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Mechanisms of medicinal plants in the treatment of diabetic wound

Oluwakemi V. Adeleke[1,2]✉, Stephen A. Adefegha[1], Ganiyu Oboh[1]

[1]*Functional Foods, Nutraceuticals and Phytomedicine Laboratory, Department of Biochemistry, Federal University of Technology Akure, Akure, Nigeria*

[2]*Department of Science Laboratory Technology, Ekiti State University, Ado Ekiti, Nigeria*

ABSTRACT

Wound repair is noticeably prolonged in a diabetic state due to a faulty inflammatory process and an underlying neuropathy. Several medicinal plants and their products have been of prime importance for the management of wounds over the years. Various mechanisms whereby medicinal plants elicit their action in wound repair are revealed and some plants are proven to be experimentally effective in enhancing wound closure and achieving healing. The mechanisms identified include hyperglycemic control, alleviation of physiological inflammation, controlled oxidative stress, infection control, and influence on gene expression. Information in this review was sourced from research and review articles in electronic databases such as Web of Science, Scopus, PubMed, and Google Scholar.

KEYWORDS: Diabetes; Infection; Inflammation; Medicinal plants; Wound healing; Oxidative stress

1. Introduction

The prevalence of diabetes was globally estimated to be 415 million in 2015 and 451 million in 2017 which is about 6% and 6.8% of the world's population, respectively. In 2021, it was reported to affect about 537 million worldwide and is expected to increase by the year 2030 and 2045 to 643 million and 783 million, respectively[1,2]. Diabetes mellitus, a multifactorial metabolic disease, is a group of disorders characterized by hyperglycemia and glucose intolerance. This unique characteristic "hyperglycemia/glucose intolerance" arises from insulin insufficiency and/or insulin insensitivity[3]. Foot ulcers and altered wound healing processes are inevitable vascular complications in diabetes which most times are presented as a long-term condition[4]. There is a 19%-34% chance that this will develop in diabetic patients and a 6.3% global incidence annually with North America having the highest prevalence rate of 13.0% followed by Africa (7.2%), Asia (5.5%), Europe (5.1%) and Oceania (3.0%)[5].

Wound repair is a coordinated process mediated by cytokines and growth factors. These mediators are secreted by different cells and actively participate in the phases of wound healing: hemostasis, inflammation, proliferation, and remodeling. Diabetic wound does not follow these well-defined processes; they often exhibit an inflammatory phase that is delayed by alterations in the inflammatory response and related growth factors[6].

Healthy living with a well-planned dietary and lifestyle pattern is required for the prevention and management of several diseases. Medicinal plants contain diverse bioactive components having a wide range of therapeutic potentials that are effective against diabetes and its complications. They are essential to consumers' well-being as they strengthen the body system specifically and selectively with little or no side effects. Several plant products and their extracts have been of prime importance to wound healing and used for the potential management of wounds over the years. Their bioactive compounds with healing potential include glycosides, steroids, essential oils, saponins, resins, mucilage, and flavonoids amongst others[7]. It is well known that healing in a diabetic wound

✉To whom correspondence may be addressed. E-mail: oluwakemi.adeleke@eksu.edu.ng

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is slow, difficult, and prolonged with a high cost of treatment and a resultant morbidity or mortality. It is, thus, important to find natural, safe, cheap, and effective ways of management. The findings from studies on medicinal plants could be useful for the development of therapeutic products for the treatment of diabetic wounds. Information on various medicinal plants in the treatment of diabetic wounds was sourced from research and review articles from electronic databases like Web of Science, Scopus, PubMed, and Google Scholar.

2. Hyperglycemia in diabetic complication

Hyperglycemia from insulin deficiency or insulin insensitivity is a common feature associated with diabetes mellitus. It initiates the activation of different signaling pathways that increases the rate at which reactive oxygen species (ROS) are produced; this drives complication in people with diabetes mellitus[8]. A damage to blood vessels (angiopathy) always existed from chronic elevation of blood glucose leading to "micro-vascular complications" (affecting small blood vessels) and/or "macro-vascular complications" (affecting arteries). Nephropathy, retinopathy and neuropathy are the micro-vascular while cardiovascular disorders associated with diabetes are considered macro-vascular complications.

The healing process in diabetic wounds is delayed by hyperglycemia which is a long-term microvascular complication of diabetes[4]. Signaling pathways such as the hexosamine, polyol, protein kinase C pathways and advanced glycation end product (AGEs) formation activate uncontrolled inflammatory cascades, resulting in cell damage and death[9]. Activation of these signaling pathways alters biological process essential for wound healing like growth factor production and cell proliferation. According to Pan *et al*.[10], a number of growth factors (PDGF, TGFβ, and VEGF) are influenced by prolonged activation of protein kinase C. Furthermore, hyperglycemia alters the production of nitric oxide which creates a highly reactive (oxygen species) environment and consequent damage to small vessels of peripheral nerves eventually leading to peripheral neuropathy[11].

One of notable complications of diabetes is diabetic peripheral neuropathy which presents signs of peripheral nerve degeneration in diabetic people. It is a chronic complication of the lower limb that makes people prone to ulceration and amputation with a global prevalence of over 60% in people with diabetes mellitus[12]. The ability to respond to pain, temperature, pressure, and touch that are external stimuli is affected due to nerve damage. This results in an undiagnosed neuropathy until ulcer forms or pain develops. Autonomic neuropathy affects autonomic nerves that control functions such as heart rate, sweating, and blood pressure, thus, reducing sweat while increasing temperature. Neuropathy of the motor nerves (sends impulses to the muscles from the brain and spinal cord) can affect the foot muscles causing limited joint mobility combined with undetected injuries, poor blood circulation and impaired healing leads to the development of a diabetic foot ulcer[4]. Generally, wounds are either external (cuts, injuries, burns and bruises) or internal (like skin ulcers and calluses) based on their origin. External wounds are somewhat unnoticeable because of pre-existing neuropathy and those of internal origin cause damages that have a high rate of bacterial infection. Diabetic wound, either internal or external, is chronic, non-healing wound with a prolonged inflammatory phase.

3. Prolonged inflammatory phase and impaired wound healing in diabetic wound

Normally, healing process starts with hemostasis and a coagulation cascade that checkmates bleeding and microbial invasion to wound area[13]. The inflammatory phase takes over allowing neutrophils and macrophages to clean up pathogens and other dead cells[14]. New tissues and blood vessels through angiogenesis and matrix reconstruction which are cascades of proliferative phase succeed in inflammation and are initiated to fill the wound area[13]. Matrix remodeling strengthens the matrix and reduces the supply of blood to affected area in the final phase of healing[15]. In this maturation phase, collagen synthesis equilibrates with collagen breakdown, and enzymes like matrix metalloproteinases (MMPs), and their inhibitors, tissue inhibitors of metalloproteinases are released. Diverse cells participate actively in wound repair through the production and regulation of cytokines and growth factors. Neutrophils in conjunction with T and B cells significantly produce TNF-α and IL-10 and also partly contribute to the release of growth factors TGF-β, VEGF, and IGF-1. Monocyte that transforms into matured macrophages (for phagocytosis) is the foremost producer of IL-1β, TNF-α, IL-6, and also growth factors.

A complex mechanism revolves around delayed healing in diabetic wounds as it does not follow the efficient and orderly wound-healing process. Formation of AGEs, microbial colonization, and unregulated infiltration of neutrophils (inflammatory cells) are mechanisms that prolong the inflammatory phase and produce ROS (Figure 1). Wound healing in diabetes is delayed by other factors like metabolic deficiencies, hypoxia, or deficient nutrient supply due to glycation of hemoglobin and narrowed blood vessels. Despite all these factors, a high percentage of cases of diabetic wounds is closely related to a chronic inflammatory process[16].

3.1. Role of inflammatory cells

During the inflammatory process activated within a day of wound formation, inflammatory cells are released at the wound site to produce cytokines, growth factors, and some enzymes. In response to chemotactic signals, neutrophils migrate with the help of functional

cell adhesion molecules to facilitate healing[17]. In a non-healing wound typical of a diabetic wound, there is uncontrolled neutrophil infiltration (Figure 1) leading to up-regulation of inflammatory mediators (cytokines, elastase, and MMPs). Elastases inhibit growth factors essential for healing while MMPs degrade and inactivate the component of the extracellular matrix. The physiological role of MMPs is to destroy dysfunctional structural proteins and release ones that provide support for the remodeled extracellular matrix but unregulated MMPs can overwhelm and destroy old extracellular matrix in addition to new structural proteins.

3.2. Role of infection

Infection in diabetic wounds occurs in almost 58% of diabetic patients. This aggravates the healing process resulting in frequent hospital visits and sometimes amputation of the affected parts[18]. The rate at which microorganism colonizes wound is a determinant of their prognosis since colonies of microorganism can form a biofilm that shields them from agents that are active against them. This delays healing and causes immune suppression[19]. Furthermore, neutrophils use free radicals generated through the myeloperoxidase (MPO) pathway to debride wounds of infection (Figure 1). Pathological production of these radicals together with pro-inflammatory cytokines resulting from excess neutrophil infiltration poses a further threat to wounds.

3.3. Role of AGEs

AGE formation is a distinct pathway influencing prolonged inflammatory phase. AGE precursor or activation of the AGE-RAGE (receptor for AGE) signaling axis causes cell dysfunction, modification of intracellular protein, loss of cell functions, and apoptosis. The binding and activation of the AGE-RAGE signaling axis lead to downstream activation of transcription factors/target genes that mediate the inflammatory process[20]. Nuclear factor kappa beta (NF-κB) is one such transcription factor (Figure 1) that modulates the expression of pro-inflammatory genes (cytokines).

4. Management of diabetic wounds: the present and future perspectives

Despite the up-to-date advances in the world of medicine and surgery, the prevalence of diabetic wound complications remains high[21]. Approaches employed for wound care should debride wounds of infection with adequate blood supply. This ensures a rapid rate of healing without spreading infection, decreases the risk of amputation and improves the quality of living[22,23].

Research on diabetic wounds is presently focused on tissue engineering approaches such as cytokine inhibitors, recombinant growth factors, MMP inhibitors, skin substitutes, stem cell/laser, stimulators of extracellular matrix and angiogenesis, and platelet-rich plasma amongst others. Living cells such as fibroblasts, keratinocytes, and stem cells, are skin substitutes used either singly or in combination with growth factors or components of the extracellular matrices[24].

As effective as these treatment approaches may be, it comes along with some risk and disadvantages which might limit their usage. Tissue engineering, one of the commonly used approaches is believed to exert its action by inducing the expression of cytokines

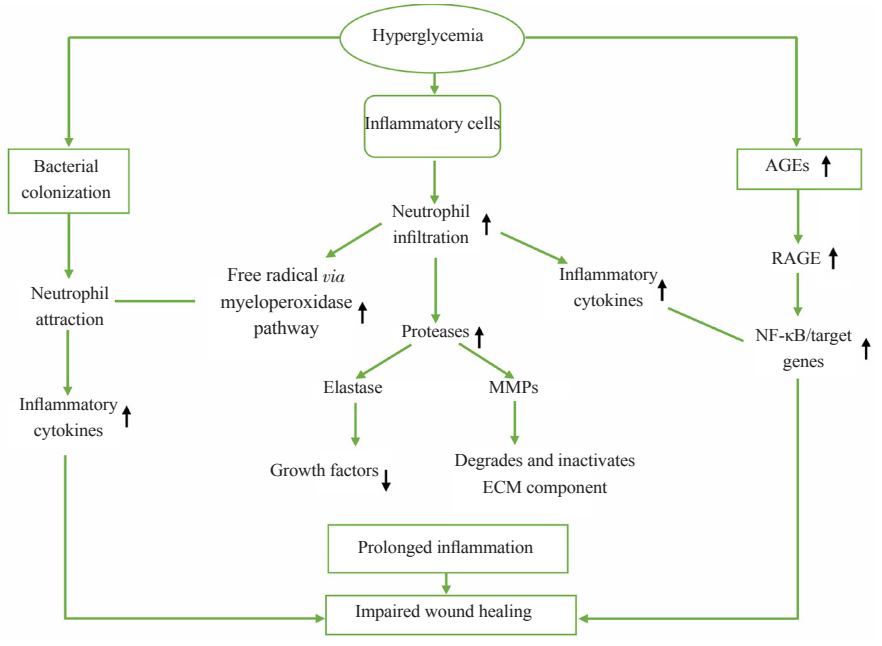

Figure 1. Mechanisms involved in prolonged inflammatory phase and impaired wound healing. AGEs: advanced glycation end products; RAGE: receptor for AGE; MMP: matrix metalloproteinases; ECM: extracellular matrix.

and growth factors in wounds. Epidermal growth factor (EGF) has shown a high cure rate in patients with diabetic foot ulcers[25], however, the use of other growth factors has no solid scientific evidence on safety profiles and benefits of their use. Use of polymers is also a current wound dressing approach involving synthetic polymers and natural ones such as cellulose, chitosan, collagen, and gelatin hyaluronic acid, but they have several disadvantages, especially a lack of antimicrobial properties[11]. Above all, these treatment approaches are expensive and may be inaccessible to a common man whose health is uninsured especially in undeveloped countries and with limited access to technological advancement.

Although complete wound closure without scar is not always achieved in diabetic patients, healing outcomes like reduced risk of infection and amputation with improved quality of life are somewhat important to these patients[22]. Therapeutic measures in managing diabetic wounds should under no circumstances alter any steps or phases involved in wound healing and should positively influence gene expression, reduce microbial invasion, and control inflammatory processes, oxidative stress, and blood glucose.

Phytomedicine which is the therapeutic use of medicinal plants has formed part of history of several cultures and in the modern world today. These medicinal plants have been discovered to effectively strengthen the body system with little or no side effects. Herbal medicines with their nutritional value and pharmacological properties possess health-promoting substances in the form of secondary metabolites[26], which are essential in health care system worldwide. Due to the antioxidant nature of these bioactive substances, they are preferable to synthetic ones avoiding safety concerns.

Traditionally, plants obtained from different natures (sources): turmeric, neem bark, and ginseng are of tremendous significance to wound healing. Their bioactive components with healing properties include glycosides, steroids, essential oils, saponins, resins, mucilage, and flavonoids amongst others[7,27]. They are involved in several healing processes which include control of the inflammatory process, collagen deposition, granulation tissue formation, and increased lesion contraction[28,29]. The use of natural product-based treatment in phytomedicine is highly celebrated globally and for these natural products to be considered for use in treatment of wounds, they must possess distinct properties. These include but are not limited to control of hyperglycemia, physiological inflammation, oxidative stress, and infection, as well as modulation of the expression of key proteins involved in the healing process[7,30].

5. Mechanisms of wound healing action of medicinal plants

A healing wound should show a rapid wound closure rate, controlled microbial colonization, moderate secretion of growth factors and cytokines, and a controlled blood glucose level[27,31,32]. All of these factors when neglected allow persistent inflammation over a long period. Diabetic wound has a poor prognosis and there is a dearth of information on effective therapy successfully used for its management. In addition, the detailed mechanism underlying efficient healing needs to be fully understood. Therefore, targeting these mechanisms specifically with medicinal plants either singly or in combination might be a promising approach to managing diabetic wounds[33].

5.1. Controlling blood glucose level

Hyperglycemia drives complications in a diabetic state by activating different signaling pathways leading to overexpression of ROS. Consistent hyperglycemia initiates the AGEs formation pathway resulting in rapid and intense accumulation of AGEs. This creates a free radical environment that negatively affects wound healing[34]. High glucose concentration also promotes the establishment of a microbial environment by supplying nutrients for microorganisms and decreasing innate immunity. Furthermore, hyperglycemia inhibits nitric oxide production creating a wound bed of reactive species and consequent neuropathy[35]. *Curculigo orchioides* Gaertn and *Sphenocentrum jollyanum* (*S. jollyanum*) improved wound healing by increasing nitric oxide in streptozotocin-induced diabetic animals[32,36].

Controlling the glycemic state of diabetes mellitus is necessary for adequate repair of wounds. Although neuropathic damage from high glucose concentration is sometimes inevitable, ensuring a normal blood glucose level could prevent progression to chronic wounds and also speed up the healing process. Moreover, inhibition of AGEs and the downstream activation of transcription factors/target genes that mediate prolonged inflammation also plays a key role in wound healing. Activation of the AGE axis together with its receptor (RAGE) is associated with chronic wounds in humans. Inhibiting this axis can accelerate wound healing by moderating epithelialization, angiogenesis, inflammation, and tissue remodeling, as well as enhancing wound closure[37-39].

Medicinal plants can target the enzymatic hydrolysis of carbohydrates and effectively slow down the absorption of their end product and control a rise in post-prandial glucose[40]. Enzymes that hydrolyze carbohydrates greatly influence their digestion and several studies confirm the potential of medicinal plants in repressing the activities of these enzymes[32,41]. Polyphenols from plants with antioxidative and antihyperglycemic effects elicit their action by inhibiting carbohydrate metabolizing enzymes α-amylase and α-glucosidase[42-45].

5.2. Redox balance via controlling oxidative stress

A physiological level of ROS initiates processes that are beneficial to healing including platelet aggregation through an expression

of adhesion molecule, stimulation of chemotaxis, stimulation of angiogenesis, and migration of endothelial cells for blood vessel reformation *via* VEGF expression[46]. In addition, free radicals induce death of microorganisms at the wound site through the MPO pathway. MPO predominantly expressed in neutrophils can produce ROS and thus has potential as an antimicrobial and antiviral agent. Through utilization of H_2O_2, MPO can generate tyrosyl free radicals and hypochlorous acid (HOCl)[47].

During oxidative stress, reactive species initiate a modification and damage to cellular components (macromolecules) such as lipids, proteins, and nucleic acids. They also can trigger a number of signaling cascades leading to the erroneous expression of many genes and consequent onset and progression of complications[30]. Uncontrolled neutrophil migration during an injury generates a cycle of recruitment that leads to excessive ROS production[48]. Oxidative burst is a primary mechanism of killing bacteria and preventing wound infection but during these processes, there exists a downregulation of enzymes that are known to scavenge ROS[30,49]. Several gene functions are known to be altered by ROS like those coding for antioxidant enzymes, VEGF, and other cellular growth factors as well as cytokines[50].

A balance of ROS generation and its scavenging is required for efficient wound healing. Activation and interaction of signaling pathways involved in overproduction of ROS alter gene expression, deplete antioxidant reservoirs, and favors the production of AGEs. Control of signaling pathways: hexosamine, polyol, protein kinase C, and formation of AGEs positively modulates the expression of genes that favor the production of antioxidants, inhibition of ROS generation, and consequent redox balance. ROS scavenging enzymes as well as glutathione and vitamin E which are small molecule antioxidants tightly regulate ROS generated in wounds and are substantially upregulated in healing wounds[51,52].

Diabetic wound studies involving different animal models have considered plants and their involvement in wound healing *via* management of oxidative stress (Table 1). *Curculigo orchioides* improved wound healing in diabetic mice by increasing superoxide dismutase and decreasing lipid peroxidation[36]. *Curcuma longa* (*C. longa*) of the family Zingiberaceae with an active component of curcumin increased wound closure rate in a diabetic experimental animal model by increasing antioxidant activity[53,54]. Genistein (*Genista tinctoria* L.) and *Astragalus membranaceus* (*A. membranaceus*) improved wound healing by suppressing FoxO1 and inducible nitric oxide synthase activity, and attenuating oxidative stress in type 1 diabetic mice and diabetic rats with hind limb ischemia, respectively[55,56]. According to Lodhi and Singhai[57], flavonoid-rich fraction and luteolin isolated from *Martynia annua* Linn. enhanced wound healing in streptozotocin-induced diabetic rats possibly by free-radical scavenging activity.

5.3. Physiological inflammatory process

Inflammation (the second phase of wound healing) is a necessity during wound repair where inflammatory cells secrete cytokines and growth factors. Inflammatory cells enter apoptosis, followed by initation of proliferation (the third phase of wound repair). Inflammation, although essential, can generate deleterious effects when it occurs repeatedly and excessively. In a chronic wound with no sign of efficient healing, there is abundant/uncontrolled

Table 1. Mechanistic effects of medicinal herbs and compounds on diabetic wound repair.

Phase	Mechanism	Medicinal herbs or compounds	Molecular target	References
Inflammation	Regulation of gene expression	*Sphenocentrum jollyanum*	SOD-1, VEGF	[27]
		Astragalus membranaceus	VEGF, eNOS	[56]
		Curcuma longa	VEGF, TGF-β, HIF-1α, stromal cell-derived growth factor-1α, heme oxygenase-1	[69]
		Naringin	VEGF, TGF-β	[70]
	Infection control	*Sphenocentrum jollyanum*	MPO	[27]
	Cytokine regulation	*Sphenocentrum jollyanum*	TNF-α, IL-6	[27]
		Rosmarinus officinalis	IL-3, IL-10	[59]
		Curcuma longa	TNF-α, IL-1	[54,60]
	Reduction of oxidative stress	*Curculigo orchioides*	SOD, MDA	[36]
		Curcuma longa	Antioxidant	[53,54]
		Genista tinctoria L	FoxO1, iNOS	[55]
		Astragalus membranaceus	FoxO1, iNOS	[56]
		Martynia annua Linn	Free radicals	[57]
	Prevention of hyperglycemia	*Sphenocentrum jollyanum*	α-Amylase, α-glucosidase	[32]
Proliferation	Epithelization, granulation, collagen deposition, angiogenesis	*Sphenocentrum jollyanum*, *Annona squamosa* L, *Angelica sinensis*, curcumin	-	[27,70–72]
Remodeling	-	*Sparassis crispa*	-	[73]

SOD-1: superoxide dismutase 1; VEGF: vascular endothelial growth factor; eNOS: endothelial nitric oxide synthase; TGF-β: transforming growth factor β; HIF-1 alpha: hypoxia inducible factor-1 alpha; MPO: myeloperoxidase; TNF-α: tumor necrosis factor α; IL: interleukin; MDA: malondialdehyde; FoxO1: forkhead box protein O1; iNOS: inducible nitric oxide synthase.

infiltration of inflammatory cells specifically neutrophils which release cytokines and interleukins.

A controlled level of inflammation is needed for wound progression to the proliferative phase. However, a modification of wound repair process resulting from cytokine dysregulation exists in patient with diabetes mellitus[58]. Overproduction of inflammatory cytokines either from abundant release of inflammatory cells or signaling from AGEs must be tightly controlled for perfect wound repair. Several plants have shown effectiveness in controlling inflammation in animal models of diabetic wounds. *Rosmarinus officinalis* reduced inflammation and increased wound contraction[59]. *C. longa* decreased inflammation in streptozotocin-induced diabetic mice and consequently increased wound closure rate[54,60]. Similarly, *A. membranaceus* and *S. jollyanum* inhibited inflammation, increased tissue regeneration, and promote angiogenesis in streptozotocin-induced diabetic rats[27] (Table 1). A study on diabetic patients revealed that *Melilotus officinalis* induced micro-vascularization and had anti-inflammatory activity[61].

5.4. Controlling microbial infection

Colonization of wounds by complex communities of microbe progresses to a chronic infection that negatively affects and prolongs wound repair. Microbes like bacteria and fungi which are from different kingdoms and species can cohabit and interact within the same biofilm and can temporarily shift their phenotypes and influence their virulence. This ability is another factor that impacts the persistence and aggressiveness of an infection. Furthermore, the presence of multidrug-resistant organisms in diabetic wounds is another factor that makes treatment more difficult or impossible[62].

A therapeutic agent is expected to control microbial colonization to avoid infections that can intensify the wound and delay healing. Commonly used antibiotics may have minimal effectiveness in interfering with microbiome of diabetic wound. A change in the bacteriome (bacterial community) which is targeted by antibiotics may permit fungal infection (colonization and expansion) for which there is limited treatment options[63]. Targeting all species of pathogens with compounds that successfully manipulate and destroy microbial biofilm of chronic wounds is essential and a promising bedrock of research. In a recent research by Adeleke *et al*.[27], the root and leaf of *S. jollyanum* exhibited anti-microbial activity *in vitro* and also reduced the microbial load on wounds of high-fat diet/streptozotocin-induced diabetic rats.

5.5. Influence of medicinal plant on gene expression

The extent to which a gene can be expressed is observed by measuring the quantity of mRNA that corresponds to the gene's DNA. Mechanisms through which gene expression is being modulated by medicinal plants have been extensively studied. The most prominent point of regulation affected by medicinal plants and its product is the DNA-binding capacity of transcription factors like Nrf2 and NF-κB. Through this, genes that code for key proteins in signal transduction pathway are modulated[64–66]. The expression of gene that modulates inflammation, hypoxia, and oxidative stress will influence the transition from inflammation to proliferation and the remodeling phase of healing[7,30]. Growth factor initiates and sustains wound repair. In chronic wound, there is reduced bioavailability of growth factors due to excess proteases (elastases) released by active neutrophils. Suppressing these proteases and expression of growth factors ensure bioavailability of growth factors like vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and insulin-like growth factor (IGF-1) that promote proliferation, angiogenesis, and matrix remodeling[67].

Transcription factors, Nrf2 and NF-κB, have different modulatory roles in wound healing. Nrf2 controls inflammation and ROS generation through the expression of antioxidant enzymes, which is altered in response to foot ulceration in diabetic patients according to Wang *et al*[68]. Activation of NF-κB and its downstream pro-inflammatory gene is increased following the initiation of the AGE/RAGE signaling axis. NF-κB activation alters the proliferation and migration of cells and also activates metalloproteinases which degrade the component of the extracellular matrix and alter growth factor function[65]. The DNA binding capacity of both Nrf2 and NF-κB should be tightly regulated for a wound to be repaired completely without delay.

Several plants are notable in modulating the expression of genes essential for wound healing (Table 1). *C. longa* L. increases the expression of growth factors (VEGF, TGF-β, hypoxia-inducible factor-1 alpha, stromal cell-derived growth factor-1α), and heme oxygenase-1 in diabetic rats[69]. According to Tam *et al*.[56], *A. membranaceus* influenced VEGF and eNOS expression in streptozotocin-induced rats with hind limb ischemia. Naringin found in the skin of grapefruit and orange induced angiogenesis and up-regulated the expression of VEGF and TGF-β in diabetic rats[70]. Furthermore, *S. jollyanum* increased the expression of VEGF and superoxide dismutase while downregulating the mRNA level of MPO in high-fat diet/streptozotocin-induced diabetic rats[27].

A focus on these mechanisms can lead to achievement of faster wound closure and complete healing by quickening the transition from inflammation to proliferation and remodeling. The proliferative and remodeling ability of plants has also been studied in animal models. Curcumin, *Annona squamosa* L., and *Angelica sinensis* increased granulation tissue, cellular proliferation, epithelialization rate, collagen synthesis, and deposition, thus enhancing angiogenesis and reducing neutrophil infiltration[71,72].

6. Conclusion

The transition from inflammation to proliferation and the remodeling phase of wound healing is very important and this physiological process needs to be accelerated for adequate wound repair. The use of medicinal plant can effectively manage diabetic wound by preventing infection and persistent inflammation on the wound. Identification and isolation of bioactive compounds with the development of natural products for the treatment of diabetic wound need to be carried out in future research and this review provides insight into the mechanisms of medicinal plant in treating diabetic wound.

Conflict of interest statement

All authors declare no conflict of interest.

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Authors' contributions

OVA contributed to design, literature search, and manuscript preparation and editing. SAA and GO contributed to conceptualization, design and manuscript reviewing. All authors read and agreed to the published version of this manuscript.

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