Exploring Molecular Targets to Treat Neurodegenerative Disorders

Exploring Molecular Targets to Treat Neurodegenerative Disorders

Edited by

Prashant Tiwari and K Sunil Kumar

Cambridge
Scholars
Publishing

Exploring Molecular Targets to Treat Neurodegenerative Disorders

Edited by Prashant Tiwari and K Sunil Kumar

This book first published 2024

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-0364-0476-5
ISBN (13): 978-1-0364-0476-5

TABLE OF CONTENTS

CHAPTER 1

EXPLORING THE NEUROPROTECTIVE EFFECT OF POTENTIAL INDIAN MEDICINAL PLANTS

R.VENU PRIYA[1], SUNIL KUMAR KADIRI[2], PRASHANT TIWARI[2], AND HANNAH NAQUIB[2]

Abstract

Neurodegenerative disorders, including conditions such as Parkinson's, Alzheimer's, and Huntington's disease, pose serious issues for global health due to their progressive nature and lack of effective treatments. Recent years have seen a rise in interest in studies examining the therapeutic benefits of natural products, notably herbal remedies used in the diagnosis and treatment of neurodegenerative diseases. In-depth information about the ongoing studies looking into the neuroprotective properties of possible Indian medicinal herbs is provided in this article. India is a prospective source for the development of new therapeutic agents because of its well-known vast biodiversity and traditional expertise in herbal medicine. In this work, bioactive substances found in Indian medicinal plants that have neuroprotective effects are identified, their mechanisms of action are clarified, and their efficacy is assessed utilizing in vitro and in vivo models. According to preliminary research, a number of Indian medicinal herbs have promising neuroprotective qualities. These include, but are not limited to, Curcuma longa (turmeric), Withania somnifera (ashwagandha), Centella asiatica (gotu kola), Bacopa monnieri, alsoknown as brahmi, and Withania somnifera. Alkaloids, flavonoids, terpenoids, and polyphenols, active chemicals produced from

[1]Department of Pharmaceutics, Anwarul Uloom College of Pharmacy,Mallepally, Hyderabad-500001, Telangana, India
[2]Department of Pharmacology, College of Pharmaceutical Sciences, Dayananda Sagar University, Bengaluru-560111,India

these plants, have shown promise in lowering oxidative stress, reducing neuro inflammation, modifying neurotransmitter levels, and promoting neurogenesis.Validating the effectiveness, safety, and recommended dosage of these chemicals obtained from plants will require more investigation. Investigations on their long-term effects and possible interactions with already used pharmacotherapies are also crucial. If successful, the discovery of neuroprotective compounds from Indianmedicinal plants could offer a practical and affordable strategy for battling neurodegenerative illnesses, opening up new therapeutic choices, and enhancing the standard of living for those who suffer from them.

Keywords: neurotransmitter, biodiversity, Withania somnifera, Centella asiatica, reactive oxygen species, neuroinflammation.

Introduction

The most prevalent form of dementia, Alzheimer's disease (AD), is getting worse and costing more to treat. A large portion of therapeutic research has focused on the connection between the distinctive histopathology of AD, cortical amyloid deposits and neurofibrillary tangle structures, and dementia-causing changes pertaining to their two most unaltered portion proteins, the amyloid-peptide (A) and the microtubule-associatedprotein tau. Alzheimer's disease (AD) pathological changes can occasionally coexist with a variety of other conditions, including diffuse Lewy body disease (DLB disease) and vascular-ischemic brain damage [1,2]. Alois Alzheimer, a German physician, is credited with establishing AD as a neurodegenerative disease after examining Auguste Deter, a 51-year-old woman who was experiencing forgetfulness, speech impairment, confusion, and hallucinations. During her autopsy, both tangles and plaques were found in her brain cortex, which prompted him to conclude that what had occurred was not your normal case of dementia. As a result of his discovery, additional studies have verified that dementia sufferers have neuritic amyloid (Aβ) plaques [3].

Age, family history, apolipoprotein E4 genetic makeup, diabetes, obesity, high cholesterol, high blood pressure, injury to the brain from trauma, and low educational attainment are all risk factors for AD [4]. Initial, predominant impairments in the visual, verbal, executive, behavioral, and motor domains are used to categorize non-amnestic phenotypes. Those with young-onset dementia, whose symptoms start before age 65, are disproportionately affected by these presentations (also known as

"atypicalAD"). Younger patients without 'typical' hippocampus volume reduction or non-amnesticsymptomsmay not have AD dementia [5]. The amyloid protein (A) can exist as soluble monomers, soluble aggregates of varying sizes (such as oligomers and protofibrils), insoluble fibrils, and plaque. It has been demonstrated that soluble A aggregates are more hazardous than monomers or insoluble fibrils[6]. A preliminarydiagnosis of AD in a living patient can be made using the cerebrospinalfluid, or CSF, and PET, or positron emission tomography, biomarkers in combination with other relatively innovative clinical criteria; however, a definitive diagnosis of AD needs post-mortem evaluation of brain tissue[7, 8]. Even though there are only a few effective pharmaceuticals for symptom management and the usual course of care for AD hasn't changed much in recent years, recent developments in inherited research and immuno therapy give hope that AD might one day be postponed for longer than the six to eighteen months provided by available pharmaceutical therapies. Particularly intriguing are treatments that could slow the development of AD in the initial phase of the illness[9]. Although numerous therapeutic approaches have been tested over a long period of time in clinical trials, the medicines that are currently accessible are generally symptomatic rather than curative. As a result, the emphasis has shifted to preventing or lowering the risk of AD. According to research, around the world, risk factors that can be changed may account for over thirty percent of occurrences of AD. This offers intriguing and possible targets for preventative measures to reduce the probability of cognitive loss brought on by AD and maybe ND in general. A significant problem is enhancing early disease detection in the preclinical stage [10].

Neuropathology

The brain of a person with Alzheimer's undergoes numerous molecular and cellular alterations long before memory loss symptoms manifest. The tools that scientists and medical professionals can use to detect and treat these diseases have been revolutionized by neuropathology research, which has been crucial in identifying these molecular changes, known as biomarkers [11]. Understanding the pathophysiology of neurodegenerative illnesses, such as NBIA-related forms of neurodegeneration, depends heavily on neuro pathology. Despite significant genetic diversity, several variants of NBIA also have other characteristics in common besides iron deposition, such as the existence of neuro axonal spheroids. Numerous NBIA types exhibit tau or synucleinpathology, indicating similarities to both Alzheimer's and Parkinson's disorders [12].

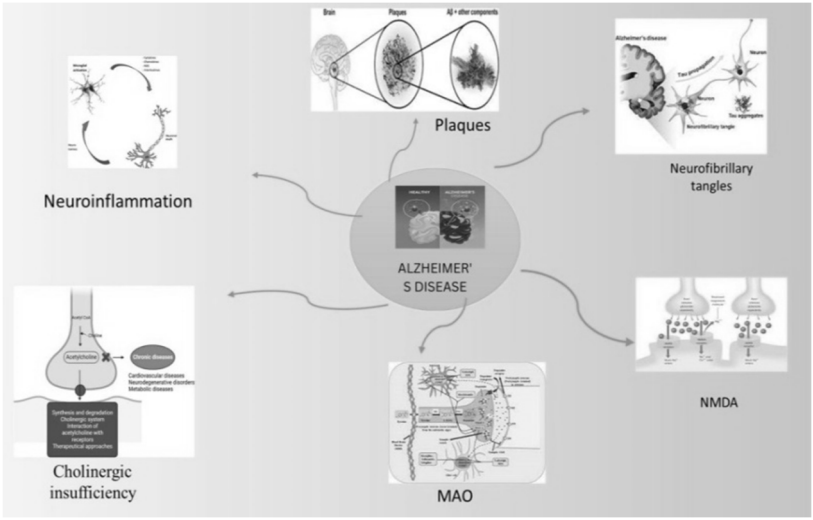

Figure 1:Neuropathology of Alzheimer'sdisease

Amyloid plaques

The amyloid hypothesis of AD, which focuses on the incorrect break down of the protein known as amyloid precursor protein (APP), which creates amyloid beta (A), witnessed an increase in research in the 1990s [13]. The aberrant break down of the cell's plasma membrane protein APP by α-secretases (BACE1) and β-secretases, whichresults in the formation of insoluble A-fibrils, is the initial stage in the pathophysiology of amyloid. After then, Aβ keeps oligomerization, diffuses into synaptic clefts, and interferes with synaptic transmission. After that, plaques are produced when clump-like stationary amyloid fibrils polymerize. The microtubule-associated protein is hyper phosphorylated as a result of this polymerization, which creates insoluble NFTs. After tangled structures and plaques form, the tiny cells that surround them are recruited. This promotes neurotoxicity by fostering regional swelling and microglial activation [14].

Neuro fibrillary tangles

In Alzheimer's land mark publication, neurofibrils, which formed dense bundles close to the cell surface of afflicted neurons, were the first to be described as neuro fibrillary tangles (NFTs). Aggregates of the tau protein,

which is associated with microtubules, are the second main pathologic finding in AD [15]. These could be seen with the help of the Bielschowsky silver stain and were connected to neuronal death and disintegration, leading to what are now known as extracellular or ghost tangles [16]. Memory problems in AD are closely tied to hippocampal synaptic deficits. It has been suggested that tau controls the formation of axonal microtubules, maintains neuronal projections, and influences synaptic function. Therefore, decreased tau's ability to connect to microtubules could be a factor in synaptic dysfunction [17].

In the postsynaptic compartment, normal tau is discovered to be engaged in synaptic activation. It has been found that regular tau is involved in synaptic activation in the post synaptic compartment. Tau can bedrawn to dendrites and the post-synapse, where it normally connects primarily with microtubules in axons, in either healthy or diseased conditions. Synaptic activity attracts tau to post synaptic densities, where it reacts with proteins there. The majority of the tau within dendritic tissue is hyperphosphorylated, free of microtubules, and associated with the deterioration of dendritic spines [18]. In AD and othert aupathies, these dendritic tau species play a substantial role in cognitive dysfunction, abnormal postsynaptic activity, and dendritic degeneration. The molecular mechanisms are probably in charge of controlling the NMDA or AMPA receptors. For instance, it has been shown that dendritic tau interacts with Fyn kinase to phosphorylate the NMDA receptor, which mediates A-dependent excito toxicity. Tau phosphorylation has been closely associated with AD and has been the topic of extensive investigation, partly because NFTs isolated from AD brains contain higher levels of highly phosphorylated tau species [19].

Glutamate

Increased homocysteine levels are influenced by a number of variables, including sex, age, heredity, and lifestyle choices. This riskfactor's occurrence in the population has a variety of origins, including both genetic and nongenetic factors. Hyperhomocysteinemia in the general population may be caused by vitamin B12, folate, and pyridoxine deficiency. According to pharmacological evidence, homocysteine promotes lipid build up, inflammatory reactions, and NMDA receptor activation. In AD models, NMDA receptors have been demonstrated to mediate the Aβ-peptide's down stream effects, and pharmacological

suppression of this receptor's activity eliminates the detrimental effect of the Aβ-peptide [20,21].

Cyclooxygenase enzymes

Since COX-2 over expression has been linked to some of these disorders, a lot of research has been done on COX-2's function in neuroinflammatory and neurodegenerative diseases (Minghetti, 2004). Central and peripheral nerve systems are among the primarytargets of PGs. The synaptic activity of specific types of mammalian neurons "dynamically regulates" the production of COX-2 in these neurons [22]. Cyclooxygenases (COX) convert arachidonic acid into prostanoids. The COX isoforms COX-1, COX-2, and COX-3 are all recognized. Neurological problems have been linked to COX-1 and COX-2. The combination of COX-2 expressed in a small number of brain cell masses has been demonstrated to elevate COX-2 in the presence of inflammatory substances such as cytokines, TNF, IL-1, and IL-2. According to studies, COX-2 expression is mostly found in pyramidal neurons and is absent from astrocytes but increases throughout the early stages of the disease [23].

Cholinergic system

Despite the fact that NPs and NFTs are the primary AD indicators, basal fore brain cholinergic hypofunction plays a significant role in the pathophysiology of the disease since the loss of basal cholinergic neuronsis linked to severe neurodegeneration [24]. Cholinergic signaling requires the synthesis and release of the neurotransmitter acetylcholine (Ach). The degradation of these neurons is thought to be a key element in the onset of dementia, more specificallyAlzheimer'sdisease (AD), because the majority of the brain regions activated by cholinergic neurons have roles in memory, cognition, responses to stress, and cognitive performance. These areas consist of the cerebral neocortex, hippocampus, basal forebrain, and nucleus basalis of Meynert[25].

The rate of action of an enzyme called ChAT, the ratio of choline uptake to choline acetyltransferase level, which is usually lower than that found in the brains of control subjects but is not significantly greater except in some brain regions, and the likelihood of increasing brain neurotransmitter levels by using precursors to neurotransmitters or cholinesterase inhibitors have all been studied. Relevant to these studies is the change in the cholinergic pathway for neurotransmitters in the brain. At the molecular

level, it is believed that the brain choline deficit first hypothesized by Wurtman is a transmissible component of dementia and AD. Severalfacts, including a 40%–50% fall in cerebral acetylcholinelevels, a reduction in choline-dependent membrane components, and an increase in choline-dependentaminoacids, are in favor of this theory[26].

Mono AminoOxidase

The cellular enzymes MAO-A and MAO-B, which catalyze the oxidative deamination of numerous natural and xenobiotic amines, including monoamine neurotransmitters like 5-HT, noradrenaline, and dopamine, may also contribute to oxidative stress in the brain. This mechanism results in the simultaneous production of aldehydes and H_2O_2. [27]. The transmembrane helices at the C-terminal sections of MAOs attach the enzymes to the mitochondrial outer membrane while leaving the remaining protein accessible to the cytoplasm. It is anticipated that a substrate or inhibitor will enter the MAO's active site close to where the enzyme and membrane surface intersect. Different parts of the human brain have different MAO activity.The basal ganglia and the hippocampus have the highest levels, whereas the cerebellum and the neocortex have the lowest levels. According to immuno histochemical studies, catecholaminergic neurons primarily contain MAO A while serotonergic neurons and astrocytes primarilycontain MAO B. Only MAO-A is present in caudate dopaminergic nerve ends, and trace levels of this isoform are also present in serotonergic nerve terminals. Species-to-species variations in dopamine metabolism have been noted. For instance, only the MAO-A isoform is active in the rat brain, but the humanbrain's MAO-B is primarily in charge of dopamine metabolism [28].

Herbalmedicine

Conventional Chinesemedicine (TCM), which has been practiced by the Chinese population for more than 2000 years and is a vital inspiration for the development of modern medications, has a long history. Nowadays, many of the sophisticated drugs used in clinical trials come from plants. TCM can be used to treat symptoms of neurodegenerative diseases (NDs), including cramping, insomnia, forgetfulness, confusion, and loss of consciousness [29]. Researchers have become interested in naturalbenefits such as a hugevariety, a widearray of sources of information, and a large variety of natural compounds. Herbs, fruits, and vegetables are frequent sources of naturalgoods in the natural world. They can be classified

structurally as glycosides, phenylpropanoids, alkaloids, flavonoids, and others [30]. Interesting pharmacological qualities include those that are anti-tumor, antioxidant compounds, antibacterial, anti-inflammatory, anti-diabetic, hypoglycemia, neuroprotective, etc., and are present in almost all natural products. Natural goods are frequently extremely safe and less toxic than artificial ones, which makes them a vital alternative source for many different kinds of drugs [31].

Medicinal plants

Ashwagandha

Among the most well-liked medications for AD brain rejuvenation is ashwagandha. It is also referred to as winter cherry or Indian ginseng. It is suggested for enhancing vitality, extending life, and acting as a brain tonic. Ashwagandha's anti-inflammatory properties, free radical-scavenging, andantioxidant activities have been proven [32]. The traditional name for the root, "ashwagandha," refers to the root's smell, which is evocative of a horse. The name is made up of the Sanskrit terms "ashva," which means "horse," and "gandha," which means "smell." The scientificname of the species, "somnifera," emphasizes how important itis for reducing stress. The plant has short stems, oval-shaped, petiolate foliage, and terminal greenish, bisexual blooms. It is an upright, grayish, ever green shrub. It also has extensive tuberous roots. It may also flourish at greater altitudes of 1700 m in the Himalayas region, primarily in the Indian states of Himachal Pradesh, Uttarakhand, and Jammu and Kashmir. This is in addition to the drier regions of India [33].

These characteristics are brought about by its constituent chemicals, Withaferin A and Withanolide A, which are similar in their pharmacokinetic activities but differ in their oral bioavailability, with Withaferin A having a higher oral bioavailability than Withanolide A [34]. WS is widely used in Ayurvedic medicine because of its supposed medicinal qualities, and it has also been investigated as a potential treatment for a number of medical diseases, including anxiety, insomnia, Parkinson'sdisease (PD), and cognitive impairment. Additionally, withania somnifera is used as an immunostimulant for persons with low white blood cell counts and as a soothing substance for people who have weariness, sleep problems, and stress-relatedconcerns [35].

Through cognitively enhancing effects and neuronal development, it also offers anti-neurodegenerative activity. It actually belongs to the rasayana subgroup known as medhya rasayana. Medhya literally means "mind" and "mental power." Numerous scientific studies have has demonstrated how Ashwagandha slows, stops, and reverses synaptic loss and neurotic atrophy. As a result, it can be used to treat neurodegenerative illnesses like Alzheimer's, Parkinson's, Huntington's, and others in their early and middle stages. Ashwagandha is frequently seen in Ayurvedic tonics since it has been recognized as a powerful nervine tonic in Ayurveda. Ayurvedic tonics, rejuvenators, and vitalizers seem to prevent disease, boost immunity, and length enusers' lives [36]. Fifty people with mild dementia participated in an eight-week prospective, randomized, double-blind, and vehicle-controlled pilot study.They were given either ashwagangha root extract (300 mg twicedaily) or a placebo. In comparison to the placebo group, the Ashwagandha treatment group showed noticeable gains in long-term as well as short-term memory tests after eight weeks of study. Executive function, persistent focus, as well as information processing speed,were markedly improved in the therapy group. These studies support the idea that ashwagandha helps those with SCI or MCI improve their memory and executive function [37]. Aphrodisiac, alterative, adaptogenic, a pain reliever, antiarthritic, antiasthmatic, an antibiotic, antidyspeptic, anti-inflammatory, antimitotic, antiproliferative, antitumor, diureticdrugs, relaxing immune-modulating, febrifuge, fungicide, emetic, and hypnotic are some of its other properties. In addition, it has the potential to be cytotoxic, radio sensitizing, and chemopreventive.

Brahmi

Brahmi, also known as Bacopa monnieri, is a helpful medicinal plant that improves brain and memory. It belongs to the 220-genus family Scrophulariaceae and is a little perennial creeping herb. Brahmi is derived from the Hindupantheon's mythical "builder" and Bramai. The plant's delicate stem measures 10–30 cm in length and 1-2 mm in thickness. The leaves are oppositely placed on the stem, sessile, succulent, and range in size from 0.6 to 2.5 cm long and 0.2-1 cm thick. It has a wide range of pharmacological effects since it contains several chemicals, including alkaloids, saponins, glycosides, flavonoids, and stigmasterols [38].

Antioxidant, anti-inflammatory, anticonvulsant, cardiotonic, bronchodilator, and pepticulcer protection are its chief pharmacological effects. Brahmi is used for a number of purposes in Ayurvedic medicine, including memory

enhancement, epileptic treatment, insomnia treatment, and anxiolytic treatment. Its effects on memory function are more focused on reducing forgetfulness than on enhancing learning [39]. Bacopa monnieri contains the alkaloids herpestine and brahmine, among others. The primary phytochemicals found include tannins, the terpenoids monnierin and hersaponin, and the flavonoid glycosides, Bacoside A and Bacoside B. Saponins, also known as pseudojujubogenin and jujubogenin glycosides, are thought to be a crucial component of the plant. Bacosides A and B are known to improve memory, and Bacoside A includesnitric oxide, makingthis important plant a nootropic medicine by facilitating easier blood circulation throughout the body by loosening the aorta and veins [40].

Contrary to the possible addictive and intense effects of regularly used psychostimulants, prolonged and moderate treatment with Bacopamonnieri (BM) seems to replenish rather than destroy neurons, a pattern confirming 1400 years of traditional research. In various animal studies and in vitro experiments, harmfuleffects have been seen in abundance at recommended levels. BM possesses antioxidant, hepatoprotective, and neuroprotective properties. Only a few of the mechanisms of action revealed by this research include acetylcholinesterase inhibition, choline acetyltransferase activation, amyloidreduction, increased cerebral blood flow, and monoamine potentiation. Numerous randomized, double-blind, placebo-controlled experiments have been conducted to establish the efficacy of BM as a nootropic in humans [35]. Although the precise mechanism of Bacopa monnieri action is not fully understood, Bacopa monnieri herbal extracts are able to boost the enzymatic antioxidant activities of superoxide dismutase and catalase. This suggests that the neuroprotective action of Bacopamonnierimay be linked to a combination of cholinergic modulation and antioxidant effects [41].

Cat’sclaw

Uncaria tomentosa, frequently referred to as "Ua de Gato" (in Spanish) or "cat's claw" (in English), is a woody vine that grows subtly throughout the Amazon jungle. The vine known as "cat'sclaw" gets its name from the unusual claw-like thorns that emerge from the base of the leaves. The vine wraps itself around the near by trees and clings to them. After 20 years, it matures and reaches an extended length of more than 100 feet [42]. Uncaria tomentosa and Uncaria guianensis are two common species of cat's claw, both valued for their anti-inflammatoryeffects in South

America. Compared to the stem, bark, and branches of the plant, the leaves have a higher concentration of oxindolealkaloid. Proanthocyanidins, a newly discovered polyphenolic compound in U. toemntosa, have inhibitory and lowering effects on plaque and tangle [43].

Uncaria tomentosa has been reported to treat wounds, abscesses, fever, urinary tract infections, and asthma in the past. Additionally, it is said to be helpful as an antioxidant, antibacterial, anti-inflammatory, and immune system booster. The most effective complementary herb for treating most parasites is U. tomentosa. The extracts of U. tomentosa include a variety of chemical components, and their biological activity is documented [44]. U. tomentosa reportedly produces a potent medicinal extract that successfully removes A plaques, making it a viable herb for Alzheimer's Disease (AD) treatments. This happened because U. tomentosa contained freshly discovered polyphenolic compounds, such as particular proanthocyanidins that inhibited growth and decreased "plaque and tangles," which decreased plaque and tangles. Proanthocyanidins, a newly discovered polyphenolic substance in U. toemntosa, have an inhibitory and decreasing effect on plaque and tangles. Proanthocyanidin B2 is a more powerful inhibitor of cerebrum aggravation and reduces brain plaque while enhancing short-term memory [45].

Ginkgo Biloba

The ginkgo biloba is the oldest surviving tree species in the world. Ginkgo species were first observed throughout the period known as the Permian Period, between 286 and 248 million years ago. Ginkgo biloba is the sole survivor of the Ginkgo family. The trees' extraordinary malleability, resilience to illness, and the Buddhist monks who looked after and protected them on sacred land are all credited, according to mythology, for their continuing existence [46]. Ginkgo originated in China and makes up roughly 70% of all resources in the world. Ginkgo biloba leaves currently contain more than 160 different chemicals, but the three most effective ones are ginkgo flavonoids, ginkgolide, and ginkgolicacid [47]. It demonstrates the neuroprotective properties of Ginkgo biloba extract. Since inflammation, oxidative stress, and neuronal death cause neurodegeneration in Alzheimer's disease, most research focuses on avoiding or treating these conditions. Ginseng lupulin minimizes the memory and cognitive decline that lead to Alzheimer's disease [48]. Ginkgo biloba use can aid in lowering mental health issues and emotional tension, enhancing memory, enhancing patients' capacity to handle their

daily lives, minimizing depression and hallucinations, protecting nerve cells, enhancing blood circulation, and many other advantages [49].

Due to the fact that ginkgo biloba extract has multiple targets and that its mechanism of action is unclear, it is a hot subject for research. Ginkgo biloba has shown neuroprotective and antioxidant qualities in numerous studies, which are attributed to the flavonoids and terpenoids that make up the extract. These investigations showed that ginkgo biloba has the capacity to lessen amyloid build up, which slows the advancement of disease and lessens its symptoms. Because flavonoids are believed to function as antioxidants, they have been demonstrated in multiple research projects on Alzheimer's disease to improve cognition and memory. Growing evidencealso points to ginkgo biloba extract's ability to lower oxidative stress, which, as was previously indicated, contributes to Alzheimer's disease [50].

Strong antioxidants found in G. biloba extract protect vascular endothelial cells from oxidative stress by scavenging free radicals. By improving cerebral and peripheral circulation through blood flow modulation, lowering vascular permeability, stimulating the nervoussystem's functions through neurons, and reducing platelet aggregation by prohibiting the reaction biochemistry in platelets, G. biloba can beused to enhance the neuroprotective effect. Additionally, it is well known that the flavonoid components in G. biloba extract have anti-inflammatory properties that are linked to the inhibition of the lipoxygenase and cyclooxygenase (COX) enzymes. Inhibiting phospholipase-A2, hydrolyzing membrane glycerophospholipids, and releasing arachidonic acid—a precursor to eicosanoids, prostaglandins, and leukotrienes—are all effects of biflavoneginkgetin, which is obtained from the leaves of the Ginkgo biloba plant. The flavonoids G. biloba, also known as ginkgolide A and B, also suppress proinflammatory cytokines such as TNF- and IL-1.3 [51–52].

Gotu Kola

Centella asiatica, also known as gotukola, is a widely used medicinal plant that has a variety of positive properties, including antioxidant effects, effects against Alzheimer's disease, effects against inflammation, effects against infertility, actions against tumors, and effects against microbes [53]. A few nations throughout the world use Centella asiatica, often known as gotu kola, as a medicinal herb and green leafy vegetable. Additionally, research-

backed multifunctional qualities make it a promising potential medication to target many pathways in neurogenerative illnesses, adding to its reputation in conventional medicine as a memory enhancer, including Alzheimer's. This plant, which is abundant in many phytochemicals, has been reported to produce these metabolites in chemotype variations depending on its origin and growth circumstances [54].

India is home to Centella asiatica, an annual plant from the Apiceae family commonly known as jalbrahmi or mandukparni. It produces small, oval fruits and has green, fan-shaped leaves. The flowers are white, light purple, or pink [55]. Gotu kola is effective at inhibiting the amyloid cell, according to in vitro research, suggesting that it can beused to treat amyloid poisoning in Alzheimer's patients. Fresh leaf extract from Centella asiatica (Linn) increased learning ability and memory retention in Wistar rats. It is used to treat rheumatism, epilepsy, mental weakness, and gastrointestinal discomfort. Centella asiatica was also discovered to reduce the oxidative stress response and reverse A pathogenesis [56].

When compared to streptozotocin, Centella asiatica has neuroprotective action and the ability to avoid cognitive impairment. This includes defending cholinergic neurons against aluminum's toxic effects and aiding in the treatment of AD neuropathy. Some research suggests that administering Centella Asiatica extract (CaE) to trans genic mice may aid in the treatment and prevention of Alzheimer's disease. Additionally, it can alter PSAPP (presenilin 'Swedish' amyloidresponse) modifications that result from the disease's amyloid pathology in the brains of affected individuals [57].

A neuroprotective effect of gotu kola extract with triterpenoid saponin glycoside phytochemical content, such as asiaticoside, asiaticacid, made cassoside, and madecasicacid, is to improve nerve function by activating the Krox-20 regulatory gene as a transcription factor from NRG-protein 1. However, because the phytochemical components of gotu kola have a tendency to be polar, it is necessary to study the pharmacokinetics of active extracts utilizing phytosome technology. In TBI model mice, phytosomegotu kola extract boosted NRG-1 levels and myelin thickness. It can make the active ingredient in gotu kola more soluble in fat, increasing the organic/water partition. As a result, the therapeutic effects and absorption of active substances are greatly increased. This is because the chemical interactions between phosphatidyl choline and phyto constituents are more apparent [58].

Lion’smane

A medicinal fungus called Hericiumerinaceus (H. erinaceus), popularly known as lion's mane, has been discovered to have a number of beneficial neurocognitive effects that may work as a delaying tactic for the development of AD. Due to its many health benefits, H. erinaceusis a highly valued edible fungus [59]. The substance has an extensive history of usage in traditional Chinese therapy because of its nutritional content and health benefits, and it is frequently consumed in Asian nations. This species may help to minimize or even avoid the severity of many significant ailments, including tumors, obesity, depressive disorders, and neurological issues [60]. The fruiting body is globular in shape and has long, shaggy spines that are initially white but eventually become brown or yellow. It is a significant edible fungus that is widely available in China, Japan, Europe, North America, and other continents. It has positive dietary and medicinal advantages without any negative side effects [61].

The hericenones A and B found in lion's mane mushrooms are special bioactive substances that have aided in the growth and development of neurons and other accessory structures. They also aid in the coordination of neurons that are linked to complex neurodegenerative diseases like Alzheimer's disease, depression disorder, and anxiety [62]. It is also known by a variety of other names, including bear's head mushroom, bear dedhedgehog mushroom, beardedtooth fungus/mushroom, hog head mushroom, Hou TouGu (Chinese), lion's mane mushroom, monkey head mushroom, old man's beard mushroom, Pom Pom mushroom, Satyr'sbeard fungus, white beard mushroom, and Yamabushitake [63].

The two significant groups of compounds identified from the fruiting body and mycelium of H. erinaceus, respectively, are hericenones and erinacines. Low-molecular-size, moderately hydrophobic compounds such as hericenones and erinacines have been demonstrated to promote NGF synthesis and neurite out growth in nerve cells in vitro [64].

The bioactive substances in H. erinaceus include glucan polysaccharides, isoindolinones, hericenones, and erinacineterpenoids, as well as myconutrients, which may have both neuro protective and neuro degenerative effects. For neurological disorders, H. erinaceus is helpful. In a few trials, it was shown that people with Alzheimer's disease who took anti-inflammatory medications had fewer symptoms of the disease [65–66].

Saffron

Extracts from the blue-purple saffron flower, Crocus sativus L., have been the subject of intense research by a number of scientists lately. Native to the Middle East, Crocus sativus East and belongs to the iris family, the Iridaceae. Because the stigmas of saffron flowers contain a lot of carotenoid pigment, its name is derived from an Arabic word for yellow [67]. Saffron may be helpful for treating a number of illnesses, including depression, respiratory, and cardiovascular ailments. To improve and restore memory, saffron has also been utilized in conventional Persian and Chinese medicine [68].

Fromits bulbs, this perennial bloom develops to an elevation of 10 to 25 cm. The sub-ovoid bulb comes in a variety of sizes and shapes. Its considerable structure is covered with a multitude of concentric spathes. Each mother bulb creates one to three large daughter bulbs from the apical buds and several smaller daughter bulbs from the lateral buds. Both contractile roots, which develop at the base of lateral buds, and thin, fibrous roots, which begin at the base of the mother bulb, are present in saffron. Five to eleven leaves are present in each bud. They range in size from 1.5 to 2.5 mm and have a dark green colour. They range in height from 20 to 60 cm and feature an inner pale stripe [69]

The use of saffron in traditional medicine is centuries old. This plant has been used to ease coughing, loosen phlegm, treat asthma, and treat whoopingcough. Saffron is also used to treat heartburn, discomfort, hemoptysis, Alzheimer's disease, depression, terror, shock, and dry skin [70].

The main phytochemicals in saffron are picrocrocin, kaempferol, safranal, phenol, delphinidin, flavonoid, and crocetin, all of which have high bioactivity and antioxidant potential. Saffron stigmas contain secondary metabolites such anthocyanins, carotenoids, flavonoids, and terpenes as well as lipids, carbohydrates, minerals, and vitamins, according to chemical analysis. The bioactive elements of stigma include anthocyanins, pigments, flavonoids, volatile aromatic essences, and vitamins [71-72].

Shankhpushpi

Ayurveda recognizes sankhpushpi as "Medhya Rasayana," a substance that revitalizes, upholds, and sharpens memory and intellect [73].

Convolvulus spluricaulis, also known as sankh pushpi, is a plant that is frequently found in India and isused as a nervous system tonic. Cortisol and adrenaline were controlled by Shankh pushpi. It could be used to treat insomnia, stress, and anxiety [74]. Traditional uses of Shankh pushpi, also known as Convolvulus pluricaulis Choisy, a member of the Convolvulaceae family, include the treatment of nervous system problems. As a nervine tonic, it increases functions of learning and memory [75]. Due to its potential bioactive components, the herb is employed by many Ayurvedic practitioners in traditional therapeutic practice as a single herb as well as in formulations. It has been used as a natural booster for children's brain growth by numerous Ayurvedic doctors to thisday [76].

Although preclinical research suggests that shankhpushpi may have memory-improving, antioxidant, and anti-inflammatory properties, human data from well-planned, well-controlled medical trials is still lacking, which is quite significant. When used in accordance with instructions, sankh pushpi is generally safe, although it can also significantly reduce blood pressure and interfere with some medications [77]. Alkaloids (shankhpushpine and convolamine), volatile oils, favanoid-kampferol, phytosterol, aminoacids, fatty acids, scopoletin, and beta-sitosterol are the main chemical constituents (Sethiya NK) [78]. Winfornine-F, Paniculatine-A, and Paniculatine-B are alkaloids discovered in the plant's stem, while Celastrine, Celapagine, Celpanigine, and Celapanine are alkaloids found in the seed. The antioxidant enzymes present in the extract may partially prevent hydrogen peroxide-driven cell death, and they can also enhance memory by raising dopamine levels in the brain [79].

The plant is effective in reducing psychological, chemical, and traumatic stress, among other types of stress. It has been demonstrated that the roots of CP increase brain protein concentration while lowering total serum cholesterol, triglycerides, and phospholipids. Further evidence of the plant's neuroprotective potential came from its capacity to prevent the buildup of lipid and protein damage. Additionally, CP extract administration lessened alterations in endogenous antioxidant enzyme levels linked to Al administration when compared to the common AD therapy rivastigmine. According to an in vitro study, the ethanolic extract of CP demonstrates considerable antioxidant activity [80].

It was demonstrated that the water, acetate (ethylacetate), and ethanol-based extracts of this substance considerably improved learning and memory in rats. Scopolamine's neurotoxic effects were lessened in AD rat

models through the administration of C. pluricaulis oral therapy, which reduced the brain's synthesis of tau and APP. Triterpenoids, flavanol glycosides, anthocyanins, and steroids, which are assumed to be the cause of conventional medicine's nootropic and memory-improving benefits, have been discovered as the active components of this plant, making it a potential treatment for AD.

Turmeric

The mostpopular and oldest spice, noted for its use in many Asian dishes, is turmeric. This herbal spice is utilized as medication in addition to being a common ingredient in Asian cuisine [81]. The primary ingredient in turmeric, curcumin, was discovered roughly 200 years ago. It is made from the dried rhizomes of the ginger family member plant Curcuma longa L [82]. Turmeric's main active components include curcuminoids that are water-soluble, such as curcumin, and turmerone oil. Studies have been done on curcumin's medicalbenefits, specifically its anticancer activity. Additionally, it has been claimed that curcumin has potential in a transgenic mouse model of AD and demonstrates antioxidant and anti-inflammatory properties [83]. Though turmeric has been traditionally used medicinally for a very long time, only recently have its precise mechanisms of action and its active ingredients been investigated. Because of its anti-inflammatory, anti-oxidant, anti-migraine, antimicrobial, and anti-tumor properties, it has an extended tradition of use as a herbal remedy in Asian countries. However, due to its wide variety of probable applications, it is now known and used globally [84].

Through the inhibition of peroxidases, turmeric can pass the blood-brain barrier and demonstrate therapeutic potential. It also reduces A-protein aggregation and neuro inflammation. Macrophages and turmeric together increased the uptake and consumption of A plaque in AD patients, according to a UCLA study [85].

Curcumin has anti-inflammatory characteristics by reducing the amount of TNF-, IL-1, and other pro-inflammatory cytokines in microglia and astrocytes, including IL-8, MIP-1, and MCP-1. Additionally, it stops the phospholipids in neural membranes from being converted into prostaglandins by the enzyme’s phospholipase A2 and cyclooxygenase (COX-2), which reduces neuro inflammation. It reduces oxidative damage and boosts cognitive ability, especially in situations of aging, by altering the Nrf2-Keap1 (Kelch-like ECH-associatedprotein 1) pathway. Keap1 is

bound to curcumin, which releases Nrf2, which is located in the cytoplasm and is connected to Keap1. When the protein moves to the nucleus and forms a heterodimer with antioxidant-sensitive regions in DNA, it then targets the genes that control the development of antioxidant enzymes, DNA repair enzymes, molecular chaperones, and anti-inflammatory response proteins [86]. Studies on epidemiology have shown that long-termusers of nonsteroidal anti-inflammatorydrugs (NSAIDs) have a decreased incidence of Alzheimer's disease (AD). This may draw attention to the role that inflammation of the brain plays in Alzheimer's disease. It has also been demonstrated with increased cytokine levels and activated microglia. It has been shown that curcumin works similarly to NSAIDs and also lessens oxidative damage [87].

Panax Gensing

Many valuable scientific medications have been made possible by the long history and wealth of folk medicine in the nations of the Far East, and ginseng holds a special place among this significant group [88]. Panax ginseng, the widely recognized and precious medicinal herb ginseng, also known as C.A. Mey, has long been used in China and other East Asian countries for food and traditional Chinese medicine. According to recent studies, ginseng extracts, active components (ginsenosides and gintonin), and ginseng compositions aid AD patients in having fewer symptoms and a slower course of the disease by reducing the degree of A and tau protein hyperphosphorylation. These effects may be mediated by the production of reactive oxygen species (ROS), neuronal exchange, death of cells, ions of calcium, and mitochondrial activity [89–90]. Almost 200 active ginseng components, including ginsenosides, poly- and sugars that are mono vitamins, aminoacids, and organic acids, and non-saponin-soluble water glycosides, have been identified by contemporary pharmacological studies. Alzheimer's disease, carcinoma, cardiac ischemia, Parkinson's disorder, insulin resistance, heart disease, and depression are just a few of the illnesses that can be treated using Panax ginseng's active components [91]. The primary components and primary active components of ginseng are known as ginsenosides, which are a subclass of triterpenoid saponins and steroid glycosides. These substances interact with cell membranes, ion channels, and receptors dueto their four-ring steroidal structure and linked sugar moieties, which account for their pharmacological effects. The A-panaxadiol group (Rb1, Rb2, Rb3, Rc, Rd, Rg3, and Rh2), the B-panaxatriol group (Re, Rg1, Rg2, and Rh1), and the C-oleanolicacid group (Ro) are the three groups into which ginsenosides can bedivided [92].

P. ginseng is also referred to as an adaptogen because of its capacity to preserve homeostasis in the host by posing possible restorative and therapeutic effects. As an adaptogen, ginseng improves physical performance, boosts vitality, and fights anxiety and getting older by means of immune-modulating agents (which involve both immunostimulatory and immunosuppressive effects), neuromodulatory, and vasomodulatory actions, which may explain its hypertension or anti-hypotensive impact. Managing elevated blood pressure and vascular endothelium tone are examples of these effects. Additionally, P. ginseng's cardioprotective properties have been demonstrated [93].

Ginsenoside Rg1, one of the main ginseng constituents, has a number of neuroprotective effects against dementia and Alzheimer's disease (AD), such as enhancing cognitive function, preventing neuronal death, lowering oxidative stress, and minimizing mitochondrial dysfunction. Ginsenoside Rg1 has been found to have A-scavenging abilities. By boosting PPAR binding to the Bace1 promoter, for instance, ginsenoside Rg1 inhibits both translation and transcription of amyloid cleavage enzyme 1 (Bace1), a target gene of PPAR. This decreases BACE1 activity, which in turn decreases PPAR production. Additionally, ginsenoside Rg1 increases PPAR expression in the rat hippocampus AD model, which increases the production of the gene for insulin-degrading enzyme (Ide), another PPAR targetgene, and speeds up the clearance of A1-42 from the hippocampus [94].

Coriander

The annual herb coriander, or Coriandrum sativum L. (C. sativum), is native to the Mediterranean region. White flowers, short branches and sub branches of leaves, and nearly oval globular fruits with numerous longitudinal ridges on the surface. This plant's entire structure is edible, and it has long been used to heal a variety of ailments [95]. The "herb of happiness" is a plant that has several uses and has a protective and preventing effect on a variety of chronic illnesses, earning it the nick name. The primary chemical components of the plant have been demonstrated to beflavonoids, polyphenols, and carotenoids [96]. Linaloolis the primary flavoring compound in coriander, whereas the essential oil of the leaves and seeds contains polyphenols and terpenes. Coriander has been used in traditional medicine as an antibiotic, called a pain killer, as a treatment for dementia and appetite loss, as well as for digestive and respiratory disorders [97].

In recent decades, studies have focused on the chemical components, biological traits, and molecular mechanisms underlying its biological activities. Antioxidant, antidiabetic, antimutagenic, antihelminthic, anticonvulsant, anxiolytic, and liver-protective characteristics are among the pharmacological traits that Coriandrum sativum exhibits. These results could be attributed to this plant's potent antioxidant activity and the main ingredient, linalool. [98]. Essential oil inhalation significantly decreased LDH and MDA levels while raising glutathione peroxidase levels in the rat hippocampus area. Additionally, rats receiving EO had fewer amyloid deposits. Since linalool was discovered to be the compound in the EO that was most active, it may be assumed that linalool is what causes the cognitive-improving effects and antiapoptotic activity in rats given A1-42 treatment. Linalool's potential role in neuroprotection could be associated with antioxidant defense and a decline in lipid peroxidation [99]. Coriandrum sativum has been shown through pharmacological research to have hypoglycemic, hypolipidemic, antimutagenic, antihypertensive, antioxidant, anxiolytic, antibacterial, and post-coitalantifertility actions. It has also been applied to the detoxification of heavymetals. [100]. Additionally, itfunctions as a stimulant, flavoring, tonic, and diuretic. It may help with rheumatism and aching joints. The antioxidant content of the food will be increased by adding coriander seeds and leaves, likely preventing oxidative food deterioration. Additionally, adding antioxidants can extend the shelf-life of food, and coriander is a high source of these antioxidants, so flavoring food with this herb will keep it from going bad [101].

Table1: Plants and theirphytochemical

PLANT	PHYTOCHEMICAL
Ashwagandha	Withaferin A and Withanolide A
Brahmi	Tannins, Flavonoids, Glycosides, Bacoside A, Bacoside B, Terpenoids, Monnierin, Hersaponin, Saponin
Cat’sclaw	Oxindole, Indole Alkaloids, Glycosides, Organicacids, Proanthocyanidins, Sterols, Triterpenes
Ginkgo Biloba	Ginkgo Flavonoids, Ginkgolide, Ginkgolicacid
Gotu Kola	Isoprenoids and Phenylpropanoidderivatives

Lion'smane	Hericenones A and Hericenones B
Saffron	Picrocrocin, Kaempferol, Safranal, Phenol, Delphinidin, Flavonoid, Crocetin
Shankhpushpi	Alkaloids, Volatile oils, Flavonoid-Kaempferol, Phytosterol, Amino Acid, Fatty Acid, Scopoletin, Beta-Sitosterol
Turmeric	Curcuminoids
Panax Ginseng	Gensenoids
Coriander	Linalool, Polyphenols, Terpenes

Conclusion

In the hunt for cutting-edge treatment therapies for neurodegenerative illnesses, investigating the neuroprotective effects of possible Indian medicinal plants offers a viable route. India's diverse flora and ancient knowledge of medicinal plants offer an enormous variety of natural substances with potential neuroprotective qualities. Numerous Indian medicinal plants have been the subject of substantial research, and the findings of preclinical studies have been encouraging. Their anti-inflammatory, antioxidant, anti-apoptotic, and neurotrophic capabilities have all been shown to have neuroprotective effects. These plants include a wide range of bioactive substances that can target several neurodegenerative pathways, such as polyphenols, alkaloids, terpenoids, and flavonoids. To convert these encouraging results from preclinical investigations to clinical applications, additional study is required. Validating the efficacy, safety, and dosing regimens of these natural substances requires thorough assessment through carefully planned clinical trials. Additionally, the discovery of bioactive elements and the clarification of their particular mechanisms of action will advance our knowledge of their neuroprotective potential and support the creation of specialized treatments. In conclusion, investigating the neuroprotective effects of possible medicinal plants from India offers enormous promise in the search for strong remedies for neurodegenerative diseases. We can uncover these natural chemicals' therapeutic potential and help create new neuroprotective therapies by fusing conventional wisdom with cutting-edgescientific methodologies. Our understanding must be improved, and

these discoveries must be applied in clinical practice in order to better the lives of people with neurodegenerative disorders. This requires ongoing study, collaboration, and careful use of medicinal plant resources.

References

1. Silva, M.V.F., Loures, C.d.M.G., Alves, L.C.V. et al. Alzheimer's disease:riskfactors and potentially protective measures. J Biomed Sci, 2019, 26, 33.
2. DeTure, M.A., Dickson, D.W. The neuropathological diagnosis of Alzheimer's disease. Mol Neurodegeneration 2019, 14, 32.
3. Allsop D. Introduction to Alzheimer's disease. Methods Mol Med. 2000;32:1-21.
4. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: A retrospective study. Lancet Neurol. 2011;10:785–96.
5. Graff-Radford J, Yong K, Apostolova LG, Bouwman FH, Carrillo M, Dickerson BC, Rabinovici GD, Schott JM, Jones DT, Murray ME. New insights into atypical Alzheimer's disease in the era of biomarkers. Lancet Neurol. 2021, 20(3), 222-234
6. Barnes J, Dickerson BC, Frost C, Jiskoot LC, Wolk D, van der Flier WM. Alzheimer's disease first symptoms are age dependent: Evidence from the NACC dataset. Alzheimers Dement. 2015;11:1349–57.
7. Cameron Wells, Samuel Brennan, Matt Keon, Lezanne, The role of amyloidoligomers in neurodegenerative pathologies, International Journal of Biological Macromolecules, 181, 2021, 582-604,
8. Tolar M, Hey J, Power A, Abushakra S. Neurotoxic Soluble Amyloid Oligomers Drive Alzheimer's Pathogenesis and Represent a Clinically Validated Target for Slowing Disease Progression. International Journal of Molecular Sciences. 2021; 22(12), 6355.
9. Cummings, J., Aisen, P.S., Du Bois, B. et al. Drug development in Alzheimer's disease: the path to 2025. AlzRes Therapy 2016, 8, 39.
10. Fogel DB. Factors associated with clinical trials that fail and opportunities for improving the likelihood of success: A review. Contemp Clin Trials Commun. 2018, 7;11:156-164.
11. Jahn H. Memory loss in Alzheimer's disease. Dialogues Clin Neurosci. 2013;15(4):445-54.
12. Sarah Wiethoff, Henry Houlden, Chapter 11 – Neurodegeneration with brain iron accumulation, Editor(s): Gabor G. Kovacs, Irina Alafuzoff, Hand book of Clinical Neurology, Elsevier, 2018,145, 157-166,

13. Sehar U, Rawat P, Reddy AP, Kopel J, Reddy PH. Amyloid Beta in Aging and Alzheimer's Disease. International Journal of Molecular Sciences. 2022; 23(21):12924.
14. Gendron, T.F., Petrucelli, L. The role of tau in neurodegeneration. Mol Neurodegeneration 2009, 4, 13.
15. Brion JP, Anderton BH, Authelet M, Dayanandan R, Leroy K, Lovestone S, Octave JN, Pradier L, Touchet N, Tremp G. Neurofibrillarytangles and tau phosphorylation. Biochem Soc Symp. 2001;(67):81-8.
16. Natalia Crespo-Biel, Clara Theunis, Fred Van Leuven, "ProteinTau: Prime Cause of Synaptic and Neuronal Degeneration in Alzheimer's Disease", International Journal of Alzheimer's Disease, vol. 2012, Article ID 251426, 13 pages, 2012.
17. Simic G, Babic Leko M, Wray S, Harrington C, Delalle I, Jovanov-Milosevic N, Bažadona D, Buée L, De Silva R, Di Giovanni G, et al. Tau ProteinHyperphosphorylation and Aggregation in Alzheimer's Disease and Other Tauopathies, and Possible Neuroprotective Strategies. Biomolecules. 2016; 6(1):6.
18. Meaghan Morris, Sumihiro Maeda, Keith Vossel, Lennart Mucke, The Many Faces of Tau, Neuron, 2011, 70, 3, 410-426,
19. Dorostkar, M.M., Zou, C., Blazquez-Llorca, L. et al. Analyzing dendritic spine pathology in Alzheimer's disease:problems and opportunities. Acta Neuropathol 130, 2015, 1–19.
20. E.Siobhan Mitchell, Nelly Conus, Jim Kaput, B vitamin polymorphisms and behavior: Evidence of associations with neurodevelopment, depression, schizophrenia, bipolardisorder and cognitive decline, Neuroscience & Biobehavioral Reviews, 2014, 47, 307-320,
21. Tinelli C, Di Pino A, Ficulle E, Marcelli S, Feligioni M. Hyperhomocysteinemia as a Risk Factor and Potential Nutraceutical Target for Certain Pathologies. Front Nutr. 2019, 24;6:49.
22. Yagi A, Kamal MA, Poddar NK. Integrated Pathways of COX-2 and mTOR: Roles in Cell Sensing and Alzheimer's Disease. Front Neurosci. 2020, 9(14), 693.
23. Minghetti L. Cyclooxygenase-2 (COX-2) in inflammatory and degenerative brain diseases. J Neuropathol ExpNeurol. 2004;63(9):901-10.
24. Chen ZR, Huang JB, Yang SL, Hong FF. Role of Cholinergic Signaling in Alzheimer's Disease. Molecules. 2022, 10;27(6):1816.
25. Frinchi M., Scaduto P., Cappello F., Belluardo N., Mudo G. Heat shockprotein (Hsp) regulation by muscarinic acetyl-choline receptor

(mAChR) activation in the rat hippocampus. J. Cell Physiol.2018;233:6107–6116.
26. Ramos-Rodriguez J.J., Pacheco-Herrero M., Thyssen D., Murillo-Carretero M.I., Berrocoso E., Spires-Jones T.L., Bacskai B.J., Garcia-Alloza M. Rapid β-amyloiddeposition and cognitive impairment after cholinergic denervation in APP/PS1 mice. J. Neuropathol. Exp. Neurol. 2013;72:272–285.
27. Bortolato M, Chen K, Shih JC. Monoamine oxidase inactivation: from pathophysiology to therapeutics. Adv Drug Deliv Rev. 2008;60(13-14):1527-33.
28. Tomas Herraiz, Hugo Guillen, "Monoamine Oxidase-A Inhibition and Associated Antioxidant Activity in Plant Extracts with Potential Antidepressant Actions", Bio Med Research International, 2018,10, 2018.
29. Marshall AC. Traditional Chinese Medicine and Clinical Pharmacology. Drug Discovery and Evaluation: Methods in Clinical Pharmacology. 2020, 2:455–82.
30. Yuan H, Ma Q, Ye L, Piao G. The Traditional Medicine and Modern Medicinefrom Natural Products. Molecules. 2016 Apr29;21(5):559.
31. Lei Wu, Wanyue Chen, Zhang Wang, Traditional Indian medicine in China: The status quo of recognition, development and research, Journal of Ethnopharmacology, 279, 2021, 114317.
32. Kelgane SB, Salve J, Sampara P, Debnath K. Efficacy and Tolerability of Ashwagandha Root Extract in the Elderly for Improvement of General Well-being and Sleep: A Prospective, Randomized, Double-blind, Placebo-controlledStudy. Cureus. 2020, 23;12(2):e7083.
33. Zahiruddin S, Basist P, Parveen A, Parveen R, Khan W, Gaurav, Ahmad S. Ashwagandha in braindisorders: A review of recent developments. J Ethnopharmacol. 2020 Jul15;257:112876.
34. Gupta SK, Jadhav S, Gohil D, Panigrahi GC, Kaushal RK, Gandhi K, Patil A, Chavan P, Gota V. Safety, toxicity and pharmacokinetic assessment of oral Withaferin-A in mice. Toxicol Rep. 2022, 18;9:1204-1212.
35. Gregory J, Vengala setti YV, Bredesen DE, Rao RV. Neuroprotective Herbs for the Management of Alzheimer's Disease. Biomolecules. 2021, 8;11(4):543.
36. Rao RV, Descamps O, John V, Bredesen DE. Ayurvedic medicinal plants for Alzheimer's disease: a review. Alzheimers Res Ther. 2012, 29;4(3):22.
37. Dennis Chang, Jianxun Liu, Kellie Bilinski, Li Xu, Genevieve Z. Steiner, Sai W. Seto, Alan Bensoussan, "Herbal Medicine for the