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## Acknowledging the use of botanicals to treat diabetic foot ulcer during the 21<sup>st</sup> century: A systematic review

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### Abstract

#### BACKGROUND

Diabetic foot ulcer (DFU) is a serious health issue of diabetes mellitus that affects innumerable people worldwide. Management and treatment of this complication are challenging, especially for those whose immune system is weak.

#### AIM

To discuss the plants and their parts used to heal DFU, along with the mode of their administration in diabetic patients.

#### METHODS

The original articles on “the plants for the treatment of DFU” studied in clinical cases only were obtained from various bibliographic databases using different keywords.

#### RESULTS

The search resulted in 22 clinical cases records with 20 medicinal plants belonging

to 17 families on 1553 subjects. The fruits and leaves were the most preferentially used parts for DFU treatment, regardless of whether they were being administered orally or applied topically. Of the 20 medicinal plants, 19 reported their effectiveness in increasing angiogenesis, epithelialization, and granulation, thus hastening the wound-healing process. The efficacy of these botanicals might be attributed to their major bioactive compounds, such as actinidin and ascorbic acid (in *Actinidia deliciosa*), 7-O-( $\beta$ -D-glucopyranosyl)-galactin (in *Ageratina pichinchensis*), omega-3-fatty acid (in *Linum usitatissimum*), isoquercetin (in *Melilotus officinalis*), anthocyanins (in *Myrtus communis*), and plantamajoside (in *Plantago major*).

### CONCLUSION

The validation of mechanisms of action underlying these phytochemicals contributing to the management of DFU can aid in our better understanding of creating efficient treatment options for DFU and its associated problems.

**Key Words:** Diabetic foot ulcer; Phytochemicals; Wound healing; Angiogenesis; Medicinal plants

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**Core Tip:** Due to the fact that diabetic foot ulcer (DFU) may result in osteomyelitis and lower limb amputation in diabetic patients, this exhaustive systematic review can offer clinically relevant treatments for DFU using natural remedies. This review focuses on metabolites from 19 medicinal plants that could contribute to DFU healing. The recovery time for DFU, the route of administration of medicinal plants, and a comparison of the treated group to the positive and negative control groups were also included in this study to better understand the beneficial effects of using botanicals in the management of DFU.

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## INTRODUCTION

The present scenario of human civilization has become prone to several forms of disharmony and the development of different forms of diseases responsible for the curtailment of life in every possible way. Among those varieties of disease conditions, diabetes mellitus (DM), a state of elevated blood sugar level in the body, in the long run of disease format, has paved the path for living in anguish and suffering both physically and mentally. Several aetiological factors are responsible for the development of DM. Anxiety and stress are only two of the numerous issues that have become a matter of concern in the medical field today. In the modern world, the younger generation has abandoned physical exercise in favour of social media and other technologies for entertainment and other purposes, resulting in obesity and a sedentary lifestyle. Many Western countries have witnessed the early onset of DM (type 2) in children between 1990 and 2000[1]. Remarkably, between 1998 and 2005, there was an eight-fold rise in prescriptions for reducing glucose levels in the United Kingdom[1]. Nearly 200 million people worldwide have DM, with type 2 being the most frequent. It is expected to rise exponentially to 300 million people in the next two decades[2] or 439 million by 2030[3]. The predicted increase in the number of diabetic cases by Shaw *et al*[3] has been reached in just eight years, which was actually expected to occur over a span of 20 years[4]. Additionally, every year, nearly 400 million people suffer from DM and around 1.6 million people die from it; the vast majority of them are from low-income families[5,6].

Among all the consequences, diabetic foot ulcer (DFU) is one of the most significant complications that DM patients face. Some of the significant causes of DFU include poor glycemic management, repetitive trauma, underlying neuropathy, peripheral vascular disease, and poor foot care. The prevalence of DFU is increasing globally, and more people are suffering due to inadequate information and precarious economic conditions. The global DFU incidence was 8.5% [7], with North America (13%) having the highest incidence and Europe (3%) and Africa (7.2%) having the lowest[8]. DFU has been reported to be more prevalent in males than females[9]. According to DFU statistics in India, 25% acquire DFU, 50% become infected, and around 20% require amputation. Notably, DFU contributes to nearly 80% of amputations in India each year[10].

Neuropathy is the underlying cause of DFU. The polyol pathway converts hexose sugar into polyols, which is an important element during nerve injury. In a normal physiological state, glucose is metabolized through the hexokinase route. However, in a hyperglycemic condition, the hexokinase pathway becomes saturated, allowing the polyol pathway to take over. The enzyme aldose reductase converts glucose to sorbitol. Sorbitol is difficult to break down, resulting in increased cellular osmolarity and cell damage. The activation of the polyol pathway, which also participates in numerous metabolic processes, reduces the concentration of pyridine nucleotides. This results in a drop in glutathione, nitric oxide, myoinositol and taurine concentrations[11]. The chemical conversion of sugar affects the reserves of nicotinamide adenine dinucleotide phosphate (NADP), which are responsible for the vasodilator nitric oxide. Vasoconstriction and ischemia are caused by NADP disruption, resulting in nerve cell injury and cell death. These factors cause a chain reaction that affects the body's motor, autonomic, and sensory systems, as well as the foot muscles, resulting in the deformity in the flexion and extension of the affected foot, the development of broken skin, and the creation of ulceration. The changes in autonomic nervous system function affect sweat and oil production; this causes the skin on the feet to dry out, leading to recurrent tears and infections. The loss of sensation induced by peripheral neuropathy worsens the development of ulcers. The repeated damage to the afflicted area goes undetected by the patient and, in the long term, becomes painful, necessitating hospitalization and, in many cases, amputation and death[12]. Plants and their secondary metabolites have been demonstrated to be beneficial in treating and controlling diabetes[13]. Particularly, *Vaccinium arctostaphylos* L[14], *Securigera securidaca* L[15], *Gymnema sylvestre* L[16], *Atriplex halimus* L[17], *Allium cepa* L[18], *Citrullus colocynthis* (L.) Schrad[19], *Silybum marianum* (L.) Gaertn[20], *Trigonella foenum-graecum* L[21] and *Allium sativum* L[22] have traditionally been related to an antioxidant mechanism and the treatment of diabetes by lowering blood glucose levels.

This review aims to clarify the scientific data supporting the ethnobotanical use of plant parts as treatment options for DFU. Therefore, this systematic review intends to explore the many therapeutic cases addressing this significant issue with a special emphasis on the potential routes of administration of the compounds derived from plants for treating DFU.

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## MATERIALS AND METHODS

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This systematic review of the clinical cases on the use of plants to treat DFU was performed as per the PRISMA guidelines[23].

### **Information sources and search strategy**

Original research articles were searched in various bibliographical databases like PubMed, Scopus, and Google Scholar, using the various keywords (Figure 1) listed below:

#### **For PubMed: Accessed on 07.12.2022**

("diabetic foot"[MeSH Terms] OR ("diabetic"[All Fields] AND "foot"[All Fields]) OR "diabetic foot"[All Fields] OR ("diabetic"[All Fields] AND "foot"[All Fields] AND "ulcer"[All Fields]) OR "diabetic foot ulcer"[All Fields]) AND ("plants"[All Fields] OR "planted"[All Fields] OR "planting"[All Fields] OR "plantings"[All Fields] OR "plants"[MeSH Terms] OR "plants"[All Fields] OR "plant"[All Fields]) AND "clinic"[All Fields] OR "clinics"[All Fields] OR "clinical"[All Fields] OR "clinically"[All Fields] OR "clinical"[All Fields] OR "clinics"[All Fields]) AND ("cases public health commun mark"[Journal] OR "cases"[All Fields]).

#### **For Scopus: Accessed on 07.12.2022**

TITLE-ABS-KEY (diabetic AND foot AND ulcer AND clinical AND cases) AND PUBYEAR >2000 AND PUBYEAR >2000; TITLE-ABS-KEY (diabetic AND foot AND ulcer AND clinical AND cases) AND PUBYEAR >2000 AND PUBYEAR >2000; TITLE-ABS-KEY (diabetic AND foot AND ulcer AND plant AND clinical AND cases) AND PUBYEAR >2000 AND PUBYEAR >2000; TITLE-ABS-KEY (dfu AND plant AND clinical AND cases) AND PUBYEAR >2000 AND PUBYEAR >2000.

#### **For Scholar Google: Accessed on 07.12.2022**

"Diabetic foot ulcer", "plant" and "clinical cases".

### **Inclusion criteria**

The publications of the last decade (published between 1<sup>st</sup> January 2000 to 7<sup>th</sup> December 2022) that focused on the clinical cases carried out to validate the effects of plants on DFU were set as the inclusion criteria for selecting the relevant reports in this study. Only the abstracts and full-text articles that met the aforementioned requirements were taken into account for interpretation.

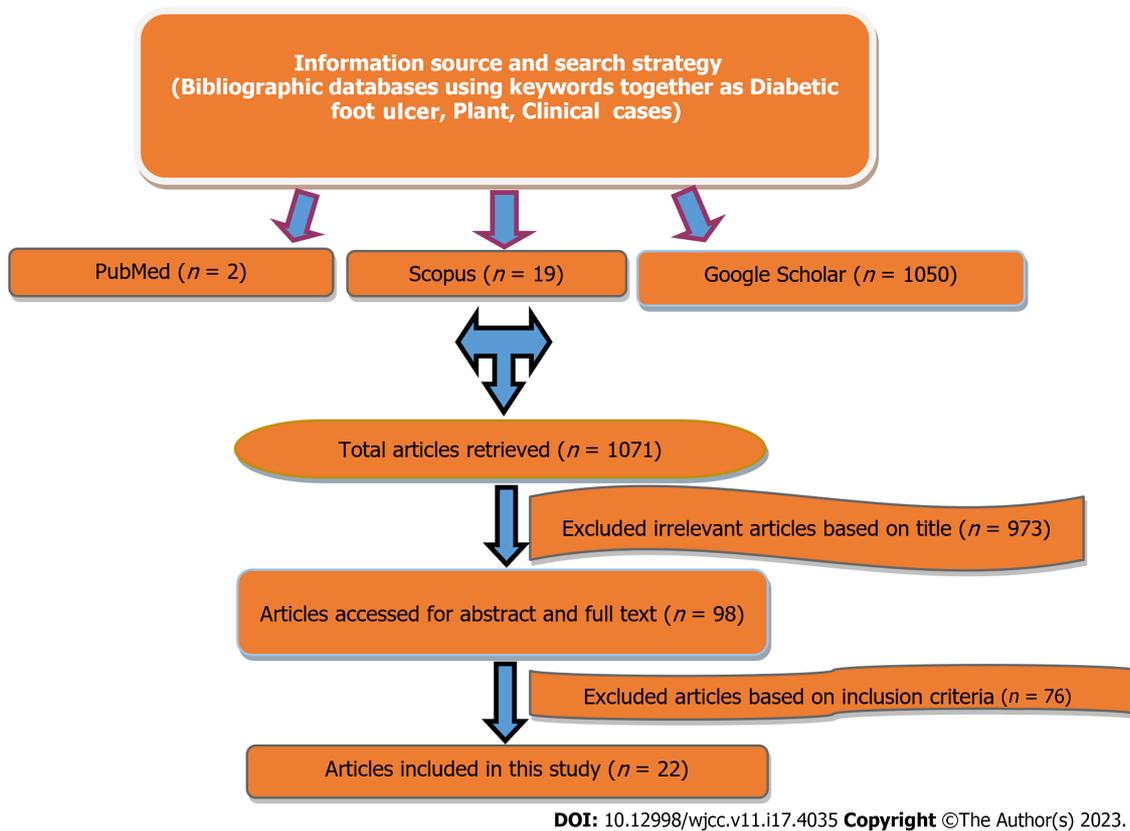


Figure 1 Schematic representation of the methodology adopted for screening and analyzing the reports available in the literature.

### Exclusion criteria

The research studies not published in English were not included. In addition, any information about injuries other than DFU and information not involving human subjects were categorically omitted.

### Data retrieval

The information relevant to the investigation, including metabolites, sample size, length of therapy, country of treatment, parts used, and manner of administration, retrieved from full-text papers, was entered into an Excel sheet from full-text articles (Microsoft Office Version 2018 for Windows, Washington, United States). The Excel sheet was used as a means of gathering data.

## RESULTS

After preliminary screening, a total of 1071 abstracts/citations were obtained from several bibliographic databases, including 2 from PubMed, 19 from Scopus, and 1050 from Google Scholar. Ninety-eight (98) papers were considered full-text examination studies after removing duplicates, and the titles and abstracts were screened for relevance. Finally, 22 clinical case-related articles fulfilled both the inclusion and exclusion criteria. A flowchart showing the selection strategy of the research studies and publication number at each stage is shown in Figure 1.

There were 1553 subjects enrolled in total among the 22 investigations. The countries that attracted the most interest were Iran (45.45%,  $n = 10$ ), Brazil (13.64%,  $n = 3$ ), Nigeria and India (9.09%,  $n = 2$  each), Mexico, Thailand, Taiwan, Indonesia, and the West Indies (4.55%,  $n = 1$  each), and other countries. The majority (13.64%,  $n = 3$  each) of the research publications were reported in 2020 and 2021. The most often used mode of administration of the herbal preparation in the chosen cases was by topical delivery (45.45%,  $n = 10$ ), followed by oral (18.18%,  $n = 4$ ) and intravenous (13.64%,  $n = 3$ ) routes. The herbal therapies to treat DFU were given orally in five trials. One of the five trials failed to show a meaningful effect on DFU compared to the control group. Three studies involving oral treatment (Bolajoko *et al*[24], Soleimani *et al*[25], and Bolajoko[26]) combined herbal and conventional therapy to improve the impact of conventional therapy on DFU. The most often used plant parts utilized in those studies were the leaf (22.7%,  $n = 5$ ), followed by the fruit (18.18%,  $n = 4$ ), the seed, the bloom, and the aerial part (9.09%,  $n = 2$  each). Except for one experiment, all investigations concluded well, with recovery times ranging from 9 to 112 d (Table 1).

Table 1 Clinical cases assessing the role of medicinal plants in the treatment of diabetic foot ulcer

Scientific name	Family	Sanskrit name	Country	Parts used	Sample size	Other ingredients	Mode of administration	Metabolites or nutraceuticals along with result	Duration	Inference of the study	Ref.
<i>Actindia deliciosa</i>	Actinidiaceae	Kiwi	Iran	Fruit	37	NR	Injection (3 mm thick layer) every 12 h	Actinidin and ascorbic acid/angiogenesis (increased), epithelialization, vascularization and granulation. Ulcer size (decreased)	11.24 ± 3.66 d (experimental), 17.76 ± 4.88 d (control)	Complete wound healing and effective	Mohajeri <i>et al</i> [35]
<i>Actindia deliciosa</i>	Actinidiaceae	Kiwi	Iran	Fruit	18	Eucerin cream	Topical (wound was covered with the mixture) every 24 h	Actinidin, wound size (decreased) (0.94 ± 0.58 cm <sup>2</sup> ), experimental <i>vs</i> control (% change in wound size: -1.25 ± 0.21 <i>vs</i> 0.21 ± 0.05)	28 d	Reduction in wound size and effective	Kardoust <i>et al</i> [36]
<i>Ageratina pichinchensis</i>	Asteraceae	-	Mexico	Aerial part	36	Cold cream	Topical one a week	7-O-(β-D-glucopyranosyl)-galactin/wound size (decreased)	65.47 ± 47.08 d (experimental); 77.46 ± 50.80 d (control)	Complete wound healing and effective	Romero-Cerecero <i>et al</i> [37]
<i>Calendula officinalis</i>	Asteraceae	Zergul	Brazil	Flowers	32	NR	Topical (5 mL) once a day	Calendula oil/wound healing (increased), pain (decreased)	30 d	Reduction in wound size and effective	Carvalho <i>et al</i> [73]
<i>Calendula officinalis</i>	Asteraceae	Zergul	Brazil	Flowers	84	NR	Spray twice daily	Wound healing (increased), 78% had complete healing after 30 wk	15.5 ± 6.7 wk	Reduction in wound size and effective	Buzzi <i>et al</i> [74]
<i>Garcinia kola</i>	Clusiaceae	Balya	Nigeria	Seed	120	NR	Oral (capsule) 250-500 mg	Wound healing (increased), Reduction in wound size by 63.30% in experimental group	63-84 d	Reduction in wound size and effective	Bolajoko <i>et al</i> [24]
<i>Kalanchoe pinnata</i>	Crassulaceae	Pranabijah	West Indies	Leaves	478	NR	Plaster (boiled leaf) and poultice once to thrice daily	Wound healing (increased)	9 d	Effective	Cawich <i>et al</i> [99]
<i>Linum usitatissimum</i>	Linaceae	Atasi	Iran	Seed oil	60	NR	Supplement (1000 mg/d omega-3 fatty acid from flaxseed oil)	Omega-3- fatty acid/ulcer length (decreased), width and depth, experimental <i>vs</i> control % change in (ulcer length: -2.0 ± 2.3 <i>vs</i> -1.0 ± 1.1 cm; width: -1.8 ± 1.7 <i>vs</i> -1.0 ± 1.0 cm; and depth: -0.8 ± 0.6 <i>vs</i> -0.5 ± 0.5 cm)	84 d	Reduction in wound size and effective	Soleimani <i>et al</i> [25]
<i>Melilotus officinalis</i>	Fabaceae	Vanamethika	Iran	NR	10	NR	Intravenous infusion	Melilotus/wound (decreased) size (reduced by 50%), experimental <i>vs</i> control (wound size: 6.69 ± 60 <i>vs</i> 12.32 ± 11 cm <sup>2</sup> )	56 d	Reduction in wound size and effective	Bagheri <i>et al</i> [113]
<i>Melilotus officinalis</i>	Fabaceae	Vanamethika	Iran	NR	40	NR	Orally twice a day	Melilotus/wound healing (increased), experimental <i>vs</i> control (completely healed: 90.0% <i>vs</i> 70.0%)	84 d	Complete wound healing and effective	Bahrami <i>et al</i> [114]
<i>Momordica</i>	Cucurbitaceae	Karavella	Indonesia	Leaf	30	NR	Oral (6 g) per day	Wound healing (increased), experimental	28 d	Not effective	Rosyid <i>et al</i>

<i>charantia</i>								<i>vs</i> control: [TNF- $\alpha$ serum levels (pg/mL): -29.50 $\pm$ 8.6 <i>vs</i> -202.47 $\pm$ 610.2; PEDIS degree (decreased): 1.9 $\pm$ 0.6 <i>vs</i> 2.2 $\pm$ 0.8]			[122]
<i>Olea europaea</i>	Oleaceae	Jaitun	Iran	Fruit	60	NR	Topically (oil) once a day	Wound healing (increased), experimental <i>vs</i> control (completely healed: 76.60% <i>vs</i> 0.00%)	28 d	Complete wound healing and effective	Abdoli et al [130]
<i>Olea europaea</i>	Oleaceae	Jaitun	Iran	Fruit	34	NR	Topical (oil) once a day	Wound healing (increased). Ulcer area (decreased) and depth, experimental <i>vs</i> control (completely healed: 73.33% <i>vs</i> 13.30%; change in ulcer (area: -54.7% $\pm$ 28.8% <i>vs</i> +2.7% $\pm$ 47.2%), depth (area: -60.1% $\pm$ 13.8% <i>vs</i> -29.6% $\pm$ 12.6%))	28 d	Complete wound healing and effective	Nasiri et al [131]
<i>Plantago major</i>	Plantaginaceae	Asvagola	Iran	Leaves	94	Gel	Topically (oil) once a day	Plantamajoside/wound healing (increased), experimental <i>vs</i> control (completely healed: 64.00% <i>vs</i> 20.50%)	14 d	Complete wound healing and effective	Ghanadian et al [125]
<i>Plantago major</i> and <i>Aloe vera</i>	Plantaginaceae, Asphodelaceae	Asvagola and Ghrit kumara	Iran	NR	40	NR	Intervention twice a day	Ulcer surface decreased, ulcer depth decreased	28 d	Reduction in wound size and effective	Najafian et al [55]
<i>Plectranthus amboinicus</i> and <i>Centella asiatica</i>	Lamiaceae and Apiaceae	Yavani, Mandukaparni	Taiwan	NR	24	Cream (composed of cetostearyl alcohol, ireine, liquid petrolatum, methyl paraben propyl paraben, Span 60, Tween 60, white petrolatum, water, and pigments)	Topically (2 mm thickness) twice a day	Wound healing (increased), experimental <i>vs</i> control [improved Wagner grade: 90.9% <i>vs</i> 70.0% (% change in wound size: -27.18 <i>vs</i> -22.64)]	14 d	Reduction in wound size and effective but not significant compared to controlled group	Kuo et al [84]
<i>Quercus infectoria</i>	Fagaceae	Mayakku	Thailand	Nutgalls	51	Ethanol	Topical once a day	Wound healing (increased), experimental <i>vs</i> control (80.7% <i>vs</i> 20.0%)	96 d	Complete wound healing and effective	Chokpaisarn et al [152]
<i>Sesamum radiatum</i> and <i>Azadirachta indica</i>	Pedaliaceae and Meliaceae	Tila, Nimba	India	Seed and leaves	15	Ghee and honey	Topically (3 mm thick) once a day	Wound size and exudates (decreased), no granulation, reduction in wound size by 88.0% in the experimental group	45 d	Complete wound healing and effective	Tripathy et al [160]
<i>Teucrium polium</i>	Lamiaceae	-	Iran	Aerial part	70	Eucerin	Topically twice daily	Wound healing (increased), experimental <i>vs</i> control; ulcer area (decreased): 0.717 $\pm$ 0.19 cm <sup>2</sup> <i>vs</i> 1.63 $\pm$ 0.72 cm <sup>2</sup>	28 d	Reduction in wound size and effective	Fallah Huseini et al [169]
<i>Tinospora cordifolia</i>	Menispermaceae	Guduchi	India	NR	50	NR	Intervention	Wound healing (increased), experimental <i>vs</i> control (change in ulcer area: 0.15 cm <sup>2</sup> /d <i>vs</i> 0.07 cm <sup>2</sup> /d; ulcer perimeter: 0.09 cm <sup>2</sup> /d <i>vs</i> 0.07 cm <sup>2</sup> /d; ulcer depth: 2.20 cm <sup>2</sup> /d <i>vs</i> 1.40 cm <sup>2</sup> /d; wound score: 14.40 cm <sup>2</sup> /d <i>vs</i> 10.60 cm <sup>2</sup> /d; no. of debridements: 1.90 cm <sup>2</sup> /d <i>vs</i> 2.50 cm <sup>2</sup> /d)	28 d	Reduction in wound size and effective	Purandare and Supe [176]
<i>Vasconcellea</i>	Caricaceae	-	Brazil	Latex	50	NR	Intervention thrice	Wound healing (increased), experimental	112 d	Complete	Tonaco et al

<i>cundinamarcensis</i>							a week	<i>vs</i> control. Completely healed: 68.7% <i>vs</i> 31.3%)		wound healing and effective	[182]
<i>Vernonia amygdalina</i>	Asteraceae	-	Nigeria	Leaves	120	NR	Oral (capsule) 250-500 mg/kg body weight	Wound healing (increased), reduction in wound size by 60.0% in experimental group	63-84 d	Complete wound healing and effective	Bolajoko[26]

NR: Not reported; TNF- $\alpha$ : Tumour necrosis factor alpha.

## DISCUSSION

Diabetes-related foot ulceration is common and incapacitating, frequently necessitating limb amputation[27]. It is associated with worsening the patient's condition and a significant negative economic impact[28]. There are several ways to treat diabetic wounds, but one option that has attracted attention internationally in the recent two decades is the use of medicinal plants[29]. Twenty medicinal plant species from 17 different families have been reported in the current review, with the majority of the plants coming from the Asteraceae family.

### *Actinidia deliciosa*

*Actinidia deliciosa* (*A. deliciosa*) is a Chinese native plant, later made available by cultivation in New Zealand and the United States[30]. In an experiment by Masoudpour *et al*[31], third-degree burn wounds were generated on rats that were infected by *Pseudomonas aeruginosa*. The first group received topical silver sulfadiazine, the second a slice of fresh *A. deliciosa* fruit, and the third did not receive any treatment. In terms of wound healing and contraction, the study found that *A. deliciosa* fruit was much more successful than silver sulfadiazine. In another animal experiment in 2010, *A. deliciosa* was reported to heal wounds faster with ulcer debridement, angiogenesis and disinfection compared to a group treated with Vaseline sterile gauze and silver sulfadiazine cream[32]. The major compound present in *A. deliciosa* is actinidin which is responsible for the fruit's well-known proteolytic and meat-tenderizing actions, making it a good choice for herbal debridement[33]. The inclusion of key ingredients such as lutein, beta-carotene, fisetin, and vitamins C, E, and K supports that *A. deliciosa* might be used as an herbal debridement agent[34]. Mohajeri *et al*[35] studied the effect of topical *A. deliciosa* treatment on neuropathic DFU. When comparing the *A. deliciosa*-treated group to the control group, the authors observed a mean reduction in the surface area of foot ulcers. They also detected enhanced angiogenesis and vascularization, as well as an increase in collagen and granulation tissue. Actinidin has been reported to be responsible for the wound-healing process. Kardoust *et al*[36] conducted a study with 18 DFU patients who were randomly allocated to either the control or experimental groups. The control group was given Eucerin as a basic ointment, whereas a conventional wound dressing added with *A. deliciosa* extract was applied to the experimental group. The mean wound area of the experimental group was significantly less than that of the control group after 4 wk of treatment. The difference in average wound size between the experimental and control groups showed that *A. deliciosa* could help with wound healing. Thus, a wound dressing with *A. deliciosa* extract may help reduce the treatment time and be used in place of surgical debridement in DFU patients.

### ***Ageratina pichinchensis***

*Ageratina pichinchensis* (*A. pichinchensis*) is a wild plant native to Mexico[37]. In the Mexican state of Morelos, this plant is used in traditional medicine to prepare a remedy for skin lesions[38]. A chemical examination of this plant's extract indicated the presence of chromones and compounds from the benzofurane group[39,40]. The antifungal efficacy of *A. pichinchensis* extracts against *Trichophyton rubrum* and *Trichophyton menthagrophytes* bacterial strains have also been reported[41]. In an *in-vivo* animal study, the *A. pichinchensis* aqueous extract completely cured the lesions in all cases at the end of the dosing period, forming a large number of fibroblasts, collagen fibers, elastin, hair follicles, vascular neoplasms, and a bridging cell-by-cell regeneration process, compared to the control group treated with fibrinolysin (Fibrase SA®)[42]. The aqueous and hexane-ethyl acetate (EA) extract of *A. pichinchensis* were investigated for wound healing activity in a DFU rat model. The results showed that 100% of animals treated with *A. pichinchensis* extracts healed the wounds between days 4 and 11; however, the positive and negative control groups exhibited only 70% and 40% of wound healing, respectively, at day 11. 7-O-( $\beta$ -d-glucopyranosyl)-galactin molecule has been found to be responsible for the healing effect of *A. pichinchensis*[43]. Romero-Cerecero *et al*[44] studied the effectiveness and tolerability of a phytopharmaceutical made from a standardized extract (5% cream formulation) of *A. pichinchensis* in DFU patients, where micronized silver sulfadiazine (1%) was employed as a control. All the subjects who finished the study had their ulcers totally cured. The patients in the experimental group had a wound-healing rate of 77.5% after six weeks of treatment, compared to 69.8% in the control group. The average time required for complete wound healing for patients in the experimental group was  $65.47 \pm 47.08$  d, whereas patients in the control group needed  $77.46 \pm 50.80$  d. Thus, *A. pichinchensis* extract has shown the ability to enhance wound healing in DFU patients.

### ***Aloe vera***

*Aloe vera* (*A. vera*) is a native of North Africa and Spain, but it is currently grown throughout hot, arid parts of Asia, Europe, and America[45]. Cancer, free radical activity, diabetes, inflammation, microbiological infections, tyrosinase activity, spermatogenic activity,  $\beta$ -secretase inhibitory effect, and proliferative activity have all been reported to be reduced by anthraquinones and glycosides contained in *A. vera* sap[46]. Thirty patients with multi-drug-resistant organisms infected leg ulcers were treated with topical *A. vera* gel and thirty with topical antibiotics. Bacterial growth in the study group was reduced from 100% (30 instances) to 6.7% (2 cases) by day 11, but bacterial growth in the control group remained unchanged by day 11. *A. vera* gel is less expensive and more effective against multi-drug resistant pathogens when compared to commonly used topical antimicrobial medicines[47]. In an interesting study, ultraviolet (UV)-induced polymerization was used to create polyvinylpyrrolidone-based hydrogels containing *A. vera* juice and L-ascorbic acid. It was observed that the polymer structure became more wrinkled as the amount of crosslinker increased. Following that, it was demonstrated that as the amount of crosslinker grew, the crosslinking density of hydrogels rose, and therefore their swelling ratio dropped. The hydrogels generated with a higher average molecular weight crosslinking agent demonstrated greater swelling ability than materials prepared with a lower average molecular weight crosslinking agent. Furthermore, as the amount of crosslinking agent grew, so did the tensile strength and % elongation of the hydrogels[48]. The experiments were carried out on three types of diabetic rats: Non-diabetic (ND), type I (IDDM), and type II (NIDDM). *A. vera* leaf pulp or gel extracts did not affect the blood sugar levels of ND rats. In IDDM and NIDDM rats, *A. vera* leaf pulp extract demonstrated hypoglycemic effectiveness, with type II diabetes benefiting more than glibenclamide. On the other hand, *A. vera* leaf gel extract revealed hyperglycemic activity in NIDDM rats. Consequently, it was concluded that non-gel *A. vera* leaf pulps might be beneficial in treating non-insulin-dependent DM [49]. In another study, regular post-treatment with *A. vera* for 21 d indicated possible hypoglycemic action in oral glucose tolerance tests and normoglycemic rats, as well as the antidiabetic effect in alloxanized rats[50]. One study demonstrated that aloe emodin (AE), an anthraquinone in the *A. vera* plant, inhibits hemoglobin (Hb) aggregation. To confirm this finding, UV-visible spectroscopy, intrinsic fluorescence, thioflavin T, Congo red test, and transmission electron microscopy were utilized. Data from Fourier transform infrared (IR) spectroscopy and circular dichroism showed that sheet structure has been removed and helices have been formed[51]. In one investigation, *in-vitro* cell proliferation and migration assays were performed on normal primary human skin fibroblasts and keratinocytes in the growth medium containing *A. vera* solution and preservatives at varied doses. The findings imply that *A. vera* promotes wound healing by boosting fibroblast and keratinocyte proliferation and migration, as well as shielding keratinocytes against preservative-induced mortality[52]. The prophylactic effectiveness of *A. vera* gel ethanolic extract in Wistar rats was examined using a DFU paradigm. The results provide scientific support for the use of *A. vera* gel ethanolic extract, revealing that the gel decreased diabetic foot lesions in rats[53]. The *A. vera* cream was compared to normal saline dressings (NSDs) for infected diabetic leg ulcers. Sixty patients with infected lower leg ulcers were placed into two groups: One received daily *A. vera* dressings, while the other received daily saline-soaked dressings. The efficacy of *A. vera* cream dressing was recorded to be higher than that of NSD[54]. Najafian *et al*[55] evaluated the efficacy of *Aloe vera/Plantago major* gel (Plantavera gel) in treating DFU, which was a randomized clinical trial with 40 DFU patients. The patients in the intervention group were randomly assigned to receive

topical Plantavera gel in addition to standard care, whereas the patients in the control group received topical Placebo gel in addition to standard care. At the end of the study, a significant difference between the two groups in terms of total ulcer score was observed, and Plantavera gel significantly reduced the ulcer surface compared to the control group with no adverse effects.

### ***Azadirachta indica***

*Azadirachta indica* (*A. indica*), sometimes known as neem, is an Indian native that has been naturalized in most tropical and subtropical areas[56]. A phytochemical screening study revealed the presence of steroids, triterpenoids, reducing sugars, alkaloids, phenolic compounds, flavonoids, and tannins[57,58]. The anti-inflammatory and antipyretic effects of *A. indica* extract were investigated; the extract showed strong anti-inflammatory and antipyretic properties in rabbits[59]. An aqueous extract of *A. indica* leaves was tested for anthelmintic efficacy against *Pheretima posthuma*, *Raillietina spiralis* and *Ascaridia galli*. The extract exhibited antihelmintic action, showing that the aqueous extract possesses vermifugal activity and is an efficient anthelmintic[60]. *A. indica* leaf extract inhibited *Plasmodium falciparum in vitro* and *Plasmodium vivax in vivo*. As a result, using *A. indica* to treat various medical conditions, particularly infectious disorders, is strongly warranted[61]. When compared to the control group of adult male Wistar rats, *A. indica* extract significantly accelerated the day of complete wound closure in the experimental group. The aqueous leaf extract of *A. indica* promoted wound healing by boosting inflammatory response and neovascularisation[62]. When diabetes was adequately compensated at the Wound Care Units of Pisa, Ragusa and Modena - Italy, 16 DFUs from a study were managed at home with a blend of *Hypericum perforatum* and *Azadirachta indica* (Hyperoil™). DFUs were recovered in all patients between 2 and 10 mo after beginning Hyperoil™ therapy. During this period, all patients' HbA1c levels declined, DFU discomfort was reduced, and hypertension was well compensated. These preliminary data showed that utilizing Hyperoil™ in conjunction with strict diabetes control might be a low-cost and effective new home care option for severe DFUs[63]. Following the successful use of a *Hypericum* flower extract (*Hypericum perforatum*) and neem oil (*Azadirachta indica*; Hyperoil) in foot wounds with exposed bone in a patient with bilateral advanced diabetic ulcers, it was hypothesized that the improvement was due to improved glycemic control and peripheral microvascular circulation. A case study recounts the extraordinarily positive outcome of another patient who utilized Hyperoil for an infection-damaged diabetic foot without prior surgical intervention. DFU healing was associated with decreased local infection and better glycemic control. This patient's outcome illustrates that the efficacy of a low-cost Hyperoil therapy for the diabetic foot is connected not only with the presence of significant microvascular dysfunction but also with appropriate local treatment[64].

### ***Calendula officinalis***

*Calendula officinalis* (*C. officinalis*) is indigenous to the region stretching from Macaronesia East across the Mediterranean region to Iran[65]. The phytochemical investigation of *C. officinalis* revealed the presence of carbohydrates, amino acids, lipids, volatile oils, fatty acids, carotenoids, terpenoids, flavonoids, quinones, and coumarins[66-68]. The *C. officinalis* flower extracts inhibited the proliferation of the human immunodeficiency virus-type 1 (HIV-1). The organic extract demonstrated significant anti-HIV efficacy in an *in-vitro* MTT/tetrazolium-based test. The organic extract was also demonstrated to inhibit HIV-1 reverse transcription activity in a dose- and time-dependent manner. These studies have shown that an organic extract of *C. officinalis* flowers had anti-HIV properties with therapeutic potential[69]. In traditional medicine, *C. officinalis* is used to treat wounds, ulcers, herpes, scars, skin damage, frostbite, and blood purification. According to pharmacological studies, calendula extracts have antiviral and antigenotoxic properties *in vitro*[70]. In another research study, biologically active compounds were discovered and measured in *C. officinalis* flowers. The UV-visible (UV-VIS) spectroscopy enabled the identification and characterization of the whole range of phenolic and flavonoid acids, while high-performance liquid chromatography (HPLC) was used to detect and quantify phenolic compounds. In methanolic extracts, the polyphenol content was shown to be related to antioxidant activity. The UV-VIS spectra of assimilator pigments (*e.g.*, chlorophylls), polyphenols, and flavonoids extracted from *C. officinalis* flowers were a quantitative evaluation of compounds that absorb at wavelengths greater than 360 nm[71]. A study looked at the molecular mechanism underlying the wound healing properties of *Calendula* extracts. The effects of three *Calendula* flower extracts (n-hexanic, ethanolic, and aqueous) on the inflammatory phase of wound healing in immortalized human keratinocytes and human dermal fibroblasts were studied. *Calendula* flower n-hexanic and ethanolic extracts influence the inflammatory phase in human immortalized keratinocytes by activating the transcription factor nuclear factor-kappa B and increasing the amount of the chemokine interleukin (IL)-8 at both the transcriptional and protein levels. The ethanolic extract inhibited collagenase activity *in vitro* while increasing the amount of collagen in the supernatant of human dermal fibroblasts, indicating that the granulation tissue was affected[72]. Carvalho *et al*[73] evaluated the effects of low-level laser therapy on DFUs alone and in conjunction with *C. officinalis* oil. The research study involved a group of 32 diabetics of both sexes. At random, the participants were divided into four groups. Low-level laser treatment and low-level laser therapy combined with essential fatty acids groups had reduced pain. All groups had the same ankle-brachial index and Doppler ultrasound. The study indicated that low-level laser therapy, either alone or in conjunction with *C. officinalis* oil, was effective in lowering pain and accelerating tissue repair in the

diabetic foot. Buzzi *et al*[74] performed a prospective, descriptive pilot study to determine the therapeutic effectiveness of *C. officinalis* hydroglycolic extract in the treatment of DFUs. The ulcers were treated twice daily with a spray solution of *C. officinalis* hydroglycolic extract and coated with sterile, saline-moistened gauze and bandages, followed by foot unloading with suitable protective footwear. 54%, 68%, and 78% of patients had complete wound closure after 11, 20, and 30 wk of treatment, respectively. The quantity of exudate, fibrin slough, and necrotic tissue was significantly reduced after treatment with *C. officinalis* hydroglycolic extract, with no adverse reactions.

### **Centella asiatica**

*Centella asiatica* has been used as a medicinal plant in India for thousands of years, and it is mentioned in the well-known 'Sushruta Samhita', an ancient Indian medical text[75]. Among the active compounds found in it include pentacyclic triterpenes such as asiaticoside, madecassoside, asiatic acid, and madecassic acid[76,77]. An HPLC technique employing an octadecyl silylated silica column quantified the amount of such bioactive terpene acids[78]. Its chemical elements have several medicinal uses with antibacterial, anti-inflammatory, anticancer, neuroprotective, antioxidant, and wound healing properties[79]. Keloids, leg ulcers, phlebitis, slow-healing wounds, leprosy, surgical lesions, striae distensae, and cellulitis are all well treated with *Centella asiatica* extract[80]. Animal studies have revealed that *C. asiatica* improves memory, increases response time, and aids in wound healing. *C. asiatica* aqueous extract in dose-dependent amounts decreased the appearance of aging skin, collagen, and topical scars[81]. *In vivo* and *in vitro* studies of the methanolic fraction of *C. asiatica* exhibited great polyvalent activity, indicating that it has the potential to be an efficient wound healer[82]. In a pre-clinical study, the wounds of 64 male Sprague-Dawley rats were treated with a placebo, *C. asiatica* Linn., *Garcinia mangostana* Linn., and neomycin. The rats were divided into two groups: Normal control and diabetes-induced, with each group divided into four groups. The results demonstrated that the 'wounds of the treated group epithelialized and contracted faster than the non-treated groups, proving the validity of traditional usage of *C. asiatica* Linn. and *Garcinia mangostana* Linn.[83]. A clinical study by Kuo *et al*[84] demonstrated the treatment of a topical cream containing *P. amboinicus* (Lour.) Spreng. (Lamiaceae) and *C. asiatica* (L.) Urban (Umbelliferae) resulted in the reduction of a greater portion of the wound size when compared to the hydrocolloid fiber dressing group.

### **Garcinia kola**

*Garcinia kola's* (*G. kola*) trade name is bitter cola, which is highly regarded in African ethnomedicine, making the plant an important component in folk medicine[85]. According to one study, the most prevalent medical uses of *G. kola* were for treating cough, mouth infection, liver problems, diarrhea, and dysentery[86]. The pharmacologic studies on this plant's seed, leaf, and root demonstrated antibacterial, antiviral, antiulcer, anti-inflammatory, antihepatotoxic, antidiabetic, antihypertensive, adaptogenic, aphrodisiac, and anti-asthmatic activities[87]. The phytochemical analysis of the plant extract revealed the presence of flavonoids, tannins, cardiac glycosides, saponins, steroids, reducing sugars, phlobatannins, polyphenols, pydroxymethyl anthraquinones, glucides and alkaloids[88,89]. The saponin extract from *G. kola* root showed substantial antioxidant and free radical scavenging activity *in vitro* and *in vivo* experiments on alloxan-induced diabetic rats, indicating it might be employed as a natural antioxidant[90]. Using the excision wound and dead wound space experimental models, researchers investigated the effect of *Garcinia* hydroxyl biflavanonol (GB1) on wound healing in streptozotocin-induced diabetic rats. Topical GB1 treatment reduced excision wound dimensions and epithelialization time in a concentration-dependent manner. Furthermore, GB1 dramatically reduced malondialdehyde (MDA) levels compared to the negative control, suggesting that GB1 activities may aid in diabetic wound healing[91]. The antioxidant and antidiabetic effects of *G. kola* ethanolic seed extract on alloxan-induced diabetic albino rats were investigated. Standard procedures were used for the *in-vitro* antioxidant test. In the *in-vivo* investigation, 36 albino rats were fasted for 16-18 h before being injected intraperitoneally with 150 mg/kg body weight of alloxan monohydrate to induce diabetes. The animals were placed into six groups: Normal, positive, negative, and groups that received 500, 250, and 125 mg/kg of the extract, respectively. The 500 mg/kg extract-treated group had lower blood glucose levels than the positive control. The antioxidant studies revealed a considerable dose-dependent improvement in free radical scavenging activity[92]. Bolajoko *et al*[24] compared glycemic control and oxidative stress levels in type 2 diabetics with or without chronic foot/leg ulcer to NDs with or without chronic foot/leg ulcer after an 8-wk freeze-dried *G. kola* dosage. All participants were given conventional treatment (metformin, glibenclamide, or insulin alone, or metformin with glibenclamide or metformin with insulin). The study participants included 30 diabetics with foot/leg ulcers (DFU), 30 diabetics without ulcers (T2DM), 30 NDs with chronic foot/leg ulcers, and 30 NDs without ulcers were divided into three groups: Subgroup-1 (250 mg *G. kola*), subgroup-2 (500 mg *G. kola*), and subgroup-3 (no-supplementation). The individuals that took 250 or 500 mg *G. kola* for 8 wk had lower total plasma peroxides (TPP), oxidative stress index and plasma glucose, as well as improved wound healing, higher total antioxidant status (TAS) and antioxidant-micronutrients. The findings showed that *G. kola* supplementation might be utilized as an adjuvant in the prevention and treatment of type 2 diabetes with or without foot/leg ulcers.

### ***Kalanchoe pinnata***

*Kalanchoe pinnata* (*K. pinnata*) is a succulent plant from Madagascar[93]. *K. pinnata* include anthocyanins and flavonoids, which have antibacterial, antioxidant, cytotoxic, anticancer, antiparasitic, antiallergic, and hepatoprotective properties[94]. An excision wound model was used to assess the wound-healing activities of *K. pinnata* extract in rats. When compared to the control and the mupirocin-treated standard, animals given with the ethanolic leaf extract exhibited less wound area and higher hydroxyproline concentration. *K. pinnata* leaf extract showed high wound-healing capability, enhanced wound contraction rate, and hydroxyproline content in extract-treated mice that were validated by histological studies[95]. According to one research, hydroethanolic *K. pinnata* leaf extracts suppressed phospholipase activity, demonstrating antiophidic action against the effects of *B. jararaca* snake venom, implying that they might be exploited as a novel source of bioactive molecules against bothropic venom [96]. A chloroform/aqueous extract of *K. pinnata* leaves was evaluated *in vitro* against MTCC 78pBR322 *Escherichia coli*, MTCC 227 *Candida albicans*, MTCC 265 *Rhodococcus rhodochrous*, and MTCC 2682 *Arthrobacter protophormial*. When compared to the standard antibiotic used as a control, the aqueous extract considerably suppressed the zone of bacterial growth, suggesting its antibacterial properties[97]. A research study developed and compared two creams comprising an aqueous leaf extract of *K. pinnata* and its major flavonoid. When administered topically to a rat excision model, both creams healed the wound by increasing re-epithelialization and collagen fibers. According to HPLC-ESI-MS/MS investigation, the primary phenolics in *K. pinnata* leaf extract were identified to be flavonol glycosides. The wound-healing capacity of *K. pinnata* was demonstrated by the outcomes of treatment following both creams[98]. In a research study, Cawich *et al*[99] divided individuals with diabetic foot infections into two groups: The study group, which utilized topical *K. pinnata*, and the medical therapy group, which used conventional therapy. The medical therapy group had 382 patients, whereas the study group had 96. The study and medical therapy groups had an identical incidence of all amputations and death. The study showed that using topical *K. pinnata* to treat diabetic foot infections might be beneficial.

### ***Linum usitatissimum***

*Linum usitatissimum* or linseed is a native crop of West Asia and the Mediterranean coastal nations, Asia Minor, Egypt, Algeria, Tunis, Spain, Italy, and Greece[100]. According to phytochemical screening studies, the principal chemical components of *L. usitatissimum*, include secoisolariciresinol diglucoside (major bioactive compound), omega-3 fatty acids, phenols, flavonoids, sterols, proteins, antioxidants, and numerous soluble and insoluble fibers[101,102]. The fatty acid components, particularly polyunsaturated fatty acids like linoleic acid, are thought to play an important role in wound healing[103]. A study investigated the antibacterial and antibiofilm properties of *L. usitatissimum* crude extract (Lu. Cr). The bacterial strains found on diabetic foot bandages were investigated and the Gram-positive bacteria were identified to be the most common in all the studied groups. Lu. Cr has the most bactericidal activity against *Staphylococcus aureus* (*S. aureus*) compared to other bacteria in the study. This research revealed that linseed had antibacterial properties that might be utilized to treat diabetic foot[104]. *L. usitatissimum* oil and mucilage were investigated for antiulcer activity in a rat model of ethanol-induced stomach ulcer. Pre-treatment of rats with flaxseed oil and mucilage significantly reduced the incidence and duration of ethanol-induced stomach ulcers. An oral dose of flaxseed oil (5 mL/kg) reduced ulcer severity more than ranitidine (50 mg/kg). According to this study, both flaxseed oil and flaxseed mucilage can provide cytoprotection against ethanol-induced stomach ulcers in rats[105]. Soleimani *et al* [25] conducted a study on 60 people with grade 3 DFU. All the subjects received conventional treatment [ciprofloxacin (Cipro) 400 mg IV plus clindamycin 900 mg IV]. The subjects were randomly grouped into one of two groups for 12 wk: Those receiving 1000 mg omega-3 fatty acids from flaxseed oil supplements or those receiving a placebo. After a 12-wk intervention, omega-3 fatty acid supplementation resulted in a significant decrease in ulcer length, width and depth, and found substantial reductions in blood insulin levels compared to the placebo. Overall, omega-3 fatty acid supplementation improved ulcer size measurements, insulin metabolic markers, serum high-sensitivity C-reactive protein, plasma total antioxidant capacity, and glutathione levels in DFU patients. Furthermore, the effects of omega-3 fatty acids in flaxseed oil on improving metabolic profiles may have indirectly impacted wound healing.

### ***Melilotus officinalis***

*Melilotus officinalis* (*M. officinalis*) is native to the United States and Canada[106]. *Melilotus officinalis* contains coumarins, melilotoin, phenolic acids, flavonoids, steroids, saponins, volatile oils, lipids, triterpenes, carbohydrates, sugar, anthraquinone glycosides, mucilage, tannin, bishydroxycoumarin, choline, alcohols, and uric acid[107]. The antimicrobial, antioxidant, anticancer, antiinflammatory, neural, protective, sedative, anxiolytic, smooth muscle relaxant and hypotensive activities are among the many pharmacological effects of this plant[108]. The effects of 0.25% coumarin *M. officinalis* extract on acute inflammation produced by the oil of turpentine in male rabbits were investigated. In this *in vivo* study, *M. officinalis* inhibited circulating phagocyte activation and citrulline production, indicating its anti-inflammatory property[109]. A three-layer electrospun nanofiber wound dressing was developed in a study, with the scaffold's external, middle, and inner layers made of polycaprolactone

(PCL), PCL/collagen, and collagen nanofibers, respectively. Various amounts of *M. officinalis* extract were also added to the collagen nanofibers as a physiologically active component. The effectiveness of the produced dressings as wound-healing agents were tested in streptozotocin-induced diabetic rats. The histopathological and histomorphometry evaluations demonstrated that herbal extract-loaded electrospun dressings (especially those containing 0.08 g of extract) are promising in promoting diabetic ulcer healing[110]. A study examined the phytochemicals responsible for the antifungal activity of *M. officinalis*, which is frequently grown in Iraq. The agar diffusion method was used to study the antifungal activity of the water-soluble fraction and pinpoint the key ingredient. At 1% and higher dosages, Iraqi *M. officinalis* demonstrated significant antifungal effectiveness against five diagnostic fungi. When compared to a standard, thin-layer chromatography of the acid-hydrolyzed glycoside shows the presence of kaempferol flavonoid, which was supported by high-performance thin-layer chromatography, UV, and IR spectroscopy. The major phytochemical in the extract's polar component, kaempferol glycoside, is responsible for its potent antifungal effect[111]. In Iran, *M. officinalis* dry extract is marketed under the trade name Semelil (ANGIPARS™) and is used to treat chronic wounds, particularly DFUs[112]. Bagheri *et al*[113] investigated the safety and healing rates of DFUs in people who were given ANGIPARS™. Ten diabetic patients participated in this single-arm trial before-after clinical research. The wound area was calculated using planimetry. According to this research study, the medication may reduce wound size by at least 50% over the course of eight weeks with no discernible side effects. In a study by Bahrami *et al*[114], 40 patients with DFUs that had been present for at least 4 wk were randomly assigned to receive either oral ANGIPARS or a placebo twice a day for a maximum of 6 wk, and they were observed for up to 12 wk. The results showed a significant reduction in wound surface area in both groups. In the ANGIPARS group, the mean improvement ratio was 95.8%, compared to 79.2% in the placebo group. 90% of the ANGIPARS group and 70% of the placebo group had fully healed wounds after 12 wk. At weekly evaluations, the former group had a larger mean percent of wound area decrease than the placebo group.

### **Momordica charantia**

*Momordica charantia* (*M. charantia*), a medicinal plant, is native to India and is widely grown in Asian nations[115]. The primary metabolites of *M. charantia* include common sugars, proteins and chlorophyll, whereas secondary metabolites include alkaloids, flavonoids, tannins, saponins, diosgenin, proteins, calcium, and copper[116]. A qualitative phytochemical study on *M. charantia* indicates the presence of phytochemicals such as flavonoids, saponins, terpenoids, coumarins, emodins, alkaloids, proteins, cardiac glycosides, anthraquinones, anthocyanins, and steroids[117]. The aqueous and ethanolic extracts of *M. charantia* inhibited the growth of *S. aureus*, *Bacillus subtilis*, *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa*. The findings of this study backed up the use of *M. charantia* in herbal medicine and suggested that it might be utilized as a source of antibacterial agents for treating disorders caused by the pathogenic bacteria investigated[118]. The wound-healing efficacy of *M. charantia* fruit powder was studied in rats utilizing an excision, incision, and dead space wound model. The powder ointment showed a statistically significant response in wound-contracting ability, wound closure time, length of epithelization, wound tensile strength, and wound tissue regeneration compared to the control group [119]. A study evaluated the alterations in transforming growth factor (TGF) expression in diabetic lesions treated with topical *M. charantia* fruit extract. Fifty-six male Sprague-Dawley rats were divided into five diabetes groups of 10 rats each, as well as a normal control group. Diabetes was induced in diabetic groups by intravenous injection of 50 mg/kg streptozotocin. Full-thickness excision wounds were created on the thoracodorsal region of the animals; these wounds were then treated for 10 d with vehicle, *M. charantia* powder, *M. charantia* ointment, and povidone ointment or ointment base. The wound closure was substantially quicker in the *M. charantia* ointment group than in the untreated diabetes group. The study demonstrated that *M. charantia* ointment has good potential for use as an alternative topical therapy for diabetic wounds that accelerates wound healing by increasing TGF expression[120]. In another study, the impact of bitter melon leaves extract supplementation on glycemic status in DFU patients was investigated. Thirty DFU patients with PEDIS 1-8 scores who satisfied the criteria were split into two groups: 15 as a treatment group receiving bitter melon leaves extract and 15 as a control group receiving placebo. After 4 wk of therapy, the baseline value of glycated albumin in the treatment group increased, whereas it decreased in the control group. However, the examination of the effect of bitter melon leaves extract supplementation on the value of glycated albumin yielded no significant findings[121]. The impact of bitter melon leaves extract on blood tumor necrosis factor (TNF)- $\alpha$  levels and DFU improvement was studied by Rosyid *et al*[122]. Thirty DFU patients took part in the experiment and were separated into two groups based on PEDIS scores, with 15 patients in the treatment group receiving bitter melon leaves extract at a dose of 6 g/d and the remaining 15 patients in the control group receiving a placebo. The baseline blood TNF- $\alpha$  levels in both the treatment and control groups decreased after four weeks of therapy. PEDIS degrees decreased in the extract treatment and control groups from baseline, weeks 2, 3, and 4, but there was no effect on DFU improvement.

### ***Olea europaea***

*Olea europaea* leaves have long been used in traditional medicine in Greece, Spain, Italy, France, Turkey, Israel, Morocco, and Tunisia[123]. *O. europaea* known as the olive, has traditionally been used as a diuretic, hypotensive, emollient, laxative, febrifuge, skin cleanser, cholagogue, and treatment of urinary infections, gallstones, bronchial asthma, and diarrhea, as they have antioxidant, anticarcinogenic, anti-inflammatory, antimicrobial, antihypertensive, antidyslipidemic, cardiotoxic, and antiplatelet properties [124,125]. The antimicrobial activity of *O. europaea* leaves extract against *Campylobacter jejuni*, *Helicobacter pylori*, and *S. aureus* [including methicillin-resistant *S. aureus* (MRSA)] was discovered[126]. In an *in-vivo* investigation, wound contraction and healing activity were best observed in normal and diabetic experimental rats treated with a newly developed ointment of *O. europaea* leaf extracts combined with Shea butter[127]. When compared to a regularly used amorphous hydrogel, the unique *O. europaea* leaf extract hydrogel (EHO-85) was tested for its capacity to expedite wound healing. Compared to a control amorphous hydrogel, EHO-85 significantly accelerated wound healing regardless of ulcer etiology (pressure, venous leg, or diabetic foot) or prognosis, doubling the median wound area decrease. An intention-to-treat analysis was performed on 195 patients. This novel medication modulates the ulcer microenvironment by altering reactive oxygen species and pH, which explains the demonstrated granulation formation and pain-relieving powers of EHO-85[128]. In one case study, a 45-year-old lady with T2DM had a big toe wound and was given propolis and olive oil. The patient had a 2 cm<sup>2</sup> wound on her foot and was told to wash it with serum, apply topical admixture to the lesion, and change it every 12 h. The ulcer healed entirely within a week after therapy, proving that propolis with olive oil may cure DFU[129]. Abdoli *et al*[130] wanted to see how topical olive oil dressing combined with standard therapy compared to standard care alone for treating grade 1 and 2 DFUs in T2DM patients. The research study used 60 T2DM patients. For four weeks, the intervention group got standard treatment, including wound irrigation with normal saline, oral antibiotics, and daily topical olive oil dressing, whereas the control group received just standard care. At weeks one, two, three, and four, the olive oil group had significantly higher scores for ulcer degree, colour, drainage, and surrounding tissue healing than the control group. As a result, topical olive oil dressing aided in the healing of DFU. Nasiri *et al*[131] conducted a double-blind, randomized clinical trial on 34 patients with Wagner's ulcer DFU grade 1 or 2. The patients in the intervention group got topical olive oil in addition to routine treatment, whereas the patients in the control group only received normal care. At the conclusion of the fourth week, there were significant variations between the two groups in three ulcer parameters: Degree, colour, and surrounding tissues, as well as total ulcer status. When compared to the control group, olive oil dramatically reduced ulcer area and depth and completed higher ulcer healing at the end of the study. The findings showed that using olive oil in conjunction with routine care is more beneficial than using routine care alone to treat DFU.

### ***Plantago major***

According to academics, *Plantago major* (*P. major*) has been present for over 4000 years, especially in Europe, America, and Asia[132]. Based on phytochemical investigations, *P. major* contains volatile compounds, triterpenoids, phenolic acids, and flavonoids[132]. Traditional Persian medicine describes the benefits of *P. major* on wound healing, treatment of intestinal ulcers, hematemesis, upper and lower gastrointestinal bleeding, dyspepsia, hemorrhoids, stomachache, and dysentery[133]. A case study discovered that decoction of *P. major* alleviated patient symptoms within a few days of starting therapy, indicating the potential benefits of *P. major* for treating pancolitis[134]. Supplementation with two capsules of *P. major* seed (500 mg per capsule) decreased blood levels of alanine aminotransferase, aspartate aminotransferase, and triglyceride in non-alcoholic fatty liver disease patients in a clinical trial research[135]. A pilot study on wound healing in a rat model discovered that *P. major*'s leaf extract might accelerate wound healing[136]. The therapeutic benefits of *P. major* topical formulation on stage 1 pressure ulcers in 130 patients were studied. The study's findings revealed a substantial difference in damage resolution between the test and control groups. HPLC was used to standardize the topical formulation based on the amount of quercetin, one of the phytochemicals in *P. major* and no adverse effect was observed[137]. A research study evaluated the therapeutic impact of *P. major* extract with 1% sulfadiazine on the healing of second-degree burn wounds in a control group. The investigation and control groups received 10% *P. major* ointment and 1% silver sulfadiazine ointment, respectively. The average complete healing time in the *P. major* and control groups was 11.73 d and 13 d, respectively. The study discovered that *P. major* ointment is a safe and efficient herbal product for the treatment of second-degree burn wounds since it not only cures the lesion but also serves as an analgesic and antibacterial agent[138]. Ghanadian *et al*[125] conducted a clinical study where patients with DFU or pressure ulcers were randomly assigned to medication (*P. major*) or control groups. In the medicine treatment group, a 10% *Plantago* extract topical gel was used on the wound once daily for two weeks, whereas the control group utilized an acceptable fresh dressing. *Plantago* extract gel significantly decreased wound size when compared to the control. Furthermore, the treatment group had significantly more patients who healed completely than the control group. According to the findings of the study, using *P. major* topical gel expedited the healing of DFUs and pressure ulcers.

### ***Plectranthus amboinicus***

*Plectranthus amboinicus* (*P. amboinicus*) is a medicinal herb that has been used in traditional medicines for therapeutic purposes in the form of syrup[139]. It is mainly found on the Maluku Islands, close to Indonesia[140]. According to a phytochemical research investigation, *P. amboinicus* contains flavonoids such as apigenin, luteolin, and salvigenin[141]. Swamy *et al*[141] indicated that the therapeutic properties of this plant are due to the existence of secondary metabolites such as flavonoids, glycosides, phenols, tannins, and steroids. The capacity of *P. amboinicus* (Lour.) Spreng. to resist clinical isolates of MRSA was examined. Using broth microdilution and bioautography, the *in vitro* efficacy of the hydroalcoholic extract (HE), EA fraction, and its subfractions against MRSA clinical isolates were assessed. Bacterial suspensions were combined with Citodex and administered subcutaneously into male Swiss mice to stimulate abscess formation. Two doses of HE, the EA fraction, or vancomycin were delivered intraperitoneally to mice at 3 and 12 h after infection. The lowest minimum inhibitory concentrations (MIC, 0.25 to 0.5 mg/mL) were found in the EA fraction and its subfractions. The plant samples were tested bacteriostatic at 2 × and 4 × MIC and bactericidal at 100 mg/mL. The abscess volume, bacterial cell counts in abscess slurries, and inflammatory ratings decreased significantly in the HE and EA fraction-treated groups. The samples were effective in treating the animals in a dose-dependent manner, confirming the efficiency of *P. amboinicus* fractions against MRSA both *in vitro* and *in vivo*[142]. Kuo *et al* [84] examined and compared the effects of a topical cream comprising *P. amboinicus* (Lour.) Spreng. (Lamiaceae) and *C. asiatica* (L.) Urban (Umbelliferae) on DFUs in comparison to the effects of hydrocolloid fiber wound dressing. The study comprised of 24 type 1 or type 2 diabetes patients, aged 20 and above, with Wagner grade 3 foot ulcers following surgical debridement. Twelve patients were randomly assigned to receive WH-1 cream containing *P. amboinicus* and *C. asiatica* for two weeks, and another 12 patients were treated with hydrocolloid fiber dressings. Wagner grade improvement was noted in a relatively greater proportion of patients in the WH-1 cream group (10 of 12; 90.9%) than in the hydrocolloid fiber dressing group.

### ***Quercus infectoria***

*Quercus infectoria* (*Q. infectoria*) is a tiny tree or shrub endemic to Turkey, Greece, Iran, and Syria[143]. Pharmacological studies on *Q. infectoria* revealed that acetone-treated methanolic extract was an active analgesic and reduced blood sugar levels in rats, but chloroform-treated methanolic extract worked as a central nervous system (CNS) depressant and an efficient local anesthetic[144]. The presence of three compounds, syringic, gallic, and ellagic acids, as well as CNS activity, were reported in an alcoholic extract of *Q. infectoria* galls[145]. The alcoholic extract of *Q. infectoria* galls also demonstrated anti-inflammatory activity both *in vitro* and *in vivo*. In a research study, oral gall extract therapy inhibited carrageenan, histamine, serotonin, and prostaglandin E<sub>2</sub> (PGE<sub>2</sub>)-induced paw oedemas, whereas local application prevented phorbol myristate acetate (PMA)-induced ear irritation. *In vitro* exposure of rat peritoneal macrophages to gall extract increased lipopolysaccharide-stimulated PGE<sub>2</sub> and NO production as well as PMA-stimulated superoxide formation[146]. By determining the MIC and minimum bactericidal concentration values, the aqueous and acetone extracts of galls of *Q. infectoria* demonstrated to have antimicrobial activity against Gram-negative and Gram-positive bacterial species, indicating that the galls of *Q. infectoria* are a potentially good source of antimicrobial agents[147]. The effects of an ethanolic extract of shade-dried *Q. infectoria* leaves on wound healing in rats were studied using incision, excision, and dead-space wound models. The plant increased the levels of the antioxidant enzymes, superoxide dismutase and catalase, in the granuloma tissue, showing a clear, beneficial effect on wound healing[148]. A study was carried out to look at the use of *Q. infectoria* as a topical medicine for the treatment of chronic wounds. Twenty *Q. infectoria* formulations (QiFs) were created pharmaceutically and evaluated for antibacterial effectiveness. The wound-healing activities in streptozotocin-induced diabetic rats and control rats were investigated. When compared to citrate injection controls, streptozotocin administration (50 mg/kg) caused substantial hyperglycemia. Three days after wounding, QiF was applied topically to one of each animal's identical wounds, while physiological saline (control) was applied to the other. QiF10 exhibited antibacterial and antioxidant activities, which may aid in wound healing in diabetic mice[149]. An alcoholic extract of the plant *Q. infectoria* was studied for its antibacterial, cytotoxic, and antioxidant activities. A crude extract inhibited *C. albicans* growth the most, followed by *S. aureus* and *E. coli*. Treatment with alcoholic extract also inhibited cell growth of the human breast cancer MCF-7 cell line in a concentration-dependent manner. The findings indicate that the plant *Q. infectoria* is an excellent source of antiproliferative and cytotoxic chemicals. The DPPH experiment also revealed that the extract had higher antioxidant activity[150]. In one study, the wound-healing effectiveness of topical co-administration of hydroethanolic extracts of *Pistacia atlantica* (*P. atlantica*) hulls and *Q. infectoria* galls in streptozotocin-induced diabetic mice was assessed using an excision wound model. The diabetic mouse model was divided into four groups: Control (soft yellow paraffin), *P. atlantica* 5%, *Q. infectoria* 5%, and *Q. infectoria* 5% + *P. atlantica* 5% mixed soft yellow paraffin. On the back of each mouse, two circular, full-thickness skin incisions were made. According to the findings, topical treatment of each hydroethanolic extract of *P. atlantica* and *Quercus infectoria* extract alone or in combination improves the wound-healing activity in diabetic mice by decreasing inflammatory stages, edema, and immune cell migration scores and increasing new

vascular creation, fibroblast infiltration, collagen production scores, and GLUT-1- and GPC3-positive cells[151]. Chokpaisarn *et al*[152] assessed the clinical effectiveness of a pharmaceutically prepared *Q. infectoria* solution for the treatment of chronic diabetic ulcers in patients. The diabetic patients with ulcers (Wagner Ulcer Classification grade 1-3) were randomized to receive traditional wound treatment (normal saline solution) plus *Q. infectoria* solution or the standard solution alone for three months. At week 12, the decrease in wound size in the study and control groups were 91.51% and 76%, respectively, with the study group having more patients with complete wound closure than the control group. The solution of *Q. infectoria* has been clinically proven to have tremendous potential as an alternate therapy for DFUs.

### **Sesamum radiatum**

Despite being native to Africa, *Sesamum radiatum* (*S. radiatum*) is extensively dispersed throughout Asia's tropical and subtropical climates[153]. The nutritional properties of *S. radiatum* leaves revealed a significant amount of protein, high values of macronutrients and micronutrients, phenolic compounds, and a good antioxidant capacity<sup>[154]</sup>. During the phytochemical examination, quinones, tannins, alkaloids, sterols, terpenes, polyphenols, saponosides, and reducing compounds were detected in *S. radiatum* leaf extract[155]. *Sesamum* gum was discovered to include glucuronic acid, mannose, galactose, and xylose, as well as trace levels of glucose, rhamnose, and arabinose[156]. The essential oil isolated from the dried leaves of *S. radiatum* indicated that the predominant ingredient was n-hexadecanoic acid, followed by 9,12,15-octadecanoic acid-(Z,Z,Z), dodecanoic acid, and tetradecanoic acid. The findings suggest its usefulness for cardiovascular and estrogenic activity, male infertility, constipation, fungal and bacterial infections, and bruising[157]. Using the agar diffusion technique, ethanolic, methanolic, and aqueous extracts of *S. radiatum* leaves were tested for antibacterial activity against Gram-positive and Gram-negative bacteria and yeast. The presence of carboxylic acids and phenolic groups in essential oils, and antioxidants such as sesamol, sesamol, and sesamin, were shown by gas chromatography-mass spectrometry (GC-MS) phytochemical screening of methanolic extract. Both the methanolic and ethanolic extracts exhibit wide antibacterial activity against all the microorganisms supporting folkloric assertions of antibacterial efficacy[158]. Using the agar diffusion technique, ethanolic and aqueous extracts of *S. radiatum* leaves were tested for antibacterial activity *in vitro*. The phytochemical screening using GC-MS revealed the presence of essential oils, namely the phenolic and carboxylic acid groups. The ethanolic extract modestly inhibited *Streptococcus pneumoniae* and *C. albicans*, whereas *S. aureus*, *Pseudomonas aurogenosa*, and *E. coli* were not. The aqueous extract, on the other hand, had no inhibitory impact in any of the tested microorganisms[159]. Tripathy *et al*[160] studied the wound-healing potential of Nimbadi Kalka, an Ayurvedic paste in which *S. radiatum* is the primary major ingredient, on 15 DFU patients with baseline HbA1c levels. *S. radiatum* was administered daily to the wound site for 45 d, showing a significant decrease in wound size and exudates. In the case of granulation tissue, there was a peak rise on the 15<sup>th</sup> d of therapy, showing the creation of granulation tissue. As a result, Nimbadi Kalka enhanced wound healing by lowering ulcer size in DFU patients.

### **Teucrium polium**

*Teucrium polium* (*T. polium*) is a flowering plant native to Europe, North Africa, and Southwest Asia [161]. *T. polium* has been used to treat diabetes, rheumatologic diseases, inflammation, and gastrointestinal disorders[162,163]. *T. polium* L. methanolic extract (rutin and apigenin) was also discovered to have antioxidant effects[164]. *T. polium* extracts showed *in vitro* antibacterial activity against *Bacillus anthracis*, *Bordetella bronchiseptica*, and *Salmonella typhi*, indicating that it might be used as a source of antiseptic compounds for medicinal applications[165]. *T. polium* honey-treated animals improved wound contraction, closure time, and tensile strength, as well as epithelium proliferation, angiogenesis granulation, and fibrous connective tissue in an *in vivo* rat skin wound healing study[166]. A test was done on diabetic rats to see how well *T. polium* extract ointment treated wounds. 64 male Wistar rats were made diabetic by inducing alloxan and wounds made in their bodies for the experimental purpose. Eight groups of eight rats each were formed using the following treatments: Control, eucerin, phenytoin, 2%, 3%, 4%, 5%, and 10% *T. polium*. The ointment was administered to the wound twice daily. *T. polium* extract ointment with a 10% ointment accelerates wound healing in diabetic rats and is equivalent to the phenytoin group, according to the wound healing process of *T. polium* ointments with base ointment (eucerin) and phenytoin ointment[167]. A study looked at the effect of the co-administration of ointments produced from *T. polium* hydroethanolic extract (TPEO) and *Aloe vera* gel (AVGO) on excisional wound healing in a diabetic mice model. The mice were divided into six groups after diabetes induction and a circular excisional wound: Control mice given mupirocin (a traditional drug), mice given 5 and 10% TPEO, mice given 5 and 10% AVGO, and mice given a combination of 5% TPEO and 5% AVGO (TPEO + AVGO). The results showed that using the ointments, especially in combination, shortened the inflammatory phase and reduced tissue MDA, TNF- $\alpha$ , and IL-1 levels compared to the mupirocin group[168]. Fallah Huseini *et al*[169] performed an experiment with 70 diabetic patients with foot ulcers, scoring 1 or 2 on the Wagner's scale to investigate the safety and efficacy of topical *T. polium* ointment in addition to conventional care. The patients were randomly divided into two groups and both groups of patients got normal therapy for DFUs. Furthermore, for four weeks, group one received topical *T. polium* ointment, whereas group two received topical placebo

ointment. The result showed reduced mean ulcer surface area in the *T. polium* group compared to the placebo group, and the *T. polium* group had a higher percentage of patients who healed completely at the end of the study. The inclusion of *T. polium* ointment in normal therapy sped up the healing period of diabetic non-infected foot ulcers.

### ***Tinospora cordifolia***

*Tinospora cordifolia* (*T. cordifolia*), often known as Gulbel or Indian Tinospora in English and Guduchi in Sanskrit, is an Indian plant[170]. The leaf extract has been proven to be effective against infections caused by *E. coli*, *S. aureus*, *S. pyrogens*, *B. subtilis* and *P. vulgaris*, as well as helping in cell repair and rejuvenation[171]. Plant phytochemicals such as alkaloids, terpenoids, lignans, and steroids contributed to the pharmacological activities; also, its chloroform fraction contains pharmacologically active substances like rutin and quercetin, which have anticancer activity in MDA-MB-231 and MCF 7 breast cancer cells[172,173]. *In vitro* and *in vivo* studies demonstrated that the alkaloid present in *T. cordifolia* contributes to the antihyperglycemic effect *via* insulin-releasing and insulin-mimicking pathways, hence reducing postprandial hyperglycemia[174]. The excision wounds, resutured incision wounds, and dead space wounds were inflicted on male Wistar rats ( $n = 6$ , in each group) under mild thiopentone anesthesia to investigate the effect of *T. cordifolia* on wound healing. Planimetry was used to investigate the effects of a 250 mg/kg methanol extract of *T. cordifolia* stem delivered orally once a day for 10 d in the resutured incision, dead space, and excision wounds. In all three models, *T. cordifolia* promotes wound healing, including increased wound contraction and shorter days for complete epithelization in excision wounds, increased breaking strength in resutured incision wounds, and increased granuloma dry weight and cellular infiltration in granulation tissue[175]. Purandare and Supe[176] conducted a double-blind, randomized, controlled research on 50 patients to evaluate the role of *T. cordifolia* as an adjuvant for the treatment of DFU. The mean ulcer size, depth, and perimeter were assessed, and swabs were collected for culture. Blood was drawn to determine the percentage of polymorphonuclear phagocytosis. Medical therapy, glycemic management, wound care, and debridement were all optimized. Net improvement was reported in 17 patients in the trial group and 13 patients in the control group. Thus, diabetic patients with foot ulcers who received *T. cordifolia* as adjuvant treatment had a considerably superior end result, with enhanced wound healing, decreased debridements and increased phagocytosis.

### ***Vasconcellea cundinamarzensis***

*Vasconcellea cundinamarzensis* native to tropical America[177]. The *in vivo* investigation revealed that the proteolytic fraction (P1G10) is composed of 14 proteolytic isoforms that protect and repair the stomach by raising mucus content, lowering gastrin levels to avoid hyperacidity, improving excisional wound healing, and boosting PGE2 production[178]. P1G10 was investigated as a natural antifungal and shown to be capable of inhibiting mycelium development and cell adhesion in *B. cinerea* by inducing membrane integrity and cell wall degradation[179]. In a cutaneous wound excision model, P1G10 treatment accelerated the onset of the early inflammatory phase and reduced the negative effects generated by residual TGF- or MMPs, therefore enhancing scar quality[180]. The corneal healing capability of P1G10 was investigated using an ethanol-chemical burn in rabbit eyes. Except when administered at 10 g/mL, P1G10 is safe for ocular administration. P1G10 at 1 g/mL stimulates corneal re-epithelization, resulting in full wound healing 72 h after the chemical burn. P1G10 also influenced the arrangement of collagen fibers in the stroma and modulated the inflammatory response, indicating its potential corneal healing characteristics[181]. Tonaco *et al*[182] engaged 50 patients in a prospective, randomized, double-blind study to assess the efficacy and safety of a wound healing topical dressing containing 0.1% P1G10 to a hydrogel (control) regimen. The results showed that 5 patients in the control group had 100% ulcer healing, 3 had  $\geq 80\%$  healing, 11 had  $\leq 80\%$  ulcer changes, and the remainder had no changes or their wounds became worse. Meanwhile, 11 patients in the P1G10 group had complete healing, 4 had  $\geq 80\%$  healing, 5 had ulcer alterations of less than 80%, and the remainder had no changes or their wounds deteriorated. Thus, the P1G10 group outperformed the control group in wound healing.

### ***Vernonia amygdalina***

*Vernonia amygdalina* (*V. amygdalina*) sometimes known as the bitter leaf, is found across tropical Africa [183]. Traditional healers utilize the plant as an antihelminth, antimalarial, laxative, digestive tonic, appetizer, febrifuge, and for wound healing[184]. According to phytochemical research, this plant is high in proteins, lipids, fibers, amino acids, minerals, vitamins and carbohydrates[185]. In an *in vitro* study, the methanol extract of *V. amygdalina* leaves was shown to be effective against bacterial isolates [186]. An *in-vivo* testing of extracts from the leaves and root bark of *V. amygdalina* for antimalarial efficacy against drug-sensitive *Plasmodium berghei* in mice resulted in a reduction of parasitaemia[187]. The antibacterial and antifungal activity of vernolide and vernodalol, two known sesquiterpene lactones produced from *Vernonia amygdalina* leaves, was investigated. Both are bactericidal to Gram-positive bacteria and fungal species supporting the ethnomedical uses in the treatment of infectious diseases [188]. *V. amygdalina* leaves juice improved cutaneous wound healing in rats. Compared to the negative

control, there was an increase in fibroblast recruitment, epithelial cell migration, neovascularization, and a decrease in polymorphonuclear leukocyte infiltration[189]. The impact of a cod liver oil (CLO)-enriched *V. amygdalina* leaf-based diet (CLVA) on wound healing in type 2 diabetic rats was studied. Thirty-six albino rats were divided into six groups at random: Control (C), diabetic untreated control (DC), reference drug control (RD), 10% CLVA, 20% CLVA, and 30% CLVA. Except for C, all groups were diabetic rats with wounds, while C group comprised of ND rats with wounds. The diets of groups C, DC, and RD were devoid of CLO and *V. amygdalina* leaves. The final three groups were provided 10, 20, and 30% *V. amygdalina* leaves and CLO in their diet. When compared to DC, the wound contraction rate rose considerably, with wound area pictures suggesting progressive wound closure in CLVA-fed animals[190]. Bolajoko[26] examined the effects of freeze-dried *V. amygdalina* leaves on glycemic indices and oxidative stress indicators in type 2 diabetics with or without chronic foot/leg ulcers to NDs with or without chronic foot/leg ulcers. All participants were given conventional treatment (metformin, glibenclamide, or insulin alone, or metformin with glibenclamide or metformin with insulin). One hundred and twenty people were recruited and divided into four groups. Each group was separated into three subgroups: Subgroup-1 (250 mg *V. amygdalina*), subgroup-2 (500 mg *V. amygdalina*), and subgroup-3 (500 mg *V. amygdalina*) (no supplementation). Decrease in fasting plasma glucose and HbA1c, TPP and OSI, as well as substantial increase in TAS, vitamin A, vitamin C, and vitamin E were seen in the subgroups with herbal supplements. Increases in formamidopyrimidine DNA glycosylase, HbA1c, and exacerbation of wounds, TPP, OSI, reductions in TAS and antioxidant micronutrients were identified in no supplementation subgroups.

### Limitations and future perspectives

The absence of blood glucose monitoring during therapy is the first possible constraint. Except for three research, none of the others mentioned managing blood glucose levels. The second identified barrier is a scarcity of clinical case records. The remaining plant species, with the exception of five, have only undergone one clinical study. It would be difficult to extrapolate the statistical outcomes of one therapy study to a larger cohort. None of the experiments dealing with the oral administration of the medicinal plants on DFU could shed light on the influence of herbal medication on circulatory, cardiovascular or neurological activities. Aspects to consider in the future is the monitoring of blood glucose levels for each plant species. Conducting clinical cases with more patients for each species to improve research accuracy.

## CONCLUSION

Twenty different medicinal plants were tested in clinical research for their capacity to treat DFUs by fostering wound healing. All 19 plant species, except one, have led to wound healing. Ten plant species demonstrated total wound healing, while the others demonstrated significant healing. These plant species have a great potential for skin lesion healing, with substantial changes compared to various controls. With significant differences compared to controls, these plant species have a high potential for healing skin lesions. According to this review, the medicinal plants that were investigated and their derivatives can be used to create effective oral and topically applied treatments for DFUs with dermatological effects, providing dermatologists with a new tool in their toolbox.

## ARTICLE HIGHLIGHTS

### Research background

Diabetes has been a major health issue for centuries. Though the basic understanding regarding the incidence of diabetes is still at a rudimentary level, it is associated with a number of factors, which, if not monitored, may lead to severe consequences. Diabetic foot ulcer (DFU) is one of the most significant complications faced by diabetic patients worldwide. Poor glycemic management, repetitive trauma, underlying neuropathy, peripheral vascular disease, and poor foot care are the major causes leading to DFU.

### Research motivation

Currently, a number of drugs (like insulin, sulphonylureas, biguanides, *etc.*) are used as antihyperglycemic medications to regulate blood glucose levels. Although synthetic oral antihyperglycemic drugs are effective, they are still accompanied by undesirable side effects; so, in recent years, interest has gradually shifted towards herbal medications. Since time immemorial, plants and plant-derived products have been used to prevent or treat a host of illnesses, including diabetes, and thus could be of potential benefit for DFU therapy.

### Research objectives

This systematic review aims to summarize the therapeutic cases addressing the use of botanicals for treating DFU.

### Research methods

The original articles on “the plants for the treatment of DFU” studied in clinical cases only were obtained from various bibliographic databases like PubMed, Scopus, and Google Scholar using different keywords.

### Research results

A total of 19 clinical cases were recorded employing the use of 20 medicinal plants belonging to 17 families on 1347 subjects. The fruits and leaves were the most preferred plant parts used to treat DFU, regardless of their oral or topical routes of administration.

### Research conclusions

Of the 20 different medicinal plants, 19 plant species showed potential benefits toward wound healing. Fifty percent of the plant species demonstrated total wound healing, while the others demonstrated significant partial healing. The enlisted medicinal plants can be used to create effective oral and topically applied treatments for DFU.

### Research perspectives

The effect of these plants on the sugar levels might be studied along with DFU treatment. The effect of these plants on the circulatory, cardiovascular and neurological systems can also be studied in the future to understand their mechanisms of action and develop effective treatments for DFU.

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## FOOTNOTES

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