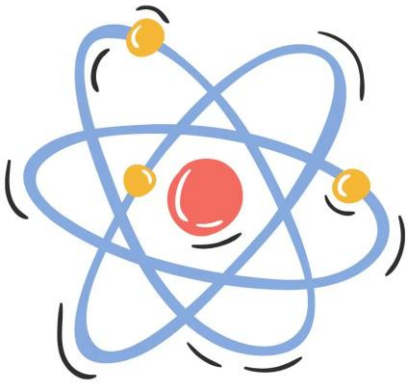

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Abstract: *The nootropic drug piracetam, a cyclic derivative of γ-aminobutyric acid (GABA), is well known for its hemorheological, antioxidant, and neuroprotective qualities. Its possible significance in cutaneous wound healing has not gotten much attention, despite being thoroughly studied in neurological illnesses. With a focus on oxidative stress, inflammation, mitochondrial dysfunction, microcirculatory impairment, and platelet-derived growth factor-β (PDGF-β) and vascular endothelium growth factor (VEGF) associated regenerative signalling, this study assesses the mechanistic justification for piracetam's repurposing in wound healing. Excessive reactive oxygen species formation, ongoing inflammatory cytokine release, mitochondrial dysfunction, decreased tissue perfusion, and flawed cellular repair responses are all indicators of impaired wound healing. According to experimental research, piracetam reduces oxidative stress, replenishes endogenous antioxidant defences, maintains the potential of the mitochondrial membrane, inhibits pro-inflammatory mediators, and enhances microcirculation when tissue damage occurs. The cellular milieu needed for fibroblast proliferation, angiogenesis, extracellular matrix remodelling, and growth factor mediated tissue repair may be improved by these pharmacological characteristics. Additionally, preliminary data from experimental burn wound models indicates that piracetam has positive effects on wound closure, collagen organization, and epithelialisation. However, there is currently little direct validation in wound-healing models, and the majority of the evidence is preclinical and indirect. All things considered, piracetam is a potential multi-target candidate for wound healing that merits additional mechanistic and translational research.*

Keywords: *Piracetam, wound healing, oxidative stress, inflammation, microcirculation, mitochondrial dysfunction, PDGF-β signaling.*

Introduction

The skin, the body's largest organ, constitutes roughly 16% of total body weight and plays a critical role in maintaining homeostasis while acting as a protective barrier against external insults [1]. Preservation of skin integrity is essential for overall health, as damage caused by chronic diseases, burns, trauma, or surgical interventions can result in functional impairment and significant psychological distress. Collectively, these complications impose a substantial burden on healthcare systems worldwide [2]. Chronic wounds have emerged as a significant and expanding clinical

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challenge, with rising incidence rates contributing to a considerable economic burden on healthcare systems. This increase is largely driven by an aging population and the global surge in obesity and diabetes. As a result, the costs associated with the management and treatment of these persistent, non-healing wounds have escalated substantially [3]. Pressure ulcers and diabetic foot ulcers are major causes of morbidity rates and have a high financial cost [4]. Traditional wound management relies on basic interventions, including infection control, regular dressing changes, and the removal of necrotic tissue through debridement [5]. There is no reliable pharmacological agent that targets multiple healing pathways. Drug repurposing, which is also referred to as drug repositioning, reconfiguration, or re-tasking. Compared to creating completely novel medications for a particular indication, pharmacological repurposing has definite advantages. Since these medications have previously shown acceptable safety profiles in preclinical research and human use, the most important advantage is a decreased risk of failure. Timelines and development expenses are also much reduced. Crucially, repurposing can also reveal biological pathways and targets that were previously unknown, opening doors for additional therapeutic innovation [6] , This approach is suitable for complex processes like wound healing. Piracetam was initially synthesized in 1964s by a scientist named Dr. Corneliu E. Giurgea in UCB Pharm in Belgium. It is a cyclic derivative of gamma amino butyric acid (GABA) and was the first nootropic drug [7], demonstrated antioxidant effects, microcirculatory improvement, mitochondrial support and anti-inflammatory effects. [8,9]These mechanisms are not limited to the brain, in fact piracetam explored in burn wound [10]. Piracetam has been extensively studied for its neuroprotective properties; however, its role in wound healing remains largely unexplored. This review aims to critically evaluate whether the established pharmacological actions of piracetam can be mechanistically translated into cutaneous wound healing.

Biology of Wound Healing

i. Hemostatic Phase

The hemostatic phase, which includes coagulation as well as primary and secondary hemostasis, starts wound healing right after tissue damage. Fibrinogen, a plasma protein produced by hepatocytes, is transformed into fibrin by this process, which is mostly mediated by platelets and the coagulation cascade. The ensuing fibrin network creates a temporary matrix that sets the basis for later stages of wound repair and stabilizes the initial platelet plug [11]. When a vessel wall is damaged, the tunica media's vascular smooth muscle cells quickly constrict as a result of the immediate neurogenic reflex responses. The release of endothelin from damaged endothelium cells is the main mediator of this reaction, and circulating catecholamines released from injured tissues further strengthen it. The combined impact limits blood loss at the site of damage and temporarily reduces blood flow [12]. Vasoconstriction is essential for avoiding excessive blood loss, as is the creation of a platelet-rich thrombus by platelet aggregation and plug formation (primary

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haemostasis). Subendothelial collagen exposure after vascular damage starts this process by activating platelets through G protein-coupled receptors, which promotes adhesion, activation, and aggregation at the site of injury [13]. Vasoconstriction, however, is a temporary reaction that is only useful for a brief period of time. Tissue hypoxia causes metabolic acidosis in the artery wall, which causes vascular smooth muscle to passively relax and vasodilate. Increased vascular permeability, fluid extravasation, and tissue edema accompany this change, which may jeopardise haemostasis and cause bleeding to resume [14]. Adhesive glycoproteins and bioactive mediators like sphingosine-1-phosphate are released at the site of vascular damage, facilitating platelet adhesion and aggregation. These elements increase thrombus formation by improving platelet–matrix interactions and increasing the recruitment and activation of extra platelets [15]. In addition to preventing blood loss, the development of a stable thrombus, which is made up of a platelet plug strengthened by a fibrin mesh produced by activation of the coagulation cascade (secondary hemostasis), also starts the initial signaling processes in wound healing. Epidermal growth factor (EGF), transforming growth factor (TGF)-α and TGF-β, insulin-like growth factor (IGF), interleukin-1 (IL-1), platelet-derived growth factor (PDGF) and vascular endothelium growth factor(VEGF) are among the many growth factors and cytokines released by activated platelets [16].

ii. Inflammatory Phase

After tissue damage, the inflammatory phase of wound healing begins within 24 hours and can last up to two weeks, especially in complex wounds. Rapid inflammatory cell recruitment and the production of a wide range of enzymes, cytokines, and bioactive mediators are the hallmarks of this phase, which together result in the traditional indicators of inflammation—dolor, rubor, calor, and tumour. The early response is dominated by neutrophils, which mediate debris removal and pathogen clearance. Macrophages then coordinate phagocytosis, cytokine signalling, and the proliferative phase shift. T-lymphocytes further control the immune response by regulating repair processes through cytokines, The first cells to react to the chemotactic platelet products are neutrophils [17]. Circulating leukocytes migrate transendothelially into the extravascular space after undergoing margination and adhering to the vascular endothelium at the site of damage. Cell adhesion molecules (CAMs), which mediate contacts between cells and the extracellular matrix, closely control this process. During wound healing, CAMs serve as transmembrane receptors that promote cellular adhesion, motility, and intracellular signalling. Despite not being CAM carriers, fibroblasts have adhesion receptors, especially integrins, which provide coordinated cell-to-cell communication and allow contact with the extracellular matrix. Migration, proliferation, and matrix deposition all depend on these interactions. Adhesion molecule dysregulation or lack hinders cellular recruitment and signalling, which eventually slows down the healing process [18]. Effective infiltration of the wound site is made possible by the release of proteolytic enzymes like collagenase

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and elastase, which promote neutrophil transmigration across the endothelial basement membrane and into the extracellular matrix. These enzymes promote cellular motility, phagocytosis, and the removal of necrotic tissue by breaking down damaged structural proteins. Neutrophils secrete pro-inflammatory cytokines, such as TNF-α and IL-1, in addition to their proteolytic activity. These cytokines are essential for attracting and activating fibroblasts and epithelial cells, which starts the proliferative phase of wound repair, Following monocyte recruitment, macrophages enter the wound site and are essential for both phagocytosis and immunological control. They secrete a variety of growth hormones and cytokines, such as PDGF, TGF-β, FGF, TNF-α, IL-1, and IL-6, while also using phagocytic activity to remove pathogens and cellular waste. These mediators facilitate the change from the inflammatory to the proliferative phase of wound healing by promoting fibroblast recruitment, angiogenesis, and extracellular matrix formation [19]. During the later phases of the inflammatory phase, lymphocytes penetrate the wound site and predominantly use cytokine secretion to regulate healing. Interleukin-2 (IL-2), which is produced by activated T cells, is essential for regulating immunological responses and boosting fibroblast infiltration, proliferation, and metabolic activity. Furthermore, lymphocyte-derived cytokines facilitate tissue healing and the transition to the proliferative phase by coordinating interactions between immune and stromal cells [20].

iii. Proliferation Phase

Fibroblasts migrate into the wound site to initiate the proliferative phase of wound healing. This process is mainly triggered by platelet-derived growth factor (PDGF), which is generated from platelets and macrophages. PDGF facilitates extracellular matrix remodelling and tissue repair by promoting chemotaxis, fibroblast proliferation, and collagenase synthesis [17]. PDGF promotes collagenase synthesis, chemotaxis, and fibroblast proliferation [21]. Fibroblasts produce and deposit structural proteins, especially collagen, which gives the regenerating tissue its tensile strength and structural integrity [22]. Matrix metalloproteinases (MMPs), a class of proteolytic enzymes that aid fibroblast migration through the extracellular matrix, are also produced by fibroblasts. In order to restore tissue integrity, fibroblasts gradually decrease their proteolytic activity as wound healing advances and start producing and depositing structural proteins, especially collagen. Connective tissue growth factor (CTGF), which is generated by fibroblasts themselves, and transforming growth factor-β (TGF-β), which is secreted by platelets and macrophages, are the main factors controlling this transformation [23]. During the proliferative stage of wound healing, angiogenesis creates granulation tissue to repair damaged vasculature. Growth factors including basic fibroblast growth factor (βFGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF) are secreted by epidermal cells, fibroblasts, vascular endothelial cells, and macrophages. VEGF, a member of the PDGF family of growth factors, has potent angiogenesis, as well as vasopermeability, activity which led to its initial

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designation as vasopermeability factor (VPF) [24] and essential for the growth and neovascularisation of endothelial cells [17]. The expression of vascular endothelial growth factor (VEGF) and its receptor is greatly stimulated by low oxygen tension, as seen during tissue hypoxia. This promotes angiogenesis and vascular remodelling during wound healing [24–26].

iv. Remodelling Phase

The resolution stage of wound healing, known as remodelling, is characterised by a steady loss of inflammatory cells and a decrease in the quantity of cells that secrete growth factors. Fibroblasts continue to produce and deposit collagen, helping to reconstruct the extracellular matrix and restore tissue strength, even as their numbers also start to decline [27]. Collagen fibres undergo gradual covalent cross-linking and reorganisation during remodelling, which increases the regenerated tissue's tensile strength. The ultimate tensile strength of a well-healed wound may be about 80% of that of healthy, uninjured tissue [17].The precise coordination of several overlapping biological processes, such as angiogenesis, growth factor-mediated cellular signalling, extracellular matrix remodelling, and inflammatory control, is ultimately necessary for efficient wound healing. The preservation of oxidative balance, sufficient mitochondrial energy production, efficient microcirculatory perfusion, and persistent action of growth factors like platelet-derived growth factor-β (PDGF-β) and VEGF all have a significant impact on these events [28,29]. When these interrelated processes are disrupted, fibroblast function is compromised, collagen deposition is compromised, inflammation persists, and tissue regeneration is delayed, all of which lead to chronic or non-healing wounds. As a result, pharmaceuticals that may concurrently alter these pathways may have substantial therapeutic promise for wound healing, all phases depicted in fig **1**.

Figure **1** : **Biology of Wound Healing**

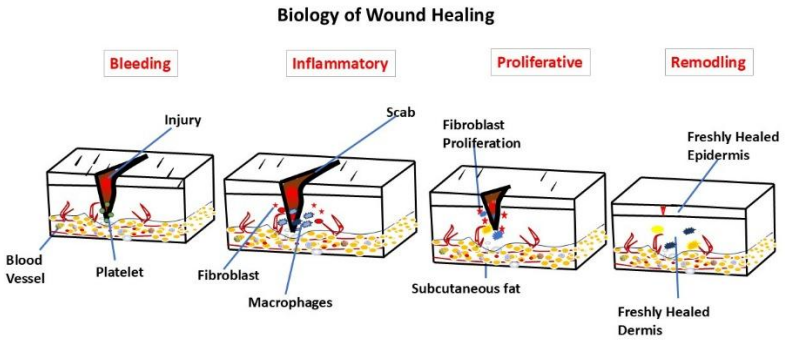

Fig 1: Schematic representation of the sequential phases of cutaneous wound healing, including hemostasis (bleeding/coagulation), inflammation, proliferation, and remodeling. Each phase is characterized by distinct cellular and molecular events that collectively contribute to tissue repair, re-epithelialization, extracellular matrix deposition, and restoration of skin integrity.

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Pharmacological Profile and Pleiotropic Properties of Piracetam

Piracetam, a cyclic derivative of γ-aminobutyric acid (GABA), was the first compound introduced under the class of nootropic agents [7]. Initially developed for its cognitive-enhancing properties, piracetam has since demonstrated a wide range of pharmacological effects extending beyond memory and learning modulation. Although the mechanism of action of piracetam is not fully elucidated till now [7]. Experimental and clinical studies have reported its potential roles in improving microcirculation, enhancing erythrocyte deformability, stabilizing cellular membranes, modulating mitochondrial function, and reducing oxidative and inflammatory injury [8]. Owing to these pleiotropic properties, piracetam has been investigated in various neurological and ischemic conditions, including stroke, neuroinflammation, epilepsy, traumatic brain injury, and oxidative stress-associated disorders [9]. Importantly, many of the mechanisms implicated in piracetam-mediated neuroprotection such as attenuation of oxidative stress, preservation of mitochondrial integrity, suppression of pro-inflammatory cytokines, and improvement of tissue perfusion are also critically involved in the regulation of wound healing [30]. These mechanistic overlaps suggest that piracetam may possess potential translational relevance in cutaneous wound repair, despite the current lack of direct experimental evidence in wound-healing models.

Pathophysiological Barriers in Impaired Wound Healing and the Potential Role of Piracetam

i. Oxidative Stress Modulation

The condition known as oxidative stress, which is brought on by an imbalance in the form of excess ROS, may be a contributing factor to the development of chronic wounds [31].While excessive ROS formation is detrimental to wound healing, ROS production is necessary to start wound repair. It has been demonstrated that persistent oxidative stress, which is linked to lipid peroxidation, protein modification, and DNA damage, hinders wound healing processes by increasing cell senescence and apoptosis,[32–36] and also involved in dysregulated re-epithelialization and a prolonged pro-inflammatory environment during wound healing [37].Given the critical role of oxidative stress in impaired wound healing, pharmacological agents capable of restoring redox homeostasis may provide therapeutic benefit in tissue repair. Experimental studies have demonstrated that piracetam possesses significant antioxidant properties in conditions associated with inflammatory oxidative injury. In lipopolysaccharide (LPS)-induced neuroinflammation models, piracetam restored glutathione (GSH) levels and glutathione reductase activity, indicating enhancement of endogenous antioxidant defense mechanisms [8].Furthermore, piracetam significantly attenuated lipid peroxidation, suggesting protection against reactive oxygen species (ROS)-mediated membrane damage and cellular injury [8]. Since excessive ROS generation in chronic wounds contributes to fibroblast dysfunction, impaired re-epithelialization, persistent inflammation, and increased cellular apoptosis, the antioxidant effects of piracetam may help create a more favorable microenvironment for tissue repair as depicted in figure **2**. Although these findings

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are primarily derived from neuroprotective models, the underlying oxidative mechanisms are highly relevant to wound healing pathology.

ii. Mitochondrial Dysfunction

Mitochondria are essential regulators of cellular homeostasis and serve as the primary source of intracellular energy in eukaryotic cells[38]. Through the electron transport chain (ETC), comprising complexes I–IV, coenzyme Q, cytochrome c, and ATP synthase (complex V), mitochondria generate ATP required for various energy-dependent cellular processes involved in tissue repair [39]. Disruption of mitochondrial function impairs ATP synthesis, alters cellular metabolism, and contributes to defective wound healing [40]. In response to tissue injury, damaged mitochondria may release mitochondrial damage-associated molecular patterns (DAMPs), which amplify inflammatory signaling and further aggravate cellular dysfunction [41,42]. In addition, fibrinogen, which acts as a DAMP under pathological conditions, has been reported to reduce mitochondrial membrane potential and promote inflammatory responses [43].Mitochondrial membrane potential (MMP) is critical for maintaining mitochondrial integrity and efficient ATP production. Loss of MMP disrupts oxidative phosphorylation, enhances reactive oxygen species (ROS) generation, and promotes cellular injury. In chronic wounds, mitochondrial dysfunction contributes to impaired fibroblast proliferation, defective collagen synthesis, delayed re-epithelialization, and persistent inflammation [44]. Experimental studies in lipopolysaccharide (LPS)-induced neuroinflammation models demonstrated that piracetam restored mitochondrial membrane potential while simultaneously reducing pro-inflammatory cytokines such as TNF-α, IL-1β, and IFN-γ. These findings suggest that piracetam may help preserve mitochondrial integrity under inflammatory oxidative conditions as depicted in figire **2** . Although these observations originate from neuroprotective models, maintenance of mitochondrial function and cellular bioenergetics is equally critical in wound healing, where energy-demanding processes such as cell migration, extracellular matrix synthesis, and angiogenesis are required for effective tissue regeneration [8,44].

Fig 2: Key pathological mechanism in impared wound healing and potential beneficial action of piracetam

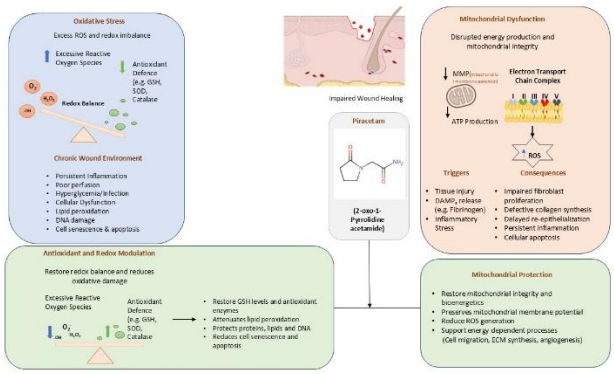

Fig 2-Piracetam is thought to work by reducing oxidative stress and mitochondrial malfunction, which hinders

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wound healing. Piracetam promotes efficient wound healing by restoring redox balance, strengthening antioxidant defences, maintaining mitochondrial integrity, lowering ROS generation, and supporting cellular repair processes.

iii. Inflammatory Dysregulation in Impaired Wound Healing

Persistent inflammation is a major pathological feature of impaired wound healing and contributes to extracellular matrix degradation, fibroblast dysfunction, delayed re-epithelialization, and prolonged tissue injury [45–47]. Excessive production of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and activation of nuclear factor-kappa B (NF-κB), sustains a chronic inflammatory microenvironment that interferes with normal tissue repair processes [48]. Experimental evidence from doxorubicin (DOX)-induced inflammatory injury models has demonstrated that piracetam possesses significant anti-inflammatory properties. DOX-induced oxidative stress markedly increased inflammatory mediators and cytokine expression [49], whereas piracetam treatment significantly reduced TNF-α levels and suppressed the expression of key inflammatory mediators, including cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), and NF-κB. In addition, piracetam attenuated inflammatory cytokine dysregulation associated with elevated acetylcholinesterase activity [50]. These findings suggest that piracetam may help limit excessive inflammatory signaling and improve the wound microenvironment by reducing cytokine-mediated tissue injury as depicted in figure **3**. Although these observations are derived primarily from non-wound experimental models, the underlying anti-inflammatory mechanisms are highly relevant to chronic wound pathology and may support progression toward effective tissue repair.

iv. Microcirculatory Impairment

A crucial pathological characteristic of chronic and non-healing wounds is microcirculatory impairment, where decreased blood perfusion restricts the delivery of nutrients, oxygen, immune cells, and growth factors necessary for efficient tissue repair. Insufficient microvascular circulation delays fibroblast proliferation, collagen production, angiogenesis, and re-epithelialization by causing tissue hypoxia, chronic inflammation, oxidative stress, and altered cellular metabolism. Furthermore, altered blood rheological characteristics and endothelial dysfunction further impair capillary perfusion in the wound microenvironment. Therefore, sustaining tissue oxygenation and meeting the high metabolic requirements of regenerated tissue during wound healing depend on adequate microcirculatory activity. Research has shown that angiogenesis and extracellular matrix remodeling—both essential for appropriate wound closure and tissue maturation—are severely disrupted by poor oxygen delivery [29,51–55]. Experimental evidence suggests that piracetam may exert beneficial effects on microcirculatory function through its hemorheological and antioxidant properties. In rotenone-induced oxidative injury models, piracetam significantly reduced malondialdehyde (MDA) levels while restoring glutathione (GSH) content in several brain regions,

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indicating attenuation of oxidative tissue injury [56]. Beyond its antioxidant effects, piracetam has also been reported to improve cerebral blood flow, thereby enhancing oxygen and glucose availability to metabolically stressed tissues [57]. These effects are believed to be mediated, at least in part, through improved erythrocyte deformability and enhanced microvascular perfusion. Although these observations were primarily reported in neuroprotective experimental models, the underlying mechanisms are highly relevant to wound healing, where restoration of local perfusion and oxygen supply is essential for fibroblast activity, angiogenesis, collagen deposition, and overall tissue regeneration as depicted in figure **3**. Consequently, piracetam may indirectly support wound repair by improving the microcirculatory environment required for effective healing.

Fig 3: Key pathological mechanism in impared wound healing and potential beneficial action of piracetam

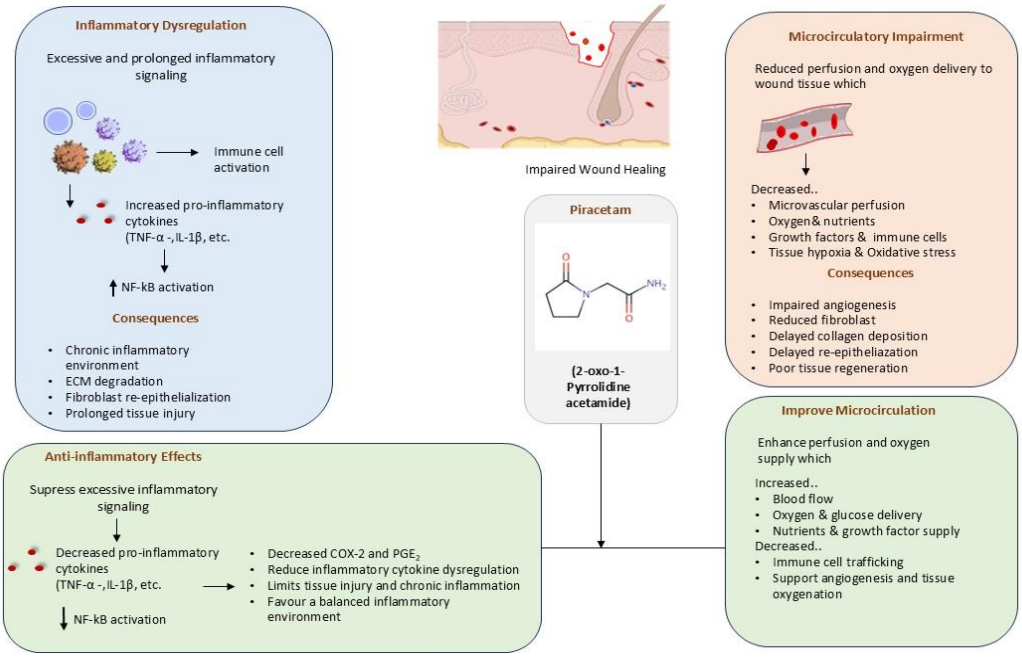

Fig 3-Piracetam may play a part in poor wound healing by modifying inflammatory dysregulation and impairing microcirculation. In order to promote efficient wound healing, piracetam inhibits excessive inflammatory signalling, lowers pro-inflammatory cytokines, enhances microvascular perfusion and oxygen delivery, and promotes angiogenesis and tissue regeneration.

Interrelationship Between Oxidative Stress, Inflammation, Mitochondrial Dysfunction, Microcirculatory Impairment, and PDGF-β Signaling in Wound Healing

The pathogenic mechanisms that interfere with normal wound healing and growth factor-mediated tissue repair include oxidative stress, mitochondrial dysfunction, prolonged inflammation, and decreased microcirculation. Platelet-derived growth factor-β (PDGF-β), one of the growth factors involved in wound regeneration, is essential for controlling angiogenesis, chemotaxis, fibroblast proliferation, and extracellular matrix deposition. However, PDGF-mediated cellular responses can

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be adversely affected and successful tissue regeneration compromised by increased production of reactive oxygen species, inflammatory cytokine signalling, cellular energy depletion, and decreased tissue perfusion [29,58–60]. Piracetam may indirectly support PDGF-β-associated wound healing processes by improving the cellular and metabolic microenvironment required for efficient growth factor signalling because it has shown antioxidant, anti-inflammatory, mitochondrial-protective, and microcirculatory-enhancing properties in a variety of experimental models.

Translational and Therapeutic Potential of Piracetam in Wound Healing

i. Potential Role of Piracetam in Acute Wound Healing

Acute wounds, including surgical incisions, traumatic injuries, and burn wounds, generally undergo an organized sequence of hemostatic, inflammatory, proliferative, and remodeling phases that culminate in tissue repair. However, excessive oxidative stress and uncontrolled early inflammatory responses following tissue injury can disrupt this tightly regulated process and contribute to secondary cellular damage. During the early stages of acute wound healing, reactive oxygen species (ROS) are rapidly generated at the injury site. Although physiological ROS levels are required for antimicrobial defense and signaling, excessive ROS production may induce lipid peroxidation, cellular membrane damage, endothelial dysfunction, and impaired fibroblast activity, thereby delaying tissue repair [29,54,55]. In addition, early inflammatory cytokine release can amplify tissue injury and prolong local edema and vascular dysfunction. Experimental evidence from multiple non-wound models suggests that piracetam possesses antioxidant and anti-inflammatory properties that may be relevant during the early stages of acute wound repair. Piracetam has been shown to restore endogenous antioxidant defenses, reduce lipid peroxidation, and attenuate inflammatory cytokines such as TNF-α and IL-1β under oxidative and inflammatory conditions.[8,50] Furthermore, adequate tissue perfusion and oxygen delivery are essential during acute wound healing to support angiogenesis, fibroblast migration, collagen synthesis, and re-epithelialization [14,35,52]. Piracetam has also demonstrated hemorheological and microcirculatory-enhancing properties, including improved blood flow and increased oxygen and glucose availability in experimental studies [56,57]. These findings suggest that piracetam may help support the early wound-healing environment by limiting oxidative tissue injury, modulating excessive inflammation, and improving local tissue perfusion as depicted in figure **4**. Nevertheless, direct experimental studies evaluating piracetam in acute cutaneous wound models remain unavailable.

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Fig 4: Potential role of Piracetam in Acute Wound Healing

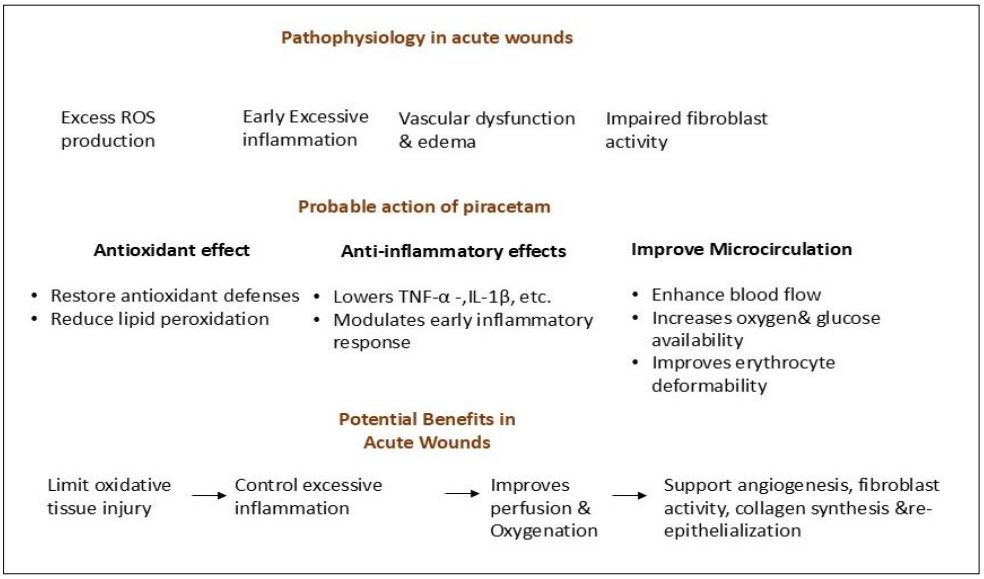

Fig 4: Piracetam's potential contribution to acute wound healing through the regulation of oxidative stress, inflammation, and microcirculation.

ii. Potential Relevance of Piracetam in Chronic and Diabetic Wounds

Chronic wounds, especially diabetic ulcers, often get stuck in a chronic inflammatory state and are characterised by impeded progression through the typical phases of healing. Chronic and diabetic wounds, in contrast to acute wounds, show persistent oxidative stress, prolonged generation of inflammatory cytokines, mitochondrial dysfunction, reduced angiogenesis, faulty extracellular matrix remodelling, and microvascular insufficiency [29,55].Reactive oxygen species (ROS) overproduction linked to hyperglycemia impedes successful wound closure by causing endothelial dysfunction, fibroblast senescence, poor collagen deposition, and delayed re-epithelialization. Pro-inflammatory mediators including TNF-α and IL-1β are also persistently elevated, which prolongs tissue damage and interferes with the transition from inflammation to proliferation [28]. Another major factor in the pathophysiology of diabetic wounds is mitochondrial dysfunction. Energy-dependent cellular processes necessary for tissue healing, such as fibroblast proliferation, angiogenesis, collagen synthesis, and keratinocyte migration, are compromised by impaired mitochondrial bioenergetics and decreased ATP production. Diabetic microvascular dysfunction-induced chronic tissue hypoxia further restricts the transport of nutrients and oxygen to the wound bed, exacerbating cellular metabolic impairment and slowing recovery [53,54].Furthermore, platelet-derived growth factor-β (PDGF-β)-mediated signalling pathways may be compromised by long-term oxidative and inflammatory stress, which would decrease fibroblast responsiveness and extracellular matrix synthesis, both of which are essential for wound regeneration. Piracetam's pharmacological characteristics in several experimental settings exhibit significant mechanistic

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overlap with similar pathological anomalies found in chronic wounds. In situations of oxidative and inflammatory damage, piracetam has been shown to improve microcirculatory function, lower lipid peroxidation, maintain mitochondrial membrane potential, decrease inflammatory cytokines, and restore glutathione levels [56,61,62]. Growth factor-mediated tissue repair processes may be indirectly supported by these effects, which may also help to alleviate the dysfunctional wound microenvironment. In diabetic wounds, where poor microcirculation and ongoing inflammation continue to be significant obstacles to healing, piracetam-mediated improvement of tissue perfusion and decrease of oxidative cellular damage may be particularly pertinent as depicted in figure **5.** The molecular parallels between piracetam-responsive pathways and chronic wound pathology offer a biologically plausible justification for further translational research, notwithstanding the current lack of direct proof in diabetic wound models.

Fig 5 : Potential Relevance of Piracetam in Chronic and Diabetic Wounds

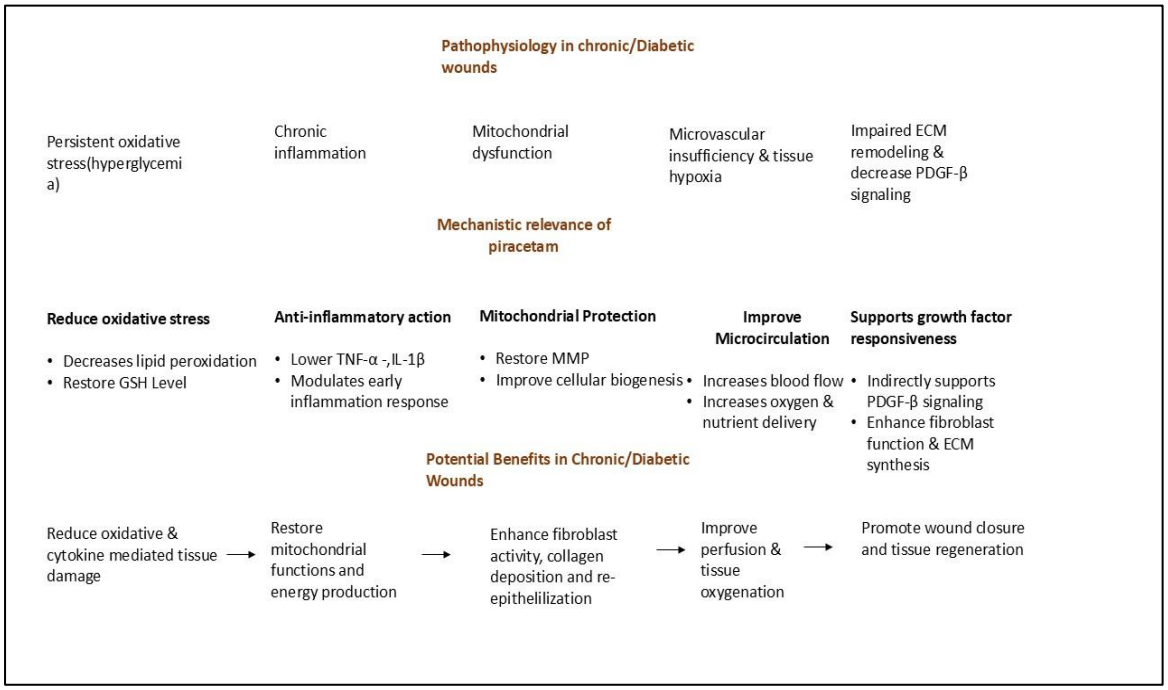

Fig 5: suggested molecular explanation for piracetam's possible contribution to diabetic and chronic wound healing. Piracetam may promote fibroblast activity, extracellular matrix remodelling, tissue oxygenation, and PDGF-β-associated regeneration processes by reducing oxidative stress, chronic inflammation, mitochondrial dysfunction, and microcirculatory impairment.

iii. Potential Role of Piracetam in Combination and Adjunctive Wound Therapy

Combination-based therapy techniques are often necessary for effective wound management since chronic and complex wounds engage numerous pathogenic processes concurrently[29,55].Piracetam has been found to have direct positive benefits in an experimental full-thickness burn wound model in addition to its experimentally proven antioxidant, anti-inflammatory, mitochondrial-protective, and microcirculatory-enhancing qualities. In comparison

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to untreated controls, topical and systemic piracetam administration in rabbits enhanced the quality of epithelialisation, collagenization, skin organization, lowered inflammation and necrosis, and markedly reduced ulcer diameter depicted in figure **6.** Additionally, wounds treated with piracetam showed better healing without significant hypertrophic scarring and more regular connective tissue architecture [10]. These results imply that piracetam may have adjunctive therapeutic potential in the treatment of wounds, especially when paired with well-known wound-healing techniques such growth factor therapy, sophisticated wound dressings, antioxidant formulations, or diabetic wound care techniques. To confirm its translational application in chronic and non-healing wounds, more mechanistic and clinical research is required.

Fig 6: Potential Role of Piracetam in Combination and Adjunctive Wound Therapy

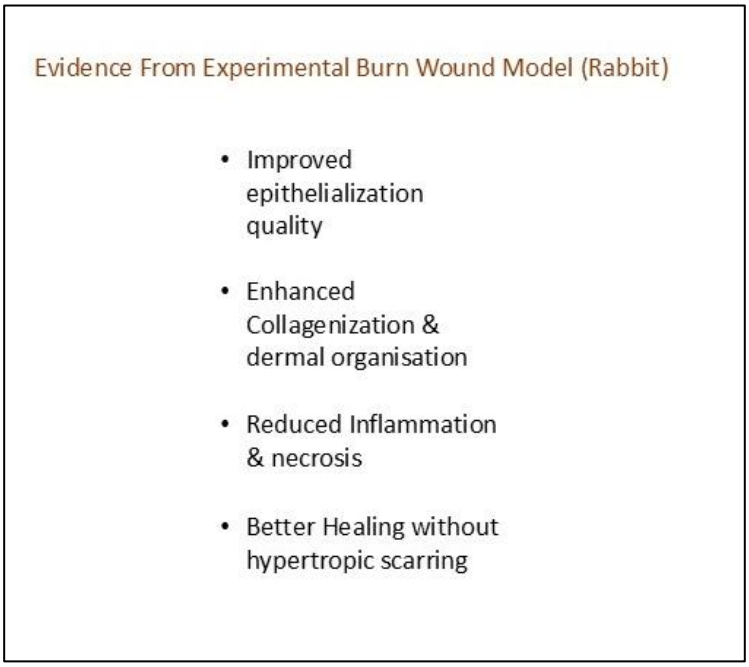

Fig 6: Piracetam's wound-healing properties, such as increased epithelialisation, improved collagen organization, decreased inflammation and necrosis, and improved tissue regeneration with less hypertrophic scarring, were demonstrated experimentally in a rabbit burn wound model.

Limitations

Piracetam's potential as a wound-healing drug is supported by a promising molecular explanation, however there are a number of limitations to be aware of. There are still few direct studies on wound-healing systems, and the majority of the evidence that is now available comes from neurological and non-cutaneous experimental models [8,10,56]. Piracetam has been shown to have positive effects on epithelialisation, collagen organization, inflammation, and wound closure in an experimental burn wound investigation [8,10], although there is currently insufficient evidence in

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chronic and diabetic wound models. Additionally, no research has examined how piracetam and platelet-derived growth factor-β (PDGF-β) signalling pathways interact during tissue repair. Additionally, the majority of current research is preclinical, which restricts direct clinical translation. Furthermore, piracetam's ideal therapeutic dosage, mode of administration, length of treatment, and long-term safety profile for wound-healing applications have not yet been determined. Therefore, rather than being clinically validated, the suggested effect of piracetam in cutaneous wound healing should still be regarded as exploratory and hypothesis-driven.

Future Directions

Future studies should concentrate on verifying piracetam's ability to cure wounds utilising standardised experimental wound models, such as burn, excision, incision, and diabetic wound models. Mechanistic research assessing piracetam's impact on oxidative stress regulation, mitochondrial function, inflammatory signalling, angiogenesis, collagen deposition, fibroblast proliferation, and PDGF-β-associated cellular responses during tissue repair should receive special attention. Its translational significance in wound care may further be clarified by additional research into topical formulations, localised drug delivery devices, and combination-based therapy approaches. To identify the best therapeutic approach for cutaneous applications, pharmacokinetic and dose-optimization studies are also required. The effectiveness, safety, and therapeutic application of piracetam in acute and chronic wound healing will ultimately need to be established through well planned clinical trials.

Conclusion

Piracetam has a wide range of pharmacological characteristics, including as antioxidant, anti-inflammatory, mitochondrial-protective, and microcirculatory-enhancing actions, that are mechanistically relevant to wound healing. These mechanisms strongly correspond with a number of important pathogenic processes, including oxidative stress, persistent inflammation, mitochondrial dysfunction, tissue hypoxia, and poor growth factor-mediated regeneration, that are implicated in deficient wound repair. Piracetam's precise molecular mechanism is still unknown, but experimental data indicates that it may enhance the cellular microenvironment required for successful tissue repair and indirectly support angiogenesis, extracellular matrix remodelling, and platelet-derived growth factor-β (PDGF-β) signalling. Crucially, the biological plausibility of its wound-healing ability is further reinforced by preliminary data from experimental burn wound models. However, there is currently little direct validation in cutaneous wound-healing models, and the majority of the evidence is preclinical and indirect. Therefore, even though piracetam is a promising multi-target candidate for wound-healing applications, its therapeutic significance in wound management cannot be confirmed unless thorough mechanistic research and carefully planned experimental and clinical studies are conducted.

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