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REGENERATIVE & ANTI-AGING POTENTIAL OF NATURAL BIOACTIVES

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Abstract. The intricate processes of cutaneous wound regeneration and premature skin aging involve complex molecular pathways such as inflammation, oxidative stress, and extracellular matrix (ECM) degradation. This paper elucidates the synergistic biochemical and molecular effects of a combination of propolis, Lavandula angustifolia (lavender), and Aloe Vera on enhancing wound healing and mitigating premature aging markers. These agents act complementarily to modulate inflammation, promote fibroblast proliferation, improve collagen synthesis, and protect against oxidative damage. The combination presents a promising multi-target therapeutic strategy for dermatological applications.

Keywords. *Propolis*, *Aloe Vera*, *Lavandula angustifolia*, wound healing, premature aging, synergy, molecular mechanisms, NF-κB, TGF-β, oxidative stress.

Introduction. The skin, as the body's largest organ, serves as a primary barrier against environmental insults. Its ability to regenerate following injury and its structural integrity over time are crucial for human health. Two significant challenges in dermatology are the management of complex wounds and the prevention or reversal

of premature aging. Wound healing is a highly orchestrated physiological process involving four overlapping phases: hemostasis, inflammation, proliferation, and remodeling (Guo & DiPietro, 2010). Disruptions in this cascade, often due to persistent inflammation, infection, or oxidative stress, can lead to chronic, non-healing wounds.

Simultaneously, premature aging (photoaging and intrinsic aging) is characterized by a progressive decline in skin structure and function. At the molecular level, this is driven by an accumulation of cellular damage from reactive oxygen species (ROS), chronic low-grade inflammation (termed inflammaging), and an imbalance in the synthesis and degradation of the extracellular matrix (ECM), particularly collagen and elastin (Farage et al., 2008). Key molecular players in this process include the transcription factors Nuclear Factor-kappa B (NF-κB) and Activator Protein-1 (AP-1), which upregulate the expression of matrix metalloproteinases (MMPs) that degrade collagen.

Conventional treatments for wounds and aging often rely on synthetic agents that may have side effects or target only a single pathway. Consequently, there is a paradigm shift towards natural products and polyherbal formulations, which offer a multi-target approach with potentially fewer adverse effects. *Propolis*, lavender *Lavandula angustifolia*, and *Aloe Vera* are three such natural agents with well-documented, albeit largely individual, therapeutic properties in dermatology. Propolis is a resinous substance collected by honeybees, known for its potent antimicrobial, anti-inflammatory, and antioxidant properties (Kuropatnicki et al., 2013). Lavender essential oil is widely used for its antiseptic and anxiolytic effects, and recent research highlights its role in promoting collagen synthesis (Mori et al., 2016). Aloe Vera gel is a classic remedy for burns and skin irritation, attributed to its ability to stimulate fibroblast activity and moisturize the skin (Hekmatpou et al., 2019).

While the individual effects of these substances are recognized, their potential synergistic interactions at the molecular level have not been comprehensively investigated. A formulation combining these three agents practically stimulate wound healing and aging by simultaneously controlling inflammation, fighting oxidative stress, preventing infection, and stimulating tissue regeneration.

The aim of the study. This paper aims to elucidate the biochemical and molecular mechanisms underlying the synergistic effects of a combination of propolis, Lavandula angustifolia, and *Aloe Vera* (L.) on accelerating wound regeneration and mitigating the markers of premature aging.

Materials and Methods. This study was conducted as a comprehensive practical research elucidating the biochemical and molecular mechanisms underlying the synergistic effects of *Propolis*, *Lavandula angustifolia* (lavender), and *Aloe Vera*

on wound regeneration and premature skin aging. Analysis was performed using practical and experimental reports, and molecular studies relevant to dermatology, wound healing, and cellular aging. Some aspects are focused on studies detailing of the bioactive compounds, molecular targets, and therapeutic outcomes associated with each agent individually and in combination. Data were extracted regarding their anti-inflammatory, antioxidant, antimicrobial, and pro-regenerative activities, as well as their influence on key molecular pathways, including NF-κB, TGF-β, and matrix metalloproteinases (MMPs).

Results and Discussion. In the present study, a comparative synthesis of experimental data and results was conducted to assess synergistic interactions throughout the wound healing continuum. The research focused on key biological processes – including inflammatory regulation, fibroblast proliferation, collagen synthesis, and extracellular matrix remodeling. Results indicated that coordinated modulation of these processes enhanced tissue regeneration efficiency and contributed to a measurable reduction in oxidative stress markers. Furthermore, the findings suggest that promoting balanced wound healing responses may mitigate inflammaging mechanisms associated with premature skin aging, highlighting potential therapeutic targets for regenerative skin care applications.

To understand the synergy, it is essential first to dissect the individual contributions of each component.

Propolis is a complex mixture of plant resins, beeswax, and bee enzymes, containing a large number of bioactive compounds. Its primary active constituents are polyphenols, including flavonoids (e.g., chrysin, galangin, pinocembrin) and phenolic acids, most notably caffeic acid phenethyl ester (CAPE) (Wagh, 2013).

Anti-inflammatory mechanism. The potent anti-inflammatory action of propolis is largely attributed to CAPE. CAPE is a highly specific inhibitor of the transcription factor NF-κB (Natarajan et al., 1996). NF-κB is a master regulator of the inflammatory response, controlling the expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), chemokines, and enzymes like cyclooxygenase-2 (COX-2). By blocking NF-κB activation, propolis effectively dampens the inflammatory cascade, which is crucial for preventing chronic inflammation in wounds and for combating inflammaging.

Antioxidant mechanism. The flavonoids in propolis are powerful antioxidants. They act by directly scavenging free radicals (ROS and RNS), chelating metal ions like Fe^{2+} and Cu^{2+} that catalyze ROS production, and upregulating endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) (Viuda-Martos et al., 2010). This action protects cellular structures from oxidative damage, a key factor in both wound chronicity and skin aging.

Antimicrobial and pro-regenerative effects. Propolis exhibits broad-spectrum activity against bacteria (including MRSA), fungi, and viruses. This is critical in wound care to prevent infection. Furthermore, some studies suggest propolis can increase collagen content and promote angiogenesis (the formation of new blood vessels), essential steps in the proliferative phase of wound healing (Olczyk et al., 2013).

Lavandula angustifolia. The Pro-collagen and remodeling agent. Lavender essential oil is primarily composed of the monoterpenes linalool and linalyl acetate. Its benefits extend beyond its well-known calming aroma.

Wound Healing Acceleration. A seminal study by Mori et al. (2016) demonstrated that topical application of lavender oil on wounds in animal models significantly increased the expression of Transforming Growth Factor-beta (TGF-β). TGF-β is a pivotal growth factor that stimulates fibroblast differentiation into myofibroblasts, which are responsible for wound contraction and the synthesis of Type I and Type III collagen. This direct stimulation of the ECM-building machinery accelerates the proliferative and remodeling phases of healing.

Anti-inflammatory activity. Linalool has been shown to reduce the production of inflammatory mediators. It can inhibit the activation of inflammatory pathways and reduce edema, contributing to a more controlled inflammatory phase in wound healing (Peana et al., 2002).

Aloe Vera. The Fibroblast Stimulator and Moisturizer. The gel from the leaves of Aloe Vera is a complex mixture of water, polysaccharides, vitamins, enzymes, and glycoproteins. Its most researched bioactive polysaccharide is acemannan.

Stimulation of Cellular Proliferation: Acemannan is a potent macrophage activator, leading to the release of cytokines and growth factors like Fibroblast Growth Factor (FGF) and Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) (Zhang & Tizard, 1996). More directly, *Aloe Vera* gel has been shown to stimulate the proliferation and activity of fibroblasts and keratinocytes. This leads to increased synthesis of collagen and hyaluronic acid, improving skin elasticity and hydration (Surjushe et al., 2008).

Anti-inflammatory and moisturizing effects. *Aloe Vera* inhibits the COX pathway and reduces prostaglandin E2 production, contributing to its anti-inflammatory effects. Its high water content and muco-polysaccharides create a moist wound environment, which is known to facilitate cell migration and re-epithelialization, preventing scab formation and scarring.

Synergistic mechanisms in wound regeneration. A combination of these three agents creates a multi-target therapeutic system that addresses the entire wound healing continuum.

Phase 1. Inflammation Control. In the initial phase, the combination provides a powerful, multi-pathway anti-inflammatory effect. Propolis (via CAPE) blocks the central NF-κB pathway, lavender reduces inflammatory cytokine expression, and *Aloe Vera* inhibits the prostaglandin pathway. This rapid and comprehensive suppression of excessive inflammation prevents the wound from becoming chronic and sets the stage for efficient healing. Simultaneously, the antimicrobial properties of propolis and lavender create a sterile field, preventing infection, a common complication.

Phase 2. Proliferation enhancement. As inflammation subsides, the focus shifts to tissue formation. Aloe Vera stimulates the proliferation of fibroblasts, the primary cells of this phase. Lavender then upregulates TGF-β, signaling these newly proliferated fibroblasts to produce vast amounts of collagen. Propolis may further support this phase by promoting angiogenesis, ensuring the new tissue receives adequate blood supply (Martinotti & Ranzato, 2019). The moisturizing effect of aloe provides the ideal physical environment for these processes.

Phase 3. Optimized Remodeling. In the final phase, the newly deposited collagen is reorganized into a strong, functional scar. Lavender's role in promoting organized collagen III to collagen I transition is crucial. By concurrently reducing Matrix metalloproteinase (MMP) activity (an effect noted for some propolis flavonoids), the formulation may prevent excessive collagen degradation, leading to minimized scarring and improved tensile strength of the healed tissue.

Synergistic Mechanisms in Combating Premature Aging. The same molecular pathways involved in wound healing are implicated in skin aging. The synergy of the combination is therefore equally applicable to anti-aging strategies.

Comprehensive antioxidant defense: the combination provides a robust defense against oxidative stress. Propolis flavonoids, lavender's terpenes, and the vitamins (C and E) in *Aloe Vera* form an antioxidant complex that can neutralize a wide spectrum of free radicals. This reduces the cumulative oxidative damage to DNA, proteins, and lipids that drives cellular senescence.

Combating Inflammaging. Premature aging is intrinsically linked to chronic, low-grade inflammation. The potent, multi-target anti-inflammatory action of the combination, particularly the NF-κB inhibition by propolis, directly counteracts this process. By keeping chronic inflammation in check, the formulation helps preserve cellular function and prevent the inflammatory-driven degradation of the ECM.

Preservation and restoration of the extracellular matrix. This is the base of a potent anti-aging strategy. The combination acts on the ECM in two synergistic ways:

Inhibition of degradation. Flavonoids in propolis have been shown to inhibit the activity of MMPs (MMP-1, MMP-3, MMP-9), the enzymes responsible for breaking

down collagen and elastin in response to UV radiation and inflammation (Chen et al., 2018).

Lavender extract, through activation of transforming growth factor beta (TGF-β) signaling, and *Aloe Vera*, via fibroblast stimulation, both enhance the biosynthesis of collagen and hyaluronic acid. This complementary mechanism – concurrently suppressing matrix metalloproteinase (MMP) activity and stimulating fibroblast-mediated matrix production – results in a net increase in the structural integrity and density of the dermal extracellular matrix. Consequently, these effects contribute to a reduction in wrinkle formation, improved dermal firmness, and enhanced skin hydration [17].

Table 1.

Structured table summarizing the main points, mechanisms, and synergistic effects of *Propolis, Lavandula angustifolia* and *Aloe Vera* in wound healing and anti-aging applications

Component	Key bioactive compounds	Primary mechanisms	Effects on wound healing	Effects on premature aging
Propolis	Flavonoids (chrysin, galangin, pinocembrin), CAPE, phenolic acids	NF-κB inhibition (anti-inflammatory), antioxidant (ROS scavenging, metal chelation), antimicrobial	Reduces inflammation, prevents infection, promotes angiogenesis, increases collagen synthesis	Reduces oxidative stress, inhibits MMP activity, protects ECM
***Lavandula angustifolia* (Lavender)**	Linalool, linalyl acetate	Upregulates TGF-β (procollagen), anti-inflammatory, promotes organized collagen deposition	Stimulates fibroblast differentiation, enhances collagen synthesis, accelerates wound contraction	Enhances ECM integrity, reduces wrinkle formation
Aloe Vera	Acemannan, polysaccharides, vitamins, glycoproteins	Stimulates fibroblast proliferation, anti-inflammatory (COX inhibition), moisturizing	Promotes cell proliferation, collagen and hyaluronic acid synthesis, maintains moist wound environment	Improves dermal hydration, stimulates ECM production, enhances skin elasticity
Synergistic Combination	Propolis + Lavender + Aloe Vera	Multi-target: anti-inflammatory, antioxidant, antimicrobial, pro-regenerative	Controls all wound healing phases: inflammation, proliferation, remodeling; reduces	Counteracts inflammaging, protects against oxidative damage, stimulates ECM

			scarring; promotes robust tissue regeneration	restoration, improves skin firmness

Table 2.

Phase-wise table showing how the combination of *Propolis*, *lavender* and *Aloe Vera* acts during each wound healing stage, including their synergistic mechanisms

Wound Healing Phase	Role of *Propolis*	Role of *Lavender*	Role of *Aloe Vera*	Synergistic Effects
1. Inflammation Control	Inhibits NF-κB → reduces pro-inflammatory cytokines (TNF-α, IL-1β, IL-6); antimicrobial	Reduces inflammatory mediators (linalool), decreases edema	Inhibits COX pathway → lowers prostaglandins; maintains moist environment	Comprehensive suppression of inflammation, prevents chronic wounds, reduces infection risk
2. Proliferation (Tissue Formation)	Promotes angiogenesis, supports collagen deposition	Upregulates TGF-β → stimulates fibroblast differentiation and collagen synthesis	Stimulates fibroblast and keratinocyte proliferation; enhances collagen & hyaluronic acid production	Accelerated tissue formation, robust collagen synthesis, optimal cell proliferation, moist environment for healing
3. Remodeling / Maturation	Reduces MMP activity → prevents excessive collagen degradation	Promotes organized transition from collagen III to I → improves tensile strength	Maintains hydration → facilitates ECM remodeling	Strong, functional tissue; minimized scarring; improved dermal structure and elasticity
Anti-aging / ECM Preservation	Antioxidant → scavenges ROS; inhibits MMPs	Enhances TGF-β signaling → boosts ECM synthesis	Stimulates fibroblast-mediated ECM production; improves skin hydration	Reduced oxidative damage, preserved ECM integrity, reduced wrinkles, improved skin firmness and elasticity

Conclusions. Combination of *Propolis, Lavender*, and *Aloe Vera* functions as a powerful synergistic formulation for promoting wound regeneration and mitigating the signs of premature aging. The synergy arises from the complementary, multi-target

actions of their respective bioactive compounds. This formulation effectively modulates all phases of wound healing by controlling inflammation, preventing infection, and stimulating robust tissue proliferation and remodeling. In the context of aging, it provides a comprehensive strategy to combat the root causes of skin deterioration by neutralizing oxidative stress, quelling chronic

The studies continue on optimizing the ratios of the components within a stable formulation, prolong to conducting research to quantify the synergistic effects on wound closure rates and collagen deposition, for both wound care and anti-aging dermatological applications.

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THE EFFECT OF COFFEE DRINKS ON THE BIOCHEMICAL PROCESSES OF BLOOD CLOTTING

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