

UNVEILING THE WOUND HEALING POTENTIAL OF FABACEAE PLANTS IN
DIABETIC FOOT ULCER TREATMENTDeepak Muthu S.¹, Ayesha Lubaba M.¹, Nivedha V.¹, Nithyapriya R.², Sathiyabalan G.^{1*} and
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625020, Tamilnadu, India.**ABSTRACT**

Diabetic foot ulcers (DFUs) are a common complication of diabetes, leading to significant morbidity, mortality, and healthcare costs. Traditional medicine has utilized plants from the Fabaceae family to treat various ailments, including wounds and ulcers. This review aims to summarize the current evidence on the use of Fabaceae family plants in treating DFUs. A comprehensive literature search identified several Fabaceae plants with promising wound healing properties including *Melilotus officinalis*, *Buteo monosperma*, *Prosopis farcta*, *Tephrosia purpurea*, *Astragalus propinquus*, *Cassia auriculata*, *Acacia catechu*, *Cicer arietinum*, *Vigna unguiculata*, *Phaseolus vulgaris*, *Prosopis africana* and *Senna occidentali*. These plants possess bioactive compounds with antimicrobial, anti-inflammatory and antioxidant properties, which may aid in wound healing and tissue repair. While the available evidence is promising, further clinical trials are necessary to fully elucidate the efficacy and safety of these plants in treating DFUs. This review highlights the potential of Fabaceae family plants as adjunct therapy for managing DFUs and emphasizes the need for continued research in this area.

KEYWORDS: Diabetic foot ulcers, Fabaceae, Traditional medicine, Antioxidant and Wound healing.**INTRODUCTION**

Diabetic Foot Ulcer (DFU) is a serious and devastating result of unmanaged and extended diabetes, typically appearing on bottom of the foot.^[1] It may result in diminished quality of life and high medical expenses for those affected.^[2] About 18.6 million people around the globe deal with diabetic foot ulcer.^[3] Approximately, 25% of individuals with diabetes in India are expected to develop diabetic foot ulcer. This may worsen due to insufficient general awareness, inadequate medical infrastructure and economic constraints.^[4] The process of abnormal foot ulcer in diabetic patient is characterized by several factors, including chronic inflammation, impaired angiogenesis, abnormal proliferation and migration of keratinocytes and extra cellular matrix remodeling. Furthermore, diabetic patients frequently experience foot ulcers that are linked to bacterial infections.^[5]

Fabaceae are among the largest families of flowering plants, containing more than 727 genera. Fabaceae is also known as Leguminosae. Fabaceae plants produce a wide variety of natural substances including flavors, toxins, dyes and they play an essential role in medicine.^[6] *Acacia catechu*, *Bauhinia variegata*, *Cassia*

fistula, *Erythrina suberosa*, *Lathyras aphaia*, *Medica polymorpha*, *Mimosa pudica*, *Saraca indica*, *Tamarindus indica* are the some reported medicinal plants belonging to Fabaceae.^[7] Fabaceae family plants contain phytoconstituents such as polyphenols, flavonoids, tannins, terpenes, alkaloids, steroids and carbohydrates. Due to these bioactive compounds, Fabaceae plants exhibit diverse pharmacological activities such as estrogenic, antibacterial, antioxidant, antifungal, ulcer protective, anti-inflammatory, sedative, neuroprotective and digestive properties.^[8,9] The Fabaceae family includes some of the most thoroughly researched medicinal plants, with numerous scientific publications addressing their applications in treating diabetic foot ulcer. Consequently, this review intends to deliver an updated overview of some species belonging to Fabaceae, concentrating on the active constituents extracted from the plants used in the treatment of diabetic foot ulcer.

Botanical characterization of fabaceae species

Fabaceae is the third largest family of flowering plants, characterized by significant diversity.^[10] It includes woody plants, shrubs and flowering perennials or annuals, which might be easily recognized by their

legume shape and unique leaves.^[11] Fabaceae family contains 727 genera and 19,373 species. It classified into six subfamilies Caesalpinioideae, Dialioideae, Detarioideae, Cercidoideae, Duparquetioideae, and Papilionoideae.^[12,13]

Table1: Taxonomy of Fabaceae.

TAXONOMICAL CLASSIFICATION	
Kingdom	Plantae
Subkingdom	Tracheobionta
Superdivision	Spermatophyta
Division	Magnoliophyta
Class	Magnoliopsida
Subclass	Rosidae
Order	Fabales
Family	Fabaceae

Phytochemistry of fabaceae

The Fabaceae family is rich in phytochemicals, which contribute to its medicinal, nutritional and pharmacological properties. It is a major source of compounds such as flavonoids, lectins, saponin, alkaloids, carotenoids and phenolic acids which are responsible for treating diabetic foot ulcer.^[14] Phytoconstituents such as 3-nitropropanoic acid, gallic acid, protocatechuic acid, caffeic acid, coumaric acid, ferulic acid, rutin, rosmarinic acid, resveratrol, quercetin, kaempferol, epicatechin and polyphenols are present in the plants of Fabaceae family.^[15] Species within the fabaceae family primarily synthesize secondary metabolites, including flavonoids, isoflavones and saponins. These substance play a crucial role in protecting the plants from herbivores, pathogens and they also have potential health benefits for human through their antioxidant and antimicrobial effects.^[16] The hydroalcoholic extracts of *Melilotous officinalis*, *Coronilla varia*, *Ononis spinosa* and *Robino pseudoacacia* which belongs to the Fabaceae family contain tannins and flavonoids that exhibit antimicrobial effects against the bacterial strains.^[17] Aqueous and ethanolic extracts derived from *Acacia nilotica*, *Bauhinia reticulata* and *Tamarindus indica* have been traditionally utilized in Northern Cameroon for the treatment of cancer.^[18] The buds and fruits of *Saphora japonica*, commonly cultivated in China produce flavones that serves as hemostatic agents in Traditional Chinese Medicine. The seeds of this species are composed of various phytoconstituents such as triterpenes, phospholipids, alkaloids, amino acids, polysaccharides and fatty acids. Pharmacological and clinical studies have demonstrated its antitumor and antifertility properties.^[19] The Fabaceae family includes genera such as *Indigofera*, *Senna*, *Albiza*, *Rhynchosia*, and *Vachellia* which are recognized for their significant medicinal properties. The species belonging to these genera are utilized in traditional medicine to treat 134 medical complications, primarily focusing on gastrointestinal ailments, female reproductive issues and respiratory infections due to presence of terpenes, tannins, saponins, phenolic compounds and alkaloids.^[20]

Research outcome: phytochemical and pharmacological analysis of fabaceae family plants for diabetic foot ulcer management

Melilotus officinalis

Melilotus officinalis Linn. classified under the family Fabaceae, is widely known as yellow sweet clover. This biennial herb grows up to 1 meter height and is characterized by trifoliate leaves with obviate leaflets and are oblong in shape. The flowers are arranged in loose racemes. The pods are ovoid. The seeds are oval measuring 2-3mm diameter and characterized by a yellowish green colour.^[21] This species originates from Europe & Asia.^[22]

The preliminary phytochemical analysis of the *M.officinalis* revealed the presence of various constituents such as coumarone, melilotin, phenolic acids, flavonoids, steroids, saponin, volatile oils, fat, triterpenes, carbohydrates, sugars, anthroquinone glycosides, mucilage, tannins, bishydroxy coumarin, choline, alcohols and uric acids.^[23] As a result of the of these compounds *M.officinalis* shows anti-inflammatory, swelling and antitumor properties.^[24]

A newly introduced treatment for diabetic foot ulcer involves the oral and topical use of natural extract derived from *M.officinalis*. Clinical trials have evaluated Semelil, a formulation containing coumarin and flavonoids, administered through intravenous and oral route, as well as applied topically as a gel, highlighting its potential as a novel therapeutic approach for diabetic foot ulcer. In phase I-II clinical trials involving nine patients with diabetic foot ulcer, Semelil was administered in doses ranging from 2ml to 13.5ml daily over a period of 28 days. The primary objective of the study was to determine the optimal intravenous dosage of semelil for treating diabetic foot ulcer while assessing the safety parameters. Laboratory assessment, including complete blood count, creatinine levels and liver function test were conducted at baseline, after two weeks, after four weeks of treatment initiation and at the end of four weeks, dose escalation has been performed. Other patient group received intravenous semelil at doses of 4, 6, 7, 10 & 13.5ml respectively. Treatment continued for 28 days in the absence of toxic effects, while it was discontinued for patients who experienced worsening ulceration or adverse drug reaction. If a patient exhibited dose-limiting toxicity at a specific dose level, dose elevation was stopped and the next lower dose was established as the maximum tolerated dose. A reduction of one dose level was considered for patients who experienced dose –limiting toxicity. Patients were monitored for an additional four weeks. The maximum tolerated dose was identified as 10ml/day, with local phlebitis being the dose-limiting toxicity observed. The study reported a significant reduction in ulcer area with doses up to 10ml Semelil.^[25]

Buteo monosperma

Buteo monosperma belongs to the Papilionoideae – Fabaceae family.^[26] It is otherwise known as the flame of the forest.^[27] It is a small to deciduous tree, leaves are trifoliolate, flowers in racemes, seeds are broad leafed and flattened about 3cm long.^[28] The leaves are thought to possess astringent and diuretic properties. They also are known to enhance diuresis and stimulate menstrual flow. The seeds exhibit anthelmintic effects and when mixed with lemon juice and applied to the skin, they function as rubefacient.^[29] The various parts of the contain triterpenes, glycosides, tannins, enzymes, esters, polyphenols, fatty acids, amino acids and steroids.^[30] *B. monosperma* significant shows anti-diabetic, anti-conceptive, anti-diarrheal, anti-convulsive, anti-inflammatory, antifertility, anti-estrogenic, anti-bacterial and antifungal activity.^[31] A study was conducted in diabetic animal model to assess the wound healing potential of the methanolic extract from the flowers of the *B.monosperma* Linn. The extract was prepared by continuous hot percolation method using Soxhlet apparatus. Preliminary phytochemicals screening indicated the presence of flavonoids, phenolic compounds and glycosides. Diabetes was induced in wistar albino rats by administration of single dose of alloxan monohydrate, followed by the measurement of their blood glucose level. An excision wound model was utilized to create wounds in diabetic animals, and the methanolic extract was administered to observe the effects. The results indicated that the methanolic extract significantly reduced blood glucose levels and improve the wound contraction among the diabetic animals. This wound healing effect of *B.monosperma* may be attributed to the presence of flavonoids in the plant.^[32]

Prosopis farcta

Prosopis farcta belonging to Fabaceae is commonly known as Syrian mesquite. This plant is characterized as a woody, perennial dwarf shrub, typically ranging from 0.4 to 1 meter in height. The leaves are bipinnately compound and herbaceous featuring 9 to 13 leaflets. Its shrub produces one or two fruiting spikes, containing numerous ovate seeds.^[33] *P.farcta* is a significant source of medicinal plants rich in phytochemicals. It contains a variety of compounds such as alkaloids, phenolic acids, flavonoids, glycosides, steroids, tannins & triterpenoids which are increasingly recognized for their therapeutic effects.^[34] This plant is rich in flavonoids and it may be effective against viruses & cancer. The fruit extract contains corsetine, quercetin which is used for the treatment of viral infection, heart and blood vessels problems in traditional medicine.^[35] Aqueous extract of *P.farcta* fruits which contain high concentration of phenols & flavonoids which is directly responsible for managing diabetic foot ulcer.^[36] The effect of the aqueous extract derived from the roots of *P.farcta* was evaluated for the diabetic wound healing property in diabetes rats. Total 18 male wistar rats were randomly assigned to three equal groups: a normal control group, a diabetic group, and an experimental group receiving

treatment with the root extract. Diabetes was induced through intraperitoneal injection of Streptozocin. Subsequently, three holes, each measuring 4mm in diameters, were created in the lateral posterior regions of all animal groups. For a duration of two days, the experimental group received local treatment with aqueous extract of *P.farcta* root three times daily, while the control group were treated with normal saline in the same manner. On the 4th, 8th and 10th days post-punching, samples were collected from the healing sites, which had expanded to 6mm in diameter. Histological analysis indicated the presence of inflammatory cells, re-epithelization and neovascularization in the affected areas. Significant changes in proliferation of inflammatory cells (on the 10day), epithelial thickness (on the 4th and 8th days), an increased angiogenesis (from the 4th to 10th day) in the experimental wounds compared to the diabetic group (P<0.001, P<0.01 respectively). The above results suggest that the extract of *P.farcta* root plays a significant role in foot ulcers in diabetic rats, likely due to its anti-inflammatory, re-epithelization and neovascularization properties.^[37]

Tephrosia purpurea

T.purpurea, commonly known as Sarpunkha, belongs to the Fabaceae family, and is classified under the subfamily Papilionaceae. The genus *Tephrosia* includes around 300 to 400 species of woody herbs, both annual and perennial, that are distributed throughout tropical and subtropical regions worldwide.^[38]

Methylene chloride extracts of the *T.purpurea* were successfully isolated and structurally characterized, including compounds such as aromatic esters, sesquiterpene and prenylated flavonoids.^[39] Numerous studies on *T.purpurea* have indicated the presence of flavones, flavanones, chalcones, prenylated flavonoids and rotenoids.^[40] The therapeutic properties attributed to their phytoconstituents includes anticancer, antipyretic, antidiabetic, anti-inflammatory, antioxidant and antimicrobial activities.^[41] The wound healing activity of hydroalcoholic extract of *T.purpurea* was investigated in diabetic rats induced by Streptozotocin, using excision and dead space wound models. The application of 5% w/w *T. purpurea* extract ointment twice daily resulted in a significantly greater (P<0.001) rate of wound contraction in both normal & diabetic subjects compared to the control group. Additionally, oral administration of 200mg/kg body weight per day notably enhanced the weight of both wet & dry granulation tissue in comparison to the control. So, this research significantly shows the potential effect of *T. purpurea* against diabetic foot ulcer.^[42]

Astragalus propinquus

A.propinquus commonly referred to as Mongolian milk vetch, is a flowering plant recognized for its numerous potential pharmacological benefits. This plant is rich in various chemical constituents including flavonoids, saponins and polysaccharides.^[43] The pharmacological

effects of *A.propinquus* are diverse, which includes the enhancement of immune function, anti-aging effects, antitumor properties, lowering blood glucose level, anti-fibrosis, antibacterial and antiviral effects.^[44] *A.propinquus* and *Radix rehmannie* is the Traditional Chinese Medicine (TCM) for treating diabetic foot ulcer. A 2:1 ratio of the two herb formula (NF3) has been studied *in-vitro* for its effects on fibroblast proliferation. HS-27 fibroblasts were cultured in 96-well and subjected to different concentration of NF3, following this, MTT solution was introduced and the plates were incubated at 37°C for a duration of 4 hours. The optical density was measured at 540nm. The proliferation of fibroblast is essential for effective wound healing and tissue regeneration. The results demonstrated that the treatment with NF3 resulted in a significant enhancement of viability in HS-27 fibroblasts at concentration of 625, 1250 & 2500µg/ml (P<0.01-0.001), achieving proliferation rates of 122.7%, 130% and 125.3% respectively.^[45]

Cassia auriculata

C.auriculata Linn, belonging to the Caesapiniace – Fabaceae family is commonly referred to as Tanner’s senna and is found across the warm deciduous forests of India. It is esteemed for its importance in the Ayurvedic and Siddha systems of medicine.^[46] This plant contains polysaccharides, flavonoids, anthracene derivatives and dimeric procyanidins, quercetin, hesperidin, phenolic acids, theobromine, theophylline, steroids, fatty acids and tannins, which are present in the various parts such as leaves, flowers, stem and bark.^[47] Systematic documentation demonstrated that this plant possess the anti-inflammatory, antioxidant, hypoglycemic,

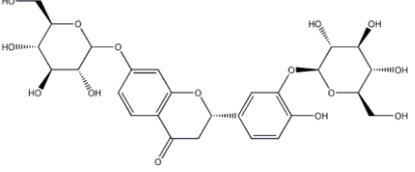
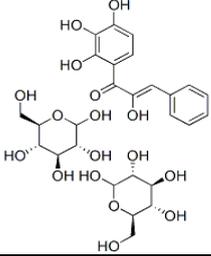
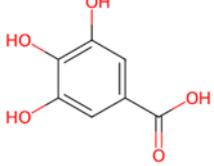
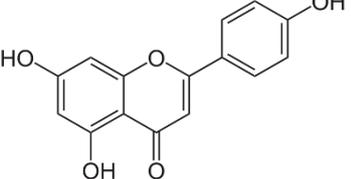
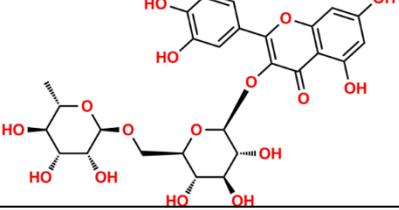
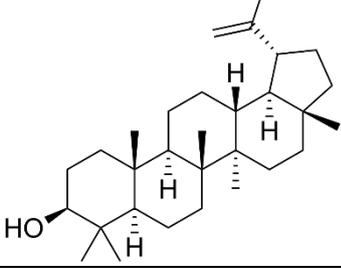
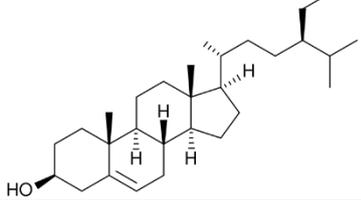
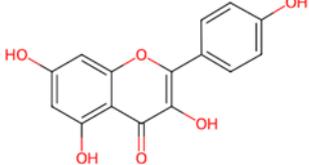
anthelmintic and antibacterial activities.^[48] This plant widely is used for the management of diabetes. Traditionally, it used for the treatment of ulceration. Further studies are needed to confirm its effectiveness in treating diabetic foot ulcers.^[49]

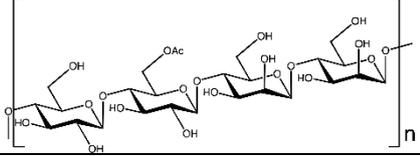
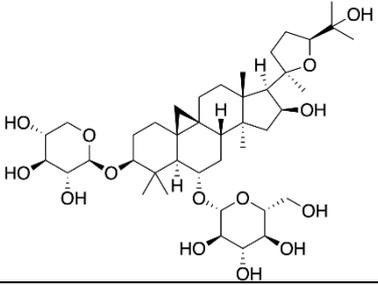
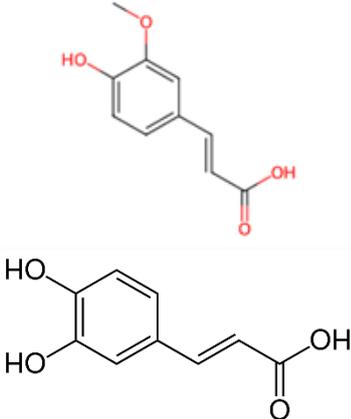
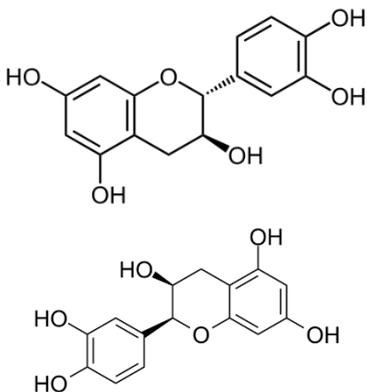
Acacia catechu

A.catechu belonging to the Mimosoideae - Fabaceae family, is prevalent throughout the forests in India. It is most commonly found in the sub-himalayan region, from Punjab to Assam at elevations of up to 1200 meters. These species are commonly found in the drier regions of Madhya Pradesh, Maharashtra, Gujarat, Bihar, Rajasthan, Tamilnadu and along the eastern slopes of the western ghats.^[50] The primary phytochemicals found in *A.catechu* includes protocatechuic acid, taxifolin, epicatechin, epigallocatechin, aldobiuronic acid, gallic acid, D-galactose, L-arabinose, D-rhamnose and quercetin. *A.catechu* serves as an important source of bioactive compounds, which are applicable in biological and pharmaceutical applications, including antidiabetic, antioxidant, antimicrobial, anticancer, antidiarrheal, anti-inflammatory, antiviral, hepatoprotective and immunomodulatory properties. (-) epicatechin is the major constituent of the *A.catechu*. the ethanolic extract of *A.catechu* was analyzed by HPLC, which revealed the presence of (-) epicatechin. The results of the molecular docking studies have confirmed that (-)epicatechin plays a crucial role in stabilizing human inducible nitric oxide synthase by interacting with the inhibitor, exhibiting a binding energy of -8.31kcal/mol. This investigation highlights (-) epicatechin as a primary active constituent in the diabetic wound healing efficacy of *A.catechu*.^[51]

Table 2: Phytoconstituents of Medicinal plants.

PLANT	PHYTOCHEMICALS	STRUCTURE
<i>Melilotus officinalis</i>	Polyphenol	
	Coumarin	
	Flavonoid	
	Quercetin	
	Luteolin	

<i>Butea monosperma</i>	Flavonoids Butrin	
	Isobutrin	
<i>Prosopis farcta</i>	Phenolic acid a) Gallic acid	
	Flavonoid Apigenin	
<i>Tephrosia purpurea</i>	Flavonoid a) Rutin	
	Triterpenoid Lupeol	
	Sterol β - sitosterol	
<i>Astragalus propinquus</i>	Flavonoid Kaempferol	

	<p>Polysaccharide</p> <p>Astragalus polysaccharide</p>	
	<p>Saponin</p> <p>Astragalosides</p>	
<i>Cassia auriculata</i>	<p>Phenolic acids</p> <p>Ferulic acid</p> <p>Caffeic acid</p>	
<i>Acacia catechu</i>	<p>Flavonoid</p> <p>Catechin</p> <p>Epicatechin</p>	

Some other fabaceae species for DFU

- ***Cicer arietinum* (Chickpea):** The extracts exhibit antioxidant, anti-inflammatory and antimicrobial properties, which can aid in diabetic wound healing.
- ***Vigna unguiculata* (Cowpea):** The extracts demonstrated antioxidant and anti-inflammatory activities, which help in managing diabetic foot ulcer.
- ***Phaseolus vulgaris* (Common bean):** The extracts shown to have antioxidant and anti-inflammatory properties, which can aid in wound healing and tissue repair.
- ***Prosopis africana* (African mesquite):** The tree's extract has shown to promote wound healing in diabetic rats by enhancing collagen synthesis and improving tissue strength.
- ***Senna occidentalis* (Coffee senna):** The extracts exhibit anti-inflammatory, which may help with wound healing and pain management.^[52]

CONCLUSION

Diabetic foot ulcers pose a significant burden on healthcare systems worldwide, necessitating effective and alternative treatment strategies. Fabaceae plant species have been traditionally used and scientifically explored for their potential in treating diabetic foot ulcers. This review highlights the medicinal properties of various Fabaceae plants, such as *Melilotus officinalis*, *Buteo monosperma*, *Prosopis farcta*, *Tephrosia purpurea*, *Astragalus propinquus*, *Cassia auriculata*, *Acacia catechu*, *Cicer arietinum*, *Vigna unguiculata*, *Phaseolus vulgaris*, *Prosopis Africana*, *Senna*

occidentalis. The bioactive compounds present in these plants such as flavonoids, alkaloids, and glycosides exhibit antioxidant, anti-inflammatory, antimicrobial, and wound-healing properties. These findings suggest that Fabaceae plant species may be a valuable adjunct or alternative therapy for managing diabetic foot ulcers. However, further rigorous clinical trials are necessary to fully elucidate the efficacy and safety of these plants for this indication. Moreover, standardized extraction and formulation methods are required to ensure consistency and quality of these plant-based treatments. By exploring the therapeutic potential of Fabaceae plant species, we may uncover novel and effective solutions for the prevention and treatment of diabetic foot ulcers.

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