Exploration of the potential effect of some selected Indian medicinal plants against Alzheimer's disease

Synopsis submitted

By

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1. Title of the thesis:

Exploration of the potential effect of some selected Indian medicinal plants against Alzheimer's disease

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1. Background of the study

Alzheimer's Disease (AD) is a long-term, progressive neurodegenerative disorder marked by gradual deterioration in memory, thinking abilities, speech, behavior, and the capacity to perform routine tasks. While AD is not the immediate cause of death, it markedly heightens vulnerability to associated complications, which can ultimately may lead to mortality. Presently, around 44 million individuals worldwide are affected by dementia, and this figure is projected to exceed 152 million by the mid-21st century. Given the complex pathogenesis of AD, several hypotheses have been put forwarded to explain its progression. Among the most prominent are the amyloid-β (Aβ) cascade hypothesis, tau protein hypothesis, cholinergic deficit hypothesis, neuroinflammatory hypothesis, and oxidative stress hypothesis. Currently, no curative therapy exists for AD. Though, some treatment options are available that provide symptomatic benefits and slow functional decline. The U.S. Food and Drug Administration (FDA) has approved acetylcholinesterase inhibitors (AChEIs), namely donepezil, rivastigmine, and galantamine together with the NMDA receptor antagonist memantine. These medications, however, only alleviate symptoms and fail to reverse the underlying disease process.

For centuries, medicinal plants have been widely employed in alleviating AD symptoms and improving cognitive functions. Traditional medical systems such as Ayurveda, Unani, Siddha, and Homeopathy preserve extensive knowledge on the use of natural remedies for neurological health. Moreover, many modern pharmaceuticals are derived from plant-based compounds or their synthetic analogs. In recent decades, the global demand for herbal medicines has risen sharply, owing to their therapeutic potential and relatively lower risk of adverse effects. Historical records demonstrate that nearly every culture has relied on herbal medicines to enhance memory and cognitive performance. Plants such as *Allium sativum* L., *Punica granatum* L., *Carum carvi* L., *Bacopa monnieri* (L.) Pennell, and *Centella asiatica* (L.) Urban have been traditionally valued for their memory-enhancing effects.

Zingiber officinale Roscoe (commonly known as ginger) is another medicinally important plant, enriched with secondary metabolites and diverse phytochemicals, traditionally utilized to promote memory and manage neurological ailments. Among its constituents, 6-gingerol is recognized as the major bioactive compound responsible for several pharmacological effects.

The phytochemical content of herbal remedies, however, can vary substantially depending on ecological and agronomic conditions such as soil characteristics, altitude, rainfall, cultivation methods, and genetic diversity maintained through traditional agricultural practices. Thus, the present research undertakes a detailed phytochemical and pharmacological evaluation of chemo-varieties of *Zingiber officinale* collected from nine distinct geographical zones of Northeast India, particularly Manipur, a biodiversity-rich state with diverse agro-climatic conditions.

2. Work performed

The current research incorporates a comprehensive phytochemical and pharmacological evaluation of chemo-type *Zingiber officinale* (ginger) collected from nine distinct geographical locations across Northeast India, especially Manipur, a region recognized for its rich biodiversity and agro-climatic variation.

The phytochemical profiling will include determination of Total Phenolic Content (TPC) and Total Flavonoid Content (TFC), in-vitro antioxidant activity assays, and chromatographic characterization using High-Performance Liquid Chromatography (HPLC) and High Performance Thin Layer Chromatography (HPTLC). Statistical analysis through Pearson's correlation will be performed to establish relationships between phytochemical constituents and antioxidant activities.

Further, the extracts will be evaluated for their neuroprotective potential via in-vitro Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE) enzyme inhibition assays. The most potent ginger sample, based on the analytical procedures and in-vitro screening, will be subjected to High-Resolution Liquid

Chromatography-Mass Spectrometry (HR-LCMS) analysis to identify and characterize its major bioactive constituents and in-vivo anti-Alzheimer's evaluation using behavioral assays such as the Morris water maze, Y-maze, and Novel Object Recognition (NOR) test to assess memory and learning efficacy. Subsequent biochemical analysis will measure brain AChE, BChE, and Acetylcholine (ACh) levels, along with antioxidant parameters, to elucidate the underlying mechanisms. Histopathological examination of brain tissue will provide further morphological evidence of neuroprotection. Molecular docking studies will be undertaken to predict interactions of major bioactive constituents with target enzymes, thus correlating in-silico results with experimental findings.

Chapter 1 offers a comprehensive overview of AD, including its global epidemiology, pathogenic mechanisms, and currently available therapeutic approaches. The discussion emphasizes the roles of oxidative damage, Aβ deposition, tau hyperphosphorylation, and cholinergic dysfunction in disease progression. In addition, the neuroprotective effects of herbal medicines and plant-derived phytochemicals are reviewed, highlighting their antioxidant, anti-inflammatory, and cholinesterase-inhibiting activities. This provides the foundation for exploring ginger as a potential neuroprotective resource.

Chapter 2 investigates the chemical diversity of ginger, emphasizing its phytoconstituent composition and in-vitro anti-Alzheimer's activity. It starts with a taxonomic classification, morphological features, and a survey of various ginger types, followed by a discussion on its traditional medicinal applications in different cultural systems. The phytochemical section underscores the key bioactive molecules, notably phenolic acids, flavonoids, gingerols, shogaols, and other secondary metabolites that contribute to the therapeutic potential of ginger.

Chapter 3 presents the research framework and objectives, outlining the methodology and experimental strategies adopted to achieve the study's goals.

Chapter 4 explores the collection of ginger specimens from various locations, their authentication, extraction, and subsequent assessment of phytochemical characteristics. For this purpose, nine ginger accessions from different regions of Manipur were gathered, authenticated, and subjected to hydroalcoholic extraction. The phytochemical evaluation included estimation of total phenolic content (TPC), total flavonoid content (TFC), and measurement of antioxidant potential using DPPH, hydroxyl, and ABTS radical scavenging assays. Advanced chromatographic approaches such as HPLC and HPTLC were utilized to quantify 6-gingerol, which displayed significant variation across the samples. Pearson's correlation analysis indicated strong positive associations among phenolic content, 6-gingerol concentration, and antioxidant capacity. Additionally, in-vitro cholinesterase inhibition studies confirmed the neuroprotective efficacy of the extracts. Notably, sample GV6 showed the highest levels of phenolics, antioxidant activity, 6-gingerol content, and the most potent inhibition of AChE and BChE. Overall, the chapter emphasizes the significance of comprehensive phytochemical profiling and standardization of herbal formulations to ensure consistency, safety, and therapeutic effectiveness.

Chapter 5 explores the metabolite profiling, in-vivo neuroprotective evaluation, and molecular docking studies of the most potent sample, GV6. Selected for its high 6-gingerol concentration and strong enzyme inhibition, GV6 was subjected to LC-MS analysis, which identified 39 metabolites, including phenolics, flavonoid, terpenoids, diarylheptanoids, fatty acids, amino alcohols, cinnamic acid derivatives, fatty amide, alkanolamine, co-enzyme Q10, and galactosyl-glycerol derivative. Twelve compounds were recognized for their established anti-Alzheimer's activities. Noteworthy constituents such as 6-gingerol, 6-shogaol, 6-paradol, α-linolenic acid, oleamide, cymene, limonene, ubiquinol-10, zingerone, coumaric acid, dehydrozingerone, and rhamnetin were highlighted for their antioxidant, anti-amyloid, anti-inflammatory, and neurotrophic properties. In-vivo studies using a scopolamine-induced memory deficit model in Swiss albino mice

demonstrated the safety of GV6, with no toxic effects observed at 2000 mg/kg. Behavioral assays, including the Morris water maze, Y-maze, and the NOR tests, showed significant dose-dependent improvements in spatial learning, short-term memory, and recognition memory. Biochemical studies revealed that GV6 reduced AChE and BChE activity, restored ACh levels, enhanced antioxidant defenses, and decreased Tumor Necrosis Factor-alpha (TNF-α) levels. Histological analysis confirmed protection of hippocampal neurons from scopolamine-induced degeneration. Molecular docking indicated strong interactions of 6-gingerol with key active sites of AChE and BChE, comparable to the reference standard galantamine, further validating its enzyme inhibitory effects.

Chapter 6 serves as the concluding section of the thesis, bringing together the findings from all the preceding chapters into a coherent summary. It summarizes the overall objectives, methodologies, and key results of the research, emphasizing how each stage of the study contributed to the understanding of the chemo-diversity and neuroprotective potential of *Zingiber officinale*. The chapter restates the global significance of AD, the limitations of existing therapies, and the rationale behind exploring herbal medicine as a safer alternative. It then focuses the outcomes of phytochemical characterization, in-vitro assays, in-vivo experiments, and molecular docking studies, highlighting the promising role of the GV6 chemo-type as a multi-target therapeutic candidate. Finally, the chapter reflects on the broader implications of the work, underscoring its relevance to ethnomedicine, modern pharmacology, and future drug discovery, while also providing directions for further research in the field.

The study as a whole emphasizes the therapeutic promise of *Zingiber officinale*, particularly the GV6 chemo-type, as a multi-targeted intervention for AD. The research highlights the significance of chemical diversity in ginger, demonstrating how variability in phytoconstituents influences pharmacological activity. GV6,

enriched with 6-gingerol and synergistic phytochemicals, exhibited potent antioxidant, anti-inflammatory, cholinesterase inhibitory, and neuroprotective properties. These findings validate the ethnomedicinal applications of ginger and establish its importance as both a culinary spice and a potential phytopharmaceutical resource. Overall, the work confirms the relevance of ginger in modern drug discovery and supports its development as a safe and effective natural candidate for managing complex neurodegenerative disorders such as AD.

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