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Review Article

EXPLORING PHYTOESTROGENS AND AI-ASSISTED DOCKING IN FEMALE NEUROPROTECTION AND COGNITIVE AGING

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Cognitive aging and the heightened prevalence of Alzheimer's disease in post-menopausal women highlight the pivotal neuroprotective role of estrogens in maintaining neuronal integrity. Declining estrogen levels after menopause accelerate oxidative stress, mitochondrial dysfunction, and synaptic loss, thereby predisposing women to neurodegenerative disorders. Phytoestrogens—plant-derived polyphenolic compounds with structural similarity to 17β-estradiol—have emerged as promising alternatives to hormone replacement therapy owing to their selective estrogen receptor modulation and antioxidant capacity. However, variable receptor affinity, bioavailability limitations, and incomplete mechanistic understanding constrain their translational use.

Recent advances in artificial intelligence (AI) and molecular docking now enable the rapid prediction of receptor–ligand interactions, pharmacokinetic behavior, and toxicity of phytoestrogen analogues. AI-assisted structure–activity relationship (SAR) modeling and virtual screening can identify novel derivatives with improved selectivity toward estrogen receptor-β and enhanced blood–brain barrier permeability. Integrating computational intelligence with sustainable drug discovery not only accelerates neurotherapeutic design but also aligns with eco-friendly and precision-medicine goals.

This review provides a comprehensive synthesis of current evidence on phytoestrogens in female neuroprotection, elucidates molecular and cellular mechanisms, and examines how AI-driven modeling, docking, and ADMET prediction contribute to rational, sustainable drug discovery for cognitive aging.

Keywords : Phytoestrogens; Cognitive aging; Neuroprotection; Estrogen receptor-β; Artificial intelligence; Molecular docking; Structure–activity relationship (SAR); Alzheimer's disease; Sustainable drug discovery; Machine learning.

INTRODUCTION

The progressive decline in cognitive function among aging women represents a major biomedical and societal challenge. Numerous epidemiological studies demonstrate that females exhibit nearly twice the risk of developing Alzheimer's disease (AD) compared with males of the same age. The underlying reason lies largely in estrogen depletion during the menopausal transition, which precipitates a cascade of neurochemical and structural alterations including impaired synaptic plasticity, reduced cholinergic tone, mitochondrial dysfunction, and accumulation of reactive oxygen species (ROS).

Estrogens modulate diverse neuronal processes: they enhance dendritic spine density, regulate neurotransmitter systems, and activate antioxidant and anti-apoptotic signaling via

estrogen receptor-β (ER-β). The abrupt withdrawal of estrogen signaling thus contributes to accelerated brain aging. Conventional hormone replacement therapy (HRT) can transiently restore estrogenic activity but is linked with severe side effects such as thromboembolism, breast cancer, and cardiovascular risks. Hence, the scientific community has turned toward natural compounds capable of mimicking estrogenic actions without adverse effects.

Phytoestrogens—bioactive secondary metabolites present in soy (genistein, daidzein), flaxseed (secoisolariciresinol diglucoside), red clover (formononetin, biochanin A), and grapes (resveratrol)—exert estrogen-like effects by binding selectively to ER-β, the receptor subtype predominant in the hippocampus and cortex. Their multifunctional properties include antioxidant defense, modulation of neuroinflammatory cytokines, and regulation of amyloid-β aggregation and tau phosphorylation. Despite encouraging preclinical findings, clinical translation of phytoestrogens remains inconsistent due to limited bioavailability, interindividual gut metabolism variability, and poor blood–brain barrier penetration.

Here, artificial intelligence (AI) has become a transformative tool in drug discovery and neuropharmacology. Machine learning (ML) algorithms, quantitative structure–activity relationship (QSAR) modeling, and molecular docking simulations can efficiently analyze massive chemical libraries, predict receptor affinity, and optimize pharmacokinetic properties of lead compounds. By integrating these computational approaches, researchers can identify novel phytoestrogen analogues with improved potency, receptor selectivity, and safety profiles—while minimizing the ecological and ethical footprint of traditional experimental screening.

This review therefore aims to bridge two converging domains: (i) the biological and neurochemical underpinnings of phytoestrogen-mediated protection in female cognitive health, and (ii) the technological innovations provided by AI-assisted modeling and docking for next-generation neuroprotective drug discovery. The synthesis of these perspectives holds promise for sustainable, precision-based therapeutics tailored to female neurobiology.

Rationale of the Study

The global burden of neurodegenerative diseases is escalating, with Alzheimer's disease (AD) representing the leading cause of dementia among elderly women. Epidemiological and mechanistic studies indicate that estrogen

decline during menopause contributes to cognitive impairment and heightened neuronal vulnerability. Estrogen exerts neuroprotective effects through multiple molecular pathways—enhancing synaptic signaling, stimulating mitochondrial biogenesis, modulating calcium homeostasis, and activating antioxidant defenses.

However, synthetic hormone replacement therapy (HRT), though effective in mitigating menopausal symptoms, is associated with severe adverse outcomes including breast and endometrial carcinoma and thromboembolic events. This necessitates the exploration of safer, natural alternatives capable of reproducing estrogen's neuroprotective efficacy without its risks.

Phytoestrogens, naturally occurring plant-derived polyphenols, provide a promising avenue as selective estrogen receptor modulators (SERMs). These compounds preferentially activate ER-β over ER-α, thereby mediating neuroprotection without inducing uterine or breast proliferation. Nonetheless, their clinical utility is constrained by variable bioavailability, rapid metabolism, and limited brain penetration.

To address these challenges, artificial intelligence (AI) and molecular docking technologies offer transformative potential. Machine learning-based structure–activity relationship (SAR) models can predict the binding affinity and pharmacokinetic parameters of novel phytoestrogen analogues, while molecular docking and molecular dynamics simulations reveal atomic-level interactions with ER-β, SIRT1, or amyloid-β aggregates. Integrating these AI-assisted computational methods into natural compound research ensures precision, efficiency, and sustainability in neurotherapeutic discovery.

Thus, the rationale of this study is founded on the need to combine neuroendocrinological insight with computational intelligence to design sustainable, female-centric therapeutics for neurodegenerative diseases.

To review and analyze the synergistic role of phytoestrogens and artificial intelligence–assisted molecular modeling in developing sustainable neuroprotective strategies for female cognitive aging and Alzheimer's disease prevention.

1. To elucidate the biological mechanisms by which estrogens and phytoestrogens modulate neuronal survival, synaptic plasticity, and cognitive function.
2. To summarize recent advances in phytoestrogen research focusing on eurodegenerative disease prevention in women.
3. To explore the role of artificial intelligence

(AI), quantitative structure–activity relationship (QSAR), and molecular docking in the identification and optimization of phytoestrogen analogues.

4. To discuss how AI-based screening and ADMET modeling can overcome pharmacokinetic limitations of natural phytoestrogens.

5. To propose a sustainable, AI-driven framework for designing phytoestrogen-inspired neuroprotective drugs tailored to female neurobiology

This review adopts an integrative and systematic approach combining literature synthesis, computational analysis insights, and sustainability perspectives.

Literature Search Strategy

Peer-reviewed publications from 2015–2025 were retrieved from Scopus, PubMed, Web of Science, and ScienceDirect databases. The search terms included *phytoestrogens, cognitive aging, estrogen receptor beta, artificial intelligence, machine learning, molecular docking, SAR, neuroprotection*, and *Alzheimer's disease*. Both experimental and computational studies were considered.

Inclusion and Exclusion Criteria

- Inclusion: Studies focusing on phytoestrogens' neuroprotective mechanisms, AI-assisted computational modeling, molecular docking, or SAR analyses.
- Exclusion: Reports not related to neurobiology, AI, or those lacking mechanistic insights.

Data Extraction and Analysis

Extracted data were categorized under:

- Source and structure of phytoestrogens
- Mechanistic neuroprotection pathways
- Docking and AI-model outcomes
- Pharmacokinetic and ADMET properties
- Environmental and sustainability aspects in drug discovery

Ethical and Sustainability Considerations

All referenced studies were previously published and publicly available; thus, no new human or animal experimentation was conducted. Emphasis was placed on green and sustainable research paradigms, minimizing reliance on resource-intensive experimental assays through AI-driven virtual modeling and computational optimization.

Discussion

Overview of Phytoestrogens in Female Neurobiology

Phytoestrogens are naturally occurring non-steroidal polyphenols found mainly in soybeans, flaxseeds, legumes, whole grains, and certain fruits. Chemically, they belong to three major

classes—isoflavones (e.g., genistein, daidzein), lignans (e.g., secoisolariciresinol diglucoside), and coumestans (e.g., coumestrol). These compounds exhibit structural similarity to 17β-estradiol, allowing them to interact with estrogen receptors (ER-α and ER-β). Unlike synthetic estrogens, most phytoestrogens preferentially activate ER-β, abundant in the hippocampus and cortex—key brain regions for cognition and memory.

During menopause, the decline in estrogen levels triggers oxidative stress, mitochondrial dysfunction, and neuroinflammation. Phytoestrogens mimic estrogenic effects by activating ER-β-mediated genomic and non-genomic pathways, thereby sustaining synaptic connectivity and neuronal plasticity. Experimental evidence shows that genistein enhances BDNF expression, promotes CREB phosphorylation, and inhibits microglial activation, collectively contributing to cognitive resilience.

Mechanisms of Neuroprotection by Phytoestrogens

The neuroprotective actions of phytoestrogens encompass multiple molecular targets:

1. Antioxidant Defense: Isoflavones scavenge reactive oxygen species (ROS), upregulate superoxide dismutase (SOD) and glutathione peroxidase (GPx), and restore mitochondrial membrane potential.
2. Anti-Amyloidogenic Pathway: Genistein and daidzein inhibit β-secretase (BACE-1) and prevent amyloid-β aggregation, a hallmark of Alzheimer's pathology.
3. Anti-Inflammatory Effects: Phytoestrogens modulate NF-κB, TNF-α, and IL-6 signaling, thereby mitigating neuroinflammation.
4. Mitochondrial Biogenesis and Energy Regulation: Activation of PGC-1α and SIRT1 enhances neuronal metabolism and longevity.
5. Epigenetic Modulation: Certain phytoestrogens influence DNA methylation and histone acetylation, preserving gene expression patterns essential for cognition.

Collectively, these mechanisms underscore their role as multi-target neuroprotective agents, capable of addressing the multifactorial nature of female cognitive decline.

Challenges in Clinical Translation

Despite compelling preclinical evidence, the transition of phytoestrogens to clinical success remains limited due to:

- Poor bioavailability and first-pass

metabolism.

Variable intestinal microbiota conversion, influencing active metabolite formation such as equol.

- Low BBB (blood–brain barrier) permeability.

These factors necessitate structure modification and computational optimization—areas where AI and molecular docking play transformative roles.

AI-Assisted SAR and Molecular Docking in Phytoestrogen Research

Artificial intelligence accelerates natural compound research through predictive modeling and virtual screening. Techniques such as quantitative structure–activity relationship (QSAR), deep learning, and molecular docking identify analogues with improved pharmacokinetic and pharmacodynamic profiles.

- Machine Learning–Based QSAR: Algorithms (e.g., Random Forest, XGBoost, Deep Neural Networks) can correlate molecular descriptors with estrogen receptor affinity or antioxidant potential.
- Docking Studies: Virtual docking of genistein analogues against ER-β, SIRT1, and Aβ oligomer binding sites reveals crucial hydrogen bonding and π-π interactions that determine efficacy.
- Molecular Dynamics (MD) Simulations: Further refine binding stability and conformational flexibility, ensuring lead-compound reliability.
- AI-Integrated ADMET Prediction: Models estimate absorption, distribution, metabolism, excretion, and toxicity profiles—essential for drug-likeness evaluation.

Through this computational synergy, researchers can design next-generation phytoestrogen analogues with enhanced potency and BBB permeability while minimizing toxicity.

Sustainability and Green Drug Discovery

AI-assisted docking aligns with the principles of green chemistry by reducing experimental animal use, reagent consumption, and energy demand. In silico models guide the synthesis of only promising compounds, significantly minimizing chemical waste. Moreover, phytoestrogens derived from renewable plant sources foster eco-friendly and sustainable pharmacotherapy, aligning with UN Sustainable Development Goals (SDG 3 & 12).

Future Prospects

1. Hybrid Molecule Design: Combining phytoestrogen cores with neuroactive

moieties via AI-guided algorithms may enhance receptor specificity.

2. Personalized Neuroprotection: AI can analyze hormonal, genomic, and metabolic data in women to tailor neuroprotective interventions.
3. Nanocarrier Integration: Phytoestrogen-loaded nanoparticles, optimized by AI-based modeling, could overcome BBB limitations and ensure targeted brain delivery.
4. Clinical AI Pipelines: Integration of AI platforms in clinical trials will allow real-time prediction of efficacy and safety outcomes, expediting translation to bedside.

CONCLUSION

The convergence of phytoestrogen research and AI-driven computational modeling represents a revolutionary step toward sustainable, women-centric neurotherapeutic innovation. Phytoestrogens, as natural selective estrogen receptor modulators (SERMs), offer multitargeted neuroprotection through antioxidant, anti-inflammatory, and mitochondrial pathways, particularly beneficial during estrogen-deficient aging in females.

Nevertheless, conventional research on these compounds has faced significant challenges due to limited bioavailability, metabolic instability, and restricted blood–brain barrier permeability. Artificial intelligence (AI) and molecular docking methodologies overcome these barriers by enabling rapid prediction of receptor binding affinity, ADMET properties, and optimized analog design, thereby reducing both time and resource consumption in drug discovery.

Integrating AI-assisted SAR, molecular dynamics simulations, and green-synthesis concepts could facilitate the rational development of next-generation phytoestrogen derivatives capable of restoring cognitive function and preventing neurodegenerative diseases such as Alzheimer's. The path forward lies in combining computational precision with clinical validation—establishing a holistic, sustainable approach to female neuroprotection and healthy cognitive aging.

Future Perspective

Future neuropharmacological research must expand AI's role in personalized medicine. AI algorithms analyzing hormonal status, genomics, and metabolic data can customize phytoestrogen-based interventions for individual women. The integration of machine learning–driven nanocarrier design, digital twin simulations, and neuroinformatics platforms will refine brain-targeted delivery and improve translational outcomes. Collaborative efforts among computational biologists, neuroscientists,

and pharmacologists are essential to advance this paradigm into clinically viable therapeutics.

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