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INNOVATIVE STRATEGIES FOR NEUROLOGICAL DISEASES:

FROM NUTRACEUTICALS TO NANOMEDICINE

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TABLE OF CONTENTS

PREFACE.....i

CHAPTER 1
NATURE-BASED SOLUTIONS FOR NEUROHEALTH: NUTRACEUTICALS TO COMBAT NEURODEGENERATION
Huma IKRAM 1

CHAPTER 2
POTENTIAL DRUG IDENTIFICATION FOR CREUTZFELDT-JAKOB DISEASE (CJD) THROUGH THE BIOINFORMATICS APPROACH
Celine Eleora WIHARJA
Caitlin Rania SUJENDRO
Gregorius KEVIN
Matthew Aurelius TIRTA
Arli Aditya PARIKESIT.....36

CHAPTER 3
GOLD NANOPARTICLES FOR NEUROPROTECTION: A REVIEW OF THERAPEUTIC APPLICATIONS AND EMERGING STRATEGIES IN NEUROLOGICAL DISEASES
Sriram R.
Parthasarathi. V.
M. SANJAI
Prof. Dr. DEVI
Prof. Dr. R. SRINIVASAN.....53

PREFACE

Neurological and neurodegenerative diseases remain among the most complex and challenging areas of contemporary biomedical research. Their multifactorial nature requires innovative approaches that combine biological knowledge, therapeutic exploration, computational analysis, and advanced biomedical technologies. In recent years, increasing attention has been given to interdisciplinary strategies that may contribute to the prevention, understanding, and treatment of neurological disorders.

The chapters in this volume address current developments in neurohealth and neurotherapeutic research from different scientific perspectives. The discussion of nature-based solutions highlights the potential role of nutraceuticals in combating neurodegeneration and supporting neurological wellbeing. The bioinformatics-based study on Creutzfeldt-Jakob Disease demonstrates how computational approaches can assist in identifying potential drug candidates for complex and rare neurological conditions. In addition, the review of gold nanoparticles explores their neuroprotective potential and their emerging applications in the management of neurological diseases.

By bringing together studies on nutraceuticals, bioinformatics, and nanomedicine, this volume emphasizes the importance of multidisciplinary research in modern neuroscience and biomedical sciences. The integration of natural therapeutic agents, computational drug discovery, and nanoparticle-based strategies offers valuable insights into future directions for neurological disease research and treatment.

It is hoped that this book will serve as a useful academic resource for researchers, healthcare professionals, students, and scholars interested in neurodegenerative diseases, biotechnology, pharmacology, nanomedicine, and related fields. We extend our sincere appreciation to all contributing authors for their valuable scholarly efforts.

Editorial Team
June, 2026
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CHAPTER 1
NATURE-BASED SOLUTIONS FOR NEUROHEALTH: NUTRACEUTICALS TO COMBAT NEURODEGENERATION

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INTRODUCTION

The escalating prevalence of neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, presents one of the most formidable challenges to global healthcare systems in the 21st century. These complex, age-related conditions are characterized by the progressive loss of neuronal structure and function, leading to profound cognitive and motor impairments. Current pharmacological interventions remain largely symptomatic and are often hampered by significant side effects and limited efficacy in halting disease progression. This therapeutic impasse has intensified the search for alternative and complementary strategies that can target the multifactorial pathophysiology of these diseases. Among these, nature-based solutions have garnered significant attention, offering a rich reservoir of bioactive compounds with potential neuroprotective properties (Wang et al., 2024). Consequently, the exploration of nutraceuticals food-derived products with purported health benefits has emerged as a promising frontier in the fight against neurodegeneration.

Nutraceuticals encompass a diverse array of natural compounds, including polyphenols, flavonoids, alkaloids, and omega-3 fatty acids, which are derived from various botanical and marine sources. Their proposed mechanisms of action in the context of neuroprotection are remarkably multifaceted, directly addressing key pathological hallmarks such as oxidative stress, mitochondrial dysfunction, and chronic neuroinflammation. For instance, many of these compounds act as potent antioxidants, scavenging free radicals and bolstering the endogenous antioxidant defense systems within the brain. Furthermore, they have been shown to modulate critical signaling pathways involved in neuronal survival, synaptic plasticity, and the clearance of toxic protein aggregates like amyloid-beta and tau (Fatima et al., 2025). This ability to intervene simultaneously on multiple fronts distinguishes nutraceuticals from conventional single-target drugs. It is this polypharmacological profile that positions them as particularly compelling candidates for the development of effective neuroprotective therapies.

The concept of "neurohealth" extends beyond the mere absence of disease, encompassing the proactive maintenance of cognitive function and mental well-being throughout the lifespan.

In this context, nutraceuticals are increasingly viewed not only as potential therapeutic agents but also as key components of preventive strategies to build cognitive reserve and delay the onset of neurodegeneration (Ristori et al., 2025). Dietary patterns rich in these bioactive compounds, such as the Mediterranean diet, have been epidemiologically linked to a lower risk of cognitive decline. However, the translation of these observational findings into effective clinical applications requires rigorous scientific investigation to establish bioavailability, optimal dosages, and long-term safety profiles. This chapter will critically examine the current scientific evidence supporting the use of various nutraceuticals in combating neurodegeneration, exploring their mechanisms of action, preclinical and clinical findings, and the challenges that must be overcome to integrate these nature-based solutions into mainstream neurohealth paradigms.

1. DEFINING NATURE-BASED SOLUTIONS

The concept of Nature-Based Solutions (NBS) has gained considerable traction as a framework for addressing societal challenges through the responsible application of natural processes and ecosystems (Sowińska-Świerkosz et al., 2024). While initially prominent in environmental management and urban planning, the core principles of NBS are now being recognized for their profound relevance to health innovation, particularly in the search for sustainable therapies. At its heart, NBS is defined by actions that are inspired by, supported by, or copied from nature, and they are designed to deliver multiple benefits across ecological, social, and economic dimensions. In the context of neurohealth, this translates to developing interventions—such as nutraceuticals—that harness the inherent therapeutic potential of biodiversity while promoting conservation and sustainable sourcing. This approach moves beyond a purely extractive model of drug discovery to one that values the integrity of the ecosystems from which these compounds are derived. The fundamental principle is that human health is inextricably linked to the health of our planet, and sustainable innovation must therefore protect both. A key principle underpinning NBS for neurohealth is the emphasis on systemic thinking and multifunctionality.

Unlike synthetic drugs designed for a single, potent effect, nature-derived compounds often operate through complex, synergistic networks, reflecting the intricate relationships found within their native ecosystems (Jiao et al., 2024). This aligns perfectly with the need to target the multiple interconnected pathways involved in neurodegeneration, such as inflammation, oxidative damage, and protein aggregation. Furthermore, NBS promotes the use of locally available resources and traditional knowledge, which can enhance the resilience and cost-effectiveness of health interventions, particularly in underserved regions. By valuing and integrating indigenous practices related to medicinal plants, researchers can uncover novel bioactive compounds while supporting cultural preservation. This systemic approach ensures that the pursuit of neurohealth does not occur in a silo but contributes to broader goals of environmental stewardship and social equity.

Ultimately, applying NBS principles to nutraceutical development necessitates a life-cycle perspective that prioritizes sustainability from source to patient. This involves establishing ethical supply chains that prevent over-harvesting of endangered plant species and promote agroecological farming practices over destructive wild collection (Djekic et al., 2025). It also calls for green extraction and manufacturing technologies that minimize energy consumption and waste, ensuring that the cure does not come at the cost of further environmental degradation. The long-term viability of nature-based neurohealth strategies depends on this commitment to sustainability, as the erosion of biodiversity directly diminishes the library of potential therapeutic compounds for future generations. Therefore, the integration of NBS principles provides an ethical and practical roadmap for developing nutraceuticals that are not only effective against neurodegeneration but also contribute positively to the health of the planet. This holistic perspective redefines innovation in neurohealth as a practice that must be regenerative and restorative, rather than merely extractive.

Figure 1. Nature-based solutions for Neurohealth

2. THE UNMET NEED

The global demographic landscape is undergoing a profound transformation, with the proportion of individuals aged 60 years and older growing at an unprecedented rate. This "silver tsunami" represents one of the greatest public health achievements of our time, yet it simultaneously presents society with immense socioeconomic challenges. Among the most pressing of these is the sharply rising incidence of age-related neurodegenerative disorders, which predominantly affect this vulnerable segment of the population (Gianfredi et al., 2025). Alzheimer's disease, Parkinson's disease, and related dementias have thus transitioned from relatively rare conditions to leading causes of disability and dependency worldwide. The personal toll on individuals and families is immeasurable, eroding memories, motor function, and identity itself over prolonged periods. Concurrently, the economic burden on healthcare systems, social services, and informal caregivers has reached unsustainable levels, creating an urgent imperative for effective solutions.

The pathophysiology underlying these disorders is notoriously complex and remains incompletely understood, which has significantly hampered the development of curative interventions.

Common features include the progressive accumulation of misfolded proteins, such as amyloid-beta plaques and tau tangles in Alzheimer's disease, alongside chronic neuroinflammation, oxidative stress, and mitochondrial dysfunction (Zhang et al., 2025). These interconnected pathological cascades begin years or even decades before the appearance of clinical symptoms, creating a lengthy prodromal phase that may offer a critical window for intervention. The clinical consequences are devastating, manifesting as progressive cognitive decline, behavioral changes, and loss of motor control that ultimately renders individuals entirely dependent on others. Current pharmacological options are limited to a handful of drugs that provide modest symptomatic relief for some patients but do not modify the underlying disease trajectory. This stark reality leaves millions of patients and their families without meaningful hope for altering the course of their illness.

The failure of conventional drug development pipelines to deliver disease-modifying therapies has exposed critical gaps in the current therapeutic paradigm. Numerous high-profile clinical trials for promising drug candidates have yielded disappointing results, leading some pharmaceutical companies to retreat entirely from neuroscience research (Dominguez-Gortaire et al., 2025). This attrition reflects, in part, the reductionist approach of targeting single molecular pathways in diseases now recognized as systemic and multifactorial in nature. Furthermore, the blood-brain barrier presents a formidable obstacle to drug delivery, preventing many potentially therapeutic compounds from reaching their intended targets within the central nervous system. There is also a growing recognition that intervention may need to commence during the preclinical phase, before irreversible neuronal loss has occurred, necessitating reliable biomarkers and preventative strategies. Collectively, these challenges underscore the critical unmet need for innovative approaches that embrace the complexity of neurodegeneration and offer sustainable, accessible, and multitargeted therapeutic options for our aging global population.

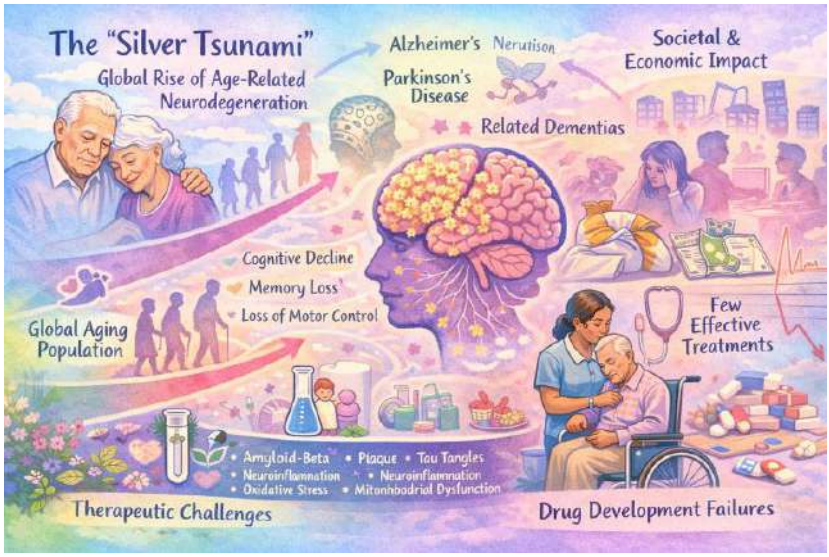

Figure 2. Global rise of age-related neurodegeneration

3. BIODIVERSITY AS A RESERVOIR

The extraordinary diversity of life on Earth, encompassing millions of plant, microbial, and marine species, represents an immeasurably rich repository of chemical innovation honed over billions of years of evolution. Each organism produces a vast array of secondary metabolites—compounds not essential for basic survival but synthesized to confer ecological advantages such as defense against predators, competition with neighboring species, or adaptation to environmental stressors (Karthikeyan et al., 2022). It is precisely these bioactive molecules, refined through natural selection for their potent biological effects, that hold immense promise for human therapeutic applications. The plant kingdom alone has historically provided the foundation for numerous essential medicines, from the analgesic morphine derived from opium poppy to the antimalarial artemisinin from sweet wormwood. This evolutionary pharmacopoeia is now being systematically explored for compounds capable of modulating the complex pathological cascades underlying neurodegenerative diseases. The fundamental premise is that nature has already conducted millions of years of research and development, presenting humanity with a pre-screened library of bioactive structures awaiting discovery and characterization.

Among the most intensively investigated categories of neuroprotective natural products are the polyphenols, a large family of compounds abundant in fruits, vegetables, tea, and medicinal herbs. These molecules, including resveratrol from grapes, epigallocatechin-3-gallate from green tea, and curcumin from turmeric, exhibit remarkable multifunctional bioactivity relevant to neurodegeneration (Srinivasan et al., 2021). Their neuroprotective effects stem from their ability to scavenge reactive oxygen species, chelate pro-oxidant metal ions, and upregulate endogenous antioxidant defense mechanisms within neuronal cells. Furthermore, numerous polyphenols have been shown to modulate key inflammatory pathways, suppressing the chronic neuroinflammation that characterizes diseases like Alzheimer's and Parkinson's. They also influence intracellular signaling cascades governing neuronal survival, synaptic plasticity, and the autophagic clearance of toxic protein aggregates. This pleiotropic mechanism of action aligns ideally with the multifactorial etiology of neurodegeneration, offering a distinct advantage over conventional single-target pharmaceuticals.

Beyond terrestrial plants, the world's oceans and extreme environments are emerging as particularly promising frontiers for neuroactive compound discovery. Marine organisms, including sponges, tunicates, algae, and microorganisms, inhabit competitive and challenging ecosystems that drive the evolution of unique and often highly potent chemical defenses (Karthikeyan et al., 2022). These marine-derived compounds frequently possess novel chemical scaffolds not found in terrestrial sources, expanding the structural diversity available for drug development. Similarly, extremophiles—organisms thriving in volcanic springs, deep-sea vents, or polar ice—produce specialized molecules that maintain functionality under extreme conditions, offering insights into mechanisms of cellular resilience. The ongoing loss of biodiversity due to habitat destruction, climate change, and overexploitation therefore represents not only an ecological tragedy but also a direct threat to the future of neurohealth innovation. Protecting these natural reservoirs through conservation and sustainable bioprospecting is thus an urgent priority for preserving access to the next generation of neuroprotective therapeutics.

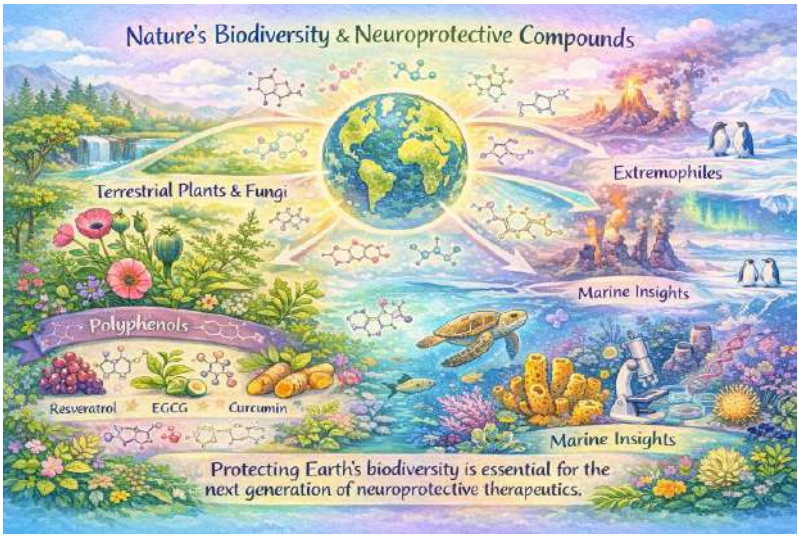

Figure 3. Biodiversity of neuroprotective agents

4. MOLECULAR MECHANISMS

The neuroprotective potential of nutraceuticals resides in their remarkable capacity to simultaneously modulate multiple interconnected pathological pathways that drive neurodegeneration. Unlike conventional pharmaceuticals designed for high-affinity binding to a single molecular target, natural bioactive compounds typically exert their effects through what is termed "polypharmacology"—the concurrent modulation of numerous cellular signaling cascades. This multitargeted approach is particularly well-suited to complex disorders like Alzheimer's and Parkinson's diseases, which involve the progressive dysfunction of multiple interrelated systems rather than a single linear pathway. The molecular mechanisms through which these compounds operate span a continuum from direct antioxidant and anti-inflammatory actions to the regulation of gene expression and cellular survival programs (Giri & Chandra, 2025).Understanding these mechanisms at the molecular level is essential for rationalizing the traditional use of medicinal plants and for optimizing their application in modern neurotherapeutics. Furthermore, this mechanistic insight provides the scientific foundation for developing evidence-based nutritional strategies for maintaining cognitive health throughout the lifespan.

A primary mechanism by which nutraceuticals confer neuroprotection is through the amelioration of oxidative stress, a unifying feature of virtually all neurodegenerative conditions. The brain is particularly vulnerable to oxidative damage due to its high oxygen consumption, abundant lipid content, and relatively limited antioxidant defense capacity. Many plant-derived polyphenols, such as resveratrol, curcumin, and quercetin, function as direct free radical scavengers, neutralizing reactive oxygen and nitrogen species before they can damage cellular lipids, proteins, and DNA (Borrego-Ruiz & Borrego, 2025). Beyond this direct scavenging activity, these compounds also activate endogenous antioxidant defenses by upregulating the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Nrf2 serves as a master transcriptional regulator that coordinates the expression of a battery of cytoprotective enzymes, including heme oxygenase-1, catalase, and superoxide dismutase. Through this dual mechanism of direct radical neutralization and reinforcement of intrinsic cellular defenses, nutraceuticals establish a comprehensive shield against oxidative injury in vulnerable neuronal populations.

Chronic neuroinflammation represents another critical pathological driver that nutraceuticals effectively target through multiple molecular pathways. Microglia, the resident immune cells of the central nervous system, can become persistently activated in neurodegenerative diseases, releasing a barrage of pro-inflammatory cytokines and neurotoxic factors that exacerbate neuronal injury. Numerous natural compounds have demonstrated potent anti-inflammatory effects by inhibiting key signaling nodes such as nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs). For instance, curcumin has been extensively documented to suppress NF-κB activation, thereby reducing the transcription of inflammatory mediators including tumor necrosis factor-alpha and interleukin-1 beta. Additionally, certain nutraceuticals promote the autophagic clearance of aggregated proteins, facilitating the removal of toxic species like amyloid-beta and hyperphosphorylated tau that would otherwise propagate inflammatory responses and synaptic dysfunction (Adamu et al., 2024).

The convergence of nutraceuticals upon these fundamental molecular hubs oxidative stress, inflammation, and proteostasis explains their capacity to modify disease trajectories and supports their integration into comprehensive neurohealth strategies.

Figure 4. Neuroprotective potential of natural compounds

5. THE GUT-BRAIN AXIS

The bidirectional communication network linking the gastrointestinal tract and the central nervous system, known as the gut-brain axis, has emerged as a fundamental determinant of neurological health and disease. This complex system encompasses neural pathways, endocrine signaling, immune mediators, and increasingly recognized, the vast community of microorganisms residing within the gut—the microbiota. Compelling evidence now implicates gut dysbiosis, an imbalance in this microbial ecosystem, in the pathogenesis of various neurodegenerative disorders, including Parkinson's and Alzheimer's diseases (Liu et al., 2025). The microbiota and its collective genome, the microbiome, influence brain function through the production of neuroactive metabolites, modulation of immune responses, and regulation of intestinal barrier integrity. This revelation has profound implications for neurotherapeutics, suggesting that interventions targeting the gut microbial community could exert meaningful effects on brain health.

Within this paradigm, nature-based solutions offer particularly promising strategies, as many nutraceuticals possess prebiotic properties that selectively nurture beneficial microbial populations.

Dietary polyphenols and polysaccharides derived from botanical sources serve as key substrates for microbial fermentation in the colon, directly modulating the composition and metabolic output of the gut microbiota. These compounds, often poorly absorbed in the small intestine, reach the large intestine where they are metabolized by specific bacterial species into smaller bioactive metabolites with enhanced bioavailability and neuroactivity (Li et al., 2025). For instance, the metabolism of flavonoids from berries and tea by gut bacteria generates phenolic acids that can cross the blood-brain barrier and exert direct neuroprotective effects. Concurrently, these prebiotic compounds promote the growth of beneficial genera such as Bifidobacterium and Lactobacillus while suppressing potentially pathogenic species. The resulting shift toward a healthier microbial profile enhances the production of short-chain fatty acids—metabolites with demonstrated anti-inflammatory and neuroprotective properties that signal directly to the brain via vagal and circulatory routes. This intricate interplay between dietary nutraceuticals, gut microbiota, and neural function exemplifies the systemic nature of nature-based solutions for neurohealth.

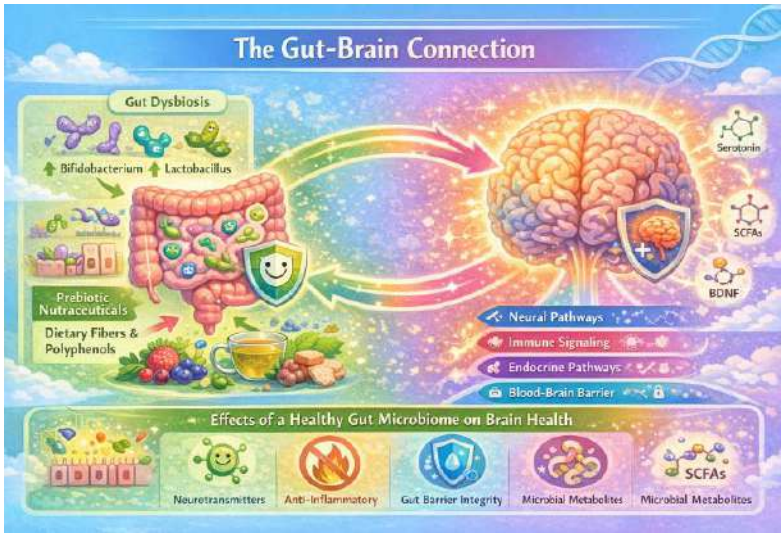

Figure 5. Gut-brain connection and its benefits

The therapeutic implications of harnessing the gut-brain axis through prebiotic nutraceuticals extend beyond direct symptomatic relief to encompass disease modification and prevention. By restoring microbial equilibrium and reinforcing intestinal barrier function, these interventions may reduce the systemic inflammation and leaky gut phenomena increasingly linked to neuroinflammatory processes within the brain (Alkuwaiti et al., 2025). Furthermore, the capacity of certain prebiotic compounds to enhance the production of neurotrophic factors and neurotransmitters within the gut provides an additional mechanism for supporting cognitive function and mood regulation. This gut-centered approach also aligns with the NBS principle of multifunctionality, as dietary interventions that benefit the microbiota simultaneously support metabolic health, immune function, and environmental sustainability through responsible sourcing. The recognition that neurohealth begins in the gut fundamentally expands the therapeutic landscape, positioning prebiotic nutraceuticals as foundational components of comprehensive strategies to combat neurodegeneration. Future research directed at understanding individual variability in microbiome composition and response will be essential for personalizing these nature-based interventions and maximizing their clinical impact.

6. ETHNOPHARMACOLOGY

Ethnopharmacology, the scientific study of traditionally used medicinal substances, represents a vital bridge between indigenous healing practices and contemporary biomedical research. For millennia, human cultures across the globe have accumulated empirical knowledge regarding the therapeutic properties of plants, fungi, and other natural materials found within their local environments. This vast repository of traditional knowledge, passed down through generations via oral traditions and written texts, encodes countless observations about which natural substances can alleviate suffering and promote health (Tadesse et al., 2025). In the context of neurodegeneration, numerous botanical remedies have been employed traditionally to enhance memory, sharpen cognition, and age-related mental decline, long before the molecular basis of these conditions was understood.

The systematic documentation and analysis of these traditional uses provide modern researchers with invaluable information or identifying potentially neuroactive compounds worthy of further investigation. Ethnopharmacology thus functions as a sophisticated filtering system, directing scientific attention toward those natural products with the greatest likelihood of yielding clinically relevant bioactivity.

The methodological approach of ethnopharmacology begins with meticulous fieldwork, wherein ethnobotanists and anthropologists collaborate with indigenous communities to document traditional medicinal practices and the specific plants employed. This process requires cultural sensitivity, mutual respect, and adherence to protocols ensuring that communities retain agency over their knowledge and receive fair benefit-sharing from any commercial developments that may ensue. Once a plant with traditional neurocognitive indications is identified, phytochemical analysis proceeds to isolate and characterize its constituent compounds, which are then subjected to a battery of in vitro and in vivo assays to evaluate neuroprotective properties (Balkrishna et al., 2026). This pipeline has yielded numerous successes, including the isolation of galantamine from Caucasian snowdrop and related species, traditionally used for cognitive support and now approved for Alzheimer's disease treatment. The investigation of Bacopa monnieri, a cornerstone of Ayurvedic medicine for memory enhancement, has similarly generated extensive preclinical evidence supporting its neuroprotective effects through multiple mechanisms. These examples illustrate how traditional knowledge can dramatically accelerate the drug discovery process by providing validated starting points for scientific inquiry.

Despite its immense potential, the integration of ethnopharmacological knowledge into mainstream neurotherapeutic development faces significant challenges and ethical responsibilities. Biopiracy—the appropriation of traditional knowledge and genetic resources without authorization or compensation—remains a persistent concern, particularly when pharmaceutical interests exploit indigenous wisdom for commercial gain while excluding source communities from benefits (Patwardhan & Aswar, 2025).

The Convention on Biological Diversity and the Nagoya Protocol establish international frameworks for access and benefit-sharing, but implementation remains inconsistent across jurisdictions. Additionally, the standardization and quality control of traditional preparations pose scientific challenges, as plant composition varies with growing conditions, harvesting practices, and processing methods. The validation of traditional claims through rigorous clinical trials is essential but resource-intensive, often deterring commercial investment in botanicals that cannot be patented in their natural form. Nevertheless, the ethical integration of ethnopharmacology offers a pathway to neurotherapeutic innovation that honors cultural heritage, promotes biodiversity conservation, and expands the repertoire of nature-based solutions available to combat neurodegeneration in our aging global population.

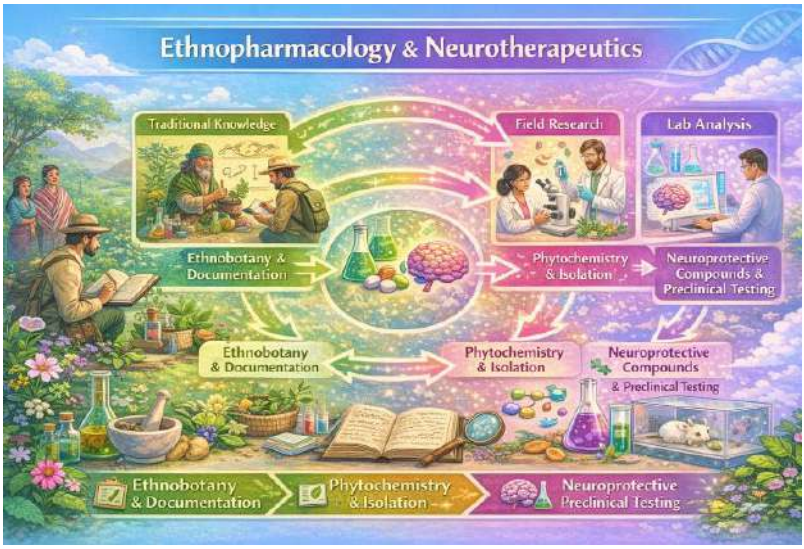

Figure 6. Blend of ethnopharmacology and modern neurotherapeutics

7. SUSTAINABLE SOURCING

The therapeutic promise of nature-based solutions for neurodegeneration rests fundamentally upon the continued availability of the botanical and marine resources from which neuroprotective compounds are derived.

As demand for these natural products escalates in response to aging populations and growing consumer interest in cognitive health, the imperative for sustainable sourcing becomes increasingly urgent. Unsustainable wild harvesting practices have already driven numerous medicinal plant species toward endangerment or extinction, simultaneously threatening biodiversity and the livelihoods of communities dependent on these resources (Toulis et al., 2025). The transition from wild collection to regulated cultivation represents a critical step in ensuring both conservation and supply chain reliability for the nutraceutical industry. This shift must be guided by ecological principles that maintain genetic diversity within cultivated populations and prevent the domestication bottleneck that can reduce bioactive potency. Sustainable sourcing thus emerges not merely as an ethical consideration but as a fundamental prerequisite for the long-term viability of nature-based neurohealth interventions.

Cultivation strategies for neuroactive medicinal plants must integrate agricultural science with ecological wisdom to optimize both yield and phytochemical quality. The concentration of bioactive compounds in plants is profoundly influenced by growing conditions, including soil composition, water availability, light exposure, and symbiotic relationships with beneficial microorganisms. Implementing Good Agricultural and Collection Practices (GACP) ensures that cultivation methods produce consistent, high-quality raw materials while minimizing environmental impact through reduced pesticide use and water conservation (El-Saadony et al., 2025).Agroforestry systems, wherein medicinal plants are cultivated alongside food crops or within forest understories, offer particular promise for reconciling production with biodiversity conservation. These multifunctional landscapes provide habitat for pollinators and wildlife, enhance soil carbon sequestration, and diversify farmer incomes, embodying the NBS principle of generating multiple simultaneous benefits. Furthermore, cultivation initiatives can be designed to empower local communities, particularly in regions of high biodiversity where traditional knowledge of medicinal plants resides, creating economic incentives for conservation.

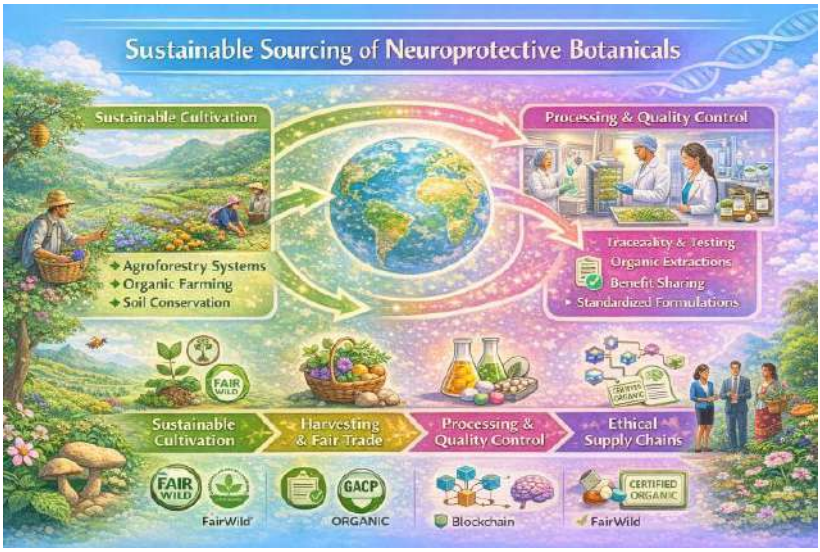

Figure 7. Therapeutic promise of nature-based solutions

The journey from cultivated crop to finished nutraceutical product involves complex supply chains that must maintain traceability, quality, and ethical integrity at every stage. Post-harvest processing, including drying, extraction, and formulation, presents opportunities for the introduction of contaminants or the degradation of bioactive constituents if not carefully controlled. Transparent supply chain management, enabled by technologies such as blockchain and chemical fingerprinting, allows consumers and regulators to verify the authenticity and sustainability credentials of finished products (Manzoor et al., 2024). Equitable benefit-sharing mechanisms, as established under international agreements like the Nagoya Protocol, ensure that source communities receive fair compensation for their genetic resources and traditional knowledge. The adoption of certification schemes, such as FairWild and organic certifications, provides market-based incentives for sustainable practices while communicating these values to increasingly conscientious consumers. Ultimately, the development of robust, ethical, and ecologically sound supply chains for neuroactive nutraceuticals represents a complex but essential endeavor that will determine whether nature-based solutions fulfill their potential to combat neurodegeneration without compromising the natural systems that sustain them.

8. ETHICAL FRAMEWORKS

The exploration of nature's pharmacological richness for neuroprotective compounds, known as bioprospecting, carries profound ethical obligations that extend far beyond the laboratory. Historically, the collection of genetic resources and traditional knowledge from biodiversity-rich nations, often in the Global South, has proceeded without meaningful consent or compensation to source communities, a practice rightly condemned as biopiracy. This exploitative legacy has fostered deep mistrust between indigenous peoples, local communities, and the commercial entities seeking to develop nature-based therapeutics (Rodrigues, 2024). In response to these injustices, the international community has developed ethical frameworks centered on the principle of Access and Benefit-Sharing (ABS), which asserts that countries have sovereign rights over their genetic resources and that benefits arising from their utilization must be equitably shared. The fundamental premise of ABS is that those who contribute genetic materials and associated traditional knowledge should participate fairly in the financial and non-financial rewards generated through product development. This framework transforms bioprospecting from a potentially extractive enterprise into a collaborative partnership between resource providers and users. For the field of neurohealth, implementing robust ABS mechanisms ensures that the development of nutraceuticals to combat neurodegeneration contributes positively to the well-being of communities who serve as custodians of this invaluable biodiversity.

The Convention on Biological Diversity (CBD), adopted at the 1992 Earth Summit in Rio de Janeiro, established the foundational legal architecture for ABS by affirming national sovereignty over genetic resources and requiring prior informed consent for their collection. Building upon this foundation, the Nagoya Protocol on Access and Benefit-Sharing, which entered into force in 2014, provides a more detailed and legally binding international framework for implementing ABS principles (Lachenmeier & Montagnon, 2024). Under the Nagoya Protocol, countries are required to establish clear and transparent procedures for accessing genetic resources, including requirements for obtaining permits and negotiating mutually agreed terms with provider countries.

These terms specify how benefits which may include monetary royalties, technology transfer, research collaboration, or capacity-building support—will be shared with source communities. For researchers and companies developing neuroprotective nutraceuticals, compliance with ABS regulations is not merely a legal obligation but an opportunity to build enduring partnerships that enhance the quality and sustainability of their work. The protocol also includes specific provisions protecting traditional knowledge associated with genetic resources, requiring that indigenous and local communities give their approval for its use and participate in benefit-sharing arrangements.

Despite the elegant architecture of international ABS frameworks, their practical implementation in the context of neurohealth research faces numerous challenges requiring ongoing attention and refinement. The administrative burden of navigating diverse national ABS laws, each with unique permitting procedures and contractual requirements, can be particularly daunting for academic researchers and small enterprises with limited legal resources (Ljungqvist et al., 2025). Furthermore, the complexity of modern bioprospecting, wherein genetic sequence data may be accessed digitally from open repositories rather than through physical samples, raises unresolved questions about whether and how ABS principles apply to such "digital sequence information." The long time horizon between initial sample collection and eventual product commercialization—often spanning decades—complicates the prediction and distribution of benefits, particularly when multiple compounds from various sources contribute to a final formulation. Despite these challenges, the ethical imperative underlying ABS remains clear: communities who have conserved biodiversity and developed traditional knowledge about its uses deserve recognition and fair compensation when these resources contribute to neurohealth innovations. The maturation of ethical frameworks for bioprospecting thus represents an essential foundation for ensuring that nature-based solutions for neurodegeneration advance both scientific progress and global justice.

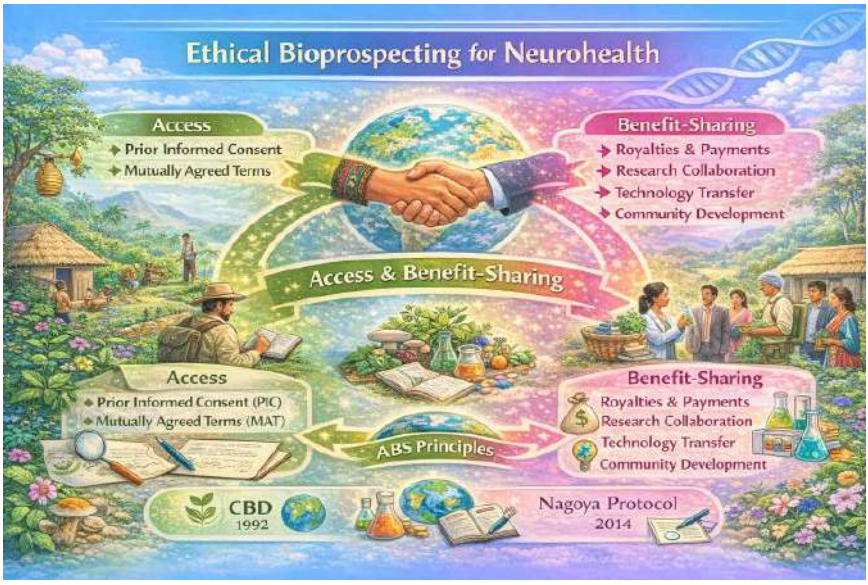

Figure 8. Ethical bioprospecting for neurohealth purposes

9. STANDARDIZATION AND QUALITY CONTROL

The translation of neuroprotective nutraceuticals from traditional remedies to evidence-based therapeutic interventions necessitates rigorous standardization and quality control protocols. Unlike synthetic pharmaceuticals with well-defined chemical structures and purity profiles, natural extracts comprise complex mixtures of hundreds or even thousands of constituents, many of which remain unidentified or poorly characterized. This inherent complexity presents formidable challenges for ensuring batch-to-batch consistency, which is essential for both clinical research reproducibility and reliable therapeutic outcomes (Bhargavi et al., 2025). The bioactivity of a given extract depends not only on the presence of specific "active" compounds but also on the synergistic interactions among multiple constituents that may modulate each other's absorption, metabolism, and target engagement. Furthermore, natural variations in plant genetics, cultivation conditions, harvest timing, and post-harvest processing can dramatically influence phytochemical profiles, introducing variability that must be controlled through systematic quality management.

The development of robust standardization methods therefore represents a critical prerequisite for integrating nature-based solutions into mainstream neurohealth paradigms.

Modern analytical chemistry provides an increasingly sophisticated toolkit for characterizing and standardizing complex botanical extracts destined for neurotherapeutic applications. High-performance liquid chromatography (HPLC) coupled with mass spectrometry and diode array detection enables the simultaneous identification and quantification of multiple marker compounds within a single analytical run (Sica et al., 2025). The selection of appropriate markers for standardization requires careful consideration, balancing the need to represent known bioactive constituents with the practical reality that bioactivity often arises from the entire phytochemical ensemble. Chemometric approaches, including principal component analysis and hierarchical clustering analysis, allow researchers to compare comprehensive chemical fingerprints across different batches and identify unacceptable deviations from established reference profiles. Nuclear magnetic resonance (NMR)-based metabolomics offers an even more holistic view of extract composition, capturing information on both primary and secondary metabolites that may contribute to neuroprotective effects. These advanced analytical methods must be complemented by validated reference materials and proficiency testing programs to ensure accuracy and comparability across laboratories. The integration of multiple orthogonal analytical techniques provides the comprehensive characterization necessary for meaningful standardization of complex natural products.

Beyond chemical characterization, quality control for neuroactive nutraceuticals must address potential safety concerns including contaminants, adulterants, and toxic constituents that may compromise patient health. Botanical extracts are susceptible to contamination with heavy metals, pesticides, mycotoxins, and microbial pathogens, all of which require rigorous testing with established safety limits (Kanugo & Agrawal, 2026). Deliberate adulteration, wherein lower-cost materials or synthetic compounds are substituted for authentic botanical ingredients, represents an additional quality concern that undermines both therapeutic efficacy and consumer trust.

DNA barcoding and other molecular authentication methods provide powerful tools for verifying species identity and detecting adulteration at the raw material stage. The establishment of pharmacopoeial standards, such as those developed by the United States Pharmacopeia or European Pharmacopoeia, provides authoritative benchmarks for identity, purity, and strength that facilitate regulatory compliance and international commerce. Ultimately, the maturation of standardization and quality control practices for complex natural extracts will determine whether neuroprotective nutraceuticals can achieve the reliability and credibility required for widespread clinical adoption, transforming nature-based solutions from anecdotal traditions into rigorously validated components of neurohealth therapeutics.

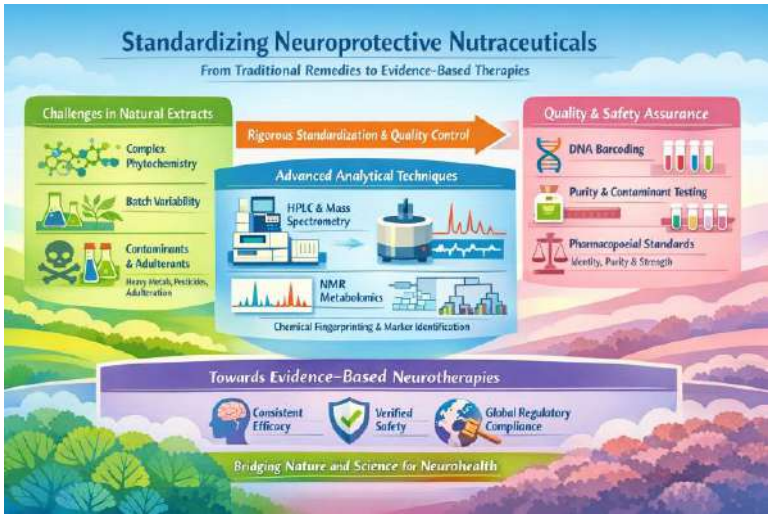

Figure 9. Standardizing neuroprotective nutraceuticals infographic

10. OVERCOMING BIOAVAILABILITY BARRIERS

The translation of promising neuroprotective nutraceuticals from laboratory discoveries to clinically effective interventions is profoundly constrained by the formidable challenge of bioavailability. Bioavailability, defined as the fraction of an administered compound that reaches systemic circulation and becomes available at the site of action, represents a critical determinant of therapeutic efficacy.

Many polyphenolic compounds with demonstrated neuroprotective activity in vitro, such as curcumin, resveratrol, and epigallocatechin-3-gallate, exhibit notoriously poor bioavailability following oral administration (Żurek & Adamczyk, 2025). This discrepancy between potent in vitro bioactivity and disappointing in vivo performance has historically undermined the credibility of nutraceutical research and contributed to inconsistent clinical trial outcomes. The underlying causes of poor bioavailability are multifactorial, encompassing physicochemical properties of the compounds themselves and physiological barriers within the human body. Addressing these bioavailability barriers through innovative formulation strategies is therefore essential for realizing the full therapeutic potential of nature-based solutions for neurodegeneration.

The journey of an orally administered nutraceutical from ingestion to neuronal target involves navigating a series of formidable obstacles that progressively reduce the available dose. Many neuroactive polyphenols are characterized by poor aqueous solubility, limiting their dissolution in gastrointestinal fluids and consequently their availability for absorption. Those compounds that do solubilize must then traverse the intestinal epithelial barrier, a process often hampered by high molecular weight, extensive hydrogen bonding, and efflux transporters such as P-glycoprotein that actively pump xenobiotics back into the intestinal lumen. Following absorption, compounds enter the hepatic portal circulation and undergo extensive first-pass metabolism, wherein phase I and phase II enzymes in the liver and intestine conjugate the parent molecules with glucuronide, sulfate, or methyl groups to enhance their elimination. These conjugated metabolites typically possess reduced biological activity compared to their parent aglycones and are rapidly excreted in bile or urine (Domínguez-López et al., 2025). The small fraction of intact compound that survives these barriers and enters systemic circulation must finally cross the blood-brain barrier, a tightly regulated endothelial interface that restricts the entry of most hydrophilic and large molecules into the central nervous system. This cumulative attrition explains why nanomolar or picomolar plasma concentrations are often observed following administration of gram quantities of neuroactive nutraceuticals.

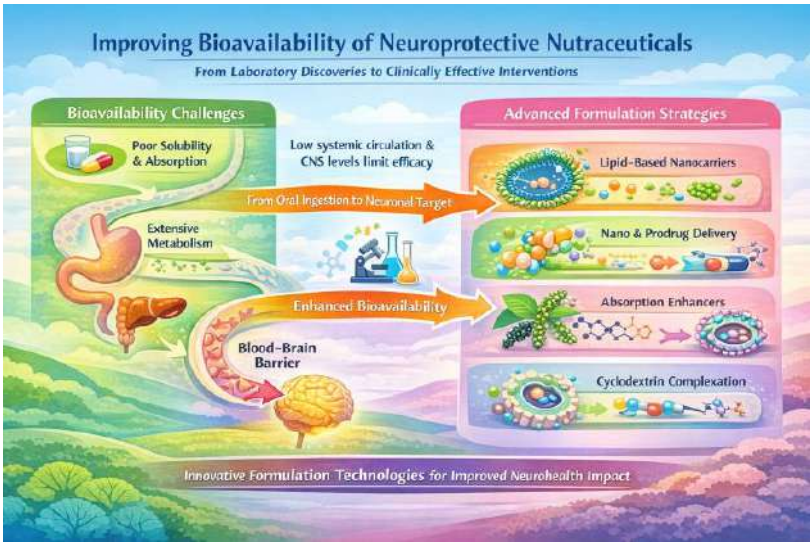

Figure 10. Improving neuroprotective nutraceutical bioavailability

In response to these formidable bioavailability challenges, pharmaceutical scientists have developed an array of innovative formulation technologies designed to enhance the delivery of neuroprotective compounds to their intended targets. Lipid-based formulations, including liposomes, phytosomes, and nanoemulsions, have demonstrated particular promise by incorporating hydrophilic polyphenols into lipid matrices that mimic cell membrane composition and facilitate absorption (Patel et al., 2024). Particle size reduction to the nanometer range through techniques such as nanomilling and high-pressure homogenization increases surface area and dissolution rate, dramatically improving the bioavailability of poorly soluble compounds. The incorporation of absorption enhancers, such as piperine from black pepper, can inhibit intestinal and hepatic metabolism, effectively increasing the systemic exposure of co-administered nutraceuticals. Cyclodextrin complexation encapsulates hydrophobic molecules within hydrophilic cavities, enhancing solubility and stability while potentially masking undesirable organoleptic properties. Prodrug strategies, wherein the active compound is chemically modified to improve absorption and subsequently converted to the parent molecule in vivo, offer an additional approach for specific nutraceutical candidates.

The application of these enabling formulation technologies is rapidly transforming the bioavailability landscape, positioning neuroprotective nutraceuticals for more rigorous clinical evaluation and ultimately for meaningful impact on cognitive health in aging populations.

11. SYNERGISTIC FORMULATIONS

The conventional pharmaceutical paradigm has long pursued therapeutic efficacy through the isolation and purification of single active compounds, a reductionist approach that assumes maximal benefit derives from a singular molecular entity. While this strategy has yielded numerous life-saving medications, its application to complex neurodegenerative diseases has proven disappointingly limited, perhaps because these conditions arise from the dysregulation of multiple interconnected pathways rather than a single defect. Nature-based solutions offer an alternative philosophical framework grounded in the recognition that plants and other organisms produce complex chemical mixtures precisely because synergy the enhanced effect resulting from combined constituents confers evolutionary advantages (Shaharyar et al., 2025). The concept of synergistic formulations acknowledges that the therapeutic whole of a botanical extract may exceed the sum of its isolated parts, with multiple compounds working in concert to enhance bioavailability, modulate diverse targets, and mitigate potential toxicity. This holistic approach aligns with the traditional wisdom underlying many medicinal plant practices, wherein whole extracts or multi-herb formulas have been preferred over isolated constituents for generations. Embracing this complexity in the development of neuroprotective nutraceuticals requires sophisticated experimental designs capable of detecting and quantifying synergistic interactions, as well as manufacturing processes that preserve the integrity of the original phytochemical ensemble. The mechanistic basis for synergy in neuroprotective natural product formulations operates through several distinct but potentially overlapping phenomena that collectively enhance therapeutic impact. Pharmacodynamic synergy occurs when multiple compounds within a mixture engage different molecular targets involved in the same pathological cascade, producing combinatorial effects that exceed what would be predicted from their individual activities.

For example, one constituent might inhibit neuroinflammation through NF-κB suppression while another simultaneously enhances neuronal resilience through BDNF upregulation, together providing more comprehensive neuroprotection than either alone. Pharmacokinetic synergy involves compounds that improve each other's absorption, distribution, metabolism, or elimination, effectively increasing the concentration and duration of active principles at target sites (Irum et al., 2025). The classic example is piperine from black pepper, which inhibits intestinal and hepatic metabolism of co-administered curcumin, dramatically increasing its systemic bioavailability. Additionally, certain constituents may suppress the activity of efflux transporters at the blood-brain barrier, facilitating the central nervous system penetration of neuroactive compounds that would otherwise be excluded. The suppression of potential toxicity through buffering or antagonistic interactions represents another form of synergy, wherein companion compounds mitigate adverse effects associated with primary active constituents, thereby widening the therapeutic window.

The scientific validation and commercialization of synergistic nutraceutical formulations present unique challenges that distinguish them from conventional single-compound drug development. Experimental approaches for demonstrating synergy require careful dose-response studies comparing the full mixture against its individual constituents and against theoretical additive models. These studies must account for the inherent variability in natural product composition, ensuring that observed synergistic effects are reproducible across different batches and representative of the intended commercial formulation. Regulatory pathways for complex mixtures remain less clearly defined than those for single compounds, creating uncertainty for manufacturers seeking to substantiate health claims or achieve approval in different jurisdictions. Intellectual property protection for synergistic formulations often relies on composition patents covering specific ratios or extraction methods, rather than claims on individual compounds that may exist in the public domain (Uniyal et al., 2026). Despite these challenges, growing consumer interest in holistic approaches to cognitive health, coupled with accumulating scientific evidence supporting the superiority of certain complex extracts over isolated constituents, is driving continued innovation in this space.

The future of neuroprotective nutraceuticals likely lies not in the pursuit of a single magic bullet, but in the thoughtful formulation of nature's multifaceted chemical libraries into standardized, evidence-based products that honor the synergistic wisdom encoded within biodiversity.

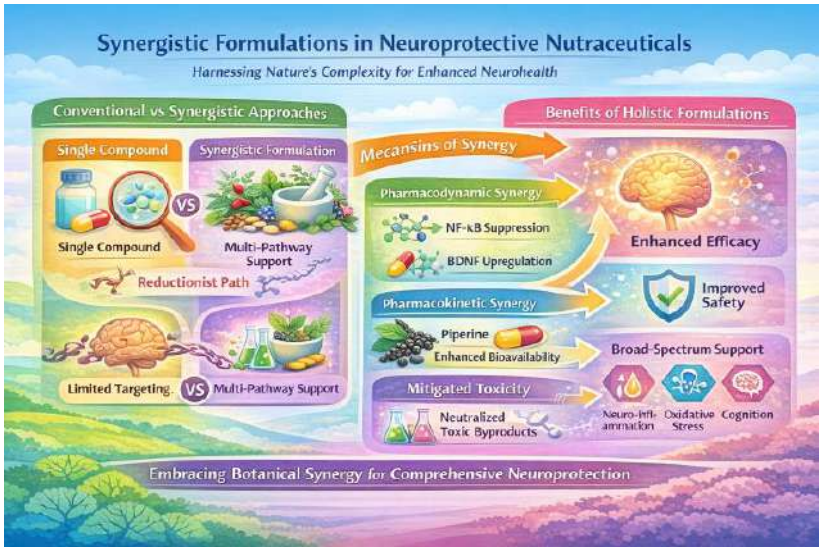

Figure 11. Neuroprotective nutraceutical synergy infographic

12. INTEGRATING INTO POLICY

The convergence of the neurodegenerative disease pandemic with the biodiversity crisis demands policy responses that transcend traditional sectoral boundaries, uniting public health and environmental conservation under a shared framework. Historically, health policy and environmental policy have operated in parallel silos, with ministries of health focused on healthcare delivery while environmental agencies addressed conservation concerns independently. This fragmentation has obscured the fundamental interdependence between ecosystem integrity and human well-being, particularly in the context of nature-based solutions for neurohealth (Velikic et al., 2025). The recognition that the same natural resources providing neuroprotective compounds also deliver essential ecosystem services clean air, water purification, climate regulation creates a compelling rationale for integrated policy approaches.

Furthermore, the disproportionate burden of both neurodegeneration and biodiversity loss falls upon vulnerable populations, including indigenous communities and those in low-income regions, introducing equity considerations that demand coordinated action. Integrating nature-based solutions into policy frameworks offers an opportunity to simultaneously advance cognitive health, environmental sustainability, and social justice through coherent, cross-sectoral strategies.

The translation of nature-based neurohealth solutions from scientific concept to policy reality requires the development of enabling regulatory environments across multiple governance levels. At the international level, conventions including the Convention on Biological Diversity and the World Health Organization's traditional medicine strategy provide platforms for harmonizing approaches to access and benefit-sharing, quality standards, and biodiversity conservation in the context of health product development. National governments must establish clear legal frameworks governing sustainable harvesting, cultivation incentives, and equitable benefit-sharing arrangements that protect both biodiversity and the rights of source communities (de Leeuw et al., 2026). Agricultural policies can play a transformative role by providing subsidies and technical support for farmers transitioning from conventional monoculture to diversified agroecological systems that produce medicinal plants while enhancing ecosystem services. Health systems and insurance providers may increasingly recognize the preventive potential of nutritional interventions, creating reimbursement mechanisms for evidence-based nutraceuticals that reduce long-term healthcare costs associated with neurodegenerative diseases. Urban planning policies that preserve green spaces and promote biodiversity within cities simultaneously support mental well-being and provide accessible reservoirs of plant genetic resources. These interconnected policy interventions exemplify the multifunctional benefits central to the nature-based solutions philosophy.

Figure 12. Integrating nature for neurohealth and conservation

Realizing the vision of integrated nature-based solutions for neurohealth requires overcoming significant implementation barriers rooted in institutional inertia, competing economic interests, and insufficient cross-sectoral collaboration. The dominance of short-term economic valuations that fail to account for the long-term costs of biodiversity loss or the societal burden of neurodegenerative disease perpetuates underinvestment in preventive and nature-based approaches. Powerful pharmaceutical and agribusiness interests may resist policy shifts that prioritize sustainable harvesting and equitable benefit-sharing over extractive, profit-maximizing models (Nail-Beatty et al., 2024). Furthermore, the evidence base linking specific nature-based interventions to measurable neurohealth outcomes must be strengthened through rigorous, policy-relevant research that meets the standards of both scientific and regulatory communities. Educational initiatives targeting policymakers, healthcare providers, and the public are essential for building awareness of the connections between biodiversity conservation and cognitive health, fostering demand for integrated approaches. Despite these challenges, the mounting urgency of both the neurodegeneration pandemic and the biodiversity crisis creates unprecedented political opportunity for transformative change.

The integration of nature-based solutions into public health and environmental policy represents not merely an incremental adjustment but a fundamental reconceptualization of how societies can simultaneously nurture human and planetary health for generations to come.

CONCLUSION

The convergence of the neurodegeneration pandemic with the accelerating biodiversity crisis demands therapeutic innovation grounded in ethical stewardship and ecological wisdom. Nature's chemical libraries, refined through millions of years of evolution, offer unparalleled bioactive compounds capable of targeting the multifactorial pathophysiology of neurodegenerative diseases. However, realizing this therapeutic promise requires rigorous attention to bioavailability enhancement, standardization, and clinical validation through innovative formulation technologies and analytical methodologies. Equally critical is the implementation of Access and Benefit-Sharing frameworks that ensure equitable partnerships with source communities and incentivize biodiversity conservation. The integration of synergistic formulations and the translation of these strategies into coherent public health policy represent the final frontiers for mainstream adoption. Ultimately, nature-based solutions for neurohealth affirm the fundamental truth that human health is inseparable from the health of the planet that sustains us.

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CHAPTER 2
POTENTIAL DRUG IDENTIFICATION FOR CREUTZFELDT-JAKOB DISEASE (CJD) THROUGH THE BIOINFORMATICS APPROACH

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INTRODUCTION

Creutzfeldt–Jakob disease (CJD) is a human prion disease noted by rapid neurodegeneration resulting from a conformational change in the prion protein. The term "prion" comes from "proteinaceous infections" and was first described by Stanley Prusiner. Soon after, abnormal prion proteins were identified as the cause of the disease (Mackenzie & Will, 2017). CJD is rare, affecting about one in one million people worldwide each year, with around 350 cases in the USA annually (Salehian et al., 2021). The altered protein conformation leads to an aberrant structure, which can spread and damage the brain (Al-Ansari & Robertson, 2017). CJD has three forms: genetic, sporadic, and acquired, with sporadic being the most common (Uttley et al., 2020).

The etiology of this is the abnormal accumulation of the prion protein (PrPSC). The normal prion protein, PrPC, is encoded by the prion gene (PRNP) on human chromosome 20. However, the function of PrPC is not really well understood (Mackenzie & Will, 2017). The accumulation and aggregation of prions result in abnormally folded proteins with a higher proportion of β-pleated sheets than the typical α-helices in the posttranslational conformation of typical proteins. They are resistant to proteases and serve as templates for the rapid misfolding of native proteins into these abnormal proteins (Baldwin & Correll, 2019). The misfolding and aggregation of prions would result in forms linked with diseases, such as the proteinase K (PK)-resistant scrapie forms.

Additionally, the CJD disease may also be caused by the somatic PRNP mutation. The human PRNP gene harbors 70 variants that encode different mutations, some of which cause inherited prion diseases (Jones & Mead, 2020). Patients with CJD have a polymorphism at codon 129 of the PRNP gene between Met and Val (Hermann et al., 2021). Aside from the PRNP gene, several risk loci were identified, including polymorphisms in STX6 that drive prion expression in brain zones associated with disease (Jones & Mead, 2020).

These factors will cause neuronal death, gliosis, vacuolation, and nerve cell loss, overall causing the pathognomonic spongiform appearance of the brain (Baldwin & Correll, 2019). The concentration of prions fluctuates throughout an infected person's body, but the brain and posterior eye, particularly the optic nerve and retina, are the most concentrated.

This condition could result in neurological symptoms such as extrapyramidal and cerebellar symptoms, quickly progressing dementia, as well as myoclonus and visual signs. Clinically diagnosed CJD patients usually die within a year of exhibiting symptoms (Uttley et al., 2020).

Creutzfeldt-Jakob disease is difficult to diagnose because its signs and symptoms vary widely from patient to patient. This disease is characterized by focal lesions of the nervous system, including the cerebral cortex, basal ganglia, and spinal cord (Hai et al., 2021). If left untreated, this disease can be fatal and even lead to death. The other issue that is appealing about the devastating CJD disease is that its medical strategies and treatment are still problematic to combat (Gitler et al., 2017). Creutzfeldt-Jakob disease currently has no cure, as the process of finding and diagnosing the pathological PrPSc protein in the patient's nervous system lacks standardized procedures (Ciepierski et al., 2019). However, several possible treatments can help limit symptoms, such as doxycycline (Al-Ansari & Robertson, 2017). The treatments for these prion diseases target symptomatic relief and improvements in quality of life, including pharmacologic and nonpharmacologic care, education, and psychosocial support (Appleby & Yobs, 2018).

Genomics can be used to identify mutations in the gene that cause the disease. The drug target can be determined using transcriptomic data or by comparing proteomes of the control group to those of the patient, which will later be processed through phenotypic screening. Comparing the BLAST sequences of proteins with a comparable structure to prions will also help elucidate structure-function relationships and identify binding partners of a query to assess its capability as a drug candidate or target (Xia, 2017).

This study focuses on Creutzfeldt-Jakob disease, the prion protein, drug design, bioinformatics, and molecular docking. Our goal is to find and describe possible treatments and effective strategies to address Creutzfeldt-Jakob disease using bioinformatics methods.

1. MATERIALS AND METHOD

1.1 Study Design Overview

To find potential drug candidates for Creutzfeldt-Jakob disease (CJD), we used a bioinformatics pipeline that combined genomic, structural, and chemical analysis methods. Each step was planned to make the results as reliable and useful as possible, considering the unique challenges of prion biology and the rarity of CJD. The next sections explain each method in detail, including why we chose them and which tools and databases we used.

The overall study design consisted of (1) target protein selection and mutation analysis, (2) retrieval and preparation of mutated protein structures, (3) identification and curation of potential drug candidates, (4) molecular docking and validation, and (5) analysis of docking results and binding site characterization. This section was developed by deploying our previously published pipeline with slight modification as stipulated in the following subsections (Siddique et al., 2025; Mauliana et al., 2025; Rubani and Parikesit, 2024).

1.2 Protein Target Selection and Sequence Analysis

The primary focus of this study was the human cellular prion protein (PrP^C), encoded by the PRNP gene. To secure accurate targeting, the canonical sequence of PRNP was retrieved from UniProt (Bagyinszky et al., 2018) and compared against the NCBI protein database to check consistency. Special emphasis was placed on identifying clinically relevant mutations linked to CJD pathogenesis. Among more than 70 documented PRNP mutations, the E200K variant—resulting from the substitution of glutamic acid (E) with lysine (K) at codon 200—was selected for in silico modeling due to its well-established association with familial CJD (Hermann et al., 2021; Jones & Mead, 2020). Multiple sequence alignment and variant annotation were performed to confirm the precise location and possible structural implications of the E200K mutation.

1.3 Structural Modeling and Protein Preparation

The three-dimensional structure of the human prion protein harboring the E200K mutation was obtained from the RCSB Protein Data Bank (PDB; Rose et al., 2021). In cases where a mutant-specific structure was unavailable, homology modeling was proposed as a backup strategy using SWISS-MODEL or similar platforms, guaranteeing the highest possible accuracy for subsequent docking simulations. The downloaded structure underwent several pre-processing steps, including removal of water molecules, addition of missing hydrogen atoms, assignment of correct bond orders, and minimization of steric clashes. These steps were performed using UCSF Chimera and SwissDock's built-in preparation protocols to make certain the protein structure was suitable for molecular docking.

1.4 Identification and Retrieval of Potential Drug Candidates

We reviewed the literature and searched databases to find molecules that might work against prion protein aggregation. Using DrugBank (Ishibashi et al., 2016) and PubChem, we looked for small molecules and biologics like acridines, anti-PRP monoclonal antibodies (PRN100), Anle138b, doxycycline, tetracyclines, and gabapentin. We chose candidates based on three criteria: previous experimental evidence of anti-prion or anti-aggregation activity, proven safety in humans, and the availability of good 3D structural data. All ligand structures were downloaded in SDF or MOL2 format and converted to PDB format for docking.

1.5 Molecular Docking Protocol and Validation

SwissDock, a widely used molecular docking platform, was used to predict binding affinities and orientations of each drug candidate with the E200K prion protein (Bitencourt-Ferreira & Azevedo, 2019). The docking protocol was configured in 'accurate' mode, utilizing the CHARMM force field for energy calculations. A blind docking approach was implemented, allowing the entire protein surface to be sampled for possible binding pockets. The exhaustiveness parameter was set to 50, balancing the computational cost with thoroughness of search. Docking grid parameters were automatically generated to encompass all plausible interaction sites.

For quality assurance, the docking protocol was validated by redocking known ligands of the prion protein, comparing predicted binding poses to experimentally determined structures where available. This step ensured the reliability of binding mode predictions and the reproducibility of free energy estimations (FullFitness and ΔG scores).

1.6 Binding Site Characterization and Post-Docking Analysis

We analyzed the docking results in detail using UCSF Chimera, looking at hydrogen bonds, hydrophobic contacts, pi-pi stacking, salt bridges, and specific residue contacts in the active sites. CASTp (Computed Atlas of Surface Topography of proteins) helped us find and visualize the shapes of surface pockets and cavities, which gave us insight into how druggable these regions are (Jiang et al., 2019). If there was any uncertainty about the main active site, we compared CASTp pocket mapping with the clustering of top docking poses to reach a consensus.

1.7 Ethical Issues and Data Reproducibility

All data used in this study came from public databases, and no human or animal subjects were involved. Our computing workflows, scripts, and parameter files are available upon request to ensure reproducibility and transparency. By using this thorough and validated pipeline, we aimed to lay a strong foundation for future practical validation and to guide upcoming drug discovery efforts for CJD and related prion diseases.

2. RESULTS

2.1 Overview of Docking Results

To provide a complete analysis of potential drug candidates for CJD, molecular docking was performed for seven compounds—gabapentin, flupirtine, tetracycline, Anle138b, acridines, anti-PRP monoclonal antibody (PRN100), and doxycycline—against the E200K mutant prion protein. Each compound was docked using SwissDock, and binding energies, FullFitness scores, and predicted binding sites were systematically compared.

The docking simulations generated multiple binding poses for each molecule, which were then clustered based on their predicted Gibbs free energy (ΔG) and spatial proximity within the protein structure. The top-ranked binding mode for each compound was selected for further analysis.

Table 1 summarizes the key binding metrics, including the lowest binding energy (ΔG), FullFitness score, and the rank of the most favorable pose for each candidate. Gabapentin consistently presented the most negative binding energy and FullFitness values, denoting a particularly strong and stable interaction with the E200K prion protein. Flupirtine, while exhibiting a favorable ΔG, did not achieve as low an energy or FullFitness score as gabapentin. Tetracycline, in contrast, had the highest (least favorable) binding energy, suggesting weak or unstable binding under these conditions. These results are visualized in Figure 1, which maps the binding site locations and illustrates the spatial grouping of high-affinity poses.

2.2 Detailed Binding Affinity and Pose Analysis

Gabapentin achieved a binding energy of -22.70 kcal/mol and a FullFitness score of -847.26, both of which were the most favorable among the drugs tested. Its optimal docking pose was localized near a hydrophilic pocket formed by key residues, including glutamine and lysine, and was stabilized through multiple hydrogen bonds and electrostatic interactions. Flupirtine, with a ΔG of -8.35 kcal/mol, was the next strongest binder, but its FullFitness was less favorable and its predicted pose had fewer hydrogen bonds and less overall interaction surface with the protein.

Among the other candidates, Anle138b and doxycycline displayed moderate binding energies, forming interactions mainly with the protein's surface and exhibiting less residue-specific engagement in the active site region. The anti-PRP monoclonal antibody (PRN100) was modeled as a large ligand and, while capable of interacting with the protein in theory, its size and shape resulted in less precise pocket binding according to the docking algorithm's constraints. Acridines, though known for their anti-aggregation activity in prion models, showed only modest affinity in these in silico experiments. A summary of the quantitative docking results is presented below:

Table 1. Molecular Docking Results of the Potential CJD Drugs Tested. Gabapentin shows the lowest energy and the highest fitness.

Drug Name	Energy (kcal/mol)	Full Fitness (kcal/mol)	Delta G (kcal/mol)
Gabapentin	-22.6968	-847.25836	-6.7599874
Memantine	-6.88016	-804.72424	-6.9482837
Flupirtine	0.364374	-832.95435	-8.354856
Donepezil	14.22	-761.601	-8.222172
Acridine	22.3716	-742.3936	-5.9274607
Diphenylhydantoin	26.6003	-780.1249	-6.055657
Tetracycline	28.5228	-831.49	-6.9662466

The results show that gabapentin had the lowest values for energy and full fitness, but not necessarily the lowest delta G value, as flupirtine did. The energy and full fitness values for gabapentin were -22.6968 and -847.25836, respectively, while flupirtine had a delta G value of -8.354856. Tetracycline had the highest energy, with a value of 28.5228. In addition, the binding site for the prion protein itself was tested using CASTp (Figure 1), and the results indicated that the active sites were located at the amino acids leucine, glutamine, tyrosine, histidine, threonine, and lysine, as depicted in Table 2.

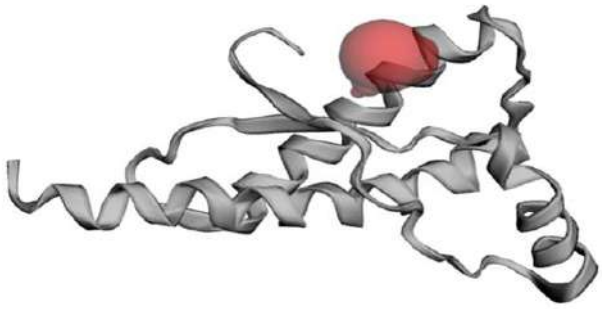

Figure 1. CASTp test result for P04126 E200K mutated protein. The active site is located at leucine, glutamine, tyrosine, histamine, threonine, and lysine. The red ball is designated as the active and/or binding site of the protein.

2.3 Binding Site and Active Site Characterization

To further understand the molecular basis of the interactions, CASTp analysis was used to identify surface pockets and internal cavities that could serve as potential drug binding sites. The primary active site for the E200K prion protein was mapped to a pocket involving leucine, glutamine, tyrosine, histidine, threonine, and lysine residues. Figure 2 visualizes this active site, with the red sphere indicating the centroid of the predicted druggable region. Table 2 lists the amino acids comprising the major active site, as identified both by CASTp and clustering of high-affinity docking poses.

Table 2. Amino acids contained within the active sites of the P04156 E200K mutated protein for CJD

Sequence ID	Amino Acid	Atom
130	Leucine	CD1
130	Leucine	CD2
160	Glutamine	CB
160	Glutamine	CD
162	Tyrosine	CE1
162	Tyrosine	OH
187	Histamine	ND1
187	Histamine	CE1
187	Histamine	NE2
190	Threonine	OG1
190	Threonine	CG2
191	Threonine	CA
191	Threonine	OG1
194	Lysine	CE
194	Lysine	NZ

2.4 Comparison Across Drug Candidates

Notably, the binding mode of gabapentin allowed for more extensive interaction with the center of the active site pocket than any other compound tested. Its shape and electrostatic profile were complementary to the pocket defined by CASTp, resulting in a higher number of stabilizing contacts and a more deeply buried binding orientation.

This is in contrast to larger or more rigid molecules, such as PRN100, which tended to interact towards surface residues rather than penetrate the well-defined pocket.

The comparison of binding energies and docking poses supports the selection of gabapentin for further preclinical investigation. While flupirtine's ΔG was slightly lower, gabapentin's overall binding profile—including FullFitness, hydrogen bonding, and safety factors—was superior for the purposes of CJD therapy development. These results illustrate the relevance of integrating multiple docking metrics and structural analyses when evaluating candidate drugs in silico.

3. DISCUSSION

This study shows the feasibility and promises of using in silico bioinformatics approaches to identify novel therapeutic candidates for Creutzfeldt-Jakob disease (CJD), a fatal neurodegenerative disorder with limited treatment options. By targeting the E200K mutation in the prion protein, one of the most clinically relevant genetic variants linked to familial CJD, we intended to bridge the gap among molecular pathogenesis and drug discovery using computational tools.

The biological plausibility of gabapentin's potency in CJD is additionally emphasized by its known effects on neurotransmission regulation. Gabapentin's modulation of GABAergic and glutamatergic transmission could help counteract the neurotoxicity and synaptic dysfunction characteristic of prion diseases (Bartoletti-Stella et al., 2019; Cai et al., 2012). Not only does this provide a mechanistic rationale for its repurposing in CJD, but it additionally highlights the value of repositioning well-characterized drugs for orphan neurodegenerative conditions, possibly accelerating the translational timeline.

A important aspect of this research was the thorough characterization of the prion protein's active site. Through integrating CASTp analysis and pose clustering, we identified a recurring set of residues leucine, glutamine, tyrosine, histidine, threonine, and lysine forming the principal druggable pocket in the E200K mutant.

This pocket's physicochemical characteristics and geometric accessibility reinforce its suitability as a pharmacological target, not only for gabapentin but also for future structure-based drug design campaigns. The convergence of docking predictions and active site mapping strengthens confidence in the computational pipeline and its usefulness for rare disease drug discovery.

In this research, the gabapentin result was used and discussed further as it showed the most negative value. When a drug binds to a target, the binding energy is released, which decreases the overall energy of the complex (Fouejio et al., 2021). According to Garbett & Chaires (2012), the free binding energy can be associated with the drug's binding affinity. The binding strength between a ligand and a receptor is indicated by the binding affinity (Nusantoro & Fadlan, 2021). A higher binding affinity results in a stronger, tighter interaction between the ligand and receptor. Higher binding affinity can be achieved when the free binding energy is low (Garbett & Chaires, 2012). Therefore, it can be inferred that the drug is more stable and preferred when the binding energy is lower (Fouejio et al., 2021). From the results obtained in Table 1, among the seven drugs tested through molecular docking, the drug with the lowest binding energy is gabapentin, with a value of -22 kcal/mol.

The molecular docking results show gabapentin as the most promising candidate among the drugs tested, based on its lowest binding energy, most favorable FullFitness score, and negative Gibbs free energy. These parameters jointly indicate a strong, stable, and spontaneous interaction with the mutant prion protein, supporting the hypothesis that gabapentin could interfere with pathogenic protein aggregation. Importantly, the complementary shape and electronic configuration of gabapentin allowed it to bind strongly with the predicted druggable pocket, maximizing key interactions such as hydrogen bonding and electrostatics. Although flupirtine displayed a slightly more favorable ΔG, gabapentin's global binding profile combined with its established clinical safety and CNS pharmacology makes it a more attractive lead for subsequent experimental and clinical evaluation. Gabapentin also has the lowest level of full fitness, which means averaging the 30% most favorable effective energies of the element to reduce the risk that a few complexes disrupt the whole cluster (Rosell & Fernandez-Recio, 2018).

As the risk of a few complexes forming is minimal, the reaction between the ligand (drug molecule) and the cell receptor can occur effectively and efficiently. In addition to its energy-binding affinity, gabapentin has the lowest values for these two aspects (Table 1).

The value of gabapentin's Gibbs free energy (Delta G) is negative; hence, the reaction is exothermic and spontaneous, making the binding between the drug molecule and the receptor favorable. This negative value is created by the energy of binding, which is released to the surrounding environment during the formation of a new chemical bond and is used to lower the Delta G value (Omar et al., 2020). Although the Delta G value of flupirtine is the lowest among the drugs tested, given the other two aspects discussed above, gabapentin remains the best candidate for treating Creutzfeldt-Jakob Disease (CJD).

Gabapentin is a drug used to treat patients with seizure disorders, but it has recently been found to have a role in ameliorating neuropathic pain in clinical settings as well. It has low safety concerns around drug interactions as well as no interference with hepatic enzymes (Kukkar et al., 2013). Genes that were involved in the uptake, signaling, and metabolism of GABA are downregulated in sporadic CJD patients, specifically in their frontal cortex. It was also found that GABRB1 is associated with the formation of PrPSc and the selective impairment of GABAergic transmission in sCJD patients (Bartoletti-Stella et al., 2019). Gabapentin is thought to increase GABA levels, but this is associated with an inverse correlation between baseline GABA concentrations and the magnitude of the increase. The highest concentration of GABA obtained with this drug would be 79% above baseline. However, it is essential to note that it also decreases glutamate production by reducing calcium influx into glutamatergic terminals (Cai et al., 2012). Treatment using this drug would partially decrease neuronal degeneration that was induced by acute status epilepticus (Rossi et al., 2013).

As for the active sites of the P04126 E200K variant of the human prion protein, it was predicted that the protein active sites are located at the amino acids leucine, glutamine, tyrosine, histamine, threonine, and finally lysine, as shown in Table 2. These active sites are pockets within proteins that allow drugs to bind and activate their mechanisms. Identifying active sites is important for drug design and for determining drug effectiveness (Jiang et al., 2019).

The research encountered several limitations, such as a lack of the mutated protein structure in the PDB associated with CJD. Only 3 proteins were found, and only 1 was applicable in SwissDock. Limited access to drugs and literature was also encountered during the project. Moreover, this study concentrates on the E200K mutation, which is a frequent mutation in Creutzfeldt-Jakob disease; however, it is not the only one. Further studies are needed to examine other genetic or protein mutations associated with the disease and to determine the ultimate treatment. As this study only examined potential drug design, clinical trials and drug testing must be conducted before concluding that the drug molecule is indeed a suitable treatment for Creutzfeldt-Jakob disease.

Moreover, several limitations also warrant discussion. The scarcity of experimentally resolved mutant prion structures in public databases constrained the breadth of proteins available for docking, possibly limiting the generalizability of findings across the heterogeneous spectrum of CJD. The dependence on a single, albeit clinically important, mutation (E200K) means that other PRNP variants and their associated conformational states remain unexplored in this context. Future studies should incorporate a wider array of mutations and implement emerging techniques such as molecular dynamics simulations to more effectively capture protein flexibility and ligand-induced fit.

Further, while molecular docking gives valuable insights into binding energetics as well as site complementarity, it does not account for cellular uptake, blood-brain barrier penetration, or the complex pharmacodynamics of drug action in neural tissue. Gabapentin's established CNS bioavailability and tolerability profile offer some reassurance, but in vitro and in vivo studies are still essential to confirm these interactions, assess neuroprotective efficacy, and rule out off-target effects. Additionally, expanding the chemical diversity of screened compounds possibly through virtual high-throughput screening or AI-based molecular generation may discover new scaffolds with even greater activity and specificity against pathogenic prion conformers.

Finally, the wider public health context should be considered. As CJD is a rare but devastating disease, even incremental advances in therapy can have deep impact for patients and families.

The computational workflow described here provides a scalable and adaptable blueprint for similar drug discovery efforts in other neurodegenerative and protein misfolding disorders, including Alzheimer's, Parkinson's, and Huntington's diseases, where protein aggregation is central to pathology.

CONCLUSION

To summarize, this study leveraged bioinformatics and molecular docking to identify gabapentin as an encouraging drug candidate for Creutzfeldt-Jakob disease, precisely targeting the E200K mutant prion protein. Gabapentin's strong predicted binding affinity, favorable drug profile, and capacity to engage key residues within the prion protein's active site collectively support its prioritization for further empirical confirmation. While these findings deliver an important foundation, translation to clinical application will require extensive laboratory and animal studies, as well as eventual clinical trials, to confirm efficacy and safety in the context of prion disease.

The success of this computationally-based pipeline illustrates the game-changing potential of bioinformatics in accelerating drug discovery for rare and neglected diseases. Ongoing refinements in protein structure determination, virtual screening, and integrative modeling will further improve our ability to uncover new therapies for CJD and related neurodegenerative disorders. The approach outlined here holds offers promise not only for CJD, but for the wider field of protein misfolding diseases giving hope for patients afflicted by these difficult conditions.

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CHAPTER 3
GOLD NANOPARTICLES FOR NEUROPROTECTION: A REVIEW OF THERAPEUTIC APPLICATIONS AND EMERGING STRATEGIES IN NEUROLOGICAL DISEASES

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INTRODUCTION

Neurological diseases constitute one of the most significant global health challenges of the 21st century, both because of their increasing prevalence and the enormous personal, social, and economic burdens they impose. Disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), ischemic stroke, multiple sclerosis (MS), traumatic brain injury (TBI), and amyotrophic lateral sclerosis (ALS) collectively impact hundreds of millions of people worldwide, with incidence rising sharply due to aging populations and environmental risk factors. Dementia alone affects over 55 million individuals globally, with projections estimating this number will surge to 139 million by 2050, making neurodegenerative disorders the fastest-growing cause of disability and dependency among older adults.

A major challenge in managing neurological diseases is their complex, multifactorial pathophysiology, which typically involves several interconnected mechanisms. These include chronic oxidative stress leading to lipid, protein, and DNA damage; neuroinflammation mediated by hyperactive microglia and astrocytes; mitochondrial dysfunction and impaired cellular energetics; protein misfolding and aggregation, such as Aβ plaques or α-synuclein fibrils; excitotoxicity driven by dysregulated glutamatergic signaling; synaptic loss and structural degeneration; impaired autophagy–lysosomal pathways; and the activation of apoptotic or necroptotic cell death cascades [6]. Because these pathways operate synergistically, therapies that target only one mechanism frequently fail to produce meaningful or sustained clinical improvement.

Compounding these biological complexities is the formidable challenge posed by the blood–brain barrier (BBB) a specialized endothelial interface designed to protect the brain from toxins, pathogens, and fluctuations in systemic biochemistry. While physiologically essential, the BBB severely restricts the delivery of therapeutic agents. More than 98% of small molecules and nearly 100% of large-molecule biologics fail to cross the BBB at therapeutic concentrations. Many drugs with strong neuroprotective potential in vitro exhibit disappointing in vivo outcomes precisely because they cannot reach neuronal tissues in meaningful quantities. This barrier remains one of the greatest obstacles to developing effective treatments for CNS diseases.

Due to these combined challenges multifactorial disease mechanisms, BBB impermeability, and limited efficacy of single-target drugs there is urgent need for innovative therapeutic strategies. Over the past decade, nanotechnology has emerged as a promising frontier in this regard. Among various nanomaterials, gold nanoparticles (AuNPs) have gained exceptional attention due to their unique combination of physicochemical, optical, and biological properties. AuNPs offer highly tunable size, shape, and surface chemistry, enabling precise control over their biological interactions, biodistribution, and therapeutic functions. Their inherent biocompatibility and chemical stability further support their suitability for long-term neurological applications.

A defining advantage of AuNPs is their ability to cross or modulate the BBB. Ultra-small AuNPs (<20 nm) can penetrate the BBB via passive diffusion or transcytosis, whereas functionalization with targeting ligands such as transferrin, lactoferrin, TGN peptide, and RVG29 significantly enhances selective uptake by brain endothelial cells and neurons. PEGylation improves colloidal stability, circulation time, and immune evasion, while plant-, polymer-, or membrane-based coatings reduce toxicity and microglial activation. This tunability enables AuNPs to serve not only as therapeutic agents but also as drug delivery carriers, transporting small molecules, nucleic acids, peptides, and antibodies into the CNS with high efficiency.

Beyond their delivery capabilities, AuNPs exhibit intrinsic neuroprotective properties. They can act as nanozymes nanomaterials with enzyme-like catalytic activity mimicking superoxide dismutase (SOD), catalase, or peroxidase to neutralize reactive oxygen species (ROS) and restore redox balance. They modulate key signaling pathways such as Nrf2/ARE, thereby promoting endogenous antioxidant defenses. AuNPs also suppress neuroinflammation by inhibiting NF-κB signaling and reducing the release of pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6. Furthermore, they prevent mitochondrial membrane depolarization, enhance ATP production, and regulate mitochondrial biogenesis by influencing PGC-1α and TFAM expression, thereby stabilizing neuronal energetics.

In apoptosis-related pathways, AuNPs increase anti-apoptotic Bcl-2 protein levels while reducing the activation of Bax, caspase-3, and caspase-9, preserving neuronal survival during disease progression.

A particularly promising feature is the ability of AuNPs to interact with pathological proteins. Studies demonstrate that AuNPs inhibit amyloid-beta (Aβ) fibrillation, destabilize β-sheet–rich aggregates, reduce Aβ toxicity, and even disassemble pre-formed fibrils in AD models. Similarly, AuNPs interfere with α-synuclein aggregation in PD, providing direct protection to dopaminergic neurons. These anti-aggregation properties are further enhanced when AuNPs are conjugated with functional biomolecules such as antibodies, peptides, and phytochemicals.

Importantly, AuNPs also support neuroregeneration. They promote neurite outgrowth, enhance axonal repair, upregulate neurotrophic factors such as NGF and BDNF, and even facilitate neural stem cell differentiation into functional neurons. These regenerative benefits are particularly relevant for chronic neurological diseases and post-injury repair, including after stroke or TBI.

Despite their promise, AuNPs are not without challenges. Concerns include biodistribution, long-term tissue accumulation, dose-dependent toxicity, immune activation, and regulatory hurdles related to clinical translation. However, ongoing advancements in surface engineering, biomimetic coatings, and nanozyme optimization continue to refine AuNP safety and therapeutic performance.

Given their multifunctionality direct neuroprotection, BBB transport, anti-inflammatory effects, anti-aggregation activity, mitochondrial stabilization, gene/drug delivery, and regenerative potential—gold nanoparticles represent a transformative platform in the pursuit of next-generation neurotherapeutics. This review therefore aims to provide a comprehensive and mechanistically detailed analysis of the neuroprotective roles of AuNPs, summarize their applications across major neurological diseases, evaluate safety considerations, and discuss future strategies for clinical translation.

1. PHYSICOCHEMICAL PROPERTIES OF GOLD NANOPARTICLES RELEVANT TO NEUROPROTECTION

Gold nanoparticles (AuNPs) are distinguished from other nanomaterials by a constellation of interrelated physicochemical properties size, shape, surface chemistry, surface charge, crystallinity, optical/plasmonic characteristics, colloidal stability, and dissolution behavior that collectively determine their interactions with biological systems and therefore their suitability for neuroprotective applications. Rational design of AuNPs for central nervous system (CNS) therapy depends on a comprehensive understanding of how each of these properties modulates biodistribution, blood–brain barrier (BBB) transport, cellular uptake, subcellular localization, therapeutic action (e.g., antioxidant nanozyme activity, anti-aggregation binding), and safety (toxicity, clearance, immunogenicity). This section systematically examines each physicochemical parameter, explains mechanistic links to neurobiology, outlines methods for tuning these parameters in synthesis, and summarizes practical recommendations for designing AuNPs intended for neuroprotection.

1.1 Particle Size Ranges, Mechanisms, and Biological Consequences

Why Size Matters in Neurotherapeutics

Particle size is arguably the single most influential descriptor of nanoparticle (NP) behavior in vivo. Size affects: (a) hydrodynamic behavior in blood and interstitial fluids, (b) propensity to cross biological barriers including the BBB, (c) routes and rates of cellular uptake, (d) subcellular localization (e.g., ability to access mitochondria or nucleus), (e) catalytic surface area (per mass), and (f) routes of clearance (renal versus hepatic). For CNS-targeted therapies these effects are amplified because the BBB imposes strict size-dependent constraints on what can or cannot reach parenchymal neural tissue.

Size Regimes and Their Functional Correlates

- Ultra-small AuNPs / nanoclusters (< 2–5 nm) These behave almost like small molecules: they often exhibit partial renal clearance, lower long-term accumulation in liver/spleen, and can penetrate tight biological barriers more readily. They also possess very high surface-to-volume ratios, which maximizes catalytic (nanozyme) activity per particle mass and enhances ROS scavenging capacity. However, extremely small sizes sometimes increase reactivity and can lead to unintended interactions with biomacromolecules or DNA if not properly passivated.
- Small AuNPs (5–20 nm)Widely used in neuro applications because they provide a favorable balance: sufficient surface area for functionalization and catalytic activity, yet small enough to exploit transcytosis and adsorptive-mediated uptake at the BBB when appropriately surface-modified. Many examples of BBB crossing and neuronal uptake use AuNPs in this size window.
- Medium AuNPs (20–50 nm) Tend to be taken up robustly by phagocytic cells (including microglia) and enter cells through clathrin-mediated endocytosis and macropinocytosis. They are excellent for payload carriage (drug, peptide, oligonucleotide) because they provide surface area for conjugation while maintaining good colloidal stability. However, hepatic accumulation increases as size grows, and BBB penetration becomes less efficient without active targeting.
- Large AuNPs (> 50–100 nm) Useful in local or topical brain applications (e.g., implanted devices or focal photothermal therapy) but generally poor candidates for systemic CNS delivery because they are efficiently sequestered by the mononuclear phagocyte system (MPS) and have limited BBB transit.

Subcellular Targeting Via Size Tuning

Size also controls subcellular access. Very small AuNPs (< 10 nm), when properly functionalized, may localize to mitochondria or nuclei, enabling direct modulation of mitochondrial respiration, ROS detoxification at the source, or interference with transcriptional programs that regulate oxidative stress and apoptosis . This property has been exploited in preclinical models where AuNPs aided mitochondrial protection and restored ATP production.

Practical Synthesis and Measurement

- Synthesis approaches that reliably produce narrow size distributions include Turkevich citrate reduction (good for ~10–20 nm spheres), seed-mediated growth (for rods & larger shapes), and ligand-assisted reduction for ultra-small clusters.
- Hydrodynamic size (by dynamic light scattering, DLS) differs from the core size (by TEM); both values are critical: hydrodynamic size reflects the effective size in biological fluids including ligand shells and adsorbed corona proteins.
- Zeta potential and polydispersity index (PDI) should be reported alongside size; PDI < 0.2 is desirable for reproducible biological behavior.

Design guideline: for systemic neuroprotection with BBB penetration, target 5–20 nm core size; for mitochondrial targeting prefer ultra-small ~2–5 nm clusters with strong, biocompatible surface passivation.

1.2 Particle Shape and Morphology Spheres, Rods, Stars, Shells

Shape influences optical/plasmonic behavior, surface curvature (affects ligand density and protein adsorption), cell membrane interactions, and photothermal conversion efficiency. Shape tuning is thus central to both therapeutic action and safety.

Spheres (isotropic)

Spherical AuNPs are the most common due to straightforward synthesis and predictable biological behavior.

They are typically least inflammatory, show stable colloidal properties, and provide a uniform platform for ligand attachment. For antioxidant and drug-delivery applications where steady biodistribution is required, spheres are an excellent default choice.

Rods (anisotropic)

Gold nanorods (AuNRs) exhibit two plasmon bands (transverse and longitudinal) and robust NIR absorption when aspect ratio is tuned; this makes them ideal for photothermal applications and remote activation of cargo release or neuromodulatory heating. In neural contexts, NIR-activated AuNRs have been used experimentally for photothermal modulation of neural activity and to enhance clearance/disruption of protein aggregates. However, rods often require careful surface chemistry to reduce cytotoxicity associated with residual CTAB used in common syntheses.

Stars, Cages, Shells, and Nanoshells

Nanostars and nanocages present sharp protrusions and hollow volumes which increase surface area and electromagnetic field enhancement; they are thus highly effective for both SERS sensing and efficient photothermal conversion at lower light intensities. Nanoshells (dielectric core + Au shell) shift SPR into the NIR and permit payload encapsulation; they have been explored for targeted photothermal disruption of aggregates and as theranostic platforms combining imaging and therapy.

Design guideline: choose spheres for biocompatibility and cargo delivery; rods/stars/cages when photothermal activation, imaging contrast, or enhanced catalytic surface is required while carefully optimizing coatings to minimize toxicity from synthesis residues.

1.3 Surface Chemistry and Functionalization Stability, Targeting, and Stealth

Surface chemistry is the modular knob with the greatest leverage over biological fate. It dictates protein corona composition, circulation time, immune recognition, receptor engagement, and drug release behavior.

Passivation and Stealth: Pegylation and Alternatives

Polyethylene glycol (PEG) grafting reduces nonspecific protein adsorption and MPS clearance, prolonging circulation time and improving the probability of BBB interaction. Alternatives and complements include zwitterionic coatings, PVP, and albumin (or engineered plasma proteins) which can offer "stealth" while tuning receptor interactions.

Targeting Ligands for BBB Crossing and Neuronal Specificity

Active targeting strategies use ligands that bind receptors on brain endothelium or neurons to promote receptor-mediated transcytosis or selective uptake:

- Transferrin / transferrin receptor (TfR) exploited for BBB transcytosis (requires care to avoid TfR saturation).
- Apolipoprotein E (ApoE) peptides hitchhike lipoprotein transport mechanisms across the BBB.
- RVG29 & TGN peptides target neuronal nicotinic acetylcholine receptors and facilitate neuronal uptake.
- Antibodies or antibody fragments can provide high affinity for pathological assemblies (Aβ, α-syn), enabling targeted binding and plaque localization.

Multi-Functional Coatings and Stimuli Responsiveness

Coatings can be engineered to be stimuli-responsive: acid-labile linkers for endosomal escape, ROS-sensitive linkers for disease microenvironments, or light-activated tethers for remote control of payload release. Dual coatings (PEG + targeting ligand) are common: PEG provides stealth while the terminal functional group presents the ligand.

Conjugation Chemistries and Ligand Density

Covalent thiol−Au bonds (Au–S) are a gold standard for stable functionalization; yet ligand density and orientation matter high density may sterically hinder receptor binding, whereas too low density reduces targeting efficacy. Spacer lengths and flexible linkers (PEG spacers of controlled length) help optimize effective presentation.

Design guideline: use PEGylation for in vivo stealth, then append receptor-targeting ligands at controlled densities using robust Au–S linkages and spacer arms for optimal accessibility.

1.4 Surface Charge (Zeta Potential) Uptake vs. Safety Trade-Off

Zeta potential influences colloidal stability and electrostatic interactions with cell membranes and serum proteins.

Cationic Surfaces

Cationic AuNPs show rapid cellular uptake due to electrostatic attraction to negatively charged cell membranes; this property is exploited for nucleic acid delivery (siRNA, DNA). However, cationic particles commonly induce membrane destabilization, hemolysis risk, and potentiate complement activation — increasing inflammation and cytotoxicity in brain tissue.

Anionic and Neutral Surfaces

Negatively charged or near-neutral surfaces decrease nonspecific interactions and immune activation, often translating to improved biocompatibility and longer circulation times. For CNS delivery, many successful formulations use near-neutral PEGylated surfaces with a small fraction of targeting ligands.

Modulating Charge Dynamically

Some smart designs present a neutral surface in circulation and expose cationic moieties in the target microenvironment (e.g., via pH-sensitive linkers), enabling both stealth and enhanced uptake at the diseased site.

Design guideline: prioritize near-neutral/PEGylated surfaces for systemic CNS administration; reserve cationic strategies for local delivery or transient exposure where toxicity can be controlled.

1.5 sOptical Properties: Surface Plasmon Resonance (SPR), Photothermal Conversion, and Sensing

SPR endows AuNPs with strong light–matter interactions; tuning SPR into the NIR "biological window" (650–900 nm, even into NIR-II > 1000 nm) enables deep tissue photothermal therapy and imaging.

Photothermal Neuromodulation & Aggregate Disruption

NIR illumination of AuNRs or nanostars causes localized heating that can:

- Modulate neuronal excitability (transiently opening ion channels) neuromodulation applications.
- Disrupt amyloid fibrils and α-syn aggregates via localized thermal denaturation, facilitating clearance.
- Trigger heat-induced release of heat-labile payloads or activation of heat shock responses promoting cellular repair.

Careful dosing and thermal mapping are required to prevent collateral thermal injury to brain tissue.

Imaging and Theranostics

AuNPs facilitate high-contrast photoacoustic and SERS imaging; theranostic AuNPs combine imaging tags with therapeutic payloads for guided delivery and real-time biodistribution monitoring. This capability is invaluable in evaluating BBB penetration efficiency, plaque targeting, and accumulation at lesions.

Design guideline: shift SPR into NIR using rods/stars/cages for photothermal and imaging applications while ensuring coatings mitigate phototoxic byproducts and that illumination protocols avoid exceeding safe temperature thresholds in brain tissue.

1.6 Crystallinity, Atomic Surface Features, and Defects

The atomic structure (crystallinity, facets, defects) of AuNPs influences catalytic activity, surface binding, and protein interactions.

Facet-Dependent Chemistry

Different crystalline facets (e.g., {111}, {100}, {110}) show varied binding affinities for thiols and biomolecules; facets influence adsorption geometry of peptides and proteins and therefore affect anti-aggregation or enzyme-like activity. Tailoring growth conditions to expose specific facets can optimize desired interactions (e.g., higher binding to Aβ monomers).

Defects Increase Catalytic Sites

Grain boundaries and surface defects can serve as active catalytic sites that enhance nanozyme activity desirable when ROS scavenging is the therapeutic aim. Conversely, defects might increase dissolution rates and unintended ion release.

Design guideline: consider controlled defect engineering (via annealing or selective growth) to achieve optimal nanozyme activity while balancing stability.

1.7 Colloidal Stability, Aggregation, and the Protein Corona

Aggregation A Critical Risk Factor

Aggregation alters effective size and surface properties, increasing clearance and potentially increasing toxicity. Stabilizing ligands (PEG, PVP) and appropriate ionic strength buffers minimize aggregation in biological fluids.

Protein Corona Formation Identity And Function

Upon exposure to biological fluids, AuNPs acquire a protein corona that redefines their biological identity: opsonins, apolipoproteins, complement factors, and albumin may adsorb, altering cell uptake, circulation half-life, and immune visibility. For instance, ApoE adsorption can serendipitously enhance BBB transcytosis because BBB receptors recognize ApoE-containing complexes . Conversely, opsonin-rich coronas accelerate MPS clearance.

Strategies To Control The Corona

- Pre-coating with chosen proteins (biomimicry) to dictate corona composition and exploit endogenous transport pathways.

- PEGylation and zwitterionic surfaces to resist nonspecific adsorption.
- "Hard" corona stabilization with covalent grafting to maintain predictable biological identity.

Design guideline: deliberately control corona formation through surface chemistry choices and consider exploiting beneficial corona components (e.g., ApoE) to enhance BBB transport.

1.7 Dissolution, Ion Release, and Long-term Stability

Gold is chemically inert relative to many metals, but ultra-small AuNPs and certain surface chemistries may release Au ions under oxidative biological conditions, which can contribute to toxicity or catalytic activity.

Mechanisms of Dissolution

- Oxidative environments (inflamed tissue, phagolysosomes) can catalyze partial dissolution.
- Ligand exchange processes in vivo can destabilize surface passivation and increase ion liberation.

Biological Consequences

Controlled ion release can augment redox chemistry beneficially (nanozyme function), but uncontrolled release risks genotoxicity, altered redox signaling, or systemic deposition.

Design guideline: for chronic CNS applications, design for minimal dissolution (robust thiol or multidentate ligand shells) unless controlled ion release is an intended therapeutic mechanism .

1.8 Synthetic Methods and Their Impact on Physicochemical Properties

Synthesis approaches define core size, shape, surface chemistry, and residual reagents all of which bear on biological performance.

Common Synthesis Methods

- Turkevich–Frens citrate reduction produces spherical AuNPs typically 10–20 nm, citrate-capped (biocompatible after ligand exchange).
- Seed-mediated growth enables precise control of rods, stars, and larger shapes; however, surfactants (CTAB) used for rod growth can be cytotoxic and must be replaced/coated post-synthesis .
- Green synthesis (plant/biomolecule-mediated) yields biocompatible surfaces and intrinsic antioxidant coatings; appealing for translational safety but can produce heterogeneous products.
- Ligand-assisted cluster formationused for producing ultrasmall, atomically precise clusters with strong catalytic behavior.

Post-Synthesis Modification

- Ligand exchange (e.g., displace citrate with PEG-thiol) stabilizes colloids for biological use.
- Encapsulation in lipid vesicles or polymer shells can provide controlled release and mitigate opsonization.
- Biomimetic camouflaging with cell membranes (e.g., RBC or neuron membrane coatings) can confer immunological stealth and homotypic targeting.

Practical note: avoid residual toxic surfactants (CTAB); rigorous purification (centrifugation, dialysis, ultrafiltration) is mandatory for in vivo applications.

1.9 Characterization Techniques and Quality Control

Robust characterization ensures reproducibility, safety, and regulatory compliance:

- Transmission electron microscopy (TEM) core size and shape.
- Dynamic light scattering (DLS) hydrodynamic diameter & PDI in suspension.
- UV–vis spectroscopy SPR peak (size/shape indicator).
- Zeta potential surface charge and colloidal stability.

- X-ray diffraction (XRD) / Selected area electron diffraction (SAED) crystallinity/facet analysis.
- X-ray photoelectron spectroscopy (XPS) / FTIR surface chemistry and ligand confirmation.
- Inductively coupled plasma mass spectrometry (ICP-MS) metal concentration, biodistribution assays.
- Thermogravimetric analysis (TGA) quantify ligand density.
- SDS-PAGE & proteomics protein corona composition after exposure to serum.

Stringent batch-to-batch QC is required for translational work and regulatory filings.

1.10 Biological Interactions: Cellular Uptake Pathways and Immune Effects

Endocytosis Routes

- Clathrin-mediated endocytosis: common for receptor-targeted AuNPs.
- Caveolae-mediated: favors transcytosis across endothelium and may facilitate BBB passage.
- Macropinocytosis & phagocytosis: dominant in microglia/macrophages and mononuclear phagocytes.

Ligand design can bias uptake routes (e.g., caveolae favor transport across endothelia with minimal lysosomal degradation; clathrin routes may lead to lysosomal processing).

Microglial Activation and Immunotoxicity

Microglia respond to NP physicochemical cues: size, charge, and corona composition modulate activation state (M1 pro-inflammatory vs M2 reparative). Designs that favor M2 polarization (neutral surfaces, specific biomimetic coatings) may reduce chronic neuroinflammation.

BBB Interactions And Transcytosis Mechanisms

Receptor-mediated transcytosis (TfR, LRP1 via ApoE/pathways) is widely exploited for AuNP entry into brain parenchyma.

Adsorptive-mediated transcytosis (via cationic surfaces) is less specific and riskier due to endothelial perturbation.

Design guideline: employ targeted receptor ligands (Tf, ApoE mimic, RVG) combined with stealth coatings to maximize safe BBB transport and minimize endothelial toxicity.

1.11 Manufacturing, Scalability, and Regulatory Considerations

Translation requires scalable, GMP-compatible synthesis with stringent control over size, charge, ligand density, residual reagents, and endotoxin levels. Regulatory bodies demand reproducible QC, long-term toxicity data, and well-defined characterization endpoints. Early engagement with regulatory authorities will streamline requirements for first-in-human trials [19, 26].

1.12 Practical Design Recommendations for Neuroprotective AuNPs

- Size: 5–20 nm core for systemic CNS delivery; 2–5 nm for mitochondrial-targeted strategies.
- Surface: PEGylated with 2–5 kDa PEG for stealth; include a small fraction (1–5%) of targeting ligand at controlled density.
- Charge: near-neutral to mildly negative zeta potential (–5 to –20 mV) to minimize immune activation.
- Shape: spherical for drug delivery; rods/stars/cages only when photothermal or imaging function is essential and toxicity mitigated.
- Ligands: choose receptor ligands validated for brain transport (TfR, ApoE, RVG29) with spacers to present epitopes effectively.
- Coating: consider biomimetic membrane coatings where immune evasion and homotypic targeting are advantageous .
- Nanozyme activity: if antioxidant catalysis is the aim, prefer highly crystalline small clusters with defect sites optimized for catalysis but with stable ligands to prevent uncontrolled ion release.

- Manufacture/Characterization: define batch release specs for core size, hydrodynamic size, PDI, zeta, ligand density, endotoxin, Au concentration (ICP-MS).

2. MECHANISMS OF NEUROPROTECTION

AuNPs protect neurons using several interlinked molecular and cellular mechanisms.

Antioxidant Activity

- AuNPs can scavenge reactive oxygen species (ROS), reducing oxidative stress—a critical driver of neuronal damage in many neurological diseases.
- By maintaining redox balance, they help preserve cellular homeostasis.

Anti-Inflammatory Effects

- AuNPs modulate immune signaling, reducing pro-inflammatory cytokines such as TNF-α and IL-1β, and potentially increasing anti-inflammatory mediators like IL-10.
- They can inhibit inflammasome activation, thereby decreasing release of pro-inflammatory cytokines.
- By modulating toll-like receptor (TLR) signaling and gene expression, they dampen the neuroinflammatory cascade.

Anti-Apoptotic and Pro-Survival Signaling

- AuNPs influence apoptosis regulators (e.g., Bcl-2 family proteins, caspases), reducing programmed cell death.
- They support mitochondrial health, stabilizing mitochondrial membrane potential, enhancing ATP production, and preventing the release of pro-apoptotic factors.
- They can activate survival pathways such as PI3K/Akt and MAPK/ERK, promoting neuronal resilience.

Neurotrophic Effects and Synaptic Connectivity

- AuNPs enhance secretion of neurotrophic factors such as BDNF and NGF, which are essential for neuronal growth and maintenance.
- They also stimulate neurite outgrowth and boost synaptic connectivity, helping maintain or restore neural networks.

Anti-Aggregation of Pathological Proteins

- A critical mechanism: AuNPs interfere with misfolded protein aggregation (e.g., Aβ in Alzheimer's, α-synuclein in Parkinson's).
- For example, by binding or chelating metal ions, they may prevent fibrillogenesis.
- Other studies (outside the core review) show that citrate-stabilized AuNPs can inhibit amyloid fibril formation (such as β2-microglobulin variants), suggesting that surface chemistry strongly affects aggregation dynamics.

Photothermal and Catalytic Effects

- Upon irradiation (e.g., near-infrared), AuNPs generate local heat, which might be harnessed for photothermal therapy.
- Heat-shock responses (e.g., upregulation of heat-shock proteins) may contribute to neuroprotection.
- Certain AuNPs and gold nanocrystals have catalytic activity, which might modulate cellular metabolism (e.g., redox balance, NAD^+/NADH) – though more research is needed in this area.

3. THERAPEUTIC APPLICATIONS IN NEUROLOGICAL DISEASES

Here, we examine how the above mechanisms translate into preclinical disease models.

Alzheimer's Disease (AD)

- Pathology addressed: Aβ aggregation, oxidative stress, neuroinflammation, mitochondrial dysfunction.

- Preclinical evidence: In an in vivo rat model (okadaic acid–induced neurotoxicity), 20 nm AuNPs (2.5 mg/kg, every 48 h for 21 days) helped to restore mitochondrial function, antioxidant enzyme activities (e.g., SOD, catalase), glutathione levels, and cognitive performance.
- In in vitro SH-SY5Y neuroblastoma cells exposed to Aβ, AuNPs inhibited fibril formation and provided neuroprotection, possibly via metal chelation and direct interaction with Aβ.
- Implication: AuNPs have the potential to act on multiple pathological axes in AD (aggregation + inflammation + oxidative stress), making them attractive multi-mechanistic agents.

Parkinson's Disease (PD)

- Challenges in PD: Dopaminergic neuron degeneration, α-synuclein aggregation, neuroinflammation, synaptic dysfunction.
- Therapeutic strategies:
- AuNP-DNA/ribonucleic acid composites: Studies have used plasmid DNA (pDNA) or siRNA carried by AuNPs to modulate α-synuclein expression. For example, in mouse models, such composites reduced α-synuclein aggregation in the substantia nigra, preserved tyrosine hydroxylase–positive neurons, and improved behavior and long-term potentiation.
- Inti-inflammatory / neuroprotective AuNPs: Some AuNPs suppress microglial activation and decrease pro-inflammatory cytokines, limiting neurotoxicity.
- Outcome: These multifaceted approaches may slow down or reverse neuronal loss and functional decline in PD models.

Stroke (Ischemic / Cerebral Ischemia)

- Pathophysiology: Ischemia–reperfusion injury triggers inflammation, oxidative stress, excitotoxicity, apoptosis, and blood–brain barrier (BBB) disruption.
- Application of AuNPs:

- Delivery of neuroprotective agents: AuNPs can carry anti-inflammatory or antioxidant drugs directly to ischemic regions, minimizing collateral damage.
- Apoptosis inhibition and mitochondrial protection: By preserving mitochondrial function and reducing apoptotic signaling, AuNPs may limit neuronal death.
- Clot targeting: An intriguing future strategy is to use AuNPs to deliver thrombolytics directly to clots, improving efficacy and reducing systemic side effects.
- Empirical findings: Animal models of stroke treated with AuNPs show reduced infarct volume and improved functional recovery.
- Implication: AuNPs may function both in acute neuroprotection and in facilitating post-stroke repair.

Other Applications: Radiation-Induced Brain Injury

- Beyond classical neurodegenerative diseases, AuNPs have been studied in models of radiation-induced brain damage. For instance, a mixture of AuNPs with α-lipoic acid showed a neuroprotective effect in irradiated rat brains — reducing oxidative damage, inflammation, and preserving neuronal integrity.
- This suggests that AuNPs might be broadly applicable across CNS injuries where oxidative stress and inflammation are central.

4. CELLULAR AND ANIMAL STUDIES: EVIDENCE BASE

In Vitro Studies

- AuNPs reduce pro-inflammatory cytokine production (e.g., TNF-α, IL-6) in activated microglia or astrocyte models.
- They reduce oxidative stress markers and increase survival in neuronal cell lines under stress.
- AuNPs modulate intracellular signaling (e.g., PI3K/Akt, MAPK) and support viability via anti-apoptotic pathways.

In Vivo Studies

- Rodent AD models: Behavioral improvement, restored antioxidant enzyme levels, normalized mitochondrial function.
- PD models in mice: AuNP composites carrying gene therapy or anti-aggregation cargo protect dopaminergic neurons, improve motor and cognitive outcomes.
- Stroke models: AuNP treatment reduces infarct size and improves neurological recovery.
- Biodistribution and Pharmacokinetics: AuNP toxicity and accumulation depend heavily on size, coating, and dose.

5. CHALLENGES AND TRANSLATIONAL BARRIERS

Translating AuNP-based neurotherapeutics from bench to bedside involves major hurdles:

Toxicity and Long-Term Safety

- Potential accumulation in non-target organs (liver, spleen) depending on nanoparticle size and coating.
- Long-term immunological responses: repeated dosing may provoke immune reactions.

Blood–Brain Barrier (BBB) Delivery

- Even though AuNPs can cross the BBB, achieving sufficiently high and selective delivery to diseased brain regions remains challenging.
- Novel approaches (e.g., focused ultrasound) are promising but need more preclinical and clinical validation.

Manufacturing and Reproducibility

- Consistency in AuNP synthesis (size, shape, surface chemistry) is essential for reproducible bioactivity and safety.
- Scaling up production under good manufacturing practices (GMP) for clinical use is nontrivial.

Regulatory and Clinical Trial Design

- Lack of standardized toxicity assays for nanoparticles.
- Designing trials: determining optimal dose, frequency, route of administration, and patient population (which disease stage to treat) are open questions.

Immune Response and Biocompatibility

- Engineering "stealth" particles (e.g., PEGylated or biomimetic coatings) to evade immune detection may be necessary.

6. EMERGING STRATEGIES AND FUTURE DIRECTIONS

Moving ahead, several innovative strategies may help harness the full potential of AuNPs in neuroprotection:

Targeted Functionalization

- Surface ligands (antibodies, peptides) directed to disease-specific markers (e.g., Aβ plaques, α-synuclein aggregates) to improve specificity.
- Stimuli-responsive systems: AuNPs that release therapeutic payloads in response to pH, enzymes, or oxidative stress in diseased microenvironments.

Gene/RNA Therapy Delivery

- Use of AuNP–nucleic acid composites (siRNA, miRNA, plasmids) to modulate disease-relevant genes (e.g., silencing α-synuclein in PD).
- Combining gene therapy with other modalities (anti-inflammatory, antioxidant) for synergistic effects.

Catalytic and Metabolic Modulators

- Leveraging the catalytic potential of gold nanocrystals to influence cellular metabolism (e.g., the NAD^+/NADH ratio), which may boost neuronal energy homeostasis.

- Recent research into gold nanocrystals acting as nanozymes or "metabolic catalysts" may open up novel therapeutic mechanisms.

Theranostics (Therapy + Diagnostics)

- Design of AuNPs that are both therapeutic and diagnostic — carrying imaging agents (e.g., fluorescent dyes, MRI contrast) along with drugs.
- Use photothermal properties to trigger controlled release or to activate cellular stress response pathways (e.g., heat-shock proteins).

Personalized Nanomedicine

- Tailoring AuNP formulations to patient-specific pathology (genetics, disease stage).
- Biomimetic coatings (e.g., cell membrane–derived vesicles or exosomes) to enhance targeting and biocompatibility.

Advanced Delivery Techniques

- Non-invasive BBB opening strategies: Focused ultrasound, receptor-mediated transcytosis, exosome-mediated transport.
- Intranasal delivery: using the olfactory route to bypass the BBB.

7. SAFETY, TOXICITY, AND REGULATORY CONSIDERATIONS

Ensuring the clinical safety of AuNPs is paramount:

- Pharmacokinetics & Biodistribution: Detailed studies are required to trace where AuNPs accumulate, how they are cleared, and whether they persist long term.
- Size- and Surface-dependent Toxicity: Smaller particles may be more reactive, but coating can mitigate this.
- Immune and Inflammatory Responses: Chronic administration could lead to immune activation; strategies like PEGylation or biomimicry may reduce this.

- Genotoxicity and Long-Term Effects: Requires extended animal studies to assess mutagenesis, neuronal network integrity, and behavior over months to years.
- Regulatory Pathway: Nanoparticles are still relatively novel in clinical settings; regulatory guidelines for their safety, manufacturing, and quality control need to be clearly defined.

CONCLUSION

Gold nanoparticles (AuNPs) represent one of the most promising nanotechnology platforms capable of addressing the intricate and multifactorial pathology characteristic of neurological diseases. Unlike conventional therapeutics, which often target a single molecular pathway, AuNPs possess a multifaceted biological profile that enables them to intervene at multiple stages of neurodegeneration. Their unique physicochemical features—including tunable size, geometry, surface charge, and optical properties—allow them to interact with neural tissue in ways that traditional small-molecule drugs or biologics cannot achieve. When engineered appropriately, AuNPs demonstrate potent antioxidant, anti-inflammatory, anti-apoptotic, mitochondrial-stabilizing, and anti-protein-aggregation effects, while simultaneously serving as versatile carriers for drug and gene delivery. This synergistic combination positions AuNPs as an emerging, next-generation neurotherapeutic platform with broad applicability across diverse neurological disorders, including Alzheimer's disease, Parkinson's disease, ischemic stroke, multiple sclerosis, traumatic brain injury, and amyotrophic lateral sclerosis.

A central advantage of AuNPs lies in their intrinsic ability to modulate oxidative stress—one of the earliest and most persistent drivers of neurodegeneration. AuNPs possess catalytic nanozyme-like properties that mimic the activity of natural antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. These pseudoenzymatic functions enable them to neutralize reactive oxygen species (ROS), inhibit lipid peroxidation, and restore intracellular redox equilibrium. Additionally, AuNPs can activate endogenous antioxidant signaling pathways, including Nrf2/ARE, increasing expression of heme oxygenase-1, superoxide dismutase, and glutathione-related enzymes.

By attenuating oxidative damage at both the mitochondrial and cytosolic levels, AuNPs protect neurons from excitotoxicity, metabolic dysfunction, and ROS-induced apoptosis, thereby preserving neuronal viability and synaptic integrity.

Beyond their antioxidant capacity, AuNPs exhibit powerful anti-inflammatory actions. Neuroinflammation, driven by chronic activation of microglia and astrocytes, contributes to progressive neuronal loss in nearly all neurodegenerative diseases. AuNPs have been shown to attenuate microglial activation, shifting cells away from the pro-inflammatory M1 phenotype toward the neuroprotective M2 phenotype. They also suppress key inflammatory mediators such as TNF-α, IL-1β, IL-6, COX-2, and inducible nitric oxide synthase (iNOS), while inhibiting central inflammatory signaling pathways including NF-κB, JNK, and p38 MAPK. By dampening these inflammatory cascades, AuNPs reduce secondary neuronal injury, maintain glial homeostasis, and promote a microenvironment conducive to repair and regeneration. This immunomodulatory capacity is especially valuable for chronic diseases such as Alzheimer's disease, Parkinson's disease, and multiple sclerosis, in which prolonged inflammation leads to cumulative neuronal deterioration.

Another major therapeutic advantage of AuNPs is their demonstrated ability to inhibit or reverse pathogenic protein aggregation. Misfolded protein species such as amyloid-β, tau, and α-synuclein play central roles in the pathogenesis of Alzheimer's and Parkinson's disease. AuNPs can prevent aggregation at multiple stages—interfering with nucleation, destabilizing fibril formation, blocking oligomerization, or disassembling existing aggregates. Functionalized AuNPs, such as those conjugated with peptides, antibodies, or polyphenols, show enhanced specificity in binding pathological proteins and disrupting their assembly. These interactions help prevent the formation of toxic oligomers, reduce aggregate-induced oxidative stress, preserve synaptic function, and mitigate downstream neurotoxicity. As such, AuNPs stand out as a novel anti-aggregation therapeutic class with significant implications for slowing or halting disease progression.

AuNPs also demonstrate anti-apoptotic effects, which are critical for protecting neurons that are highly susceptible to programmed cell death under stress conditions. AuNPs regulate mitochondrial pathways by stabilizing mitochondrial membrane potential, reducing cytochrome c release, and modulating Bcl-2 family proteins (increasing anti-apoptotic Bcl-2 while inhibiting pro-apoptotic Bax). They also reduce activation of caspase-3 and caspase-9, thereby preventing the execution of apoptosis. Furthermore, AuNPs help maintain calcium homeostasis, reduce excitotoxic glutamate signaling, and preserve synaptic communication. Through these combined effects, AuNPs enhance neuronal survival and counteract the progressive, irreversible cell loss that characterizes most neurological diseases.

One of the most transformative advantages of AuNPs is their utility as drug and gene delivery vehicles. Their high surface-to-volume ratio allows for dense loading of multiple drugs or biomolecules—including small molecules, peptides, growth factors, antibodies, siRNA, miRNA, and CRISPR components. AuNPs can penetrate the blood–brain barrier (BBB) via passive diffusion when sufficiently small (<10 nm), or via receptor-mediated transcytosis when conjugated with targeting ligands such as transferrin, lactoferrin, RGD peptides, or apolipoprotein E. This enables highly efficient delivery of therapeutics to specific brain regions or cell types that are otherwise difficult to target. Moreover, AuNPs provide controlled or stimuli-responsive release triggered by pH, enzymes, or external energy sources such as near-infrared light. Their multifunctional capabilities open the door to personalized, precision-targeted therapies for heterogeneous neurological disorders.

Despite their immense therapeutic potential, several challenges must be addressed before AuNP-based neurotherapies can achieve widespread clinical application. Safety concerns remain a primary obstacle. Although gold is generally biocompatible and inert, the long-term effects of chronic AuNP exposure—particularly regarding accumulation, clearance, and potential interference with cellular homeostasis—are not yet fully understood. The biodistribution of AuNPs depends heavily on size, shape, and surface chemistry, and excessive accumulation in organs such as the liver, spleen, or kidneys could pose toxicity risks.

Rigorous in vivo studies are needed to establish optimal dosing parameters, clearance mechanisms, and long-term safety. Another major challenge involves ensuring reproducibility and scalability of AuNP synthesis. Small variations in manufacturing conditions can significantly alter biological performance, including BBB permeability, immunogenicity, and neuroprotective efficacy. Regulatory agencies require precise control over nanoparticle characteristics before approving clinical translation, making standardization essential. Additionally, the complexity of neurological diseases means that single-function nanoparticles may be insufficient; combinatorial, multifunctional, or hybrid nanoplatforms may be required to simultaneously target multiple pathological pathways.

Nevertheless, rapid progress in nanomaterial engineering continues to refine AuNP design and functionality. Emerging innovations include biomimetic AuNPs coated with cell membranes (e.g., microglial, neuronal, or stem-cell membranes) to improve targeting and immune evasion; hybrid nanozyme-AuNP systems with enhanced catalytic functionality; multi-metallic nanoparticles for improved redox modulation; and theranostic AuNPs integrating drug delivery with real-time imaging or diagnostic monitoring. Photothermal neuromodulation using gold nanorods or nanostars is also gaining attention for its potential to modulate neural circuits with exceptional spatial precision. These futuristic strategies hold enormous promise for ushering in a new era of nanomedicine-based treatment for neurological disorders.

In conclusion, AuNPs offer a comprehensive, multifunctional approach to treating neurological diseases, addressing oxidative stress, inflammation, protein aggregation, apoptosis, and mitochondrial dysfunction while enabling precise drug and gene delivery across the blood–brain barrier. Their versatility, biocompatibility, and capacity for multimodal therapeutic action position them as highly promising candidates for next-generation neurotherapeutics. Although challenges related to safety, biodistribution, regulatory approval, and large-scale synthesis remain, continuous advancements in nanotechnology, neuroscience, and bioengineering are steadily accelerating their path toward clinical translation.

With ongoing interdisciplinary collaboration and innovation, AuNP-based strategies may soon emerge as transformative interventions capable of altering the trajectory of currently incurable neurological diseases.

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