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REVIEW ARTICLE

Recent Advances in Natural Hydrolates for Burn Care: Anti-Inflammatory, Antioxidant and Antimicrobial Perspectives

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Abstract

Burn injuries represent a significant global health burden, characterised by complex pathophysiology that extends far beyond the initial thermal insult. The healing process is profoundly influenced by a cascade of molecular and cellular events, including acute and chronic inflammation, oxidative stress and microbial colonisation. These interconnected challenges frequently lead to severe complications such as delayed wound closure, impaired tissue regeneration and pathological scarring. A critical and escalating issue in contemporary burn care is the pervasive rise of antibiotic resistance, which severely compromises treatment efficacy, prolongs hospital stays and significantly increases both patient morbidity and mortality. This literature review critically examines the multifaceted aspects of burn wound healing, focusing on the intricate interplay between inflammation, oxidative stress and infection. It delves into the molecular mechanisms underlying these processes, including the dual role of reactive oxygen species (ROS) in cellular signalling and tissue damage and the dysregulation of key pathways that perpetuate chronic inflammation and promote fibrosis. The alarming rise of multidrug-resistant pathogens (eg *Pseudomonas aeruginosa, Klebsiella pneumoniae, Staphylococcus aureus*, etc) further exacerbates these challenges, highlighting the urgent need for novel therapeutic strategies. The limitations of conventional therapies in precisely modulating these complex biological processes and effectively countering resistant microorganisms are thoroughly discussed. Special attention is given to the therapeutic potential of natural compounds, particularly hydrolates, as innovative and complementary interventions. Current evidence in specific literature demonstrates their anti-inflammatory, antioxidant and antimicrobial properties, supporting their capacity to create a favourable healing microenvironment and mitigate the impact of antibiotic resistance. By elucidating the mechanisms through which these botanical extracts may influence wound healing, this review seeks to identify critical knowledge gaps and provide a robust foundation for future research into integrative approaches that can optimise burn wound outcomes and address urgent clinical needs.

Key words: Burns; Inflammation; Drug resistance, microbial; Hydrolates; Wound healing; Natural compounds; Oxidative stress.

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Introduction

Burn injury represents a major global health problem, imposing a profound physical, psychological and socioeconomic burden on millions each year.[1] The catastrophic wildfires in Los Angeles in 2025, which resulted in a surge of severe burn cases, underscored the critical importance of advancing burn care and the broader implications for public health systems worldwide.[2] The complex pathophysiology of burn wounds arises from cascading inflammatory responses, oxidative stress and impaired healing: it often culminates in infection, delayed closure, pathological scarring and, in severe cases, multi-organ failure and psychosomatic complications.[3] Current clinical practice relies on advanced surgical interventions and established supportive therapies, yet infection control and the accelerating threat of antimicrobial resistance remain formidable challenges.[4] These realities emphasise the urgent need for innovative, biologically based strategies that not only mitigate excessive inflammation and address the global crisis of antimicrobial resistance but also actively promote effective re-epithelialisation and optimal skin tissue regeneration, ultimately improving long-term outcomes for burn patients.

One of the most alarming threats in modern burn care is the growing crisis of antibiotic resistance. The widespread and often indiscriminate use of antibiotics, although crucial for the prevention and treatment of infections in burn patients, inadvertently favours the emergence and spread of multidrug-resistant (MDR) bacterial strains.[5] This phenomenon renders conventional antimicrobial therapy ineffective, resulting in prolonged hospital stays, increased treatment costs, increased incidence of adverse events (ie sepsis) and increased mortality.[6] Environmental studies are a clear illustration of this global problem: for example, a study by Kristiansson et al demonstrated alarmingly high concentrations of active pharmaceutical ingredients, including antibiotics, in wastewater from pharmaceutical plants in Hyderabad, India, with levels in the Musi River downstream exceeding those found in the blood of treated patients.[7] This environmental reservoir of resistance genes not only fuels the clinical burden of antimicrobial resistance but also represents a growing threat to global health and the well-being of future generations.

In response to these growing challenges, clinical guidelines from organisations like the American Burn Association and the World Health Organisation offer standard protocols for the management of burns that emphasise early excision, wound closure and infection prevention.[8–11] However, these recommendations primarily focus on traditional pharmacological and surgical interventions, often leaving a critical gap in addressing the nuanced modulation of the wound microenvironment and the ongoing threat of resistant pathogens. The limitations of conventional therapies combined with the increasing prevalence of MDR organisms necessitate the search for new, complementary therapeutic strategies.

In the context of this topic, natural compounds with inherent antimicrobial, anti-inflammatory and regenerative properties are of particular interest to many researchers.[12, 13] Among them, hydrolates (or "hydrosol" can also be found in specialised literature) – aqueous by-products of distillation of essential oils of medicinal plants, represent a promising but still insufficiently studied area. Unlike essential oils, hydrolates have a milder chemical profile, making them potentially safer for topical application on damaged skin, while retaining a complex array of water-soluble bioactive compounds.[14] Preliminary studies suggest that these plant extracts may modulate inflammatory mediators, exhibit antioxidant activity and have direct antimicrobial effects, offering a mild but effective means of supporting the healing process and combating microbial colonisation.[15, 16]

Given the multifaceted challenges of burn wound management, in particular the dual burdens of inflammation and increasing antibiotic resistance, a comprehensive understanding of alternative therapies is essential. This review aimed to critically assess the current landscape of burn wound healing, with a particular focus on the growing problem of antibiotic resistance and the potential of plant-derived hydrolates as innovative therapeutic tools. By summarising the available evidence and highlighting knowledge gaps, we aim to lay the groundwork for future research into integrative strategies that can optimise burn wound outcomes, mitigate complications and address the urgent need for novel antimicrobial and anti-inflammatory agents.

Methods

A comprehensive literature search was systematically performed across *PubMed*, *Scopus*, *Web of Science* and *Google Scholar*. The search was performed using a combination of keywords and Medical Subject Headings (MeSH) terms, tailored to each database's indexing system. Key search terms included, but were not limited to: "burn injury", "wound healing", "inflammation", "oxidative stress", "antibiotic resistance", "multidrug-resistant bacteria", "hydrolates", "hydrosols", "herbal medicine", "plant extracts", "antimicrobial activity", "antioxidant properties" and "clinical applications".

Only peer-reviewed original research, systematic reviews, meta-analyses and clinical guidelines published in English that directly addressed the pathophysiology of burn wounds, antimicrobial resistance, or the therapeutic role of natural compounds were included. Data were extracted by three independent researchers.

Molecular pathways of burn wound healing

Burn wound healing is a regulated biological process, involving a complex interplay of cellular and molecular events. This intricate cascade can be broadly divided into three overlapping phases: inflammation, proliferation and maturation (commonly referred to as the remodelling phase in specialised literature).[17] Each of these phases is meticulously regulated by a myriad of signalling pathways, growth factors, cytokines and extracellular matrix components. Even minor dysregulation at any stage can cause molecular disfunction, delayed healing, chronic wounds, or pathological scarring. In this section, we examine the three key phases of burn wound repair through their molecular and cellular mechanisms.

The inflammatory phase. The initial response to burn injury is an acute inflammatory phase that plays a central role in clearing cellular debris, controlling microbial invasion and initiating tissue repair (Figure 1). This stage is characterised by vasodilation, increased vascular permeability and rapid recruitment of immune cells to the wound site (primarily neutrophils and macrophages).[18] As emphasised by Chen et al, the inflammatory response is indispensable for wound debridement and pathogen control; however, when it becomes excessive or prolonged, it contributes to collateral tissue damage, delays epithelialisation and can trigger systemic inflammatory response syndrome (SIRS).[19]

At the molecular level, early inflammation is initiated and regulated by pro-inflammatory cytokines, including interleukin-1 (IL-1), IL-6, IL-8 and tumour necrosis factor-alpha (TNF-α), which act as key mediators of leukocyte recruitment and activation.[20–22] These cytokines activate major intracellular signalling cascades: most notably the NF-kB (nuclear factor-kappa B) and MAPK (mitogen-activated protein kinase) pathways.[23]

NF-kB is a core regulator of the inflammatory response: once stimulated by TNF-α, IL-1β, or pathogen-associated molecular patterns (MAMP), it translocates into the nucleus and induces the expression of pro-inflammatory genes, chemokines, adhesion molecules and inflammatory enzymes like iNOS and COX-2 (Figure 2). Persistent NF-kB activation in burn wounds has been directly linked to systemic inflammation and tissue injury.[24]

In parallel, the MAPK family (ERK, JNK and p38) mediates cellular responses to stress. As noted by Johnson et al, p38 MAPK predominantly drives stress-related and pro-inflammatory signalling, whereas ERK activation is often associated with cell survival and proliferative responses.[25] This contrast illustrates the context-dependent duality of MAPK signalling in burn injury.

Beyond cytokine-driven pathways, reactive oxygen species (ROS) play a dual role in the inflammatory phase. These highly reactive molecules arise primarily from mitochondrial respiration and enzymatic reactions (eg NADPH oxidase activity and the Fenton reaction), generating superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH^-), nitric oxide (NO^-), peroxynitrites ($ONOO^-$) and hypochlorite (OCl^-), etc.[26–28] While physiological levels of ROS are crucial for essential cellular processes, including microbial clearance and intracellular signalling pathways vital for tissue repair and regeneration, their excessive accumulation, particularly during ischaemia-reperfusion injury and acute inflammation, leads to a state of oxidative stress.[29]

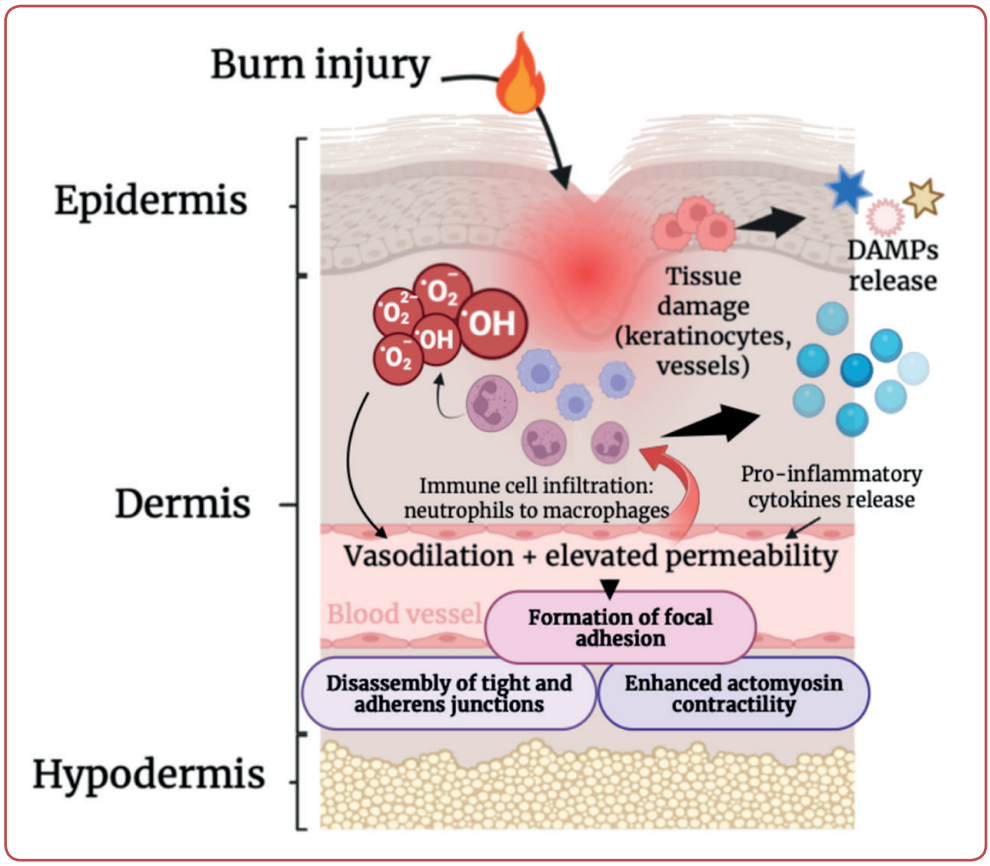

Figure 1: Early inflammatory phase of burn wound healing. Thermal injury induces keratinocyte and vascular damage, leading to damage-associated molecular patterns (DAMP) and reactive oxygen species (ROS) release. These signals activate IL-1, IL-6, IL-8 and TNF-α pathways, driving endothelial activation, vasodilation and cytoskeletal remodelling. The resulting permeability promotes neutrophil and macrophage infiltration, initiating debridement and amplifying local inflammation

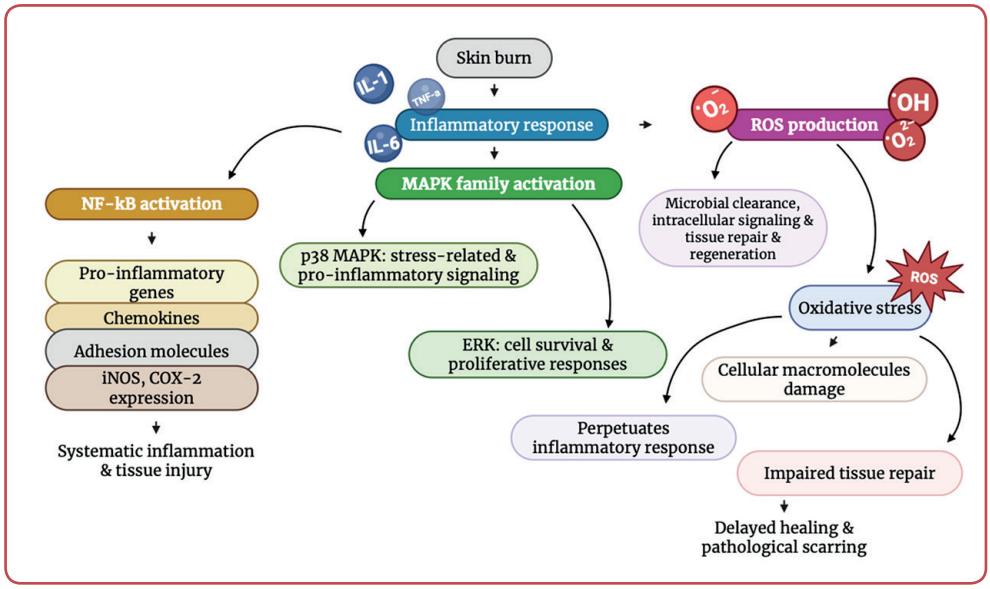

Figure 2: Key pathways of burn injury: ROS – reactive oxygen species, NF-kB – nuclear factor kappa-B, MAPK – mitogen-activated protein kinase, ERK – extracellular signal-regulated kinase, iNOS – inducible nitric oxide synthase, COX-2 – cyclooxygenase-2;

Oxidative stress, driven by an imbalance between pro-oxidants and antioxidants, damages cellular macromolecules: cellular lipids, proteins and DNA. This damage perpetuates the inflammatory response and severely impairs tissue repair, leading to delayed healing and pathological scarring (Figure 2).[30]

In response to this oxidative challenge, the nuclear factor erythroid 2-related factor-2 (Nrf-2) pathway emerges as a pivotal endogenous defence mechanism.[31] Nrf-2, a core regulator of antioxidant and detoxification responses, is activated under conditions of oxidative stress.[29] Upon activation, Nrf-2 translocates to the nucleus, where it binds to antioxidant response elements (AREs) in the promoter regions of target genes, upregulating the expression of a battery of cytoprotective enzymes, for example heme oxygenase-1 (HO-1), NAD(P)H quinone oxidoreductase-1 (NQO1) and glutathione S-transferases (GSTs).[32] The robust activation of the Nrf-2 pathway has been consistently shown to mitigate oxidative damage, reduce inflammation and promote more efficient tissue regeneration in various models of burn injury.[33, 34]

The proliferative phase. Following the initial inflammatory response, the wound healing cascade transitions into the proliferative phase, a critical period characterised by interdependent processes including angiogenesis, granulation tissue formation, collagen synthesis and re-epithelialisation. This phase is meticulously regulated by a diverse array of growth factors and cytokines (vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), epidermal growth factor (EGF) and transforming growth factor-beta (TGF-β).[35]

Central to the cellular and molecular tools of this phase are several keys signalling pathways. The phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway serves as a fundamental regulator of cell growth, proliferation, survival and angiogenesis.[36] In the context of burn wound healing, activation of this pathway has been shown to significantly promote fibroblast proliferation, enhance collagen synthesis and facilitate endothelial cell migration (all of which are indispensable for robust granulation tissue formation and effective revascularisation).[37] However, dysregulation of the PI3K/Akt/mTOR pathway can contribute to pathological scarring, highlighting the importance of its precise control.[38]

Concurrently, the Wnt/β-catenin pathway plays a pivotal role in cell proliferation, differentiation and overall tissue regeneration. Interesting, that in wound healing, Wnt signalling is intricately involved in modulating fibroblast activity, promoting epithelial cell migration and critically, facilitating hair follicle regeneration, thereby contributing to efficient re-epithelialisation and dermal repair.[39] Mi et al, in a recent study, showed that activation of the Wnt/β-catenin pathway promotes fibroblast proliferation and migration, which are critical for wound closure.[40]

Furthermore, transforming growth factor-beta (TGF-β) is a pleiotropic cytokine with multifaceted roles in wound healing.[41] While its presence is essential for physiological collagen synthesis and extracellular matrix deposition, excessive or prolonged TGF-β signalling, particularly through the canonical Smad pathway, is a well-established major contributor to the development of hypertrophic scarring and fibrosis, common and debilitating complications of deep burn injuries.[42] Studies have indicated that fibroblasts derived from hypertrophic scars exhibit altered TGF-β signalling, underscoring its role in pathological outcomes.[43]

The remodelling phase. The final and often most protracted phase of wound healing is maturation (or remodelling), a dynamic process that can extend for months to several years post-injury.[44] This phase is anatomically characterised by the gradual maturation and reorganisation of the newly synthesised collagen fibres within the scar tissue, leading to a progressive increase in the wound's tensile strength.[45] Morphologically, this involves a transition from the initial haphazard deposition of type III collagen to a more organised, cross-linked network predominantly composed of stronger type I collagen.[46] This intricate process is governed by a delicate balance between collagen synthesis (primarily by fibroblasts) and collagen degradation, mediated by a diverse family of matrix metalloproteinases (MMPs) and their specific tissue inhibitors (TIMPs).[47] Dysregulation of this finely tuned equilibrium can lead to adverse outcomes, ranging from insufficient scar formation and wound dehiscence to excessive, pathological scarring, clinically manifesting as hypertrophic scars and keloids, which are characterised by aberrant collagen accumulation and architectural disorganisation.[48]

Understanding the molecular, cellular and genetic

pathways that govern burn healing is critical for designing targeted therapies. Precise modulation of these streams could enhance tissue regeneration, accelerate recovery and reduce complications, for example pathological scarring. The key challenge lies in developing agents that promote reparative signalling while suppressing harmful responses.

The role of inflammation in burn pathology

Inflammation is an indispensable physiological response to injury, protecting from infection and initiating tissue repair. In burn injuries, however, this response is often excessive and prolonged – especially in the case of additional microbiological contamination of the wound, large lesion area and delayed therapy; shifting from a protective mechanism to a driver of tissue damage and systemic complications.[49] Focus of this paper was on investigating this dual nature of inflammation, aiming to unravel its underlying mechanisms and translate these insights into targeted therapeutic strategies.

Acute inflammatory response. A rapid localised inflammatory response arises immediately after thermal injury. This critical initial phase is characterised by the release of damage-associated molecular patterns (DAMPs) from necrotic and damaged cells like high-mobility group box 1 (HMGB1) and S100 proteins.[50] These DAMPs act as endogenous danger signals, activating innate immune cells, including resident macrophages and mast cells, through pattern recognition receptors like Toll-like receptors (TLRs).[51] This activation initiates a cascade of molecular events, leading to increased vascular permeability, localised oedema and the rapid recruitment of neutrophils and macrophages to the wound site (Figure 3). The phagocytic cells are essential for the enzymatic debridement of necrotic tissue and the efficient phagocytosis of pathogens, crucial steps for preventing infection and preparing the wound bed for subsequent healing phases.[52]

However, in severe burn injuries, this normally protective localised response can rapidly escalate into a SIRS.[53] This systemic amplification is driven by the massive and sustained release of potent pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), into the systemic blood circulation.[54] SIRS can lead to widespread endothelial dysfunction, remote organ damage and significantly contributes to the high morbidity and mortality associated with severe burns, often culminating in sepsis and multiple organ failure. The sustained activation of key intracellular signalling pathways (NF-kB and MAPK), plays a central role in perpetuating chronic and detrimental systemic inflammation by upregulating the expression of pro-inflammatory genes and adhesion molecules.[23] Therefore, a comprehensive understanding of these complex molecular, cellular and genetic pathways is paramount.

Chronic inflammation and impaired healing. While acute inflammation is an indispensable component of the initial wound healing response, its persistence beyond the necessary early stages can severely impede wound closure and predispose to pathological scarring.[55] This transition to chronic inflammation (particularly prevalent in deep burn injuries) is morphologically characterised by a sustained influx and presence of immune cells, notably macrophages and lymphocytes, alongside activated fibroblasts, leading to continuous tissue destruction and aberrant extracellular matrix (ECM) remodeling.[56, 57] Anatomically, this manifests as a non-healing wound bed, often with friable granulation tissue, impaired re-epithelialisation and progressive fibrotic changes in the surrounding dermis.

At a biochemical level, this prolonged inflammatory state drives a cascade of detrimental processes. Persistent activation of neutrophils and macrophages leads to the continuous production of excessive ROS via enzymatic systems like NADPH oxidases and myeloperoxidase.[58, 59] The resulting oxidative burst overwhelms endogenous antioxidant defences, including superoxide dismutase, catalase and glutathione peroxidase, causing the accumulation of ROS and reactive nitrogen species (RNS).[60] This imbalance inflicts widespread oxidative damage on lipids through peroxidation, on proteins via carbonylation and nitration and on nucleic acids, ultimately disrupting cellular function and viability. Damaged and oxidised cellular components further amplify inflammatory signalling pathways, creating a self-perpetuating cycle of tissue injury and inflammation.[61]

In addition, chronic inflammation is intrinsically

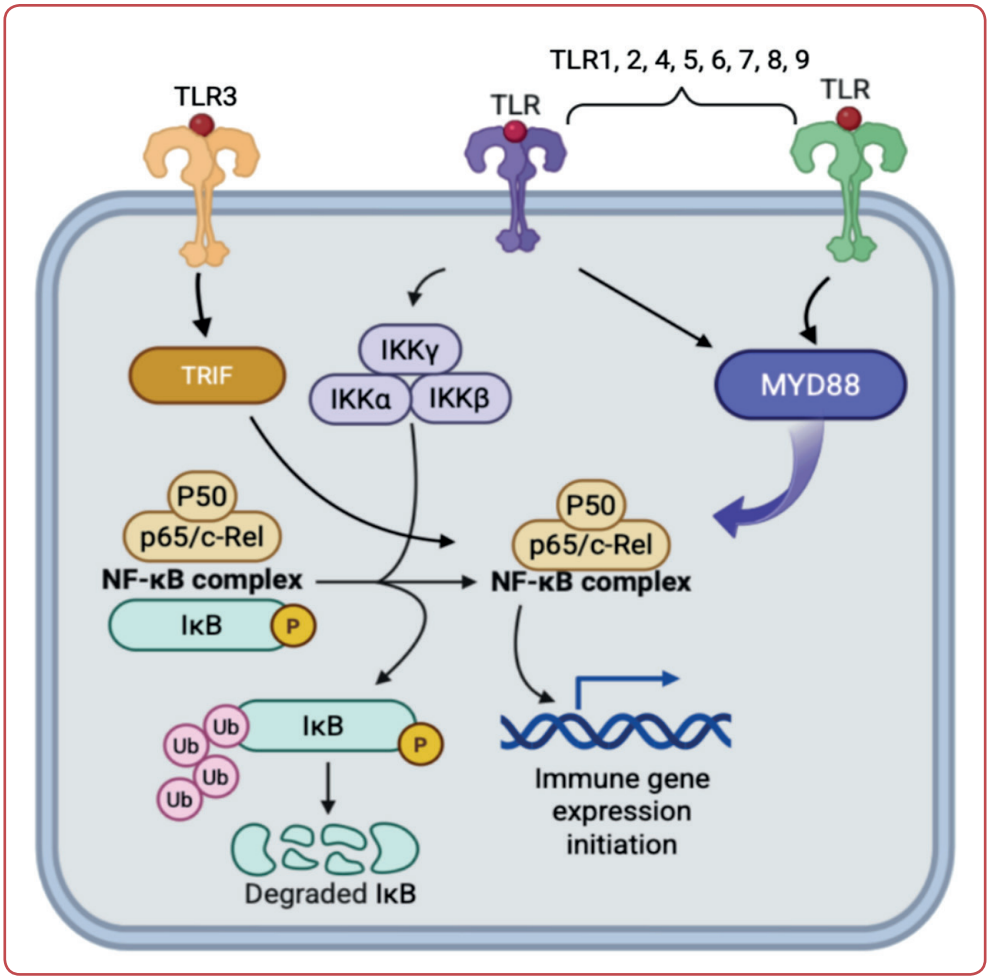

Figure 3: TLR-mediated activation of NF-kB signalling in burn injury: TLR – Toll-like receptor, TRIF – TIR-domain-containing adapter-inducing interferon-β, MYD88 – myeloid differentiation primary response 88, IKK – inhibitor of nuclear factor kB kinase, NF-kB – nuclear factor kappa-B, IkB – inhibitor of NF-kB, Ub – ubiquitin, p65/c-Rel – NF-kB subunits.

Following burn injury, damage-associated molecular patterns (DAMPs) released from necrotic cells bind to Toll-like receptors (TLR1–9) on innate immune cells. Most TLRs signal via the adaptor protein MYD88, while TLR3 and partially TLR4 can signal through TRIF. These adaptors recruit and activate the IKK complex (IKKα, IKKβ, IKKγ), which phosphorylates the NF-kB inhibitor IkB. Phosphorylated IkB undergoes ubiquitination (Ub) and proteasomal degradation, releasing the NF-kB complex (p50/p65 or p65/c-Rel). The active NF-kB translocates into the nucleus, initiating transcription of immune and pro-inflammatory genes, thereby amplifying the inflammatory response in the burn wound.

linked to an upregulation and dysregulation of proteolytic enzymes (PE). Specifically, an excessive activity of matrix metalloproteinases (MMPs): MMP-1, -8 and -9, along with serine proteases like elastase and cathepsins, leads to the uncontrolled degradation of vital ECM components, including collagen, elastin and fibronectin.[62, 63] This biochemical imbalance between synthesis and degradation of ECM components prevents proper tissue reconstruction, impairs growth factor bioavailability and contributes significantly to the chronicity of non-healing burn wounds by creating a hostile microenvironment for cellular migration and proliferation.[64]

Prolonged inflammation creates a microenvironment that favours fibrosis, where excessive fibroblast proliferation and disorganised ECM deposition disrupt normal tissue architecture.[65] In this setting, persistent pro-fibrotic signalling – exemplified by the chronic activation of the TGF-β/Smad axis, drives myofibroblast differentiation and uncontrolled collagen synthesis. The resulting hypertrophic scars and keloids exhibit dense, irregular collagen bundles, increased cellularity and a loss of the skin's native architecture, causing both functional impairment and aesthetic morbidity in burn patients.[42, 43]

Therapeutic modulation of inflammation. Given the critical yet complex role of inflammation in burn trauma, therapeutic strategies must focus on targeted modulating, rather than completely suppressing, the inflammatory response. The core goal is to attenuate the detrimental, self-perpetuating aspects of excessive inflammation while meticulously preserving its beneficial functions in pathogen clearance, debridement of necrotic tissue and initiation of repair. Traditional pharmacological approaches have included corticosteroids, utilised with caution due to their broad immunosuppressive effects and potential to impair wound healing and non-steroidal anti-inflammatory drugs (NSAIDs), which offer symptomatic relief but may also carry risks in burn patients.[66] More targeted biological agents (like monoclonal antibodies) against specific cytokines (eg TNF-α, IL-6), represent a promising, albeit often costly, avenue for precise immunomodulation.[67]

However, there is a burgeoning interest in natural compounds with potent anti-inflammatory properties that can offer a safer, more nuanced and holistic approach to burn care. For instance, research by Professor Chen and colleagues highlighted the anti-inflammatory and wound healing properties of natural extracts, demonstrating their potential to modulate the inflammatory cascade without severe systemic side effects.[68] Similarly, studies by Wang et al have explored novel hydrogel systems incorporating anti-inflammatory agents, showcasing their efficacy in reducing excessive inflammation and promoting angiogenesis in burn wounds.[69]

Hydrolates, with their complex phytochemical profiles derived from aromatic plants, represent a particularly promising avenue for such gentle yet effective immunomodulation. Their inherent ability to scavenge free radicals, as demonstrated by research from Süntar et al on the antioxidant capacity of various plant extracts and to modulate key inflammatory mediators positions them as valuable candidates for integrative burn care strategies.[32] Also, recent work by Professor Demyashkin et al further supports the therapeutic potential of plant-based formulations, showing that hydrogels containing water extracts of medicinal plants significantly enhance burn wound healing, stimulate keratinocyte proliferation and reduce local inflammation in *Pseudomonas aeruginosa*-infected models.[70] This approach moves burn care beyond nonspecific suppression toward targeted molecular modulation of the healing microenvironment.

The challenge of antibiotic resistance in burn wounds

Burn wounds create an ideal environment for microbial colonisation and different infections, complicating patient management and sharply increasing morbidity and mortality. A disrupted skin barrier, necrotic tissue and a transiently suppressed immune response provide favourable conditions for diverse microorganisms to proliferate.[71] The growing crisis of antibiotic resistance intensifies this risk, rendering conventional antimicrobial therapies less effective and underscoring the urgent need for innovative treatment strategies.

The microbial landscape of burn wounds. The microbial landscape of burn wounds is dynamic and complex, evolving significantly over time and posing a formidable challenge to effective clinical management. Initially, burn wounds are often colonised by the patient's endogenous skin flora, predominantly gram-positive (G+) bacteria like *Staphylococcus aureus* (including both *methicillin-sensitive S aureus* (MSSA) and *methicillin-resistant S aureus* (MRSA)) and coagulase-negative staphylococci, notably *Staphylococcus epidermidis*.[72, 73] However, within days, a critical shift often occurs, with gram-negative (G–) bacteria emerging as dominant pathogens. Prominent among these are *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*, frequently originating from the patient's gastrointestinal tract or the hospital environment (an additional critical factor is hospital-acquired antimicrobial resistance) (Table 1).[74]

Beyond bacterial threats, opportunistic fungal infections, primarily caused by *Candida* species, are a significant concern, particularly in immunocompromised patients or those undergoing prolonged antibiotic therapy.[84] Other notable bacterial species that can colonise and infect burn wounds include *Proteus mirabilis* and *Enterococcus species*, further diversifying the microbial challenge.[87, 88]

Among these, *Pseudomonas aeruginosa* stands out as a particularly pathogen in burn units due to its intrinsic resistance to numerous antibiotics, its remarkable ability to form robust biofilms and its production of various virulence factors that contribute to extensive tissue damage and systemic infection.[89] Biofilm formation, a complex

Table 1: Major microbial pathogens in burn wounds: taxonomic classification, origin, resistance traits and clinical impact

Microorganism	Class	Primary origin	Main resistance mechanisms	Clinical relevance	Ref
Staphylococcus aureus (MSSA/MRSA)	Gram + cocci	Skin flora, healthcare environment	β-lactamase production (MSSA), mecA-mediated PBP2a expression (MRSA)	Common early coloniser; MRSA causes severe invasive infections	75, 76
Staphylococcus epidermidis	Gram + cocci	Skin flora	Biofilm formation, multidrug efflux pumps, β-lactam resistance	Opportunistic infections, biofilm-associated device infections	77
Pseudomonas aeruginosa	Gram – rod	GI tract, hospital environment	Efflux pumps, β-lactamases, porin loss, biofilm formation	Major burn pathogen; high intrinsic and acquired resistance	78–80
Klebsiella pneumoniae	Gram – rod	GI tract, hospital environment	ESBL and carbapenemase production	Causes wound infection and sepsis; often multidrug-resistant	81
Acinetobacter baumannii	Gram – rod	Hospital environment	Carbapenemases, efflux pumps, desiccation resistance	Highly resistant; associated with outbreaks in burn units	76, 82
*Candida spp.**	Yeast	Endogenous mucosal flora, hospital environment	Azole resistance via ERG11 mutations, efflux pumps	Opportunistic fungal infections; more frequent after antibiotics	83, 84
Proteus mirabilis	Gram – rod	GI tract	β-lactamases, swarming motility aiding biofilm	Secondary coloniser, often in mixed infections	85
*Enterococcus spp.***	Gram + cocci	GI tract	Vancomycin resistance (van genes)	Causes wound infections; problematic in immunocompromised patients	85, 86

MSSA: methicillin-sensitive Staphylococcus aureus; MRSA: methicillin-resistant Staphylococcus aureus; PBP2a: penicillin-binding protein 2a; mecA: gene encoding PBP2a, conferring β-lactam resistance; GI tract: gastrointestinal tract; ESBL: extended-spectrum β-lactamase; ERG11: gene encoding 14α-demethylase (azole target); Van genes: genes mediating vancomycin resistance (vanA, vanB). Candida spp includes C albicans, C glabrata, C parapsilosis, C tropicalis; Enterococcus spp includes E faecalis and E faecium.

aggregation of bacteria encased within an extracellular polymeric substance, provides a formidable protective barrier against both antibiotic penetration and host immune defences, rendering eradication exceedingly difficult.[90] Similarly, MRSA represents a significant threat due to its widespread resistance to β-lactam antibiotics and its capacity to cause severe, invasive infections, often leading to prolonged hospital stays and increased morbidity.[91]

The widespread and often indiscriminate use of antibiotics in burn care has inadvertently contributed to the alarming emergence and dissemination of multidrug-resistant (MDR) strains. This phenomenon, termed antibiotic resistance, occurs when bacteria develop sophisticated mechanisms to withstand the effects of antimicrobial agents, rendering these crucial drugs ineffective. The implications for burn patients are dire, leading to prolonged hospitalisation, escalated treatment costs, higher rates of sepsis and significantly elevated mortality.[5, 92]

Mechanisms of antibiotic resistance are diverse and include enzymatic inactivation of antibiotics (eg β-lactamases that degrade penicillin and cephalosporin derivatives), alteration of target sites (eg mutations in ribosomal subunits affecting aminoglycoside binding), the activation of efflux pumps that actively expel antibiotics from the bacterial cell and reduced permeability of the bacterial cell wall.[93–95]

Horizontal gene transfer, a process where bacteria share resistance genes via plasmids or transposons, further accelerates the rapid spread of resistance within and between bacterial populations, complicating infection control efforts.[96, 97]

The inherent presence of biofilms in burn wounds further exacerbates the issue, as bacteria within these structured communities exhibit significantly higher resistance to antibiotics compared to their planktonic (free-floating) counterparts, often requiring substantially higher antibiotic concentrations for effective treatment.[98]

Therapeutic potential of hydrolate compositions in burn wound healing

Hydrolats (hydrosol or floral water) are aromatic waters obtained in the process of steam distillation (of medical plant raw materials for the extraction of essential oils. Unlike essential oils, which are lipophilic and highly concentrated, hydrolats are hydrophilic, containing water-soluble volatile compounds and trace amounts of essential oils.[99, 100] This unique composition endows them with pronounced therapeutic properties, making them attractive candidates for dermatological applications, especially in the delicate context of burn wound healing.

Antioxidant properties. One of the most significant challenges in burn wound healing is the excessive production of ROS and the resultant cumulative oxidative stress, which can damage cellular components, perpetuate inflammation and impair tissue regeneration.[101]

Hydrolates, particularly those derived from plants rich in phenolic compounds and flavonoids, exhibit potent antioxidant activities.[99] Recent studies indicate that hydrolates from *Origanum vulgare L*, *Thymus vulgaris L* and *Melissa officinalis L* exhibit notable antioxidant activity and can protect human skin fibroblasts from ROS.[102, 103] This effect is particularly relevant in burn wounds, where limiting oxidative damage supports a healthier cellular environment and accelerates healing (it is important to consider the cumulative impact of oxidative stress on cellular signalling, particularly how cells respond to ROS and how peroxisomal molecules may enter the blood circulation).[104] The presence of bioactive compounds: for example thymol, neral and geranial likely contributes to these effects, partly through the modulation of endogenous antioxidant pathways.[105]

Modulating the immune response. As mentioned, excessive and prolonged inflammation (eg chronic inflammation) is a major impediment to optimal burn wound healing. Hydrolates have anti-inflammatory properties that may help modulate the immune response, reducing the deleterious effects of chronic inflammation without completely suppressing the necessary initial inflammatory cascade.[99] While direct studies of hydrosols in models of burn-induced inflammation are just emerging, works in context of essential have already been widely described in the medical literature. For example, Rosanna Avola et al demonstrated that *Origanum vulgare L* essential oil reduces pro-inflammatory mediators, including ICAM-1, iNOS and COX-2, in human keratinocytes and inhibits DNA damage induced by inflammatory stimuli.[106] Given that hydrolates contain water-soluble anti-inflammatory compounds (primarily low-molecular-weight terpenoids, phenolic acids and flavonoid glycosides[107]), they are expected to exert similar effects to the parent essential oils, albeit in a milder and more skin-tolerant form This makes them particularly suitable for application on sensitive and inflamed burn tissue, where harsh synthetic anti-inflammatory agents might cause irritation or side effects. The ability of hydrolates to modulate pathways like NF-kB and MAPK,[108] which are central to inflammatory responses and need for further investigation.

Antimicrobial properties. Bacterial infection, especially caused by multidrug resistant strains, is a major issue of morbidity and mortality among burn patients.[109] The antimicrobial properties of certain hydrolates offer a promising adjunctive strategy to combat these pathogens and reduce the reliance on conventional antibiotics. Studies have demonstrated that hydrolates from plants like *Origanum vulgare L, Satureja montana L* and *Coriandrum sativum L* exhibit antibacterial activities against common skin-infecting bacteria, including *Staphylococcus spp.* and *Pseudomonas aeruginosa*.[70] While the concentrations of active compounds are lower than in essential oils, the aqueous nature of hydrolates allows for direct application and penetration into the wound bed.[14] Their multi-component nature may also make it more difficult for bacteria to develop resistance compared to single-target antibiotics.[99]

A significant advantage of hydrolates is their generally favourable safety profile, making them suitable for topical application, even on compromised skin. Their acidic to neutral pH help restore the skin's natural acid mantle, which is often disrupted in burn injuries.[99]

However, as with any natural product, standardisation and formulation, validation of vapor droplet manufacturing processes, quality control and thorough safety assessment are essential. The efficacy of hydrolates can also be enhanced by advanced formulation strategies: for example, in-

corporation into hydrogels, emulsions, nanopolymers or liposomes to improve stability, bioavailability and targeted delivery to the wound site.

Conclusion

This review underscores the intricate and dynamic nature of burn wound healing, a process profoundly influenced by a delicate balance of inflammatory responses, cellular proliferation and tissue remodelling. The critical challenges posed by dysregulated inflammation and the escalating threat of antibiotic resistance is highlighted, both of which significantly impede optimal patient outcomes and contribute to long-term morbidity. The current therapeutic landscape, while offering essential interventions, often falls short in providing nuanced modulation of these complex biological processes, particularly in the face of microbial threats.

Presented findings highlight an urgent need for targeted, mechanism-based therapies in burn care. Plant-derived hydrolates offer a promising alternative: these complex botanical distillates possess anti-inflammatory, antioxidant and antimicrobial properties that may help curb excessive inflammation and combat resistant infections, without the collateral damage of broad-spectrum antibiotics.

To realise their clinical potential, future research must rigorously assess efficacy, safety and mechanisms of action through robust preclinical and clinical studies. Standardised methods for extraction, characterisation and quality control are essential to ensure consistency. Ultimately, the integration of validated hydrolates into burn care may improve outcomes and help mitigate the growing threat of antibiotic resistance.

Ethics

This study was a secondary analysis based on the currently existing data and did not directly involve with human participants or experimental animals. Therefore, the ethics approval was not required in this paper.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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