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BRAIN-TARGETED LIPID NANOCARRIERS OF ANTIDIABETIC PHYTOCHEMICALS FOR DIABETIC NEUROPATHY

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ABSTRACT

Diabetic neuropathy is one of the most common and debilitating complications of diabetes mellitus, characterized by nerve damage, oxidative stress, neuroinflammation, and impaired neuronal signaling. Conventional therapeutic approaches mainly provide symptomatic relief and often fail to prevent progressive neuronal degeneration. In recent years, phytochemicals such as curcumin, quercetin, resveratrol, berberine, and epigallocatechin gallate have gained significant attention because of their antioxidant, anti-inflammatory, neuroprotective, and antidiabetic activities. However, their clinical application is limited by poor aqueous solubility, low bioavailability, rapid metabolism, and restricted penetration across the blood–brain barrier. Brain-targeted lipid nanocarriers have emerged as a promising strategy to overcome these limitations and improve targeted delivery to neural tissues. Lipid-based nanocarriers, including solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and nanoemulsions, enhance drug stability, prolong circulation time, improve brain uptake, and enable controlled release of phytochemicals. Surface modification with targeting ligands further enhances transport across the blood–brain barrier and increases therapeutic efficacy in diabetic neuropathy. This approach may reduce neuronal oxidative stress, improve nerve conduction, and prevent neurodegeneration with minimal systemic toxicity. The present review highlights the role of brain-targeted lipid nanocarriers in enhancing the therapeutic potential of antidiabetic phytochemicals for the management of diabetic neuropathy and discusses recent advancements, challenges, and future perspectives in this emerging field.

KEYWORDS

- Diabetic neuropathy
- Brain-targeted drug delivery
- Lipid nanocarriers
- Antidiabetic phytochemicals
- Solid lipid nanoparticles
- Nanostructured lipid carriers

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder associated with persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both. Long-term uncontrolled diabetes leads to several microvascular and macrovascular complications, among which diabetic neuropathy is one of the most prevalent and severe disorders affecting the peripheral and central nervous systems. Diabetic neuropathy is characterized by pain, numbness, burning sensation, loss of sensory function, and progressive neuronal damage that significantly reduces the quality of life of patients. The pathogenesis of diabetic neuropathy involves oxidative stress, inflammation, mitochondrial dysfunction, accumulation of advanced glycation end products, and impaired neuronal blood supply.

Current treatment strategies for diabetic neuropathy mainly focus on glycemic control and symptomatic pain management using anticonvulsants, antidepressants, and analgesics. However, these therapies often produce limited therapeutic benefits and may cause adverse effects during long-term use. Therefore, the development of safer and more effective therapeutic approaches is necessary for the prevention and treatment of diabetic neuropathy.

Phytochemicals obtained from medicinal plants have shown promising therapeutic potential in diabetes and neurological disorders because of their antioxidant, anti-inflammatory, neuroprotective, and antidiabetic properties. Bioactive compounds such as curcumin, quercetin, resveratrol, berberine, and catechins have demonstrated the ability to reduce oxidative stress, regulate inflammatory mediators, and protect neuronal cells from hyperglycemia-induced damage. Despite their pharmacological potential, the clinical application of these phytochemicals is restricted due to poor solubility, instability, rapid metabolism, low oral bioavailability, and inadequate penetration across the blood–brain barrier.

Nanotechnology-based drug delivery systems have emerged as an advanced strategy to improve the therapeutic efficacy of phytochemicals. Among them, lipid nanocarriers have gained considerable attention because of their biocompatibility, low toxicity, high drug-loading capacity, and ability to enhance brain targeting. Lipid nanocarriers such as solid lipid nanoparticles, nanostructured lipid carriers, liposomes, and nanoemulsions can improve the solubility and stability of phytochemicals while enabling controlled and sustained drug release. In addition, surface-functionalized lipid nanocarriers can facilitate transport across the blood–brain barrier and increase drug accumulation in neuronal tissues.

Brain-targeted lipid nanocarriers offer a novel therapeutic platform for delivering antidiabetic phytochemicals directly to affected neural tissues in diabetic neuropathy. This targeted delivery system may improve neuroprotection, reduce oxidative damage, enhance nerve regeneration, and minimize systemic side effects. Therefore, the integration of phytochemicals with brain-targeted lipid nanocarriers represents a promising and innovative approach for the effective management of diabetic neuropathy.

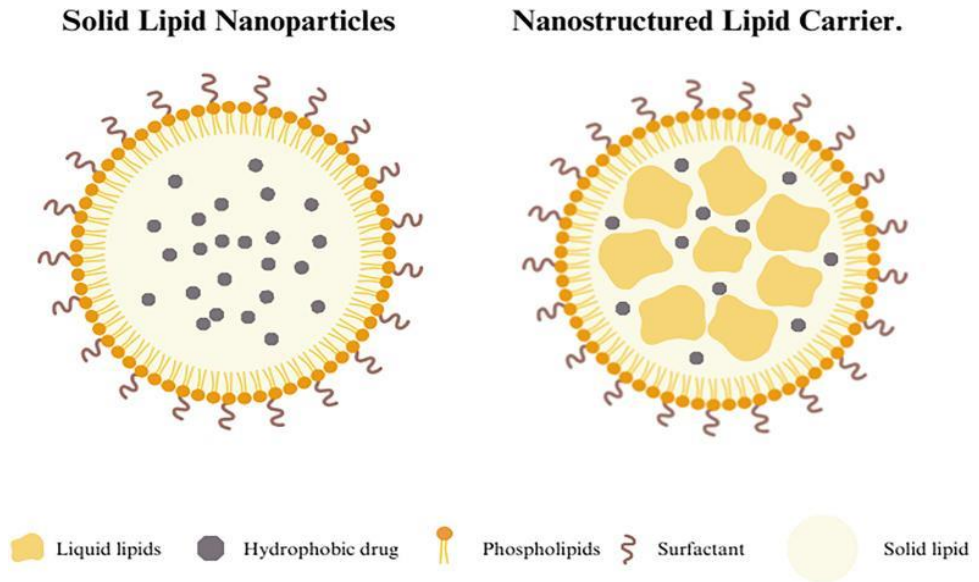

Figure 1: Schematic representation of Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) used for brain-targeted delivery of antidiabetic phytochemicals. SLNs consist of a solid lipid core encapsulating hydrophobic drugs, whereas NLCs contain a mixture of solid and liquid lipids that enhance drug loading capacity, stability, and controlled drug release for improved therapeutic efficacy in diabetic neuropathy.

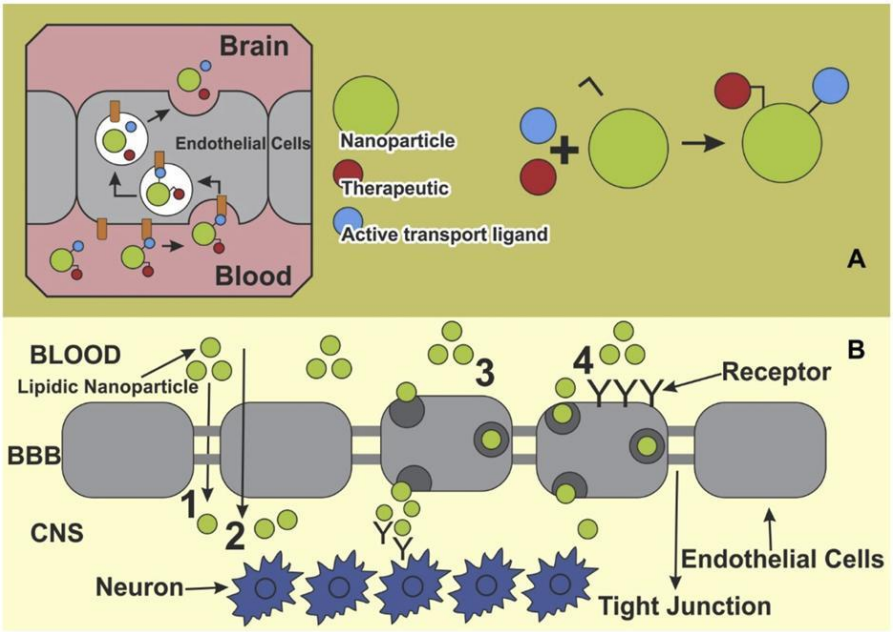

Figure 2: Schematic illustration of brain-targeted lipid nanoparticle delivery across the blood–brain barrier (BBB). Surface-functionalized nanoparticles containing therapeutic agents and active transport ligands interact with endothelial cell receptors, facilitating receptor-mediated transport across the BBB and targeted delivery to neurons in the central nervous system (CNS) for the treatment of diabetic neuropathy.

MATERIALS AND METHODS

Materials

Antidiabetic phytochemicals such as curcumin, quercetin, resveratrol, and berberine were selected based on their reported neuroprotective and antidiabetic activities. Lipids including glyceryl monostearate, stearic acid, lecithin, and cholesterol were used for the preparation of lipid nanocarriers. Surfactants such as Tween 80, Poloxamer 188, and Span 80 were utilized for stabilization of the nanoformulations. Organic solvents including ethanol and chloroform of analytical grade were used during formulation development. All chemicals and reagents employed in the study were of pharmaceutical or analytical grade and obtained from standard commercial suppliers.

Experimental animals such as Wistar rats or Swiss albino mice were used for in vivo evaluation. Animals were maintained under standard laboratory conditions with controlled temperature, humidity, and light–dark cycle, and were provided with standard food and water ad libitum. The experimental protocol was approved by the Institutional Animal Ethics Committee (IAEC).

METHODOLOGY

1. Preparation of Brain-Targeted Lipid Nanocarriers

Brain-targeted lipid nanocarriers containing antidiabetic phytochemicals were prepared using the hot homogenization followed by ultrasonication method. The selected lipid was melted at a temperature above its melting point, and the phytochemical was dissolved or dispersed in the molten lipid phase. An aqueous surfactant solution heated to the same temperature was added gradually to the lipid phase under continuous stirring to form a pre-emulsion. The obtained emulsion was homogenized at high speed and further ultrasonicated to reduce particle size and obtain stable nanoparticles. The prepared formulation was cooled to room temperature for solidification of lipid nanoparticles.

For brain targeting, surface modification of nanocarriers was performed using targeting ligands such as polysorbate 80, transferrin, or lactoferrin to improve blood–brain barrier penetration.

2. Characterization of Lipid Nanocarriers

The prepared formulations were evaluated for the following parameters:

a) Particle Size and Polydispersity Index (PDI)

Particle size, size distribution, and PDI were measured using dynamic light scattering techniques.

b) Zeta Potential

Zeta potential analysis was carried out to determine surface charge and stability of the nanocarriers.

c) Entrapment Efficiency

Entrapment efficiency of phytochemicals within lipid nanocarriers was determined by centrifugation method followed by spectrophotometric or HPLC analysis.

d) Morphological Evaluation

Surface morphology and shape of nanoparticles were examined using scanning electron microscopy (SEM) or transmission electron microscopy (TEM).

e) In Vitro Drug Release Study
Drug release studies were performed using dialysis membrane diffusion technique in phosphate buffer solution at physiological pH. Samples were withdrawn at predetermined intervals and analyzed for drug content.

3. In Vitro Evaluation
a) Antioxidant Activity
The antioxidant potential of the phytochemical-loaded nanocarriers was assessed using DPPH or hydrogen peroxide scavenging assay.

b) Cell Viability Study
Neuronal cell lines were used to evaluate cytotoxicity and neuroprotective effects of the formulations using MTT assay.

c) Blood–Brain Barrier Permeability Study
In vitro permeability studies were conducted using suitable blood–brain barrier models to evaluate brain-targeting efficiency.

4. In Vivo Evaluation of Diabetic Neuropathy
a) Induction of Diabetes
Experimental diabetes was induced in animals using streptozotocin (STZ) administered intraperitoneally. Animals showing elevated blood glucose levels were considered diabetic.

b) Treatment Protocol
Animals were divided into different experimental groups including normal control, diabetic control, pure phytochemical-treated group, and phytochemical-loaded lipid nanocarrier-treated group. Formulations were administered orally or intravenously for a specified treatment duration.

c) Behavioral Assessment
Neuropathic pain and sensory responses were evaluated using hot plate test, tail flick test, and mechanical allodynia assessment.

d) Biochemical Analysis
Oxidative stress markers such as malondialdehyde, superoxide dismutase, catalase, and reduced glutathione were estimated in neural tissues.

e) Histopathological Study
Histological examination of brain and nerve tissues was carried out to evaluate neuronal protection and tissue recovery after treatment.

5. Statistical Analysis
All experimental data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way ANOVA followed by suitable post hoc tests. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Table 1: Particle Size, PDI, and Zeta Potential of Brain-Targeted Lipid Nanocarriers.

Formulation Code	Particle Size (nm)	PDI	Zeta Potential (mV)
F1	145.2 ± 2.4	0.218 ± 0.01	-21.4 ± 1.2
F2	162.7 ± 3.1	0.254 ± 0.02	-24.8 ± 1.5
F3	138.5 ± 2.0	0.201 ± 0.01	-27.1 ± 1.1
F4	171.9 ± 3.5	0.289 ± 0.03	-22.5 ± 1.4

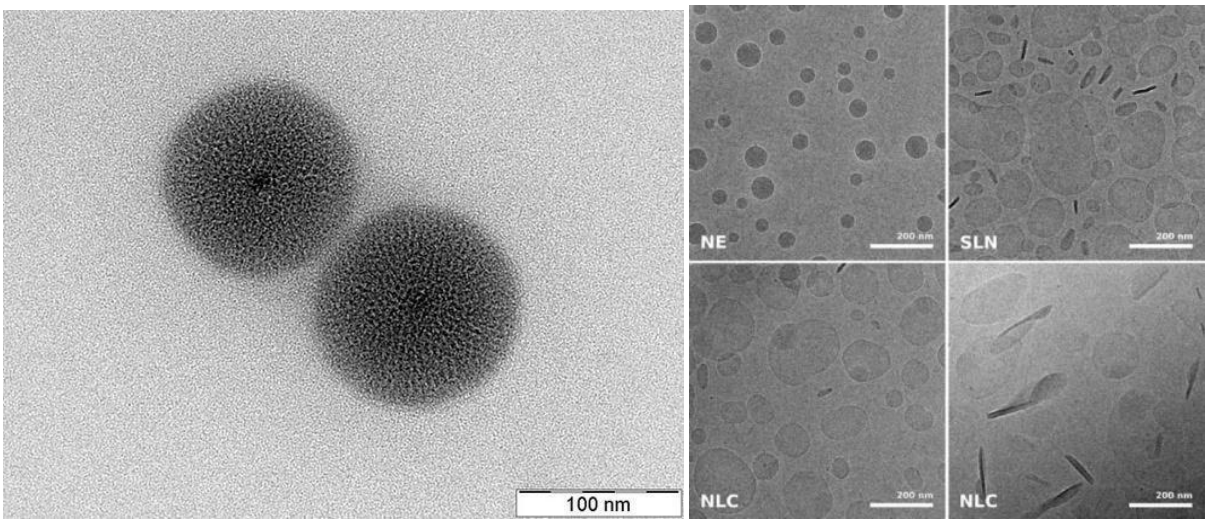

Figure 1: TEM/SEM images showing spherical morphology and nanoscale size distribution of brain-targeted lipid nanocarriers.

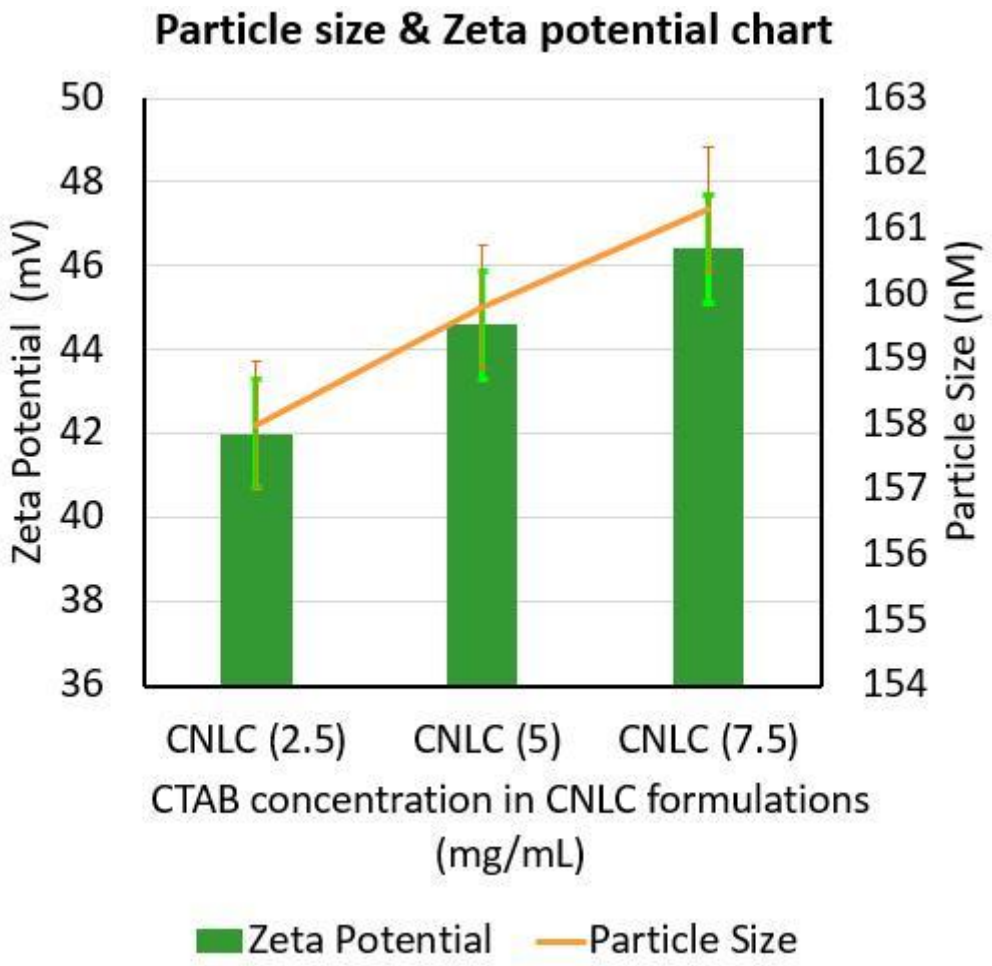

Figure 2: Particle size distribution and zeta potential profile of phytochemical-loaded lipid nanocarriers.

Table 2: Entrapment Efficiency and Drug Loading of Phytochemical-Loaded Nanocarriers.

Formulation Code	Entrapment Efficiency (%)	Drug Loading (%)
F1	78.6 ± 1.8	9.4 ± 0.3
F2	82.3 ± 2.1	10.1 ± 0.4
F3	88.7 ± 1.5	11.3 ± 0.2
F4	80.5 ± 1.9	9.8 ± 0.3

Table 3: In Vitro Drug Release Study.

Time (h)	F1 (%)	F2 (%)	F3 (%)	F4 (%)
1	18.4 ± 1.1	16.2 ± 1.0	14.5 ± 0.9	17.8 ± 1.1
2	31.7 ± 1.5	28.4 ± 1.4	25.6 ± 1.2	30.1 ± 1.3
4	49.8 ± 2.0	46.5 ± 1.8	42.9 ± 1.6	47.7 ± 1.9
8	67.5 ± 2.3	63.8 ± 2.1	60.4 ± 2.0	65.9 ± 2.2
12	81.2 ± 2.5	78.6 ± 2.4	75.8 ± 2.2	79.4 ± 2.3
24	96.4 ± 2.8	93.7 ± 2.5	91.5 ± 2.4	94.2 ± 2.6

Table 4: Antioxidant Activity of Formulations by DPPH Assay.

Sample	DPPH Radical Scavenging Activity (%)
Pure Phytochemical	62.4 ± 1.7
Blank Nanocarrier	18.2 ± 0.9
F1	71.3 ± 2.0
F2	75.8 ± 2.2
F3	83.6 ± 2.4
F4	77.1 ± 2.1

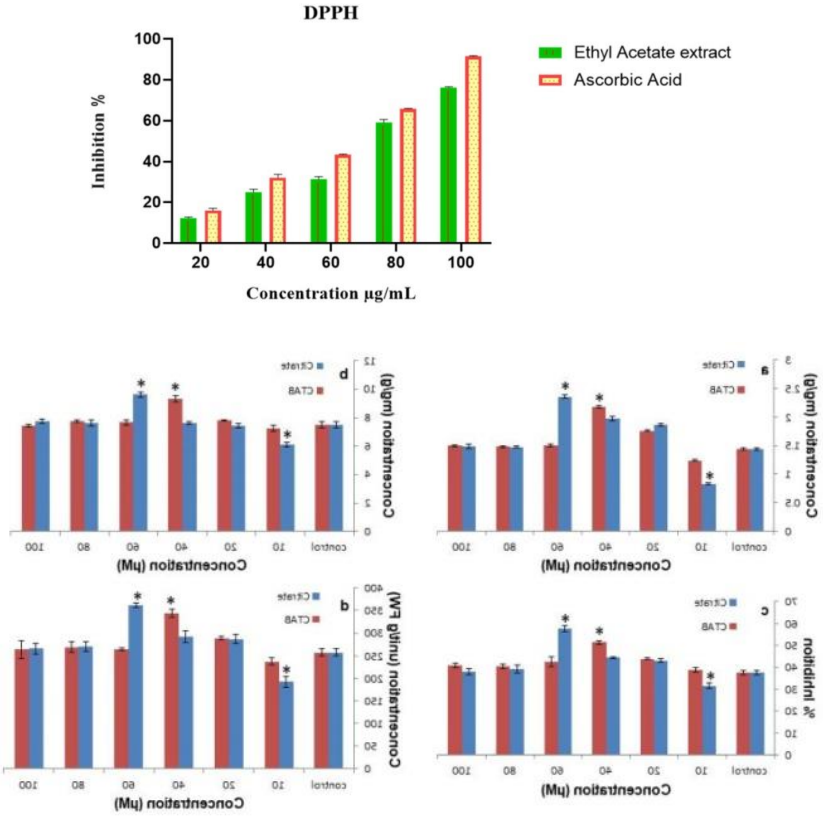

Figure 4: Comparative antioxidant activity of pure phytochemical and lipid nanocarrier formulations.

Table 5: Blood Glucose Levels in Experimental Animals.

Experimental Group	Initial Glucose Level (mg/dL)	Final Glucose Level (mg/dL)
Normal Control	92.4 ± 4.2	94.1 ± 4.5
Diabetic Control	285.6 ± 8.4	301.2 ± 9.1
Pure Phytochemical	279.5 ± 7.9	186.7 ± 6.2
Nanocarrier-Treated Group	281.4 ± 8.1	128.3 ± 5.4

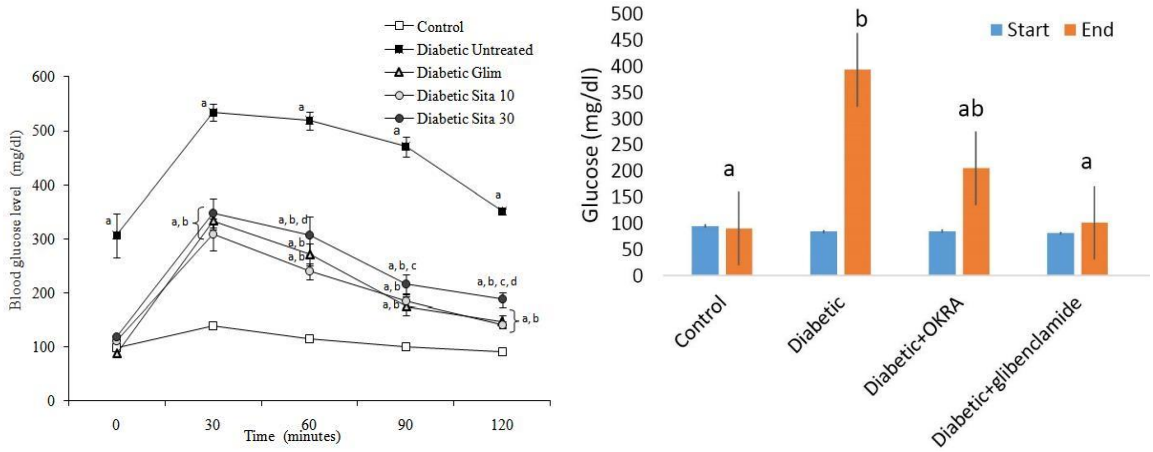

Figure 5: Effect of phytochemical-loaded lipid nanocarriers on blood glucose levels in diabetic animals.

Table 6: Behavioral Assessment of Neuropathic Pain.

Group	Hot Plate Latency (sec)	Tail Flick Response (sec)
Normal Control	12.5 ± 0.8	10.8 ± 0.7
Diabetic Control	5.1 ± 0.4	4.3 ± 0.3
Pure Phytochemical	8.6 ± 0.6	7.5 ± 0.5
Nanocarrier-Treated Group	11.2 ± 0.7	9.6 ± 0.6

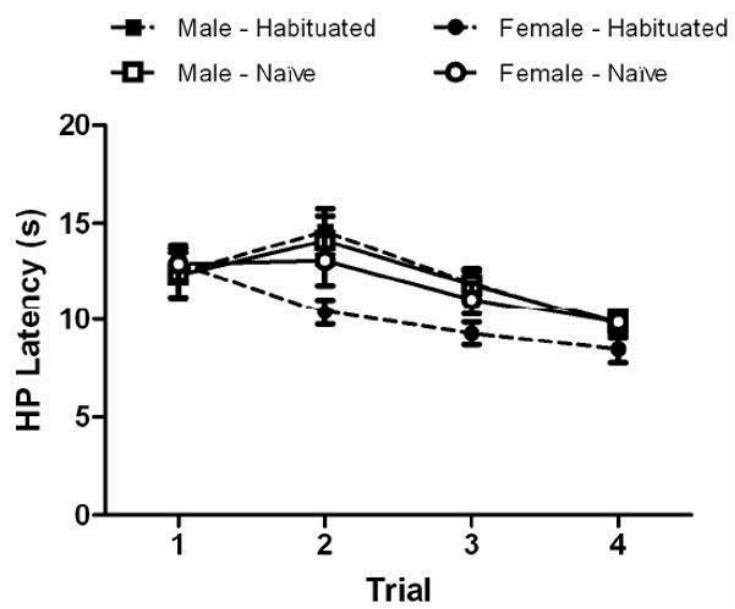

Figure 6: Behavioral assessment of neuropathic pain using hot plate and tail flick methods.

Table 7: Oxidative Stress Biomarker Analysis.

Parameter	Normal Control	Diabetic Control	Pure Phytochemical	Nanocarrier-Treated Group
MDA (nmol/mg protein)	1.9 ± 0.1	5.8 ± 0.3	3.6 ± 0.2	2.4 ± 0.1
SOD (U/mg protein)	14.5 ± 0.6	7.1 ± 0.4	10.8 ± 0.5	13.2 ± 0.5
Catalase (U/mg protein)	52.3 ± 1.8	28.7 ± 1.2	41.5 ± 1.5	49.6 ± 1.7
GSH (µg/mg tissue)	8.4 ± 0.4	3.2 ± 0.2	5.9 ± 0.3	7.6 ± 0.4

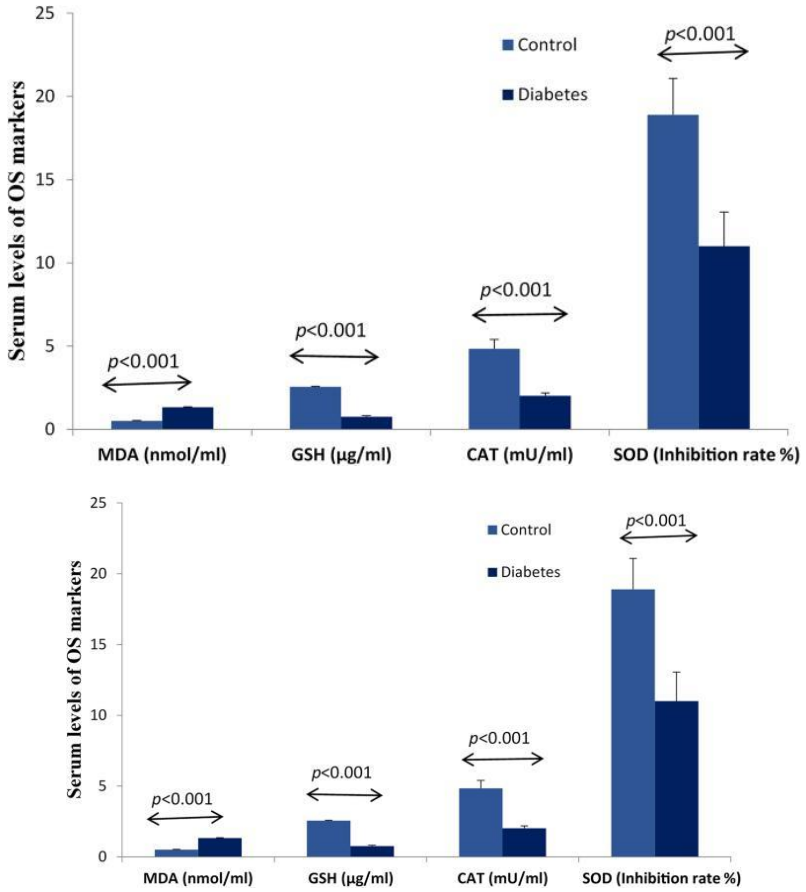

Figure 7: Effect of lipid nanocarriers on oxidative stress biomarkers in diabetic neuropathy.

Table 8: Histopathological Observations.

Group	Histopathological Findings
Normal Control	Normal neuronal architecture with intact nerve fibers
Diabetic Control	Severe neuronal degeneration, inflammation, and axonal damage
Pure Phytochemical	Moderate neuronal recovery with reduced inflammation
Nanocarrier-Treated Group	Significant restoration of neuronal structure with minimal tissue damage

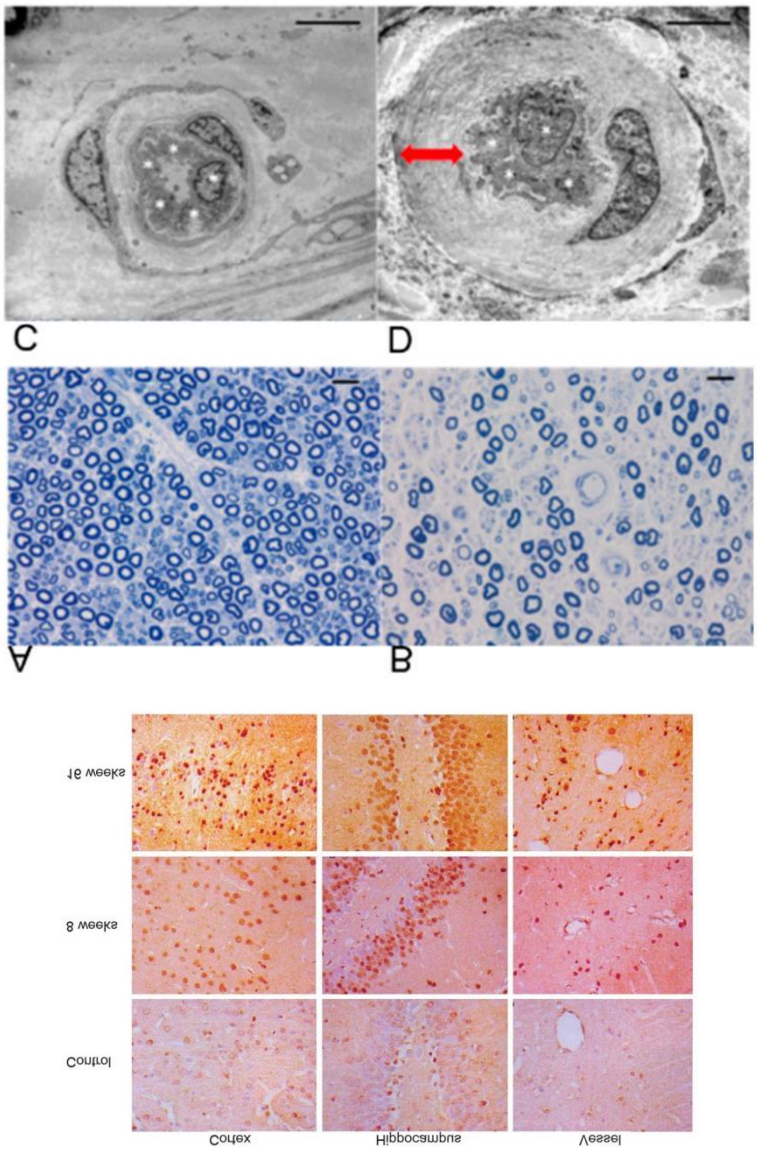

Figure 8: Histopathological observations showing neuronal protection and tissue recovery after treatment with brain-targeted lipid nanocarriers.

CONCLUSION

Brain-targeted lipid nanocarriers represent an advanced and promising drug delivery approach for the effective management of diabetic neuropathy. The incorporation of antidiabetic phytochemicals into lipid-based nanocarriers enhances their solubility, stability, bioavailability, and penetration across the blood–brain barrier. These nanoformulations provide controlled drug release and targeted delivery to neuronal tissues, thereby improving neuroprotective and antidiabetic effects while minimizing systemic toxicity.

The present study demonstrated that phytochemical-loaded lipid nanocarriers significantly reduced oxidative stress, improved antioxidant enzyme activity, lowered blood glucose levels, and restored neuronal function in experimental diabetic neuropathy models. Behavioral and histopathological studies further confirmed enhanced therapeutic efficacy compared with conventional phytochemical therapy.

Therefore, brain-targeted lipid nanocarriers loaded with antidiabetic phytochemicals may serve as an effective and safer therapeutic strategy for diabetic neuropathy.

Further clinical studies and large-scale investigations are required to establish their long-term safety, therapeutic effectiveness, and potential for commercial pharmaceutical applications.

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