International Journal of Pharmaceutical Drug Design (IJPDD)
Website: https://ijpdd.org/
ISSN: 2584-2897
Vol. 2, Issue 4, April, 2025
Page No.: 38-48

Review

# Management of Diabetic Foot Infection with Plant-Based Metabolite

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***DOI:*** *10.62896/ijpdd.2.4.5*

***Conflict of interest:*** *NIL*

**Article History**
Received: 01/03/2025
Accepted: 26/03/2025
Published: 26/03/2025

**Abstract**

Diabetic foot infections (DFIs) are severe complications of diabetes mellitus, often resulting in chronic wounds, gangrene, and amputations due to impaired wound healing and immune dysfunction. Conventional therapies, including antibiotics and debridement, are often insufficient and accompanied by side effects, necessitating alternative treatments. This review highlights the potential of plant metabolites, particularly bioactive compounds from *Ocimum sanctum* (Tulsi) and *Catharanthus roseus* (Periwinkle), in managing DFIs. Compounds such as eugenol, ursolic acid, rosmarinic acid, and alkaloids exhibit anti-inflammatory, antioxidant, and antimicrobial properties, promoting wound healing through enhanced angiogenesis, collagen synthesis, and fibroblast activity. The integration of these phytochemicals into therapeutic strategies may offer a cost-effective, side-effect-free adjunct to existing treatments for DFIs. Further clinical research is required to validate these findings and establish their efficacy in patient care.

**Keywords:** Plant metabolites, Diabetic foot infection, Wound healing, Ocimum sanctum, Catharanthus roseus



## Introduction

Diabetes mellitus (DM) is an endocrine disease caused by high blood sugar. It occurs when the body's ability to produce or effectively use insulin, a hormone that regulates blood sugar, is impaired.[1] It is classified as an epidemic due to its widespread prevalence and impact on mortality rates. It is among the top ten leading causes of death worldwide and affects over 10.5% of the adult population.

There are several types of diabetes, including type 1 diabetes, type 2 diabetes, and gestational diabetes. 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. [2]

Diabetes Mellitus can lead to several complication over time such as neuropathy, 25%; retinopathy, 32%; and nephropathy, 23%. [3] Macrovascular, microvascular, and diabetic foot ulcers with mortality rate of diabetic foot ulcer and Gangrene 17 -23%. [4]

Diabetic foot ulcer is a chronic and serious complication that can occur in individuals with diabetes. It refers to an open sore or wound that develops on the foot of a person with diabetes. These ulcers typically occur due to a combination of factors, including poor circulation, nerve damage (neuropathy), and impaired wound healing, all of which are common complications of diabetes. [5]

Diabetes affects the body's ability to regulate blood sugar levels properly. Continuous high blood sugar levels can lead to damage to the blood vessels and nerves. If the nerves of the feet are damaged can cause lose sensation. Generally, it has been seen in

some cases reduced supply of blood in the affected areabecause of poor healing process. [6]

The development of a diabetic foot ulcer often follows a pattern. It usually starts as a small sore or blister on the foot, which may go unnoticed due to the lack of sensation. Without prompt and proper treatment, the ulcer can progress and deepen, affecting deeper layers of the skin, tendons, and bones. In severe cases, it can lead to serious infections, gangrene, and potential amputation if left untreated. [7]

Several factors increase the risk of developing diabetic foot ulcers, including:

- **Poor glucose control:** Consistently high blood sugar levels contribute to nerve damage and impaired wound healing.
- **Peripheral neuropathy:** Nerve damage in the feet reduces sensation, making it harder to detect injuries or pressure.
- **Peripheral artery disease:** Poor blood circulation in the feet impairs the delivery of oxygen and nutrients necessary for wound healing.
- **Foot deformities:** Conditions like bunions or hammertoes can cause increased pressure on specific areas of the foot.
- **Poor foot hygiene:** Neglecting foot care and failing to keep feet clean and dry can increase the risk of infection.
- Smoking: Smoking damages blood vessels and reduces circulation, exacerbating the risk of complications.

**Etiology of Diabetic Foot Ulcer**

Many factors are responsible for the appearance of DFU like a history of foot ulcer, hyperglycaemia, trauma, callus, dry skin, peripheral arterial disease, and peripheral neuropathy lack of proper treatment may lead to partial or complete limbamputation.

**Diabetic Peripheral Neuropathy**

Diabetic peripheral nephropathy (DPN) is one of the most severe chronic complications of Diabetes Mellitus characterized by peripheral nerve malfunction. The progression of the disease starts with the loss of sensory and autonomic reflexes that results in the inhibition of sweating, temperature, and pain sensation. Chronic cases can lead to bone deformities, necrosis, and sepsis.

**Peripheral Arterial Disease**

In diabetic patients with arterial disease oxidative stress and atherosclerosis cause inflammation in lower limb microcirculation. 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. [8] Additionally Hyperglycaemia produces endothelial injury and preferentially involves theposterior and anterior tibial arteries with less common involvement of the femoropopliteal arterial segment, and often sparing of the aortoiliac artery segment. With the development of diffuse tibial artery occlusive disease, perfusion of the foot below a level adequate to maintain skin integrity anddevelops in ischemic ulcer or gangrene. [9]

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. [10]

**Other Contributively Factors**

Recent studies have highlighted several key factors causing DFU, such as prolonged hyperglycaemia, gender (male), advanced age (approximately 65 years), obesity, retinopathy, peripheral neuropathy, high glycated haemoglobin levels, and nicotine intake. Bacteria collect and convert in the form of wounds which are nearby extracellular polymeric substances containing polysaccharides and lipids. This microbial volume, called biofilm, increases resistance to antimicrobial, immunological, and antibacterial drugs. [4] DFU connects with crucial diseases ranging from manageable cellulitis to life-threatening necrotizing fasciitis. Hyperglycemia-mediated immune dysfunction often leads to infection, resulting in bacterial infections such as Escherichia coli, methicillin-resistant Staphylococcus aureus, and Staphylococcus aureus, which lead to poor skin and soft tissue perfusion, skin damage, and eventually sepsis. The risk of amputation increases the presence of infection, sepsis, and antibiotics. [5]

**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. Diabetic ulcers can be classified by the Wagner ulcer classification system. [11]

**Wagner-Meggitt Classification of Diabetic Foot**

- Grade 0 - Foot symptoms like pain, only
- Grade 1 - Superficial ulcers involving skin and subcutaneous tissue

- Grade 2 - Deep ulcers involving ligaments, muscles, tendons, etc
- Grade 3 - Ulcer with bone involvement
- Grade 4 - Forefoot gangrene
- Grade 5 - Full-foot 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.

- **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. [12]

**Pathophysiology**

The development of a diabetic ulcer is usually in 3 stages. The initial stage is the development of a callus. The callus results from neuropathy. The motor neuropathy causes physical deformity of the foot, and sensory neuropathy causes sensory loss which leads to ongoing trauma. Drying of the skin because of autonomic neuropathy is also another contributing factor. Finally, frequent trauma of the callus results in subcutaneous hemorrhage and eventually, it erodes and becomes an ulcer. [13]

In addition, atherosclerosis in the microcirculation causes neovascularization and inflammation, contributing to the delayed healing of wounds, necrosis, and gangrene.10

Neuropathy in DM manifests against motor, sensory and autonomic. Damage to the innervation of the leg muscles causes an imbalance between flexion and leg extension, resulting in deformity and change of pressure points. Gradually, it will cause skin damage that develops into ulcers. Autonomic neuropathy lowers the activity of oil glands and sweat so that the foot moisture is reduced and susceptible to injury. Sensory neuropathy lowers the pain threshold so that it is often unaware of the existence of the wound until the wound worsens. [14]

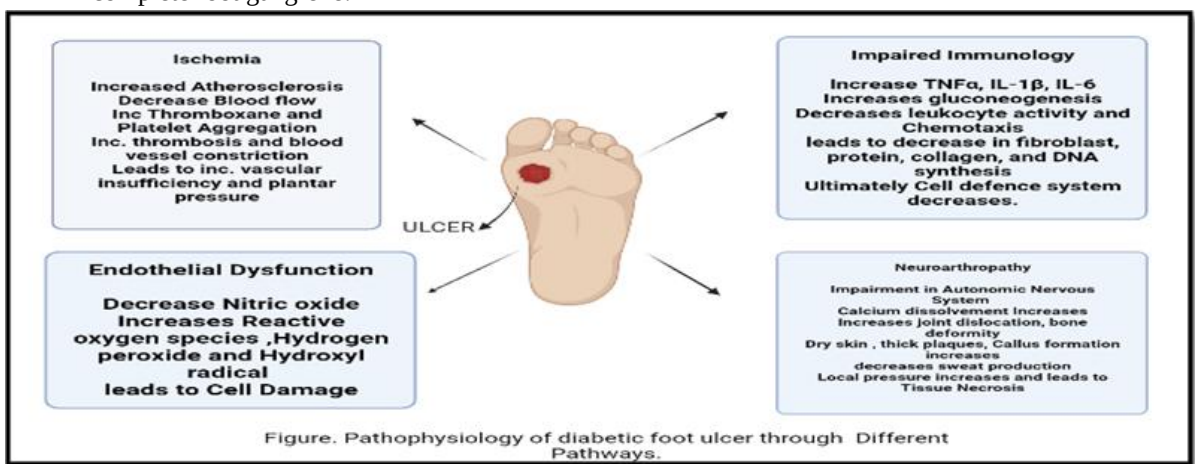


Figure. Pathophysiology of diabetic foot ulcer through Different Pathways.

In hyperglycaemia, 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 radical 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. 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. [15,16]

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. [17,18] The immune system of diabetic patients becomes weaker than normal and the hyperglycaemic state increases the number of pro-inflammatory cytokines, affecting cell defences 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. [19] Generally, hyperglycaemia, vascular insufficiency, arterial diseases, neuroarthropathy, and impaired immunology all contribute to the pathophysiology of diabetic foot ulcers.

**Conventional Therapies for Diabetic Foot Management**

Management of DFUs requires the correct classification of stage and severity. The basic care for the control and treatment of DFUs involve targeting wound healing, controlling the spread of infection, relieving pressure, and improving blood flow. [20] 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, there frequent use causes nausea, constipation, drowsiness and confusion. [21]

Many antibiotics such as nafcillin, flucloxacillin, dicloxacillin, ceftazidime, cefazolin, ceftriaxone, dalbavancin, oritavancin, telavancin, doxycycline, sulfamethoxazole or trimethoprim, which are used successfully in the treatment of diabetic foot, are ineffective. [22] It should be noted that many factors will contribute to the recovery of antibodies, such as the age of the wound, the host's immune system, polymicrobial infection, hygiene, and previous antibiotic therapy. [23] In addition, the cost of anti-diabetic drugs for the treatment of diabetes mellitus is less recommended. This leads to severe diabetes that cannot be treated in healthcare. [22,23] Debridement is the most important first step in wound healing and reducing the risk of complications in DFU patients. This includes removing dead and old tissue from the wound, as well as foreign matter and infection. Debridement appears to reduce bacterial count, reduce and promote wound drainage while increasing local growth of the product. [10] The primary goal of surgical debridement is to transform chronic disease into acute disease. This has been shown to be more successful in the treatment of DFU than mechanical, biological, enzymatic, or autolytic debridement methods.

**Alternative Therapy for Diabetic Foot**

The global burden of DFU has expanded unexpectedly over the past few decades as the incidence of DM has increased. The cost of DFU treatment is estimated to be one-third of the total cost of diabetes management alone. Full spending and low cuts reduce patients' quality of life and create stigma among people. In order to reduce this public health problem, alternative treatments can be offered to DAU patients as adjunctive treatments with fewer side effects and cost advantages. [24]

Synthetic drugs, alone or in combination with insulin, are often used as the first line of therapy to manage DM and its complications. These drugs may not work as intended and may have adverse effects on the patient's health. Therefore, people are looking for other sources of anti-diabetic drugs based on natural sources such as plants and animals. [25] Plants are the best source of medicine and have been used as anti-inflammatory for centuries. Many drugs currently used in the treatment of DM are also obtained directly or indirectly from medicinal plants. [26] Traditional medicine has many therapeutic effects, such as wound healing, antioxidant, antibacterial, anti-inflammatory, and anti-hyperglycemic activity. The most recent studies show that medicinal drugs are used mainly as wound dressings and rarely as oral drugs for DFU. [27]

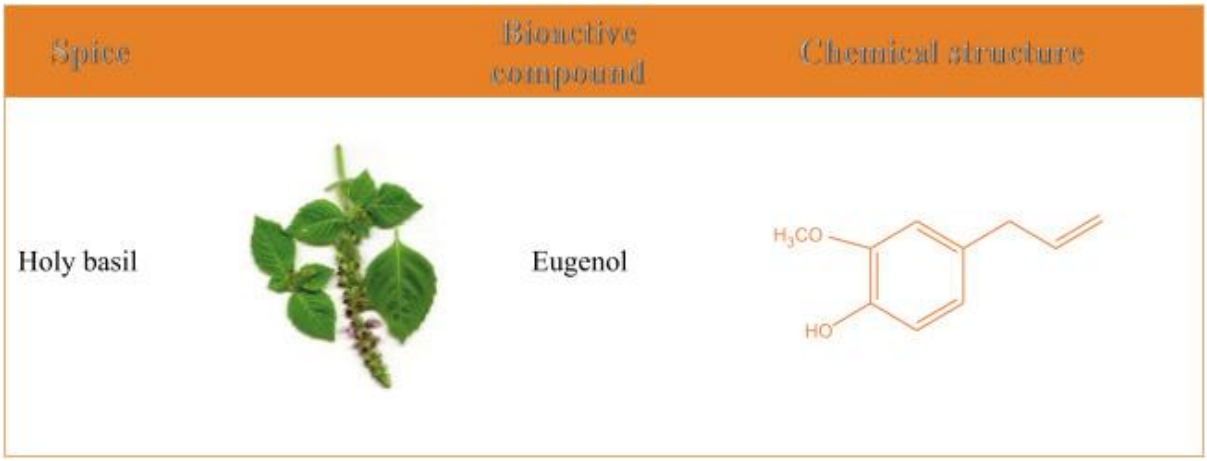
**Treatment Approach and Applicability in Diabetic foot infection with Bioactive Compounds of *Vinca rosea* and *Ocimum sanctum***

***Ocimum sanctum Linn.*** (Lamiaceae), commonly known as holy basil, is a herbaceous plant native to Southern Asia. It belongs to the Lamiaceae family and is commonly known as Tulsi in India. The plant grows in India but is also widely grown in homes and temple gardens. [28] In addition to its religious significance, it has a long history of medicinal use and is mentioned in the ancient

Ayurvedic text Charak Samhita. All herbs, Lamiaceae basil has the best healing properties. The leaves of O. sanctum have been shown to have hypoglycemic effects in animals. The ethanol (70%) extract of O. sanctum leaves caused a significant reduction of blood glucose in normal, glucose-fed hyperglycaemic and streptozotocin-treated diabetic rats. [28]

**Bioactive Volatile Compounds Present in Tulsi**

***Ocimum sanctum*** *(OS)* is also known as Holy Basil or Tulsi, and belongs to the family of Lamiaceae. This plant is well known for its medicinal and spiritual properties in Ayurveda which includes aiding cough, asthma, diarrhea, fever, dysentery, arthritis, eye diseases, indigestion, gastric ailments, etc. Major Phytoconstituents of OS are eugenol, ursolic acid, rosmarinic acid, apigenin, myretenal, luteolin, β-sitosterol, and carnosic acid.




Tulsi essential oil contains a valuable source of bioactive compounds such as camphor, eucalyptol, eugenol, alpha bisabolene, beta bisabolene, and beta caryophyllene. These compounds are proposed to be responsible for the antimicrobial properties of the leaf extracts. [29]

**1. Eugenol** has dual mode of action in treating diabetes; it lowers blood glucose level by inhibiting α-glucosidase and prevents AGE formation by binding to ε-amine group on lysine, protecting it from glycation, offering potential utilizationin diabetic management. [30] It also possesses potent anti-oxidative and anti-inflammatory effect in HFD/STZinduced diabetic rats and facilitates insulin sensitivity and stimulate skeletal muscle glucose uptake via activation of the GLUT4-AMPK signalling pathway. [31] Eugenol is also used in the treatment of Diabetic Foot Infection as it is highly bactericidal against the pathogen Staphylococcus aureus and Pseudomonas aeruginosa which are the mainmicrobial inhabitants of infected DFUs. [32]

2. **Ursolic acid** (UA, C 30 H48 O 3, molecular weight: 456.68) is one of themain effective components of herbal compounds, and is widelydistributed within plants.Ursolic acidpossesses a variety of biological activities includinganti-tumor, anti-oxidation, anti-inflammatory, anti-diabetic, and liverprotective and lipid-lowering effects. [33]

A study reveals that Ursolic acid improves diabetic nephropathy via suppression of oxidative stress and inflammationand reduces FBG, KW/BW, BUN and SCr levels in STZ-induced diabetic nephropathy rats, hence, improving renal function, ameliorating oxidative damage, and attenuating the inflammatory injury of kidney via inhibiting the expressions of TNFα, MCP-1 and IL-1β. [34] Ursolic acid encapsulated into electrospun nanofibers decreased the release levels of TNF-α and IL-6 inflammatory factors, and suppressed oxidative stress responses by reducing the generation of reactive oxygen species (ROS) which improve the closure rate, and also promote the revascularization and re-epithelization,andremodeling of collagen matrix and the regeneration of hair follicles for diabetic wounds thus promoting diabetic wound healing. [35]

**3. Rosmarinic acid** ($C_{18}H_{16}O_8$), is a natural Polyphenolicacids widely occurringin almost each herbal plant, and is present in over 160 species belonging to many families, especially the Lamiaceae. [36] Rosmarinic acidis found to have multiple biological activity, including anti-inflammatory and antitumour effects, which are a consequence of its inhibition of the inflammatory

processes and of reactive oxygen species scavenging.

The anti-inflammatory mechanisms mainly include decreasing the release of histamine in mast cells, suppressing the activities of lipoxygenase, cyclooxygenase and phospholipase, and reducing the production of nitric oxide and reactive oxygen species, blocking the activation of the signal pathway, down regulating the expression of inflammatory factors, and inhibiting the activities of elastase and complement thus prevent diabetic foot ulcer. [37] Phenolics (rosmarinic acid) have been shown to significantly reduce tissue lipid peroxidation level. [38]

**4. Apigenin** (4′,5,7-trihydroxyflavone) is one of the most widely distributed in the plant kingdom, and one of the most studied phenolics. Apigenin is present principally as glycosylated in significant amount in vegetables (parsley, celery, onions) fruits (oranges), herbs (chamomile, thyme, oregano, basil), and plant-based beverages (tea, beer, and wine). [39]

The anti-diabetic properties of apigenin may be attributed to its capacity to inhibit α-glucosidase activity, increase secretion of insulin, [40] to interact with and neutralize reactive oxygen species (ROS) in the cell, which together contribute to the prevention of diabetic complications. [41]

Apigenin also improved there epithelialisation and inflammation of the skin, and favoured neo vascularisation of the wounds. [42]

**5. Luteolin** is a naturally occurring flavonoid that is effective in the treatment of diabetes as it act by inhibiting alpha- glucosidase enzyme. [43] The formation of free radicals accompanied by oxidative damage to the pancreatic islet cells causes' diabetes. By inhibiting the enzymes that produce ROS, luteolin may prevent the development of reactive oxygen species (ROS) and can absorb ROS and secure the constituents of other antioxidant systems. [44] Luteolin significantly reduce blood glucose level and improves impaired healing and accelerates re-epithelization of skin wound in diabetic rats. [45]

**6. β-sitosterol** is a plant sterol that increase insulin release throughthe regeneration of b-cells thus effective in the management of diabetes. [46] Beta-sitosterol and naringeninhave a synergistic effect on wound closure without decreasing the viability of fibroblasts. The combination alleviated oxidative stress via increasing SOD activity and decreased IL-1β level in wounded fibroblasts, thus restore wound. [47]

7**. Carnosic acid** is a phenolic (catecholic) diterpene, endowed with antioxidative and antimicrobial properties. [48]

Carnosic acid is a natural compound found in rosemary (Rosmarinus officinalis) and other plants from the Lamiaceae family. It is known for its antioxidant and anti-inflammatory properties, and research suggests that it may have potential benefits for wound healing. [49]

Wound healing is a complex process that involves various stages, including inflammation, tissue formation, and tissue remodeling. [50] Carnosic acid's potential role in wound healing is attributed to its ability to modulate oxidative stress, reduce inflammation, and promote tissue regeneration.

Here are some ways in which carnosic acid may contribute to wound healing: [51]

**Antioxidant Properties:** Carnosic acid is a potent antioxidant that helps protect cells and tissues from oxidative damage caused by free radicals. Oxidative stress can delay wound healing by damaging cells involved in the healing process. By reducing oxidative stress, carnosic acid may support the body's ability to repair and regenerate damaged tissue. [52]

**Anti-Inflammatory Effects:** Inflammation is a natural response to tissue injury and is necessary for wound healing. However, excessive inflammation can hinder the healing process. Carnosic acid has been shown to possess anti-inflammatory properties by inhibiting the production of pro-inflammatory molecules. By controlling inflammation, carnosic acid may create a more conducive environment for healing. [53]

**Stimulation of Cell Proliferation:** Carnosic acid has been investigated for its ability to promote the proliferation of fibroblasts and keratinocytes, which are essential for tissue regeneration and wound closure. By enhancing cell proliferation, carnosic acid could potentially accelerate wound healing. [54]

**Collagen Synthesis:** Collagen is a major component of the extracellular matrix that provides structural support to healing tissues. Carnosic acid may stimulate collagen synthesis, thereby contributing to the formation of stronger and more resilient tissue at the wound site. [55]

**Angiogenesis Promotion:** Angiogenesis is the process of forming new blood vessels, which is crucial for supplying nutrients and oxygen to

healing tissue. Some research suggests that carnosic acid may promote angiogenesis, facilitating the transport of essential resources to the wound site. [56]

*Catharanthus roseus* (L) G. Don (Family: Apocynaceae), also known as periwinkle, is a beautiful evergreen plant. It grows to 100 cm tall and is in Madagascar. Vinca is a source of commercial bioactive alkaloids, including vinblastine and vincristine, which have anti-cancer properties. [57,58] It also contains many bioactive compounds with antidiarrheal, antidiabetic, hypoglycemic, antibacterial, wound-healing, and antioxidant activities such as anthocyanins, flavonol glycosides, phenolic acids, saponins, steroids, and terpenoids. [59,60]

Roses bloom year-round, the flowers are pink, purple, or white, fragrant, and beautiful. It is generally grown as an ornamental plant in Africa, Australia, China, Europe, and the United States . [61]

Several alkaloids, such as ajmalicine, vindoline, catharanthine, vinblastine, and vincristine, were successfully obtained from C. roseus shoot cultures. A study reports the in vitro antioxidant and antidiabetic activities of the major alkaloids isolated from Catharanthus roseus leaves extract. Four alkaloids—vindoline I, vindolidine II, vindolicine III and vindolinine IV—were isolated and identified from the dichloromethane extract (DE) of this plant's leaves. [62]

***Catharanthus roseus* contribute to diabetic wound healing by:**

**Antioxidant Activity:** Diabetic wounds are often associated with increased oxidative stress, which can impair the wound healing process. The antioxidant compounds in *Catharanthus roseus*, such as flavonoids and alkaloids, may help neutralize free radicals and reduce oxidative stress at the wound site. This can create a more favorable environment for wound healing to progress. [62]

**Anti-Inflammatory Properties:** Chronic inflammation is a common characteristic of diabetic wounds and can delay healing. Certain phytochemicals in *Catharanthus roseus* have demonstrated anti-inflammatory effects by inhibiting pro-inflammatory cytokines and enzymes. By reducing inflammation, these compounds may promote a faster healing response. [63]

**Angiogenesis Promotion:** Diabetic wounds often suffer from impaired blood flow and reduced angiogenesis (formation of new blood vessels). Some phytochemicals in *Catharanthus roseus* have been shown to stimulate angiogenesis, which can enhance the supply of oxygen and nutrients to the wound area, aiding in tissue regeneration. [64]

**Collagen Synthesis:** Diabetic wounds tend to have altered collagen metabolism, which can result in delayed wound closure and weak scar formation. Certain constituents of *Catharanthus roseus*, such as alkaloids, may influence collagen synthesis, thereby promoting better wound closure and tissue remodelin. [65]

**Enhancement of Fibroblast Activity:** Fibroblasts are essential cells involved in wound healing, as they produce extracellular matrix components and contribute to tissue repair. Some compounds in *Catharanthus roseus* may enhance fibroblast proliferation and activity, which can expedite wound healing. [64]

**Wound Contraction:** The wound contraction phase is crucial for closing the wound and reducing its size. Certain bioactive compounds in *Catharanthus roseus* may influence the contractile properties of myofibroblasts, helping to accelerate wound closure. [66]

It's important to note that while the potential of *Catharanthus roseus* and its phytochemicals in diabetic wound healing is promising; more research is needed to fully understand the mechanisms of action and to validate these effects in clinical settings. Additionally, individual responses to phytochemical treatments can vary, so it's crucial to consult with a healthcare professional before using any plant-based remedies, especially for individuals with diabetes or other health conditions.

**Conclusion**

Plant metabolites hold significant promise in the management of diabetic foot infections by addressing key challenges such as oxidative stress, inflammation, and microbial resistance. Bioactive compounds from *Ocimum sanctum* and *Catharanthus roseus* have demonstrated remarkable therapeutic potential, including improved wound healing, enhanced immune responses, and reduced bacterial infections. These findings suggest that plant-derived treatments could serve as valuable adjuncts to conventional therapies, offering a natural, cost-effective, and sustainable approach to managing DFIs. However, more extensive clinical trials and mechanistic

studies are essential to translate these promising results into practical medical applications.

**List of Abbreviations**

**Declarations**

**Conflict of Interest:** None declared.

**Financial support and sponsorship:** Nil

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