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REVIEW ARTICLE

α-Mangostin in Diabetic Wound Healing: Roles of Growth Factors and Endothelial Dysfunction

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ABSTRACT

Diabetic foot ulcers (DFUs) represent one of the most debilitating complications of diabetes mellitus, largely driven by impaired wound healing processes, endothelial dysfunction, and dysregulated growth factor activity. Normal wound repair is orchestrated by a coordinated sequence of cellular and molecular events involving macrophages, fibroblasts, and endothelial cells, with growth factors such as PDGF, VEGF, TGF-β, bFGF, and CTGF playing central roles. In diabetic conditions, however, hyperglycemia-induced oxidative stress, reduced nitric oxide availability, and chronic inflammation disrupt these pathways, leading to delayed angiogenesis and poor tissue regeneration. Natural products have emerged as promising alternatives for chronic wound management, owing to their antioxidant, anti-inflammatory, and pro-angiogenic properties. Among these, α-mangostin, the predominant xanthone in the mangosteen (Garcinia mangostana) pericarp, has demonstrated potent anti-inflammatory and proliferative effects in vitro, accelerating fibroblast migration and suppressing cytokines such as IL-6 and IL-8. While most studies to date have focused on normal wound models, evidence suggests that α-mangostin may also modulate endothelial function and growth factor signaling under diabetic conditions. This review synthesizes current knowledge on growth factor regulation, endothelial dysfunction, and the therapeutic potential of α-mangostin in diabetic wound healing. Understanding

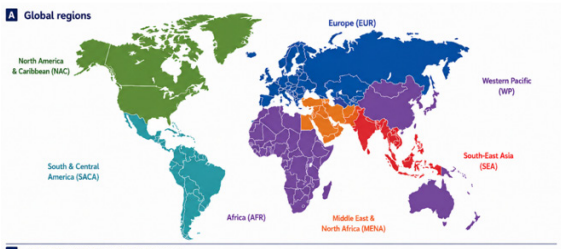
these mechanisms may provide a foundation for developing cost-effective, locally sourced, natural product-based therapies to reduce the clinical and economic burden of DFUs.

INTRODUCTION

Diabetes mellitus is a chronic and multifactorial metabolic disorder marked by persistent hyperglycaemia, resulting from impaired insulin secretion, insulin resistance, or both. Prolonged hyperglycaemia contributes to progressive damage across multiple organ systems, ultimately leading to complications such as blindness, kidney failure, and cardiovascular disease (Maurya, Varma, Chaurasia, Vishwakarma, & Reviews, 2019; Pan, Kaminga, Wen, Acheampong, & Liu, 2019).

Malaysia is also experiencing an alarming rise in diabetes prevalence. The proportion of Malaysian adults with the disease increased from 8.3% in 1996 to 14.9% in 2006, and further to 18.3% in 2019. By 2025, projections indicate that nearly 7 million Malaysian adults will be affected (Akhtar et al., 2022; Ganasegeran et al., 2021). This rapid increase prompted the Ministry of Health to launch a nationwide healthy lifestyle campaign aimed at strengthening screening and management of diabetes in both primary and secondary healthcare settings, accompanied by the establishment of a national steering committee (Yun et al., 2007). Figure 1 shows the global trend of diabetes.

If diabetes is not adequately controlled, patients may develop chronic complications that progress gradually over time. These complications are generally classified into macrovascular, microvascular, and immunosuppressive categories. Macrovascular complications include cerebrovascular, cardiovascular, and peripheral vascular diseases, while microvascular complications give rise to diabetic nephropathy, retinopathy, and neuropathy. Immunosuppression, on the other hand, predisposes individuals to diabetic foot ulcers, impaired wound healing, and a heightened risk of infection. Such conditions are frequently observed among the diabetic population in Malaysia. In particular, the interplay of immunosuppression, peripheral vascular disease, microangiopathy, neuropathy, and weakened immune responses significantly contributes to poor wound healing and the development of diabetic foot ulcers (DFU), which may ultimately progress to gangrene and necessitate amputation (Deshpande, Harris-Hayes, & Schootman, 2008; Ganasegeran et al., 2020).



B Population projections by region (millions)

Year	North America & Caribbean (NAC)	South & Central America (SACA)	Africa (AFR)	Middle East & North Africa (MENA)	Europe (EUR)	Western Pacific (WP)	South-East Asia (SEA)
2021	51 million	32 million	24 million	73 million	61 million	206 million	90 million
2030	57 million	40 million	33 million	95 million	67 million	238 million	113 million
2045	63 million	49 million	55 million	136 million	69 million	260 million	152 million
Increase (2021–2045)	↑ 24%	↑ 50%	↑ 134%	↑ 87%	↑ 13%	↑ 27%	↑ 68%

Figure 1: Global and regional distribution and projected number of adults with diabetes from 2021 to 2045. The figure presents estimates across seven geographical regions for 2021, with projections for 2030 and 2045 and the corresponding percentage increase. The figure was created by the authors using numerical data from Magliano et al. (2021).

Diabetic foot ulcer (DFU) is a serious and debilitating complication of poorly controlled and long-standing diabetes, typically manifesting as ulcerations on the plantar surface of the foot. Owing to its high morbidity, often associated with severe infections such as osteomyelitis and the risk of lower-limb amputation, it is crucial to address and treat the underlying causes of DFU promptly and effectively (Raja, Maturana, Kayali, Khouzam, & Efeovbokhan, 2023). Diabetic wounds exhibit several abnormalities indicative of localized endothelial dysfunction. Evidence from experimental diabetic animal models of acute cutaneous wound healing has shown a reduction in nitric oxide (NO)

expression, which correlates with impaired healing characterized by diminished collagen deposition and reduced wound tensile strength. Additionally, altered expression of both endothelial and inducible nitric oxide synthase (NOS) has been reported in diabetic wound tissues compared to those of non-diabetic controls (Laing, Hanson, Chan, & Bouchier-Hayes, 2007).

Numerous studies have demonstrated that natural products possessing anti-inflammatory, antioxidant, antibacterial, and collagen-promoting properties contribute positively to wound healing (Thakur, Jain, Pathak, Sandhu, & medicine, 2011).

The phytochemical constituents of medicinal plants are known to enhance key processes such as tissue remodeling, epithelial regeneration, and angiogenesis (Hsu, 2005; Thangapazham, Sharad, & Maheshwari, 2016; Vanden Berghe & Haegeman, 2010). Such effects are particularly valuable in the management of chronic wounds, including diabetic foot ulcers, which often demand costly and prolonged treatment, imposing a significant socio-economic burden on both patients and healthcare systems (Shearer, Scuffham, Gordois, & Oglesby, 2003; Wild, Roglic, Green, Sicree, & King, 2004).

Given this challenge, the search for novel therapeutic agents and a deeper understanding of their underlying mechanisms remain essential (Jivad, Bahmani, & Asadi-Samani, 2016; Naji, Zarei, Pourjabali, & Mohammadi, 2017).

Among natural products, mangosteen has attracted increasing scientific interest as a potential candidate for diabetic wound healing. Recent years have witnessed a growing number of publications highlighting its role in accelerating wound repair. In this context, the present study specifically investigates the effect of α-mangostin, the most abundant xanthone derived from the mangosteen pericarp on wound healing using an in vitro diabetic wound model (Obolskiy, Pischel, Siriwatanametanon, Heinrich, & Derivatives, 2009; Yang et al., 2017).

Previous studies have reported the positive effects of α-mangostin on wound-healing processes, demonstrating its ability to modulate key growth factors and matrix-regulating enzymes. In the present study, α-mangostin at 2.5 µg/mL markedly increased the secretion of platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), while reducing matrix metalloproteinase-9 (MMP-9) levels compared to glucose-induced controls. These findings further support earlier evidence suggesting that α-mangostin enhances angiogenesis and tissue regeneration through the up-regulation of PDGF and VEGF signaling pathways and inhibition of excessive matrix degradation (Patrick, Zohdi, Abd Muid, & Omar, 2024).

In this review, we discuss the roles of growth factors and endothelial dysfunction in diabetic wound healing and highlight the novel therapeutic potential of α-mangostin based on its reported in vitro mechanisms.

Diabetic foot ulcers

The term 'diabetic foot ulcers' (DFU) typically refers to a non-healing, chronic foot ulceration with superimposed infection (Craus, Mula, & Coppini, 2023). It is estimated that 2 to 3% of patients with diabetes mellitus have an active foot ulcer, with the lifetime risk of developing a foot ulcer as high as 25% (Lim, Ng, & Thomas, 2017). DFU is currently considered to be one of the most significant causes of morbidity and the primary reason for hospitalisation in diabetic patients (Shahbazian, Yazdanpanah, & Latifi, 2013).

Individuals with a history of lower extremity amputation, previous foot ulcers, foot deformities, peripheral vascular disease, or diabetic nephropathy, particularly those undergoing dialysis are at greater risk of

developing diabetic foot ulcers (DFU) (Aumiller & Dollahite, 2015; Panneerselvam, Vijayakumar, Raja, & Venkatesan, 2021). Walking barefoot or without appropriate footwear or foot protection further increases this risk (Chavan, 2018). A meta-analysis involving 542 patients with DFU reported that 46 cases were associated with peripheral arterial disease (PAD) as a contributing factor (Z. H. Huang et al., 2019). Similarly, in a study by Yazdanpanah et al., several clinical features were identified as significant risk factors: among 566 diabetic patients, 474 presented with foot dryness, 52 with foot deformities, and 12 with a history of foot ulcers or amputations. These findings emphasise the critical need to address and manage modifiable risk factors to reduce the incidence of DFU among diabetic individuals (Yazdanpanah et al., 2018).

A diabetic foot ulcer (DFU) is defined as a full-thickness wound that penetrates through the dermis, vascular, and collagen-rich layer of the skin occurring below the ankle. Once ulceration develops, the affected area becomes highly vulnerable to infection (Bakker et al., 2016; Jalilian, Sarbarzeh, Oubari, targets, & therapy, 2020). Multiple factors, including inadequate tissue perfusion (oxygen delivery), bacterial infection, malnutrition, and poor glycaemic control, can impair the wound healing process by disrupting the body's ability to repair and regenerate damaged tissue (Ontario, 2017) . Evidence indicates that approximately 78% of individuals with DFU exhibit microvascular complications associated with peripheral arterial disease (PAD), primarily due to endothelial cell dysfunction, which reduces blood supply and further predisposes to ulcer formation (Baig et al., 2022). These conditions demand prompt medical intervention to prevent progression and worsening of DFU if left untreated.

Normal wound healing

Normal wound healing is defined by the body's ability to repair tissue through a well-organised and efficient process that restores both structure and function. Typically, uncomplicated wounds heal within 5 to 10 days. This natural repair mechanism proceeds through four overlapping but distinct phases: hemostasis (blood clotting), inflammation, proliferation (involving angiogenesis, granulation, and re-epithelialisation), and tissue remodelling (Salazar-Gómez & Alonso-Castro, 2022).

Each phase has a specific duration, cellular activity, extracellular mediators, and growth factors that act as signals, suppressors, or promoters of healing. The acute inflammatory response plays a crucial role at the beginning of tissue repair. It not only initiates blood clotting to minimise blood loss but also helps clear bacteria and foreign debris from the wound, thereby creating the conditions necessary for healing to proceed (Demidova-Rice, Hamblin, Herman, & care, 2012; Slavich & Irwin, 2014).

Once the inflammatory phase subsides, the wound enters the proliferative stage, marked by fibroblast proliferation, angiogenesis, and re-epithelialisation of the wound surface. This is followed by the remodelling phase, characterised by reduced angiogenesis and increased deposition of collagen and extracellular matrix components. During this stage, the new tissue gradually gains strength and flexibility, signalling the near completion of the healing process (Nussbaum et al., 2015). Cells such as macrophages, endothelial cells, and fibroblasts actively participate throughout these stages by secreting cytokines and growth factors including interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). These mediators establish a complex signalling network that coordinates interactions among the various cell types involved in healing. Endothelial cells, which line the vasculature and supply oxygen, nutrients, and circulating cells, are particularly important. Their integrin–matrix interactions are modulated by extracellular matrix remodelling, thereby enhancing angiogenesis during the repair process (Agyare, Osafo, & Boakye, 2018; Lindley, Stojadinovic, Pastar,

Tomic-Canic, & surgery, 2016; Yussof, Omar, Pai, & Sood, 2012).

Growth factor activities in normal wound healing

Growth factors are essential regulators of the wound healing process, coordinating the transition from the inflammatory phase to tissue repair. They not only modulate immune defense mechanisms during inflammation but also initiate the proliferative phase by stimulating key cellular activities, including migration, proliferation, angiogenesis, and tissue formation (Werner & Grose, 2003).

These mediators, secreted by endothelial cells, fibroblasts, keratinocytes, macrophages, and neutrophils, play critical roles in wound repair. Among the most important are platelet-derived growth factor (PDGF), connective tissue growth factor (CTGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and transforming growth factor-β (TGF-β). In normal wound healing, the levels of these growth factors are upregulated to facilitate tissue regeneration (Barrientos et al., 2008).

During controlled inflammation, PDGF released by macrophages stimulates collagen synthesis, a key event in wound closure. Numerous studies have shown that PDGF not only enhances cell proliferation but also modulates inflammatory responses, thereby supporting skin regeneration [34]. Drawina et al. reported that elevated PDGF expression was strongly associated with accelerated wound closure in non-diabetic animal models with full-thickness wounds. The authors proposed that PDGF promotes wound repair by activating pathways such as MAPK, which stimulate cell proliferation and new tissue formation, ultimately contributing to faster wound closure (Drawina et al., 2022).

Connective tissue growth factor (CTGF), a cysteine-rich peptide with biological and immunological similarities to PDGF, also plays a vital role in tissue repair. It regulates cell adhesion and migration, stimulates fibroblast proliferation, and promotes extracellular matrix production and granulation tissue formation (Leask & Abraham, 2004). A study on diabetic mice with full-thickness cutaneous wounds demonstrated that topical application of recombinant human CTGF significantly accelerated epithelial closure compared to untreated diabetic controls. The authors attributed this effect to enhanced collagen deposition at the wound site, which increased wound stiffness and strength, thereby facilitating improved healing (Henshaw, Boughton, Lo, McLennan, & Twigg, 2015).

The growth factor basic fibroblast growth factor (bFGF) is a potent mitogen that regulates proteins responsible for stimulating the proliferation of multiple cell types, particularly endothelial and fibroblast cells (Matsumoto et al., 2013). bFGF plays a critical role in accelerating wound healing by promoting neovascularisation, enhancing angiogenesis, and increasing collagenase synthesis (Nakamichi et al., 2016). Huang et al. demonstrated that FGFs influence the proliferative phase of diabetic wounds in mice by facilitating angiogenesis and epithelial formation, thereby significantly accelerating tissue regeneration while reducing scar formation (C. Huang et al., 2016; Liu, Liu, Deng, Li, & Nie, 2021). Clinical studies further support these findings, showing that the topical administration of bFGF—commercially available in Japan—effectively enhances wound healing outcomes (Akita, Akino, Imaizumi, & Hirano, 2005; Kinoshita et al., 2012).

Vascular endothelial growth factor (VEGF), also known as vascular permeability factor, is another key angiogenic molecule that enhances capillary permeability. Forough et al. reported that increased VEGF expression improves angiogenesis and granulation tissue formation during wound healing (Shams et al., 2022). In diabetic mouse models, VEGF levels were found to be diminished; however,

treatment with the natural product Aloe vera elevated VEGF expression, leading to improved angiogenesis and significantly accelerated wound closure (Sargowo, Handaya, Widodo, Lyrawati, & Tjokroprawiro, 2011). The role of VEGF in wound healing is largely attributed to its ability to enhance vascular permeability through nitric oxide (NO)-mediated mechanisms, which cause plasma proteins such as fibrinogen to leak into the extracellular space. Fibrinogen is subsequently converted into a fibrin gel, providing a provisional matrix that supports cell migration and tissue repair (Bao et al., 2009).

Transforming growth factor-β (TGF-β) plays a pivotal role in wound healing by stimulating tissue repair and regeneration (Savari, Shafiei, Galehdari, & Kesmati, 2019). Following tissue injury, blood vessel disruption results in the extravasation of blood into the surrounding tissue. The coagulation cascade is then activated, leading to the formation of a fibrin clot that restores haemostasis and provides a temporary extracellular matrix scaffold to support cell migration. Platelets trapped within this clot release multiple growth factors, including TGF-β. This growth factor facilitates the recruitment of key wound-healing cells such as neutrophils, macrophages, and fibroblasts, thereby initiating subsequent stages of the repair process (Klass, Grobbelaar, & Rolfe). In a prior study, Roghaye et al. observed the TGF-β gene expression in healthy (non-diabetic) rats increased after being induced with treatment (Phenytoin). This could be attributed to TGF-β stimulating cells to enhance the synthesis of extracellular matrix proteins while simultaneously reducing collagen proteases (Savari et al., 2019).

Growth factor activities in abnormal wound healing

As research continues to elucidate their role in chronic wound pathophysiology, growth factors are increasingly recognised for their potential to enhance the effectiveness of wound care interventions (Park, Hwang, & Yoon, 2017; Yamakawa, Hayashida, & trauma, 2019). In chronic wounds, growth factor signalling is often dysregulated, resulting in an inadequate physiological response that compromises healing. Evidence indicates that growth factor levels in chronic wounds are markedly lower compared to those in acute wounds (Koob et al., 2013).

Chronic wounds commonly fail to heal within the expected timeframe due to factors such as vascular insufficiency, infection, or pressure necrosis. Key angiogenic mediators such as bFGF and VEGF stimulate granulation tissue formation; however, when these growth factors are deficient, angiogenesis is impaired, granulation tissue becomes scarce, and the healing process is delayed (Yu et al., 2016). Experimental studies using full-thickness dorsal skin wounds in non-diabetic rats further demonstrated that chronic wounds exhibit significantly reduced bFGF expression compared with treated wounds. Subsequent angiogenesis assays confirmed diminished angiogenic activity in chronic wounds (Nakamichi et al., 2016).

Similarly, a review by Deng et al. reported that growth factor deficiency contributes to the development of chronic pressure ulcers. Specifically, levels of PDGF were significantly lower in chronic dermal ulcers compared with acute wounds. These findings suggest that insufficient growth factor activity is a major factor underlying chronic wound persistence. Thus, incorporating growth factors into wound treatment strategies may help prevent or slow the transition from acute to chronic wounds (Deng, Gould, & Ali, 2022).

Diabetic endothelial dysfunction

Endothelial cell dysfunction (ECD) refers to the disruption of normal endothelial functions, encompassing impaired barrier integrity, reduced vasodilation, alterations in proliferative capacity, diminished migration and tube formation, compromised angiogenic potential, weakened synthetic activity,

and decreased ability to prevent leukocyte adhesion and diapedesis. Multiple factors contribute to the development of ECD, including smoking, hypertension, diabetes, hyperlipidemia, obesity, hyperglycemia, advanced glycation end products (AGEs), and genetic predisposition (Kolluru, Bir, & Kevil, 2012). During endothelial injury, several changes are commonly observed, including impaired vasodilation, dysregulated production and secretion of bioactive substances, altered energy metabolism, and structural damage. The key pathophysiological mechanisms involved are oxidative stress and mitochondrial dysfunction, accompanied by inflammation, immune activation, increased vascular permeability, and barrier disruption (Xia et al., 2025).

Wound healing relies heavily on angiogenesis, and any disruption to this process can severely hinder tissue repair. In diabetic wounds, endothelial dysfunction plays a critical role by impairing angiogenesis and further complicating the healing process. Evidence shows that prolonged hyperglycemia in diabetic patients leads to reduced levels of key pro-angiogenic mediators, including vascular endothelial growth factor A (VEGFA), angiopoietin-1 (ANGPT1), and stromal cell-derived factor-1 (SDF-1). These factors are essential for endothelial cell proliferation, migration, and lumen formation (J. Zhang et al., 2025). According to Zhang et al., growth differentiation factor 11 (GDF11) promotes diabetic wound healing by mobilizing endothelial progenitor cells and enhancing neovascularization through activation of the HIF-1α–VEGF/SDF-1α signaling pathway. Likewise, transforming growth factor-beta 1 (TGF-β1) serves as a key regulator of angiogenesis, facilitating wound repair by activating the Akt, Erk, and TGF-β/Smad3 signaling cascades(Zong et al., 2020).

Hyperglycemia hinders angiogenesis by decreasing nitric oxide (NO) production and elevating reactive oxygen species (ROS). This oxidative stress compromises endothelial cell function, thereby limiting their angiogenic potential. Thus, restoring endothelial function to enhance angiogenesis may offer an effective therapeutic approach for promoting wound healing in diabetes (Malone-Povolny, Maloney, & Schoenfisch, 2019; Xiong et al., 2023).

The role of medicinal plants in diabetic wound healing

Extensive research has demonstrated that natural products with anti-inflammatory, antioxidant, antibacterial, and collagen-stimulating properties exhibit promising wound-healing potential (Thakur et al., 2011). The phytochemical constituents of medicinal plants can promote tissue remodelling, epithelial regeneration, and angiogenesis, thereby supporting the repair of chronic wounds (Hsu, 2005; Thangapazham et al., 2016; Vanden Berghe & Haegeman, 2010). This is particularly relevant for diabetic foot ulcers, which often demand prolonged and costly treatments that place a significant socio-economic burden on both patients and healthcare systems (Shearer et al., 2003; Wild et al., 2004).

Given these challenges, the search for novel therapeutic agents derived from medicinal plants is crucial, not only to identify effective treatments but also to clarify their mechanisms of action in chronic wound repair (Jivad et al., 2016; Naji et al., 2017).
Among these, mangosteen (Garcinia mangostana) has attracted considerable attention for its potential in diabetic wound healing.

In recent years, the number of studies investigating mangosteen's wound-healing effects has increased substantially. Of particular interest is α-mangostin, the most abundant xanthone in the mangosteen pericarp, which has been explored for its therapeutic properties. The present study focuses on evaluating the effect of α-mangostin on wound healing using an in vitro diabetic wound-healing model.

Mangosteen pericarp and wound healing

Mangosteen (Garcinia mangostana Linn., GML), commonly referred to as the "Queen of Fruits" (Figure 2.3), is a well-documented plant with notable biological and therapeutic potential. Traditionally, it has been used to manage infections, diarrhoea, dysentery, inflammation, skin disorders, and wounds (Obolskiy et al., 2009; Yang et al., 2017), and it continues to play an important role in traditional Chinese, Thai, and Ayurvedic medicine (Sultan et al., 2022).

The mangosteen pericarp is considered non-toxic and has shown no apparent adverse effects, making it a promising candidate for biomedical applications (S. Zhang et al., 2020). Recent studies have reported its positive impact on wound healing. For instance, Shafy et al. demonstrated that an ointment enriched with mangosteen pericarp accelerated wound closure and improved the tensile strength of healed skin in mice, with no observed side effects (Shafy, Jassim, & Mohammed, 2019). Figure 2 shows the image of the mangosteen pericarp.

Figure 2: The mangosteen fruit, also known as the "Queen of fruits"

The pericarp of mangosteen is particularly rich in phenolic compounds, notably xanthones, which are regarded as the primary bioactive constituents (Suttirak, Manurakchinakorn, & technology, 2014).

More than 50 different xanthone derivatives have been identified in the mangosteen pericarp (Pedraza-Chaverri, Cárdenas-Rodríguez, Orozco-Ibarra, Pérez-Rojas, & toxicology, 2008). These compounds display a wide range of biological activities, including antibacterial, antimalarial, anti-inflammatory, anticancer, antioxidant, and wound-healing effects (Febrina, Milanda, & Muchtaridi, 2018). Xanthones have been shown to promote fibroblast proliferation, an essential marker of effective wound healing, as increased fibroblast activity contributes to tissue repair and regeneration (Hanafiah, Abidin, Ilyas, Nainggolan, & Syamsudin, 2019).

Alpha(α)-mangostin

The most abundant xanthone present in the mangosteen pericarp is α-mangostin. Xanthones are organic polyphenolic compounds with the molecular formula $C_{13}H_8O_2$, characterised by a tricyclic skeleton that largely determines their biological activities. The specific properties of these molecules vary depending on the position and nature of functional groups and substitutions. Among the xanthone derivatives, α-, β-, and γ-mangostins have been the most extensively studied for their pharmacological potential, with α-mangostin being the predominant and most concentrated form found in the mangosteen pericarp (Jiang, Dai, & Li, 2004; K.-j. Zhang, Gu, Yang, Ming, & Wang, 2017). Figure 3 illustrates the chemical structure of α-mangostin.

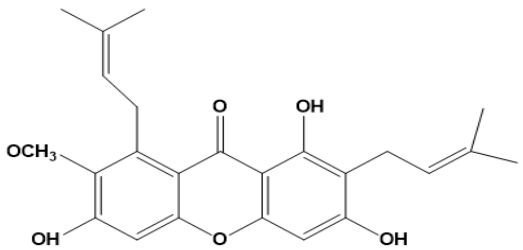


Figure 3: Chemical structure for α-mangostin

Owing to its wide-ranging biological

and pharmacological activities, particularly in the context of wound management, α-mangostin has attracted significant interest in medicinal plant research (Rizaldy, Hartati, Nadhifa, & Fidrianny, 2021). Studies have demonstrated that α-mangostin exhibits stronger antioxidant activity than several well-known reference compounds. In addition, it possesses notable anti-inflammatory and antibacterial properties, further supporting its potential as a therapeutic agent for wound healing (Abate et al., 2022; McFarland, Hahn, Combs, & Supp).

Effect of α-mangostin in In-vitro study

A scratch assay investigation revealed that α-mangostin accelerates wound closure within 24 hours compared to the control group by enhancing both cell proliferation and migration. This assay, performed using a fibroblast cell line in a non-diabetic in vitro wound-healing model, suggests that α-mangostin may play a beneficial role in promoting wound repair (M. Siriwattanasatorn, A. Itharat, P. Thongdeeying, B. J. E.-B. C. Ooraikul, & A. Medicine, 2020).

To illustrate the potential mechanisms underlying these findings, Figure 4 presents a schematic pathway summarising the proposed actions of α-mangostin across different phases of diabetic wound healing. The compound exerts anti-inflammatory effects by reducing IL-6 secretion, stimulates angiogenic growth factors and modulates matrix remodeling through MMP-9 suppression and TIMP-2 upregulation. Collectively, these actions contribute to enhanced endothelial repair, fibroblast proliferation, and overall wound closure.

Further evidence supports its anti-inflammatory potential, as α-mangostin has been shown to suppress the expression of pro-inflammatory cytokines, particularly IL-6 and IL-8, in human gingival fibroblasts (Yiemwattana & Kaomongkolgit, 2015).

To date, however, most studies investigating α-mangostin have focused on its role in normal wound healing. Its specific effects on diabetic wound healing, especially regarding cell migration, inflammatory modulation, and growth factor regulation, remain poorly understood.

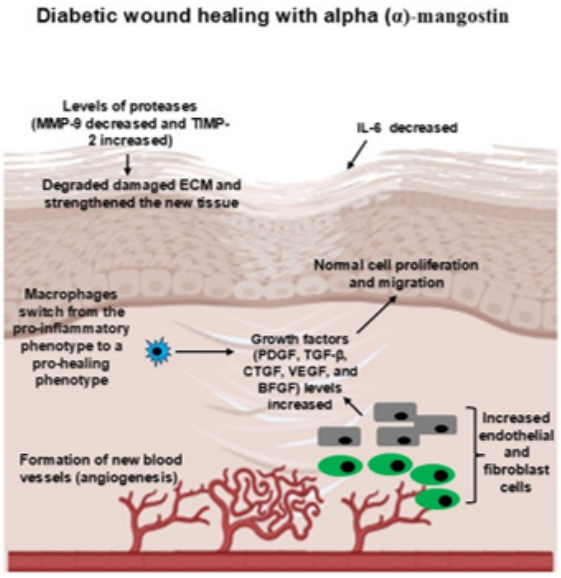


Figure 4: Proposed pathways of α-mangostin in diabetic wound healing

DISCUSSION

Although α-mangostin has shown strong biological activity, its use as a wound-healing therapy is still limited. For diabetic foot ulcers and other chronic wounds, effective formulations must improve skin absorption, stability, and controlled release. Delivery systems such as nanoemulsions, hydrogels, liposomes, and nanoparticle-based ointments can enhance the solubility and retention of α-mangostin at the wound site. Among these, natural polysaccharide-based hydrogels, such as gellan gum, are preferred because they keep the wound moist, adhere well to tissue, and are non-irritating. Recent studies reported that gellan gum (GG) hydrogel films containing α-mangostin showed good thickness, flexibility, and uniformity, along with strong antibacterial and antioxidant properties that increased with higher α-mangostin content. These features make GG hydrogels a promising option for delivering α-mangostin directly to

Table 1: *In-vitro* evidence of α-mangostin in wound healing

Study / Year	Model / Cell Type	Experimental Design / Treatment	Dose / Formulation	Measured Parameters	Main Findings
Ennesta Asri et al. (2021) (Asri11, Gustia, Sari, Wirman, & Aidi, 2025)	Human keloid fibroblasts	In-vitro treatment of keloid fibroblasts to evaluate collagen and TGF-β/SMAD pathway expression	20 µM α-mangostin	TGF-β1, SMAD3, Type I collagen (ELISA) and cell migration (scratch assay)	↓ TGF-β1 and SMAD3 expression and ↑ Type I collagen; reduced fibroblast proliferation and migration
Siriwattanasatorn et al. (2021)(M. Siriwattanasatorn, A. Itharat, P. Thongdeeying, B. J. E. B. C. Ooraikul, & A. Medicine, 2020)	Human dermal fibroblasts (scratch assay)	In-vitro wound-healing assay	1-10 µg/mL	% wound closure at 24 h, fibroblast proliferation	Accelerated scratch closure within 24 h and increased fibroblast proliferation
Yiemwattana et al. (2021) (Yiemwattana & Kaomongkolgit, 2015)	Fibroblast	Anti-inflammatory evaluation	0.5- 2.0 µg/mL	IL-6, IL-8 release	Significant suppression of IL-6 and IL-8 expression
Kevin L. McFarland et al. (2021) (McFarland et al.)	Human normal and keloid fibroblasts	Cells from three donors treated with α-mangostin; assessed for gene expression and protein secretion	5 µg/mL	COL1A1, MMP1, MMP3, MMP13, pro collagen I (gene expression)	↓ COL1A1 and pro-collagen I and ↑ MMP1 and MMP13 secretion
Menik Sayekti et al. (2022) (Sayekti et al., 2022)	Osteoblast 7F2 cell line	Four group post-test only design with LPS and α-mangostin induction	Not specified	IL-10 and Collagen 1A1 gene expression (qPCR)	↓ IL-10 expression (anti-inflammatory) and ↑ COL1A1 expression
Patrick et al. (2024) (Patrick et al., 2024)	Macrophage cells under glucose-induced stress	Comparative in-vitro diabetic wound model	2.5 µg/mL α-mangostin	PDGF, VEGF, MMP-9, IL-6, TIMP-2 levels	↑ PDGF & VEGF and ↓ MMP-9; no change in IL-6 or TIMP-2 vs. glucose controls

wounds for better healing and minimal side effects (Shahzad, Khan, & Khalid, 2025).

Previous studies have provided strong evidence supporting the efficacy of the NLC-P-αM (nanostructured lipid carrier-phytosomal α-mangostin) formulation in promoting diabetic wound healing. Across multiple biological assays, this nanoformulation consistently outperformed both the free α-mangostin compound and control treatments, meeting essential criteria for an effective wound-healing agent. Incorporating α-mangostin into lipid-based nanoparticles has been shown to markedly enhance its therapeutic stability, solubility, and bioavailability. Furthermore, in vivo diabetic wound-healing experiments demonstrated that NLC-P-αM significantly accelerated wound closure and facilitated advanced tissue regeneration, as evidenced by histological observations showing reduced inflammation and restoration of normal skin architecture. Collectively, these findings indicate that NLC-P-αM represents a promising and innovative strategy for improving the clinical translation of α-mangostin in chronic and diabetic wound management (Suhandi et al., 2025).

From a safety perspective, at concentrations less than 10 µg/mL, α-mangostin has shown minimal cytotoxicity in fibroblast and macrophage models. Higher concentrations (>20 µM), particularly in fibroblast cells, have been linked to decreased cell viability and apoptotic induction. In order to balance pro-healing benefits and avoid delayed remodelling as a result of excessive matrix breakdown, dose optimisation is essential. Before moving on to human testing, toxicological profiling in skin irritation, sensitisation, and phototoxicity assays is advised (Asri11 et al., 2025; Patrick et al., 2024). Pharmacodynamically, rather than directly

stimulating angiogenesis, α-mangostin's antioxidant and anti-inflammatory properties seem to be the main source of its therapeutic benefits in diabetic wound models (Shahzad et al., 2025). The lack of in-vivo diabetes evidence calls for careful interpretation, despite the current in-vitro results showing up-regulation of PDGF and VEGF and down-regulation of MMP-9. Until they are confirmed in animal models of diabetes, mechanistic assertions beyond these measurable parameters especially those pertaining to growth-factor receptor signalling or molecular crosstalk should remain theoretical (Patrick et al., 2024). Furthermore, in vivo research should be carried out to verify the safety and therapeutic selectivity of α-mangostin before to moving forward with clinical use. Assessments of wound contraction, re-epithelialization, and skin cell migration should be part of these studies, along with an analysis of potential side effects including undesired apoptosis or altered collagen turnover. For α-mangostin to effectively promote healing without causing unfavourable scarring or fibrosis, preclinical validation is crucial (Sarian, Zulkefli, ZAIN, Maniam, & Fakurazi, 2023; Sawaragi et al., 2025).

CONCLUSION

Diabetic wounds are challenging to cure due to chronic inflammation, endothelial dysfunction, and decreased activity of growth factors as PDGF, VEGF, bFGF, CTGF, and TGF-β. There is limited information on the therapeutic efficacy of α-mangostin in this situation. However, current findings suggest it can promote cell migration, reduce pro-inflammatory cytokines, and restore growth-factor activity to facilitate angiogenesis and tissue healing. Further in-vivo investigations with diabetic animal models are required to corroborate these results, notably in terms of wound contraction, re-epithelialization, and long-term tissue remodelling. To ensure reproducibility and translational relevance, comprehensive preclinical testing should consider safety, dosage optimisation, bioavailability, and formulation stability. Early-phase clinical trials can test the effectiveness of topical α-mangostin formulations in diabetic patients, with an emphasis on wound closure rate, infection control, and healing quality. Developing α-mangostin as an inexpensive, locally obtained natural-product therapy could enhance diabetic wound management, reduce healthcare expenses, and alleviate the burden of persistent, non-healing lesions like diabetic foot ulcers.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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