



Plant Based Therapeutics in Diabetic Foot Ulcer: Evidence Based Insights on Grape Seed and Lotus Seed Extracts

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Abstract

AIM: The purpose of the study was to examine the potential therapeutic benefits of extracts from *Vitis vinifera* (grape seed) and *Nelumbo nucifera* (lotus seed) in the management of diabetic foot ulcers (DFU) by utilizing its anti-inflammatory, antioxidant, and wound-healing qualities. **METHOD:** A comprehensive literature search was conducted using PubMed, Google Scholar, Cochrane Library, and other relevant medical databases to gather studies related to diabetic foot ulcers, *Vitis vinifera*, and *Nelumbo nucifera*. Prior to screening, 400 duplicate entries were eliminated from the initial 700 records. The remaining papers were screened for titles and abstracts before 200 articles were evaluated for full-text eligibility using predetermined inclusion and exclusion criteria. After, a detailed evaluation of methodology, study outcomes, and relevance to the research objectives, 30 studies were found suitable and were included in the final review. **RESULT AND DISCUSSION:** The pharmacological potential of lotus and grape seed extracts in wound healing was significant. With minimal adverse effects, grape seed extract, which is high in proanthocyanidins, demonstrated improved healing via modulating TGF- β 1, IL-10, and TNF- α . Neferine alkaloid, which is found in lotus seed extract, inhibited oxidative stress and inflammatory mediators to enhance wound contraction and epithelialization. Their combined function in enhancing tissue regeneration and regulating inflammatory pathways such as NF- κ B and Nrf2 is supported by literature. The herbal ointment's non-irritating qualities, spreadability, and stability were all deemed satisfactory. **CONCLUSION:** A safe and efficient natural option for the treatment of diabetic foot ulcers is provided by the combination formulation of extracts from *Vitis vinifera* and *Nelumbo nucifera*. Neferine and proanthocyanidins, two of their bioactive substances, improve healing by encouraging tissue repair, lowering inflammation, and offering antioxidant protection. To maximize dosage, formulation, and synergistic efficacy, more clinical and mechanistic research is advised.

Keywords

Diabetic foot ulcers, *Vitis vinifera*, *Nelumbo nucifera*, Proanthocyanidins, Neferine

INTRODUCTION

Diabetes mellitus (DM) is commonest endocrine disorder. It is caused by deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood. It is found to damage many of body systems particularly blood vessels, eyes, kidney, heart and nerves ^[1]. According to epidemiological studies, the number of patients with DM increased

from about 30 million cases in 1985, 177 million in 2000, 285 million in 2010, and estimated if the situation continues, more than 360 million people by 2030 will have DM ^[2].

Diabetic foot ulcers are chronic wounds that are difficult to heal, with a high rate of recurrent hospitalizations ^[3]. A diabetic foot ulcer is the general term to describe a full-thickness wound below the ankle in a patient with diabetes ^[4]. People with

diabetes have a 12– 25% lifetime risk of developing a foot ulcer ^[5]. Worldwide, approximately 18.6 million people with diabetes develop a foot ulcer each year ^[6].

The six grade Wagner-Meggitt classification, which has been used for decades, classifies wounds by the depth of ulceration and extent of gangrene ^[7].

Wagner's Classification:

- Stage 0 - Skin intact but bony deformities lead to "foot at risk"
- Stage 1-Superficial Diabetic ulcer
- Stage 2-Ulcer extension, Involves ligament, tendon, joint capsule, no abscess or Osteomyelitis
- Stage 3 -Deep ulcer with abscess or osteomyelitis

- Stage 4 - Partial Gangrene of forefoot
- Stage 5- Extensive Gangrene of foot ^[8]

Unfortunately, treatment provided for foot ulcers is often inadequate ^[9]. Primary prevention is the aim of diabetes management, but secondary prevention is the goal of good foot-ulcer care ^[10]. Commonly Diabetic foot ulcers can be treated with the following,

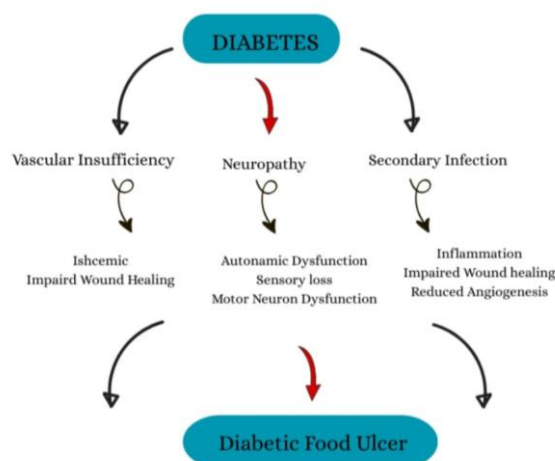
1. Patient Education
2. Blood-Sugar Control
3. Decreasing Pressure, preventing further or new trauma
4. Improve Peripheral Vascular Circulation
5. Prevent or Control Infection
6. Topical Ulcer Care ^[11]

The following herbal ointments are used for diabetic foot ulcers,

OINTMENT	HERB USED
Honeyderm	Honey
MEBO (most exposed burn ointment)	Sesame oil and bees wax
Jatyadi taila ointment	Neem, til oil, haritaki
Patanjali herbal ointment	Neem, Turmeric and honey
Neem-based ointment	Neem leaf extract
Himalayan antiseptic cream	Neem, Turmeric and Aloe vera
DermaID herbal ointment	Tea tree oil, Turmeric, Aloe vera.

PATHOPHYSIOLOGY:

Pathophysiology of Diabetic Foot Ulcer ^[12]



PLANT PROFILE

LOTUS SEED (*Nelumbo nucifera*):

CHEMICAL CONSTITUENTS:

The Lotus seed (*Nelumbo nucifera*) contains 61%– 62% of carbohydrates, 16%–21% of total protein, and 2.40%– 3% of crude fat with 5%–9% of moisture content ^[13]. Prebiotic ^[14], vitamin C is found in maximum concentration (20–24 mg/100 g). Minerals, namely iron (13–18 mg/100 g), calcium (30–31 mg/100 g), sodium (30–35 mg/100 g), and

potassium (16–20 mg/100 g) ^[15]. Alkaloids, terpenoids and phenolic compound ^[16].

USES:

- Anti- obesity ^[17] and Anti – inflammatory ^[18]
- Hypoglycaemia ^[19] and treat diabetic foot ulcer ^[20]
- Cardiovascular, hepatic protective, and immune regulatory ^[19]
- Anti-viral ^[19], wound healing ^[20] and anti-oxidant ^[21]

GRAPE SEED (*Vitis vinifera*):

CHEMICAL CONSTITUENTS:

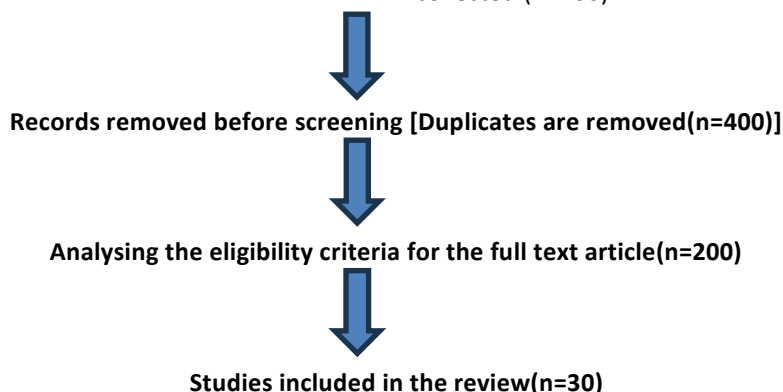
Grape seed is a complex matrix that consists of 40%, fibre, 16% oil, 11% protein and 7% complex phenols and tannins besides sugars, mineral salts etc ^[22]. Grape seeds also contain flavonoids (4–5%), including kaempferol-3-O-glucosides, quercetin-3-O-glucosides, quercetin and myricetin ^[23]. The slimy film, that surrounds the seeds are rich in polyphenolic compounds such as monomeric, dimeric, trimeric and tetrameric procyanidins ^[24].

USES:

- Antimicrobial Activity
- CVS
- Anticancer activities
- Treatment of peptic ulcer ^[25]
- Diabetic mellitus ^[26]
- Diabetic foot ulcer ^[27]

METHODOLOGY

A comprehensive literature search was conducted using PubMed, Google Scholar, Cochrane Library, and other relevant medical databases to gather studies related to diabetic foot ulcers, *Vitis vinifera*, and *Nelumbo nucifera*. Prior to screening, 400 duplicate entries were eliminated from the initial 700 records. The remaining papers were screened for titles and abstracts before 200 articles were evaluated for full-text eligibility using predetermined inclusion and exclusion criteria. After a detailed evaluation of methodology, study outcomes, and relevance to the research objectives, 30 studies were found suitable and were included in the final review. Use internet resources like Pubmed, Google Scholar, Cochrane Library and relevant medical publications to start a through literature search. Use a mix of terms that are associated with Diabetic foot ulcers, *Vitis vinifera*, *Nelumbo nucifera* the articles are collected. (n=700)



RESULT AND DISCUSSION

Grape seed extract is rich in powerful antioxidant compounds such as Proanthocyanidin and Polyphenol. By neutralizing the impact of free radicals these antioxidant compounds prevent cell damage caused by free radicals. For this reason, grape seed extract is used in the treatment of disorders associated with increased free radicals. It is reported that grape seed possesses good preventive effects against oxidative damage to DNA ^[28]. Curing skin lesions with grape seed extract caused proliferation areas with protected boundaries in epithelium, increased cell density and increased deposition of connective tissue at the wound site which in general improves cellular structure in wound. Proanthocyanidins in grape seed extract trigger the release of vascular endothelial growth factor and its topical application causes wound contraction and closure. In addition, its anti-inflammatory and anti-microbial properties are effective in wound healing ^[29]. Grape seed extract, rich in phenolics, fatty acids, and vitamins, shows

promise for its anti-inflammatory, antimicrobial, and antioxidant benefits. ^[30]

Compound found in lotus, neferine its effects on wound healing in diabetic rats, particularly for diabetic foot ulcers (DFUs). It shows that neferine speeds up wound closure, helps the skin heal faster, and increases the production of collagen and proteins in the treated group compared to the untreated group. ^[31] At the molecular level, neferine reduces certain markers related to inflammation and increases markers related to healing, such as Kaep-1. It also decreases oxidative stress and boosts antioxidant levels, which are important for healing wounds. ^[32] Additionally, neferine helps control insulin and lipid levels, further aiding the healing process. Overall, neferine has a significant impact on speeding up and improving wound healing in diabetic rats by reducing inflammation, promoting tissue repair, and improving metabolic factors like insulin and lipid levels ^[33]. Phytoconstituents, including Neferine emerge from these studies as promising agents for diabetic wound healing through the

inhibition of the NF- κ B pathway ^[34]. However, in diabetic wounds, an overexpression of NF- κ B leads to an undesirable outcome an escalated production of cytokines that lean towards fostering inflammation and oxidative stress ^[35]. The topical application of neferine in streptozotocin- induced diabetic incision wound models in rats effectively promotes wound healing ^[36]. In vitro and in vivo findings from the researchers suggests that lotus seed extracts have important anti-cancer, anti-proliferation, anti-diabetic, anti- inflammatory, Neuroprotective, antioxidant, and immunomodulatory activities ^[37]. Natural ingredients are increasingly used in drug formulations due to concerns about chemical side effects. In wound care, many current treatments struggle with issues like biofilms, inflammation, and oxidation, prompting the need for better, cost-effective options.

The present study was done to collect the complete details of *Nelumbo Nucifera* and *Vitis Vinifera* it is quite versatile. The Grapes seed extract (GSE) (*Vitis Vinifera*) topical application improved the skin homogenate contents of TGF- β 1(Transforming Growth Factor Beta 1), IL-10 (Interleukin)and TNF- α (Tumor Necrosis Factor) denoting the immunological effect of GSE on wound healing.^[38] On the other hand, grape seed, leaf and fruit extracts are well tolerated with no or minimal side effects. Adverse events reported in clinical trials have included mild degrees of itchy skin, dizziness, headache, and nausea but a similar incidence of these adverse events was often found in patients receiving placebos. At the same time *Nelumbo Nucifera* also promising the diabetic wound healing activity through improved wound contraction, epithelialization, and modulation of inflammatory mediators. It also has the various properties such as anti-inflammatory, diabetes, weight loss, anti-aging etc.

This review shows the importance and need to explore the detailed mechanisms behind these differences and to determine the potential benefits of these two extracts. Future research should also focus on optimizing dosage, treatment duration, and possible synergistic effects and identify which of the two compounds is more effective to maximize therapeutic outcomes for diabetic foot ulcer patients.

CONCLUSION

In *Nelumbo Nucifera* and *Vitis Vinifera* used for their various medicinal properties like Diabetic foot ulcer, wound healing, Anti-inflammatory, Anti-oxidant, etc. Ointment is viscous semi-solid preparation, the ointment has higher patient compliance because of

its long- term healing capacity. The primary goal of the antimicrobial and antibacterial ointment formulation was to cure or treat diabetic foot ulcers and injuries in diabetic patients. It was concluded that the foot ulcer healing ointment from natural sources has no side effects as compared to ointments from synthetic compounds. This ointment can kill targeted microbes, which are responsible for diabetic foot ulcers. This ointment is effective for wound healing properties compared to other treatment used in this study. The Phytochemical constituents such as alkaloids (Neferine), flavonoids (Proanthocyanidine), glycosides, tannins, carbohydrates, sterols saponins, protein, and other phenolic compounds bare believed to play a pivotal role in the healing of the wound by significantly increasing the rate of wound closure and epithelization. The mechanisms of action for neferine and proanthocyanidin include TGF- β modulation, Nrf2 activation, and NF- κ B inhibition. Clinical trials, as well as in vivo and in vitro studies, have reported promising outcomes for wound healing, particularly in preventing or treating diabetic foot ulcers. Future research in this area could focus on comparative studies, standardization and formulation processes, combination therapies, or detailed mechanistic studies to further understand their therapeutic potential.

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