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"A BRIEF REVIEW ON PHYTOCHEMICALS REPORTED TO PREVENT ALZHEIMER'S DISEASE"

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ABSTRACT: Alzheimer's disease (AD) is a multifaceted, progressive neurodegenerative illness marked by memory loss, personality changes, and cognitive impairment. While the actual origin of AD is unknown, recent research points to lifestyle, nutrition, environmental, and genetic factors. Genetic factors play a role in illness progression. To present, pharmaceutical therapies have not affected disease progression. Over the last decade, more than 200 potential therapeutic candidates have failed clinical trials, indicating that the disease and its causes are likely to be complicated. Since, a long time ago, products made from natural resources, such as medicinal plants, have been used to treat various memory diseases, including amnesia, dementia, Alzheimer's, and Parkinson's. Various studies have shown the use of medicinal herbs in treating Alzheimer's. Despite this, it is still unclear exactly how they act. Numerous bioactive chemicals, including polyphenols, tannins, flavonoids, triterpenes, alkaloids, and sterols, have been found in diverse plant components after phytochemical examinations. These substances have various pharmacological properties, including antioxidant, anticholinesterase, anti-inflammatory, anti-amyloidogenic, and anti-inflammatory effects. Several medicinal plants against AD are described in this review.

INTRODUCTION: Neurodegenerative diseases are a wide range of genetic disorders that cause loss of neuronal structure and function and, in many cases, neuronal death. These conditions may result directly from specific neuronal population degeneration or indirectly from glial supporting cell changes. These conditions are characterized by an abnormal accumulation of proteins or other accumulations of biological material inside or outside the nerve cell.

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These aggregates are structurally different and lead to dysfibrillation in AD, Lewy bodies in Parkinson's disease, and glycogen and polyglucosan bodies in Lafora disease. AD is thought to cause 60% of mental disorders in middle-aged and older adults and affects more than 5 million Americans, estimated to increase to 7.7 million by 2030 [1].

The progression and symptoms of AD are indicated by two categories of neuropathological alterations, which include: (i) Positive lesions, which are characterized by the build-up of neurofibrillary tangles, amyloid plaques, dystrophic neurites and neuropil threads additional deposits discovered in patients with AD's brains. Additionally, there are (ii) Two negative lesions (caused by losses), characterized by significant atrophy brought on by

neuronal, neuropil, and synaptic loss. In addition, other variables like neuroinflammation, oxidative stress, and damage to cholinergic neurons might result in neurodegeneration [2]. Particularly in the hippocampus, amygdala, entorhinal cortex, and the cortical association areas of the frontal, temporal, and parietal cortices, but also with other brain regions, neuronal loss and/or disease may be observed. The cholinergic basal nucleus, the noradrenergic locus coeruleus, and the serotonergic dorsal raphe are examples of subcortical nuclei. The trans-entorhinal cortex is where tangles first begin to accumulate, followed by the entorhinal cortex, the cornu Ammonis (CA1) region of the hippocampus, and finally, the cortical association areas, where the frontal, parietal, and temporal lobes are most severely impacted. Much more so than the number of amyloid plaques, the degree and location of tangle development correlate well with the severity of dementia [3]. Herbal medicine has long been used worldwide as therapy for dementia. Herbal medicines have, however, hardly ever been authorized as therapy for dementia over the past ten decades. Overall, a systematic review has found a couple of single herbs and herbal sources as potentially effective medicine for AD **Table 1**. According to current evidence, some of these therapies have potential cognitive benefits. It is presently unknown whether herbal therapy could be a new way of treating AD based on the findings of clinical trials and the implications for possible treatment of AD pathophysiology.

Phytochemicals and Herbal Plants and their Extracts: Table 1. Different medicine and herbal sources are effective in the treatment of AD.

TABLE 1:

S. no.	Herbal drug	Formulation of a mixture of herb extracts	Sources
1	*Uncaria rhynchophylla* Miq.	Aqueous extract of *Uncaria rhynchophylla*	JiWook Jung *et al*[4].
2	Huperzine	A from Lycopodium alkaloid isolated from Chinese herb *Huperzia serrata*	Hai-yanet et al[5].
3	*EGb761*	A standardized extract of GinkoBiloba	Charles Ramassamyet*et al*[6].
4	Reveratrol	Extract grapes, apples, blueberries, plums, and peanuts.	Alex J. T. Yang*et al*[7]. Teng Mae*et al*[8]. J. Gambini et al[9].
5	Curcumin	Extracted from the dried root of the rhizome Turmeric (Curcuma Longa) by solvent extraction.	Min Chen*et al*.[10] Tian Jiang*et al*[11].
6	Omega 3 PUFA	Extract fish, vegetable oils, nuts (especially walnuts), flax seeds, flaxseed oil, and leafy vegetables.	Harimana Yves*et al*[12]. Burckhardt M*et al*[13].
7	Quarcetin	Free-form from leaf surfaces, fruits, or bud extracts.	Haroon Khan*et al*[14].
8	Protopine	Solid-liquid extraction of protopine from *Fumaria officinalis*	Sravan Gopalkrishna shetty Sreenivas murthy et al[15].
9	Spinosin	Isolated from *Zizyphus jujuba* var. spinosa.	Mudan Cai*et al*[16].
10	Nobeletin	Apolymethoxylated flavone from the peel of Citrus depressa.	Akira Nakajima*et al*[17].
11	Galantamine	Maryllidaceae plants including Narcissus, Galanthus, Lycoris, and Leucojum species are used for extraction.	Özlem Bahadır Acikara *et al*[18].
12	Rivastigmine	Hydro-alcoholic extract of Salvia haematodes Wall root.	Mohammad Shawwal *et al*[19].
13	Berberine	Extracts roots and rhizomes of various plants including barberry, Oregon grape, goldenseal, and tree turmeric.	Maria A. Neag *et al*[20].

Bioactive Components in Plant Extracts:

***Ginkgo biloba*:** The use of *Ginkgo biloba* extract (GBE) is utilized to enhance cognitive function. Numerous investigations were done to learn more about its phytomedicines and effectiveness in various contexts. Many studies support the use of GBE in conditions such as cerebrovascular insufficiency, AD, multi-infarct dementia, resistant depression, peripheral artery insufficiency, venous insufficiency, asthma, and memory loss in the elderly. Due to its high tolerability and the limited or complete failure of conventional treatments for certain conditions, GBE for tinnitus, schizophrenia, psychotic organic brain syndrome, vertigo of unclear origin, and premenstrual syndrome merits thorough investigation even if it is less well

supported [21]. Ginkgolides are the basic terpenoids. As per **Fig. 1**. The GB standard extract has a bilobalide content of 2.6 to 3.2%, ginkgolides (A, B, and C) of 2.8 to 3.4%, and flavone glycosides of 24%. (quercetin, isorhamnetin, and kaempferol) [22]. Like most plant-based medicines, *Ginkgo biloba* has a variety of active ingredients that are thought to work in concert. Ginkgo is hypothesized to have its therapeutic effects due to flavonoids like quercetin, kaempferol, and isorhamnetin, tri lactonic diterpenes like Ginkgolide A, B and C, a tri lactonic sesquiterpene called bilobalide, and proanthocyanidins. Additional components include D-glucaric acid, ginkgolide acid, related alkylphenols, glucose, rhamnose, hydroxykinurenic, kynurenic, protocatechuic, vanillic, and shikimic acids [21].

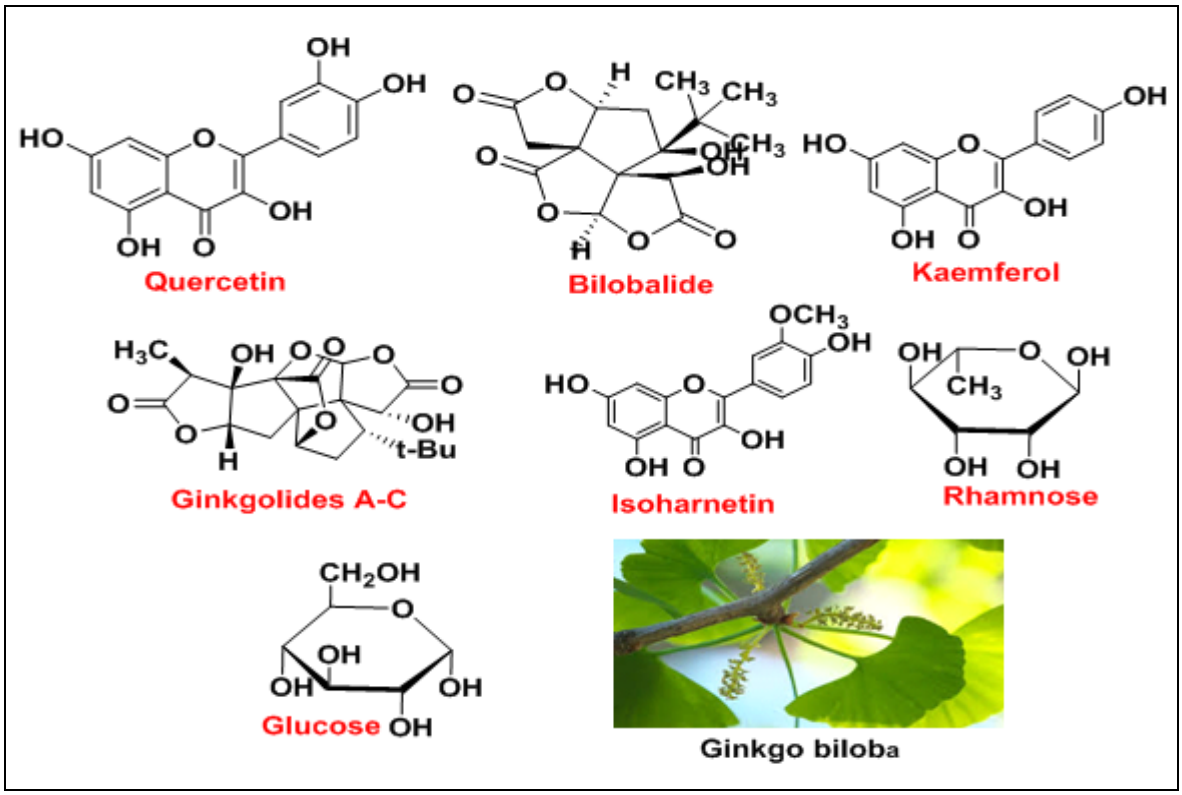

FIG. 1: SCHEMATICS OF THE PRINCIPLE COMPONENTS FOUND IN *GINKGO BILOBA* EXTRACT. (GBE) OBSERVE THE VARIOUS BIOACTIVE AGENT GROUPS. (TERPENOIDS AND FLAVONOIDS)

One of the world's most thoroughly researched plant extracts is the *Ginkgo biloba* L. [*Ginkgoaceae*] unique extract *EGb761*. Using that extract as a paradigm, we describe insights into how the climate, the harvest region, the processing of the plant material, the drying process, the extraction solvents, and the specifics of the subsequent process steps significantly impact the quality and uniformity of the final extract. We stress the significance of controlling the concentrations of useful constituents and steadily lowering the amounts of undesirable compounds in herbal extracts. *Ginkgo biloba* leaf extracts distributed under the brand name *EGb761* have been promoted as therapeutic herbal supplements to treat a range of neurological conditions, including AD [23]. Strong experimental evidence shows that *EGb761* protects the brain in humans and animals. Nootropics and vasodilators, medications given particularly for memory loss, are clear candidates for therapies to stop cognitive aging. *Ginkgo biloba* extract *(EGb761H*- Tanakan) has been supplied as a memory aid in France for over thirty years, and it is also sold as a dietary supplement in the *US*. While protecting neuronal cell membranes from free radical damage is arguably the most well-known benefit of *G. biloba* extract, *EGb761*'s characteristics go beyond that basic antioxidant process. It has been demonstrated that it can increase hippocampus neurogenesis, engage in mitochondrial defence, and lessen *Aβ* aggregation and toxicity. *EGb761H* has been demonstrated to decrease blood viscosity and increase microperfusion. Moreover, several rat model

studies demonstrated that *EGb761* enhances neurotransmission, particularly in glutamatergic, dopaminergic, and cholinergic systems. As a result, *EGb761* can be regarded as a medication with multiple targets [24]. Recent reviews and meta-analyses of randomized controlled trials concluded that *EGb761* successfully treats individuals with dementia, including those with AD, vascular dementia, and mixed forms, especially those with neuropsychiatric symptoms [25]. As shown in **Fig. 1**, all of these bioactive constituents are found in *EGb761*.

Mechanisms of the Neuroprotective Effect of *EGb761 In-vitro* and Animal Studies: The striatum, *Substantia nigra*, and hippocampus of rats showed potent antioxidant and scavenging activities against various reactive oxygen species (including superoxide, peroxyl, and hydroxyl radicals), increased the activities of superoxide dismutase and catalase, and decreased lipid Peroxidation [26]. In rat cerebellum cultures, had protective effects against apoptosis induced by oxidative stress [27]. High levels of peroxide generation did not influence the enzyme activities of the mitochondrial respiratory chain, protecting against age-related mitochondrial DNA damage and glutathione oxidation in rats. This prevented the loss of plasma superoxide dismutase activity and significantly improved spatial memory in a gerbil model of vascular dementia.

It also preserved the hippocampus CA1 neurons had positive effects on synaptic efficacy and plasticity in the hippocampus CA1 area in elderly animals, improved spatial learning and memory, and improved synaptic effectiveness. Enhanced cell proliferation in both young and old mice's hippocampi and a dose-dependent rise in the total number of neural precursor cells. through anti-excitotoxicity, suppression of free radical formation, scavenging of reactive oxygen species, and modulation of mitochondrial gene expression, safeguarded against ischemia and glutamate-induced neuronal death. altered the activity of transcription factors and target genes, particularly those involved in the stress response [26].

***EGb761*in Preclinical and Clinical Dementia: Evidence of Efficacy:** Although it has been used for many years to treat neuro-cognitive disorders, *EGb761* has recently received unanimously positive expert reviews. As noted in the treatment guidelines for cognitive disorders, the success of *EGb761* as a drug for dementia can be attributed to the results of recent scientific reviews and meta-analysis studies. The various forms of dementia are with the various pharmaceutical therapies that are now available [28].

***Withania somnifera* (Ashwagandha):** Ashwagandha, also known as *Withania somnifera*, is a *Solanaceae* family perennial plant. One of the most notable plants frequently given for AD is *W. somnifera*. It is typically administered as an energy and nerve tonic. As an adaptogen, *W. somnifera* has been shown to have free radical scavenging, antioxidant, and immune-boosting properties. As per **Fig. 2** Withanolides A-Y, withanone, withasomniferols A to C, dehydrowithanolide-R, withasomidienone, and other ergostane-type steroidal lactones are just a few of the bioactive substances of medical significance found in *W. somnifera*.

The plant also comprises alkaloids, beta-sitosterol, and phytosterols sitoindosides VII-X. Several of these components have been shown to remove free radicals created during the development of AD pathology [29]. This herb's aqueous extracts have been found to boost cholinergic activity, including acetylcholine content and choline acetyl activity may partially explain this describe the effects that improve memory and intellect.

Additionally, new reports have revealed fascinating details about this herb's capacity to promote neurite outgrowth. Treatment with the methanol extract of Ashwagandha in human neuroblastoma cells human neuroblastoma cells, treatment with the methanol extract of Ashwagandha resulted in dose- and time-dependent neurite sprouting. In cells treated with Ashwagandha, the levels of two dendritic markers, microtubule-associated protein-2 and postsynaptic density-95, were found to be significantly elevated, indicating that it promotes dendrite formation [30, 31]. In the subsequent investigation, the same research team exposed cultured rat cortical neurons to amyloid peptide, which caused axonal and dendritic atrophy as well as loss of pre-and postsynaptic stimuli. Following therapy with an Ashwagandha methanol extract,

axons, and dendrites were significantly regenerated. Methanol extracts of Ashwagandha restored amyloid peptide-induced memory deficit in mice and reconstructed pre- and postsynapses in neurons. These *in vivo* effects of Ashwagandha persisted even after the drug's delivery was stopped. Similarly, preliminary research from this lab found that dentate gyrus neurogenesis was significantly increased only in *J20* mice fed a diet containing the entire herb (Ashwagandha root powder, *2.5* g/kg body weight), as opposed to *J20* mice that only received normal food. *J-20* mice that express the mutant form of human amyloid precursor protein (APP) bearing both the Swedish *(K670N/M671L)* and the Indiana *(V717F)* mutations. (Unpublished data). Additional clinical trials must be carried out to support Ashwagandha's therapeutic use, even though the data stated above are quite encouraging for its use as an anti-AD agent. Although the herb has been effectively used in Ayurvedic medicine for centuries, a systematic investigation of the acute or chronic toxicity of this herb or its various constituents is still missing, and more research is necessary to confirm the therapeutic significance of this herb [32].

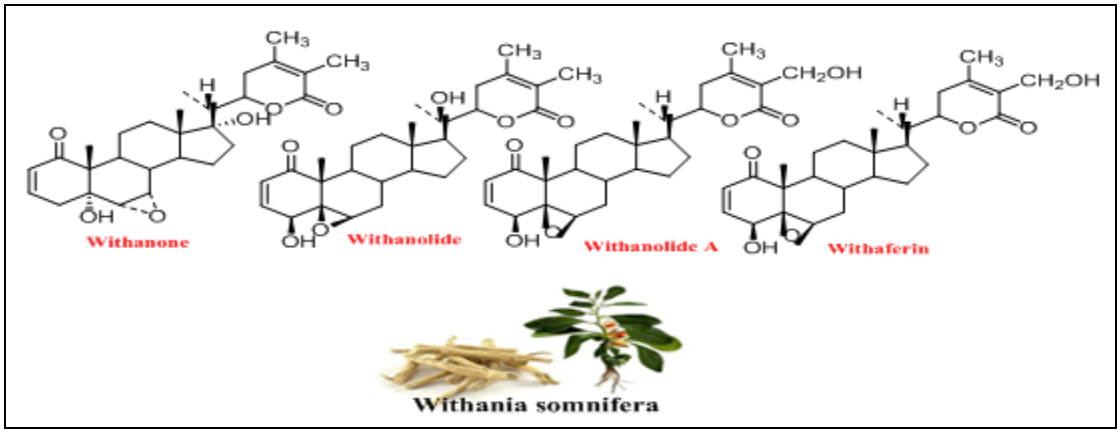

FIG. 2: SCHEMATICS OF THE PRINCIPLE COMPONENTS FOUND IN *WITHANIA SOMNIFERA* EXTRACT OF THE VARIOUS BIOACTIVE AGENT GROUPS

Pinax Ginseng: For thousands of years, countries in the far east, including China, Japan, and Korea, have used ginseng (Panax ginseng Meyer) root extensively as a traditional tonic for longevity. Ginseng was decocted with water and made into a drink in traditional medicine Fig. 3 The body is rejuvenated or has more vital energy due to ginseng extract, as does mood and longevity. While its mode of action is unknown, ginseng extract has traditionally been thought of as an adaptogen for enhanced resilience to many diseases and stresses. Ginseng is currently used all around the world as a functional food, alternative medicine, and supplementary medicine. Ginseng-containing commercial products are made by extracting the ginseng's water-soluble and/or water-insoluble constituents with water and/or alcohol. One of the main merits of ginseng extract is that it exhibits a variety of effects with fewer side effects than those exhibited by other herbal medicines [33]. Gintonin's potential in preventing and managing. Gintonin affects the cholinergic system, neurotrophic factors, autophagy, and apoptosis, as well as G protein-coupled lysophosphatidic acid (LPA) receptors to exercise its anti-AD actions. Gintonin injection improves memory impairment in AD mice by inhibiting A plaque deposition and promoting amyloid precursor proteins *(sAPP)* release. This suggests that gintonin causes the production of sAPP rather than the harmful [34]. In a transgenic AD mouse model, gintonin can boost the expression of choline acetyltransferase, resulting in the release of Acetylcholinesterase and attenuating induced cholinergic deficits [33]. Gintonin stimulates the release and expression of vascular endothelial growth factor (VEGF), which may be mediated through the LPA1/3 receptor or other receptors, in cortical astrocytes, providing neuroprotective effects against hypoxic shocks [35]. Gintonin can also effectively reduce no generation via controlling the Mitogen-activated protein kinase (MAPK) and nuclear factor (NF-B) pathways, as well as stimulate autophagic flux in astrocytes by activating the adenosine monophosphate-activated protein kinase (AMPK) inhibits target of rapamycin (mTOR) signaling pathway. Gintonin is an LPA

receptor ligand that interacts with the abundantly expressed LPA receptors in astrocytes to temporarily elevate intracellular calcium (Ca2+) concentrations, which in turn affects neurotransmitter release and synaptic transmission and ultimately improves cognition. Nevertheless, ginsenosides or other ginseng-active ingredients did not affect Ca2+, which may be connected to gintonin's chemical properties and how it interacts with G protein-coupled receptors [33].

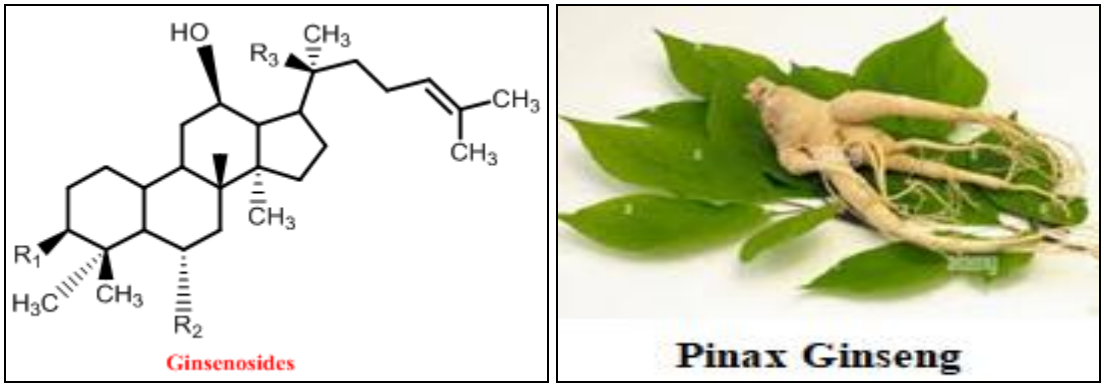

FIG. 3: CHEMICAL STRUCTURES OF GINSENOSIDES; R1, R2 AND R3 = GLC–B-D-GLUCOPYRANOSYL; ARAP-A-L-ARABINOPYRANOSYL; ARAF- A-L-ARABINOFURANOSYL; RHA- A-L-RHAMNOPYRANOSYL

***Bacopa monnieri* (Brahmi):** Brahmi is a creeping plant that grows to a height of two to three feet, with branching leaves and purple blooms. It lives in wet, marshy places. Formerly addressed in Ayurveda as a 'medhyarasayana', or "the memory enhancer herb" [36]. Brahmi extract underwent phytochemical research, which identified numerous bioactive components in the extract [37].

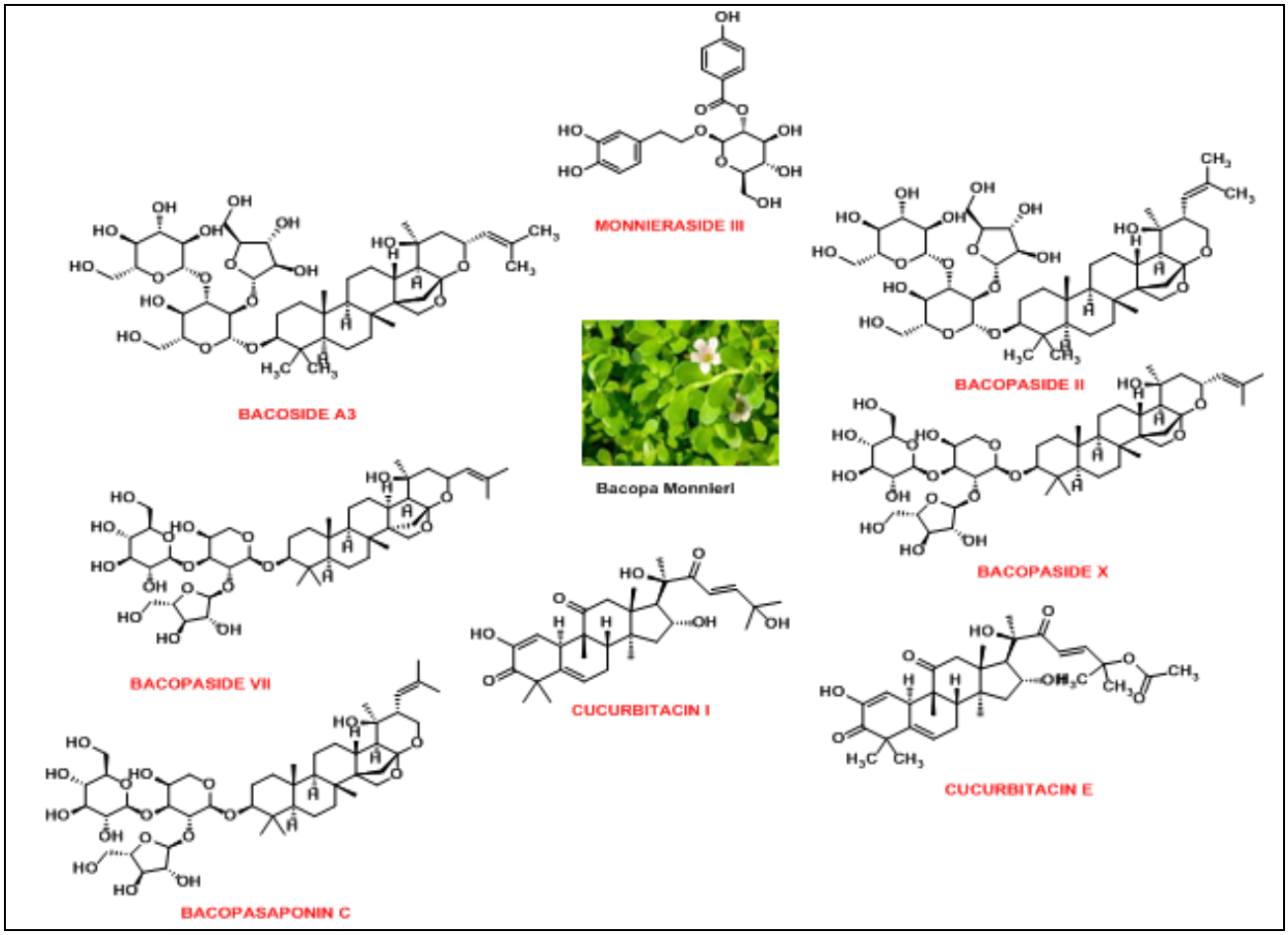

FIG. 4: SCHEMATICS OF THE PRINCIPLE COMPONENTS FOUND IN *BACOPA MONNIERI* EXTRACTOBSERVE THE VARIOUS BIOACTIVE AGENT GROUPS

According to reports, the Brahmi extract contains triterpene-containing saponins, alkaloids, glycosides, and alcohols. Alkaloids such as "Brahmine," "Nicotine," and "Herpestine" are present in the Brahmi extract. One of the main bioactive components of Brahmi is thought to be the dammarane type triterpenoids saponins, such as Bacoside A [3-(L-arabinopyronsyl)-O-D-glucopyronaside, 20-dihydraoxy-16-keto-dammar-24-ene]. Further research has revealed the presence of a triterpenoid saponin called Bacoside A3 that is 3 - [O - D-glucopyronosyl (1 - 3) – O - [L-arabinofuranosy (1-2)] – O -D-glucopyranosyl)oxy. Chemicals like pseudojujubogenin, which is technically known as 3-O-[-1-arabinofuranosyl (1-2) -d-glucopyranosyl], are present in the glycoside component of Brahmi extract **Fig. 4**. Brahmi's methanolic extract produced two 3-O-Larabinofuranosyl-1 pseudojujubogenin glycosides (1-2)-[6 - O - sulphonyl – β – D - glucopyranosil-(1-3)]3 – O – L – arebinofuranosyl - (1-2) - [-D-glucopyronosil-1(1-3)] and -L-arabinopyranosyl pseudo jujubogeninp seudo jujubogenin -D-glucopyranosyl [38]. From an ethanolic extract of Brahmi, a new saponin known as bacopasaponin G was discovered. Its chemical name is 3-O-[-1-arabinofuranosyl-1(1-2)] Jujubogenin L-arabinopyrosyl. A 5-O-p-hydroxybenzoyl-D-apifuranosyl-phenylethyl alcohol, 3,4-dihydroxyphenylethyl alcohol (2-Oferulolyl)—D-glucopyronoside, and phenylethanoid glycoside (1-2) -β-Dglucopyranoside [39]. "The two primary substances believed to be responsible for Brahmi's effectiveness as a neuroprotectant are 'Bacoside A' and 'Bacoside B. Bacoside A is a blend of several saponins, including jujubogenin, bacopaside, and bacoposaponin C. Mevalonate (MVA) and methyl-D-erythritol-4-phosphate (MEP) pathways were used to create bacoside [37] **Fig. 4.**

***Melissa officinalis* (Lemon balm):** *Salvia officinalis* and *Melissa officinalis*, two plants in the labiatae family, may be able to treat AD naturally. Originally from Europe, *Melissa officinalis* is currently grown all over the world. It provides calming and carminative properties in addition to anxiolytic, sedative/hypnotic, and relaxing effects. *Melissa officinalis* contains nicotinic and muscarinic acetylcholine receptor activation in the central nervous system.

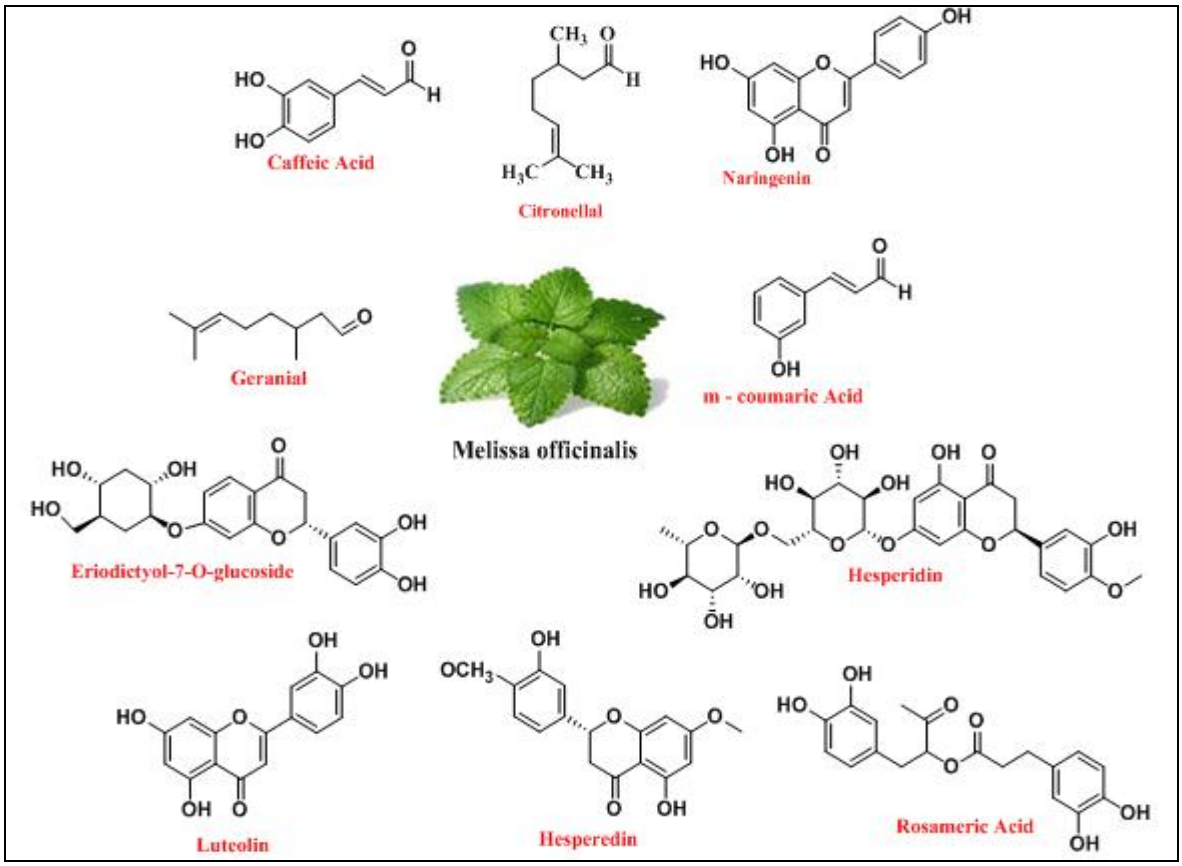

FIG. 5: SCHEMATICS OF THE PRINCIPLE COMPONENTS FOUND IN *MELISSA OFFICINALIS* EXTRACT OF THE VARIOUS BIOACTIVE AGENT GROUPS

In addition, a recent study found that this herb alters the mood and cognitive function in healthy young volunteers when administered acutely. There have not been any side effects or toxicology symptoms associated with its use [40]. According to chemical studies, *Melissa officinalis* includes flavonoids, terpenoids, phenolic acids, tannins, and essential oil. Melissa Officinalistive constituents are volatile compounds (geranial, neral, citronellal). phenolic substances (rosmarinic acid, caffeic acid, and protocatechuic acid), and flavonoids (quercetin, rhamnocitrin, and luteolin)are shown in **Fig. 5**.

The therapeutic principle responsible for most biological activities is generally thought to be essential oil, but polyphenols are also involved. *Melissa officinalis* essential oil, obtained by water steam water-steam extraction from this plant's fresh or dried blossom, leaf, and branches, has a fresh lemon odour and a light golden colour [41]. Polyphenols, on the other tandem, remain a potential source of new drugs, and there is a great deal of interest in understanding their mechanisms in the prevention and treatment of AD. We looked into a crude extract from *Melissa officinalis* leaf, not a single pure chemical compound, it should be emphasised. This plant extract is a complex mixture, and it may have its effects as a consequence of the combined effects of several of its constituents (such as the additive or synergistic effects of caffeic acid with salvianolic acids and rosmarinic acid, among others) [42].

***Centella asiatica* (Gotu Kola):** Being natural sources of a wide range of phytochemical components and sites of action, herbal treatments have a promising future as treatments for AD. For its alleged benefits on brain health, the herb Centellaasiatic, often known as gotu kola, has a long history of usage in traditional Chinese and Ayurveda medicine. Although the mechanisms behind the cognitive-improving and neuroprotective properties of *Centella asiatica* are yet unknown, preclinical and clinical evidence strongly supports these results [35]. In mice, ageing and AD models have shown that a water extract of *Centella asiatica* (CA) exhibits cognitive-improving effects [43]. Asiaticoside, a component of CA, has been demonstrated to support angiogenesis and collagen production, two processes that aid in wound healing. Asiaticoside has been shown to increase the tensile strength of freshly formed skin, aiding in wound healing and boosting the production of collagen in numerous cell types. Moreover, it has been shown to enhance capillary permeability and reduce inflammation, which can result in scar hypertrophy. In one experimental animal study, the effects of asiaticoside on antioxidant levels were examined because it has been hypothesised that antioxidants play a role in the process of wound healing [44].

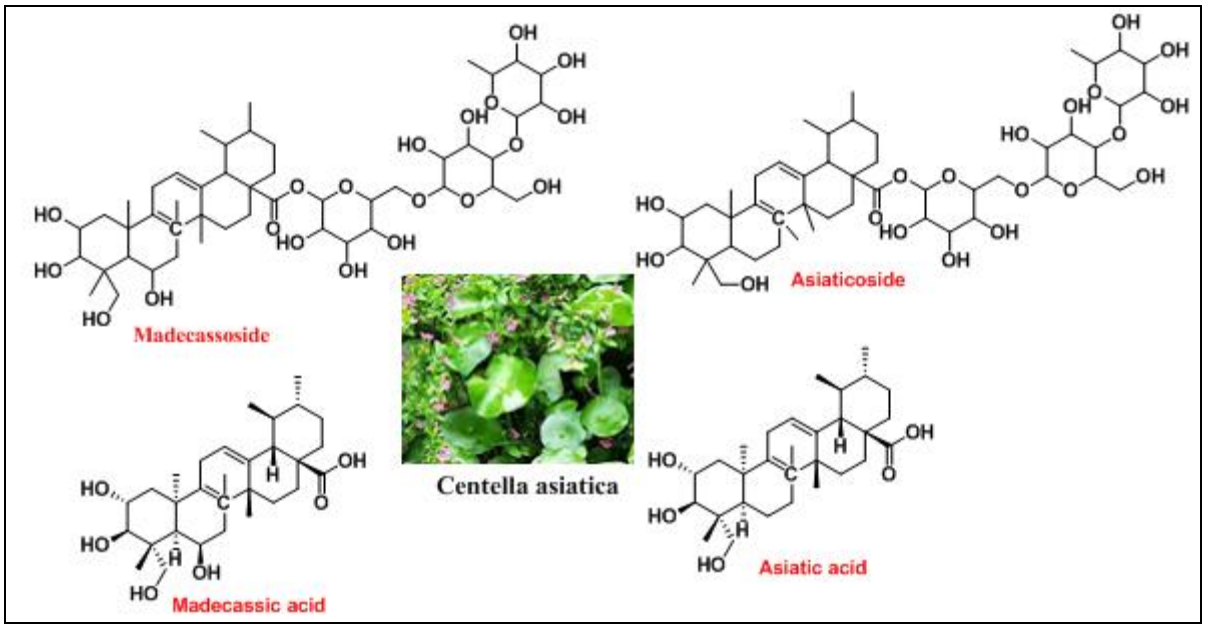

FIG. 6: SCHEMATICS OF THE PRINCIPLE COMPONENTS FOUND IN THE EXTRACT OF *CENTELLA ASIATICA* AND THE VARIOUS BIOACTIVE AGENT GROUPS

There might be a role for gotu kola in treating and preventing AD and beta-amyloid toxicity. Asiaticoside derivatives, such as Asiatic acid and asiaticoside, have decreased hydrogen peroxide-induced cell death, decreased free radical concentrations, and inhibited beta-amyloid cell death *in-vitro*. Gotu kola extracts changed the oxidative stress response elements and reversed beta-amyloid pathology in the brains of *PSAPP* mice [45].

***Rosmarinus officinalis* L. (Rosamary):** The woody perennial herb *Rosmarinus officinalis* (*R. officinalis*), which belongs to the *Lamiaceae* family, is native to the Mediterranean region and has long been used as a seasoning as well as for a variety of medical conditions. It is known for its stimulant, mild analgesic, choleretic, anticancer, and hepatoprotective properties. As a rich source of phytochemicals such as Carnosicacid (CA), rosmarinic acid (RA), ursolic acid (UA), and camphor, which exhibit antioxidant, anti-inflammatory, and anticarcinogenic characteristics, *R. officinalis* has attracted enough attention from other herbs and spices. Moreover, it has analgesic, anti-anxiety, and memory-improving benefits, demanding additional research on its active ingredients tolerate therapeutics for nervous system illnesses like AD, Parkinson's disease, and epilepsy [46]. Pharmacologically active components found in *R. officinalis* include phenolic diterpenes, triterpenes, and phenolic acids including carnosic acid (CA), carnosol, rosmanol, ursolic acid, betulinic acid, and rosmarinic acid (RA), as well as nepitrin.

CA and *RA* have been demonstrated to have the most pervasive pharmacological effects and interact with various molecular targets among the isolated phenolic compounds from *R. officinalis*. *R. officinalis* potential effects on cognitive disorders and their impact on cognitive function have not yet been thoroughly examined. To describe the qualitative and quantitative effects of *R. officinalis* and its active ingredients on cognition in preclinical experiments and to pinpoint the underlying mechanisms is the goal of the current study [47].

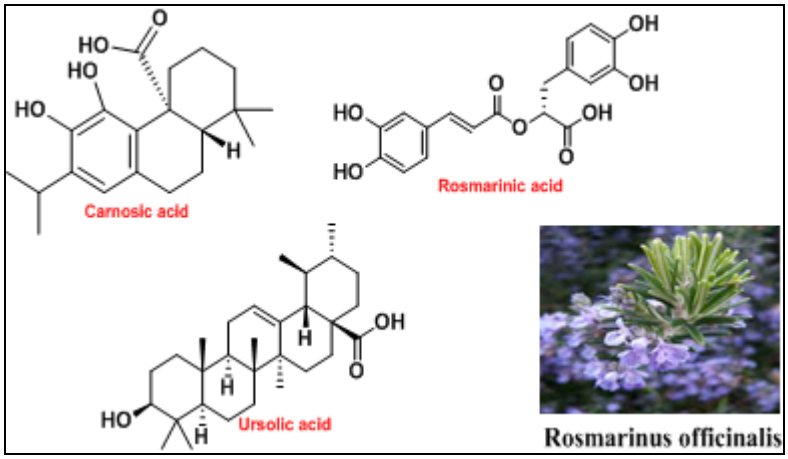

FIG. 7: SCHEMATICS OF THE PRINCIPLE COMPONENTS FOUND IN THE EXTRACT OF *ROSMARINUS OFFICINALIS* THE VARIOUS BIOACTIVE AGENT GROUPS

***Valeriana officinalis* (Valerian):** The term "valerian" relates to a perennial herb plant that is native to different parts of America, Europe, and Asia and belongs to the *Caprifoliaceae* family. The *Valeriana officinalis* L. species, one of over *200 species* that have been identified so far, is the one that is most frequently used medicinally. Between 150 and 200 different compounds can be found in valerian, including volatile oils, ketones, phenols, iridoid esters like valreotriate and valeric acid, alkaloids, and amino acids like glutamine, arginine, aminobutric acid, and aminobutric acid as well as noncyclic, monocyclic, and bicyclic hydrocarbons. This herbaceous perennial plant, common in temperate Asia, Europe, and North America and has good benefits for the heart, brain, and stomach, has short rhizomes that produce underground creeping stems [48]. According to reports, several valerian species have been used for millennia as mild sedatives and sleep aids in Europe and North America. Pharmacological activity on the Valeriana genus, including anxiolytic, depressive,

antispasmodic, sedative, anticancer, and anti-HIV activities, and its application in treating neurological illnesses after studying ancient manuscripts and contemporary pharmacological research [49]. Lignans and flavonoids with central nervous system action. It is believed that valerenic acid is the main component. The two primary groups of components in the roots and rhizomes of *V. officinalis* are sesquiterpenes of the volatile oil, which include valerenic acid and its derivatives valeranone, valeranal and kessyl esters, and valepotriates, which include valtrate, didrovaltrate, acevaltrate, and isovaleroxyhydroxyvaltrate. Sesquiterpenoids of several different types, such as volvalerenals A–F, volvalerenic acids A–D, volvalerelactones A–B, and valeneomerins A–D, have been found in *V. officinalis* [50].

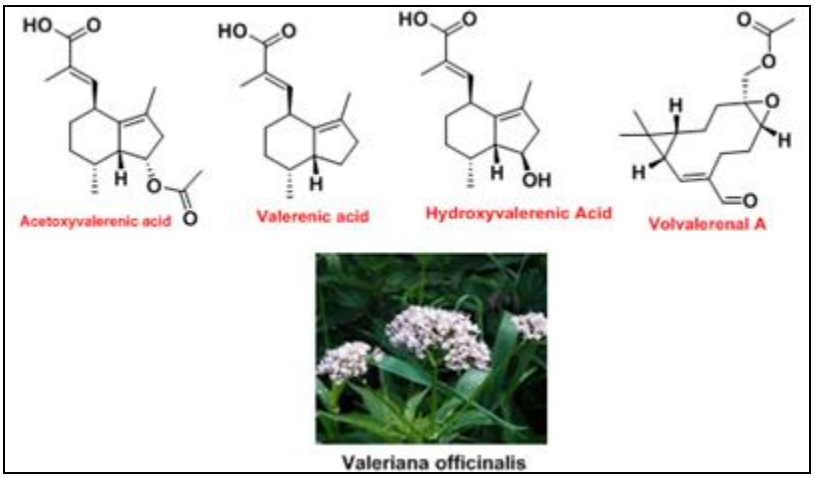

FIG. 8: SCHEMATICS OF THE PRINCIPLE COMPONENTS FOUND IN THE EXTRACT OF *VALERIANA OFFICINALIS* THE VARIOUS BIOACTIVE AGENT GROUPS

***Curcuma longa* (Curcumin):** Turmeric, which is derived from the plant *Curcuma longa* - Haldi, is used in curries and other hot cuisines from India, Asia, and the Middle East. Similar to many other herbal treatments, curcumin was first utilised as a meal before people realised it also had powerful therapeutic properties. It has been widely utilised in Ayurveda (Indian system of medicine) as a painkilling and anti-inflammatory substance to treat pain and inflammation in the muscles and skin. Moreover, it has demonstrated anti-cancer effects. As a "cleanser of the body," curcumin is highly revered in Ayurveda medicine. Today, science is discovering a rising number of sick illnesses that the active elements in curcumin 51 can treat. Turmeric's active ingredients are water-soluble curcuminoids and turmerone oil. Demethoxy curcumin (DMC), bisdemethoxycurcumin (BDMC), and cyclo curcumin are examples of curcuminoids. The main curcuminoid has anti-inflammatory properties and is linked to a lower risk of AD. Curcumin was several times more effective than vitamin E in blocking lipid peroxidation and neutralizing reactive oxygen species *in-vitro* tests [52]. The main polyphenol present in turmeric stew is curcumin. (*Curcuma longa*). Numerous laboratory and clinical studies have demonstrated the anti-AD properties of curcumin and its new formulations. In addition to having antioxidant, anti-inflammatory, and neurotrophic qualities, curcumin has also been shown to inhibit apoptosis and hyper-phosphorylation of tau protein [53]. The potent antioxidant and anti-inflammatory qualities of curcumin also reduced the symptoms of AD that are characterised by oxidation and inflammation.

Additionally, a modest dose of turmeric (160 ppm) decreased proinflammatory cytokine levels, which are connected to the neuroinflammatory cascades involved in the pathogenesis of neuritic plaques. Curcumin may be several times more effective than vitamin E at inhibiting lipid degradation and neutralizing reactive oxygen species *in-vitro* [30]. The National Cancer Institute, among other organizations, conducted toxicity tests by feeding groups of male and female rats and mice for 13 weeks and for two years turmeric oleoresin (an organic turmeric extract toxicity toxicology investigations by feeding groups of male and female rats and mice for 13 weeks and for two

years turmeric oleoresin (an organic extract of turmeric). No toxicity-related acute or long-term clinical findings were observed in rodents or mice given doses of turmeric oleoresin of 2,000, 10,000, or 50,000 ppm [45].

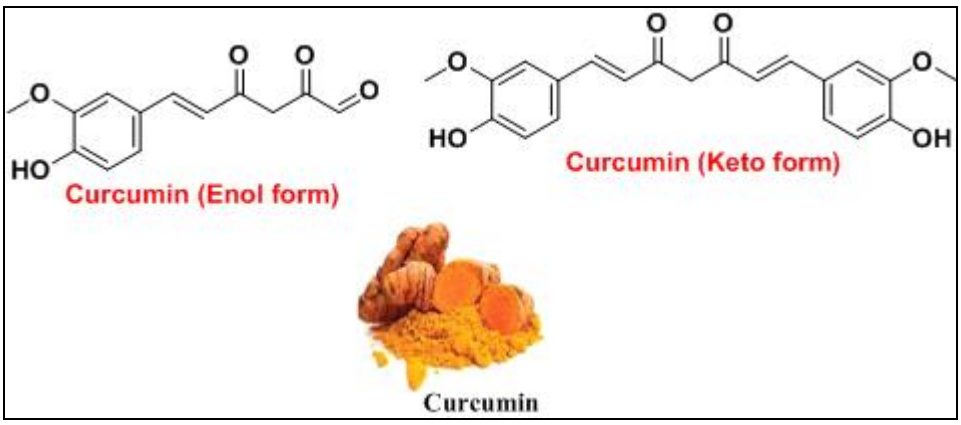

FIG. 9: SCHEMATICS OF THE PRINCIPLE COMPONENTS FOUND IN THE EXTRACT OF *CURCUMA LONGA* THE VARIOUS BIOACTIVE AGENT GROUPS

***Convolvulus pluricaulis* (Shankhpushpi):** The Convolvulus pluricaulis (CP), Convolvulus microphyllus, Evolvulusalsinoides, and Clitoriaternatea (CT) are a few of the varieties that have been identified as belonging to the genus Shankapushpi. In India, the common plant sankhpushpi is used in various formulas as a nervine tonic to enhance memory and cognitive performance [54].

Various secondary metabolites have been identified and may be in charge of Shankhpushpi's nootropic and memory-improving qualities and other pharmacological actions. These include tri terpenoids, flavonol glycosides, anthocyanins, and steroids. According to popular belief, Shankhpushpi soothes nerves by controlling the body's production of cortisol and adrenaline stress chemicals [55].

The alkaloids convolving, convolamine, phyllabine, convolidine, confoline, convoline, subhirsine, convosine, and convolvidine, as well as scopoline and -sitosterol, are important phytoconstituents in the extract of this plant **Fig. 10** [56].

The ethanol that is derived from CP aids in the body's reduction of toxic fatty acids, phospholipids, and total serum cholesterol. Convolvine has been identified to specifically inhibit M2 and M4 cholinergic muscarinic receptors by its pharmacological activity. Additionally, it was shown that convolvine amplifies the benefits of arecoline, a muscarinic memory booster that improves AD-related cognitive deficiencies. Additionally, it is advised for nervous system disorders like tension, anxiety, mental exhaustion, and insomnia. Rats' learning and memory were significantly enhanced by the ethanolic extract of CP and its ethyl acetate and aqueous components. When tested *in-vitro*, the ethanolic extract of CP also exhibits significant antioxidant action.

When given to gerbils served a diet high in cholesterol, an ethanolic extract of the entire plant significantly decreased serum cholesterol, LDL cholesterol, triglycerides, and phospholipids. When rodents were given CP extracts, a dose-dependent memory improvement was seen. Similarly to this, giving old mice CP extracts for 7 days improved their recall.

The CA1 and CA3 areas of the hippocampal regions linked to learning and memory revealed a dose-dependent rise in acetylcholine esterase activity with CP treatment. In particular, administering CT's aqueous root extract to newborn rat pups enhanced retention and spatial learning abilities, demonstrating CT's memory-improving ability. Additionally, acetylcholine levels in CT-treated rodents' hippocampi were significantly higher than those of age-matched control rats. Their enhanced learning and memory may have a neurochemical foundation in the hippocampus' increased acetylcholine content [57].

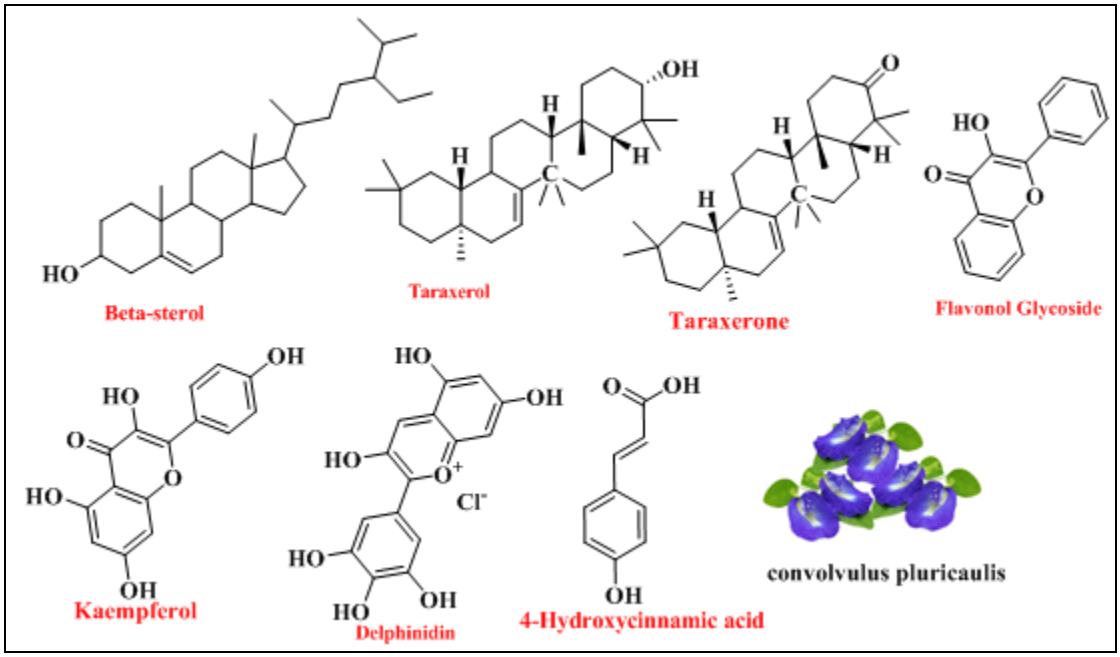

FIG. 10: SCHEMATICS OF THE PRINCIPLE COMPONENTS FOUND IN THE EXTRACT OF *CONVOLVULUS PLURICAULIS* THE VARIOUS BIOACTIVE AGENT GROUPS

***Alpinia Officinarum* (Galangal):** *Alpinia galanga* (L.) Wildis a medicinal plant native to China, India, and Southeast Asia that belongs to the Zingiberaceae family. This plant's rhizomes are widely used to flavor food and are also used in traditional medicine to treat a variety of diseases. *Alpinia galanga* comprises anticancer, antibacterial, antifungal, HIV 1 replication suppression, and anticholinesterase effects [58].

In Europe and Indonesia, the rhizomes of Temu Lawak, *Alpinia officinarum* (Zingiberaceae), have been used as choleretic medicines. Two diarylheptanoids have been identified as this plant's chemical components. Two new diarylheptanoids (Ia and II) and three known diarylheptanoids (curcumin (V), hexahydrocurcumin (IV), and dihydro curcumin (III) have been isolated and their structures have been determined in the current research. We also want to describe a novel diarylheptanoid (VIa) that was discovered in the rhizomes of *Alpinia officinarum* [59]. Diarylheptanoid (DAH) is a class of chemicals with the potential to be used to create natural products. Its unique feature is that it has a 1,7-diphenylheptane skeleton. Many DAH compounds have been identified, and their structural characterization and biological activity have been published. Due to their capacity to scavenge reactive oxygen species (ROS), polyphenols and flavonoids belong to a different class of substances that are of interest. The effectiveness of antioxidants in reducing 2,2'-diphenyl-1-picrylhydrazyl (DPPH) radicals is gauged by the decline in their absorbance at 517 nm. DPPH can cause many antioxidants to react slowly or even inertly, reacting quickly with peroxyl radicals [60]. *Alpinia officinarum* (*A. officinarum*) contains several acetylcholinesterase inhibitors, including galantamine, huperzine, and rivastigmine.

Galangin demonstrated a potential effect to reduce the synthesis of b-amyloid and acetyl cholinesterase for treating AD. Galangin, a flavonoid isolated from A. officinarum, had the greatest inhibitory impact on acetylcholinesterase out of all well-known flavonoids. It is a naturally occurring flavonoid that prevents the synthesis of b-amyloid. Galangin also has antioxidant and free radical scavenging properties. One of the main flavonoids in *A. officinarum* is galangin, which has a 3-hydroxy flavone backbone. The regulation of signaling pathways may be connected to the process. Gene alteration at the transcriptional level, particularly methylation, and acetylation, is the principal mechanism implicated in inhibition. Therefore, the aforementioned indicates that flavonoid galangal is important for future therapeutic development. Natural Chemicals that Prevent AD. As a result, *A. officinarum* has significant and growing applications in therapeutic herbs [61].

A. galanga contains a high concentration of phenolic compounds **Fig.11**such as phenylpropanoids. 1′S-1′-acetoxychavicol acetate, one of the primary phenylpropanoids, is recognized as the source of *A. galanga's* distinct pungent and aroma component. Flavonoids discovered in A. galanga rhizomes include galangin (3,5,7-trihydroxyflavone) and galangoisoflavonoid. The primary ingredients of *A. officinarum* include nine flavanols, galangin-3-methyl ether, galangin, kaempferide, kaempferol, quercetin-3-methyl ether, quercetin, apigenin, isorhamnetin, and rhamnocitrin; two flavanonols, pinobanksin, and pinocembrin; and epicatechin. Galangin is the main component discovered in high concentrations in *A. officinarum* [58].

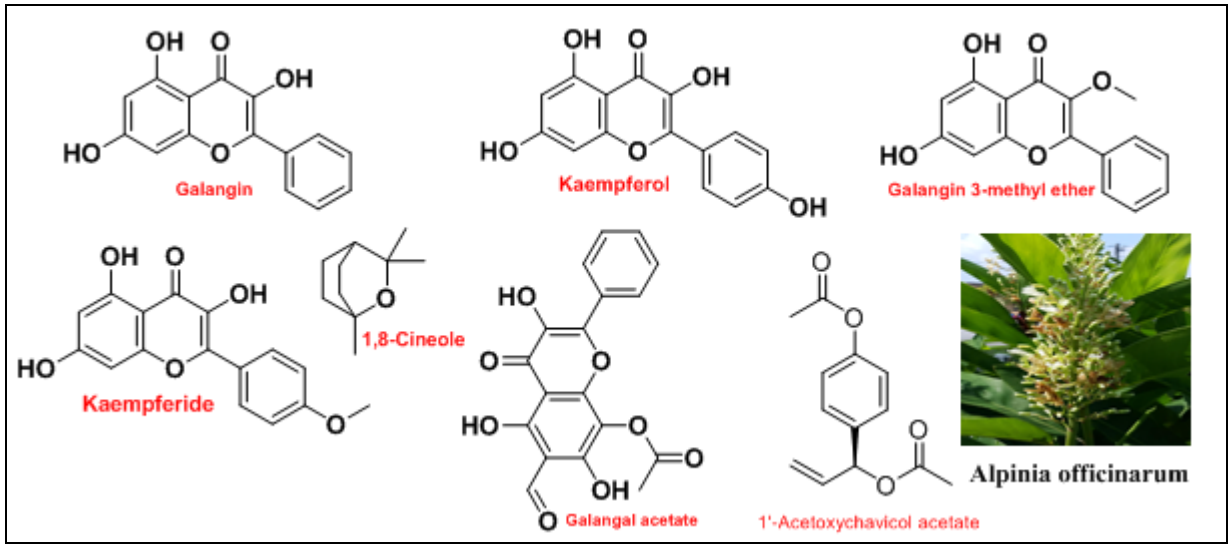

FIG. 11: SCHEMATICS OF THE PRINCIPLE COMPONENTS FOUND IN THE EXTRACT OF ALPINIA OFFICINARUM, THE VARIOUS BIOACTIVE AGENT GROUPS

CONCLUSION: The world of medicine is confronting significant challenges as the drug discovery process for neurodegenerative diseases becomes increasingly expensive, risky, and inefficient. A significant change from a single-target to a multi-target drug strategy is being observed, particularly for chronic and complex disease syndromes. Reverse pharmacology approaches (from the clinic to the bedside) also provide efficient research platforms for herbal formulations. In terms of diet and treatment options, the Ayurvedic medicine method has gained increasing attention in recent years. Without the knowledge of the mode of action, the early development of Ayurvedic herbal supplements needed only anecdotal or epidemiologic information (as well as both). The traditional Ayurvedic medicine sector has gone a long way since it was thought unnecessary to test Ayurvedic formulations before use, to several randomized, double-blind, controlled studies and to introduce industry-wide good manufacturing practice guidelines. 'Proof of thought' and a scheme of action shall be provided, it has adopted a more rigorous scientific and quality-enhanced approach. Since Ayurvedic therapeutics have been prescribed for decades for neurodegenerative diseases (including dementias), Western, mechanistic research investigations on AD have only recently been conducted; however, these mechanistic studies point to the same mechanisms addressed by Ayurvedic therapeutics (for example, increased in nerve growth factors and neurotrophic factors and reduction in inflammation and oxidative damage), providing strong support. It is hoped that Ayurveda's strong knowledge base, combined with combinatorial sciences and High-throughput screening methods will increase how simple it is to use Ayurvedic products. And formulations can be used in drug discovery campaigns and development processes, resulting in new functional leads for AD and other age-related neurodegenerative diseases. The goal is to provide new functional leads for AD and other age-associated neurodegenerative diseases, it is hoped that the robust Ayurvedic knowledge base will be combined with combinatorial sciences and high-throughput screening techniques to make it easier to use Ayurvedic products and formulations in drug discovery campaigns and development processes.

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CONFLICTS OF INTEREST: Nil

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