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THE JOURNEY OF SOME MEDICINAL PLANTS FROM TRADITIONAL CONSUMPTION TO MODERN RESEARCH ON ALZHEIMER'S DISEASE

Nithya Rajamanickam[1], Prashant Tiwari[2*], Sonal Dubey[3] and Bincy Raj[4]

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Abstract

The Neurodegenerative disease which pushes heart disease to second place due to severe health disorders is Alzheimer's disease. The main pathological emblem identified is the Cholinergic hypothesis and the Amyloid-Beta hypothesis. The currently available medications can be used to manage the disease and these synthetic medicines are working as per the Cholinergic hypothesis. The recently FDA- approved biological medicine Aducanumab which is an amyloid beta-directed monoclonal antibody which reduces amyloid beta plaques. Alternatively, many plants which are in traditional use as well as in multi-cuisine also help to manage the disease. The mechanism of action of phytomedicines which were identified from medicinal plants for neuroprotective activity is ongoing research. This Review discusses the neuroprotective properties and the probable mechanism of the plants consumed in day-to-day south India.

Keywords: *Alzheimer's, Medicinal plants, Neuroprotective, Withania somnifera, Clitoria ternatea, Centella asiatica, Bacopa monnieri, Curcuma longa, Commiphora wightii, Tinospora cordifolia, Glycyrrhiza glabra, Terminalia chebula, Vitis vinifera*.

[1]*Research Scholar, College of Pharmaceutical Science, Dayananda Sagar University, Bengaluru-560111, India, RNithya.res-soe-chemistry@dsu.edu.in*

[2]*Associate professor, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru-560111, India,* cologyprashant87@gmail.com

[3] Professor, Department of Pharmacy, College of Pharmaceutical Sciences, , *Dayananda Sagar University, Bengaluru-560111, India*

[4] Professor, T John college of Pharmacy, Bangalore- 560083, India

***Corresponding author:** *Prashant Tiwari, Associate professor, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru-560111, India,* cologyprashant87@gmail.com

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INTRODUCTION:

The age-related disease which causes the leading illness followed by death overall world is Alzheimer's disease. There are over 10 million new cases of dementia each year worldwide, implying one new case every 3.2 seconds. According to WHO, lower and middle economic countries showing an increasing the Alzheimer's disease population in recent years. The disease statistics are predicted that in the year of 2030, the affected population would be 82 million, and in 2050, it would be 152 million which alarming the world. The current synthetic medicines which are in use are Donepezil, Galantamine, and Rivastigmine. All three medicines are cholinesterase inhibitors. The recently approved biological medicine Aducanumab is an amyloid beta-directed monoclonal antibody and it reduces beta-amyloid plaques.

There are 100 billion nerve cells are available in the human brain. These cells are interlinked and responsible for all the functions in the human body. The important requirements of the Human being are creative thinking, Presence of mind, five senses, timely responding, memory, feeling hungry, remembering old memories, etc. The brain keeps on working like industry to maintain all the requirements and different nerve cells in the brain are doing these jobs.

Among many requirements of the human, memory is an important requirement for the human body, for this, the nerve transmitter acetylcholine should pass the intra requirements. In Alzheimer's the nerve transmitter acetylcholine will not be available in enough quantity since the enzyme Acetylcholinesterase will break the acetylcholine. [1].

Another important requirement for the brain is proper blood flow, if the blood flow is decreased due to a single major stroke or series of very small strokes, clogs the tiny arteries. This causes vascular dementia which gives memory problems, confusion, and difficulty in following anything.[1]

To diagnose Alzheimer's disease, human neuronal tests are to be performed including psychiatric history, neurological examination, Vitamin deficiencies, Mental status, etc. [2]

There are two types of neuropathological evidence that can be identified for Alzheimer's 1. Extra deposits such as neurofibrillary tangles, amyloid plaques, dystrophic neurites, neuropil threads and are called positive lesions. 2. Loss in the neuropil, neural and synaptic, are called negative lesions. Other factors also may be identified as injuries on cholinergic neurons, oxidative stress, and neuroinflammation.

Alzheimer's disease has developed in many stages and the severity of the symptom in every stage increases. In the early stage, the symptoms are unable to identify easily, mild symptoms produce difficulty in daily life like memory and mood change, the next moderate stage produces severe memory problems by difficulty identifying family members, difficulty in reading and writing, and the next severe stage produces progressive functional impairment and the patient will be bedridden. [3]

Among the main pathology models, extracellular deposits of Amyloid β (Aβ) protein due to the cleavage of Amyloid precursor protein and abnormal intraneuronal accumulation of phosphorylated protein forming neurofibrillary tangles are playing roles along with cholinergic pathway [3].

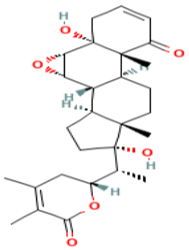
There are two Hypothesis models used for Alzheimer's one is the cholinergic hypothesis and Amyloid Hypothesis. The Aβ is affecting the Acetylcholine release by reducing the choline uptake due to affecting the cholinergic neurotransmission.[3]. And due to the Aβ peptide accumulation resulting the amyloid fibril formation and resulting neurotoxicity [3].

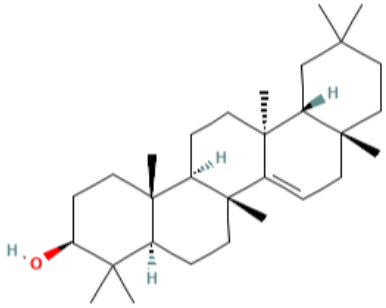
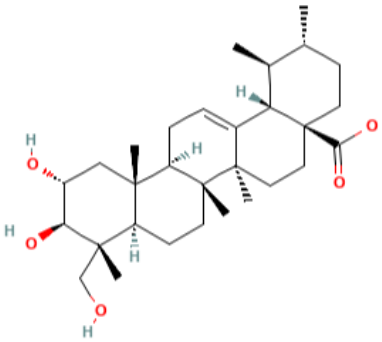
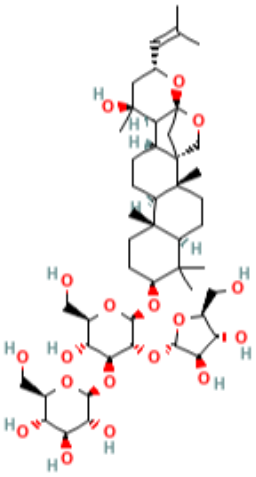
MECHANISM FOR ALZHEIMER'S TREATMENT:

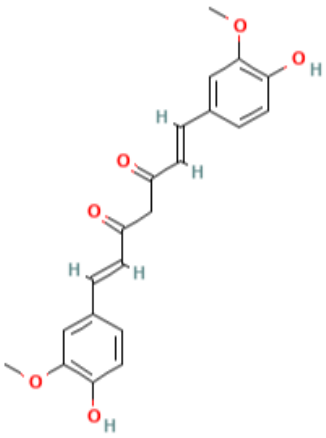
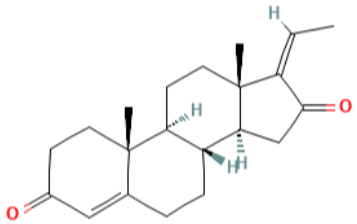
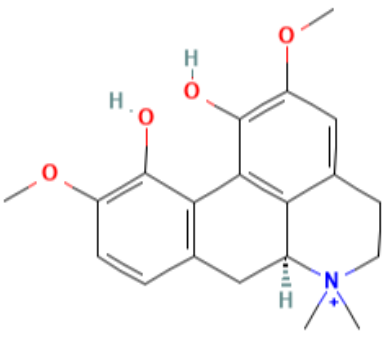
The natural anti-oxidants Vitamin E, C, and beta carotene will help in the initial stage of Alzheimer's since they scavenge free radicals.[1]. Since the reduction of Acetylcholine production is also a reason for AD, the drugs which are helping to increase Acetylcholine production are used for the management of AD. Currently, two, classes of drugs are approved for AD treatment. Cholinesterase enzyme inhibitor which helps to improve Acetylcholine production and improve memory. The second class is N-Methyl D-Asparate antagonist which prevents the NMDAR glutamate overactivation resulting in Ca2+ influx and normal activity will be restored. However, these drugs are to manage the disease only not for a complete cure [3]. Hence, focusing on the good mechanisms of action from the traditional plants used daily is an immediate requirement.

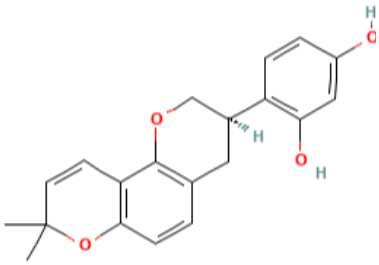
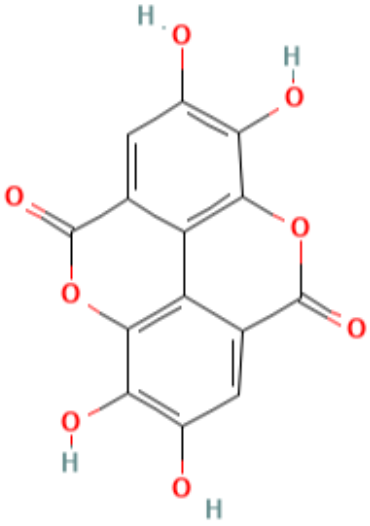
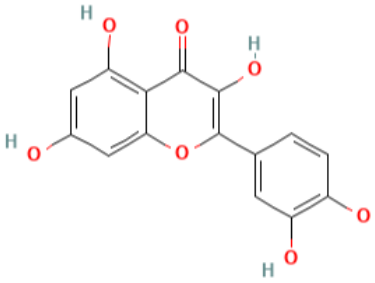
In the plant world, many plants are in use to cure various chronic diseases since ancient times. They are still in use for the same since the plants are the potential source for the many alkaloids, flavonoids, phenolic compounds, etc., Due to the antioxidant properties of the alkaloids and flavonoid compounds, inflammatory-related disorders have been treated with medicinal plants, and the effect has also been observed well. As part of that, many plants are being investigated for their neuroprotective properties. In this review, we will discuss some plants which are part of day-to-day life in south India and investigated for their neuroprotective properties. The plants are *Withania somnifera, Clitoria ternatea, Centella asiatica, Bacopa monnieri, Curcuma longa, Commiphora wightii, Tinospora cordifolia, Glycyrrhiza glabra, Terminalia chebula, Vitis vinifera.* These plants are involved in many aspects of south Indian daily life. The isolated compounds from these plants and their action are listed in Table 1.

Table 1: Medicinal plants and Mechanism of Action on Alzheimer's Disease

S. No	Botanical Name	Type of usage in south India	Isolated compounds investigated	Mechanism of action on Alzheimer's study
1`.	*Withania somnifera*, *Family:* Solanaceae	energy booster	Withanone, Obtained from Chloroform and n-butanol extracts [17]  Molecular Formula: $C_{28}H_{38}O_6$	Increasing the Acetylcholine levels and inhibiting the Amyloid β dividing, inhibiting the β-secretase and r-secretase, free radicals and modulating the peripheral cytokines [18].
2.	*Clitoria ternatea* *Family:* Fabaceae	To treat cough, For improving eye sight. memory power	pentacyclic triterpenoids-Taraxerol [22]	Increasing the serotonin level and decreasing the brain glutamate level [19].

			 Molecular Formula: $C_{30}H_{50}O$	
3.	*Centella asiatica* *Family:* Apiacae	For memory power.	Asiatic acid [25],  Molecular Formula: $C_{30}H_{48}O_5$	Preservation of mitochondrial function by reducing the cytochrome C release by elevating calcium levels, H_2O_2, nitric oxide radical concentration [25].
4.	*Bacopa monnieri* *Family:* Plantaginaceae	For memory power and hair growth	Bacoside A3 [28]  Molecular Formula: $C_{47}H_{76}O_{18}$	Decreasing the A β production by anti-oxidant activity and modulation of Ca2+ homeostasis as calcium channel blocker by anti-inflammatory activity, ethanolic extract also shows the same. [27, 28]

5.	*Curcuma longa* *Family:* Zingiberaceae	Part of cooking ingredient. To increase immunity and fight with bacteria and fungus this is used.	curcumin,  Molecular Formula: $C_{21}H_{20}O_6$	Curcumin crosses the blood brain barrier due to its lipophilic nature and binds to plaques and inhibits A-beta aggregation. protecting the PC12 and HUVEC cells from beta Amyloid (1±42) insult through the anti-oxidant properties of curcuminoids. This was proven through MTT assay [29, 30].
6.	*Commiphora wightii* *Family:* Burseraceae	Smoke of the gum for good fragrance to heal headaches	Guggulsterone  Molecular Formula: $C_{21}H_{28}O_2$	Inhibiting the NO due to the presence of Guggulsterone [31]
7.	*Tinospora cordifolia* *Family:* Menispermaceae	For gonorrhoea, liver and spleen disorder	**Magnoflorine [33]**  Molecular Formula: $C_{20}H_{24}NO_4^+$	Increasing the CAT level and restoring the GSH level due to anti-oxidant property [32

8.	*Glycyrrhiza glabra* *Family:* Fabaceae	To improve immunity	Glabridin [35]  Molecular Formula: $C_{20}H_{20}O_4$	Inhibits the inflammation related protein and pro-inflammatory mediator like NO, iNOS, COX-2, IL-1β, and IL-6 [34]
9.	*Terminalia chebula* *Family:* Combretaceae	Immunity booster, good digestion, get rid of cough.	Ellagic acid [36]  Molecular Formula: $C_{14}H_{6O}8$	Protecting the PC12 cells from toxicity by inhibiting ROS production as well as reducing calcium ion influx due to its OH and H_2O_2 scavenging activity and anti-inflammatory as well as anti-oxidant properties [37]
10.	*Vitis vinifera* *Family:* Vitaceae	reduced blood pressure	Quercetin [38]  Molecular Formula: $C_{15}H_{10}O_7$	Regulating the anti-oxidant levels in brain, regularizing the levels of . Al. Serum glucose, TG, TC, ALP and ALT and improving the activity of enzyme acetylcholinesterase.[39]

Note: The chemical structure is referred from PubChem.

DISCUSSION:

From the above data, it was found that medicinal plants have many important chemical compounds which will help to solve the related issues. *Withania somnifera is* regularly used as a powder to boost energy and the same is used in Ayurveda for many purposes. Ayurveda is prescribing *Withania somnifera* for getting long life means it boosts the immunity power which helps to lead the life in long span. As well as it gives good intellectual power also. A daily oral dose of Withanone reduced the increased levels of pro-inflammatory mediators TNF-α, IL-1β, IL-6, and MCP-1 [41].

Clitoria ternatea, *Centella asiatica*, and *Bacopa monnieri* are the general plants that are consumed in daily life for many purposes, and their usage is starting to fight the common cold, cough, and not ending for the particular diseases since multiple benefits noted when these are consumed regularly.

Curcuma longa is a special herb that is used from very ancient times in all Indian cuisines regularly, which gives various health benefits from antibacterial to anti-cancer strength. The same herb is proven for its neuroprotective properties also, the main important content, curcumin is proven for its neuroprotective properties.

Tinospora cordifolia, Glycyrrhiza glabra, and Terminalia chebula are used as part of spices in south Indian cuisines. These have been used in Ayurveda for important treatments. *Viti's vinifera* seeds used to be consumed for getting immunity power. At the same time, this is proven to the neuroprotective property. Due to the presence of alkaloids, flavonoids, and steroids, these plants show rich antioxidant properties which help with their Neuroprotective property. Majorly the anti-oxidant potential and anti-inflammatory potential of these medicinal plants might be helpful for their neuroprotective nature.

The neurotoxicity can be induced in several ways such as Aβ deposition, excess glutamate concentration, apoptosis, overloading calcium to mitochondria, intracellular cholesteryl esters, etc., The neurotoxicity can be reduced in multiple ways as follows, protecting neurons and cholinergic neurons from damage [27] through AChE inhibition [40], reducing the glutamate concentration [19], protecting reactive oxygen species generation, presenilin 1, preseniline2 and activation of signaling pathways [41].

The neuronal damage and death is endorsed due to the β- amyloid (Aβ) deposition, The Aβ produced in two sequential cleavages. These cleavages are induced on the beta-amyloid precursor protein by beta- and gamma-secretases. The treatment with Withanone from *Withania somnifera* decreases the enzymatic activity of both β- and γ- secretase and provides the protective potential. [41]. *Bacopa Monnieri* also protects in a similar manner [28].

The signal conductors are available in the brain and spinal cord, in that glutamate is also one of the primary signal conductors. Glutamate contributes an important role in brain development and also contributes to general learning and memory. If the glutamate level is excess in the brain it becomes neurotoxin and creates neuronal cell death, Ethanol extract of *Clitoria ternatea* reduces the Glutamate concentration significantly [42].

It is also harmful if any defect in the metabolism of mitochondrial energy, and it might be the reason for the secondary damage. The secondary damage may occur slowly and generate endogenous glutamate which makes toxic neurons. Another reason

for stroke-related cell death and tissue damage is oxidative stress and overloading Calcium to mitochondria. Asiatic acid which is a major phytochemical in *Centella asiatica* is significantly reducing cytochrome c release from isolated brain mitochondria preparations exposed to elevated calcium levels, H_2O_2, or nitric oxide and hence it protects mitochondria [26]

Another possibility of amyloid plaques is an intracellular accumulation of cholesteryl esters. Due to lifestyle and fast food consumption, blood cholesterol level is increasing and it is linked to amyloid plaque increment. Curcumin, the main active phytochemical from *Curcuma longa* fights against Alzheimer's by preventing the formation of cholesterol and lowering the serum peroxides. Curcumin is a lipophilic compound and it can bind to plaques by crossing the blood and brain barrier and also destabilizes the A-beta polymer and good A-beta 40 aggregation inhibitor. Peroxynitrite will be created from the reaction of nitric oxide with superoxide. This peroxynitrite can attack a range and destabilizes the fA-beta (1-40) and fA-beta(1-42) as well as their extension since it is a versatile oxidant. The pre-consumption of Curcumin can protect mitochondria from peroxynitrite [30]

Commiphora wightii is helping by inhibiting the NO action, and *Tinospora cordifolia* and *Terminalia chebula help* by their anti-oxidant properties.

Apoptosis is an active energy-dependent mode of cell death that is controlled by tightly controlled intracellular signaling events. Intrinsic and extrinsic are the signaling pathways.

The intrinsic pathway involves in DNA damage which is also called severe cellular stress and cell cycle defects. In this pathway, the bcl-2 (B-cell leukemia/lymphoma 2) family and apoptosis-inducing factors will be activated by the mitochondria. The extrinsic pathway involves members of the tumor necrosis factor superfamily. The inappropriate activation of apoptosis may contribute to a variety of pathogenic processes such as the loss of neuronal cells in Alzheimer's disease and stroke. Glabridin, the main compound in *Glycyrrhiza glabra* is up-regulating the bcl-2 and gcl-2 has an important role in cell growth and apoptosis [43].

Resveratrol main phytochemical available in *Vitis vinifera* has antioxidant properties and scavenges free radicals and helps with Alzheimer's disease.

There are many studies proving the neuroprotective properties of these plants and the availability of possible phytochemicals. And also the Alzheimer's disease population is less in India when compared to America and European countries because in south India these herbs are part of life and are consumed regularly as food but not as medicine. It may be the reason for the less population of Alzheimer's in India.

Conclusion:

If we look at the mechanism of action of these plants, these are not directly acting on plaque or tau. These are targeting the backbone reasons due to which these plaque or tau are forming. Then the action is starting to manage the backbone issues like correcting the acetylcholine level, Increasing the serotonin level and decreasing the brain glutamate level, and controlling the calcium, H_2O_2, NO_2 levels. Since the presence of multiple alkaloids and other phytochemicals, plant medicine can work for multiple targets at one time. Hence regular consumption of these plants will lead to the management of the disease. The proper intake of these plant medicine for a long time along with exercise and well-balanced lifestyle may lead to a cure for the disease.

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