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Nature's Arsenal Against Alzheimer's: A Comprehensive Review of Herbal Remedies and their Therapeutic Potential

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Abstract:- Extracellular amyloid-beta (Aβ) plaques and intracellular accumulation of neurofibrillary tangles are indicative of the prevalence of Alzheimer's disease (AD), a neurological illness that impairs memory and learning. It is now imperative to find new therapeutic medicines with more efficacy and fewer adverse effects due to the aging population and rising incidence of AD. Conventionally, a range of synthetic drugs are used to treat symptoms and prevent the advancement of the condition. These drugs include tacrine, donepezil, galantamine, rivastigmine, memantine, glutathione, ascorbic acid, ubiquinone, ibuprofen, and ladostigil .The spotlight has shifted to herbal medicines due to their perceived effectiveness and minimal side effects. Due to their potential to alleviate symptoms associated with neurological illnesses, Lavandula angustifolia, Ginkgo biloba, Melissa officinalis, Crocus sativus, ginseng, Salvia miltiorrhiza, and Magnolia officinalis have become more well-known. This article provides an overview of the therapeutic effects of these phytomedicines, showcasing their impact on various factors related with Alzheimer's.

Keywords:- *Alzheimer, Traditional use, Phytochemistry, Pharmacology, Therapeutic.*

I. INTRODUCTION

Alzheimer's disease (AD) is a neurological illness that is more common in the elderly. In 1906, German neuropathologist and psychiatrist Alois Alzheimer made the discovery of AD. Alzheimer's disease accounts for the majority of dementia cases, which affect over 24 million individuals globally (Ballard et al., 2011). Memory loss, behavioral issues, cognitive impairment, and cognitive delay are characteristics of AD. Major depression and this circumstance are comparable (Squire, 1992). Cognitive and mental problems result from the accumulation of oxidative damage to proteins, mitochondria, and nucleic acids in the brain. SMC prevalence, age, gender, education, mood, and cognitive function were all related.. 24% of adults between the ages of 65 and 69 have SMC. SMC rose by 57% in those 90 years and older. The incidence of cognitive impairment in individuals with anxiety and depression stands at 52.8%, as reported by Montejo et al. in 2011. Amnesia can be induced by psychological stress or substance abuse. While numerous allopathic medications are available for Alzheimer's disease (AD) patients, they often come with adverse effects. Consequently, herbal remedies may offer a viable alternative for the treatment of Alzheimer's and memory deficiencies, with minimal to no side effects. This article explores various herbs with demonstrated efficacy in managing Alzheimer's and memory-related disorders. In the hippocampus, cortex, and subcortical brain regions, neuronal degeneration and the loss of synaptic connections are the main pathogenic processes driving these diseases. Serious repercussions in the impacted areas may result from this loss, such as amnesia, difficulties learning new knowledge, mood fluctuations, decreased functional capability, and an inability to carry out daily tasks (ADLs). Because they have lost their memory and their sense of time and location, patients in the advanced stages of AD require continuous care. It is generally accepted that treatments that can postpone the start or course of AD will help lower the number of individuals afflicted with this illness during the next fifty years.[1,2] Intracellular neurofibrillary tangles (NFTs), which are made up of abnormally folded and hyperphosphorylated isoforms of the microtubule-associated protein tau, are frequently seen within Alzheimer's disease (AD)-affected cells. [3, 4]. According to research, the inability of these mutant, erratic, and hyperphosphorylated tau proteins to correctly regulate microtubule growth and function leads to microtubule network instability, which is a hallmark of Alzheimer's disease.[5] With the failure of beta-amyloid-targeting clinical studies, attention is now being directed toward targeted therapeutics. However, recent failures involving targeted drugs have revealed a basic ignorance regarding the pathophysiology of AD [6]. This emphasizes the need to take into account additional pathophysiological factors that may contribute to AD. These factors may include autophagy, unfolded protein response, oxidative stress, neuroinflammation, metal ion toxicity, neurotransmitter excitotoxicity, intestinal dysbiosis, cholesterol metabolism, and insulin/glucose dysregulation [7]. Alternative therapeutic approaches that address all of these pathophysiological aspects are crucial given the history of failed pharmacological therapies targeting tau or amyloid and the urgent need for a safe and effective treatment for AD. [8,9]

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II. ETIOPATHOGENESIS

The neuropathological changes associated with Alzheimer's disease (AD) are twofold and provide information about the course and manifestations of the disease. Neurofibrillary tangles, amyloid plaques, dystrophic accumulating neurites, neuropil, and other brain deposits are indicative of positive disease symptoms. Macroscopic atrophy is linked to this disorders. The loss of blood vessels, nerves, and synapses in AD patients causes negative disease symptoms. Neurodegeneration may also be exacerbated by elements like oxidative stress, neuroinflammation, and harm to cholinergic neurons.

Senile Plaques (SP): Neuritic, diffuse, dense, classical, and dense plaques are among the different morphologies of extracellular deposits of β-amyloid (Aβ). Proteases such as β- and γ-secretase mediate the biosynthesis of Aβ deposits from the transmembrane amyloid precursor protein (APP). Aβ40 and Aβ42 are two prominent examples of the Aβ fragments that are produced by this process. There are two types of Aβ: soluble oligomers that can travel throughout the brain and insoluble amyloid fibrils that help form amyloid plaques. The presence of dense plaques in areas such as the hippocampus, amygdala, and cerebral cortex causes brain damage, axon and dendrite loss, synaptic damage, and harm to microglia and astrocytes. Aβ is closely associated with neurotoxicity and neurological function. Hyperphosphorylated tau protein can form abnormal fibers called neurofibrillary tangles (NFTs), which can also take the form of paired helical fibers (PHF). The pericytoplasm, axons, and dendrites become clogged with these tangles, which leads to the loss and deterioration of cytoskeleton proteins. In the AD brain, hyperphosphorylated tau makes up a significant portion of NFTs. These tangles progress through several stages: the mature NFT stage (marked by filamentous tau protein aggregates), the extracellular tangle stage (located extraneurally), and the pre-entanglement stage (PHF without phosphorylated tau). early stages of synaptic loss.[10] [11] [12]

III. DIAGNOSIS

Routine clinical examinations did not reveal any specific abnormalities. Standard tests, including complete blood count (CBC), complete metabolome (CMP), thyroid stimulating hormone (TSH), and vitamin B12 levels, are typically conducted to rule out other potential causes. Brain CT scans indicated brain atrophy and an enlarged third ventricle, but these findings are not exclusive to Alzheimer's disease and can also be observed in individuals with various other conditions and age-related changes [5].In the preclinical stage, low β-amyloid 42 levels and high tau protein levels in cerebrospinal fluid (CSF) analysis provide supportive evidence for the diagnosis. Electroencephalograms (EEGs) often display slow wave patterns without specific focal points, which can be informative but not entirely conclusive. The most reliable method for detecting early-stage suspicions of the disease is through neuropsychological examinations. Recently, volumetric MRI has been employed to assess brain changes. In Alzheimer's disease, volumetric MRI typically reveals atrophy of the middle temporal lobe. However, it's important to note that hippocampal atrophy can also be associated with normal age-related memory changes, raising questions about the utility of volumetric MRI for early Alzheimer's disease detection.[13] [14] [15]

➢ *Clinical Interventions used for Alzheimer's:*

- *Tacrine (Cognex):*

Tacrine is an inhibitor of cholinesterase that also affects ion channels and monoamines. Under the commercial name Cognex, it was first created in 1945 by Adrian Albert at the University of Sydney and is presently used to treat Alzheimer's disease. Moreover, it inhibits the enzyme histamine N-methyltransferase. Tacrine has poor cholinesterase activity (48.2%) and limited efficacy (41.2%) in treating Alzheimer's disease, but it has strong anti-inflammatory qualities (74.1%) and can be used as a breath stimulant(68.4%) as per PASS data..

- *Memantine (Namenda):*

An NMDA receptor antagonist called memantine is used to treat Alzheimer's symptoms. It was first created and patented by Eli Lilly and Company in 1968 as an anti-diabetic medication. Later, it was shown to have activity in the central nervous system, and in 1989 it was made available as a dementia treatment in Germany under the brand name Axura. Memantine is now sold all over the world under a number of brand names, including Namenda in the US.

- *Velnacrine:*

A tacrine derivative called velnacrine was once used to treat Alzheimer's patients. However, because of the drug's toxicity to the central nervous system, the FDA's Peripheral Drugs Advisory Committee recommended against using it in 1994. It is less successful in treating Alzheimer's disease (46.5%) despite having similar acetylcholinesterase inhibitory characteristics (50.1%).

- *Rivastigmine:*

Marta Weinstock originally created rivastigmine at the Hebrew University of Jerusalem School of Pharmacology. Novartis eventually purchased the drug for use in commercial applications. Since 1997, this medication—a semisynthetic derivative of the hazardous alkaloid physostigmine—has been offered in liquid and capsule form. It was the first medication licensed globally in 2006 to treat mild to moderate dementia brought on by Parkinson's disease. High acetylcholinesterase activity (70.4%) but comparatively poor treatment efficacy (50.7%) for Alzheimer's disease are suggested by PASS analysis.

- *Donepezil (Aricept):*

In more than 50 countries, donepezil, also known as Aricept, is a drug used to treat Alzheimer's disease. One of the more selective acetylcholinesterase inhibitors, both natural and synthetic, donepezil is known for its advantageous pharmacological profile when it comes to improving cognitive function. PASS findings show that it

works well as an acetylcholinesterase inhibitor (85.7%), is well suited for treating myasthenia gravis (91.1%), and has a moderate efficacy (49.6%) in treating Alzheimer's disease. Furthermore, 51.2% of respondents believe that this medication may be useful in avoiding Huntington's disease.[16][17][18}

➢ *Herbal Drugs used in Alzheimer :*

- *Salvia Miltiorrhiza :*

Salvia miltiorrhiza is a member of the Lamiaceae family and has widely spaced, branching stems and leaves. There is a long history of using this plant to cure a variety of illnesses. As seen in Figure 5, the main active ingredient in S. miltiorrhiza is cryptotanshinone. It exhibits diverse pharmacological properties, including anti-acetylcholinesterase (AChE) activity, neuroprotection against toxicity, anti-inflammatory effects , antioxidative properties , and anti-apoptotic actions . It has been observed that cryptotanshinone can improve deficiencies in spatial learning and lessen the accumulation of amyloid-beta (Aβ). Through modulating the gamma-secretase pathway, it prevents the production of Aβ plaque and lessens the harm that glutamate causes to neurons . Cryptotanshinone has been shown to have a major positive effect on memory impairment and to mitigate cognitive impairments. Another polyphenolic product from S. miltiorrhiza, salvanolide acid, has an impact on Alzheimer's disease (AD) symptoms and exhibits antioxidant and anti-inflammatory properties. It demonstrates dose-dependent characteristics in inhibiting Aβ self-aggregation and deconstructing Aβ fibrils, protecting cells from the neurodegenerative consequences of Aβ fibrils. Salianolic acid promotes neuronal development and increases the expression of brain-derived neurotrophic factor (BDNF), as Zhang et al. have shown. Salvianolic acid lowers lipid peroxidation and shields the PC12 cell line from H2O2-induced neurotoxicity. It preserves the activity of antioxidant enzymes, intracellular calcium levels, and caspase-3 enzyme under normal conditions. Zhang and colleagues have also shown that salvianolic acid decreases lactate dehydrogenase leakage, thereby safeguarding neuronal cells against H2O2-induced damage.[19]

- *Panax Ginseng :*

The root of a plant belonging to the Panax genus in the Araliaceae family, Panax Ginseng, is used extensively in traditional medicine. The principal pharmacological actions of this hand-picked herb are attributed to its high concentration of triterpene glycosides, also referred to as ginsenosides, which are naturally found in hilly places. The polyphenol-rich ginseng aqueous extract exhibits strong antioxidant qualities. This herbal treatment increases the activity of the SOD enzyme while efficiently scavenging free radicals, including hydroxyl and superoxide anions [20].Ginseng extract has been proven in studies by Choi and colleagues to be able to prevent neuro-inflammation and neuronal death. By impeding the hyperphosphorylation of tau proteins, ginseng prevents the formation of neurofibrillary tangles. Moreover, it efficiently inhibits the BACE1 enzyme, which lowers the amounts of Aβ. Ginsenosides stimulate the hippocampal production of brain-derived nerve factor (BDNF), an essential neuromodulator of learning and memory functions. This is supported by biochemical and behavioural tests that validate ginseng's capacity to reduce stress-related deficits in memory and learning. As a result, it is hypothesized that this herbal medicine may be useful in reducing the memory loss associated with Alzheimer's disease (AD).According to studies, ginsenoside increases the level of acetylcholine (ACh) in cultivated PC12 cell lines by inhibiting the activities of butyrylcholinesterase (BchE) and acetylcholinesterase (AChE). Furthermore, in an animal model of AD, it reinstates choline acetyltransferase activity . Ginseng also exhibits neuroprotective properties by suppressing glutamate-induced toxicity in AD .[21]

- *Melissa Officinalis:*

Lemon balm, or Melissa officinalis, is a plant that belongs to the Lamiaceae family. This herbal remedy has been employed to improve motivation and behaviour in individuals with dementia disorders .[22] It offers a range of health benefits, including antioxidant , antidepressant , anxiolytic , and anti-inflammatory activities. Its main active ingredients, flavonoids, phenolic acids, and triterpenes, are responsible for these medicinal effects[23]. Ez and associates carried out an investigation that confirmed M. officinalis's ability to lower intracellular ROS production in both aqueous and methanol extract forms. It has been demonstrated that certain M. officinalis compounds, including flavonoids, caffeic acid, and rosmarinic acid, have antioxidant qualities. Through lowering MDA levels, raising GSH, and improving the activity of Paraoxonase 1, one of the key enzymes involved in detoxifying oxidative stress mediators, this herbal remedy demonstrates its strong antioxidant impact. It also exhibits antioxidant activity through lipid peroxidation inhibition, free radical scavenging, and protection against H2O2-induced oxidative stress. In a scopolamine-induced dementia model, Soodi and colleagues showed that the ethanol extract of M. officinalis improves learning and memory. They attributed this cognitive support to its inhibitory effect on AChE activity. For those suffering from Alzheimer's disease (AD), the herb improves cognitive function and reduces neural excitability. Research suggests that M. officinalis may alleviate certain symptoms in AD patients by acting on ligand-gated and ion channels, as well as the serotonergic system. It has been demonstrated that gallic acid, an important component of M. officinalis, lowers matrix metalloproteinase-2 activity, which is pertinent to AD. Additionally, this medicinal plant reduces Aβ-induced neurotoxicity, demonstrating neuroprotective properties. All things considered, M. officinalis's many medicinal properties—especially its anti-cholinesterase, antioxidant, and anti-neurotoxicity properties—make it a strong contender to reduce the symptoms of neurodegenerative illnesses like Alzheimer's disease.[24]

- *Crocus Sativus :*

Saffron, or Crocus sativus, is a plant that belongs to the Iridaceae family and has been used in traditional medicine for a very long time. Numerous health advantages, such as anti-inflammatory effects, free radical scavenging

properties, and neuroprotective qualities, are linked to this herbal plant. Saffron's primary sources of antioxidant activity can be traced back to its phenolic and carotenoid compounds . Many of saffron's therapeutic effects can be attributed to one of its primary active phytochemical constituents, known as crocin. Crocin exerts multifaceted pharmacological activities, encompassing antioxidant functions , inhibition of peroxidized lipid formation , restoration of superoxide dismutase (SOD) activity , preservation of neuronal integrity , and maintenance of neuronal morphology . This chemical has strong reactive oxygen species (ROS) scavenging abilities despite its comparatively low stability. The good effects of crocin on memory enhancement and cognitive improvement are supported by empirical evidence. Additionally, crocin plays a critical function in altering the plasticity of synaptic transmission within neural circuits, which is a crucial neuronal process underlying learning and memory events.Research has also shown that mild to moderate depression and other mental health issues can be effectively treated with this stemless flowering plant.[25]

- *Lavandula Angustifolia:*

Lavender, or Lavandula angustifolia, is a native aromatic shrub of the Lamiaceae family that grows naturally in the Mediterranean region. Traditional medical practices have long used this plant's essential oil, aqueous extract, alcoholic extract, hydroalcoholic extract, and phenolic extract, among other extract types. The main ingredients of lavender essential oil are linalool and linalyl acetate, whereas the main ingredients of the aqueous extract are luteolin and caffeic acid. The results of our investigation show that the Hep G2 cell line is not harmed by the lavender aqueous extract. Regarding neuronal activity, the aqueous extract of lavender administered to rats injected with Aβ has shown a restorative impact on the altered plasticity of glutamatergic synaptic transmission in the hippocampus. Furthermore, it has been demonstrated that Aβ injections intracerebroventricularly change the expression of some proteins in the hippocampus p0. Notably, the aqueous extract of lavender demonstrates a dose-dependent suppression of Aβ monomer polymerization, preventing the thickening of Aβ fibrils, as per our in vitro investigation conducted using an atomic force microscope. Additionally, in a rat model of Alzheimer's disease, histological evaluations have verified that the lavender aqueous extract successfully lowers brain Aβ plaques.[26]

- *Ginkgo Biloba:*

The huge tree Ginkgo biloba, sometimes referred to as ginkgo, is distinguished by its angular crown and long, uneven limbs. This well-known traditional Chinese medicinal herb has been used for hundreds of years in folk medicine to treat a wide range of illnesses. It has numerous therapeutic properties.G. biloba has been shown in numerous clinical studies involving people with Alzheimer's disease (AD) to have a beneficial effect on cognitive impairment and the course of the disease, especially in the early stages of the condition. Acetylcholine (ACh) receptors in the hippocampus have been shown to be able to be restored by G. biloba, which improves neurotransmitter activity and aids in learning and memory in AD patients. Interestingly, research has demonstrated that G possesses strong acetylcholinesterase (AChE) inhibitory action of G biloba . By protecting brain cells from the toxicity linked to Aβ plaques, bilabia extract demonstrates neuroprotective qualities. In addition, it affects a number of Aβ-induced processes, such as apoptosis suppression, mitochondrial dysfunction mitigation, and reduced formation of reactive oxygen species (ROS). This herbal remedy also prevents free cholesterol from circulating and obstructs the production of Aβ. Consistent with these results, studies have demonstrated that G. biloba extract can block Aβ oligomerization and fibril formation in vitro. There is evidence to suggest that G. biloba may prevent the generation of Aβ via stimulating the gamma-secretase pathway during the cleavage process of the amyloid precursor protein (APP) . Additionally, G. biloba has neuroprotective effects via promoting the manufacture of growth factors, removing amyloid plaques, regulating tau phosphorylation, and preserving calcium homeostasis in astrocytes inside the rat hippocampus.[27]

IV. CONCLUSION

Herbal remedies have the ability to prevent and treat Alzheimer's disease (AD) due to their promising anti-oxidative, anti-inflammatory, and anti-neurotoxic qualities as well as their capacity to limit the generation of Aβ and increase cholinergic activity. The review in this research emphasizes the medicinal value of many herbal plants in treating symptoms associated with AD. Even though there is a wealth of preclinical data supporting the effectiveness of medicinal plants in neurodegenerative illnesses like AD, more clinical research is necessary to confirm the use of herbal medicine in reducing AD symptoms.

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