Perspectives on recent advance in the understanding and treatment of Alzheimer's disease

Sachin P. Bhatt*, Shruti M. Panchal, Rudri V. Diyora, Rudrika S. Gauswami,
Hema C. Rathod, Avani N. Joshi

Assistant Professor, Gyanmanjari Pharmacy College, Gujarat Technological University, Bhavnagar.
Student, Gyanamanjari Pharmacy College, Gujarat Technological University, Bhavnagar.
Student, Gyanamanjari Pharmacy College, Gujarat Technological University, Bhavnagar.
Gyanamanjari Pharmacy College, Gujarat Technological University, Bhavnagar.
Gyanamanjari Pharmacy College, Gujarat Technological University, Bhavnagar.
Assistant Professor, Gyanmanjari Pharmacy College, Gujarat Technological University, Bhavnagar.

ABSTRACT:
The most frequent cause of dementia in elderly people is Alzheimer's disease (AD), which is also a significant public health issue. Age, cerebral ischemia, toxin exposure, and oxidative stress are a few of the variables that contribute to the pathogenesis and progression of dementia. The current dementia treatments, such as cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) antagonists (memantine), only temporarily alleviate symptoms without addressing the primary underlying pathogenesis. Curcuma longa, Ginkgo biloba, Nigella sativa, Withaniasomnifera, Bacopamonnieri, convolvulus pluricaulis, Glycyrrhiza species, Saliva officinalis, Mellisaofficinalis, Centellaasiatica, Celastruspaniculatus, etc. are examples of ayurvedic medications. drugs are included in this, which is used for stress management through frequent exercise, acupuncture, and meditation. These methods have been shown to be effective in treating AD. Less than 105 people with Alzheimer's disease experience early onset, which is unusual. Although there is no known cure for Alzheimer's, there are treatments that could lessen some of the signs. Alzheimer's disease symptoms vary depending on the illness's stage. Loss of episodic short-term memory with comparatively preserved long-term memory is the initial and most prevalent presenting symptom, and it can be evoked in the majority of patients even when it's not present.Alzheimer's disease is an untreatable, progressive brain condition that gradually robs people of their ability to think clearly and perform even the most basic activities. Some of these are etiological risk factors for Alzheimer's disease, such as high blood pressure, head injuries, diabetes, ageing, genetics, and environmental variables.

I. A SUMMARY OF ALZHEIMER'S DISEASE:

Worldwide, Alzheimer's disease (AD) is regarded as a pandemic issue (Soheiliet al., 2020). It is a type of dementia that develops later and is characterised by progressive synaptic dysfunction and neuronal degeneration (Salami et al., 2020). The primary cause of dementia and one of the biggest medical care challenges of the twenty-first century is Alzheimer's disease (AD) (Konstantinaet al., 2020).

The world's population is ageing quickly, and by 2030, 65 million more people are anticipated to have dementia than there are now (Igor et al., 2014). Alzheimer's illness affects 5 million Americans, or 1 in 9, who are over the age of 65 (Igor et al., 2014). Progressive memory loss, impaired executive function, and challenges carrying out everyday tasks are all clinical signs of AD. Affective or unconscious shifts in behaviour are among the early signs of AD (Holtzmanet al., 2012).

A collection of clinical symptoms affecting memory, thinking, and social skills collectively referred to as dementia are characterised by a progressive decline in memory capacity and cognitive abilities. Age, cerebral ischemia, toxin exposure, and oxidative stress are a few of the variables that contribute to the pathogenesis and progression of dementia. Both clinically and in experimental animal models, dementia and Alzheimer's disease (AD) share a great deal in common. The most common type of dementia, AD, is defined by beta-amyloid protein buildup and deficiencies in cholinergic

neurotransmission in the brain (Alzobaidiet al., 2021). The current dementia therapy options, such as choline esterase inhibitors and N-methyl-D-aspartate (NMDA) antagonists (memantine), only provide temporary relief from symptoms without addressing the primary underlying pathogenesis. Many animal studies and clinical trials are being carried out to explain the trust elements and hopeful approaches in the prevention or treatment of dementia and to provide a rational approach to these medicinal plants and their derived lead molecules (Alzobaidiet al., 2021).

In late stage clinical studies, the majority of candidate drugs that target AB have failed to demonstrate clinical efficacy (Foroutanet al., 2019). The fundamental pathophysiology and neuropathology of AD, which is what motivates current research, indicates that the extracellular and amyloid plaques and the intracellular Tau neurofibrillary tangles (NFTS) are the main histopathologic lesions of AD (Yiannopoulouet al., 2013). Elderly patients with dementia will be seen by both primary care physicians and specialists more frequently as they advance in their professions (Igor et al., 2014).

An extensive range of tests are used in the examination of a person with suspected memory loss in order to characterise the cause of cognitive decline and pinpoint pathologies that are incurable. These evaluations consist of a thorough medical history, physical and mental state checks, fundamental lab work, and neuroimaging tests. Advanced brain imaging methods and neurophysiological tests may also be used as additional resources (E Bonsanget al.,2022). The search for particular causes of major neurocognitive disorder begins once reversible factors have been ruled out. For instance, a history of numerous strokes could indicate vascular dementia. Traumatic encephalopathy may be suggested by a history of brain trauma. The identification of an alcohol-related dementia may be supported by a history of chronic alcohol use disorder. The most common reason for progressive cognitive decline in people over 60 AD2(E Bonsanget al., 2022).

II. HISTORY OF DEMENTIA :-
Long before it was given a label, dementia has existed in human history. Ancient Egyptians were conscious that memory deteriorates with age around 2000 B.C. (Signoretet al., 2016).

Greek physician and mathematician Pythagoras (570–495 B.C.) divided a person's lifespan into six stages: infancy (ages 0–6), adolescence (ages 7–21), adulthood (ages 22–49), middle age (ages 50–62), senescence (ages 63–79), and old age (age 80 or older). Senescence and old age were among these phases, and some people who survived to this point were anticipated to degenerate in mind to the level of a suckling baby and eventually become stupid (Hyun et al., 2016).

Greek physicians Hippocrates (460–370 B.C.) and Plato (428–347 B.C.) held that brain damage causes cognitive disorders, and that old age itself is the primary cause of dementia because mental capacity is bound to inevitably decline. Instead, Marcus Tullius Cicero (106-43 B.C.), a Roman philosopher, politician, and jurist, noted that, with the exception of those with weak wills, ageing does not always result in a decline in mental function. He briefly stated that dementia is not a necessary result of ageing (Cicero et al., 2016).

Aretheus, a physician in Turkey in the second century A.D., classified dementia into two categories: dementia, an irreversible chronic disorder, and delirium, a reversible acute disorder of brain function (Donnetet al., 2016).

With the fall of the Roman empire in the fifth century and the subsequent reduction in funding, the medical and scientific research of dementia experienced a setback. Due to theocracy's dominance in the middle times as the era's spirit, there was a propensity to view dementia and other abnormal symptoms such as senility as a result of man's original sin (Albert et al., 2016).

In his play King Lear, which was published in 1608, the British playwright William Shakespeare (1564–1616) symbolically depicted the dementia symptom. King Lear is now regarded as one of the four greatest tragedies in English writing(Roman et al.,2016).

The most typical cause of progressive dementia in the elderly populace is Alzheimer's disease. It is a long-term neurodegenerative condition that causes progressive disturbances in memory, judgement, decision-making, orientation to one's bodily environment, and speaking (Ellis et al., 2003). Selective neuronal and synaptic losses, extracellular neuritic plaques containing the beta-amyloid peptide, and neurofibrillary tangles (NFTs) made up of hyperphosphorylated tau protein are typical neuropathological observations (Delacourte et al., 1995). The German psychiatrist Alois Alzheimer first reported the clinical symptoms of dementia in 1906 at a conference in Tübingen, along with the histological findings of amyloid

plaques and NFTs (Maurer et al., 1997).An estimated 5% of people over the age of 65 are thought to have Alzheimer's disease (Bullock et al., 2004). Beyond age 65, the prevalence doubles roughly every five years, and some studies indicate that nearly half of those 85 and later suffer from this devastating condition (Forsyth et al., 1998). Acetylcholinesterase (AchE) inhibitors for mild to moderate cases and memantine, an NMDA (N-methyl-D-aspartate)-receptor antagonist for the treatment of moderate to severe Alzheimer dementia are among the current medicines approved by the FDA for the treatment of Alzheimer's disease. Some of the patients appear to benefit modestly from symptomatic benefits from all of these medications(Clarket al., 2003).A small percentage of Alzheimer's disease (1%–2%) is transmitted in an autosomal dominant manner (ADAD), which can cause very early onset and a rapid rate of progression. It is also occasionally accompanied by other neurologic symptoms that are less common in sporadic AD (Bateman et al., 2012).

III. EPIDEMIOLOGY :-

Alzheimer's disease epidemiology Due in part to their longer lifespans, women have a greater incidence and prevalence of AD, which rises with age. Between the ages of 65 and 70 and over the age of 85, AD prevalence is between 1% and about 4%. More than 1.3 million new instances are anticipated in the United States annually by 2050, up from about 420,000 in 2000. (Hebert et al., 2005). The lowest reported estimate of AD prevalence is 3% of the population at age 65, and the highest reported estimate is 47% of persons over the age of 85. The number of Americans with AD was expected to be 4.5 million in 2000 (Hebert et al., 2005).This figure will nearly triple by 2050, reaching 13.2 million. With about 63,000 deaths annually and a death rate of 21.8 per 100,000 people in the US, AD is presently the eighth leading cause of death (Hoyeret al., 2005). Approximately 6% more people die from AD every year. Recent estimates place the median survival from the time of the initial diagnosis at 4.2 years for males and 5.7 years for women (Larson et al., 2005).
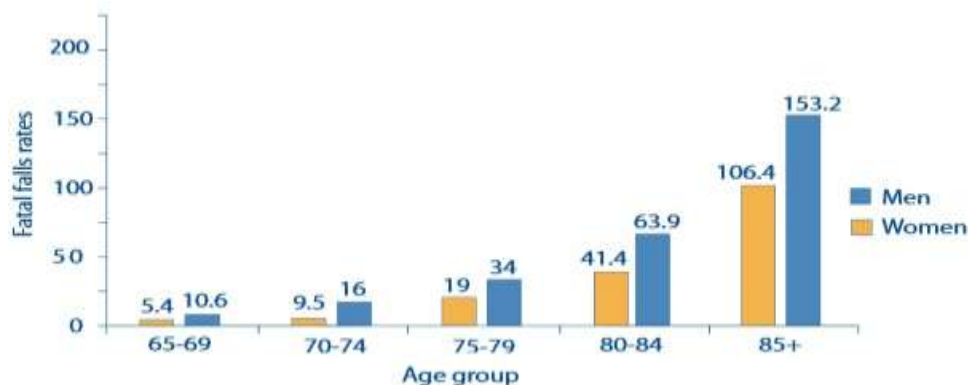

Figure 1: Fatal fall rates by age and sex group for epidemiology of Alzheimer disease (Adopted From: Aysegulet al., 2015).

By age category and gender, fatal falls are shown in Figure 1. For both sexes, the incidence of fatal falls rises with age, reaching its peak at 85 years and older. Men described being in worse health and having more underlying conditions than women, according to research. These include an elevated chance of hip fracture and demise (Aysegulet al., 2015).
ETIOLOGY :-
Risk factors from both the surroundings and genetics can contribute to the development of AD. Age is the biggest risk factor; at age 65, the chance of having AD is only about 3%, but by age 85, it is over 30%. Uncertainty surrounds the prevalence of AD in people under the age of 65, but estimates place the number of cases in this age category at about 3%. Age-specific incidents appear to be declining in a number of nations, despite the fact that total numbers are rising due to the ageing population (Sheppard et al.,2020).

AD can be categorised according to when it appears and whether it is hereditary. Early-onset Alzheimer's disease (EOAD) develops before the age of 65, while late-onset Alzheimer's disease (LOAD), which affects 95% of cases, does not appear until after the age of 65. Mendelian inheritance is evident in common AD, but there is

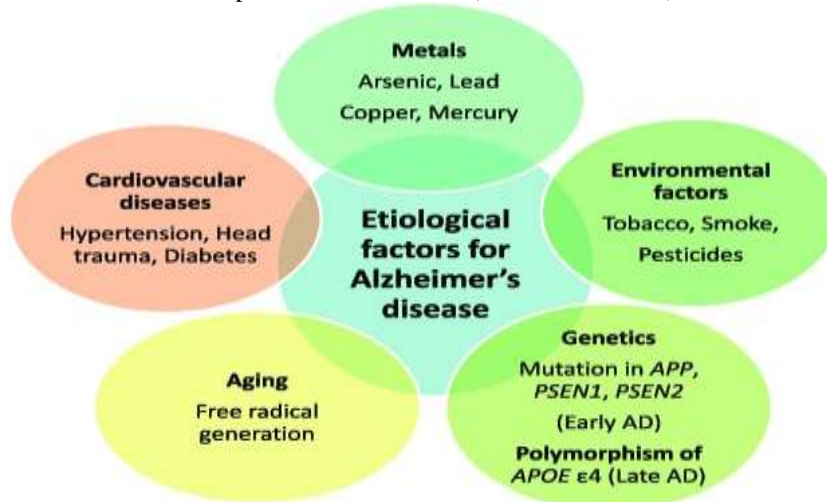no clear familiar connection in sporadic AD (Mihaelet al.,2020).

Figure 2: Etiological factors for Alzheimer's disease (Adopted From: Pallaviet al., 2019).
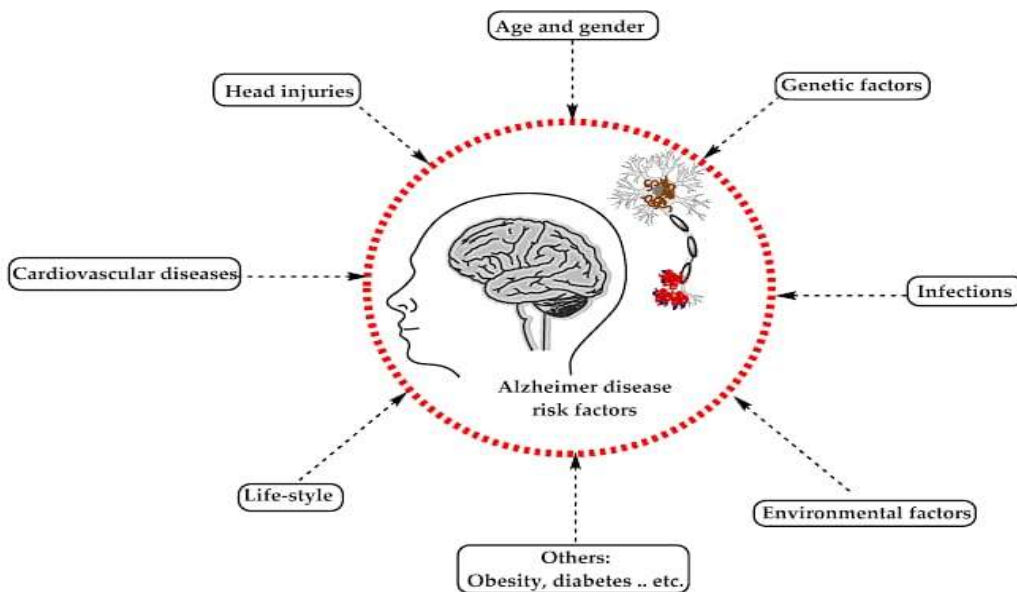
IV. RISK FACTOR:-

Figure 3: Risk factors for Alzheimer Disease (Adopted From: Zeinab et al., 2020)

V. SIGN AND SYMPTOMS :-

The management of these incapacitating non-cognitive dementia manifestations depends heavily on recognition and thorough evaluation. Families and carriers of BPSD experience substantial distress, and the condition is linked to high rates of carrier depression, stress, and burden. Additionally, BPSD frequently triggers the need for residential care, results in substantial declines in function and quality of life, and is linked to a higher mortality rate for dementia patients. Studies examining the incidence and persistence of BPSD have been highly heterogeneous (Eratneet al., 2018).In general, BPSD will manifest itself in the majority of dementia patients at some point during their disease. Before cognitive and functional deterioration and the diagnosis of AD, depressive symptoms may be present. 1 As the disease worsens, irritability, agitation, and psychosis frequently appear. The prevalence of BPSD tends to increase during the moderate to severe phases of dementia and decline during the disease's final stages. Apathy and hyperactivity are examples of symptoms that typically exhibit high persistence,

whereas sadness and psychosis exhibit low to moderate and low persistence, respectively

(Eratneet al., 2018).

Figure 4: Symptoms for Alzheimer Disease (Adopted From: Jadoopat et al., 2018)
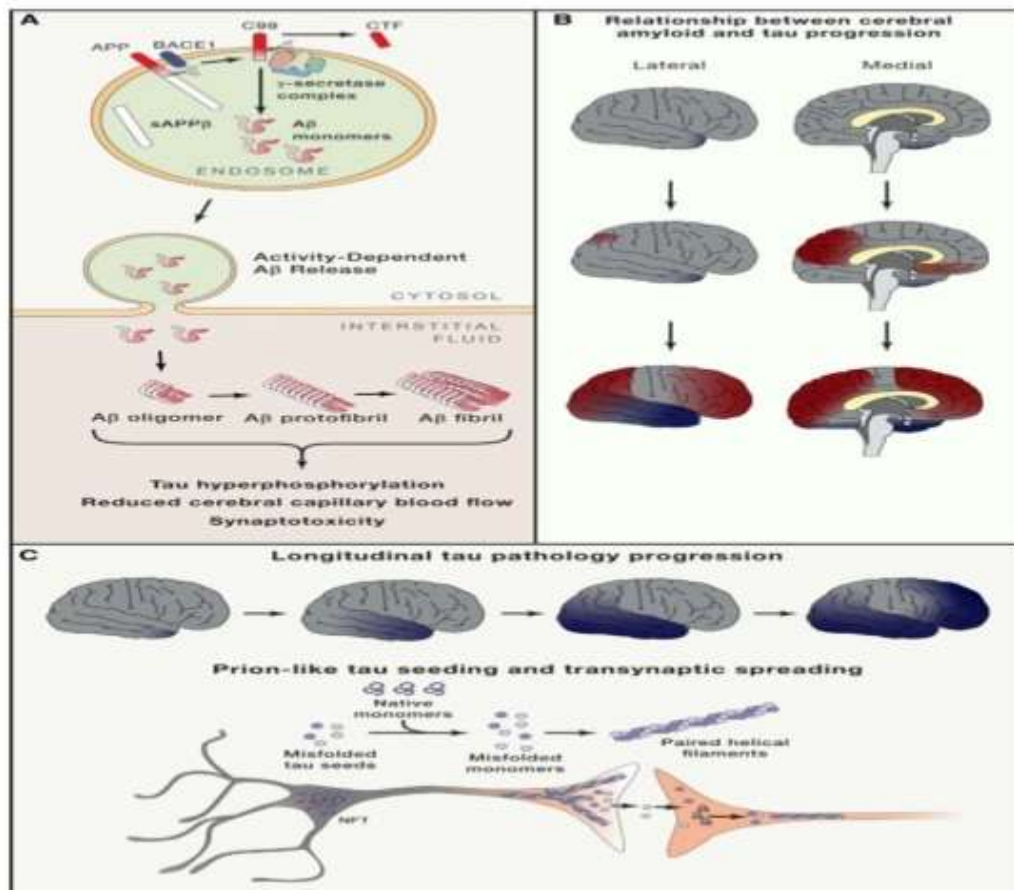
VI. PATHOPHYSIOLOGY :-

Figure 5: Pathophysiology of Alzheimer Disease (M. long et al., 2019).

HERBAL TREATMENT OF ALZHEIMER'S DISEASE :-

Amyloid protein buildup and deficiencies in cholinergic neurotransmission are hallmarks of ageing or cognitive disorders. Unfortunately, existing dementia therapies like choline esterase inhibitors, N-methyl-D-aspartate (NMDA) antagonists (memantine), and calcium channel blockers only temporarily relieve symptoms. They do not address the primary underlying pathogenesis

of the disease (Alzobaidiet al., 2021).Memantine, a relatively weak NMDA receptor antagonist, was authorised by the FDA for use in AD patients in 2003 who had moderate to severe cognitive impairments. It is known to stop synaptic loss and neuronal damage brought on by the upregulation of NMDA receptors. Natural products and non-pharmacological interventions seem to be promising and safer alternative approaches with a positive impact on cognitive behaviours, thus they should be the main strategies in the treatment of memory impairment. Conventional therapies have numerous side effects and fail to improve cognitive decline (Alzobaidiet al., 2021).

1)   Ginkgo Biloba :
        One of the most unique plants in the Ginkgoaceae family is Ginkgo Biloba. The genome of ginkgo biloba is vast, and it has a high level of plant resistance. Pathogens and additional environmental factors, such as hot temperatures, elevated soil temperatures, and salinity (Alzobaidiet al., 2021). Ginkgo extract contains flavonoids, terpenoids (including Ginkgolides A, B, C and J and bilobalide), glycosides (including quercetin, kaempferol, isorhamnetin, etc.), and organic acids (Sharma et al., 2019). Ginkgo Biloba extract has demonstrated efficacy in the treatment of Alzheimer's disease, cancer, neurovascular disease, deafness, and other age-related conditions(Gregory et al.,2021).In several experimental rat models of dementia and chronic stress, standardised GB extracts significantly ameliorate cognitive dysfunction, attenuate oxidative stress, and decrease tissue damage after brain ischemia (Alzobaidiet al., 2021).

        A single dose of EGb761 (90 mg/kg) in the rat brain achieves its peak concentration after 1 hour and maintains measurable levels for 6 hours, demonstrating the high cerebral bioavailability of ginkgo biloba. To evaluate the safety issues and possible drug interactions, additional animal studies and clinical trials are needed (Alzobaidiet al., 2021).

2)   Withaniasomnifera :
        A common ayurveda herb known as Indian ginseng, Withaniasomnifera, ashwagandha, or other members of the Solanaceae family are used for their teratogenic and anti-stress properties (Alzobaidiet al., 2020). President has found that withaniasomnifera treatment significantly lowers corticosterone levels in mice than vehicle treatment does in mice that are exposed to restraint stress for 30 days (John et al., 2020). It is well known to have a variety of medicinal uses, including as a nerve tonic, a memory enhancer, and a plant medicine with anti-stress, immunomodulatory, and anti-oxidant qualities (Alzabaidiet al.,2021).

        When examining the therapeutic potential of an unidentified substance, toxicology studies are crucial to take into account. There is a dearth of systematic research on W. somnifera that examined the acute, subacute, subchronic, or chronic toxicity of the root powder, as well as the whole plant powder of various plant extracts (water, alcohol, petroleum ether, purified alkaloids, and glycosides) (Singh et al., 2017).

        50 participants with mild cognitive impairment participated in a prospective, randomised, double-blind, placebo-controlled pilot trial where they were given either ashwagandha root extract (300 mg twice daily) or a placebo for eight weeks following the study (Gregory et al., 2021).

3) Bacopamonnieri :
        Brahmi, also known as bacopamonnieri, is a creeping, succulent plant grown in the wetlands of the Indian subcontinent. It is a member of the scrophulariaceae family. Brahmi herb has been used for a long time in Indian ayurvedic medicine to treat cognitive impairments brought on by ageing of the brain (Alzobaidiet al., 2021). Brahmi'sbacoside metabolites can pass through the blood-brain barrier (BBB) with ease and enhance cognition by boosting blood flow, though not necessary through direct interactions with neutral cells. The impact of brahmi extract on amyloid-induced AD in PSAPP rodents was examined by Holcomb et al.The results of the research showed that brahmi extract can reverse Y-maze performance and open field hyperlocomotion in mice, as well as reduce amyloid plaque in their cortex. Behaviour It was discovered that taking brahmi extract orally for 14 days at a dose of 30 mg/kg greatly improved learning and memory (Alzobaidiet al.,2021).

Le et al. assessed in vitro and in vivo the effects of an ethanolic extract of B. monnieri that contained 22% bacoside-A and 11% bacopaside on cognitive function (Fuentes et al., 2021). Rats given centellaasiatica extract showed a substantial improvement in their cognitive behaviours. After extract was given at doses of 200 and 300 mg/kg, the greatest reaction was seen (Fuentes et al., 2021).

4) Convolvuluspluricaulis :

Convolvulus pluricalius is a perennial, wild, prostrate plant that is primarily found in northern India. It is a member of the Convulvulaceae family. It is typically utilised in the ayurveda medical system as a nervine tonic (Mehlaet al., 2020).

Ayurveda recognises sankhpushpi as a "medhyarasayana," or a substance that revitalises, sustains, and enhances memory and intelligence. based on their capacity to treat conditions linked to memory and their flower-like shape. Triterpenoids, flavanol glycosides, anthocyanins, and steroids are the main molecular components and are what give Cp its nootropic and memory-improving effects (Gregorgyet al., 2021).

5)Curcuma longa:

The spice turmeric is derived from a plant called curcuma longa-haldi, and it is used in curries and other hot foods from India, Asia, and the Middle East. Similar to many other herbal medicines, curcumin was first used as a food before people realised it also had powerful medicinal properties (Shrikantet al., 2008). The ginger plant, Curcuma longa, is believed to have originated on the Indian subcontinent and is a part of the zingiberaceae family. It is produced commercially in India, China, and many other tropical south Asian countries. To flourish, it requires temperatures between 20 and 30 °C and a sizable amount of annual rainfall(Niteshet al., 2012).

Dietary curcumin has shown preventive action against carcinogenesis in the skin, colon, forestomach, and duodenum in studies on rodents and mice. Curcumin inhibits specific T-cell proliferation pathways that are resistant to cyclosporine, making it a possible adjuvant immunosuppressive agent for the therapy of cancer. A study of curcumin in 60 individuals with HIV infection was prompted by case reports of decreases in p24 antigen following consumption of 2.5 g of curcumin daily for seven days. (Hataet al., 2012).

6)Glycyrrhiza Genus:

Liquorice, also known as glycyrrhiza, is a perennial herb that grows in Iran, Southern Russia, Asia, and the Mediterranean area. Glycyrrhiza comes from the Greek words glykys, which means "sweet," and rhiza, which means "root" (Alzobaidiet al., 2021). The sweet-tasting triterpenesaponin glycyrrhizin (glycyrrhizic acid) and the phenolic compound isoliquiritigenin are the primary bioactive phytoconstituents of glycyrrhizaglabra (liquorice) root (Tewariet al., 2018).

Several isoflovonoid derivatives, such as shinpterocarpil, glabrone, glabridin, glabrene, and lico-isoflavones A and B, are also significant components (Tiwari, et.al 2018). Asthma, tonsillitis, sour tongue, hyperdipsia, flatulence, epilepsy, fever, sexual debility, paralysis, coughs, stomach ulcers, indigestion, colic, swellings, skin conditions, and jaundice are just a few of the diseases that licorice has historically been used to treat (Mohamed et al., 2020).

7)SalivaOfficinalis:

There are about 900 species in the genus Saliva (Lamiaceae), some of which are commercially significant due to their use as spices and flavourings (Longarayet al., 2007). Saliva officinalis L. is grown as both a culinary herb and a plant with significant medicinal value. Sage's therapeutic benefits have long been known, and antihydrotic effects have been documented.(Kintzioset al., 2000).

Chinese medicine uses the plant Saliva officinalis L. for a variety of purposes. As an antibiotic, antihydrotic, astringent, and antifungal agent, it has a lengthy history of use. The plant S officinalis is well known for its antioxidant properties because its leaf extract contains the primary component ursolic acid, a pentacyclictriterpenoid carboxylic acid, which can successfully lower the level of lipid peroxidation and effectively reverse D-galactose-induced learning and memory impairment.(Tzonget al., 2011).

8)MellisaOfficinalis:

The age-related neurodegenerative disease AD is acknowledged as one of the major health issues impacting the elderly. It is known that excessive neuronal loss, a drop in Ach levels, a rise in inflammation, and OS all contribute to brain ageing (Nieet al., 2009).

The most popular AD therapy method has involved using "cholinesterase inhibitors" in an effort to restore acetylcholine levels in the brain, according to the "cholinergic hypothesis" of AD (Perry et al., 1986). However, it has been demonstrated that some of these AD medications have a number of side effects and provide only a modest advantage (Van et al., 2008).

As a result, there is still a high demand for the development of novel therapeutic options for the treatment of AD. Due to their anti-

amyloidogenic, antioxidant, and anti-inflammatory properties, some naturally occurring dietary phytochemicals have drawn significant attention as alternative options for AD therapy (Francis et al., 1999).

9)Centellaasiatica:

Alzheimer's disease (AD) is a neurological condition that progresses and causes severe dementia in older people. The appearance of abnormal tau protein filaments in the form of neurofibrillary tangles and deposits of amyloid fibrils in sensile plaques are two of the neuropathological hallmarks of AD (Anil et al., 2009). The main neural systems involved in the pathophysiology of AD are the cortex, limbic system, and hippocampal regions. Oxidative stress has been implicated in the onset and development of AD, and the etiopathogenesis of this disease is multifactorial. Given the mechanistic elements, it has been determined that -amyloid aggregates and iron accumulation both work in concert to produce free radicals, which in turn cause oxidative damage (dograet al., 2009).

10)NigellaSativa:

The annual herbaceous plant Nigella sativa L. (also known as N. sativa) is extensively cultivated throughout the Mediterranean region, western Asia, the Middle East, and Eastern Europe. It is a member of the ranuncuiaceae family. For seasoning, N. sativa seeds have been used in a variety of Iranian dishes, including bread, pickles, sauces, and salads (Mohammad et al., 2015). Thymoquinone (TQ), which is the main component of N. sativa that is active, has the ability to treat a variety of inflammatory conditions such as encephalomyelitis, colitis, edoema, and arthritis by inhibiting prostaglandins and leukotrienes, two inflammatory mediators (Mohammad et al., 2015).

The safety profile of NS for human consumption and conventional nutritional applications has undergone considerable research (Ramadan et al., 2007). In various animal models, it has neuroprotective, nephroprotective, lung protective, cardioprotective, and hepatoprotective properties.
Traditional medicine has recognised the curative properties of Nigella sativa (NS). It has been used in the Middle East and the Far East to address conditions like gastrointestinal issues, asthma, headaches, dysentery, infections, obesity, and back pain. Islamic belief is that NS is beneficial for all illnesses, with the exception of mortality.(Beheshtiet al., 2014).

11)Celastruspaniculatus:

It is also known as malkangni, a climber and a popular medicinal plant that is a member of the Celastraceae family. Celastrine, paniculatine, celapanin, celapanigin, and celapagin compounds are present in the plant (Khandayet al., 2019).
Malkangani was discovered to increase cholinergic activity in a study, which adds to its capacity to enhance memory function. Another research found that malkangni's aqueous extract has antioxidant and brain-improving qualities (Bashir et al., 2019).

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No.	Short name	Full form
1.	NMDA	N-methyl D- aspartate
2.	NFTs	Neurofibrillary tangles
3.	FDA	Food and drug administration
4.	AchE	Acetylcholinesterase
5.	ADHD	Attention deficit hyperactivity disorder
6.	BPSD	Behavioral and psychological symptoms of dementia
7.	BBB	Blood brain barrier
8.	HIV	Human immunodeficiency virus
9.	AD	Alzheimer disease