REVIEW ARTICLE

Molecular Docking Approaches in Evaluating Antidiabetic, Neuroprotective, and Wound Healing Potential of Plant-based Nanosuspensions

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Abstract

Diabetes mellitus is a chronic metabolic disorder associated with debilitating complications such as cognitive dysfunction and impaired wound healing. Conventional therapies largely focus on glycemic control and remain insufficient to address the complex molecular mechanisms underlying these complications. Plant-derived bioactive compounds exhibit antidiabetic, neuroprotective, and wound-healing properties; however, their clinical application is limited by poor solubility and low bioavailability. Plant-based nanosuspensions have emerged as an effective delivery strategy to enhance the pharmacological performance of phytochemicals. Molecular docking plays a crucial role in elucidating ligand–protein interactions and identifying key molecular targets involved in glucose metabolism, neuroinflammation, neurodegeneration, angiogenesis, and extracellular matrix remodeling. This review highlights docking-guided insights into the multitarget activity of phytochemicals incorporated into nanosuspensions and correlates *in silico* predictions with experimental evidence. Advances in docking methodologies, nanotechnology, and systems pharmacology support the rational development of multifunctional herbal nanosystems for the management of diabetes and its associated complications.

Key words: Diabetes mellitus, molecular docking, herbal nanosuspensions, phytochemicals, neuroprotection, wound healing, multitarget therapy

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The global prevalence of diabetes has increased at an alarming rate over the past few decades, making it a major public health concern worldwide. According to the International Diabetes Federation, diabetes affects hundreds of millions of individuals globally, with projections indicating a substantial rise in prevalence in coming years, particularly in low- and middle-income countries.[1] In addition to metabolic dysregulation, diabetes is associated with a wide range of microvascular and macrovascular complications that significantly contribute to morbidity, mortality, and healthcare expenditure.[2]

Among these complications, cognitive dysfunction and impaired wound healing have emerged as critical yet underappreciated consequences of chronic diabetes. Increasing clinical and experimental evidence indicates that prolonged hyperglycemia adversely affects central nervous system function, leading to deficits in learning, memory, and executive functions.[3] The underlying mechanisms include oxidative stress, neuroinflammation, mitochondrial dysfunction, insulin resistance in the brain, and accumulation of advanced glycation end products (AGEs).[2,3] Parallel to neurological impairment, diabetes profoundly disrupts the normal wound healing process by impairing angiogenesis, collagen deposition, immune cell function, and

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epithelialization, resulting in chronic non-healing wounds and diabetic foot ulcers.[4] These pathological conditions often coexist, reflecting shared molecular pathways and systemic metabolic disturbances.

Despite the availability of multiple classes of antidiabetic drugs and adjunctive therapies, conventional treatment strategies remain largely inadequate in preventing or reversing diabetes-associated cognitive decline and delayed wound repair. Many antidiabetic agents primarily focus on glycemic control without sufficiently addressing the oxidative stress, inflammation, and tissue regeneration.[2] Similarly, currently available neuroprotective drugs exhibit limited clinical success due to poor blood–brain barrier penetration, adverse effects, and lack of disease-modifying potential.[3] Standard wound care approaches in diabetic patients often fail to restore normal healing, frequently resulting in recurrent infections, hospitalization, and limb amputation.[4] These limitations highlight the need for therapeutic strategies capable of simultaneously targeting multiple pathological processes. Plant-derived bioactive compounds have gained considerable attention due to their broad pharmacological activities, including antidiabetic, antioxidant, anti-inflammatory, neuroprotective, and wound-healing effects. However, the clinical translation of phytoconstituents is often hindered by poor aqueous solubility, low oral bioavailability, chemical instability, and rapid metabolism.[5] Nanotechnology-based drug delivery systems have been explored as an effective approach to overcome these limitations, with nanosuspensions emerging as a particularly promising strategy for herbal drug delivery. Plant-based nanosuspensions enhance dissolution rate, improve bioavailability, promote cellular uptake, and enable targeted delivery of phytochemicals, thereby amplifying their therapeutic potential.[5,6] Due to these advantages, herbal nanosuspensions are increasingly being investigated as multifunctional systems for managing complex diabetic complications.

Molecular docking has become an essential computational technique in modern drug discovery and development, providing valuable insights into ligand–protein interactions at the atomic level. Docking studies enable the prediction of binding affinity, interaction patterns, and key molecular targets involved in disease pathways.[7] In the field of herbal nanomedicine, molecular docking plays a crucial role in elucidating the mechanisms underlying the antidiabetic, neuroprotective, and wound-healing activities of phytoconstituents incorporated into nanosuspensions. By identifying multitarget interactions and prioritizing bioactive compounds, docking approaches support rational formulation design and complement experimental pharmacological studies.[7] The integration of molecular docking with nanotechnology-based herbal therapeutics offers a systematic framework for understanding and optimizing their therapeutic efficacy.

DIABETES AND ITS ASSOCIATED COMPLICATIONS

Pathophysiology of diabetes mellitus

Diabetes mellitus is a heterogeneous metabolic disorder primarily characterized by persistent hyperglycemia arising from insulin resistance, β-cell dysfunction, or a combination of both. Insulin resistance, particularly in skeletal muscle, adipose tissue, and liver, leads to impaired glucose uptake and increased hepatic glucose production. In response, pancreatic β-cells initially compensate by increasing insulin secretion; however, prolonged metabolic stress ultimately results in β-cell exhaustion, dysfunction, and apoptosis, contributing to progressive disease severity.[8,9]

A central feature of diabetic pathophysiology is the excessive generation of reactive oxygen species, which overwhelms endogenous antioxidant defense systems and leads to oxidative stress. Hyperglycemia-induced oxidative stress activates multiple stress-sensitive signaling pathways, including nuclear factor-κB and mitogen-activated protein kinases, thereby promoting chronic low-grade inflammation.[10] This inflammatory milieu exacerbates insulin resistance, impairs β-cell function, and contributes to the development of diabetic complications.

AGEs play a pivotal role in mediating long-term tissue damage in diabetes. AGEs are formed through non-enzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids under hyperglycemic conditions. Interaction of AGEs with their receptor triggers the oxidative stress, inflammation, endothelial dysfunction, and altered gene expression, thereby accelerating vascular damage and organ dysfunction.[11] The accumulation of AGE's has been concerned with neurodegeneration, impaired wound healing, and microvascular complications associated with diabetes.

Diabetic cognitive dysfunction

Diabetic cognitive dysfunction is increasingly recognized as a significant complication of both Type 1 and Type 2 diabetes. Chronic hyperglycemia adversely affects brain structure and function, leading to deficits in learning, memory, attention, and executive function. Multiple mechanisms have been anticipated to clarify the link between hyperglycemia and neurodegeneration, including insulin resistance in the brain, mitochondrial dysfunction, oxidative stress, and impaired glucose utilization by neurons.[12,13]

Interruption of the blood–brain barrier (BBB) represents a critical pathological event in diabetes-associated cognitive impairment. Hyperglycemia and oxidative stress compromise the integrity of tight junction proteins, increasing BBB permeability and facilitating the entry of inflammatory mediators and neurotoxic substances into the central nervous

system.[14] This vascular dysfunction contributes to neuronal injury and synaptic loss.

Neuroinflammation is another key contributor to diabetic cognitive decline. Activation of microglia and astrocytes respond to metabolic stress results in the release of pro-inflammatory cytokines, chemokines, and reactive oxygen species, which interfere with synaptic plasticity and neurotransmission.[13,15] Alterations in synaptic proteins and impaired long-term potentiation further exacerbate cognitive dysfunction, highlighting the multifactorial nature of diabetes-induced neurodegeneration.

Delayed and impaired wound healing in diabetes

Delayed and impaired wound healing is a common and serious complication of diabetes, often culminating in chronic ulcers and limb amputation. Normal wound healing involves a coordinated sequence of hemostasis, inflammation, proliferation, and remodeling; however, diabetes disrupts each of these phases. One of the hallmark features of diabetic wounds is impaired angiogenesis, resulting from reduced expression of vascular endothelial growth factor and endothelial dysfunction.[4] Insufficient neovascularization limits oxygen and nutrient supply to wound site, thereby delaying tissue repair.

Collagen synthesis and extracellular matrix remodeling are also adversely affected in diabetes. Hyperglycemia impairs fibroblast function and reduces collagen deposition, leading to weakened wound tensile strength and delayed closure.[16] In addition, re-epithelialization is markedly delayed due to impaired keratinocyte migration and proliferation, further prolonging wound healing time.

Oxidative stress is a key contributor to the development of diabetic wounds, as it induces damage to cellular macromolecules and leads to a sustained inflammatory response. Elevated levels of reactive oxygen species disrupt normal cellular repair processes and impair immune cell activity, thereby increasing vulnerability to microbial infections and delaying wound healing.[4,17,18] Diabetic wounds are frequently colonized by pathogenic microorganisms, which further exacerbate inflammation and tissue damage, creating a hostile microenvironment that impedes effective healing.

PLANT-BASED BIOACTIVE COMPOUNDS IN DIABETES MANAGEMENT

Plant-derived bioactive compounds have long been utilized in traditional medicine systems for the management of diabetes and its associated complications. Advances in phytochemistry and pharmacology have identified numerous classes of secondary metabolites with proven antidiabetic, neuroprotective, and wound-healing activities. These compounds act through multiple molecular targets, making them particularly relevant for complex metabolic disorders such as diabetes.

Antidiabetic phytoconstituents

Flavonoids, alkaloids, terpenoids, and phenolic compounds represent the major classes of phytoconstituents exhibiting antidiabetic activity. Flavonoids such as quercetin, kaempferol, and catechins have been shown to improve glucose homeostasis by enhancing insulin secretion, increasing insulin sensitivity, and modulating glucose transporter activity in peripheral tissues.[19,20] Their antioxidant properties further contribute to the protection of pancreatic β-cells from oxidative damage.

Alkaloids, including berberine and vindoline, exert antidiabetic effects by activating adenosine monophosphate-activated protein kinase, suppressing hepatic gluconeogenesis, and improving insulin signaling pathways.[21] Terpenoids such as gymnemic acids and triterpenes have demonstrated the ability to regenerate pancreatic β-cells and inhibit intestinal glucose absorption.[22] Phenolic compounds, including gallic acid and chlorogenic acid, are known to reduce postprandial hyperglycemia through inhibition of carbohydrate-digesting enzymes.

One of the most significant mechanisms of antidiabetic phytoconstituents is the inhibition of α-glucosidase and α-amylase enzymes, which delays carbohydrate digestion and glucose absorption in the intestine.[23] In addition, several phytochemicals enhance insulin sensitivity by modulating peroxisome proliferator-activated receptor-γ and insulin receptor signaling pathways, thereby improving peripheral glucose utilization.[20,24]

Neuroprotective phytochemicals

Neuroprotective phytochemicals play a crucial role in mitigating diabetes-associated cognitive dysfunction through their antioxidant and anti-inflammatory activities. Chronic hyperglycemia induces excessive production of reactive oxygen species in neural tissues, leading to neuronal damage and synaptic dysfunction. Polyphenols and flavonoids scavenge free radicals, enhance endogenous antioxidant defenses, and protect neuronal cells from oxidative stress-induced apoptosis.[25]

In addition to antioxidant effects, many plant-derived compounds exhibit potent anti-inflammatory actions by inhibiting pro-inflammatory mediators such as tumor necrosis factor-α, interleukin-1β, and cyclooxygenase-2.[26] These effects contribute to reduced microglial activation and attenuation of neuroinflammation, which is a key pathological feature of diabetic cognitive impairment.

Phytochemicals also modulate neurotransmitter systems and intracellular signaling pathways involved in cognition and neuronal survival. Compounds such as curcumin, resveratrol, and ginsenosides have been shown to regulate acetylcholine levels, enhance brain-derived neurotrophic factor expression, and activate signaling pathways such as phosphoinositide 3-kinase/protein kinase B and mitogen-activated protein kinases, thereby improving synaptic plasticity and cognitive function.[27,28]

Wound healing phytochemicals

Plant-derived bioactive compounds contribute significantly to wound healing through angiogenic, antimicrobial, and collagen-promoting effects. Flavonoids and terpenoids stimulate angiogenesis by upregulating vascular endothelial growth factor and nitric oxide production, thereby enhancing blood supply to the wound site.[29] Improved angiogenesis facilitates oxygen and nutrient delivery, which is critical for effective tissue repair in diabetic wounds.

Many phytochemicals possess broad-spectrum antimicrobial activity against pathogenic bacteria commonly associated with diabetic wound infections. Phenolic compounds and essential oils disrupt microbial cell membranes and inhibit biofilm formation, thereby reducing infection-induced inflammation and tissue damage.[30] In parallel, phytochemicals promote fibroblast proliferation and collagen synthesis, leading to improved extracellular matrix formation and increased wound tensile strength.[31]

Beyond antimicrobial and angiogenic effects, plant-based compounds actively participate in tissue regeneration by regulating growth factors, cytokines, and matrix remodeling enzymes. These actions support re-epithelialization, granulation tissue formation, and remodeling of damaged tissue, which are often compromised under diabetic conditions.[32]

Linking phytochemicals to molecular docking targets

Molecular docking studies have demonstrated that plant-derived phytochemicals interact with multiple protein targets involved in glucose metabolism, neurodegeneration, inflammation, angiogenesis, and tissue repair. These interactions provide mechanistic justification for their observed pharmacological effects and support their incorporation into nanosuspension-based delivery systems. Frequently docked targets include carbohydrate-hydrolyzing enzymes, insulin signaling proteins, neurodegenerative markers, inflammatory mediators, and wound-healing–related growth factors.[52-55,56-63]

Docking analysis typically reveals hydrogen bonding, hydrophobic interactions, and π–π stacking between phytochemicals and active site residues of target proteins, resulting in enzyme inhibition or pathway modulation. Such multitarget engagement is particularly relevant for managing diabetes and its complications, which involve interconnected molecular pathways, has been tabulated in Tables 1-4 and picturized in Figure 1.[43-45,52,56]

NANOTECHNOLOGY IN HERBAL DRUG DELIVERY

Nanotechnology has emerged as a transformative approach in herbal drug delivery, addressing major limitations associated with plant-derived bioactive compounds, such as poor solubility, low bioavailability, and inconsistent therapeutic performance. Among various nanocarriers, nanosuspensions have gained considerable attention for delivering hydrophobic phytoconstituents and enhancing their pharmacological efficacy in complex disorders such as diabetes and its associated complications.[33-35]

Concept and advantages of nanosuspensions

Nanosuspensions are colloidal dispersions of drug particles in the nanometer size range, typically stabilized by surfactants or polymers. Unlike polymeric nanoparticles or lipid-based systems, nanosuspensions consist primarily of pure drug particles, making them particularly suitable for poorly water-soluble phytochemicals.[33] Reduction of particle size to the nanometer scale significantly increases surface area, leading to enhanced dissolution rate and improved solubility.

Enhanced solubility directly translates into increased oral bioavailability, especially for plant-derived compounds that exhibit limited gastrointestinal absorption. Nanosuspensions also improve pharmacokinetic profiles by promoting rapid dissolution, prolonged residence time, and improved absorption across biological membranes.[34] In addition, nanoscale particles exhibit improved tissue targeting and cellular uptake due to enhanced permeation and retention effects, as well as endocytic internalization by target cells.[35] Another key advantage of nanosuspensions is the reduction in the required therapeutic dose. Improved bioavailability allows lower drug concentrations to achieve desired pharmacological effects, thereby minimizing systemic toxicity and adverse effects.[36] This is particularly relevant for herbal compounds that may exhibit dose-dependent toxicity or off-target effects at higher concentrations.

Preparation methods of plant-based nanosuspensions

Several bottom-up and top-down techniques have been employed for the preparation of plant-based nanosuspensions, each offering distinct advantages and limitations. High-pressure homogenization is one of the most widely used

Table 1: Antidiabetic phytochemicals and their molecular docking targets involved in glucose homeostasis and insulin signaling[52,55]

Phytochemical	Chemical class	Docking target	Target role	Mechanism of action
Quercetin	Flavonoid	α-Glucosidase	Carbohydrate digestion	Competitive inhibition, reduced postprandial glucose
Kaempferol	Flavonoid	α-Amylase	Starch breakdown	Suppresses glucose release
Chlorogenic acid	Phenolic acid	Glucose-6-phosphatase	Hepatic gluconeogenesis	Reduces hepatic glucose output
Berberine	Alkaloid	AMPK	Energy metabolism	Enhances insulin sensitivity
Gymnemic acid	Triterpenoid saponin	PPAR-γ	Insulin signaling	Improves glucose uptake
Catechin	Flavonoid	DPP-4	Incretin degradation	Prolongs GLP-1 activity

AMPK: Adenosine monophosphate-activated protein kinase, PPAR-γ: Peroxisome proliferator-activated receptor gamma, DPP-4: Dipeptidyl peptidase-4, GLP-1: Glucagon-like peptide-1

Table 2: Neuroprotective phytochemicals and molecular docking targets relevant to diabetic cognitive dysfunction[56-60]

Phytochemical	Chemical Class	Docking Target	Target Role	Mechanism of Action
Curcumin	Polyphenol	AChE	Neurotransmitter degradation	Inhibits AChE, improves cholinergic signaling
Resveratrol	Stilbene	SIRT1	Neuronal survival	Enhances mitochondrial function
Ginsenoside Rg1	Triterpenoid	NMDA receptor	Excitotoxicity	Modulates glutamate signaling
Epigallocatechingallate	Flavonoid	β-Amyloid	Protein aggregation	Prevents amyloid fibril formation
Luteolin	Flavonoid	COX-2	Neuroinflammation	Reduces inflammatory mediator production
Apigenin	Flavonoid	MAPK	Stress signaling	Suppresses neuronal apoptosis

AChE: Acetylcholinesterase, COX-2: Cyclooxygenase-2, NMDA: N-methyl-D-aspartate, MAPK: Mitogen-activated protein kinases, SIRT1: Sirtuin 1

Table 3: Wound-healing phytochemicals and their docking-validated molecular targets[61-64]

Phytochemical	Chemical class	Docking target	Target role	Mechanism of action
Asiaticoside	Triterpenoid	TGF-β receptor	Collagen synthesis	Promotes fibroblast proliferation
Quercetin	Flavonoid	VEGF receptor	Angiogenesis	Enhances neovascularization
Curcumin	Polyphenol	MMP-9	ECM degradation	Controls matrix remodeling
Eugenol	Phenolic compound	Bacterial DNA gyrase	Microbial survival	Antimicrobial action
Catechin	Flavonoid	iNOS	Nitric oxide production	Reduces oxidative damage
Aloin	Anthraquinone	NF-κB	Inflammation	Suppresses pro-inflammatory signaling

TGF-β: Transforming growth factor-beta, VEGF: Vascular endothelial growth factor, MMP-9: Matrix Metalloproteinase-9, iNOS: Inducible nitric oxide synthase, NF-κB: Nuclear Factor kappa B, ECM: Extracellular matrix

top-down approaches, wherein coarse drug suspensions are subjected to intense shear forces, cavitation, and particle–particle collisions under high pressure. Repeated homogenization cycles result in uniform nanosized particles with a narrow size distribution.[37] This method is scalable and suitable for industrial production of herbal nanosuspensions.

Antisolvent precipitation is a bottom-up technique based on controlled nucleation and crystal growth. In this method, the drug is dissolved in a suitable solvent and rapidly mixed with a non-solvent, leading to supersaturation and precipitation of nanosized drug particles.[38] Antisolvent precipitation is particularly useful for thermolabile phytochemicals and allows better control over particle size when combined with stabilizers. Media milling involves mechanical attrition of drug particles using milling beads under controlled conditions. Continuous collision between the milling media and drug particles results in progressive size reduction to the nanometer range.[39] This method is effective for producing stable nanosuspensions of poorly soluble herbal compounds, although prolonged milling may induce crystal defects or contamination.

Table 4: Multitarget phytochemicals relevant for docking-guided nanosuspension development in diabetic complications[52,56,66]

Phytochemical	Diabetes target	Neuro target	Wound target	Therapeutic significance
Quercetin	α-Glucosidase	AChE	VEGF	Multifunctional anti-diabetic and regenerative agent
Curcumin	AMPK	AChE	MMP-9	Metabolic, neuroprotective, and wound repair
Resveratrol	PPAR-γ	SIRT1	VEGF	Insulin sensitization and neurovascular protection
Catechin	DPP-4	β-Amyloid	iNOS	Antioxidant and anti-inflammatory
Berberine	AMPK	MAPK	NF-κB	Glycemic control and inflammation modulation

AChE: Acetylcholinesterase, DPP-4: Dipeptidyl peptidase-4, AMPK: Adenosine monophosphate-activated protein kinase, MAPK: Mitogen-activated protein kinases, VEGF: Vascular endothelial growth factor, MMP-9: Matrix Metalloproteinase-9, iNOS: Inducible nitric oxide synthase, NF-κB: Nuclear Factor kappa B, PPAR-γ: Peroxisome proliferator-activated receptor gamma

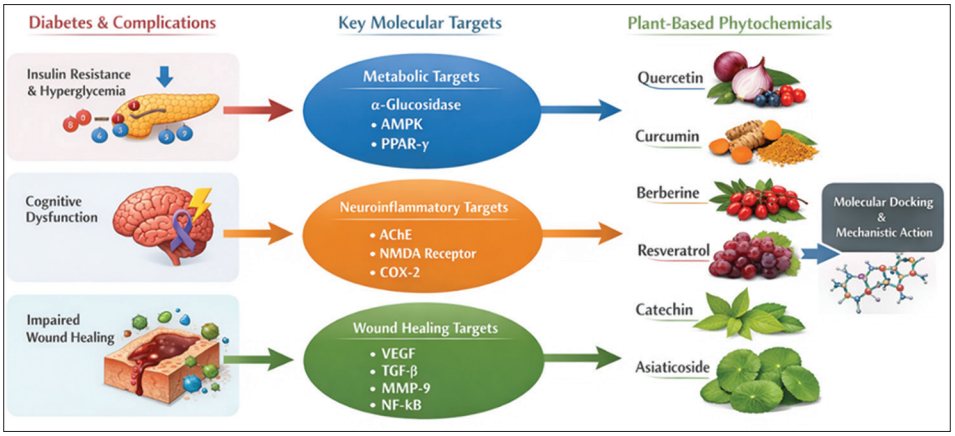

Figure 1: Phytochemical intervention in diabetes and its complications

Characterization parameters

Comprehensive physicochemical characterization is essential to ensure the quality, stability, and performance of herbal nanosuspensions. Particle size and polydispersity index (PDI) are critical parameters that influence dissolution rate, bioavailability, and physical stability. Smaller particle size and low PDI values indicate uniform particle distribution and reduced risk of aggregation.[40] Zeta potential reflects the surface charge of nanosuspension particles and serves as an indicator of colloidal stability. High absolute zeta potential values, either positive or negative, promote electrostatic repulsion between particles, thereby preventing aggregation and enhancing long-term stability.[41]

Drug loading and stability are equally important parameters for evaluating nanosuspension performance. High drug loading ensures efficient delivery of phytoconstituents, while physical and chemical stability studies assess changes in particle size, crystallinity, and drug content during storage. Stability evaluation under different temperature and humidity conditions is essential for predicting shelf life and ensuring reproducibility of therapeutic outcomes has shown in Figure 2.[42]

MOLECULAR DOCKING IN HERBAL NANOMEDICINE RESEARCH

Molecular docking has emerged as a powerful computational technique in herbal nanomedicine research, enabling the exploration of molecular interactions between plant-derived bioactive compounds and disease-relevant protein targets. When combined with nanotechnology-based delivery systems, docking studies provide mechanistic insights that strengthen the scientific basis for the development of plant-based nanosuspensions in the management of diabetes and its associated complications; a clear outline pictorial representation has been given in Figure 3.[7,43-48]

Principles of molecular docking

Molecular docking is based on the theoretical framework of ligand–protein interaction, wherein a small molecule ligand binds to a specific active or allosteric site of a target protein to form a stable complex. The docking process involves predicting the optimal orientation, conformation, and position of the ligand within the protein binding site, governed by non-covalent interactions such as hydrogen bonding, hydrophobic interactions, electrostatic forces, and π–π stacking.[43,44]

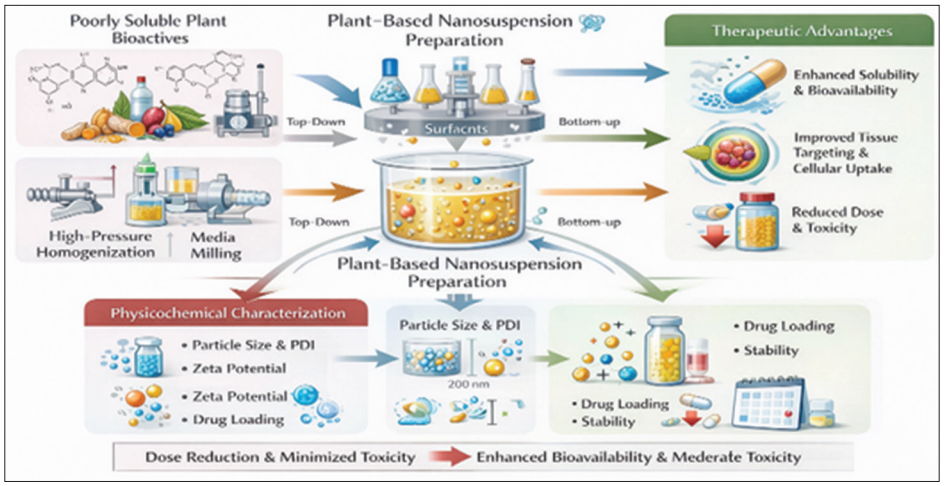

Figure 2: Plant-based nanosuspensions in herbal industry (Biorender software)

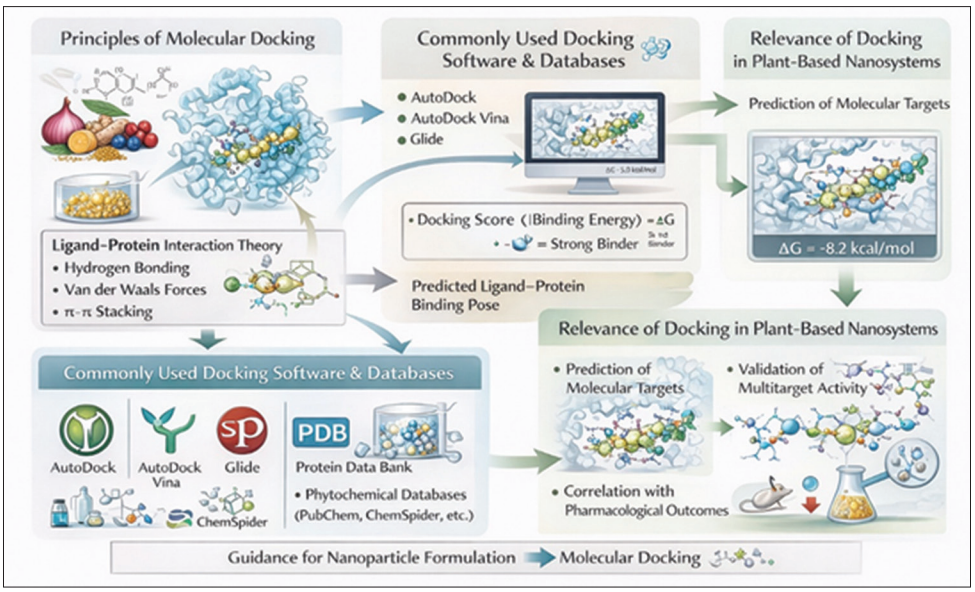

Figure 3: Molecular docking in herbal nanomedicine research (Biorender software)

Binding affinity is a key outcome of docking analysis and reflects the strength of interaction between the ligand and the target protein. It is typically expressed as binding energy (kcal/mol), with more negative values indicating stronger interactions. Scoring functions are mathematical models used to estimate binding affinity by evaluating energetic contributions from intermolecular forces, desolvation effects, and conformational entropy.[45] These scoring functions enable ranking of ligands and identification of potential lead compounds from large phytochemical libraries.

Commonly used docking software and databases

Several molecular docking software tools are widely employed in herbal drug and nanomedicine research. AutoDock and AutoDockVina are among the most commonly used open-source docking programs, known for their flexibility, reliability, and ability to handle a wide range of ligand types, including phytochemicals.[46] AutoDockVina offers improved speed and accuracy through an enhanced scoring function and efficient optimization algorithm. Glide, a proprietary docking tool, is frequently used for high-precision docking and virtual screening. It employs hierarchical filtering and refined scoring algorithms to predict ligand–protein interactions with high accuracy.[47] Glide is particularly useful for validating docking results obtained from open-source platforms. Protein structures required for docking studies are primarily obtained from the Protein Data Bank, which provides experimentally determined three-dimensional structures of proteins, enzymes, and receptors.[48] For ligand preparation, phytochemical structures are retrieved from curated databases such as PubChem, ChemSpider, and traditional medicine-specific phytochemical repositories. These databases facilitate the systematic screening of plant-derived compounds against multiple molecular targets.[7,48-49]

Relevance of docking in plant-based nanosystems

Molecular docking plays a critical role in predicting potential molecular targets of phytochemicals incorporated into plant-based nanosuspensions. By identifying specific protein targets involved in glucose metabolism, neurodegeneration, inflammation, and wound healing, docking studies guide the rational selection of bioactive compounds for formulation development.[7] An important advantage of docking in herbal nanomedicine is its ability to validate multitarget activity, a hallmark of phytochemicals. Docking analysis often reveals that a single compound can interact with multiple disease-related targets, supporting the use of herbal nanosuspensions for managing complex, multifactorial disorders such as diabetes and its complications.[49] Furthermore, docking studies enable correlation between *in silico* predictions and experimental pharmacological outcomes. Binding affinity and interaction profiles obtained through docking frequently align with observed *in vitro* and *in vivo* activities, such as enzyme inhibition, antioxidant effects, and tissue regeneration. This correlation enhances confidence in docking-guided drug development and reduces reliance on extensive trial-and-error experimentation.[50]

Docking targets relevant to antidiabetic activity

Molecular docking studies targeting proteins involved in glucose metabolism have provided mechanistic insight into the antidiabetic effects of plant phytochemicals. α-Glucosidase and α-amylase are carbohydrate-digesting enzymes; docking analyses frequently demonstrate strong binding of flavonoids and phenolics to their active sites, supporting enzyme inhibition and attenuation of postprandial hyperglycemia. Dipeptidyl peptidase-4 inhibition through phytochemical docking suggests prolonged incretin function and enhanced insulin secretion. Docking with peroxisome proliferator-activated receptor-γ indicates modulation of insulin sensitivity and glucose uptake regulation. Phytochemicals also show favorable interactions with the insulin receptor and glucose transporters, supporting improved insulin signaling and peripheral glucose uptake *in silico*.[51-54] When formulated as nanosuspensions, these bioactive often display enhanced docking relevance correlated with increased systemic exposure and bioactivity.

Docking targets in neuroprotection

Neuroprotective docking studies emphasize enzymes and receptors relevant to cognitive function and neurodegeneration. Acetylcholinesterase and butyrylcholinesterase are targeted to preserve cholinergic neurotransmission, with many flavonoids and polyphenols showing high binding affinity within their catalytic sites. Docking against N-methyl-D-aspartate receptors highlights potential regulation of excitotoxicity. In addition, interactions with β-amyloid and Tau protein binding regions suggest a mechanism for inhibiting protein aggregation linked to cognitive decline. Docking toward neuroinflammatory mediators such as cyclooxygenase-2 and inducible nitric oxide synthase underscores potential anti-inflammatory activity relevant to diabetes-associated neurodegeneration.[55-62]

Docking targets in wound healing

Wound healing–related docking studies focus on proteins central to angiogenesis, matrix remodeling, and infection control. Vascular endothelial growth factor and associated signaling proteins are common targets, and phytochemicals often show interactions that suggest enhancement of neovascularization. Docking with transforming growth factor-β and collagen synthesis–related pathways indicates potential for accelerated fibroblast activity and matrix deposition. Matrix metalloproteinases (MMPs), particularly MMP-2 and MMP-9, are targeted to modulate extracellular matrix turnover, while docking against microbial enzymes implicated in wound infection points to possible antimicrobial action supportive of diabetic wound management.[62,63]

Correlation between *in silico* docking and experimental evidence

Strong correlations have been reported between docking predictions and experimental pharmacological outcomes. Phytochemicals with high predicted binding affinity toward antidiabetic targets frequently exhibit significant *in vitro* α-glucosidase inhibition, antioxidant activity, and insulin sensitization. Similarly, favorable docking against neuroprotective targets aligns with *in vivo* cognitive improvements and attenuation of neuroinflammation in animal models. In wound healing studies, docking interactions with angiogenic and matrix-related proteins correlate with accelerated wound closure, enhanced collagen deposition, and infection control. The incorporation of phytochemicals into nanosuspension formulations further enhances these effects by improving solubility, bioavailability, and targeted delivery, resulting in synergistic outcomes that validate docking predictions.[62-66]

Advantages of molecular docking–guided herbal nanosuspension development

Molecular docking–guided development of herbal nanosuspensions offers several strategic advantages. It supports cost-effective identification of lead phytochemicals and molecular targets, reducing time and resource expenditure in early drug discovery. Docking assists in reducing animal experimentation by prioritizing compounds with favorable binding profiles. Insights from docking contribute to rational formulation design, enabling selection of phytochemicals with optimal multitarget affinity that benefit from nanosuspension delivery. Crucially, docking reveals multitarget

Table 5: Summary of molecular docking targets and representative phytochemicals involved in diabetes and its associated complications[52-66]

Disease/ Complication	Key docking targets	Representative phytochemicals	Docking outcome	Therapeutic relevance
Diabetes mellitus	α-Glucosidase, α-Amylase	Quercetin, Catechin	Active site binding	Reduced postprandial hyperglycemia
	DPP-4	Berberine, Luteolin	Enzyme inhibition	Enhanced incretin activity
	PPAR-γ	Curcumin, Resveratrol	Agonist-like interaction	Improved insulin sensitivity
	Insulin receptor, GLUTs	Genistein, Catechin	Stable domain interaction	Increased glucose uptake
Diabetic cognitive dysfunction/ Neurodegeneration	AChE, BchE	Curcumin, Apigenin	Catalytic gorge binding	Enhanced cholinergic signaling
	NMDA receptor	Ginsenosides, Resveratrol	Modulation of ligand site	Reduced excitotoxicity
	β-Amyloid, Tau	EGCG, Luteolin	Aggregation inhibition	Neuroprotection
	COX-2, iNOS	Quercetin, Kaempferol	Anti-inflammatory docking	Reduced neuroinflammation
impaired wound healing	VEGF	Quercetin, Resveratrol	Receptor interaction	Enhanced angiogenesis
	TGF-β	Asiaticoside, Curcumin	Fibroblast pathway activation	Increased collagen synthesis
	MMP-2, MMP-9	Catechin, Curcumin	Enzyme inhibition	Controlled ECM remodeling
	Microbial enzymes	Eugenol, Berberine	Antimicrobial docking	Infection control
Multisystem diabetic complications	Multiple targets	Quercetin, Curcumin	Multitarget affinity	Synergistic therapeutic action (nanosuspensions)

AChE: Acetylcholinesterase, DPP-4: Dipeptidyl peptidase-4, PPAR-γ: Peroxisome proliferator-activated receptor gamma, GLUTs: Glucose transporters, BchE: Butyrylcholinesterase, NMDA: N-methyl-D-aspartate, COX-2: Cyclooxygenase-2, iNOS: Inducible nitric oxide synthase, VEGF: Vascular endothelial growth factor, TGF-β: Transforming growth factor-beta, MMP-2: Matrix Metalloproteinase-2, MMP-9: Matrix Metalloproteinase-9, EGCG: Epigallocatechin gallate, ECM: Extracellular matrix

therapeutic potential, which is particularly valuable for complex, multifactorial disorders such as diabetes, neurodegeneration, and impaired wound healing, it has been summarized in Table 5.[52,56,66]

FUTURE PERSPECTIVES

Future research in docking-guided herbal nanomedicine is expected to evolve toward more integrative and predictive approaches. The integration of molecular dynamics simulations with docking studies will allow better assessment of binding stability, protein flexibility, and time-dependent ligand target interactions, thereby improving the reliability of computational predictions. The application of artificial intelligence–assisted docking and network pharmacology is anticipated to transform herbal drug discovery. Machine learning algorithms can analyze large phytochemical datasets, predict multitarget interactions, and uncover complex signaling networks involved in diabetes, neurodegeneration, and wound healing. Such approaches align well with the polypharmacological nature of plant-based therapeutics.

Advances in systems biology and biomarker discovery may enable personalized herbal nanotherapy, where docking-guided selection of phytochemicals and nanosuspension formulations is tailored to individual disease profiles and genetic backgrounds. Furthermore, emphasis on clinical translation of docking-guided nanosystems, supported by robust preclinical validation, standardized manufacturing practices, and regulatory alignment, will be essential for successful bench-to-bedside progression.

CONCLUSION

Molecular docking has emerged as a valuable computational tool for elucidating the molecular mechanisms underlying the antidiabetic, neuroprotective, and wound-healing activities of plant-derived phytochemicals. By identifying key ligand protein interactions and multitarget binding profiles,

docking studies have significantly enhanced understanding of how phytoconstituents modulate complex pathological pathways associated with diabetes and its complications. The incorporation of phytochemicals into plant-based nanosuspensions further amplifies their therapeutic potential by improving solubility, bioavailability, tissue targeting, and safety profiles. Together, molecular docking and nanotechnology provide a rational and complementary framework for the development of multifunctional herbal therapeutics. Overall, docking-driven herbal nanomedicine represents a promising interdisciplinary strategy that bridges computational modeling with experimental pharmacology. Continued integration of advanced computational techniques, innovative formulation approaches, and translational research is expected to accelerate the development of effective, safe, and multitarget therapies for diabetes and related disorders.

AUTHORS' CONTRIBUTIONS

Charritha Rangam: Writing–review and editing, writing–original draft, investigation, data curation; Mohammad Ali: Writing–review and editing, writing–original draft, methodology, validation, supervision.

CONSENT FOR PUBLICATION

All authors have approved the manuscript and consent to publication.

DATA AVAILABILITY

All data are available in the main text.

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