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Synergistic effects of polyherbal combination in wound healing: Mechanism and therapeutic insights

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The biological process of wound healing is intricate and includes remodeling, collagen formation, tissue proliferation and inflammation. Even with the advent of contemporary synthetic medications, delayed wound healing is still a significant clinical problem, especially in wounds that are chronic or diabetic. Polyherbal formulations, which combine several plant extracts to produce synergistic therapeutic effects, present a promising alternative in traditional medicine. The goal of this review is to investigate how polyherbal combinations can improve the healing process of wounds through synergistic processes, phytochemical interactions and therapeutic potential. Through a variety of multi-targeted actions, including as antioxidant activity that counteracts reactive oxygen species, anti-inflammatory effects that control the generation of cytokines and antimicrobial actions that prevent infection, polyherbal formulations aid in wound recovery. Furthermore, bioactive phytoconstituents such alkaloids, terpenoids, flavonoids and tannins promote collagen deposition, angiogenesis and fibroblast proliferation. When compared to formulations made with just one herb, the synergistic interaction of several ingredients improves bioavailability, increases efficacy and reduces negative effects. Because polyherbal mixtures target several physiological targets at once, they provide a comprehensive and synergistic approach to wound healing. Their potential use as affordable natural substitutes for artificial wound-healing agents is supported by their integration of many phytochemicals, which improves therapeutic efficacy and safety. To standardize formulations, validate mechanisms and create optimal polyherbal therapeutics for efficient wound management, more experimental and clinical research is necessary.

Keywords: Herbal therapy, Phytochemicals, Antioxidant activity, Wound healing, Polyherbal formulation, Synergistic action

Introduction

It is clear that polyherbal preparations are very successful in accelerating wound healing when taking into account the main findings from the literature review. They may start several physiological processes that hasten the healing of wounds. Consequently, these formulations should be investigated further in clinical studies and increasing production capacity and eliminating the previously described bottlenecks will help provide new opportunities for polyherbal wound-healing treatments that are more potent and less harmful[1].

Overview of wound healing process

There is much more to comprehending wound healing nowadays than just mentioning the three phases: inflammation, proliferation and maturation. A complicated

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chain of events including interactions and reactions between cells and "mediators" makes up wound healing. New mediators are found every year and our knowledge of inflammatory mediators and cellular interactions expands. Wound healing is influenced by numerous intrinsic and extrinsic factors and a vast industry gives the doctor a vast and sophisticated toolkit to combat those issues. An overview of wound healing, including issues and remedies, will be given in this article[2]. The intricate process of wound healing necessitates the coordinated responses of several cell types to a range of distinct cytokines and microenvironmental factors. In order to optimize effective wound healing and lower morbidity and mortality from disrupted wound healing, surgeons must have a thorough understanding of the major physiological processes involved and the significant variables that might impact them[3].

Limitation of conventional therapies

The world's antimicrobial resistance crisis has intensified due to a number of serious constraints with conventional antibiotic therapy. Antibiotic abuse and misuse have led to the rise of multidrug-resistant (MDR) microorganisms, making many conventional therapies useless. Chronic infections are challenging to treat because antibiotics frequently cannot break through biofilms. Because of their limited range of action, non-target species may be subject to selective pressure, which could increase resistance. Nephrotoxicity and ototoxicity are serious adverse effects of many antibiotics, particularly aminoglycosides like plazomicin. Outpatient use is restricted by the fact that some more recent medications, including eravacycline, are only available intravenously[4].

Only roughly 70% of the original tissue strength is restored after wound healing. Underlying diseases like diabetes or vascular disease cause chronic wounds to halt, interfering with the natural healing processes. Topical antimicrobials like iodine and silver have a limited effectiveness and can irritate or cause resistance. While sophisticated dressings are expensive and not always effective, traditional ones have the potential to harm tissue. With the exception of PDGF, growth factor treatments are costly and have little advantages. There is little data on hyperbaric oxygen therapy and there may be adverse effects. Skin replacements such as Derma graft and Apligraft work well but are very costly. All things considered, traditional treatments are frequently single-target, expensive and unavailable for broad use[5].

Importance of herbal and polyherbal approaches

Active phytochemicals are frequently found in trace amounts in single plants, which might not be enough to produce the intended therapeutic effects. According to the Sarang Dhar Samhita, polyherbal compositions blend several herbs in particular ratios to increase effectiveness and lower toxicity. Compared to isolated drugs, this synergy enables multi-targeted action, better addressing complicated diseases. By combining several therapeutic effects into a single formulation, lowering pill burden and improving convenience, Polyherbal also increases patient compliance[6]. For herbal and polyherbal compositions to be safe, effective and reproducible, phytochemical standardization is necessary. To ensure constant quality, methods including marker compound measurement and fingerprint profiling are used. These methods combine the beneficial benefits of several plant components to provide affordable, multipurpose treatments, which are particularly helpful for complicated and chronic illnesses. Standardization allows for dependable incorporation into mainstream healthcare by bridging the gap between traditional knowledge and contemporary research[7].

For polyherbal wound healing to be safe, effective and high-quality, pharmacovigilance is essential. Because polyherbal preparations have complicated phytochemical profiles, they may result in unpleasant responses or herb-drug interactions despite their medicinal promise. Systematic monitoring aids in risk identification, formulation standardization and sensible usage guidance. Strong pharmacovigilance frameworks are necessary to convert traditional remedies into clinically validated, multifunctional medications as the demand for plant-based diabetic wound therapy rises8.

Concept of polyherbal formulation

Extracts from several medicinal plants are combined in a polyherbal formulation to target various wound healing pathways, improving angiogenesis, collagen synthesis and epithelialization, particularly in complex diabetic wound settings[9]. In diabetic models, its bioactive components demonstrated synergistic antibacterial, anti-inflammatory and antioxidant qualities that sped up tissue regeneration. These results provide credence to its promise as a safe, multipurpose and reasonably priced treatment for the treatment of chronic wounds[10].

Historical and ayurvedic background

Ancient cultures employed beer and sesame oil, the Egyptians applied honey and bandages, the Greeks placed a strong emphasis on wound closure and Ayurveda described plant-based healing, all of which have influenced modern wound care techniques[11]. Originating in India's Vedic traditions more than 5,000 years ago, Ayurveda developed via classical texts and oral tradition. These days, it incorporates holistic remedies, herbal medicine and lifestyle. Globally acknowledged, Ayurveda has potential for individualized, integrative treatment and long-term wellness, but it has difficulties with standardization and evidence-based validation[12]. Herbal treatment, Ayurveda, honey therapy, maggot debridement, stem cell therapy and low-level laser therapy are examples of alternative wound healing techniques. Each of these methods offers a special mechanism to improve tissue repair, lessen infection and encourage regeneration[13].

Ayurvedic medications are categorized into three groups based on their source: herbal, mineral and animal. Among these, herbal formulation has lately become increasingly significant and well-known worldwide. This situation is clear given the significant rise in the use of herbal formulations in the developed world over the past several years[14]. A coordinated interaction of macrophages, fibroblasts, keratinocytes, epithelial cells and signalling molecules is necessary for the proper wound healing process, which includes overlapping phases of haemostasis, inflammation, proliferation and remodeling. By eliminating infections, removing damaged tissue and generating growth factors that promote angiogenesis, collagen deposition and wound closure, macrophages are essential to the inflammatory stage of wound healing[15].

Rationale behind combining herbs

Kerry Bone's A Clinical Guide to Blending Liquid Herbs provides a useful framework for customized herbal prescriptions. It describes dose methods, herbal selection, formulation principles and therapeutic synergy. By providing case studies and justification, it enables medical professionals to customize liquid herbal mixes for particular patient requirements, improving clinical results, safety and efficacy[16].

Multi-target analysis of Ayurvedic formulations for wound healing, such as triphala, is made possible by network pharmacology. Synergistic interactions are revealed by methods like bioactive mining, target prediction using Binding DB and network creation using Cytoscape. By identifying important pathways associated with inflammation and angiogenesis, such as AGE-RAGE and NF-κB, these techniques validate conventional treatments using systems biology. This method for managing diabetic wounds combines traditional knowledge with contemporary medication discoveries[17].

Synergistic vs. additives effects

Although herbal synergism has been extensively documented, few investigations have clarified the underlying mechanisms. Both pharmacodynamic and pharmacokinetic synergism have been defined, much like medication combinations. The majority of publications (74%) assume synergism when combinations lower dosage or improve effects by comparing effective concentrations or therapeutic outcomes. But this method frequently misses the difference between additive effects and real synergy. To more precisely measure synergistic interactions, exacting techniques including isobolographic analysis, interaction index and ANOVA are being employed more frequently[18].

Combinations of cumin and fenugreek and cumin and mustard had strong synergistic antibacterial activity, suppressing S. aureus, L. monocytogenes and E. coli. No hostility was seen. Additionally, extracts decreased spoilage bacteria and maintained probiotic viability, enabling a variety of food safety uses[19]. When combined, the essential oils of clove, cinnamon and thyme demonstrated potent synergistic antibacterial activity against *P. aeruginosa, S. aureus* and *E. coli,* lowering MICs by up to four times. Antioxidant synergy outperformed individual oils and supported multifunctional therapeutic potential by considerably improving DPPH and ABTS radical scavenging[20].

Mechanism of wound healing

In order to restore tissue integrity, wound healing is a dynamic and intricate biological process that involves several overlapping phases. It starts with haemostasis, in which platelet aggregation and vascular constriction cause a clot to form. After then, there is an inflammatory phase marked by the invasion of neutrophils and macrophages, which removes debris and pathogens while producing growth factors and cytokines. Granulation tissue is formed as a result of fibroblast stimulation, angiogenesis and re-epithelialization during the proliferative phase. In order to reinforce the healed tissue, collagen and extracellular matrix components are finally rearranged throughout the remodeling process. Both local and systemic variables, such as oxygenation, infection, diabetes and nutritional status, have an impact on the process. Targeted therapeutic measures are necessary for chronic wounds, which are frequently caused by disruption or prolongation of one or more phases (Table 1 and 2)[21].

Proliferation, remodeling, inflammation and haemostasis are all involved in wound healing. Cellular senescence, persistent inflammation and defective re-epithelialization hinder repair in diabetes and aging, resulting in chronic wounds with inadequate matrix deposition and an increased risk of infection[22].

Phases of wound healing (inflammation, proliferative, remodeling)

Inflammation

Redrawn from Nedelec, B et al. Inflammatory responses mediated by cytokines, chemokines, growth factors and their effects on cellular receptors dominate the first stage following cutaneous damage (Fig. 1). Activation of intracellular signalling cascades promotes cell motility, proliferation and differentiation. Additionally, several cell types, including granulocytes and macrophages, are drawn to the wound site by chemoattractant factors, which starts the healing process. Cellular activities are significantly impacted by the wound milieu, which is made up of different proteinases, cytokines, chemokines, pH gradients

Table 1. Haemostatic derived factors affecting wound healing

Haemostatic factors	**Function**
Fibrin, plasma fibrinogen	Coagulation, chemoattraction, adhesion, scaffolding for cell migration
Factor XIII (fibrin stabilizing factor)	Induces chemoattraction and adhesion
Circulatory growth factors	Regulation of chemoattraction, mitogenesis, fibroplasia
Complement	Antimicrobial activity, chemoattraction

Table 2. Platelets derived factors affecting wound healing

Platelet derived factors	**Function**
Cytokines, growth factors	Regulation of chemoattraction, mitogenesis, fibroplasia
Fibronectin	Early matrix, ligand for platelet aggregation
Platelet-activating factor (PAF)	Platelet aggregation
Thromboxane A2	Vasoconstriction, platelet aggregation, chemotaxis
Platelet factor IV	Chemotactic for fibroblast and monocytes, neutralizes activity of heparin, inhibit collagenase
Serotonin	Induces vascular permeability, chemoattractant for neutrophils
Adenosine dinucleotide	Stimulate cell proliferation and migration, induces platelet aggregation

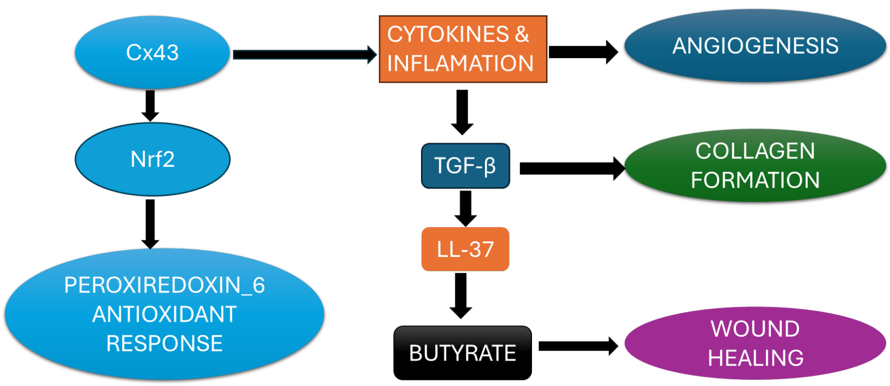

Figure 1. Inflammation process during causes of wound

and pO2 gradients[23].

Cx43- connexin 43, Nrf2- nuclear factor erythroid 2 – related factor 2

TGF-β-Transforming growth factor-beta, LL-37 – Human catholicising antimicrobial peptide

The phase of proliferative

Neo angiogenesis, granulation tissue and extracellular matrix production and re-epithelialization are all components of the proliferative phase.

Neo angiogenesis

Proper wound healing requires Neo angiogenesis, one of the key processes in wound healing. TLR cross-talk with adenosine A2A receptors regulates the transition of macrophages from generating proinflammatory cytokines to secreting VEGF. This change is brought about by the cytoplasmic adaptor protein for TLR signalling, myeloid differentiation primary response gene (MyD-88). Myeloid differentiation primary response protein-88 e/e mice's wounds heal noticeably more slowly than those of wild-type mice[24].

Tissue formation

Redrawn from Mosser, D. M. et al. in the proliferative phase (Fig. 2): nutrients and oxygen are limiting factors because of the tremen dous metabolic activity. Just as in Neoangiogenesis, macrophages are also being rediscovered in their interaction with fibroblasts. A special subtype of wound healing macrophages is induced mainly by IL-4-mediated T helper cell type 2 (TH2) responses[25].

Re-epithelialization

(Fig. 3) Redrawn from Fathke, C. *et al.* is based on the differentiation, proliferation and migration of epidermal keratinocytes. The process can begin once the wound bed has been appropriately established with proliferating fibroblasts, a new collagen matrix and new vessels. Keratinocytes are activated and migrate into the wound site from the edges; even highly conserved pathways like

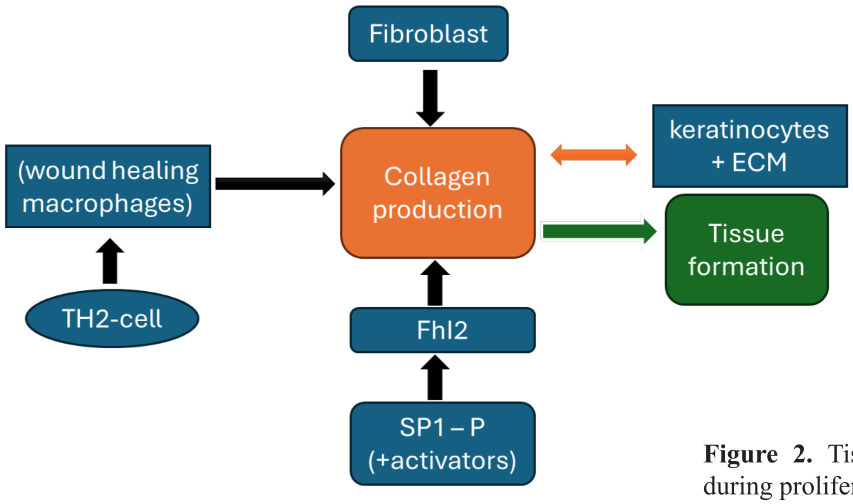

Figure 2. Tissue and collagen synthesis formation during proliferative phase

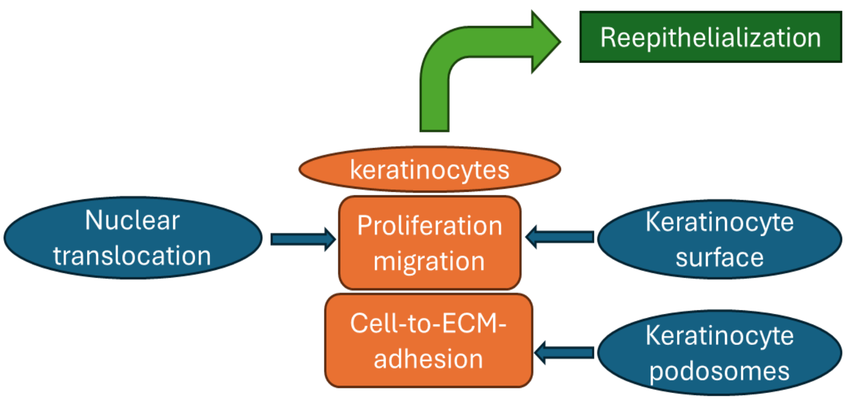

Figure 3. Process of Re-epithelialization during last phase of proliferative phase

the Wnt (combined from wingless Wgand Int) pathway are involved[26].

Phases of remodeling

(Fig. 4) Redrawn from Braunwarth, H. *et.al*, can begin as soon as a few days following an injury and continue for up to two years. A range of proteinases, which are controlled by time-dependent and geographic changes in expression patterns, aid in coordinated wound healing during this phase. Aside from this control, the wound milieu itself modifies the activity and confirmation of nearly all proteinases, such as through changes in pH brought on by wound healing in contrast to physiological settings[27].

Role of antioxidant, collagen synthesis, growth factors and cytokines

Antioxidant

Excess reactive species harm DNA, proteins and lipids, causing oxidative stress. By scavenging radicals, chelating metals and blocking oxidative enzymes, antioxidants combat this. Their combined effects shield cells, but taking too much of them can damage them by interfering with redox signalling[28].

DPPH radical scavenging activity

By providing hydrogen, an antioxidant can stop a molecule from oxidizing. One method that is frequently used in the industry to assess antioxidants based on their ability to reduce stable free radical DPPH is radical scavenging activity with DPPH. Since the DPPH solution changes from deep violet to light yellow when it is lowered, the spectrophotometer's drop in absorbance value indicated the antioxidant activity. The samples' antioxidant qualities are shown by the colour changes.

Ferric reducing antioxidant power (FRAP)

The reduction of Fe3+-tripyridyl triazine (colourless ferric complex) to Fe2+-tripyridyl triazine (blue colour ferric complex) at low pH was used to calculate the plant's ferric reducing power. Antioxidants that donate electrons caused the decrease[29].

Collagen synthesis

Using collagen dressings to treat wounds Given that collagen dressings provide the following purposes, their use may seem appealing: Deactivate or inhibit MMPs to promote fibroblast

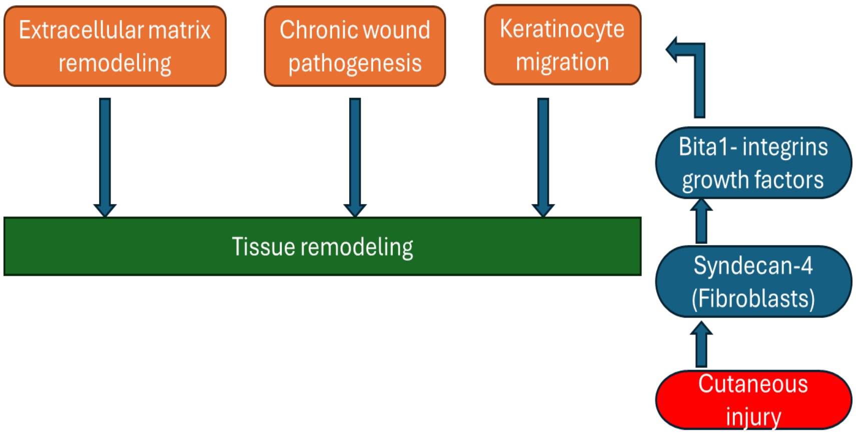

Figure 4. Remodeling/maturation process in last mechanism during wound healing

penetration and production. Leukocytes, macrophages, fibroblasts and epithelial cells are preserved with the aid of fibronectin absorption and bioavailability. support the preservation of the wound's chemical and thermal microenvironment[30].

Growth factors

Cytokines

By controlling inflammation, angiogenesis and fibroblast activity, cytokines such as TGF-β, IL-1, IL-6, TNF-α and PDGF orchestrate wound healing. Dysregulated cytokine signalling, particularly increased TGF-β, encourages excessive extracellular matrix deposition in fibrotic disorders, which results in scarring. The goal of cytokine therapy is to promote tissue regeneration and restore equilibrium[32].

Synergistic mechanism in polyherbal formulation

Phytochemical interaction

Amruthotharam kashayam, a significant Ayurvedic polyherbal compound, was the subject of the study, which assessed the synergistic effects of many phytochemicals derived from diverse plant ingredients. The final formulation's chemical components differ from those of individual plant extracts, according to chromatographic profiling and spectrophotometric analyses. The FTIR spectrum shift provides proof of the process's synergistic chemical interaction. The same was confirmed by tandem mass spectroscopy investigations. The investigation confirmed that the active ingredients in an Ayurvedic polyherbal formulation interacted synergistically[33].

If taken concurrently with pharmaceutical medications, liquorice root extracts may disrupt their metabolism and clearance. Extracts that have been shown to dramatically improve the metabolism of medications that are substrates of these enzymes, leading to quicker clearance and perhaps decreased effectiveness and treatment failure. An increasing amount of research suggests that liquorice may interact with prescription drugs. Glabridin and glycyrrhetinic acid are two components of liquorice that can disrupt medication metabolism by altering the CYPs, particularly the CYP3A4 isozyme. For some individuals with chronic illnesses who need to take certain types of clinical medications for the rest of their lives, such protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (NNRTI): which are substrates of CYP3A4, this condition may be very crucial[34].

Enhanced bioavailability and pharmacodynamic synergy

The oral bioavailability of polyherbal nanoparticles containing quercetin and gallic acid was four times higher than that of polyherbal extract in rats with DMH-induced colorectal cancer. Improved serum concentration levels and sustained release characteristics were found via pharmacokinetic study. Additionally, these nanoparticles showed exceptional anticancer activity, indicating that they may be a unique therapeutic approach for the prevention and treatment of colon cancer[35].

This study included 5666 phytochemicals and 361 medicinal plants in 522 Indian polyherbal preparations. Pharmacokinetics, structural characteristics and drug-likeness were examined for every molecule. Interactions between illness, formulation and plant were discovered using a network pharmacology method. The information is digitally preserved, facilitating the use of traditional expertise in drug development[36].

Molecular targets involved in healing

Molecular targets for diabetic wound healing were found in a patent review and were categorized as growth factors, neuropeptides, immunomodulators and miscellaneous substances. These affect the four main stages of wound healing: haemostasis, remodeling, angiogenesis and inflammation. All stages are affected by growth factors, whereas immunomodulators and neuropeptides control angiogenesis and inflammation[37].

Table 3. Role in wound healing, different type of growth factors 4[31]

Growth factor	Cell source	Activity
TGF- α	Platelets, macrophages, keratinocytes	Activates neutrophils, fibroblast mitogen, stimulates angiogenesis
TGF- β	Platelets, macrophages, lymphocytes	Stimulates fibroplasia and angiogenesis, induces proliferation of many different cells
PDGF	Platelets, macrophages, keratinocytes, endothelial cells	Chemoattractant for neutrophils, fibroblasts, mitogen for smooth muscle cells and fibroblast
FGF	Macrophages, neural tissue, nearly ubiquitous	Stimulates endothelial cell growth, mitogen for mesodermal and neuroectodermal- derived cells
EGF	Platelets, keratinocytes, salivary gland	Mitogens for keratinocytes, endothelial cells and fibroblasts
Interleukin-1	Platelets, leukocytes	Vascular permeability increased
TNF- α	Platelets	Chemotaxis, nitric oxide release, other growth factors activate
VEGF	Platelets, neutrophils, keratinocytes	Neovascularization, angiogenesis stimulates

TGF, transforming growth factor; IL, interleukin; PDGF, platelet derived growth factor; FGF, fibroblast growth factor; EGF, epidermal growth factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor

Table 4. New molecular targets that have been developed to help diabetic wounds heal

Class	Molecular target
Immunomodulators	Lactoferrin
	Thymosin beta 4 (T $beta_4$)
	T cell immune response cDNA 7
	Putative chemokines
Neuropeptides	Substance P
	Neuropeptide Y
Growth factors	Vascular endothelial growth factors
	Fibroblast growth factors
	Nerve growth factors
	Connective tissue growth factors
	Hepatocyte growth factors
Other agents	Homeobox genes
	Treprostinil

Phytochemical and pharmacological insights

The potent wound-healing properties of polyherbal ointments are made possible by the complex phytochemical profiles of *Thymus vulgaris, Nigella sativa and Ziziphus nummularia*, which include flavonoids, phenolics, saponins and essential oils. Together, these elements affect inflammation, microbial load and oxidative stress. Pharmacologically, by promoting epithelialization, preventing cytokine release and rupturing bacterial membranes, they offer broad-spectrum antibacterial and anti-inflammatory benefits for faster wound healing38.

Under the effect of the plant extract formulation, it was shown that L929 fibroblasts and HaCaT cells move toward the artificially induced cell damage at varying speeds. Based on their innate traits, keratinocytes were shown to be pickier than L929 fibroblasts.

Through the proliferation and mobilization of fibroblasts and keratinocytes, a polyherbal formulation made from plant extracts (*V. negundo, E. officinalis* and *T. procumbens)* speeds up the healing process of wounds and encourages angiogenesis at the site of damage[39].

Key active constituents involved: like - flavonoid, alkaloid, terpenoids, phenolic etc.

Through bioactive components such flavonoids, alkaloids, tannins, terpenoids, saponins and phenolic compounds, medicinal plants aid in the healing of wounds. These have anti-inflammatory, antibacterial and antioxidant properties that work at various stages of healing. They improve tissue regeneration and repair by promoting collagen production, cell proliferation, angiogenesis and modulating cytokines including TNF-α and IL-6[40].

Flavonoids

It promotes collagen production, angiogenesis and fibroblast activity while suppressing microbial virulence factors. Certain flavonoids, such as luteolin, rutin, apigenin and catechins, have demonstrated effectiveness in a variety of wound models. By altering signalling pathways including PI3K/Akt, MAPK and PKC, they affect gene expression and cellular reactions that are essential for tissue regeneration[41].

Terpenoid

Prominent monoterpenes and iridoid derivatives with wound-healing qualities include aucubin, thymol, α-terpineol, genipin and borneol. Inhibiting proinflammatory cytokines, fibroblast activity and leukocyte migration are all boosted by Borneol. Thymol has antibacterial properties, growth-promoting properties for fibroblasts and regulates prostaglandin production. By blocking COX enzymes and NF-κB signalling, α-terpineol lowers TNF-α and IL-1β. Collagen deposition and epithelialization are stimulated by genipin inherent crosslinking properties. NF-κB activation is suppressed, inflammatory cytokines are inhibited and skin regeneration is promoted by aucubin[42].

Alkaloids

Alkaloids that have been identified from Colletotrichum species, like quinine, have antibacterial and anti-inflammatory qualities that aid in the healing of wounds. Although some alkaloids, such as vinblastine and camptothecin, prevent healing, quinine has been used traditionally to treat infected wounds by lowering inflammation and microbial burden, indicating its potential for use in skin regeneration and wound care.

Phenolic

These endophytic fungal phenolic compounds include benzoic acid, 4-hydroxybenzaldehyde, flavones, stilbenes, flavanonols, isoflavonoids, phenolic glycosides and phenol derivatives. They have antibacterial, antioxidant and biofilm-inhibiting actions. In diabetic and infected wound models, these components increase wound contraction, epithelialization and tissue regeneration, demonstrating encouraging wound-healing potential[43].

Formulation strategies and evaluation parameters

Phytochemical fingerprinting: To choose appropriate plants and guarantee consistency in polyherbal mixes, HPLC is utilized to produce comprehensive chemical profiles of herbal extracts. Quantification of marker compounds: In multi-herb formulations, uniformity across batches is crucial and this is made possible by the identification and measurement of bioactive markers. Detection of adulterants and contaminants: guarantees purity and safety, which is crucial when mixing different plants. Complex combination quality control: HPLC makes it possible to track the stability and deterioration of active ingredients in polyherbal formulations. Synergy effect validation**:** HPLC data can help synergy research by linking compound ratios with bioactivity, even though this isn't investigated in the study[44].

Combining several medicinal plant extracts had synergistic effects that improved wound-healing and antibacterial activity. Every extract contributed distinct bioactivities, such as antibacterial, antioxidant, or anti-inflammatory qualities and the components were chosen based on their ethnomedical significance and previous pharmacological data. Agar well diffusion was used to assess the antimicrobial activity against Pseudomonas aeruginosa, Escherichia coli and Staphylococcus aureus. The results demonstrated distinct zones of inhibition as a result of the combined phytoconstituent action. To guarantee stability and efficient topical performance, physicochemical characteristics such as pH, viscosity, spreadability and extrudability were methodically adjusted and verified using pharmacopeial standards. Strong shelf-life and resistance under stress circumstances were indicated by accelerated stability testing, which verified no appreciable changes in appearance, pH, or microbiological contamination over time[45].

Ointment formulation strategies and evaluation parameters

Formulation processes

The ointment with 5% extract, beeswax and soft paraffin was made using the fusion process. A crucible containing a weighed quantity of extract was set on a hot plate that was heated at 131 °C. After melting, beeswax was added in a geometric dilution while being stirred to guarantee uniform mixing. After lowering the temperature to 55 ± 3 ^{0}C, soft paraffin was added by geometric dilution to the molten extract-beeswax combination. After removing the crucible from the heat, the ointment was agitated in a storage container until it solidified[46].

Evaluation parameter

Measurements of the manufactured ointments' appearance, Odor, colour, homogeneity, pH, spread-ability, hardness, water number and viscosity were among the factors that were examined[47].

Hydrogel formulation strategies and evaluation parameters

Formulation processes

The method outlined by Ali et al. (2021) was used to create herbal hydrogel. At 40 to 50 degrees Celsius, one gram (1g) of carbopol 940 was dissolved in 50 milliliters of distilled water, followed by 0.2 grams of potassium sorbate and well mixed with the aid of a magnetic stirrer. After the mixture was left overnight, 50 milliliters of distilled water were added. The addition of 10 mL of propylene glycol and 5 mL of ethanol, respectively, continued the stirring. Add two to three drops of 10% 0.1M NaOH and mix until the pH of the gel solutions reaches 7.0[48].

Evaluation parameter

Measurements of the manufactured hydrogel Physical Examination such as colour, homogeneity and consistency visually, pH measurement, spreading coefficient, Rheological studies and finally stability testing is involved[49].

Cream formulation strategies and evaluation parameters

Formulation of creams based on absorption extract from hot infusion oil

10 ml of olive oil was combined with 1g of the extract (the mixture that produced the best results) and heated to 60–70°C in a water bath. After cooling, 10 milliliters of this mixture were filtered through cotton fabric. After being collected, the filtrate was boiled once again in a water bath. When the solution was heated, 2.8g of beeswax was added to this combination. Await the melting of the solution. This is the cream's oil phase.

Extract of water

Ten milliliters of water were combined with one gram of extract (the mixture that produced the greatest results). After that, this combination was heated to 60–70°C in a water bath. After cooling to room temperature, a cotton towel was used to filter it. The water extract is the filterate that was gathered.

Blending

To combine the two processes, a mortar and pestle were used. Prior to solidification, the oil phase was put into the mortar. This oil phase was supplemented with five drops of mineral oil. Drop by drop, the water extract was added and the mixture was constantly stirred. This was carried out until a cream-like consistency was achieved[50].

Evaluation parameter

Measurements of the manufactured hydrogel Physical Examination such as colour, homogeneity and consistency visually, pH measurement, spreading coefficient, Rheological studies and finally stability testing is involved.

Challenges and future prospect

Challenges in polyherbal formulation

Regulations' effects on the status and safety of herbal medicines, difficulties with herbal-allopathic drug interactions, difficulties with herbal drug quality control, difficulties with herbal safety monitoring and difficulties with clinical research on herbal medicines[51].

Better techniques for quality control

Due to their complex chemical compositions, insufficient pharmacological data and the shortcomings of existing standardization techniques, polyherbal products provide significant quality control issues. Functional significance is lacking in conventional methods such as marker quantification and DNA barcoding. Batch consistency and biological potency require sophisticated techniques like omics, Phytomics QC and BioReF.

Comprehending molecular, cellular and organism-level herb-herb interactions

Managing large amounts of data from multi-component investigations, interpreting intricate herb interactions, confirming synergy using cellular and molecular tests and using computer models like NIMS to find active combinations are some of the difficulties.

Research studies on herbal products

The high expense of thorough studies, limited sample size, poor methodology and poor-quality control are among the difficulties. Reliable effectiveness validation of herb-herb mixtures in clinical settings is hampered by these variables[52].

The potential of polyherbal formulations in the future

It is believed that local medicine provided the lead for the discovery of roughly three-fourths of the herbal medications used globally. About 25% of contemporary medications, according to the WHO, are derived from plants that were once used in traditional medicine. In India, natural ingredients constitute the source of over 70% of contemporary medications[53].

Current status of polyherbal formulations

In both clinical and experimental trials, polyherbal formulations for diabetes exhibit encouraging antidiabetic benefits. Although they provide multiple mechanisms, less adverse effects and synergistic benefits, they struggle with standardization, dose consistency and regulatory validation for wider clinical acceptability.

Polyherbal formulations' prospects for the future

Prospects for the future centre on combining polyherbal treatments with traditional medicine, maximizing synergistic pairings, enhancing safety assessment and carrying out thorough clinical trials to confirm effectiveness and reduce side effects[54].

Conclusions

Recently, we have observed a widespread issue with wound healing globally, highlighting the need to study and identify suitable treatments to minimize or resolve this problem. Some broad-spectrum antibiotics are produced to address this issue; however, they often cause significant side effects and are unsuitable for long-term treatment. Additionally, their high cost and the development of antibiotic resistance contribute to their limited use. Some other treatments are also presented for treatment, which is not available for everyone due to high cost. After these causing problems, this shows the low efficacious diversity for the treatment in wound healing. The synergistic effect of antibiotics can provide effective treatment; however, prolonged use may lead to side effects and antibiotic resistance. Finally, a suitable treatment is required for this problem. Herbal treatment comes to show no side effects and show the high efficacy and attack on different mechanisms, but the problem is when a single herbal use only shows some specific wound-healing mechanisms. After approaching a single herbal treatment, it was converted into a polyherbal treatment approach to show the better efficacy and effective treatment for this broad-level problem. The benefit of a polyherbal synergistic approach is treating a multi-type mechanism, which is the process of wound healing and showing no or minimum side effects. It is very low cost and also a natural source for this formulation. After all, this paper focused on the synergistic effect due to multiple types showing the mechanism like anti-inflammation, the proliferative phase and remodeling from one approach and the result is very good for the present and future prospects. It will be easily available for every person and also low-cost treatment.

Reference

1. **Dubey, S. and Dixit, A.K. (2023).** Preclinical evidence of polyherbal formulations on wound healing: A systematic review on research trends and perspectives. Journal of Ayurveda and Integrative Medicine. 14(2): 100688.
2. **George Broughton, I.I., Janis, J.E. and Attinger, C.E. (2006).** Wound healing: an overview. Plastic and Reconstructive Surgery. 117(7S): 1e-S.
3. **Harper, D., Young, A. and McNaught, C.E. (2014**). The physiology of wound healing. Surgery (Oxford): 32(9): 445-450.
4. **Alaoui Mdarhri, H., Benmessaoud, R., Yacoubi, H., Seffar, L., Guennouni Assimi, H., Hamam, M. and Kettani-Halabi, M. (2022).** Alternatives therapeutic approaches to conventional antibiotics: advantages, limitations and potential application in medicine. Antibiotics. 11(12): 1826.
5. **Han, G. and Ceilley, R. (2017).** Chronic wound healing: a review of current management and treatments. Advances in Therapy. 34(3): 599-610.
6. **Parasuraman, S., Thing, G.S. and Dhanaraj, S.A. (2014).** Polyherbal formulation: Concept of ayurveda. Pharmacognosy Reviews. 8(16): 73.
7. **Rajani, M. and Kanaki, N.S. (2008**). Phytochemical standardization of herbal drugs and polyherbal formulations. In Bioactive molecules and medicinal plants (pp. 349-369). Berlin, Heidelberg: Springer Berlin Heidelberg.
8. **Gupta, D., Sudan, P., Imran, M. and Wal, A.** (2024).The Importance of Pharmacovigilance in the Polyherbal Sector: Challenges and Future Potential. International Journal of Pharmaceutical Quality Assurance. 5(2): 950-956.
9. **Gupta, A., Upadhyay, N.K., Sawhney, R.C. and Kumar, R. (2008).** A poly-herbal formulation accelerates normal and impaired diabetic wound healing. Wound Repair and Regeneration. 16(6): 784-790.
10. **Panwar, A.S., Panwar, V. and Darwhekar, G.N. (2013).** Wound healing activity of prepared polyherbal formulation. Asian Journal of Pharmaceutical Research and Development. 16-21.
11. **Ahmad, W., Aquil, Z. and Alam, S.S. (2020).** Historical background of wound care. Hamdan Medical Journal. 13(4): 189-195.
12. **Kizhakkeveettil, A., Parla, J., Patwardhan, K., Sharma, A. and Sharma, S. (2024). History**, Present and Prospect of Ayurveda. In History, Present and Prospect of World Traditional Medicine. (pp. 1-72).
13. **Majumdar, A. and Sangole, P. (2016).** Alternative approaches to wound healing. Alexandrescu VA. Wound Healing: New insights into Ancient Challenges., IntechOpen. 459.
14. **Parasuraman, S., Thing, G.S. and Dhanaraj, S.A. (2014).** Polyherbal formulation: Concept of ayurveda. Pharmacognosy Reviews. 8(16): 73.
15. **Mandrika, I., Kumar, S., Zandersone, B., Eranezhath, S.S., Petrovska, R., Liduma, I. and Tracevska, T. (2021).** Antibacterial and Anti-Inflammatory Potential of Polyherbal Formulation Used in Chronic Wound Healing. Evidence-Based Complementary and Alternative Medicine. 2021(1): 9991454.
16. **Bone, K. (2003).** A clinical guide to blending liquid herbs: herbal formulations for the individual patient. Elsevier Health Sciences.
17. **Chandran, U., Mehendale, N.E.E.L.A.Y., Tillu, G.I.R.I.S.H. and Patwardhan, B.H.U.S. H.A.N. (2015).** Network pharmacology: an emerging technique for natural product drug discovery and scientific research on ayurveda. In Proc. Indian Natn. Sci. Acad. 81(3): 561-8.
18. **Ma, X.H., Zheng, C.J., Han, L.Y., Xie, B., Jia, J., Cao, Z.W. and Chen, Y.Z. (2009).** Synergistic therapeutic actions of herbal ingredients and their mechanisms from molecular interaction and network perspectives. Drug Discovery Today. 14(11-12): 579-588.
19. **Das, S., Anjeza, C. and Mandal, S. (2012).** Synergistic or additive antimicrobial activities of Indian spice and herbal extracts against pathogenic, probiotic and food-spoiler micro-organisms. International Food Research Journal. 19(3): 1185.
20. **Bag, A. and Chattopadhyay, R.R. (2015).** Evaluation of synergistic antibacterial and antioxidant efficacy of essential oils of spices and herbs in combination. PloS One. 10(7): e0131321.
21. **Witte, M.B. and Barbul, A. (1997).** General principles of wound healing. Surgical Clinics of North America. 77(3): 509-528.
22. **Wilkinson, H.N. and Hardman, M.J. (2020).** Wound healing: cellular mechanisms and pathological outcomes. Open Biology. 10(9): 200223.
23. **Nedelec, B., De Oliveira, A., Saint-Cyr, M. and Garrel, D.R. (2007).** Differential effect of burn injury on fibroblasts from wounds and normal skin. Plastic and Reconstructive Surgery. 119(7): 2101-2109.
24. **Schreml, S., Szeimies, R.M., Prantl, L., Landthaler, M. and Babilas, P. (2010).** Wound healing in the 21st century. Journal of the American Academy of Dermatology. 63(5): 866-881.
25. **Mosser, D.M. and Edwards, J.P. (2008).** Exploring the full spectrum of macrophage activation. Nature Reviews Immunology. 8(12): 958-969.

26. **Fathke, C., Wilson, L., Shah, K., Kim, B., Hocking, A., Moon, R. and Isik, F. (2006).** Wnt signaling induces epithelial differentiation during cutaneous wound healing. BMC Cell Biology. 7(1): 4.
27. **Braunwarth, H., Brill, F.H. and Brill, H. (2011).** Results of in vitro testing of wound dressings with sustained release of polyhexanide (PHMB) and silver-ions at different pH-values. Wund Manage. 3: 119-125.
28. **Pisoschi, A.M. and Pop, A. (2015).** The role of antioxidants in the chemistry of oxidative stress: A review. European Journal of Medicinal Chemistry. 97: 55-74.
29. **Rahim, N.F.A., Muhammad, N., Abdullah, N., Talip, B.A. and Poh, K.H. (2020).** The interaction effect and optimal formulation of selected polyherbal extracts towards antioxidant activity. Food Research. 4(6): 2042-2048.
30. **Rangaraj, A., Harding, K. and Leaper, D. (2011).** Role of collagen in wound management. Wounds UK. 7(2): 54-63.
31. **Steed, D.L. (1997).** The role of growth factors in wound healing. Surgical Clinics of North America. 77(3): 575-586.
32. **Gharee-Kermani, M. and Pham, S.H. (2001).** Role of cytokines and cytokine therapy in wound healing and fibrotic diseases. Current Pharmaceutical Design. 7(11): 1083-1103.
33. **Sulaiman, C.T., Anju, K., Anandan, E.M. and Balachandran, I. (2021).** Synergistic interactions of phytochemicals in polyherbal formulation enhance the chemical transformations of active constituents. Journal of Applied Spectroscopy. 88(1): 181-186.
34. **Haron, M.H., Avula, B., Ali, Z., Chittiboyina, A.G., Khan, I.A., Li, J. and Khan, S.I. (2023).** Assessment of herb-drug interaction potential of five common species of licorice and their phytochemical constituents. Journal of Dietary Supplements. 20(4): 582-601.
35. **Patil, P. and Killedar, S. (2021).** Improving gallic acid and quercetin bioavailability by polymeric nanoparticle formulation. Drug Development and Industrial Pharmacy. 47(10): 1656-1663.
36. **Gogoi, D., Kiewhuo, K., Chutia, H., Vaikundamani, S., Sastry, G.N. and Mahanta, H.J. (2025).** A systemic investigation of the phytochemical space in polyherbal formulations of India: A curated database. Computers in Biology and Medicine. 196, 110760**.**
37. **Pradhan, L., Andersen, N.D., LoGerfo, F.W. and Veves, A. (2007).** Molecular targets for promoting wound healing in diabetes. Recent Patents on Endocrine, Metabolic and Immune Drug Discovery. 1(1): 1-13.
38. **Nayeem, N., Soomro, S., Alshehri, S., Alsanie, W.F., Alamri, A.S., Alhomrani, M. and Asdaq, S.M.. (2025).** Development and Evaluation of a Polyherbal Ointment for Enhanced Wound Healing and Antimicrobial Activity. International Journal of Pharmacology. 21(1): 78-85.
39. **Talekar, Y.P., Apte, K.G., Paygude, S.V., Tondare, P.R. and Parab, P.B. (2017). Studies** on wound healing potential of polyherbal formulation using in vitro and in vivo assays. Journal of Ayurveda and Integrative Medicine. 8(2): 73-81.
40. **Cedillo-Cortezano, M., Martinez-Cuevas, L.R., López, J.A.M., Barrera López, I.L., Escutia-Perez, S. and Petricevich, V.L. (2024).** Use of medicinal plants in the process of wound healing: a literature review. Pharmaceuticals. 17(3): 303.
41. **Ahmad, M.S., Riaz, H., Qureshi, O.S. and Maria, P. (2018).** Role of flavonoids as wound healing agent. *Phytochemicals:* Source of Antioxidants and Role in Disease Prevention. 95-102.
42. **Barreto, R.S., Albuquerque-Júnior, R.L., Araújo, A.A., Almeida, J.R., Santos, M.R., Barreto, A.S. and Quintans-Júnior, L.J. (2014).** A systematic review of the wound-healing effects of monoterpenes and iridoid derivatives. Molecules.19(1): 846-862.
43. **Calvo-Gomez, O., Eshboev, F., Mullaiarova, K. and Egamberdieva, D. (2025). Endophytic** Bioactive Compounds for Wound Healing: A Review of Biological Activities and Therapeutic Potential. Microorganisms. 13(7): 1691.
44. **Sarker, S.D. and Nahar, L. (2015).** Applications of high-performance liquid chromatography in the analysis of herbal products. In Evidence-based validation of herbal medicine (pp. 405-425). Elsevier.
45. **Bhinge, S.D., Bhutkar, M.A., Randive, D.S., Wadkar, G.H., Todkar, S.S., Kakade, P.M. and Kadam, P.M. (2017).** Formulation development and evaluation of antimicrobial polyherbal gel. In Annales pharmaceutiques francaises (Vol. 75, No. 5, pp. 349-358). Elsevier Masson.
46. **Allen, L. and Ansel, H.C. (2013).** Ansel's pharmaceutical dosage forms and drug delivery systems. Lippincott Williams and Wilkins.
47. **Maru, A.D. and Lahoti, S.R. (2019).** Formulation and evaluation of ointment containing sunflower wax. Asian J. Pharm. Clin. Res. 12(8): 115-120.
48. **Ali, A., Garg, P., Goyal, R., Kaur, G., Li, X., Negi, P. and Kulshrestha, S. (2020).** RETRACTED: A Novel Herbal Hydrogel Formulation of *Moringa oleifera* for Wound Healing. Plants. 10(1): 25.
49. **Yuniarsih, N., Hidayah, H., Gunarti, N.S., Kusumawati, A.H., Farhamzah, F., Sadino, A. and Alkandahri, M.Y. (2023).** Evaluation of Wound Healing Activity of Hydrogel Extract of *Sansevieria trifasciata* Leaves (Asparagaceae). Advances in Pharmacological and Pharmaceutical Science. 2023(1): 7680518.
50. **Zaman, S.U. and Akhtar, N. (2013).** Effect of turmeric (*Curcuma longa* Zingiberaceae) extract cream on human skin sebum secretion. Tropical Journal of Pharmaceutical Research. 12(5): 665-669.
51. **Saggar, S., Mir, P.A., Kumar, N., Chawla, A., Uppal, J. and Kaur, A. (2022).** Traditional and herbal medicines: opportunities and challenges. Pharmacognosy Research. 14(2):
52. **Che, C.T., Wang, Z.J., Chow, M.S.S. and Lam, C.W.K. (2013).** Herb-herb combination for therapeutic enhancement and advancement: theory, practice and future perspectives. Molecules. 18(5): 5125-5141.
53. **Verma, S. and Singh, S.P. (2008).** Current and future status of herbal medicines. Veterinary World. 1(11): 347.
54. **Ghorbani, A. (2014).** Clinical and experimental studies on polyherbal formulations for diabetes: current status and future prospective. Journal of Integrative Medicine. 12(4): 336-345.