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Review Article

A Proposed Framework for *Gliricidia sepium*-Derived Exosome-like Nanoparticles in Diabetic Wound Repair

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Diabetic wounds pose a major clinical challenge due to the lack of angiogenesis, presence of chronic inflammation, oxidative stress, and delayed tissue regeneration. Exosome-based nanotherapeutics have emerged as promising tools for wound repair by enabling nanoscale delivery of bioactive cargo; however, mammalian exosomes face limitations related to scalability, cost, and biosafety. Plant-derived exosome-like nanoparticles (PELNs) have been recognized as a precision nanomedicine platform due to their biocompatibility, eco-friendliness, reduced immunogenicity, and scalable production. *Gliricidia sepium*, a medicinal plant rich in flavonoids, saponins, phenolics, and fatty acid derivatives, presents a compelling source of bioactive compounds for regenerative applications. This review critically integrates the phytochemical profile of *Gliricidia sepium* with emerging evidence on plant-derived exosome-like nanoparticles, proposing a cargo-driven mechanism that may regulate inflammation, angiogenesis, oxidative stress, and cellular migration within the diabetic wound microenvironment. This review propose a novel concept that Plant-derived exosome-like nanoparticles will deliver the vesicle-associated phytochemicals of *Gliricidia sepium* that molecularly (inflammatory signalling, angiogenesis and oxidative stress) target diabetic wound healing. The researchers show size control of vesicles, cargo composition and biological targeting impact reproducibility and translational potential of therapy. They also address isolation, characterization and standardization as critical challenges. Most importantly, the preclinical validation and future directions, necessary to evaluate the feasibility of *Gliricidia sepium*-associated exosome-like nanoparticles as a clinical approach.

Introduction

Diabetes mellitus is a persistent metabolic condition associated with a combination of environmental and genetic variables that either cause the pancreas to produce insufficient amounts of insulin or reduce the body's responsiveness to the insulin that is produced. Numerous other health issues are frequently linked to the development of this illness [1]. The most common endocrine condition, diabetes, is primarily caused by a lack of insulin secretion, damage to the pancreatic â cell, and a decline in insulin function (insulin resistance). Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) are the three main types of diabetes. Autoimmune B-cell destruction is the etiology of type 1 diabetes mellitus (T1DM), which usually results in a complete lack of insulin. A progressive decline of insulin production by B-cells, along with increasing insulin resistance, is the etiology of type 2 diabetes (T2DM)[2].

Non-healing skin ulcers and a number of micro and macrovascular issues are brought on by diabetes mellitus. Long-term, poorly controlled diabetes can lead to the common and extremely morbid condition known as diabetic foot ulcers (DFU). Diabetic foot ulcers can be classified as neuropathic, ischemic, or neuroischemic, and each type has a different impact on a patient's level of disability. Oxidative stress, adenosine triphosphate deficit, protein kinase C activity, immune-mediated inflammatory activity, and the glucose-to-sorbitol conversion pathway are all implicated in the mechanisms by which hyperglycemia damages peripheral neurons (both motor and sensory). The patient may not react to variables that harm the foot tissues because of reduced or absent pain, warmth, vibration, and tactile feeling in the foot [3].

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The emerging issues have resulted in the discovery of plant-derived exosome-like nanoparticles (PELNs) as a potential for regenerative medicine therapy, revolutionizing therapeutic interventions in the field of medicine. Regenerative medicine uses cutting-edge techniques, such as plant-derived exosome-like nanoparticles-based treatments, to promote skin regeneration and wound healing by facilitating intercellular signalling through bioactive molecules like lipids, proteins and miRNAs. By reducing inflammation, encouraging tissue remodelling, and enhancing cellular processes essential for healing, PELNs - nanosized extracellular vesicles-speed up wound healing. Despite issues with scalability and uniformity, these developments place PELNs-based therapies as game-changing instruments in customized and scalable regenerative medicine for wound care [4]. Plant-derived exosome-like nanoparticles, or PELNs, generated from medicinal herbs and edible plants, have recently emerged as a unique, biocompatible substitute for mammalian exosomes. PELNs are excellent candidates for clinical translation because of their low immunogenicity, improved safety, and scalable manufacturing [5].

Using medicinal herbs to treat wounds has been shown to help prevent infection and promote the healing process. Numerous therapeutic herbs possess antibacterial and antioxidant qualities [6]. *Gliricidia sepium* is a species within the Fabaceae family and is a leguminous tree. Medium in size, *Gliricidia sepium* trees can reach heights of 10 to 12 meters. Its composite leaves have a maximum length of 30 cm. The leaflets that make up each leaf are roughly 2 to 7 cm in length and 1 to 3 cm in width. The unleafed branches are where the blossoms are found. These blossoms are violet to brilliant pink with a hint of white [7]. *Gliricidia sepium* leaf extracts are used locally by traditional healers to cure phlegm, skin infections, rashes and itching, while decoctions and shoot extracts are used to treat skin irritations, wounds and even ringworm. *Gliricidia sepium* is also used in traditional medicine for alopecia, burns, skin tumours, bruises, debility, fever, colds, fractures, gangrene, headache, rheumatism and ulcers [8]. Plant aqueous and organic extracts have been used as CNS depressants, mosquito repellents, fumigants, wound dressings, antibacterial, antifungal, and antiviral medications, and to induce vomiting. Herbal medicine made from plant parts has been proven to be successful, and serves as the main healthcare source for over 80% of people [9]. This review article is intended to be presented as a framework for nanomedicine in diabetic wounds. Instead of simply being a review article on existing literature on diabetic wounds, this article attempts to bring together existing knowledge on diabetic wounds, regenerative medicine approaches to diabetic wounds, and plant-based exosome-like nanoparticles to propose a potential approach to diabetic wounds. Within this framework, this review article examines the phytochemical content and existing uses of *Gliricidia sepium* in wound healing to propose a rationale for its application in plant-derived exosome-like nanoparticles (PELNs)-based diabetic wound healing. This review article proposes a framework for the application of *Gliricidia sepium*-based nanotechnology in diabetic wounds based on existing knowledge on regenerative medicine, nanotechnology, and phytotherapy.

Diabetic Wound Pathophysiology and the Four Phases of Healing

The multifaceted physiological mechanism of wound healing is governed by a series of coordinated biological interactions among different cell types, mediated by growth factors, cytokines, chemokines, and metabolites, which preserve tissue integrity [10]. Hemostasis, inflammation, proliferation, and remodelling are the four overlapping phases that traditionally contribute to this biological process. For tissue repair to be successful, these phases must occur in a timely and effective manner [11]. However, this highly regulated process is often disrupted in the pathological conditions associated with diabetes, leading to the sustained presence of chronic non-healing wounds that fail to improve through the necessary stages of repair [12].

Hemostasis phase dysregulation in diabetes

The hemostatic phase, which is critical for initiating wound repair through vasoconstriction and clot formation, is frequently disrupted in diabetic patients due to underlying metabolic aberrations [13]. Specifically, hyperglycemia induces platelet hyperactivity and alters coagulation factor levels, leading to an unstable fibrin clot that fails to provide an adequate provisional matrix for subsequent cellular migration [14,15]. This dysregulation is further compounded by endothelial dysfunction and impaired fibrinolysis, which collectively disturb the delicate balance required for effective hemostasis and transition into the inflammatory phase [15,16].

Inflammation phase dysregulation in diabetes

In diabetes, the inflammatory phase is greatly prolonged and dysregulated with pro-inflammatory M1 macrophages and high levels of cytokines like TNF-α and IL-1β that impede the progression to the proliferative phase [17]. A degenerative microenvironment that actively inhibits tissue regeneration is created by the accumulation of senescent cells, such as macrophages and fibroblasts, which have a senescence-associated secretory phenotype that continuously releases reactive oxygen species and pro-inflammatory mediators and worsens this chronic inflammation [11]. Therefore, if inflammation is not reduced, the cells that restore damaged tissues cannot be recruited and activated on time, creating a barrier that needs to be removed in order to resume the physiological progression of wound healing.

Proliferation phase impairment in diabetes

The proliferative phase of diabetic wounds, which is crucial for reepithelialization, formation of granulation tissue, and

Table 1: Healing Phases in Diabetic Wounds

Wound Healing Phase	Impairment in Diabetes	Effect of *Gliricidia sepium*
Inflammation	Extended inflammation, increased cytokines	Anti-inflammatory action, cytokine regulation
Proliferation	Reduced fibroblast activity, poor angiogenesis	Stimulate fibroblast proliferation and neovascularization
Remodelling	Delayed collagen deposition and tissue regeneration	Boost collagen synthesis and matrix remodeling
Oxidative Stress	Excessive ROS production, impaired redox balance	Antioxidant activity reduces oxidative stress and protects tissue
Infection Control	Higher susceptibility to bacterial colonization	Antibacterial action prevents infection and biofilm formation
Epithelialization	Delayed keratinocyte migration and wound closure	Stimulates epithelial cell migration and accelerates re-epithelialization
Pain and Discomfort	Persistent inflammation leads to chronic pain	Anti-inflammatory compounds may contribute to pain relief indirectly

Table 2: Bioactive Compounds of *Gliricidia sepium* Leaf Extract

	Compound Name	Molecular Formula	Biological Activity	Potential Role in Exosome-Like Vesicles / Synergistic Function
1	Hexadecane	$C_{16}H_{34}$	Antibacterial [26], Antioxidant [27]	Long-chain hydrocarbon that may contribute to hydrophobic packing within vesicle membranes, improving lipid bilayer stability and protecting encapsulated phytochemicals.
2	Phytol	C20H40O	Antimicrobial, Anti-inflammatory [28]	Amphiphilic diterpene that may assist membrane anchoring of bioactive molecules while providing antioxidant protection to vesicle membranes.
3	Neophytadiene	C20H38	Antimicrobial [29], Antioxidant [30], Anti-inflammatory [31]	Hydrophobic terpene that may support membrane fluidity and enhance vesicle stability, indirectly facilitating delivery of therapeutic phytochemical cargo.
4	Lupeol acetate	C32H52O2	Antimicrobial, Anti-inflammatory, Antioxidant [32]	Triterpenoid compound that may function as a bioactive vesicle cargo capable of modulating inflammatory signaling pathways during wound repair.
5	3,7,11,15-Tetramethyl-2-hexadecen-1-ol	C20H40O	Anti-inflammatory, Antioxidant [33]	Lipid-like molecule that may participate in vesicle membrane organization while contributing antioxidant protection within the wound microenvironment.
6	Dodecane, 4,6-dimethyl-	C14H30	Antibacterial [26]	Hydrocarbon component that may contribute to lipid matrix structure of vesicles, improving membrane integrity and stability during transport.
7	Hexadecenoic acid ethyl ester	C18H36O2	Antibacterial, Antioxidant [34]	Fatty acid ester that may integrate into vesicle membranes, contributing to lipid bilayer formation and sustained delivery of encapsulated bioactives.
8	Squalene	C30H50	Antibacterial, Antioxidant, Immunostimulant [28]	Highly unsaturated lipid known to enhance membrane flexibility and stability, potentially improving vesicle persistence and bioactive delivery efficiency.
9	n-Hexadecanoic acid	C16H32O2	Antioxidant, Anti-inflammatory, Antibacterial [28]	Fatty acid that may participate in vesicle lipid bilayer assembly while contributing anti-inflammatory effects within the wound environment.
10	Kaempferol	C15H10O6	Antidiabetic [35]	Flavonoid cargo molecule capable of modulating angiogenic signaling pathways such as VEGF, promoting endothelial cell migration and wound repair.
11	Luteolin	$C_{15}H_{10}O_6$	Antimicrobial, Antioxidant, Antidiabetic [36]	Flavonoid that may function as a therapeutic vesicle cargo with antioxidant and anti-inflammatory effects supporting tissue regeneration.
12	Isoquercitrin	$C_{21}H_{20}O_{12}$	Antioxidant, Anti-inflammatory [37]	Glycosylated flavonoid that may act as a protective cargo molecule capable of reducing oxidative stress and inflammatory signaling in diabetic wounds.

neovascularization, is severely impaired due to cellular dysfunction and reduced sensitivity of cells to growth factors. Specifically, hyperglycemia causes cellular dysfunction in keratinocytes and fibroblasts, leading to a decrease in migration capacity, proliferation, and synthesize extracellular matrix components that are essential for the formation of granulation tissue [18]. In addition, the process of angiogenesis is significantly repressed, due to endothelial cells decreased responsiveness to pro-angiogenic factors like VEGF, leading to inadequate blood flow and tissue hypoxia that further inhibits the sustained release of nutrients and oxygen necessary for healing [16].

Remodelling phase deficiencies in diabetes

The final remodelling phase is characterized by a pathological imbalance between extracellular matrix synthesis and degradation, driven by the sustained overexpression of matrix metalloproteinases and the diminished activity of tissue inhibitors of metalloproteinases, which results in the degradation of newly formed collagen and the formation of weak, disorganized granulation tissue [19,20]. The extracellular matrix's cohesiveness is mostly dependent on endopeptidases, including tissue inhibitors of metalloproteinases (TIMP) and matrix metalloproteinases (MMP). There is an overexpression of MMP and an underexpression of TIMP in diabetic wounds that are inflammatory.MMP-9 is a key player in cell migration and proliferation, which advances the wound-healing process by accelerating the series of events that include collagen synthesis, cell migration, and proliferation [21]. Table 1 summarizes these phase-specific deficits in diabetic wound healing as well as the related reparative effects linked to *Gliricidia sepium*.

Phytochemical Composition of *Gliricidia sepium*

The therapeutic value and pharmacological effects of medicinal plants largely depend on their phytochemical composition. A previous study revealed the existence of bioactive constituents such as alkaloids, flavonoids, glycosides, polyphenols, and tannins, in which the alkaloids showed the highest amount, followed by flavonoids and glycosides (table 2) [22].

Solvent selection is critical in determining the recovery of phytochemicals of *Gliricidia sepium*. Organic solvents work better for extracting bioactive phenolics and flavonoids rather than aqueous solvents. Previous phytochemical investigations have consistently demonstrated that total phenolic and flavonoid contents generally increase with extract concentration, irrespective of solvent system employed. Among the solvents studied, dichloromethane extracts are often reported to have higher total phenolic content (47.19 ± 0.02 mg GAE/g), while aqueous extracts show the lowest levels (6.19 ± 0.01 mg GAE/g).

Similarly, flavonoid distribution is strongly influenced by solvent polarity, with non-polar solvents such as n-hexane yielding notably high flavonoid concentrations at higher extract doses, whereas water extracts consistently contain very little amounts. Methanolic extracts are often highlighted for their efficiency in extracting phenolic compounds at lower

concentrations [23]. These phytochemicals should not be viewed merely as free bioactive compounds but as potential endogenous cargos that could be associated with or incorporated into plant-derived exosome-like nanoparticles. Encapsulation within lipid bilayer vesicles may enhance their stability, protect labile molecules from degradation, and enable controlled delivery to target cells within the diabetic wound microenvironment. This conceptual cargo-centric interpretation bridges classical phytochemistry with precision nanotherapeutic design principles. In this context, lipidic constituents such as hexadecane, squalene, and phytol may play complementary roles within vesicular membranes. Long-chain hydrocarbons like hexadecane can enhance hydrophobic packing of the lipid bilayer, while squalene may contribute to membrane flexibility and resistance to mechanical stress. Phytol, owing to its amphiphilic structure, may facilitate membrane anchoring of bioactive molecules while providing antioxidant protection. Together, these lipids may synergistically improve vesicle integrity and persistence, thereby supporting efficient cargo delivery in the hostile diabetic wound microenvironment [24,25].

Within a vesicle-based delivery framework, lipidic molecules such as squalene and hexadecane may form part of the structural membrane matrix, whereas flavonoids such as kaempferol function as biologically active cargo. This lipid–cargo coupling may provide a synergistic mechanism in which membrane lipids stabilize the vesicle and protect encapsulated phytochemicals, enabling targeted delivery and sustained bioactivity within the diabetic wound microenvironment

Pharmacological Activities of *Gliricidia sepium*

Antioxidant activity

The oxidative destruction of biological constituents like DNA, proteins, and lipids is considerably postponed or prevented by antioxidants. The genesis and progression of cardiovascular and neurological disorders have been linked to elevated oxidative stress, which has sparked a lot of interest in plants' antioxidant capacity [39,40]. A common technique to assess the antioxidant capacity of plant-derived phytochemicals, such as essential oils, is the DPPH (2,2-Diphenyl-1-picrylhydrazyl) radical-scavenging assay. The DPPH's characteristic absorption takes place at 517 nm. It falls with antioxidant treatment that can scavenge its free radical by providing either an electron or a hydrogen atom [40].

The current study found that the *Gliricidia* plant extract is high in antioxidants, and all of the solvents examined had good antioxidant levels. Studies have shown that *Gliricidia sepium* contains flavonoids. Because of their well-known antioxidant qualities, flavonoids are essential for scavenging free radicals and supporting the defense systems of plants. *Gliricidia sepium* is known to contain phenolic acids, such as variants of ferulic acid along with caffeic acid. These substances have been found to have antibacterial, tissue regeneration, prevention of aging, reduction of inflammation, and cancer-fighting effects in addition to their antioxidant qualities [41].

Antimicrobial properties

According to research, the phytochemicals in *Gliricidia sepium* extracts have antimicrobial effects by interfering with vital bacterial metabolism and inhibiting the growth of *E.coli*. Similar to this, plant extracts have shown substantial effects on *Staphylococcus aureus* by interfering with enzyme activity, bacterial membranes, and essential cellular processes. Environmental conditions, extract quantities, and differences in bacterial strains all determine how effective they are [41].

According to research, plant extracts of *Gliricidia sepium* have the potential to become novel agents with antimicrobial activity targeting both Gram-positive and Gram-negative bacterial strains. They may also be more advantageous than conventional types due to their low toxicity to mammals, quick degradation, and local availability. Therefore, even at lesser quantities, the chemical components found in them are probably physiologically active. The chemicals found in the extract, such as flavonoids and phenolic acids, or the combined action of the major and minor components may be responsible for this antibacterial activity. Although the major components of plant extracts often have the most antibacterial activity, the extract's overall activity is also significantly increased by minor components, as opposed to the synergistic combination of key components. It may therefore be employed as a possible antimicrobial agent [7].

Anti-inflammatory activity

Currently, there is a scarcity of direct experimental evidence on the ability of the extract from the plant *Gliricidia sepium* to downregulate the matrix metalloproteinase-9, a key pro-inflammatory mediator in the degradation of the extracellular matrix during the healing process. However, the plant is rich in flavonoids such as kaempferol glycosides and isorhamnetin, which have been found to affect the inflammatory pathway. However, currently, there is a scarcity of research on the molecular mechanisms of the action of the plant extract on the inflammatory pathway. Therefore, the anti-inflammatory benefits are on the same scale as the downregulation of the MMP-9 by the flavonoids present in the extracts of other plants. Kaempferol and other flavonoids present in the extract from *Gliricidia sepium* have been found to inhibit the NF-êB pathway in other plant systems. The NF-κB pathway is a key inflammatory pathway. The inhibition of the pathway has been found to downregulate the transcription of inflammatory mediators and matrix metalloproteinases such as MMP-9. This inhibits the degradation of the extracellular matrix and the healing process [42,43]. Further research reported that *Gliricidia sepium* leaves have strong ant-inflammatory effects due to their bioactive compounds, which improve wound healing. These compounds possess their anti-inflammatory properties by blocking the activity of cyclooxygenase enzymes, which are the key connections in inflammatory pathways. This control of inflammatory reactions is essential because persistent inflammation can prevent the proliferative and remodelling stages of wound healing [44,45].

Antidiabetic activity

The emerging antidiabetic potential of *Gliricidia sepium* has been identified, although the current scientific evidence is limited to in vitro studies only. *Gliricidia sepium* methanolic leaf extract inhibited α-amylase and α-glucosidase activity in a moderate fashion, which are major enzymes in the digestion of carbohydrates and can cause an increase in blood glucose levels [46]. These antidiabetic effects of *Gliricidia sepium* are in agreement with the action of various antidiabetic agents of medicinal plants that often possess phenolic and flavonoid constituents which show their effect by the inhibition of enzymes [47,48]. There were no studies relating to the effect of *Gliricidia sepium* extract on the antidiabetic potential of the plants in in vivo and clinical studies. While *Gliricidia sepium* shows lower systemic antidiabetic potency than acarbose, its localized antioxidant and anti-inflammatory profile makes it an ideal candidate for topical wound-site delivery where systemic glucose-lowering is not the primary objective.

Cytotoxicity of *gliricidia sepium*

The evaluation of cytotoxicity and cell proliferation is essential for determining the safety profile and therapeutic potential of *Gliricidia sepium* extracts, particularly in the context of wound healing where cellular viability and growth are critical parameters. Studies on the cytotoxicity of *Gliricidia sepium* leaf extracts using L929 fibroblast cells revealed no evidence of cytotoxic effects, with high cell viability (>80–100%) over a dosage range of 0.1–100 μg/mL. The extract's biocompatibility is further supported by the lack of an IC_{50} value, which makes them appropriate for topical treatments such diabetic wound healing. Further, the *Gliricidia sepium* could potentially decrease the formation of matrix metalloproteinases, maintaining the integrity of the extracellular matrix, increase the availability of growth factors, and help diabetic wounds move from persistent inflammation to successful tissue regeneration [49]. Despite there is currently little information on the specific cytotoxicity of *Gliricidia sepium*, studies on poly-herbal formulations with comparable phytoconstituents have shown high cell viability, more than 90% in HepG2 cells even at high concentrations, suggesting an acceptable safety profile for possible therapeutic development [50]. However, there is a lack of information on cytotoxicity profiles of exosome-like

Figure 1: Overview of *Gliricidia sepium* Leaf Extract Action in Promoting Efficient Diabetic Wound Healing

nanoparticles derived from *Gliricidia sepium*. As such, concentration-dependent cytotoxicity profiles and IC_{50} determination are crucial experiments that should be carried out to validate the safety profile of this proposed nanomedicine strategy.

Scratch wound healing assay of *gliricidia sepium*

In vitro scratch wound healing assays have proved to be highly valuable indicators of understanding the capacity of migration of fibroblasts and keratinocytes, being vital factors in the wound healing process, particularly during re-epithelialization, a phase that is usually compromised under a range of hyperglycemic factors that normally inhibit cellular function. Although there has been a lack of direct evidence for *Gliricidia sepium* in scratch assays, deeper studies on a range of polyherbal formulations have indicated that certain bioactive compounds stimulate the migratory capacity of fibroblasts towards the damaged tissue with enhanced rates compared to positive controls, despite a range of high glucose concentrations [51,52]. Based on evidence from comparable phytochemicals and animal wound models, *Gliricidia sepium* is thought to modulate the balance between matrix metalloproteinases and their tissue inhibitors to promote Vascular Endothelial Growth Factor. Additionally, it may directly activate VEGF ligand-receptor interactions, which are crucial for angiogenesis and tissue repair. According to evidence from comparable species, phytochemicals including triterpenes and flavonoids can enhance VEGF/VEGFR interactions and successfully modify the MMP/TIMP balance to promote these activities[53]. In particular, bioactive substances like kaempferol have been shown to enhance angiogenic activities in endothelial cell cultures by directly interacting with VEGF. Furthermore, kaempferol has also been found to block the nuclear factor kappa-B (NF-κB) pathway, which is responsible for the regulation of inflammatory genes and matrix metalloproteinases, such as MMP-9. NF-κB pathway inhibition by kaempferol may help in the prevention of degradation of the extracellular matrix by MMP-9, while at the same time promoting VEGF-mediated endothelial cell migration. This improves the receptor-ligand interaction and triggers downstream signalling cascades that are essential for the migration and proliferation of endothelial cells [54,55]. Under a range of excision wound

Table 3: Wound Healing Potential of *Gliricidia sepium* and Selected Medicinal Plants

Plant	Bioactive Constituents	Biological Activities	Major Wound Healing Actions	Advantages /Limitations	Ref
Gliricidia sepium	Flavonoids, phenolics, tannins, saponins, coumarins	effective antioxidant, broad-spectrum antimicrobial, and inhibitors of inflammatory mediators	Stimulates angiogenesis, collagen deposition, and fibroblast proliferation; regulates MMP activity and oxidative stress.	Multi-target effect that is balanced; especially beneficial for diabetic and chronic wounds	[57], [56]
Centella asiatica	Triterpene saponins, asiaticoside, madecassoside	Weak antibacterial; moderate anti-inflammatory and antioxidant	Promotes collagen maturation and fibroblast proliferation.	Excellent collagen remodeling; limited infection control	[58]
Ocimum sanctum (Tulsi)	Ursolic acid, rosmarinic acid, eugenol	Strong antioxidant; anti-inflammatory; antimicrobial	Promotes tissue regeneration and lowers inflammation and oxidative stress	Good immunomodulation and a moderate biological ability for regeneration	[59]
Aloe vera	Polysaccharides (Acemannan), saponins, naftoquinone vitamins, sterols and triterpenoids.	Mild antibacterial, anti-inflammatory with moderate antioxidant	Boosts hydration, keratinocyte migration, and re-epithelialization	Better epithelial healing but less effective antimicrobial protection	[60]
Bougainvillea spp.	Flavonoids, alkaloids, betacyanins, terpenoids, phenolics	Anti-inflammatory, powerful antibacterial, and slightly antioxidant	77% wound area reduction, decreases microbial burden	Strong antibacterial action with little indication of angiogenic effects	[61]
Azadirachta indica (Neem)	Nimbin, azadirachtin, quercetin	Strong antibacterial; moderately anti-inflammatory and antioxidant	Prevents infections in wounds and promotes granulation tissue	Slower epithelialization and remarkable antibacterial activity	[62]
Curcuma longa (Turmeric)	Demethoxycurcumin, bisdemethoxycurcumin, curcumin	Strong anti-inflammatory and antioxidant properties; mild antibacterial	Inhibits inflammation mediated by NF-κB and encourages granulation	Strong anti-inflammatory; lack of formulation leads to poor bioavailability	[63]
Calendula officinalis	Triterpenoids, flavonoids, carotenoids	Mild antibacterial, antioxidant, and anti-inflammatory	Stimulates fibroblast activity, epithelialization, and angiogenesis.	Strong releiving and anti-inflammatory properties; less effective against bacteria that are resistant	[64], [65]

Table 4: Key differences between mammalian and plant-derived exosome-like nanoparticles [68]

Feature	Mammalian-Derived Exosome-Like Nanoparticles	Plant-Derived Exosome-Like Nanoparticles
Size range	30–150 nm	30–500 nm (optimal therapeutic window: 80–150 nm)
Immunogenicity	Moderate	Low
Scalability	Limited	High
Batch variability	High	Lower with standardized plant sources
Cost	High	Relatively low

models, it has been evident that a range of wound contraction activities is promoted significantly with enhanced re-epithelialization, with a notable rise in collagen synthesis and formation [56]. In a range of diabetic animal models, the extract of *Gliricidia sepium* has significantly promoted a range of wound closure activities with a notable reduction in inflammation, coupled with a range of collagen synthesis and re-epithelialization processes under hyperglycemic concentrations [57]. There are no published reports on quantitative scratch assay data on exosome-like nanoparticles derived from *Gliricidia sepium*. Future studies must establish the IC_{50} of *Gliricidia sepium*-derived PELNs to confirm that the nano-encapsulation does not increase cytotoxicity compared to the bulk extract and validate the proposed role of these nanoparticles in diabetic wound healing through concentration-dependent effects on fibroblast migration and wound closure rates.

Plant-derived Exosome-like Nanoparticles (PELNs) in Regenerative Medicine

Plant-derived exosome-like nanoparticles, which have a diameter of 30 to 150 nm, are a subset of tiny lipid bilayer Extracellular vesicles (EVs). Multivesicular bodies (MVBs), consisting of immune cells and stem cells participating in wound repair, release them into the extracellular fluids from the majority of cells. By transporting their cargo - proteins, RNA, lipids, and other physiologically active substances - to the target cell's cytoplasm, exosomes play a crucial role in intercellular communication and alter the recipient cell's biological characteristics (figure 2). PELNs can accelerate wound healing by reducing inflammation, enhancing neovascular development, promoting cell proliferation, and stimulating collagen deposition, according to established research. PELNs have a lot of potential to speed up the healing of skin wounds, but how to optimize their therapeutic effect depends on a number of variables, including exosome engineering and exosome delivery techniques [66].

Over the past few years, researchers have progressively identified, isolated, and described exosomes from plants with heterogeneous size distribution (50–500 nm), precision nanomedicine applications preferentially focus on smaller vesicle subpopulations (approximately 80–150 nm) due to their superior tissue penetration, cellular uptake, and therapeutic reproducibility. A variety of fruits, vegetables, and even certain traditional herbs and fungi have been shown to contain plant-derived exosomes. PELNs have a unique subcellular structure and vary depend-

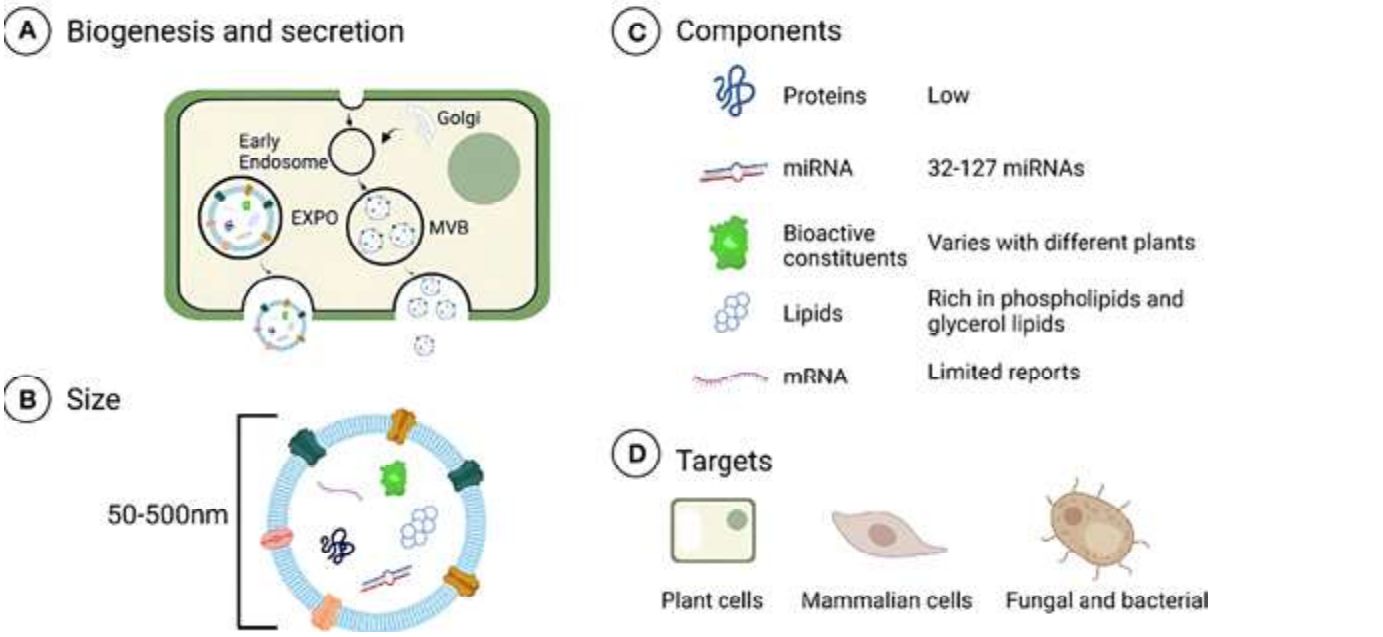

Figure 2: PELN Contents. (A)Biosynthesis and production: Exocyst positive organelles (EXPO) and Multivesicular bodies (MVB) are two means by which plant cells could produce PELNs. (B) Size: PELNs are approximately 30 to 500nm in size. (C) Components: PELNs usually have less proteins and miRNAs. (D) Targets: Plant, Mammalian, fungal and bacterial cells can absorb PLENs [69]

ing on the sources. Proteins, siRNA, and therapeutic medicines are just a few of the therapeutic molecules that PELNs can transport to the appropriate disease sites, in addition to serving as therapeutic agents for disease intervention. Clinical efficacy can be greatly improved by the synergistic therapeutic effects of their endogenous bioactive components. PELNs have distinct advantages over mammalian exosomes, including lower toxicity, increased bioavailability, and difficulty being recognized by the immune system [67].

Mechanistic insights into exosome-mediated wound healing

PELNs, as nanosized extracellular vesicles, regulate vital biological processes such as angiogenesis, immune responses, fibroblast function and oxidative stress, which are important for effective wound repair. They facilitate the transport of diverse cargoes, including mRNA, microRNA, proteins and lipids by altering recipient cell behaviour and promoting tissue regeneration [70]. PELNs produced specifically from mesenchymal stem cells have shown remarkable therapeutic potential in wound healing by enhancing cell migration, proliferation, angiogenesis, collagen deposition and re-epithelialization, besides regulating macrophage polarization [71]. In comparison to mammalian counterparts, plant-derived exosome-like nanovesicles offers a promising substitute by avoiding problems like immunogenicity, pathogen transmission and high production costs while maintaining strong anti-inflammatory, antioxidant and wound healing qualities (table 4). Additionally, traditional Chinese medicine derived from exosome-like nanovesicles have shown potential in reducing oxidative stress, promoting angiogenesis, activating fibroblasts and keratinocytes and modulating inflammation providing insights into possible mechanisms for *Gliricidia sepium*-derived exosomes exosome-like nanovesicles. These plant-derived nanovesicles contain a wide range of endogenous phytochemicals, including ginsenosides, polyphenols and flavonoids, which substantially improve their therapeutic effectiveness and may play a role in vesicle transport mechanisms used in diabetic wound healing (figure 3) [12].

Isolation and purification techniques for plant exosomes

Plant-derived exosome-like nanoparticles are isolated using multiphase process which includes differential centrifugation, ultrafiltration and size-exclusion chromatography to separate the nanovesicles from cellular debris and other impurities [72]. The isolation process starts with the mechanical disruption of plant tissues, such as mixing, crushing and squeezing in buffer solutions to release exosomal content. The extract often contains a heterogeneous mixture of vesicles and other cellular components, which need to undergo a series of purification procedures to enrich for exosomes based on their size, density and particular surface markers [73]. Alternative advanced techniques such as immunoaffinity capture-based isolation, microfluidics-based techniques and aqueous two-phase systems can be used to enhance isolation efficiency and purity, overcoming the drawbacks of conventional methods that have challenges with large-scale, high-quality extraction [74]. A critical limitation in the isolation of plant-derived exosomes is the lack of standardized isolation and characterization procedures which results in significant variation in reported exosome characteristics and functional analyses across studies, thereby limiting translational research. The di-

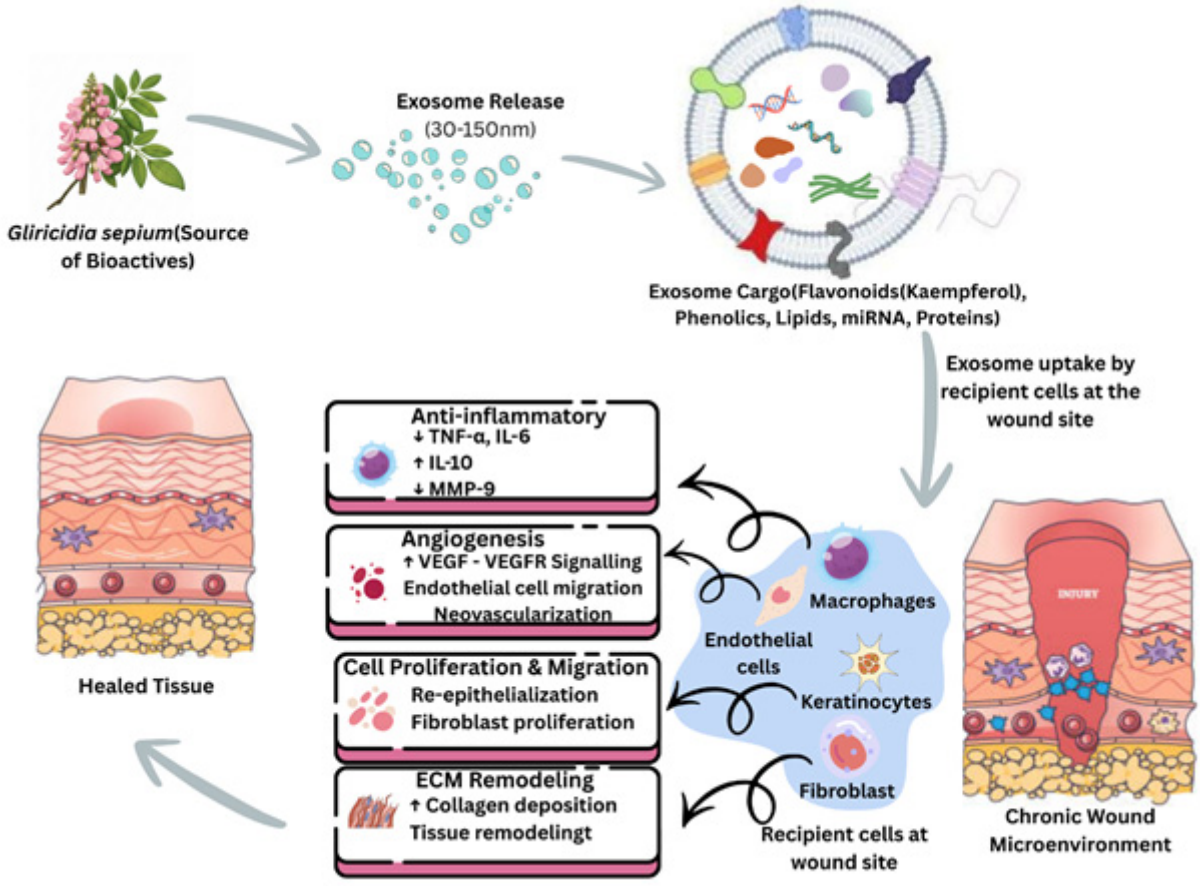

Figure 3: Proposed framework for vesicle-mediated delivery of *Gliricidia sepium* phytochemicals in diabetic wound repair. Plant-derived exosome-like vesicles deliver flavonoids and lipid molecules to wound-site cells, where they may suppress inflammation via MMP-9 inhibition and promote angiogenesis through VEGF signaling, enhancing collagen deposition, fibroblast migration, and re-epithelialization

verse nature plant matrices further makes the isolation difficult because the chemical compositions and physical characteristics differ significantly between species, necessitating method optimization for each plant source.

Characterization methods for plant-derived exosomes-like nanoparticles

Characterization techniques are necessary to confirm the exosomal nature of isolated vesicles. It is done by evaluating their size, morphology, concentration and molecular cargo. These characterization techniques are essential for distinguishing plant-derived exosome-like vesicles from other nanoparticles and cellular debris, in order to ensure the integrity and functional relevance of further investigations [75]. Key techniques include Scanning Electron Microscopy (SEM), Nanoparticle Tracking Analysis (NTA), Atomic Force Microscopy (AFM), Transmission Electron Microscopy (TEM), Flow Cytometry, Dynamic Light Scattering and Zeta Potential [76]. Adoption of standardized isolation, characterization, and reporting guidelines will be essential to ensure reproducibility, regulatory acceptance, and translational feasibility of plant-derived exosome-based nanotherapeutics.

Rationale for Exploring *Gliricidia sepium*-Derived Exosome-like nanoparticles for Diabetic Wound Repair

In spite of the fact that there are no direct studies reported in the application or isolation of *Gliricidia sepium*-derived exosomes for the treatment of diabetic wounds, existing evidence from associated research gives a strong scientific rationale for their exploration. Plant-derived exosome-like nanoparticles isolated from various medicinal and edible plants have been suggested to have biological effects including anti-inflammatory, antioxidant and regenerative effects. Studies on extracellular vesicles derived from *Aloe saponaria* have been demonstrated to have strong anti-inflammatory effects by suppressing pro-inflammatory cytokines like IL-6 and IL-1β while concurrently stimulating fibroblast migration, proliferation, and endothelial tube formation [77]. Kim *et al.* 2022 [78] reported that the *Aster yomena callus*-derived extracellular vesicles (AYC-EVs) have strong immunomodulatory effects by inhibiting the maturation of dendritic cells, lowering the production of pro-inflammatory cytokines, and reducing the activation of CD4 and CD8 T cells in vitro. Taken together, the findings indicate the therapeutic potential of plant-derived extracellular vesicles as natural biomaterials in the management of chronic inflammatory conditions and wound healing. Thus, exosome-like nanoparticles isolated from *Gliricidia sepium* are proposed to have therapeutic potential in the healing of diabetic wounds, and further studies are required to explore the bioactive content, such as regulatory RNAs, and the ability to modulate pathways critical for healing.

Challenges and Future Directions

Plant-derived exosome-like nanoparticles research has made encouraging improvements, but there are still a number of issues with their standardized isolation, characterization, and quality control all of which are essential for reliable therapeutic results. The clinical translation of plant-derived exosome-like nanoparticles depends on their standardized and scalable production, which requires for the improvement of extraction procedures that will ensure constant vesicle yield and purity. Further, by understanding the particular mechanisms of exosome biogenesis in plants, targeted strategies to improve the delivery and efficacy of therapeutic molecules can be developed [79]. Due the variety of molecules contained in plant exosome-like nanovesicles, future research must also address potential immunogenicity and guarantee long-term safety[12]. Furthermore, thorough analyses of the pharmacokinetics and pharmacodynamics of plant-derived extracellular vesicles are necessary to guide clinical application, even though their fundamental stability and biocompatibility provide significant advantages [80]. Additionally, problems with purification techniques result in problems with exosome yield and purity, requiring the creation of more effective and economic isolation technologies to strike a balance between purity and sufficient production volumes [81]. Addressing these issues through standardized isolation, characterization, and quality-control protocols will be essential for reproducible precision nanomedicine applications.

Conclusion

The increasing burden of diabetes-associated complications, particularly chronic non-healing wounds, underscores the urgent need for safe, scalable, and mechanistically defined therapeutic strategies. *Gliricidia sepium*, a medicinal plant rich in flavonoids, saponins, tannins, and other bioactive compounds, represents a promising biological source for regenerative applications when integrated within a nanomedicine framework.

This review highlights the emerging potential of plant-derived exosome-like nanoparticles as precision nanotherapeutic systems capable of delivering phytochemical cargos in a controlled, reproducible, and biologically targeted manner. By shifting from conventional bulk plant extracts to nanoscale vesicle-mediated delivery, *Gliricidia sepium*-derived nanoparticles offer a rational strategy to modulate inflammation, oxidative stress, angiogenesis, and cellular migration in the diabetic wound microenvironment.

Despite this promise, successful clinical translation will require rigorous standardization of isolation and purification methods, scalable manufacturing, and robust quality-control metrics to ensure vesicle consistency and therapeutic reproducibility. Future research should prioritize systematic profiling of lipid, protein, and RNA cargos, along with mechanistic validation through preclinical models and well-designed clinical studies. Addressing these precision-related challenges will be critical to establishing *Gliricidia sepium*-derived exosome-like nanoparticles as a credible and translational nanomedicine platform for diabetic wound repair.

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