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Review Article

Pathogenesis, Molecular Mechanism, Targets and Treatment Strategies to Accelerate Diabetic Wound Healing

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterised by the inability to mobilise the glucose in proper way, which severely retards the healing process of the wound. Chronic hyperglycaemia causes vascular dysfunction, oxidative stress, and chronic inflammation, ultimately leading to poor tissue repair, increased risk of infection, and potential amputation. Although conventional therapies are available, the management of diabetic wounds remains a significant clinical challenge due to low efficacy and associated side effects. Natural bioactive compounds, in the recent past, have received a significant amount of attention as a potential alternative in wound management. Isorhamnetin is one of compound which is a naturally occurring flavonoid that has demonstrated remarkable potential in enhancing diabetic wound healing due to its multifaceted biological properties. This review describes the pathogenesis of diabetic wounds and details the molecular mechanisms underlying isorhamnetin's therapeutic effects, including anti-inflammatory, antioxidant, and pro-angiogenic effects. It has a special focus on isorhamnetin's regulation of major signalling pathways such as PI3K/Akt and MAPK, which are important in cellular proliferation, migration and tissue regeneration. Overall, this review indicates that isorhamnetin is a promising natural primary therapeutic agent that can accelerate the healing of diabetic wounds by modulating various molecular processes that play a role in the inflammatory response, oxidative stress, and angiogenesis.

Keywords: Isorhamnetin, Diabetic wound healing, Natural remedy, Flavonoid, Molecular mechanisms.

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic disease affecting millions worldwide. It causes complications such as delayed wound healing, which can lead to ulcers and even amputation. Diabetic wounds are persistent and they may develop into ulcer or amputation leading to severe physical, emotional, and economic implications. The traditional treatment of diabetic wounds is not always sufficient, as persistent inflammation, oxidative stress and poor angiogenesis continue to impair healing. This has fueled interest in natural compounds that have multi-targeted actions and superior safety profiles. Isorhamnetin is a dietary flavonoid found in many fruits and other medicinal plants; it promotes wound healing through its anti-inflammatory, antioxidant and pro-angiogenic activity (Herman 2025; Kalai *et al.*, 2022).

The is an urgent need for effective and safe alternatives to hasten the repair of diabetic wounds. Isorhamnetin provides such an opportunity, as its target multiple molecular pathways involved in tissue regeneration.

The purpose of this review is to discuss (1) the pathogenesis of diabetic wounds, (2) the PI3K / Akt and MAPK signaling pathways, and (3) the therapeutic value and clinical evidence of isorhamnetin in diabetic wounds healing. Isorhamnetin bridges natural medicine and functional therapeutics, offering promise for patient suffering from severe effects of delayed wound healing in diabetes (Khaled 2020).

Pathogenesis of Diabetic foot ulcer

Diabetic wounds result from impaired normal healing due to disrupted molecular signaling. Among these pathways, the MAPK pathway plays a key role: ERK, JNK, and p38 regulate cell growth, migration, and inflammation. In diabetes, overactivation of JNK and p38 enhances inflammation and apoptosis, whereas downregulation of ERK inhibits angiogenesis and collagen production. Such disproportion causes non-healing wounds, which are chronic in nature, and MAPK modulation is exposed as a possible remedy (Figures 1 and 2) (Antonetti, Silva, and Stitt 2021).

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Neuropathy (Peripheral Neuropathy)

Diabetes can cause peripheral neuropathy, leading to loss of sensation and nerve damage, particularly in the lower limbs. This decreased sensation predisposes patients to unnoticed injuries and ulcers (Figure 3).

Ischemia (Peripheral Arterial Disease)

Diabetic Peripheral Artery Disease (PAD) decreases blood flow to the limbs, impairing oxygen and nutrients to the tissue, which hinders immune function and wound healing (Figure 3).

Foot Deformities

Prolonged elevated blood glucose can lead to Charcot foot deformities, creating pressure points that lead to calluses, blisters, and ulcers (Figure 4) (Dawi *et al.,* 2025).

Microvascular Changes

Diabetes-induced microangiopathy reduces the supply of blood, oxygen, and immune cells to tissues, thereby severely impairing wound healing (Figure 4) (Spampinato *et al.,* 2020).

Infection

Diabetes impairs immunity, increasing susceptibility to infection and making it more difficult to heal wounds or ulcers (Figure 5) (Burgess *et al.,* 2021).

Impaired Immune Response

Diabetes suppresses immune function, and elevated blood sugar facilitates bacterial growth, impairing infection control and wound healing (Figure 5) (Berbudi *et al.,* 2019).

Glycation

High glucose-induced protein glycation decreases the blood vessels elasticity and impairs connective tissue function, thereby affecting the wound healing (Figure 5) (Dasari *et al.,* 2021).

Inflammatory Response

Chronic inflammation in diabetes prolongs the inflammatory phase of wound healing, delays progression to the proliferative and remodeling stages, and ultimately impairs healing (Figure 5) (Cai *et al.,* 2023).

Pressure and Friction

Due to neuropathy, individuals with diabetes may not perceive excessive pressure or friction, leading to calluses, blisters, and ulcers in affected areas (Figure 6).

Poor Self-Care

Proper diabetes management, including foot care, is critical for preventing foot ulcers. Poor adherence to self-care practices (e.g., neglecting daily foot inspections, not wearing proper footwear, or failing to treat minor injuries) can increase the risk of developing foot ulcers (Figure 6).

Receptors involved in biochemical mechanisms

The biochemical processes depend on different receptors that mediate and facilitate cellular communication, signal transduction, and the regulation of physiological functions.

G Protein-Coupled Receptors (GPCRs)

The seven-membrane receptors (also known as G Protein-Coupled Receptors or GPCRs) are used to conduct external signals into the cell, which controls hormones, neurotransmission and sensory perception through the G proteins (Figure 6) (Nguyen *et al.,* 2018).

Receptor Tyrosine Kinases (RTKs)

Receptor Tyrosine Kinases (RTKs) are cell surface receptors that regulate cell survival growth, proliferation, migration, and survival through phosphorylating tyrosine residues when activated by ligands (Figure 7).

Ion Channel Receptors

The ion channel receptors are membrane proteins which selectively permeable the cell membrane with neurotransmitter-gated channels changing the membrane potential during signaling (Figure 8).

Nuclear Receptors

Nuclear receptors are intracellular receptors that control gene transcription and regulate metabolism, immune response and development when the receptor binds a ligand (Figure 9).

Enzyme-Linked Receptors

Enzyme-linked receptors are receptors on cell surfaces and when connecting ligands, phosphorylate or dephosphorylate target proteins, which controls immunity and growth signaling (Figure 9).

Toll-Like Receptors (TLRs)

TLRs sense Pathogen-Associated Molecular Patterns (PAMPs) and trigger innate immunity and inflammatory reactions in combating pathogens (Figure 10).

Cytokine Receptors

Cytokine receptors are immune and inflammatory response mediators which bind cytokines and cause cell-to-cell signaling events (Figure10).

Chemoreceptors

Chemical changes are sensed by the chemoreceptors and regulate the taste, smell and control the respiratory and cardiovascular functions (Figure 10).

MATERIALS AND METHODS

A literature search was performed in PubMed, Scopus, and Google Scholar using the keywords "diabetic wound healing," "molecular mechanisms," "isorhamnetin," "natural therapy," and "advanced wound care." Publications from the past ten years were given priority. The retrieved literature was critically reviewed and categorized into thematic subheadings, including molecular physiology, signaling pathways, and current treatment approaches, encompassing both experimental and clinical data.

Molecular physiology of diabetic wounds

The molecular physiology of diabetic wounds involves a complex interplay of various cellular and molecular processes, often disrupted, or dysregulated in individuals with diabetes. These alterations may result in persistent, non-healing lesions, like diabetic foot ulcers, and poor wound healing. Below is the molecular physiology of diabetic wounds, highlighting key factors and mechanisms involved (Figure 11) (Pandey *et al.,* 2025).

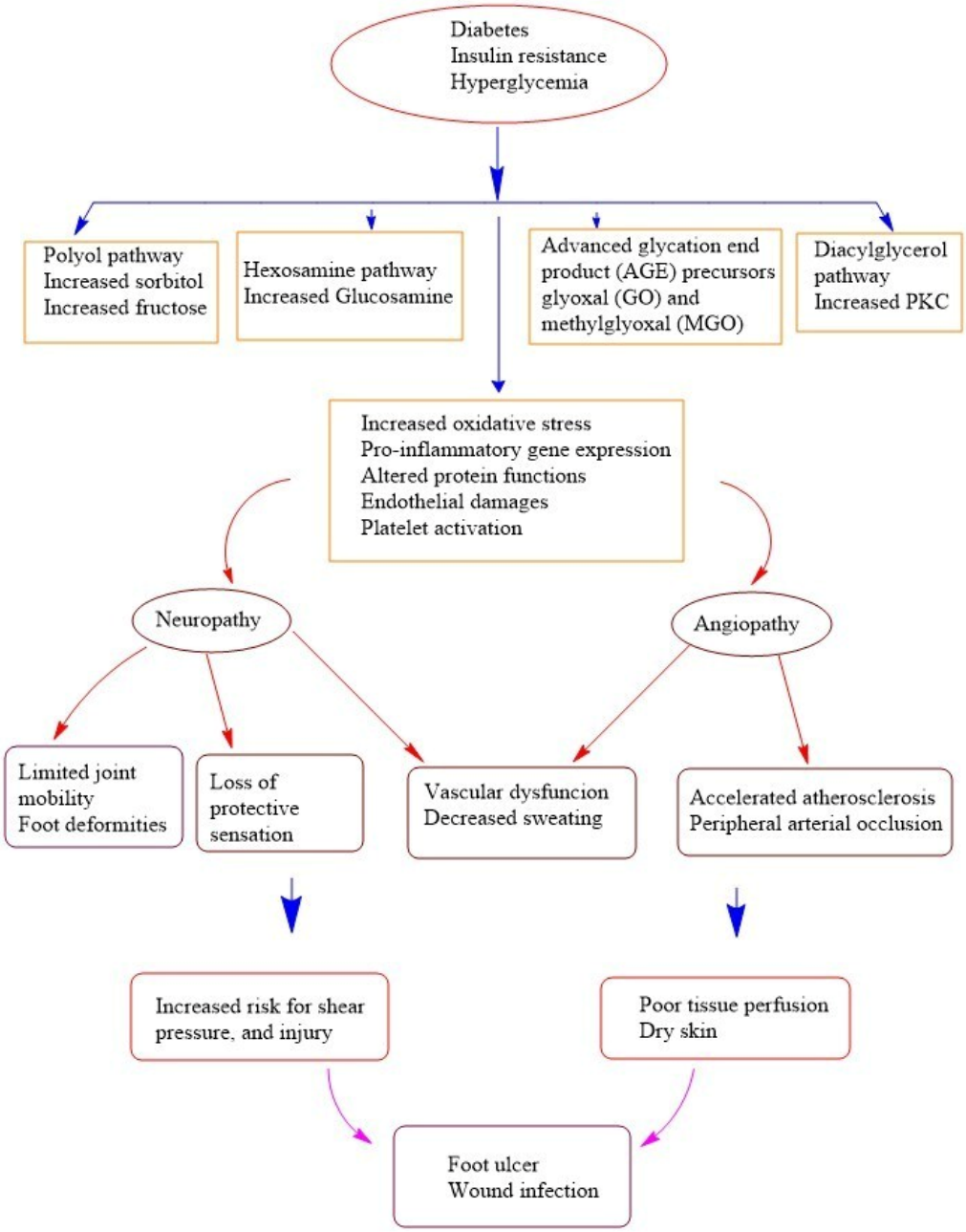

Figure 1: Diabetic foot ulcer pathogenesis Made with Perkin Elmer chemdraw 2020.

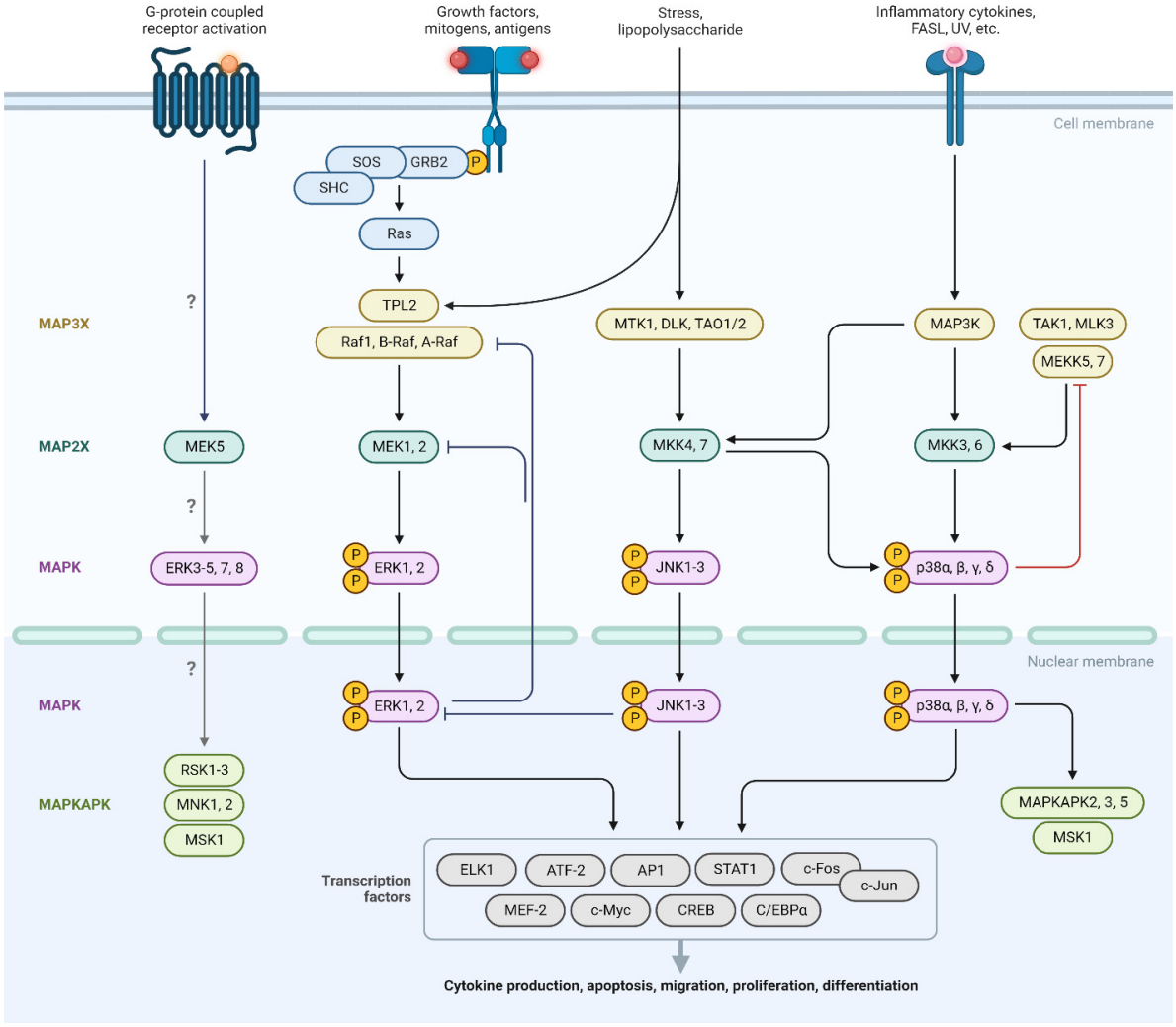

Figure 2: Molecular physiology of diabetic wounds essential variables and processes Diabetic wounds have a complex molecular physiology that is often disturbed or dysregulated (Made with Bio-render).

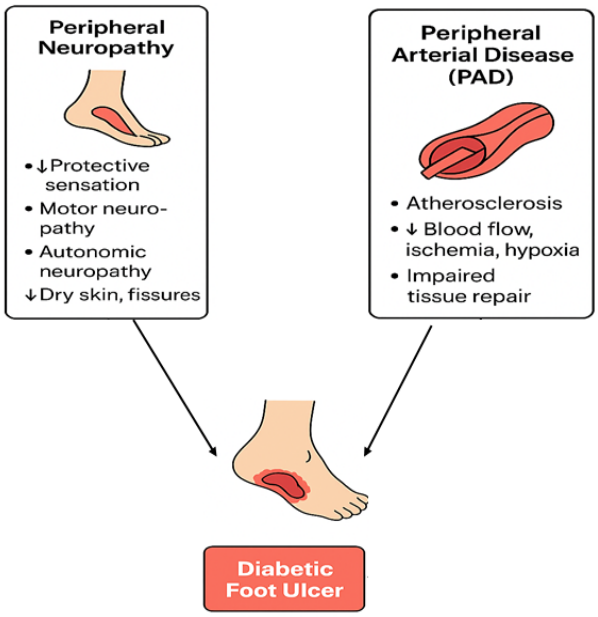

Figure 3: Neuropathy and Ischemia in Diabetic Foot Ulcer Development (Made with M. S. PowerPoint Professional 2021).

Hyperglycemia and Glycation

Persistent high blood glucose levels in diabetes contribute to glycation. Excess glucose molecules bind to proteins, altering their structure and function. This can lead to the dysfunction of various molecules involved in wound healing, such as collagen, growth factors, and enzymes, impairing the formation of a healthy extracellular matrix (Figure 11) (Singh *et al.*, 2014).

Oxidative Stress

Diabetes raises the risk of oxidative stress because it lowers antioxidant defenses and produces too many Reactive Oxygen Species (ROS). Oxidative stress can harm biological structures, including proteins, lipids, and DNA and hinder wound healing (Figure 11) (Caturano *et al.*, 2023).

Inflammation

Diabetes is characterized by chronic inflammation, which has a major impact on wound healing. Persistent inflammation may

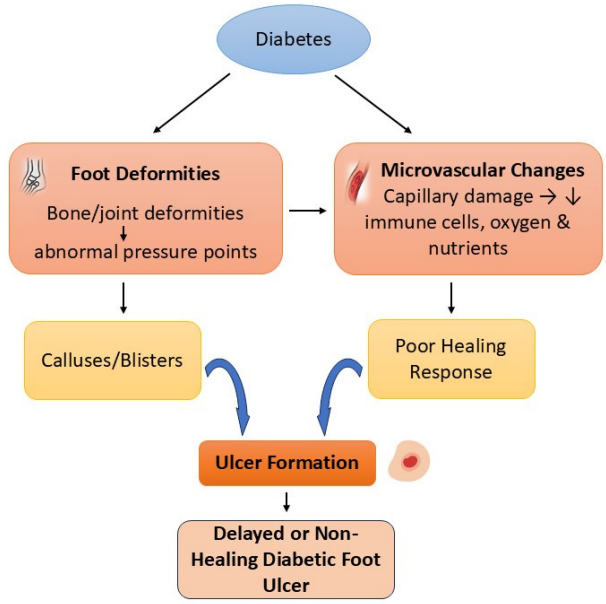

Figure 4: Mechanism of diabetic foot ulcer formation. Chronic hyperglycaemia causes foot deformities and microvascular changes both contributing to delayed or non-healing diabetic foot ulcers (Made with M. S. PowerPoint Professional 2021).

slow down the inflammatory to the proliferative and remodelling stages of wound healing. Chemokine and cytokine production Interleukin-6 (IL-6) and Tumor Necrosis Factor-alpha (TNF-a) can worsen inflammation (Figure 12) (Sathya Preiya and Kumar 2023).

Angiogenesis

Since blood provides nutrition and oxygen to the healing tissue, a sufficient blood flow is necessary for wound healing. Diabetes can impede the development of new blood vessels (angiogenesis) because it reduces the production of Vascular Endothelial Growth Factor (VEGF), which slows healing and prevents tissue perfusion (Figure 13) (Okonkwo and Dipietro 2017).

Neuropathy

Diabetes frequently results in peripheral neuropathy, which damages the autonomic and sensory nerves in the limbs. Autonomic neuropathy decreases sweat gland function, causing the skin to become dry and more prone to cracks and ulcers, whereas sensory neuropathy lessens pain perception, making injuries go unreported (Feher 2023).

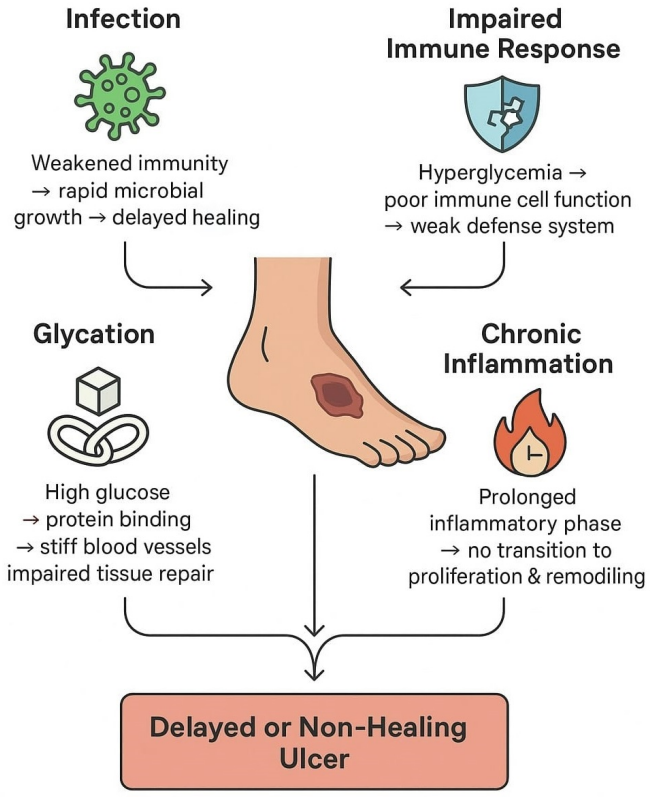

Figure 5: Mechanisms of impaired wound healing in diabetes: Diabetes causes increased infection susceptibility, weakened immune responses, protein glycation, and inflammation, ultimately leading to slow or non-healing ulcers (Made with M. S. PowerPoint Professional 2021).

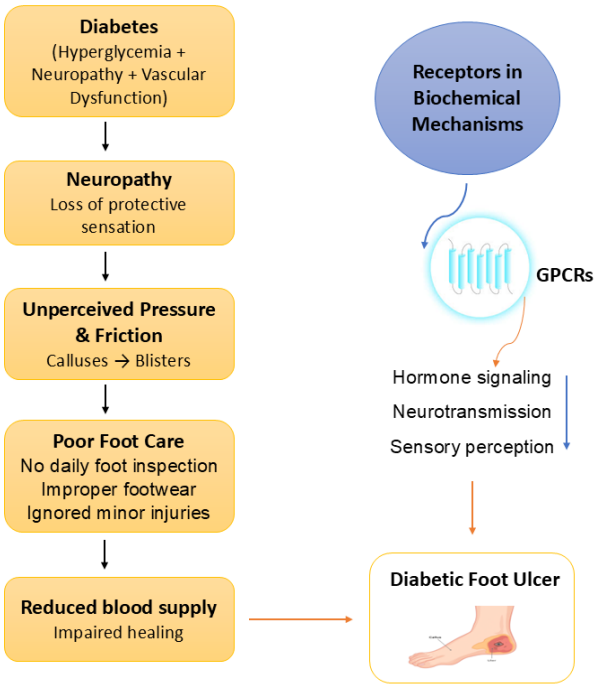

Figure 6: Mechanistic diagram of diabetic foot ulcer formation showing clinical factors (neuropathy, pressure/friction, poor foot care, vascular impairment) and biochemical receptor involvement (GPCRs) contributing to impaired healing (Made with M. S. PowerPoint Professional 2021).

Excessive Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases, the enzymes that degrade extracellular matrix during wound healing, can become more active in diabetics. Tissue deterioration and slowed healing can result from high MMP activity (Ayuk, Abrahamse, and Houreld 2016).

Delayed Reepithelialization

The migration and proliferation of keratinocytes to cover the wound's surface (reepithelialization) are essential for wound closure. Diabetes can impair this process by affecting keratinocyte function and altering gene expression in epithelial repair (Hosseini Mansoub 2022).

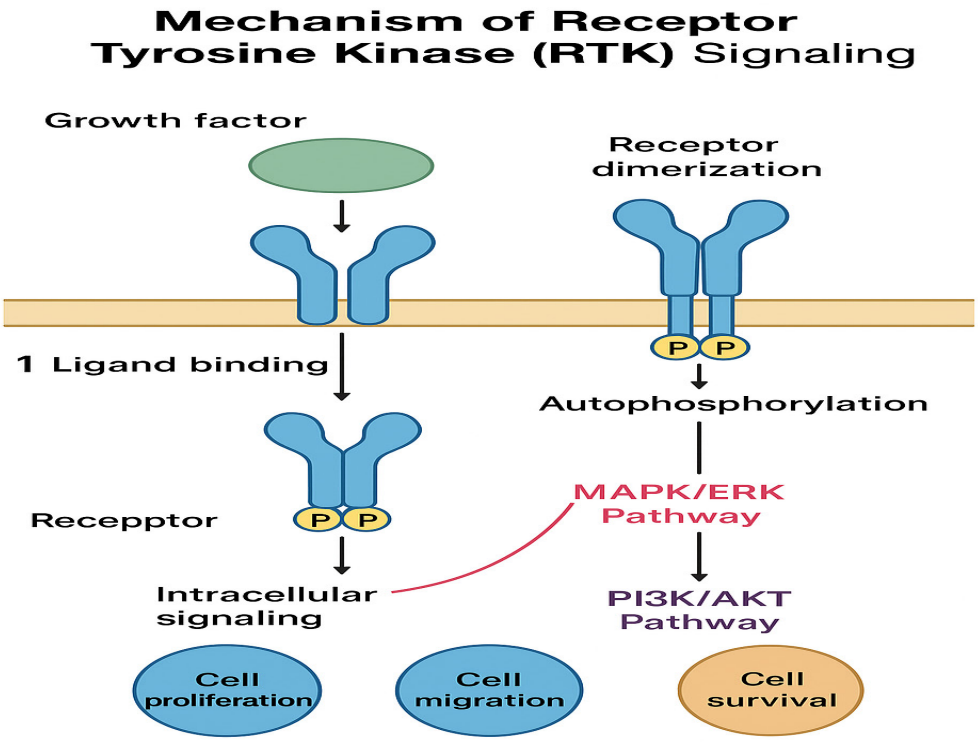

Figure 7 : Mechanism of Receptor Tyrosine Kinase (RTK) signaling in wound healing (Made with M. S. PowerPoint Professional 2021).

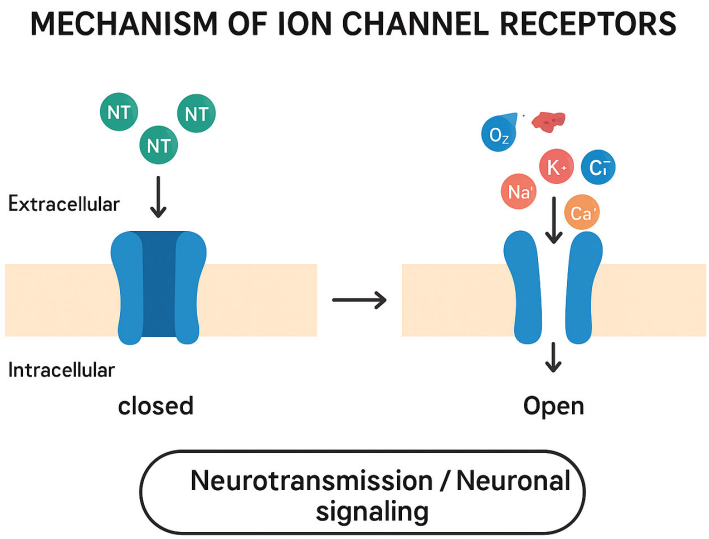

Figure 8: Ion channel receptors are selective ionic conductors that permit ionic flux to occur on a signal-dependent basis, and mediate processes such as neurotransmission and membrane potential changes (Made with M. S. PowerPoint Professional 2021).

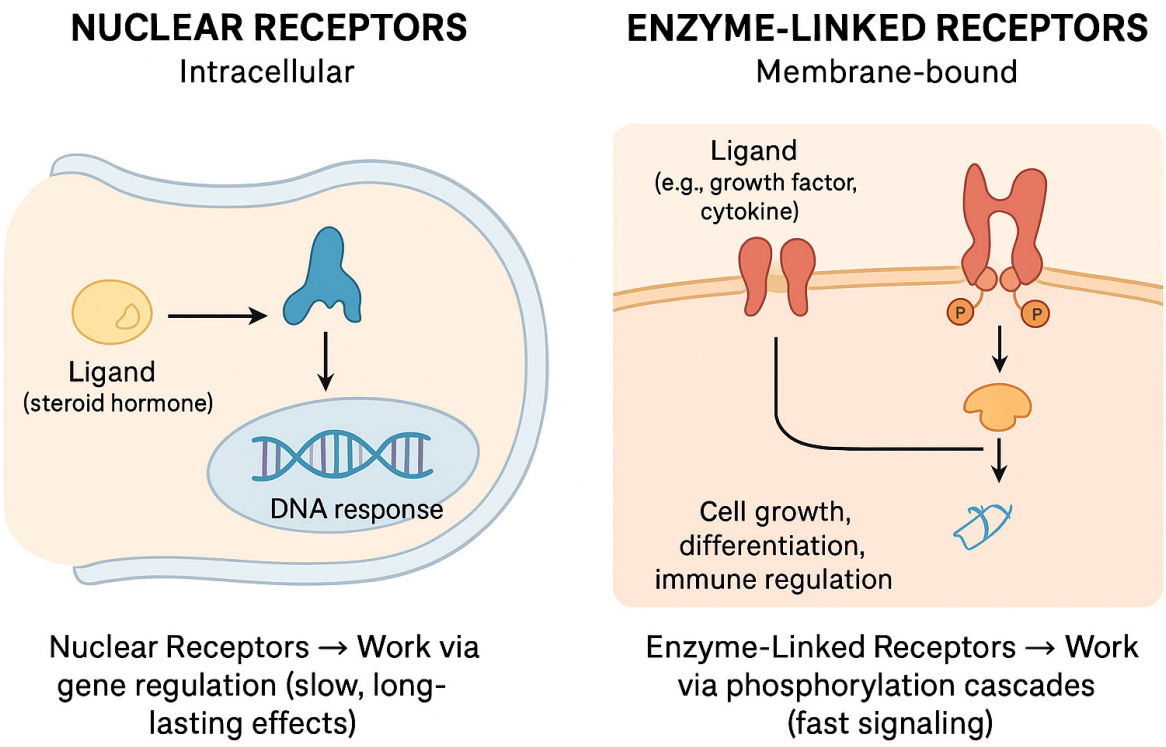

Figure 9: Mechanisms of Nuclear and Enzyme-Linked Receptors in Cellular Signalling (Made with M. S. PowerPoint Professional 2021).

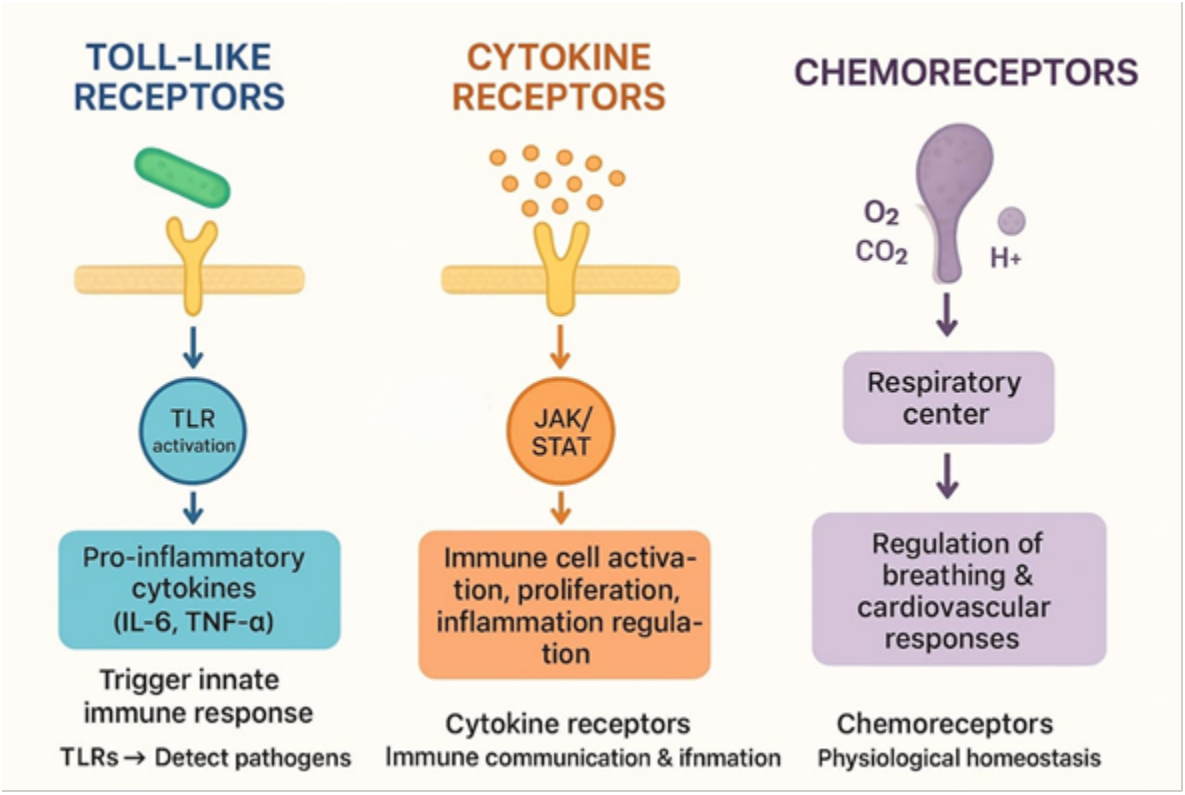

Figure 10: The TLRs activate innate immunity; cytokine receptors facilitate immune signaling; chemoreceptors respond to the chemical changes and can be used in sensory and physiological regulation (Made with M. S. PowerPoint Professional 2021).

Defects in Fibroblast Activity

Fibroblasts play a key role in the production of collagen and remodeling of tissues during wound healing. Diabetes may hamper the growth and functioning of the fibroblast and cause delayed collagen deposition and poor wound healing (Cialdai, Risaliti, and Monici 2022).

Advanced Glycation End Products (AGEs)

AGEs are formed when there is non-enzymatic interaction of sugars and proteins. AGEs may accumulate and block angiogenesis, collagen cross-linking and cell activity in diabetic wounds (Twarda-clapa *et al.*, 2022).

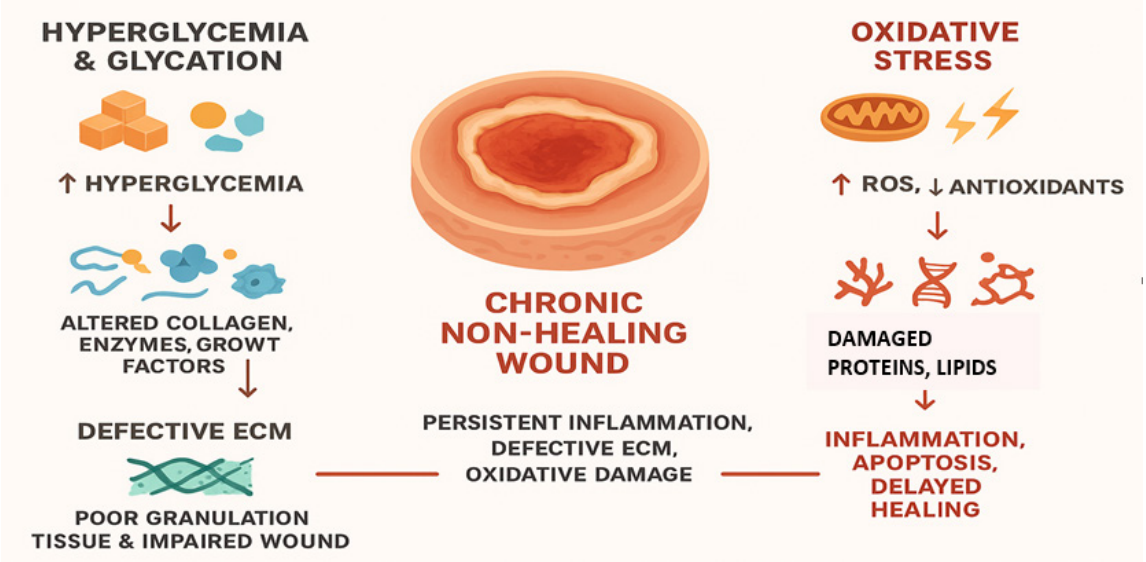

Figure 11: Molecular physiology of diabetic wounds (Made with M. S. PowerPoint Professional 2021).

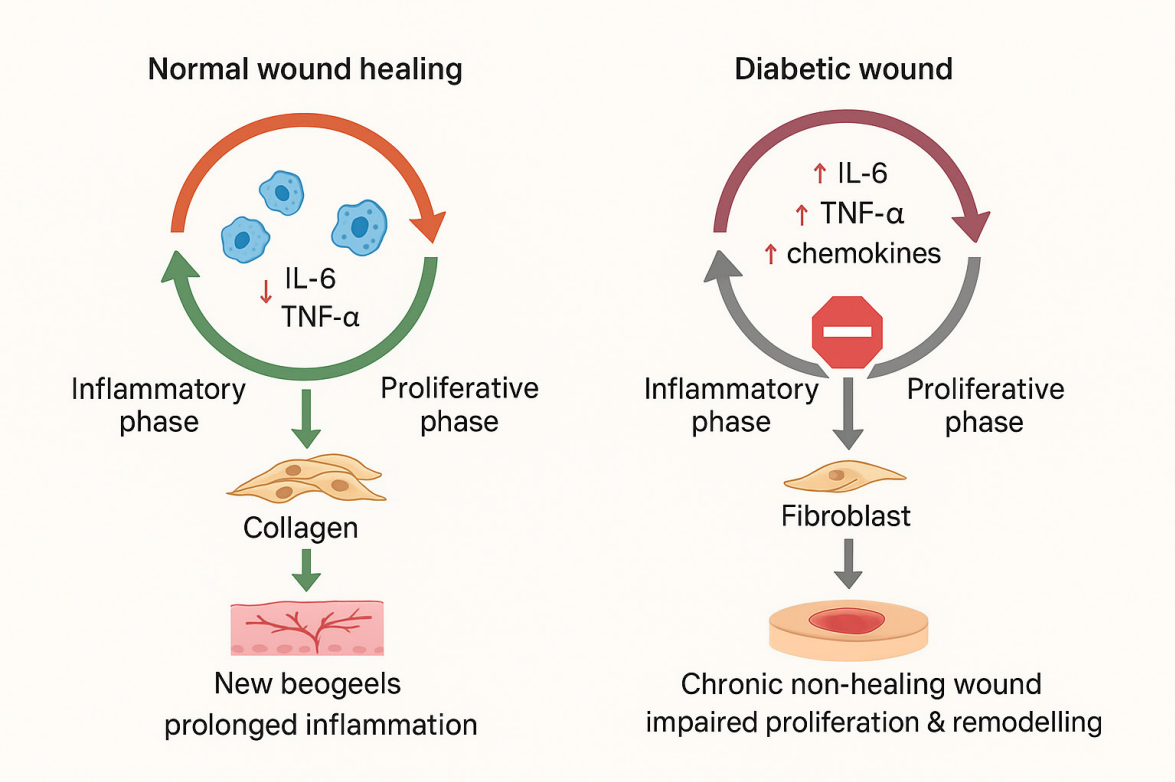

Figure 12: Cytokine-induced chronic diabetes-related Inflammation (IL-6, TNF-a) slows the inflammatory-proliferative and remodelling phases, which delays wound healing (Made with M. S. PowerPoint Professional 2021).

Weakened Immune Response

Diabetes may disrupt the ability of the immune system to combat infection, thereby enhancing susceptibility of microbial colonization and delayed healing of diabetic wounds (Larkin, Frier, and Ireland 1985).

Current Therapies in Diabetic Wound

The management of diabetic wounds is usually a multidisciplinary process that incorporates contemporary medical treatment and complementary and alternative therapies (Table 1). This is a summary of the different strategies employed in the management of diabetic wounds (Varma, Haponiuk, and Gopi 2021).

Modern Medical Therapy

Topical Antibiotics and Antiseptics

It is commonly applied to prevent or treat the infection in diabetic wounds. Topical antibiotics, such as mupirocin, and antiseptics such as iodine-based solution are the common agents (Table 2).

Modern Wound Dressings

The wound dressings used are advanced and they regulate exudate, retain a moist wound environment and promote healing. Hydrocolloids, foams and hydrogel are examples of such dressings (Berry-Kilgour, Cabral, and Wise 2021).

Negative Pressure Wound Therapy (NPWT)

It involves the dressing of the wound site with a vacuum dressing. It also accelerates wound healing by removing additional fluid, increasing the blood circulation, and promoting the growth of tissue granulation.

Growth Factors and Cytokines

Some advanced wound care products contain recombinant cytokines or growth factors (e.g., Platelet-Derived Growth Factor, PDGF) to promote tissue repair.

Table 1: Herbal Therapy.

Herbal Therapy	Chemical Constituents	Mechanism	Signaling Pathways	Applications
Calendula (*Calendula officinalis*)	Triterpenoids (calendic acid, faradiol), flavonoids (quercetin, rutin), carotenoids (lutein, beta-carotene), polysaccharides.	Anti-inflammatory: Calendic acid inhibits inflammatory cytokines and prostaglandins; Wound healing: Flavonoids stimulate collagen synthesis, fibroblast proliferation, and angiogenesis; Antioxidant: Carotenoids scavenge free radicals.	NF-κB, MAPK, PI3K/Akt	Topical use in ointments and creams for minor burns, cuts, and abrasions.
Comfrey (*Symphytum officinale*)	Allantoin, rosmarinic acid, tannins, choline, pyrrolizidine alkaloids (trace amounts).	Tissue regeneration: Allantoin promotes cell proliferation and migration; Anti-inflammatory: Rosmarinic acid inhibits inflammatory mediators; Astringent: Tannins promote wound closure.	TGF-β, Wnt/β-catenin, EGFR	Topical application for wound healing
Chamomile (*Matricaria chamomilla*)	Essential oils (chamazulene, bisabolol), flavonoids (apigenin, quercetin), coumarins, matricine.	Anti-inflammatory: Chamazulene inhibits leukocyte migration and inflammatory mediators; Soothing: Bisabolol has analgesic and antispasmodic properties; Antioxidant: Flavonoids and coumarins scavenge free radicals.	NF-κB, COX-2, Jak-STAT	Topical use in tea or oil for minor burns, cuts, and eczema
Echinacea (*Echinacea* spp.)	Alkyl amides, caffeic acid derivatives, polysaccharides, echinacoside.	Immune system booster: Alkyl amides and polysaccharides stimulate white blood cell activity; Antibacterial: Caffeic acid derivatives may aid in wound healing by preventing infection.	Toll-Like Receptors (TLRs), interferon pathways	May aid in immune response to infections and support wound healing

Biologic Agents

Biologic dressings, such as skin substitutes and tissue-engineered grafts, may be used for severe diabetic wounds that do not respond to traditional treatments.

Hyperbaric Oxygen Therapy (HBOT)

In this therapy, patients breathe pure oxygen in a pressurized chamber. This can enhance angiogenesis, improve tissue oxygenation, and promote wound healing.

Ayurvedic Therapy

Neem (Azadirachta indica)

Neem leaves and oil are used in Ayurvedic medicine for their antimicrobial properties; they can be applied topically to help prevent wound infection (Neem 1992).

Dimethyl (2a*R*,2a^1*R*,3*S*,4*S*,4a*R*,5*S*,7a*S*,8*S*,10*R*,10a*S*)-10-(acetyloxy)-3,5-dihydroxy-4-[(1a*R*,2*S*,3a*S*,6a*S*,7*S*,7a*S*)-6a-hydroxy-7a-methyl-3a,6a,7,7a-tetrahydro-2,7-methanofuro[2,3-*b*]oxireno[2,3-*e*]oxepin-1a(2*H*)-yl]-4-methyl-8-{[(2*E*)-2-methylbut-2-enoyl]oxy}octahydro-1

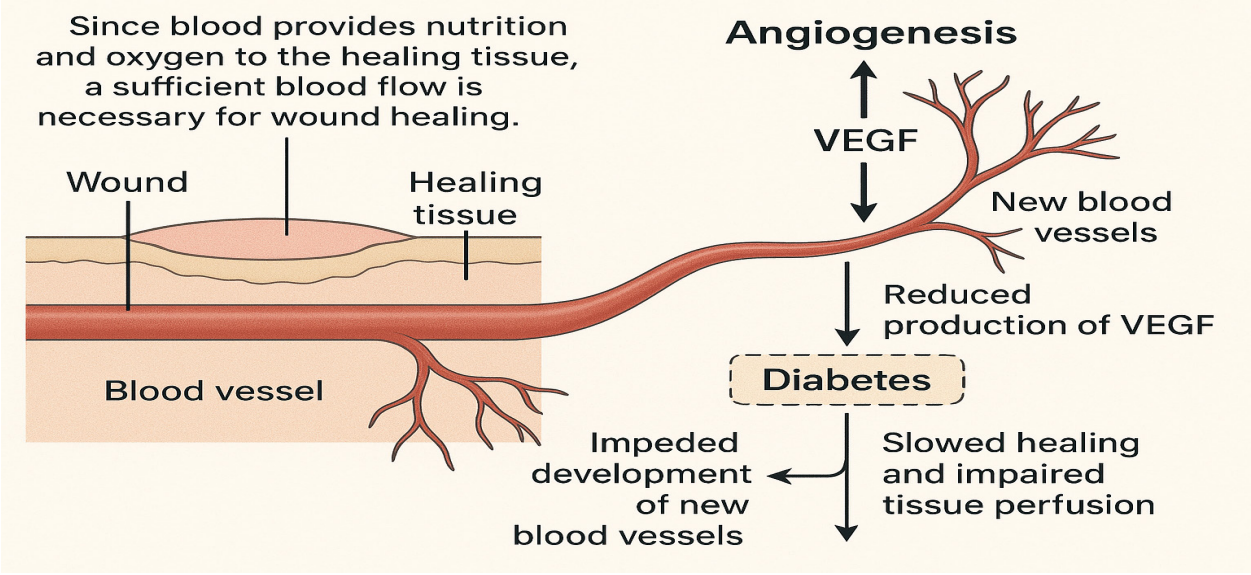

Figure 13: In diabetes, impaired angiogenesis reduces VEGF production and, thereby, reduces the formation of new blood vessels, inadequate tissue perfusion, and wound healing (Made with M. S. PowerPoint Professional 2021).

Table 2: Modern Medications and Treatments for Diabetic Wounds.

Category	Medications/Treatments
Topical Antibiotics and Antiseptics	- Mupirocin
	- Silver Sulfadiazine
	- Iodine-Based Antiseptics (e.g., povidone-iodine)
Systemic Antibiotics	- Prescribed for severe infections or cellulitis
Growth Factors	- Becaplermin (recombinant human PDGF gel)
Enzymatic Debridement Agents	- Collagenase
Pain Management Medications	- NSAIDs or opioids (as needed)
Antiplatelet Agents	- Aspirin or other antiplatelet medications (improve blood flow)
Hyperbaric Oxygen Therapy (HBOT)	- Increases tissue oxygenation
Angiogenesis Promoters	- Experimental medications to promote new blood vessel formation
Pentoxifylline	- Improves blood flow and reduces inflammation in chronic wounds
ACE Inhibitors and ARBs	- May be used to manage blood pressure and improve blood flow
Blood Sugar Control Medications	- Adjustments to existing diabetes medications for better glucose control

H,7*H*-naphtho[1,8-*bc*:4,4a-*c*′]difuran-5,10a(8*H*)-dicarboxylate. (Azadirachtin)

Turmeric (*Curcuma longa*)

Turmeric possesses antioxidant and anti-inflammatory qualities. It can be applied locally or taken internally to promote the healing of wounds and lower inflammation (Prasad and Aggarwal 2011).

1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione. (Curcumin)

Aloe Vera (*Aloe barbadensis*)

Aloe vera gel is calming and therapeutic. It can be administered topically to lessen pain and encourage the healing of wounds (Hekmatpou *et al.,* 2019).

(10*S*)-10-Glucopyranosyl-1,8-dihydroxy-3-(hydroxymethyl)-9(10*H*)-anthracenone. (Aloin)

Triphala

An herbal mixture called Triphala, consisting of three fruits, is used in Ayurvedic medicine to support overall health and may help improve wound healing when consumed orally (Peterson, Denniston, and Chopra 2017).

3,4,5-Trihydroxybenzoic acid. (Gallic acid)

Jatyadi Taila

This herbal oil is used in Ayurvedic practice for wound care. It has various herbs and can be applied topically to promote wound healing (Patwardhan, Datta, and Mitra 2011).

3,3′,4′,5,7-Pentahydroxyflavone. (Quercetine)

Amla (*Emblica officinalis*)

Rich in vitamin C, promotes collagen synthesis and tissue regeneration (Fujii *et al.,* 2008).

(5*R*)-[(1*S*)-1,2-Dihydroxyethyl]-3,4-dihydroxyfuran-2(5*H*)-one. (Ascorbic acid)

Babchi (*Psoralea corylifolia*)

Antibacterial, antifungal, promotes wound contraction and reduces scar formation (Alam, Khan, and Asad 2018).

7*H*-Furo[3,2-*g*][1]benzopyran-7-one. (Psoralen)

Brahmi (*Bacopa monnieri*)

Promotes nerve healing and reduces pain, beneficial for chronic wounds.

Table 3: Plants Containing Isorhamnetin.

Plant Name	Isorhamnetin Content	Parts of the Plant Used
Onion (*Allium cepa*)	Has isorhamnetin derivatives, primarily in the outer layers of the bulb	Bulbs, outer layers
Red Grapes (*Vitis vinifera*)	Red grapes, skins, and seeds have isorhamnetin	Skins, seeds
Apples (*Malus domestica*)	Apples and apple products hold isorhamnetin	Whole fruit, peels
Capers (*Capparis spinosa*)	Capers are a rich source of isorhamnetin	Flower buds
Green Tea (*Camellia sinensis*)	Green tea has isorhamnetin glycosides	Leaves
Tomatoes (*Solanum lycopersicon*)	Tomatoes and tomato products contain isorhamnetin	Fruits
Chili Peppers (Capsicum spp.)	Some chili pepper varieties contain isorhamnetin	Fruits
Ginkgo Biloba (*Ginkgo biloba*)	Ginkgo leaves contain isorhamnetin derivatives	Leaves
Gourd Family (Cucurbitaceae)	Various members of the gourd family may contain isorhamnetin	Leaves, fruits
Dill (*Anethum graveolens*)	Dill leaves and seeds contain isorhamnetin glycosides	Leaves, seeds
Parsley (*Petroselinum crispum*)	Parsley is a source of isorhamnetin glycosides	Leaves
Kaempferia galanga (Galangal)	Galangal root contains isorhamnetin derivatives	Rhizomes
Fennel (*Foeniculum vulgare*)	Fennel seeds contain isorhamnetin glycosides	Seeds
Rutin (*Sophora japonica*)	The Japanese pagoda tree yields Rutin, a glycoside of isorhamnetin	Flowers, buds, leaves
Hawthorn (Crataegus spp.)	Some species of hawthorn may have isorhamnetin	Leaves, berries
Buckwheat (*Fagopyrum esculentum*)	Buckwheat has isorhamnetin glycosides in the seeds	Seeds
Spinach (*Spinacia oleracea*)	Spinach leaves may have isorhamnetin	Leaves
Bilberry (*Vaccinium myrtillus*)	Bilberries have isorhamnetin glycosides	Berries
Horse Chestnut (*Aesculus hippocastanum*)	Horse chestnut seeds contain isorhamnetin glycosides	Seeds

Table 4: Natural Remedies: Exploring the Therapeutic Potential of Plant-Derived Compounds

Plant Name	Parts Used	Main Chemical Compounds	Mechanism of Action	Pharmacological Activity
Amla (*Emblica officinalis*)	Fruits	Vitamin C, Emblicanin A & B	Antioxidant, Collagen synthesis, Tissue regeneration	Anti-inflammatory, Wound healing
Babchi (*Psoralea corylifolia*)	Seeds	Bakuchiol, Isopsoralen	Antibacterial, Antifungal, Wound contraction	Anti-inflammatory, Scar reduction
Brahmi (*Bacopa monnieri*)	Leaves	Bacoside A & B, Hersaponin	Nerve healing, Pain reduction	Anti-inflammatory, Chronic wound healing
Chamomile (*Matricaria chamomilla*)	Flowers	Chamazulene, Apigenin, Quercetin	Anti-inflammatory, Soothing, Antioxidant	Wound healing, Pain relief
Comfrey (*Symphytum officinale*)	Roots	Allantoin, Rosmarinic acid, Tannins	Tissue regeneration, Anti-inflammatory, Astringent	Wound healing, Pain relief
Calendula (*Calendula officinalis*)	Flowers	Calendic acid, Faradiol, Flavonoids	Anti-inflammatory, Wound healing, Antioxidant	Wound healing, Pain relief
Echinacea (Echinacea spp.)	Roots	Alkyl amides, Caffeic acid derivatives	Immune system booster, Antibacterial	Wound healing (prevent infection)
Curcuma longa (Turmeric)	Rhizomes	Curcumin	Anti-inflammatory, Antioxidant, Collagen synthesis	Wound healing, Pain relief
Aloe vera	Leaves	Acemannan, Polysaccharides	Antibacterial, Anti-inflammatory, Wound healing	Wound healing, Pain relief, Skin hydration
Centella asiatica (Gotu kola)	Leaves	Asiaticoside, Triterpenoids	Collagen synthesis, Tissue regeneration, Nerve healing	Wound healing, Anti-inflammatory, Scar reduction
Neem (*Azadirachta indica*)	Leaves	Azadirachtin, Nimbolide	Antibacterial, Antifungal, Wound closure	Wound healing, Pain relief, Anti-inflammatory
Guggulu (*Commiphora mukul*)	Resin	Guggulsterones	Anti-inflammatory, Analgesic, Tissue repair	Wound healing, Pain relief

19,20-Dihydroxy-16-oxodammar-24-en-3-yl 4-O-α-L-arabinopyranosyl-β-D-glucopyranoside. (Bacoside A)

Chirata (*Swertia chirata*)

Antiseptic, anti-inflammatory, promotes tissue granulation and wound closure (Kumar and Van Staden 2016).

(4a*S*,5*R*,6*S*)-5-Ethenyl-1-oxo-4,4a,5,6-tetrahydro-1*H*,3*H*-pyrano[3,4-c]pyran-6-yl β-D-glucopyranoside 2-(3,3′,5-trihydroxy[1,1′-biphenyl]-2-carboxylate). (Amarogentin)

Durva (*Cynodon dactylon*)

Antiseptic, astringent, promotes wound healing and reduces scar formation.

4′,5,7-Trihydroxyflavone. (Apigenin)

Guggulu (*Commiphora mukul*)

Anti-inflammatory, analgesic, promotes tissue repair, and reduces pain.

Pregna-4,17-diene-3,16-dione. (Guggulsterone)

Haritaki (*Terminalia chebula*)

Antiseptic, astringent, promotes tissue regeneration and immune function.

(2R)-2-[(3S)-3-carboxy-5,6,7-trihydroxy-1-oxo-3,4-ihydroisochromen-4-yl]butanedioic acid. (Chebulic acid)

Karpura (*Cinnamomum camphora*)

Antiseptic, analgesic, promotes blood circulation and wound healing.

1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one. (Camphor)

Lodh (*Symplocos racemosa*)

Anti-inflammatory, astringent, promotes wound healing and reduces scar tissue formation.

7-O-Glucoside of 3′-methoxy-4′,5,7-trihydroxyflavanone. (Symplocoside)

Punarnava (*Boerhavia diffusa* leaves)

Diuretic, anti-inflammatory, promotes blood flow and wound healing (Mishra *et al.,* 2014).

6,9,11-Trihydroxy-10-methylchromeno[3,4-b]chromen-12(6H)-one. (Boeravinone B)

Saraswathi (*Sarsaparilla parvifolia*)

Antiseptic blood purifier, which enhances tissue regeneration and wound healing.

(25*S*)-5β-Spirostan-3β-ol (Sarsasapogenin)

Shatavari (*Asparagus racemosus*)

Immunomodulatory effect, antioxidant effect, tissue repair, and inflammation decrease.

Tagar (*Alpinia galanga*)

Antiseptic, anti-inflammatory, facilitates tissue regeneration and scars epithelial tissue (Cahyono, Suzery, and Amalina 2023).

3,5,7-Trihydroxyflavone (Galangin)

Vacha (*Acorus calamus*)

Antiseptic, pain reliever, promotes nerve healing and decreases pain (Sharma *et al.,* 2020).

1,2,4-Trimethoxy-5-[(*Z*)-prop-1-enyl] benzene (β). (β-Asarone)

Vidanga (*Embelia ribes*)

Anti-inflammatory, helps to heal wounds and prevent scars (Sharma *et al.,* 2022).

2,5-Cyclohexadiene-1,4-dione, 2,5-dihydroxy-3-undecyl- (Embelin)

Yashtimadhu (*Glycyrrhiza glabra* root)

Anti-inflammatory, antioxidant, stimulates tissue regeneration, decreases scar formation (Matte *et al.,* 2025).

α-D-glucopyranosiduronic acid (glycyrrhizin or glycyrrhizinic acid).

DISCUSSION

Diabetes mellitus is a chronic metabolic disease that is a central issue in the management of modern healthcare because of ability to derail wound healing mechanisms. Traditional treatment strategies have proved to be not very effective in dealing with these issues. Natural compounds which are potential alternatives to diabetic wound healing have also been discovered like Isorhamnetin which is a widely occurring flavonoid in many plants (Jiang *et al.,* 2023). This is a review study, in which the role of isorhamnetin in accelerated wound healing in diabetics is critically analyzed. It examines the molecular mechanisms behind its therapeutic effects which may include its pro-angiogenic, antioxidant, and anti-inflammatory properties (Table 3). It also examines the effect of isorhamnetin on the regulation of important cellular processes such as PI3K/Akt and MAPK signaling pathways during wound healing (Duan *et al.,* 2020). By discussing its different sources, pharmacokinetics, and safety profiles, the paper identifies the promise of isorhamnetin as a safe and readily available therapeutic agent in treating diabetic wounds. It gives understanding of several of the experimental and clinical studies on the effectiveness of Isorhamnetin in enhancing wound healing in diabetic patients with encouraging results.

The pathogenesis of diabetic foot ulcer is a multifactorial and complex process which develops due to many factors associated with diabetes mellitus. It is important to be aware of the underlying mechanisms to prevent and manage diabetic foot ulcers. The pathogenesis is mainly associated with peripheral neuropathy, ischemia, foot deformities, microvascular alterations, infection, impaired immune response, glycation, inflammation, pressure, and friction, and inadequate self-care. Isorhamnetin is a natural product that has an extraordinary ability to speed up the healing process of diabetic wounds (X. Wang *et al.,* 2022). This is because its mechanism of action is versatile, safe, and rich, thereby making it an excellent option to be further developed and researched on to minimize the burden of diabetes. Biochemical receptors of the human body are of many types: G Protein-Coupled Receptors (GPCRs), ion channel receptors, nuclear receptors, enzyme-linked receptors, Toll-Like Receptors (TLRs), cytokine receptor, Chemical Sensors and Receptor Tyrosine Kinases (RTKs) (Zheng *et al.,* 2024). These receptors play a significant role in navigation, communication and body functions (Varney and Benovic 2024). The combination of cellular and molecular mechanisms can result in diabetes Mellitus causing chronic pain, poor wound healing and inability to heal the wounds. These factors and mechanisms include hyperglycemia (with glycation), oxidative stress, chronic inflammation, impaired angiogenesis, peripheral neuropathy, excessive Matrix Metalloproteinases (MMPs), delayed epithelial re-epithelialization, impaired fibroblast activity, Advanced Glycation End products (AGEs), and compromised immunity. High blood sugar and glycation can impair key molecules involved in wound healing (e.g., collagen, growth factors, and enzymes). Oxidative stress, inflammation, angiogenesis, peripheral neuropathy, matrix metalloproteinases, slow epithelial regeneration, impaired fibroblast activity, advanced glycation end products, and impaired immunity (R. Wang *et al.,* 2025). Factors such as impaired blood circulation, dysfunctional VEGF signaling, excessive matrix metalloproteinase activity,

sluggish epithelial repair, and compromised immunity further contribute to chronic diabetic wounds. Such injuries may result in the inability to heal wounds and the emergence of chronic diseases like diabetic foot ulcers. Diabetic wound management includes various approaches, encompassing modern medical treatments as well as complementary and alternative therapies such as Ayurveda and herbal medicine. Topical agents such as mupirocin (an antibiotic) and iodine (an antiseptic) are commonly used to control infection. Modern wound dressings are designed to manage exudate, maintain a moist wound environment, and promote healing (Ahmad *et al.,* 2025). Examples include hydrocolloids, foams, and hydrogels. Hydrocolloids, foams and hydrogels are examples of such dressings. Negative Pressure Wound Therapy (NPWT): This technique uses a vacuum dressing over the wound site, which removes excess fluid, increases blood circulation, and promotes granulation tissue growth to accelerate healing. Tissue repair is stimulated using growth factors and cytokines (Normandin *et al.,* 2021). Severe diabetic wounds that do not respond to conventional treatment may also be treated with biologic agents, including skin substitutes and tissue-engineered grafts. Hyperbaric Oxygen Therapy (HBOT) facilitates angiogenesis, augmented wound healing and tissue oxygenation by breathing pure oxygen in a pressurized chamber (Wu *et al.,* 2024). Neem leaves and oil are used as Ayurvedic medicine, due to its antibacterial properties. Turmeric, Aloe vera, triphala, and Jatyadi taila are used to treat wounds. Herbal therapies include Calendula, chamomile, and echinacea extracts are used as their anti-inflammatory and wound-healing properties. Current therapies for diabetic wounds include topical antibiotics, growth factors, pain medications, antiplatelet agents, hyperbaric oxygen therapy, angiogenesis promoters, pentoxifylline, ACE inhibitors, ARBs, and strict blood sugar control (Oyebode, Jere, and Houreld 2023). Isorhamnetin is present in various plants such as onions, red grapes, apples, capsicum, Ginkgo biloba, members of the gourd family (Cucurbitaceae), fennel, buckwheat, spinach, and horse chestnut because they enhance healing and address different factors about wound pathophysiology (Gong *et al.,* 2020). The important pharmacological actions are anti-inflammatory, antioxidant, promotion of angiogenesis, collagen synthesis, antibacterial and antifungal actions, analgesia, stimulation of growth factor, wound clean and debridement, tissue regeneration, immunomodulatory activities, anti-glycation, and wound hydration and moisture regulation. Flavonoids, curcumin, and resveratrol from plants exhibit potent anti-inflammatory effects, while antioxidants and vitamins combat oxidative stress. New blood vessels and collagen secretion are stimulated by plant compounds as well. They also possess antifungal and antibacterial effect which helps in prevention and treatment of wounds. Plant chemicals are important in wound healing generally (Jhamb, Vangaveti, and Malabu 2016).

Some important pharmacological activities of plant-derived compounds in diabetic wound healing are summarized in Table 4. The following are some of the important pharmacological activities of the plant chemicals as applied to the healing of diabetic wounds. These are some of the important pharmacological activities of plant chemicals in the healing of diabetic wounds (Kizhakkeveettil, Smirl, and Parla 2018).

CONCLUSION

This review revealed the possibility of using Isorhamnetin which is a plant flavonoid in enhancing wound healing in diabetic individuals. The diabetic patients were demonstrated to have impaired wound healing, which contributed to persistent ulcers with great health and financial costs. Isorhamnetin studies indicated that Isorhamnetin had an anti-inflammatory, antioxidant, and pro-angiogenic effect and regulated main cellular pathways, including PI3K/Akt and MAPK, which play role in wound healing. It also had a promising therapeutic effect due to its pharmacokinetics, safety profile, and natural availability. The proposed studies in the future will be based on clinical trials, optimization of formulation, and extensive molecular investigations to make Isorhamnetin an effective and accessible therapy of diabetic wounds.

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ABBREVIATIONS

DM: Diabetes Mellitus; **ROS:** Reactive Oxygen Species; **IL-6:** Interleukin-6; **TNF-α:** Tumor Necrosis Factor-alpha; **VEGF:** Vascular Endothelial Growth Factor; **MMPs:** Matrix Metalloproteinases; **AGEs:** Advanced Glycation End Products; **GPCRs:** G Protein-Coupled Receptors; **RTKs:** Receptor Tyrosine Kinases; **TLRs:** Toll-Like Receptors; **PDGF:** Platelet-Derived Growth Factor; **NPWT:** Negative Pressure Wound Therapy; **HBOT:** Hyperbaric Oxygen Therapy; **MAPK:** Mitogen-Activated Protein Kinase; **ERK:** Extracellular Signal-Regulated Kinase; **JNK:** c-Jun N-terminal Kinase; **PI3K:** Phosphoinositide 3-Kinase; **Akt:** Protein Kinase B; **COX-2:** Cyclooxygenase-2; **NSAIDs:** Non-Steroidal Anti-Inflammatory Drugs; **ARBs:** Angiotensin Receptor Blockers; **EGFR:** Epidermal Growth Factor Receptor; **TGF-β:** Transforming Growth Factor-beta; **Wnt:** Wingless-related integration site; **NF-κB:** Nuclear Factor-kappa B.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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