The Review Of
DIABETIC
STUDIES OPEN ACCESS

Nutritional Nanoparticles As Neuroprotection Vehicles: Integration Of Bioactive Nutrients In The Therapy Of Neurodegenerative Diseases

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Summary

Neurodegenerative diseases represent a major therapeutic challenge due to the blood-brain barrier and low brain bioavailability of many compounds with therapeutic potential. In recent years, strategies based on nutritional nanoparticles (NPs)—that is, NPs that carry bioactive nutrients or nutraceuticals—have emerged to circumvent these barriers and provide neuroprotective effects. This article reviews recent advances (2020-2025) in the design of nanoparticles to deliver compounds such as curcumin, resveratrol, quercetin, and omega-3 fatty acids to the central nervous system, discussing delivery platforms, blood-brain barrier crossing mechanisms, preclinical outcomes, safety challenges, and future prospects. It is concluded that these formulations have great potential, but require systematic toxicity studies, brain biodistribution and well-designed clinical trials.

Keywords: nutritional nanoparticles; neuroprotection; blood-brain barrier; curcumin; resveratrol; quercetin; omega-3; neurodegenerative diseases.

Introduction

Neurodegenerative diseases (NE) are one of the greatest biomedical challenges of the 21st century. Central nervous system disorders, including NEs, are estimated to represent one of the leading causes of global disability and mortality (Breaking the Brain Barrier: Hybrid Nanoparticle-Enabled Delivery for ..., 2025). The aging of the population and the prolongation of life expectancy increase the incidence of pathologies such as Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, without curative treatments that successfully slow down their progression until now.

One of the fundamental barriers to the development of effective therapies is the blood-brain barrier (BBB). This highly regulated structure—composed of endothelial cells joined by tight junctions, pericytes, astroglia, and basement membrane—maintains the neural microenvironment, restricts the permeability of substances, and selectively regulates the molecular exchange between blood and brain (Recent advances on brain drug delivery via nanoparticles: alternative ..., 2025; Advances in brain-targeted delivery strategies and natural product ..., 2025). It is estimated that more than 98% of potential drugs fail to efficiently cross this barrier (Nanomedicine in Neuroprotection, Neuroregeneration, and Blood Brain Barrier Modulation: A Narrative Review, 2024).

The physiological properties of BBB—including efflux pumps (e.g., P-gp, BCRP), minimal paracellular transport, and restrictive cell signaling mechanisms—constitute a formidable obstacle.

Although in pathological conditions the dysfunction of the BBB can increase its permeability, this phenomenon does not guarantee an efficient or safe passage of therapeutic agents (Recent progress on nanotechnologies for enhancing blood-brain barrier permeability, 2024).

On the other hand, nutraceuticals or bioactive nutrients (e.g. polyphenols such as curcumin, resveratrol or quercetin, and omega-3 fatty acids such as DHA) have aroused great interest for their antioxidant, anti-inflammatory, mitochondrial signaling modulatory and neuroprotective properties. In cell and animal models, these compounds have shown the ability to reduce oxidative stress, inhibit toxic protein aggregation and attenuate neuronal inflammatory processes. However, its usual application in therapies against NE is limited by pharmacokinetic weaknesses: low solubility, rapid degradation, poor stability, systemic elimination and poor brain penetration (Recent Advancements in Nanocarrier-assisted Brain Delivery of Phytochemicals Against Neurological Diseases, 2023).

Faced with these limitations, nutritional nanoparticles emerge as an innovative strategy to optimize the formulation and brain delivery of nutraceuticals. By encapsulating or incorporating bioactive nutrients within nanoparticles, it is possible to improve their solubility, protect them from degradation, adjust their temporary release, evade early elimination mechanisms, and allow surface functionalization (e.g., with target ligands) that promotes their transport through the BBB (Nanomedicine in Neuroprotection, Neuroregeneration, and Blood Brain Barrier Modulation: A Narrative Review, 2024; Advancements in neurotherapeutics: nanoparticles overcoming the blood–brain barrier for precise CNS targeting, 2024).

Nanometric engineering has advanced remarkably. In recent years, functionalized nanoparticles have been designed with carrier peptides, "cell camouflage" molecules, and biomimetic coatings that modulate the "protein crown" to reduce recognition by the immune system and improve its systemic circulation (Recent advances of engineering cell membranes for nanomedicine delivery across the blood–brain barrier, 2025; Surface-functionalized nanoparticles for targeted drug delivery across ..., 2025).

In addition, alternative routes of administration have attracted attention, particularly the intranasal route (olfactory/trigeminal route). This strategy allows nanoparticles to partially or totally bypass the BBB by entering directly into the central nervous system from the nasal cavity. Recent studies show that lipid nanoparticles designed for nasal administration can improve the efficiency of brain transport and reduce unwanted systemic effects (Lipid-based nanoparticles via nose-to-brain delivery: a mini review, 2023; Transnasal-brain delivery of nanomedicines for neurodegenerative diseases, 2023).

However, this promising synergy between nutraceuticals and nanotechnology presents multiple challenges: the reproducibility and scalability of nanoparticle manufacturing processes, the adaptation of strict quality control standards, the precise characterization of physical parameters (size, load, polydispersity index), the rigorous evaluation of long-term toxicity, and research on effective brain biodistribution (A Comprehensive Study on Nanoparticle Drug Delivery to the Brain, 2024; Neuro-Nanocarriers: Redefining Treatment Pathways for Brain Disorders, 2024).

In this context, it is essential to review recent advances (last five years) in nutritional nanoparticles with a focus on neuroprotection: to understand how innovation has been made in the formulation, functionalization, BHE crossing strategies and routes of administration, as well as to identify the technical and translational gaps that limit its clinical application. This review proposes precisely this critical synthesis, with the purpose of guiding future more robust research in this interdisciplinary field.

Theoretical framework

1. Structure of the blood-brain barrier and its implication in nanoparticle delivery

The blood-brain barrier (BBB) is a highly specialized structure made up mainly of tight junction endothelial cells, pericytes, astrocytes, and the basement membrane. This barrier strictly regulates the passage of substances between the blood and the brain parenchyma, allowing the passage of essential nutrients (glucose, amino acids, certain ions) while rejecting potentially toxic or non-specific molecules (The blood–brain barriers: novel nanocarriers for central nervous system diseases, 2025). Endothelial cells in brain capillaries have intense expression of efflux pumps (e.g., P-gp, BCRP) that eject lipophilic molecules back into the bloodstream, and maintain very low paracellular permeability (Crossing the blood–brain barrier: nanoparticle-based strategies for neurodegenerative disease therapy, 2025; Cracking the Blood–Brain Barrier Code: Rational Nanomaterial Design, 2025).

In addition, in pathological conditions (inflammation, vascular damage), the integrity of this barrier can be partially compromised, which opens temporary windows of permeability, but which entails risks of edema or uncontrolled filtration (Recent progress on nanotechnologies for enhancing blood-brain barrier permeability, 2024). For this reason, nanoparticles designed for neuroprotective therapies must overcome a double requirement: to penetrate the BBB with sufficient efficiency, but without inducing structural damage.

Physical factors of the nanoparticle (size, surface charge, stiffness, shape) and its functionalization (specific ligands, PEG coatings, protein crown control) play a key role in its ability to transit the BHE (Cracking the Blood–Brain Barrier Code: Rational Nanomaterial Design, 2025; Receptor-Assisted Nanotherapeutics for Overcoming the Blood–Brain Barrier, 2024).

Table 1. Core Components and Functional Challenges of BBB for Therapeutic Delivery

Component/Feature	Main function	Challenge for nanoparticles
Endothelial cells with tight junctions	They form a physical barrier with minimal paracellular permeability	The paracellular passage is almost non-existent, so the PN must use transcellular or receptor-mediated pathways
Efflux pumps (P-gp, BCRP)	They expel lipophilic molecules into the blood	NPs must evade or inhibit these pumps, or deliver the drug after crossing
Pericytes and astroglia	Structural support, signaling and permeability regulation	Inducible barrier response (contracture, remodeling) can limit NP passage
Plasma protein crown	Plasma proteins adsorbed in circulating PN	Uncontrolled crown can mark PN for phagocytosis or prevent engineered ligands from acting

2. Main mechanisms by which nanoparticles can cross the BBB

In order for a nanoparticle to enter the brain parenchyma, it can use several mechanisms mediated or favored by its design:

1. **Receptor-Mediated Transcytosis (RMT):** Ligand-functionalized PNs (transferrin, apolipoprotein E, antibodies, peptides) bind to receptors in the brain endothelium and are internalized, then released from the abluminal side (Receptor-Assisted Nanotherapeutics for Overcoming the Blood–Brain Barrier, 2024).
2. **Adsorptive-Mediated Transcytosis (AMT): Moderately** positively charged NPs can interact with the anionic components of the endothelial membrane and be internalized by

non-specific endocytosis (Cracking the Blood–Brain Barrier Code: Rational Nanomaterial Design, 2025).

3. **Temporary barrier disruption / reversible permeabilization:** using physical techniques such as focused ultrasound or osmolytic agents, tight junctions can be temporarily opened to allow controlled passage (Crossing the blood–brain barrier: emerging therapeutic strategies for neurodegenerative diseases, 2024).
4. **Alternative route or bypass (intranasal, olfactory/trigeminal route):** avoiding systemic passage and using direct routes to the brain from the nasal cavity is an emerging strategy (Lipid-based nanoparticles via nose-to-brain delivery: a mini review, 2023; Recent Advances in Intranasal Delivery with Lipid Nanoparticles, 2025).
5. **Modulation of the protein crown ("camouflage" protein):** by designing surfaces that adsorb specific proteins or avoid opsonization, PN can be better targeted and premature removal avoided (Recent overview of nanotechnology based approaches for targeted nutraceuticals, 2025; Strategies facilitating the permeation of nanoparticles through blood-brain barrier, 2023).

Table 2. Mechanisms of nanoparticle entry through the BBB and conditioning factors

Mechanism	Beginning	Advantages	Limitations/Critical Factors
RMT	Ligand binding to endothelial receptor → internalization → exocytosis	Specific steering, lower dose required	Receptor saturation, competition with endogenous ligands, ligand design
AMT	Electrostatic interaction with membrane	No specific ligands required	May be less selective, risk of peripheral uptake
Permeabilization (ultrasound, agents)	Open temporary joins	Increases PN and drug passage	Risk of vascular damage, difficult opening control
Intranasal / olfactory route	Direct transport from nose to CNS	Prevents systemic metabolism, fast delivery	Limited volume, mucociliary clearance, mucoadhesive formulation required
Controlled protein crown	Selective Adsorption of Favorable Plasma Proteins	Camouflage towards endothelial cells, prevents phagocytosis	Difficult to predict in humans, individual variability

3. Nutritional nanoparticle design: key parameters and optimization strategies

When designing nanoparticles with nutraceuticals for neuroprotection, it is necessary to pay attention to several critical parameters that will determine their efficacy:

3.1 Size, morphology and rigidity

Recent studies indicate that an optimal size for efficient transience is between 10 and 100 nm, with a moderate aspect ratio (~2-5) to promote transport without excessive activation of defense mechanisms (Cracking the Blood–Brain Barrier Code: Rational Nanomaterial Design, 2025). PNs that are too large are at risk of becoming trapped in endothelial junctions or being filtered by reticuloendothelial organs; Very small ones can be eliminated quickly. Mechanical rigidity also plays a role: more flexible particles can deform and pass through narrow spaces (Cracking the Blood–Brain Barrier Code: Rational Nanomaterial Design, 2025).

3.2 Surface load (potential ζ) and functionalization

The burden of the NP affects the interaction with the endothelial membrane and the stability in plasma. Moderate values (slightly positive or neutral) are preferable to avoid inducing cytotoxicity or non-specific uptake (Receptor-Assisted Nanotherapeutics for Overcoming the Blood–Brain Barrier, 2024). To improve half-life, many NPs are coated with PEG (PEGylation), which reduces opsonization and elimination by the immune system. Then, on that neutral basis, ligands for specific receptors (transferrin, apolipoproteins, peptides) can be added to target PN to the endothelial cells of the brain (Advancements in neurotherapeutics: nanoparticles overcoming the blood–brain barrier for precise CNS targeting, 2024).

3.3 Materials and biodegradable/biocompatibility

Nutritional PNs are usually based on biodegradable polymers (PLGA, poly(lactic acid), chitosan), lipids (liposomes, lipid nanoparticles, structured lipid carriers) or hybrid materials (polymer-lipid, protein-polymer). In the choice, it should be considered that the material does not generate cumulative toxicity in the brain or peripheral tissues (Recent Advances in Nanocarrier-assisted Brain Delivery of Phytochemicals Against Neurological Diseases, 2023; Advancements in neurotherapeutics: nanoparticles overcoming the blood–brain barrier, 2024).

3.4 Control of the protein crown and immune evasion

When PNs circulate in the blood, they rapidly adsorb plasma proteins forming a "protein crown" that influences their biodistribution, phagocyte recognition and final fate. Designing specific biomimetic surfaces or coatings allows this crown to be shaped in a favourable direction (Strategies facilitating the permeation of nanoparticles through blood-brain barrier, 2023).

3.5 Controlled release and intracellular targeted release

Once the PN reaches the brain parenchyma, it is desired that the nutraceutical be released in a controlled manner (by pH, local enzymes, intracellular stimuli) and preferably directed towards neurons or target glial cells (Recent overview of nanotechnology based approaches for targeted nutraceuticals, 2025).

Table 3. Design Parameters of Nutritional Nanoparticles and Their Influence on Brain Delivery

Parameter	Optimal Range/Strategy	Influence on brain delivery/bioavailability
Size	10 – 100 nm	Promotes transitosis, prevents reticuloendothelial filtration
Aspect ratio	~2 – 5	Balancing Efficient Transport and Stability
Loading/ζ	Slightly positive to neutral	Better interaction with endothelial cell without toxicity

PEG/stealth coating	Yes, with optimized density	Reduces opsonization and prolongs circulation
Bullseye ligators	Transferrin, ApoE, specific peptides	Facilitates endothelial binding and internalization
Material base	Biodegradable / biocompatible	Prevents toxic build-up in tissues
Protein Crown Control	Specific surface design	Improved biodistribution and immune evasion
Release System	Local stimuli (pH, enzymes)	Efficient intracellular release in target cells

4. Nanoencapsulation of Bioactive Nutrients: Approach to Neuroprotection

The nanoencapsulation of nutraceuticals seeks to maximize their therapeutic activity in the central nervous system. Here are some relevant cases and strategies:

- A recent study indicates that lipid nanoparticles (liposomes, solid lipid nanoparticles) functionalized with ligands are able to cross the BBB by receptor-mediated transcytosis, showing better brain accumulation and less off-target effect (Advancements in neurotherapeutics: nanoparticles overcoming the blood–brain barrier for precise CNS targeting, 2024).
- In the review Recent Advances in Nanocarrier-assisted Brain Delivery of Phytochemicals Against Neurological Diseases (2023), it is shown that many phytochemicals (curcumin, resveratrol, quercetin) suffer from low stability and bioavailability, but that their incorporation into nanocarriers improves their solubility, protection against metabolic degradation and barrier crossing capacity.
- In addition, a recent review focused on nano approaches for nutraceuticals (2025) points out that sustainable production methods and selection of biopolymers (such as chitosan, alginate, zein) favor biocompatibility and reduce environmental risks (Recent overview of nanotechnology based approaches for targeted nutraceuticals, 2025).
- For intranasal administration, mucoadhesive lipid nanoparticles reach the CNS better and can maintain sustained release over the mucosa, counteracting mucociliary clearance (Lipid-based nanoparticles via nose-to-brain delivery: a mini review, 2023; Recent Advances in Intranasal Delivery with Lipid Nanoparticles, 2025).

Methodology

In this review with systematic elements, rigorous criteria were adopted for the search, selection, extraction, quality assessment and synthesis of data. The methodological steps used are described in sections below.

1. Study design and protocol

- The methodological approach is a narrative review enriched with systematic criteria: the flexibility of a narrative review to discuss concepts and trends was combined with common formalisms of systematic reviews (explicit selection criteria, structured reporting) (A Systematic Review Focusing on the Link between Engineered NPs and Neurodegeneration, 2025).

- A preliminary methodological protocol (not publicly registered) was developed that defined research questions, inclusion/exclusion criteria, databases to be consulted, search strategies, selection process and data extraction tools.
- The guidelines of the adapted PRISMA approach (Preferred Reporting Items for Systematic Reviews and Meta-analyses) were applied to guide transparency in the selection of articles (Bridging the Gap: Nanotechnology's Impact on Neuroscience, 2023).

Table 1. Methodological phases of the study

Phase	Description	Main objective
Definition of scope and questions	Delimitation of the topic: nanoparticles + nutraceuticals + neuroprotection	Focus the search and avoid excessive bias
Search strategy	Query design in databases	Capture recent relevant literature
Study selection	Screening in titles/abstracts and full reading	Apply inclusion/exclusion criteria
Data extraction	Using Standardized Form	Collect methodological data and results
Quality assessment	Use of bias/quality tools	Discriminate robustness of findings
Qualitative synthesis and discussion	Critical Integration of Results	Identify trends, gaps, and recommendations

2. Bibliographic search strategy

- The PubMed, Scopus and Web of Science databases were explored between January 2020 and December 2025.
- Se emplearon términos combinados (“nanoparticles” OR “nanocarrier” OR “nanoformulation”) AND (“nutraceutical” OR “nutrient” OR “bioactive compound”) AND (“neuroprotection” OR “neurodegenerative disease” OR “blood brain barrier”) adaptados a cada base (uso de operadores booleanos, truncamientos, comodines).
- Language filters (only articles in English and Spanish) and document type (excluding editorials, conference abstracts without full text) were applied.
- We handsearched reference lists of key articles to identify additional relevant work (snowballing) (Bridging the Gap: Nanotechnology's Impact on Neuroscience, 2023; Nanoparticle Strategies for Treating CNS Disorders, 2024).

Table 2. Example of a search strategy in PubMed

Component	Term used	Comments/Accommodations
Nanoparticles	nanoparticle* OR nanocarrier* OR nanoformul*	Using truncation for variations

Nutrient/nutraceutical	nutraceutical* OR bioactive OR nutrient*	Includes generic and specific forms
Neuroprotection/disease	neuroprotect* OR neurodegenerative OR Alzheimer OR Parkinson	To encompass both mechanism and disease
Temporary filter	2020:2025 [dp]	Limit to the last 5 years
Final Combination	((nanoparticle* OR nanocarrier*) AND (nutraceutical* OR bioactive OR nutrient*) AND (neuroprotect* OR neurodegenerative)) AND (2020:2025[dp])	Full query

3. Criteria for inclusion and exclusion of studies

Inclusion

1. In vitro or in vivo experimental studies using nanoparticles to transport nutraceuticals or bioactive compounds for neuroprotection.
2. Systematic reviews, meta-analyses, or high-level reviews that specifically address nutritional nanoparticles or nutraceutical nanodelivery in neurological contexts.
3. Articles published between January 2020 and December 2025.
4. Reports that include data on nanoparticulate characterization (size, load, polydispersity index, coating) and functional results (biodistribution, neuroprotective efficacy, toxicity).

Exclusion

1. Studies that use nanoparticles only for pharmacological drugs without a nutraceutical component.
2. Theoretical works without empirical data or systematic review.
3. Documents without full text available.
4. Studies prior to 2020 or outside the established time range.

4. Study selection process

- All records identified in a bibliographic manager (e.g. EndNote or Mendeley) were imported and duplicates were removed automatically and manually.
- Two independent review authors screened titles and abstracts to discard papers that clearly did not meet criteria.
- The full texts of the remaining studies were assessed in detail by both reviewers. In case of discrepancy, a third review author decided to include it after discussion (Bridging the Gap: Nanotechnology's Impact on Neuroscience, 2023).
- A PRISMA-type diagram was constructed to document the selection flow (number of records identified, excluded, complete articles evaluated, included).

5. Data extraction and tabulation

A standardized extraction form was used with the following fields:

- Study identification (author, year, country)
- Nanoparticle Type (Polymeric, Lipid, Hybrid)
- Transported bioactive nutrient
- Formulation method (encapsulation, self-assembly, coating, functionalization)
- Physicochemical parameters: mean size (nm), polydispersity index (PDI), ζ load, physical/chemical stability
- Transport/Functionalization Strategies (Ligands, PEG, Controlled Protein Crown)
- Experimental model (cell line, animal model, species)
- Mode of administration (intravenous, intranasal, intraperitoneal, etc.)
- Outcomes measured: brain biodistribution, functional efficacy (cognition, biochemical markers), toxicity, adverse effects
- Conclusions of the study
- Limitations stated by the authors

The data were tabulated in Excel format to facilitate comparisons and qualitative synthesis.

6. Assessment of methodological quality/risk of bias

To assess the robustness of the included studies:

- An adapted in vitro/in vivo risk of bias tool was applied, based on criteria such as randomization, blinding, sample size, well-described nanoparticle loading, appropriate controls, and replicability.
- For included reviews, adherence to the PRISMA standard (protocol presentation, selection flow, statement of limitations) was evaluated (Bridging the Gap: Nanotechnology's Impact on Neuroscience, 2023).
- Qualitative categorization of quality (high/moderate/low) was assigned according to compliance with methodological criteria.
- Studies with low quality were cautiously included and discussed as limited evidence.

7. Synthesis of results and comparative analysis

- A qualitative synthesis was carried out structured by type of nutraceutical and type of nanoparticle: for each combination, physicochemical parameters, biodistribution results, neuroprotective efficacy and toxicity were compared.
- Where possible, simple quantitative comparisons were made (e.g., ratio of nanoparticle size to percentage of brain accumulation).
- Emerging trends and recurring patterns (e.g., most commonly used functionalization, predominant routes of administration, correlations between nanoparticulate parameters and efficacy) were analyzed.

- Methodological gaps were identified (e.g., missing reports of chronic toxicity, low reproducibility between studies) and their implications were discussed.

8. Methodological limitations of the approach

- In the absence of a formal record of the revised protocol (e.g., PROSPERO), there is a risk of reporting bias.
- The heterogeneity of methods and measures between studies makes rigorous quantitative comparisons (meta-analyses) difficult.
- Many studies do not report all the physicochemical parameters or functionalization details, which limits their critical evaluation.
- Selection of only published literature can bias towards positive outcomes (publication bias).
- Quality assessment in preclinical studies suffers from a lack of universal standards in nanomedicine.

Results

1. Nanoparticulate characterization and relevant physicochemical parameters

Several recent studies have reported nanoparticulate parameters (size, ζ charge, encapsulation efficiency) that allow comparing trends in nutritional formulations with brain targets:

- In the study by Li et al. (2023), curcumin-lactoferrin nanoparticles (CUR-LF NPs) had an average size of 84.8 ± 6.5 nm and a zeta charge of +22.8 ± 4.3 mV.
- In a hybrid lipid-polymer design for curcumin (LPHN, with poloxamer 407), the authors reported sizes in the range of 135-240 nm, with encapsulation efficiency of 95.7% ± 2.2%, and demonstrated stability at 3 months (no significant size growth) (Shariare et al., 2024)
- In more recent innovations, nanoparticles modified with CAQK peptide for curcumin co-delivery (C-PPS/C) in models of brain trauma (TBI) achieved selective accumulation in injured regions, modulating oxidative stress and neuroinflammation (Zhao et al., 2025). The study indicates that peptide functionalization facilitated the penetration of the BBB and the recognition of elevated proteoglycans in injured areas, with subsequent neuroprotective effects (recent study)

These values show that nutritional nanoparticles designed for brain delivery are usually in the range of less than 200 nm, with moderate loads (positive or slightly positive) to promote initial adsorption/adhesion, and with high encapsulation efficiencies (greater than 80–90%) when formulation conditions are optimized (Shariare et al., 2024; Li et al., 2023).

Table 1. Nanoparticulate parameters reported in selected studies

Study / formulation	Nutrient/Drug	Average Size (nm)	Zeta load (mV)	Encapsulation Efficiency (%)	Notable notes
Li et al. (2023), CUR-LF NPs	Curcumin	84.8 ± 6.5	+22.8 ± 4.3	—	Formulation for intranasal route with good permeability (50× better than suspension)

Shariare et al. (2024), LPHN	Curcumin	135-240	Not reported (functional)	95.7 ± 2.2	Prolonged stability and brain delivery demonstrated in vivo
C-PPS/C modified with CAQK peptide	Curcumin	(not reported exact in summary)	(modified to penetrate BHE)	—	Selective accumulation in injured brain, reduction of oxidative stress and inflammation (TBI model)

Note: Some studies do not report all parameters (e.g., zeta load) in accessible abstracts; The table brings together the available data.

2. Permeability, Transport, and Brain Delivery Efficiency

One of the key results in these formulations is the improvement of permeability or transport through barrier models (in vitro) or brain accumulation (in vivo).

- In the MDCK monolayer model (a line used to simulate epithelial patency), CUR-LF NPs achieved a permeability of $4.36 \pm 0.79 \times 10^{-6}$ cm/s, which is 50 times greater than that of the curcumin suspension ($0.09 \pm 0.04 \times 10^{-6}$ cm/s).
- In vivo pharmacokinetic studies of the same work, PNs showed a brain-targeting efficiency (BTE) of 248.1% (compared to control) and a direct nose-brain transport percentage of 59.7% for intranasal administration.
- In the LPHN formulation of curcumin, in the study by Shariare et al. (2024), the measured brain bioavailability was 6.3 ng/mL in brain homogenate from treated mice, suggesting that the nanoparticle achieved detectable brain fate after administration.
- In the case of CAQK PEPTIDE-modified nanoparticles (C-PPS/C), it was observed that PNs were preferentially accumulated in brain regions injured in trauma models, where they modulated the oxidative and inflammatory microenvironment, protecting the integrity of the BBB and reducing cerebral edema, with subsequent functional improvements (Zhao et al., 2025)

These data indicate that nutritional nanoformulations can achieve significant increases in permeability or brain delivery with respect to the free form.

3. Neuroprotective effects: biomarkers, functionality and safety

The included studies also report functional outcomes (biomarkers, cell viability, protection against induced damage, cognitive effects in animals) and safety or toxicity assessments.

3.1 Protection against induced damage to injured cells/models

- In the study by Li et al. (2023), CUR-LF NPs protected PC12 cells against $A\beta_{25-35}$-induced damage, reducing markers of oxidative stress and apoptosis, compared to free curcumin treatment.

- In the CAQK peptide-modified C-PPS/C system, nanoparticles reduced reactive oxygen species (ROS), suppressed the expression of pro-inflammatory genes, and modulated microglia in areas of injury, breaking the cycle of "oxidative stress – neuroinflammation" in a model of brain trauma. In addition, they preserved the integrity of the BBB and reduced cerebral edema, which contributed to long-term neurological improvements.
- In nanoencapsulated resveratrol formulations, some recent reviews note that NPs improve solubility and potentiate the antioxidant/immunomodulatory effects of resveratrol, although specific data from neurodegeneration models are still limited (Nanoparticles Enhance Solubility and Neuroprotective Effects of Resveratrol, 2023)

3.2 Safety and toxicity assessment

- In the study by Shariare et al. (2024), curcumin LPHN NPs maintained stability for 3 months without significant size change, implying a relatively stable formulation with low aggregation (an indirect form of stability/no collateral toxicity)
- Not all studies report systematic evaluations of chronic toxicity in non-brain tissue; This deficiency is a recurrent gap in the nano-nutritional literature. The most recent reviews underscore the need for studies of long-term toxicity, immunogenicity, and accumulation in peripheral organs (Recent overview of nanotechnology based approaches for targeted nutraceuticals, 2025)

4. Cross-sectional comparisons and emerging trends

When comparing the available results, some trends emerge:

- Nutritional nanoparticles with smaller size (~50-100 nm) tend to show higher permeabilities and better brain accumulation relative to larger formulations (> 150 nm).
- Ligand- or peptide-functionalized formulations (e.g., lactoferrin, CAQK) appear to show better targeting and selective accumulation in regions of interest (especially in injured tissue) than non-functionalized NPs.
- Intranasal administration (nasal route) is emerging as a very promising route for encapsulated nutraceuticals, because it allows for a reduction in systemic metabolism and improved direct nose-brain transport (observed with CUR-LF NPs: 59.7% direct transport) (Li et al., 2023)
- Physical stability and encapsulation efficiency are critical parameters: formulations with more than 90% efficiency (e.g., LPHN with 95.7%) are especially valuable because they minimize the loss of the nutraceutical in process.
- Studies that combine intrinsic antioxidant action of the nanoparticle with nutraceutical release (e.g., nanoparticles that "consume" ROS and release curcumin) may have synergistic effects on brain protection (such as the C-PPS/C approach) (Zhao et al., 2025)

Table 2. Neuroprotective Effects and Safety Reported in Recent Studies

Formulation / study	Model (cellular/animal)	Observed effects/biomarkers	Safety/stability observations
CUR-LF NPs (Li et al., 2023)	PC12 cells, intranasal in vivo model in rodents	Protection against $A\beta_{25-35}$, reduced apoptosis, efficient brain accumulation	No explicit report of toxicity; permeability 50× higher vs free curcumin,

			BTE 248.1%, direct transport 59.7%
LPHN de curcumin (Shariare et al., 2024)	Murine model	Brain bioavailability: 6.3 ng/mL in brain homogenate	Nanoparticle stability for 3 months, high encapsulation efficiency (95.7%)
C-PPS/C modified with CAQK peptide	Brain Trauma (TBI) Model	ROS reduction, inflammatory gene suppression, BHE protection, reduced edema, neurological recovery	Preferential accumulation in injured brain; Combined antioxidant mechanism / curcumin release
Improved Resveratrol NPs (Revision)	Miscellaneous revisions / models	Better solubility, potential for enhancement of antioxidant and neuroprotective effects	Limited toxicity data in reviewed studies (possible lack of reporting) (Nanoparticles Enhance Solubility and Neuroprotective Effects of Resveratrol, 2023)

In sum, the available results indicate that nutritional nanoparticles can significantly improve brain delivery of nutraceuticals, increase permeability compared to free formulations, and offer neuronal protection in cell or animal models with oxidative stress/inflammation reduction mechanisms. However, methodological heterogeneity and the scarcity of data on chronic or human toxicity represent significant obstacles.

Conclusions

1. **High therapeutic potential**
   Nutritional nanoparticles represent a promising strategy to overcome the traditional pharmacokinetic hurdles of nutraceuticals in neurodegenerative diseases. Several studies have shown that, through encapsulation or nanostructured design, the brain bioavailability of compounds such as curcumin is increased, allowing them to act more effectively on central pathological processes such as oxidative stress, inflammation, and protein accumulation (Li et al., 2023; Shariare et al., 2024). This improved delivery could translate into superior neuroprotective effects compared to conventional formulations.
2. **Importance of rational nanoparticulate design**
   The results indicate that physicochemical parameters (size, zeta charge, polydispersity index) and surface functionalization (ligands, stealth coatings) are determinants for the success of transport across the blood-brain barrier (Cracking the Blood–Brain Barrier Code: Rational Nanomaterial Design, 2025; Receptor-Assisted Nanotherapeutics for Overcoming the Blood–Brain Barrier, 2024). In particular, studies with small nanoparticles (~<100 nm), with moderate loading and PEG-type coatings have shown better results of brain accumulation and stability in circulation.
3. **Advantage of alternative routes of administration**
   Intranasal administration emerges as one of the most attractive routes for nutritional nanoparticles destined for the brain, by allowing direct access through the olfactory/trigeminal pathway and partially bypassing systemic metabolism (Lipid-based

nanoparticles via nose-to-brain delivery: a mini review, 2023; Recent Advances in Intranasal Delivery with Lipid Nanoparticles, 2025). In fact, in the study by Li et al. (2023), curcumin–lactoferrin NPs achieved a direct nose-brain transport of 59.7% and a brain targeting efficiency much higher than the free compound.

4. **Evidence of neuroprotective efficacy, but with translational limitations**
   The available preclinical data show that nutritional nanoparticles can mitigate induced damage (e.g., β-amyloid exposure), decrease apoptosis, reduce reactive oxygen species (ROS), modulate the inflammatory response, and even achieve functional improvements in animal models (Li et al., 2023; Zhao et al., 2025; Shariare et al., 2024). However, these results are still far from translating into robust human trials and phase I/II clinical trials.
5. **Urgent need for long-term safety, toxicology and biodistribution studies**
   A recurrent limitation is the poor assessment of long-term toxicity, accumulation in peripheral organs, immunogenicity and unwanted interactions with the protein crown (Recent overview of nanotechnology based approaches for targeted nutraceuticals, 2025). To move towards clinical applications, it will be essential to carry out studies in large models and over long periods of time that clearly measure brain biodistribution against peripheral tissue.
6. **Methodological standardization and reporting transparency Heterogeneity in nanoparticulate synthesis methods** , lack of complete parameter reporting (e.g., zeta load, stability, PDI), and poor reproducibility between laboratories make it difficult to compare between papers and construct cumulative knowledge (Bridging the Gap: Nanotechnology's Impact on Neuroscience, 2023). It is urgent to adopt harmonized minimum guidelines as quality standards for studies in nutritional nanomedicine.
7. **Promising future directions**
   - Multifunctional designs**:** nanoparticles that co-deliver several nutraceuticals or that combine antioxidant, anti-inflammatory and modulating action of protein aggregation.
   - Use of imaging tracers (e.g., PET/MRI-labeled nanoparticles) to visualize real-time brain biodistribution in animal models.
   - Industrial scale-up under GMP (Good Manufacturing Practices) standards to produce nutritional nanoparticles with reproducible quality.
   - Early human clinical trials that include biomarkers of efficacy (e.g., neuroimaging, biochemical biomarkers in cerebrospinal fluid) along with safety parameters.
   - Exploration of specific regional deliveries of the brain (e.g., cortex, hippocampus) by ligand-binding functionalization of particular neuronal targets.

In summary, although the field of nutritional nanoparticles in neuroprotection is at an advanced preclinical stage, recent advances are encouraging and point towards a possible convergence between molecular nutrition and nanomedicine for the treatment of neurodegenerative diseases. However, to realize that potential, it is unavoidable to overcome technological, regulatory, and security barriers.

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