AI-Driven Scientific Prompting and Sequential Discovery Pipeline for Nrf2-Targeted Predictive Modeling and Therapeutic Insights in Alzheimer's Disease Using Glucomoringin from *Moringa oleifera*

Siddik Bagwan

Sinhgad College of Pharmacy Pune, India

Corresponding author Email: bagwansiddik50@gmail.com

Doi: 10.5281/zenodo.19727414
Received: 16 February 2026
Accepted: 02 March 2026

ABSTRACT

Alzheimer's disease (AD) remains a major global health challenge with limited disease-modifying therapies. The nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a central regulator of antioxidant and anti- inflammatory responses, has emerged as a promising therapeutic target. Natural products, particularly glucosinolates, provide diverse scaffolds for Nrf2 modulation. This review synthesizes current evidence on the neuroprotective potential of glucomoringin, a major glucosinolate from *Moringa oleifera*, as an Nrf2 activator in AD, and proposes an AI-driven sequential discovery pipeline to accelerate therapeutic development. A systematic literature search (2010–2025) across PubMed, Scopus, Web of Science, and Google Scholar identified studies on Nrf2 signaling in AD, glucomoringin neuroprotection, and AI applications in drug discovery. Evidence indicates diminished Nrf2 activity in AD brains, contributing to oxidative stress and neuroinflammation. Glucomoringin and its metabolite moringin significantly activate Nrf2 in neuronal and microglial models, enhancing antioxidant enzymes (HO-1, NQO1, SOD) and suppressing NF-κB-mediated inflammation. In silico studies confirm favorable Keap1 binding and drug-like properties. AI-driven approaches, including large language model (LLM)-based hypothesis generation, molecular docking, machine learning prediction, and ADMET modeling, are transforming natural product discovery by enabling rapid screening, property prediction, and iterative optimization. Integrating scientific prompting with predictive modeling and experimental validation offers a powerful strategy to overcome traditional bottlenecks. Glucomoringin thus represents a promising phytochemical for Nrf2-targeted AD intervention, and AI-enabled sequential pipelines may accelerate its translation into effective neuroprotective therapies.

Keywords: Alzheimer's disease; Nrf2 pathway; glucomoringin; *Moringa oleifera*; AI in drug discovery; predictive modeling; neuroprotection; oxidative stress

1. INTRODUCTION

Alzheimer's disease (AD) stands as the most prevalent form of dementia, affecting an estimated 50 million individuals worldwide, with projections anticipating a tripling of this number by 2050 as populations age [1, 2]. This escalating global burden extends beyond patient suffering to encompass profound socioeconomic costs, positioning AD as one of the twenty-first century's most pressing public health challenges [3]. Despite decades of intensive research and substantial investment in drug development, the therapeutic landscape for AD remains notably barren. Current pharmacologic interventions primarily acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine -offer modest symptomatic relief without altering disease progression [4]. Even the recent regulatory approvals of anti-amyloid monoclonal antibodies (lecanemab, donanemab), while representing a significant milestone, have yielded marginal clinical benefits accompanied by substantial treatment burden and safety concerns [5, 6]. This persistent therapeutic gap underscores an urgent need for innovative approaches targeting fundamental disease mechanisms.

The pathophysiological complexity of AD necessitates a re-evaluation of conventional drug discovery paradigms. While amyloid-beta (Aβ) plaques and tau neurofibrillary tangles remain neuropathological hallmarks, accumulating evidence implicates oxidative stress and neuroinflammation as critical drivers of disease initiation and progression [7, 8]. The brain's high oxygen consumption, abundant polyunsaturated fatty acids, and relatively limited antioxidant capacity render it uniquely vulnerable to oxidative damage [9]. In AD, this vulnerability is compounded by mitochondrial dysfunction, metal dyshomeostasis, and chronic microglial activation, creating a self-perpetuating cycle of neuronal injury [10].

Central to cellular defense against these insults is the nuclear factor erythroid 2-related factor 2 (Nrf2)-Kelch- like ECH-associated protein 1 (Keap1)-antioxidant response element (ARE) signaling pathway. Often termed the guardian of redox homeostasis, Nrf2 orchestrates the transcriptional activation of over 200 cytoprotective genes encoding antioxidant enzymes (heme oxygenase-1, HO-1; NAD(P)H:quinone oxidoreductase 1, NQO1; glutathione S-transferases), phase II detoxifying enzymes, and proteins involved in mitochondrial biogenesis and inflammation resolution [11, 12]. In AD-afflicted brains, however, Nrf2 nuclear translocation and transcriptional activity are markedly diminished, despite cytosolic retention of the transcription factor a paradoxical finding suggesting impaired activation mechanisms rather than reduced protein expression [13]. This functional deficit renders neurons and glia vulnerable to oxidative injury, creating a rational therapeutic opportunity for Nrf2 augmentation.

Within this context, natural products have historically served as invaluable reservoirs of structurally diverse and biologically active compounds. Among the myriad medicinal plants with neuroprotective potential, *Moringa oleifera* Lam. (Moringaceae) has attracted considerable scientific attention. Indigenous to the Himalayan foothills and widely

cultivated throughout tropical and subtropical regions, *M. oleifera* commonly designated the drumstick tree or miracle tree exhibits an extensive ethnopharmacological profile encompassing antioxidant, anti-inflammatory, and neuroprotective properties [14]. Its major bioactive constituents include glucosinolates, particularly glucomoringin (4-(α-L-rhamnopyranosyloxy) benzyl glucosinolate), which upon enzymatic hydrolysis by myrosinase yields the corresponding isothiocyanate, moringin [15]. Emerging experimental evidence suggests that glucomoringin and its metabolites exert neuroprotective effects through Nrf2 pathway activation, positioning this phytochemical as a compelling candidate for AD therapeutic development [16, 17].

Concurrent with advances in understanding AD pathogenesis and natural product bioactivity, the application of artificial intelligence (AI) and machine learning (ML) is fundamentally transforming drug discovery. AI methodologies now enable the rapid screening of vast chemical libraries, prediction of molecular targets and bioactivity, optimization of pharmacokinetic properties, and even de novo generation of compound libraries with desired characteristics [18, 19]. Particularly relevant to natural product research, AI-driven approaches can navigate the structural complexity of phytochemicals, predict their interactions with biological targets such as Keap1, and prioritize candidates with optimal drug-like properties [20]. Moreover, the emergence of large language models (LLMs) and generative AI has introduced the concept of scientific prompting the use of natural language interfaces to generate hypotheses, design experiments, and orchestrate multi-step discovery workflows [21].

This review synthesizes current knowledge regarding the neuroprotective potential of glucomoringin from *M. oleifera* as an Nrf2-targeted therapeutic agent in AD. We critically evaluate the evidence for Nrf2 dysregulation in AD pathogenesis, examine the mechanistic basis of glucomoringin-mediated neuroprotection, and assess the role of AI-driven approaches in accelerating discovery. Furthermore, we propose an integrated sequential discovery pipeline that combines AI-based scientific prompting, predictive modeling, and experimental validation to systematically develop Nrf2-activating therapeutics. By bridging natural product chemistry, neuropharmacology, and computational innovation, this framework aims to address the translational challenges that have historically impeded the development of effective AD therapies.

2. LITERATURE REVIEW

2.1 Alzheimer's Disease Pathophysiology: Beyond Protein Aggregation

Alzheimer's disease is a progressive neurodegenerative disorder characterized by insidious cognitive decline, ultimately culminating in complete functional dependence. While the extracellular accumulation of Aβ peptides in senile plaques and intraneuronal aggregation of hyperphosphorylated tau protein in neurofibrillary tangles remain definitive neuropathological diagnostic criteria [22], contemporary understanding recognizes AD as a multifactorial disease process involving complex interactions among genetic, environmental, and metabolic factors [23].

The amyloid cascade hypothesis, initially proposed in the early 1990s, posits that Aβ

accumulation serves as the initiating event in AD pathogenesis, triggering a cascade of downstream events including tau hyperphosphorylation, synaptic dysfunction, and neuronal death [24]. This hypothesis derives substantial support from the genetics of early-onset familial AD, wherein mutations in amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) uniformly enhance Aβ production or aggregation [25]. However, the imperfect correlation between plaque burden and cognitive decline, together with the presence of substantial amyloid pathology in cognitively normal elderly individuals, has prompted refinement of this model to emphasize soluble oligomeric Aβ species as the primary neurotoxic moieties [26].

Tau pathology demonstrates stronger correlation with cognitive status than amyloid burden, supporting the concept that tau aggregation represents a critical downstream effector of neurodegeneration [27]. Hyperphosphorylated tau sequesters normal tau and other microtubule-associated proteins, disrupting axonal transport, impairing synaptic function, and ultimately contributing to neuronal death. Moreover, emerging evidence indicates that pathological tau species can propagate trans-synoptically throughout neural circuits in a prion-like manner, providing a mechanistic basis for the stereotyped progression of neurofibrillary pathology observed in AD brains [28].

Beyond proteinopathies, neuroinflammation has emerged as a third core pathological feature of AD. Genome- wide association studies (GWAS) have consistently identified AD risk variants in genes encoding microglial receptors (TREM2, CD33) and inflammatory mediators, implicating innate immune dysfunction in disease pathogenesis [29]. In AD, microglia undergo phenotypic transformation from homeostatic surveillant cells to chronically activated phenotypes, releasing pro-inflammatory cytokines (interleukin-1β, tumor necrosis factor-α), reactive oxygen species, and neurotoxic factors that exacerbate neuronal injury [30]. This sustained inflammatory response, rather than promoting resolution and repair, becomes self-perpetuating and contributes to progressive neurodegeneration.

Oxidative stress represents a unifying mechanism linking these pathological features. Reactive oxygen species (ROS) are generated through multiple AD-associated processes: mitochondrial dysfunction, metal-catalyzed reactions, microglial NADPH oxidase activation, and Aβ-membrane interactions [31]. Elevated oxidative damage to lipids, proteins, and nucleic acids is consistently documented in AD brains, with evidence of such damage preceding the appearance of frank pathology in Down syndrome and mild cognitive impairment [32]. The brain's particular vulnerability to oxidative insult stems from its high metabolic rate, abundant oxidizable polyunsaturated fatty acids, and regionally variable antioxidant capacity [33]. In AD, this vulnerability is compounded by age-related decline in endogenous antioxidant defenses, creating a permissive environment for oxidative injury.

Synaptic dysfunction and loss constitute the pathological correlate most closely associated with cognitive impairment in AD. Dendritic spine loss, reduced synaptic density, and impaired long-term potentiation precede frank neuronal death and correlate strongly with dementia severity [34]. Both soluble Aβ oligomers and hyperphosphorytau tau disrupt

synaptic structure and function through multiple mechanisms: interference with glutamatergic signaling, impairment of mitochondrial trafficking, and activation of apoptotic pathways [35]. The selective vulnerability of specific neuronal populations particularly cholinergic neurons of the basal

forebrain and glutamatergic neurons of the hippocampus and entorhinal cortex reflects differential expression of molecular risk factors and adaptive capacity.

2.2 Nrf2-Keap1-ARE Signaling Pathway in Neuroprotection

The Nrf2-Keap1-ARE pathway represents the primary cellular defense mechanism against oxidative and electrophilic stress. Nrf2 (encoded by *NFE2L2*) is a basic leucine zipper (bZIP) transcription factor belonging to the cap 'n' collar (CNC) subfamily. Under basal conditions, Nrf2 is maintained at low levels through Keap1- mediated ubiquitination and proteasomal degradation. Keap1, a cysteine-rich substrate adaptor protein for the Cullin-3/Rbx1 E3 ubiquitin ligase complex, binds Nrf2 and targets it for rapid turnover, with a half-life of approximately 20 minutes [36].

The structural basis of Keap1-mediated Nrf2 regulation involves a cycling mechanism wherein Keap1 functions as a molecular sensor for electrophiles and oxidants. Keap1 contains 27 cysteine residues, several of which (particularly Cys151, Cys273, and Cys288) are highly reactive and serve as sensors for oxidative stress [37]. Upon exposure to electrophiles or ROS, these cysteine residues undergo modification, inducing conformational changes in Keap1 that impair its ubiquitination activity. This results in stabilization of newly synthesized Nrf2, which translocates to the nucleus, heterodimerizes with small Maf proteins, and binds to antioxidant response elements (AREs) in the regulatory regions of target genes [38].

The transcriptional program governed by Nrf2 encompasses a broad array of cytoprotective enzymes and proteins with diverse functions. Direct antioxidant enzymes include catalase, superoxide dismutase (SOD), glutathione peroxidase (GPx), and peroxiredoxins. Phase II detoxifying enzymes such as NQO1, glutathione S-transferases (GSTs), and UDP-glucuronosyltransferases (UGTs) facilitate the metabolism and elimination of xenobiotics and endogenous toxins [39]. Heme oxygenase-1 (HO-1) degrades pro-oxidant heme to generate biliverdin (subsequently converted to antioxidant bilirubin), carbon monoxide (a signaling molecule with anti- inflammatory properties), and ferrous iron (sequestered by ferritin) [40]. Additionally, Nrf2 regulates genes involved in glutathione synthesis (glutamate-cysteine ligase catalytic and modifier subunits, GCLC/GCLM), thioredoxin system components (thioredoxin, thioredoxin reductase), and proteins supporting mitochondrial function and biogenesis (Nrf1, mitochondrial transcription factor A) [41].

In the central nervous system, Nrf2-mediated neuroprotection operates through both cell-autonomous and non-cell-autonomous mechanisms. Within neurons, Nrf2 activation enhances intrinsic antioxidant capacity, protects mitochondrial function, and reduces excitotoxicity [42]. However, astrocytes with their larger cytoplasmic volume and higher baseline antioxidant capacity may serve as the primary effectors of Nrf2- dependent neuroprotection. Activated astrocytes export glutathione and other antioxidants to support

neighboring neurons, while Nrf2-driven metabolic reprogramming in astrocytes enhances neuronal survival [43]. Microglial Nrf2 activation suppresses pro-inflammatory phenotypes, reducing the release of neurotoxic cytokines and ROS while promoting phagocytic clearance of debris and protein aggregates [44].

In AD, compelling evidence documents impaired Nrf2 function despite preserved or even elevated Nrf2 protein levels. Postmortem studies reveal reduced nuclear Nrf2 localization in hippocampal neurons of AD patients compared to age-matched controls, with corresponding decreases in NQO1 and HO-1 expression [45]. This functional deficit appears attributable to multiple mechanisms: sequestration of Nrf2 in cytoplasmic aggregates, competition for transcriptional coactivators, epigenetic silencing of ARE-containing genes, and dysregulation of autophagy pathways that normally facilitate Keap1 degradation [46]. Importantly, genetic ablation of Nrf2 in AD mouse models accelerates pathology, exacerbates oxidative damage, and worsens cognitive deficits, while pharmacological Nrf2 activation attenuates these phenotypes [47, 48].

2.3 Natural Nrf2 Activators in Neurodegenerative Diseases

The recognition of Nrf2 as a promising therapeutic target has stimulated intensive investigation of Nrf2- activating compounds, particularly those derived from natural sources. Phytochemicals with electrophilic properties can modify Keap1 cysteine sensors, disrupting the Nrf2-Keap1 interaction and stabilizing Nrf2. This mechanism, shared with endogenous electrophiles and oxidants, forms the basis for the neuroprotective effects of numerous dietary and medicinal plant constituents [49].

Curcumin, the principal curcuminoid from *Curcuma longa* (turmeric), represents the most extensively studied natural Nrf2 activator. Curcumin's α,β-unsaturated carbonyl moiety serves as a Michael acceptor capable of alkylating Keap1 cysteine residues, leading to Nrf2 nuclear translocation and ARE-driven gene expression [50]. In cellular and animal models of AD, curcumin attenuates oxidative stress, reduces Aβ aggregation and toxicity, suppresses neuroinflammation, and improves cognitive performance [51]. However, clinical translation has been hindered by poor bioavailability, rapid metabolism, and limited brain penetration, prompting development of various formulation strategies (nanoparticles, liposomes, adjuvants like piperine) to enhance therapeutic utility [52].

Sulforaphane, an isothiocyanate derived from glucoraphanin in cruciferous vegetables (particularly broccoli), stands as one of the most potent naturally occurring Nrf2 activators. As a highly reactive electrophile, sulforaphane readily modifies Keap1 cysteines, inducing Nrf2-dependent transcription of antioxidant and phase II enzymes with remarkable potency (low micromolar range) [53]. In AD models, sulforaphane protects neurons from Aβ toxicity, reduces oxidative damage, suppresses microglial activation, and improves cognitive function [54]. Notably, sulforaphane's isothiocyanate structure generated through myrosinase-mediated hydrolysis of its glucosinolate precursor serves as a direct chemical analog to moringin from *M. oleifera*, highlighting the mechanistic commonality among this compound class.

Resveratrol, a stilbenoid polyphenol abundant in grapes and red wine, activates Nrf2

through multiple mechanisms including sirtuin-1 (SIRT1) activation, AMPK phosphorylation, and direct Keap1 modification [55]. Beyond Nrf2 induction, resveratrol exhibits pleiotropic neuroprotective effects including Aβ clearance enhancement, tau dephosphorylation, mitochondrial biogenesis, and anti-inflammatory activity [56]. Despite extensive preclinical evidence, clinical translation has been constrained by rapid glucuronidation and sulfation, resulting in low oral bioavailability and limited brain exposure.

Apigenin, a flavonoid abundantly present in chamomile, parsley, and celery, activates Nrf2 through both transcriptional and post-transcriptional mechanisms [57]. In neuronal and microglial models, apigenin upregulates HO-1, NQO1, and glutathione synthesis while suppressing NF-κB-driven inflammation, effects attenuated by Nrf2 silencing [58]. Importantly, apigenin demonstrates favorable brain penetration and has shown cognitive benefits in multiple AD animal models, supporting its therapeutic potential.

Other notable Nrf2-activating phytochemicals include epigallocatechin-3-gallate (EGCG) from green tea, quercetin (ubiquitous in fruits and vegetables), luteolin (present in celery, thyme, and chamomile), and hydroxytyrosol (the major polyphenol in olive oil) [59]. The diversity of chemical scaffolds capable of Nrf2 activation encompassing flavonoids, isothiocyanates, curcuminoids, stilbenes, and phenolic acids reflects the broad electrophilic sensitivity of Keap1 and offers multiple opportunities for therapeutic development.

2.4 Glucomoringin from *Moringa oleifera*: Phytochemistry and Neurobiological Properties

Moringa oleifera Lam. (Moringaceae), a fast-growing tree native to the Indian subcontinent, has been employed in traditional medicine systems for centuries to treat diverse ailments including inflammation, infections, and metabolic disorders [60]. Phytochemical investigation has revealed a complex array of bioactive constituents, with glucosinolates and their isothiocyanate hydrolysis products recognized as principal contributors to the plant's pharmacological properties.

Glucomoringin (4-(α-L-rhamnopyranosyloxy) benzyl glucosinolate) constitutes the predominant glucosinolate in *M. oleifera* tissues, particularly abundant in seeds and leaves [61]. Structurally, glucomoringin consists of a β-D-glucopyranose moiety linked via a sulfur atom to an (E)-N- hydroximinosulfate ester, with the aglycone portion comprising 4-(α-L-rhamnopyranosyloxy) benzyl alcohol (Figure 1). Upon tissue disruption, glucomoringin meets endogenous thioglucosidase (myrosinase), which hydrolyzes the thioglycosidic linkage, yielding glucose, sulfate, and the unstable aglycone intermediate that spontaneously rearranges to form the corresponding isothiocyanate, moringin (4-(α-L-rhamnopyranosyloxy)benzyl isothiocyanate) [15]. This enzymatic activation mirrors the glucoraphanin- sulforaphane system in broccoli, positioning glucomoringin as a prodrug requiring bioactivation for optimal biological activity.

The biosynthesis of glucomoringin follows the general glucosinolate pathway, beginning with chain elongation of phenylalanine-derived aromatic amino acids, followed by formation of the core glucosinolate structure through sequential oxidation, conjugation with

glutathione, and glycosylation [62]. The unique rhamnosylation of the benzyl aglycone distinguishes *Moringa* glucosinolates from those of Brassicaceae and contributes to their distinctive physicochemical properties and biological activities.

Experimental investigations have established a robust neuroprotective profile for glucomoringin-derived isothiocyanates. In neuronal cell models, moringin pretreatment attenuates hydrogen peroxide (H_2O_2)-induced cytotoxicity, reduces ROS accumulation, preserves mitochondrial membrane potential, and prevents apoptotic cell death [16]. These protective effects are associated with upregulation of Nrf2 target genes, including *HO- 1*, *NQO1*, and *GCLC*, and are abrogated by Nrf2 silencing, confirming pathway dependence. Mechanistically, moringin's electrophilic isothiocyanate group serves as a Michael acceptor capable of alkylating specific Keap1 cysteine residues, particularly Cys151, disrupting the Nrf2-Keap1 interaction and stabilizing Nrf2 [63].

Concurrent with Nrf2 activation, moringin suppresses pro-inflammatory signaling through NF-κB pathway inhibition. In lipopolysaccharide-stimulated microglial cells, moringin reduces nuclear p65 translocation, decreases phosphorylation of IκBα, and attenuates expression of inflammatory mediators (iNOS, COX-2, TNF-α, IL-1β) [17]. This dual modulation enhancing antioxidant defenses while restraining neuroinflammation positions glucomoringin-derived isothiocyanates as particularly attractive candidates for AD intervention, given the intertwined roles of oxidative stress and inflammation in disease progression.

In vivo evidence, while primarily derived from Parkinson's disease models, supports the neuroprotective potential of moringin. In MPTP-induced mouse models of Parkinsonism, moringin administration preserves nigrostriatal dopaminergic neurons, reduces oxidative damage, suppresses microglial activation, and improves motor function [64]. Importantly, comparisons between glucomoringin and its bioactivated form (moringin plus myrosinase) demonstrate superior efficacy of the isothiocyanate, underscoring the importance of enzymatic activation for optimal neuroprotection.

Despite this promising preclinical profile, significant knowledge gaps remain regarding glucomoringin's therapeutic potential in AD. Direct evidence in AD transgenic models is limited, pharmacokinetic characterization is incomplete, and the compound's ability to penetrate the blood-brain barrier requires systematic investigation. Moreover, the structural similarity between moringin and sulforaphane a well- characterized Nrf2 activator with established safety but limited brain penetration raises questions about relative efficacy and bioavailability that warrant rigorous comparative study.

2.5 Artificial Intelligence in Modern Drug Discovery: Transforming Natural Product Research

The application of artificial intelligence to drug discovery has undergone exponential growth over the past decade, driven by advances in machine learning algorithms, increasing computational power, and the

accumulation of vast biomedical datasets [65]. AI methodologies now permeate virtually every stage of the drug discovery pipeline, from target identification and validation through hit discovery, lead optimization, preclinical development, and clinical trial design [66].

In the context of natural product drug discovery, AI offers advantages in addressing the unique challenges posed by phytochemical complexity. Natural products occupy chemical space distinct from synthetic compound libraries, featuring greater stereochemical complexity, higher molecular weight, and more diverse ring systems characteristics that historically complicated their inclusion in high-throughput screening campaigns [67]. Machine learning models trained on large natural product databases can now predict bioactivity, toxicity, and pharmacokinetic properties, enabling efficient prioritization of compounds with optimal characteristics [20].

Target identification represents a critical application of AI in natural product research. Computational approaches including similarity ensemble searching, reverse pharmacophore mapping, and machine learning- based target prediction can rapidly identify potential protein targets for phytochemicals based on structural features [68]. For Nrf2-activating compounds like glucomoringin, such approaches can predict interactions with Keap1 cysteine residues, guide structure-activity relationship studies, and identify off-target effects that might influence therapeutic utility.

Molecular docking and molecular dynamics simulations, while predating the current AI revolution, have been substantially enhanced through integration with machine learning. Scoring functions trained on large protein- ligand interaction datasets improve docking accuracy, while machine learning potentials enable longer timescale simulations with quantum mechanical accuracy [69]. These approaches enable detailed characterization of glucomoringin-Keap1 interactions, prediction of binding modes, and identification of structural modifications that might enhance affinity and selectivity.

ADMET (absorption, distribution, metabolism, excretion, toxicity) prediction has emerged as a particularly valuable AI application for natural product development. Machine learning models trained on large experimental datasets can predict intestinal absorption, blood-brain barrier penetration, cytochrome P450 metabolism, and potential toxicities with reasonable accuracy [70]. Such predictions enable early elimination of compounds with unfavourable properties and guide medicinal chemistry optimization to enhance drug-like characteristics.

Recent advances in generative AI and large language models have introduced transformative capabilities for drug discovery. Generative adversarial networks (GANs) and variational autoencoders (VAEs) can generate novel molecular structures with desired properties, enabling de novo design of Nrf2 activators inspired by natural product scaffolds [71]. Transformer-based models trained on chemical reaction data can predict synthetic routes, facilitating access to complex phytochemical analogs [72].

The concept of scientific prompting the use of natural language interfaces to interact with AI systems represents an emerging paradigm with profound implications for drug discovery. Rather than requiring specialized programming expertise, researchers can

articulate discovery goals in natural language, with AI systems translating these prompts into executable workflows encompassing data retrieval, computational modeling, and experimental design [21]. This democratization of AI capabilities has the potential to accelerate discovery by enabling broader participation and more rapid iteration of hypotheses.

Recent industry-led initiatives have demonstrated the feasibility of fully integrated, AI-driven drug discovery pipelines. The from prompt to drug framework, proposed by researchers at Insilico Medicine and Eli Lilly, envisions autonomous AI systems capable of orchestrating target discovery, generative chemistry, experimental validation, and clinical development with minimal human intervention [73]. While such pharmaceutical superintelligence remains aspirational, incremental integration of AI capabilities into discovery workflows is already yielding tangible advances in speed and efficiency.

For Nrf2-targeted natural product discovery, AI integration offers particular promise. Machine learning models trained on known Nrf2 activators can identify structural features predictive of Keap1 interaction, enabling virtual screening of natural product databases to identify novel candidates. Generative models can explore chemical space around glucomoringin's scaffold, proposing analogs with optimized potency and drug-like properties. Predictive ADMET models can prioritize compounds with favorable brain penetration, addressing a critical barrier to CNS drug development. And LLM-based scientific prompting can integrate these capabilities into coherent discovery workflows, accelerating the translation of phytochemical leads like glucomoringin toward clinical evaluation.

3. MATERIALS AND METHODS

3.1 Literature Search Strategy

A systematic literature search was conducted to identify relevant studies on Nrf2 signaling in Alzheimer's disease, the neuroprotective effects of glucomoringin from *Moringa oleifera*, and AI applications in natural product drug discovery. The following electronic databases were searched: PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar. The search period encompassed January 2010 to December 2025, capturing both foundational studies and recent advances.

Search strategies employed combinations of Medical Subject Headings (MeSH) and keywords, adapted for each database. Primary search terms included: Alzheimer disease OR Alzheimer's AND Nrf2 OR NFE2L2 OR Keap1 OR antioxidant response element; glucomoringin OR moringin OR Moringa oleifera AND neuroprotection OR neuroprotective OR oxidative stress OR inflammation; artificial intelligence OR machine learning OR deep learning OR neural networks AND drug discovery AND natural products OR phytochemicals. Reference lists of included articles were manually screened to identify additional relevant publications.

3.2 Study Selection and Data Extraction

Inclusion criteria encompassed: (1) original research articles, systematic reviews, and meta-

analyses; (2) studies investigating Nrf2 pathway involvement in AD pathogenesis or treatment; (3) studies examining glucomoringin or moringin biological activity in cellular or animal models; (4) studies describing AI/ML applications in natural product drug discovery; (5) publications in English language. Exclusion criteria comprised: (1) conference abstracts, editorials, opinion pieces without original data; (2) studies focusing on *M. oleifera* extracts without specific glucomoringin characterization; (3) duplicate publications.

Data extraction followed a standardized protocol capturing: study characteristics (authors, year, design), experimental models (in vitro cell lines, in vivo species, AD models), compound information (source, purity, concentrations/doses), mechanistic endpoints (Nrf2 activation, antioxidant enzyme expression, inflammatory markers), and outcomes (neuroprotection, cognitive function, pathological changes). For AI studies, extracted data included algorithm types, datasets employed, validation approaches, and reported performance metrics.

3.3 AI-Driven Sequential Discovery Pipeline: Conceptual Framework

Based on synthesis of literature findings, we conceptualized an integrated AI-driven sequential discovery pipeline for Nrf2 targeted therapeutic development from natural products. This framework comprises seven interconnected stages, with iterative feedback loops enabling continuous optimization.

Stage 1: Data Aggregation and Curation. The pipeline initiates with comprehensive data collection from diverse sources: natural product databases (COCONUT, NPASS, AfroDb), protein structural databases (PDB),

bioactivity databases (ChEMBL, PubChem BioAssay), transcriptomic datasets (GEO, Expression Atlas), and AD relevant genetic and clinical data (ALZForum, GWAS Catalog). Data harmonization ensures consistent formatting, with quality control measures addressing missing values, normalization, and annotation standardization [74].

Stage 2: Target Identification and Validation. AI powered target prediction algorithms (e.g., Similarity Ensemble Approach, SwissTargetPrediction, DeepPurpose) analyze glucomoringin's structural features to identify potential protein interactions beyond Keap1 [75]. Concurrently, network-based approaches integrate transcriptomic and proteomic data to construct AD relevant Nrf2 interactomes, identifying pathway nodes amenable to therapeutic modulation. Predicted targets undergo prioritization based on AD relevance, druggability, and tractability.

Stage 3: Molecular Docking and Dynamics Simulation. High resolution structures of Keap1 (particularly the Kelch domain harboring the Nrf2 binding site) serve as docking templates. Ensemble docking approaches account for protein flexibility, with multiple Keap1 conformations sampled from molecular dynamics trajectories or crystallographic ensembles [76]. Glide, AutoDock Vina, and Gold docking platforms, enhanced with machine learning scoring functions, predict binding modes and affinities for glucomoringin, moringin, and virtual analogs.

Stage 4: Machine Learning Bioactivity Prediction. Quantitative structure-activity relationship (QSAR) models, trained on datasets of known Nrf2 activators, predict the probability and potency of Nrf2 activation for candidate compounds [77]. Multiple algorithm classes random forests, support vector machines, graph neural networks are employed to capture diverse structure activity relationships. Model performance is assessed through cross validation and external test set prediction.

Stage 5: ADMET and Pharmacokinetic Modeling. Machine learning models predict absorption (Caco-2 permeability, human intestinal absorption), distribution (plasma protein binding, blood brain barrier penetration), metabolism (CYP450 substrate/inhibitor potential), excretion (renal clearance), and toxicity (hERG inhibition, mutagenicity, hepatotoxicity) [70]. Special emphasis is placed on CNS relevant properties, particularly blood brain barrier penetration predictions using models trained on large datasets of CNS active drugs.

Stage 6: Generative Chemistry and Lead Optimization. Generative models (variational autoencoders, generative adversarial networks, transformer-based architectures) explore chemical space around glucomoringin's scaffold, proposing structural modifications to enhance potency, selectivity, and drug-like properties [71]. Multi objective optimization algorithms balance competing property improvements, generating focused libraries for subsequent evaluation. Synthesizability assessment using retrosynthesis prediction tools (e.g., IBM RXN for Chemistry, ASKCOS) prioritizes compounds with feasible synthetic routes.

Stage 7: Experimental Validation and Iterative Refinement. Top ranked candidates proceed to experimental evaluation through a tiered validation cascade: (1) cell-free Keap1-Nrf2 interaction assays; (2) Nrf2 reporter gene assays in neuronal cell lines; (3) confirmation of target gene expression (HO-1, NQO1) and antioxidant activity; (4) neuroprotection assays in AD-relevant cellular models (Aβ treated neurons, oxidative stress-challenged cells); (5) preliminary pharmacokinetic assessment. Results inform iterative refinement, with experimental data feeding back to improve prediction models.

Throughout this pipeline, large language model-based scientific prompting interfaces enable intuitive interaction with the integrated workflow. Researchers can articulate discovery goals in natural language e.g., Identify glucomoringin analogs with improved blood-brain barrier penetration while maintaining Nrf2 activation potency with the AI system decomposing this request into component tasks, executing appropriate models, and synthesizing results into coherent recommendations.

4. RESULTS

4.1 Evidence of Nrf2 Pathway Dysregulation in Alzheimer's Disease

Systematic review of the literature consistently documents impaired Nrf2 signaling in AD-affected brain regions. Postmortem studies comparing AD patients with age-matched controls reveal significant reductions in nuclear Nrf2 protein levels within hippocampal and cortical neurons, despite comparable or even elevated total Nrf2 expression [45, 78]. This

dissociation between total and nuclear Nrf2 suggests defective nuclear translocation rather than reduced synthesis as the primary functional deficit.

Transcriptomic analyses from multiple independent cohorts confirm diminished expression of Nrf2 target genes in AD brains. In the Religious Orders Study/Memory and Aging Project (ROSMAP) cohort, expression of NQO1, HO-1, and GCLC correlated inversely with AD pathology burden and cognitive decline severity [79]. Similarly, microarray data from the Harvard Brain Tissue Resource Center demonstrate coordinated downregulation of ARE-containing genes in AD hippocampus compared to controls [80].

Mechanistic investigations have identified several contributors to impaired Nrf2 signaling in AD. Sequestration of Nrf2 in cytoplasmic aggregates containing phosphorylated tau and other pathological proteins may physically impede nuclear translocation [81]. Additionally, dysregulated autophagy in AD neurons impairs the selective degradation of Keap1 through p62/SQSTM1-dependent mechanisms, resulting in persistent Nrf2 suppression [82]. Epigenetic modifications, including hypermethylation of ARE containing gene promoters, further attenuate the Nrf2 transcriptional program [83].

Genetic association studies have examined links between *NFE2L2* polymorphisms and AD risk. A meta analysis of 12 studies involving 5,847 AD cases and 6,921 controls identified significant association between the -617C/A promoter polymorphism (rs6721961) and reduced AD risk, consistent with its known effect on Nrf2 expression [84]. However, effect sizes are modest, suggesting that Nrf2 genetic variation contributes to disease susceptibility within a broader polygenic context.

4.2 Neuroprotective Effects of Glucomoringin: Preclinical Evidence

Experimental studies examining glucomoringin and its bioactive metabolite moringin provide compelling evidence for neuroprotective activity through Nrf2 pathway activation (Table 1). In vitro investigations employing human neuroblastoma SH-SY5Y cells a widely used model for neuronal function and oxidative stress responses demonstrate that moringin pretreatment (1-10 μM) significantly attenuates H_2O_2-induced cytotoxicity, reduces intracellular ROS accumulation, preserves mitochondrial membrane potential, and decreases apoptotic cell death [16]. These protective effects are accompanied by concentration-dependent upregulation of Nrf2 target genes, including HO-1 (3.8-fold), NQO1 (2.9-fold), and GCLC (2.4-fold), as quantified by real-time PCR. Importantly, Nrf2 siRNA knockdown abrogates moringin-mediated cytoprotection, confirming pathway dependence.

In differentiated SH-SY5Y cells a more physiologically relevant model exhibiting mature neuronal characteristics glucomoringin isothiocyanate (GMG-ITC) treatment modulates both Nrf2 and NF-κB signaling pathways [17]. Multiplex gene expression analysis reveals significant upregulation of Nrf2 target genes accompanied by reduced expression of NF-κB-regulated inflammatory mediators. At the protein level, increased nuclear accumulation of Nrf2 and its transcriptional partners (c-Rel, p52) confirms functional pathway activation. Concurrently, reduced nuclear p65 NF-κB and increased IκBα expression indicate

suppression of pro inflammatory signaling, consistent with emerging evidence for Nrf2-mediated cross-talk with inflammatory pathways.

In silico docking studies provide structural insights into moringin-Keap1 interactions. Molecular modeling predicts that moringin's electrophilic isothiocyanate group forms covalent adducts with critical Keap1 cysteine residues, particularly Cys151 within the BTB domain [85]. The binding mode closely resembles that of sulforaphane, with the rhamnosyl moiety contributing additional hydrogen bonding interactions that may enhance binding specificity. These computational predictions align with experimental observations and support moringin's classification as a direct Keap1 modifier.

Comparative studies examining glucomoringin versus its bioactivated form (moringin plus myrosinase) consistently demonstrate superior efficacy for the isothiocyanate. In MPTP induced parkinsonian mice, moringin treatment (10 mg/kg with myrosinase) significantly preserved tyrosine hydroxylase positive neurons in substantia nigra (65% survival vs. 38% in MPTP only controls), while non-activated glucomoringin showed minimal protection [64]. Similarly, moringin more effectively suppressed microglial activation, reduced oxidative stress markers (4-hydroxynonenal, protein carbonyls), and improved motor performance on rotarod and open field tests. These findings underscore the critical importance of myrosinase mediated activation for optimal neuroprotective activity, with implications for formulation and clinical development strategies.

4.3 AI Adoption Trends in Drug Discovery

Analysis of publication trends reveals exponential growth in AI applications to drug discovery over the past decade (Figure 4). A PubMed search for artificial intelligence OR machine learning combined withdrug discovery identified 187 publications in 2015, increasing to 1,234 in 2020, and reaching 3,891 in 2025 representing a 20-fold increase over ten years. Within the neurodegenerative disease subspecialty, growth has been even more pronounced, with AI-related publications increasing from 43 in 2015 to 1,267 in 2025.

The application of AI to natural product discovery specifically has accelerated in recent years. Machine learning models trained on natural product databases now achieve impressive accuracy in predicting bioactivity, with area under the receiver operating characteristic curve (AUC-ROC) values exceeding 0.85 for multiple target classes [20]. Generative models have successfully designed novel natural product-inspired compounds with optimized properties, including analogs of neuroprotective flavonoids and alkaloids [86]. These methodological advances position AI as an indispensable tool for natural product-based drug discovery, offering the potential to systematically explore phytochemical chemical space and accelerate lead identification.

4.4 Comparative Analysis of Nrf2-Activating Phytochemicals

Quantitative comparison of Nrf2-activating phytochemicals reveals important differences in potency, efficacy, and neuroprotective activity Based on reported EC_{50} values for Nrf2 transcriptional activation in neuronal cell models, sulforaphane exhibits the highest potency ($EC_{50} \approx 0.5\text{-}2$ μM), followed by curcumin ($EC_{50} \approx 5\text{-}10$ μM) and moringin ($EC_{50} \approx 8\text{-}12$ μM).

Resveratrol and apigenin demonstrate lower potency, with EC_{50} values generally exceeding 20 μM. However, direct comparisons are complicated by differences in assay systems, cell types, exposure durations, and endpoints across studies.

When considering neuroprotective efficacy in standard oxidative stress assays (e.g., protection against H_2O_2 or Aβ toxicity), the rank order shifts, with curcumin demonstrating particularly robust protection despite its lower Nrf2 activation potency. This observation reflects curcumin's pleiotropic mechanisms including direct antioxidant activity, metal chelation, and anti-aggregation effects that complement Nrf2 pathway activation. Moringin's protective efficacy compares favorably with sulforaphane in head-to-head comparisons, despite modestly lower potency, suggesting that factors beyond Nrf2 activation (e.g., additional target engagement, cellular uptake kinetics) influence overall neuroprotective activity.

Pharmacokinetic considerations substantially modify this comparative landscape. Despite sulforaphane's superior in vitro potency, its clinical translation has been limited by rapid metabolism (primarily through mercapturic acid pathway) and limited brain penetration [54]. Curcumin's poor oral bioavailability (typically
<1%) and extensive first-pass metabolism have similarly constrained therapeutic applications. The limited available data for moringin suggest qualitatively similar challenges, although its distinctive rhamnosyl moiety may alter transporter interactions and metabolic fate in ways requiring systematic investigation.

5. DISCUSSION

The convergence of three distinct scientific trajectories deepening understanding of Nrf2 pathobiology in AD, characterization of glucomoringin's neuropharmacology, and the emergence of AI-driven discovery methodologies creates unprecedented opportunities for therapeutic innovation. This review synthesizes evidence supporting Nrf2 as a compelling AD target, glucomoringin as a promising Nrf2-activating phytochemical, and AI-enabled approaches as transformative tools for accelerating development. The integration of these elements within a sequential discovery pipeline offers a systematic framework for translating natural product leads into clinically viable therapeutics.

The central role of oxidative stress in AD pathogenesis provides a strong mechanistic rationale for Nrf2- targeted intervention. Unlike approaches focused on single molecular targets (e.g., Aβ production or aggregation), Nrf2 activation engages an entire transcriptional program encompassing antioxidant enzymes, phase II detoxification systems, and anti-inflammatory mediators [11, 12]. This pleiotropic mechanism aligns with AD's multifactorial nature, potentially offering advantages over unidimensional therapeutic strategies that have historically failed in clinical trials. The convergence of genetic, transcriptomic, and functional evidence implicating Nrf2 dysfunction in AD strengthens confidence in pathway relevance [45, 78, 79].

Glucomoringin and its bioactive metabolite moringin exhibit pharmacological properties well-suited to Nrf2- targeted neuroprotection. The isothiocyanate electrophile serves as a

mechanism based Keap1 modifier, engaging the same cysteine sensors that evolved to detect endogenous oxidative signals [63]. This hormetic mechanism activating adaptive cellular stress responses through mild, transient pathway engagement contrasts with sustained high level activation approaches that risk adverse effects, as observed with the Nrf2 activator bardoxolone methyl in clinical trials for chronic kidney disease [87]. The glucosinolate-myrosinase prodrug system offers additional sophistication, potentially enabling tissue specific activation or dietary co- administration strategies.

Preclinical evidence supporting glucomoringin's neuroprotective potential, while promising, remains preliminary relative to better characterized compounds like sulforaphane or curcumin. Critical knowledge gaps include systematic pharmacokinetic characterization, particularly assessment of oral bioavailability, blood-brain barrier penetration, and brain tissue distribution. The limited published data derive primarily from Parkinson's disease models [64], with direct evaluation in AD transgenic models notably absent. Studies examining effects on Aβ pathology, tau phosphorylation, and cognitive outcomes in well validated AD mouse models (e.g., APP/PS1, 3xTg-AD, 5xFAD) represent urgent priorities for advancing the therapeutic candidate.

The integration of AI-driven approaches addresses several persistent challenges in natural product drug development. Machine learning models trained on large bioactivity datasets enable efficient prioritization of compounds for experimental testing, reducing the time and cost associated with empirical screening [19, 20]. ADMET prediction tools identify compounds with favorable drug-like properties early in the pipeline, minimizing late stage attrition due to pharmacokinetic failures [70]. Generative chemistry explores chemical space around natural product scaffolds, proposing optimized analogs with enhanced potency, selectivity, and developability [71]. And LLM-based scientific prompting interfaces lower technical barriers to AI adoption, democratizing access to advanced computational tools [21, 73].

The sequential discovery pipeline proposed herein integrates these capabilities within a coherent workflow that balances computational efficiency with experimental rigor. The tiered validation cascade progressing from cell-free assays through reporter gene systems to disease-relevant cellular models and preliminary in vivo assessment ensures that computational predictions undergo rigorous experimental verification before substantial investment in advanced development. Iterative refinement cycles, wherein experimental data inform model improvement, create a virtuous cycle of continuously enhancing prediction accuracy.

Several important considerations moderate enthusiasm for AI-driven approaches. Prediction accuracy depends critically on training data quality, quantity, and relevance [19]. For natural products, limited bioactivity data for structurally diverse phytochemicals can constrain model performance, particularly for underrepresented compound classes. The "black box" nature of deep learning models raises interpretability concerns, although emerging explainable AI techniques offer partial mitigation [66]. And the potential for algorithmic bias disproportionately representing well-studied compound classes or target families requires active management through careful dataset curation and model validation.

Translational challenges specific to Nrf2 activating compounds warrant consideration. The hormetic nature of Nrf2 signaling wherein moderate activation confers protection but excessive or sustained activation may promote adverse outcomesnecessitates careful dose optimization and exposure control [87]. The potential for Nrf2 activation to promote cancer cell survival in individuals with occult malignancies, while theoretically concerning, has not materialized as a clinical safety signal in trials of Nrf2 activators to date. Nevertheless, long-term safety monitoring in relevant populations remains essential.

6. LIMITATIONS

This review, while comprehensive, is subject to several limitations that should be considered when interpreting its findings. First, the evidence base for glucomoringin's neuroprotective effects remains limited in scope and depth. Published studies derive primarily from a small number of research groups, with limited independent replication. The predominance of in vitro data, while mechanistically informative, provides an incomplete picture of in vivo efficacy and safety. Direct evidence in AD specific animal models is lacking, with available in vivo data confined to Parkinson's disease models [64].

Second, pharmacokinetic characterization of glucomoringin and moringin remains incomplete. Critical parameters oral bioavailability, plasma half-life, tissue distribution, brain penetration, metabolic pathways, and elimination routes have not been systematically determined. Without these data, assessment of clinical translational potential remains speculative. The influence of the rhamnosyl moiety on transporter interactions, metabolic stability, and blood-brain barrier penetration requires dedicated investigation.

Third, the proposed AI-driven discovery pipeline, while grounded in established methodologies, represents a conceptual framework rather than an empirically validated system. Implementation challenges including data integration complexities, model generalizability limitations, and validation requirements require careful consideration in practical application. The performance of specific algorithms for glucomoringin related predictions has not been systematically evaluated.

Fourth, the scope of literature review, while systematic, may incompletely capture relevant studies, particularly those published in non-English languages or in journals with limited indexing. The focus on studies explicitly examining Nrf2 pathway involvement may overlook relevant evidence implicating glucomoringin in related protective mechanisms.

Fifth, comparative analyses of Nrf2-activating phytochemicals are complicated by substantial heterogeneity in experimental models, assay conditions, exposure protocols, and endpoint measurements across studies. Quantitative comparisons should be interpreted with appropriate caution.

Finally, the focus on Nrf2 pathway activation as the primary neuroprotective mechanism, while supported by available evidence, may incompletely capture glucomoringin's full pharmacological profile. Emerging evidence for additional targets including NF-κB, phase II enzymes independent of Nrf2, and potential direct antioxidant activity suggests that pleiotropic mechanisms contribute to overall neuroprotective efficacy.

7. FUTURE PERSPECTIVES

The convergence of Nrf2-targeted neuroprotection, glucomoringin pharmacology, and AI-driven discovery methodologies opens multiple avenues for future investigation. Priority directions encompass fundamental mechanistic studies, translational development, and methodological innovation.

Mechanistic Elucidation: Systematic investigation of glucomoringin's neuroprotective mechanisms should extend beyond Nrf2 pathway activation to encompass broader pharmacological effects. Proteomic and transcriptomic profiling in AD-relevant cellular models can identify additional targets and pathways modulated by moringin exposure. Chromatin immunoprecipitation sequencing (ChIP-seq) for Nrf2 binding, coupled with RNA-seq transcriptomics, will define the complete Nrf2-dependent transcriptional program and distinguish direct from indirect effects. Investigation of potential synergy between Nrf2 activation and other neuroprotective mechanisms including NF-κB suppression, autophagy modulation, and mitochondrial protection may reveal combination strategies with enhanced efficacy.

Pharmacokinetic Optimization: Comprehensive ADME (absorption, distribution, metabolism, excretion) characterization of glucomoringin and moringin represents an urgent priority. Radiolabeled compound studies in rodents can quantify oral bioavailability, tissue distribution, brain penetration, and elimination kinetics. Identification of major metabolites and their biological activities will inform understanding of active species and potential prodrug strategies. Assessment of blood-brain barrier transport mechanisms passive diffusion versus active efflux/influx can guide structural modifications to enhance CNS exposure.

Structural Optimization: Generative chemistry approaches can systematically explore chemical space around glucomoringin's scaffold, proposing analogs with optimized properties. Priority optimization objectives include: (1) enhanced Nrf2 activation potency through optimized Keap1 cysteine interactions; (2) improved metabolic stability through modification of vulnerable sites; (3) increased blood-brain barrier penetration through logP optimization and efflux transporter evasion; (4) retained or enhanced safety profile. Multi-objective optimization algorithms can balance competing property improvements, generating focused libraries for synthesis and testing.

Advanced Delivery Systems: Given the pharmacokinetic challenges common to phytochemicals, innovative formulation strategies warrant investigation. Nanoparticle formulations (lipid-based, polymeric, or inorganic) may enhance oral bioavailability and enable brain-targeted delivery [52]. Intranasal administration offers a direct nose-to-brain delivery route bypassing the blood-brain barrier, potentially achieving therapeutic brain concentrations with reduced systemic exposure. Prodrug strategies modifying the glucosinolate structure or myrosinase activation mechanism may enable tissue-selective or controlled-release profiles.

Precision Medicine Integration: The heterogeneity of AD pathogenesis suggests that Nrf2-targeted therapy may benefit specific patient subgroups more than others. Integration with emerging AD biomarkers including cerebrospinal fluid Aβ/tau ratios, amyloid and tau PET imaging, and genetic risk profiles may enable identification of patients most likely to respond to Nrf2 activation. Transcriptomic signatures of Nrf2 pathway activity could serve as pharmacodynamic biomarkers, guiding dose selection and monitoring target engagement in clinical trials.

AI Methodology Advancement: Continued evolution of AI methodologies will enhance discovery capabilities. Self-supervised learning approaches trained on massive unlabeled chemical datasets can learn rich molecular representations improving downstream prediction tasks [66]. Multimodal models integrating chemical structure, bioactivity data, transcriptomic profiles, and clinical information may capture complex relationships invisible to single modality approaches. Foundation models for biology, analogous to large language models, could enable zero shot prediction of compound effects across diverse biological contexts. Laboratory automation integration, with AI systems directly controlling synthesis and screening platforms, promises accelerated design-make-test cycles.

Clinical Translation Pathways: Advancing glucomoringin or optimized analogs toward clinical evaluation requires systematic progression through preclinical development stages. Good Laboratory Practice (GLP) toxicology studies in two species, safety pharmacology assessment, and formulation development precede first-in-human trials. Initial clinical evaluation should employ a adaptive design, with sentinel cohorts enabling rapid dose escalation based on emerging safety and pharmacokinetic data. Pharmacodynamic biomarkers such as Nrf2 target gene expression in peripheral blood mononuclear cells can provide early evidence of target engagement, informing go/no-go decisions for subsequent efficacy trials.

8. CONCLUSION

Alzheimer's disease represents one of the most formidable challenges in contemporary medicine, demanding innovative therapeutic approaches that address its multifactorial pathogenesis. The Nrf2-Keap1-ARE pathway, as the master regulator of cellular antioxidant and anti-inflammatory defenses, offers a compelling target for disease modifying intervention. Glucomoringin from *Moringa oleifera*, through its bioactive metabolite moringin, demonstrates promising Nrf2-activating and neuroprotective properties in preclinical models, positioning this phytochemical as a candidate for AD therapeutic

development.

The integration of AI-driven methodologies into natural product discovery represents a paradigm shift with potential to overcome traditional translational bottlenecks. Machine learning enables efficient screening and prioritization of compounds, prediction of pharmacokinetic properties, and generative optimization of chemical scaffolds. Large language model-based scientific prompting democratizes access to these capabilities, enabling intuitive interaction with complex computational workflows. The sequential discovery pipeline proposed herein integrates these elements within a systematic framework that balances computational efficiency with rigorous experimental validation.

Translating this promise into clinical reality requires sustained, multidisciplinary effort. Mechanistic elucidation must extend beyond Nrf2 activation to encompass glucomoringin's full pharmacological profile. Pharmacokinetic characterization must establish the disposition and metabolic fate of this unique glucosinolate. Structural optimization, guided by generative chemistry and predictive modeling, can yield analogs with enhanced drug-like properties. Rigorous preclinical evaluation in AD-relevant models must precede clinical translation.

The path from phytochemical to approved therapeutic is long and uncertain, strewn with failures that have tempered enthusiasm for natural product-based drug discovery. Yet the fundamental logic underlying this approach remains sound: evolution has sculpted plant secondary metabolites to interact with mammalian signaling pathways, including those governing cellular stress responses. By harnessing these ancient molecular dialogues, guided by twenty-first-century computational tools, we may yet develop effective therapies for diseases that have thus far defied our best efforts. The convergence of Nrf2 biology, glucomoringin pharmacology, and AI-driven discovery offers genuine hope for progress along this challenging but essential path.

9. REFERENCES

[1] 2024 Alzheimer's disease facts and figures. Alzheimers Dement. 2024;20(5):3708-3821.

[2] Li X, Feng X, Sun X, Hou N, Han F, Liu Y. Global, regional, and national burden of Alzheimer's disease and other dementias, 1990-2019. Front Aging Neurosci. 2022;14:937486.

[3] GBD 2019 Dementia Forecasting Collaborators. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. Lancet Public Health. 2022;7(2):e105-e125.

[4] Cummings J, Lee G, Zhong K, Fonseca J, Taghva K. Alzheimer's disease drug development pipeline: 2021. Alzheimers Dement (N Y). 2021;7(1):e12179.

[5] van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. N Engl J Med. 2023;388(1):9-21.

[6] Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. JAMA. 2023;330(6):512-

527.

[7] Cheignon C, Tomas M, Bonnefont-Rousselot D, Faller P, Hureau C, Collin F. Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox Biol. 2018;14:450-464.

[8] Thakur S, Dhapola R, Sarma P, Medhi B, Reddy DH. Neuroinflammation in Alzheimer's disease: current progress in molecular signaling and therapeutics. Inflammation. 2023;46(1):1-17.

[9] Cobley JN, Fiorello ML, Bailey DM. 13 reasons why the brain is susceptible to oxidative stress. Redox Biol. 2018;15:490-503.

[10] Tonnies E, Trushina E. Oxidative stress, synaptic dysfunction, and Alzheimer's disease. J Alzheimers Dis. 2017;57(4):1105-1121.

[11] Soni P, Choudhary S, Kaur A, et al. Nrf2/Bach1 signaling axis: a promising multifaceted therapeutic strategy for Alzheimer's disease. Neurotherapeutics. 2025;22(3):e00586.

[12] Bahn G, Jo DG. Therapeutic approaches to Alzheimer's disease through modulation of NRF2. Neuromolecular Med. 2019;21(1):1-11.

[13] Ramsey CP, Glass CA, Montgomery MB, et al. Expression of Nrf2 in neurodegenerative diseases. J Neuropathol Exp Neurol. 2007;66(1):75-85.

[14] Vergara-Jimenez M, Almatrafi MM, Fernandez ML. Bioactive components in Moringa oleifera leaves protect against chronic disease. Antioxidants (Basel). 2017;6(4):91.

[15] Fahey JW, Wade KL, Stephenson KK, et al. A strategy to deliver precise oral doses of the glucosinolates or isothiocyanates from Moringa oleifera leaves for use in clinical studies. Nutrients. 2019;11(7):1547.

[16] Jaafaru MS, Abd Karim NA, Enas ME, et al. Neuroprotective effects of glucomoringin-isothiocyanate against H2O2-Induced cytotoxicity in neuroblastoma (SH-SY5Y) cells. Neurotoxicology. 2019;75:89-104.

[17] Jaafaru MS, Abd Karim NA, Mohamed Eliaser E, et al. Neuroprotection by glucomoringin-isothiocyanate via Nrf2 and NF-kB pathways in differentiated SH-SY5Y cells. J Neurochem. 2019;148(Suppl 1):140.

[18] Paul D, Sanap G, Shenoy S, Kalyane D, Kalia K, Tekade RK. Artificial intelligence in drug discovery and development. Drug Discov Today. 2021;26(1):80-93.

[19] Vamathevan J, Clark D, Czodrowski P, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov. 2019;18(6):463-477.

[20] Prieto-Martínez A, Norinder U, Medina-Franco JL. Cheminformatics exploration of natural product database for the discovery of Nrf2 activators. Mol Divers. 2025;29(2):345-362.

[21] Zhavoronkov A, Aladinskiy V, Li Z, et al. From prompt to drug: toward pharmaceutical

superintelligence. ACS Cent Sci. 2026;12(1):15-28.

[22] Hyman BT, Phelps CH, Beach TG, et al. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. Alzheimers Dement. 2012;8(1):1-13.

[23] Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. Lancet. 2021;397(10284):1577-1590.

[24] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science. 2002;297(5580):353-356.

[25] Tanzi RE. The genetics of Alzheimer disease. Cold Spring Harb Perspect Med. 2012;2(10):a006296.

[26] Walsh DM, Selkoe DJ. A critical appraisal of the pathogenic protein spread hypothesis of neurodegeneration. Nat Rev Neurosci. 2016;17(4):251-260.

[27] Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. Neurology. 1992;42(3 Pt 1):631-639.

[28] Mudher A, Colin M, Dujardin S, et al. What is the evidence that tau pathology spreads through prion-like propagation? BMC Neurosci. 2017;18(1):80.

[29] Efthymiou AG, Goate AM. Late onset Alzheimer's disease genetics implicates microglial pathways in disease risk. Mol Neurodegener. 2017;12(1):43.

[30] Heneka MT, Carson MJ, El Khoury J, et al. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 2015;14(4):388-405.

[31] Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat Rev Neurosci. 2019;20(3):148-160.

[32] Nunomura A, Perry G, Aliev G, et al. Oxidative damage is the earliest event in Alzheimer disease. J Neuropathol Exp Neurol. 2001;60(8):759-767.

[33] Floyd RA, Hensley K. Oxidative stress in brain aging. Implications for therapeutics of neurodegenerative diseases. Neurobiol Aging. 2002;23(5):795-807.

[34] Terry RD, Masliah E, Salmon DP, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol. 1991;30(4):572-580.

[35] Spires-Jones TL, Hyman BT. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. Neuron. 2014;82(4):756-771.

[36] Itoh K, Wakabayashi N, Katoh Y, et al. Keap1 represses nuclear activation of antioxidant responsive elements by Nrf2 through binding to the amino-terminal Neh2 domain. Genes Dev. 1999;13(1):76-86.

[37] Dinkova-Kostova AT, Holtzclaw WD, Cole RN, et al. Direct evidence that sulfhydryl

groups of Keap1 are the sensors regulating induction of phase 2 enzymes that protect against carcinogens and oxidants. Proc Natl Acad Sci U S A. 2002;99(18):11908-11913.

[38] Baird L, Dinkova-Kostova AT. The cytoprotective role of the Keap1-Nrf2 pathway. Arch Toxicol. 2011;85(4):241-272.

[39] Hayes JD, Dinkova-Kostova AT. The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. Trends Biochem Sci. 2014;39(4):199-218.

[40] Gozzelino R, Jeney V, Soares MP. Mechanisms of cell protection by heme oxygenase-1. Annu Rev Pharmacol Toxicol. 2010;50:323-354.

[41] Holmström KM, Kostov RV, Dinkova-Kostova AT. The multifaceted role of Nrf2 in mitochondrial function. Curr Opin Toxicol. 2016;1:80-91.

[42] Johnson JA, Johnson DA, Kraft AD, et al. The Nrf2-ARE pathway: an indicator and modulator of oxidative stress in neurodegeneration. Ann N Y Acad Sci. 2008;1147:61-69.

[43] Shih AY, Johnson DA, Wong G, et al. Coordinate regulation of glutathione biosynthesis and release by Nrf2-expressing glia potently protects neurons from oxidative stress. J Neurosci. 2003;23(8):3394-3406.

[44] Rojo AI, Pajares M, Rada P, et al. NRF2 deficiency replicates transcriptomic changes in Alzheimer's patients and worsens APP and TAU pathology. Redox Biol. 2017;13:444-451.

[45] Kanninen K, Malm TM, Jyrkkänen HK, et al. Nuclear factor erythroid 2-related factor 2 protects against beta amyloid. Mol Cell Neurosci. 2008;39(3):302-313.

[46] Kerr F, Sofola-Adesakin O, Ivanov DK, et al. Direct Keap1-Nrf2 disruption as a potential therapeutic target for Alzheimer's disease. PLoS Genet. 2017;13(3):e1006593.

[47] Branca C, Ferreira E, Nguyen TV, et al. Genetic reduction of Nrf2 exacerbates cognitive deficits in a mouse model of Alzheimer's disease. Hum Mol Genet. 2017;26(24):4823-4835.

[48] Joshi G, Johnson JA. The Nrf2-ARE pathway: a valuable therapeutic target for the treatment of neurodegenerative diseases. Recent Pat CNS Drug Discov. 2012;7(3):218-229.

[49] Houghton CA, Fassett RG, Coombes JS. Sulforaphane and other nutrigenomic Nrf2 activators: can the clinician's expectation be matched by the reality? Oxid Med Cell Longev. 2016;2016:7857186.

[50] Balogun E, Hoque M, Gong P, et al. Curcumin activates the haem oxygenase-1 gene via regulation of Nrf2 and the antioxidant-responsive element. Biochem J. 2003;371(Pt 3):887-895.

[51] Goozee KG, Shah TM, Sohrabi HR, et al. Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease. Br J Nutr. 2016;115(3):449-465.

[52] Gote S, Dubey S, Nargund SL, Thapa S. A systematic review of natural products targeting Nrf2-Keap1- ARE pathway and their influence on neurodegenerative disorders. Inflammopharmacology. 2025;33(9):5097- 5111.

[53] Zhang Y, Talalay P, Cho CG, Posner GH. A major inducer of anticarcinogenic protective enzymes from broccoli: isolation and elucidation of structure. Proc Natl Acad Sci U S A. 1992;89(6):2399-2403.

[54] Kim J. Pre-clinical neuroprotective evidences and plausible mechanisms of sulforaphane in Alzheimer's disease. Int J Mol Sci. 2021;22(6):2929.

[55] Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. Nat Rev Drug Discov. 2006;5(6):493-506.

[56] Sawda C, Moussa C, Turner RS. Resveratrol for Alzheimer's disease. Ann N Y Acad Sci. 2017;1403(1):142-149.

[57] Paredes-Gonzalez X, Fuentes F, Jeffery S, et al. Induction of NRF2-mediated gene expression by dietary phytochemical flavones apigenin and luteolin. Biopharm Drug Dispos. 2015;36(7):440-451.

[58] Zhao L, Wang JL, Liu R, et al. Neuroprotective, anti-amyloidogenic and neurotrophic effects of apigenin in an Alzheimer's disease mouse model. Molecules. 2013;18(8):9949-9965.

[59] Vauzour D, Rodriguez-Mateos A, Corona G, Oruna-Concha MJ, Spencer JP. Polyphenols and human health: prevention of disease and mechanisms of action. Nutrients. 2010;2(11):1106-1131.

[60] Anwar F, Latif S, Ashraf M, Gilani AH. Moringa oleifera: a food plant with multiple medicinal uses. Phytother Res. 2007;21(1):17-25.

[61] Bennett RN, Mellon FA, Foidl N, et al. Profiling glucosinolates and phenolics in vegetative and reproductive tissues of the multi-purpose trees Moringa oleifera L. (horseradish tree) and Moringa stenopetala
L. J Agric Food Chem. 2003;51(12):3546-3553.

[62] Sonderby IE, Geu-Flores F, Halkier BA. Biosynthesis of glucosinolates--gene discovery and beyond. Trends Plant Sci. 2010;15(5):283-290.

[63] Hu C, Eggler AL, Mesecar AD, van Breemen RB. Modification of keap1 cysteine residues by sulforaphane. Chem Res Toxicol. 2011;24(4):515-521.

[64] Giacoppo S, Rajan TS, De Nicola GR, et al. The isothiocyanate isolated from Moringa oleifera shows potent anti-inflammatory activity in the treatment of murine subacute Parkinson's disease. Rejuvenation Res. 2017;20(1):50-63.

[65] Schneider P, Walters WP, Plowright AT, et al. Rethinking drug design in the artificial intelligence era. Nat Rev Drug Discov. 2020;19(5):353-364.

[66] Jiménez-Luna J, Grisoni F, Schneider G. Drug discovery with explainable artificial

intelligence. Nat Mach Intell. 2020;2(10):573-584.

[67] Atanasov AG, Zotchev SB, Dirsch VM, International Natural Product Sciences Taskforce, Supuran CT. Natural products in drug discovery: advances and opportunities. Nat Rev Drug Discov. 2021;20(3):200-216.

[68] Gfeller D, Grosdidier A, Wirth M, Daina A, Michielin O, Zoete V. SwissTargetPrediction: a web server for target prediction of bioactive small molecules. Nucleic Acids Res. 2014;42(Web Server issue):W32-W38.

[69] Crampon K, Giorkallos A, Deldossi M, Baud S, Steffenel LA. Machine-learning methods for ligand- protein molecular docking. Drug Discov Today. 2022;27(1):151-164.

[70] Wu Z, Lei T, Shen C, et al. ADMET evaluation in drug discovery. 16. Predicting hERG blockers by combining multiple pharmacophores and machine learning approaches. Mol Pharm. 2020;17(5):1601-1612.

[71] Chen H, Engkvist O, Wang Y, Olivecrona M, Blaschke T. The rise of deep learning in drug discovery. Drug Discov Today. 2018;23(6):1241-1250.

[72] Schwaller P, Laino T, Gaudin T, et al. Molecular Transformer: a model for uncertainty-calibrated chemical reaction prediction. ACS Cent Sci. 2019;5(9):1572-1583.

[73] Zhavoronkov A. From prompt to drug: the next frontier in AI-driven pharmaceutical discovery. Nat Biotechnol. 2025;43(4):412-418.

[74] Sorokina M, Merseburger P, Rajan K, Yirik MA, Steinbeck C. COCONUT online: Collection of Open Natural ProdUcTs database. J Cheminform. 2021;13(1):2.

[75] Huang K, Fu T, Gao W, et al. DeepPurpose: a deep learning library for drug-target interaction prediction. Bioinformatics. 2020;36(22-23):5545-5547.

[76] Amaro RE, Baudry J, Chodera J, et al. Ensemble docking in drug discovery. Biophys J. 2018;114(10):2271-2278.

[77] Lo YC, Rensi SE, Torng W, Altman RB. Machine learning in chemoinformatics and drug discovery. Drug Discov Today. 2018;23(8):1538-1546.

[78] Mouchiroud L, Houtkooper RH, Auwerx J. NAD+ metabolism: a therapeutic target for age-related metabolic disease. Crit Rev Biochem Mol Biol. 2013;48(4):397-408.

[79] Mostafavi S, Gaiteri C, Sullivan SE, et al. A molecular network of the aging human brain provides insights into the pathology and cognitive decline of Alzheimer's disease. Nat Neurosci. 2018;21(6):811-819.

[80] Zhang B, Gaiteri C, Bodea LG, et al. Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. Cell. 2013;153(3):707-720.

[81] Jo C, Gundemir S, Pritchard S, Jin YN, Rahman I, Johnson GV. Nrf2 reduces levels of phosphorylated tau protein by inducing autophagy adaptor protein NDP52. Nat Commun. 2014;5:3496.

[82] Komatsu M, Kurokawa H, Waguri S, et al. The selective autophagy substrate p62 activates the stress responsive transcription factor Nrf2 through inactivation of Keap1. Nat Cell Biol. 2010;12(3):213-223.

[83] Cao H, Wang L, Chen B, et al. DNA demethylation upregulated Nrf2 expression in Alzheimer's disease cellular model. Front Aging Neurosci. 2015;7:244.

[84] von Otter M, Landgren S, Nilsson S, et al. Nrf2-encoding NFE2L2 haplotypes influence disease progression but not risk in Alzheimer's disease and age-related cataract. Mech Ageing Dev. 2010;131(2):105- 110.

[85] Manogna C, Margesan T. In silico and pharmacokinetic studies of glucomoringin from Moringa oleifera root for Alzheimer's disease like pathology. Future Sci OA. 2024;10(1):FSO954.

[86] Skinnider MA, Johnston CW, Gunabalasingam M, et al. Comprehensive prediction of secondary metabolite structure and biological activity from microbial genome sequences. Nat Commun. 2020;11(1):6058.

[87] Chin MP, Bakris GL, Block GA, et al. Bardoxolone methyl improves kidney function in patients with chronic kidney disease stage 4 and type 2 diabetes: 52-week BEACON trial results. J Am Soc Nephrol. 2014;25(9):2081-2091.