodeling | Enhancement of fibroblast proliferation; stimulation of collagen I and III synthesis; downregulation of TGF-β1 and inhibition of TGF-β/SMAD pathway; inhibition of MMP-2 and MMP-9 | 189, 190 |
| Immunomodulation | Restoration of Th1/Th2 cytokine balance; promotion of Treg function; macrophage M1 to M2 polarization; increased lymphocyte proliferation and macrophage phagocytosis; inhibition of NLRP3 inflammasome via AMPK activation | 189,191, 192, 193 |
| Neurogenic and Pain Modulation | TRPV1 desensitization reducing nociceptive signaling; regulation of neuropeptides, substance P and CGRP to mitigate neurogenic inflammation | 194, 195 |
| Cellular Signaling Pathway Modulation | Activation of PI3K/Akt/mTOR pathway promoting EMT, proliferation, and protein synthesis; enhancement of MAPK/ERK pathway for keratinocyte proliferation and migration; suppression of Wnt/β-catenin signaling to reduce scar formation | 196, 197, 198, 200, 201, 202, 203 |
| Mitochondrial and Bioenergetic Enhancement | Enhancement of ATP production via CB2 receptor activation; upregulation of PGC-1α promoting mitochondrial biogenesis through SREBP-1c/PPARγ and AMPK/AKT-mTOR; preservation of mitochondrial integrity by preventing MPTP opening and apoptosis | 204, 205, 206,207, 208, 209, 210, 211 |
| Epigenetic Regulation | Pan-HDAC inhibition leading to histone acetylation and chromatin remodeling; modulation of miRNAs (miR-21, miR-146a, miR-155) involved in fibroblast proliferation, inflammation resolution, angiogenesis, and ECM remodeling | 212, 213, 214, 219, 220, 221, 222, 223, 224 |
| Stem Cell Recruitment and Activation | Modulation of wound microenvironment to support MSC homing and retention; enhancement of MSC proliferation, survival, and differentiation; activation by β-caryophyllene promoting regenerative pathways | 225,226, 227,228 |
| Skin Barrier Recovery and Keratinocyte Function | Activation of EGFR pathway promoting keratinocyte migration and differentiation; upregulation of involucrin, filaggrin, loricrin; inhibition of STAT6 phosphorylation restoring barrier protein expression; stimulation of EGF expression | 229, 230, 231, 232 |
| Psychoneuroimmune Modulation | Elevation of hypothalamic and hippocampal serotonin and dopamine; MAO inhibition sustaining neurotransmitter levels; HPA axis regulation lowering cortisol and oxidative stress; increased BDNF expression improving neuroplasticity and immune function | 233, 234, 235 |
| Enhancer of Drug Bioavailability | Inhibition of hepatic AHH and UDP-glucuronyltransferase reducing glucuronidation; inhibition of P-gp and CYP450 enzymes (CYP3A4, CYP1A1, CYP1B1, CYP1B2, CYP2E1); receptor sensitization and modulation of membrane dynamics improving absorption; synergy with antibiotics enhancing efficacy | 237, 238 |

TGF-β1 and the TGF-β/SMAD pathway, mitigating fibrosis and enabling organized matrix remodeling [190]. Additionally, piperine downregulates MMP-2 and MMP-9, reducing ECM degradation and preserving tissue structure [66]. These combined effects support balanced ECM remodeling, wound contraction, and restoration of tensile strength in chronic, irradiated wound environments.

## Immunomodulatory Properties of *Piper nigrum* in Wound Healing

Post-mastectomy wound healing is hindered by cancer-associated immune dysregulation and treatment-induced immunosuppression. Piperine restores immune balance by modulating Th1/Th2 cytokine responses and enhancing regulatory T cell (Treg) function in immunocompromised models [189]. It promotes macrophage polarization from M1 to M2 phenotypes, facilitating inflammation resolution, extracellular matrix (ECM) remodeling, and tissue regeneration [191]. Piperine also enhances lymphocyte proliferation and macrophage phagocytosis, counteracting tumor-associated immunosuppression and supporting microbial clearance [192]. Furthermore, it inhibits NLRP3 inflammasome activation via AMPK signaling, reducing pyroptosis and proinflammatory cytokine release [193]. These effects collectively reestablish immune homeostasis and promote wound healing in compromised post-surgical environments.

## Immunomodulatory Properties of *Piper nigrum* in Wound Healing

Post-mastectomy wound healing is often compromised by cancer-induced immune dysregulation and therapy-related immunosuppression. Piperine restores immune balance by modulating Th1/Th2 cytokine responses and enhancing regulatory T cell (Treg) function [189]. It promotes macrophage polarization from the pro-inflammatory M1 to the reparative M2 phenotype, supporting inflammation resolution and tissue regeneration [191]. Piperine also stimulates lymphocyte proliferation and macrophage phagocytic activity, mitigating tumor-associated immunosuppression and aiding microbial clearance [192]. Additionally, it inhibits NLRP3 inflammasome activation via AMPK signaling, reducing pyroptosis and pro-inflammatory cytokine release [193]. These immunoregulatory effects facilitate immune homeostasis, limit chronic inflammation, and enhance wound repair in immunocompromised post-surgical settings.

## Neurogenic and Pain-Modulating Actions of *Piper nigrum*

Chronic post-mastectomy wounds are often exacerbated by neurogenic inflammation and persistent pain, which impair healing and reduce therapeutic compliance. Piperine modulates transient receptor potential vanilloid 1 (TRPV1) channel, inducing desensitization and thereby attenuating nociceptive signaling and neuronal hyperexcitability [194]. It also downregulates neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), limiting neurogenic inflammation, vasodilation, and peripheral sensitization [195]. These neuromodulatory effects reduce pain, suppress neuroinflammation, and restore neuroimmune balance, creating a regenerative microenvironment conducive to wound healing submission.

## Modulation of Cellular Signaling Pathways by *Piper nigrum*

*Piper nigrum* facilitates wound healing through regulation of key signaling cascades governing inflammation resolution, cell proliferation, migration, and extracellular matrix (ECM) remodeling. Piperine activates the PI3K/Akt/mTOR pathway, enhancing epithelial–mesenchymal transition (EMT), fibroblast and keratinocyte proliferation, and protein synthesis—accelerating the proliferative phase of repair [196-198]. It also stimulates the MAPK/ERK cascade via ERK phosphorylation, promoting keratinocyte migration and re-epithelialization; conversely, ERK inhibition impairs epidermal regeneration [199-201]. Additionally, piperine downregulates β-catenin, COX-2, and c-Myc within the Wnt/β-catenin axis, preventing hyperproliferation and favoring organized, scar-free healing [202,203]. Through coordinated modulation of PI3K/Akt/mTOR, MAPK/ERK, and Wnt/β-catenin pathways, *Piper nigrum* supports functional tissue regeneration in chronic wound environments.

## Mitochondrial and Bioenergetic Enhancement by *Piper nigrum*

Efficient wound healing depends on intact mitochondrial function and energy homeostasis, which are compromised under hypoxic, ischemic, or nutrient-deprived conditions common in chronic and post-mastectomy wounds. Piperine enhances mitochondrial bioenergetics through multiple mechanisms. Black pepper essential oil (BPEO) increases metabolic activity in human dermal fibroblasts, promoting matrix remodeling [204]. Trans-β-caryophyllene (BCP), a BPEO constituent, activates cannabinoid receptor 2 (CB2), improving tricarboxylic acid cycle flux and ATP synthesis [205,206]. Piperine upregulates PGC-1α, the key regulator of mitochondrial biogenesis, through activation of SREBP-1c/PPARγ and AMPK/AKT-mTOR signaling, enhancing oxidative phosphorylation [207,208]. It also stabilizes mitochondrial membrane potential, inhibits mitochondrial permeability transition pore (MPTP) opening, and prevents calcium overload and apoptosis—key contributors to cellular dysfunction and impaired healing [209-211]. These actions position *Piper nigrum* as a bioenergetic modulator that restores mitochondrial function and supports tissue regeneration in metabolically compromised wound environments.

## Epigenetic Regulation and Stem Cell Recruitment by *Piper nigrum*

Piperine facilitates wound healing in chronic and post-surgical settings by epigenetically reactivating silenced regenerative pathways. As a pan-histone deacetylase (HDAC) inhibitor, it induces histone acetylation, loosening chromatin structure and restoring transcription of genes essential for proliferation, angiogenesis, and extracellular matrix (ECM) synthesis [212-214]. HDAC inhibition disrupts histone-DNA affinity, alters protein-protein interactions, and stabilizes transcriptional complexes to refine gene regulation [215-218]. Piperine also modulates microRNAs—miR-21, miR-146a, and miR-155—that control fibroblast activation, inflammatory resolution, angiogenesis, and ECM remodeling by targeting untranslated mRNA regions to suppress or degrade transcripts [213,219-224]. Through combined modulation of histone acetylation and miRNA networks, *Piper nigrum* reprograms impaired wound microenvironments and enhances stem cell recruitment, supporting its potential as a regenerative therapy for fibrotic, non-healing post-mastectomy wounds.

## Stem Cell Recruitment and Activation by *Piper nigrum*

Healing of chronic and post-mastectomy wounds requires activation of endogenous stem and progenitor cells to restore tissue architecture. Piperine enhances this process by modulating the wound microenvironment—reducing inflammation, stimulating angiogenesis, and promoting mesenchymal stem cell (MSC) homing, retention, and function [225]. It also supports MSC proliferation, survival, and differentiation, thereby enhancing collagen deposition and neovascularization [226,227]. Additionally, β-caryophyllene, a key component of black pepper essential oil, activates regenerative pathways while suppressing inflammation, further potentiating stem cell-mediated tissue repair [228].

## Enhanced Epidermal Barrier Repair and Keratinocyte Function by *Piper nigrum*

Restoration of the epidermal barrier requires coordinated keratinocyte activation, migration, and differentiation. Piperine and its metabolite piperonylic acid enhance these processes by activating the epidermal growth factor receptor (EGFR) pathway, with piperonylic acid directly binding EGFR to upregulate genes essential for re-epithelialization [229]. Piperine also increases the expression of involucrin, filaggrin, and loricrin—key barrier proteins—by inhibiting STAT6 phosphorylation in keratinocytes, countering inflammation-induced suppression [230,231]. Additionally, piperonylic acid stimulates epidermal growth factor (EGF) expression, promoting keratinocyte proliferation and migration [232]. These effects position *Piper nigrum* as a promising agent in topical therapies for post-surgical wound management.

## Psychoneuroimmune Modulation by *Piper nigrum* in Wound Healing

Psychological stress impairs wound healing via immune dysregulation, glucocorticoid elevation, and systemic inflammation—particularly relevant in post-mastectomy breast cancer patients. *Piper nigrum*, via piperine, exerts psychoneuroimmune effects that support tissue repair. Piperine increases serotonin and dopamine in the hypothalamus and hippocampus, improving mood and reducing stress-induced healing delays [233]. It inhibits monoamine oxidase (MAO), prolonging monoamine activity essential for neuroendocrine stability [234]. Additionally, piperine downregulates cortisol and oxidative stress, while upregulating brain-derived neurotrophic factor (BDNF) mRNA, enhancing neuroplasticity and immune function [235]. These mechanisms collectively reduce systemic inflammation and restore immune competence, positioning *Piper nigrum* as a psychoneuroimmune adjunct in wound healing.

## Preclinical and Experimental Evidence

Preclinical models demonstrate that both topical and oral administration of piperine or *Piper nigrum* extracts accelerate wound closure, enhance collagen deposition, stimulate angiogenesis, and reduce infection rates [189]. Co-administration with turmeric shows synergistic effects, further promoting tissue regeneration [236]. However, high topical concentrations of piperine may induce dermal irritation, highlighting the need for optimized formulations. Additionally, piperine's inhibition of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) necessitates caution in patients receiving chemotherapy or hormonal therapies due to potential drug

interactions.

## Enhancer of Drug Bioavailability

Piperine significantly enhances the systemic bioavailability of co-administered agents—including curcumin, antibiotics, and antioxidants—by inhibiting hepatic aryl hydrocarbon hydroxylase (AHH) and UDP-glucuronyltransferase, thereby reducing glucuronidation and metabolic clearance (Bhardwaj, 2002). It also inhibits key enzymes and transporters, including P-glycoprotein (P-gp) and cytochrome P450 isoforms CYP3A4, CYP1A1, CYP1B1, CYP1B2, and CYP2E1, altering first-pass metabolism and drug pharmacokinetics (237). Additional mechanisms include receptor sensitization, receptor mimetic effects, increased gastrointestinal vasodilation, and modulation of membrane dynamics to facilitate absorption [237,238]. Piperine further exhibits synergistic antimicrobial activity, enhancing antibiotic efficacy, lowering required dosages, and reducing resistance risk.

## Pharmaceutical Formulation and Mechanisms of Medicinal Cannabis in Wound Care

This study employed a pharmaceutical-grade sublingual formulation of medicinal cannabis (MC) containing both tetrahydrocannabinol (THC) and cannabidiol (CBD), phytocannabinoids with immunomodulatory, analgesic, and pro-regenerative properties relevant to chronic, non-healing wounds. Sublingual administration bypasses hepatic first-pass metabolism, enhancing systemic bioavailability and enabling rapid onset (15–30 minutes), with peak plasma levels at ~45 minutes and duration of action of 4–6 hours [239-241]. The high lipophilicity of THC and CBD facilitates distribution to central and peripheral tissues, including immune and adipose compartments [242]. The formulation is pharmacologically analogous to Sativex® (1:1 THC:CBD), which is approved for neuropathic pain and spasticity, supporting its clinical applicability [243,244]. Sublingual MC offers a mechanistically targeted intervention for neuroinflammation, nociceptive sensitization, and stress-mediated immune dysregulation in wound environments.

## Endocannabinoid System Modulation by Sublingual THC/CBD

Sublingual THC and CBD promote wound healing via modulation of the endocannabinoid system (ECS), which regulates immune homeostasis, inflammation resolution, and tissue regeneration. THC acts as a partial agonist at CB1 and CB2 receptors, located primarily in the central nervous system and immune cells, respectively [245]. CBD, while exhibiting low receptor affinity, inhibits FAAH, increasing endogenous cannabinoids (AEA, 2-AG) and enhancing CB receptor activation [246]. CB2 activation suppresses pro-inflammatory cytokines (IL-2, IL-1β, TNF-α, IL-6, IL-8), while promoting M2 macrophage polarization—key to resolving chronic inflammation and initiating tissue repair [247,248]. These ECS-driven effects underpin the immunoregulatory role of sublingual THC/CBD in chronic wound environments.

## Anti-Inflammatory Effects of Sublingual CBD/THC

Sublingual administration of cannabidiol (CBD) ensures rapid systemic absorption and exerts potent anti-inflammatory effects via activation of CB2 and PPARγ receptors, suppressing IL-6, TNF-α, and IL-1β [249-252]. CBD also inhibits NF-κB nuclear translocation, downregulating COX-2 expression [252], and increases extracellular adenosine, activating A2A receptors to further reduce TNF-α [249,253]. Additionally, through PPARγ, CBD acts as an E3 ubiquitin ligase targeting NF-κB p65, reinforcing suppression of pro-inflammatory mediators [250-252]. These mechanisms support sublingual CBD/THC as a therapeutic strategy in chronic wound inflammation.

## Analgesic Effects of Sublingual THC/CBD in Chronic Wound Management

Sublingual THC and CBD provide analgesia via central and peripheral pathways, making them effective for chronic wound pain. THC activates CB1 receptors in the periaqueductal gray and spinal substantia gelatinosa, inhibiting glutamate and GABA release to suppress nociceptive transmission [254,255]. CBD exerts peripheral analgesic effects by inhibiting COX-2 and prostaglandin synthesis, modulating α3 glycine receptors, and reducing neuropeptides such as substance P and CGRP that mediate neurogenic inflammation [256]. Additionally, oral or sublingual THC, CBD, or their 1:1 combination attenuates sensory hyperactivity and modulates immune signaling in early peripheral nerve injury models [257], highlighting their dual analgesic and immunomodulatory potential in wound care.

## Epigenetic Modulation by Sublingual THC/CBD in Wound Healing

Sublingual THC and CBD rapidly engage the endocannabinoid system (eCBD), exerting epigenetic effects critical for chronic wound resolution. These cannabinoids modulate DNA methylation, histone acetylation, and chromatin remodeling by regulating TET dioxygenases, DNMTs, and HDACs, thereby controlling gene expression linked to inflammation, fibrosis, and epithelial repair [258,259]. They also downregulate microRNAs such as miR-155, miR-146a, miR-21a, miR-31, and miR-33—key mediators of immune dysregulation—via CB receptor activation, promoting regenerative signaling [260,261]. Additionally, cannabinoids enhance keratinocyte migration and differentiation through epigenetic remodeling of cytoskeletal gene networks [262, 263], and act as PPARγ ligands to suppress inflammatory and fibrotic transcription through chromatin modification [259]. Together, these mechanisms position sublingual THC/CBD as epigenetic regulators of immune resolution, epithelial regeneration, and matrix remodeling in chronic wound repair.

## Peripheral Vasodilation and Microcirculation Enhancement via Sublingual CBD/THC

Sublingual CBD and THC improve microvascular perfusion by activating CB2 and TRPV1 channels, enhancing oxygen delivery, nutrient transport, and metabolic waste clearance in hypoxic wound beds. These cannabinoids induce vasorelaxation through CB1/CB2 and TRP channel signaling, potassium channel activation, and inhibition of calcium influx, while promoting the release of nitric oxide (NO), prostanoids, EDHF, $H_2O_2$, and CGRP, which collectively drive smooth muscle relaxation and peripheral vasodilation [264]. Additional modulation of GPR55, PPARs, 5-HT1A, and prostanoid receptors contributes to their hemodynamic effects. Sublingual delivery enables rapid systemic uptake, making it an effective strategy for restoring microcirculatory function in chronic or ischemic

**Table 4:** Mechanisms of Action of Sublingual THC/CBD in Wound Healing.

| Mechanistic Domain | Biological Actions | Supporting References |
|---|---|---|
| Analgesia & Neuromodulation | - THC activates CB1 receptors in the CNS, modulating nociceptive pathways and reducing neuropeptide-mediated inflammation (e.g., substance P, CGRP). - CBD enhances spinal glycine receptor function, reducing pain transmission. - TRPV1 desensitization contributes to neurogenic inflammation suppression. | 254; 255, 256; 269 |
| Peripheral Vasodilation & Perfusion | - Activation of CB2, TRPV1, and GPR55 leads to release of vasodilators (NO, prostanoids, CGRP), opening of potassium channels, and calcium influx inhibition. - Improves microcirculation and oxygen delivery to hypoxic wound beds. | 264 |
| Oxidative Stress Regulation | - CBD activates Nrf2, enhancing HO-1 and glutathione peroxidase expression. - Reduces ROS accumulation and NLRP3 inflammasome activation. - Comparable antioxidant efficacy to vitamins C and E. | 276,227;278, 279,280 |
| Mitochondrial Bioenergetics | - CBD enhances ATP production and stabilizes mitochondrial membrane potential. - Modulates calcium homeostasis and prevents proton overload. - THC demonstrates biphasic effects: supportive at low doses, suppressive at higher doses. | 281, 282, 283,284 |
| Lipid Mediator Modulation | - Promotes lipid mediator class switching to SPMs (resolvins, lipoxins, maresins). - Suppresses neutrophil recruitment and enhances macrophage efferocytosis and re-epithelialization. - Resolves chronic inflammation and promotes tissue regeneration. | 265, 266,267, 268 |
| Immune Modulation | - Promotes M2 macrophage polarization, suppresses neutrophil ROS production. - Enhances FoxP3□ Treg function and immune tolerance. - Modulates cytokine production and inflammatory cell recruitment via CB1/CB2 and PPARγ. | 293, 294, 291, 295 |
| Angiogenesis Promotion | - Increases VEGF expression, endothelial cell migration, and tubulogenesis. - M2 macrophage transition promotes pro-angiogenic signaling. - Reduces oxidative and cytokine-mediated endothelial dysfunction. | 28,52,91,292 |
| Antimicrobial & Antibiofilm Effects | - Disrupts bacterial membranes and inhibits biofilm formation. - Effective against MRSA, S. aureus, S. pyogenes, and C. difficile. - Synergistic with cannabis terpenes and flavonoids. | 286, 285,287,278, 288, 289, 26,290 |
| Neuroimmune Crosstalk | - Modulates TRPV1, CB1, and microglial activity to reduce nociception and local inflammation. - Regulates immune cell signaling (macrophages, mast cells, T cells, dendritic cells). - Alters microRNA and epigenetic profiles associated with chronic inflammation. | 269, 270,271,272, 273,275, 2011,274 |
| Gut–Skin Axis Modulation | - Rebalances intestinal microbiota, reduces dysbiosis-related inflammation. - Improves gut barrier integrity and systemic immune tone. - Modulates skin ECS and cytokine signaling. | 287, 279,299,300 |
| Neuroendocrine and HPA Axis Regulation | - Reduces cortisol via ECS-mediated HPA axis suppression. - Improves sleep quality and melatonin/GH secretion. - Modulates circadian rhythm, enhancing regeneration. | 263, Sohn, 2024 |
| Neuropsychiatric Stress Buffering | - CBD modulates 5-HT1A and GABA receptors, reducing anxiety and improving sleep. - THC induces sedation at low doses via CB1 agonism. - ECS restores emotional and physiological homeostasis under stress. | 263,301, 303,297 |
| Stem Cell Recruitment & Regeneration | - Activates MAPK (p42/44) pathway to recruit MSCs. - Enhances keratinocyte and fibroblast migration and viability. - Supports extracellular matrix remodeling. | 304, 305,303 |

wounds.

## Lipid Mediator Regulation by Sublingual CBD/THC

Sublingual cannabidiol (CBD) and tetrahydrocannabinol (THC) regulate lipid-derived signaling critical for inflammation resolution and wound healing. By modulating N-acylethanolamines (NAEs), prostaglandins, lipoxins, and resolvins, these cannabinoids promote lipid mediator class switching from pro-inflammatory prostaglandins and leukotrienes to specialized pro-resolving mediators (SPMs) such as lipoxins, resolvins, protectins, and maresins [265-267]. This shift enhances macrophage efferocytosis, limits neutrophil infiltration, and promotes re-epithelialization [150]. Lipoxins initiate resolution, followed by PUFA-derived mediators, restoring immune balance and epithelial integrity. Impaired SPM signaling perpetuates inflammation and delays repair [268]. By facilitating SPM biosynthesis and lipid class switching, sublingual CBD/THC reinforces immune resolution and tissue regeneration in chronic wounds.

## Neuroimmune Modulation at the Wound Site by Sublingual THC/CBD

Sublingual cannabidiol (CBD) and tetrahydrocannabinol (THC) rapidly engage the endocannabinoid system (ECS), bypassing hepatic metabolism to modulate neuroimmune crosstalk essential for wound healing. Cannabinoids desensitize TRPV1 channels, reducing nociceptive transmission and neuropeptide-driven neurogenic inflammation [269]. Sublingual and oromucosal delivery enhance systemic bioavailability [270,271]. THC activates CB1-mediated neuroprotective and immunosuppressive pathways [272,273], while both cannabinoids regulate microglial function via microRNA and epigenetic mechanisms [273]. Through interaction with immune cells—including macrophages, mast cells, dendritic cells, and lymphocytes—cannabinoids suppress neuroinflammation and promote immune tolerance [274]. ECS activation further modulates lymphocyte proliferation, macrophage cytotoxicity, and cytokine expression [275], collectively optimizing the wound immune microenvironment and supporting resolution of chronic inflammation.

## Oxidative Stress Modulation by Sublingual THC/CBD in Wound Healing

Excessive reactive oxygen species (ROS) disrupt wound healing by damaging tissue and sustaining inflammation. Cannabidiol (CBD) mitigates oxidative stress through direct ROS scavenging and activation of the Nrf2 pathway, which induces cytoprotective genes such as HO-1 and glutathione peroxidases, suppressing NLRP3 inflammasome activity [276,277]. Sublingual delivery of CBD and THC ensures rapid systemic absorption and facilitates antioxidant synergy from cannabinoids, terpenes, and flavonoids at the wound site [278]. These effects are mediated via CB1, CB2, PPARs, TRP channels, and PUFA-derived mediators [279]. Preclinical data show antioxidant efficacy of cannabinoids comparable to vitamins C and E [280], supporting sublingual THC/CBD as a redox-stabilizing intervention for chronic, nonhealing wounds.

## Mitochondrial and Bioenergetic Effects of Sublingual CBD/THC in Wound Healing

Mitochondrial dysfunction impairs cell proliferation, migration,

and matrix remodeling in chronic wounds. Cannabidiol (CBD) enhances mitochondrial efficiency and ATP production, supporting reparative activity in fibroblasts, keratinocytes, and immune cells [281]. In contrast, THC exhibits dose-dependent effects: low doses may improve respiration, while higher levels impair ATP synthesis via CB1-mediated pathways, affecting calcium uptake and membrane potential [281,282]. CBD preserves mitochondrial integrity by restoring calcium homeostasis, reducing oxidative stress, and maintaining membrane potential critical for cell viability [283,284]. These bioenergetic mechanisms position sublingual THC/CBD as a therapeutic strategy for metabolically impaired, non-healing wounds.

## Antimicrobial Effects of Sublingual THC/CBD in Chronic Wound Management

Cannabidiol (CBD) and $\Delta^9$-tetrahydrocannabinol (THC), the principal phytocannabinoids in medicinal cannabis, exhibit potent antimicrobial properties relevant to chronic wound care. They are effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive pathogens that commonly colonize chronic wounds and impair healing. Clinical evidence reports a wound closure rate of 3.3 $cm^2$ over 30 days with cannabinoid therapy, and a case series of 17 patients using oral THC/CBD oils and topical cannabinoid-terpene formulations achieved a mean healing time of 54 days [285]. In murine models, THC reduced MRSA burden comparably to 2% mupirocin by day five [286].

Mechanistically, cannabinoids disrupt bacterial membranes and penetrate biofilms—key for overcoming multidrug resistance [287,278]. They inhibit *Streptococcus pyogenes* [69], *S. pneumoniae*, and *Clostridium difficile* [287]. Additionally, cannabis extracts contain antimicrobial flavonoids, terpenes, alkaloids, and phenolics; essential oils such as α-pinene display broad-spectrum activity against Gram-positive and Gram-negative organisms [288,289]. The *Cannabis sativa* cultivar Futura 75 exhibits bactericidal activity against multidrug-resistant *S. aureus*, biofilm disruption, and inhibition of *Listeria monocytogenes* [290].

## Angiogenic Effects of Sublingual CBD/THC in Wound Healing

Angiogenesis is essential for repairing chronic and ischemic wounds. Sublingual cannabidiol (CBD) and $\Delta^9$-tetrahydrocannabinol (THC) promote neovascularization by inducing vascular endothelial growth factor (VEGF), enhancing endothelial migration, and stimulating tubulogenesis [285,291]. They also drive macrophage polarization from M1 to reparative M2 phenotypes, which secrete VEGF and matrix metalloproteinases (MMPs) that remodel the extracellular matrix and support vascular sprouting [291,292]. Cannabinoids concurrently reduce oxidative stress and pro-inflammatory cytokines, preserving endothelial integrity and angiogenic signaling. By restoring immune-endothelial balance and tissue perfusion, sublingual THC/CBD facilitates regeneration in hypoxic wound environments, highlighting angiogenesis as a central mechanism in their wound-healing efficacy.

## Immunomodulatory Effects of Sublingual THC/CBD in Wound Healing

Sublingual cannabidiol (CBD) and $\Delta^9$-tetrahydrocannabinol (THC) modulate immune responses to resolve chronic inflammation and support tissue repair. Enhanced bioavailability via sublingual delivery promotes M2 macrophage polarization while reducing neutrophil infiltration and ROS production [293,294]. Acting through CB1 and CB2 receptors on macrophages, neutrophils, dendritic cells, and T lymphocytes, cannabinoids suppress pro-inflammatory cytokines and reprogram immune cells toward reparative phenotypes [291]. They also enhance adaptive immunity by expanding FoxP3® regulatory T cells and boosting their suppressive function, facilitating immune tolerance and regeneration [283,295,296]. These dual effects on innate and adaptive immunity highlight the endocannabinoid system as a therapeutic target in managing chronic, nonhealing wounds.

## Modulation of the Gut–Skin Axis by Sublingual THC/CBD

Sublingual cannabidiol (CBD) and tetrahydrocannabinol (THC) may promote systemic wound healing by modulating the gut–skin axis—a bidirectional pathway linking intestinal microbiota, immune function, and cutaneous repair. Dysbiosis impairs cytokine regulation, immune tolerance, and nutrient absorption, contributing to delayed wound healing; CBD has been shown to reverse dysbiosis and restore immune function [287]. The endocannabinoid system (ECS), expressed in gut epithelial, neuronal, and immune cells, regulates intestinal barrier integrity and cytokine signaling relevant to systemic immunity [297]. Cannabinoid activation of CB1 and CB2 receptors enhances mucosal resilience, reduces gut inflammation, and preserves epithelial barrier function. Additionally, cannabinoids modulate the microbiota–gut–brain axis via microbial metabolites and vagal pathways, attenuating systemic inflammation [298,299]. THC and CBD also act on the cutaneous ECS, where endocannabinoids like anandamide and 2-AG regulate immune responses and barrier repair [300]. These mechanisms support the therapeutic potential of cannabinoids in managing chronic wounds via gut–skin axis modulation.

## Hormonal and Neuroendocrine Modulation by Sublingual THC/CBD

Sublingual cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) modulate the hypothalamic–pituitary–adrenal (HPA) axis through endocannabinoid system (ECS) activation, reducing stress-induced cortisol elevations that impair immunity, suppress collagen synthesis, and delay wound healing [232]. By restoring neuroendocrine balance, cannabinoids foster a hormonal milieu favorable to tissue repair. Additionally, they improve sleep architecture by enhancing slow-wave sleep and promoting circadian release of growth hormone (GH) and melatonin—key regulators of angiogenesis, immune function, and extracellular matrix remodeling. Melatonin also exerts antioxidant, anti-inflammatory, and epithelial regenerative effects, further supporting wound healing [273].

## Neuropsychiatric Modulation by Sublingual THC/CBD in Wound Healing

Cannabidiol (CBD) exerts anxiolytic and sleep-promoting effects via 5-HT1A receptor agonism and modulation of GABAergic and glutamatergic neurotransmission [263,301], while acting as a non-competitive CB1 antagonist with antidepressant and analgesic properties [302]. Tetrahydrocannabinol (THC), a partial CB1 agonist, induces dose-dependent sedation that enhances sleep at low doses but may be stimulatory at intermediate levels [303]. Psychological stress and mood disturbances impair wound healing by activating the HPA axis and elevating cortisol, which suppresses immune function and tissue repair [263]. The endocannabinoid system (ECS), a key

regulator of neuroendocrine responses, modulates HPA activity and behavioral adaptation [297]. ECS dysregulation exacerbates stress, inflammation, and impaired healing. By restoring ECS tone and enhancing serotonergic pathways, sublingual THC/CBD may counter stress-induced neuroimmune dysfunction and improve healing outcomes in patients with anxiety, depression, or sleep disturbances.

## Stem Cell Recruitment and Tissue Regeneration by Sublingual THC/CBD

Cannabinoid signaling via the endocannabinoid system (ECS) enhances mesenchymal stem cell (MSC) recruitment and migration to injury sites through activation of the p42/44 MAPK pathway, which regulates motility, proliferation, and extracellular matrix remodeling [304]. Additionally, cannabinoids promote keratinocyte proliferation and fibroblast migration—key processes in granulation and re-epithelialization—at non-cytotoxic concentrations (0.625–2.5 μg/mL), demonstrating a favorable therapeutic profile [305]. These mechanisms underscore the regenerative potential of sublingual THC/CBD in managing chronic, nonhealing wounds, particularly in immunocompromised individuals.

## Synergistic Topical Phytotherapy in Wound Healing

In this case, a synergistic topical botanical formulation was applied directly to the wound, combining turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), and black pepper (*Piper nigrum*) in a sweet almond oil base to enhance dermal absorption and bioavailability.

Curcumin, the principal active compound in turmeric, is known to promote fibroblast proliferation, angiogenesis, and collagen synthesis by inhibiting NF-κB and COX-2 while upregulating TGF-β and VEGF [9,13]. Piperine from *Piper nigrum* enhances curcumin bioavailability by inhibiting glucuronidation and facilitating transdermal delivery [122].

Bioactives from *Zingiber officinale*—including gingerols and shogaols—further contributed by suppressing TNF-α and IL-6, enhancing VEGF-mediated angiogenesis, and promoting keratinocyte migration [87,278]. These effects were complemented by *Piper nigrum* essential oil, which is rich in β-caryophyllene and piperine, and provided additional antimicrobial, anti-inflammatory, and analgesic properties [189,306]. The sweet almond oil carrier served to support skin barrier repair and facilitate phytochemical diffusion [307].

This polyherbal formulation targeted overlapping mechanisms central to wound healing—reducing oxidative stress and lipid peroxidation, suppressing leukocyte infiltration, and enhancing angiogenesis and extracellular matrix remodeling [308]. Freshly prepared extracts preserved volatile and thermolabile components, and patch testing confirmed safety, with no adverse reactions observed.

In this patient, the topical regimen was well tolerated and contributed to progressive epithelialization and stable closure. These findings support the clinical potential of synergistic phytotherapeutic formulations in managing chronic nonhealing wounds, particularly in oncology patients with impaired regenerative capacity.

## Mind–Body Interventions and Psychophysiological Resilience

In this patient, chronic nonhealing wounds were profoundly influenced by psychoneuroendocrine dysregulation, a common barrier in immunocompromised cancer contexts. Psychological stress is well established to impair wound healing by activating the hypothalamic–pituitary–adrenal (HPA) axis, elevating cortisol levels, and suppressing both inflammatory and proliferative wound phases [37,309]. Persistent sympathetic overactivation and diminished vagal tone further disrupted immune trafficking and cytokine balance, perpetuating local wound inflammation.

To address this psychophysiological dimension, the integrative protocol for this case incorporated evidence-based mind–body therapies: mindfulness-based stress reduction (MBSR) following Kabat-Zinn's model, forest bathing, neurofeedback-assisted meditation, and pulsed electromagnetic field (PEMF) therapy. These interventions are known to enhance autonomic regulation, increase parasympathetic tone, and reduce systemic inflammation [128,310].

Heart rate variability (HRV), a validated biomarker of autonomic function, showed progressive improvement in this patient, reflecting restored vagal modulation. Enhanced HRV correlates with improved immune competence, reduced allostatic load, and accelerated wound repair under chronic stress conditions [127].

PEMF therapy, delivered via an FDA-cleared infrared photon mat with conductive minerals, was employed to improve microcirculatory perfusion, mitochondrial biogenesis, and tissue oxygenation—factors crucial for reversing ischemic wound pathology [152,167]. Additionally, neurofeedback and EEG-guided brainwave entrainment facilitated alpha-theta modulation, a state associated with reduced anxiety and enhanced immune surveillance [84].

By mitigating psychophysiological barriers, these mind–body interventions likely augmented immune coherence and systemic homeostasis, thereby promoting tissue repair in a high-stress, immunocompromised breast cancer patient. In this case, they complemented the anti-inflammatory, immunomodulatory, and regenerative effects of botanical and cannabinoid therapies, forming a comprehensive strategy for chronic wound management [263,264].

Together with phytotherapy and sublingual cannabinoid interventions, these mind–body modalities contributed to a holistic framework that addressed both the biological and psychosocial barriers to wound healing, ultimately supporting complete tissue repair in this patient.

## Clinical Implications and Integrative Medicine Perspective

Chronic nonhealing wounds in post-mastectomy breast cancer patients pose significant therapeutic challenges, often exacerbated by chemotherapy-induced immunosuppression, surgical trauma, and persistent infection, which delay reconstruction and impair quality of life. Conventional wound management frequently fails to address the multifactorial biological and psychosocial barriers to healing, underscoring the need for integrative, multimodal strategies that target systemic dysfunction.

This case demonstrates that a personalized integrative protocol—including phytotherapy, sublingual cannabinoids, nutritional optimization, topical botanicals, and evidence-based mind–body interventions—can safely accelerate epithelial closure within four weeks in a medically complex, immunocompromised patient without disrupting oncologic treatments. These findings align with mechanistic insights on the anti-inflammatory, antioxidant, immunomodulatory,

and pro-angiogenic properties of compounds such as curcumin, gingerols, piperine, and cannabinoids [13,264,285,291].

Nutritional support integrated principles from Ayurvedic and traditional Chinese medicine (TCM), emphasizing doshic balance, digestive fire, spleen Qi, and kidney essence to enhance systemic resilience and metabolic function [32]. Complementary therapies, including guided meditation, chakra visualization, yoga, and meridian massage, were applied to modulate the hypothalamic–pituitary–adrenal (HPA) axis and improve autonomic regulation, as evidenced by improved heart rate variability (HRV) and reduced stress biomarkers [128,263].

Neurofeedback and biofeedback modalities further supported neural coherence and parasympathetic activation, fostering a neuroimmune milieu conducive to tissue repair [84,310]. This biopsychosocial framework directly addressed the patient's barriers to recovery, including unresolved inflammation, oxidative stress, immune dysregulation, impaired angiogenesis, and neuroendocrine imbalance [68,264].

Although limited by its single-patient design and lack of controls, this report provides valuable clinical insight and highlights the potential role of integrative, systems-based protocols in complex oncology settings. The observed outcome supports the need for rigorous randomized trials to validate such approaches as adjuncts to conventional wound care, particularly for cancer patients at elevated risk for impaired healing and psychosomatic burden. With further study, these strategies may help redefine chronic wound management through personalized, holistic care.

## Limitations and Considerations

This case report provides preliminary evidence supporting the feasibility and potential efficacy of a systems-based integrative protocol in promoting wound healing for a post-mastectomy breast cancer patient with a chronic nonhealing wound. However, as a single uncontrolled case, it cannot establish causality, limit statistical generalizability, and precludes attribution of outcomes to specific therapeutic components. Instead, it offers a valuable clinical signal and hypothesis-generating evidence for future controlled studies.

The multimodal nature of the protocol—encompassing dietary, phytochemical, topical, neuroimmune, and mind–body interventions—reflects a real-world, patient-centered approach that emphasizes therapeutic synergy. While this integrative complexity limits the ability to isolate individual effects, it is consistent with systems biology and the holistic management of multifactorial wound pathophysiology.

Individual clinical context, including cancer stage, treatment history, and immune status, may have influenced wound trajectory. Nevertheless, the patient achieved complete epithelial closure within four weeks, with sustained functional skin integrity and no signs of infection or recurrence during the short-term follow-up period. Longer-term monitoring would be necessary to evaluate durability and relapse risk.

Assessment of wound healing relied on clinical examination, patient-reported outcomes, and photographic documentation. Future investigations should incorporate objective measures such as histological analysis, quantitative biomarkers, and imaging modalities to enhance scientific rigor. Importantly, the integrative regimen—including oral turmeric, ginger, and black pepper; sublingual THC/CBD; and freshly prepared botanical dressings—was well tolerated with no reported adverse effects. Herb–drug interaction risks were mitigated through interdisciplinary collaboration with oncology teams, demonstrating safety and compatibility within conventional cancer care frameworks.

## Strengths

This case report highlights several important strengths that enhance its clinical and scientific relevance. It represents one of the first structured applications of a multimodal integrative protocol for managing a chronic nonhealing post-mastectomy wound in a breast cancer patient. The intervention combined oral turmeric–ginger–black pepper formulations, sublingual THC/CBD, and freshly prepared botanical dressings, integrated with conventional wound care.

The inclusion of individualized nutritional support—drawing from Ayurvedic and traditional Chinese medicine (TCM)—together with evidence-informed mind–body therapies, reflects a comprehensive, systems-based approach. This design leveraged pharmacodynamic synergies, including piperine-enhanced curcumin bioavailability and cannabinoid-mediated immune modulation, aligning with contemporary models of personalized and integrative medicine.

Despite the patient's complex oncologic background, which included surgical trauma, immune compromise, and delayed wound healing, complete epithelial closure was achieved within four weeks. This outcome underscores the protocol's feasibility and translational potential in medically complex settings. Importantly, no adverse events or treatment-related complications occurred, and herb–drug interaction risks were proactively monitored through interdisciplinary collaboration with oncology providers.

Together, these strengths support the safety, adaptability, and clinical promise of integrative wound care protocols as adjuncts within conventional cancer management frameworks.

## Conclusion and Future Directions

Chronic nonhealing post-mastectomy wounds in immunocompromised breast cancer patients represent a formidable clinical challenge, characterized by persistent inflammation, oxidative stress, immune dysregulation, and impaired tissue regeneration. This case report presents preliminary evidence that a multimodal integrative medicine protocol—encompassing phytotherapeutics, sublingual cannabinoids, targeted nutrition, and mind–body therapies—can facilitate successful wound closure and systemic recovery in a high-risk oncology patient.

The protocol combined oral and topical administration of turmeric (*Curcuma longa*), ginger (*Zingiber officinale*), and black pepper (*Piper nigrum*), leveraging synergistic anti-inflammatory, antioxidant, and antimicrobial mechanisms [9,13,48,87,306]. Piperine was included to enhance curcuminoid bioavailability [122], while sublingual THC/CBD targeted the endocannabinoid system, modulating immune responses, oxidative pathways, angiogenesis, pain perception, and sleep quality [263,291,294]. The patient achieved complete epithelial closure within four weeks without adverse effects or interference with oncologic treatments.

Complementary therapies—including mindfulness meditation, chakra-based visualization, PEMF therapy, neurofeedback, HRV-

guided biofeedback, Ayurvedic digestive support, and TCM-based meridian stimulation—were integrated to address neuroimmune and neuroendocrine dysregulation. These modalities supported vagal activation, HPA axis normalization, and autonomic recalibration, factors known to influence wound repair [127,128,182,197,206].

Observed improvements likely resulted from systems-level synergy rather than isolated effects. Mechanistic pathways include M2 macrophage polarization and Treg function [244,264], VEGF-driven angiogenesis [271], and restoration of mitochondrial bioenergetics [281]. This supports the potential role of integrative strategies in overcoming multifactorial barriers to healing in oncology patients.

While encouraging, this case report is limited by its uncontrolled design, treatment complexity, and single-patient focus, which preclude definitive attribution of outcomes to specific interventions. Nevertheless, the complete healing observed in an immunocompromised patient highlights the translational promise of integrative wound care protocols.

Emerging evidence further supports combining turmeric, ginger, and black pepper in inflammatory and wound-healing contexts. Preclinical data show that topical curcumin and ginger accelerate wound closure, epithelial regeneration, and collagen deposition (Bhagavathula, 2009). Clinical trials demonstrate synergistic oral blends reduce prostaglandin $E_2$ ($PGE_2$) levels, with efficacy comparable to NSAIDs and *in vitro* studies confirm turmeric–ginger synergy [185]. However, no clinical trial has yet examined this tri-herbal protocol in cancer-related chronic wounds, underscoring the need for formal evaluation.

Future research should prioritize randomized controlled trials of standardized integrative protocols in oncology settings, with mechanistic endpoints including cytokine panels, angiogenic markers, oxidative stress indicators, and microbiome analyses. Longitudinal measures such as HRV, NK cell activity, Treg function, sleep architecture, and patient-reported outcomes would clarify systemic recovery and resilience.

In summary, this case report demonstrates the feasibility, safety, and potential efficacy of a personalized integrative approach to chronic wound healing in an immunocompromised breast cancer patient. By targeting intersecting immune, endocrine, vascular, microbial, and neurocognitive systems, this model aligns with emerging paradigms in precision and whole-person oncology. With further validation, such protocols may provide valuable adjuncts to conventional wound care in refractory post-surgical contexts.

## Ethics Statement and Patient Consent

This case report was conducted in accordance with the ethical principles of the Declaration of Helsinki. All potentially identifying patient information has been fully de-identified to ensure anonymity. The patient declined photographic documentation of her wound healing due to severe psychological distress and depersonalization related to her cancer treatment and surgery, requesting complete privacy. Nevertheless, she provided written informed consent for the publication of her clinical details under the explicit condition that no images or personal identifiers would be included. Wound healing assessments were therefore based on serial clinical examinations and patient-reported outcomes, without photographic evidence.

## Acknowledgments

The authors extend their heartfelt gratitude to the patient who entrusted us with her care and healing. Her patience, trust, and unwavering commitment to this journey were instrumental in the success of this work. It is through her courage and generosity that we were able to explore and document this integrative approach to wound healing.

This case report was conducted without external funding or sponsorship. The authors declare no conflicts of interest. The work was undertaken with the sole intention of advancing clinical knowledge and alleviating the suffering experienced by breast cancer patients facing complex, non-healing wounds. Our efforts were guided by a deep sense of compassion and a shared commitment to improving the lives of current and future patients, while contributing meaningfully to the broader scientific and medical community.

## Dedication

This work is dedicated to all women who face the challenges of breast cancer with courage and resilience. May it serve as a step toward advancing compassionate, integrative approaches to healing and improving the quality of life for those on this journey.

## Glossary

1,8-Cineole (Eucalyptol)

A monoterpene with anti-inflammatory, antioxidant, and cortisol-lowering properties.

2-AG – 2-Arachidonoylglycerol

A principal endocannabinoid that activates both CB1 and CB2 receptors; regulates inflammation and neuroprotection.

5-HT1A – 5-Hydroxytryptamine (Serotonin) Receptor 1A

A serotonin receptor subtype involved in mood, anxiety, and vascular tone; activated by CBD for anxiolytic effects.

5-LOX – 5-Lipoxygenase

An enzyme converting arachidonic acid to leukotrienes; involved in inflammatory responses.

AEA – Anandamide (N-arachidonoylethanolamine)

An endogenous ligand for CB1 and CB2 receptors; involved in pain, mood, and immune regulation.

AHH – Aryl Hydrocarbon Hydroxylase

A detoxification enzyme involved in metabolism of toxins and drugs.

Akt / AKT – Protein Kinase B

A kinase downstream of PI3K; promotes cell survival, metabolism, and angiogenesis.

AMPK – AMP-Activated Protein Kinase

An energy-sensing enzyme that promotes catabolic processes, mitochondrial function, autophagy, and resolution of inflammation.

AP-1 – Activator Protein-1

A transcription factor regulating inflammation, proliferation, and differentiation in response to stress and cytokines.

ARE – Antioxidant Response Element

DNA sequence activated by Nrf2 to promote expression of

antioxidant and detoxification genes.

ATP – Adenosine Triphosphate

The primary energy carrier in cells, essential for biosynthesis, proliferation, and tissue regeneration.

Bax – Bcl-2-Associated X Protein

A pro-apoptotic protein; its downregulation supports cell survival during tissue regeneration.

BCP – Beta-Caryophyllene

A CB2 receptor agonist with anti-inflammatory and tissue-repair effects.

BDNF – Brain-Derived Neurotrophic Factor

Supports neuroplasticity, mood regulation, and neuroimmune interactions; elevated BDNF mRNA is associated with tissue repair.

BECN1 – Beclin-1

An essential protein in autophagy that promotes autophagosome formation and cellular recycling.

bFGF – Basic Fibroblast Growth Factor

A mitogenic and angiogenic factor stimulating endothelial and fibroblast proliferation.

Caspase-3 – Cysteine-aspartic Acid Protease-3

An executioner enzyme of apoptosis that clears damaged cells during wound resolution.

Catalase / CAT – Catalase

An antioxidant enzyme that converts hydrogen peroxide into water and oxygen.

CB2 – Cannabinoid Receptor Type 2

Predominantly expressed on immune cells; modulates immune responses and inflammation.

CGRP – Calcitonin Gene-Related Peptide

A neuropeptide involved in pain, vasodilation, and neurogenic inflammation.

CNS – Central Nervous System

Integrates neural and endocrine signals for systemic stress and immune responses.

COX-1 – Cyclooxygenase-1

A constitutive enzyme producing prostaglandins for physiological functions like gastric protection.

COX-2 – Cyclooxygenase-2

An inducible enzyme catalyzing prostaglandin synthesis; contributes to pain and inflammation.

DIEP Flap – Deep Inferior Epigastric Perforator Flap

An autologous breast reconstruction using abdominal fat while preserving muscle.

DNA – Deoxyribonucleic Acid

The molecule encoding genetic instructions for cellular structure and function.

DNMTs – DNA Methyltransferases

Enzymes that add methyl groups to DNA, repressing gene transcription; affected by phytocannabinoid signaling.

ECM – Extracellular Matrix

A scaffold of proteins and polysaccharides supporting adhesion, migration, and tissue structure.

EDHF – Endothelium-Derived Hyperpolarizing Factor

A factor released from endothelial cells that contributes to vasodilation and vascular tone regulation.

EEG – Electroencephalogram

A diagnostic tool to measure brainwave activity; used in neurofeedback applications.

EGF – Epidermal Growth Factor

Promotes keratinocyte proliferation, migration, and re-epithelialization.

EGFR – Epidermal Growth Factor Receptor

Drives keratinocyte proliferation and migration during wound healing.

Egr-1 – Early Growth Response Protein 1

A transcription factor regulating genes involved in inflammation and fibrosis.

EMT – Epithelial–Mesenchymal Transition

A process enabling epithelial cells to gain migratory capacity for wound closure.

EP300 / CBP – E1A Binding Protein p300 / CREB-Binding Protein

Coactivators with HAT activity that regulate chromatin and gene transcription.

ERK – Extracellular Signal-Regulated Kinase

A MAPK involved in cell proliferation and survival.

ER-positive – Estrogen Receptor-Positive

A breast cancer subtype with tumors responsive to hormone therapy.

E3 Ubiquitin Ligase

Enzyme that tags proteins (e.g., NF-κB subunits) for degradation, suppressing inflammatory signaling.

eCBD – Endocannabinoid-Based Drug / Endocannabinoid Pathway

Refers to modulation of endogenous cannabinoid pathways by phytocannabinoids like THC and CBD.

FAAH – Fatty Acid Amide Hydrolase

Enzyme that degrades endocannabinoids; inhibition by CBD enhances endocannabinoid tone.

FGF – Fibroblast Growth Factor

Promotes fibroblast proliferation and angiogenesis.

FoxP3® – Forkhead Box P3 Positive

A transcription factor required for the development and function of regulatory T cells (Tregs).

FOXO1 – Forkhead Box Protein O1

Regulates autophagy, oxidative stress responses, and survival.

GABA – Gamma-Aminobutyric Acid

Principal inhibitory neurotransmitter; CB1 activation enhances GABA release.

GCLC – Glutamate-Cysteine Ligase Catalytic Subunit

Rate-limiting enzyme in glutathione synthesis, boosting antioxidant capacity.

GEO – Ginger Essential Oil

Volatile oil from *Zingiber officinale* with antimicrobial, anti-inflammatory, and antioxidant effects.

GH – Growth Hormone

Enhances tissue growth, repair, and immune modulation.

GPx – Glutathione Peroxidase

Enzymes reducing lipid hydroperoxides and hydrogen peroxide using glutathione.

GPR55 – G Protein-Coupled Receptor 55

A putative cannabinoid receptor potentially involved in inflammation, pain, and metabolism.

GSH – Glutathione

A tripeptide that maintains redox balance and detoxifies reactive species.

$H_2O_2$ – Hydrogen Peroxide

A reactive oxygen species that also acts as a secondary messenger.

HA – Hyaluronic Acid

A glycosaminoglycan with anti-inflammatory, hydrating, and tissue-repairing properties.

HATs – Histone Acetyltransferases

Add acetyl groups to histones, loosening chromatin for transcriptional activation.

HDACs – Histone Deacetylases

Enzymes that compact chromatin; inhibition enhances gene expression.

HIF-1α – Hypoxia-Inducible Factor 1-alpha

Promotes VEGF expression under hypoxia to stimulate angiogenesis.

HMTs – Histone Methyltransferases

Methylate histones to regulate gene expression.

HO-1 – Heme Oxygenase-1

An Nrf2-inducible enzyme with antioxidant and cytoprotective functions.

HPA Axis – Hypothalamic–Pituitary–Adrenal Axis

Coordinates stress responses and cortisol regulation; chronic activation impairs healing.

HRV – Heart Rate Variability

A measure of autonomic flexibility; higher HRV reflects better stress resilience.

HSF-1 – Heat Shock Factor 1

Induces heat shock proteins for cell protection and survival.

IκBα – Inhibitor of kappa B alpha

Prevents NF-κB nuclear translocation.

IFN-γ – Interferon-gamma

Activates macrophages and T cells; excessive levels delay healing.

IKK – IκB Kinase

Activates NF-κB by phosphorylating IκB.

IL-1β / IL-2 / IL-6 / IL-8 – Interleukins

Pro-inflammatory cytokines involved in immune activation and chemotaxis.

IL-10 – Interleukin-10

An anti-inflammatory cytokine that limits immune activation.

IL-12 – Interleukin-12

Promotes Th1 responses; overexpression impairs repair.

IL-18 – Interleukin-18

Enhances IFN-γ production and Th1 responses.

iNOS – Inducible Nitric Oxide Synthase

Produces nitric oxide during inflammation; excess contributes to tissue damage.

IP-10 (CXCL10) – Interferon Gamma-Induced Protein 10

A chemokine that recruits immune cells; elevated in chronic wounds.

JAK/STAT – Janus Kinase / Signal Transducer and Activator of Transcription

A pathway controlling immunity, inflammation, and proliferation.

LOX – Lysyl Oxidase

Crosslinks collagen and elastin to stabilize ECM.

MAPK – Mitogen-Activated Protein Kinase

A family of kinases mediating responses to inflammation and stress.

MAO – Monoamine Oxidase

Degrades neurotransmitters like serotonin and dopamine; inhibition enhances mood.

MBSR – Mindfulness-Based Stress Reduction

A program combining meditation and yoga to reduce stress.

MDA – Malondialdehyde

A biomarker of lipid peroxidation and tissue damage.

MD2 – Myeloid Differentiation Protein 2

TLR4 co-receptor for LPS detection.

miRNAs (e.g., miR-21, miR-146a, miR-155, miR-20a)

Small RNAs regulating inflammation, fibrosis, and wound healing.

MMPs – Matrix Metalloproteinases

Proteolytic enzymes that degrade ECM during remodeling; overactivity delays healing.

mMPGES-1 – Microsomal Prostaglandin E Synthase-1

Catalyzes final step in PGE2 synthesis.

mRNA – Messenger Ribonucleic Acid

Carries genetic instructions for protein synthesis.

MRSA – Methicillin-Resistant Staphylococcus aureus

A multidrug-resistant bacterium often found in chronic wounds.

MSC – Mesenchymal Stem Cell

Multipotent stromal cells essential for regeneration and angiogenesis.

mtDNA – Mitochondrial DNA

Mitochondrial genetic material; indicator of energy capacity.

M2 Macrophage – Alternatively Activated Macrophage

Anti-inflammatory subtype promoting repair and angiogenesis.

MyD88 – Myeloid Differentiation Primary Response 88

Adaptor protein linking TLRs to NF-κB and MAPK pathways.

NAEs – N-acylethanolamines

Bioactive lipids (e.g., anandamide) involved in ECS-mediated repair.

NF-κB – Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells

A transcription factor governing inflammatory gene expression.

NK Cell – Natural Killer Cell

Cytotoxic lymphocytes targeting virally infected and malignant cells.

NO – Nitric Oxide

A signaling molecule regulating vasodilation, angiogenesis, and antimicrobial activity.

NLRP3 – NOD-, LRR-, and Pyrin Domain-Containing Protein 3

A central inflammasome component activating IL-1β and IL-18.

NQO1 – NAD(P)H Quinone Dehydrogenase 1

An antioxidant enzyme induced by NRF2.

P450 – Cytochrome P450 Enzymes

Liver enzymes for drug metabolism; inhibited by piperine.

P-gp – P-glycoprotein

A membrane efflux transporter inhibited by piperine.

PDGF – Platelet-Derived Growth Factor

Promotes fibroblast recruitment, angiogenesis, and ECM remodeling.

PGC-1α – Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha

Master regulator of mitochondrial biogenesis.

PI3K–AKT–mTOR Pathway

Central axis regulating survival, metabolism, and proliferation.

PKCα – Protein Kinase C-alpha

Involved in inflammation and cytokine production.

PPARγ – Peroxisome Proliferator-Activated Receptor Gamma

Regulates inflammation, fibrosis resolution, and metabolism.

PUFA – Polyunsaturated Fatty Acids

Precursors to inflammatory and pro-resolving mediators.

RAB7 – Ras-related Protein Rab-7a

Mediates endosome maturation and autophagosome-lysosome fusion.

RAGE – Receptor for Advanced Glycation End Products

Promotes chronic inflammation by binding ligands.

RNS – Reactive Nitrogen Species

Reactive nitrogen-based molecules including peroxynitrite.

ROS – Reactive Oxygen Species

Reactive oxygen-containing molecules; cause tissue damage when unregulated.

S. aureus, S. pyogenes, S. pneumoniae

Common Gram-positive pathogens in wound infections.

SOD – Superoxide Dismutase

Antioxidant enzyme converting superoxide to hydrogen peroxide.

SPMs – Specialized Pro-Resolving Mediators

PUFA-derived lipids (e.g., resolvins, lipoxins) that resolve inflammation.

SREBP-1c – Sterol Regulatory Element-Binding Protein 1c

Regulates lipid biosynthesis.

STAT / STAT6 – Signal Transducer and Activator of Transcription

Cytokine-activated transcription factors; STAT6 inhibition supports keratinocyte repair

Substance P

A neuropeptide that induces vasodilation, mast cell activation, and pain signaling.

TCA cycle – Tricarboxylic Acid Cycle (Krebs cycle)

Central metabolic pathway generating ATP.

TET – Ten-Eleven Translocation Enzymes

Mediators of DNA demethylation and epigenetic regulation.

Th1 / Th2 – T-helper 1 and 2 Cells

CD4 subsets mediating cell-mediated (Th1) and humoral (Th2) immunity.

TGF-β1 / TGF-β2 / TGF-β3 – Transforming Growth Factor Beta

Cytokines regulating immune responses, angiogenesis, and remodeling.

- TGF-β1: Promotes inflammation and angiogenesis.
- TGF-β2: Enhances ECM production and migration.
- TGF-β3: Supports scarless healing.

TIMPs – Tissue Inhibitors of Metalloproteinases

Inhibit MMPs to regulate ECM remodeling.

TLR4 – Toll-Like Receptor 4

Recognizes bacterial LPS, activating innate immune responses.

TNF-α – Tumor Necrosis Factor Alpha

A pro-inflammatory cytokine central to chronic inflammation.

TRPV1 – Transient Receptor Potential Vanilloid 1 Channel involved in nociception, thermoregulation, and inflammation.

Tregs – Regulatory T Cells (FoxP3®) Suppress immune responses and promote tolerance.

UDP-glucuronyltransferase A Phase II enzyme responsible for glucuronidation and detoxification.

VEGF – Vascular Endothelial Growth Factor

Stimulates angiogenesis for wound healing.

Wnt/β-catenin Pathway

Regulates proliferation and tissue repair; dysregulation leads to fibrosis.

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