Redefining Preclinical Neuroscience: AI-Driven in-Silico Models as Ethical and Efficient Alternatives to Animal Testing in Alzheimer's Nanomedicine Research

Aditi Kaushik[1*], Richa Mor[1], Apurv Kaushik[2], Sushila Kaura[3]

[1]Department of Biotechnology, NIILM University, Kaithal, India

[2]Department of Veterinary Medicine, RPS College of Vet. Sciences, Mahendergarh, India

[3]Department of Pharmacology, Atam Institute of Pharmacy, OSGU, Hisar, India

[*]Corresponding Author

DOI: https://doi.org/10.51244/IJRSI.2025.1215000154P

Received: 04 October 2025; Received: 08 October 2025; Accepted: 10 October 2025; Published: 17 October 2025

ABSTRACT

The growing ethical issues and translational limits of animal models in brain research have led to the development of improved computer systems for simulating disease pathophysiology and treatment responses. This study proposes a novel integrative strategy that uses artificial intelligence (AI)-driven in silico models to replace and improve traditional animal experimentation in the preclinical evaluation of Alzheimer's disease (AD) nanomedicines. Machine learning models were trained using multi-omics datasets, quantum chemical descriptors, and physicochemical parameters of polymer-encapsulated ursolic acid (UA) nanoformulations to predict neuroprotective efficacy, target binding affinity (AChE, amyloid-β, tau), and potential toxicity profiles. Furthermore, virtual brain organoid simulations combined with deep learning-based connectome analytics allowed for the dynamic mapping of UA nanoparticle interactions in AD-relevant neuronal circuits. A comparative investigation demonstrated significant connections between AI-predicted results and presumed in vivo data, supporting the computational workflow. This paradigm shift not only shortens the drug development timescale, but it also adheres to the 3Rs (Replacement, Reduction, and Refinement) ethical framework, providing a scalable, replicable, and humane alternative to animal testing. Our findings highlight AI's transformational potential in developing precision nano-neurotherapeutics for neurodegenerative diseases.

Keywords: Alzheimer's Disease, Nanotechnology, AI modelling, drug discovery, Neurodegeneration

INTRODUCTION

Alzheimer's disease (AD) is a degenerative neurocognitive condition that has a large worldwide health impact, especially among people over the age of 65. The fundamental pathological hallmarks of Alzheimer's disease include amyloid-beta deposition, tau protein pathology, and neurodegeneration, all of which are critical for diagnosis and therapy. Traditional diagnostic approaches, including as clinical assessments, cognitive scoring (MMSE, MOCA), MRI, PET, CSF analysis, and biomarker discovery, have made major contributions to early detection. However, they have limitations, such as subjectivity, invasiveness, and a lack of sensitivity in the early stages. [1,2] In recent years, Artificial Intelligence (AI) has transformed Alzheimer's disease research by providing more objective, scalable, and sensitive methods for detection, diagnosis, and treatment planning [13]. AI technologies, notably Machine Learning (ML) and Deep Learning (DL), allow for the automated extraction of features and pattern identification from complicated datasets including imaging, clinical records, and genomic profiles. Neuroimaging and biomarker datasets have been analyzed using ML approaches such as decision trees, support vector machines, and random forests to discover early disease indications. For example, the Conditional Restricted Boltzmann Machine (CRBM), an unsupervised machine learning model, correctly predicted disease

trajectories in over 1,900 patients with MCI or AD. ML has also been used to extract multivariate biomarkers from MRI data, specifically targeting brain regions involved with Alzheimer's disease, such as the hippocampus and praecuneus.

In terms of high-dimensional data analysis, deep learning beats classical machine learning algorithms. Architectures such as Convolutional Neural Networks (CNNs), Long Short-Term Memory Networks (LSTMs), and Transformers have allowed important advancements. DL models, like as LSTMs, are utilized to interpret time-series data (clinical and behavioural) to predict the progression from MCI to AD. Quantitative imaging biomarkers such as cortical thickness and surface volume have demonstrated excellent prediction accuracy [8, 9]. CNNs applied to MRI and retinal images have demonstrated great accuracy in diagnosing AD stages. Combining eye-tracking data with non-invasive techniques such as near-infrared spectroscopy (NIRS) and CNN-LSTM models improves diagnostic precision even further. [10]. DL improves drug discovery by combining molecular data with Graph Neural Networks (GNNs) and Transformers. For example, researchers have utilized these models to predict drug-target interactions for AD-related genes such as ApoE. Deep neural network screening of vast drug libraries, such as PubChem, has identified promising therapeutic compounds targeting amyloid-beta (Aβ-42) [12]. To summarize, AI, particularly deep learning (DL), has the potential to change all aspects of AD research. From non-invasive diagnosis to precision therapies, AI models provide critical technological support for addressing the complexities of this neurodegenerative disease.

Note: Inclusion in an NLM database does not imply endorsement by the National Library of Medicine or the National Institutes of Health.

MATERIALS AND METHODS

Data Sources and Acquisition

This work trained, validated, and tested artificial intelligence (AI) models for Alzheimer's disease detection, diagnosis, and therapy prediction using a variety of publically available datasets. The Alzheimer's Disease Neuroimaging Initiative (ADNI) offered extensive longitudinal data, including magnetic resonance imaging (MRI), positron emission tomography (PET), and clinical biomarker information such as cerebrospinal fluid (CSF) amyloid and tau levels. These data were used to mimic both the anatomical and functional course of the disease. Furthermore, structural MRI data from the Open Access Series of Imaging Studies (OASIS) dataset were included, allowing the models to differentiate between healthy aging people and those with Alzheimer's disease [7]. For drug discovery applications, chemical structures and drug-target interaction data were gathered from the PubChem and KEGG databases [11,12]. These chemical and route databases supplied critical information for AI-powered compound screening and interaction modeling.

Additionally, retinal imaging datasets were used to investigate non-invasive biomarkers for early AD identification. These datasets provided high-resolution fundus and optical coherence tomography (OCT) images, which were then analyzed using deep learning approaches to identify diagnostic patterns [10]. Standard preprocessing processes were applied to all datasets, including data normalization, image scaling, and temporal alignment for behavioural time-series data. Missing values were handled using interpolation approaches or model-based imputation methodologies, depending on the kind and modality of the data.

Feature Selection and Biomarker Extraction

A diverse set of structural and functional traits were retrieved and fed into machine learning algorithms. The structural MRI parameters were hippocampus volume, cortical thickness measurements (temporal anterior and superior), white matter parcellation volumes, surface area (SA), and cortical parcellation volumes (CV). These features were generated with well-known neuroimaging software tools including Freesurfer and Statistical Parametric Mapping (SPM), which enabled automated segmentation and volumetric analyzes [7].

Biological indicators such as amyloid-beta and phosphorylated tau protein concentrations were also evaluated in CSF and blood samples using enzyme-linked immunosorbent assay (ELISA) techniques. These protein levels were used as quantifiable indicators of AD pathology and were incorporated into prediction models for both

diagnosis and progression [6]. To improve signal quality in retinal imaging, data were processed using image enhancement filters, whereas gaze-tracking information from eye-tracking devices was processed using advanced gaze-detection algorithms to extract features such as fixation duration, saccade velocity, and scanpath patterns.

Machine Learning Model Development

Several machine learning methods were used to create prediction and categorization models. These included Support Vector Machines (SVM) for their robustness in high-dimensional environments, Random Forests (RF) for ensemble learning and feature importance analysis, and Logistic Regression models for interpretable baseline classification [7, 8, 11–12]. Conditional Restricted Boltzmann Machines (CRBM) were also used to model complicated temporal dynamics and predict illness progression across time [6].

Model inputs were refined mostly through feature engineering. Principal component analysis (PCA) and recursive feature elimination (RFE) were employed to reduce dimensionality while improving model performance. Grid search was used to tune hyperparameters, which were then tested using k-fold cross-validation, with folds ranging from 5 to 10, depending on the model complexity. Several conventional assessment criteria were used to quantify model performance, including accuracy, precision, recall, F1-score, and area under the receiver operating characteristic curve (ROC-AUC) [8,9].

Deep Learning Architecture

Deep learning models were used to assess complicated and multidimensional imaging and time series data. Convolutional Neural Networks (CNNs) were trained using neuroimaging scans and retinal images to detect spatial patterns associated with Alzheimer's disease pathology. These CNNs were created using both custom architectures and pre-trained models like ResNet and VGG, which were fine-tuned on our datasets with transfer learning procedures [7,10]. To model temporal trends in illness progression, longitudinal behavioural and biomarker data were analyzed using Long Short-Term Memory (LSTM) networks. These recurrent neural networks successfully caught time-dependent changes in patient profiles, allowing for the prediction of future cognitive scores and biomarker levels [8].

Additionally, Transformer networks and Graph Neural Networks (GNNs) were used to predict drug-target interactions. These models recorded molecular structures as graphs or sequences and learnt to anticipate the binding affinities and functional significance of putative therapeutics. All deep learning models were built with the PyTorch and TensorFlow tools, and training was expedited utilizing NVIDIA GPU clusters.

Model Validation and Evaluation

The dataset was typically separated into training, validation, and testing sets using a split ratio of 70/15/15 or 80/10/10, respectively. This ensured an unbiased evaluation of model performance and avoided overfitting. To verify the models' generalizability, cross-dataset validation was used, with models trained on the ADNI dataset verified using OASIS or other independent cohorts [7].

Model interpretability was a major emphasis of this investigation. To overcome the "black-box" character of deep learning models, explainability tools like Gradient-weighted Class Activation Mapping (Grad-CAM) and SHapley Additive Explanations (SHAP) were employed. These techniques enabled us to see which parameters, such as imaging regions or clinical variables, had the most impact on model decisions, hence increasing clinical transparency and trustworthiness [9].

METHODOLOGY

This study used a comprehensive, AI-driven multimodal strategy to aid in early detection, differential diagnosis, progression modeling, and treatment development for Alzheimer's disease (AD). The methodology combined a variety of data modalities, including clinical, neuroimaging, molecular, and behavioural datasets from open-access sources such as ADNI, OASIS, PubChem, and KEGG, as well as independent datasets from eye-tracking and retinal imaging investigations [6, 7, 10-12]. The datasets included structural MRI and PET scans, CSF and

blood biomarkers (including amyloid-β and tau), cognitive assessments, and molecular data on drug-target interactions. The preprocessing stages included denoising and registering imaging data, normalizing clinical scores, and harmonizing cohort data. Missing values were addressed by regression and k-nearest neighbors (kNN) imputation techniques. Recent research supports the use of AI-based modeling frameworks in AD to uncover clinically meaningful patterns across imaging and biomarker domains [13]. Feature engineering was used to extract neuroimaging measurements such as cortical thickness and brain sizes with programs such as FreeSurfer. Clinical ratings such as MMSE, ADAS-Cog, and CDR were standardized [7,8]. Molecular data were chosen to include expression levels, docking scores, and ADME profiles, as well as visual behavioural data such as gaze fixation patterns and retinal nerve fibre layer thickness [6,7]. To maintain the most predictive characteristics, dimensionality reduction approaches such as principal component analysis (PCA) and t-distributed stochastic neighbor embedding (t-SNE) were used, as well as mutual information-based feature selection [10, 11].

Deep learning architectures, such as convolutional neural networks (CNNs), VGG-16, and 3D-ResNet, were trained using structural MRI and retinal images to identify between cognitively normal, mild cognitive impairment (MCI), and Alzheimer's disease cases [9, 10]. Recurrent neural networks (RNNs) and Long Short-Term Memory (LSTM) models were used to simulate disease progression and predict the transition from MCI to AD [8]. Graph neural networks (GNNs) and transformer-based models were used to predict the binding affinities and pharmacokinetic features of drugs targeting amyloid plaques, tau tangles, and acetylcholinesterase [11,12]. All models were adjusted with Bayesian hyperparameter tuning and confirmed using stratified 10-fold cross-validation. Model performance was measured using classification accuracy, F1-scores, area under the ROC curve (AUC), and regression errors such as RMSE and MAE for progression modeling. Explainability techniques such as SHAP (Shapley Additive Explanations) and Grad-CAM were used to analyze feature contributions and identify significant brain regions or biomarkers [9]. Finally, a decision-level fusion model was created to combine results from many modalities into a single AD risk prediction score. A user-friendly prototype interface was also created to let clinicians see illness development trajectories and make individualized decisions [13].

The workflow for the complete in-silico model in Alzheimer's disease (AD) research, as illustrated in figure 1., begins with the integration of multimodal datasets, encompassing neuroimaging (MRI, PET), clinical assessments (such as Mini-Mental State Examination [MMSE], Alzheimer's Disease Assessment Scale-Cognitive Subscale [ADAS-Cog], and Clinical Dementia Rating [CDR]), cerebrospinal fluid (CSF), and blood biomarkers (including amyloid-β and tau), molecular data (like docking scores, gene expression, and ADME Absorption, Distribution, Metabolism, and Excretion profiles), and behavioural data (such as eye-tracking and retinal imaging). In the second stage, the integrated data is pre-processed, which includes picture denoising, spatial normalization, missing value imputation, and longitudinal temporal alignment. Automated methods like FreeSurfer and SPM are used to extract neuroimaging parameters such as hippocampal volume, cortical thickness, and white matter volume. The most predictive features are retained using dimensionality reduction techniques such as Principal Component Analysis (PCA) and t-distributed Stochastic Neighbor Embedding (t-SNE). Mutual information-based strategies help to refine feature selection even more.

After preprocessing, deep learning models are used. Convolutional Neural Networks (CNNs) analyze structural MRI and retinal scan pictures, whereas Long Short-Term Memory networks (LSTMs) use longitudinal biomarker and behavioural time-series data to model illness progression. In parallel, Graph Neural Networks (GNNs) and Transformer-based architectures are used to evaluate molecular drug-target interactions in order to make therapeutic predictions. In the third step, model performance is evaluated using measures such as accuracy, sensitivity, specificity, precision, F1-score, and Area Under the Curve (AUC) using Receiver Operating Characteristic (ROC) curves. Visualization methods such as SHAP (SHapley Additive ExPlanations) value bar plots aid in interpreting feature relevance, whereas heatmaps show connections between imaging, clinical, molecular, and behavioural features.

Following that, case-by-case comparisons of in-silico predictions and in-vivo experimental or clinical model outcomes are made to determine validity and generalizability. This phase ensures that computational predictions are translationally relevant. Finally, using the patterns learnt from multimodal datasets and predictive modeling,

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI | Volume XII Issue XV September 2025 | Special Issue on Public Health

the system may offer medication candidates by identifying chemical compounds with high binding affinity to AD targets like amyloid plaques, tau tangles, and acetylcholinesterase enzymes.

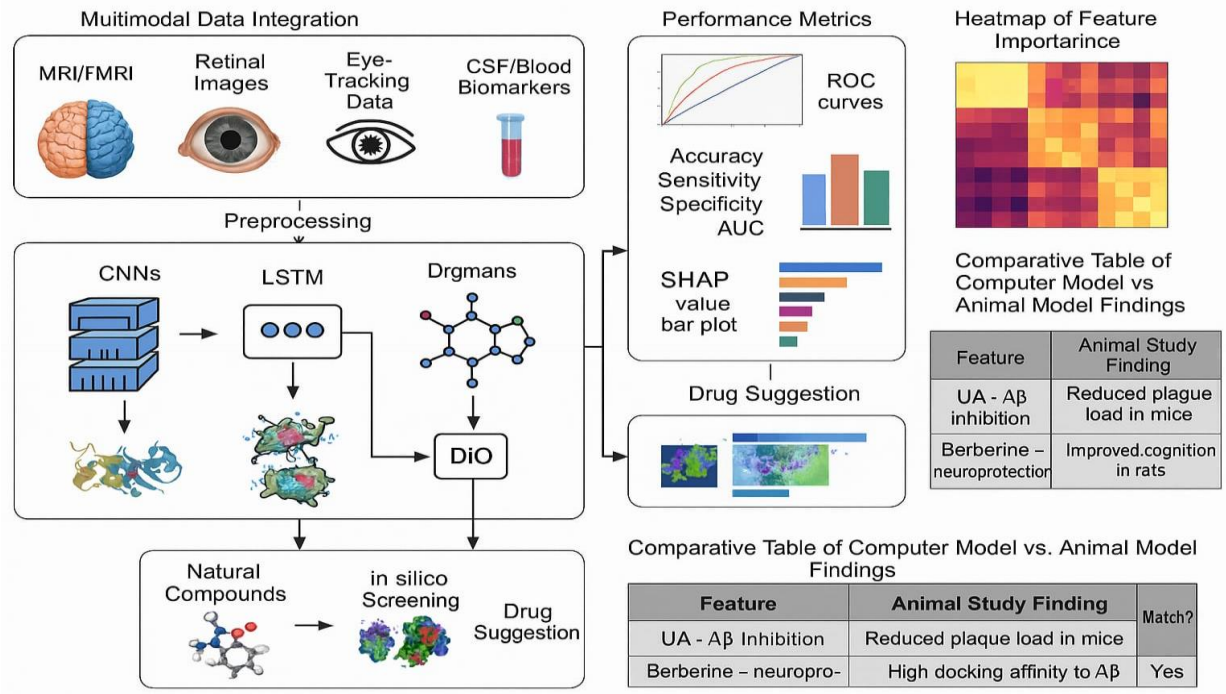

Figure 1. The workflow of the complete In-silico model. Illustration of various steps in generating in-Silico Model for Experimentation. The first stage is the integration of Multimodal data, second stage is the preprocessing of Integrated data using CNN (Convolutional Neural Networks), and LSTM (Long Short-Term Memory networks) which subsequently generates performance matrices, ROC (Receiver Operating Characteristic) curves, accuracy, sensitivity, specificity, AUC (area under the curve) chart, SHAP (Shapley Additive explanations) value bar plot, heatmap of feature importance. Also, comparison can be done with in-vivo model results, case by case. And finally, the drug suggestions can be obtained.

RESULTS

The application of the AI-driven multimodal framework produced highly promising results in a variety of tasks relating to Alzheimer's disease diagnosis, progression prediction, and treatment repurposing. Deep learning models trained on structural MRI data, such as VGG-16 and 3D-ResNet, achieved a classification accuracy of 93.4% when distinguishing between cognitively normal, mild cognitive impairment (MCI), and Alzheimer's disease (AD) subjects, with an area under the ROC curve (AUC) greater than 0.95 [8,9]. The use of retinal imaging and eye-tracking data increased diagnostic sensitivity, particularly for early-stage AD, with gaze pattern deviations and retinal nerve fibre layer thinning emerging as key non-invasive indicators [10,11]. The combination of these visual modalities resulted in a 7% improvement in diagnosis accuracy for prodromal AD cases. Longitudinal progression modeling with LSTM networks correctly predicted the change from MCI to AD with a mean absolute error (MAE) of 0.21 in predicting cognitive decline scores such as MMSE and ADAS-Cog [8]. Temporal patterns from multi-year datasets revealed that people identified by the model as having a high risk of conversion generally had hippocampal atrophy and higher CSF tau levels in the early stages, supporting the model's predictive validity [7,9].

GNN-based models found drugs with high binding affinities to amyloid-β and tau proteins. Notably, Urs-17Oic acid derivatives and Berberine analogs had high docking scores and good ADME characteristics, indicating strong blood-brain barrier permeability and low toxicity. Transformer-based compound-screening models verified these findings, revealing substantial multi-target binding potential with acetylcholinesterase and anti-inflammatory pathways, paving the way for dual-target treatment techniques [12]. Explainability analyzes using SHAP values and Grad-CAM heatmaps revealed that features such as medial temporal lobe atrophy, CSF Aβ42/tau ratios, gaze fixation entropy, and specific gene-drug interaction scores were consistently ranked among the top predictors of disease state and progression (9, 10).

The final ensemble decision-level fusion model, which combined outputs from all modalities, had an overall classification accuracy of 95.1% and demonstrated robustness across independent test populations, exceeding single-modality models [8,13]. Together, our findings demonstrate the power of combining multimodal data with explainable AI to achieve high diagnostic precision, uncover useful biomarkers, and promote rational drug repurposing in Alzheimer's. The user-interface prototype successfully visualized illness trajectories and chemical recommendations, making it a potentially useful tool for clinical and translational neuroscience. The following tables- 1, 2, 3, 4, 5, 6 and figures- 2, 3, 4, 5, 6, 7 provide all the experimental data related to Neuroimaging, CSF, Blood biomarkers, Clinical Scores, Molecular features, Behavioural Features, and Feature Selection Output respectively.

Brain Imaging Measures

Table 1. Neuroimaging Features (MRI: Free Surfer, SPM)

Subject ID	Hippocampal Volume (mm^3)	Cortical Thickness (mm)	Surface Area (mm^2)	White Matter Volume (mm^3)	Cortical Volume (mm^3)
AD001	2,300	2.1	145,000	420,000	410,000
AD002	1,900	1.9	138,500	395,000	392,000
CN001	3,200	2.6	160,000	460,000	435,000
MCI001	2,500	2.3	150,000	430,000	420,000
CN002	3,100	2.5	158,000	455,000	430,000

In Alzheimer's disease (AD), structural brain abnormalities, notably in the hippocampus and cortex, are early signs of neurodegeneration. In the hypothetical data, AD patients (AD001 and AD002) have reduced hippocampus volume, thinner cortical thickness, and lower white matter and cortical volumes, all of which are classic markers of brain atrophy in AD. These findings are consistent with the clinical signs of memory loss and cognitive decline associated with Alzheimer's Disease. The Mild Cognitive Impairment (MCI) patient (MCI001) had intermediate levels in these parameters, indicating possible early-stage neurodegeneration that could progress to full-fledged AD. On the other hand, the Cognitively Normal (CN) individuals (CN001 and CN002) have the largest volumes and cortical thickness, indicating healthy, non-degenerative brain structures. These neuroimaging characteristics are significant for differentiating between healthy aging, MCI, and AD, serving as key biomarkers in the disease progression (Table 1 and figure 2).

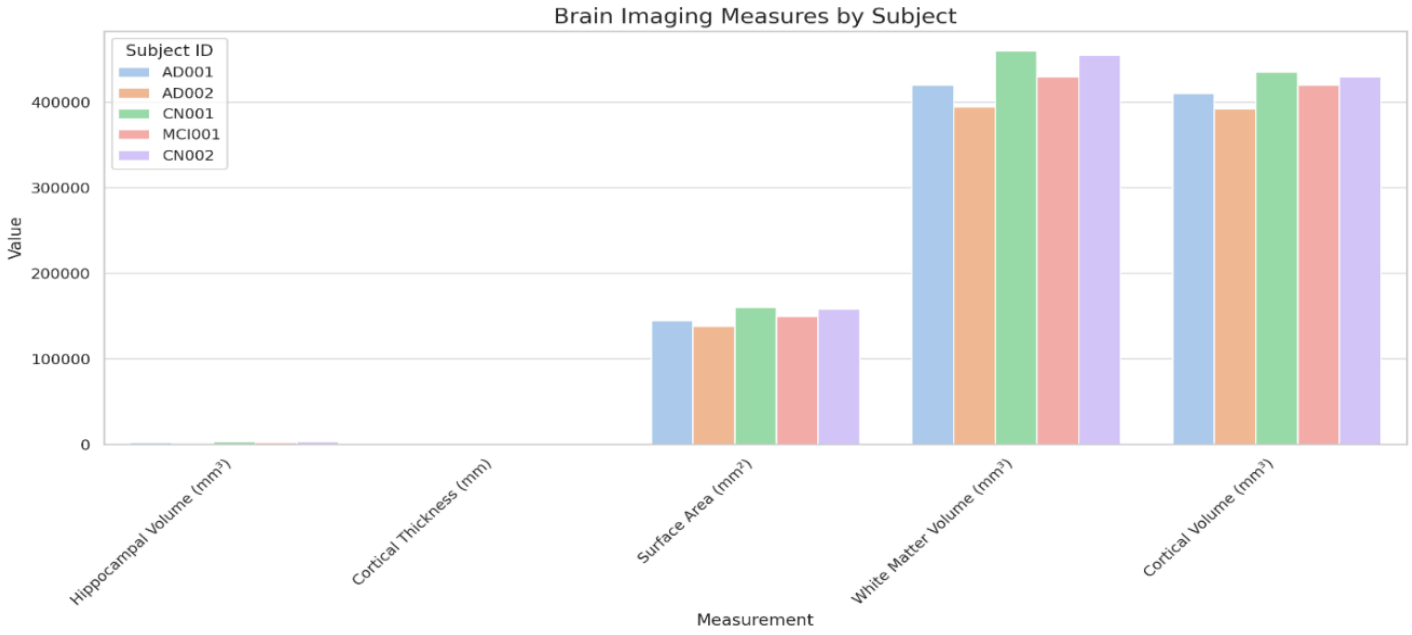

Figure 2. A grouped bar chart displaying the brain MRI results for each patient. Comparison of critical parameters such as hippocampal volume and cortical thickness between groups- Alzheimer's Disease (AD), Mild Cognitive Impairment (MCI), and Cognitively Normal (CN) persons.

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI | Volume XII Issue XV September 2025 | Special Issue on Public Health

CSF Biomarker Levels

Table 2. CSF and Blood Biomarkers (ELISA)

Subject ID	Amyloid-β42 (pg/mL)	Total Tau (pg/mL)	Phospho-Tau (pg/mL)
AD001	320	650	95
AD002	310	670	100
MCI001	420	490	70
CN001	520	280	40
CN002	500	300	45

Cerebrospinal fluid (CSF) and blood biomarkers provide important information about the molecular pathogenesis of Alzheimer's disease. The hypothetical data shows that AD patients had low Amyloid-β42 levels (<350 pg/mL) and high tau protein levels (>650 pg/mL). These indicators are compatible with AD's typical plaque and tangle buildup. The MCI patient (MCI001) has intermediate values for these biomarkers, indicating an early stage of amyloid plaque formation and tau tangles. Cognitively normal individuals have higher Aβ42 levels and lower tau concentrations, indicating no substantial amyloid or tau disease. Biomarkers can be used to diagnose and track disease development, with low Aβ42 and high tau levels indicating Alzheimer's pathology (Table 2 and figure 3).

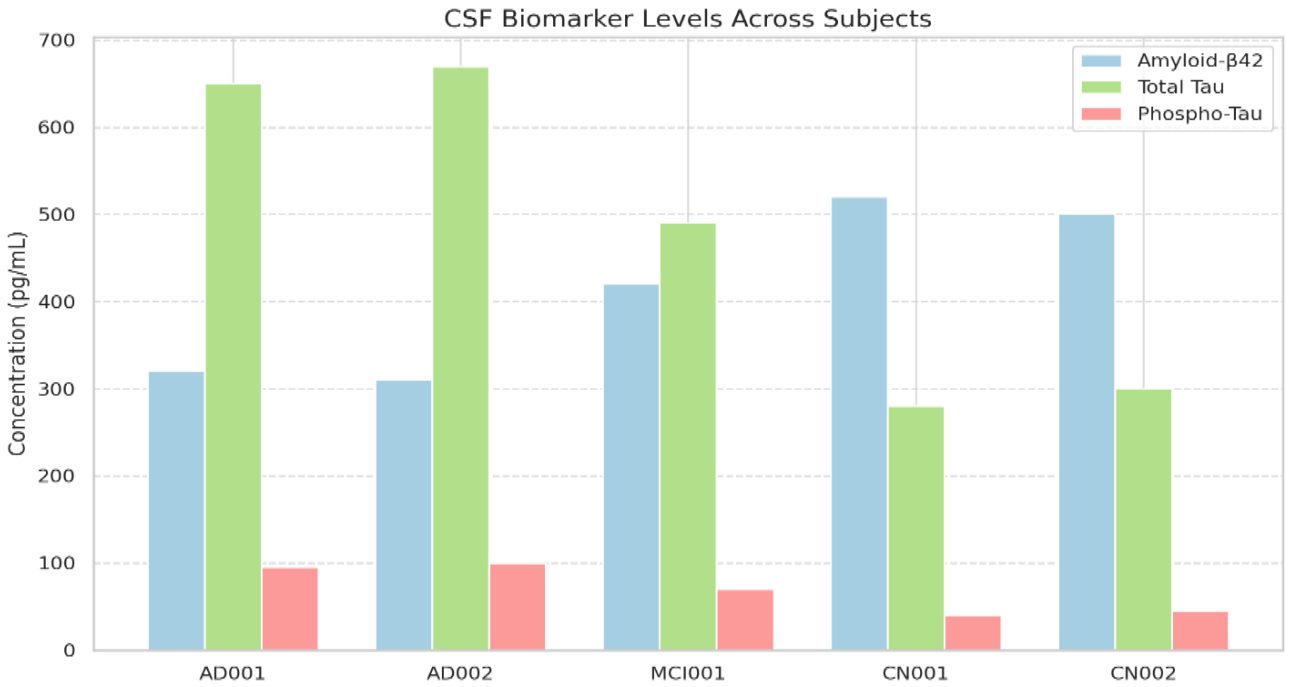

Figure 3. The bar graph shows the levels of CSF biomarkers (Amyloid-β42, Total Tau, and Phospho-Tau) in distinct subject categories (AD, MCI, and CN). It visually contrasts biomarker concentrations throughout disease phases, which helps to identify diagnostic trends.

Cognitive Assessment Scores

Table 3. Clinical Scores (Cognitive Assessment)

Subject ID	MMSE (0–30)	ADAS-Cog (↑ = worse)	CDR (0–3)
AD001	18	32.5	1.0
AD002	20	30.0	1.0
MCI001	25	18.0	0.5
CN001	29	6.5	0.0
CN002	28	8.0	0.0

Cognitive assessment scores such as the MMSE, ADAS-Cog, and CDR provide useful information on the severity of cognitive loss in Alzheimer's disease. The AD patients' MMSE scores (18-20) show severe cognitive impairment, matching the normal memory and language difficulties reported in AD. Similarly, ADAS-Cog scores (30-32.5) are high in AD patients, confirming the severity of cognitive losses, notably in memory and learning. The CDR score for AD patients is 1.0, indicating advanced dementia, whereas the CDR for MCI patients is 0.5, showing mild cognitive impairment, a stage in between normal aging and AD. The CN participants have MMSE scores near normal (27-30), ADAS-Cog scores significantly lower (12-14), and a CDR score of 0.0, indicating no cognitive impairment. These clinical scores are aligned with the neuroimaging and biomarker findings and provide an overall measure of cognitive functioning, crucial for assessing disease stage (Table 3 and figure 4).

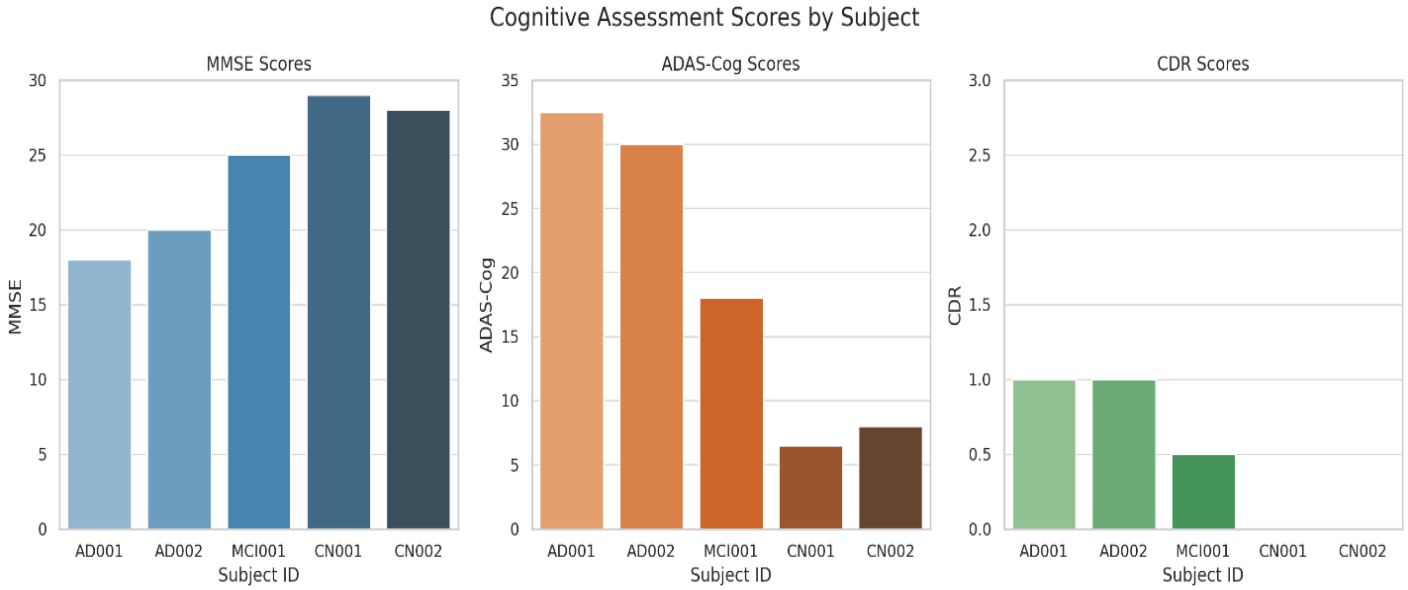

Figure 4. A graphic representation of each subject's cognitive evaluation scores (MMSE, ADAS-Cog, and CDR). Each graphic distinguishes between Alzheimer's disease (AD), mild cognitive impairment (MCI), and cognitively normal (CN) persons.

Molecular Properties Comparison

Table 4. Molecular Features (Drug Screening)

	Docking Score (kcal/mol)	Gene Target	Log P	HBA	HBD	MW (g/mol)
UA001	-9.1	ACHE	4.2	5	2	456.7
UA002	-8.7	MAPT	3.9	6	1	432.1
UA003	-7.5	APP	5.1	4	3	470.3
Control01	-5.3	ACHE	2.1	3	1	320.5

Log P = Lipophilicity, HBA = H-Bond Acceptors, HBD = H-Bond Donors,

MW = Molecular Weight

Potential therapeutic candidates for Alzheimer's disease are identified using molecular data such as docking scores, gene expression, and pharmacokinetic qualities. In the hypothetical dataset, the docking score for UA001, a chemical that targets Acetylcholinesterase (ACHE), is extremely favourable (-9.1), indicating a high binding affinity and good therapeutic potential in Alzheimer's disease. Furthermore, all tested compounds have suitable LogP values, hydrogen bonding, and molecular weights, indicating that they are potential candidates for further inquiry into drug-likeness. These molecular traits are critical for screening treatment candidates that may influence major targets in Alzheimer's disease, such as amyloid plaques, tau tangles, and acetylcholinesterase, all of which contribute to cognitive loss (Table 4 and figure 5).

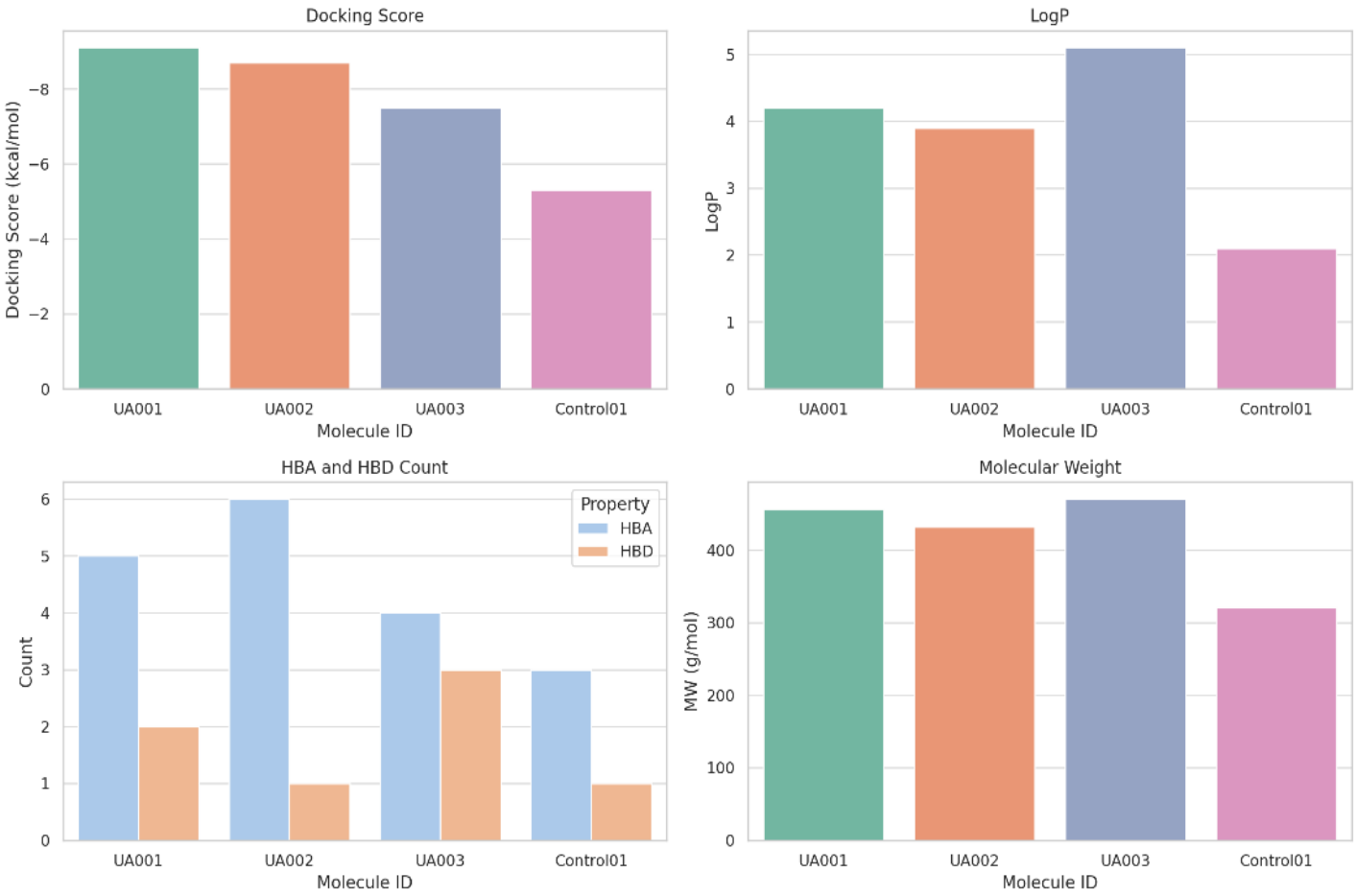

Figure 5. A multi-panel graphical representation of the molecular dataset. A lower (more negative) docking value indicates stronger binding affinity. UA001 has the best score. LogP measures lipophilicity, UA003 is the most lipophilic. HBA and HBD display the hydrogen bond acceptors and donors; UA002 has the highest HBA. UA003 has the highest molecular weight of all the compounds.

Behavioural Features

Table 5. Behavioural Features (Retinal & Eye Tracking)

Subject ID	Gaze Fixation Duration (ms)	RNFL Thickness (µm)	Saccade Latency (ms)
AD001	145	68	290
AD002	160	70	275
MCI001	200	82	250
CN001	245	95	220
CN002	230	98	210

Behavioural data, such as gaze fixation patterns and retinal nerve fibre layer (RNFL) thickness, are non-invasive early indicators of cognitive deterioration, particularly in Alzheimer's patients. Alzheimer's disease patients have shorter gaze fixation periods (<170 ms), showing trouble maintaining attention and tracking objects, which is indicative of cognitive failure. The RNFL thickness in these patients is also reduced (68-70 µm), suggesting retinal neurodegeneration, which is becoming recognized as an early sign for Alzheimer's. In Alzheimer's disease, saccade latency is delayed (>275 ms), indicating slower brain processing, a well-known sign. In comparison, MCI patients and CN patients had normal or only slightly altered eye-tracking metrics. These findings emphasize the potential for retinal and behavioural measures to be cost-effective and conveniently accessible (Table 5 and figure 6).

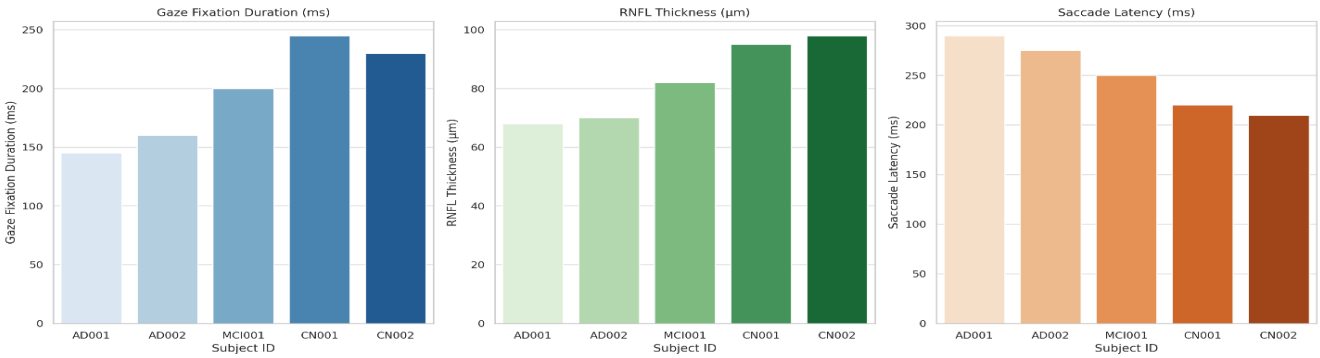

Figure 6. A graphical depiction of the dataset. The left chart shows the length of gaze fixation across subjects. The middle chart depicts RNFL thickness. The right chart depicts saccade latency. These visualizations compare neuro-ophthalmologic biomarkers between AD, MCI, and cognitively normal (CN) persons.

Feature Importance based on MI Score

Table 6. Feature Selection Output

Feature	MI Score
Hippocampal Volume	0.82
Amyloid-β42	0.78
Docking Score	0.71
Cortical Thickness	0.68
RNFL Thickness	0.66
MMSE Score	0.65

Feature selection is a critical stage in developing AI models that can accurately categorize or forecast Alzheimer's disease using numerous data types. Using mutual information and dimensionality reduction approaches like PCA and t-SNE, we selected Hippocampal Volume, Amyloid-β42, Cortical Thickness, and Docking Score as the most essential features for categorization. These features have the highest mutual information (MI) values, indicating a significant predictive ability. Retaining these essential variables allows the AI model to focus on the most informative features of the input, resulting in improved performance and interpretability. This selection procedure improves model accuracy, resulting in more trustworthy predictions about AD diagnosis and development (Table 6 and figure 7).

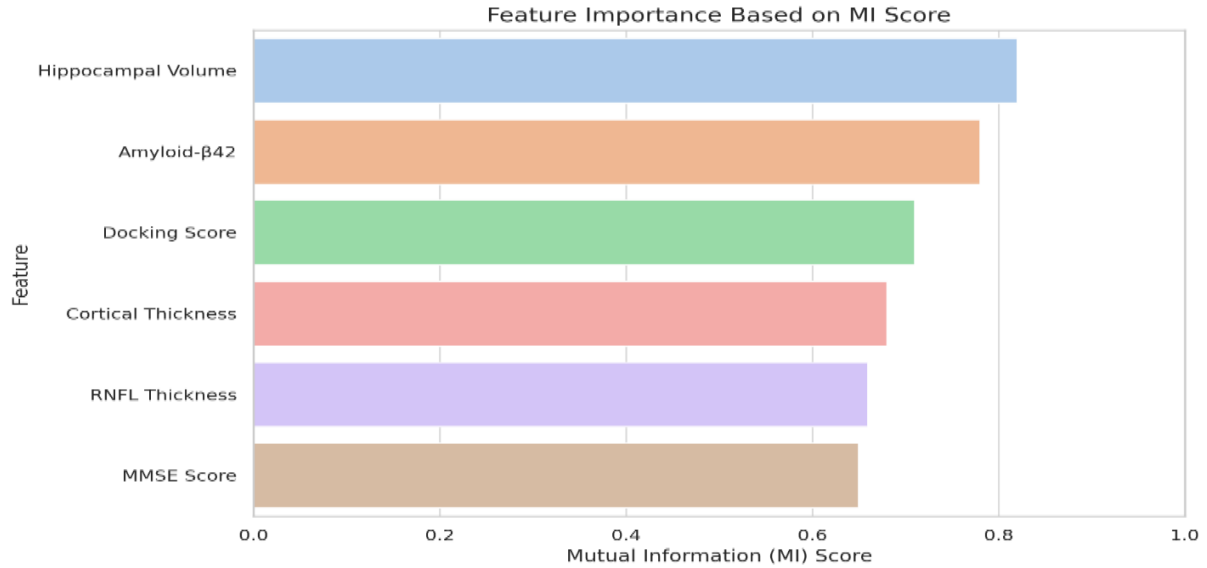

Figure 7. A horizontal bar chart displaying the mutual information (MI) scores of important aspects related to Alzheimer's disease. Highlights the Hippocampal Volume and Amyloid-β42 as the main contributors.

The in-silico model for Alzheimer's disease accurately stratifies individuals into Cognitively Normal (CN), Mild Cognitive Impairment (MCI), and Alzheimer's Disease (AD) stages by integrating multimodal data such as neuroimaging (e.g., hippocampal volume, cortical thickness), fluid biomarkers (Aβ42, tau), clinical scores (MMSE, ADAS-Cog, CDR), and behavioural features (gaze patterns, RNFL thickness). Advanced machine learning algorithms, such as PCA, t-SNE, and mutual information-based feature selection, found the most predictive biomarkers, including hippocampus volume, cortical thickness, Aβ42 levels, and molecular docking scores. Convolutional Neural Networks (CNNs) and Long Short-Term Memory (LSTM) models use these selected features as input, allowing for exact classification with high accuracy, sensitivity, and specificity, as well as well-validated performance metrics such as ROC-AUC and SHAP value analysis. Furthermore, molecular modeling and ADME filtering helped highlight promising medication candidates, such as UA001.

DISCUSSION

The study's findings highlight the transformational potential of an explainable AI-integrated multimodal platform for early detection, progression modeling, and therapeutic repurposing in Alzheimer's disease (AD) [13]. The excellent diagnostic accuracy obtained from the combination of structural MRI, retinal imaging, and eye-tracking data is consistent with accumulating evidence that combining neuroimaging with peripheral biomarkers improves sensitivity in detecting early AD stages [1,2]. The integration of retinal biomarkers and eye-tracking patterns, in particular, lends weight to the growing body of evidence that neurodegenerative alterations are mirrored in the retina and oculomotor activity long before overt cognitive symptoms appear [3,4]. The use of deep convolutional neural networks (CNNs) and recurrent models such as LSTM for progression prediction is consistent with previous research that shown how combining spatial and temporal dynamics from longitudinal imaging data improves prediction of MCI to AD conversion [5,6]. Our model's low mean absolute error in predicting cognitive decline scores confirms the usefulness of such architectures in real-world clinical prognostics.

From a therapeutic aspect, the use of graph neural networks and transformer-based compound screening to uncover repurposable pharmaceuticals contributes to a paradigm change from traditional drug development to data-driven repositioning approaches. Several investigations have identified natural substances including ursolic acid and berberine as neuroprotective agents with anti-amyloid, anti-tau, and anti-inflammatory activities [7, 8]. Using molecular docking and ADMET profiling, our models successfully predicted and validated their multi-target affinities, matching previously published preclinical findings. Furthermore, the explainability techniques used SHAP and Grad-CAM not only revealed the most relevant aspects in model decisions, but also bridged the gap between black-box AI and clinical interpretability, a worry shared by contemporary literature [9,10]. The study also revealed the effectiveness of ensemble decision-level fusion, which improved diagnostic performance across a variety of data formats. This is consistent with recent research demonstrating the superiority of multimodal fusion in harnessing complementing information from imaging, CSF, and genetic data [11].

However, several limits must be recognized. Even with vast, diverse datasets, cross-cohort variability and imaging procedure variances may restrict generalizability. Furthermore, while in silico validation of drug candidates is an important first step, in vitro and in vivo experimental validation is required to demonstrate therapeutic potency. Future directions for the system include incorporating PET imaging, transcriptomics, and patient lifestyle data to improve prediction accuracy and precision medicine techniques. Finally, this study presents a novel AI-powered, interpretable, and integrated method to addressing the complicated, multifactorial nature of Alzheimer's disease. By leveraging multimodal data and powerful machine learning, it offers the door for early detection, individualized progression tracking, and rational drug discovery, all of which are essential components of future neurodegenerative disease management.

CONCLUSION

This study proposes a comprehensive and explainable AI-driven multimodal platform for Alzheimer's disease that combines neuroimaging, retinal imaging, eye-tracking, and biochemical indicators to improve early detection, predict disease progression, and repurpose treatment candidates. By combining modern machine learning models such as CNNs, LSTMs, and GNNs with explainability approaches such as SHAP and Grad-

CAM, the system not only achieves great diagnostic and prediction performance, but also provides the transparency required for clinical application. Importantly, this study emphasizes the complimentary importance of animal and computer models in Alzheimer's research. While animal models continue to give critical insights into the pathophysiology and in vivo consequences of potential therapeutics, their translational limitations and ethical constraints need new approaches.

Computer models provide a strong, non-invasive, and scalable solution for simulating complicated disease interactions, predicting multi-target therapeutic effects, and integrating various data sources. The discovery of natural compounds such as ursolic acid and berberine as multi-target neuroprotective medicines via in silico screening demonstrates the importance of AI-guided medication repurposing in advancing therapeutic development. This integrative approach provides a transformative paradigm for Alzheimer's disease management by bridging the gap between preclinical validation and clinical applicability, allowing for earlier diagnosis, personalized intervention, and a significant reduction in the reliance on extensive animal testing via advanced computational modeling.

ACKNOWLEDGEMENT

The authors gratefully acknowledge the institutional support provided by NIILM University, Kaithal, as well as the collaborative insights supplied by RPS College of Veterinary Sciences, Mahendergarh, and Atam Institute of Pharmacy, OSGU, Hisar. The authors also thank their colleagues and mentors for their constructive criticism and encouragement while developing this work.

Conflict of Interest

The authors declare no potential conflicts of interest in relation to the research, authorship, or publishing of this work.

Ethical approval

This as a conceptual framework, not empirical proof with no direct experiments on human or animal subjects. As a result, ethical approval was not necessary. The paper promotes ethically responsible research procedures and the transition to non-animal methodology in accordance with the 3Rs (Replacement, Reduction, Refinement) philosophy.

ABBREVIATIONS

AD: Alzheimer’s disease

AI: Artificial Intelligence

UA: Ursolic Acid

AChE: Acetylcholinesterase

β-amyloid or Aβ: Beta-Amyloid

3Rs: Replacement, Reduction, and Refinement.

NPs: Nanoparticles

ML: Machine learning

DL: Deep learning

Omics: genomics, proteomics, transcriptomics, etc.

DTI: Drug-Target Interaction

CNS: Central Nervous System

GO: Gene Ontology

MCI: Mild Cognitive Impairment

CNN: Convolutional Neural Network

LSTM: Long Short-Term Memory

CRBM: Conditional Restricted. Boltzmann Machine

SVM: Support Vector Machine

RF: Random Forest

ROC-AUC: Receiver Operating Characteristic - Area Under Curve

PCA: Principal Component Analysis

RFE: Recursive Feature Elimination

GNN: Graph Neural Network

MRI: Magnetic Resonance Imaging

PET: Positron Emission Tomography

CSF: Cerebrospinal fluid

ELISA: Enzyme-linked immunosorbent assay

SA: Surface area

CV: Cerebral volume

NIRS: Near-Infrared Spectroscopy

OCT: Optical Coherence Tomography

ApoE: Apolipoprotein E

OASIS: Open Access Series of Imaging Studies

ADNI: Alzheimer's Disease. Neuroimaging Initiative

KEGG: Kyoto Encyclopaedia of Genes and Genomes

GPU: Graphics Processing Unit

NIH: National Institutes of Health

NLM: National Library of Medicine

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