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EFFICACY OF *Curcuma longa, Withania somnifera, Ginkgo biloba* IN CURING DEMENTIA: A SYNERGISTIC PHARMACOTHERAPY

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ABSTRACT

Dementia, a neurodegenerative disease, manifests as a gradual deterioration in cognitive function and memory. Given the substantial side effects associated with current dementia therapeutics, this review aims to identify traditionally used plants that could potentially provide a lasting remedy without causing much side effects. Specifically, the review delves into the compatibility of three such plants—*Curcuma longa, Withania somnifera,* and *Ginkgo biloba*—examining their pharmacotherapeutic and neuroprotective efficacy at different stages of neuropathological mechanism cascade. Data of various clinical trials, using these plant products or their active constituents, done so far is also compiled and compared. This data holds the potential to further investigate the feasibility of employing these plants or their active constituents in a synergistic manner for the treatment of dementia patients. This review work can further contribute to standardizing the drug composition and determining its effective dosage.

INTRODUCTION

Dementia, a neurodegenerative disease, refers to a gradual and ongoing decline in cognitive functions and memory. While it predominantly impacts geriatric populations, it can also occur in younger individuals (Rossor *et al.,* 2010). The World Health Organization predicts a dramatic rise in global dementia cases, projecting an increase from the current 50 million to 82 million in 2030 and a staggering 152 million in 2050, resembling an epidemic (World Health Organization 2019),(Ravindranath and Sundara kumar 2021).

In dementia, faulty protein accumulates either within or outside the neurons, leading to the death of these cells (Arya *et al*., 2014), (Srivastava *et al*., 2018). These protein aggregates adversely affect neuroplasticity, cellular activity, and contribute to the emergence of cognitive and mood-related disorders. Dementia manifests in various forms, such as Alzheimer's disease, Parkinson's disease, and Creutzfeldt-Jakob Disease (CJD)(Breijyeh and Karaman 2020), (DeMaagd and Philip 2015), (Mackenzie and Will 2017). Accumulation of hyperphosphorylated tau protein and β-amyloid peptide (Aβ-40) indicate Alzheimer's disease (AD), while Lewy bodies containing α-synuclein (α-syn) and altered dopamine transporter (DAT) imaging point to Parkinson's disease (PD). Familial amyotrophic lateral sclerosis (ALS) is associated with SOD mutations (Rosen *et al*., 1993), Huntington's disease (HD) with CAG repeats (Walker 2007) and an elevated plasma concentration of MR-proANP serves as an indicator for vascular dementia. The detection of reliable causes is crucial for predicting the risk of neurodegenerative disorders and facilitating the development of early-stage therapeutic interventions.

Presently, no permanent cure is available for these neurodegenerative disorders; instead, treatments center around managing symptoms by adjusting neurotransmitter levels and delaying the onset of the disease, such as Donepezil, Galantamine, and cholinesterase inhibitors for Alzheimer's diseases (Birks 2006) NMDA receptor antagonists and Memantine for severe Alzheimer's disease and vascular dementia (Koch, Uyanik, and Fischer-Barnicol 2005); and blood pressure and cholesterol-lowering drugs for preventing further brain damage from hypertension and cholesterol (World Health Organization 2019). Additionally, the prolonged usage of synthetic drugs can lead to various side effects, such as insomnia, dizziness, confusion, decreased concentration, and drug resistance affecting multiple proteins (Jones 2011), (Hoffman and Bloemer 2021). Consequently, researchers have shifted their focus towards exploring new therapies for example natural therapy using plant products which have shown promises in treatment of various diseases (Yogaraj *et al*., 2020). Natural compounds are considered safe, easily accessible, cost-effective, provide etiological treatment, and exhibit neuroprotective properties. Extensive

research and indigenous practices have documented the effectiveness of diverse plant products in ameliorating symptoms of various forms of dementia, which occur due to complex cellular mechanisms. It is also evident from recent studies that a single plant product may not be effective at all stages of this mechanism cascade, limiting its potential for offering a permanent cure and also their pharmacovigilance is needed (Arya *et al*., 2023). However, natural substances vary in their efficacy, with some providing neuroprotection, others having anti-amyloid and anti-tau properties, modulating neurotransmitter systems, enhancing mitochondrial function, inhibiting cholinesterase, or possessing antioxidant and anti-inflammatory properties.

This major goal of the present study is to explore the potential of particular plants and their active ingredients in combating the processes that lead to the aberrant synthesis, accumulation, and hindered clearance of faulty protein aggregates, as well as the effects these processes have on brain health. The findings from this study have the potential to contribute towards the development of a suitable and effective therapeutic approach that combines multiple plant products in optimal dosages, to provide both therapeutic and neuroprotective benefits. Consequently, our literature search aimed to identify plants capable of crossing the blood-brain barrier, reaching the affected areas of the brain, and addressing the root cause of the problem. Additionally, we focused on identifying plants that can be used synergistically in the treatment of dementia patients, and our search ends at three notable natural compounds such as curcumin from *Curcuma longa* (turmeric), *Ginkgo biloba* and *Withania somnifera* (ashwagandha) which have shown promising pharmacotherapeutic and neuroprotective options. Comparative study is summarised in table-1, 2 and 3.

General characteristics of the chosen plants:

Curcuma longa (turmeric)'s active ingredients are water-soluble curcuminoids and turmerone oil. Demethoxycurcumin (DMC), bisdemethoxycurcumin (BDMC), and cyclocurcumin are all examples of curcuminoids(Gregory *et al*., 2021)(Sarangthem 2010)(Gururani *et al*., 2023). Curcumin is known for its health benefits in various disorders (Navyashree, Koulagi, and Kumar,2018). On an average 1 gm of turmeric contains 60 to 200 mg of curcumin and this much amount is traditionally used in many Asian countries which are known to have less cases of dementia. The enol structure of curcumin and the presence of a central methyl group as the H-atom donor both significantly increase the free radical scavenging activity of curcumin (Ohara *et al*., 2005), (Toniolo *et al*., 2002), (Priyadarsini *et al*., 2003).

The two primary biologically active substances in *Ginkgo biloba* are terpene lactones (ginkgolides and diterpenes) and ginkgo flavone glycosides (ginkgetin, bilobetin, and sciadopitysin). The most widely used extract of *Ginkgo biloba* is EGb 761 which comprises of flavonoids (22–27%), terpene lactones (5-7%), including bilobalide (2.6–3.2%) and ginkgolides A, B, and C (2.8–3.4%), organic acids, proanthocyanidins, and proanthocyanidins with a reduced level of ginkgolic acid (5 ppm)(Nowak *et al*., 2021). The ginkgolides (1-100 M in vitro or 50-100 mg/kg in vivo), bilobalides (25-100 M in vitro or 10 mg/kg in vivo), and, in rare circumstances, the flavonoid fraction (25-100 g/ml in vitro or 40-100 mg/kg in vivo) have all documented the neuroprotective properties of EGb 761 (Singh *et al*., 2019).

A few of the bioactive compounds of high interest found in ashwagandha in general are withanolides A–Y, dehydrowithanolide–R,withasomniferin–A,withaso midienone, withasomniferols A–C, withaferin–A, withanone, phytosterols, sitoindosides, alkaloids and flavonoids(L. C. Mishra, Singh, and Dagenais 2000), (Dar, Hamid, and Ahmad 2015), (Mirjalili *et al*., 2009), (Farooqui *et al*., 2018), (Gregory *et al*., 2021). Despite the fact that withaferin A (WL-A) has a 1.44 times higher oral bioavailability than withanolide A, both of these substances exhibit equivalent pharmacokinetic properties (Patil *et al*., 2013).

MATERIALS AND METHODS

We started our literature survey in June 2023 with key words neuroprotective plants, medicinal plants, dementia, Curcumin, Ashwagandha, *Ginkgo biloba* and neuropathology on the following databases: Google Scholar, Research Gate, Medline and Embase. All searched papers were further reviewed for cross references related to neuropathological cascade like amyloidogenesis, Aβ clearance, neurofibrillary tangles, aggregation of.α-Syn, synaptic dysfunction, degeneration of neurons, neurotransmitters malfunctioning, permeability to blood brain barrier, mitochondrial dysfunction and ROS, neuroinflammation and clinical trials. We selected the papers on the basis of the availability of the plant, their ability to cross the blood-brain barrier and having the potential to provide cure against dementia through clinical trials.

Out of thousands of papers at first search, around 900 papers were screened on the basis of title, then, further these papers were reviewed on the basis of abstract, finally 45 research papers were selected for full text reading.

Pharmacodynamics of Plant Products against Neurop athological Cascade

1.1 Amyloidogenesis

Amyloid formation occurs due to misfolding of proteins that may form smaller aggregates- oligomers which later turn into mature insoluble fibrils. These fibrils, having a distinctive β-sheet structure,tend to build up in extracellular spaces, diffuse into the synapses of local neurons, hindering, and disturbing synaptic signalling (Qiu *et al*., 2015), (Doecke *et al*., 2020), (Baweja *et al*., 2021) and thus interfere with proper tissue function.

Hypercholesterolemia and hyperlipidemia enhance the formation of β-amyloid plaques (Tokuda *et al*., 2000). Aβ aggregations constitute two kinds of Aβ polymers: Aβ40 and Aβ42. Aβ40 is more abundant and less neurotoxic than Aβ 42. According to Prasansuklab and Tencomnao high levels of Aβ cause RAGE (Receptor for Advanced Glycation End Products) to be upregulated, which in turn causes a higher buildup of faulty proteins in the brain (Prasansuklab and Tencomnao 2013).

Type of amyloid depositions varies with different forms of dementia, for example, α-Syn amyloid deposition occurs in Parkinson disease (Bloem, Okun, and Klein 2021) and prion protein amyloids in CJD (Iwasaki 2017).

Table-1: Clinical Trials Investigating the Therapeutic Effects of *Curcuma Longa*

No. of Subjects	Severe AD patients (n = 3)	AD patients (n = 60)	Adults with mild to moderate AD (n = 36)	Healthy adults (n = 1010)	Diseased old adults (n = 24)	Diseased volunteers	Diseased volunteers (n = 30)	Healthy adults (n = 60) (n = 132)	AD patients (n = 27)
Age (in years)	none	60–85 years	above 48 years	60–93 years	older adults	none	none	60-85 years	50-80 years
Dose	100 mg/d oral Optimized Curcumin,	80 mg/d with yoga	2g, 4 g/day	80–200 mg	100 mg/day	800 mg/day	180 mg/day	400 mg Longvida® containing approximately 80 mg curcumin in a solid lipid formulation	1-4 g/day
Treatment Time	12 weeks	Acute (1 h post dose) and chronic (1-month duration)	24 weeks ption from years	Daily consum	3 months	12 months	18 months	One/day for 4 weeks	6 months
Effects	Reduction in agitation, anxiety and irritability	Improved working memory, mood, alertness and contentedness	No significant difference	Lower incidence and prevalence of AD	Improvement in cognitive function, pain and inflammation	Cognitive changes, reduction in accumulation of A^2 and tau	Cognitive changes inflammatory markers	Safe and well tolerated, Improve important cognitive functions, reduce fatigue	Slower AD progression, No adverse effects even at 4 g, Rise in serum A^240 levels
References	(M. Chen et al. 2018)	(DiSilvestro et al. 2012)	(Ringman et al. 2012)	(Chandra et al. 2001)	(M. Chen et al. 2018)	(M. Chen et al. 2018)	(M. Chen et al. 2018)	(Cox, Pipingas, and Scholey 2015)	(Baum et al. 2008)

Curcumin binds to the amyloid (Ryu *et al*., 2006), (Reinke and Gestwicki 2007), and directly lowers Aβ formation by blocking β-site APP cleaving enzyme (BACE), which cleaves the transmembrane amyloid precursor protein (APP) at the N-terminal (Lin *et al*., 2008).

It may also indirectly lower BACE levels due to its anti-inflammatory nature (Morihara *et al*., 2005), (Howes and Perry 2011). Curcumin has been shown to cross the toxic oligomeric stage of amyloid formation in various neurodegenerative diseases (Ono *et al*., 2004), (F. Yang *et al*., 2005), (Garcia-Alloza *et al*., 2007), (Begum *et al*., 2008).

Additionally, curcumin may inhibit GSK3-mediated activation of PS1 and the subsequent cleavage of APP into Aβ (Xiong *et al*., 2011). γ-secretase inhibitory properties have also been reported for a few synthesised curcumin derivatives (Howes and Perry 2011). By preventing the synthesis of cholesterol and lowering serum peroxides, evidence suggests that curcumin may have therapeutic effects for AD (Soni and Kuttan 1992).

Different signalling pathways in affected people have been explored which show improvement by using curcumin. For example, Aβ pathway is manipulated by reducing amyloid load and improving brain signalling, tau pathway by inhibiting hyperphosphorylation and reducing the formation of tangles and help in signalling. Low doses of curcumin reduced the amount of Aβ plaques in the mice with AD's brains by 40 to 43% (Mishra and Palanivelu 2008), (Shytle *et al*.,2009). The potential of curcumin to disaggregate Aβ deposits in the brain, freeing the Aβ for circulation and disposal, was observed to cause a rise in serum Aβ40 in a placebo controlled double blind clinical trial (Baum *et al*., 2008). In Tg2576 mice, a dose of 5000 ppm curcumin enhanced Aβ monomer levels while lowering Aβ oligomer concentration. According to Hamaguchi *et al*., 2009, curcumin may inhibit Aβ polymerization but not Aβ deposition. Similarly, Ashwagandha and *Ginkgo biloba* has been studied for its neuroprotective, anti-inflammatory, and antioxidant properties, which may contribute to its effects on signalling pathways in dementia (Pahal *et al*., 2022). Both the plants have been shown to promote the production of nerve growth factors like brain-derived neurotrophic factor (BDNF), which in turn helps neurons to survive and maintain their functions. Their anti-inflammatory qualities reduce the generation of pro-inflammatory molecules such as tumor necrosis factor-α (TNF-α) and Interleukin (IL-6), enhancing signalling pathways impacted by chronic inflam mation(Venkatesan, Ji, and Kim 2015). Furthermore, both herbs include antioxidants that scavenge free radicals, decrease oxidative stress, and aid in the maintenance of healthy signalling pathways (Fig-1).

Studies using molecular modelling demonstrated that ashwagandha's withanamides A and C specifically bind to the active motif of Aβ25-35 and stop the development of fibrils. Ashwagandha is well known for preventing Aβ-induced cell death in PC-12 cells and rat neural cells(Gregory *et al*., 2021). Sehgal *et al*. (2012) observed a notable decrease in amyloid plaques in the brain and improvement in cognitive functions after administering oral doses of ashwagandha extract for 30 days to genetically modified mice with Alzheimer's disease. The results of this study also showed that Hsp70 serves as an

Table-2: Clinical Trials Investigating the Therapeutic Effects of *Ginko biloba*

No. of Subjects	Healthy adults (n = 20)	Dementia patients (n = 222)	Adults with mild to moderate dementia (n = 25)	Adults with cognitive impairment and dementia (n = 60)	Adults with cognitive impairment and dementia (n = 60)	AD patients (n = 400)	Healthy adults or with mild cognitive impairment
Age (in years)	21	> 55	50-80	25-61	50-65	> 50	> 75
Dose	GK501-360 mg	EGb 761 at 240 mg	EGb 761 at 160 mg	EGb 761 at 240 mg	EGb 761 at 240 mg	EGb 761 at 240 mg	G. biloba ext at 120 mg
Treatment Time	Single dose	Once a day-24 weeks	Once a day-24 weeks	Once a day-22-26 weeks	Once a day-f or 56(± 4) days	Once a day-22 weeks	Twice a day
Effects	Improved cognitive abilities, self-esteem, mood	Improvement in cognitive functions	No significant difference between EGb 761 and donepezil in the treatment of mild to moderate dementia	Stabilized or slow decline in cognition function	Greater cognitive flexibility without altering brain activity in the elderly	Less apathy and indifference, reduced anxiety, depression and irritability and improved sleep	Reduced progression of dementia in elderly and AD patients
References	(Scholey and Kennedy 2002)	(Herrschaft *et al*. 2012)	(Mazza *et al*. 2006)	(Tan *et al*. 2015)	(Beck *et al*. 2016)	(Scripnikov *et al*. 2007)	(DeKosky *et al*. 2008)

Table-3: Clinical Trials Investigating the Therapeutic Effects of *Withania somnifera*

No. of Subjects	Adults with mild cognitive impairment (n = 50)	Healthy adults (n = 13)	Healthy male (n = 20)	Healthy adult (n = 130)
Age (in years)	> 35 years	18 to 59 years	20-35 years	20-55 years
Dose	300 mg of ashwagandha root extract in capsule form, twice daily with water for eight weeks	400 mg of a proprietary ashwagandha root and leaves	250 mg capsules twice daily	300mg capsule one in a day
Treatment Time	from December 2013 to May 2014.	30 days	14 days	90 days
Effects	Significantly greater improvement in executive function, sustained attention, and information-processing speed	Improved selected measures of executive function. Sustain attention and increase short-term/working memory in healthy young adults.	Improvement in cognitive and psychomotor performance	Improvement in memory and focus, psychological well being, sleep quality, and reduced stress levels
References	(Choudhary, Bhattacharyya, and Bose 2017)	(Xing *et al*. 2022)	(Pingali, Pilli, and Fatima 2014)	(Gopukumar *et al*. 2021)

intracellular chaperone for aggregated tau or Aβ. It aids in the disassembly of aggregated tau protein and improves the ability of the LRP receptor to act as a sponge to draw out these disaggregated segments.

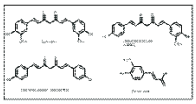
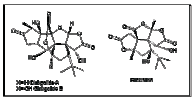
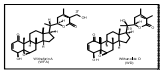
The aqueous extract of ashwagandha root is also neuroprotective against H_2O_2 and Aβ-induced cytotoxicity (S. Kumar *et al*., 2010). Withanone, a component of Ashwagandha, shows significant inhibition of Aβ42(A. Pandey *et al*., 2018). All four derivatives of Ashwgandha (Withanolide A, Withanolide B, Withanoside IV, and Withanoside V) have effective inhibitory activities against oligomeric peptide synthesis. In the oligomeric stage of Aβ42, withanolides and withanosides bind with the hydrophobic core, inhibiting further contact with the monomers and reducing aggregation(Jin *et al*., 2018),(Dubey, Kallubai, and Subramanyam 2021). According to the research by Kumar *et al*. (2012) the aqueous extract of Ashwagandha root can prevent the development of mature Aβ fibrils and consequently amyloid plaques in vivo.

Molecular docking studies showed that withanolides A, B, IV, and V bind to the Aβ's LVFFA residue area, a favoured location too for many small-molecule inhibitors of Aβ-42 peptide aggregation (Dubey, Kallubai, and Subramanyam 2021).

According to Dubey *et al*., 2021(Dubey, Kallubai, and Subramanyam 2021) research, withanolide A interacts with residues Leu17 and Leu19, withanolide B with residues Phe19 and Phe20, withanoside IV with residues Asp23, Val24, and Ser26, and withanoside V, which is bound in the same site as withanolide A and B. Additionally, their in-silico research revealed that withanoside IV is in the β-turn region of the amyloid peptide and is effective, with a binding energy of -7.4 kcal/mol, compared to the molecules of ashwagandha A, B, and V, which have binding energies of -6.4, -6.8, and -6.3 kcal/mol, respectively.

Ginkgo biloba is known for its ability to improve blood circulation and enhance vasodilation. By increasing blood flow to the brain, it may enhance oxygen and nutrient delivery, thereby optimizing signalling pathways involved in cognitive function. *Ginkgo biloba* was found to inhibit Aβ-peptide aggregation in AD (S. K. Singh *et al*., 2019), (Gregory *et al*.,

Table4 : Comparing the Efficacy of Phytochemicals from Three Distinct Sources in the Treatment of Dementias: A Comprehensive Analysis.

Parameters	***Curcumin longa***	***Gingko biloba***	***Withania somnifera***
Active Components	turmerone oil, curcumin, demethoxycurcumin, & cyclocurcumin	terpene lactones (blsdemethoxycurcumin and ginkgo ûavone glycos ides (ginkgetin, bilobetin & sciadopitysin)	withanolides A - Y, ginkgolides & diterpenes) dehydrowithanolide R, withasomniferin - A, withasomidienone, withasomniferols AC, withaferin A, withanone, phytosterols & withanamides
Structure			
Permeability of BBB	- (in water) + (in other solvents)	+	+
Production of amyloid beta plaque	-	-	-
A^2 Clearance	+	+	+
NFT Dissolution	+	+	+
Mitochondrial Dysfunction and ROS Production	-	-	-
References	(Srivastava *et al.* 2015), (S. Mishra and Palanivelu 2008), (Frautschy *et al.* 2001), (Cole *et al.*, 2004), (L. Zhang *et al.*, 2006), (S. Hu *et al.*, 2015), (Soni and Kuttan 1992), (Soudamini *et al.* 1992), (F. Yang *et al.*, 2005), (Bhat *et al.*, 2019)	(Konczol *et al.*, 2016), (Liang *et al.*, 2020), (Vareed et al. 2014), (Y. Luo *et al.*, 2002), (S. K. Singh *et al.* 2019), (Ramassamy 2006), (Bridi *et al.*, 2001), (Ahlemeyer and Krieglstein 2003), (Nowak *et al.*, 2021)	(Konczol *et al.* 2016), (Liang *et al.*, 2020), (Vareed *et al.*, 2014), (Haass and Selkoe 2007), (Dubey, Kallubai, and Subr amanyam 2021), (Tjernberg *et al.*, 1996), (Soto *et al.*, 1996), (Jayaprakasam, Padmanabhan, and Nair 2010), (Jayaprakasam, Padmanabhan, and Nair 2010)

β

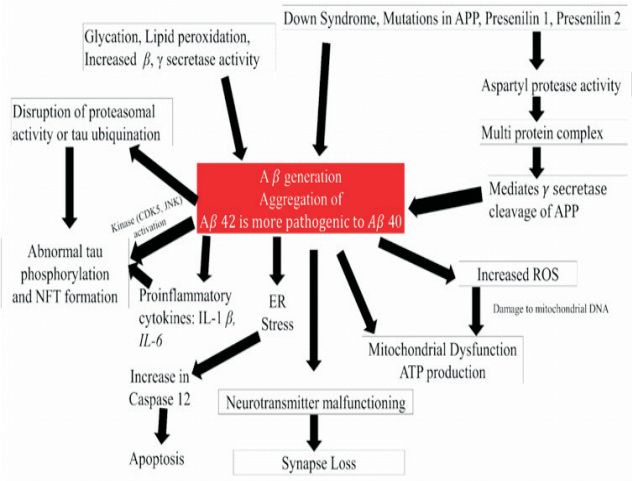


Fig-1: Illustration depicting the intricate process of A β aggregation and the resultant deposition of amyloid plaques within and around neuronal cells. The mechanism highlights the molecular events leading to the formation of amyloid aggregates, their impact on cellular function, and their subsequent accumulation both intracellularly and extracellularly. This portrayal elucidates the pivotal role of A β aggregation in the pathogenesis of conditions such as Alzheimer's disease.

2021),(Ramassamy, Longpre, and Christen 2007), (Yao *et al.*, 2004), (Verma *et al.*, 2020). GBE (*Ginkgo biloba* extract) has the ability to disrupt the formation of A oligomers (Y. Luo *et al.*, 2002), (Ramassamy 2006). The β-sheet structure of A β oligomers is widely recognized as the main contributor to A β neurotoxicity and can hinder A β clearance through proteolytic cleavage (Ramassamy 2006), (Pike *et al.*, 1991), (Simmons *et al.*, 1994), (Soto *et al.*, 1998). Therefore, inhibiting the formation of the β-sheet structure in Aβ oligomers emerges as a significant strategy to counteract Aβ toxicity (S. K. Singh *et al.*, 2019). GB derivatives support the accumulation of microglia around amyloid plaques, and also lead to a reduction in the production of pro-inflammatory cytokines (IL1β , IL6, TNFα) and to increase the production of anti-inflammatory cytokines (IL4, IL13, TGFα)(Nowak *et al.*, 2021).

1.2 Aβ Clearance:

Aβ clearance is the brain's natural process of removing toxic Aβ protein, which can accumulate and form harmful plaques. Normally, the brain has mechanisms to clear Aβ , and a delicate balance exists between its production and elimination. Effective clearance takes place either by proteolytic degradation, phagocytosis by microglia or clearance via BBB and lymphatic system. Removal of Aβ is essential for maintaining brain health and preventing neurodegenerative diseases like Alzheimer's. Impaired clearance leads to Aβ buildup, contributing to cognitive decline and neuron damage.

Studies showed that curcumin enhances the removal of Aβ from the brain by boosting the phagocytic activity of microglia, which are the brain's immune cells and the elimination of Aβ across the blood-brain barrier in various human cell and rodent AD models (Frautschy *et al.*, 2001), (Cole *et al.*, 2004), (L. Zhang *et al.*, 2006). Further, Curcumin has been reported to enhance the activity of enzymes responsible for degrading Aβ, such as neprilysin and insulin-degrading enzymes(P. Wang *et al.*, 2014), (Reddy *et al.*, 2018). By promoting the breakdown of Aβ, curcumin may help in reducing its accumulation in the brain.

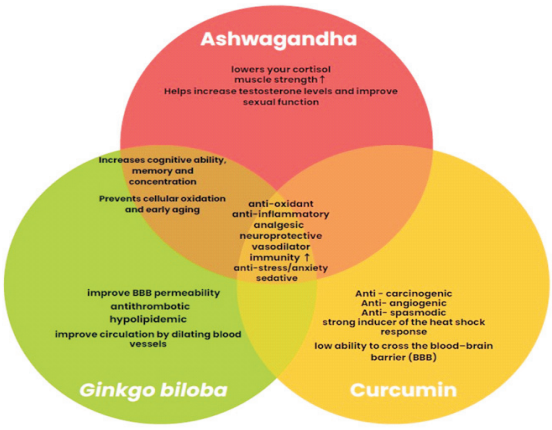


Fig-2: Comparative Analysis of Curcumin, *Ginkgo biloba*, and Ashwagandha Extracts: Highlighting Shared and Unique Therapeutic Attributes Across Various Disorders

It has been hypothesised that Ashwagandha acts like a chaperone which aids in the proper folding of proteins and the removal of misfolded proteins, such as amyloid formations. Limanaqi *et al*., 2019 reported that Ashwagandha reduces misfolded protein aggregation and may boost autophagy, which could further help in the breakdown and removal of amyloid aggregates from the cells and make it easier for them to be eliminated from the body.

Ashwagandha is shown to have neuroprotective qualities, which may help in maintaining the functionality of clearance pathways involved in eliminating amyloid aggregates by defending neurons from harm and enhancing their health. Sehgal *et al*. (2012) demonstrated the potential of a partially purified extract derived from ashwagandha to reverse Alzheimer's disease (AD) pathology in mice carrying the APP/PS1 genetic background. This extract contained 75% withanolides and 20% withanosides. The researchers observed that the ashwagandha extract effectively increased the clearance of the toxic Aβ peptide from the brain, leading to its sequestration in the bloodstream and subsequent degradation in peripheral tissues. Consequently, the mice showed improvements in AD-related pathology as a result of this treatment. Furthermore, Sehgal *et al*. (2012) also studied that ashwagandha extract enhances the expression of liver low-density lipoprotein receptor-related protein (LRP) and neprilysin (NEP) that leads to a decrease in Aβ in the brain and plasma of 3-month-old wild type WT mice.

Specific substances found in *Ginkgo biloba* extracts have the ability to chelate or bind to metal ions like copper and zinc. The formation and toxicity of amyloid can be facilitated by metal ions. *Ginkgo biloba* may inhibit the interaction of metal ions with amyloid proteins and thus facilitate their removal by attaching to these ions. It has been claimed that *Ginkgo biloba* increases cerebral blood flow and overall blood circulation which is essential for the transport of nutrients and oxygen to brain cells as well as the elimination of waste materials and clearance of amyloid (Singh *et al*., 2019).

1.3 Formation of Neurofibrillary tangles

Tau protein is an important microtubule-associated protein, thus it plays a vital role in stabilizing and regulating the structure of microtubules, which are essential components of the cell's cytoskeleton. In certain neurodegenerative diseases, such as AD and other tauopathies, tau undergoes abnormal hyperphosphorylation that disrupts tau's ability to interact with microtubules effectively, causing it to detach and aggregate as neurofibrillary tangles (NFT). The accumulation of NFTs inside neurons leads to cell dysfunction, impaired communication between neurons, cognitive decline and ultimately, neuronal death. Accumulated Aβ and hyperphosphorylated tau (pTau) are thought to be coexistent (Zheng *et al*., 2002), (H.C. Huang and Jiang 2009). Aβ fibrils are strongly associated with the phosphorylation of tau at Ser-202 and Ser-396/Ser-404, causing a shift in the tau M(r) in human cortical neurons. In neurons treated with fibrillar Aβ, pTau accumulates in the somatodendritic compartment in a soluble form that is not bound to microtubules in vitro (Busciglio *et al*., 1995). Furthermore, Aβ triggers a significant inflammatory response, and pro-inflammatory cytokines may indirectly influence tau phosphorylation. Additionally, there is growing evidence suggesting that Aβ might inhibit tau protein degradation through the proteasome, (Blurton-Jones and Laferla 2006).

Curcumin reduces the accumulation of soluble tau aggregates, which are a major cause of synapse loss. It achieves this through multiple actions. Firstly, it directly reduces the activation of tau kinases, such as c-Jun N terminal kinase (JNK) and GSK3β, in neurons, resulting in reduced levels of pTau. Additionally, curcumin reduces the production of inflammatory cytokines by glial cells, which helps to prevent the activation of NF*k*B and Activator Protein 1 (AP1), both of which can activate tau kinases in neurons. Moreover, curcumin limits the oxidation of tau, which promotes its activation, and can also reduce the acetylation of tau by affecting CBP/p300 histone acetyltransferase (HAT) (S. Hu *et al*., 2015).

Data suggest curcumin interferes with the homodimerization of the TLR4 receptor complex that is responsible for NF*k*B activation (Youn *et al*., 2006), which limits PPAR α activation. Curcumin also increases peroxisome proliferator-activated receptor - γ (PPAR γ) expression (Wang *et al*., 2010), which forms heterodimers with RXR alpha to regulate microglial activation and phagocytosis (Yamanaka *et al*., 2012). PPAR will downregulate inflammatory cytokines that contribute to tau kinase hyperactivity, tau accumulation and oxidative damage.

Curcumin binds to neurofibrillary tangles (NFTs) in human AD brain and animals (Mohorko *et al*., 2010), (Mutsuga *et al*., 2012), reduces soluble pTau oligomers and is also identified as significant tau aggregation inhibitors (Brunden *et al*., 2010), (Park *et al*., 2008). In *Caenorhabditis elegans* with human tau mutations, curcumin improves coordinate movement, reduces neuritic abnormalities (Miyasaka *et al*., 2016). Curcumin protects neuron-like PC12 rat cells and umbilical endothelial cells against A toxicity and reduces tau hyperp hosphorylation (Park *et al*., 2008).

Ashwagandha is known for its neuroprotective and antidementia properties that was evident through the upregulation of the low-density lipoprotein receptor, leading to the reversal of neurodegenerative tauopathies and enhanced cognitive functioning in a mouse model of Alzheimer's disease (AD) (Sehgal *et al*., 2012). In a study done on genetically induced human neurodegenerative disease (α-

synucleinopathy and tauopathy) models of Drosophila, it was found that the Ashwagandha treatment significantly reduced microtubular instability, mitotic arrest and neuronal death in photoreceptor neurons (Murthy and Shyamala 2024).

EGb761, a standardized *Ginkgo biloba* extract, was found to be efficacious in inhibiting the zinc-induced tau phosphorylation at Ser262 through its anti-oxidative actions involving the regulation of GSK3β (Kwon *et al*., 2015).

1.4 Aggregation of α-Syn

Dementia with Lewy bodies (DLB) is the second most common form of dementia after Alzheimer's disease (AD) and is also characterized by the aggregation of α-Syn in cortical and subcortical neurons. The ultrastructure of α-Syn aggregates is structurally similar to the Aβ aggregates(Conway, Harper, and Lansbury 2000) and therefore Pandey *et al*., 2008 propounded that the compounds which disrupt Aβ aggregates would have similar effect on α-syn aggregates. Various studies conducted demonstrated that curcumin binds to the β-pleated sheet structures of α-syn (Ono and Yamada 2006), (Pandey *et al*., 2008), (Ahmad and Lapidus 2012).

Moreover, curcumin effectively reduces cell toxicity of α-Syn aggregates by binding to preformed oligomers and fibrils, altering their hydrophobic surface exposure. It specifically binds to oligomeric intermediates rather than monomeric α-Syn, as supported by fluorescence and two-dimensional nuclear magnetic resonance (2D-NMR) data. The degree of curcumin binding is proportional to the extent of α-Syn oligomerization, indicating that the ordered protein structure is crucial for its effective binding (P. K. Singh *et al*., 2013).

Curcumin also increases α-syn solubility, inhibits α-syn aggregation and prevents the formation of high molecular weight α-syn aggregates in a dose-dependent manner. Cells treated with 10.6 M curcumin demonstrated reduction in aggregation. Experimental results of Pandey, *et al*., 2008 further demonstrated that treatment with curcumin at doses of 10^{6-} 10^{-7} M significantly increases the soluble fraction of α-syn in the form of monomers, dimers and oligomers whereas the aggregates in the absence of curcumin treatment are >200 kDa .

Benameur *et al*., 2021 explored the potential of curcumin to reduce misfolded α-Syn by stimulating autophagy. In cellular models for Parkinson's disease (PD), curcumin therapy resulted in increased expression of autophagy-related proteins such as lysosome membrane protein 2 (ALAMP2A), nuclear plasma protein determination of nuclear transcription factor EB (TFEB), and microtubule-associated protein 1 light chain 2 (LC3-II). This stimulation led to an increase in the synthesis of autophagy-lysosomes and improved autophagic clearance of α-Syn.

Studies investigating the neuroprotective properties of ashwagandha in an α-syn induced cellular model (Choudhary, Bhattacharyya, and Bose 2017) and in animal models and a reduction in α-syn aggregation is observed (Mikulska *et al*., 2023).

Several studies have explored the potential impact of *Ginkgo biloba* extract on the formation of α-Syn, a protein associated with neurodegenerative disorders, particularly Parkinson's disease. Effects of *Ginkgo biloba* extract EGb761 on α-Syn aggregation in cellular models and found that it significantly reduced the formation of α-Syn aggregates is investigated (Qiu *et al*., 2015). Additionally, Zhang *et al*. (2018) conducted in vivo experiments on animal models and reported that *Ginkgo biloba* extract showed a promising inhibitory effect on the aggregation of α-syn in the brain.

These findings suggest that *Ginkgo biloba* may hold potential as a therapeutic agent in targeting α-syn related pathologies. However, further research is needed to better understand the underlying mechanisms and potential clinical implications.

1.5 Synaptic dysfunction:

Synaptic dysfunction is triggered by changes in synaptic structure and neurochemicals induced by oligomerized Aβ rather than amyloid plaques (Prasansuklab and Tencomnao 2013). Synaptic deterioration occurs early in the disease, even before the formation of amyloid plaques and neuron loss. This initial synaptic impairment affects brain areas crucial for cognitive processes and memory formation, such as the hippocampus and entorhinal cortex (Thompson *et al*., 2003), (Arendt 2009). The process of synaptic damage may initiate with dysregulation of glutamate receptors and essential scaffold molecules like PSD95 and Shank1(Overk and Masliah 2014). PSD-95, a crucial regulator of synaptic structure and plasticity, actively promotes synapse formation (Nikonenko *et al*., 2008). As a membrane-associated guanylate kinase (MAGUK), it plays a significant role in regulating the synaptic expression of NMDA receptors, which are essential for long-term potentiation, synaptogenesis, and memory formation.

Curcumin induces down-regulation of PSD95 that is associated with synaptic plasticity and causes impairment of learning and memory ability in rats. It also improved the structure and function of synapses in the hippocampus by increasing the expression of the synapse-related proteins PSD95 and Shank1 in the early stage of AD and showed a therapeutic effect after short-term treatment (H. Chen, Zhou, and Zhao 2018). Curcumin is believed to enhance the removal of Aβ from the brain, leading to improved synapses (Reddy *et al*., 2018). Curcumin's presence may also promote the production of the protein brain-derived neurotrophic factor (BDNF), which supports the development, maintenance, and functionality of neurons and synapses.

The active components of ashwagandha such as withanolide A (first isolated withanolide from ashwagandha), withanolide IV, withanolide VI possess the ability of reconstructing the pre-synapses and post- synapses; and also involves in the regeneration of neuronal axons and dendrites (Ratheesh *et al*., 2017).

Bilobalide was demonstrated to have facilitative effects on synaptic transmission and plasticity in hippocampal CA1 and MPP-DG synapses, respectively (Suzuki *et al*., 2011). Moreover, bilobalide blocks glycine receptors and also inhibits GABA receptors more potently than ginkgolide B, and ginkgolide B, C, and M are significantly more potent than ginkgolide A and J for blocking glycine receptors (Ivic *et al*., 2003).

Findings of Mango *et al*., 2016 indicated that Ginkgolic Acid (GA) can reverse the Aβ-induced changes in both pre- and post-synaptic functions. GA has been further shown to inactivate the PI3K/Akt/mTOR pathway (Baek *et al*., 2017) which is vital for regulating autophagy and synaptic plasticity.

Dysregulation of this pathway is commonly observed in the brains of AD patients and AD model mice, induced by Aβ-promoted autophagy (Heras-Sandoval *et al.*, 2014).

1.6 Neuron degeneration

In Alzheimer's disease (AD), the deposition of nonvascular Aβ and pTau in the brain activates caspases, initiating and accelerating the further degeneration of neurons. Consequently, hippocampus and cerebral cortex undergo apoptotic neuronal death. Various categories of caspases play specific roles in apoptosis, with Caspase 8/10 serving as initiators by activating other caspases, namely caspase-3, -6, and -7, which execute the apoptotic process. The apoptotic pathway in AD is also triggered through diverse molecular pathways, including Ras-ERK, JNK, GSK-3, BDNF/TrkB/CREB, and PI3K/AKT/mTOR signalling (Kumari, Dhapola, and Reddy 2023).

Curcumin, in a randomized, pilot II, double blind pilot study which was done on 36 participants, found to treat cognitive impairments by inhibiting JNK-3 phosphorylation and dramatically decreased levels of amyloid, oxidised proteins, and isoprostanes in the brain (Ying Xu *et al.*, 2007), (Lauretti, Dincer, and Pratico 2020). At low concentrations, curcumin promotes neurogenesis through the promotion of brain-derived neurotrophic factor (BDNF) expression (Ying Xu *et al.*, 2007) and the proliferation of adult hippocampal progenitor cells (Kim *et al.*, 2008). Curcumin nanoparticles have been shown to induce neurogenesis in an AD model by suppressing the Wnt/β-catenin signalling pathway, which regulates GSK3 β activity (Tiwari *et al.*, 2014).

Administering Withanolide A (WL-A) from the root of Ashwagandha at a dosage of 10 □mol/kg/day for 13 days orally restores Aβ-induced memory deficit in mice. Additionally, it helps in the recovery of the axons, dendrites, and synapses in the cerebral cortex and hippocampus (Sun *et al.*, 2016), (Tohda, Kuboyama, and Komatsu 2000), (Kuboyama, Tohda, and Komatsu 2005). Withanolide A and withanosides IV and VI extend axons and dendrites, respectively, in vitro, and withanolide A is considered to reconstruct neuronal networks in vivo(Kuboyama, Tohda, and Komatsu 2005). However, withanoside-IV restored synapses in rat cortical neurons that were damaged by Aβ (dose: 10 μM/kg/day)(Kuboyama *et al.*, 2002). Derivatives of WS root extract promoted neurite outgrowth extension in the cell lines of human neuroblastoma (Zhao *et al.*, 2002).

In a study it was found that *Ginkgo* flavonoids increases the cell viability in TNF-α induced cultures of primary hippocampal neurons of rat brains (Guo *et al.*, 2015).

1.7 Neurotransmitters malfunctioning

Chronic administration of curcumin reversed the levels of 3,4-dihydroxyphenylacetic acid, noradrenaline, serotonin and 5-hydroxyindoleacetic acid in the hippocampus region of male albino rats. Curcumin helps to normalize the levels of dopamine, noradrenaline, and 5-hydroxyindoleacetic acid in the frontal cortex of rats (Ratheesh *et al.*, 2017).

Aqueous extracts of Ashwagandha increased acetylcholine (ACh) content and choline acetyltransferase activity in rats, which might partly explain the cognition-enhancing and memory-improving effects (Gregory *et al.*, 2021). There is evidence suggesting that EGb 761 (*Ginkgo* extract) has an impact on the dopaminergic system. In a mouse model of MPTP-induced toxicity, the extract demonstrated an ability to inhibit the degeneration of dopaminergic neurons in the striatum.

Ashwagandha acts by GABAergic system and antioxidant potential restores acetyl cholinesterase and glutathione enzyme levels and improves cognitive function (P. Kumar and Kumar 2008). Moreover, ashwagandha increases the expression of acetylcholine and dopamine receptors, contributing to improved cognitive function in cases of cognitive impairment and Parkinson's disease and inhibits acetylcholinesterase activity and the increase in acetylcholine receptor expression, which is beneficial in anti-Alzheimer's strategies. Furthermore, Ashwagandha has been observed to inhibit glucocorticoids and increase serotonin concentration, offering potential benefits in stress and related conditions (Durg *et al.*, 2015).

Ashwagandha has been found as a modulator of the cholinergic system, which is essential for learning, memory, and cognition. It may improve cholinergic signalling by boosting acetylcholine levels or regulating acetyl cholinesterase activity, an enzyme that degrades acetylcholine. Ginkgo biloba also has the capacity to influence numerous neurotransmitter systems in the brain, such as acetylcholine, dopamine, and serotonin (Venkatesan, Ji, and Kim 2015)

EGb 761 impede the degeneration of dopaminergic neurons in the striatum of a mouse model induced with MPTP toxicity (S. F. Yang *et al.*, 2001) but did not alter the density of dopamine (D2) receptors, however, reversed the age-related decrease in the density of acetylcholine receptors and serotonin (5-HT) receptors in the rat brain that might be due to the inhibitory effect of EGb 761 on lipid peroxidation and membrane destruction. Additionally, bilobalide, terpenoid trilactone found in *G. biloba*, elevated the level of gamma-aminobutyric acid (GABA) and activity of glutamic acid decarboxylase in the mouse hippocampus (Ahlemeyer and Krieglstein 2003) (Fig-2).

1.8 Permeability to blood brain barrier (BBB)

Penetrating the BBB to reach the brain is a challenge for natural chemicals. Some plant-derived compounds can cross the BBB, many cannot thus limit their effectiveness. The ability to cross BBB varies widely depending on their molecular size, chemical properties, their lipophilicity, active transport and binding to carrier proteins.

Curcumin can be transported across the barrier with the help of particular receptors that are expressed on the surface of BBB endothelial cells. Curcumin is delivered to the brain more effectively by using receptor-mediated transport mechanisms to conjugate it with ligands that can bind to these receptors. Microbubbles and focused ultrasound have the ability to temporarily rupture the BBB, enhancing the delivery of therapeutics like curcumin into the brain. The oscillations caused by the ultrasonic waves in the microbubbles enable enhanced medication penetration and localised BBB opening.

The uptake of curcumin into the brain is severely restricted by its low ability to cross the blood–brain barrier (BBB). The combination of Curcumin and GBE has been shown to improve BBB permeability (Assi *et al.*, 2023).

The components of *Ginkgo biloba* and ashwagandha (Choudhary, Bhattacharyya, and Bose 2017), (Liang *et al.*, 2020)are reported to be BBB+ that means these can cross the blood brain barrier (Vareed *et al.*, 2014).

Studies have shown that the concentration of ginkgo flavonoids and terpene trilactones increases in the plasma of rodents and humans after administering G biloba extract orally and many such compounds reach CNS after crossing blood-brain barrier in rats (Ude, Schubert-Zsilavecz, and Wurglics 2013).

1.9 Mitochondrial dysfunction and ROS

Human body can be exposed to free radicals through several mechanisms, such as aging, inflammation and environmental factors, such as nutrition, stress, and viruses, which result in further ROS accumulation and make NDDs a progressively deteriorating disease (Z. Liu *et al.*,2017), (Elyasi *et al.* 2022).

Spuch *et al.*, 2012 reported that mitochondrial malfunctions occur as a consequence of membrane-localized Aβ include the inhibition of protein transport into mitochondria, the disruption of the electron transport chain leading to impaired glucose utilization in neurons, and mitochondrial damage due to an increase in reactive oxygen species (ROS) production. Increased oxidative stress, in turn, also promotes APP processing through the upregulation of BACE1 gene expression, which leads to an increase in AB generation (Tong *et al.*, 2005), (Coma *et al.*, 2008), (Quiroz-Baez, Rojas, and Arias 2009).

In vitro studies revealed curcumin's ability to block lipid peroxidation and neutralize reactive oxygen species, which was several times more potent than vitamin E (Butterfield *et al.*, 2002).

It is a known fact that curcumin is a strong anti-oxidant compound with great ability to scavenge the oxygen-derived free radicals (Soni and Kuttan 1992), (Soudamini *et al.*, 1992), (F. Yang *et al.*, 2005), (Bhat *et al.*, 2019). Curcumin increases HO-1 (Haem Oxygenase-1) in astrocytes and neurons where it mediates neuroprotection against oxidative stress(Scapagnini *et al.*, 2006).

Dietary curcumin (2000 ppm) succeeded in reducing oxidative damage and increased microglial reaction near A deposits (F. Yang *et al.*, 2005). Both Ashwagandha and *G biloba* include antioxidants that scavenge free radicals, decrease oxidative stress, and aid in the maintenance of healthy signalling pathways (Venkatesan, Ji, and Kim 2015).

Flavonoid and ginkgolide of *Ginkgo biloba* derivatives exhibit protective effects against various mechanisms, like, they directly trap reactive oxygen species (ROS), chelate active metal ions, deliver antioxidant proteins, reduce lipid peroxidation, and inhibit NO synthesis. Additionally, these derivatives enhance antioxidant defense by upregulating the expression of antioxidant enzyme genes and inhibiting caspase 3, thereby reducing oxidative stress (Bridi *et al.*, 2001), (Ahlemeyer and Krieglstein 2003), (S. K. Singh *et al.*, 2019), (Nowak *et al.*, 2021). Moreover, mitochondrial oxidative phosphorylation (OXPHOS) against Aβ-induced oxidative stress has also been regulated by GBE for maintaining the equilibrium of ROS/RNS (reactive oxygen species/reactive nitrogen species) in cells

(Kaur *et al.*, 2015).

The antioxidative effects of EGb 761 have been confirmed in several studies, which are attributed to the free radical scavenging properties of this compound and its protection against ROS and inflammasomes in the CNS (Q. Liu *et al.*, 2019), (Singh *et al.*, 2019).

Similar to curcuminoids and ginkgolides, withanamides from ashwagandha fruit showed potent antioxidant activity as indicated by its ability to inhibit LPO. Withanamides block the methionone and other amino acid residues of the BAP motif involved in the oxidation and generation of free radicals in vitro(Jayaprakasam, Padmanabhan, and Nair 2010).

Ashwagandha has demonstrated potential in preventing oxidative stress on dopaminergic neurons and decreasing neuroinflammation, two major factors in the pathogenesis of Parkinson's disease. In case of Alzheimer's disease, it has a role in preventing oxidative stress on neurons, lowering Aβ aggregation, and enhancing synaptic function.Besides, antioxidant activity of ashwagandha is also attributed to the reduction or normalization of reversed lipid peroxidation levels (Bhattacharya *et al.*, 2000) and the increase or normalization of elevated superoxide dismutase levels, notably in key brain regions such as the cerebellum, striatum, hippocampus, frontal cortex. This is further supported by the activation of enzymes like catalase(Prakash, Shur, and Kumar 2013) and glutathione peroxidase (Gupta, Dua, and Vohra 2003)across various brain regions including the striatum, cortex, hippocampus.

Ashwagandha extract effectively mitigates LPS-induced NO and ROS in astrocytes (Martorana *et al.*, 2015), LPS-induced COX-2 expression and PGE2 release in BV-2 cells and rat primary microglia (S.W. Min *et al.*, 2010), and stimulates Nrf2 pathway and HO-1 production in microglial cells (Narayan, Seeley, and Jinwal 2015).

1.10 Inflammation

The deposition of Aβ plaques triggers a complex cascade of events within the brain, leading to the activation of microglia, the resident immune cells to clear the plaques via phagocytosis and chronic inflammation may persist. Over time, the persistent inflammation can lead to the release of inflammatory molecules, such as cytokines and chemokines, which can further attract immune cells and exacerbate the inflammatory response. This inflammatory environment can be damaging to surrounding neurons and can contribute to the progressive neurodegeneration.

Curcumin has potent anti-inflammatory properties. Research has shown that curcumin aids macrophages in effectively clearing amyloid plaques that are associated with Alzheimer's Disease. In a study when macrophages,treated with curcumin, were exposed to amyloid plaques, it was found that curcumin-treated macrophages exhibited greater uptake and ingestion of the plaques compared to macrophages that were not treated with curcumin. Various studies reveal the anti-inflammatory property of curcumin and also have a potent role in preventing Aβ oligomer and fibril formation (Ratheesh *et al.*, 2017).

Curcumin exhibits anti-inflammatory property (Frautschy *et al.*, 2001), (Zhang *et al.*, 2006), (Lim *et al.*, 2005) primarily by reducing inflammation in THP-1 cells (a major inflammatory transcription factor) through the inhibition of Egr-1 DNA binding activity (Giri, Rajagopal, and Kalra 2004), (Pendurthi and Rao 2000).

Curcumin reduces elevations in the inflammatory cytokines

Interleukin 1β and TNFα in the Tg2576 AD mouse model (Monroy, Lithgow, and Alavez 2013), (S. Mishra and Palanivelu 2008), (Maiti and Dunbar 2018) and also in LPS-stimulated BV2 microglia (Cho, Lee, and Kim 2007), (Gulcubuk *et al.*, 2006).

Under homeostatic conditions curcumin regulates inflammation by inhibiting p300 histone acetyltransferase (HAT) activity, even at very low levels. The HAT p300 contributes to chronic inflammation by acetylating and stabilizing NFéB, while counteracting deacetylases like sirtuins that can resolve inflammation and thus it downregulates NF-kB, a neuroinflammatory marker protein(Biswas *et al.*, 2005). Inflammatory diseases, as well as tau aggregation, are influenced by hyperacetylation (Maiti and Dunbar 2018), (K.-J. Min, Choi, and Kwon 2011).

Curcumin also restricts the production of arachidonic acid (AA) substrates and abnormal inflammatory cytokines. Although it does not directly inhibit cyclooxygenase unless at high concentrations (50-100 μM) curcumin modulates multiple AA metabolites (M. T. Huang *et al.*, 1991). It reduces the induction of cyclooxygenase-2, inhibits 5-lipoxygenase (IC50 ~ 0.7 μM), and suppresses the phosphorylation and activation of cytosolic phospholipase A2 (Park and Kim 2002), (Hong *et al.*, 2004), (Maiti and Dunbar 2018).

Ginkgo biloba extract has anti-inflammatory activity on primary microglia stimulated by LPS.EGB can reduce neuro inflammatory activation by targeting the Cox/PGE2 pathway(Gargouri *et al.*, 2018), (C. Luo *et al.*, 2018), (Wan *et al.*, 2016), (Cruz *et al.*, 2010).

Ginkgo flavone exhibited significant inhibitory effects on the abnormal expression of the Akt and p38 pathways in A549 cells, which were stimulated by human neutrophil elastase. Additionally, in treated mice, there was a reduction in inflammatory cells and cytokines, including IL-8. Other compounds found in *Ginkgo biloba*, such as ginkgo bilobalide, ginkgolide A, ginkgolide B, ginkgolide C, ginkgolide J, ginkgolide K, and bilobalide, have also been reported to possess anti-inflammatory properties (H. Hu *et al.*, 2018), (Tao *et al.*, 2019), (Mohammadi Zonouz, Ghasemzadeh Rahbardar, and Hosseinzadeh 2024), (Ge *et al.*, 2020), (Sarkar *et al.*, 2020), (Yiling Xu *et al.*, 2020), (Chu *et al.*, 2011), (S. Zhao *et al.*, 2021).

Withanone was found to intensify the activity of acetylcholine, glutathione and secretase enzymes (β and γ) and improved the elevation in pro-inflammatory cytokines levels (Pandey *et al.*, 2018). Oral administration of WS root extract powder (500 and 1000 mg/kg body weight) was found to be effective against reducing pro-inflammatory cytokines (IL-6), Tumor necrosis factor (TNF)-α, reactive oxygen species (ROS) and nitric oxide (NO) in female Balb/c mouse models(U. Minhas, Minz, and Bhatnagar 2011), (Ujla Minhas *et al.*, 2012).

1.11 Clinical Trials:

The incidence and prevalence of AD were shown to be lower in India (Chandra *et al.*,1998;2001)in a cross-national epidemiological (Indo-US) study comparing rural people in northern India (n = 4,450) with southwestern Pennsylvania (n = 886).

Clinical trials have shown no significant evidence of curcumin toxicity, even with long-term use of doses up to 5,000 ppm or below (National Toxicology Program 1993). Furthermore, treatment of curcumin increases HDL cholesterol and reduces LDL cholesterol, triacylglycerols and total cholesterol, particularly in the 1 g group of a six month double blind clinical trial (Baum *et al.*, 2008). In another study, three patients with advanced stage dementia were administered turmeric (764 mg turmeric/day) capsules with bioavailable curcumin (100 mg/day) over a one-year period. All the patients showed improvement in neuropsychiatric inventory scores and cognition and reduction in caregiver burden (Hishikawa *et al.*, 2012).

In a randomized, double-blind, placebo-controlled, parallel groups trial done by Cox *et al.*, 2015 (Cox, Pipingas, and Scholey 2015) showed that 400 mg of Longvida® curcumin, given daily for 4 weeks, was safe and well tolerated in an elderly population. Behavioral measures showed that curcumin even at low dose (approximately 80 mg) has the potential to enhance cognitive functions, reduce fatigue, and improve resilience to the detrimental effects of psychological stress on mood.

Curcumin also showed indirect antioxidant action by elevating plasma activities of the endogenous antioxidant enzyme catalase but there was no change in the readings of other two antioxidant enzymes glutathione peroxidase and erythrocyte superoxide dismutase (DiSilvestro *et al.*, 2012) (Table-4).

The ginkgolides (1–100 μM in vitro or 50–100 mg/kg in vivo), bilobalide (25–100μM in vitro or 10 mg/kg in vivo), and in some cases also the flavonoid fraction (25–100 μg/ml in vitro or 40–100 mg/kg in vivo) have been shown to contribute to the neuroprotective effect of EGb 761 (Gohil and Packer 2002). Administration of GBE (100 mg/kg body weight) in SD rats resulted in decrease in Aβ aggregation, ubiquitin deposition, accompanying a significant decline in APP and Tau protein hyperphosphorylation which can be attributed to activation of Heat shock factor (HSF-1) and upregulation in the protein expression of HSPs (Verma *et al.*, 2020).

Ashwagandha was found to significantly improve immediate and general memory in a study of 50 patients aged over 35. The treatment group, after eight weeks, displayed notable enhancements compared to the placebo group, suggesting potential benefits for mild cognitive impairment and executive function, attention, and processing speed (Choudhary, Bhattacharyya, and Bose 2017).

Studies by Xing *et al.*, 2022 showed that acute supplementation with 400 mg of ashwagandha improved executive function, sustained attention, and short-term/working memory. Furthermore, 600 mg and 500 mg doses taken over eight weeks improved memory, executive function, processing speed, and certain cognitive functions in adults with early dementia and bipolar disorder, respectively. A 14-day trial with 1000 mg of ashwagandha extract in healthy participants aged 25 demonstrated enhanced cognitive and psychomotor performance.

Improved cognitive and psychomotor performance was also reported in another similar study done on 20 healthy males using a dose of two 250 mg capsules of root and leaf extract of ashwagandha twice daily for a period of 14 days(Pingali, Pilli, and Fatima 2014).

Furthermore, the treatment with one Ashwagandha SR capsule (300mg) once daily for 90 days improved memory and focus, psychological well-being, and sleep quality, reduced stress levels, and was safe and well-tolerated (Gopukumar *et al.*,

2021).

3. Challenges and Limitations

Our study found that the chosen plants, curcumin, ashwagandha, and *Ginkgo biloba* for neuroprotection have many potential benefits since these have been used traditionally in India and other Asian countries but the use of these in pharmaceutical therapeutics still requires more robust clinical research with large sample size, long study periods nd a good number control group. The data on the combined use of these plants is also scanty.

Furthermore, these natural products can vary in quality and content if these are used in their unpurified forms, which make it difficult to ensure consistent dosing and effectiveness. The use of curcumin has many limitations like poor bioavailability, limited water solubility, quick metabolism and inability to cross the blood brain barrier to reach the target areas of the brain. A lot of research on nano formulations are going on to protect curcumin from premature degradation, clearance and help them to reach the brain cells via crossing BBB.

Curcumin, ashwagandha and *Ginkgo biloba* components may also interact with pharmaceuticals which are blood thinners and those that are broken down by particular liver enzymes. The effectiveness or safety of curcumin and the other drugs may be impacted by these interactions. To completely comprehend these interactions and offer precise recommen dations for using it in combination with other medications, more research is required.

CONCLUSION

Polyherbal formulations contain a number of phyto-components that aim to ease out the health issues with their synergistic, potentiating, agonistic, or antagonistic actions. Numerous plant products have garnered global attention for their potential neuroprotective effects, including memory enhancement, antioxidative, and anti-inflammatory properties. These plant products possess a significant advantage over conventional mono-component drugs due to the presence of multiple active compounds that can address multiple goals simultaneously, providing holistic relief.

This is corroborated by the findings of Assi *et al*., in 2023 where the combination of curcumin and *Ginkgo biloba* extract (GBE) revealed a substantial increase in curcumin levels in both brain and plasma within 30 minutes to 1 hour after oral administration of CUR + GBE, particularly in an AD rat model compared to when curcumin alone was administered in the same model. CUR + GBE was reported to reverse learning and memory deficits up to some extent. This effect was linked to a more pronounced inhibitory impact on acetylcholinesterase (AChE), caspase-3, hippocampal amyloid beta (Aβ1-42), phosphorylated tau protein (p-tau) levels, as well as pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-1beta (IL-1β), when compared to treatment with curcumin alone. Furthermore, the combined therapy significantly reduced lipid peroxidation (MDA) and increased reduced glutathione (GSH) levels, unlike the curcumin-alone group.

Similarly, in another study the combination of *Ginkgo biloba,* sesame and turmeric specifically increased the density of terpene lactones in the mouse brain in comparison to GBE alone (Iwamoto *et al*., 2019), (Nakase *et al*., 2023). Terpene lactone is known to protect neurons by inhibiting caspase-3 activity and amyloid-β aggregation (Wu *et al*., 2006). Likewise, the combination of *Withania somnifera, Boswellia serrata, Curcuma longa* and Zinc was safely tested against osteoarthritis patients and reported to be effective in minimizing pain.

Our systematic search led us to three plants, *Curcuma longa, Withania somnifera* and *Ginkgo biloba* that have constituents with similar therapeutic activities which have been pharmacologically proven effective in treating various forms of dementia, such as Parkinson's disease (PD) and Alzheimer's disease (AD). These plants have shown the potential to slow down disease progression and alleviate symptoms.

Further, the findings of this research provide support for the notion that the polyherbal approach may serve as an alternative therapeutic strategy for the management and prevention of neurological disorders. This study introduces a novel avenue for exploring phytotherapies for dementia and underscores the importance of future research focusing on the synergistic effects of herbal medications.

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