REVIEW PAPER

In-vivo Evaluation Parameters of Polyherbal Formulations for Wound Healing: Mechanistic Insights and Experimental Models

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ABSTRACT

Wound healing is a complex, spatiotemporally regulated biological continuum governed by four overlapping phases: haemostasis, inflammation, proliferation, and remodelling, each orchestrated by distinct cellular programs, growth factor gradients, and extracellular matrix (ECM) remodelling cascades. The persistent limitations of conventional wound management, including antimicrobial resistance, biofilm formation, high treatment costs, and narrow molecular targeting, underscore the urgent need for biologically compatible alternatives. Polyherbal formulations (PHFs), which combine two or more medicinal plants in defined proportions, exploit phytochemical synergy to simultaneously modulate haemostasis, inflammation, angiogenesis, collagen synthesis, and tissue remodelling, and offer inherent multi-target pharmacological advantages over single-agent therapies. In vivo parameters are employed to assess PHFs in wound healing, integrating macroscopic indices, histopathological assessment, and biochemical biomarkers (hydroxyproline, hexosamine, SOD, CAT, GSH, MDA, NO, MPO), and molecular pathway analyses (NF-κB, Nrf2, TGF-β1, VEGF, MAPK, PI3K/Akt). A structured comparison of seven experimental wound models is provided, along with evaluation frameworks for each parameter class. Emerging nanoherbal delivery systems, electrospun scaffolds, smart hydrogels, and AI-assisted phytochemical screening are enabling technologies for translational advancement. A standardised interdisciplinary evaluation strategy that integrates classical wound metrics with advanced molecular biomarkers is essential to accelerate the regulatory acceptance and clinical translation of polyherbal wound therapeutics.

Keywords: Polyherbal formulations; wound healing; In-vivo evaluation; wound contraction; hydroxyproline; NF-κB; TGF-β1; phytomedicine; excision wound model; collagen synthesis.

How to cite this article: Mishra S, Singh AK, Singh A, Yadav J. In-vivo Evaluation Parameters of Polyherbal Formulations for Wound Healing: Mechanistic Insights and Experimental Models. Int J Drug Deliv Technol. 2026;16(51s): 324-342. DOI: 10.25258/ijddt.16.51s.24

Source of support: Nil.

Conflict of interest: None

1. INTRODUCTION

Wound healing is one of the most evolutionarily conserved and complex physiological processes in humans. Once the integrity of the tissue is disrupted (by trauma, surgery, infection, or metabolic disease), the organism triggers a carefully orchestrated sequence of cellular and molecular responses to restore functional capacity and anatomical continuity. Although biomedical science has made tremendous strides, non-healing and chronic wounds remain a problem in modern medicine and are becoming a growing health threat worldwide. The burden of wound care is enormous, from an epidemiological standpoint. In the United States alone, an estimated 6.5 million patients suffer from chronic wounds every year, with more than USD 25 billion in direct healthcare costs being spent each year on these wounds [1]. Skin Wound Care. The global wound care market is projected to grow, driven by conditions such as diabetes mellitus and peripheral vascular disease. The World Health Organization (WHO) estimates that diabetes mellitus affects over 537 million adults globally, and a diabetic foot ulcer is likely to develop in 15–25% of these during their lifetime, with up to 20% of these cases eventually leading to amputation [2]. Traditional wound care techniques include debridement, moist wound care, antimicrobials, growth factors, negative pressure wound therapy, and skin grafting. Although both methods have advantages, several challenges remain: antimicrobial resistance, high treatment costs, delayed healing in immunocompromised patients, biofilm formation, and side effects of synthetic pharmaceuticals [3]. For centuries, medicinal plants have been the foundation of wound care in various traditional healing practices. Hundreds of botanicals have been documented in Ayurveda, Traditional Chinese Medicine (TCM), Unani, and other ethnobotanical traditions, each with empirically demonstrated wound-healing properties [4]. All these plants have been scientifically validated and found to contain a wealth of bioactive phytoconstituents that can modulate distinct yet related components of the wound repair continuum, including flavonoids, terpenoids, tannins, alkaloids, phenolic acids, saponins, and polysaccharides [5]. The idea of polyherbal formulations (PHFs), which are combinations of two or more medicinal plants in specific proportions, is scientifically interesting and a more practical option for wound management. PHFs exploit phytochemical synergy to simultaneously modulate haemostasis, inflammation, proliferation, and tissue remodelling, thereby mimicking the multifactorial pharmacologic needs of each phase of wound healing [6]. This

multi-target action reduces the risk of therapeutic resistance, increases efficacy at lower individual-plant doses, and generally improves the safety profile compared to isolated phytoconstituents or synthetic drugs [6]. In vivo evaluation of PHFs is a crucial step in the drug development process. Animal wound models are physiologically relevant and cannot be replicated in cell culture or ex vivo systems, enabling the study of wound-healing events using macroscopic, histological, biochemical, and increasingly sophisticated molecular methods [7].

Table 1. Medicinal Plants Commonly Used in Polyherbal Wound Healing Formulations

Plant (Family)	Part Used	Key Phytochemicals	Pharmacological Activity	Reference
Centella asiatica (Apiaceae)	Aerial parts	Asiaticoside, madecassoside, asiatic acid	Collagen synthesis↑, fibroblast proliferation↑, TGF-β1↑, anti-inflammatory	[8]
Curcuma longa (Zingiberaceae)	Rhizome	Curcumin, demethoxycurcumin	NF-κB↓, COX-2↓, antioxidant, angiogenesis↑, antimicrobial	[9]
Aloe vera (Asphodelaceae)	Gel/leaf	Acemannan, aloin, polysaccharides	Re-epithelialization↑, anti-inflammatory, immunomodulatory	[10]
Terminalia chebula (Combretaceae)	Fruit	Chebulagic acid, ellagic acid, gallic acid, tannins	Antioxidant, antimicrobial, collagen maturation↑, epithelialization↑	[11]
Azadirachta indica (Meliaceae)	Leaf/bark	Nimbidin, nimbolide, quercetin	Antimicrobial, anti-inflammatory, wound contraction↑	[12]
Ocimum sanctum (Lamiaceae)	Leaves	Eugenol, ursolic acid, rosmarinic acid, apigenin	COX inhibition, antimicrobial, angiogenesis↑, antioxidant	[13]
Calendula officinalis (Asteraceae)	Flowers	Isorhamnetin, quercetin, oleanolic acid, saponins	Anti-inflammatory, collagen deposition↑, epithelialization↑, antifungal	[14]
Tridax procumbens (Asteraceae)	Aerial parts	Luteolin, quercetin, kaempferol, flavones	Hemostasis↑, antimicrobial, wound contraction↑, anti-inflammatory	[15]
Berberis aristata (Berberidaceae)	Root/bark	Berberine, oxyberberine, berbamine	NF-κB↓, IL-6↓, TNF-α↓, antimicrobial, collagen synthesis↑	[16]
Glycyrrhiza glabra (Fabaceae)	Root	Glycyrrhizin, glabridin, liquiritin	Anti-inflammatory, Nrf2↑, antimicrobial, fibroblast proliferation↑	[17]
Withania somnifera (Solanaceae)	Root	Withanolides, withaferin A	Adaptogenic, anti-inflammatory, collagen synthesis↑, immunomodulatory	[16]
Eclipta alba (Asteraceae)	Whole plant	Wedelolactone, ecliptine, coumestans	Hemostasis↑, anti-inflammatory, wound contraction↑	[18]

Methodology

Systematic electronic databases including PubMed, Scopus, Web of Science, Google Scholar, were explored with a strategy to gather experimental, mechanistic effects of gut microbiota on different endocrine-axis accompanying conceptually relevant peer-reviewed articles published primarily from 2000 - 2025. Keywords used were -*:* Polyherbal formulations; wound healing; *In-vivo* evaluation; wound contraction; hydroxyproline; NF-κB; TGF-β1; phytomedicine; excision wound model; collagen synthesis. The eligible studies included original research studies, high impact reviews published in the English language that had evidence of gut-microbiota biological effects or mechanistic relevance to gut-endocrine axis.

2. BIOLOGY OF WOUND HEALING

Wound healing is a dynamic, spatiotemporally regulated continuum of overlapping cellular programs, growth factor gradients, cytokine signalling networks, and remodelling cascades of ECM molecules, spanning four interdependent phases [19].

2.1 Hemostasis

Hemostasis (0-6 hours) helps to stop bleeding and creates a temporary ECM framework [20]. Primary plug formation begins with platelet adhesion via vWF-glycoprotein Ib-IX-V interactions, and activation of the extrinsic coagulation pathway leads to thrombin generation and the formation of a stable fibrin clot. The fibrin-platelet matrix stores PDGF, TGF-β, VEGF, and EGF, which orchestrate subsequent inflammatory recruitment [21].

2.2 Inflammatory Phase

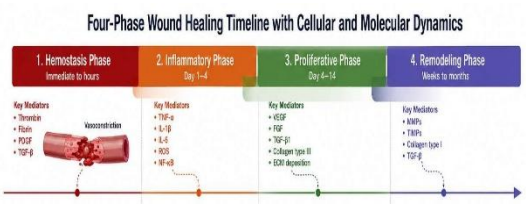
The inflammatory phase (0–72 h) is characterised by the sequential infiltration of neutrophils and macrophages, which is mediated by complement fragments, DAMPs (HMGB1), and PAMPs [22]. Neutrophils perform debridement using matrix metalloproteinases (MMPs), reactive oxygen species (ROS), and antimicrobial peptides. Activation of the NF-κB pathway by TLR–DAMP interactions promotes transcription of TNF-α, IL-1β, IL-6, iNOS, and COX-2. The shift from M1 to M2 macrophages is a key step in the transition to repair, with M2 macrophages secreting TGF-β, IL-10, and VEGF, which recruit fibroblasts and promote angiogenesis [23].

2.3 Proliferative Phase

During the proliferation phase (days 2–21), keratinocytes migrate toward the centre in response to EGF, KGF, and HGF [24] via the MAPK/ERK and PI3K/Akt pathways [25]. PDGF stimulates the recruitment of fibroblasts, and TGF-β1 stimulates collagen synthesis and induces the differentiation of fibroblasts into myofibroblasts (α-SMA expression). VEGF stimulates angiogenesis via VEGFR-2, PI3K/Akt, and eNOS pathways, which are crucial for granulation tissue oxygenation [26].

2.4 Remodelling Phase

During remodelling (3 weeks to 2 years), the MMP/TIMP regulatory axis is responsible for replacing type III collagen with type I collagen. Lysyl oxidase (LOX) cross-links mature collagen fibers, and healed tissue will have approximately 80% of the original tensile strength [27]. Hypertrophic scarring results from the failure of myofibroblast apoptosis, driven by the lack of regulation of TGF-β1-Smad2/3 signaling.



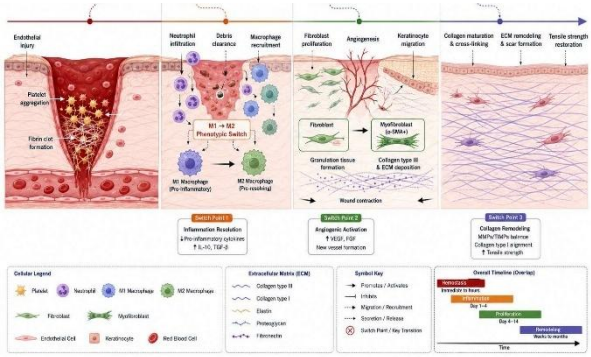


Fig 1: Schematic representation of the four overlapping phases of wound healing—hemostasis, inflammation, proliferation, and remodelling—highlighting key cellular events, molecular mediators, macrophage polarisation, angiogenesis, extracellular matrix (ECM) deposition, and collagen remodelling during tissue repair.

Table 2. Phases of Wound Healing: Cellular Events, Biomarkers, Molecular Mediators, and Therapeutic Targets

Phase	Duration	Key Cells	Cellular Events	Molecular Mediators	Biomarkers	Therapeutic Targets	References
Hemostasis	0–6 h	Platelets, endothelial cells	Vasoconstriction, platelet aggregation, fibrin clot, growth factor release	vWF, TXA2, thrombin, fibrin, PDGF, TGF-β, EGF	PT, aPTT, fibrinogen	Coagulation cascade, PDGF	[28]
Inflammation	Hours–3 days	Neutrophils, M1 macrophages, mast cells	Phagocytosis, ROS production, cytokine secretion, DAMPs signaling	TNF-α, IL-1β, IL-6, NF-κB, ROS, MMP-8,	MPO, CRP, IL-6, TNF-α, MDA	NF-κB, COX-2, iNOS, IL-1β	[29]

				iNOS			
Proliferation	Day 2–21	Fibroblasts, myofibroblasts, keratinocytes, endothelial cells, M2 macrophages	Re-epithelialization, fibroplasia, granulation tissue, angiogenesis, collagen synthesis	TGF-β1, VEGF, FGF-2, KGF, EGF, IL-10, α-SMA	Hydroxyproline, VEGF, α-SMA, Ki-67, type III collagen	TGF-β1, VEGF, EGFR, PI3K/Akt, MAPK/ERK	[30]
Remodeling	3 wks–2 yrs	Fibroblasts, myofibroblasts (apoptosis), endothelial cells	Collagen I replaces III, cross-linking, MMP remodeling, myofibroblast apoptosis	MMP-1/2, TIMP-1/2, LOX, TGF-β3, Smad7, FasL	Tensiometry, collagen I/III ratio, MMP activity	MMP/TIMP balance, LOX, TGF-β1/3 ratio	[31]

3. RATIONALE AND DESIGN OF POLYHERBAL FORMULATIONS FOR WOUND HEALING.

Classical Ayurvedic medicine has been used for centuries, and the principle of 'yogavahi" (botanical combinations) predates the modern concept of polypharmacology [32]. This empiricism is confirmed by modern molecular pharmacology: phytochemical mixtures can simultaneously modulate NF-κB, MAPK, PI3K/Akt, TGF-β, and Nrf2 pathways [33–35]. There is also pharmacokinetic synergy, as curcumin absorption is improved by up to 2000% when combined with piperine from Piper nigrum, which inhibits intestinal glucuronidation [36]. Curcumin and quercetin target hub proteins (TNF, AKT1, IL-6, VEGFA, EGFR) involved in wound healing [37, 38]. Topical dosage forms, such as ointments, gels, creams, hydrogels, films, and nano-engineered systems, are widely used in wound care in PHF because they allow for direct application to the wound microenvironment and optimal moisture. The major dosage forms and their clinical uses are summarised in Table 3.

Table 3. Polyherbal Dosage Forms for Wound Healing: Advantages, Limitations, and Applications

Dosage Form	Base/Matrix	Advantages	Limitations	Wound Application	Reference
Ointment	Petrolatum/lanolin	Occlusive moisture retention, extended release, cost-effective	Too occlusive for exudative wounds; maceration risk	Dry/chronic ulcers, pressure injuries	[10]
Hydrogel	Carbopol, HPMC, alginate	Moist environment, cooling, transparent (allows monitoring), autolytic debridement	Limited strength; frequent changes; peri-wound maceration	Burns, donor sites, diabetic ulcers	[18]
Film	HPMC/PVA/gelatin	Transparent, flexible, controlled release, gas exchange	Fragile, limited drug loading, unsuitable for exuding wounds	Donor sites, minor surgical wounds	[39]
Nanoherbal gel	Nanoparticle-embedded gel	Enhanced penetration, improved bioavailability, sustained release	Complex formulation, stability concerns, regulatory ambiguity	Biofilm-infected wounds, deep injuries	[14]
Smart hydrogel	pH/thermo-responsive polymers	On-demand release triggered by wound microenvironment signals	Complex synthesis, limited *In-vivo* validation, high cost	Infected/diabetic chronic wounds	[16]
3D-printed	Alginate/gelatin/chitosan bioinks	Patient-specific geometry,	High cost, bioink optimi	Large tissue defects, reconstr	[40]

scaffold		precise drug localization, cell co-delivery	zation required, limited clinical studies	uctive wounds	

4. *IN-VIVO* WOUND MODELS: PRINCIPLES AND COMPARATIVE EVALUATION

A wound model should be reproducible, ethically acceptable, technically feasible, and physiologically relevant to human wound conditions. There is no single model that meets all the requirements; often, a combination of models is used [41].

4.1 Excision Wound Model

A standardised full-thickness circular cut (2 cm) on the dorsal region of the rat can be used for simultaneous macroscopic, histological, and biochemical evaluations. Photographic planimetry was performed every day to measure wound contraction, and biopsies were taken at days 4, 8, 12, 16, and 21 to obtain temporal data. This is ideal for topical PHF gels, ointments, and creams [18].

4.2 Incision Wound Model

Two parallel paravertebral incisions (6 cm in length) were sutured and tested on day 10 using a tensiometer for breaking strength. This model was specifically designed to assess ECM quality and collagen cross-linking maturity, which are important when using PHFs derived from collagen-modulating plants, such as *Centella asiatica* [42].

4.3 Dead Space (Granuloma) Model

Dry granuloma weight and hydroxyproline content are direct biochemical markers of collagen synthesis and can be quantified by implanting a subcutaneous cotton pellet (10 ± 1 mg), which is particularly well suited for systemic PHF preparations (oral or parenteral) [42].

4.4 Diabetic Wound Model

STZ-induced diabetes (55–65 mg/kg i.p., with blood glucose ≥250 mg/dL) and excision wound generation mimic the impaired angiogenesis, chronic inflammation, and impaired fibroblast function observed in patients with diabetic foot ulcers, whereas the db/db and ob/ob genetic models provide complementary phenotypes [43].

4.5 Infected Wound Model

Standardised S. aureus/MRSA suspensions (10^7–10^8 CFU/mL) applied topically to fresh excision wounds allow direct assessment of the PHF's antimicrobial and antibiofilm activity via serial colony-forming unit (CFU) counts and confocal laser scanning microscopy (CLSM) [44, 45].

Table 4. Comparative Analysis of *In-vivo* Wound Models Employed in Polyherbal Formulation Evaluation

Wound Model	Animal	Wound Induction	Key Parameters	Primary Endpoints	Advantages	Limitations	References
Excision	Rat, mouse, rabbit	2 cm biopsy punch, full-thickness excision	Wound contraction %, epithelialization period, histopathology, hydroxyproline, VEGF	Day 21 wound closure, H&E histology, collagen quantification	Simple, reproducible, multi-parameter, widely validated	Rat panniculus carnosus inflates contraction vs. humans	[46]
Incision	Rat, mouse	6 cm parallel incisions, sutured	Breaking strength (tensiometer), wound index, Masson's collagen alignment	Day 10 tensile strength	Quantitative mechanical endpoint	Requires specialized equipment; limits histological sampling	[47]
Dead Space	Rat	Cotton pellet (10 mg) s.c. implantation	Granuloma dry weight, hydroxyproline, hexosamine, hexuronic acid	Granuloma weight at day 7/10	Directly quantifies collagen synthesis; suits systemic PHF	No epidermal component; no contraction measurement	[48]
Burn	Rat, rabbit	Brass rod 100°C/10 s or scald 80°C/10 s	Eschar separation, wound contraction, bacterial colonization, cytokines	Day 14 eschar score, bacterial count, collagen density	Clinically relevant; tests antimicrobial + anti-inflammatory activity	Variable injury depth; analgesic complexity	[45]
Diabetic	STZ rat, db/db	STZ 65 mg/kg i.p. + excision punch	Wound closure vs. non-diabetic, VEGF IHC,	Day 28 wound area, angiogenesis score,	Most clinically translatable; tests multip	STZ toxicity limits duration; geneti	[6]

	mouse		AGE deposits, M1/M2 ratio	VEGF expression	le dysfunctional pathways	c models expensive	
Infected	Rat, mouse	Excision + S. aureus /MRSA 10^8 CFU topical	CFU/cm², wound pH, biofilm density (CLSM), cytokines	Day 7 bacterial count, biofilm score	Evaluates antimicrobial PHF component directly	Biosafety requirements; variable infection establishment	[49]
Ischemic	Rat	Bipedicle flap / femoral artery ligation	Laser Doppler perfusion, micro-CT angiography, necrotic area%, VEGF	Day 14 perfusion ratio, collateral vessel density	Evaluates pro-angiogenic activity; relevant for PAD/ pressure injuries	Technically demanding; requires perfusion imaging equipment	[50]

5. IN-VIVO EVALUATION PARAMETERS: A COMPREHENSIVE ANALYTICAL FRAMEWORK

The PHF assessment framework is broad and covers many levels of biology, ranging from macroscopic wound contraction to modulation of molecular pathways. Each cardinal evaluation parameter is discussed in detail in the following sections.

5.1 Macroscopic Evaluation Parameters

Wound Contraction

Wound area reduction due to contraction (myofibroblasts) [51] was determined by digital planimetric analysis (ImageJ) of standardised photographs. It is typically calculated as a percentage of initial wound area. The Wound Healing Index (WHI) is a metric that can represent overall healing efficiency.

Epithelialization Period and Granulation Tissue

Epithelialisation is the process of wound closure by the formation of new epithelial tissue. Vascularisation and maturity of the granulation tissue were scored semi-quantitatively (0–4 scale). Thermal imaging and chromametry can be used to objectively evaluate tissue hyperaemia and vascularity [52].

Tensile strength and breaking strength

In incision models, the mechanical property of breaking strength (g/mm ²) obtained from a universal testing machine is a direct mechanical measure of the maturity of the collagen cross-links and the quality of the ECM, which is correlated with the histological collagen score [53].

Table 5. Macroscopic Evaluation Parameters: Methods, Formulas, Reference Values, and Interpretation

Parameter	Assessment Method	Formula / Unit	Reference Range (Rats)	PHF Positive Response	Limitations	References
Wound Contraction %	Digital planimetry (ImageJ); calibration grid photography	$[(A_0-A_n)/A_0]\times100$ (%)	Day 14: 70–85% (vehicle); Day 21: >95 %	PHF > control indicates enhanced myofibroblast activity	Photographer variability; 2D ignores wound depth	[54]
Epithelialization Period	Daily clinical inspection + histological confirmation	Days to complete closure	18–22 days (vehicle); 12–16 days (standard drug)	Reduction of 4–7 days = clinically significant; correlates with KGF/EGF expression	Subjective; eschar may obscure early epithelium	[55]
Granulation Tissue Score	Semi-quantitative visual scoring (0–4 scale)	0 (absent) to 4 (abundant)	Score 2–3 at day 7 in vehicle group	Score 3–4 with PHF at day 7 = enhanced angiogenesis and fibroplasia	Inter-observer variability; requires blinded assessment	[56]
Wound Healing Index (WHI)	Composite of contraction + epithelialization	WHI = (% contraction × 100) / EP (days)	~4–5 units in vehicle group	Higher WHI = better overall healing; useful single metric	Combines independent variables; lacks	[57]

					mechanistic specificity	
Tensile/ Breaking Strength	Universal testing machine or spring balance (incision model)	g/mm² or N/mm²	~200–350 g/mm² at day 10 (vehicle)	>400 g/mm² indicates enhanced collagen cross-linking; correlates with hydroxyproline	Technique-dependent; only applicable to incision wounds	[27]

5.2 Histopathological Evaluation Parameters

The gold standard for assessing wound healing is histopathological examination at the cellular level [56]. The wound tissue was formalin-fixed, paraffin-embedded (FFPE), and cut into 4–5-µm sections. Objectivity is achieved through blind, semi-quantitative scoring by a qualified histopathologist using standard criteria

Haematoxylin and Eosin (H&E) Staining

H&E staining allows the quantification of inflammatory cell infiltration, fibroblast density, epidermal continuity, dermal appendage preservation, and neovascularization. Each parameter was scored on an ordinal scale (0–4), which allowed for statistical comparisons between groups.

Masson's Trichrome and Picrosirius Red

Masson's trichrome (collagen=blue) allows quantitative collagen area fraction analysis and provides information on the organisation of the collagen fibres: parallel bundles (mature scar) and disorganised thin fibres (immature ECM) [58]. Under polarised light, Picrosirius is red and can distinguish between collagen type I (orange-red, mature) and type III (green, immature) [59]. Collagen I/III ratio, measured by digital image analysis, is a good indicator of the progression of the remodelling phase [60].

Table 6. Histopathological Scoring System for Wound Healing Evaluation

Histological Parameter	Staining	Scoring Criteria	Scale	PHF Positive Response Indicator	Clinical Significance	References
Inflammatory cell infiltration	H&E	0=absent; 1=mild (few PMNs); 2=moderate; 3=severe dense infiltrate	0–93	Score 0–1 at day 14 (vs. 2–3 in vehicle) = reduced chronic inflammation	Indicates inflammatory phase resolution; score >2 at day 14 predicts delayed healing	[61]
Fibroblast proliferation	H&E	0=absent; 1=sparse; 2=moderate; 3=abundant dense fibroblasts	0–3	Score 3 at day 7–14 = vigorous proliferative phase	High fibroblast density correlates with collagen synthesis capacity	[62, 63]
Collagen deposition density	Masson's trichrome	0=absent; 1=thin scattered; 2=moderate; 3=dense parallel bands	0–3	Score 2–3 with organized fibers = mature functional ECM	Dense organized collagen correlates with tensile strength	[27, 64]
Collagen type I/III ratio	Picrosirius red (polarized)	% orange-red (type I) vs. % green (type III) fibers	Ratio	Ratio >2 at day 21 = advanced remodeling	Ratio >3 in mature scar; ratio <1 = immature/fibrotic matrix	[65]
Angiogenesis (MVD)	H&E / CD31 IHC	Count of capillary lumens per HPF (×200)	Vessels/HPF	MVD >8/HPF at day 7–10 in PHF vs. <5 in vehicle	MVD correlates with VEGF expression and wound oxygenation	[66, 67]

Re-epithelialization	H&E	0=none; 1=partial (<50 %); 2=>50 %; 3=complete with stratification	0–3	Score 3 at day 14 vs. 1–2 in vehicle	Complete stratified epithelium validates epithelialization period data	[68, 69]
Granulation tissue maturity	H&E + Trichrome	0=no GT; 1=immature loose; 2=maturing; 3=organized collagenous	0–3	Score 3 with vascularized collagen-rich GT at day 14	Mature GT precedes successful scar remodeling	[70, 71]

5.3 Biochemical Evaluation Parameters

Wound tissue homogenates were analysed biochemically for quantitative molecular evidence of macroscopic and histological healing responses.

Collagen Markers: Hydroxyproline, Hexosamine and Hexuronic Acid: Hydroxyproline is a key biochemical index of collagen metabolism and can be quantified using the colorimetric method of Woessner after acid hydrolysis (absorbance at 550–560 nm) [72]. Hexosamine (measured using the Elson-Morgan reaction) is related to the glycosaminoglycan/proteoglycan content and hydration capacity of the ECM [73]. Hyaluronic acid and chondroitin sulfate contents were measured using hexuronic acid (Bitter-Muir carbazole method), which provides information on the compositional maturation of the temporal ECM [74].

Antioxidant Panel: SOD, CAT, GSH and MDA

The combined values of SOD (NBT reduction assay), CAT (UV absorbance at 240 nm), and GSH (Ellman's DTNB method) represent the endogenous antioxidant capacity**,** which is important for PHFs containing flavonoids and terpenoids. Lipid peroxidation was quantified using MDA/TBARS (TBA assay at 532 nm), providing direct biochemical evidence of antioxidant protective action in the presence of PHF [75].

Inflammatory Markers: Nitric Oxide (NO) and Myeloperoxidase (MPO)

NO has two roles: Physiological NO (cGMP-VEGF pathway) and Excessive NO (iNOS-derived peroxynitrite). Nitrite was measured at 540 nm using the Griess reagent assay. Normalised MPO (days 7–10) is a specific marker of neutrophil infiltration quantified by TMB oxidation (460 nm) and represents PHF-facilitated inflammation resolution [76].

Table 7. Biochemical Biomarkers: Biological Roles, Assay Methods, Reference Ranges, and PHF Interpretation

Biomarker	Biological Role	Assay Method	Expected Value	PHF Positive Response	Molecular Target/Pathway	References
Hydroxyproline	Collagen content; ECM maturity marker	Woessner colorimetric; acid hydrolysis; 550 nm	40–80 µg/mg dry wt (day 14–21)	Significantly elevated vs. vehicle ($p<0.05$)	Prolyl 4-hydroxylase; TGF-β1-Smad; ascorbate-dependent	[77]
Hexosamine	GAG/proteoglycan content; ECM hydration	Elson-Morgan colorimetric; acetylacetone; 530 nm	15–35 µg/mg dry wt	Elevated hexosamine = improved ECM glycoprotein matrix quality	Hyaluronan synthase (HAS); chondroitin sulfate biosynthesis	[78]
Hexuronic Acid	Hyaluronic acid / chondroitin sulfate content	Bitter-Muir carbazole-H_2SO_4; 530 nm	10–30 µg/mg dry wt	High early; normalized by day 21 = orderly ECM transition	Hyaluronidase regulation; CD44-HA signaling	[79]
SOD Activity	Superoxide dismutation; ROS quenching	NBT reduction inhibition; 560 nm	15–30 U/mg protein	Elevated SOD = flavonoid/terpenoid antioxidant action	Nrf2-ARE pathway; Cu/Zn-SOD, Mn-SOD genes	[80]
CAT Activity	H_2O_2 decomposition; secondary antioxid	Clairborne UV method; 240 nm	25–60 nmol/min/mg protein	Elevated CAT = enhanced antioxidant	Nrf2 regulation; FOXO3a pathway	[81]

	ant defense			defense in inflammatory phase		
GSH Level	Primary intracellular redox buffer	Ellman's (DTNB) colorimetric; 412 nm	1.5–4.0 µmol/mg protein	Preserved/elevated GSH = protection against oxidative depletion	Nrf2-GCL axis; glutathione reductase	[82]
MDA (TBARS)	Lipid peroxidation; oxidative membrane damage	TBA colorimetric; 532 nm	0.5–2.0 nmol/mg protein (decreasing with healing)	Significantly reduced MDA = antioxidant protection; correlates with Nrf2 upregulation	PUFA oxidation; NF-κB activation by lipid aldehydes	[83]
Nitric Oxide (NO)	Dual: angiogenesis (eNOS) vs. cytotoxic (iNOS)	Griess reagent; 540 nm (nitrite)	15–40 µM/mg protein (phase-dependent)	↓ NO at day 7 (iNOS inhibition) + sustained NO at day 14 (eNOS support) = ideal PHF profile	iNOS: NF-κB; eNOS: PI3K/Akt; cGMP-PKG pathway	[84]
Myeloperoxidase (MPO)	Neutrophil infiltration marker; antimicrobial defense	TMB oxidation; 460 nm	High at day 1–3; <50 U/mg at day 7	Normalized MPO at day 7 = accelerated neutrophil resolution	NF-κB-mediated iNOS/MPO; IL-8-CXCR1/2 axis	[85]

5.4 Molecular Evaluation Parameters

Gene Expression Analysis (RT-qPCR)

RT-qPCR enables the precise quantification of mRNA transcripts for TGF-β1, VEGF, IL-1β, TNF-α, iNOS, α-SMA, COL1A1, COL3A1, MMP-1/9, TIMP-1, HO-1, NQO1, and GCLC [86]. ΔΔCt analysis normalised to GAPDH/β-actin with a minimum of three biological replicates is the accepted standard [86, 87].

Protein expression (Western Blotting, ELISA, IHC). Western blotting was used to quantify the total and phosphorylated amounts of NF-κB p65, IκBα, Nrf2, HO-1, p-Akt (Ser473), p-MAPK, p-Smad2/3, VEGF, and α-SMA. ELISA was used to quantify cytokines (TNF-α, IL-1β, IL-6, IL-10, TGF-β1, and VEGF) in wound exudates or tissue lysates in a high-throughput manner. Immunohistochemistry (IHC) on FFPE sections allowed for protein quantification and spatial localisation (VEGF in endothelial cells, α-SMA in myofibroblasts, CD68 in macrophages, and Ki-67 in proliferating keratinocytes), and digital analysis (QuPath, HALO) allowed for quantification of the H-score [88].

Key Signalling Pathway Analysis

NF-κB status was evaluated based on the nuclear translocation of the p65 subunit (IHC or nuclear/cytoplasmic fractionation western blot) and the stability of IκBα, as well as the expression of NF-κB target genes [89]. Nrf2 activity was measured by western blotting for nuclear accumulation and quantification of target genes (HO-1, NQO1, GCLC) that are regulated by the ARE [90]. Evaluation of TGF-β1/Smad signalling was performed by western blotting for phospho-Smad2/3 and by measuring COL1A1/COL3A1 gene expression [91]. The VEGF angiogenic axis was confirmed using VEGF ELISA, VEGFR-2 phosphorylation, and CD31 microvessel density [92]. A dual pharmacological profile of NF-κB (anti-inflammatory) and Nrf2 (antioxidant) activation is characteristic of certain PHFs, such as curcumin, quercetin, and kaempferol Furthermore, systemic assessments of granulation tissues rely on the standardized quantification of cellular populations, including myofibroblasts and macrophages, which correlate directly with the modulation of these signaling cascades [93].

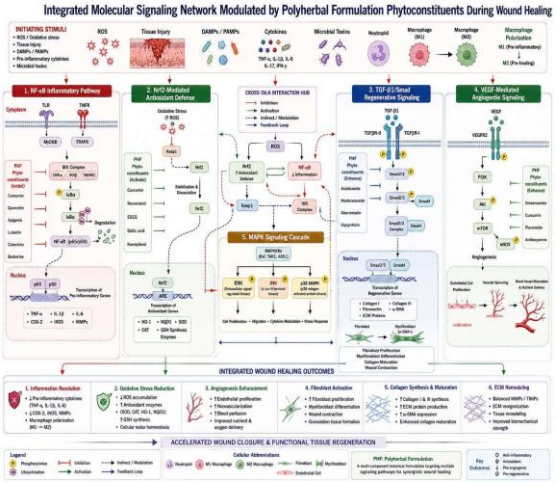


Fig 2: Integrated molecular signalling network illustrating the coordinated modulation of

inflammatory, antioxidant, angiogenic, and regenerative pathways by polyherbal formulation (PHF) phytoconstituents during wound healing. The figure highlights NF-κB, Nrf2/Keap1, TGF-β/Smad, VEGF/PI3K/Akt, and MAPK signaling crosstalk leading to inflammation resolution, oxidative stress suppression, angiogenesis, extracellular matrix (ECM) remodeling, and accelerated wound closure.

Table 8. Molecular Markers and Signaling Pathways in PHF Wound Healing Evaluation

Pathway/Marker	Analytical Method	Key Proteins/Genes	Expected Change with PHF	Biological Significance	Phytochemical Modulators	References
NF-κB Signaling	Western blot (p65, IκBα); IHC (p65 nuclear); RT-qPCR (IL-1β, TNF-α, iNOS, COX-2)	p65, IκBα, IKKβ, IL-1β, TNF-α, iNOS	p65 nuclear translocation↓; IκBα stability↑; inflammatory mRNA↓	Anti-inflammatory: resolves chronic inflammation driving wound chronicity	Curcumin, berberine, quercetin, eugenol, nimbolide, glycyrrhizin	[94]
Nrf2/ARE Pathway	Western blot (Nrf2 nuclear); RT-qPCR (HO-1, NQO1, GCLC); enzyme activities (SOD, CAT, GSH)	Nrf2, Keap1, HO-1, NQO1, GCLC, TXNRD1	Nrf2 nuclear accumulation↑; HO-1↑; SOD/CAT/GSH↑; MDA↓	Antioxidant defense: prevents ROS-mediated cellular damage in wound tissue	Curcumin, withanolides, kaempferol, ursolic acid, asiaticoside	[95]
TGF-β1/Smad2/3	Western blot (p-Smad2/3, Smad7); RT-qPCR (COL1A1, COL3A1, α-SMA); ELISA (TGF-β1)	TGF-β1, TβRII, Smad2/3, Smad7, CTGF, α-SMA	TGF-β1↑ early (pro-fibroplasia); Smad7↑ prevents fibrosis; COL1A1/COL3A1↑	Drives fibroplasia, collagen synthesis, myofibroblast differentiation; excess → fibrosis	Asiaticoside, madecassoside, aloe-emodin, punicalagin, resveratrol	[96]
VEGF/Angiogenesis	ELISA (VEGF); IHC (CD31, VEGFR-2); Western blot (p-VEGFR2, p-Akt); LDPI	VEGF-A, VEGFR-2, CD31, CD34, Ang-1, Tie-2	VEGF expression↑; MVD↑; VEGFR-2 phosphorylation↑; Akt activation↑	Neovascularization: restores oxygenation to wound bed; critically impaired in diabetic wounds	Quercetin, kaempferol, curcumin, scopoletin, asiaticoside, damnacanthal	[97]
MAPK/ERK1/2	Western blot (p-ERK1/2, p-p38, p-JNK); RT-	ERK1/2, p38 MAPK, JNK, MEK, Raf	p-ERK1/2↑ (keratinocyte proliferation); p-p38↓; p-JNK↓	Regulates keratinocyte proliferation/migration and fibroblast activation	EGCG, quercetin, resveratrol, wedelolactone	[98]

	qPCR (FGF-2, EGF)					
PI3K/Akt/mTOR	Western blot (p-PI3K, p-Akt Ser473, p-mTOR)	PI3K, Akt, mTOR, PTEN, S6K1	p-Akt↑; mTOR activation↑; PTEN↓	Promotes cell survival, proliferation, and glucose uptake; impaired in diabetes	Berberine, curcumin, quercetin, β-sitosterol, catechins	[99]
MMP/TIMP Balance	Gelatin zymography (MMP-2/9); ELISA (MMP-1, TIMP-1/2); IHC	MMP-1, MMP-2, MMP-9, MMP-13, TIMP-1, TIMP-2	MMP-9/MMP-1↓ (anti-inflammatory); TIMP-1↑; MMP-2 normalized in remodeling	Controls ECM degradation/remodeling balance; excessive MMPs destroy ECM in chronic wounds	Ellagic acid, EGCG, kaempferol, luteolin, wedelolactone	[100]

6. PHARMACOLOGICAL MECHANISMS OF POLYHERBAL FORMULATIONS IN WOUND HEALING.

6.1 Antioxidant Mechanisms

Flavonoids, phenolic acids, and tannins exhibit direct free radical scavenging activity through HAT/SET mechanisms. The antioxidant activities of curcumin, withanolides, and sulforaphane analogues are sustained, as they activate Nrf2 by modifying the cysteine residues (C151, C273, C288) of Keap1, leading to Nrf2 nuclear translocation and ARE-dependent upregulation of HO-1, NQO1, GCLC, and ferritin [101].

6.3 Antimicrobial and Antibiofilm Mechanisms.

Tannins (Terminalia, Punica) act as antibacterial agents and protein coagulants. Phenolics (eugenol, carvacrol, thymol) insert into the hydrophobic part of the membrane and cause leakage of potassium ions. Alkaloids (berberine) intercalate with DNA and inhibit topoisomerase. Lipophilic PHF components can pass through biofilm exopolysaccharide matrices, which is an advantage over conventional antibiotics that are 1000-fold resisted by biofilm communities [102].

6.4 Angiogenesis Promotion

PHF phytoconstituents induce neovascularization by upregulating VEGF-A through PHD stabilisation of HIF-1α (via quercetin inhibition of PHD), activation of VEGFR-2 (via scopoletin), and activation of eNOS (via PI3K/Akt-Ser1177) (via resveratrol). Endothelial tube formation is stimulated by the activation of integrin αvβ3, which is stimulated by saponin-rich plants (Centella asiatica and Astragalus membranaceus) [103].

6.5 Collagen Synthesis and ECM Remodeling

Asiaticoside and madecassoside (Centella asiatica) are activators of Smad2/3 and direct transcription factors that upregulate COL1A1/COL3A1 . Acemannan (Aloe vera) activates fibroblast proliferation through the mannose receptor. The cofactor for collagen cross-linking is ascorbic acid, which is a component of several PHFs. EGCG chelates Zn^{2+}, which is required for the activity of MMP-1 and MMP-9; EGCG flavonoids increase TIMP-1 levels, thereby preventing the over-activity of matrix-degrading proteases [104].

7. Advanced and emerging approaches in polyherbal wound healing

The combination of nanotechnology, bioengineering, and artificial intelligence with traditional phytomedicine has overcome the long-standing limitations of PHF, including poor bioavailability, formulation instability, and inconsistent release profiles (Bonifácio et al., 2014). The topical bioavailability of PHF phytoconstituents is significantly enhanced by nanoencapsulation in PLGA, chitosan, or lipid nanoparticles, which can permeate the stratum corneum barrier and provide sustained controlled release (e.g., curcumin-loaded PLGA nanoparticles have 15-fold higher wound tissue distribution compared to free curcumin suspension) [105]. Phytosome complexes (phosphatidylcholine-polyphenol) significantly increase the permeability of the membrane of hydrophilic polyphenols (Bhattacharya, 2009). Nanofibres (100–2000 nm in diameter) electrospun from polymers, such as PCL, PLGA, gelatin, and chitosan, closely resemble the architecture of native ECM collagen fibres and allow for controlled release of phytochemicals (Zahedi et al., 2010). Smart hydrogels that release antimicrobial/antioxidant PHFs on demand in response to wound microenvironmental signals [106] (acidic pH of infected wounds and high ROS) have been developed. Patient-specific wound treatment geometries and the co-delivery of cells and herbal actives are possible using 3D bioprinting [107] with bioinks containing herbs. AI/machine learning methods have been used to predict wound healing bioactivity based on databases of phytochemicals, predict ADMET parameters, and facilitate the rational design of PHFs by network pharmacology.

Table 9. Advanced Evaluation Techniques and Emerging Delivery Systems in PHF Wound Healing Research

Technology	Principle	Application in PHF Wound Healing	Advantages	Current Limitations	References
Nanoherbal particles (PLGA/chitosan NPs)	Polymer encapsulation + controlled release	Topical delivery of curcumin, quercetin, essential oils to wound bed	Enhanced penetration, biofilm penetration, sustained release	Scale-up challenges; regulatory ambiguity; shelf-life stability	[10]
Phytosome complexes	Phosphatidylcholine-polyphenol complex	Improved oral/topical bioavailability of polar PHF polyphenols	Traverses lipid and aqueous barriers; improved cellular uptake	Complex characterization; higher cost than free extract	[108]
Electrospun nanofibers	High-voltage electrospinning of polymer-herb solution	ECM-mimicking scaffolds releasing PHF actives during wound contraction	Biomimetic architecture; high surface area; sustained drug release	Limited hydrophilic drug loading; mechanical fragility when wet	[109]
Smart/stimuli-responsive hydrogels	pH/ROS/enzyme-responsive polymer matrices	On-demand PHF release triggered by wound microenvironment signals	Self-regulating delivery; infection-responsive; prevents overdosing	Complex synthesis; limited *In-vivo* validation; regulatory pathway unclear	[107]
3D bioprinting with herb bioinks	Layer-by-layer biofabrication with cell-laden herb bioinks	Custom wound dressings with spatial PHF gradients and cell co-delivery	Patient-specific geometry; co-delivery of cells + herbs	Equipment cost; bioink rheology optimization; limited clinical data	[110]
AI/machine learning screening	QSAR, network pharmacology, molecular docking pipelines	Virtual PHF optimization; target identification; ADMET prediction	Reduces experimental burden; identifies novel targets; predicts synergy	Requires validated training data; in silico predictions need *In-vivo* conformation	[111]

8. LIMITATIONS OF CURRENT PHF WOUND HEALING

There are a number of common methodological shortcomings. Insufficient statistical power: Usually, the number of animals in each study arm (4–6) is insufficient to detprimarily by contraction, whereas in humans, it heals predominantly by re-epithelialization; the panniculus carnosus represents a significant difference in healing mechanisms; porcine models offer significantly improved translational fidelityng rates; in rats, the skin heals by contraction by 70–80%, whereas in humans, it heals by contraction by 40–60%; the panniculus carnosus represents a significant difference; porcine models offer significantly improved translational fidelity [112, 113]. Third, there is a gap in molecular validation: a significant number of published studies are limited to basic and macroscopic histological information, without any evidence of a mechanistic pathway, and provide a literature with good outcomes but lacking mechanistic lack of adequate controls: individual plant extract groups lity to assess synergistic versus additive PHF effects, which is the major theoretical basis for the polyherbal approach. Lastly, only a few PHFs have moved to clinical evaluation after 30 years of preclinical data, due to limited pharmacokinetic data, lack of safety data in target populations, and the lack of clarity in the regulatory pathway [114].

9. FUTURE PERSPECTIVES

Precision phytomedicine, in which the composition of the PHF is optimised for each wound phenotype by profiling the wound microenvironment through

biosensing of cytokines, metabolomics, and sequencing of the microbiome, has the most near-term clinical impact. A diabetic wound that is VEGF-deficient is treated with an angiogenesis-stimulating, antioxidant-rich formulation of PHF, whereas an infected wound with biofilm-derived inflammation is treated with an antimicrobial, NF-κB-inhibiting formulation of PHF [115]. The rational assembly of PHFs with pre-specified molecular target profiles is significantly reduced through the use of AI-guided PHF design, which combines molecular docking, ADMET prediction, and generative AI molecular design. Mechanistic clarity will be reinforced in regulatory evidence dossiers by systems pharmacology approaches [116]. The wound microbiome is becoming an important factor in wound healing. Future PHFs could be used to alter the microbiome composition, favouring S. epidermidis and Lactobacillus species and inhibiting pathogenic species, thus creating a new paradigm in wound therapy targeting the microbiome. The use of stem cell-integrated PHF systems with the pro-healing molecular milieu developed by PHF phytochemicals is a powerful approach for full-thickness wound repair [117].

10. CONCLUSION

PHFs have strong therapeutic potential for wound healing. The outcomes are indicative of coordinated interactions of multi-component phytochemical profiles with complex molecular machinery of wound repair, and are consistently observed in PHFs, indicative of coordinated interactions of multi-component phytochemical profiles with complex molecular machinery of wound repair, and are consistently observed in PHFs. No single evaluation parameter reflects the therapeutic aspect of PHF activity. Macroscopic wound contraction, myofibroblasts, histopathology, biochemical quantification (hydroxyproline, antioxidant enzymes, and MPO) is the quantitative molecular scaffold, and pathway-level molecular analysis. The pharmacological signatures of PHF wound healing are suppression of NF-κB, activation of Nrf2, stimulation of fibroplasia by TGF-β1/Smad2/3, stimulation of angiogenesis by VEGF-PI3K/Akt, and rebalancing of MMP/TIMP, provide a scientifically credible and pharmacologically actionable mechanism. To realise the potential, a standardised, context-specific evaluation framework that combines classical metrics with advanced molecular biomarkers, a new reporting guideline (ARRIVE 2.0), and the development of internationally harmonised regulatory protocols for PHF evaluation are needed. Precision phytomedicine, AI-assisted design, smart biomaterial delivery, and wound microbiome modulation are scientifically sound and clinically promising concepts that make polyherbal wound therapeutics an unmissable opportunity for serious international collaboration to develop the formulations.

Statements and Declarations

1. **Competing Interests:** The authors have no competing interests to declare that are relevant to the content of this article.
2. **Funding:** The authors did not receive support from any organization for the submitted work.
3. **Financial or non-financial interests:** The authors have no relevant financial or non-financial interests to disclose.
4. **Data Availability Statement:** The data that support the findings of this study are openly available in Google Scholar database at https://scholar.google.com/, reference number from 1-117.

Acknowledgments:
The authors would like to thank specially to Vice-chancellor and administration of Chhatrapati Shahu Ji Maharaj University, Kanpur, India, an internationally recognized and well ranked by QS, NAAC, NIRF. Special thanks to our own research team members for their invaluable contributions to this article.

Ethics statement:
This review paper, "In-vivo Evaluation Parameters of Polyherbal Formulations for Wound Healing: Mechanistic Insights and Experimental Models," involves no experimental research, human subjects, or animal studies that need ethical approval. For academic openness and integrity, all acknowledged sources were appropriately referenced.

Author Contribution declaration/ CREDIT Roles:
Sameer Mishra: Idea for article, literature search and**,** writing the draft**. Mr. Ajay Kumar Singh** has supervised and critically revised the manuscript. **Jyoti Yadav, Anurag Singh:** Reviewed and edited the manuscript.

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