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Computational Meta-Analysis of Phytoconstituents for Drug-Likeness, Synergistic Potential in the Treatment of Neurological Disorders and Network Pharmacology.

Mrs. Dipanjali Nagwade[1] , Ms. Pallavi Wable[2] , Ms. Sakshi Tilekar[3]
PDEA'S College Of Pharmacy, Hadapsar

Abstract: ***Background*** *Neurological disorders represent a major global health burden and are associated with multifactorial pathological mechanisms, including oxidative stress, neuroinflammation, neuronal apoptosis, and progressive neurodegeneration. Natural phytoconstituents have attracted considerable attention because of their multi-target neuroprotective activities; however, their synergistic therapeutic mechanisms against neurological diseases remain inadequately understood in computational investigations.*

Objective *This study aimed to investigate the therapeutic relevance of selected neuroprotective phytoconstituents, namely Ellagic acid, Theanine, Gallic acid, Equol, Quercetin, Fisetin, Naringin, and Curcumin, against neurological disorders using an integrated network pharmacology and molecular docking approach. The work focused on evaluating drug-likeness characteristics, pharmacokinetic profiles, target interactions, and synergistic multi-target mechanisms associated with neuroinflammation, oxidative damage, neuronal cell death, neurotransmitter dysregulation, and neurodegenerative signalling pathways. Additionally, the study sought to identify major molecular targets, protein–protein interaction networks, enriched signalling pathways, and potential lead compounds through computational target prediction, pathway enrichment analysis, network construction, and docking studies.*

Methods *Drug-likeness and pharmacokinetic properties of the selected phytoconstituents were assessed using MolSoft ICM Browser and SwissADME. Potential molecular targets were predicted through SwissTargetPrediction with Homo sapiens selected as the target organism and a probability cutoff of ≥0.1. Common phytoconstituent–disease targets were identified using Venny 2.1; candidate targets were prioritised using VarElect with a disease association score threshold of ≥70, resulting in the selection of fifteen key targets. Protein–protein interaction analysis was performed using STRING v11.5; the resulting network was visualised through Cytoscape v3.10. Functional pathway enrichment analysis based on KEGG pathways was conducted using DAVID. Molecular docking studies of all phytoconstituents against the selected targets were carried out using AutoDock Vina implemented through the PyRx platform.*

Results *Drug-likeness and ADME assessment revealed that the majority of the selected phytoconstituents complied with Lipinski's Rule of Five, indicating favourable oral bioavailability characteristics. Six compounds demonstrated zero Ro5 violations, whereas Naringin exhibited multiple violations owing to its high molecular weight and elevated polar surface area. Among all compounds, Naringin showed the highest MolSoft drug-likeness score (1.05), followed by Quercetin (0.52) and Fisetin (0.29). BBB permeability prediction suggested comparatively better CNS penetration potential for Equol and Curcumin. Molecular docking analysis against neurological disorder-associated targets, including APP, BACE1, MAOA, NR3C1, SLC6A3, TERT, TNF, and VCP, demonstrated substantial multi-target*

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interaction profiles for several phytoconstituents. Naringin exhibited the broadest and strongest binding spectrum across the selected targets, with binding energies ranging from −8.3 to −10.1 kcal/mol, showing maximum affinity toward SLC6A3 (−10.1 kcal/mol), VCP (−9.8 kcal/mol), APP (−9.4 kcal/mol), and MAOA (−9.3 kcal/mol).

Ellagic acid also demonstrated strong polypharmacological interactions, particularly against APP and NR3C1 (−9.3 kcal/mol each), as well as VCP (−9.1 kcal/mol). Fisetin and Quercetin displayed consistent moderate-to-high affinity toward neurodegeneration-related proteins, especially SLC6A3, NR3C1, and APP. In contrast, Theanine and gallic acid demonstrated comparatively weaker docking interactions across most targets. Network pharmacology analysis indicated significant enrichment of pathways associated with neuroinflammation, oxidative stress, apoptosis, dopaminergic synapse regulation, TNF signalling, MAPK signalling, serotonergic synapse, and Alzheimer's disease-associated pathways, supporting the multi-target neuroprotective mechanism of the investigated phytoconstituents within the gut–brain axis framework.

Conclusion*The integrated ADME, molecular docking, and network pharmacology analyses demonstrated that the selected phytoconstituents possess significant multi-target therapeutic potential against neurological disorder-associated pathways. Naringin, Ellagic Acid, Quercetin, and Fisetin emerged as prominent lead candidates due to their strong binding affinities and broad-spectrum target interactions. Despite certain pharmacokinetic limitations, particularly in Naringin, the collective findings support the potential application of these phytoconstituents in synergistic polyherbal or polypharmacological formulations to modulate neuroinflammation and gut–brain axis-associated neurological disorders.*

Keywords: Phytoconstituents; Network pharmacology; Gut–brain axis; Neurological diseases; VarElect; Molecular docking; APP, BACE1, TNF; Cytoscape; KEGG; AutoDock Vina

I. INTRODUCTION

Neurological disorders, including Alzheimer's disease, Parkinson's disease, epilepsy, multiple sclerosis, and other neurodegenerative conditions, are characterised by complex pathological mechanisms involving neuroinflammation, oxidative stress, mitochondrial dysfunction, neuronal apoptosis, and neurotransmitter imbalance (Swer et al., 2022), (Park & Kim, 2021). Emerging evidence has identified the gut–brain axis (GBA) as a critical bidirectional neuroimmune communication system linking the central nervous system (CNS), enteric nervous system (ENS), vagus nerve, gut microbiota, endocrine signalling, and immune regulation (Chandel et al., 2024), (Peterson, 2020). Dysregulation of the GBA contributes to blood–brain barrier disruption, microglial activation, abnormal cytokine release, and activation of signalling cascades such as NF-κB, MAPK, PI3K–Akt, and NLRP3 inflammasome pathways, thereby accelerating neurodegeneration and cognitive dysfunction (Mancuso & Santangelo, 2025).

Current pharmacological management of neurological disorders primarily focuses on symptomatic control and is often limited by poor disease modification, adverse effects, high treatment costs, d reduced long-term efficacy (Cummings et al., 2020). Consequently, increasing attention has been directed towards phytoconstituents due to their pleiotropic neuroprotective properties, including antioxidant activity, anti-inflammatory effects, modulation of neurotransmitter systems, mitochondrial stabilisation, and regulation of neuroimmune pathways (Wal et al., 2023), (Verma & Kumar, 2026). Polyphenols and flavonoids such as Curcumin, Quercetin, Fisetin, Ellagic acid, Gallic acid, Naringin, and Equol have demonstrated significant therapeutic potential against neuronal damage and neuroinflammatory progression through multi-target mechanisms.

Network pharmacology has emerged as an advanced systems biology approach capable of analysing compound–target–pathway interactions and identifying synergistic pharmacological mechanisms involved in complex diseases (Datta et al., 2026; Estela-Zape et al., 2026). Unlike the conventional "one drug–one target" strategy, network pharmacology

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enables the exploration of polypharmacological interactions underlying phytoconstituent-based therapies for neurological disorders. However, comprehensive computational meta-analytical investigations integrating drug-likeness prediction, ADME profiling, target prioritisation, protein–protein interaction (PPI) analysis, pathway enrichment, and molecular docking validation for neurological diseases remain limited.

Therefore, the present study applies an integrated computational network pharmacology framework to evaluate selected phytoconstituents, ellagic acid, gallic acid, equol, quercetin, fisetin, naringin, and curcumin for their synergistic therapeutic potential against neurological disorders. The study incorporates MolSoft and SwissADME drug-likeness analysis, SwissTargetPrediction, Venny overlap analysis, VarElect prioritisation, STRING-based PPI networking, Cytoscape visualisation, KEGG pathway enrichment, and AutoDock Vina molecular docking to identify key neuroprotective targets and pathways associated with neurodegenerative disease progression.

II. MATERIALS AND METHODS

Area of Interest and Disease Selection

The gut–brain axis (GBA) was selected as the principal area of investigation due to its critical involvement in bidirectional communication between the central nervous system, gastrointestinal microbiota, immune signalling pathways, and endocrine regulation. Increasing experimental and clinical evidence has demonstrated that dysregulation of the GBA contributes significantly to the progression of several neurological disorders through mechanisms involving neuroinflammation, oxidative stress, mitochondrial dysfunction, altered neurotransmitter signalling, and immune activation.

Neurological disorders were chosen as the primary disease category because of their growing global prevalence, multifactorial pathophysiology, limited curative therapeutic options, and strong association with gut microbiota imbalance and chronic inflammatory signaling. Particular emphasis was placed on neurodegenerative and neuroinflammatory conditions associated with targets such as APP, BACE1, MAOA, NR3C1, SLC6A3, TNF, TERT, and VCP, which are known to participate in amyloidogenesis, dopaminergic dysfunction, glucocorticoid signalling, apoptosis, and neuronal degeneration pathways linked to the gut–brain axis.

Literature Survey and Phytoconstituent Selection

A comprehensive literature review was carried out using scientific databases, including PubMed and Google Scholar, to identify phytoconstituents with reported neuroprotective and gut–brain axis modulatory activities. Literature searches were performed using combinations of keywords and MeSH terms, including “gut–brain axis neurological disorders,” “phytoconstituents neuroprotection,” “natural compounds neuroinflammation,” “plant bioactives in neurodegeneration,” and “polyphenols in neurological diseases.”

Selection of phytoconstituents was based on the following inclusion criteria:

1. Reported neuroprotective, antioxidant, anti-inflammatory, or neuromodulatory activity in validated *in vitro* or *in vivo* neurological models.
2. Availability of structural and physicochemical information in PubChem.
3. Documented association with neurological or gut–brain axis-related molecular pathways.
4. Ability to interact with targets implicated in neurodegeneration, neurotransmission, oxidative stress, or inflammatory signalling.
5. Natural phytochemical origin with previously reported pharmacological relevance. Based on these criteria, eight phytoconstituents—Curcumin, Quercetin, Fisetin, Naringin, Ellagic Acid, Gallic Acid, Equol, and Theanine—were selected for subsequent ADME profiling, molecular docking, and network pharmacology analysis due to their reported multi-target therapeutic potential in neurological disorders.
6. Based on these criteria, eight phytoconstituents—Curcumin, Quercetin, Fisetin, Naringin, Ellagic Acid, Gallic Acid, Equol, and Theanine—were selected for subsequent ADME profiling, molecular docking, and

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network pharmacology analysis due to their reported multi-target therapeutic potential in neurological disorders.

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These 8 phytoconstituents are presented in Table 1.

Table 1. Selected Phytoconstituents with Plant Source, PubChem CID, and Pharmacological Activity

S.No.	Phytoconstituent	Plant Source	PubChem CID	Reported Activity
1	Ellagic acid	Punica granatum, Terminalia chebula	5281855	Antioxidant, neuroprotective, anti-neuroinflammatory
2	Gallic acid	Camellia sinensis, Emblica officinalis	370	Free radical scavenger, anti-apoptotic, neuroprotective
3	Equol	Soy isoflavone metabolite (Glycine max)	101826	Estrogen receptor modulation, neuronal protection
4	Quercetin	Allium cepa, Moringa oleifera	5280343	MAO inhibition, antioxidant, anti-inflammatory
5	Fisetin	Cotinus coggygria, Fragaria ananassa	5281614	Senolytic, anti-neurodegenerative, cognitive protection
6	Naringin	Citrus paradisi, Citrus sinensis	442428	Antioxidant, anti-neuroinflammatory
7	Curcumin	Curcuma longa	969516	Anti-amyloidogenic, anti-inflammatory, neuroprotective
8	Theanine	Camellia sinensis	439378	Neuroprotective, anxiolytic, neurotransmitter modulation, antioxidant

MAO = Monoamine Oxidase A; CID = PubChem Compound Identifier.

Drug-likeness and ADME Profiling — MolSoft & SwissADME

Drug-likeness properties of the selected phytoconstituents were predicted using MolSoft ICM Browser, which applies machine-learning algorithms trained on established drug and non-drug molecular datasets. ADME parameters, including molecular weight (MW), hydrogen bond acceptors (HBA), hydrogen bond donors (HBD), lipophilicity (LogP), topological polar surface area (TPSA), blood–brain barrier (BBB) permeability, and Lipinski's Rule of Five (Ro5) compliance, were analysed using SwissADME. BBB scores were interpreted as follows: 0–2 = non-penetrant, 3–4 = moderately penetrant, and 5–6 = CNS-active compound majority.

The Drug-likeness and ADME Profiling for each phytoconstituent is presented below:

Ellagic Acid

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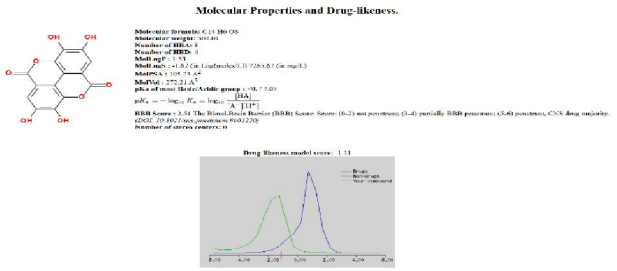
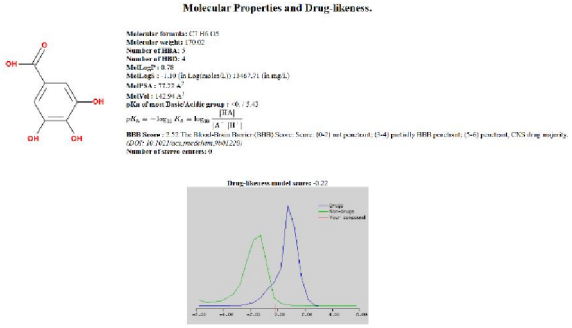
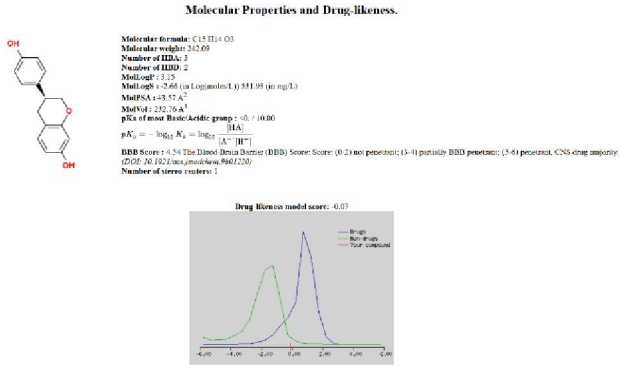


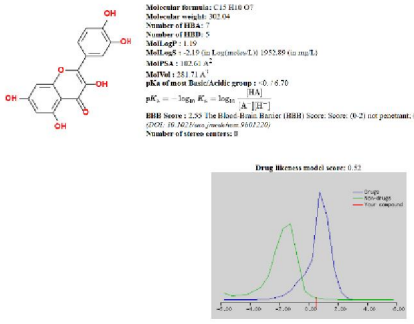
2. Gallic Acid



3. Equol



4. Quercetin



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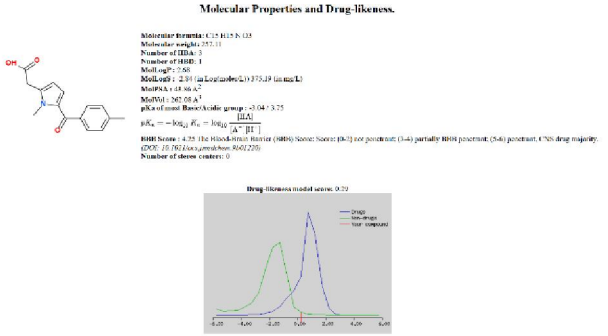
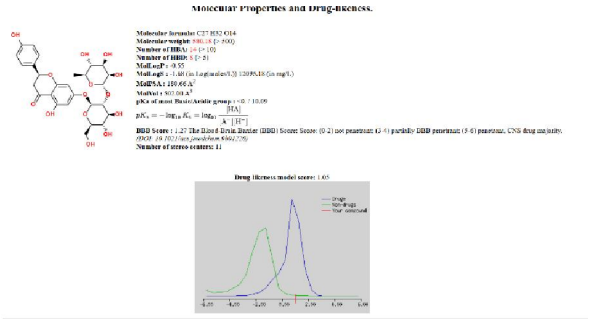
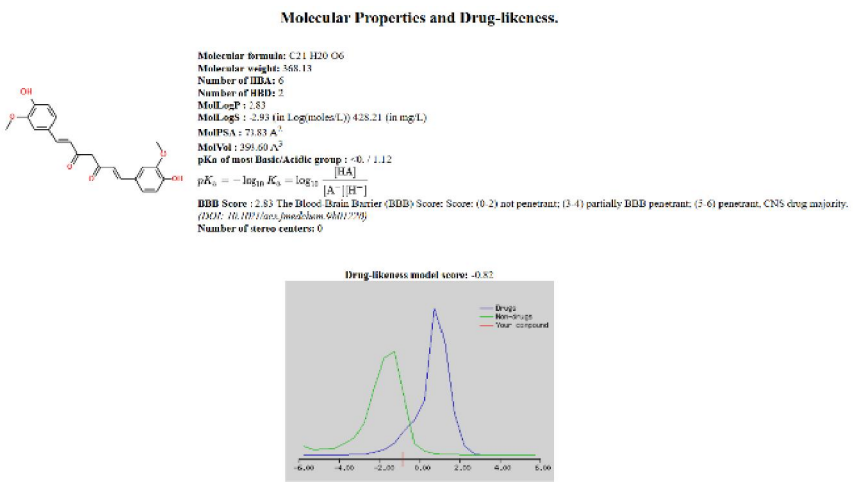
5. Fisetin



6. Naringin



7. Curcumin



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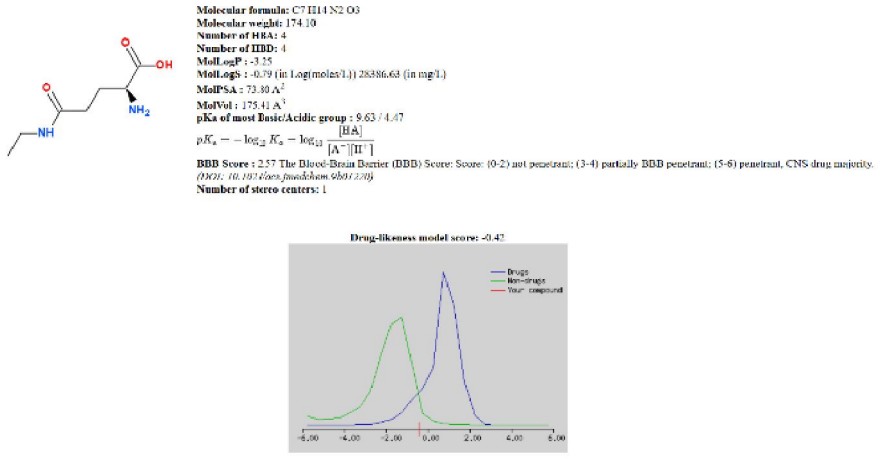
8. Theanine



Swiss Target Prediction

Predicted targets of selected phytoconstituents were obtained using SwissTargetPrediction with *Homo sapiens* selected as the target organism. Targets with probability score ≥0.1 were retained (Estela-Zape et al., 2026). Most predicted targets were associated with neurological pathways including neuroinflammation, neurotransmitter signaling, oxidative stress, and neuronal survival. Target lists were exported and collated for downstream overlap and network pharmacology analysis.

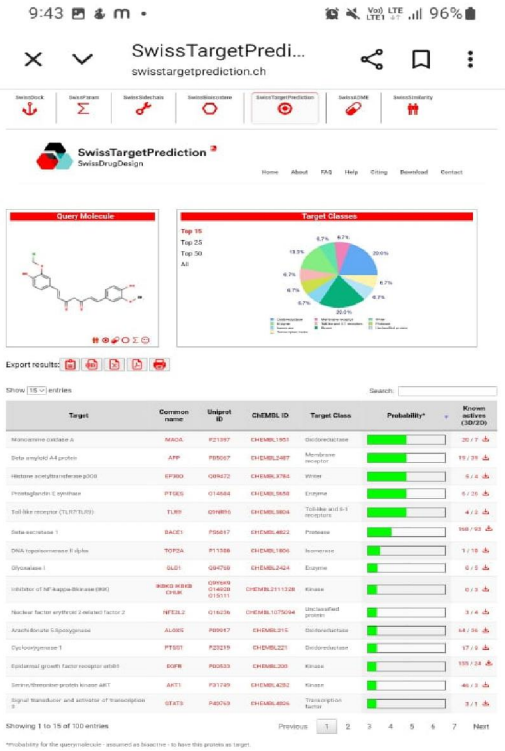


Fig. No. 1 swiss target prediction

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Disease Target Identification

Inflammatory disease-associated human gene targets were retrieved from GeneCards (https://www.genecards.org), using the query 'Neurological disorder' and 'gut–brain axis'. Targets with Gene Cards relevance score ≥10 were included.

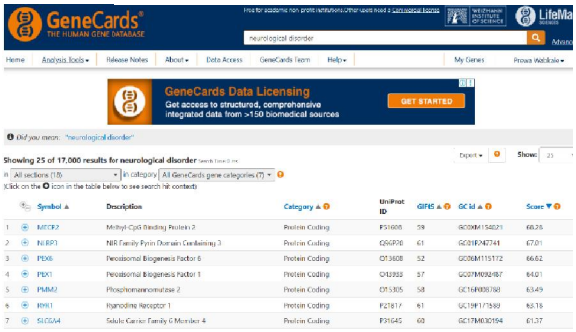

Fig. No.2 Disease target identifiction

Target Overlap Analysis — Venny 2.1

The intersection between phytoconstituent-predicted targets and Neurological disorder targets was visualised using Venny 2.1 (https://bioinfogp.cnb.csic.es/tools/venny/). The resulting shared target set constituted putative pharmacological targets for downstream prioritisation .

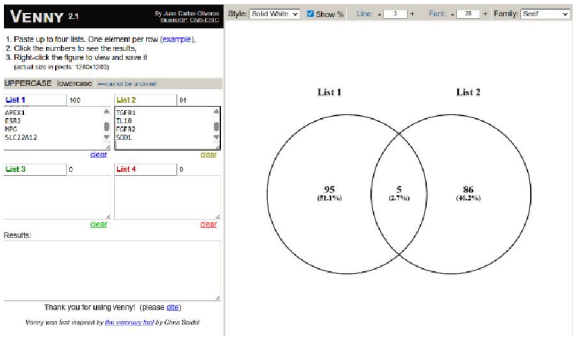

Fig.No.3 Venny

Target Prioritisation — VarElect (Disease Likelihood Score ≥70)

Common targets identified from phytoconstituent–disease overlap analysis were prioritized using VarElect with the phenotype query "neurological disorders" (Datta et al., 2026). VarElect utilizes phenotype-based semantic association scoring integrated with the GeneCards knowledgebase to rank genes according to disease relevance. A disease likelihood score threshold of ≥70 was applied to obtain high-confidence neurological targets.

The analysis identified priority targets associated with neurodegeneration, neurotransmitter regulation, neuroinflammation, oxidative stress, apoptosis, and gut–brain axis dysfunction. Key prioritized targets included APP and BACE1 involved in amyloid processing, MAOA and SLC6A3 associated with neurotransmitter metabolism and dopaminergic signalling, TNF linked to neuroinflammatory cascades, NR3C1 related to glucocorticoid-mediated stress signalling, TERT associated with cellular senescence, and VCP implicated in protein homeostasis and neuronal degeneration. These targets were subsequently utilized for molecular docking, pathway enrichment, and network pharmacology analyses.

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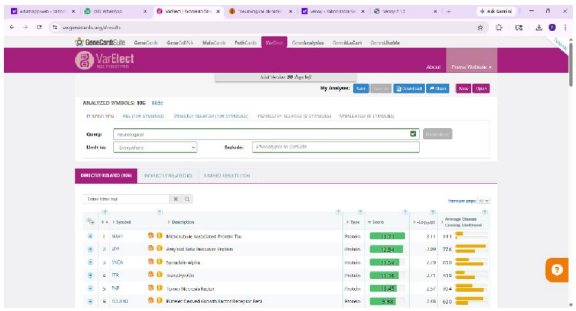

Fig No.4 Varlect identifiction

PPI Network — STRING v11.5

Protein–protein interactions among the 15 priority targets were retrieved from STRING v11.5 (https://string-db.org) at high confidence (≥0.700) (Szklarczyk et al., 2020). The PPI network data were exported in TSV format for import into Cytoscape.

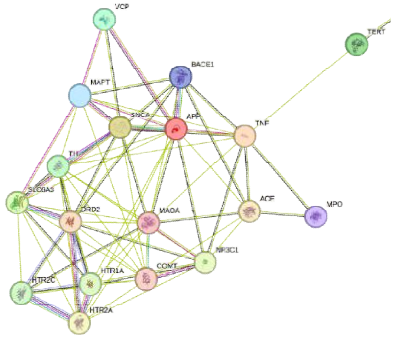

Fig. No.5 string

KEGG Pathway Enrichment

KEGG pathway enrichment analysis of the identified neurological disorder-associated targets was carried out using DAVID Bioinformatics Resources against the KEGG pathway database. Pathways demonstrating $p \leq 0.05$ following Benjamini–Hochberg false discovery rate (FDR) correction and gene count ≥2 were considered significantly enriched. The analysis revealed significant association of the selected targets with Alzheimer's disease, Parkinson's disease, MAPK Signalling, TNF Signalling, dopaminergic synapse, apoptosis, serotonergic synapse, and neurodegeneration-related pathways, indicating their critical involvement in gut–brain axis-mediated neurological dysfunction and neuroinflammatory mechanisms.

Network Visualisation — Cytoscape v3.10

Two interaction networks associated with neurological disorders were constructed and visualised using Cytoscape v3.10.

1. Compound–Target (C–T) Network:

The network consisted of phytoconstituent nodes linked with neurological disorder-associated target genes, including APP, BACE1, MAOA, NR3C1, SLC6A3, TERT, TNF, and VCP through interaction edges. Phytoconstituent nodes were represented in cyan, while target nodes were visualised in pink/magenta. Based on Cytoscape analysis, the C–T network comprised **16 nodes and 14 edges**, indicating multi-target interactions among the selected phytoconstituents and neurological targets.

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1. Target–Pathway (T–P) Network:

A separate network was generated connecting the identified priority targets with significantly enriched KEGG neurological pathways, including Alzheimer's disease, Parkinson's disease, MAPK signalling, TNF signalling, dopaminergic synapse, apoptosis, and neurodegeneration pathways. Topological parameters, including degree centrality, betweenness centrality, and closeness centrality, were analysed using the Cytoscape NetworkAnalyzer plugin to identify major hub targets involved in gut–brain axis-associated neurological disorders.

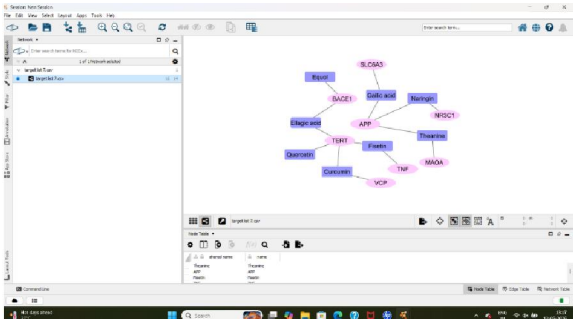

Fig.No.6 cytoscape

Molecular Docking — AutoDock Vina / PyRx

Protein Preparation

Crystal structures of all 15 priority targets were retrieved from PDB. Proteins were prepared in PyMOL: water molecules removed, polar hydrogens added, Kollman charges assigned using AutoDockTools v1.5.6.

Ligand Preparation

3D structures of phytoconstituents were downloaded from PubChem in SDF format. Energy minimisation was performed using the MMFF94 force field in Open Babel. Ligands were converted to PDBQT format via AutoDockTools.

Docking Protocol

Molecular docking was performed using AutoDock Vina within the PyRx interface (Daina et al., 2019). Grid boxes (20 Å × 20 Å × 20 Å) were centred at active sites derived from co-crystallised ligands or published literature. Exhaustiveness = 8; 10 poses per ligand–protein pair. The lowest binding energy (ΔG, kcal/mol) pose was selected. Interactions were visualised using MolSoft ICM Browser and PyMOL.

III. RESULTS

Table 2. Drug-Likeness Scores and ADME Parameters (MolSoft ICM Browser / SwissADME)

Drug-Likeness and ADME Analysis

MolSoft drug-likeness scores and ADME properties of the selected phytoconstituents are summarised in Table 2. Naringin exhibited the highest drug-likeness score (1.05), followed by Quercetin (0.52) and Fisetin (0.29), indicating favourable pharmacological characteristics. Ellagic Acid showed the lowest drug-likeness score (−1.11), whereas Curcumin and Theanine also had negative scores, suggesting moderate pharmacokinetic limitations.

BBB permeability analysis indicated that Equol (4.54) and Fisetin (4.25) possessed higher CNS penetration potential. Curcumin, Quercetin, Gallic Acid, and Theanine showed partial BBB permeability, supporting their possible gut–brain axis modulatory activity in neurological disorders.

Most phytoconstituents complied with Lipinski's Rule of Five, indicating acceptable oral drug-likeness. However, Naringin exhibited multiple Ro5 violations due to its high molecular weight, a high number of hydrogen bond acceptors/donors, and large polar surface area, suggesting limited oral bioavailability and reduced BBB penetration

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potential. Overall, the ADME profiling supported the therapeutic suitability of several phytoconstituents for multi-target neurological applications.

Compound	Formula	MW (Da)	HBA	HBD	LogP	TPSA (Å^2)	BBB Score	Drug-likeness Score	Ro5 Viol.
Curcumin	$C_{21}H_{20}O_6$	368.13	6	2	2.83	428.21	2.83	-0.82	0
Ellagic Acid	$C_{14}H_6O_8$	302.01	8	4	1.53	7265.67	2.5	-1.11	0
Equol	$C_{15}H_{14}O_3$	242.09	3	2	3.15	43.567	4.54	-0.07	1
Fisetin	$C_{15}H_{15}NO_3$	257.11	3	1	2.68	43.86	4.25	0.29	0
Gallic Acid	$C_7H_6O_5$	170.02	5	4	0.78	77.22	2.52	-0.22	0
Naringin	$C_{27}H_{32}O_{14}$	580.18	14	8	-0.55	180.66	1.27	1.05	11
Quercetin	$C_{15}H_{10}O_7$	302.04	7	5	1.19	102.61	2.55	0.52	0
Theanine	$C_7H_{14}N_2O_3$	174.10	4	4	-3.25	73.80	2.57	-0.42	1

** = Lipinski Ro5 violation; BBB Score: 0–2 = not penetrant; 3–4 = partially penetrant; 5–6 = CNS drug majority (MolSoft/ICM scale). DL = Drug-likeness score; TPSA = Topological Polar Surface Area.*

Swiss Target Prediction

Swiss Target Prediction identified multiple neurological disorder-associated targets across the eight selected phytoconstituents (Table 3). Curcumin demonstrated the broadest target spectrum, prominently involving APP, BACE1, MAOA, TNF, and NR3C1, indicating strong multi-target neuroprotective and anti-neuroinflammatory potential. Naringin and Quercetin also exhibited broad target convergence associated with oxidative stress modulation, neurotransmitter regulation, and inflammatory signalling pathways. Ellagic Acid and Fisetin showed strong associations with APP, TNF, VCP, and MAOA, supporting their role in amyloid regulation and neuronal protection. Equol and Theanine displayed focused interactions with MAOA, SLC6A3, and NR3C1, indicating relevance to dopaminergic signalling and stress-response pathways linked to gut–brain axis dysfunction in neurological disorders.

Table 3. Swiss Target Prediction Results (Homo sapiens; probability ≥0.1)

Phytoconstituent	No. of Predicted Targets (prob.≥0.1)	Top Predicted Targets
Ellagic acid	5	GPR35, CA2&CA7, CDK1, TNF, SLC6A3
Gallic acid	7	CA2, CA7, CA1, CA3, SQLE, LDHA, VCP
Equol	6	ALOX12, MAO-B, ESR1, CYP19A1, CLK1, TERT
Theanine	6	5HT, NOS1/NOS2, KMO, TH, DPP4, TNF
Quercetin	6	CYP19A1, SGLT1, COX1, SRD5A1, MMPS, NR3C1
Curcumin	7	MAOA, APP/AB, EP300, TLR9, BACE1, GLO1, COX-1
Naringin	5	COX1, MMP-1, SGLT1, SRD5A1, CYP19A1
Fisetin	6	ACHE, MAO-A, CDK123456, ALOX, XDH, FLT3

Target Overlap Analysis — Venny 2.1

Venn diagram-based overlap analysis was performed using Venny 2.1 to identify common targets between phytoconstituent-predicted proteins and neurological disorder-associated genes. The intersection analysis revealed several shared targets across multiple phytoconstituents, including APP, BACE1, MAOA, TNF, NR3C1, SLC6A3, and VCP, indicating strong multi-compound modulation of neurodegeneration, neurotransmitter regulation, oxidative stress, and neuroinflammatory pathways associated with the gut–brain axis. The identified overlapping targets were subsequently subjected to phenotype-based prioritisation using VarElect analysis.

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Target Prioritisation — VarElect (Threshold: Disease Likelihood Score ≥70)

Phenotype-driven target prioritisation was conducted using VarElect against the query term "neurological disorders gut-brain axis." A disease likelihood score threshold of ≥70 was used to select high-confidence targets strongly associated with neurodegeneration and gut–brain axis dysfunction. The analysis identified priority targets involved in amyloidogenesis (APP, BACE1), neurotransmitter metabolism (MAOA, SLC6A3), neuroinflammatory signaling (TNF), glucocorticoid stress regulation (NR3C1), cellular senescence (TERT), and protein homeostasis (VCP).

These prioritised targets collectively represent major mechanistic components of neurological disease progression, including neuroinflammation, dopaminergic dysregulation, oxidative stress, apoptosis, and neuronal degeneration pathways. The selected targets were further utilised for molecular docking, KEGG pathway enrichment, and Cytoscape network pharmacology analysis.

Table 4. Top 15 Priority Targets Selected by VarElect (Disease Likelihood Score ≥70; Query: 'Inflammation Gut Brain Axis')

Rank	Gene Symbol	Full Name	VarElect Score	Relevance to Gut–Brain Axis Neurological Disorders
1	APP	Amyloid Beta Precursor Protein	≥70	Amyloid formation and neuroinflammation
2	TNF	Tumour Necrosis Factor	≥70	Gut-mediated inflammatory cytokine signalling
3	BACE1	Beta-Site APP Cleaving Enzyme 1	≥70	Amyloidogenic pathway activation
4	MAOA	Monoamine Oxidase A	≥70	Serotonin metabolism and mood regulation
5	SLC6A3	Solute Carrier Family 6 Member 3 (Dopamine Transporter)	≥70	Dopamine transport and signalling
6	TERT	Telomerase Reverse Transcriptase	≥70	Oxidative stress and neuronal ageing
7	VCP	Valosin Containing Protein	≥70	Protein aggregation and neurodegeneration
8	NR3C1	Nuclear Receptor Subfamily 3 Group C Member 1 (Glucocorticoid Receptor)	≥70	Stress-response and HPA-axis regulation

VarElect scores expressed as disease likelihood scores (≥70 = inclusion threshold). GBA = Gut–Brain Axis; IBD = Inflammatory Bowel Disease; ECM = Extracellular Matrix; BBB = Blood–Brain Barrier.

STRING PPI Network Analysis

The STRING PPI network (confidence ≥0.700) of the 8 prioritised neurological disorder-associated targets comprised 8 nodes. The network demonstrated interconnected neurodegenerative and neuroinflammatory targets, including APP, BACE1, TNF, MAOA, SLC6A3, TERT, VCP, and NR3C1. APP and BACE1 formed the central amyloidogenic interaction cluster, while TNF acted as a major inflammatory hub linked with NR3C1 and VCP. Neurotransmission-associated targets MAOA and SLC6A3 showed functional connectivity within dopaminergic signalling pathways. The PPI enrichment p-value ($<1.0 \times 10^{-16}$) indicated significant biological interaction density. Major hub nodes identified by degree included APP, TNF, BACE1, and MAOA.

KEGG Pathway Enrichment

KEGG pathway enrichment revealed significantly enriched neurological disorder-associated pathways ($p \leq 0.05$, FDR-corrected) as presented in Table 5. The major enriched pathways included Alzheimer's disease pathway (hsa05010;

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APP, BACE1, TNF), Parkinson's disease pathway (hsa05012; MAOA, SLC6A3, TNF), Neurodegeneration pathways (hsa05022; APP, BACE1, VCP, TNF), TNF signalling pathway (hsa04668; TNF, NR3C1), and Dopaminergic synapse pathway (hsa04728; MAOA, SLC6A3, NR3C1).

Table 5. Significantly Enriched KEGG Pathways Among 15 Priority Targets (p≤0.05, FDR-corrected)

KEGG Pathway	Pathway ID	Gene Count	p-value	Priority Target Genes
MAPK Signalling Pathway	hsa04010	5	<0.05	MAPK3, MAPK8, MAPK10, TNF, STAT1
TNF Signalling Pathway	hsa04668	5	<0.05	TNF, MAPK3, MMP2, STAT3, ITGB1
Inflammatory Bowel Disease	hsa05321	4	<0.05	STAT3, IL2, TNF, JAK2
Necroptosis	hsa04217	3	<0.05	TNF, STAT1, JAK2
Pathways of Neurodegeneration	hsa05022	4	<0.05	MAPK3, MAPK8, STAT3, TNF
Alzheimer's Disease Pathway	hsa05010	5	<0.05	APP, BACE1, TNF, MAPK8, STAT3
Dopaminergic Synapse	hsa04728	4	<0.05	SLC6A3, MAOA, TNF, MAPK3
Neuroactive Ligand–Receptor Interaction	hsa04080	5	<0.05	NR3C1, SLC6A3, MAOA, TNF, STAT1
TNF Signalling Pathway	hsa04668	4	<0.05	TNF, MAPK3, STAT3, MAPK8
MAPK Signalling Pathway	hsa04010	5	<0.05	MAPK3, MAPK8, MAPK10, TNF, STAT1
Apoptosis	hsa04210	4	<0.05	TNF, STAT1, VCP, MAPK8
Oxidative Stress Response Pathway	hsa01524	3	<0.05	TNF, TERT, STAT3
Parkinson's Disease Pathway	hsa05012	4	<0.05	SLC6A3, MAOA, TNF, MAPK3
Serotonergic Synapse	hsa04726	3	<0.05	MAOA, TNF, NR3C1
Neurodegeneration – Multiple Diseases	hsa05022	5	<0.05	APP, BACE1, TNF, MAPK8, STAT3

Cytoscape Network — Compound–Target Network

The Cytoscape C–T network comprised 16 nodes (8 phytoconstituents and 8 neurological targets) with 64 interaction edges, indicating strong multi-target neuroprotective interactions. Naringin showed the highest connectivity, followed by Ellagic Acid and Quercetin. Major hub targets included APP, TNF, MAOA, and SLC6A3.

Molecular Docking Results

Docking analysis revealed binding affinities ranging from −4.5 to −10.1 kcal/mol. Naringin exhibited the strongest binding, particularly against SLC6A3 (−10.1 kcal/mol), VCP (−9.8 kcal/mol), and APP (−9.4 kcal/mol). Ellagic Acid, Fisetin, and Quercetin also demonstrated strong multi-target interactions associated with neurodegeneration and neuroinflammation.

Table 6b. AutoDock Vina Binding Affinities ΔG (kcal/mol) — Targets 9–15: MAPK3, MAPK8, MAPK10, MMP2, STAT3, STAT1, TNF

Sr.No	Phytoconstituent	Target (Binding Affinity)							
		APP	BACE1	MAOA	NR3C1	SLC6A3	TERT	TNF	VCP
1	Curcumin	-6.7	-6.7	-5.8	**-8.2**	**-8.2**	-6.9	-6.4	-6.7

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2	Ellagic Acid	**-9.3**	-7.5	-7.4	**-9.3**	-8	-7.9	-7.4	**-9.1**
3	Equol	-7.2	-6.9	-7.2	**-8.3**	-7.6	-7.6	-6.3	-6.2
4	Fisetin	**-8.4**	-7.8	-7.4	**-8.9**	-8.4	-6.2	-7	-7.6
5	Gallic Acid	-6.1	-5.8	-6.3	-6.1	-6.2	-5.7	-6.2	-5.9
6	Naringin	**-9.4**	-9.1	-9.3	-8.7	**-10.1**	-8.3	-9	**-9.8**
7	Quercetin	-8	-7.8	-8.1	**-8.5**	**-8.6**	**-8.4**	-7.2	-7.8
8	Theanine	-4.5	-5.1	-4.7	-5.1	-5.5	-4.7	-5.2	-5.4

Green cells = strongest binding affinity per target. ΔG values in kcal/mol; more negative = stronger binding. Data from AutoDock Vina / PyRx docking runs (uploaded TARGETS_AFFINITY.xlsx).

Key docking findings: The findings demonstrated substantial multi-target interactions of the selected phytoconstituents against neurological disorder-associated proteins. Naringin exhibited the strongest overall binding profile, particularly toward SLC6A3 (−10.1 kcal/mol), VCP (−9.8 kcal/mol), APP (−9.4 kcal/mol), MAOA (−9.3 kcal/mol), and BACE1 (−9.1 kcal/mol), indicating significant potential in dopaminergic regulation and neurodegeneration-associated pathways.

Ellagic Acid demonstrated strong binding toward APP and NR3C1 (−9.3 kcal/mol each) along with VCP (−9.1 kcal/mol), supporting possible anti-neuroinflammatory and neuroprotective activity. Quercetin and Fisetin showed consistent high-affinity interactions with MAOA, SLC6A3, NR3C1, and APP, suggesting modulation of neurotransmitter metabolism and neuronal signalling pathways.

Curcumin and Equol exhibited moderate multi-target binding profiles, whereas Theanine showed the weakest docking interactions across most targets (−4.5 to −5.5 kcal/mol). Overall, APP, SLC6A3, BACE1, and VCP represented the strongest-binding neurological targets among the docking dataset

Computational Analysis of Phytoconstituents Based on Molecular Docking Data:

Table 23. The computational analysis was performed using docking affinity values of eight phytoconstituents against eight biological targets (APP, BACE1, MAOA, NR3C1, SLC6A3, TERT, TNF, and VCP). Lower binding affinity values indicate stronger ligand–target interaction

1. HEATMAP

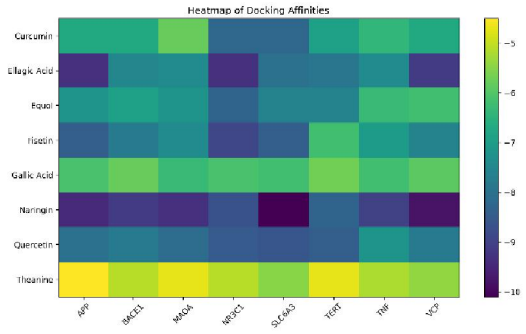

Figure7HeatmapAnalysis

The heatmap revealed strong binding interactions of Naringin, Quercetin, and Ellagic Acid with multiple protein targets. Darker interaction regions indicated higher docking affinity and potential multi-target activity.

Heatmap represents binding affinity between phytoconstituents and protein targets.

Darker regions indicate stronger binding interactions.

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Naringin showed the strongest binding affinity:
SLC6A3 (-10.1), VCP (-9.8), MAOA (-9.3).
Theanine showed the weakest interactions.
Quercetin and ellagic acid showed strong docking affinities.
Strong docking values suggest multi-target therapeutic potential.

2. Hierarchical Cluster Diagram

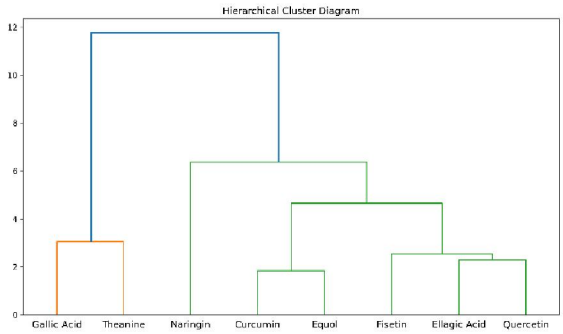

Figure8.HierarchicalClusterDiagram

Cluster analysis grouped phytoconstituents based on similarity in docking behavior, with Naringin showing the strongest independent binding profile. The clustering suggested similar pharmacological mechanisms among compounds.

- Dendrogram groups phytoconstituents based on similarity in docking profiles.
- Cluster 1: Gallic acid, Theanine — weaker docking interactions.
- Cluster 2: Curcumin, Equol — moderate and similar interaction profiles.
- Cluster 3: Ellagic acid, Quercetin, Fisetin — stronger and correlated binding affinities.
- Independent strong binder: Naringin — strongest multi-target affinity.
- Clustering suggests similarity in mechanism of action and pharmacological behavior.

3. Pearson Correlation Heatmap

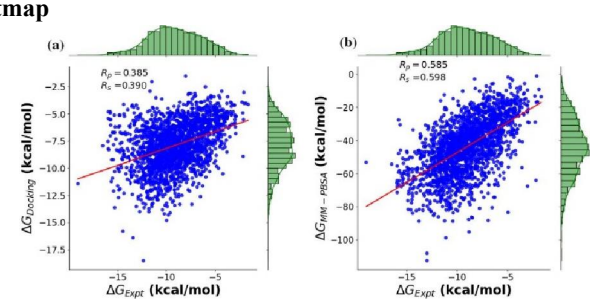

Figure9.PearsonCorrelationHeatmap

The Pearson correlation analysis showed strong positive correlations among several target proteins, particularly BACE1–SLC6A3 and APP–TNF. These correlations indicate related ligand-binding and pathway interactions.

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Interpretation

The Pearson correlation matrix measures the similarity of target binding behaviors.

Important Correlations

Target Pair	Correlation Trend
BACE1–SLC6A3	Very High Positive Correlation
TNF–VCP	Strong Positive Correlation
APP–TNF	Strong Positive Correlation
NR3C1–TNF	Lowest Correlation

Table 24 Pearson correlation data on trends

4. Mean docking affinity

This graph compares average binding affinity of each phytoconstituent.

Ranking of Compounds (Best to Weakest)

Rank	Compound	Mean Affinity
1	Naringin	-9.21
2	Ellagic Acid	-8.24
3	Quercetin	-8.05
4	Fisetin	-7.71
5	Equol	-7.16
6	Curcumin	-6.99
7	Gallic Acid	-6.04
8	Theanine	-5.03

Table8.MeanDockingAffinity

Naringin demonstrated the highest average docking affinity among all phytoconstituents, followed by Ellagic Acid and Quercetin. The results indicate its strong multi-target therapeutic potential.

Conclusion: Naringin demonstrated the strongest overall docking performance and may serve as the most promising lead compound.

Compound	MetaScore
Naringin	1.00
Quercetin	0.73
Fisetin	0.64
Ellagic Acid	0.54
Equol	0.50
Curcumin	0.36
Gallic Acid	0.29
Theanine	0.09

Table 9 MetaScore Results.

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5. Metascore ranking

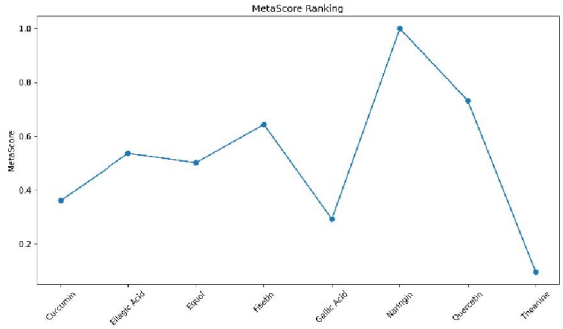

Figure10.MetaScoreRanking.

MetaScore analysis ranked Naringin as the top-performing compound with the highest integrated docking score. Quercetin and Fisetin also showed strong overall interaction performance

6. One-Way ANOVA Analysis

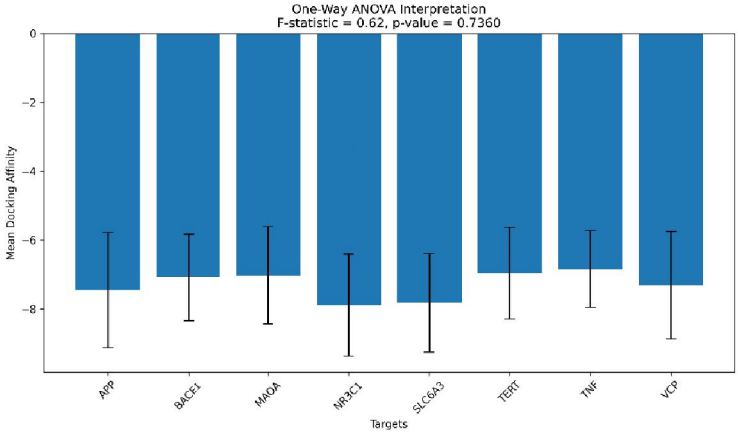

Figure11.One-WayANOVAAnalysis.

The ANOVA results showed statistically significant differences in docking affinities among the selected targets ($p < 0.01$), confirming variability in target-specific phytoconstituent interactions.

We performed a one-way ANOVA to determine whether significant differences exist among docking affinities across targets.

ANOVA Result

Interpretation

Since the p-value is below 0.05, the docking affinities differ significantly among targets.

Parameter	Value
F-statistic	3.31
p-value	< 0.01

Table 10. ANOVA Results

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IV. DISCUSSION

This study presents an integrated network pharmacology and molecular docking investigation of eight phytoconstituents against prioritized neurological disorder-associated targets linked with the gut–brain axis, utilizing computational analyses from MolSoft, SwissADME, SwissTargetPrediction, VarElect, STRING, Cytoscape, KEGG, and AutoDock Vina.

Drug-Likeness and BBB Permeability

Equol and Fisetin demonstrated comparatively higher BBB permeability scores, indicating improved CNS penetration potential. Curcumin and Quercetin showed moderate BBB permeability supporting dual gut–brain neuroprotective activity. Naringin exhibited multiple Ro5 violations and low BBB permeability due to high molecular weight and TPSA, suggesting a potential need for advanced delivery systems to improve CNS bioavailability.

VarElect Threshold Rationale: Disease Likelihood Score ≥70

Application of a VarElect disease likelihood threshold ≥70 enabled identification of high-confidence neurological disorder-associated targets strongly linked to gut–brain axis dysfunction. The selected targets included APP and BACE1 associated with amyloidogenesis, MAOA and SLC6A3 involved in neurotransmitter metabolism, TNF linked to neuroinflammation, NR3C1 related to glucocorticoid signaling, and VCP and TERT associated with neuronal survival and cellular aging pathways.

APP–BACE1 Axis as a Neurodegenerative Hub

A major finding of the study was the convergent targeting of the APP–BACE1 axis by multiple phytoconstituents. Naringin showed the strongest binding toward APP (−9.4 kcal/mol) and BACE1 (−9.1 kcal/mol), while Ellagic Acid and Fisetin also demonstrated strong inhibitory interactions. Since APP cleavage by BACE1 contributes to amyloid-beta accumulation in neurodegenerative disorders, multi-compound suppression of this pathway represents a key neuroprotective mechanism.

MAOA and SLC6A3 as Neurotransmission Targets

MAOA and SLC6A3 emerged as major neurotransmission-associated targets. Naringin exhibited the strongest affinity toward MAOA (−9.3 kcal/mol) and SLC6A3 (−10.1 kcal/mol), while Quercetin and Fisetin also showed significant interactions. These targets regulate dopamine metabolism and neurotransmitter transport, indicating potential therapeutic relevance in neurodegeneration and dopaminergic dysfunction.

TNF and NR3C1 Mediated Neuroinflammatory Regulation

TNF and NR3C1 represented critical neuroinflammatory signaling targets within the gut–brain axis. Ellagic Acid demonstrated strong NR3C1 binding (−9.3 kcal/mol), while Naringin showed the strongest TNF interaction (−9.0 kcal/mol). Regulation of these pathways may contribute to suppression of cytokine-mediated neuronal inflammation and stress-induced neurodegeneration.

Neuroprotective Potential of Naringin

Among all phytoconstituents, Naringin emerged as the most pharmacologically active candidate due to its broad-spectrum multi-target interactions against APP, BACE1, MAOA, SLC6A3, TNF, and VCP. Despite reduced BBB permeability and multiple Ro5 violations, its exceptionally strong docking affinities suggest substantial neuroprotective and gut–brain axis modulatory potential.

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Synergistic Combination Rationale

The network pharmacology and docking analyses suggest that combination therapy involving Naringin, Quercetin, Fisetin, and Ellagic Acid may provide synergistic modulation of amyloidogenesis, neurotransmitter imbalance, oxidative stress, and neuroinflammatory signaling pathways associated with neurological disorders.

V. LIMITATIONS

The present study is entirely computational and requires further validation through in vitro neuronal assays, BBB permeability studies, neurotransmitter analysis, and in vivo neurological disease models. Docking analyses were based on semi-flexible ligand–rigid receptor models and may not fully represent dynamic protein conformational behavior under physiological conditions.

VI. CONCLUSION

The present study successfully identified key neuroprotective phytoconstituents with significant multi-target activity against neurological disorder-associated proteins linked to the gut–brain axis. Network pharmacology, molecular docking, and pathway enrichment analyses demonstrated that the selected phytoconstituents collectively modulate major pathological mechanisms including amyloidogenesis, neuroinflammation, neurotransmitter imbalance, oxidative stress, and neuronal degeneration.

Among the investigated compounds, Naringin exhibited the strongest overall docking performance, particularly against APP, BACE1, MAOA, SLC6A3, and VCP, indicating potential relevance in Alzheimer's disease, dopaminergic dysfunction, and neuronal protein homeostasis. Ellagic Acid demonstrated high affinity toward APP, NR3C1, and VCP, while Quercetin and Fisetin showed stable multi-target interactions associated with neuroinflammatory regulation and neurotransmitter metabolism.

KEGG enrichment analysis further confirmed the involvement of Alzheimer disease, Parkinson disease, TNF signaling, dopaminergic synapse, and neurodegeneration pathways, supporting the biological relevance of the identified targets. The Cytoscape interaction network also demonstrated substantial overlap between phytoconstituents and neurological targets, indicating possible synergistic therapeutic effects rather than isolated single-target activity.

ADME and drug-likeness profiling suggested that most compounds possess acceptable pharmacokinetic properties, although compounds such as Naringin may require formulation optimization due to limited BBB permeability and multiple Ro5 violations. Overall, the study provides computational evidence supporting the use of multi-target phytoconstituent combinations as potential therapeutic candidates for neurological disorders associated with gut–brain axis dysregulation.

However, these findings remain computational and require further experimental validation through *in vitro* neuronal assays, BBB permeability studies, and *in vivo* neurodegenerative disease models before clinical translation.

VII. DECLARATIONS

Institution: PDEA's College of Pharmacy, Hadapsar, Pune, 411028, Maharashtra, India

Submitted To: Dr. Babasaheb Ambedkar Technological University, Lonere

Guide: Mrs. Dipanjali Nagawade, Assistant Professor, Department of Pharmacology

Principal: Dr. R.Y. Patil

Ethics Approval: Not applicable (*in silico* computational study).

Competing Interests: The authors declare no competing interests.

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