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TARGETING THE LACTYLATION-PYROPTOSIS AXIS IN CHRONIC WOUNDS: AN IMMUNOMETABOLIC FRAMEWORK FOR PHYTOCHEMICAL NANOTHERAPEUTICS

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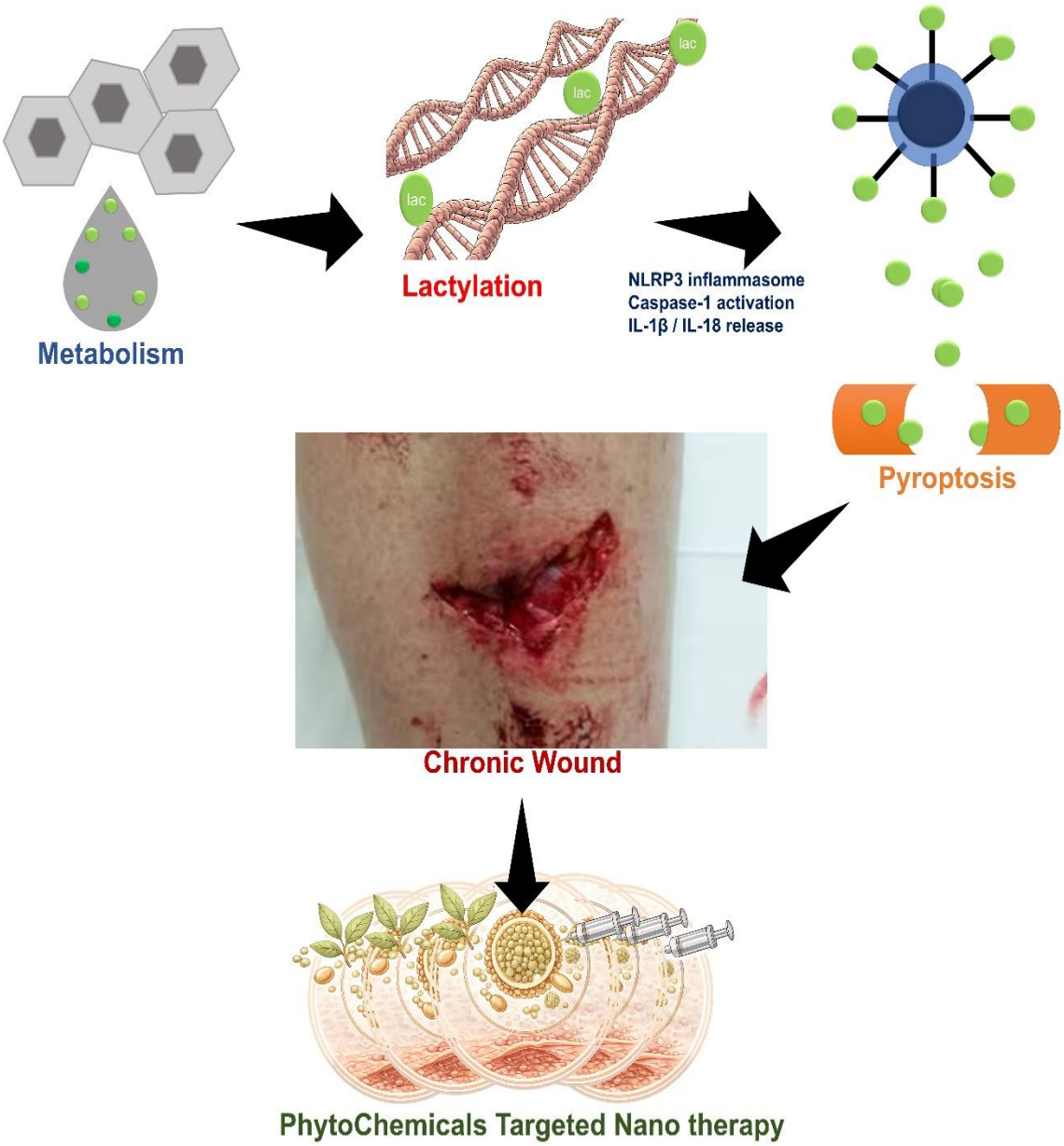
ABSTRACT
Chronic wounds represent a considerable clinical burden associated with prolonged inflammation, metabolic dysregulation, and impaired tissue regeneration. The role of metabolic reprogramming in the maintenance of non-healing wound environments is being underscored by emerging evidence from immunometabolism. In that regard, the lactylation–pyroptosis axis has been examined as a novel mechanism that integrates hypoxia-driven glycolysis, lactate accumulation, epigenetic regulation, and inflammasome-mediated inflammatory cell death. Histone lactylation serves as a metabolic–epigenetic interface, supporting lactate-derived chromatin modifications relevant to regulating immune modulation and tissue repair genes. On the contrary, pyroptosis enhances inflammation through NLRP3 inflammasome activation, caspase-1–mediated cleavage of gasdermin D, and secretion of pro-inflammatory cytokines including interleukin-1β and interleukin-18. This axis dysregulation contributes toward sustained inflammation, defective macrophage polarization, and delayed wound healing. This review offers a summary overview of the immunometabolic profile of chronic wounds, highlighting the interactions between lactylation and pyroptotic mechanisms. It continues to discuss the therapeutic effect of phytochemicals as active multifunctional modulators modulating metabolism and inflammation. This review presents the use of phytochemicals into nanocarrier systems (nanocarriers) as a novel approach for improving stability, bioavailability, targeted delivery, and controlled release in the wound microenvironment. While promising preclinical data, translational hurdles include incomplete mechanistic insights, few biomarkers, and nanotherapeutics scalability challenges. Targeting the lactylation–pyroptosis axis represents an exciting avenue for the development of next-generation therapies in chronic wound treatment**.**

KEYWORDS: Chronic wounds; Histone lactylation; Pyroptosis; Phytochemical nanotherapy.

GRAPHICAL ABSTRACT



1. INTRODUCTION

Chronic wounds are a major and growing problem for healthcare systems around the world, especially for older people and those with metabolic disorders like diabetes mellitus[1]. These wounds are characterized by their failure to advance through the standard phases of healing: hemostasis, inflammation, proliferation, and remodeling in a synchronized and timely fashion[2]. Instead, they become stuck in a state of long-term inflammation, which is marked by too much protease activity, trouble with extracellular matrix deposition, and ongoing microbial colonization[3]. This pathological stagnation not only delays tissue repair but also significantly increases the risk of complications, including infection, amputation, and mortality[4]. Even though wound care technology has come a long way, current treatment methods are still not good enough[5]. This shows how important it is to use mechanistically informed interventions that fix the underlying biological problem

A key aspect of chronic wounds is the disturbance of immune homeostasis, which is intricately linked to changes in cellular metabolism[6]. In recent years, immunometabolism has shown that metabolic pathways don't just help immune cells work; they also control how they behave and how they respond to inflammation[7]. Immune cells in the wound microenvironment undergo significant metabolic reprogramming due to hypoxia, nutrient deficiency, and continuous inflammatory signals[8]. This reprogramming is marked by a transition to aerobic glycolysis, resulting in the buildup of metabolic intermediates like lactate[9]. These metabolites act as signaling molecules that change the type of immune cells, how many cytokines they make, and how quickly tissues heal.

Macrophages are very important for wound healing and are a good example of what happens when the immune and metabolic systems are out of balance[9]. In acute wounds, macrophages change from being pro-inflammatory to pro-reparative, which helps inflammation go away and tissue regeneration begin[10]. In chronic wounds, this transition is hindered, leading to persistent pro-inflammatory activity and protracted healing[11]. Metabolic dysregulation contributes directly to this phenomenon by modifying intracellular signaling pathways and epigenetic landscapes that regulate macrophage function[12]. Glycolytic metabolism and its by-products continue to promote inflammatory signaling, leading to a self-sustaining cycle of immune activation and tissue damage.

Among the metabolic factors implicated in this process, lactate has emerged as a critical regulator of immune function[13]. Traditionally regarded as a by-product of anaerobic metabolism, lactate is now recognized as an active participant in cellular signaling and gene regulation[14]. Elevated lactate levels in hypoxic wound environments drive a novel epigenetic modification known as histone lactylation, which links metabolic status to transcriptional control[15]. This modification enables lactate-derived chemical groups to be added to histone proteins, thereby influencing gene expression programs associated with inflammation and repair[16]. Recent studies have demonstrated that lactylation serves as a molecular bridge connecting metabolic reprogramming with immune regulation and chronic inflammatory states[17]. Through this mechanism, lactate not only reflects metabolic activity but actively shapes cellular responses within the wound microenvironment.

Concurrently, programmed cell death pathways contribute significantly to the pathophysiology of chronic wounds, with pyroptosis emerging as a key mediator of inflammation[18]. Pyroptosis is a highly inflammatory form of cell death triggered by activation of inflammasomes, particularly the NLRP3 complex, leading to caspase-mediated cleavage of gasdermin proteins and subsequent membrane pore formation[19]. This process results in the release of pro-inflammatory cytokines such as interleukin-1β and interleukin-18, amplifying local inflammation and recruiting additional immune cells[20]. In chronic wounds, excessive or dysregulated pyroptotic activity contributes to sustained inflammatory signaling, tissue damage, and impaired regenerative capacity[21]. While pyroptosis plays a protective role in host defense by eliminating infected or damaged cells, its uncontrolled activation disrupts the delicate balance required for effective wound healing[22].

Importantly, emerging evidence suggests that pyroptosis is not solely detrimental but may exert context-dependent effects that influence both inflammation and repair[23]. Controlled activation of pyroptotic pathways can facilitate clearance of pathogens and promote immune activation necessary for tissue remodeling[24]. However, the transition from beneficial to pathological pyroptosis is governed by complex regulatory mechanisms that remain incompletely understood[19]. This dual role highlights the need for precise modulation rather than complete inhibition of pyroptotic signaling in therapeutic strategies.

The convergence of lactylation and pyroptosis introduces a novel conceptual framework for understanding chronic wound immunopathology[19]. Recent studies indicate that post-translational modifications, including lactylation, can regulate key components of pyroptotic signaling pathways, thereby influencing inflammasome activation and downstream inflammatory responses[25]. Moreover, lactylation has been implicated in the regulation of lytic cell death processes, suggesting a direct link between metabolic reprogramming and pyroptotic mechanisms[26]. This interplay establishes a dynamic axis in which metabolic signals modulate inflammatory cell death, while pyroptotic activity further alters the metabolic and immune landscape of the wound environment[18].

Dysregulation of this lactylation–pyroptosis axis may represent a critical determinant of chronic wound persistence[27]. Excessive lactate accumulation without appropriate epigenetic control can lead to aberrant lactylation patterns, while uncontrolled pyroptosis amplifies inflammatory signaling and tissue injury[28]. Together, these processes create a feedback loop that perpetuates immune dysfunction and prevents resolution of inflammation[29]. Understanding the mechanisms governing this axis is therefore essential for identifying novel therapeutic targets capable of restoring immune balance and promoting tissue regeneration[30].

Given these insights, targeting the lactylation–pyroptosis axis represents a promising and mechanistically grounded approach for chronic wound therapy[31]. Rather than focusing on single pathways, this strategy aims to modulate the integrated network of metabolic, epigenetic, and inflammatory processes that drive disease progression[32]. By restoring coordination between metabolic signaling and immune responses, it may be possible to shift the wound environment from a state of chronic inflammation toward effective repair and regeneration[33].

In conclusion, chronic wounds exemplify a complex interplay between immune dysregulation and metabolic dysfunction, in which traditional therapeutic approaches fail to address underlying biological mechanisms[33, 34]. The emerging recognition of lactylation as a key epigenetic mediator and pyroptosis as a central inflammatory pathway provides new opportunities for mechanistic intervention[26]. Integrating these processes into a unified framework highlights the importance of the lactylation–pyroptosis axis as a critical regulator of wound healing outcomes[35]. Future research focused on this axis holds significant potential for advancing the development of targeted, effective, and clinically translatable therapies for chronic wound management.

2. Immunometabolic Landscape of Chronic Wounds

The wound microenvironment is a highly dynamic system in which immune responses and metabolic processes are intricately interconnected[36]. In chronic wounds, this relationship becomes dysregulated, giving rise to a pathological immunometabolic landscape that perpetuates inflammation and impairs tissue repair[37]. Unlike acute healing, where metabolic adaptation supports coordinated immune resolution, chronic wounds exhibit sustained metabolic stress, altered nutrient utilization, and persistent inflammatory signaling[8]. These changes

collectively reprogram immune cell function, particularly within macrophages, and establish a self-reinforcing cycle of immune dysfunction.

2.1. Hypoxia-Driven Glycolytic Shift and Lactate Accumulation

A defining feature of chronic wounds is localized hypoxia resulting from vascular insufficiency, impaired perfusion, and high metabolic demand[38]. Oxygen deprivation profoundly influences cellular metabolism by promoting a shift from oxidative phosphorylation to aerobic glycolysis, a phenomenon often referred to as the Warburg-like effect in immune cells[39]. This metabolic transition enables rapid ATP generation and supports biosynthetic requirements; however, it also leads to the accumulation of lactate as a major metabolic by-product[40].

In immune cells, particularly macrophages and neutrophils, glycolysis becomes the dominant metabolic pathway under hypoxic and inflammatory conditions[41]. This shift is not merely an adaptive response but a regulatory mechanism that shapes immune function[42]. Elevated glycolytic flux increases intracellular levels of intermediates such as pyruvate and lactate, which act as signaling molecules influencing transcriptional and post-transcriptional processes[43]. Pro-inflammatory immune cells exhibit enhanced glucose uptake and lactate production, reflecting their reliance on glycolysis for rapid activation and cytokine synthesis[44].

Lactate accumulation within the wound microenvironment has multifaceted consequences. Traditionally considered a metabolic waste product, lactate is now recognized as a critical immunomodulatory metabolite[45]. High lactate concentrations can alter pH, inhibit antimicrobial activity, and disrupt cellular communication[46]. At the same time, lactate functions as a signaling molecule that modulates gene expression, immune cell differentiation, and inflammatory responses[47]. Emerging evidence indicates that lactate interacts with immune cells through receptor-mediated pathways and intracellular signaling cascades, thereby influencing the balance between inflammation and repair[48].

Importantly, excessive lactate accumulation in chronic wounds contributes to metabolic stress and perpetuates inflammatory signaling[45]. Instead of resolving inflammation, the hypoxia–glycolysis–lactate axis maintains immune cells in a sustained activation state[49]. This persistent metabolic reprogramming prevents the transition to reparative phases of healing, thereby reinforcing chronicity[8]. Thus, hypoxia-induced glycolytic remodeling represents a central driver of immunometabolic dysfunction in non-healing wounds[50].

2.2. Macrophage Polarization and Metabolic Plasticity

Macrophages are central regulators of wound healing and exemplify the link between metabolism and immune function[51]. Their ability to adopt distinct functional phenotypes—ranging from pro-inflammatory to pro-reparative states–is tightly coupled to their metabolic configuration[52]. In the context of immunometabolism, macrophage polarization is not solely dictated by external cytokine signals but is fundamentally governed by intracellular metabolic pathways[53].

Pro-inflammatory macrophages are characterized by a metabolic profile dominated by glycolysis, accompanied by disruptions in the tricarboxylic acid cycle and increased production of reactive oxygen species[54]. This metabolic state supports rapid energy generation and facilitates the production of inflammatory mediators[55]. In contrast, anti-inflammatory macrophages rely on oxidative phosphorylation and fatty acid oxidation, enabling efficient energy utilization and supporting tissue repair functions[10, 55]. These distinct metabolic programs are essential for functional specialization and highlight the concept of metabolic plasticity in immune cells.

However, the macrophage phenotype in chronic wounds deviates from this classical paradigm. Instead of transitioning from inflammatory to reparative states, macrophages often remain locked in a persistent pro-inflammatory phenotype[56]. This failure of phenotypic switching is driven by sustained metabolic cues within the wound environment, including hypoxia, nutrient deprivation, and chronic exposure to inflammatory mediators[57]. As a result, macrophages exhibit impaired plasticity and contribute to prolonged inflammation and delayed healing.

Recent studies suggest that macrophage polarization exists along a continuum rather than as discrete states. Hybrid phenotypes displaying both inflammatory and reparative characteristics have been identified, reflecting the complexity of immunometabolic regulation[58]. These intermediate states are influenced by dynamic metabolic inputs and microenvironmental signals, further complicating the regulation of immune responses in chronic wounds[59].

Metabolic intermediates generated during macrophage activation also play regulatory roles in gene expression and signaling pathways[60]. For instance, metabolites derived from glycolysis and the tricarboxylic acid cycle can influence epigenetic modifications, transcription factor activity, and cytokine production[61]. This integration of metabolism and gene regulation underscores the importance of metabolic plasticity in determining macrophage function. In chronic wounds, disruption of these regulatory mechanisms leads to sustained inflammatory activation and impaired tissue repair[33].

2.3. Metabolic Control of Inflammatory Persistence

The persistence of inflammation in chronic wounds is not solely a consequence of immune dysregulation but is fundamentally driven by metabolic control mechanisms[59]. Immunometabolism provides a framework for understanding how metabolic pathways influence the duration and intensity of inflammatory responses[62]. In this context, metabolic intermediates act as signaling molecules that regulate immune cell activation, cytokine production, and cell fate decisions.

One of the key features of chronic wound inflammation is the continuous activation of innate immune pathways, including inflammasome signaling[63]. Metabolic reprogramming toward glycolysis enhances the production of pro-inflammatory mediators and supports the activation of inflammasomes, thereby amplifying inflammatory responses[64]. At the same time, metabolic stress disrupts feedback mechanisms that normally limit inflammation, resulting in a failure to resolve immune activation[65].

Lactate plays a central role in this process by modulating both immune signaling and cellular metabolism[66]. Elevated lactate levels can influence the activity of transcription factors and signaling pathways associated with inflammation, thereby sustaining cytokine production and immune cell recruitment[67]. Additionally, lactate-mediated signaling may interfere with the resolution phase of inflammation, preventing the transition to tissue repair[68].

The interplay between metabolism and inflammation is further reinforced by the production of reactive oxygen species and other metabolic by-products[69]. These molecules contribute to oxidative stress, tissue damage, and activation of inflammatory pathways[70]. In chronic wounds, the accumulation of such metabolites creates a hostile microenvironment that perpetuates immune activation and impairs cellular function[34].

Importantly, metabolic control of inflammation is not unidirectional but involves complex feedback loops. Inflammatory signaling can further alter metabolic pathways, leading to increased glycolysis and lactate production, which in turn sustains inflammation[71]. This bidirectional relationship establishes a self-amplifying cycle that underlies the persistence of chronic wound pathology.

Understanding these mechanisms highlights the importance of targeting metabolic pathways as a therapeutic strategy[72]. By modulating glycolysis, lactate signaling, and associated metabolic processes, it may be possible to disrupt the cycle of persistent inflammation and restore immune balance[49]. Such approaches have the potential to shift the wound microenvironment from a state of chronic inflammation toward effective tissue repair.

3. Chronic wound pathophysiology of aetiology is the pathophysiology of pyroptosis of chronic wounds.

Pyroptosis is the predominant pathway of inflammatory cell death **Fig 1.** and also, has emerged as a major inflammatory cell death pathway supporting chronic wounds pathophysiologies[73]. While apoptosis is largely immunologically silent as this process progresses, pyroptosis induces rapid plasma membrane rupture and the secretion of potent pro-inflammatory mediators, which facilitate immune response amplification[74]. In the case of chronic wounds, where immune regulation is already compromised, disorganized pyroptotic signaling leads to increased tissue damage, extended inflammation and dysfunctional regenerative processes[37]. Moreover, modulated pyroptotic activity can promote host defense and wound debridement and demonstrates its dual and context-dependent role in tissue repair[75].

3.1. Activation of Inflammasome (NLRP3, Caspase-1)

Pyroptosis initiation is closely associated with the activation of intracellular multiprotein complexes called inflammasomes. Out of this, the NLRP3 inflammasome is the most well characterized in chronic inflammatory conditions like non-healing wounds[76]. NLRP3 acts as a cytosolic sensor that responds to numerous danger-associated molecular patterns and stressors, like reactive oxygen species, extracellular ATP, ion flux disturbances, and mitochondrial dysfunction which are all present in chronic wound environments[77]. Upon the activation of NLRP3, the protein undergoes conformational changes and these contribute to the recruitment of the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD domain) into a wound surface[78]. They collectively help form a signaling platform that recruits, activates, and binds pro-caspase-1. In the course of the autocatalytic cleavage of pro-caspase-1, active caspase-1 exists as the main effector enzyme in canonical pyroptosis[79]. The resulting activation of caspase-1 mediates two important stages of caspase-1 activation—the cytokine maturation and the cleavage of the gasdermin family[80]. In chronic wounds, chronic exposure to inflammatory stimuli induces the NLRP3 inflammasome to be chronically activated. The chronic activation is a complex biological syndrome and is caused by a myriad of reasons[81]: microbial input, oxidative stress, metabolic dysregulation, and cellular debris. Consequently, this leads to persistent caspase-1 activity and overactive inflammatory mediators production that led to the inhibition of inflammation resolution. Of considerable importance, the activation of NLRP3 has strong association with metabolic signals which, in particular, glycolysis and mitochondrial dysfunction, are known to support the correlation between immunometabolism and inflammatory cell death. As much as NLRP3-driven inflammasome activation contributes significantly to chronic inflammation, it is not entirely pathological[82]. Inflammasome signaling serves a protective role during early wound responses by signaling pathogen clearance and immune activation. Nonetheless, if inflammasome activity is not downregulated, chronic wounds are characterized by repeated activation of the immune system and tissue damage due to sustained inflammation[63]. This emphasizes the role of the temporal and spatial control of inflammasome signaling in regulating tissue homeostasis.

3.2. Gasdermin mediated membrane pore formation.

A hallmark of pyroptosis is the generation of membrane pores through the action of gasdermin proteins, and more specifically gasdermin D[83]. After activation by caspase-1, gasdermin D is cleaved into an N-terminal domain which has an important role in the pore formation and a C-terminal inhibitory domain[83]. The released N-terminal fragment moves to the plasma membrane where it undergoes oligomerization and the N-terminal fragment integrates into the lipid bilayer as large non-selective pores[84]. These pores are disruptors of cell integrity by facilitating the unregulated entry of ions and water, resulting in cell swelling and membrane disruption[85]. In addition to the induction of cell death, gasdermin-mediated pores function as translocation

mechanisms directing intracellular substances such as cytokines and damage-associated molecular patterns[86]. This release enhances inflammatory signaling and attracts extra immune cells to the site of injury. Under chronic wound conditions, extensive gasdermin activation leads to pervasive damage across all tissues[37]. Cytotoxic and pro-inflammatory molecules are released leading to local inflammation due to sustained generation of membrane pore formation from immune and resident cells[87]. Moreover, formation of pores compromises epithelial and stromal cell integrity, disrupting barrier function and delaying tissue regeneration[88]. Recent research indicates that the activity in gasdermin is regulated by regulatory mechanisms that control the formation of pores and pyroptotic properties and pyroptotic intensity[88, 89]. Lipid composition, cellular metabolism, and post-translational modifications mediate the gasdermin functionality, controlling membrane damage degree and membrane damages[90]. In chronic wounds, derangement of these regulatory factors leads to the uncontrolled pore formation and augmented tissue injury. Importantly, the gasdermin-mediated processes can offer beneficial outcomes under controlled conditions in addition to these normal functions[59]. The limited formation of pore walls can promote the release of signalling molecules that aid tissue remodeling and immune activation[91]. However, in chronic wounds, the balance of good and bad effects is disrupted and therefore leads to pathological effects.

3.3. Pyroptotic Secretome (IL-1β, IL-18) During Tissue Damage.

Pyroptotic secretome is the body's storage of cytokines, metabolites and intracellular substances produced upon pyroptotic cell death[73]. Especially, interleukin-1β and interleukin-18 are the most prominent and functionally important mediators among the above mentioned. These cytokines are produced as inactive precursors, and need caspase-1-mediated cleavage to be activated[20]. When released, they have potent pro-inflammatory actions, which promote immune cell recruitment, activation, and amplification of inflammatory signaling[92]. Higher IL-1β and IL-18 in wounds promote sustained inflammation and reduce healing. IL-1β can therefore promote expression of adhesion molecules and chemokines, promoting the uptake of neutrophils and macrophages[93]. Although this response is necessary for host defense, large and prolonged cytokine production results in tissue destruction, slowing down the transition to reparative phases. IL-18, like cytokines, also induces inflammatory responses and may contribute for different immune cell formation, creating an inflammatory process[94]. Notably, the pyroptotic secretome contains reactive oxygen species, extracellular ATP, nucleic acids, and other damage-associated molecular structures, beyond cytokines[95]. Secondary signals that activate inflammasomes, which in turn sustain inflammatory systems, are activated by these molecules[96]. The production of such factors forms a feedback loop with pyroptosis leading to increased immune activation, which maintains the pyroptotic signaling[97]. The total impact of the pyroptotic secretome is a highly inflammatory microenvironment that does not allow for tissue healing[98]. Chronic cytokine signaling derails fibroblast function, suppresses collagen deposition, and inhibits angiogenesis, all of which are essential for wound healing[99]. Moreover, high inflammation stimulates proteins to cleave matrix (inhibit repair) and decrease tissue integrity in the process[100]. Given its pathological role in chronic wounds, the pyroptotic secretome also exhibits context-specific beneficial effects. Controlled cytokines and other release can play a role in immunomodulating surveillance and will be beneficial in encouraging early wound healing[101]. But the uncontrolled magnitude and duration of this response turn a form of protective response into a driver for chronic inflammation. Pyroptosis represents crucial features of inflammatory signaling pathway between activated inflammasome expression, metabolic stress, and chronic wound pathophysiology and stress[102]. The NLRP3–caspase-1 axis triggers a series of events that will eventually disrupt membrane in a gasdermin-dependent manner and produce a powerful inflammatory secretome[103]. These processes are important to host defense but are altered when dysregulated in long-term (chronic) wounds result in sustained inflammation, local inflammation, tissue inflammation, and impaired repair[34]. It is therefore essential to address the specific regulatory processes underlying pyroptosis with respect to developing directed therapeutic strategies that can modulate the death of inflammatory cells while preserving their favorable functions.

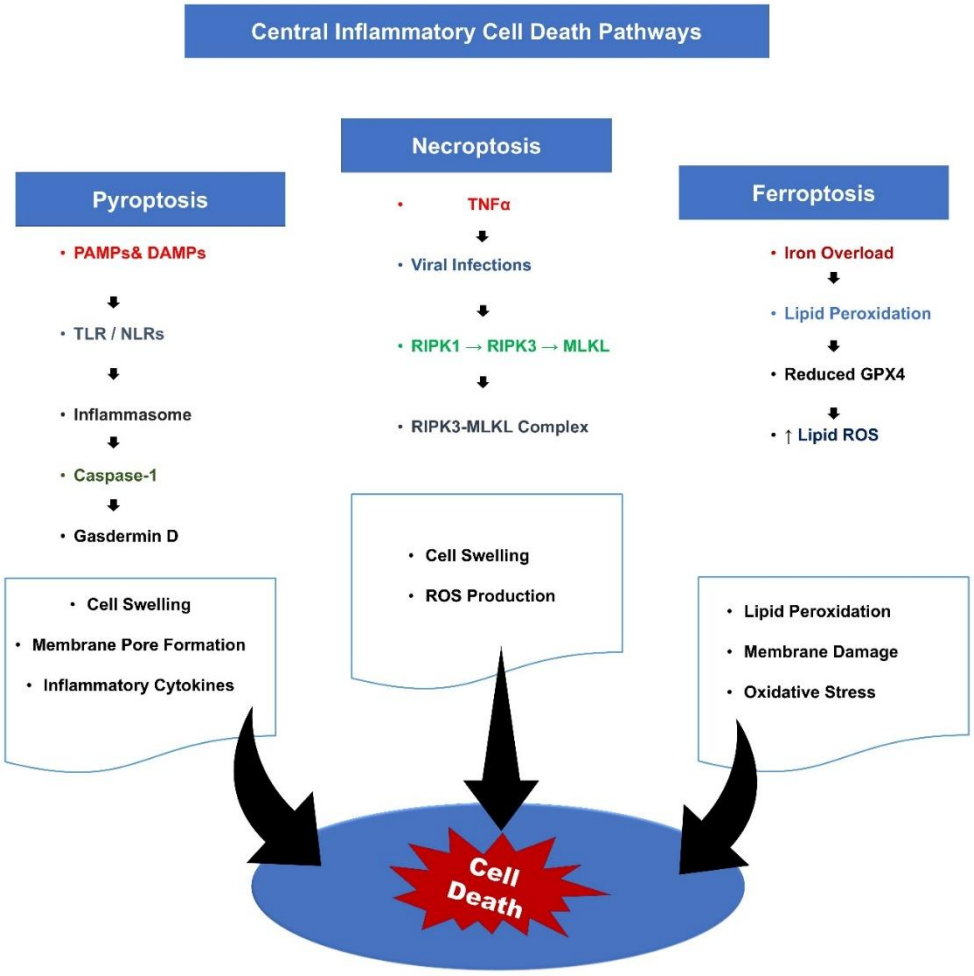


Fig 1. Central Inflammatory cell Death Pathway

4. Histone Lactylation as an Epigenetic Regulator in Chronic Wound Healing

Histone lactylation has recently emerged as a critical epigenetic modification linking cellular metabolism to gene expression, providing a mechanistic bridge between metabolic reprogramming and immune regulation[15]. In chronic wounds, where hypoxia and sustained inflammation drive profound metabolic alterations, lactylation represents a key regulatory node influencing immune cell function, inflammatory signaling, and tissue repair[45]. Unlike classical epigenetic modifications such as acetylation and methylation, histone lactylation is directly derived from lactate, positioning it as a unique metabolic-epigenetic interface that responds dynamically to the wound microenvironment.

4.1 Lactate as a Signaling Metabolite

Lactate accumulation is a hallmark of chronic wound environments, primarily driven by hypoxia-induced glycolytic metabolism[104]. Traditionally regarded as a metabolic by-product, lactate is now recognized as an active signaling molecule that modulates cellular behavior through both extracellular receptor-mediated pathways and intracellular mechanisms[14]. Elevated lactate levels influence immune cell function, angiogenesis, and fibroblast activity, thereby shaping the overall wound healing response[14].

At the intracellular level, lactate contributes to the formation of lactyl-CoA, a key intermediate required for histone lactylation[105]. This process enables the transfer of lactyl groups to lysine residues on histone proteins, altering chromatin structure and regulating gene transcription[106]. The accumulation of lactate in chronic wounds therefore not only reflects metabolic stress but actively drives epigenetic reprogramming[45]. This paradigm shift has redefined lactate as a central regulator of gene expression rather than a passive metabolic end product.

Moreover, lactate-mediated signaling exhibits context-dependent effects. Moderate lactate levels can promote angiogenesis and tissue repair, while excessive accumulation contributes to acidosis, impaired immune function, and persistent inflammation[107]. This dual role underscores the importance of tightly regulated lactate dynamics in maintaining tissue homeostasis.

4.2 Mechanisms of Histone Lactylation

Histone lactylation involves the covalent modification of lysine residues on histone tails, leading to changes in chromatin accessibility and transcriptional activity[105]. This modification is facilitated by enzymatic processes that remain under active investigation, although parallels with histone acetylation suggest the involvement of

acyltransferase-like enzymes[108]. The dynamic nature of lactylation allows cells to rapidly respond to metabolic fluctuations, integrating environmental cues into transcriptional programs.

In macrophages, histone lactylation has been shown to activate genes associated with tissue repair and immune resolution[109]. This modification promotes the expression of anti-inflammatory and pro-regenerative factors, enabling the transition from inflammatory to reparative phenotypes[10]. However, in chronic wounds, sustained metabolic stress leads to aberrant lactylation patterns, disrupting normal gene regulation and contributing to pathological inflammation.

Importantly, histone lactylation does not operate in isolation but interacts with other epigenetic modifications, including acetylation, methylation, and phosphorylation[16]. This crosstalk creates a complex regulatory network that fine-tunes gene expression in response to metabolic signals[110]. The balance between these modifications determines cellular outcomes, and disruption of this balance in chronic wounds contributes to impaired healing **Fig 2.**

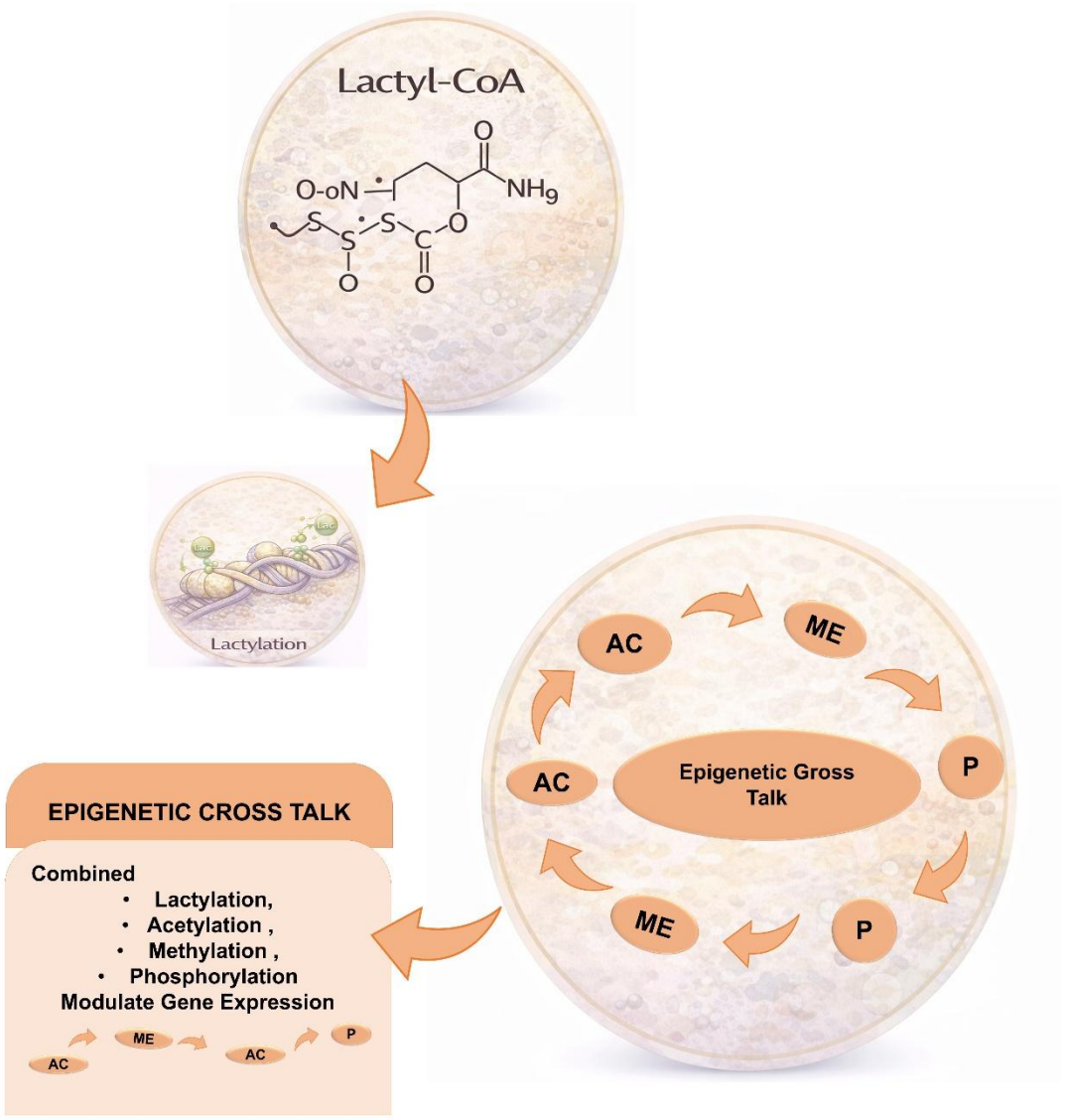


Fig 2. Epigenetic Cross Talk

4.3 Role in Macrophage Reprogramming and Immune Regulation

Macrophages are highly sensitive to metabolic cues and serve as primary mediators of lactylation-driven effects in chronic wounds[111]. The accumulation of lactate in the wound microenvironment influences macrophage phenotype by modulating epigenetic landscapes[45]. Histone lactylation promotes the expression of genes associated with tissue repair, angiogenesis, and extracellular matrix remodeling, facilitating the transition toward a pro-reparative state[112].

However, in chronic wounds, macrophage reprogramming is often incomplete or dysfunctional. Persistent lactate exposure, combined with ongoing inflammatory signaling, results in mixed or hybrid phenotypes that fail to effectively resolve inflammation[113]. This impaired reprogramming contributes to the maintenance of a pro-inflammatory environment and delays tissue regeneration.

Recent studies suggest that histone lactylation may serve as a timing mechanism that coordinates the transition from inflammation to repair[45]. Early in the wound healing process, glycolysis-driven lactate production supports inflammatory responses[114]. As lactate accumulates, lactylation-mediated gene activation promotes resolution and tissue repair. In chronic wounds, this temporal regulation is disrupted, leading to sustained inflammation and impaired healing outcomes[114, 115].

4.4 Integration with Inflammatory Signaling Pathways

Histone lactylation is closely linked to inflammatory signaling pathways, including those involved in cytokine production and inflammasome activation[16]. By regulating gene expression, lactylation influences the production of inflammatory mediators and the activation of immune pathways[16]. This integration positions lactylation as a key modulator of the balance between pro-inflammatory and anti-inflammatory responses.

Emerging evidence indicates that lactylation may directly or indirectly regulate components of inflammasome signaling, including pathways associated with pyroptosis[116]. Through epigenetic control of gene expression, lactylation can modulate the intensity and duration of inflammatory responses, thereby influencing tissue damage and repair. This interaction highlights the interconnected nature of metabolic, epigenetic, and inflammatory processes in chronic wounds.

4.5 Dysregulation in Chronic Wound Pathology

In chronic wounds, the regulatory functions of histone lactylation are disrupted due to sustained metabolic stress and persistent inflammatory signaling[117]. Excessive lactate accumulation leads to abnormal lactylation patterns, which can result in inappropriate gene activation or suppression[118]. This dysregulation contributes to impaired immune resolution, defective angiogenesis, and reduced collagen deposition.

Furthermore, the inability to properly regulate lactylation may exacerbate inflammatory pathways, reinforcing the cycle of chronic wound pathology[45]. The interplay between lactylation and other epigenetic modifications is also altered, further complicating gene regulation and cellular responses. These disruptions highlight the importance of maintaining epigenetic balance for effective wound healing.

4.6 Therapeutic Implications and Future Directions

Targeting histone lactylation represents a promising strategy for modulating immune responses and promoting tissue repair in chronic wounds[15]. Therapeutic approaches aimed at regulating lactate production, modulating epigenetic enzymes, or restoring metabolic balance may help normalize lactylation patterns and improve healing outcomes.

Phytochemical-based therapies and nanocarrier systems offer potential avenues for such interventions. These approaches can influence metabolic pathways, reduce excessive lactate accumulation, and modulate epigenetic modifications, including lactylation.[119] By targeting multiple aspects of the immunometabolic network, these strategies may provide more effective and sustained therapeutic benefits.

Despite these promising developments, significant challenges remain. The precise enzymatic mechanisms underlying histone lactylation are not fully understood, and the context-dependent effects of lactate complicate therapeutic targeting[120]. Additionally, the lack of specific biomarkers for lactylation limits the ability to monitor treatment responses and stratify patients[121].

Future research should focus on elucidating the molecular machinery governing lactylation, identifying key regulatory targets, and developing selective modulators[122]. Advanced technologies such as single-cell epigenomics and metabolomics will be essential for understanding the spatial and temporal dynamics of lactylation in wound environments. Furthermore, integrating lactylation studies with clinical research will be critical for translating these findings into effective therapies[123].

5. Lactylation–Pyroptosis Axis in Chronic Wound Immunometabolism

The convergence of metabolic reprogramming, epigenetic regulation, and inflammatory cell death defines a critical mechanistic axis governing chronic wound pathophysiology[21]. Within this framework, the lactylation–pyroptosis axis has emerged as a central integrative pathway linking hypoxia-driven metabolic alterations to inflammasome-mediated inflammatory responses. This axis represents a dynamic interface where metabolic intermediates directly influence gene expression and immune signaling, ultimately determining the balance between persistent inflammation and tissue regeneration[124]

5.1 Metabolic–Epigenetic Coupling in Chronic Wounds

Chronic wounds are characterized by sustained hypoxia, impaired perfusion, and elevated metabolic demand, leading to a persistent shift toward glycolytic metabolism[6]. This metabolic adaptation results in the accumulation of lactate, which serves not only as an energy by-product but also as a regulatory metabolite capable of influencing cellular signaling pathways[125]. The intracellular conversion of lactate into lactyl-CoA enables its utilization in histone lactylation, a post-translational modification that alters chromatin accessibility and transcriptional activity.

Histone lactylation provides a direct mechanistic link between metabolic state and gene expression. By modifying lysine residues on histone tails, lactylation promotes the transcription of genes associated with immune modulation, angiogenesis, and tissue repair[16]. In macrophages, this modification facilitates a transition toward reparative phenotypes by activating gene programs involved in extracellular matrix remodeling and growth factor production[33]. However, in chronic wounds, the sustained elevation of lactate disrupts the temporal regulation of lactylation, leading to aberrant transcriptional responses[27].

Importantly, lactylation does not function in isolation but interacts with other epigenetic modifications, including acetylation and methylation, forming a complex regulatory network[16]. This crosstalk determines the specificity and magnitude of gene expression changes. In the chronic wound microenvironment, the imbalance between these modifications contributes to dysregulated immune responses and impaired healing[126]. Thus, metabolic–epigenetic coupling represents a foundational component of the lactylation–pyroptosis axis **Fig 3.**

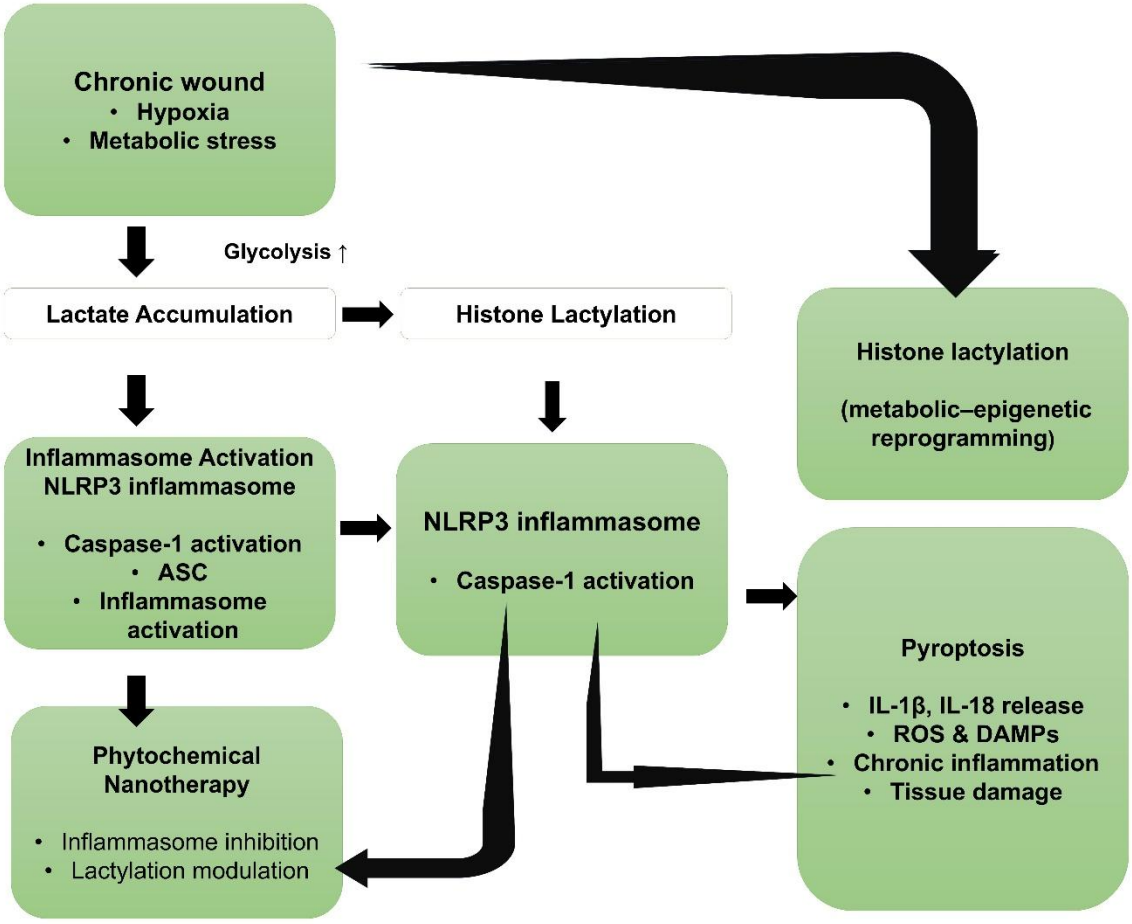


Fig 3. Lactylation -pyroptosis Axis

5.2 Regulation of Inflammasome Signaling by Lactylation

Inflammasome activation is a key driver of pyroptotic cell death and inflammatory amplification in chronic wounds. Among various inflammasome complexes, the NLRP3 inflammasome plays a predominant role due to its sensitivity to metabolic and stress-related signals[127]. Activation of NLRP3 leads to the recruitment of the adaptor protein ASC and subsequent activation of caspase-1, initiating pyroptotic signaling cascades.

Emerging evidence suggests that histone lactylation can modulate inflammasome activity at the transcriptional level[128]. By regulating the expression of genes encoding inflammasome components and associated signaling molecules, lactylation influences both the initiation and magnitude of inflammasome activation[31]. For instance, lactylation-dependent gene expression may enhance the production of anti-inflammatory mediators that suppress excessive inflammasome activation, thereby preventing uncontrolled tissue damage[129].

Conversely, dysregulated lactylation may contribute to heightened inflammasome sensitivity by promoting the expression of pro-inflammatory genes or by failing to activate regulatory pathways that limit inflammasome activity[130]. This dual role highlights the complexity of lactylation-mediated regulation and underscores its importance in maintaining immune balance.

In addition to transcriptional effects, metabolic intermediates associated with lactate metabolism can directly influence inflammasome activation through post-translational mechanisms[131]. Changes in intracellular pH,

redox status, and mitochondrial function—conditions influenced by lactate accumulation-affect the assembly and activation of inflammasome complexes[132]. These interactions further integrate metabolic signals into inflammatory pathways, reinforcing the central role of lactylation in regulating pyroptosis.

5.3 Pyroptotic Secretome and Feedback Amplification

Pyroptosis results in the release of a complex array of cytokines, metabolites, and damage-associated molecular patterns collectively referred to as the pyroptotic secretome[98]. Key components of this secretome include interleukin-1β, interleukin-18, reactive oxygen species, extracellular ATP, and nucleic acids[133]. These molecules act as potent signaling agents that amplify inflammatory responses and recruit additional immune cells to the wound site

The interaction between lactylation and the pyroptotic secretome establishes a feedback loop that perpetuates chronic inflammation[109]. Cytokines released during pyroptosis can influence metabolic pathways, promoting glycolysis and further lactate production[134]. This increase in lactate enhances histone lactylation, which in turn modulates gene expression related to inflammatory signaling[45]. The result is a self-sustaining cycle in which metabolic and inflammatory processes reinforce each other.

This feedback amplification is particularly evident in macrophages, where exposure to pyroptotic mediators alters metabolic activity and epigenetic states[135]. Lactylation-driven transcriptional changes may either attenuate or exacerbate inflammatory responses depending on the context and duration of signaling[136]. In chronic wounds, the failure to resolve this feedback loop leads to persistent immune activation and impaired tissue repair.

5.4 Impact on Cellular Crosstalk and Tissue Microenvironment

The lactylation–pyroptosis axis extends beyond individual cells to influence the broader wound microenvironment[45]. The release of cytokines and metabolic intermediates during pyroptosis affects multiple cell types, including fibroblasts, endothelial cells, and keratinocytes[98]. These interactions shape processes such as angiogenesis, extracellular matrix deposition, and epithelialization.

In fibroblasts, persistent inflammatory signaling inhibits collagen synthesis and promotes matrix degradation, contributing to impaired tissue remodeling[137]. Endothelial cells exposed to pro-inflammatory cytokines exhibit altered angiogenic responses, further limiting oxygen delivery and perpetuating hypoxia[138]. Keratinocyte proliferation and migration are similarly affected, delaying wound closure.

Lactylation-mediated gene regulation plays a critical role in modulating these cellular interactions. By influencing the expression of growth factors, cytokines, and extracellular matrix components, lactylation determines the functional state of cells within the wound microenvironment[16]. However, dysregulation of this process disrupts coordinated cellular responses, leading to a breakdown of tissue repair mechanisms

5.5 Transition from Inflammation to Regeneration

Effective wound healing requires a tightly regulated transition from inflammatory to proliferative and remodeling phases[139]. The lactylation–pyroptosis axis plays a pivotal role in orchestrating this transition by integrating metabolic and immune signals[109]. Under physiological conditions, lactate accumulation during early inflammation promotes lactylation-driven gene expression that facilitates resolution and tissue repair.

However, in chronic wounds, this transition is disrupted due to sustained metabolic stress and persistent inflammasome activation[63]. Excessive pyroptotic signaling maintains a pro-inflammatory environment, while aberrant lactylation fails to activate reparative gene programs effectively[140]. This imbalance prevents the progression to regenerative phases, resulting in chronic non-healing wounds.

Restoring the balance within this axis is therefore essential for promoting wound resolution. Therapeutic strategies that modulate lactylation and pyroptosis may help re-establish the conditions necessary for effective tissue repair[45].

5.6 Therapeutic Targeting of the Lactylation–Pyroptosis Axis

The integrative nature of the lactylation–pyroptosis axis makes it an attractive target for therapeutic intervention. Rather than targeting individual pathways in isolation, modulating this axis offers a comprehensive approach to restoring immune and metabolic balance in chronic wounds[141].

Phytochemical-based therapies have gained attention due to their ability to simultaneously influence metabolic and inflammatory pathways[142]. Many plant-derived compounds exhibit anti-inflammatory properties and can modulate glycolytic metabolism, thereby reducing lactate accumulation[143]. These compounds may also influence epigenetic modifications, including histone lactylation, by altering the availability of metabolic intermediates.

The incorporation of phytochemicals into nanocarrier systems further enhances their therapeutic potential[144]. Nanocarriers enable targeted delivery to immune cells within the wound microenvironment, improving bioavailability and reducing systemic toxicity[145]. By delivering modulators of lactylation and inflammasome activity directly to affected tissues, these systems can effectively disrupt the pathological feedback loop underlying chronic inflammation.

Additionally, emerging therapeutic strategies include the development of small molecules targeting inflammasome components, epigenetic regulators, and metabolic enzymes[146]. These approaches aim to fine-tune the balance between inflammatory and reparative processes rather than completely suppressing immune responses.

5.7 Challenges and Future Perspectives

Despite the promising potential of targeting the lactylation–pyroptosis axis, several challenges remain. The precise molecular mechanisms governing histone lactylation are not fully elucidated, and the enzymes responsible for this modification require further characterization. Moreover, the context-dependent nature of pyroptosis complicates therapeutic targeting, as both excessive and insufficient activation can be detrimental[26].

Another major challenge is the heterogeneity of chronic wounds, which vary in etiology, severity, and patient-specific factors. This variability necessitates personalized approaches to therapy, guided by biomarkers that reflect the immunometabolic state of the wound.

Future research should focus on elucidating the molecular interactions within the lactylation–pyroptosis axis, identifying key regulatory nodes, and developing targeted interventions. Advanced technologies such as single-cell sequencing and metabolomic profiling will be instrumental in understanding the spatial and temporal dynamics of this axis.

6. Phytochemicals as Immunometabolic Modulators

Phytochemicals have emerged as potent modulators of immunometabolic pathways, offering a multifaceted approach to correcting the dysregulated microenvironment characteristic of chronic wounds[147]. Unlike conventional therapeutics that often target single pathways, plant-derived bioactive compounds exert pleiotropic effects by simultaneously influencing metabolic processes, inflammatory signaling, and epigenetic regulation. This integrative capacity positions phytochemicals as promising candidates for modulating the lactylation–pyroptosis axis and restoring immune homeostasis in non-healing wounds[148]. **Table: 1**

S.no	Phytochemical	Natural Source	Primary Target Pathway	Mechanism of Action	Immunometabolic Effect	References
1	Curcumin	Curcuma longa (turmeric)	NF-κB, NLRP3 inflammasome	Inhibits NF-κB activation; suppresses inflammasome assembly	Reduces IL-1β, IL-18; attenuates pyroptosis	[149]
2	Resveratrol	Grapes, berries	SIRT1, AMPK	Activates SIRT1; enhances mitochondrial function	Reduces oxidative stress; promotes anti-inflammatory macrophage phenotype	[150]
3	Quercetin	Onions, apples	MAPK, NF-κB	Inhibits MAPK signaling; downregulates cytokine expression	Decreases TNF-α, IL-6; limits chronic inflammation	[151]

4	Epigallocatechin gallate (EGCG)	Green tea	Nrf2, NF-κB	Activates antioxidant pathways; suppresses NF-κB	Enhances redox balance; reduces inflammatory signaling	[152]
5	Berberine	Berberis species	AMPK, glycolysis	Modulates glucose metabolism; inhibits glycolytic flux	Reduces lactate accumulation; regulates metabolic stress	[153]
6	Genistein	Soybeans	PI3K/Akt, NF-κB	Inhibits tyrosine kinases; modulates signaling pathways	Promotes tissue repair; reduces inflammation	[154]
7	Luteolin	Celery, parsley	NLRP3 inflammasome	Inhibits inflammasome activation and ROS generation	Suppresses pyroptotic signaling; reduces cytokine release	[155]
8	Apigenin	Chamomile, parsley	STAT3, NF-κB	Inhibits transcriptional activation of inflammatory genes	Enhances anti-inflammatory response; supports healing	[156]
9	Baicalin	Scutellaria baicalensis	NLRP3, ROS pathways	Reduces ROS-mediated inflammasome activation	Limits pyroptosis; improves tissue repair environment	[157]
10	Sulforaphane	Cruciferous vegetables	Nrf2, epigenetic enzymes	Activates Nrf2; modulates histone modification enzymes	Regulates oxidative stress and epigenetic balance	[158]

Table :1 Phytochemicals as Immunometabolic Modulators

6.1 Natural Compounds Targeting Inflammasome Pathways

A growing body of evidence indicates that several phytochemicals can directly or indirectly suppress inflammasome activation, particularly the NLRP3 inflammasome, which plays a central role in pyroptosis[159]. These compounds interfere with upstream signaling events such as reactive oxygen species generation, mitochondrial dysfunction, and ionic fluxes that are essential for inflammasome assembly[128]. By attenuating these triggers, phytochemicals reduce the activation of caspase-1 and subsequent cleavage of gasdermin proteins, thereby limiting pyroptotic cell death[160].

In addition to inhibiting inflammasome activation, phytochemicals can modulate transcriptional pathways that regulate the expression of inflammasome components[161]. Many plant-derived compounds influence signaling cascades such as NF-κB and MAPK pathways, which are critical for priming inflammasome activation[162]. By suppressing these pathways, phytochemicals reduce the production of pro-inflammatory cytokine precursors, including pro-interleukin-1β and pro-interleukin-18, thereby diminishing the magnitude of inflammatory responses[163].

Importantly, the effects of phytochemicals on inflammasome pathways are often context-dependent, allowing for partial modulation rather than complete inhibition[164]. This selective regulation is advantageous, as it preserves essential immune functions such as pathogen clearance while preventing excessive inflammation. In chronic wounds, where persistent inflammasome activation contributes to tissue damage, such balanced modulation is particularly beneficial.

6.2 Regulation of Lactate Metabolism and Epigenetics

Beyond their effects on inflammatory signaling, phytochemicals play a significant role in regulating metabolic pathways that influence lactate production and epigenetic modifications. Chronic wound environments are characterized by enhanced glycolysis and excessive lactate accumulation, which drive histone lactylation and alter

gene expression[45, 165]. Phytochemicals can modulate these processes by influencing key metabolic enzymes and pathways involved in glucose metabolism[48, 166].

Certain plant-derived compounds have been shown to reduce glycolytic flux, thereby limiting lactate production and mitigating metabolic stress. By restoring metabolic balance, these compounds indirectly regulate histone lactylation, preventing aberrant epigenetic reprogramming associated with chronic inflammation[167]. Additionally, some phytochemicals may directly interact with epigenetic machinery, influencing histone-modifying enzymes and altering chromatin accessibility.

The ability of phytochemicals to modulate both metabolism and epigenetics underscores their role as integrators of immunometabolic regulation. By targeting the upstream drivers of lactylation, these compounds can influence downstream gene expression patterns, promoting a shift from pro-inflammatory to reparative cellular states[168]. This effect is particularly relevant in macrophages, where metabolic cues dictate functional phenotype and determine the progression of wound healing.

6.3 Anti-Inflammatory and Pro-Regenerative Signaling

Phytochemicals exert broad anti-inflammatory effects by modulating multiple signaling pathways involved in immune activation[169]. These compounds can suppress the production of pro-inflammatory cytokines, inhibit the activation of transcription factors associated with inflammation, and enhance the expression of anti-inflammatory mediators[170]. Through these mechanisms, phytochemicals reduce the intensity and duration of inflammatory responses in chronic wounds.

In parallel, phytochemicals promote pro-regenerative signaling pathways that support tissue repair and remodeling[171]. They can enhance angiogenesis by upregulating growth factors such as vascular endothelial growth factor, stimulate fibroblast proliferation and collagen synthesis, and facilitate keratinocyte migration and re-epithelialization[172]. These effects contribute to the restoration of tissue integrity and accelerate wound closure.

The interplay between anti-inflammatory and pro-regenerative effects is critical for effective wound healing. Phytochemicals achieve this balance by modulating key signaling networks that coordinate immune responses and tissue repair[173]. For instance, the suppression of excessive inflammation creates a favorable environment for regenerative processes, while the activation of repair pathways ensures the restoration of functional tissue architecture[10].

Furthermore, phytochemicals can influence the redox state of the wound microenvironment by reducing oxidative stress and enhancing antioxidant defenses[171]. This effect not only protects cells from damage but also regulates signaling pathways associated with inflammation and metabolism. By maintaining redox balance, phytochemicals contribute to the stabilization of the immunometabolic landscape.

7. Phytochemical Nanotherapy Strategies

The therapeutic potential of phytochemicals in chronic wound management is often limited by poor solubility, instability, rapid degradation, and low bioavailability[174]. To overcome these challenges, nanotechnology-based delivery systems have emerged as powerful platforms for enhancing the efficacy and precision of phytochemical interventions[175]. Phytochemical nanotherapy integrates bioactive plant-derived compounds with engineered nanocarriers, enabling targeted modulation of immunometabolic pathways, including the lactylation–pyroptosis axis[176]. By improving delivery efficiency and controlling pharmacokinetics, these systems offer a promising strategy for addressing the complex pathophysiology of chronic wounds.

7.1 Nanocarrier Systems (Nanovesicles and Nanoformulations)

Nanocarrier systems encompass a diverse range of platforms designed to encapsulate, protect, and deliver therapeutic agents. Among these, lipid-based nanovesicles, polymeric nanoparticles, nanoemulsions, and inorganic-organic hybrid systems have gained significant attention for wound healing applications[177]. These nanostructures provide a protective environment that shields phytochemicals from degradation and enhances their stability under physiological conditions[178].

Nanovesicles, including liposomes and plant-derived extracellular vesicle-like structures, are particularly advantageous due to their biocompatibility and ability to mimic biological membranes[179]. Their lipid bilayer structure facilitates efficient encapsulation of both hydrophilic and hydrophobic compounds, enabling versatile delivery of diverse phytochemicals. Polymeric nanoparticles, on the other hand, offer tunable properties such as size, surface charge, and degradation rate, allowing for precise control over drug release profiles.

Nanoformulations can also be engineered to incorporate multiple therapeutic agents, enabling synergistic effects. For example, combining anti-inflammatory phytochemicals with antioxidants or metabolic modulators within a single nanocarrier can simultaneously target multiple aspects of chronic wound pathology[180]. This multifunctional approach aligns with the complex nature of the lactylation–pyroptosis axis, which involves interconnected metabolic, epigenetic, and inflammatory pathways.

7.2 Targeted Delivery to Immune Cells in Wounds

One of the key advantages of nanocarrier-based systems is their ability to achieve targeted delivery to specific cell populations within the wound microenvironment. Chronic wounds are characterized by heterogeneous cellular composition, including macrophages, neutrophils, fibroblasts, and endothelial cells, each contributing differently to disease progression and healing[181]. Targeting immune cells, particularly macrophages, is critical for modulating inflammatory responses and promoting tissue repair.

Nanocarriers can be functionalized with surface ligands that recognize and bind to receptors expressed on target cells. For instance, mannose or other carbohydrate moieties can be used to target macrophage-specific receptors, facilitating selective uptake. Similarly, antibody-based or peptide-based targeting strategies can enhance specificity and reduce off-target effects[182].

In addition to active targeting, passive targeting mechanisms such as enhanced permeability and retention effects can facilitate the accumulation of nanocarriers at wound sites[183]. The disrupted vasculature and increased vascular permeability characteristic of chronic wounds create a favorable environment for nanoparticle retention[184]. This localized accumulation enhances therapeutic concentration at the site of injury while minimizing systemic exposure.

Targeted delivery is particularly important for modulating the lactylation–pyroptosis axis, as it allows for direct intervention in immune cells that drive inflammatory signaling[140]. By delivering phytochemicals to these cells, nanocarriers can influence metabolic pathways, epigenetic modifications, and inflammasome activity, thereby restoring immune balance.

7.3 Controlled Release and Bioavailability Enhancement

Controlled release is a defining feature of nanocarrier-based drug delivery systems, enabling sustained and localized therapeutic effects. By regulating the release kinetics of encapsulated phytochemicals, nanocarriers can maintain optimal drug concentrations within the wound microenvironment over extended periods[185]. This is particularly important in chronic wounds, where prolonged treatment is often required to achieve effective healing.

The release profile of nanocarriers can be tailored through material selection, particle size, and surface modifications. Biodegradable polymers, for example, allow for gradual degradation and controlled drug release, while stimuli-responsive systems can release their payload in response to specific environmental triggers such as pH, temperature, or enzymatic activity. Chronic wound environments, characterized by acidic pH and elevated enzyme levels, provide opportunities for designing responsive nanocarriers that release therapeutic agents selectively at the site of pathology[186].

Enhancing bioavailability is another critical advantage of nanotherapy. Encapsulation of phytochemicals improves their solubility and protects them from rapid metabolism and clearance. This results in increased systemic stability and improved therapeutic efficacy. Furthermore, nanocarriers can facilitate cellular uptake through endocytosis, ensuring efficient delivery of bioactive compounds to intracellular targets[187].

The combination of controlled release and enhanced bioavailability enables sustained modulation of key pathways involved in chronic wound pathology[188]. By maintaining consistent therapeutic levels, nanocarriers can effectively disrupt the feedback loops associated with the lactylation–pyroptosis axis, reducing inflammation and promoting tissue regeneration.

Phytochemical nanotherapy represents a transformative approach to chronic wound treatment by addressing the limitations of conventional phytochemical delivery[189]. Through the use of advanced nanocarrier systems, targeted delivery strategies, and controlled release mechanisms, these platforms enhance the stability, bioavailability, and therapeutic precision of plant-derived compounds[190]. By enabling direct modulation of immunometabolic pathways, including the lactylation–pyroptosis axis, phytochemical nanotherapy offers a comprehensive strategy for restoring immune balance and promoting tissue repair[191]. Continued advancements in nanotechnology and a deeper understanding of wound immunometabolism will be essential for translating these innovations into clinically effective therapies.

8. Translational Challenges and Future Directions

Nonetheless, although significant improvements in the knowledge of the lactylation–pyroptosis axis have been made and phytochemical nanotherapy strategies have emerged, the transfer of this knowledge onto clinical treatments for chronic wounds remains a challenging problem[140]. In view of the intricacy of wound pathophysiology and the individual variability in terms of patient-specific factors, a more integrative and sensitive approach is required in the direction of therapeutic development. Lack of mechanistic understanding of histone lactylation and its corresponding regulatory machinery has been the most profound obstacle which has been among the main hurdles faced. Although lactylation itself has been acknowledged as a critical epigenetic modification, the enzymes responsible for its addition and removal are not yet entirely well characterized. This makes it challenging to develop targeted interventions capable of selectively regulating lactylation without disturbing other epigenetic mechanisms[192]. Likewise, that pyroptosis is context-dependent presents a challenge for therapy, as not only does excessive activation of this pathway but also inhibition of pyroptosis can have deleterious effects. Therefore, controlling inflammasome activity is still a key aim. The heterogeneity of chronic wounds due to a range of disease causes (diabetes, vascular insufficiency, and pressure-related injury) represents another major limitation. All these ailments present different profiles in terms of immunometabolism that could affect activity of immune cells, metabolism, and tissue repair mechanisms[98]. The variability highlights the importance of therapy based on biomarkers to modulate the metabolic and inflammatory state of the wound microenvironment with respect to the particular therapeutic strategy. Nevertheless, reliable and clinically relevant biomarkers to monitor lactylation and pyroptosis are still lacking. From the nanotherapeutical design standpoint, scaling up, safety as well as regulations are additional hurdles. Although nanocarrier systems have exhibited promising preclinical findings, their production on a large scale in a predictable quality and reproducibility has been challenging. Moreover, long-term safety statistics are scarce, especially for the possible build-ups of nanomaterials and to what extent nanomaterials may interact with biological systems[193]. Regulatory

environments in nanomedicine remain developing, which can delay the clinical translation and approval. Nanodelivery effectiveness and specificity will also need to be improved. Although progress has been achieved with ligand-based targeting and stimuli-responsive approaches, the precise targeting of different immune cell populations within the complex wound microenvironment is challenging. These off-target and variable nanoparticle uptake may compromise therapeutic efficacy and increase risk of unintended effects. Aimed at integrative and multidisciplinary modalities using an integrated approach of immunology, metabolism, epigenetics, and nanotechnology deserves research. Advanced analytical techniques, including single-cell transcriptomics, spatial metabolomics, and high-resolution imaging, are critical for dissecting cellular and molecular dynamics within the wound context. These approaches help to explore cell-specific responses and target key regulatory nodes (notably the lactylation–pyroptosis axis) across the lactylation–pyroptosis axis. Moreover, it will be crucial to develop biomarker-driven strategies for personalized medicine. Signature discovery of metabolic imbalance, inflammasome activation, and epigenetic dysregulation associations may be used to help stratify and select for patient treatment stratification. The use of such strategies is likely to increase therapy specificity and thus therapeutic efficacy. Last but not least, phytochemicals, nanocarriers, and traditional treatments as combination therapies combining these three together could be the most effective treatment for resolving the chronic wounds of chronic lesions[194]. In targeting these pathways in parallel, they are able to overcome the shortcomings of single-modality therapies providing enhanced stability and long-lasting therapeutic effect. The translation of immunometabolic knowledge into the field of medicine will need to address formidable scientific and technological issues. The next-generation approach which fills the gaps in mechanistic understanding, enhances the design of nanocarriers, and uses personalized and integrative methods could be the means to realize the full potential of targeting the lactylation–pyroptosis axis. These developments could potentially revolutionize chronic wound care and lead to clinically significant improvement in patient outcomes.

CONCLUSION

Chronic wounds are a complicated disease state characterised by metabolic derangements, chronic inflammation, and defective tissue regeneration. A new concept, the lactylation–pyroptosis axis, emerges from these processes, uniting them and connecting hypoxia-induced metabolic reprogramming to epigenetic control and inflammasome-mediated cell death. Histone lactylation is a vital mediator that converts metabolic signals into changes in gene expression, and pyroptosis accelerates inflammatory events through cytokines released as well as other damage-associated signaling signals. The imbalance occurs between these processes, and as such, contributes to the establishment of a non-resolving inflammatory microenvironment leading to an adverse outcome in the area of wound healing. Targeting this axis is a new, therapeutically motivated, mechanism-driven approach. Because phytochemicals have an inherent capacity to modulate metabolic pathways, epigenetic alterations, and inflammatory signaling, they offer a promising avenue of treatment. Integration of these compounds into nanocarrier systems further boosts their therapeutic value by increasing their stability, bioavailability, and targeted delivery to immune cells within the wound microenvironment. Such strategies promote the exact modulation of the lactylation–pyroptosis axis and restore the immune balance and tissues. Despite this progress, more work is necessary to fully clarify the molecular mechanism of lactylation and how it relates to pyroptotic pathways, as well as translate the therapeutic strategy into practice and put into practice a nanotherapy method. Mechanistic validation, biomarker design, and personalized and molecular approaches in the future will be key. Together, promotion of this integrative paradigm has great potential for rethinking chronic wound management and discovering efficient, mechanism-dependent therapeutic alternatives.

REFERENCES

[1] Maheshwari G. Chronic wounds: A rising public health concern. Wounds Apac. 2024;7:7-11.
[2] De Francesco F, Ogawa R. From time to timer in wound healing through the regeneration. Cell Biology and Translational Medicine, Volume 22: Stem Cell Driven Approaches in Regeneration and Repair. 2024:1-18.
[3] Cavallo I, Sivori F, Mastrofrancesco A, Abril E, Pontone M, Di Domenico EG, et al. Bacterial biofilm in chronic wounds and possible therapeutic approaches. Biology. 2024;13:109.
[4] Jęczmyk A, Krych S, Jekiełek M, Jurkiewicz M, Kowalczyk P, Kramkowski K, et al. Wound healing complications after sternotomy—causes, prevention, and treatment—a new look at an old problem. Journal of Clinical Medicine. 2024;13:7431.
[5] Wang C, Shirzaei Sani E, Shih C-D, Lim CT, Wang J, Armstrong DG, et al. Wound management materials and technologies from bench to bedside and beyond. Nature Reviews Materials. 2024;9:550-66.
[6] Hunt M, Torres M, Bachar-Wikström E, Wikström JD. Multifaceted roles of mitochondria in wound healing and chronic wound pathogenesis. Frontiers in cell and developmental biology. 2023;11:1252318.
[7] Susarla S, Erbay MI, Johanis A, Abuelazm M, Ghanem AK. Role of Metabolism in Supporting Immune Responses. Metabolic Dynamics in Host-Microbe Interaction: Springer; 2025. p. 151-86.
[8] Wang Z, Zhao F, Xu C, Zhang Q, Ren H, Huang X, et al. Metabolic reprogramming in skin wound healing. Burns & Trauma. 2024;12:tkad047.
[9] Li Y, Cao Q, Hu Y, He B, Cao T, Tang Y, et al. Advances in the interaction of glycolytic reprogramming with lactylation. Biomedicine & Pharmacotherapy. 2024;177:116982.

[10] Wang L, Yang K, Xie X, Wang S, Gan H, Wang X, et al. Macrophages as multifaceted orchestrators of tissue repair: bridging inflammation, regeneration, and therapeutic innovation. Journal of Inflammation Research. 2025:8945-59.
[11] Schilrreff P, Alexiev U. Chronic inflammation in non-healing skin wounds and promising natural bioactive compounds treatment. International journal of molecular sciences. 2022;23:4928.
[12] Pokhreal D, Crestani B, Helou DG. Macrophage implication in IPF: updates on immune, epigenetic, and metabolic pathways. Cells. 2023;12:2193.
[13] Llibre A, Kucuk S, Gope A, Certo M, Mauro C. Lactate: A key regulator of the immune response. Immunity. 2025;58:535-54.
[14] Tian Z, Zhang K, Sheng S, Kan C, Han F, Sun X. The Role of Lactate Metabolism in Tumors: From Metabolic Byproduct to Signaling Molecule. American Journal of Clinical Oncology. 2025:10.1097.
[15] Zhang J, Wu D, Zeng F, Gu H, Li C, Cata JP, et al. Lactate metabolic reprogramming and histone lactylation modification in sepsis. International journal of biological sciences. 2025;21:5034.
[16] Hu Y, He Z, Li Z, Wang Y, Wu N, Sun H, et al. Lactylation: the novel histone modification influence on gene expression, protein function, and disease. Clinical epigenetics. 2024;16:72.
[17] Fang Z, song Zhu G, Nie DY, Xu B. Lactylation modification-a bridge between sepsis and macrophage metabolic reprogramming. Frontiers in Immunology. 2026;17:1738765.
[18] Harithpriya K, Kaussikaa S, Kavyashree S, Geetha A, Ramkumar KM. Pathological insights into cell death pathways in diabetic wound healing. Pathology-Research and Practice. 2024;264:155715.
[19] Liu Y, Pan R, Ouyang Y, Gu W, Xiao T, Yang H, et al. Pyroptosis in health and disease: mechanisms, regulation and clinical perspective. Signal transduction and targeted therapy. 2024;9:245.
[20] Tahmasebi S, Alimohammadi M, Khorasani S, Rezaei N. Pro-tumorigenic and anti-tumorigenic roles of pro-inflammatory cytokines in cancer. Cancer Immunology: The Immune System and Tumor: Springer; 2025. p. 529-53.
[21] Mamun AA, Shao C, Geng P, Wang S, Xiao J. Recent advances in molecular mechanisms of skin wound healing and its treatments. Frontiers in immunology. 2024;15:1395479.
[22] Zhang Y, Zhao D, Wang T, Li P, Yu D, Gao H, et al. Pyroptosis, a double-edged sword during pathogen infection: a review. Cell Death Discovery. 2025;11:289.
[23] Sendtner N, Seitz R, Brandl N, Müller M, Gülow K. Reactive oxygen species across death pathways: Gatekeepers of apoptosis, ferroptosis, pyroptosis, paraptosis, and beyond. International Journal of Molecular Sciences. 2025;26:10240.
[24] Cooper KN, Potempa J, Bagaitkar J. Dying for a cause: The pathogenic manipulation of cell death and efferocytic pathways. Molecular oral microbiology. 2024;39:165-79.
[25] Xia J, Jiang S, Dong S, Liao Y, Zhou Y. The role of post-translational modifications in regulation of NLRP3 inflammasome activation. International Journal of Molecular Sciences. 2023;24:6126.
[26] Zhang X, Luo J, Zhang Z, Yu Y, He J, Zuo Z, et al. Role of lactylation modification in regulating lytic cell death. Frontiers in Oncology. 2026;16:1718636.
[27] Hu B, Li X, Li Y, Chai S, Jin M, Zhang L. A comprehensive characterization of metabolic signatures—hypoxia, glycolysis, and lactylation—in non-healing diabetic foot ulcers. Frontiers in Molecular Biosciences. 2025;12:1593390.
[28] Ma F, Yu W. The roles of lactate and lactylation in diseases related to mitochondrial dysfunction. International Journal of Molecular Sciences. 2025;26:7149.
[29] Mehta P. Inflammation and the Immune System: A Delicate Balance. Cell Death Regulation in Pathology: IntechOpen; 2025.
[30] Xiong Y, Mi B-B, Lin Z, Hu Y-Q, Yu L, Zha K-K, et al. The role of the immune microenvironment in bone, cartilage, and soft tissue regeneration: from mechanism to therapeutic opportunity. Military Medical Research. 2022;9:65.
[31] Kunamalla RP, Panagal M, Palanisamy CP. Green-engineered multiscale starch/PVA nanofibrous scaffolds embedded with CuO nanoparticles from Sargassum ilicifolium for potent antimicrobial performance. Genetics and Molecular Research. 2026; 25 (13s): 1-8.
[32] Daniel Raja FS, Abraham L, Rangasamy K, Saikia K, Rathankumar AK, Mironescu M, Mironescu I, Palanisamy CP, Kanniappan GV. Next-Generation Microbiome Therapeutics: Psychobiotics and Fecal Microbiota Transplants (FMT) for Mental Health Treatment. Frontiers in Cellular and Infection Microbiology. 2026; 16: 1719357.
[33] Dharmaprakash S, Gunasekaran VP, Sivaramakrishnan R, Kanniappan GV, Jayaraman S, Mironescu M, Rajabathar JR, Mironescu ID, Palanisamy CP. Marine macroalgae-mediated ultrasonic-assisted green synthesis of CuO nanoparticles embedded in starch/PVA electrospun nanoscaffolds for in vitro α-amylase and α-glucosidase inhibitory activity. Scientific Reports. 2026.
[34] Surendran N, Chandrasekaran G, Raju MV, Chandrasekaran MK, Ahalliya RM, Palanisamy CP, Kanniappan GV, Arcot R, Alharbi NS, Thiruvengadam M. Anti-inflammatory potential of ethanolic extract of Maranta arundinacea L.: Insights from COX-2 modulation and oxidative stress analysis. South African Journal of Botany. 2026; 195: 142-151.

[35] Pei J, Senthilkumar MV, Hessini K, Subramaniyam S, Sivaramakrishnan R, Kanniappan GV, Jayaraman S, Palanisamy CP. Green fabrication of starch/PVA/CuO nanoscaffolds using marine macroalgae extract for enhanced anti-inflammatory activity. Sustainable Chemistry and Pharmacy. 2026; 51: 102397.
[36] Balasubramanian V, Loganathan L, Muthuswamy K, Viswanathan TM, Raju MV, Chandrasekaran MK, Ahalliya RM, Poorasamy J, Palanisamy CP, Dominic S, Kanniappan GV. Anticancer therapeutic efficacy of PEGylated β-galactosidase from Aspergillus terreus in DMBA-induced breast cancer: Toxicological, molecular and histopathological evaluation in Wistar rats. International Journal of Biological Macromolecules. 2026; 360: 151856.
[37] Jayaraman S, Eswaran A, Rajagopal P, Palanisamy CP, Veerakumar P, Veeraraghavan VP, Sirasanagandla SR. Neuroendocrine-associated epigenetic factors in cellular senescence: mechanisms and therapeutic implications. Biogerontology. 2026; 27(2): 64.
[38] Ponnusamy B, Rajagopal P, Palanisamy CP, Veeraraghavan VP, Jayaraman S. Mechanistic Exploration of the anticancer activity of Justicia adhatoda Plant Leaf Ethanolic Extract against Colon Cancer Cells: An in silico and in vitro Approach. Asian Pacific Journal of Cancer Prevention. 2026; 27(3): 1069-1080.
[39] Pei J, Saran VS, Sivaramakrishnan R, Kanniappan GV, Pandurangan V, Jayaraman S, Dhayalan VK, Mironescu M, Mironescu ID, Palanisamy CP. Ultrasonic-assisted, Sargassum ilicifolium (brown marine macroalgae)-mediated biogenic synthesis of CuO nanoparticles incorporated in starch/PVA electrospun nanoscaffolds: In vitro safety and antioxidant efficacy assessment. Bioorganic Chemistry. 2026; 173: 109679.
[40] Raj MAPA, Subramaniyam S, Kanniappan GV, Jayaraman S, Palanisamy CP. Sustainable fabrication of starch/PVA/CuO electrospun nanoscaffolds from Turbinaria ornata (marine macroalgae) extract: Physicochemical characterization and antidiabetic evaluation. Kuwait Journal of Science. 2026; 53(2): 100545.
[41] Pei J, Ganesh NS, Subramaniyam S, Sivaramakrishnan R, Kanniappan GV, Jayaraman S, Palanisamy CP. Sustainable fabrication of starch/PVA/CuO electrospun nanoscaffolds from Padina tetrastromatica (Brown macroalgae) extract: Physicochemical characterization and antidiabetic assessment. Sustainable Chemistry One World. 2026; 9: 100195.
[42] Sakthiraj A, Sivaramakrishnan R, Subramaniyam S, Kanniappan GV, Pandurangan V, Jayaraman S, Dhayalan VK, Mironescu M, Mironescu ID, Palanisamy CP. Starch/PVA electrospun nanoscaffolds loaded with ultrasonic-assisted green-synthesis of CuO nanoparticles from marine macroalgae (Gracilaria corticata) extract: Cytotoxicity and antioxidant analysis. Chemical Physics Impact. 2026; 12: 101018.
[43] Raju M, Chandrasekaran MK, Loganathan L, Ahalliya RM, Mironescu M, Mironescu ID, Palanisamy CP, Kanniappan GV. Lipid remodeling and ferroptosis in phosphatidylcholine-mediated tumor–stroma crosstalk. Frontiers in Molecular Biosciences. 2026; 13: 1742305.
[44] Kunamalla R, Panagal M, Palanisamy CP. Biogenic synthesis and fabrication of starch/PVA/CuO electrospun nanoscaffolds from Sargassum ilicifolium (brown marine macroalgae) extract for anticancer activity on HT-29 and MCF-7 cancer cells. Biocatalysis and Agricultural Biotechnology. 2026; 72: 103923.
[45] Pei J, Govindaraj H, Sivaramakrishnan R, Kanniappan GV, Pandurangan V, Dhayalan VK, Mironescu M, Mironescu ID, Jayaraman S, Palanisamy PC. Sustainable fabrication of biopolymer-based (starch/PVA) nanoscaffolds loaded with green-synthesized CuO nanoparticles from Sargassum wightii (marine macroalgae): Cytocompatibility and antioxidant activity. Biomaterials Advances. 2026; 182: 214660.
[46] Pei J, Perumal NC, Meng P, Long Q, Palanisamy CP. Extracellular vesicle-based biosensors for Alzheimer's disease: A new frontier in precision diagnostics. Ageing Research Reviews. 2026; 113: 102904.
[47] Shree P, Sivaramakrishnan R, Kanniappan GV, Pandurangan V, Jayaraman S, Dhayalan VK, Mironescu M, Mironescu ID, Palanisamy CP. Antioxidant and biocompatible CuO-starch/PVA nanoscaffolds via ultrasonic green synthesis using Turbinaria conoides (brown marine macroalgae). Medicine in Drug Discovery. 2025; 28: 100238.
[48] Gong J, Lin J, Guan T, Pei J, Palanisamy CP, El-AtyFrom AMA. selenium tolerance to nanoplastic antagonism: Comprehensive characterization of L. casei SNUT1 and its extracellular vesicle–nanoselenium complex. Food Bioscience. 2025; 74: 107749.
[49] Poochi SP, Sundarraj R, Raju MV, Chandrasekaran MK, Ahalliya RM, Palanisamy CP, Kanniappan GV, Kondapavuluri BK, Thiruvengadam M. Harnessing Nature: Computational and Experimental Insights Into Ipomoea obscura Metabolites for Bladder Cancer Therapy. Chemistry and Biodiversity. 2025; 0: e00909.
[50] Dugganaboyana GK, Kannankumar MKG, Shivaramakrishna S, Raju MV, Chandrasekaran MK, Ahalliya RM, Panneerselvam N, Palanisamy CP, Kanniappan GV. Phytochemical insights, antioxidant activity and therapeutic potential of Cassia senna against prostate cancer in Wistar albino rats. Discover Applied Sciences. 2025; 7:1206.
[51] Natarajan SR, Krishnamoorthy R, Alshuniaber MA, Gatasheh MK, Rajagopal P, Veeraraghavan VP, Palanisamy CP, Jayaraman S. KDM1A Facilitates Oncogenic Potential in Colorectal Cancer Progression Through the Activation of AXIN/GSK3β/β-Catenin Signaling Pathways: Evidence From Integrated Transcriptomics and In Vitro Studies. The Journal of Gene Medicine. 2025; 27(11): e70053.
[52] Guan T, Gong J, Lin J, Palanisamy CP, Jinjin Pei J, El-Aty AMA. Machine learning-driven multimodal optimization of selenium biotransformation and flavor profiling in fermented apple–Yacon functional beverages. Innovative Food Science & Emerging Technologies. 2025; 105: 104198.

[53] Natarajan SR, Krishnamoorthy R, Alshuniaber MA, Alsulami TS, Gatasheh MK, Rajagopal P, Palanisamy CP, Govindan R, Veeraraghavan VP, Jayaraman S. ABCE1 facilitates tumour progression via aerobic glycolysis and inhibits cell death in human colorectal cancer cells through the p53 signalling pathway. Scientific Reports. 2025; 15: 24674.
[54] Huang Y, Guo H, Liu Y, Jin W, Palanisamy CP, Pei J, Oz F, El-Aty AMA. Effects of Natural Polysaccharides on the Gut Microbiota Related to Human Metabolic Health. Molecular Nutrition & Food Research. 2025; 69:e202400792.
[55] Poornima K, Meenakshi K.C, Manikandan V.R, Shankari G, Prabhu D, Rathi M.A, Palanisamy CP, Balaji R, Gopalakrishnan V.K. Exploring the anticancer potential of Jerantinine A from Tabernaemontana coronaria against prostate, breast, and ovarian cancers: A computational approach. Journal of Complementary and Integrative Medicine, 2025 22(2): 363–372.
[56] Palanisamy CP, Poompradub S, Sansanaphongpricha K, Jayaraman S, Subramani K. Faridah Sonsudin gGreen synthesis of Nigella sativa-mediated silver nanoparticles for enhanced antibacterial activity and wound healing: Mechanistic insights and biomedical applications. Environmental Nanotechnology, Monitoring & Management. 2025; 24: 101085.
[57] Surendran N, Raju MV, Chandrasekaran MK, Ahalliya RM, Palanisamy CP, Chandrasekaran G, Kanniappan GV. Physicochemical characterization of starch from Maranta arundinacea L.(arrowroot) rhizomes and its inhibition of COX-2: In vivo validation. Bioactive Carbohydrates and Dietary Fibre. 2025; 33: 100465.
[58] Kannappan P, Chandrasekaran MK, Raju MV, Gopalakrishnan S, Dhamodharan P, Ahalliya RM, Palanisamy CP, Raju B, Kanniappan GV. Exploring the anticancer potential of Jerantinine A from Tabernaemontana coronaria against prostate, breast, and ovarian cancers: a computational approach. Journal of Complementary and Integrative Medicine. 2025; 22(02): 363-372.
[59] Pei J, Kumarasamy RV, Jayaraman S, Kanniappan GV, Long Q, Palanisamy CP. Quercetin-functionalized nanomaterials: Innovative therapeutic avenues for Alzheimer's disease management. Ageing Research Reviews. 2025; 104: 102665.
[60] Jayaraman S, Prasad M, Natarajan SR, Krishnamoorthy R, Alshuniaber MA, Gatasheh MK, Veeraraghavan VP, Rajagopal P, Palanisamy CP. Molecular mechanisms underlying the effects of beta-sitosterol on TGF-β1/Nrf2/SIRT1/p53-mediated signaling in the kidney of a high-fat diet and sucrose-induced type-2 diabetic rat. Chemico-Biological Interactions. 2025; 411: 111443.
[61] Huang Y, Guo H, Liu Y, Jin W, Palanisamy CP, Pei J, Oz F, El‐Aty AMA. Effects of Natural Polysaccharides on the Gut Microbiota Related to Human Metabolic Health. Molecular Nutrition & Food Research. 2025; e202400792.
[62] Prabhakaran P, Palanisamy CP, Shanmugam A, Damodharan P, Swaminathan H, Devaraj D, Ahalliya RM, Kanniappan GV. Isolation, structural characterization, and molecular docking studies on the bioactive compound from n-Hexane extract of Emilia sonchifolia (L.) DC against the pancreatic cancer target Aurora 2 Kinase. Journal of Complementary and Integrative Medicine. 2024; 22(1): 0290.
[63] Jiang H, Kumarasamy RV, Pei J, Raju K, Kanniappan GV, Palanisamy CP. Integrating engineered nanomaterials with extracellular vesicles: Advancing targeted drug delivery and biomedical applications. Frontiers in Nanotechnology. 2024; 6: 1513683.
[64] Guo H, Liu Y, Wan T, Song D, Palanisamy CP, Geng J, Pei J, Özmen S, El-Aty AMA. Toward personalized cancer management: Role of precision nutrition–diet interventions. Journal of Functional Foods. 2024; 123: 106584.
[65] Natarajan SR, Krishnamoorthy R, Alshuniaber MA, Al-Anazi KM, Farah MA, Rajagopal P, Palanisamy CP, Veeraraghavan VP, Jayaraman S. Identification of FOXM1 as a novel protein biomarker and therapeutic target for colorectal cancer progression: Evidence from immune infiltration and bioinformatic analyses. International Journal of Biological Macromolecules. 282 (Part 4): 137201.
[66] Rajendran MS, Jayaraman S, Khan JM, Jasmine S, Prabhakaran RK, Raju MV, Chandrasekaran MK, Ahalliya RM, Kannappan P, Palanisamy CP, Kanniappan GV. Investigating the colon toxicity and carcinogenic role of monosodium glutamate compared with Dimethylhydrazine in male Wistar rats: Exploring the link to childhood colon cancer risk. Journal of King Saud University - Science. 2024; 36(11): 103507.
[67] Kumarasamy RV, Natarajan P, Umapathy VR, Roy JR, Rab SO, Saeed M, Panagal M, Mironescu M, Srinivasan GP, Palanisamy CP. Clinical Applications and Therapeutic Potentials of Advanced Nanoparticles: A Comprehensive Review on Completed Human Clinical Trials. Frontiers in Nanotechnology. 2024; 6:1479993.
[68] Jin W, Pei JJ, Roy JR, Jayaraman S, Ahalliya RM, Kanniappan GV, Mironescu M, Palanisamy CP. Comprehensive review on single-cell RNA sequencing: A new frontier in Alzheimer's disease research. Ageing Research Reviews. 2024; 274: 102454.
[69] Pei J, Palanisamy CP, Jayaraman S, Natarajan PM, Umapathy VR, Roy JR, Panagal M, Jayaraman S. Curcumin-loaded polymeric nanomaterials as a novel therapeutic strategy for Alzheimer's disease: A comprehensive review. Ageing Research Reviews. 2024; 99: 102393.
[70] Pei J, Palanisamy CP, Jayaraman S, Natarajan PM, Umapathy VR, Roy JR, Thalamati D, Ahalliya RM, Kanniappan GV, Mironescu M. A comprehensive review on starch-based Sustainable Edible Films Loaded with Bioactive Components for Food Packaging. International Journal of Biological macromolecules. 2024; 274 (Part-1): 133332.

[71] Palanisamy CP, poompradub S, Sansanaphongpricha K, Subramani K, Sonsudin F. Increased expression levels of PDGF and VEGF magnify the wound healing potential facilitated by biogenic synthesis of silver nanoparticles. Nano-Structures & Nano-Objects. 2024; 39: 101236.
[72] Pei J, Palanisamy CP, Jayaraman S, Natarajan PM, Umapathy VR, Roy JR, Thalamati D, Ahalliya RM, Kanniappan GV, Mironescu M. Proteomics Profiling of Extracellular Vesicle for Identification of Potential Biomarkers in Alzheimer's Disease: A Comprehensive Review. Ageing Research Reviews. 2024; 99: 102359.
[73] Xi J, Wang T, Xian P, Liu X, Du M, Yang H, Palanisamy CP, Lin W, Long Q. Proteomic insights uncover enhanced neurotherapeutic potential in conditioned mesenchymal stem cell-derived extracellular vesicles. Extracellular Vesicle. 2024; 3: 100037.
[74] Pei J, Natarajan PM, Umapathy VR, Swamikannu B, Sivaraman NM, Krishnasamy L, Palanisamy CP. Advancements in the synthesis and functionalization of zinc oxide-based nanomaterials for enhanced oral cancer therapy. Molecules. 2024; 29(11): 2706.
[75] Gatasheh MK, Natarajan SR, Krishnamoorthy R, Alsulami TS, Rajagopal P, Palanisamy CP, Veeraraghavan VP, Jayaraman S. Molecular analysis to identify novel potential biomarkers as drug targets in colorectal cancer therapy: an integrated bioinformatics analysis. Molecular and Cellular Oncology. 2024; 11(1): 2326699.
[76] Pei J, Yan Y, Jayaraman S, Rajagopal P, Natarajan PM, Umapathy VR, Gopathy S, Roy JR, Sadagopan CS, Thalamati D, Palanisamy CP, Mironescu M. A review on advancements in the application of starch-based nanomaterials in biomedicine: Precision drug delivery and cancer therapy. International Journal of Biological Macromolecules. 2024; 130746.
[77] Pei JJ, Yan Y, Palanisamy CP, Jayaraman S, Natarajan PM, Umapathy VR, Gopathy S, Roy JR, Sadagopan JC, Thalamati D, Mironescu M. Materials-based drug delivery approaches: Recent advances and future perspectives. Green Processing and Synthesis. 2024; 13: 20230094.
[78] Pei JJ, Deng W, Liu Y, Guo Y, Chen J, Abdu H, Khan MR, Palanisamy CP, El-Aty AM. A Comprehensive Review of Cornus officinalis: Health Benefits, Phytochemistry, and Pharmacological Effects for Functional Drug and Food Development. Frontiers in Nutrition. 2023; 10: 1309963.
[79] Alugoju P, Palanisamy CP, Anthikapalli NVA, Jayaraman S, Prasanskulab A, Chuchawankul S, Dyavaiah M, Tencomnao T. Exploring the anti-aging potential of natural products and plant extracts in budding yeast Saccharomyces cerevisiae: A review. F1000Research. 2023; 12: 1265.
[80] Lavanya M, Krishnamoorthy R, Alshuniaber MA, Manoharadas S, Palanisamy CP, Veeraraghavan VP, Jayaraman S, Rajagopal P, Padmini R. Formulation, characterization and evaluation of gelatin-syringic acid/zinc oxide nanocomposite for its effective anticancer, antioxidant and anti-inflammatory activities. Journal of King Saud University-Science. 2023; 35: 102909.
[81] Palanisamy CP, Poompradub S, Sansanaphongpricha K, Jayaraman S, Subramani K, Sonsudin F. Biosynthesis of silver nanoparticles (AgNPs) using ethanolic extract of Nigella sativa (L.) seeds promotes wound healing via PDGF and VEGF signalling pathways activation. Biocatalysis and Agricultural Biotechnology. 2023; 54: 102970.
[82] Prasad M, Jayaraman S, Natarajan SR, Veeraraghavan VP, Krishnamoorthy R, Gatasheh MK, Palanisamy CP, Elrobh M. Piperine modulates IR/Akt/GLUT4 pathways to mitigate insulin resistance: Evidence from animal and computational studies. International Journal of Biological Macromolecules. 2023; 253: 127242.
[83] Palanisamy CP, Pei JJ, Phaniendra A, Venkata AAN, Jayaraman S, Veeraragahavan VP, Sridevi G, Roy JR, Janaki CS, Thalamati D, Mironescu M, Luo Q, Chai Y, Long Q. New Strategy of Neurodegenerative Disease Treatment with Extracellular Vesicles (EVs) Derived from Mesenchymal Stem Cells (MSCs). Theranostics. 2023; 13(12):4138-4165. doi:10.7150/thno.83066.
[84] Palanisamy CP, Phaniendra A, Jayaraman S, Poompradub S. Nigella sativa L. seed extracts promotes wound healing progress by activating VEGF and PDGF signalling pathways: An in vitro and in silico study. F1000 Research. 2023; 12: 436.
[85] Manimaran D, Elangovan N, Mani P, Subramanian K, Ali D, Alarifi S, Palanisamy CP, Zhang H, Rangasamy K, Palanisamy V, Mani R, Govarthanan K, Aruni W, Shanmugam R, Srinivasan GP, Kalirajan A. Isolongifolene-loaded chitosan nanoparticles synthesis and characterization for cancer treatment. Scientific Reports. 2022; 12:19250.
[86] Palanisamy CP, Cui B, Zhang H, Gunasekaran VP, Ariyo A, Jayaraman S, Veeraraghavan V, Rajagopal P. A critical review on starch-based electrospun nanofibrous scaffolds for wound healing application. International Journal of Biological Macromolecules. 2022; 222 (Part: B): 1852-1860.
[87] Pei J, Umapathy VR, Vengadassalapathy S, Hussain SFJ, Rajagopal P, Jayaraman S, Veeraraghavan VP, Palanisamy CP, Gopinath K. A Review of the Potential Conse-quences of Pearl Millet (Pennisetum glaucum) for Diabetes Mellitus and Other Biomedical Applications. Nutrients. 2022; 14(14):2932.
[88] Monisha P, Ponnulakshmi R, Nalini D, Vishnu P V, Palanisamy CP, Cui B, Shankargouda P, Selvaraj J. A comprehensive review on high fat diet-induced diabetes mellitus: An epigenetic view. The Journal of Nutritional Biochemistry. 2022; 2022: 109037.
[89] Monisha P, Selvaraj J, Mohamed AE, Mohamed E, Mosaab AEA, Vishnu PV, Srinivasan V, Vidhya RU, Shazia FJH, Kalaiselvi K, Durairaj S, Palanisamy CP, Surapaneni K M, Ponnulakshmi R. A Comprehensive review on therapeutic perspectives of phytosterols in insulin resistance: A mechanistic approach. Molecules. 2022; 27(5): 1595.

[90] Kannayiram K, Umapathy VR, Chamundeswari Y, Fathima JH, Govindan R, Palanisamy CP, Veeraraghavan VP, Jayaraman S, Rajagopal P. Molecular docking analysis of flavonoids with aldose reductase. Bioinformation. 2022; 18(3): 80–83.
[91] UV Rekha, Varadhachariyar R, Rajagopal P, Priya PH, Fathima JHS, Govindan R, Palanisamy CP, Veeraraghavan VP, Jayaraman S. Molecular docking analysis of bioactive compounds from Plectranthus amboinicus with glucokinase. Bioinformation. 2022; 18(3): 261–264.
[92] Umapathy VR, Rajagopal P, Varadhachariyar R, Priya PH, Fathima JHS, Govindan R, Palanisamy CP, Brindha KBA, Veeraraghavan VP, Jayaraman S. Molecular docking analysis of bioactive compounds from Cissampelos pareira with PPAR gamma. Bioinformation. 2022; 18(3): 265-268.
[93] Rajagopal P, Umapathy VR, Sandhya P, Fathima JH, Govindan R, Palanisamy CP, Veeraraghavan VP, Jayaraman S. Molecular docking analysis of metformin analogues with GSK-3β. Bioinformation. 2022; 18(3): 269-272.
[94] Adeniran LA, Palanisamy CP, Ashafa AOT. Chemical profiling, in vitro antioxidant and antidiabetic assessment of flavonoids from the ethanol extract of Hermannia geniculata root. Sokoto Journal of Veterinary Sciences. 2021; 19(1): 1-13.
[95] Sundaram S, Palanisamy CP, Subban R, Palanirajan A, Piramanayagam S, Eswaran M, Krishna CK, Kanniappan VG. 1-Pentacosanol Isolated from Stem Ethanolic Extract of Cayratia trifolia (L.) is A Potential Target for Prostate Cancer-In SILICO Approach. Jordan Journal of Biological Sciences. 2021; 14 (2): 359-365.
[96] Raj SS, Palanisamy CP, Mani P. Antioxidant, antimicrobial and cytotoxicity of n-hexane extract from Mollugo nudicaulis Lam. Bioinformation. 2021; 17 (5), 573-582.
[97] Palanisamy CP, Cui B, Zhang H, Panagal M, Paramasivam S, Chinnaiyan U, Jeyaraman S, Murugesan K, Rostagno M, Sekar V, Natarajan SP. Anti-ovarian cancer potential of phytocompound and extract from South African medicinal plants and their role in the development of chemotherapeutic agents. American Journal of Cancer Research. 2021; 11(5):1828-1844.
[98] Palanisamy CP, Pethanan S, Vincent GG, Murugesan K, Ramachandran A, Sivanandam R, Panagal M. Chemotherapeutic potential of Cayratia trifolia L nhexane extract on A2780 cells. Bioinformation. 2021; 17(8): 710–714.
[99] Palanisamy CP, Fathima JHS, Sekar R, Rajagopal P, Jeyaraman S. MTT assay based inhibition analysis of A2780 cells proliferation using Mollugo nudicaulis Lam. extract with CXCR4 and HER2 expression. Bioinformation. 2021; 17(7): 705–709.
[100] Jayaraman S, Devarajan N, Rajagopal P, Babu S, Ganesan SK, Veeraraghavan VP, Palanisamy CP, Cui B, Periyasamy V, Chandrasekar K. β-Sitosterol Circumvents Obesity Induced Inflammation and Insulin Resistance by down-Regulating IKKβ/NF-κB and JNK Signaling Pathway in Adipocytes of Type 2 Diabetic Rats. Molecules. 2021; 26: 2101.
[101] Bhuvaneswari M, Palanisamy CP, Mani P. Antioxidant, antimicrobial and cytotoxicity potential of n-hexane extract of Cayratia trifolia L. Bioinformation. 2021; 17(3): 452-459.
[102] Onwuzuligbo CC, Onwuzuligbo AU, Onwuzuligbo AJ, Obidiegwu OC, Ezeonyi EI, Onwuzuligbo CC. The dual nature of inflammation: From essential host defense to driver of chronic disease: A review. 2025.
[103] Shen C, Zhang Y, Wei C, Wang H, Zhou Y. Advances in the research of gasdermin-dependent pyroptosis mechanisms and therapeutic targets in inflammatory diseases. Apoptosis. 2026;31:38.
[104] Dilimulati D, Dilimulati D, Cui L. Alpha-ketoglutarate enhances adipose-derived stem cells survival in wound healing by hypoxia-inducible factor 1-alpha-mediated redox homeostasis and glycogen-dependent bioenergetics. World Journal of Stem Cells. 2026;18:113694.
[105] Sheng X, Lin H, Cole PA, Zhao Y. Biochemistry and regulation of histone lysine L-lactylation. Nature Reviews Molecular Cell Biology. 2025:1-15.
[106] Yang Y, Luo N, Gong Z, Zhou W, Ku Y, Chen Y. Lactate and lysine lactylation of histone regulate transcription in cancer. Heliyon. 2024;10.
[107] Ahmadi Hekmatikar Ah, Zolfaghari G, Basereh A, Awang Daud DM, Khoramipour K. Context Matters: Divergent Roles of Exercise-Induced and Tumor-Derived Lactate in Cancer. Biomolecules. 2025;15:1010.
[108] Tomczyk M. Investigating the role of SIRT3 in doxorubicin induced dilated cardiomyopathy. 2023.
[109] Shu M, Lu D, Zhu Z, Yang F, Ma Z. Insight into the roles of lactylation in macrophages: functions and clinical implications. Clinical Science. 2025;139:151-69.
[110] Mujahid M, Ambreen A, Zarlashat Y, Sarfraz Z, Iqbal MS, Waheed A, et al. Integration of light and circadian signaling in plant gene regulatory networks: implications for photomorphogenesis and stress adaptation. Biology. 2025;14:1375.
[111] Bao C, Ma Q, Ying X, Wang F, Hou Y, Wang D, et al. Histone lactylation in macrophage biology and disease: from plasticity regulation to therapeutic implications. EBioMedicine. 2025;111.
[112] Li H, Geng J, Fang Z, Ge J, Zhang Z. lactylation modification: from basic biological processes to clinical cardiovascular diseases. Research. 2026.
[113] Peng L, Luo G, He W. Masterful macrophages: understanding and targeting activation dysfunction in diabetic wounds. Burns & Trauma. 2025;13:tkaf003.

[114] Xu Y, Ma X, Ni W, Zheng L, Lin Z, Lai Y, et al. PKM2-driven lactate overproduction triggers endothelial-to-mesenchymal transition in ischemic flap via mediating TWIST1 lactylation. Advanced science. 2024;11:2406184.
[115] Bar-Or D, Banton K, Acuna D, Williams J, Palacio CH, Zaw-Mon C, et al. Lactylation as a metabolic–epigenetic switch: Mechanisms and roles in cancer, sepsis, trauma, inflammation, and tissue repair. Biochemistry and Biophysics Reports. 2026;45:102507.
[116] Liu W, Zhang T, Wang B, Yin H. Aerobic glycolysis promotes NLRP3 inflammasome activation via NLRP3 lactylation. Cell Chemical Biology. 2026.
[117] Wang J, Wang K, Hu Z, Wang Y, Kang Y, Liu X, et al. Role of lactylation-induced macrophage failed phenotypic switching in sustaining inflammation of diabetic wounds. Frontiers in Immunology. 2026;17:1777272.
[118] Lin J, Ren J. Lactate-induced lactylation and cardiometabolic diseases: from epigenetic regulation to therapeutics. Biochimica et Biophysica Acta (BBA)-molecular basis of disease. 2024;1870:167247.
[119] Prakash G, Chaudhary AA, Tanu R, Ali MA, Boufahja F, Sharma PK, et al. Harnessing Phytochemicals and Nanotechnology Synergy for Molecular, Epigenetic, and Microbiota-Driven Regulation in Type 2 Diabetes Mellitus. Pharmaceutics. 2026;18:113.
[120] Yang Q, Yang Z, Zhao H. Lactylation in cancer: mechanistic insights, tumor microenvironment, and therapeutic horizons. Frontiers in Immunology. 2025;16:1697008.
[121] Sun Z, Song Y, Li J, Li Y, Yu Y, Wang X. Potential biomarker for diagnosis and therapy of sepsis: Lactylation. Immunity, Inflammation and Disease. 2023;11:e1042.
[122] Ren H, Tang Y, Zhang D. The emerging role of protein L-lactylation in metabolic regulation and cell signalling. Nature metabolism. 2025;7:647-64.
[123] Xu Y, Zhang C, Wu J, Guo P, Jiang N, Wang C, et al. Integrated analysis of single-cell RNA-seq and spatial transcriptomics to identify the lactylation-related protein TUBB2A as a potential biomarker for glioblastoma in cancer cells by machine learning. Frontiers in Immunology. 2025;16:1601533.
[124] Liu W, Liu T, Zheng Y, Xia Z. Metabolic reprogramming and its regulatory mechanism in sepsis-mediated inflammation. Journal of inflammation research. 2023:1195-207.
[125] Liu J, Zhou F, Tang Y, Li L, Li L. Progress in lactate metabolism and its regulation via small molecule drugs. Molecules. 2024;29:5656.
[126] Chen C, Liu T, Tang Y, Luo G, Liang G, He W. Epigenetic regulation of macrophage polarization in wound healing. Burns & Trauma. 2023;11:tkac057.
[127] Mu X, Wu X, He W, Liu Y, Wu F, Nie X. Pyroptosis and inflammasomes in diabetic wound healing. Frontiers in endocrinology. 2022;13:950798.
[128] Xu J, Núñez G. The NLRP3 inflammasome: activation and regulation. Trends in biochemical sciences. 2023;48:331-44.
[129] Chu F-x, Wang X, Li B, Xu L-l, Di B. The NLRP3 inflammasome: a vital player in inflammation and mediating the anti-inflammatory effect of CBD. Inflammation Research. 2024;73:227-42.
[130] Ding J, Wang H, Yang Z, Wang X, Cao Z. Protein acylation in inflammatory diseases: from mechanisms to therapeutic strategies. Cell Communication and Signaling. 2025;23:1-23.
[131] Wu H, Huang H, Zhao Y. Interplay between metabolic reprogramming and post-translational modifications: from glycolysis to lactylation. Frontiers in Immunology. 2023;14:1211221.
[132] Wang L, Wang Y, Meng M, Ma N, Wei G, Huo R, et al. High-concentrate diet elevates histone lactylation mediated by p300/CBP through the upregulation of lactic acid and induces an inflammatory response in mammary gland of dairy cows. Microbial Pathogenesis. 2023;180:106135.
[133] Gou J, Zhang L, Wang G, Li Z, Yin Q, Pan Y. Inhalable Exosomes in Respiratory Therapies with the Transformative Potential. International Journal of Nanomedicine. 2025:14219-52.
[134] He Y, Wang Y, Jia X, Li Y, Yang Y, Pan L, et al. Glycolytic reprogramming controls periodontitis-associated macrophage pyroptosis via AMPK/SIRT1/NF-κB signaling pathway. International Immunopharmacology. 2023;119:110192.
[135] Daskalaki MG, Lapi I, Hurst AE, Al-Qahtani A, Vergadi E, Tsatsanis C. Epigenetic and metabolic regulation of macrophage responsiveness and memory. The Journal of Immunology. 2025;214:2812-21.
[136] Jiang X, Yang Y, Li X, Li T, Yu T, Fu X. Lactylation: an innovative approach to disease control. Aging and disease. 2024;16:2130.
[137] Zou AE, Kongthong S, Mueller AA, Brenner MB. Fibroblasts in immune responses, inflammatory diseases and therapeutic implications. Nature Reviews Rheumatology. 2025;21:336-54.
[138] Tóth A, Jeney V. Hypoxia-induced changes in endothelial cell phenotype and function. Antioxidants & Redox Signaling. 2025;43:849-68.
[139] Mahmoud NN, Hamad K, Al Shibitini A, Juma S, Sharifi S, Gould L, et al. Investigating inflammatory markers in wound healing: understanding implications and identifying artifacts. ACS pharmacology & translational science. 2024;7:18-27.
[140] Wu X, Liu C, Zhang C, Kuai L, Hu S, Jia N, et al. The role of lactate and lactylation in the dysregulation of immune responses in psoriasis. Clinical Reviews in Allergy & Immunology. 2025;68:28.
[141] Chen X, Yuan Y, Zhou F, Li L, Pu J, Zeng Y, et al. Lactylation: From homeostasis to pathological implications and therapeutic strategies. MedComm. 2025;6:e70226.

[142] Nisar A, Jagtap S, Vyavahare S, Deshpande M, Harsulkar A, Ranjekar P, et al. Phytochemicals in the treatment of inflammation-associated diseases: the journey from preclinical trials to clinical practice. Frontiers in pharmacology. 2023;14:1177050.
[143] Zhao M, Wei F, Sun G, Wen Y, Xiang J, Su F, et al. Natural compounds targeting glycolysis as promising therapeutics for gastric cancer: A review. Frontiers in pharmacology. 2022;13:1004383.
[144] Oladipupo S, Rotimi DE, Ezenabor EH, Ojo AB, Akinsola OA, Ojo OA. Harnessing nanoparticles for phytochemical delivery: a comprehensive review of safety and therapeutic potential. Therapeutic Delivery. 2025;16:1111-25.
[145] Rathna RP, Kulandhaivel M. Advancements in wound healing: integrating biomolecules, drug delivery carriers, and targeted therapeutics for enhanced tissue repair. Archives of Microbiology. 2024;206:199.
[146] Coll RC, Schroder K. Inflammasome components as new therapeutic targets in inflammatory disease. Nature Reviews Immunology. 2025;25:22-41.
[147] Patil AB, Raut ST, Adnaik RS. Emerging Role of Phytochemicals in Immunomodulation and Metabolic Regulation: Mechanistic Insights and Therapeutic Potential. Biopress Journal of Advanced Pharmacology (BJAP). 2025;1:49-63.
[148] Amin A, Akhtar MS, Khalil AAK, Ali S, Zaman W. Natural products in medicinal chemistry: targeting inflammatory pathways with plant-derived compounds. Medicinal Chemistry Research. 2026;35:61-84.
[149] Pandey SN, Babu MA, Goyal K, Menon SV, Ray S, Kaur M, et al. Targeting NLRP3 inflammasome with curcumin: mechanisms and therapeutic promise in chronic inflammation. Inflammopharmacology. 2025;33:5667-87.
[150] Li J, Feng Z, Lu B, Fang X, Huang D, Wang B. Resveratrol alleviates high glucose-induced oxidative stress and apoptosis in rat cardiac microvascular endothelial cell through AMPK/Sirt1 activation. Biochemistry and Biophysics Reports. 2023;34:101444.
[151] MAJEE C. TARGETING SIGNALING PATHWAYS (MAPK, NF-KB ETC.) TO HINDER INFLAMMATION. The Potential Role of Flavonoids in Mitigating Inflammatory Disorders. 2026:104.
[152] Mokra D, Joskova M, Mokry J. Therapeutic effects of green tea polyphenol (–)-Epigallocatechin-3-Gallate (EGCG) in relation to molecular pathways controlling inflammation, oxidative stress, and apoptosis. Int J Mol Sci. 2022;24:340.
[153] Li M, Zhang H, Zhang Y, Fan J, Zhu J, Gu X, et al. Berberine modulates macrophage activation by inducing glycolysis. The Journal of Immunology. 2022;208:2309-18.
[154] Naponelli V, Piscazzi A, Mangieri D. Cellular and molecular mechanisms modulated by genistein in cancer. International Journal of Molecular Sciences. 2025;26:1114.
[155] Yi Y-S. Regulatory roles of flavonoids in caspase-11 non-canonical inflammasome-mediated inflammatory responses and diseases. International Journal of Molecular Sciences. 2023;24:10402.
[156] Drif AI. Anti-inflammatory and anticancer activities of natural products and their derivatives. 2025.
[157] Li Q, Wang J, Jiang Y, Wang F, Liu M, Yang D, et al. Baicalin Attenuates Oxidative Stress and Apoptosis in Myocardial Ischemia/reperfusion Injury via Suppression of STING/NLRP3 Pathway. Journal of Cardiovascular Translational Research. 2026;19:45.
[158] Andrés CMC, Pérez de la Lastra JM, Bustamante Munguira E, Juan CA, Plou FJ, Pérez Lebeña E. Electrophilic compounds in the human diet and their role in the induction of the transcription factor NRF2. International Journal of Molecular Sciences. 2024;25:3521.
[159] Direito R, Barbalho SM, Figueira ME, Minniti G, de Carvalho GM, de Oliveira Zanuso B, et al. Medicinal plants, phytochemicals and regulation of the NLRP3 inflammasome in inflammatory bowel diseases: a comprehensive review. Metabolites. 2023;13:728.
[160] Wendlocha D, Kubina R, Krzykawski K, Mielczarek-Palacz A. Selected flavonols targeting cell death pathways in cancer therapy: the latest achievements in research on apoptosis, autophagy, necroptosis, pyroptosis, ferroptosis, and cuproptosis. Nutrients. 2024;16:1201.
[161] De Deus IJ, Martins-Silva AF, Fagundes MMdA, Paula-Gomes S, Silva FGDe, Da Cruz LL, et al. Role of NLRP3 inflammasome and oxidative stress in hepatic insulin resistance and the ameliorative effect of phytochemical intervention. Frontiers in pharmacology. 2023;14:1188829.
[162] Olędzka AJ, Czerwińska ME. Role of plant-derived compounds in the molecular pathways related to inflammation. International Journal of Molecular Sciences. 2023;24:4666.
[163] Papantoniou K, Aggeletopoulou I, Michailides C, Pastras P, Triantos C. Understanding the role of NLRP3 inflammasome in acute pancreatitis. Biology. 2024;13:945.
[164] Zheng Z, Gao J, Ma Y, Hou X. Cellular and Molecular Mechanisms of Phytochemicals Against Inflammation-Associated Diseases and Viral Infection. Cell Biology International. 2025;49:606-33.
[165] Romero BNS. Disentangling the role of Limosilactobacillus reuteri D-lactate in lipid metabolism. 2022.
[166] Yin R, Jing G, Tian Y, Ma M, Zhang M. The impact of lactate on diabetic cognitive dysfunction: insights from energy metabolism to epigenetic modulation. Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease. 2025;1871:167749.
[167] Brooks GA, Osmond AD, Arevalo JA, Duong JJ, Curl CC, Moreno-Santillan DD, et al. Lactate as a myokine and exerkine: drivers and signals of physiology and metabolism. Journal of Applied Physiology. 2023.

[168] Pan Y, Mary Peter R, Chou P, Dave PD, Xu J, Shanner A, et al. Cancer-specific regulation of metabolic and epigenetic pathways by dietary phytochemicals. Pharmaceutical research. 2025;42:1443-57.
[169] Prasad S, Kumar V, Singh C, Singh A. Crosstalk between phytochemicals and inflammatory signaling pathways. Inflammopharmacology. 2023;31:1117-47.
[170] Al-Khayri JM, Sahana GR, Nagella P, Joseph BV, Alessa FM, Al-Mssallem MQ. Flavonoids as potential anti-inflammatory molecules: A review. Molecules. 2022;27:2901.
[171] Akanda MR, Aktaruzzaman M, Tanoy NM, Supty SI, Rahman MA, Riea ATM, et al. Bioactive phytochemical-based modulation of inflammatory and oxidative pathways for enhancing tissue regeneration: A narrative review. Regenerative Medicine Reports. 2026:10.4103.
[172] Satapathy T, Yadu H, Sahu P. Protective Role of Herbal Bioactive in Modulation of PDGF-VEGF-TGFβ-EGF Fibroblast Proliferation and Re-epithelialization for the Enhancement of Tissue Strength and Wound Healing. Regenerative Engineering and Translational Medicine. 2025:1-22.
[173] Tertipi N, Grech VS, Sfyri E, Andreou E, Kefala V, Rallis E. Natural Extracts in Skin Repair and Wound Healing: Phytochemical Mechanisms and Dermopharmaceutical Perspectives. Molecules. 2026;31:967.
[174] Mashele SS. Phytochemicals as Multifunctional Agents: Antimicrobial, Enzyme Inhibitory, and Wound-Healing Potentials in the Era of Drug Resistance. 2025.
[175] Mostafa MA, Khojah HM. Nanoparticle-based delivery systems for phytochemicals in cancer therapy: molecular mechanisms, clinical evidence, and emerging trends. Drug Development and Industrial Pharmacy. 2025;51:1105-21.
[176] Parvin N, Aslam M, Joo SW, Mandal TK. Nano-phytomedicine: harnessing plant-derived phytochemicals in nanocarriers for targeted human health applications. Molecules. 2025;30:3177.
[177] Segneanu A-E, Mogoşanu GD, Bejenaru C, Kostici R, Bejenaru LE. Plant-Derived Nanocarriers for Drug Delivery: A Unified Framework Integrating Extracellular Vesicles, Engineered Phytocarriers, Hybrid Platforms, and Bioinspired Systems. Plants. 2026;15:908.
[178] Malik IM, Bhat AH, Majeed D, Nabi N. Environmental Factors Influencing Phytochemical Production for Enhanced Phytochemical Defense. Phytochemical Arsenal: Understanding Plant Defense Mechanisms Against Nematodes: Bentham Science Publishers; 2025. p. 118-50.
[179] Zhang Q, Duan H, Yang Y, Yu H, Wang W, Li B. Recent Advances in Plant-Derived Extracellular Vesicles as Nanoparticles for Cancer Drug Delivery. International Journal of Nanomedicine. 2025:14977-5016.
[180] Rahmanian M, Khosropanah S, Moghaddam SH, Vatankhah A, Haghbin A, Oroojalian F, et al. Phytochemicals and nanoformulation strategies for rheumatoid arthritis: mechanistic insights, therapeutic advances, and translational challenges. Inflammopharmacology. 2025:1-33.
[181] Ullah A, Ullah M, Lee G-J, Lim SI. A review of recent advances in nanotechnology for the delivery of therapeutics in wound healing. Journal of Pharmaceutical Investigation. 2025;55:33-54.
[182] Suvarna V, Sawant N, Desai N. A review on recent advances in mannose-functionalized targeted nanocarrier delivery systems in cancer and infective therapeutics. Critical Reviews™ in Therapeutic Drug Carrier Systems. 2023;40.
[183] Onzi G, Guterres SS, Pohlmann AR, Frank LA. Passive targeting and the enhanced permeability and retention (EPR) effect. The ADME encyclopedia: A comprehensive guide on biopharmacy and pharmacokinetics: Springer; 2022. p. 753-66.
[184] Zotikov D, Ponomareva N, Brezgin S, Kostyusheva A, Frolova A, Chulanov V, et al. Biological Nanoparticles for Enhancing Chronic Wound Regeneration. Cells. 2025;14:1637.
[185] Antonelli A, Palma F. Nanocarrier-based delivery systems for natural compounds across research stages. Materials. 2025;18:4960.
[186] Shi J, Tan C, Ge X, Qin Z, Xiong H. Recent advances in stimuli-responsive controlled release systems for neuromodulation. Journal of Materials Chemistry B. 2024;12:5769-86.
[187] Sadraei A, Naghib SM. 4D printing of physical stimuli-responsive hydrogels for localized drug delivery and tissue engineering. Polymer Reviews. 2025;65:104-68.
[188] Shen J, Tong Z, Han B, Zhang Z, Xian Z, Yuan Y, et al. Synergistic Wound Healing: Unraveling the Multi-Target Effects of Traditional Chinese Medicine and Its Biomaterials on Chronic Wound Pathways. International journal of nanomedicine. 2025:12889-912.
[189] Siafaka PI, Miliotou AN, Okur ME, Karaotmarlı Güven G, Karantas ID, Üstündağ Okur N. Nanoformulations loaded with phytochemicals for combating wound infections and promoting wound healing: current applications and innovations. Applied Sciences. 2025;15:5413.
[190] Alum EU, Nwuruku OA, Ugwu OP-C, Uti DE, Alum BN, Edwin N. Harnessing nature: plant-derived nanocarriers for targeted drug delivery in cancer therapy. Phytomedicine Plus. 2025;5:100828.
[191] Fan X, Guo S, Li W, Wang Y, Bao J, He J, et al. Natural products as metabolic modulators to enhance cancer immunotherapy: reprogramming the tumor microenvironment. Frontiers in Immunology. 2025;16:1740644.
[192] Yu X, Yang J, Xu J, Pan H, Wang W, Yu X, et al. Histone lactylation: from tumor lactate metabolism to epigenetic regulation. International journal of biological sciences. 2024;20:1833.
[193] Kardani SL. Nanocarrier-based formulations: regulatory challenges, ethical and safety considerations in pharmaceuticals. Asian Journal of Pharmaceutics (AJP). 2024;18.

[194] Kumar M, Keshwania P, Chopra S, Mahmood S, Bhatia A. Therapeutic potential of nanocarrier-mediated delivery of phytoconstituents for wound healing: their current status and future perspective. Aaps Pharmscitech. 2023;24:155.