RESEARCH PAPER

Multi-Target Therapeutic Potential of Vacha (*Acorus calamus*) in Dementia: "A Network Pharmacology and Molecular Docking Study"

Dr Praveen Mylapur[1], Dr Pradeep Agnihotri[2]*, Dr Pooja Gorobal[3], Dr Lomate Rahul[4], Dr Rajesh Arkasali[5]

[1] BAMS (MD)Ayu, 3rd Year PG Scholar Department of Rasashastra and Bhaishajya Kalpana, Ayurveda Mahavidyalaya, Hubli, Email: drpraveenmylapur99@gmail.com

[2] BAMS MD AYU, PhD, Professor, Department of Rasashastra and Bhaishajya Kalpana, Ayurveda Mahavidyalaya, Hubli, Email: docagni@gmail.com

[3] BAMS (MD)Ayu, 2nd Year PG Scholar, Department of Dravyaguna Vigyana, KAHER's Shri B M Kankanwadi Ayurveda Mahavidyalaya Shahapur, Belagavi, Email: drpoojagorobal@gmail.com

[4] BAMS (MD)Ayu, 3rd Year PG Scholar Department of Rasashastra and Bhaishajya Kalpana, Ayurveda Mahavidyalaya, Hubli, Email: rahullomate6@gmail.com

[5] BAMS (MD)Ayu, 3rd Year PG Scholar Department of Rasashastra and Bhaishajya Kalpana, Ayurveda Mahavidyalaya, Hubli, Email: arkasalirajesh55@gmail.com

**Author for correspondence:*
Dr Pradeep Agnihotri
BAMS MD AYU, PhD, Professor, Department of Rasashastra and Bhaishajya Kalpana, Ayurveda Mahavidyalya, Hubli, Email: docagni@gmail.com

ABSTRACT

Dementia is a progressive neurodegenerative disorder mainly caused by Alzheimer's disease, leading to deterioration in memory, cognition, language, and daily activities. Present treatments provide only symptomatic relief and often produce adverse effects. Network Pharmacology and molecular docking are useful approaches for exploring multi-target herbal therapies. *Acorus calamus* contains several neuroprotective phytochemicals that may be beneficial in dementia management.

AIM: Using network pharmacology and molecular docking techniques, examine the multi-target therapeutic potential and molecular processes of Vacha (*Acorus calamus*) in Dementia.

MATERIALS & METHOD: *Acorus calamus* phytochemicals were extracted from Dr. Duke's and IMPPAT databases, and SwissADME was used to screen them for oral bioavailability and drug-likeness. GeneCards and the Human Protein Atlas were searched for dementia-related targets, while BindingDB and the UniProt database were used to find possible targets. Protein-protein interaction (PPI) study, KEGG pathway enrichment analysis, and Cytoscape network construction were accomplished. PyRx and BIOVIA Discovery Studio were used to conduct molecular docking investigations.

RESULT: Among the 239 phytochemicals and 55 target genes, 26 overlapping targets linked with dementia were found. The KEGG investigation identified a number of significant pathways, such as neuroactive ligand-receptor interaction, tryptophan metabolism, and PPAR signaling. Galangin, palmitoleic acid, and linoleic acid show significant binding affinities with AKR1C3, CYP1B1, and CYP1A2, according to molecular docking. Galangin's affinity for AKR1C3 was the highest (-9.2 kcal/mol).

CONCLUSION: By altering several signaling pathways and target proteins, Acorus cala-mus has considerable multi-target therapeutic potential against dementia. Galangin may be a promising neuroprotective candidate for dementia research in the future, especially through its interaction with AKR1C3.

Keywords: Dementia, Vacha (*Acorus calamus*), Network Pharmacology, Molecular Insights.

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INTRODUCTION

The World Health Organization defines Dementia as a syndrome, not a disease, marked by a progressive loss of functioning in many cognitive domains.[1] Although "dementia" is still often used, it is referred to as “Major Neurocognitive disorder” (MND) in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5).[2] The WHO estimates that 55 million people worldwide suffer from dementia, with about 10 million new cases reported annually.[3] It is more prevalent in low and middle-income nations and is closely associated with conditions including depression, smoking, diabetes, hypertension, and age over 65 years [4] Dementia cases are predicted to increase to 131.5 million by 2050 due to the aging population.[5]

Dementia, in contrast to delirium, is a syndrome marked by continuous cognitive weakening from a person's earlier level of functioning. Mood swings are often accompanied by impairments to memory, thinking, language, learning, judgment, and direction.[6] Of the 13 causes listed in the DSM-5, Alzheimer's disease is responsible for almost 70% of cases.[7] Lewy body disease, vascular disease, frontotemporal degeneration, and traumatic brain damage are additional reasons.[8] Dementia risk factors include age (especially over 65years age) and diseases like diabetes, hypertension, smoking, and depression. Its prevalence is rising as the population ages and is more common in low- and middle-income countries.

Currently there is no definitive cure for dementia due to progressive neuronal degeneration. As a result, the cornerstone of treatment continues to be symptomatic management, which includes behavioral disorder treatment, function-supporting environmental modifications, and safety counselling. The main goal of dementia management is to reduce symptoms and slow cognitive decline using both non-pharmacological and pharmaceutical approaches. The two main approved drugs are Memantine and Cholinesterase inhibitors, depending on the form of dementia.[9] Common side effects of Memantine include fatigue, dizziness, headache, constipation, confusion, somnolence, vomiting and increased blood pressure, while cholinesterase inhibitors commonly cause dry mouth, blurred vision, constipation, urinary retention, tachycardia and confusion, with serious effects such as Stevens–Johnson syndrome, seizures, stroke and organ damage seen rarely.[10]

Vacha (*Acorus calamus* L.) is a rich source of pharmacologically important compounds, whose extracts exhibit diverse therapeutic activities such as antidiabetic, anti-obesity, anti-hypertensive, anti-inflammatory, antioxidant, anticonvulsant, antidepressant, neuroprotective, and cardioprotective effects through multiple signaling pathways.[11]

Network pharmacology provides a thorough biological understanding of disease processes and drug mechanisms by predicting intricate "drug–target–disease" connections. This is useful for assessing the efficacy and safety of clinical treatments. It is especially useful for exploring herbal medicines from a holistic standpoint because of its multi-component, multi-target, and regulatory network approach, which aids in revealing mechanisms of action.

In this regard, a drug-target network makes it easier to understand how the molecular traits and active ingredients of Vacha (*Acorus calamus* L.) relate to the treatment of dementia. In order to investigate the possible targets of *Acorus calamus* in Dementia, network pharmacology analysis is used in this study.

MATERIALS AND METHOD

Bioactive Phytochemical Screening:

Vacha's (*Acorus calamus* L.) phytochemical composition was determined by utilizing the plant's Latin name to search databases like IMPPAT [12] and Dr.Dukes [13]. Since they might not be the main targets of the drugs, duplicates and compounds with aliphatic chains were removed from the simple structural molecules. The SwissADME database was used to evaluate the oral bioavailability and drug-likeness of phytochemicals. [14] Lipinski's Rule of Five compliance ($\leq$1 violation), bioavailability $\geq$ 0.55, and high GI absorption were the criteria used to choose compounds.

Identification of Targets:

After being shortlisted, the phytochemicals' canonical SMILES and corresponding PubChem IDs were retrieved from the PubChem [15] database. These SMILES representations were then utilized to identify potential protein targets using the BindingDB, a similarity-based platform for ligand–protein interaction study [16]. Initially, a similarity criterion of 0.7 was

utilized to identify compound-related targets. Targets with a greater similarity score of ≥0.85 were designated for improved accuracy. Protein targets were then updated with gene names and UniProt IDs from the UniProt [17] database. BindingDB was used to identify Vacha targets, and phytochemicals were assessed for drug-likeness and oral bioavailability. To guarantee consistency, UniProtKB was used to standardize all targets.

Identifying objectives that complement Dementia-focused targets:

The Human Protein Atlas [18] and GeneCards [19] databases offered details on medicinal targets associated with dementia. The phrase "Dementia" was used to identify targets associated with the disease. Then, targets associated with dementia were compared with potential Vacha targets. The overlapping targets between the medication and the illness were identified using Venny 2.1.0.

Building a Network of Protein Interactions:

To collect information about the PPI network, STRING [20] version 11.0 was used to con-struct a simple interface consisting of overlapping specific genes based on the drug-protein interaction for important bioactive compounds in Vacha. In an effort to improve the accuracy of the study, the protein's interaction with the species "Homo sapiens" was calculated using a seventy percent similarity (0.700) high-assurance level.

Investigation of KEGG Pathway Enrichment:

The PPI network and the top 10 KEGG pathways were collected from the string database to assure statical relevance and minimize false positive association after intersecting targeted genes were included, Homo sapiens was selected as the species, and an FDR value of 0.05 was maintained. An FDR threshold of < 0.05 was used for KEGG pathway enrichment.

Key gene screening and the network of Protein-Protein Interactions:

The STRING database, which offers experimentally verified interaction data, was used to figure out the protein–protein interaction (PPI) network. After retrieving the KEGG path-ways, those related to dementia were found and chosen.

Building an "Herbal-Compound-Target" network:

The common targets of AC phytochemicals and Dementia were matched and sorted after the dementia-related pathways in AC phytocompounds were catalogued. Cytoscape 3.7.2 [21] was used to build the "Compound-Targets-Pathways "network.

Molecular Docking:

The RSCB PDB [22] and PubChem databases provided the crystal structures of the top three target proteins and the top three compounds, respectively. To stabilize the protein structures, water molecules were removed and polar hydrogens and Kollman charges were added & connections were formed using the Biovia DS tool. The top target proteins and ligands' binding interactions were predicted using the docking technique, and binding sites were automatically identified using PyRx software [23] The Biovia Discovery Studio program has been used to demonstrate the interaction with the best docking scores in two and three dimensions.[24]

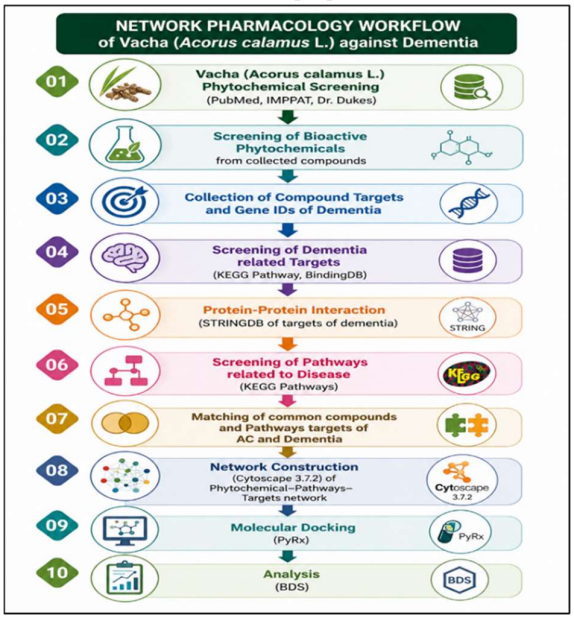

Figure 1: Process of constructing the Chemical-Target-pathways network and molecular docking of AC in Dementia.

RESULT

Analysis of the gathered phytochemicals from botanical databases:

A total of 342 phytochemicals were collected from Dr. Duke's and IMPPAT databases. There were 239 distinct phytochemicals left after duplicates were removed. The SwissADME and PubChem databases were used to further screen these compounds for toxicity and ADME features. They were carefully nominated based on factors such oral absorption, bioavailability, and Lipinski's violation. Subsequently, 55 target genes associated with these 239 active phytochemicals were found using the BindingDB and UniProt databases.

Examination of Overlapping Phyto-targets and Disease Targets:

After eliminating duplicates, searches for "Dementia" in the GeneCards and Human Protein Atlas (HPA) databases produced a total of 11751 disease-related targets. Venny 2.1 software was used to connect these disease targets with the phytochemical targets in order to find common genes. Of the 11751 targets, precisely 26 were linked to *Acorus calamus*. This led to the identification of 26 overlapping dementia targets. The overlapping targets of dementia and *Acorus calamus* are shown in the Fig.2.

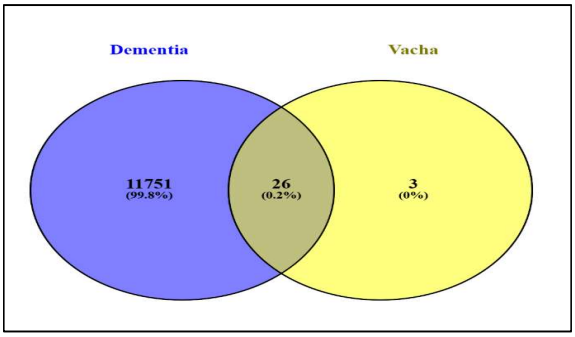

Fig.2. The overlapping targets of Dementia and *Acorus calamus*

Protein–Protein Interaction (PPI) Networks:

A protein–protein interaction (PPI) network was created using the STRING database. 26 common targets linked to Vacha for Dementia were added to the STRING database. For the analysis, "Homo sapiens" was selected as the organism, and a 0.50 confidence level was used. Following, KEGG pathway enrichment data was obtained and analyzed to identify the metabolic processes that these targets regulate. The PPI network of dementia is shown in the Fig.3.

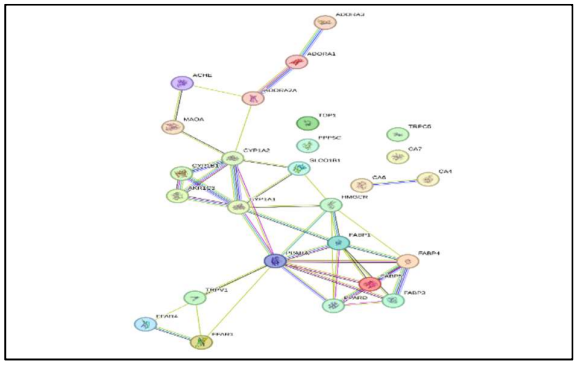

Fig.3. The PPI network of Dementia

Analysis of KEGG Pathway

KEGG functional enrichment analysis and the STRING database were used to investigate the signaling pathways. To recognize the mechanism of action of *Acorus calamus* rhizome in the selected disease, ten pathways associated with dementia were identified and studied. The involved pathways of Dementia are shown in Fig.4.

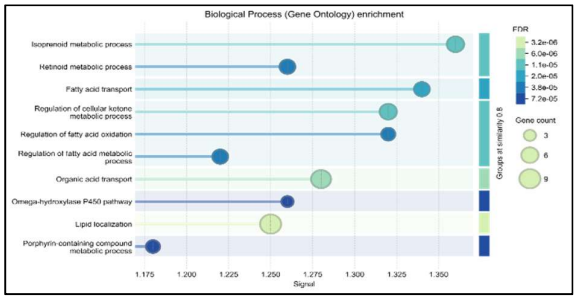

Fig.4 KEGG PATHWAY analysis revealed Ten key Dementia-related signaling pathways underlying the therapeutic action of *Acorus calamus*

Table No.1. KEGG Analysis of Selected pathways

Term ID	Term description	OGC	BGC	FDR	Protein
hsa03320	PPAR signaling pathway	6	75	5.87E-07	FABP4,FABP1,FABP5,PPARD,FABP3,PPARA
hsa00380	Tryptophan metabolism	4	41	9.04E-05	MAOA,CYP1A2,CYP1A1,CYP1B1
hsa00140	Steroid hormone biosynthesis	4	60	0.00025	CYP1A2,AKR1C3,CYP1A1,CYP1B1
hsa00910	Nitrogen metabolism	3	17	0.00027	CA4,CA7,CA6
hsa04913	Ovarian steroidogenesis	3	50	0.0043	AKR1C3,CYP1A1,CYP1B1

hsa00980	Metabolism of xenobiotics by cytochrome P450	3	69	0.0089	CYP1A2,CYP1A1,CYP1B1
hsa05204	Chemical carcinogenesis	3	76	0.0101	CYP1A2,CYP1A1,CYP1B1
hsa04976	Bile secretion	3	88	0.0134	SLCO1B1,SLCO1B3,HMGCR
hsa01100	Metabolic pathways	8	1435	0.0321	HMGCR,CA4,MAOA, CYP1A2,CA7,CA6,AKR1C3,CYP1A1
hsa04080	Neuroactive ligand-receptor interaction	4	329	0.0456	ADORA3,ADORA1, TRPV1,ADORA2A

Combined Target-Phytochemical-Pathway Network: Cytoscape 3.7.2 was used to develop the interaction network connecting 10 KEGG path-ways, 26 overlapping targets, and 6 active drugs for dementia. The network of Dementia is shown in Fig.5.

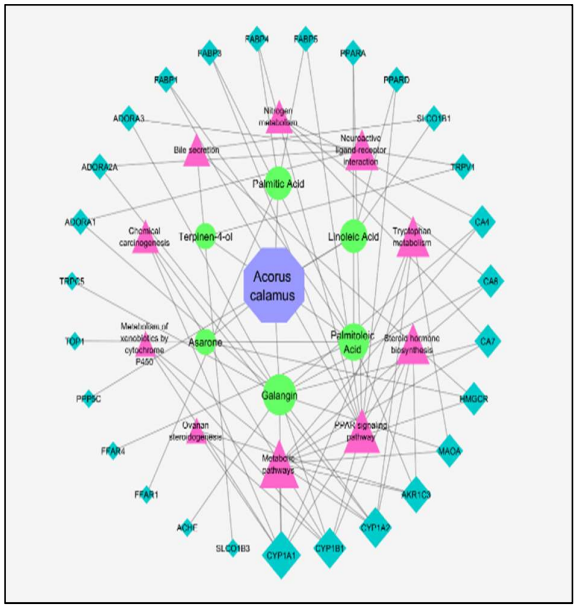

Fig.5. The interaction link between 6 key active components, 26 overlapping targets, and 10 significantly enriched KEGG pathways was created using Cytoscape 3.7.2 software.

Molecular Docking Analysis

The binding affinities of particular phytochemicals extracted from plants and the related gene targets were assessed using molecular docking. The three phytochemicals with the greatest degree values in the network- Galangin, Palmitoleic Acid, and Linoleic acid were selected for further study. Because of their significant interactions with the key phytochemicals, AKR1C3, CYP1B1 and CYP1A2 were chosen as target for dementia. Binding energy values of ≤ -5 kcal/mol, which signify strong and potentially significant molecular interactions, were used to make the selection.

Table.2. Protein Docking of *Acorus calamus* in Dementia

Phytochemicals	**Binding Affinity**		
	AKR1C3 (8BBS)	**CYP1B1 (3PM0)**	**CYP1A2 (2HI4)**
Palmitoleic Acid	**-5.1**	**-5.5**	**-5.1**
Linoleic Acid	**-5.8**	**-5.8**	**-5.4**
Galangin	**-9.2**	**-8.1**	**-7.9**

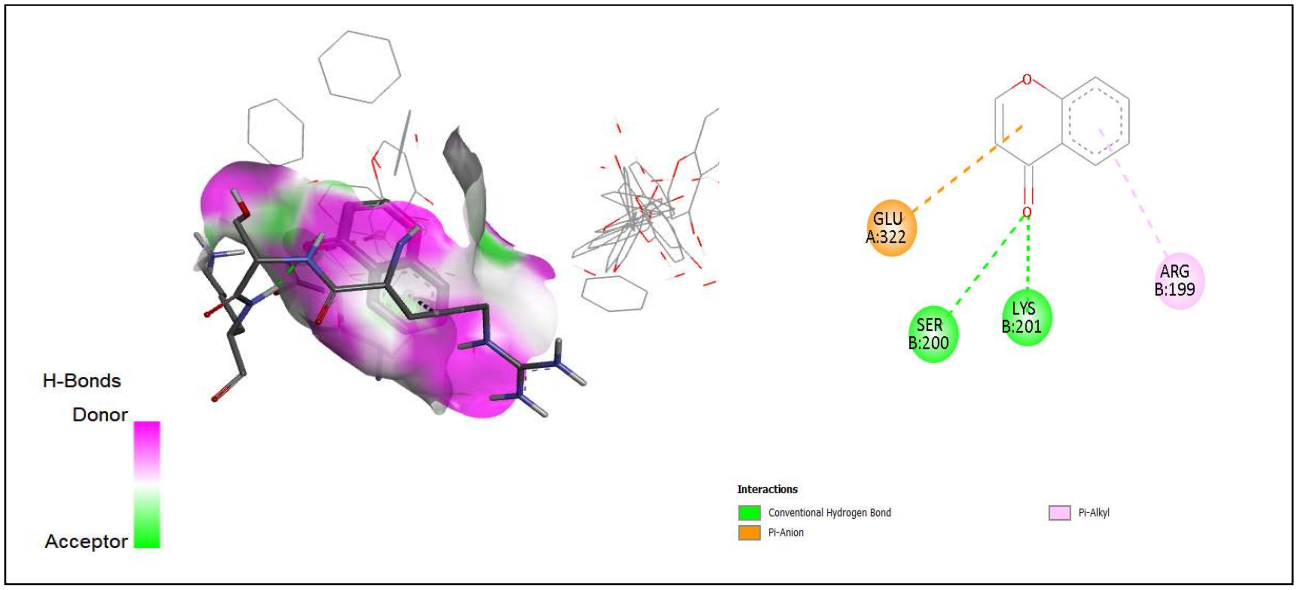

Fig.6. Interaction of Galangin with AKR1C3, 2D & 3D representation of Binding mode.

The present molecular docking study revealed that Galangin had the highest binding affinity with the target protein AKR1C3 (-9.2 kcal/mol) indicating a strong and stable association within the active binding pocket of the protein. The high negative docking score of Galangin suggests that it has good binding energy and good ligand–protein compatibility, supporting its therapeutic potential against dementia-related molecular pathways.

Visualization analysis revealed stable binding of Galangin with AKR1C3 by hydrogen bonds with SER200 and LYS201 and π-anion and π-alkyl interactions with GLU322 and ARG199, indicating a strong ligand–protein stability and molecular recognition is shown in Fig.6.

The three-dimensional image showed that Galangin is well fitted in the active binding pock-et of AKR1C3 without any steric hindrance, which indicates a positive interaction and a stable orientation. AKR1C3 has also been associated with Alzheimer's disease and other types of dementia through its roles in regulating oxidative stress, inflammation, neurosteroid me-tabolism, and ferroptosis-related pathways. Thus, Galangin may exert neuroprotective effects by modulating these pathways as evidenced by the significant interaction of Galangin and AKR1C3.

The molecular docking and visualization results suggest that Galangin exhibits strong inhibition ability against AKR1C3 and can be a promising phytochemical alternative for further pharmacological research in the treatment of dementia. However, further in vitro and in vivo studies are needed to confirm the therapeutic efficacy of Galangin and validate these computational findings.

DISCUSSION

Acorus calamus has long been utilized to treat neurological conditions, and the current network pharmacology study showed that it has significant multi-target therapeutic promise against dementia. Strong pharmacological importance in regulating neurodegeneration, oxidative stress, inflammation, and neuronal death was demonstrated by the study's discovery of 26 overlapping targets between Vacha phytochemicals and dementia-related genes.

Important pathways linked to neuroprotection, inflammation, and cognitive function were identified by KEGG pathway analysis, including PPAR signaling, tryptophan metabolism, neuroactive ligand–receptor interaction, and cytochrome P450 pathways. Strong binding affinities between phytochemicals including Galangin, Palmitoleic acid, and Linoleic acid and AKR1C3, CYP1B1, and CYP1A2 targets were also revealed by molecular docking. Among them, Galangin exhibited the best docking score, suggesting its potential neuroprotective role in dementia and Alzheimer's disease. Overall, the current study indicates that *Acorus calamus* may have substantial therapeutic promise in the treatment of dementia due to the bioactive chemical's

synergistic interactions with many molecular targets and pathways.

GALANGIN IN DEMENTIA

Galangin is a low-toxicity, naturally occurring flavonoid having anti-inflammatory and anti-cancer effects. Galangin restores defective mitophagy and increases PINK1 expression, which enhances mitochondrial quality control, protecting brain cells from Aβ1-42-induced damage, according to studies. Additionally, it promotes the proliferation and survival of neural cells and injured brain organoids, suggesting that it plays a neuroprotective role in Alzheimer's disease. Additionally, Galangin, either by itself or in conjunction with medications like metformin, urolithin A, and NAD+ boosters, may be a safe treatment option for diseases linked to impaired mitophagy.[25]

AKR1C3 IN DEMENTIA

AKR1C3 may serve as a potential biomarker and therapeutic target in dementia, mainly Alzheimer's disease It controls prostaglandins, neurosteroids and oxidative stress in the brain. is involved in the iron-dependent cell death process ferroptosis, which plays a role in neuronal damage and cognitive decline in AD. It also contributes to the maintenance of neurosteroid balance and could be involved in neuroinflammation and dysfunction of the blood–brain barrier.

AKR1C3 is thus regarded as an attractive therapeutic target given its role in neurodegeneration. Natural flavonoids such as kaempferol may attenuate neuronal ferroptosis through the GPX4/AKR1C3 pathway. Researchers are also using computer-aided drug design to develop selective inhibitors of AKR1C3 to slow or stop the progression of dementia. [26,27]

KEGG Pathways were used to investigate the mechanism of action further. The top ten KEGG signaling pathways were closely associated with Vacha's pharmacological effects on dementia.

PPAR SIGNALLING PATHWAY

A subfamily of nuclear receptors known as peroxisome proliferator-activated receptors (PPARs) is essential for controlling insulin sensitivity and may be used as treatment targets for AD. In Dementia (AD) the PPAR-γ signaling pathway is linked with important genetic risk factors such as ApoE4, TOMM40, and APOC1, which contribute to amyloid-β accumulation and disease progression. PPAR-γ regulates several AD-related genes involved in lipid metabolism, inflammation, immune response, and neuronal function, including ABCA7, ApoE, CASS4, CELF1, PTK2B, ZCWPW1, and DSG2. Activation of PPAR-γ may reduce amyloid buildup and neuroinflammation, making PPAR-γ agonists promising therapeutic agents for dementia.[28]

According to this research, Vacha may be able to cure Dementia by regulating a number of interconnected signaling pathways. The primary bioactive ingredients of Vacha, their possible targets in dementia, and their possible modes of action were all examined in this study. However, database limitations may have prevented several proteins and phytocompounds from being included in the investigation. Furthermore, additional pre-clinical and clinical research is needed to evaluate the efficacy and safety of Vacha before its medicinal usage can be confirmed.

CONCLUSION

The present study by integrated network pharmacology and molecular docking approach demonstrates the significant multi-target therapeutic potential of Vacha (*Acorus calamus* L.) in Dementia. Many bioactive phytochemicals and their molecular targets were found to be involved in neurodegenerative processes. Galangin one of the compounds found, showed the strongest interaction with the target protein AKR1C3, forming a stable ligand-protein com-plex and indicating a possible neuroprotective function.

Additionally, the study proved that the therapeutic effects of Vacha may be mediated by a number of signaling pathways, including as PPAR signaling, tryptophan metabolism, neuroactive ligand–receptor interaction, and cytochrome P450-related pathways. Oxidative stress, neuroinflammation, ferroptosis, and cognitive impairment in Dementia are all closely associated with these pathways. The strong docking affinity and useful molecular interactions between Galangin and AKR1C3 promote the possibility of using natural phytoconstituent-ents of Vacha to alter dementia-related pathophysiological pathways.

Overall, the results indicate that *Acorus calamus* has a significant multi-target and multi-component therapeutic agent for the treatment of dementia. However, additional experimental validation through in vitro, in vivo, and clinical research is required to validate its efficacy, safety, and underlying pharmacological mechanisms because the current study is based on computational analysis.

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No conflicts of interest

AI tools were used for improving language and preparation of manuscripts.

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