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Review

Hyperglycaemia-Linked Diabetic Foot Complications and Their Management Using Conventional and Alternative Therapies

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Abstract: Diabetes mellitus, a major cause of mortality around the globe, can result in several secondary complications, including diabetic foot syndrome, which is brought on by diabetic neuropathy and ischemia. Approximately 15% of diabetic patients suffer from diabetic foot complications, and among them 25% are at risk of lower limb amputations. Diabetic foot ulcers are characterized as skin lesions, gangrene, or necrosis, and may develop due to several reasons, including hyperglycemia and slower wound healing in diabetic patients. A management protocol involving wound cleaning, oral antibiotics, skin ointments, and removing dead tissue is currently followed to treat diabetic foot ulcers. In severe cases, amputation is performed to prevent the infection from spreading further. The existing therapy can be costly and present adverse side effects. Combined with a lack of vascular surgeons, this ultimately results in disability, especially in developing nations. There is a growing interest in the use of alternative therapies, such as medicinal plants, to discover more efficient and affordable treatments for diabetic foot syndrome. It has been observed that treatment with numerous plants, including *Carica papaya*, *Annona squamosa*, *Catharanthus roseus*, and *Centella asiatica*, promotes wound healing, reduces inflammation, and may decrease the number of amputations. However, little information is currently available on the prevention and management of diabetic foot ulcers, and additional research is necessary to completely understand the role of alternative therapies in the treatment of diabetic foot complications.

Keywords: hyperglycemia; diabetic foot; infection; glucose; alternative medicine

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1. Introduction

Diabetes mellitus (DM) is considered a worldwide epidemic, being one of the top ten diseases causing mortality globally and affecting more than 10.5% of the adult population [1,2]. It is a chronic metabolic disorder manifested by persistent high blood glucose levels occurring due to deficiencies in insulin production, insulin resistance, or both [3]. According to its etiology and pathogenesis, diabetes mellitus can be broadly classified into two major types: type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [4]. T1DM is a result of the autoimmune destruction of the pancreatic β-cells of the islets of Langerhans, leading to significantly diminished insulin secretion, whereas T2DM, often associated with obesity and an unhealthy lifestyle, is the outcome of either impaired insulin secretion, decreased insulin sensitivity to cells, or both [5,6]. The long-term secondary complications of diabetes include coronary heart disease, peripheral artery disease, cardiomyopathy, stroke, and cerebrovascular disease, as well as diabetic retinopathy (which causes visual impairment), diabetic nephropathy (which leads to kidney failure), and diabetic neuropathy (which increases the risk of foot ulcers) [7–9]. Individuals with long-term DM are prone to these complications, which may lead to increased morbidity and mortality [10].

Diabetic foot is a major complication of DM that affects approximately 15% of diabetic patients, with 25% of them facing the possibility of lower limb amputation [11–13]. Diabetic patients are often hospitalized due to the consequences of foot-related conditions such as infections, ulcers, and gangrene or foot necrosis [14]. The ulceration is the starting point for a severe stage of the disease, and if left untreated, this can lead to amputations. Diabetic neuropathy, neuro-ischemia, and infections all have an impact on whether lesions heal or deteriorate, and amputations in diabetic patients are often precipitated by a foot ulcer that progresses to serious gangrene or infection [12].

To accelerate the healing process of diabetic foot ulcerations, various interventions such as wound cleansing, revascularization, antibiotic therapy, dead tissue removal, and in extreme situations surgery have been implemented [15]. The conventional therapy for treating diabetic foot is often impracticable, particularly in underdeveloped countries, because of the high costs, adverse side effects, and the unavailability of vascular surgeons. In recent years, there has been a surge of interest in the search for alternative medications derived from natural resources, especially medicinal plants, for the prevention and treatment of diabetic foot [16,17].

Since ancient times, herbal remedies have been used as effective therapies to treat a wide range of ailments, including diabetic foot [16]. Recent findings have revealed that biologically-active phytomolecules present in plants demonstrate various pharmacological effects that help to prevent different forms of cell damage, including chronic wounds [17]. Numerous medicinal plants, including *Aloe vera, Annona squamosa, Azadirachta indica, Carica papaya, Catharanthus roseus, Centella asiatica, Curcuma longa, Hylocereus undatus,* and *Punica granatum,* have exhibited potential wound healing, anti-inflammatory, antioxidative, antibacterial, and other antidiabetic properties with little to no side effects, and might be considered as possible effective treatments for diabetic injuries [18–20]. Several bioactive phytomolecules such as quercetin, kaempferol, isoquercetrin, apigenin, tangeretin, naringenin, luteolin, catechin, gallic acid, methyl gallate, and rutin present in medicinal plants including *Allium cepa, Beta vulgaris, Citrus sinensis, Schinus polygamus,* and *Sorghum bicolor* exert their antidiabetic action via different mechanistic pathways to improve β-cell function and insulin secretion; enhance insulin sensitivity; increase GLUT-4 expression; decrease gluconeogenesis; and inhibit α-amylase, α-glucosidase, and DPP-IV activity and the formation of advanced glycation end products. Such phytochemicals not only ameliorate diabetic foot wounds but also contribute to the overall antidiabetic action of the medicinal plants to prevent and manage other diabetes-related complications [21,22]. Thus, due to the abundance of bioactive compounds in plants, researchers have directed their focus toward examining the significance of medicinal plants and isolating their phytoconstituents to assess their prospective wound-healing properties [18]. This review article primarily aims to explore the role of traditional medicinal plants and their isolated phytomolecules in the prevention and management of diabetic foot syndrome, as well as their future scope as antidiabetic medications.

2. Epidemiology

Nearly 537 million people are currently suffering from diabetes mellitus worldwide. This is projected to rise to 783 million by the year 2045 [2]. Diabetes mellitus is the primary cause of non-traumatic lower limb amputations across the globe [23]. This growing incidence of DM can lead to the increased prevalence of diabetic foot complications, which have become a serious medical, social, and economic concern of global importance [24]. Diabetic foot ulcers are foot lesions that damage the skin, soft tissues, and bones in the legs and feet, generating an aggravated infection in diabetic patients and potentially leading to lower limb amputations. Recent reports showed that around 60 to 80% of these ulcers can heal, 10 to 15% can stay active, and 5 to 24% eventually result in limb amputation (Figure 1) [23].

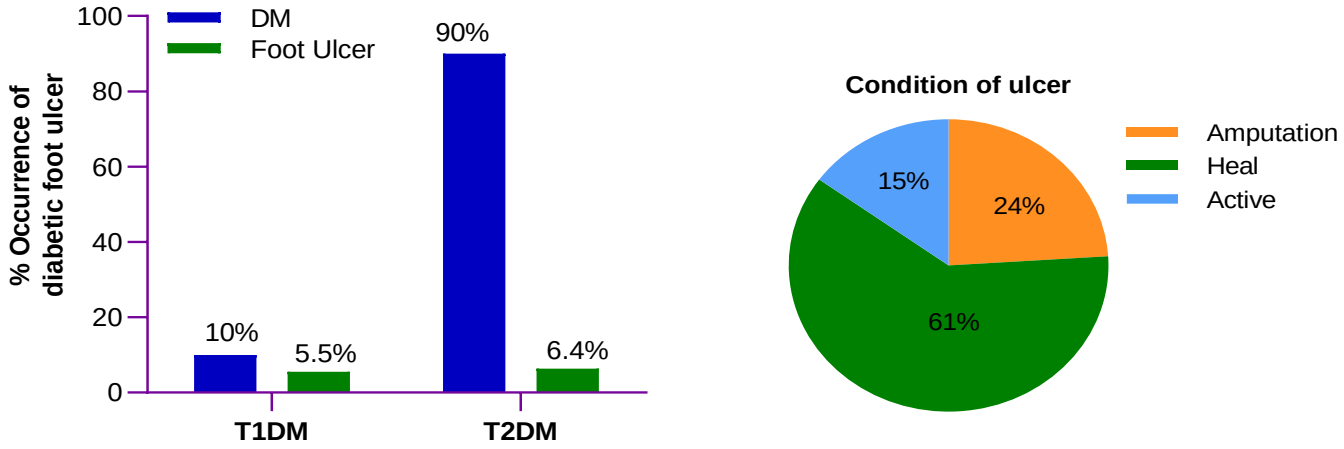

Figure 1. Incidence rates of diabetic foot ulcers in T1DM and T2DM and their conditions.

More than 85% of all amputations in diabetic foot patients are preceded by ulceration leading to severe gangrene or infection [12,25]. On average, about 6.4% of the worldwide population suffers from diabetic foot, with 2 to 5% yearly occurrence rates of ulcer or necrosis [26]. It is predicted that 19 to 34% of diabetic individuals will encounter foot disease at some stage in their lives [23]. A systemic meta-analytical review has shown that diabetic foot ulcers (DFU) are more common in men (4.5%) than in women (3.5%) and more prevalent in type 2 diabetic patients (6.4%) compared to type 1 individuals (5.5%) (Figure 1). Despite the rapidly growing prevalence of diabetic foot, only a few studies have been performed regarding its epidemiology. Thus, a detailed epidemiological study on the global update of diabetic foot is crucial in order for improved health and to minimize the financial strain on diabetic patients by preventing, controlling, and properly treating diabetic foot ulcerations [27].

3. Etiology

Diabetic foot ulcers are associated with predisposing factors such as a history of foot ulcers, hyperglycemia, calluses, foot deformity, inappropriate footwear, trauma, dry skin, underlying peripheral arterial disease, and peripheral neuropathy [28,29]. Initially, patients fail to identify the foot ulcer due to the presence of neuropathy and arterial disease, which along with the predisposing factors can ultimately progress to partial or complete limb amputation [30–33].

3.1. Diabetic Peripheral Neuropathy

Diabetic peripheral nephropathy (DPN) is one of the most severe chronic complications of DM characterized by peripheral nerve malfunction. The dysfunction of autonomic, sensory, and motor nerves in DPN inhibits sweating, pain, temperature, touch, and pressure sensations, as well as increases inflammation, dry skin, cracking, bone deformities, tissue necrosis, and weakness in patients [31,32,34]. When an individual loses their protective sensation, thermal trauma arises and the body's ability to sense the foot's position disappears. Simultaneously, motor neuropathy causes the protrusion of abnormal bones, which changes the normal structure of the foot bones and gives rise to foot deformities such as hallux rigidus and hammer toe. Finally, autonomic nerve malfunction causes dry skin, decreased sweating, and increased secondary arterial capillary refill, leading to skin fissures and crusts and diabetic foot ulcers [33].

3.2. Peripheral Arterial Disease

Hyperglycemia-induced peripheral arterial diseases are attributed to increased oxidative stress and atherosclerosis. In DM, blood sugar accumulation causes blockage, weakening, and narrowing of the arteries. Moreover, elevated oxidative stress prolongs inflammation in the microcirculation and affects the elasticity of capillaries, contributing to ischemia [31]. Additionally, atherosclerosis affects the blood vessels associated with the femoral artery and knee, contributing to developing foot ulcers two times more frequently in diabetic patients compared to non-diabetic patients [33]. The presence of atherosclerosis in the lower limbs has been documented to be 20 times more frequent in T2DM patients than in normal individuals, indicating a higher chance of developing DFU [35]. Many studies indicate that about 90% of DFU cases are attributed to neuropathy and the remaining 10% are associated with ischemia and other contributing factors [36]. A summary of the etiology of diabetic foot ulcers is illustrated in Figure 2.

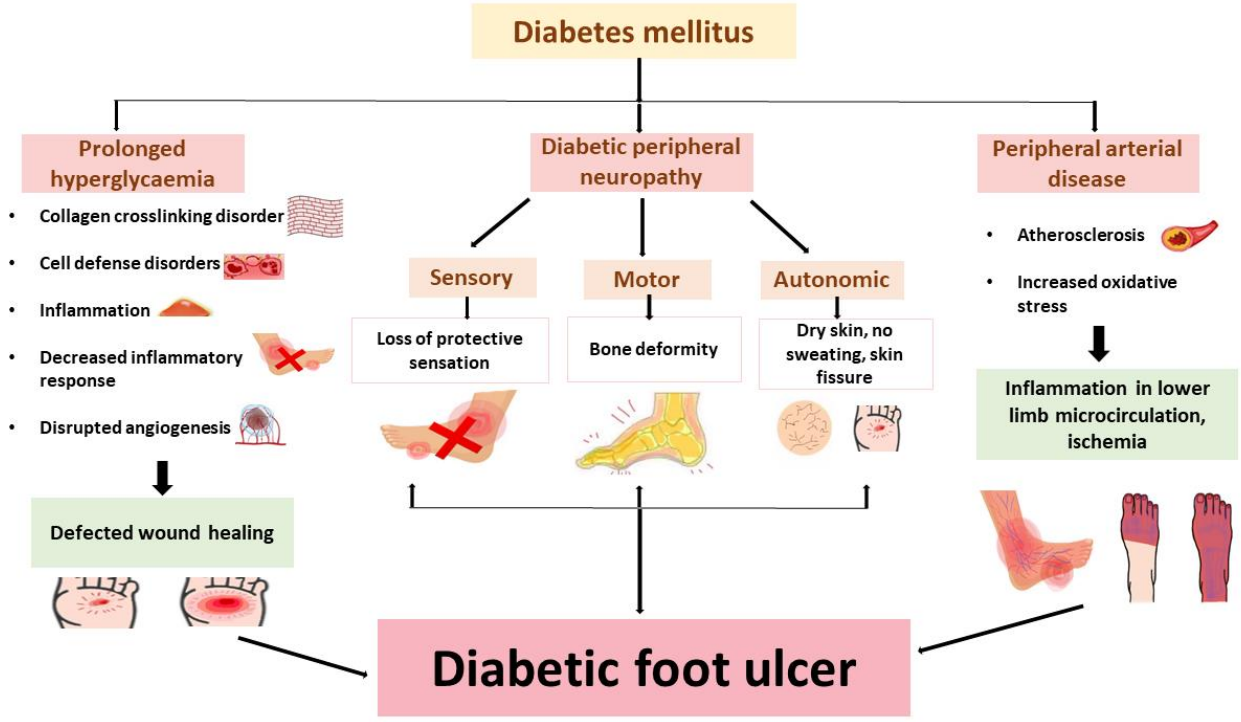

Figure 2. Diagrammatic synopsis of the etiology of diabetic foot ulcers involving prolonged hyperglycemia, diabetic peripheral neuropathy, and peripheral arterial diseases. The sustained hyperglycemia impairs the wound-healing process via collagen crosslinking disorder, cell defense disorders, decreased inflammatory response, and disrupted angiogenesis; peripheral neuropathy affects the sensory, motor, and autonomic nervous systems, causing protective sensation loss, bone deformation, dry skin, skin fissures, and infections; peripheral arterial diseases such as ischemia, inflammation in lower limb microcirculation, and high plantar pressure in the foot can occur from atherosclerosis and elevated oxidative stress.

3.3. Other Contributive Factors

Recent studies have highlighted several other important factors leading to DFU, such as prolonged hyperglycemia (>10 years), gender (male), older age (around 65), obesity, retinopathy, peripheral neuropathy, a higher glycated hemoglobin level, nicotine intake, a previously attempted amputation, a history of ulcers, elevated plantar pressure, infection, and inappropriate foot care [37–41].

In DM, the wound-healing process is hampered via collagen crosslinking disorders, immune disorders, tinea and onychomycosis infections, metalloproteinase matrix functional dysfunction, cellular defense disorders, inflammation, and neovascularization disorders.

Hyperglycemia weakens the acute inflammatory responses and disrupts angiogenesis, impairing the wound-healing process, and is considered the main culprit in the formation of DFU [42].

DFU is associated with severe infections ranging from uncomplicated cellulitis to life-threatening necrotizing fasciitis. The immunological dysfunction mediated by hyperglycemia mainly induces infection, which further leads to poor perfusion in soft tissues of the skin, damaged skin, and bacterial infections caused by bacteria such as *Escherichia coli* and *Staphylococcus aureus*, and this ultimately leads to sepsis. The risk of amputation increases if infection, sepsis, and resistant bacterial strains are present [14]. In summary, diabetic foot ulcer is a multifactorial life-threatening disease attributed to poor glycemic control.

4. Types of Diabetic Foot Complications

Diabetic foot ulcers can be classified depending on the degree of tissue loss, size, perfusion, infection site, depth, area, and sensation [43]. The changes in these parameters are based on an individual's age, sex, medical conditions, and existing comorbidities, including a loss of peripheral sensation (LOPS) and peripheral arterial diseases (PAD), which ultimately categorize diabetic foot ulcers into different grades [44].

According to Meggitt and Wagner, diabetic foot ulcers can be classified into 6 grades (Figure 3):

Grade zero: No lesion on the skin, potential bone deformity or hyperkeratotic lesion, pain;
Grade one: Superficial viable or necrotic ulcers; subcutaneous tissue loss; potential bone deformity; no penetration into the deeper layers of the skin;
Grade two: Deeper penetrates including bones, tendons, ligaments, or deep fascia; bone deformity prominent in some aspects; absence of abscess or osteomyelitis;
Grade Three: Presence of osteomyelitis, deep abscess, or tendinitis; severe infection symptoms (e.g., redness, heat, and swelling);
Grade four: Gangrene (dry, wet, infected, or non-infected) in toe or forefoot; surgical ablation of the foot required with minimal blood supply for below-knee amputations;
Grade five: Gangrene spreads to the whole foot; no healing signs; amputation below the knee is strongly recommended [28,45,46].

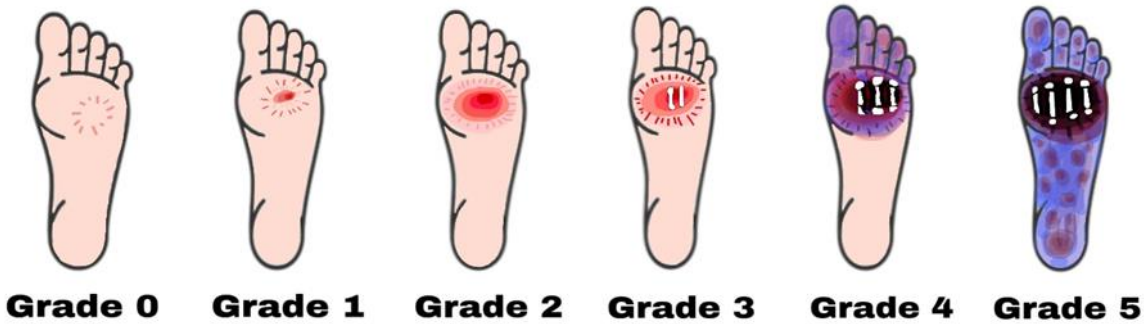

Figure 3. Diabetic foot ulcers are categorized using the Wagner–Meggitt classification. Grade 0 means no break in the skin. Grade 1 indicates a superficial ulcer. Grade 2 indicates a deep ulcer. Grade 3 shows the presence of osteomyelitis. Grade 4 is identified as forefoot gangrene. Grade 5 is recognized as complete foot exposure to gangrene.

Another scientist, named Brodsky, later discovered that the grade 4 and grade 5 foot ulcers in Wagner–Meggitt's classification were ischemic, and revised the classification in the following manner (Figure 4):

Grade 0: Intact skin; no sign of ulceration but the foot is at risk;
Grade 1: Superficial ulcer; no sign of osteomyelitis or exposed bones; no deep ulceration;

Grade 2: Deep ulceration; deeper penetration towards bones; bone deformity may be present to some extent;
Grade 3: Presence of osteomyelitis or abscess; severe infection and redness; no gangrene exposure;
Grade A: Not gangrenous; no ischemia;
Grade B: Presence of ischemia but no gangrene;
Grade C: Presence of ischemia and partial foot gangrene;
Grade D: Presence of ischemia and complete foot gangrene [47].

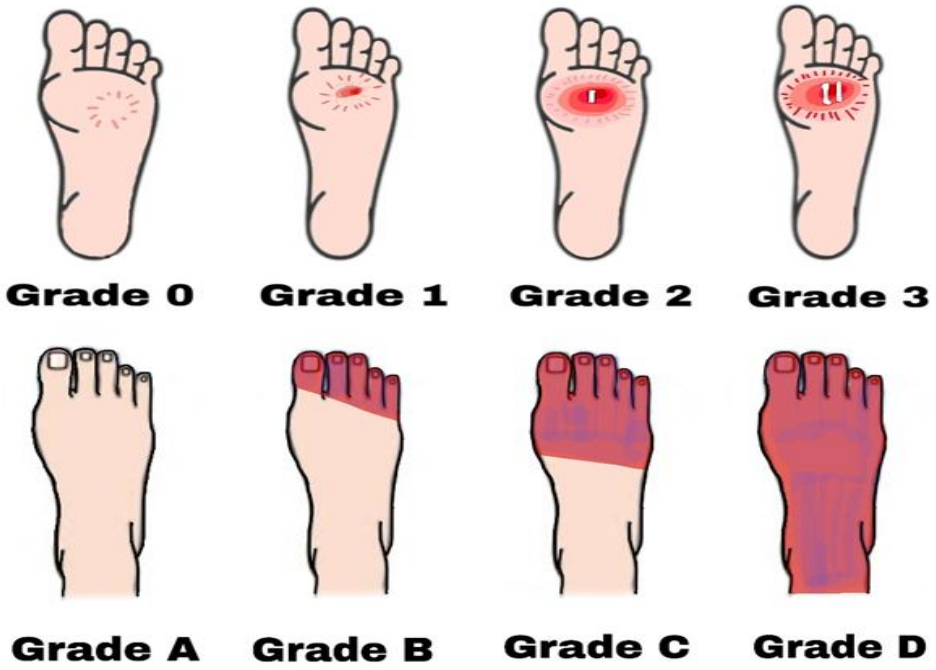

Figure 4. Diabetic foot ulcers based on Brodsky's classification. Grade 0 has no sign of ulceration but persistent pain is present. Grade 1 is a superficial ulcer. Grade 2 indicates deep ulceration towards the bones. Grade 3 means exposure to severe infection (osteomyelitis). Grade A has no ischemia. Grade B indicates ischemia but no gangrene. Grades C and D are partial and complete gangrene infections with ischemia, respectively.

5. Pathophysiology

Diabetic foot ulcers generally develop in three stages. Initially, neuropathy induces skin inflammation and forms a callus. Then, the involvement of the motor and autonomic nervous system causes bone deformation, trauma, and abnormal skin conditions. Finally, a subcutaneous hemorrhage mediated by frequent trauma erodes and forms the ulcer [48]. In addition, atherosclerosis in the microcirculation causes neovascularization and inflammation, contributing to the delayed healing of wounds, necrosis, and gangrene [28]. The stages of DFU formation and impaired wound healing are, however, associated with certain dysfunctional mechanisms in diabetic individuals [49].

The neuropathic foot is generally warm, dry, numb, and lacks pain sensations, involving neuropathic ulcers, the Charcot joint, and neuropathic edema. On the contrary, the ischemic foot is usually cold and has localized pressure necrosis and gangrene with the absence of pulses [49]. The key features of diabetes mellitus (i.e., hyperglycemia, insulin resistance, hyperlipidemia, and increased oxidative stress) are considered the main causes of endothelial dysfunction, cellular defense disorders, and other diabetes-related complications. In hyperglycemia, the endothelial nitric oxide production is suppressed by the inhibition of nitric oxide synthase, and as a result the high level of reactive oxygen species (ROS), particularly superoxide radicals, increases the hydrogen peroxide levels. This, in turn, causes the formation of highly reactive hydroxyl radicals and damages the cells. Nitric

oxide and superoxide together produce peroxynitrite, which affects the endothelial vasodilation and mediates lipid peroxidation. The concentrations of low-density lipoproteins are increased, followed by atherosclerosis in the microcirculation, increased inflammation, abnormal intimal growth, platelet aggregation, and thrombosis [50,51]. Moreover, the impairment of the autonomic nervous system is linked to degeneration of the postganglionic unmyelinated sudomotor axons, reducing sweat production. This, in turn, triggers dry skin, thick plaques, and callus formation [49]. Thus, diabetic neuropathy can be regarded as one of the key contributing factors of DFU, which proceed from a foot deformity and callus formation to increased local pressure and repeated injury, tissue necrosis, and finally ulceration [31,52].

Neuropathy, defined as a long-term painless degenerative arthropathy or Charcot neuroarthropathy, is also characterized by disrupted a sensory innervation of the foot joint. The affected autonomic nervous system increases the local and resting blood flow, causing massive calcium dissolution, leading to subluxation, joint dislocation, bone deformation, osteolysis, and soft tissue edema [53]. Studies have also reported that elevated inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β activate the nuclear factor NF-κb, leading to osteoclast maturation, ultimately contributing to bone deformities [54].

In peripheral arteries, the endothelial dysfunction elevates the vasoconstrictor thromboxane A2, which can aggregate platelets and increase the risk of plasma hypercoagulation. This can lead to ischemia in the lower limb microcirculation and eventually results in ulceration. The ulcer may become exposed and develop into gangrene and infection [55,56]. Moreover, the inhibition of nitric oxide, which is known as an anticoagulant, also contributes to the propensity of atherosclerosis, constricting the blood vessels in the microcirculation and ultimately leading to ischemia. Clinical reports suggest that DFU patients with ischemia and vascular insufficiency experience intense pain, limb hair loss, thinner skin, and a lack of peripheral pulses [54,55].

DFU gets worse over time due to the impaired healing ability existing in diabetic patients. When skin tissues, blood vessels, nerves, and other associated tissues become damaged, even controlled blood glucose levels fail to improve the condition. The slow wound-healing process deteriorates the condition and leads to life-threatening infections including cellulitis, osteomyelitis, abscesses, gangrene, and sepsis [56,57]. Additionally, the immune system of diabetic patients becomes weaker than normal and the hyperglycemic state increases the number of pro-inflammatory cytokines, affecting cell defenses such as phagocytosis, intracellular killing, chemotaxis, and leukocyte activity. The loss of leukocyte activity, decreased chemotaxis, negative nitrogen balance, and increased gluconeogenesis, as well as the impaired synthesis of fibroblasts, protein, and collagen, alter the normal wound-healing process and lead to a prolonged inflammatory state [55,58,59]. In summary, hyperglycemia, neuropathy, vascular insufficiency, arterial diseases, neuroarthropathy, and impaired immunology all contribute to the pathophysiology of diabetic foot ulcers (Figure 5) [54].

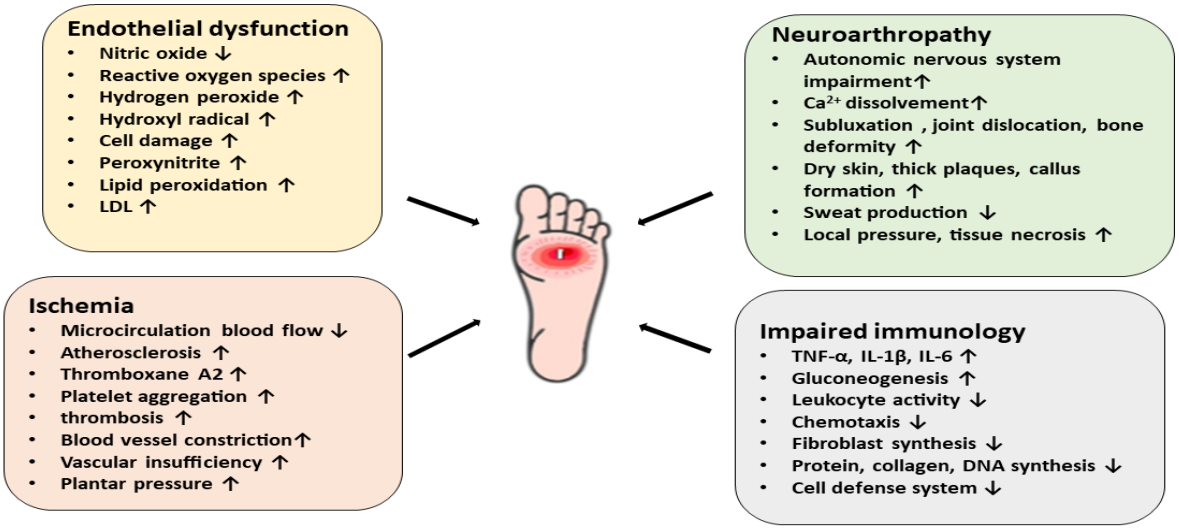

Figure 5. A schematic diagram representing the pathophysiology of diabetic foot ulcers via different mechanistic pathways. Endothelial dysfunction, ischemia, neuroarthropathy, and impaired immunology contribute to the pathophysiology of DFU.

6. Current Therapy for Diabetic Foot Complications

In order to treat and manage the diabetic foot, it is essential to properly diagnose its stage and severity. Alongside the maintenance of blood sugar levels, current therapeutic strategies involve targeting wound healing, controlling the spread of infection, relieving pressure, and improving blood flow [29]. Analgesic medications such as tapentadol, pregabalin, tramadol, duloxetine, acetaminophen, and some opioids (e.g., oxycodone) are employed to alleviate diabetic peripheral neuropathy (DPN)-associated pain. Although these drugs are effective in reducing mild to moderate pain, their frequent use causes nausea, constipation, drowsiness, and confusion [29]. Many antibiotics including nafcillin, flucloxacillin, dicloxacillin, ceftazidime, cefazolin, ceftriaxone, dalbavancin, oritavancin, telavancin, doxycycline, sulfamethoxazole, or trimethoprim have been effectively used to treat diabetic foot infections, even though no prospective comparative trials have been conducted [60]. It should be noted that several factors such as wound age, the host's immunological state, polymicrobial infection, sanitary conditions, and former antimicrobial therapy may contribute to the development of antimicrobial resistance [61]. Furthermore, the cost of antimicrobial agents recommended for the treatment of infected diabetic foot burdens a large number of diabetic patients, particularly in underdeveloped nations. This results in advanced grades of diabetic foot ulcers that are untreatable in a resource-constrained healthcare system [60,61]. The initial and most crucial step to heal wounds and lower the likelihood of amputations in patients with DFU is debridement. This involves the removal of necrotic and senescent tissues along with foreign and infectious materials from the wound. Debridement tends to lower the bacterial count while increasing the generation of local growth factors, as well as relieving pressure and facilitating wound drainage [36]. The primary purpose of surgical debridement is to transform a chronic ulcer into an acute ulcer. This has been demonstrated to be more successful in treating DFU than mechanical, biological, enzymatic, or autolytic debridement methods [36]. The use of appropriate wound dressing, revascularization for ischemia, pressure relief, laser therapy, and surgery also play an important role in the treatment and control of diabetic foot [29,36,60]. More research is needed, however, to assess the patient demographics for whom these treatments are promising, as well as their cost-to-benefit ratios. [29]. Table 1 summarizes some of the available conventional therapies and their advantages and disadvantages in the management of diabetic foot.

Table 1. Current therapeutic strategies for the treatment of diabetic foot.

Conventional Therapies for Diabetic Foot Management	Examples	Advantages	Disadvantages	References
1. Analgesics	Tapentadol, pregabalin, tramadol, duloxetine, acetaminophen, oxycodone	Alleviates diabetic peripheral neuropathy-induced pain	Constipation, nausea, drowsiness, confusion, drug abuse (opioids)	[29]
2. Antibiotics	Nafcillin, ceftazidime, cefazolin, clindamycin, dalbavancin, sulfamethoxa-zole/trimethoprim	The most common treatment for diabetic foot infections	Antibiotic resistance, high cost, unavailability	[29,61]
3. Debridement	Surgical, autolytic, mechanical, enzymatic, maggot debridement, polysaccharide beads/paste	Aids in a complete assessment of the wound, enhances breakdown of necrotic tissue, speeds up ulcer healing	High cost, time-consuming, patient reluctance, surgical debridement may increase wound size	[62–64]
4. Wound dressings	Hydrogels, hydrocolloids	Prevent infections, easy to use, effective, provides thermal insulation and mechanical protection	Costly, unavailability	[29,62,64]
5. Revascularization	-	Heals diabetic foot ulcers	Costly	[65]
6. Pressure relief	Half-shoes, rigid-soled post-operative shoes, total contact casts, accommodative dressings	Heals diabetic foot ulcers, significantly reduces pressure, high acceptability	Costly, patient compliance, ineffective against inflammation	[29,66]
7. Laser therapy	Low-level laser therapy	Effective in healing wounds, reduces inflammatory phase	High cost, discontinuous in efficacy	[29]
8. Surgery	-	Heals amputation or non-healing ulcers, one of the most effective methods to treat foot ulcers	Costly, lack of skilled surgeons	[67]

7. Alternative Therapy for Diabetic Foot

The global burden of DFU has expanded surprisingly over the last few decades with the increased incidence of DM. DFU treatment has been estimated to be as expensive as one-third of the total diabetes mellitus management alone is [68]. The overall expenditure and the amputation of lower limbs affect the quality of life of patients, as well as causing social stigma among individuals. To mitigate this public health crisis, alternative therapies can be recommended to DFU patients as adjunctive treatments with fewer side effects and promising health benefits [69].

Synthetic medicines, either alone or in conjunction with insulin, are commonly used as first-line treatments to manage DM and its complications. Such medications may occasionally fail to perform their intended effect properly and may have adverse side effects on the patient's health. As a result, there has been an increase in the pursuit of alternative sources of antidiabetic medications based on natural resources such as plants and animals [16]. Plants are a good source of medicines and have traditionally been used as antidiabetic therapies for centuries. Several drugs currently used in the treatment of DM also derive directly or indirectly from medicinal plants [70]. The use of plants solely, or in combination with existing antidiabetic agents, has been reported to minimize the

problems associated with foot conditions in diabetic individuals. Many of these herbs and their biologically active components are currently being studied to elucidate their mode of action [70].

The major challenge with DFU is the impaired and delayed wound-healing process [69,71]. Medicinal plants have long been acknowledged as a major source of therapies that are utilized both traditionally and conventionally [16]. The traditional remedies possess various therapeutic properties, such as wound healing, antioxidant, antimicrobial, anti-inflammatory, and antihyperglycemic activities. The majority of recent studies indicate that natural remedies are generally used for wound dressing, with few employed as oral drugs to treat DFU [18,71]. Among the various kinds of traditional healthcare practices, the medicinal plants used in *Ayurveda*, *Unani*, traditional Chinese medicine, and other traditional health systems have significantly contributed to the healing of wounds in diabetic foot syndrome. In Western nations, these medical systems, which integrate medicinal herbs, acupuncture, dietary therapy, massage, and therapeutic exercise for treating and preventing diseases, are regarded as a form of complementary and alternative medicine [72]. Chinese herbal medicine, the main part of traditional Chinese medicine, is extensively employed in clinical practice to treat chronic wounds of diabetic foot ulcers. Such an approach can be used either alone or in combination with conventional medicines with the intent to promote wound healing [73]. Some studies have also demonstrated that the combination of insulin with *Ayurveda* medicine has not only improved patients' treatment satisfaction but has also had a positive impact on their quality of life [74].

The numerous active phytoconstituents of medicinal herbs act via different mechanistic pathways to accelerate wound healing. This includes stimulating fibroblasts, stimulating the early expression of growth factors, displaying free radical scavenging or antioxidant activity, preventing wound bleeding, inhibiting microbial growth, stimulating collagen synthesis and improving collagen strength, improving blood circulation to wounds, preventing cell damage, promoting DNA synthesis, improving wound contraction and epithelialization, as well as increasing the production and migration of keratinocytes to the wound site [18,75–78]. Such attributes, together with various other beneficial effects, have contributed to the use of medicinal plants in the treatment of diabetic foot complications, as well as their future potential as alternative antidiabetic medicines [16]. Many phytomedicines that have been marketed and used all around the world have been developed from traditionally used medicinal plants [16]. The formulation of phytomedicines may be either single or poly-herbal. Several marketed poly-herbal formulations including Diabeta [79], Angipars [80], WinVivo [81], Jathyadi Thailam, Jatyadi Ghritam [82], and others have been employed to heal diabetic foot wounds. These products are prepared from individual ingredients from various antidiabetic herbs and are often sold with instructions regarding diet, exercise, and rest. These adjustments ultimately help the patients to re-establish a healthy lifestyle [79]. The most common medicinal plants and their isolated phytochemicals, traditional uses, and modes of action responsible for their healing effect on diabetic foot are summarized in Table 2.

Table 2. Traditional uses, isolated active phytochemicals, and mechanism of action of medicinal plants used to treat diabetic foot conditions.

	Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
1.	Acacia nilotica	Leaves, roots, bark, seeds	Gallic acid, ellagic acid, isoquercitrin, leucocianidolum, kaempferol	Diabetes, wounds, burns, stomachache, cough, malaria, pneumonia	Aqueous extract	Decreases oxidative stress; suppresses TNF-α and IL-1β activity; enhances cellular proliferation, re-epithelization of wounds, and dermal tissue regeneration	[83,84]
2.	Acalypha langiana	Leaves	Acalyphine, triacetoneamine	Diabetes, wounds, diarrhea, urinary infection, asthma, tuberculosis	Aqueous extract	Minimizes wound area, faster tissue regeneration in granulation section, improves congestion and edema	[18,85–87]
3.	Actinidia deliciosa	Fruit, stem, roots	Ursolic acid, oleanolic acid, epicatechin, quercetin, emodin	Diabetes, wound healing, fever, diarrhea, hypertension, hyperlipidemia	Pure normal concentrated kiwifruit extract	Enhances angiogenesis and vascularization, increases collagen and granulation tissues, minimizes ulcer size, initiates wound closure, inhibits bacterial infection	[88,89]
4.	Aloe vera	Leaves	Emodin, aloin, aloesin, acemannan	Diabetes, wound healing, dermatitis, constipation, infection, worm infestation	Aqueous extract	Enhances collagen cross-linking, increases DNA and glycosaminoglycans, reduces wound area, and accelerates healing rate of ulcer	[90,91]
5.	Alternanthera sessilis	Stem, leaves	Sebacic acid, bis(2-ethylhexyl) ester, neophytadiene, hexadecanoic acid	Diabetes, ulcer, wounds, lesion, fever, skin rash, burn, indigestion	Ethanol extract	Initiates wound closure, improves dermal fibroblast and keratinocyte proliferation	[92,93]
6.	Annona squamosa	Leaves	Squamosin, squamostatin, rutin, linalool, β-caryophyllene	Diabetes, ulcer, hypertension, wounds, hemorrhage, epilepsy	Ethanol extract	Increases DNA synthesis, protein and collagen contents; decreases lipid peroxidation and wound size, restores epidermis; enhances tensile strength, proliferation, epithelialization, and migration of keratinocytes	[94–96]

Table 2. *Cont.*

Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
7. Anogeissus leiocarpus	Bark, leaves	Ellagic acid, gallic acid, anogeissinin, rutin, quercetin	Diabetes, infection, wounds, diabetes, tuberculosis, hyperlipidemia	Ethanol extract	Reduces oxidative stress, lipid peroxidation, and wound area; enhances vascularity, wound contraction, and rate of epithelialization; prevents onset of cell necrosis and microbial infection	[97–99]
8. Arnebia euchroma	Roots	Naphthoquinone, shikonin, teracrylshikonin β-hydroxyisovalerylalkannin	Diabetes, eye infection, cuts, wound, toothache, earache	Aqueous, ethanol extract	Enhances granulation tissue, wound contraction, re-epithelization; restores epidermis; minimizes wound size; accelerates wound healing	[100–102]
9. Azadirachta indica	Leaves	Rutin, nimbin, deacetylnimbin, quercetin, azadiradione	Diabetes, ulcer, lesion, wounds, piles, intestinal worms, dermatitis, asthma, cough	Ethanol extract	Increases the rate of wound contraction, improves DNA content and nitric oxide level, enhances tissue regeneration, increases hydroxyproline and protein content	[16,87,103,104]
10. Balanites aegyptiaca	Bark, fruit, seed, leaves	Furanocoumarin, quercetin, diosgenin, linoleic acid, palmitic acid	Diabetes, malaria, wound healing, diarrhea, constipation, asthma	Aqueous extract	Prevents microbial infection, suppresses lipid peroxidation, enhances wound contraction, and accelerates its healing	[16,105,106]
11. Camellia sinensis	Leaves	(-) Epigallocatechin-3-gallate, quercitrin, rutin	Diabetes, wound healing, anxiety, flatulence, cardiovascular diseases	Hot water extract	Lowers blood sugar levels, increases insulin secretion, stimulates proliferation and differentiation of keratinocytes and fibroblasts, increases collagen synthesis and angiogenesis	[16,107,108]

Table 2. *Cont.*

Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
12. Carica papaya	Leaves, fruits	Apigenin, hesperitin, kaempferol, rutin, naringenin	Diabetes, dengue, malaria, ulcer, hypertension, wound, psoriasis	Aqueous, ethanol, methanol extract	Improves granulation tissue weight, collagen and hydroxyproline content, wound size, and contraction; epithelizes faster and prevents microbial infection	[18,109,110]
13. Catharanthus roseus	Flower, roots, leaves	Catharanthine, vindolinine, isorhamnetin, quercetin, kaempferol, O-feruloylquinic acids	Diabetes, sepsis, wound healing, blood dysentery, blood purification	Ethanol extract	Enhances wound contraction, tensile strength, angiogenesis, epithelialization, vascularization, granulation tissue weight, and hydroxyproline content and protects against microbial infection	[111,112]
14. Cecropia peltata	Leaves	Orientin, vitexin, rutin, chlorogenic acid, catechin	Diabetes, respiratory tract infection, wounds, kidney diseases, hypertension, sleep disorder	Aqueous, ethanol extract	Minimizes wound area; enhances hydroxyproline, protein, and hexosamine contents; accelerates wound healing	[113,114]
15. Centella asiatica	Leaves	Kaempferol, hydrochotine, linoleic, oleic, stearic, palmitic acid	Diabetes, ulcer, wounds, eczema, urinary tract infection, amenorrhea, diarrhea	Aqueous, ethanol extract	Improves angiogenesis, collagen content, fibroblast growth factor, and vascular endothelial growth factor; inhibits TNF-α, IL-6, IL-1β, COX-2, prostaglandin E2, and lipoxygenase; initiates re-epithelialization	[115,116]

Table 2. *Cont.*

Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
16. Citrus x paradisi	Peel, fruit	Narirutin, hesperidin, naringin, neohesperidin, limoline	Diabetes, hypertension, gastrointestinal problems, wound healing, infection, cold, cough	Aqueous peel extract	Reduces wound size; increases collagen synthesis, hydroxyproline and protein contents, and regeneration of tissue; initiates wound closure and healing	[117–190]
17. Citrus x sinensis	Peel, fruit	Kaempferol, naringin, hesperetin, limocitrin, naringenin	Diabetes, bronchitis, cough, obesity, hypertension, tuberculosis	Aqueous extract	Protects from oxidative damage, inflammatory cytokines, and hydrogen-peroxide-induced cellular damage; enhances cell proliferation, blood flow in tissues, angiogenesis, keratinocyte and fibroblast migration, wound healing	[120–122]
18. Citrus limon	Peel, fruit, leaves	D-limonene, naringin, hesperetin, hesperidin, apigenin, quercetin, orientin	Diabetes, cough, hypertension, sore throat, scurvy, kidney stones	Aqueous, acetone, ethanol extract	Inhibits gluconeogenesis; enhances collagen synthesis, protein and hydroxyproline contents; increases tissue growth rate; reduces wound area and healing time	[123,124]
19. Curcuma longa	Rhizome	Curcumin, curcuminoids, turmerin, vanillic acid, β-sitosterol, zingiberene	Diabetes, liver disorders, cough, inflammation, ulcer, wounds, pain, infections	Ethannol extract	Improves ulcers, inflammation, wound contraction, proliferation, fibroblast formation, collagen synthesis, granulation tissue and epithelialization; helps in tissue remodeling and wound size minimization; suppresses inflammatory cytokines	[16,76,125–127]

Table 2. *Cont.*

Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
20. Eucalyptus alba	Leaves	Chlorogenic acid, gallic acid, caffeic acid, vanillic acid, ferulic acid	Diabetes, sinusitis, bronchitis, cold, cough, wounds, sores,	Ethanol, methanol, acetone extract	Inhibits TNF-α, IL-6, and α-glucosidase enzyme; reduces oxidative stress; decreases oxidative free radicals; increases cell proliferation, collagen synthesis, and blood flow to the wound; prevents microbial attack	[128–130]
21. Euphorbia hirta	Leaves, stem, flower	Heptacosane, camphol, leucocyanidin, kaempferol, gallic acid	Diabetes, cold, asthma, dysentery, wound healing, dermatitis	Ethanol extract	Initiates wound closure and healing; restores epidermis, collagen tissue, and extensive fibrosis; improves granulation tissue weight, inflammatory cells, cellular damage, and re-epithelialization; decreases lipid peroxidation	[16,87,131,132]
22. Guiera senegalensis	Roots, leaves	Epigallocatechin, epicatechin, gallic acid, quercetin	Diabetes, wound healing, gastrointestinal disorders, cough, malaria, enteritis	Aqueous, methanol extract	Exhibits antimicrobial action, inhibits lipid peroxidation and inflammatory cytokines, minimizes wound size, improves healing time	[133–136]
23. Gymnema sylvestre	Leaves	Gymnemic acid, gurmarin, lupeol, stigmasterol, kaempferol	Diabetes, anemia, constipation, indigestion, infections, cardiopathy	Hot water, ethanol, methanol extract	Decreases blood glucose levels, bacterial growth, and inflammation; decreases formation of reactive oxidants; improves wound contraction; increases fibroblasts and enhances tissue regeneration	[137,138]

Table 2. *Cont.*

Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
24. Hibiscus rosa-sinensis	Flower, leaves, roots	Quercetin, stigmasterol, β-sitosterol, cyaniding, taraxeryl acetate	Diabetes, wounds, stomach ulcer, hypertension, hypercholesterolemia	Ethanol extract, n-butyl alcohol extract	Increases DNA, collagen, and protein contents of granulation tissues; improves rates of epithelialization and wound contraction, closure rate, granuloma weight, tensile strength	[139–141]
25. Hylocereus undatus	Peel, fruit	Gallic acid, betacyanin, lycopene, ascorbic acid	Diabetes, asthma, intestinal disease, wounds, ulcer, allergy, hypertension	Aqueous extract	Increases total protein, collagen, hydroxyproline, and DNA contents; enhances rate of epithelialization, wound size, tensile strength, and wound closure	[142,143]
26. Hypericum perforatum	Leaves, flowers	Amentoflavone, hypericin, hyperforin	Diabetes, depression, wounds healing, mycobacterium and viral infections, GIT disorders, eczema	Aqueous, ethanol extract	Improves glycemic levels, decreases inflammation, inhibits extracellular matrix degradation by matrix metalloproteinase-2 and urokinase, increases epithelial regeneration and revascularization	[103,144]
27. Kaempferia galanga	Rhizome	Ethyl p-methoxy cinnamate, 4-methoxy cinnamic acid, kaempferol, kaempferide, luteolin	Diabetes, hypertension, asthma, urticaria, rheumatism, wound healing, ulcers	Ethanol extract	Lowers blood glucose levels, exhibits anti-inflammatory and antioxidant effects, enhances wound contraction, increases rate of epithelialization	[19,145–147]
28. Lawsonia alba	Leaves	Kaempferol, quercetin, luteolin,	Diabetes, wound healing, bacterial and fungal infections, jaundice, skin problems	Aqueous, ethanol extract	Exhibits antibacterial activity, improves wound healing in fissures and cracks in diabetic foot, prevents decubitus ulcers, improves fibroblasts and collagen synthesis, increases granulation tissue	[19,148]

Table 2. *Cont.*

Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
29. Linum usitatissimum	Seeds	α- linolenic acid, omega-3-fatty acids, p-coumaric acid	Diabetes, diarrhea, skin diseases, wound healing, gastrointestinal infections	Ethanol extract	Improves insulin sensitivity; stimulates fibrin proliferation and collagen synthesis; increases granulation tissue around wounds; promotes vascular contraction, chemotaxis, adhesion, transmigration, and cell activation for tissue repair	[16,149–151]
30. Lycopodium serratum	Leaves	Lycoposerramine A, serratezomines A, B, C, α- pyridine,	Diabetes, wounds, sores, cuts, and burns, to improve learning and memory efficiency, Alzheimer's disease, otitis media	Ethanol extract	Increases rates of epithelialization and wound contraction, increases content of hydroxyproline at the wound site, and exerts antioxidant and antibacterial effects	[19,152]
31. Martynia annua	Leaves, flowers	p-hydroxy benzoic acid, chlorogenic acid, luteolin	Diabetes, epilepsy, sore throat, wounds, inflammation	Ethanol extract	Inhibits oxidative stress, exerts antibacterial action, improves angiogenesis of fibroblasts, increases collagen synthesis and hyroxyproline content, enhances epithelialization, increases wound contraction rate	[153,154]
32. Melilotus officinalis	Flowers, flowering stems	Quercetin, kaempferol, lupeol, oleanolic acid, coumarin compounds	Diabetes, intestinal worms, gastric ulcers, wound treatment, vein problems, hemorrhoids	Methanol, ethanol, hexane, chloroform extract	Stimulates the proliferation of endothelial cells and vascular neoangiogenesis, improves blood circulation, increases wound contraction and collagen synthesis, exerts anti-inflammatory and antioxidant effects	[155,156]

Table 2. *Cont.*

Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
33. Mimosa tenuiflora	Bark	Lupeol, mimonoside A,B,C, arabinogalactans, campesterol-3-O-β-D-glucopyranosyl, stigmasterol-3-O-β-D-glucopyranosyl	Diabetes, skin burns, ulcers, wounds, psoriasis, inflammation	Aqueous, ethanol extract	Enhances proliferation of dermal fibroblasts, stimulates production of keratinocytes, exerts antimicrobial activity to improve wound healing	[157,158]
34. Momordica charantia	Leaves, fruit	Momocharin, momordicin	Diabetes, wound healing, microbial infections, hypertension, inflammation, skin disease	Aqueous, ethanol, ether extract	Lowers blood glucose levels, increases insulin secretion, rectifies structural abnormalities in peripheral nerve, improves wound contraction, increases granulation tissue and neovascularization	[77,151,159]
35. Morinda citrifolia	Leaves, fruits	Rutin, quercetin, kaempferol, coumarin compounds	Diabetes, wounds, pain and inflammation, hypertension, constipation, gastric ulcers	Aqueous, ethanol extract	Reduces blood glucose levels, decreases wound size, decreases period of epithelialization, inhibits bacterial growth, reduces inflammation, exerts antioxidant action	[75,160,161]
36. Myrtus communis	Leaves, fruits	Limonene, α,β-pinene, myrtucommulone, gallic acid, ellagic acid, linalool	Diabetes, skin diseases, hemorrhage, peptic ulcers, wounds, conjunctivitis	Aqueous, ethanol extract	Lowers blood glucose levels, stimulates angiogenesis, promotes proliferation and migration of cells to wound sites, reduces inflammation, exerts free radical scavenging activity, prevents microbial infection at the wound site	[162,163]
37. Nigella sativa	Seeds	Thymoquinone, thymohydroquinone, thymol, oleic acid, linoleic acid	Diabetes, wound healing, microbial infections, rheumatism, dysentery, respiratory tract diseases	Aqueous, ethanol extract	Lowers blood glucose levels; induces angiogenesis, fibroblast proliferation, and collagen synthesis; minimizes bacterial infection; exhibits anti-inflammatory action; decreases neuronal degeneration	[16,151,164,165]

Table 2. *Cont.*

Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
38. Olea europaea	Leaves	Oleuropein, oleanolic acid, hydroxytyrosol, luteolin	Diabetes, hypertension, constipation, UTI, skin ulcers, inflammatory wounds	Ethanol extract	Decreases blood sugar levels; exhibits antioxidant activity; improves blood circulation in healing tissues; inhibits bacterial growth; enhances epithelialization, collagen synthesis, and development of fibroblasts	[16,78]
39. Orthosiphon aristatus	Leaves	Sinensetin, caffeic acid, rosmarinic acid, eupatorin, eugenol, linalool	Diabetes, nephritis, kidney and gallstones, hypertension, arteriosclerosis epilepsy, rheumatism,	Aqueous, ethanol extract	Reduces blood glucose levels; increases insulin secretion and actio;, exerts antioxidant and anti-inflammatory action; enhances epithelialization rate; increases wound contraction and collagen synthesis in fibroblasts	[166,167]
40. Prosopis cineraria	Leaves, stem bark	Pautelin, linolenic acid, luteolin, gallic acid, rutin	Diabetes, rheumatism, asthma, bronchitis, eye infections, wound healing	Ethanol extract	Increases rates of wound healing and tissue repair, enhances wound contraction and epithelialization, increases cell proliferation, exerts antioxidant and antimicrobial actions, increases collagen synthesis, regulates inflammatory markers and oxidative stress	[168,169]
41. Pterocarpus marsupium	Bark	Marsupin, marsupol, carsupin, epicatechin, pterostilbene	Diabetes, wound healing, skin diseases, ulcer, cough, diarrhea, dysentery	Ethanol extract	Lowers blood glucose levels, improves glucose tolerance, promotes re-epithelialization, exhibits free radical scavenging activity, decrease TNF-α levels, increases expression of angiogenesis-related proteins, reduces bacterial infection in wounds	[16,170]

Table 2. *Cont.*

Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
42. Punica granatum	Fruit, flowers	Ellagic acid, gallic acid, luteolin, catechin, rutin, quercetin	Diabetes, inflammation, rheumatism, sore throat, leprosy, burns	Aqueous, methanol, ethanol, ethyl acetate extract	Lowers blood sugar levels, increases wound healing rate, enhances cell proliferation and collagen synthesis, reduces inflammation	[171,172]
43. Radix Rehmanniae	Roots	Catalpol	Diabetes, ulcers, hypertension, liver and kidney diseases, depression	Aqueous extract	Reduces blood sugar levels, heals diabetic foot ulcers, promotes tissue regeneration and angiogenesis, inhibits TNF-α production, increases IL-2 and IFN-γ production	[173,174]
44. Rosmarinus officinalis	Leaves, stems, flowers	Rosmarinic acid, carnosic acid, chlorogenic acid, apigenin, luteolin	Diabetes, anxiety, inflammation, muscle, and joint pain, wound, colds	Ethanol, methanol, chloroform extract	Exhibits free radical scavenging activity, inhibits lipid peroxidation, decreases growth of microorganisms, exerts anti-inflammatory and neuroprotective actions, promotes angiogenesis, improves granulation tissue for faster wound healing	[175,176]
45. Sesamum indicum	Seeds	Sesamol, sesamin, sesamolin, sesaminol	Diabetes, healing burns and wounds, hypertension, constipation	Ethanol extract	Lowers blood glucose levels, accelerates wound healing, increases wound contraction, decreases wound inflammation, exerts neuroprotection	[19,151,177,178]
46. Syzygium cumini	Seeds, bark	Quercetin, ellagic acid, gallic acid, kaempferol, iso-coumarin	Diabetes, sore throat, constipation, wounds, skin ulcers, gastritis, constipation	Aqueous extract	Decreases blood sugar levels, enhances insulin secretion and action and re-epithelialization, increases collagen deposition, promotes neovascularization	[16,179,180]

Table 2. *Cont.*

Medicinal Plants	Parts Used	Isolated Phytochemicals	Traditional Uses	Extract Form	Mechanism of Action	References
47. Terminalia chebula	Fruit, leaves	Ellagic acid, gallic acid, tannic acid, chebulagic acid, corilagin	Diabetes, constipation, dementia, wound healing, astringent	Aqueous, methanol, ethyl acetate extract	Lowers blood glucose levels, improves rate of wound contraction, increases proliferation of keratinocytes and fibroblasts, improves free radical scavenging activity	[16,181]
48. Tinospora cordifolia	Leaves, bark, roots	Tinosporaside, tinosporine, berberine, jatrorrhizine, β-sitosterol, arabinogalactan	Diabetes, asthma, dysentery, diarrhea, jaundice, anemia, allergy, wound healing	Aqueous, methanol, ethanol extract	Exerts immunomodulatory effects, enhances wound contraction, promotes collagen synthesis, exhibits antioxidant and free radical scavenging activity levels, inhibits microbial growth at wound site	[16,182]
49. Trigonella-foenum graecum	Seeds	Galactomannan, trigonelline, 4-hydroxy isoleuscine	Diabetes, wound healing, indigestion, pneumonia, bronchitis, constipation	Aqueous, ethanol extract	Decreases blood glucose levels, increases insulin secretion, restores function of nerve fibers, improves collagen synthesis and maturation, increases granuloma tissue	[19,151,183,184]
50. Zingiber officinale	Roots, rhizome	Gingerol, paradol, shogaol	Diabetes, wound healing, microbial infections, cough, asthma	Ethanol extract	Decreases blood sugar levels, increases insulin secretion, improves collagen synthesis and maturation, increases wound contraction and epithelialization, inhibits bacterial colonization	[185,186]

8. Advantages of Alternative Therapies over Conventional Treatment Approaches for Diabetic Foot

Diabetes mellitus and its associated complications including diabetic foot have major detrimental effects on healthcare systems, particularly in poorer nations where both resources and finances are scarce. Natural compounds originating from plants have served, and continue to serve, a pivotal role in pharmaceutical research [16]. Nearly 80% of people living in developing countries rely upon traditional medicines, mostly derived from medicinal plants, to address their basic health needs [18]. Plant-based medicines have become a promising alternative source of medicines due to their ease of access, availability, low cost, and relatively low risk of adverse side effects [16]. The wide range of health benefits possessed by these plants is primarily because of the presence of numerous phytoconstituents (e.g., flavonoids, glycosides, carotenoids, terpenoids, and alkaloids) that have potent antihyperglycemic properties and are generally safe. The blood glucose-lowering effects of plants are mainly attributed to their ability to either improve the β-cell function by increasing insulin production and secretion or decrease intestinal glucose absorption [187]. Many of the studies carried out to date have proved that the bioactive compounds derived from medicinal plants have various pharmacological effects that are useful in preventing cell damage as well as chronic wounds. In addition to being traditionally used as topical formulations to treat burns, infections, inflammation, and skin problems, plants and their associated compounds have also demonstrated wound-healing characteristics in vitro, in vivo, and in clinical studies [17]. Natural products are increasingly being employed not only as therapeutic agents in their own right but also as templates for the synthesis of novel bioactive molecules. As such, it is important that extensive scientific and clinical research is carried out to validate the medicinal use of plants and phytochemicals. Finally, as plants have proved beneficial for the treatment of diabetes and its associated complications, it is reasonable to assume that the combination of herbal and synthetic medicines may help reduce some of the harmful effects of conventional drugs [175].

9. Prevention and Management of Diabetic Foot Complications

Prevention is the primary management strategy to control any lower limb injury linked to DM. Providing basic guidance to patients regarding the choice of suitable footwear and wound treatments, including a specific emphasis on foot care, has been found to help delay the occurrence or re-occurrence of DFU [188]. The use of inappropriate footwear and walking barefoot are the main contributors to foot trauma resulting in ulcers in diabetic patients with sensitive feet. Thus, people with a loss of protective sensation (LOPS) should have unrestricted access to suitable footwear and should be advised to wear them at all times, both indoors and outdoors [53,189].

Some other important aspects involved in the prevention of DFU include identifying the foot likely to be at risk of ulceration and inspecting and examining it on a regular basis, as well as treating pre-ulcerative symptoms [53]. To identify individuals who are at risk of developing foot ulcers, all diabetic patients should get their feet examined at least once annually, and those who have been identified should be checked more frequently. Diabetic patients who show symptoms of pre-ulcers should be treated accordingly. The pre-ulcerative treatments include the removal of excess calluses, the treatment of blisters and ingrown or thickened nails, the administration of antifungal medications for fungal infections, and in case of foot deformities non-surgical techniques such as orthosis may be applicable. These interventions should be carried out by an experienced foot care expert until the pre-ulcerative signs subside and do not reappear [53,189].

To control and manage DFU, it is crucial to heal the wound first. This mostly depends on the ulcer's grade and vascularity, as well as the presence of infection. The affected foot should be given adequate relaxation and pressure relief [32]. Controlling hyperglycemia accelerates wound healing and also helps to avoid negative effects on cellular immunity and infection [190]. Many antiseptic and antimicrobial agents are being investigated as topical preparations for the treatment and management of DFU. Honey, which has

antibacterial properties, has recently gained popularity as an alternative treatment for diabetic foot wounds. It provides a moist environment for wounds, and its high viscosity helps to form a protective barrier against infection. Its immunomodulatory effects are also essential for tissue repair. Much work, including performing well-designed randomized double-blind controlled studies, is still required to properly evaluate the potential of honey, design evidence-based practice guidelines, and assess the risks and benefits of such therapies [191,192]. A summary of the preventive measures and treatment strategies used for diabetic foot conditions is depicted in Figure 6.

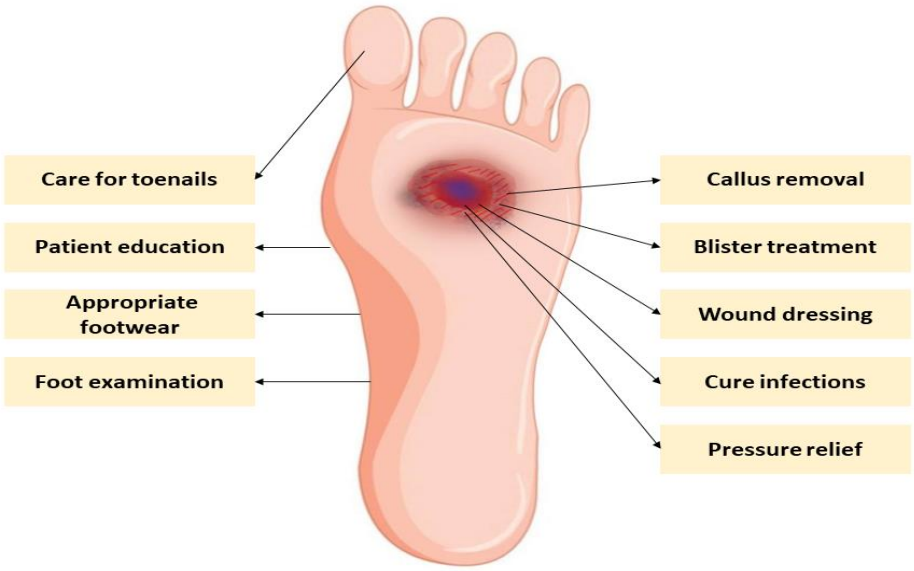

Figure 6. Prevention and management of diabetic foot conditions.

10. Future Strategies Used to Overcome the Burden of Diabetic Foot

To reduce the burden of diabetic foot, it is essential to prevent the occurrence of DFU. However, the prevention of ulcers remains underexplored both in research and clinical settings [193]. Due to the complex etiology of DFU, a multidisciplinary team approach involving diabetologists, dermatologists, primary care doctors and nurses, orthopedic and vascular surgeons, podiatrists, and orthotists is crucial. As discussed earlier, the conventional preventive and management strategies for diabetic foot conditions include local wound healing with the use of dressing, the regular removal of callus and necrotic debris, offloading, and the administration of broad-spectrum antibiotics in the case of foot infections [29,194]. These treatment approaches, however, can be adversely affected by underlying health issues that may impede recovery and be a financial burden on patients. In recent years, the use of traditional herbs as medications has received widespread attention as one of the most effective strategies to treat DFU and infections. Despite the availability of numerous medicinal plants and associated active phytoconstituents, as well as pharmaceutical preparations for the management of diabetes, additional medicinal plants with greater antidiabetic efficacy must be sought. The significance of traditional phytomedicines as one of the treatment strategies for DFU should be seriously considered, particularly in low-income nations [195]. The effects of plant extracts on diabetic wounds should be scientifically investigated in order to develop potential adjunct medications for wound treatment. Large clinical trial studies should also be performed on diabetic and non-diabetic patients to elucidate the mode of action of medicinal plants or constituents on diabetic foot-related diseases [18]. Although there are certain limitations to the extent and scope of using medicinal plants for curing diabetic foot wounds, these offer promising potential and may even lead to the discovery of novel treatment strategies for wound healing [18].

11. Conclusions

Diabetes mellitus and its related complications are on the rise globally, creating an urgent need for effective treatment strategies. The use of conventional synthetic drugs as well as surgical or non-surgical procedures has been proven to be effective in healing diabetic foot syndrome. However, these are accompanied by a number of disadvantages, which include adverse side effects, high costs, and inaccessibility to the vast majority of the global population. As a result, the current research efforts are focused on exploring novel sources of antidiabetic and wound-healing remedies, especially plant-based medicines. Medicinal plants have been documented to exhibit promising effects in treating diabetic foot ulcers and infections. Despite their limitations and the lack of clinical trials, traditional medicine remains the primary and often the only line of therapy for many people, particularly those living in poorer or developing nations, where plants are still used to treat various ailments and infections, including diabetic wounds. Thus, medicinal plants and their bioactive constituents with antidiabetic activity are being extensively studied to discover and develop novel medicines with better potency and fewer side effects. Further research and clinical studies are required to validate the efficacy and safety of herbal medicines, as well as to fully understand the molecular pathways involved in the diabetic wound-healing process.

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