Check for updates

Wiley
Advances in Pharmacological and Pharmaceutical Sciences
Volume 2025, Article ID 6634761, 30 pages
https://doi.org/10.1155/adpp/6634761

WILEY

Research Article

In Silico Pharmacological and Pharmacokinetic Study of Marmeline From Bael Fruit for the Treatment of Alzheimer's Disease

Tassanee Ongtanasup,[1,2] Onkamon Jampa,[3] Nattawan Suwannakul,[4] and Komgrit Eawsakul[1,5]

[1]*School of Medicine, Walailak University, Nakhon Si Thammarat 80160, Thailand*
[2]*Center of Excellence in Tropical Pathobiology, Walailak University, Nakhon Si Thammarat 80160, Thailand*
[3]*Department of Thai Traditional Medicine, Tak Community College, Nong Bua Tai 63000, Thailand*
[4]*Department of Molecular Biology, Umeå University, Umeå 901 87, Sweden*
[5]*Research Excellence Center for Innovation and Health Products (RECIHP), Walailak University, Nakhon Si Thammarat 80160, Thailand*

Correspondence should be addressed to Komgrit Eawsakul; komgrit.ea@wu.ac.th

Received 13 December 2024; Accepted 22 March 2025

Academic Editor: Benedetto Natalini

Copyright © 2025 Tassanee Ongtanasup et al. Advances in Pharmacological and Pharmaceutical Sciences published by John Wiley & Sons Ltd. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

Epidemiological studies identify risk factors for Alzheimer's disease (AD), which induces oxidative stress and inflammation. Pharmaceuticals aimed against the nuclear receptor PPARγ, including TZDs, have been associated with considerable negative consequences in AD treatment. The bael fruit (*Aegle marmelos*) has bioactive compounds with therapeutic promise. The purpose of our study was to investigate the pharmacological and pharmacokinetic properties of marmeline, a bioactive compound isolated from *Aegle marmelos*, as a potential therapeutic agent for AD. Specifically, we aimed to identify its molecular targets with respect to AD pathology, compare its binding affinity with important AD proteins (BACE1 and AChE) to established drugs, predict its metabolism through *in silico* liver metabolism studies, assess its pharmacokinetic properties, particularly blood–brain barrier permeability, determine optimal solvent conditions for extraction, and investigate gene expression patterns to understand its effects on AD. Network pharmacology investigation reveals that marmeline activates PPARγ in brain cells via the PPAR–PPRE pathway. Marmeline reduces BACE1 by higher binding affinity than donepezil and verubecestat, therefore, perhaps reducing amyloid-beta generation. Marmeline also targets increased CDK6 and PDE5A, which regulate cognition, amyloidogenesis, and neuroinflammation. Marmeline's cognitive advantages might result from neuroinflammation control and synaptic plasticity. Using acetone helps stable marmeline extraction remain the most effective. These results suggest that by altering amyloid-beta aggregation, tau phosphorylation, and oxidative stress, marmeline could be a possible natural AD therapy, though further *in vitro* testing is required.

Keywords: acetylcholinesterase; *Aegle marmelos* (L.) Correa ex Roxb; Alzheimer's disease; beta-secretase1; marmeline

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and behavioral changes, representing a major global health concern affecting millions of elderly individuals [1]. Presently, there are an estimated 35.6 million cases of dementia globally, a figure predicted to triple by the years 2030 and 2050 [2, 3]. In the last century, there has been substantial progress in understanding and predicting methods for this disease since it was first described. AD may be classified into two main types: familial AD (FAD), which is caused by

genetic abnormalities and results in a significantly faster onset, and sporadic AD (SAD), which is characterized by a progressive deterioration in cognitive function [4]. The importance of AD research is emphasized by its increasing incidence and the current lack of effective treatment options [5, 6]. Despite decades of research, current therapeutic options remain limited, with available treatments primarily addressing symptoms rather than modifying disease progression [7, 8]. The recent approval of amyloid-targeting therapies such as lecanemab and donanemab marks a significant advancement, as they demonstrate the ability to slow disease progression [9]. However, these treatments represent only the beginning of effective AD management, and substantial knowledge gaps remain in understanding the complex pathophysiology of AD.

Amyloid-beta (Aβ), an oligomeric peptide, is a significant component of amyloid plaques. It originates from the proteolytic cleavage of β-amyloid precursor protein (β-APP) by β- and γ-secretases. The most important enzyme for Aβ synthesis is β-secretase, also known as BACE1 [10, 11]. BACE1 inhibition is a well-known strategy for treating AD, highlighting its importance. BACE1 and the cholinergic hypothesis have helped develop AD treatments. Acetylcholinesterase (AChE) degrades acetylcholine (ACh) [12, 13]. Early AD treatment focuses on cholinergic system stimulation due to ACh depletion [14, 15]. Cholinergic inhibitors donepezil and galantamine target AChE and are essential to AD treatment [12]. In the temporal cortex of a normal brain, AChE accounts for 90% of ChE activity [16]. Thus, concomitant inhibition of AChE and BACE1 may benefit multimodal AD therapy. New drug research decision-making involves three crucial stages: lead compound discovery, new drug optimization, and clinical development, each with its own costs, length, and risks [17]. In response, pharmaceutical companies are using computational innovation to reduce research and development costs and improve medication discovery. Following years of rigorous study and development, computer-aided drug design (CADD) has become a core technique in drug research, rising in importance [18]. Computer chemistry–based CADD simulates ligand-receptor biomacromolecule interactions to optimize and create lead compounds [19]. Notably, CADD might significantly reduce medication development costs and time. Aliskiren, boceprevir, captopril, dorzolamide, nolatrexed, oseltamivir, rupintrivir, saquinavir, and zanamivir have predicted and screened several low-molecular–weight drugs using network pharmacology and molecular docking models. Further investigation of the identified chemicals after ADMET shows a variety of therapeutic uses [18].

Our investigation also showed that similar methods may be used in molecular docking analysis and network pharmacology software. CADD requires the investigation and classification of compounds with or without pharmacological activity. Previous CADD research supports this necessity. Bael or Bilwa, *Aegle marmelos*, is a perennial Rutaceae tree endemic to tropical and subtropical Southeast Asia, mostly Thailand. Most Bael components are essential in ancient therapeutic herbs, especially Ayurveda, Unani, and Siddha systems. They cure dysentery, dyspepsia, and persistent diarrhea [20]. A drink made from fruit pulp is used to regulate body temperature in Thailand's hot season. Aqueous bael fruit's extract lowers blood sugar in streptozotocin-induced diabetic mice. The extract had this effect when taken orally and intraperitoneally [21, 22]. Furthermore, The Phra Maha Kwanchai Akkachayo at Wat Kiriwong, Chumphon Province, Thailand, has used bael fruit to treat Alzheimer's patients for over 30 years. Our study aims to fill one such gap by investigating marmeline, a bioactive compound from *Aegle marmelos* (bael fruit), as a potential multitarget therapeutic for AD. We hypothesize that marmeline may provide therapeutic benefits through simultaneous inhibition of beta-secretase 1 (BACE1) and AChE, key enzymes in AD pathology.

2. Materials and Methods

2.1. Identification and Acquisition of Potential Targets. The process of identifying and acquiring potential targets for the active chemical constituents within bael fruit was executed utilizing online platforms, specifically PharmMapper [23], SEA [24], and SwissTargetPrediction [25]. The search procedure incorporated the application of the keyword "Marmeline." The resultant findings from these platforms were collated and deemed as viable objectives.

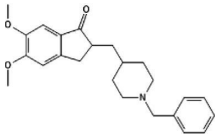
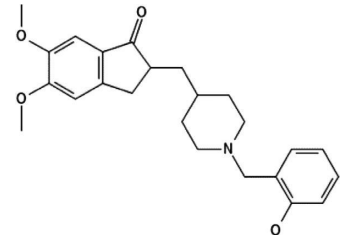
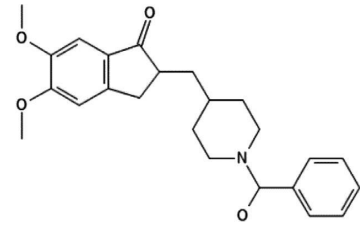
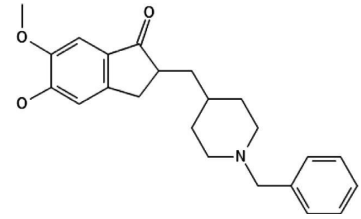
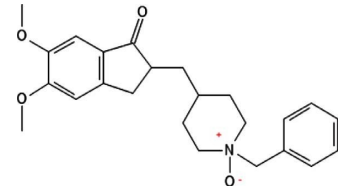
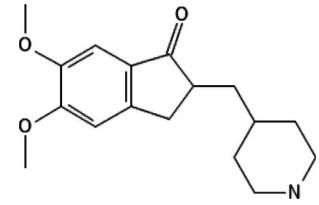
2.2. Target Acquisition for AD and Medicinal Investigation. The phrase "Alzheimer" was detected in the GeneCards Suite index [26]. The index word search was conducted on February 22, 2022. The database results were utilized to get the relevant targets related to AD. Later, the targets associated with marmeline in the context of AD were visualized and analyzed using a Venn diagram [27]. The overlapping targets were acknowledged as prospective candidates for Alzheimer's therapy in conjunction with marmeline.

2.3. Prediction of Metabolites Using Computational Methods. BioTransformer 3.0 [28] was employed to predict drug metabolism, as depicted in Table 1, utilizing the SMILES string for marmeline (CC(=CCOC1=CC=C(C=C1)C(CNC(=O)C=CC2=CC=CC=C2)O)). BioTransformer 3.0 represents a freely accessible software application explicitly designed for the efficient and accurate forecasting of metabolic processes concerning small compounds within mammals and environmental microbes. This tool facilitates the prediction of potential human metabolites of small molecules, particularly pharmaceutical medications. The construction of metabolite structures was executed through the utilization of PubChem Sketcher [29] (see Table 1).

2.4. Constructing the Protein–Protein Interaction (PPI) Network and Identifying Key Genes. Leveraging the putative target genes delineated in Table 2, we performed gene enrichment analysis and pathway through the utilization of the ShinyGo program [30], as illustrated in Figures 1 and 2.

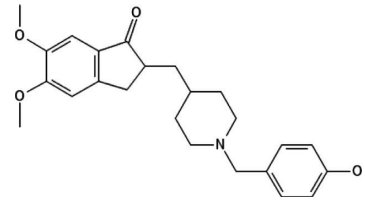
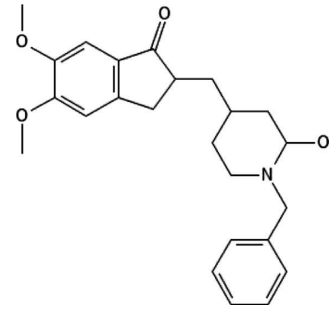
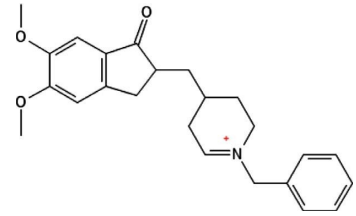
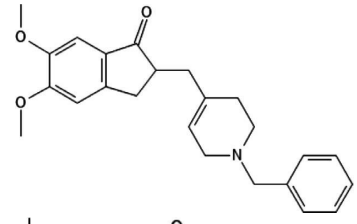
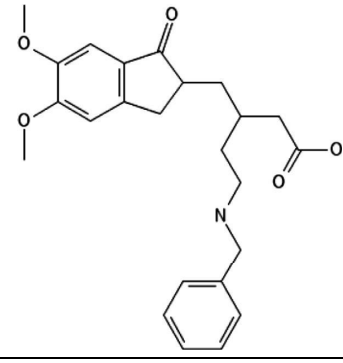
3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1: Hepatic metabolism profiling of standard drugs (donepezil and verubecestat) and marmeline, the active compound in bael fruit.

Compounds	Drug metabolism	Structure	Abbreviation
Donepezil 	O-Hydroxylation of monosubstituted benzene: cytochrome P450 1A2		D1
	Hydroxylation of nonterminal aliphatic carbon adjacent to aromatic ring: cytochrome P450 1A2		D2
	O-Dealkylation from CyProduct: cytochrome P450 1A2		D3
	N-Oxidation of alicyclic tertiary amine: cytochrome P450 1A2		D4
	N-Dealkylation of alicyclic tertiary amine from CyProduct: cytochrome P450 1A2		D5

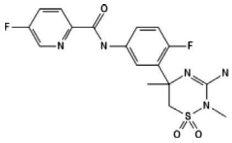
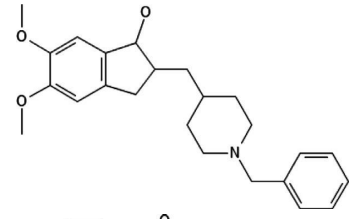
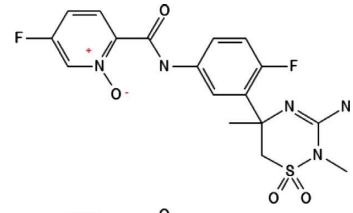
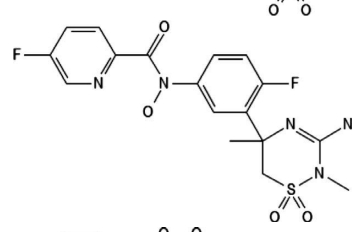
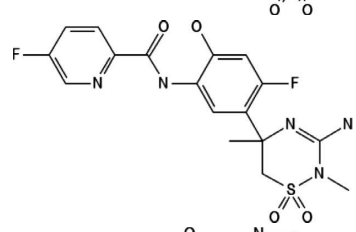
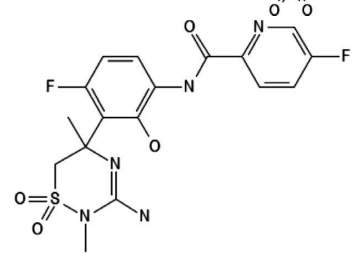
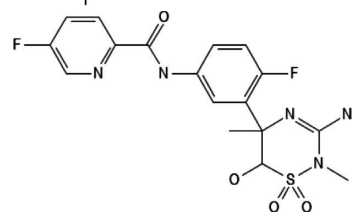
3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1: Continued.

Compounds	Drug metabolism	Structure	Abbreviation
	Hydroxylation of benzene on carbon para to electron donating group: cytochrome P450 1A2		D6
	Hydroxylation of heteroalicyclic secondary carbon: cytochrome P450 1A2		D7
	Formation of imminium ion from N-substituted piperidine: cytochrome P450 2C19		D8
	N-Dehydrogenation of aliphatic azaheterocyclene: cytochrome P450 2D6		D9
	Ring opening of N-substituted piperidine: cytochrome P450 3A4		D10

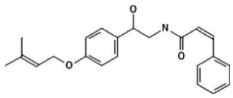
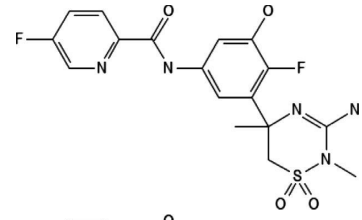
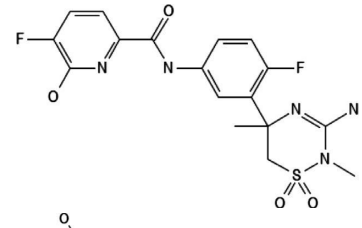
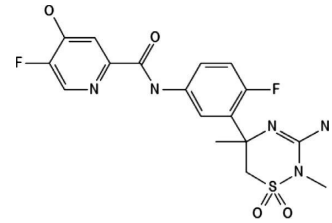
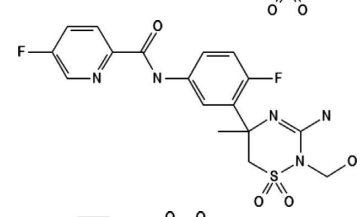
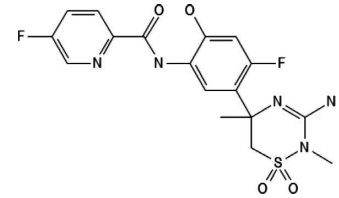
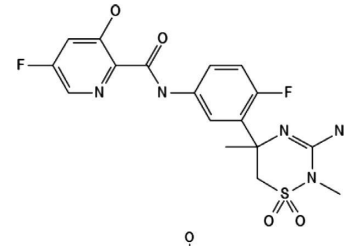
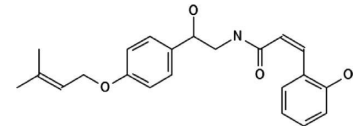
3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1: Continued.

Compounds	Drug metabolism	Structure	Abbreviation
Verubecestat 	Reduction of carbonyl: carbonyl reductase (NADPH)		D11
	Pyridine N-oxidation: cytochrome P450 1A2		V1
	N-Hydroxylation of secondary arylamide: cytochrome P450 1A2		V2
	Hydroxylation of benzene on carbon ortho to the strongly electron donating group: cytochrome P450 1A2		V3
	Hydroxylation of benzene on carbon ortho to the strongly electron donating group: cytochrome P450 1A2		V4
	Hydroxylation of heteroalicyclic secondary carbon: cytochrome P450 1A2		V5

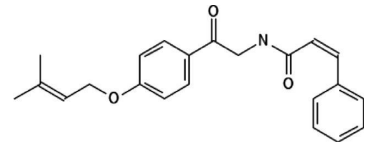
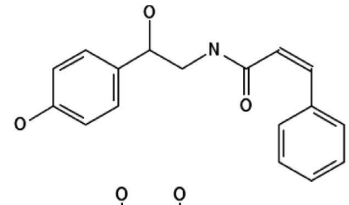
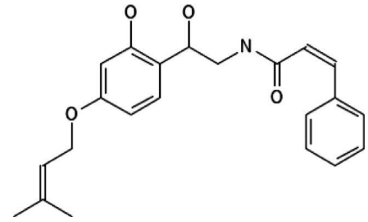
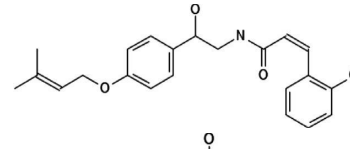
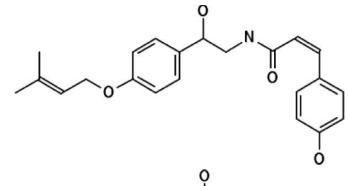
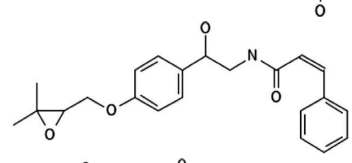
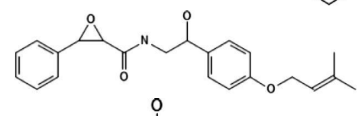
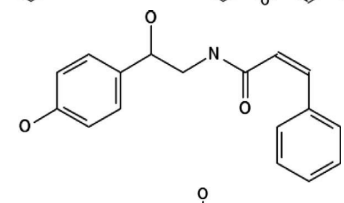
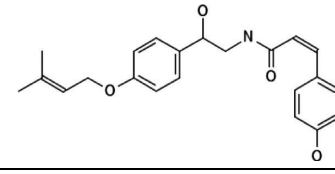
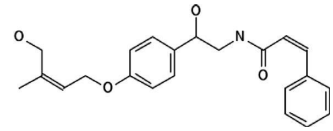
3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1: Continued.

Compounds	Drug metabolism	Structure	Abbreviation
Marmeline 	Hydroxylation of aromatic carbon ortho to the halide group: cytochrome P450 1A2		V6
	Hydroxylation of aromatic carbon ortho to the halide group: cytochrome P450 1A2		V7
			V8
	Hydroxylation from CyProduct: cytochrome P450 1A2		V9
	Hydroxylation of aromatic carbon meta to the halide group: cytochrome P450 2A6		V10
			V11
	O-Hydroxylation of monosubstituted benzene: cytochrome P450 1A2		M1

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1: Continued.

Compounds	Drug metabolism	Structure	Abbreviation
	Oxidation of secondary alcohol to ketone: cytochrome P450 1A2		M2
	O-Dealkylation from CyProduct: cytochrome P450 1A2		M3
	Hydroxylation of benzene on carbon ortho to the electron donating group: cytochrome P450 1A2		M4
	Hydroxylation of benzene on carbon ortho to the electron donating group: cytochrome P450 1A2		M5
	Hydroxylation of benzene on carbon para to the electron donating group from CyProduct: cytochrome P450 1A2		M6
	Epoxidation of alkene: cytochrome P450 1A2		M7
	Epoxidation of alkene: cytochrome P450 1A2		M8
	O-Dealkylation from CyProduct: cytochrome P450 2C9		M9
	Hydroxylation from CyProduct: cytochrome P450 2C19		M10
	Hydroxylation from CyProduct: cytochrome P450 2C9		M11

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2: Differentially expressed genes (DEGs) of Alzheimer's disease (AD) and marmeline (MML).

Names	Total	Differentially expressed genes
AD–MML	103	VDR MMP2 HCK ErbB4 ZAP70 RARG STS CCL5 C1S CDK6 HMOX1 CSK MMP7 NOS2 MMP13 LCK DCK GALE RARA FNTA CMA1 MMP3 FGFR1 FABP7 PPARA RORα ACADM JAK3 IMPA1 SETD7 BACE1 MMP8 KIT FABP4 AKT1 RXRα JAK2 NR1H2 PDPK1 RAB5A PDK2 NR1H3 TPH1 XIAP APOA2 CD1A PADI4 MDM2 MIF AKT2 EGFR NQO1 DPP4 TGM3 FCAR CDC42 ALDH2 IL2 ESR1 ACE2 PNMT GSTT2 SHBG FABP5 PAK6 PDE4D KIF11 NR1I2 MMP16 CASP7 CCNT1 THRB PDE5A QPCT ARSA CCNA2 ADK ISG20 GSK3β PPARγ DAPK1 NQO2 EPHB4 DUT STAT1 NOS3 GSTP1 ANXA5 MMP12 BST1 ST14 SRC PDE4B CASP3 NR1H4 PDE3B CBR1 MMP9 NR1I3 DPEP1 OAT FABP6 CLK1
AD	184	PPARD HMGCR LGALS2 MAN1B1 NR3C2 FECH SDS PITPNA GSR TK1 HPN HSD17B1 CYP19A1 CYP2C8 MTHFD1 GSTA1 IGF1 MAPK14 PLAU SULT1E1 KDR FABP3 PAK1 GC GLO1 CTSS TGFBR2 SOD2 PTPN1 HAGH MET AKR1C1 CRABP2 RAB11A AMY1A PRKCQ FAP GSTZ1 TTR ADAM17 MAOB LYZ FGFR2 PSAP MAPKAPK2 NMNAT1 AMY2A CSNK1G2 ADAMTS4 CTNNA1 RBP4 FHIT CFB HNMT PIK3R1 GM2A MAPK1 IMPDH2 PYGL CTSG ELANE PLEKHA4 TEK SRM OTC IMPDH1 PRKACA F2 NT5M TNK2 PTPN11 ARG1 RNASE3 PIK3CG PLAT PCK1 PLK1 SULT2A1 CBS MAP2K1 ADH1C TGFBR1 CYP2C9 ARHGAP1 HK1 PPCDC REN HEXB BHMT PLA2G2A HNF4G TPI1 WAS HSD11B1 LCN2 AKR1C3 LGALS3 GNPDA1 CYP21A2 ADH5 TYMS TRAPPC3 ALB CHEK1 TPSB2 ITK TREM1 DTYMK HRAS AZGP1 ANG HSD17B11 BIRC7 GCK FKBP1B GPI F7 MAPK8 MME ABO IGF1R BCAT2 HDAC8 F10 ESRRA MTAP DHODH ABL1 SULT2B1 CDA AR MAPK10 CALM1 CHIT1 AKR1B1 CA2 HSP90AB1 ESR2 CSNK2A1 BRAF GSTA3 CTSF FDPS SORD PLA2G10 HSPA4 FKBP1A RHOA CDK5R1 AMD1 HSPA8 SHMT1 CES1 MMP1 SERPINA1 CA12 TYMP TNNC1 AKR1C2 CFD ITGAL EPHX2 AHCY BLVRB AURKA ESRRG LSS REG1A CDK2 PAH DHFR ACP3 PGR LTA4H PNP HSP90AA1 SEC14L2 PIM1 S100A9 UCK2 PARP1 NR3C1 F11 THRA
MML	191	P03956 CALM FKB1A P49789 TPIS P78536 SAHH FABPH P14061 TGFR1 TTHY CATS P22830 Q06520 RET4 Q9NPB1 P07686 P08238 MCR VTDB TIE2 P11586 SEPR P35520 P20132 P11142 S10A9 BRAF1 MP2K1 ANDR P04179 P11309 AK1C3 O43617 AMYP TYPH CP2C9 SPYA ALDR ADHX Q96CA5 P09874 P04183 RASH O76054 O00204 ADA17 KPCT NGAL HMDH Q9UBX1 NEP GLYC MK08 P00519 RB11A PTGD2 Q16772 CAH2 CFAD Q9NP99 P49137 Q9BY41 PAK7 CAH12 PRGR P68400 P21802 Q13126 PNPH ALBU PPAP Q9BZX2 GCR O15382 P05451 P35558 MK10 DHSO Q93088 P61626 HXK4 P00326 MK01 Q14541 ANGI ELNE LGUL Q16539 P35968 G6PI P01343 TRYB2 P10827 P85A Q9H4M7 DYR FPPS KTHY ERG7 P11474 AOFB AMPM2 P29373 CP2C8 HYES CDD P63316 CHK1 P10828 Q04828 LEG2 P08263 PYRD P17900 Q03181 P06737 Q9NY01 KC1G2 P30043 LKHA4 P53350 FA10 IMDH1 P24941 CFAB FKB1B CATG ARGI1 Q16775 PTN1 LEG3 P07602 FA7 Q9HAN9 HXK1 TGFR2 P00517 DHI1 Q07960 O14965 UROK P11511 O43708 ACK1 O15496 ITAL P05981 DCAM P32589 TYSY CTNA1 P46926 PK3CG P62508 P00390 EST1 DHB11 Q13231 P37243 ATS4 TPA Q9UKM7 WASP Q08881 P04745 IMDH2 PH4H P08069 PTN11 FA11 AK1C2 Q96CD2 P12724 P14555 CATB Q62986 ST1E1 P07900 CD5R1 P50135 Q00169 P00480 P19623 A1AT CAH1 P08581 P16442 ZA2G P61586 RENI

2.5. Molecular Docking. It commences with the examination of binding interactions involving key compounds present in bael fruit, as delineated in Table 3, through the process of molecular docking. Subsequently, structures demonstrating favorable binding with target proteins underwent detailed scrutiny to identify novel features arising from metabolic processes facilitated through the liver.

The molecular structures of all marmeline metabolites were generated using PubChem software. Concurrently, the structures of BACE1 and AChE were retrieved from the PDB database. The data underwent processing with MGLTools 1.5.6 and were saved as pdbqt files [31]. Active sites and grid box coordinates of BACE1 and AChE were determined based on the analysis of robust binding sites using CavityPlus. The coordinates for BACE1 and AChE proteins were $21.565 \times 22.477 \times 44.952$ and $-0.783 \times -51.77 \times 2.859$, respectively. The dimensions of each box were $80 \times 90 \times 108$ and $62 \times 94 \times 126$ grids for BACE1 and AChE, respectively. The docking process involved small-molecule proteins and employed ArgusLab, AutoDock, and AutoDock Vina Version 1.1.2 for molecular docking analyses. Standardization of molecular structures was performed using PyMOL [32], and

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

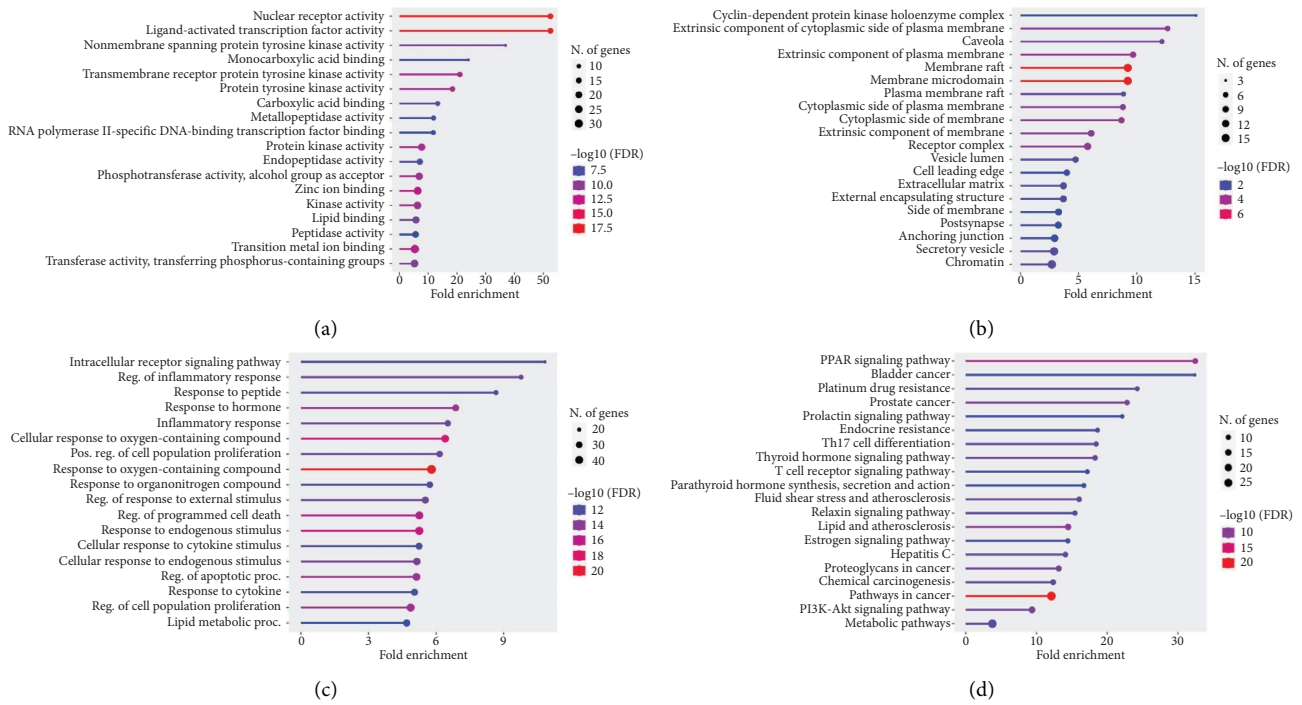


Figure 1: The results of a Gene Ontology (GO) enrichment analysis are presented graphically in the form of a bubble chart, which emphasizes the 17 most important keywords corresponding to their respective fold enrichment values for the following categories: (a) biological process (BP), (b) cellular component (CC), (c) molecular function (MF), and (d) Kyoto Encyclopedia of Genes and Genomes (KEGG). The color scheme is organized in accordance with the –log value, while the term "marmeline" signifies the number of target genes associated. The 103 components derived from the KEGG pathway analysis are presented in ascending order based on their negative logarithmic values. The intensity of the red hue signifies a higher level of enrichment.

the conformations exhibiting the highest scores were visualized and assessed using BIOVIA Discovery Studio Visualizer [33]. PubChem was utilized to depict molecular structures of compounds, subsequently transformed into three-dimensional (3D) structures with Avogadro software [34]. The refinement of these structures was realized through optimization utilizing MMFF94 force fields [35]. The 3D structures of BACE1 and AChE were sourced from the RCSB Protein Data Bank (https://www.rcsb.org), with particular emphasis on selecting the 3D structures of BACE1 (PDB ID: 2QP8) and AChE (PDB ID: 4EY6) specifically for protein docking. Conversion of both proteins and chemicals to PDBQT format was executed using AutoDockTools [36]. ArgusLab [37], AutoDock [38], and AutoDock Vina [39] are softwares which utilized the molecular docking method. To enhance computational precision, the parameter exhaustiveness was adjusted to a value of 20 [40, 41]. Default values were assigned to all parameters, except for explicitly indicated ones. Subsequently, the conformation characterized by the highest score value was selected for a thorough data analysis.

2.6. Pharmacokinetic Assessment Using the SwissADME Predictor. The SwissADME predictor [42] serves as a pivotal tool in discerning the bioavailability of compounds and their metabolites. This tool, characterized as a complementary online resource, is instrumental in evaluating the pharmacokinetics, drug-likeness, and medicinal chemistry compatibility of small compounds. In the landscape of freely available web-based tools for pharmacokinetics, advanced methodologies such as iLOGP7 or the BOILED-Egg have emerged, offering users the capability to visualize, store, and share data for individual molecules or through comprehensive intuitive and interactive graphical representations. The 2D structure of marmeline was delineated on PubChem, while the 3D structures were meticulously generated on Avogadro by minimizing energy using the MMFF94 option, with the imported structure presented in the SMILES format. Subsequently, an investigation into SwissADME medication design was undertaken, and the ensuing results were meticulously documented.

2.7. Data Mining. The Gene Expression Omnibus (GEO) database includes high-throughput gene expression data submitted by researchers worldwide. Large sample sizes were considered to provide more reliable results in the screening of differentially expressed genes (DEGs). Therefore, this research employed a gene expression profile dataset of AD that was downloaded from the GEO public database (https://www.ncbi.nlm. https://nih.gov/geo). The GSE5281 dataset containing 74 control samples and 87 AD samples based on the GPL570 platform was selected for further analysis in the present study. Data from the GEO database

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

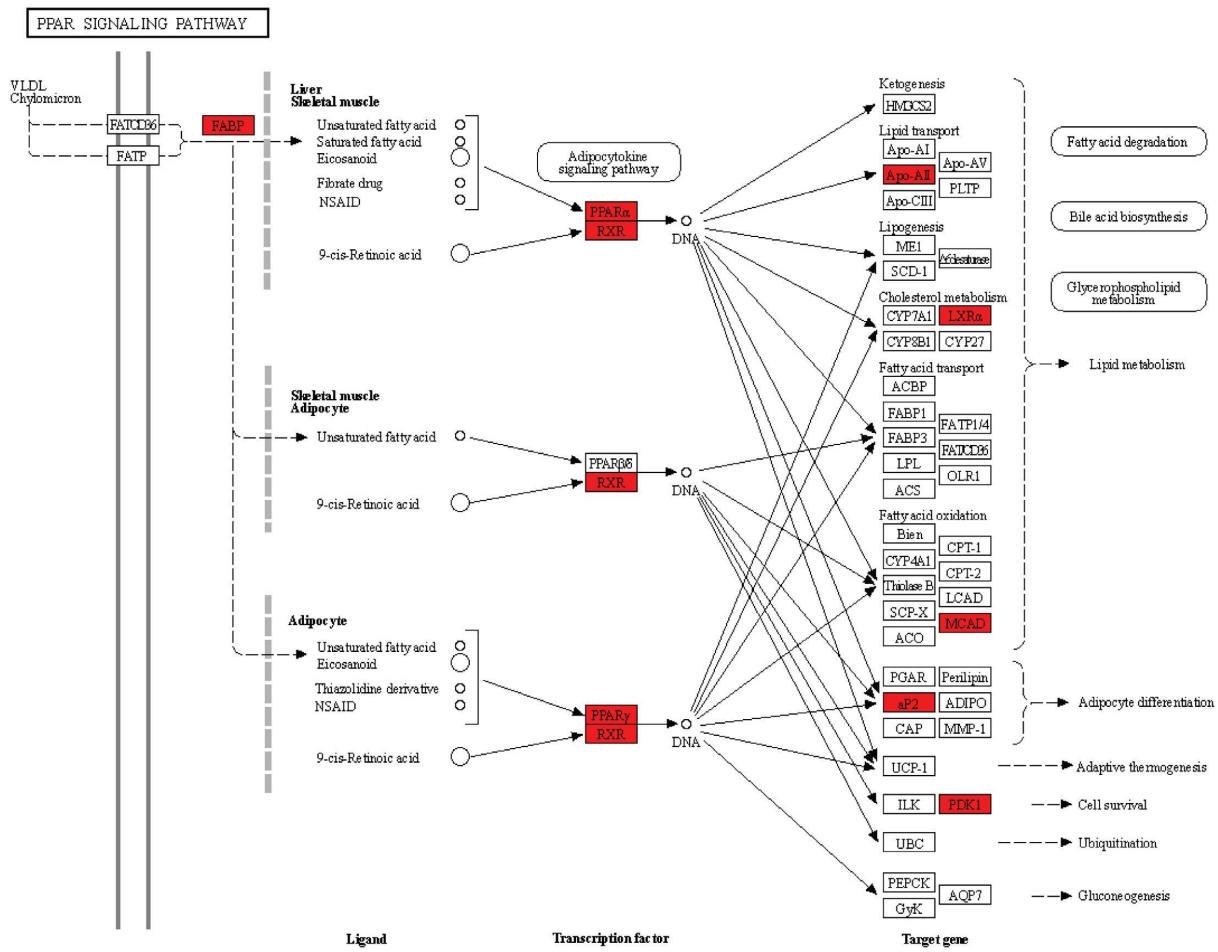


FIGURE 2: Alterations in the PPAR signaling pathway, denoted by the red color, where the entities targeted by marmeline are indicated.

are accessible and free of charge, and their utilization does not require the approval of an ethics committee.

2.8. Gene Expression Analysis (GEA). We utilize shinyGEO to procure gene expression datasets directly from the GEO. We select datasets based on the intersection with the marmeline–AD disease for analysis. Subsequently, the raw gene expression data were transformed into a log2 scale. This transformation is essential as it normalizes the data, facilitating the identification of fold changes (FCs) in gene expression. The log2 Fold-Change (log2 FC) is preferred because it simplifies statistical analysis and aids in detecting biologically relevant changes. Within shinyGEO, we define the genes by selecting samples belonging to both the healthy and AD groups. We ensure that the healthy group comprises 74 samples and the AD group consists of 87 samples to enhance the reliability of the analysis. We conduct differential expression analysis by comparing the average expression levels of genes between the AD and healthy groups. The objective is to identify genes that are significantly upregulated or downregulated in the AD group compared to the healthy group. We employ a statistical *t*-test to determine significance, using a cutoff p value of less than 0.001. We examine the results for log2 FC and p values. A positive log2 FC indicates upregulation, whereas a negative value signifies downregulation of the genes in the AD group relative to the healthy group.

2.9. Analysis of Solubility and Interaction Profiles of Marmeline With Various Solvents. The molecular structure of marmeline was obtained from PubChem, which was then used further for checking its interactions and solubility with different solvents by using COSMOquick as the earlier study [41, 43]. This method provides meaningful information regarding electrostatic characteristics and solubility behavior of marmeline under different chemical conditions. Electrostatic potential maps show the charge distribution in all solvents including acetone, ethyl acetate, ethanol, water, and heptane. The visualizations demonstrate positive and negative potentials, which allow us to understand how marmeline interacts with these different solvents. Herein, the derived structure of marmeline is given that indicates the regions of charge distribution that may interact with solvent, thus establishing the molecular basis for interpreting in a particular solvent environment. Charge density plots additionally provide a comparison of the active electronic environments of marmeline and the solvents, revealing distinct areas of positive and negative charge where the possible interaction sites that could influence solubility exist.

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 3: Binding energies of compounds isolated from bael fruit in comparison with standard inhibitors Donepezil and Verubecestat as positive controls.

Compounds	ArgusLab		AutoDock		AutoDock vina	
	AChE	BACE1	AChE	BACE1	AChE	BACE1
Donepezil	−12.2857	−10.2176	−7.63	−6.55	−8.5	−6.7
Verubecestat	−9.0988	−9.02403	−7.57	−5.48	−8.7	−7.6
Chlorogenic acid	−10.6627	−11.0622	−3.7	−3.21	−9.9	−7.8
Marmeline	−13.4258	−11.3812	−5.86	−5.55	−8.1	−7.4
Isoscoparin	−8.99362	−9.78634	−6.08	−3.51	−8.2	−7.5
Astragalin	−8.8409	−9.56985	−3.7	−2.33	−8.4	−7.4
Kaempferol 3-O-α-L-rhamnopyranosyl-(1-6)-β-D-glucopyranoside	−9.80292	−10.2305	−2.22	−2.14	−8.9	−8.5
Kaempferol 3-O-α-L-rhamnopyranosyl-(1-2)-β-D-glucoronopyranoside	−8.07306	−9.0612	−3.44	−2.17	−9.0	−8.2
Kaempferol 3-O-β-D-glucoronopyranoside	−9.39773	−10.1921	−3.47	−3.7	−8.3	−8.1
Myricetin 3′,5′-dimethyl ether 3-O-β-D-glucopyranoside	−8.9348	−9.55236	−3.43	−3.05	−8.5	−7.5
Quercetin 3-O-β-D-glucopyranoside	−9.86721	−10.0134	−3.69	−2.55	−8.9	−8.8
Isorhamnetin 3-O-β-D-glucopyranoside	−8.69247	−8.77628	−5.56	−3.86	−8.2	−7.2
Isorhamnetin 3-O-α-L-rhamnopyranosyl-(1 ⟶ 6)-β-D-glucopyranoside	−9.90749	−8.83744	−1.6	−1.61	−9.4	−8.6
β-Sitosterol glucopyranoside	−10.8543	−11.6236	−4.72	−4.37	−8.4	−6.8
Squalene	−15.4327	−13.269	−4.61	−3.53	−5.5	−5.7
Clionasterol	−9.76188	−10.5008	−7.8	−5.68	−7.9	−6.5

These profiles demonstrate the interaction of the marmeline with the hydrogen and nonhydrogen bond acceptor/donor in each solvent. A table also presents the solubility data of the marmeline across a temperature range of 25°C–100°C. The data is represented using a color-coded scheme to indicate the stepwise degree of solubility.

In summary, this investigation reveals the solubility features of marmeline due to the charge compatibilities between the types of solvents and marmeline. This research, which helps make predictions about how marmeline interacts with different solvents and its behavior in other chemical contexts as well, represents the first step in a thorough understanding of how solvents and temperature influence the energy required for a compound to transition from a solid to a liquid state. Regarding this study, the solubility of the chosen solvents in several solvents can be computationally predicted from the COSMOquick software approach according to equation (1): Estimation of the Gibbs free energy change upon melting can be used to make this estimation. In the above example, ΔG_{fus} is the Gibbs free energy change for fusion, ΔH_{fus} is the enthalpy change of fusion and T is the temperature at which the process is evaluated, and T_m is the melting point of the substance.

$$\Delta G_{fus} = \frac{\Delta H_{fus} - \Delta H_{fus}(1 - T)}{T_m}. \quad (1)$$

3. Results and Discussion

3.1. Target Identification for AD and Active Compounds. GeneCards was used to assess Alzheimer-related genes and PharmMapper, SEA, and SwissTargetPrediction were additionally utilized to identify potential targets of marmeline. Following the extensive investigation of genes listed in Table 2, 287 genes with differential expression in AD were detected. Furthermore, 294 genes manifested differential expression within the prospective targets of the marmeline

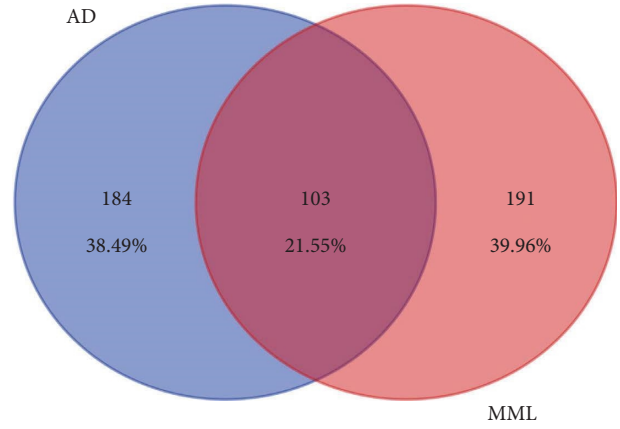


Figure 3: Comparative Venn diagram illustrating the distinct and overlapping sets of differentially expressed genes (DEGs) in Alzheimer's disease (AD) and marmeline (MML) datasets.

group. The intersection in the Venn diagram (Figure 3) representing the two distinct groups of DEGs comprised a total of 103 DEGs.

This overlap suggests that marmeline may indeed have a substantial anti-AD effect by modulating multiple genes involved in the disease pathology. The use of multiple bioinformatics tools, including GeneCards, PharmMapper, SEA, and SwissTargetPrediction, provides a comprehensive approach to target identification. This multiplatform strategy enhances the reliability of the results by cross-validating potential targets across different databases and prediction algorithms. The identification of 287 DEGs in AD highlights the complex nature of the disorder, involving numerous genetic pathways and molecular mechanisms. Similarly, the 294 genes identified as potential targets of marmeline indicate that this compound may have pleiotropic effects, potentially addressing multiple aspects of AD pathology simultaneously. The 103 overlapping DEGs between AD–related genes and marmeline targets suggest that this

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

compound may be particularly well-suited for AD treatment. These shared genes likely represent key pathways involved in AD pathogenesis that marmeline can potentially modulate. Further investigation into the specific functions and interactions of these overlapping genes could provide valuable insights into the mechanism of action of marmeline and its potential therapeutic effects in AD.

3.2. Functional Enrichment Analysis. To explore potential pathways, the DAVID database [44] was employed for comprehensive analysis encompassing biological processes (BPs), cellular components (CCs), and molecular functions (MFs). Marmeline is a compound that has the potential to help treat Alzheimer's. From the results shown in Figure 1, the mechanism of action of marmeline can be summarized as follows. In Figure 1(a), the BP enrichment analysis highlights several key activities related to AD as top enrichment such as nuclear receptor activity and ligand-activated transcription factor activity. These functions are crucial in regulating gene expression, including genes involved in neuroinflammation and neuroprotection. Activation of peroxisome proliferator–activated receptor-gamma (PPARγ), a nuclear receptor, is known to reduce inflammation and promote clearance of Aβ peptides. Nonmembrane-spanning protein tyrosine kinase activity is involved in signaling pathways that regulate cell growth, differentiation, and survival, which are critical in neuronal health. In Figure 1(b), the CC analysis shows the enrichment of components critical to Alzheimer's pathology. Cyclin-dependent protein kinase holoenzyme complex is involved in the cell cycle regulation, and dysregulation can lead to neuronal apoptosis. Changes in cytoplasmic and plasma membrane particles can affect cell signaling and integrity, which are crucial in the maintenance of synaptic function. Extrinsic components of membrane and caveola are involved in endocytosis and signal transduction, processes that are disrupted in AD. Anchoring junction and anchoring protein activity are vital for maintaining cell structure and communication, which are compromised in neurodegenerative diseases. In Figure 1(c), the MF analysis highlights several key pathways relevant to AD. The intracellular receptor signaling pathway includes nuclear receptors such as PPARγ, which are involved in modulating inflammation and metabolism in neurons. The regulation of inflammatory response is a hallmark of Alzheimer's pathology, and regulating this response is crucial for therapeutic interventions. Response to hormones and endogenous stimuli can affect brain function and is implicated in AD. Response to oxidative stress is a significant contributor to neuronal degeneration in Alzheimer's. Regulation of the apoptotic process to prevent excessive neuronal apoptosis is vital in maintaining cognitive functions in Alzheimer's patients. In addition, enrichment analysis of genomes (KEGG) was conducted for the identified targets [45, 46]. Subsequently, the top 17 outcomes were selected based on their ascending order of magnitude (Figure 1(d)). PPAR-α, a key pathway in this study, plays a crucial role in regulating the expression of genes responsible for encoding enzymes involved in the metabolism of APP [47]. It exerts inhibitory control over β-secretase (BACE1), the principal enzyme implicated in the release of Aβ peptides in AD [48].

This inhibition is characterized by multitarget and multicomponent effects, with specific targets elucidated in Figure 2. Since the focus of the study is on the genes involved in the PPAR signaling pathway, as shown in the KEGG pathway (Figure 2), it is crucial to highlight the representative target genes. The regulation of gene expression encoding enzymes implicated in the metabolism of APP is largely dependent on the PPAR signaling pathway. It has been shown that PPARγ activation selectively inhibits the activity of β-secretase (BACE1), the primary enzyme in charge of cleaving Aβ peptides, which are a hallmark of the pathophysiology of AD. Furthermore, the pathway includes the regulation of AChE activity, a neurotransmitter notably diminished in people with AD, and its levels need to be sustained. PPARγ, RXRα, and FABP4 are some of the critical genes involved in these regulatory processes. PPARγ, RXRα, and FABP4 are some of the critical genes involved in these regulatory processes. The focus of this work is on marmeline, a natural PPARγ activator with the potential to modulate these pathways and offer therapeutic benefits for AD.

Marmeline's mechanisms of action and therapeutic promise in AD can be revealed by functional enrichment analysis of its possible targets. This thorough examination of BPs, CCs, and molecular activities suggests that marmeline may treat AD's complicated pathophysiology in several ways. The enrichment of nuclear receptor activity and ligand-activated transcription factor activity implies that marmeline may modulate neuroprotection and anti-inflammatory gene expression. Active PPARγ reduces inflammation and promotes the clearance of Aβ peptides, which are crucial in AD pathogenesis. The predominance of nonmembrane-spanning protein tyrosine kinase activity suggests that marmeline may affect signaling pathways that govern neuronal health, development, and survival, which are crucial for cognitive function and AD prevention. The cyclin-dependent protein kinase holoenzyme complex, cytoplasmic and plasma membrane particles, extrinsic membrane and caveola components, and anchoring junctions are important to AD pathogenesis. These components prevent neuronal death, maintain synaptic function, facilitate signal transduction, and preserve cell shape and communication, which are commonly disrupted in neurodegenerative illnesses suh as AD. MF research suggests that marmeline may affect AD–related pathways. The intracellular receptor signaling system, inflammatory response, hormone and endogenous stimulus response, oxidative stress response, and apoptotic processes are examples. These actions are essential for treating AD pathophysiology, from neuronal inflammation and metabolism to neuronal death prevention. The KEGG pathway analysis reveals marmeline's putative mode of action, focusing on the PPAR signaling pathway. This pathway controls gene expression for enzymes that metabolize APP and block β-secretase (BACE1), which releases Aβ peptides. AChE activity, essential for neurotransmitter levels in

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

AD patients, is regulated by the PPAR signaling pathway. RXRα, FABP4, and PPARγ are the key genes in these processes.

3.3. Molecular Docking and In Silico Metabolite Prediction. The molecular docking methodology was performed in iterations. First, it was performed to identify the key compounds in bael fruit which can antagonize BACE1 and AChE proteins. Importantly, besides marmeline, the major component of bael fruit, several biologically significant compounds were detected [49]. These include chlorogenic acid [50], kaempferol 3-O-α-L-rhamnopyranosyl-(1-6)-β-D-glucopyranoside [51], kaempferol 3-O-α-L-rhamnopyranosyl-(1-2)-β-D-glucoronopyranoside [50], quercetin 3-O-β-D-glucopyranoside [52], isorhamnetin 3-O-α-L-rhamnopyranosyl-(1 ⟶ 6)-β-D-glucopyranoside [53], squalene [54], and clionasterol [55], meticulously outlined in Table 3. The presence of these compounds unequivocally demonstrated heightened efficacy in inhibiting both BACE1 and AChE proteins.

In the second phase, rigorous scrutiny was applied to marmeline extracts to elucidate their metabolic pathways within diverse physiological processes before systemic absorption and entry into the bloodstream. Cytochromes P450s, constituting a superfamily of isoenzymes accountable for the metabolism of a myriad of substances originating from both exogenous and endogenous origins, have been identified as pivotal entities associated with toxicological events [56]. Medication interactions stemming from metabolic processes pose a significant challenge in the realm of drug development. The concurrent administration of multiple pharmaceutical agents, vying for occupancy of the same P450 enzyme, wherein one drug exhibits a pronounced affinity for the enzyme either as a substrate or an inhibitor, has the potential to impede the metabolic processes of the coadministered drug [57]. This circumstance can elevate levels of the other drug in the bloodstream, heightening the risk of adverse side effects. Early identification of interactions between compounds and P450 CYP enzymes is imperative for mitigating potential issues during the initial phases of lead optimization. Pharmaceutical enterprises predominantly investigate five critical human CYP isoforms, namely, 1A2, 2C9, 2C19, 2D6, and 3A4. Cumulatively, these isoforms constitute over 60% of the overall hepatic CYPs and exert substantial influence on the metabolism of pharmaceutical agents [58].

Analysis of Table 1 reveals the distinctive metabolic pathways of three compounds, namely, donepezil, verubecestat, and marmeline, within the hepatic environment. Donepezil undergoes comprehensive structural modifications as 11 metabolites through hepatic metabolism, notably facilitated by the enzymatic activities of CYP450 isoforms 1A2, 2C9, 2D6, and 3A4. In addition, donepezil undergoes metabolic transformations catalyzed by carbonyl reductase (NADPH). The metabolic processing of verubecestat involves 11 unique metabolites. Notably, the enzymatic mediation is pronounced, primarily orchestrated by CYP450 isoforms 1A2 and 2A6. Marmeline exhibits a parallel pattern, undergoing structural alterations as 11 metabolites. The metabolic transformations are prominently guided by the enzymatic activities of CYP450 isoforms 1A2, 2C9, and 2C19. The structures of the substance, as metabolized by the liver, were subsequently re-evaluated to investigate its interactions with both proteins. It was found that the structure of the majority of marmeline, which has been altered by the liver, can interact better with both BACE1 and AChE compared to the two standard substances currently used for treatment. This observation is based on the high negative energy values [43], as shown in Figure 4.

From Table 4, it is found that the structure of D2, a metabolite of donepezil processed by the liver through the hydroxylation of nonterminal aliphatic carbon adjacent to the aromatic ring by cytochrome P450 1A2, can interact best with both AChE and BACE1 when compared to other conformations of donepezil. Meanwhile, the structure of V1, a metabolite of verubecestat processed by the liver through pyridine N-oxidation by cytochrome P450 1A2, can best interact with AChE, and V8, another metabolite of verubecestat processed by the liver through hydroxylation of aromatic carbon ortho to the halide group by cytochrome P450 1A2, can best interact with BACE1. On the other hand, the structure of M9, a metabolite of marmeline processed by the liver through O-dealkylation from CyProduct by cytochrome P450 2C9, can best interact with AChE, and M2, another metabolite of marmeline processed by the liver through oxidation of secondary alcohol to ketone by cytochrome P450 1A2, can best interact with BACE1.

When comparing the efficacy of substances that undergo liver metabolism with their effectiveness in inhibiting BACE1 and AChE through molecular docking processes, as shown in Table 4, it is found that the most effective substance is V8 of verubecestat. This is achieved through the formation of hydrogen bonds with GLN73, THR133, GLN134, and GLY291 of BACE1 (Figures 5(b) and 5(e)). Following closely is M2 of marmeline, which forms hydrogen bonds with THR133, GLN134, GLY291, and THR292 of BACE1 (Figures 5(c) and 5(f)). The least inhibitory effect is observed with D2 of donepezil, forming hydrogen bonds with THR293 of BACE1 (Figures 5(a) and 5(d)).

Regarding the inhibition of AChE, as shown in Figure 6, V1 of verubecestat (Figures 6(b) and 6(e)) is the most effective, forming hydrogen bonds with GLU313 and ARG296. The next effective substance is M9 of marmeline (Figures 6(c) and 6(f)), forming hydrogen bonds with SER293. The least inhibitory effect is observed with D2 of donepezil (Figures 6(a) and 6(d)), and no hydrogen bond formation was detected.

However, it is found that the number of modified structures capable of inhibiting both BACE1 and AChE the most is marmeline. It is observed that marmeline has structures up to 6 and 3 conformations with binding energy values in the range of −9 to −9.9 kcal/mol for inhibiting AChE and BACE1, respectively. Next in line is verubecestat, which has 1 and 2 conformations in the same range for inhibiting AChE and BACE1, respectively. Donepezil, on the other hand, has only 1 conformation capable of inhibiting AChE in the range of −9 to −9.9 kcal/mol and no conformations that can inhibit BACE1 in the same range, as shown in Figure 4.

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

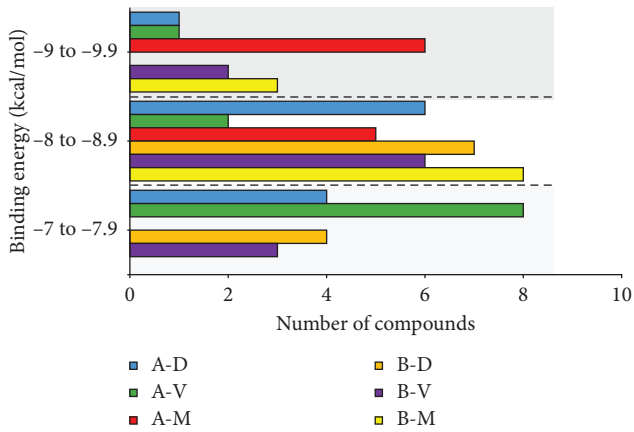


Figure 4: The quantity of metabolites produced by donepezil (D), verubecestat (V), and marmeline (M) within the human, along with their capacity to bind with the target proteins AchE (A) and BACE1 (B).

Table 4: Binding energy (kcal/mol) of metabolites produced by donepezil (D), verubecestat (V), and marmeline (M) within the human.

Metabolites	Binding energy (kcal/mol) ± SD	
	AChE	BACE1
D1	−8.51 ± 1.85	−8.06 ± 0.20
D2	−9.09 ± 0.55	−8.73 ± 0.61
D3	−8.18 ± 2.09	−8.70 ± 1.27
D4	−8.54 ± 1.32	−7.46 ± 0.65
D5	−7.23 ± 1.73	−7.51 ± 0.29
D6	−8.43 ± 2.31	−8.60 ± 0.42
D7	−7.18 ± 0.25	−8.16 ± 0.65
D8	−7.82 ± 1.87	−7.53 ± 0.75
D9	−8.87 ± 1.36	−8.33 ± 1.17
D10	−7.64 ± 1.04	−7.78 ± 0.03
D11	−8.19 ± 2.10	−8.35 ± 0.91
V1	−9.89 ± 1.81	−9.18 ± 0.70
V2	−8.08 ± 0.68	−7.77 ± 1.04
V3	−7.85 ± 0.49	−8.27 ± 0.05
V4	−7.10 ± 0.42	−7.59 ± 0.16
V5	−7.63 ± 0.39	−8.11 ± 0.01
V6	−8.09 ± 0.26	−8.82 ± 0.69
V8	−7.69 ± 0.30	−9.22 ± 0.40
V9	−7.56 ± 0.21	−8.58 ± 0.03
V10	−7.87 ± 0.05	−8.24 ± 0.08
V11	−7.78 ± 0.04	−8.70 ± 0.14
M1	−8.77 ± 3.91	−8.56 ± 2.02
M2	−8.93 ± 4.07	−9.13 ± 2.21
M3	−9.12 ± 3.62	−8.82 ± 2.64
M4	−9.08 ± 3.66	−9.06 ± 3.21
M5	−9.01 ± 3.65	−8.60 ± 2.09
M6	−8.67 ± 3.10	−8.48 ± 2.16
M7	−9.01 ± 3.66	−8.76 ± 2.55
M8	−8.78 ± 3.63	−8.45 ± 2.52
M9	−9.41 ± 2.90	−8.85 ± 2.30
M10	−8.93 ± 3.14	−8.56 ± 2.04
M11	−9.17 ± 2.55	−9.00 ± 3.00

This study's molecular docking and *in silico* metabolite prediction reveal marmeline and other bael fruit chemicals' potential to cure AD. This thorough study illuminates these drugs' metabolic pathways, medication interactions, and interactions with important AD–related proteins. Molecular docking showed that marmeline and other physiologically relevant chemicals in bael fruit inhibited BACE1 and AChE proteins. Chlorogenic acid, kaempferol, quercetin derivatives, isorhamnetin, squalene, and clionasterol demonstrate that bael fruit is rich in AD–targeting chemicals. This discovery emphasizes the relevance of natural products in developing innovative AD therapies and their synergistic potential in treating different AD disease features. The metabolism of marmeline, donepezil, and verubecestat was examined in the second phase. This study is essential for medication interactions and adverse effects. All three drugs undergo considerable metabolic changes, mostly mediated by CYP isoforms, according to the research. CYP isoforms 1A2, 2C9, 2C19, 2D6, and 3A4 metabolize nearly 60% of pharmacological drugs, making them important in drug development and medication-drug interactions. This study found that numerous liver-altered marmeline metabolites interacted better with BACE1 and AChE than conventional therapy drugs. Marmeline's metabolites may be more effective than existing AD therapies due to their strong negative energy values. The comprehensive study of particular metabolites indicated that verubecestat (V8) inhibited BACE1 best, followed by marmeline (M2) and donepezil (D2). Another verubecestat metabolite (V1) inhibited AChE best, followed by M9 and D2. The study found that marmeline produced the most BACE1 and AChE-inhibiting metabolites. For AChE and BACE1 inhibition, marmeline produced 6 and 3 conformations with binding energies of −9 to −9.9 kcal/mol. Verubecestat followed, whereas donepezil performed poorly. These data imply that marmeline may be a more effective and adaptable AD therapy than existing medications. The capacity of marmeline's metabolites to retain or increase their inhibitory effects on key AD–related proteins suggests sustained treatment activity and may be fewer adverse effects.

3.4. GEA. The relationship between certain genes and AD is complex and involves various genetic and molecular mechanisms. AD is the most common neurodegenerative disorder, characterized by progressive cognitive decline and memory loss. Several studies have identified genes that are either upregulated or downregulated in individuals with Alzheimer's, providing insights into the disease's pathophysiology. In Table 5, the relationship between marmeline and AD identified 103 genes associated with Alzheimer's. However, only 31 of these genes showed significant changes in expression in Alzheimer's patients, as indicated by a p value of less than 0.001. These genes are further categorized into those that are upregulated and downregulated.

There are 14 genes leading to being upregulated in AD. Figure 7 include ErbB4, CDK6, CSK, GALE, FGFR1, PPARγ, RORα, RXRα, AKT2, EGFR, matrix metalloproteinase 16 (MMP16), CASP7, CCNT1, and PDE5A. ErbB4 plays a role in AD pathology by mediating Aβ–induced neurotoxicity through the JNK/tau pathway, indicating involvement in tau phosphorylation and synaptic function. Upregulation of ErbB4 correlates with increased neurotoxicity and has been

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

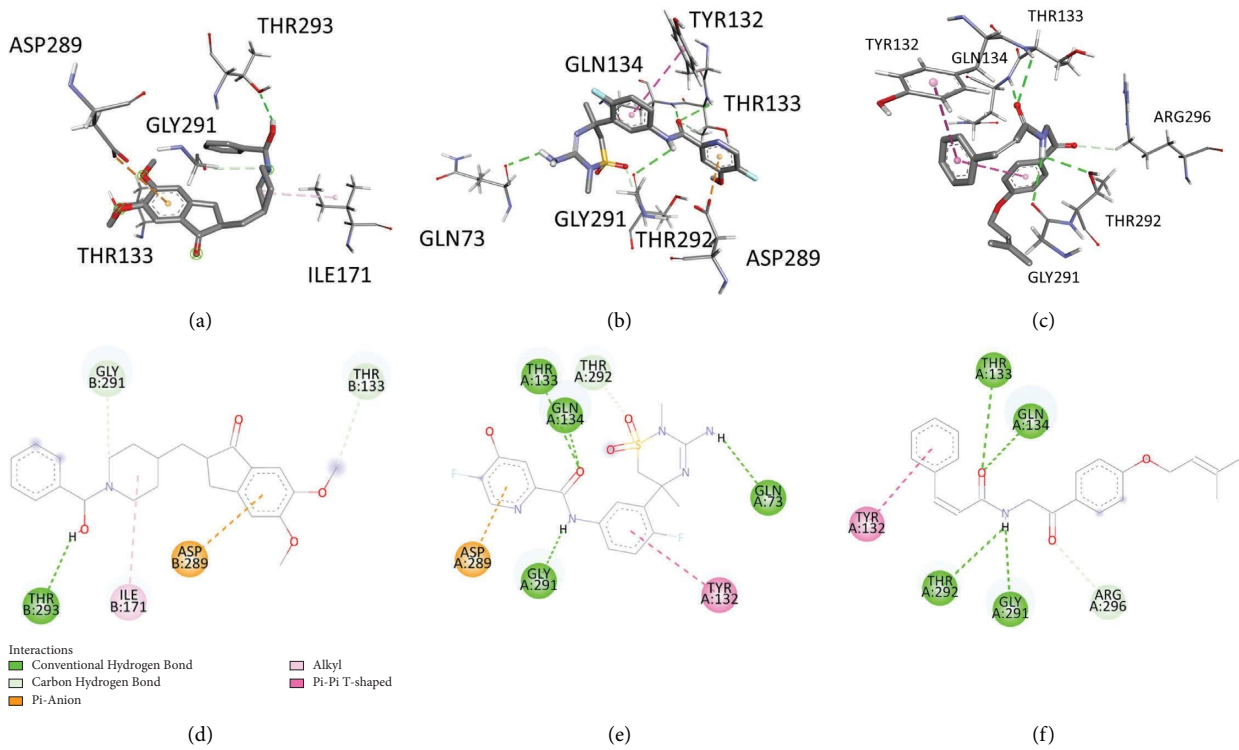


Figure 5: Molecular docking of 3D BACE1 with donepezil (a), verubecestat (b), and marmeline (c) and 2D BACE1 with donepezil (d), verubecestat (e), and marmeline (f).

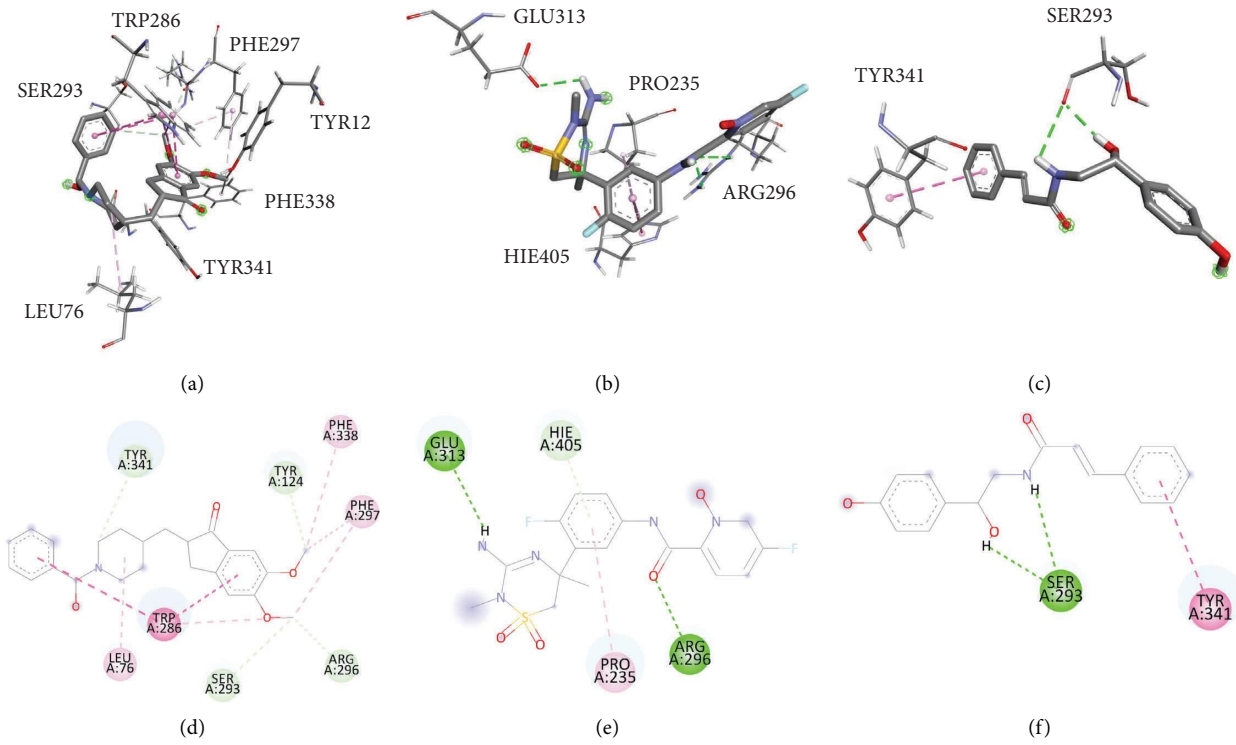


Figure 6: Molecular docking of 3D AChE with donepezil (a), verubecestat (b), and marmeline (c) and 2D AChE with donepezil (d), verubecestat (e), and marmeline (f).

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 5: Log2 fold change (Log2 FC) and p values of differentially expressed genes in Alzheimer's disease (AD) patients compared to healthy control samples.

Upregulated genes			Downregulated genes		
Name	**Log2 FC**	***p* value**	**Name**	**Log2 FC**	***p* value**
VDR	0.06	0.829	HCK	−0.08	0.716
MMP2	0.42	0.076	STS	−1.12	7.01×10^{-12}
ErbB4	1.00	3.03×10^{-8}	MMP13	−0.04	0.877
ZAP70	0.47	0.034	FNTA	−0.71	0.001
RARG	0.23	0.294	FABP7	−0.38	0.108
CCL5	0.67	0.015	JAK3	−0.36	0.017
C1S	0.07	0.789	IMPA1	−0.45	0.008
CDK6	1.06	3.30×10^{-8}	BACE1	−0.48	3.02×10^{-5}
HMOX1	0.30	0.12	KIT	−0.50	0.108
CSK	0.58	6.77×10^{-7}	FABP4	−0.11	0.661
MMP7	0.03	0.924	NR1H2	−0.12	0.472
NOS2	0.01	0.951	PDPK1	−0.01	0.933
LCK	0.42	0.07	RAB5A	−0.41	0.005
DCK	0.07	0.629	PDK2	−0.77	1.51×10^{-4}
GALE	0.67	6.94×10^{-5}	NR1H3	−0.24	0.209
RARA	0.64	0.001	MIF	−1.41	6.85×10^{-12}
CMA1	0.14	0.588	TGM3	−0.44	0.051
MMP3	0.23	0.297	FCAR	−0.21	0.377
FGFR1	0.79	6.98×10^{-5}	CDC42	−1.91	3.17×10^{-6}
PPARA	0.94	2.26×10^{-9}	ESR1	−0.88	6.15×10^{-5}
RORα	0.94	3.42×10^{-5}	ACE2	−0.41	0.16
ACADM	0.12	0.389	GSTT2	−0.91	0.001
SETD7	0.40	0.107	FABP5	−0.69	3.06×10^{-4}
MMP8	0.29	0.286	PAK6	−0.40	0.006
AKT1	0.09	0.628	PDE4D	−0.42	0.001
RXRα	0.42	5.81×10^{-4}	KIF11	−0.93	1.21×10^{-4}
JAK2	0.45	0.052	NR1I2	−0.06	0.73
TPH1	0.42	0.149	THRB	−0.26	0.087
XIAP	0.47	0.006	QPCT	−0.34	0.085
APOA2	0.25	0.304	ARSA	−0.32	0.06
CD1A	0.34	0.15	ADK	−1.07	1.81×10^{-8}
PADI4	0.22	0.386	GSK3β	−0.90	1.92×10^{-7}
MDM2	0.43	0.003	PPARγ	−1.08	3.51×10^{-5}
AKT2	0.94	1.89×10^{-5}	DAPK1	−0.76	1.88×10^{-6}
EGFR	0.81	1.02×10^{-4}	NQO2	−1.08	4.67×10^{-12}
NQO1	0.42	0.008	DUT	−0.30	0.016
DPP4	0.30	0.213	STAT1	−0.75	5.69×10^{-7}
ALDH2	0.04	0.696	NOS3	−0.28	0.211
IL2	0.10	0.724	GSTP1	−0.01	0.947
PNMT	0.27	0.217	BST1	−0.34	0.172
SHBG	0.04	0.841	PDE4B	−0.56	1.01×10^{-4}
MMP16	0.71	< 0.001	CASP3	0.00	0.957
CASP7	0.94	< 0.001	PDE3B	−0.40	0.029
CCNT1	0.79	< 0.001	CBR1	−0.60	0.003
PDE5A	1.09	< 0.001	MMP9	−0.01	0.928
CCNA2	0.29	0.014	OAT	−0.69	1.31×10^{-4}
ISG20	0.47	0.037	FABP6	−0.83	3.63×10^{-5}
EPHB4	0.58	0.007			
ANXA5	0.38	0.006			
MMP12	0.12	0.65			
ST14	0.62	0.004			
SRC	0.36	0.085			
NR1H4	0.54	0.038			
NR1I3	0.17	0.534			
DPEP1	0.45	0.070			
CLK1	0.10	0.446			

Note: The table lists both upregulated and downregulated genes identified from the GSE5281 dataset, which includes 74 control samples and 87 AD samples. Genes with p value < 0.001 are considered significantly differentially expressed.

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

linked to synaptic dysfunction in AD models [59]. CDK6 regulates AD pathology, neuroinflammation, and cognitive functions through signaling pathways impacting amyloidogenesis and tauopathy. Its dysregulation contributes to neuronal death and has been implicated in the processes of cell cycle reentry associated with neurodegenerative diseases [60]. CSK inhibits Src family kinases (SFKs) which are critical in regulating apoptosis and cellular signaling pathways in AD pathology, potentially affecting tau phosphorylation and neuronal survival [61]. UDP–galactose 4-epimerase (GALE) is an enzyme involved in the Leloir pathway of galactose metabolism, catalyzing the reversible conversion of UDP–galactose to UDP–glucose. It also interconverts UDP–N-acetylgalactosamine and UDP–N-acetylglucosamine, playing a crucial role in maintaining UDP–monosaccharide pools necessary for glycosylation processes [62]. There is no direct evidence linking GALE upregulation specifically to AD. However, understanding its metabolic roles can provide insights into its potential indirect effects. GALE's function in carbohydrate metabolism and glycosylation could influence cellular processes that are critical in neurodegenerative diseases [63]. Disruptions in these pathways might contribute to cellular stress or dysfunction, which are factors in AD pathology. Proper glycosylation is essential for protein folding and function. Misregulation in this process could theoretically affect proteins involved in AD, although specific connections to GALE have not been established. The FGFR1 gene is involved in the formation, survival, and movement of nerve cells and regulates neurogenesis and neuroinflammation, impacting neuronal functions critical for cognitive processes. It facilitates neuronal damage repair and is implicated in the pathogenesis of AD through effects on tau phosphorylation and Aβ processing activities [64]. PPARA regulates the expression of genes involved in lipid metabolism and APP metabolism, influences Aβ processing, and helps improve synaptic plasticity, which is crucial in AD pathology [65]. RORα is a nuclear receptor that is upregulated in the hippocampus of AD patients. It is involved in transcriptional regulation and may play roles in Aβ processing and tau phosphorylation, contributing to synaptic function. Studies have shown RORα's potential involvement in regulating cellular mechanisms affected by Alzheimer's pathology [66]. RXRα participates in vanilla Aβ aggregation and tau phosphorylation further procesing synaptic function and thus the pathology of AD RXR signaling when stimulated has been proven to limit amyloid deposit, reduce neurodegeneration, and dampen the AD pathology–assessed neuroinflammation [67]. The PI3K/Akt signaling pathway plays a critical role in regulating Aβ processing and tau phosphorylation, and AKT2 is involved in them. It is involved in neuronal survival and synaptic function, helping to avoid neurodegeneration in Alzheimer's [68]. Importantly, EGFR has been recognized in AD as mediating Aβ toxicity and tau phosphorylation. All of these results also suggested, implicating that it is related to synaptic dysfunction and neuroinflammation, which can all contribute to the pathogenesis of Alzheimer's. EGFR inhibitors have been identified as potential Aβ path modifiers which can ameliorate Aβ pathology and cognitive dysfunction suggesting its role within key pathways of AD [69]. Matrix metalloproteinases (MMP16) are part of a large family of enzymes that break down extracellular matrix (ECM) proteins. MMP16 is one of the MMPs that have been reported to be involved in neurodegenerative disease processes including AD. MMPs, such as MMP16, are classically recognized as ECM remodeling enzymes. While dysregulation of this process may induce pathology, it is essential for maintaining normal functioning of the brain. Dysregulated ECM remodeling in AD can alter neuronal interactions and synaptic plasticity and may be the basis for cognitive decline. MMPs play a role in the modulation of neuroinflammatory responses through cytokine and chemokine processing. MMP16 could also promote the inflammatory environment involved in this key feature of AD pathology neuroinflammation. By degrading tight junction proteins, MMPs can undermine blood–brain barrier (BBB) integrity. This disturbance contributes to leakiness and the entry of damaging materials into the brain, promoting the pathology of AD. While specific studies on MMP16's interaction with Aβ are limited, other MMPs have been shown to degrade Aβ or influence its aggregation. This alludes to a functional role for MMP16 in the regulation of Aβ dynamics, the major hallmark of AD pathology. Matrix metalloproteinase elevated levels have been found in the brains of AD cases adding to the potential role of these proteins in the clinical expression of the disease. Dysregulation of MMP activity can hamper ECM integrity, in turn, disrupting the integrity of the BBB and improving neuroinflammation, all of which are pathological to AD [70]. It is involved in the apoptotic process and microglial activation and contributes to neurodegeneration in AD. A loss-of-function variant in CASP7 protects against AD, indicating its role in AD susceptibility [71]. Cyclin T1 (CCNT1) plays a role in the regulation of transcription elongation by forming a complex with CDK9, influencing Aβ processing and synaptic functions in relation to AD pathology. It is involved in maintaining synaptic integrity and may have a role in tau phosphorylation pathways, though explicit statements connecting it directly to these processes in AD are less frequent. Therefore, it functions contextually in neuronal health and neurotransmission, contributing indirectly to AD pathologies [72]. PDE5A is involved in memory function and synaptic plasticity, and its inhibition can improve cognitive deficits in AD models by enhancing the cGMP signaling pathway and reducing Aβ and tau pathologies [73].

There are 17 genes to be downregulated in AD. Figure 8 includes STS, BACE1, PDK2, macrophage migration inhibitory factor (MIF), CDC42, ESR1, FABP5, KIF11, adenosine kinase (ADK), GSK3β, PPARγ, DAPK1, NQO2, signal transducer and activator of transcription 1-alpha/beta (STAT1), PDE4B, ornithine aminotransferase (OAT), and FABP6. Altered steroid metabolism and neurosteroid balance due to the further brought in the favor of downregulation of steryl-sulfatase (STS) have been implicated with AD since STS potentially affects neurosteroid concentrations, which are critical for critical brain activity and protection against neurodegeneration. STS play a key role in

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

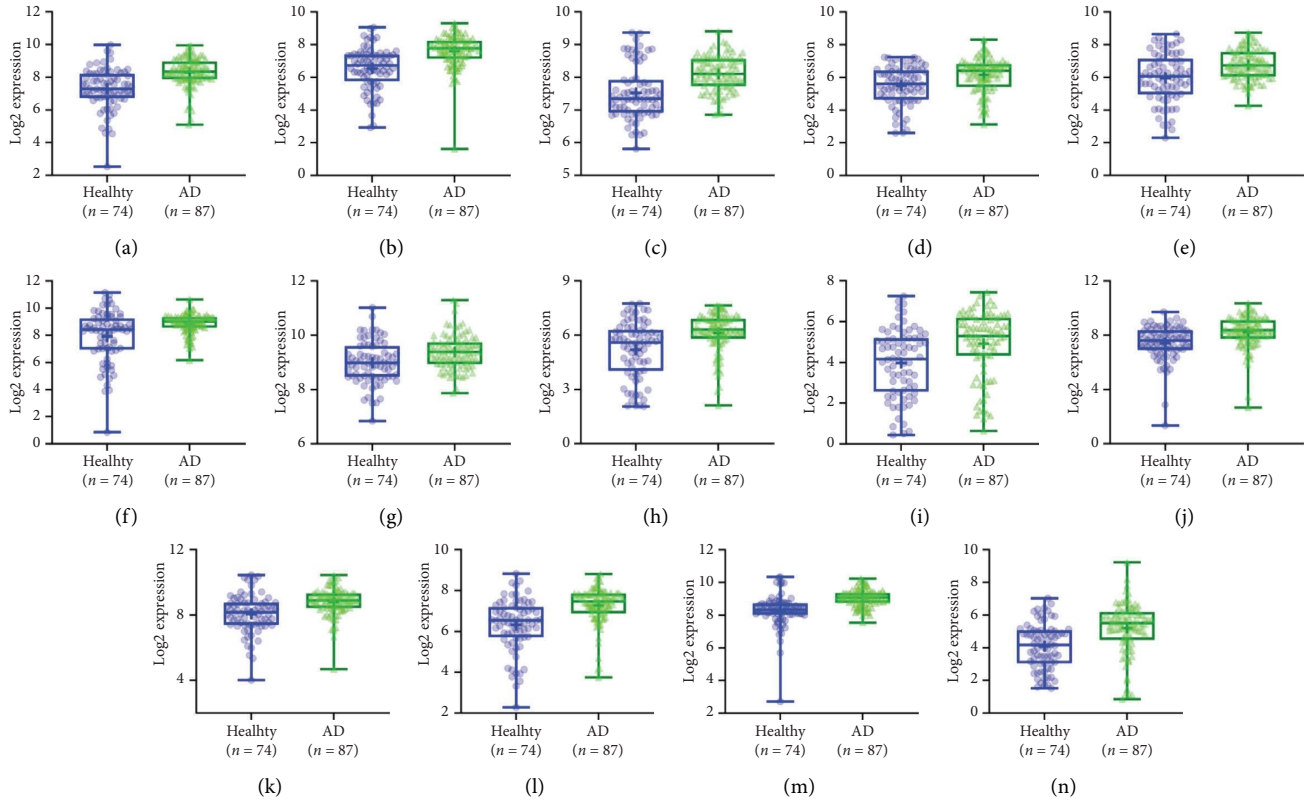


Figure 7: The gene expression levels of specific genes that are substantially upregulated in Alzheimer's disease (AD) patients in comparison to healthy control samples. The GSE5281 dataset, which comprises 74 control samples and 87 AD samples, is the source of the data. The log2 expression levels of each gene are depicted in the boxplots, with blue signifying healthy controls and green indicating AD patients. A statistically significant difference is evident in all comparisons, with a p value of less than 0.001. (a) ErbB4, (b) CDK6, (c) CSK, (d) GALE, (e) FGFR1, (f) RORα, (g) RXRα, (h) AKT2, (i) PPARα, (j) EGFR, (k) MMP16, (l) CASP7, (m) CCNT1, and (n) PDE5A.

the metabolic activation of sulfated steroids. This might play an important role in the balance between sulfated and nonsulfated neurosteroids influencing neuronal excitability and cognitive functions. Sulfated steroids, including dehydroepiandrosterone sulfate (DHEAS), play a significant neuroprotective role. Lower DHEAS levels have been observed in AD patients, implying that loss of STS activity leads to reduced neuroprotection and disease progression [74]. BACE1 plays a crucial role in adult hippocampal neurogenesis. In contrast to the recent findings in earlier development, complete loss of BACE1 activity is detrimental to adult cell proliferation and neuronal differentiation in the adult hippocampus. This reduction in neurogenesis may further aggravate cognitive decline in AD. Besides APP, BACE1 has many targets with roles in neuronal functions. However, downregulation may delve into these processes and cause neurological problems. Downregulation of BACE1 in the brain could lead to compensatory mechanisms that eventually, through alternate pathways, cause higher levels of Aβ production than expected. Studies have suggested that BACE1 may be involved in the cellular response to oxidative stress. Downregulation of it may interfere with the capacity of the brain to deal with an oxidative injury, the prominent mechanism leading to AD pathogenesis [75]. PDK2 is crucial in inhibiting pyruvate dehydrogenase complex regulatory proteins, a vital step in the conversion of pyruvate to acetyl-CoA that will serve as a substrate in the Krebs cycle. This process is critical for the neurons to be able to produce energy in a sufficient manner. However, this would result in an uncontrolled PDC activity which if not properly regulated may result in an imbalance in metabolic health leading to mitochondrial dysfunction. Mitochondrial dysfunction is one such early-hitting involuntary mechanism in the pathogenesis of AD [76]. Downregulation of MIF has a significant association with AD. AD Early onset of MIF transcription was associated with learning and memory impairments in AD model mice [77]. The neuronal cells were protected from the Aβ–induced cytotoxicity due to MIF overexpression. Neuronal cells were protected by MIF from oxidative stress mediated by disruptive caspase-3 activation. It appears that MIF does inhibit apoptosis. In MIF overexpression, the Aβ toxic effect in SH-SY5Y cells was reduced. [78]. This again points to a neuroprotective role [79]. CDC42 regulates synaptic plasticity by modulating actin dynamics in dendritic spines, which are crucial for cognitive functions. Dysregulation leads to synaptic loss, a hallmark of AD. It activates GSK3β, further exacerbating AD–like phenotypes such as increased Aβ accumulation [80]. CDC42 has a prosurvival role in neurons, and its inhibition can sensitize neurons to apoptosis under stress,

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

suggesting its potential as a therapeutic target to slow neurodegeneration [81]. The gene is involved in Aβ processing and tau phosphorylation, has neuroprotective effects, and plays a role in synaptic function. Abnormal ESR1 signaling can contribute to neuroinflammatory processes related to AD, further impacting cognitive function [82]. FABP5 contributes to the uptake of docosahexaenoic acid (DHA) across the BBB, which is crucial for maintaining cognitive function. Its deficiency results in cognitive dysfunction and increased vulnerability to AD pathology due to impaired DHA transport. FABP5 is involved in neuronal lipid metabolism, which is significant in the context of AD [83]. KIF11 is critical for maintaining synaptic structures and functions essential for learning and memory in the presence of Aβ. Overexpression of KIF11 has been shown to rescue Aβ–mediated cognitive deficits and long-term potentiation impairments, highlighting its importance in AD pathology [84]. The mechanisms that underlie the pathological features of AD are associated with the imbalance of adenosine receptor signaling and ADK. They include tau hyperphosphorylation, increased production of Aβ, deficits in memory and higher cognitive functions, impairments in synaptic physiology, and limited neurogenesis [85]. By blocking ADK, adenosine levels will be increased and neuronal activity will be modulated. A2A adenosine receptors regulate cognitive processes and their antagonists have shown beneficial results on cognition deficits resulting from AD [86]. Caffeine use has been shown to enhance cognitive performance in Alzheimer's patients, confirming the role of adenosine antagonism in ameliorating the functional decline. Antagonism of A2A adenosine receptors has been effective in reversing cognitive deficits associated with AD. These findings suggest that ADK knockdown could be used as a potential AD therapy by restoring adenosine homeostasis and hence modulating neuronal excitability [87]. GSK3β aberrancies induce tau hyperphosphorylation, increase memory impairment rate and production of Aβ peptide, perturb synaptic functions, and hinder neurogenesis, which are some of the features of the pathology of AD [88]. PPARγ downregulation has been found to have a complex interconnectivity with AD, owing to its functions as a transcription factor that modulates diverse pathways involved in the pathogenesis of AD. PPARγ has been found to influence gene expression of certain pathways including that of lipid metabolism, inflammatory response, and Aβ, all of which are relevant in AD. It has been shown that when PPARγ is downregulated, the expression of genes such as APOE, associated with late-onset AD (LOAD), which is an important genetic risk for AD, increases [89]. The relation between AD and the PPARγ agonists is according to studies of PPARγ, which is a transcription factor. The activation of PPARγ has been shown to lower inflammatory gene expression while also downregulating inflammation transcription factors [90]. PPARγ agonists aid in supplementing the degradation of Aβ, as they both raise insulin-degrading enzyme (IDE) expression and lower Aβ cleavage enzyme 1 (BACE1) expression, hence providing neuroprotection [91]. DAPK1 has an important role to play in the AD pathological mechanism, especially in regulating tau protein stability and phosphorylation, Aβ processing, and synapse loss; it is known to affect tau phosphorylation at several sites and participate in the neurodegenerative pathways of AD [92]. NQO2 downregulation is suggested to promote changes linked to AD through modulation of oxidative stress, inflammation, and neurodegeneration mechanisms. NQO2 is a flavoenzyme that contributes to quinone metabolism and is associated with several neurodegenerative diseases including AD due to its effects on redox balance and inflammatory response [93]. A lowered expression of NQO2, however, is known to disbalance reactive oxygen species (ROS) and reactive nitrogen species (RNS) leading to the neuronal effects of oxidative stress which is recognized as a hallmark of AD [94]. This disturbed oxidative homeostasis promotes the formation of Aß and tau protein aggregates resulting in aggravation of neuroinflammation and neuronal damage in AD [95]. It has been pointed out that nuclear factor is activated and a transcriptional regulation element, STAT1, is downregulated, and this downregulation is further brought into favor of AD pathogenesis because it plays a role in the transcriptional regulation and cellular signaling. STAT1 is involved in the transcriptional regulation of genes important for cellular homeostasis and immune status. In the case of AD, the loss of transcriptional control including that of STAT1 is believed to contribute towards neurodegeneration and the failure of synaptic function. This dysregulation is part of a broader pattern of transcriptional degeneration observed in AD, which affects protein degradation, neuroinflammation, and mitochondrial function. STAT1 is a central component of both the immune response and cellular signaling pathways that are impaired in AD, resulting in increased neuroinflammation and neuronal damage [96]. The suppression of STAT1 can result in transcriptional dysfunction, which may be ameliorated by promoting pathological processes in AD [97]. PDE4B is normally downregulated, but this may be an adaptive response and the downregulation can enhance memory performance, whereas it may also impair consolidation of long-term memories. Inhibition of PDE4B increases cAMP levels, which activates cAMP response element-binding protein (CREB), a crucial mediator of learning and memory [98]. Reducing PDE4B activity in mouse models of AD has been shown to enhance the short-term memory and learning abilities. Though high cAMP levels help in creating new memories, they may also interfere with the long-term memory consolidation process [99]. Involvement of proteins help in the retention of memory, such as CREB and other proteins that are essential for stabilization and storage of memory [100]. In addition, there is evidence of PDE4B being linked to psychiatric conditions such as schizophrenia and other mental illnesses. Alterations in PDE4B levels could affect mental health and mood, which may contribute to problems for some individuals. [101]. PDE4B inhibition may be beneficial for improving short-term memory, but potential long-term memory consolidation and psychiatric implications should be considered. Downregulation of OAT is involved in AD due to its involvement in the urea cycle and arginine metabolism, which are deregulated in AD pathology. The loss of function of OAT would cause

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

a disruption in these metabolic pathways and might explain the oxidative/nitrosative stress observed in AD. The stress of this over time is associated with the accumulation of neurotoxic Aβ plaques, which is a hallmark of AD. The interaction between OAT activity and Aβ metabolism may provide a basis for AD treatment. OAT is a component of the urea cycle, which is altered in AD. Changes in the expression of urea cycle enzymes including OAT have been reported in AD models and suggest a shift towards a more oxidative state [102]. The presence of metabolites such as ornithine and citrulline in AD models could be indicative of a urea cycle dysfunction, which would be potentially associated with OAT downregulation [103]. Downregulation of OAT may impair the metabolism of Aβ, as Aβ–derived ammonia is detoxified through the urea cycle. This is a crucial detoxification step to prevent memory impairment in AD [103]. Aβ peptide transport may also be influenced by proteins such as OATP1B1 that could interact with OAT–related pathways and alter the levels of Aβ in the brain [104]. The downregulation of gastrotropin (FABP6) in AD is not directly addressed by the provided papers; however, other roles of fatty acid–binding proteins (FABPs) in AD can be inferred from the FABPs. Lipid metabolism is critical in AD pathogenesis, and FABPs participate in this process. These results suggest that changes in FABP's expression (e.g., FABP6) might modulate AD through lipid metabolism and inflammatory pathways. Dysregulation of lipid metabolism is a significant factor in AD, with FABPs playing a critical role in fatty acid transport and metabolism [105]. Alterations in FABP's expression, such as potential downregulation of FABP6, could disrupt lipid homeostasis, contributing to AD progression [106].

This research examined how AD affects the expression of 31 specific genes. From this investigation, eight genes with significant changes using a log2 FC threshold of greater than 1 for upregulation or less than −1 for downregulation were identified that had notably different expression levels in AD when compared to normal brain tissue. Changes in these eight genes were either large increases in expression levels (greater than two times normal) or very large decreases in levels (less than half of what was normal). Two of the proteins made by these genes, CDK6 and PDE5A, are of particular interest because they, too, are targets of marmeline, a compound derived from bael fruit. Bael fruit is an Asian fruit that has been used for medicinal purposes. CDK6 is a protein involved in AD pathology. It has been shown to regulate neuroinflammation and cognitive functions through pathways that affect amyloidogenesis and tauopathy, which are the two main hallmarks of AD. Thus,the upregulation of these two factors, CDK6 and PDE5A, suggests that CDK6 and PDE5A may play important roles in AD progression. Considering that neuroinflammation and CDK6 play a role in neuronal damage and cognitive decline, CDK6 is important in neuroinflammation and indirectly contributes to neuronal damage and cognitive decline. Interventions against CDK6 will be able to alleviate the related effects by modulating pathways. This highlights the relevance of PDE5A in AD due to its biological function in synaptic plasticity. Strengthening cGMP signaling via targeted PDE5A inhibition may be an ideal therapeutic approach to improve cognitive defects and minimize Aβ and tau pathologies. The increased expression of PDE5A implies it is a driving force toward aggravating AD symptoms; this thus presents it as a potential therapeutic target.

Inhibitory pathways may also be represented by downregulated genes, consistent with suppression of pathways in Alzheimer's that may lead to diminished functioning of cells. For example, ADK, NQO2, and PPARγ and CDC42, MIF, and STS are downregulated. These genes have important roles in several pathways involved in the pathology of AD. Interestingly, marmeline, identified from bael fruit, showed activity as a possible new drug for targeting these proteins. ADK downregulation also has implications for AD pathobiology through the regulation of adenosine levels, an important regulator of neuronal excitability and cognitive processes. Adenosine shortage in presymptomatic AD is associated with synaptic hyperexcitability. Furthermore, downregulation of ADK restores adenosine and may convert abnormal neuronal activity back to a healthy state that mitigates AD symptoms. NQO2 is involved in both oxidative stress regulation and neurodegeneration. A reduction of its expression promotes oxidative stress, facilitating Aβ aggregation and tau protein deposition, thereby aggravating neuroinflammation and neuronal injury. PPARγ, as an agonist, exerts neuroprotective function by promoting Aβ degradation through upregulation of IDE while downregulating Aβ cleavage enzyme 1 (BACE1). CDC42 regulates synaptic plasticity by modulating actin dynamics in dendritic spines. These processes dysregulation of synaptic loss and the acceleration of Aβ deposit. The beneficial role of CDC42 in cell survival indicates that it can be a novel therapeutic target for slowing down the neurodegeneration process. The impairment of learning and memory seen in AD models could be due to decreased levels of MIF. Overexpression of it is capable of shielding neuronal cells from apoptotic damages mediated by cytotoxicity from Aβ and oxidative stress stimulation. STS transmits the metabolism of steroids and neurosteroids, which are important for the function of the brain. Decreased neuroprotection with reduced STS activity is hypothesized to occur because of decreased levels of neuroprotective STS products, such as DHEAS. Their critical roles in AD pathology are underscored by the significant downregulation of ADK, NQO2, PPARγ, CDC42, MIF, and STS. The role of each gene in the disease mechanisms is unique: ADK, for maintaining levels of the synaptic inhibitory signal adenosine, is likely to be critical in preventing synaptic hyperexcitability and cognitive decline. Targeting ADK with marmeline could rebalance adenosine in the brain and restore neuronal health. Given the role of NQO2 in the regulation of oxidative stress, the idea of inducing NQO2 activity to protect against oxidative damage and reduce disease progression is appealing. Marmeline potentially exerting effects on NQO2 could aid in restoring redox homeostasis. Therefore, targeting the ability of PPARγ to modulate the pathways of Aβ degradation may provide an attractive strategy to decrease the amyloid burden. The action of marmeline on PPARγ

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

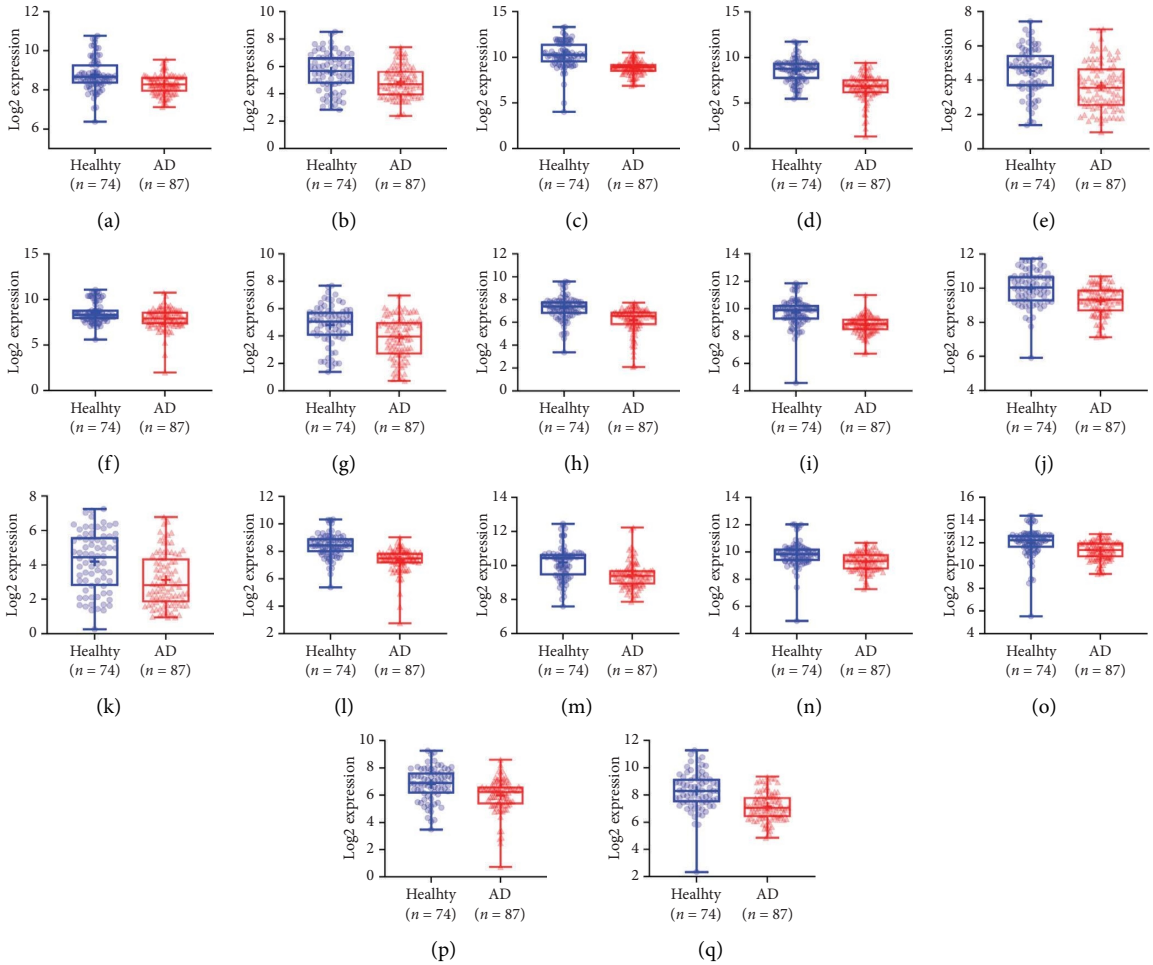


FIGURE 8: The gene expression levels of specific genes are substantially reduced in Alzheimer's disease (AD) patients when contrasted with healthy control samples. Data are obtained from the GSE5281 dataset, which comprises 87 AD samples and 74 control samples. Blue indicates healthy controls, while red indicates AD patients, as indicated by the boxplots that depict the log2 expression levels of each gene. Based on the p value, all comparisons demonstrate a statistically significant difference ($p < 0.001$). (a) BACE1, (b) PDK2, (c) MIF, (d) CDC42, (e) ESR1, (f) FABP5, (g) KIF11, (h) ADK, (i) GSK3β, (j) DAPK1, (k) PPARγ, (l) NQO2, (m) STAT1, (n) PDE4B, (o) OAT, (p) FABP6, and (q) STS.

may amplify these neuroprotective effects. Given that CDC42 regulates synaptic plasticity, it can be inferred that compromise in its function is detrimental to cognitive health. Marmeline may help stabilize actin dynamics and prevent synaptic loss. MIF's protective role against Aβ toxicity and apoptosis highlights its potential as a therapeutic target. Marmeline could enhance MIF expression or function to protect neuronal integrity. STS's influence on neurosteroid balance suggests that increasing its activity might restore neuroprotection in AD patients. Marmeline's targeting of STS could help maintain optimal steroid metabolism.

Marmeline, a bael fruit chemical, may treat AD, and gene expression research illuminates its complicated molecular underpinnings. This study found 31 genes with substantial expression changes in AD, including 8 up- or downregulated genes. CDK6 and PDE5A, increased in AD and targeted by marmeline, are of interest. Through amyloidogenesis and tauopathy pathways, CDK6 is involved in neuroinflammation and cognitive processes, suggesting it is critical to AD development. Inhibiting PDE5A might improve cognitive impairments and reduce Aβ and tau diseases due to its overexpression and synaptic plasticity. The downregulation of ADK, NQO2, PPARγ, CDC42, MIF, and STS provides vital insights into AD pathophysiology and therapeutic options. These genes control adenosine, oxidative stress, Aβ processing, synaptic plasticity, and neuroprotection. Marmeline's capacity to target downregulated genes implies a multifaceted AD treatment. Marmeline's ADK actions may restore adenosine equilibrium and reduce synaptic hyperexcitability. It may restore redox equilibrium by affecting NQO2 and PPARγ, which may lower amyloid load and neuroprotection. Marmeline's ability to control CDC42 may maintain actin dynamics and prevent AD–related synapse loss. Targeting MIF may improve protection against Aβ toxicity and apoptosis, whereas targeting STS may preserve normal steroid metabolism and neurosteroid balance. This

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

extensive gene expression research and marmeline's multitarget strategy suggest that it might treat AD.

3.5. Pharmacokinetic Assessment Using the SwissADME Predictor. In Figure 9(a), donepezil exhibits high gastrointestinal absorption (GIA) and proficient permeation through the BBB, thereby facilitating its inhibitory effects. Nevertheless, upon oral administration, the compound undergoes metabolic transformations. Notably, the structural entity denoted as D10 manifests gastrointestinal absorptivity but lacks efficient penetration through BBB. In a comprehensive study of eight distinct chemical entities (D1, D2, D3, D4, D5, D8, D9, and D11), these compounds demonstrate notable absorptive capacities within the digestive tract, giving them effective access through BBB. Moreover, the blue color representation of data points serves as indicative of pharmacological agents interacted by the human body and discerned by predictions of active efflux facilitated by P-glycoprotein (PGP+) [42]. Conversely, data points are represented in red if anticipated to be nonsubstrates of PGP− [107]. The investigative analysis reveals a consistent blue color characterizing all structural configurations of donepezil. This blue color consistency implies the universal propensity for all metabolites of varied compositions to undergo efflux from the brain compartment, thereby engendering diminished efficacy in protein inhibition and therapeutic efficacy for diseases [108].

In Figure 9(b), verubecestat demonstrates proficient absorption through the gastrointestinal tract; however, its inability to traverse the BBB renders it inefficacious in the treatment of AD, precluding the exertion of therapeutic effects within the brain compartment. Hepatic metabolism yields only two discernible structures, V1 and V2, which exhibit efficient GIA, yet none of the distinct verubecestat structures demonstrates the capacity to permeate the BBB. This inherent limitation detrimentally influences the compound's practical utility for human therapeutic outcomes, as it manifests suboptimal pharmacokinetic characteristics.

In Figure 9(c), marmeline is characterized by constituents that demonstrate notable efficacy in GIA and proficient permeability across the BBB. However, the metabolized derivative of marmeline yields a single compound, M10, which exhibits commendable absorption within the gastrointestinal system but encounters limitations in traversing the BBB. Conversely, the 4 structural components, M1, M2, M3, and M7, evince robust absorptive qualities in the gastrointestinal tract and manifest adept BBB permeability. Notably, M1, M2, and M3, by evading cerebral efflux mechanisms, engender heightened pharmacokinetic efficacy, thereby culminating in favorable therapeutic outcomes.

The SwissADME predictor helps determine donepezil, verubecestat, and marmeline's pharmacokinetic parameters, which are vital for understanding their AD therapeutic potential. Donepezil inhibits AD due to its high GIA and BBB permeability. Oral administration changes its metabolism. Most of its metabolites sustain GIA and BBB permeability, except D10, which is ineffective. All donepezil structures are projected to be PGP+ substrates, suggesting they may efflux from the brain compartment, lowering protein inhibition and therapeutic efficacy. Verubecestat has good GIA but poor BBB crossing, limiting its AD therapeutic potential. Only two hepatic metabolites (V1 and V2) sustain GIA, but no verubecestat structures can cross the BBB. Verubecestat's poor pharmacokinetics hinder its AD therapy efficacy. Most of marmeline's components pass the GIA and BBB, indicating good pharmacokinetics. One metabolite (M10) has strong GIA but low BBB permeation, whereas four others (M1, M2, M3, and M7) have both. M1, M2, and M3 may avoid brain efflux pathways, improving pharmacokinetics and therapeutic results.

3.6. Analysis of Solubility and Interaction Profiles of Marmeline With Various Solvents. The molecular electrostatic potential maps in Figure 10(a) demonstrate the varying charge distributions among the solvents, which can influence their interactions with the marmeline. Figure 10(b) shows potential interaction sites that correspond to the charge distributions. In Figure 10(c), the charge density plots reveal that marmeline has distinct positive and negative charge regions, which align with the solvent properties shown in Figure 10(a). This suggests that solvents with complementary charge distributions may enhance solubility. The interaction energy profiles in Figure 10(d) indicate that both hydrogen and nonhydrogen bonding interactions play significant roles in determining solubility.

Solvents such as acetone and ethyl acetate, which show favorable interaction energies, correlate with higher solubility levels as seen in Figure 11. Figure 11 illustrates that marmeline is most soluble in acetone across all temperatures, while its solubility in water and heptane is significantly lower. This pattern reflects the compatibility of marmeline's charge distribution with those of the solvents. Therefore, using acetone as a solvent for extracting marmeline is the most suitable choice. Not only does it provide high solubility but also eliminates the need for high temperatures that could affect the structure of the compound.

3.7. Botanical Active Compounds Demonstrating Established Efficacy Against AD. Our results on marmeline's multitarget action in AD fit the mounting data supporting the therapeutic possibilities of bioactive molecules originating from plants. By AChE inhibition and other mechanisms, some phytochemicals have shown notable anti-AD benefits. Common in Origanum and Thymus plants, carvacrol is a phenolic monoterpene with amazing anti-AD effects in *in vitro* and *in vivo* models. Recent investigations show that whilst showing strong AChE inhibitory action, carvacrol stops Aβ–induced neurotoxicity, oxidative stress, and memory impairments [109]. As a potential treatment option for AD, it can pass the BBB and produce neuroprotective benefits through several pathways, including anti-inflammatory and antioxidant activity. Likewise, some plant-derived molecules have proven effective against AD pathogenesis. Currently authorized AD medications, alkaloids include galantamine, and rivastigmine come from plants [110]. By means of several pathways, including

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

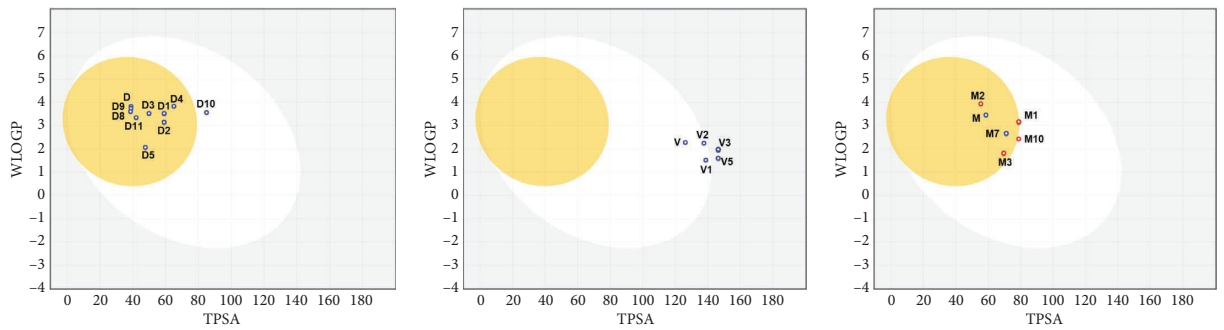


Figure 9: The bioavailability of metabolites produced by donepezil (a), verubecestat (b), and marmeline (c) using the SwissADME predictor.

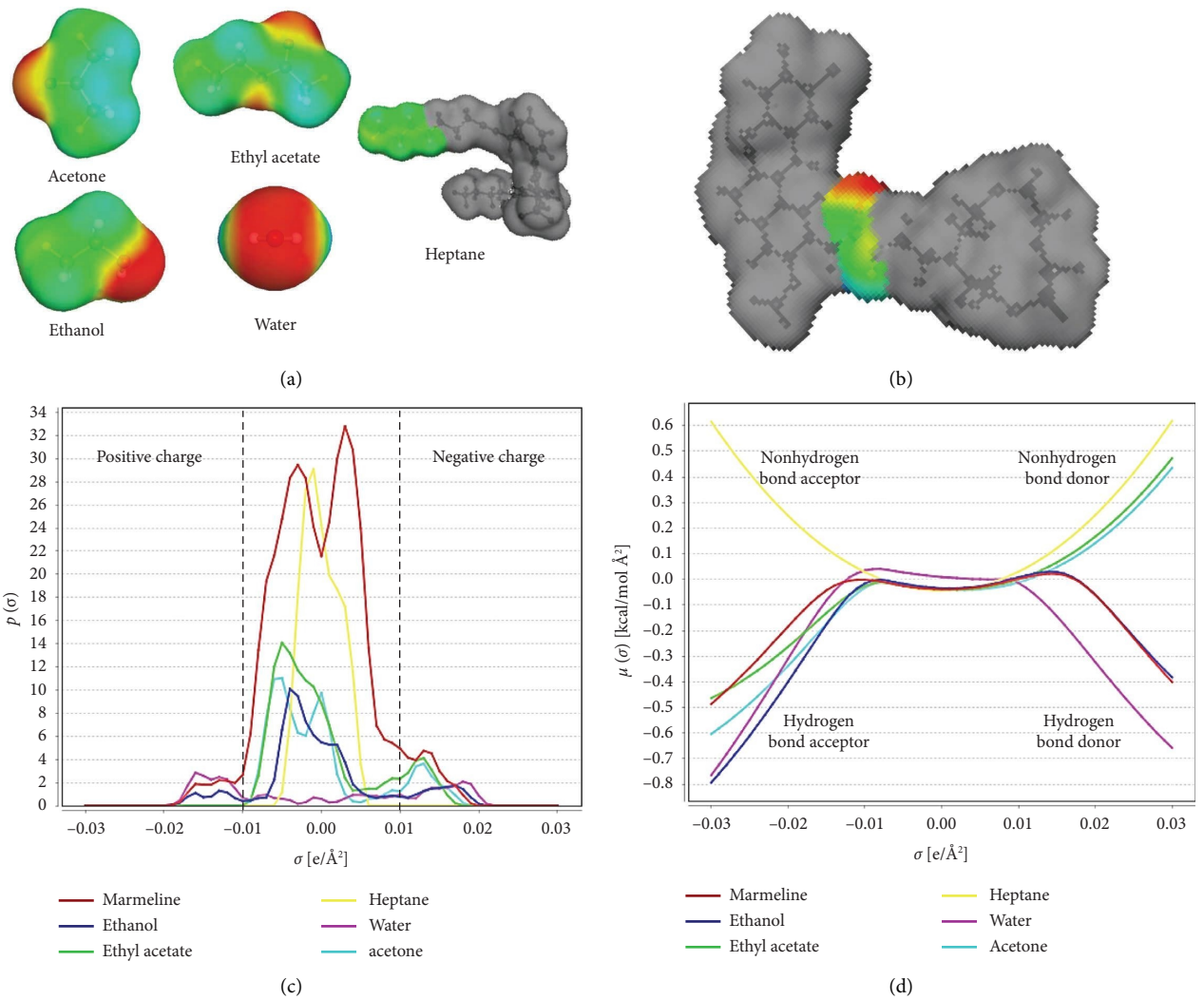


Figure 10: (a) Molecular electrostatic potential maps of solvents: acetone, ethyl acetate, ethanol, water, and heptane, showing charge distribution. (b) Structure of marmeline with highlighted regions indicating charge distribution. (c) Charge density distribution plots for marmeline and solvents, showing positive and negative charge areas. (d) Interaction energy profiles for hydrogen and nonhydrogen bond acceptors/donors in marmeline and solvents.

prevention of Aβ aggregation and decrease of neuroinflammation, curcumin, resveratrol, and other phytochemicals have shown neuroprotective effects. While *Punica granatum* has strong antidementia compounds including ellagic acid and punicalagin that operate as BACE1 inhibitors [111], extracts from *Moringa oleifera* have been demonstrated

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

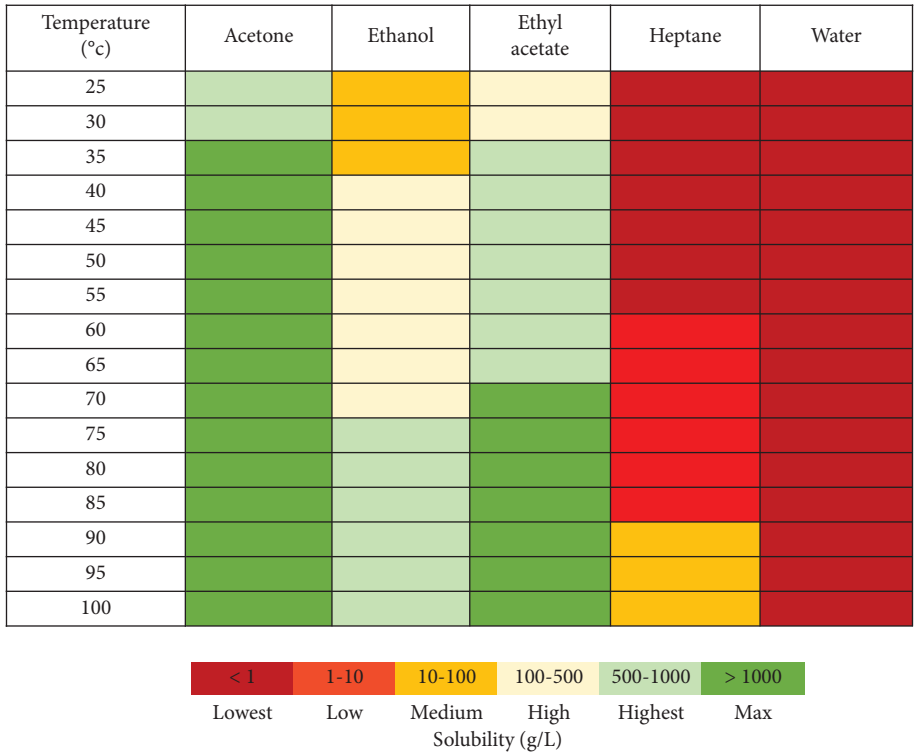


FIGURE 11: Marmeline's solubility in different solvents across temperatures from 25°C to 100°C, with colors representing solubility levels: red (< 1 g/L), orange (1–10 g/L), yellow (10–100 g/L), light green (100–500 g/L), green (500–1000 g/L), and dark green (> 1000 g/L).

to prevent dementia by replenishing depleted synaptic proteins and suppressing tau hyperphosphorylation [112]. These results point to a possible path forward for creating multitarget therapeutic strategies against AD: plant-derived bioactive compounds, including marmeline, possibly provide advantages over single-target approaches in addressing the complex pathophysiology of the disease [113].

3.8. Study Limitations. Although our computer studies offer useful insights into marmeline's potential as a therapy for AD, we recognize substantial limitations inherent to *in silico* approaches. The lack of *in vitro* and *in vivo* validation constitutes a significant limitation on the applicability of our results to actual biological systems. Molecular docking simulations, although effective for estimating binding affinities, fail to comprehensively represent the intricate dynamics of protein–ligand interactions inside biological contexts. The anticipated interactions between marmeline and its targets (BACE1 and AChE) need experimental confirmation to ascertain their biological significance. Likewise, our pharmacokinetic forecasts with SwissADME offer theoretical evaluations of absorption, distribution, metabolism, and excretion characteristics that may vary considerably in biological systems due to unconsidered aspects in computer models. The gene expression study utilizing current datasets provides correlated evidence but fails to show causation between marmeline treatment and alterations in gene expression patterns. Furthermore, our metabolite predictions, albeit grounded on recognized algorithms, need experimental validation by mass spectrometry and other analytical methods. Moreover, the sophisticated pathophysiology of AD encompasses complex cellular and systemic mechanisms that cannot be entirely replicated in computer models. The permeability of the BBB, neuroinflammatory reactions, and long-term consequences of marmeline administration can only be conclusively evaluated by meticulously prepared *in vitro* and *in vivo* research. The limitations emphasize the early nature of our findings and reinforce the need for further experimental validation via cell culture research, animal models, and ultimately clinical trials before any conclusions on marmeline's therapeutic potential can be established. Our work should be regarded as a basis for hypothesis formation that necessitates stringent experimental validation in biological systems.

4. Conclusions

The results of this extensive study provide valuable information about the compound marmeline, a bioactive component of bael fruit, which may become a novel therapeutic potential for AD. Abundant binding energies and conformations indicate that marmeline is a very promising candidate for further research and development due to the demonstrating efficacy in targeting BACE1 and AChE protein as revealed in the present study. We have also assessed its solubility and interaction profiles with different solvents through COSMOquick software which shows some interesting insights between marmeline and selected solvent solubility profiles. The results of molecular electrostatic

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

potential maps and interaction energy profiles suggest that marmeline has the potential for good solubility characteristics, especially in acetone. These data indicate that marmeline not only has suitable solubility characteristics but also circumvents the necessity for high temperatures needed to solubilize marmeline, which may lead to structural degradation of the compounds.

In addition, the mechanisms of action of marmeline, specifically its formation in the liver by CYP450 isoforms 1A2, 2C9, and 2C19 provide important information regarding potential drug interactions and modeling lead modification in the drug development pathway. The potential utility of marmeline and its metabolites in AD largely depends on the preservation of beneficial pharmacokinetic properties, namely, GIA and permeability through the BBB. The comparison with the already known therapies such as donepezil and verubecestat points out the shortcomings of the existing treatment methods, indicating the need for novel strategies. Marmeline ability to overcome BBB permeability problems and its strong inhibitory effect on both BACE1 and AChE makes it an extremely attractive compound for further preclinical and clinical testing. In addition, the recognition of potential PPARγ natural stimulation of the terminus chemical compounds of marmeline in bael fruit is another aspect of importance. The proposed mechanism in which BACE1 activity is reduced via PPARγ activation is an innovative approach towards decreasing Aβ and AChE generation. PPARγ agonists such as pioglitazone and rosiglitazone were demonstrated to have beneficial effects on AD patients, decreasing both Aβ levels and cognition [114, 115]. Marmeline was also isolated as a natural PPARγ agonist, and it may provide similar benefits with fewer side effects. Similarly, clinical trials showed a significant effect of BACE1 inhibitors (such as verubecestat) in lowering Aβ and AChE inhibitors (for instance, donepezil) in reversing cognitive impairment [116, 117]. In addition, marmeline also targets CDK6 and PDE5A, which are upregulated in AD patients. The details of this article are as follows: PDE5A and CDK6 are potential targets for the synaptic plasticity and memory regulation in AD prevention, but CDK6 also can indirectly promote AD cognitive decline via the neuroinflammation and amyloidogenesis process. In contrast, ADK, NQO2, PPARγ, CDC42, MIF, and STS, which are downregulated in AD models, are involved in oxidative stress modulation (ADK and NQO2), synaptic plasticity (NQO2 and PPARγ), neuroprotection (PPARγ, CDC42, and MIF), and steroid metabolism (STS). Since marmeline interacts with these proteins, it may help to restore balance in these disturbed pathways. Effects of marmeline on PPARγ and NQO2 may facilitate Aβ degradation and attenuation of oxidative stress. Marmeline therefore as a single drug may be a suitable treatment that has multiple effects on the key pathology factors of AD that could decelerate disease progression. This integrative dataset for molecular, metabolic, and pharmacogenomic findings will serve as a firm foundation for further preclinical analyses of marmeline as a potential treatment for AD.

Data Availability Statement

All relevant data for this research are provided in the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contributions

T.O.: conceptualization, methodology, software, formal analysis, resources, data curation, writing–original draft preparation, and funding acquisition. O.J.: validation. N.S.: investigation. K.E.: conceptualization, methodology, software, validation, investigation, resources, data curation, writing, review, editing, visualization, supervision, project administration, and funding acquisition. All authors have read and agreed to the published version of the manuscript.

Funding

The authors declare that no funding or financial support was received from any organization, institution, or individual for the research, authorship, or publication of this article. This statement is made in compliance with the policies of Advances in Pharmacological and Pharmaceutical Sciences and Wiley Publishing.

Acknowledgments

The authors express their gratitude to the Research Excellence Center for Innovation and Health Products (RECIHP), Walailak University, Nakhon Si Thammarat 80160, Thailand.

No artificial intelligence (AI) tools or systems were used in the preparation and writing of this work.

References

[1] M. Sharma, P. Pal, and S. K. Gupta, "Advances in Alzheimer's Disease: A Multifaceted Review of Potential Therapies and Diagnostic Techniques for Early Detection," *Neurochemistry International* 177 (2024): article 105761, https://doi.org/10.1016/j.neuint.2024.105761.

[2] S. J. Page and J. Connell, "Dementia as a Global Challenge: Progress and Prospects for Creating More Dementia-Inclusive Tourism Industries," *Tourism Management* 104 (2024): article 104916, https://doi.org/10.1016/j.tourman.2024.104916.

[3] Y. Goto, K. Morita, M. Suematsu, T. Imaizumi, and Y. Suzuki, "Caregiver Burdens, Health Risks, Coping and Interventions Among Caregivers of Dementia Patients: A Review of the Literature," *Internal Medicine* 62, no. 22 (2023): 3277–3282, https://doi.org/10.2169/internalmedicine.0911-22.

[4] S. Prabha, M. Sajad, G. M. Hasan, A. Islam, M. Imtaiyaz Hassan, and S. C. Thakur, "Recent Advancement in Understanding of Alzheimer's Disease: Risk Factors, Subtypes, and Drug Targets and Potential Therapeutics," *Ageing Research Reviews* 101 (2024): article 102476, https://doi.org/10.1016/j.arr.2024.102476.

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[5] H. Hampel, D. Prvulovic, S. Teipel, et al., "The Future of Alzheimer's Disease: The Next 10 Years," *Progress in Neurobiology* 95, no. 4 (2011): 718–728, https://doi.org/10.1016/j.pneurobio.2011.11.008.

[6] R. Anand, K. D. Gill, and A. A. Mahdi, "Therapeutics of Alzheimer's Disease: Past, Present and Future," *Neuropharmacology* 76 (2014): 27–50, https://doi.org/10.1016/j.neuropharm.2013.07.004.

[7] R. Das, A. Rauf, S. Akhter, et al., "Role of Withaferin A and Its Derivatives in the Management of Alzheimer's Disease: Recent Trends and Future Perspectives," *Molecules* 26, no. 12 (2021): 3696, https://doi.org/10.3390/molecules26123696.

[8] M. Singh, M. Kaur, H. Kukreja, R. Chugh, O. Silakari, and D. Singh, "Acetylcholinesterase Inhibitors as Alzheimer Therapy: From Nerve Toxins to Neuroprotection," *European Journal of Medicinal Chemistry* 70 (2013): 165–188, https://doi.org/10.1016/j.ejmech.2013.09.050.

[9] T. B. Ameen, S. N. Kashif, S. M. I. Abbas, K. Babar, S. M. S. Ali, and A. Raheem, "Unraveling Alzheimer's: The Promise of Aducanumab, Lecanemab, and Donanemab," *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery* 60, no. 1 (2024): 72, https://doi.org/10.1186/s41983-024-00845-5.

[10] R. Vassar, "BACE 1," *Journal of Molecular Neuroscience* 23, no. 1 (2004): 105–113.

[11] S. L. Cole and R. Vassar, "The Alzheimer's Disease β-Secretase Enzyme, BACE1," *Molecular Neurodegeneration* 2, no. 1 (2007): 22, https://doi.org/10.1186/1750-1326-2-22.

[12] G. T. Grossberg, "Cholinesterase Inhibitors for the Treatment of Alzheimer's Disease: Getting on and Staying on," *Current Therapeutic Research* 64, no. 4 (2003): 216–235, https://doi.org/10.1016/s0011-393x(03)00059-6.

[13] K. Sharma, "Cholinesterase Inhibitors as Alzheimer's Therapeutics (Review)," *Molecular Medicine Reports* 20, no. 2 (2019): 1479–1487.

[14] G. D. Stanciu, A. Luca, R. N. Rusu, et al., "Alzheimer's Disease Pharmacotherapy in Relation to Cholinergic System Involvement," *Biomolecules* 10, no. 1 (2020): 40.

[15] P. T. Francis, A. M. Palmer, M. Snape, and G. K. Wilcock, "The Cholinergic Hypothesis of Alzheimer's Disease: A Review of Progress," *Journal of Neurology, Neurosurgery & Psychiatry* 66, no. 2 (1999): 137–147, https://doi.org/10.1136/jnnp.66.2.137.

[16] J. Patočka, K. Kuča, and D. Jun, "Acetylcholinesterase and Butyrylcholinesterase-Important Enzymes of Human Body," *Acta Medica* 47, no. 4 (2004): 215–228, https://doi.org/10.14712/18059694.2018.95.

[17] S. Venkatesh and R. A. Lipper, "Role of the Development Scientist in Compound Lead Selection and Optimization," *Journal of Pharmaceutical Sciences* 89, no. 2 (2000): 145–154, https://doi.org/10.1002/(sici)1520-6017(200002)89:2%3A145::aid-jps2%3E3.0.co;2-6.

[18] A. Ece, "Computer-Aided Drug Design," *BMC Chemistry* 17, no. 1 (2023): 26, https://doi.org/10.1186/s13065-023-00939-w.

[19] I. M. Kapetanovic, "Computer-Aided Drug Discovery and Development (CADDD): *In Silico*-Chemico-Biological Approach," *Chemico-Biological Interactions* 171, no. 2 (2008): 165–176, https://doi.org/10.1016/j.cbi.2006.12.006.

[20] M. S. Baliga, H. P. Bhat, N. Joseph, and F. Fazal, "Phytochemistry and Medicinal Uses of the Bael Fruit (*Aegle marmelos* Correa): A Concise Review," *Food Research International* 44, no. 7 (2011): 1768–1775, https://doi.org/10.1016/j.foodres.2011.02.008.

[21] N. Kamalakkannan and P. S. M. Prince, "The Effect of Aegle Marmelos Fruit Extract in Streptozotocin Diabetes," *Journal of Herbal Pharmacotherapy* 5, no. 3 (2006): 87–96, https://doi.org/10.1300/j157v05n03_08.

[22] R. M. Hafizur, S. Momin, and N. Fatima, "Prevention of Advanced Glycation End-Products Formation in Diabetic Rats Through Beta-Cell Modulation by *Aegle marmelos*," *BMC Complementary and Alternative Medicine* 17, no. 1 (2017): 227, https://doi.org/10.1186/s12906-017-1743-y.

[23] X. Wang, Y. Shen, S. Wang, et al., "PharmMapper 2017 Update: A Web Server for Potential Drug Target Identification With a Comprehensive Target Pharmacophore Database," *Nucleic Acids Research* 45, no. W1 (2017): W356–W360, https://doi.org/10.1093/nar/gkx374.

[24] Z. Wang, L. Liang, Z. Yin, and J. Lin, "Improving Chemical Similarity Ensemble Approach in Target Prediction," *Journal of Cheminformatics* 8, no. 1 (2016): 20, https://doi.org/10.1186/s13321-016-0130-x.

[25] A. Daina, O. Michielin, and V. Zoete, "SwissTargetPrediction: Updated Data and New Features for Efficient Prediction of Protein Targets of Small Molecules," *Nucleic Acids Research* 47, no. W1 (2019): W357–W364, https://doi.org/10.1093/nar/gkz382.

[26] M. Safran, N. Rosen, M. Twik, et al., "The GeneCards Suite," in *Practical Guide to Life Science Databases* (Singapore: Springer Nature Singapore, 2021), 27–56.

[27] T. Ongtanasup, W. Tawanwongsri, C. Manaspon, S. Srisang, and K. Eawsakul, "Comprehensive Investigation of Niosomal Red Palm Wax Gel Encapsulating Ginger (*Zingiber officinale* Roscoe): Network Pharmacology, Molecular Docking, In Vitro Studies and Phase 1 Clinical Trials," *International Journal of Biological Macromolecules* 277 (2024): article 134334, https://doi.org/10.1016/j.ijbiomac.2024.134334.

[28] D. S. Wishart, S. Tian, D. Allen, et al., "BioTransformer 3.0—A Web Server for Accurately Predicting Metabolic Transformation Products," *Nucleic Acids Research* 50, no. W1 (2022): W115–W123, https://doi.org/10.1093/nar/gkac313.

[29] W. D. Ihlenfeldt, E. E. Bolton, and S. H. Bryant, "The PubChem Chemical Structure Sketcher," *Journal of Cheminformatics* 1, no. 1 (2009): 20, https://doi.org/10.1186/1758-2946-1-20.

[30] S. X. Ge, D. Jung, and R. Yao, "ShinyGO: A Graphical Gene-Set Enrichment Tool for Animals and Plants," *Bioinformatics* 36, no. 8 (2020): 2628–2629, https://doi.org/10.1093/bioinformatics/btz931.

[31] E. Di Muzio, D. Toti, and F. Polticelli, "DockingApp: A User Friendly Interface for Facilitated Docking Simulations With AutoDock Vina," *Journal of Computer-Aided Molecular Design* 31, no. 2 (2017): 213–218, https://doi.org/10.1007/s10822-016-0006-1.

[32] D. Seeliger and B. L. de Groot, "Ligand Docking and Binding Site Analysis With PyMOL and Autodock/Vina," *Journal of Computer-Aided Molecular Design* 24, no. 5 (2010): 417–422, https://doi.org/10.1007/s10822-010-9352-6.

[33] Biovia Discovery Studio, *Discovery Studio Visualizer*, 936 (San Diego, CA: BIOVIA Discovery Studio, 2017).

[34] M. D. Hanwell, D. E. Curtis, D. C. Lonie, T. Vandermeersch, E. Zurek, and G. R. Hutchison, "Avogadro: An Advanced Semantic Chemical Editor, Visualization, and Analysis Platform," *Journal of Cheminformatics* 4, no. 1 (2012): 17, https://doi.org/10.1186/1758-2946-4-17.

[35] A. V. Sulimov, D. A. Zheltkov, I. V. Oferkin, et al., "Evaluation of the Novel Algorithm of Flexible Ligand Docking

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

with Moveable Target-Protein Atoms," *Computational and Structural Biotechnology Journal* 15 (2017): 275–285, https://doi.org/10.1016/j.csbj.2017.02.004.

[36] R. Huey, G. M. Morris, and S. Forli, "Using AutoDock 4 and AutoDock Vina With AutoDockTools: A Tutorial," *The Scripps Research Institute Molecular Graphics Laboratory* 10550, no. 92037 (2012): 1000.

[37] G. Bitencourt-Ferreira and W. F. de Azevedo, "Molecular Docking Simulations With ArgusLab," in *Docking Screens for Drug Discovery* (New York, NY: Springer New York, 2019), 203–220.

[38] S. Forli, R. Huey, M. E. Pique, M. F. Sanner, D. S. Goodsell, and A. J. Olson, "Computational Protein-Ligand Docking and Virtual Drug Screening With the AutoDock Suite," *Nature Protocols* 11, no. 5 (2016): 905–919, https://doi.org/10.1038/nprot.2016.051.

[39] O. Trott and A. J. Olson, "AutoDock Vina: Improving the Speed and Accuracy of Docking With a New Scoring Function, Efficient Optimization, and Multithreading," *Journal of Computational Chemistry* 31, no. 2 (2010): 455–461, https://doi.org/10.1002/jcc.21334.

[40] T. Ongtanasup, S. Wanmasae, S. Srisang, C. Manaspon, S. Net-anong, and K. Eawsakul, "*In Silico* Investigation of ACE2 and the Main Protease of SARS-CoV-2 With Phytochemicals From *Myristica fragrans* (Houtt.) for the Discovery of a Novel COVID-19 Drug," *Saudi Journal of Biological Sciences* 29, no. 9 (2022): article 103389, https://doi.org/10.1016/j.sjbs.2022.103389.

[41] K. Eawsakul, P. Panichayupakaranant, T. Ongtanasup, S. Warinhomhoun, K. Noonong, and K. Bunluepuech, "Computational Study and In Vitro Alpha-Glucosidase Inhibitory Effects of Medicinal Plants From a Thai Folk Remedy," *Heliyon* 7, no. 9 (2021): article e08078, https://doi.org/10.1016/j.heliyon.2021.e08078.

[42] A. Daina, O. Michielin, and V. Zoete, "SwissADME: A Free Web Tool to Evaluate Pharmacokinetics, Drug-Likeness and Medicinal Chemistry Friendliness of Small Molecules," *Scientific Reports* 7, no. 1 (2017): 42717, https://doi.org/10.1038/srep42717.

[43] K. Eawsakul, T. Ongtanasup, N. Ngamdokmai, and K. Bunluepuech, "Alpha-Glucosidase Inhibitory Activities of Astilbin Contained in *Bauhinia strychnifolia* Craib. Stems: An Investigation by *In Silico* and In Vitro Studies," *BMC Complementary Medicine and Therapies* 23, no. 1 (2023): 25, https://doi.org/10.1186/s12906-023-03857-5.

[44] G. Dennis, B. T. Sherman, D. A. Hosack, et al., "DAVID: Database for Annotation, Visualization, and Integrated Discovery," *Genome Biology* 4, no. 9 (2003): R60, https://doi.org/10.1186/gb-2003-4-9-r60.

[45] W. Yu, W. Yu, Y. Yang, and Y. Lü, "Exploring the Key Genes and Identification of Potential Diagnosis Biomarkers in Alzheimer's Disease Using Bioinformatics Analysis," *Frontiers in Aging Neuroscience* 13 (2021): article 602781, https://doi.org/10.3389/fnagi.2021.602781.

[46] O. J. Olatunji, O. O. Olatunde, T. J. Jayeoye, et al., "New Insights on *Acanthus ebracteatus* Vahl: UPLC-ESI-QTOF-MS Profile, Antioxidant, Antimicrobial and Anticancer Activities," *Molecules* 27, no. 6 (2022): 1981, https://doi.org/10.3390/molecules27061981.

[47] S. Wójtowicz, A. K. Strosznajder, M. Jeżyna, and J. B. Strosznajder, "The Novel Role of PPAR Alpha in the Brain: Promising Target in Therapy of Alzheimer's Disease and Other Neurodegenerative Disorders," *Neurochemical Research* 45, no. 5 (2020): 972–988, https://doi.org/10.1007/s11064-020-02993-5.

[48] H. Hampel, R. Vassar, B. De Strooper, et al., "The β-Secretase BACE1 in Alzheimer's Disease," *Biological Psychiatry* 89, no. 8 (2021): 745–756, https://doi.org/10.1016/j.biopsych.2020.02.001.

[49] S. Chakthong, P. Weaaryee, P. Puangphet, et al., "Alkaloid and Coumarins From the Green Fruits of *Aegle marmelos*," *Phytochemistry* 75 (2012): 108–113, https://doi.org/10.1016/j.phytochem.2011.11.018.

[50] H. N. Murthy, M. A. Bhat, and D. Dalawai, "Bioactive Compounds of Bael (*Aegle marmelos* (L.) Correa)," in *Bioactive Compounds in Underutilized Fruits and Nuts* (Cham: Springer International Publishing, 2020), 459–486.

[51] A. Chinchansure, N. Shamnani, M. Arkile, D. Sarkar, and S. Joshi, "Antimycobacterium Activity of Coumarins From Fruit Pulp of *Aegle marmelos* (L.) Correa," *International Journal of Basic Applied Chemical Sciences* 5, no. 3 (2015): 39–44.

[52] N. Siddique, M. Mujeeb, M. Aamir, and A. Husain, "Simultaneous Quantification of Umbelliferone and Quercetin in Polyherbal Formulations of *Aegle marmelos* by HPTLC," *American Journal of PharmTech Research* 2 (2012): 569.

[53] D. Mammen and D. Mammen, "Phenolic Principles and Pharmacognostic Studies of Fruits of *Aegle marmelos*," *Journal of Pharmacognosy and Phytochemistry* 12, no. 5 (2023): 422–427.

[54] V. B. Tagad, A. K. Sahoo, and U. S. Annapure, "Phytochemical Study and GC-MS Analysis of Bael (*Aegle marmelos*) Fruit Pulp," *Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences* 4 (2018): 779–791.

[55] A. Chaubey and A. K. Dubey, "Chemistry and Antioxidant Potential of Phytoconstituents from *Aegle marmelos* Fruit-Shell," *Current Drug Metabolism* 21, no. 7 (2020): 525–533, https://doi.org/10.2174/1389200221666200711161056.

[56] F. P. Guengerich, "Cytochrome P450 and Chemical Toxicology," *Chemical Research in Toxicology* 21, no. 1 (2008): 70–83, https://doi.org/10.1021/tx700079z.

[57] M. A. Cerny, "Prevalence of Non-Cytochrome P450-Mediated Metabolism in Food and Drug Administration-Approved Oral and Intravenous Drugs: 2006–2015," *Drug Metabolism and Disposition* 44, no. 8 (2016): 1246–1252, https://doi.org/10.1124/dmd.116.070763.

[58] M. P. Gleeson, A. M. Davis, K. K. Chohan, et al., "Generation of In-Silico Cytochrome P450 1A2, 2C9, 2C19, 2D6, and 3A4 Inhibition QSAR Models," *Journal of Computer-Aided Molecular Design* 21, no. 10-11 (2007): 559–573, https://doi.org/10.1007/s10822-007-9139-6.

[59] H. Zhang, L. Zhang, D. Zhou, H. Li, and Y. Xu, "ErbB4 Mediates Amyloid β-induced Neurotoxicity Through JNK/tau Pathway Activation: Implications for Alzheimer's Disease," *Journal of Comparative Neurology* 529, no. 15 (2021): 3497–3512, https://doi.org/10.1002/cne.25207.

[60] H.-j. Lee and H.-S. Hoe, "Inhibition of CDK4/6 Regulates AD Pathology, Neuroinflammation and Cognitive Function Through DYRK1A/STAT3 Signaling," *Pharmacological Research* 190 (2023): article 106725, https://doi.org/10.1016/j.phrs.2023.106725.

[61] C. C. Portugal, T. O. Almeida, R. Socodato, and J. B. Relvas, "Src Family Kinases (SFKs): Critical Regulators of Microglial Homeostatic Functions and Neurodegeneration in Parkinson's and Alzheimer's Diseases," *FEBS Journal* 289, no. 24 (2022): 7760–7775, https://doi.org/10.1111/febs.16197.

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[62] A. Marín-Quílez, C. A. Di Buduo, R. Benito, A. Balduini, J. Rivera, and J. M. Bastida, "GALE Variants Associated With Syndromic Manifestations, Macrothrombocytopenia, Bleeding, and Platelet Dysfunction," *Platelets* 34, no. 1 (2023): article 2176699, https://doi.org/10.1080/09537104.2023.2176699.

[63] F. Conte, N. van Buuringen, N. C. Voermans, and D. J. Lefeber, "Galactose in Human Metabolism, Glycosylation and Congenital Metabolic Diseases: Time for a Closer Look," *Biochimica et Biophysica Acta (BBA)-General Subjects* 1865, no. 8 (2021): article 129898, https://doi.org/10.1016/j.bbagen.2021.129898.

[64] H. Yan, L. Feng, and M. Li, "The Role of Traditional Chinese Medicine Natural Products in β-Amyloid Deposition and Tau Protein Hyperphosphorylation in Alzheimer's Disease," *Drug Design, Development and Therapy* 17 (2023): 3295–3323, https://doi.org/10.2147/dddt.s380612.

[65] S. Żulińska, A. K. Strosznajder, and J. B. Strosznajder, "Current View on PPAR-α and Its Relation to Neurosteroids in Alzheimer's Disease and Other Neuropsychiatric Disorders: Promising Targets in a Therapeutic Strategy," *International Journal of Molecular Sciences* 25, no. 13 (2024): 7106, https://doi.org/10.3390/ijms25137106.

[66] G. K. Acquaah-Mensah, N. Agu, T. Khan, and A. Gardner, "A Regulatory Role for the Insulin- and BDNF-Linked RORA in the Hippocampus: Implications for Alzheimer's Disease," *Journal of Alzheimer's Disease* 44, no. 3 (2015): 827–838, https://doi.org/10.3233/jad-141731.

[67] M. Chakrabarti, A. J. McDonald, J. Will Reed, M. A. Moss, B. C. Das, and S. K. Ray, "Molecular Signaling Mechanisms of Natural and Synthetic Retinoids for Inhibition of Pathogenesis in Alzheimer's Disease," *Journal of Alzheimer's Disease* 50, no. 2 (2016): 335–352, https://doi.org/10.3233/jad-150450.

[68] M. R. Khezri, A. Esmaeili, and M. Ghasemnejad-Berenji, "Platelet Activation and Alzheimer's Disease: The Probable Role of PI3K/AKT Pathway," *Journal of Alzheimer's Disease* 90, no. 2 (2022): 529–534, https://doi.org/10.3233/jad-220663.

[69] H.-J. Choi, Y. J. Jeong, J. Kim, and H.-S. Hoe, "EGFR Is a Potential Dual Molecular Target for Cancer and Alzheimer's Disease," *Frontiers in Pharmacology* 14 (2023): article 1238639, https://doi.org/10.3389/fphar.2023.1238639.

[70] M. Brkic, S. Balusu, C. Libert, and R. E. Vandenbroucke, "Friends or Foes: Matrix Metalloproteinases and Their Multifaceted Roles in Neurodegenerative Diseases," *Mediators of Inflammation* 2015 (2015): 27, article 620581, https://doi.org/10.1155/2015/620581.

[71] X. Zhang, C. Zhu, G. Beecham, et al., "A Rare Missense Variant of CASP7 Is Associated With Familial Late-Onset Alzheimer's Disease," *Alzheimer's and Dementia* 15, no. 3 (2019): 441–452, https://doi.org/10.1016/j.jalz.2018.10.005.

[72] M. Briese and M. Sendtner, "Keeping the Balance: The Noncoding RNA 7SK as a Master Regulator for Neuron Development and Function," *BioEssays* 43, no. 8 (2021): article 2100092, https://doi.org/10.1002/bies.202100092.

[73] X.-F. Huang, Y.-H. Dong, J.-H. Wang, H.-M. Ke, G.-Q. Song, and D.-F. Xu, "Novel PDE5 Inhibitors Derived From Rutaecarpine for the Treatment of Alzheimer's Disease," *Bioorganic & Medicinal Chemistry Letters* 30, no. 9 (2020): article 127097, https://doi.org/10.1016/j.bmcl.2020.127097.

[74] P. A. Foster, "Steroid Sulphatase and Its Inhibitors: Past, Present, and Future," *Molecules* 26, no. 10 (2021): 2852, https://doi.org/10.3390/molecules26102852.

[75] T. Syeda and J. R. Cannon, "Environmental Exposures and the Etiopathogenesis of Alzheimer's Disease: The Potential Role of BACE1 as a Critical Neurotoxic Target," *Journal of Biochemical and Molecular Toxicology* 35, no. 4 (2021): article e22694, https://doi.org/10.1002/jbt.22694.

[76] N. Sheng, Z. Zhang, H. Zheng, et al., "Scutellarin Rescued Mitochondrial Damage Through Ameliorating Mitochondrial Glucose Oxidation via the Pdk-Pdc Axis," *Advanced Science* 10, no. 32 (2023): article 2303584, https://doi.org/10.1002/advs.202303584.

[77] S. Zhang, J. Zhao, Y. Zhang, et al., "Upregulation of MIF as a Defense Mechanism and a Biomarker of Alzheimer's Disease," *Alzheimer's Research & Therapy* 11, no. 1 (2019): 54, https://doi.org/10.1186/s13195-019-0508-x.

[78] W. Xia, L. Zhuang, and M. Hou, "Role of lincRNA-P21 in the Protective Effect of Macrophage Inhibition Factor Against Hypoxia/Serum Deprivation-Induced Apoptosis in Mesenchymal Stem Cells," *International Journal of Molecular Medicine* 42, no. 4 (2018): 2175–2184, https://doi.org/10.3892/ijmm.2018.3767.

[79] M. C. Petralia, G. Battaglia, V. Bruno, et al., "The Role of Macrophage Migration Inhibitory Factor in Alzheimer's Disease: Conventionally Pathogenetic or Unconventionally Protective?" *Molecules* 25, no. 2 (2020): 291, https://doi.org/10.3390/molecules25020291.

[80] M. Llorens-Martín, J. Jurado, F. Hernández, and J. Ávila, "GSK-3β, a Pivotal Kinase in Alzheimer Disease," *Frontiers in Molecular Neuroscience* 7 (2014): 46, https://doi.org/10.3389/fnmol.2014.00046.

[81] N. C. Punessen, C. Pena, A. Sandberg, L. A. Koza, and D. A. Linseman, "A Novel Anti-Apoptotic Role for Cdc42/ACK-1 Signaling in Neurons," *Molecular and Cellular Neuroscience* 126 (2023): article 103865, https://doi.org/10.1016/j.mcn.2023.103865.

[82] J. Liu, S. Yuan, X. Niu, R. Kelleher, and H. Sheridan, "ESR1 Dysfunction Triggers Neuroinflammation as a Critical Upstream Causative Factor of the Alzheimer's Disease Process," *Aging (Albany NY)* 14, no. 21 (2022): 8595–8614, https://doi.org/10.18632/aging.204359.

[83] A. Soto-Avellaneda, A. E. Oxford, F. Halla, et al., "FABP5-Binding Lipids Regulate Autophagy in Differentiated SH-Sy5y Cells," *PLoS One* 19, no. 6 (2024): article e0300168, https://doi.org/10.1371/journal.pone.0300168.

[84] E. M. Lucero, R. K. Freund, A. Smith, et al., "Increased KIF11/Kinesin-5 Expression Offsets Alzheimer Aβ-Mediated Toxicity and Cognitive Dysfunction," *iScience* 25, no. 11 (2022): article 105288, https://doi.org/10.1016/j.isci.2022.105288.

[85] C.-P. Chang, K.-C. Wu, C.-Y. Lin, and Y. Chern, "Emerging Roles of Dysregulated Adenosine Homeostasis in Brain Disorders With a Specific Focus on Neurodegenerative Diseases," *Journal of Biomedical Science* 28, no. 1 (2021): 70, https://doi.org/10.1186/s12929-021-00766-y.

[86] P. N. H. Trinh, J.-A. Baltos, S. D. Hellyer, L. T. May, and K. J. Gregory, "Adenosine Receptor Signalling in Alzheimer's Disease," *Purinergic Signalling* 18, no. 3 (2022): 359–381, https://doi.org/10.1007/s11302-022-09883-1.

[87] S. Merighi, P. A. Borea, K. Varani, et al., "Pathophysiological Role and Medicinal Chemistry of A2A Adenosine Receptor Antagonists in Alzheimer's Disease," *Molecules* 27, no. 9 (2022): 2680, https://doi.org/10.3390/molecules27092680.

[88] E. Lauretti, O. Dincer, and D. Praticò, "Glycogen Synthase Kinase-3 Signaling in Alzheimer's Disease," *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research* 1867, no. 5

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

(2020): article 118664, https://doi.org/10.1016/j.bbamcr.2020.118664.

[89] J. Barrera, S. Subramanian, and O. Chiba-Falek, "Probing the Role of PPARγ in the Regulation of Late-Onset Alzheimer's Disease-Associated Genes," *PLoS One* 13, no. 5 (2018): article e0196943, https://doi.org/10.1371/journal.pone.0196943.

[90] R. Kapadia, J. H. Yi, and R. Vemuganti, "Mechanisms of Anti-Inflammatory and Neuroprotective Actions of PPAR-Gamma Agonists," *Frontiers in Bioscience* 13 (2008): 1813–1826, https://doi.org/10.2741/2802.

[91] B. R. Sahoo, P. K. Panda, W. Liang, W.-J. Tang, R. Ahuja, and A. Ramamoorthy, "Degradation of Alzheimer's Amyloid-β by a Catalytically Inactive Insulin-Degrading Enzyme," *Journal of Molecular Biology* 433, no. 13 (2021): article 166993, https://doi.org/10.1016/j.jmb.2021.166993.

[92] T. Zhang, Y. Xia, L. Hu, et al., "Death-Associated Protein Kinase 1 Mediates Aβ42 Aggregation-Induced Neuronal Apoptosis and Tau Dysregulation in Alzheimer's Disease," *International Journal of Biological Sciences* 18, no. 2 (2022): 693–706, https://doi.org/10.7150/ijbs.66760.

[93] S. K. Beaver, N. Mesa-Torres, A. L. Pey, and D. J. Timson, "NQO1: A Target for the Treatment of Cancer and Neurological Diseases, and a Model to Understand Loss of Function Disease Mechanisms," *Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics* 1867, no. 7-8 (2019): 663–676, https://doi.org/10.1016/j.bbapap.2019.05.002.

[94] M. H. Rashid, D. Babu, and A. G. Siraki, "Interactions of the Antioxidant Enzymes NAD(P)H: Quinone Oxidoreductase 1 (NQO1) and NRH: Quinone Oxidoreductase 2 (NQO2) With Pharmacological Agents, Endogenous Biochemicals and Environmental Contaminants," *Chemico-Biological Interactions* 345 (2021): article 109574, https://doi.org/10.1016/j.cbi.2021.109574.

[95] A. K. Torres, C. Jara, H. S. Park-Kang, et al., "Synaptic Mitochondria: An Early Target of Amyloid-β and Tau in Alzheimer's Disease," *Journal of Alzheimer's Disease* 84, no. 4 (2021): 1391–1414, https://doi.org/10.3233/jad-215139.

[96] E. Butturini, D. Boriero, A. Carcereri de Prati, and S. Mariotto, "STAT1 Drives M1 Microglia Activation and Neuroinflammation Under Hypoxia," *Archives of Biochemistry and Biophysics* 669 (2019): 22–30, https://doi.org/10.1016/j.abb.2019.05.011.

[97] D. N. Clark, L. R. Begg, and A. J. Filiano, "Unique Aspects of IFN-Γ/stat1 Signaling in Neurons," *Immunological Reviews* 311, no. 1 (2022): 187–204, https://doi.org/10.1111/imr.13092.

[98] Y. Xu, N. Zhu, W. Xu, et al., "Inhibition of Phosphodiesterase-4 Reverses Aβ-Induced Memory Impairment by Regulation of HPA Axis Related cAMP Signaling," *Frontiers in Aging Neuroscience* 10 (2018): 204, https://doi.org/10.3389/fnagi.2018.00204.

[99] M. Kaushik, P. Kaushik, and S. Parvez, "Memory Related Molecular Signatures: The Pivots for Memory Consolidation and Alzheimer's Related Memory Decline," *Ageing Research Reviews* 76 (2022): article 101577, https://doi.org/10.1016/j.arr.2022.101577.

[100] V. K. Sharma and T. G. Singh, "CREB: A Multifaceted Target for Alzheimer's Disease," *Current Alzheimer Research* 17, no. 14 (2021): 1280–1293, https://doi.org/10.2174/1567205018666210218152253.

[101] T. V. Lipina, S. Li, E. S. Petrova, et al., "PDE4B Missense Variant Increases Susceptibility to Post-traumatic Stress Disorder-Relevant Phenotypes in Mice," *Journal of Neuroscience* 44, no. 43 (2024): article e0137242024, https://doi.org/10.1523/jneurosci.0137-24.2024.

[102] J. Cheng, H.-P. Liu, W.-Y. Lin, and F.-J. Tsai, "Machine Learning Compensates Fold-Change Method and Highlights Oxidative Phosphorylation in the Brain Transcriptome of Alzheimer's Disease," *Scientific Reports* 11, no. 1 (2021): 13704, https://doi.org/10.1038/s41598-021-93085-z.

[103] Y. H. Ju, M. Bhalla, S. J. Hyeon, et al., "Astrocytic Urea Cycle Detoxifies Aβ-Derived Ammonia While Impairing Memory in Alzheimer's Disease," *Cell Metabolism* 34, no. 8 (2022): 1104–1120.e8, https://doi.org/10.1016/j.cmet.2022.05.011.

[104] J. Wen, M. Zhao, W. Sun, et al., "Uptake of Aβ by OATPs Might Be a New Pathophysiological Mechanism of Alzheimer Disease," *BMC Neuroscience* 22, no. 1 (2021): 53, https://doi.org/10.1186/s12868-021-00658-9.

[105] J. Storch and A. E. A. Thumser, "The Fatty Acid Transport Function of Fatty Acid-Binding Proteins," *Biochimica et Biophysica Acta (BBA)-Molecular and Cell Biology of Lipids* 1486, no. 1 (2000): 28–44, https://doi.org/10.1016/s1388-1981(00)00046-9.

[106] X. Huang, Y. Zhou, Y. Sun, and Q. Wang, "Intestinal Fatty Acid Binding Protein: A Rising Therapeutic Target in Lipid Metabolism," *Progress in Lipid Research* 87 (2022): article 101178, https://doi.org/10.1016/j.plipres.2022.101178.

[107] F. H. Abdulredha, M. F. Mahdi, and A. K. Khan, "*In Silico* Evaluation of Binding Interaction and ADME Study of New 1,3-Diazetidin-2-One Derivatives with High Antiproliferative Activity," *Journal of Advanced Pharmaceutical Technology & Research* 14, no. 3 (2023): 176–184, https://doi.org/10.4103/japtr.japtr_116_23.

[108] W. Löscher and H. Potschka, "Drug Resistance in Brain Diseases and the Role of Drug Efflux Transporters," *Nature Reviews Neuroscience* 6, no. 8 (2005): 591–602, https://doi.org/10.1038/nrn1728.

[109] K. Celik Topkara, E. Kilinc, A. Cetinkaya, A. Saylan, and S. Demir, "Therapeutic Effects of Carvacrol on Beta-amyloid-induced Impairments in In Vitro and In Vivo Models of Alzheimer's Disease," *European Journal of Neuroscience* 56, no. 9 (2022): 5714–5726, https://doi.org/10.1111/ejn.15565.

[110] S. Dall'Acqua, "Plant-Derived Acetylcholinesterase Inhibitory Alkaloids for the Treatment of Alzheimer's Disease," *Botanics: Targets and Therapy* 3 (2013): 19–28, https://doi.org/10.2147/btat.s17297.

[111] B. A. Bhat, A. Almilaibary, R. A. Mir, et al., "Natural Therapeutics in Aid of Treating Alzheimer's Disease: A Green Gateway Toward Ending Quest for Treating Neurological Disorders," *Frontiers in Neuroscience* 16 (2022): article 884345, https://doi.org/10.3389/fnins.2022.884345.

[112] V. P. Mayookha, V. Geetha, M. Das, and S. Kumar G., "Neurodegenerative Disease: Prevention and Treatment Through Plant Extracts Therapy," *Frontiers in Clinical Drug Research-CNS and Neurological Disorders* 10 (2022): 1–59, https://doi.org/10.2174/9789815040678122100003.

[113] A. Zięba, P. Stępnicki, D. Matosiuk, and A. A. Kaczor, "What Are the Challenges With Multi-Targeted Drug Design for Complex Diseases?" *Expert Opinion on Drug Discovery* 17, no. 7 (2022): 673–683, https://doi.org/10.1080/17460441.2022.2072827.

[114] Q. Quan, Y. Qian, X. Li, and M. Li, "Pioglitazone Reduces β Amyloid Levels via Inhibition of PPARγ Phosphorylation in a Neuronal Model of Alzheimer's Disease," *Frontiers in Aging Neuroscience* 11 (2019): 178, https://doi.org/10.3389/fnagi.2019.00178.

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

[115] I. Cortez, C. M. Hernandez, and K. T. Dineley, "Enhancement of Select Cognitive Domains with Rosiglitazone Implicates Dorsal hippocampus Circuitry Sensitive to PPARγ Agonism in an Alzheimer's Mouse Model," *Brain and Behavior* 11, no. 2 (2021): article e01973, https://doi.org/10.1002/brb3.1973.

[116] S. Patel, A. V. Bansoad, R. Singh, and G. L. Khatik, "BACE1: A Key Regulator in Alzheimer's Disease Progression and Current Development of Its Inhibitors," *Current Neuropharmacology* 20, no. 6 (2022): 1174–1193, https://doi.org/10.2174/1570159x19666211201094031.

[117] B. A. Akhoon, S. Choudhary, H. Tiwari, et al., "Discovery of a New Donepezil-Like Acetylcholinesterase Inhibitor for Targeting Alzheimer's Disease: Computational Studies With Biological Validation," *Journal of Chemical Information and Modeling* 60, no. 10 (2020): 4717–4729, https://doi.org/10.1021/acs.jcim.0c00496.

3152, 2025, 1, Downloaded from https://onlinelibrary.wiley.com/doi/10.1155/adpp/6634761 by Umea University, Wiley Online Library on [03/06/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License