Phytotherapeutic alternatives for neurodegenerative dementias: Scientific review, discussion and therapeutic proposal.

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All authors have been involved in the design of the study and the systematic background investigation procedure. **Nuria Acero** reviewed the state of the art and wrote the introduction, marking the beginning of the article. **Teresa Ortega** and **Victoria Villagrasa** have developed the part on Alzheimer's disease and research in the phytotherapy field. **Gemma León** and **Dolores Muñoz-Mingarro** have developed the part on Parkinson's disease and natural products' and medicinal plants' alternatives. **Encarna Castillo** and **M. Eugenia González-Rosende** have taken care of the review of the potential of medicinal plants in Huntington's disease, also the references section, as well as the bibliographic citations throughout the document. **José Luis Ríos** and **Silvia Borrá**s have investigated the background on insomnia and anxiety linked to neurodegenerative dementias and the use of medicinal plants. **Francisco Bosch-Morell**

and **Isabel Martínez-Solís** reviewed the scientific background on medicinal plants and their phytochemicals in the case of Dementia with Lewy bodies and Mild Cognitive Impairment. They have also coordinated the work in order to obtain a harmonious and unified manuscript based on the contributions of the authors. They have also prepared the discussion, reflecting on the available information. The manuscript has been revised and corrected by all the authors and includes their suggestions.

ABSTRACT

Phytotherapy relevance: The incidence and prevalence of age-related neurodegenerative dementias has been increasing. There is no curative therapy and conventional drug treatment can cause problems for patients. Medicinal plants traditionally used for problems associated with ageing are emerging as a therapeutic resource.

Aims of the study: The main aim is to give a proposal for use and future research based on the scientific knowledge and tradition.

Material and Methods: A literature search was conducted in several searchable databases. The keywords used were related to neurodegenerative dementias, ageing and medicinal plants. Boolean operators and filters were used to focus the search.

Results: There is current clinical and preclinical scientific information on 49 species used in traditional medicine for ageing-related problems, including neurodegenerative dementias. There are preclinical and clinical scientific evidences on their properties against protein aggregates in the ~~**CNS**~~ **central nervous system** and their effects on neuroinflammation, apoptosis dysregulation, mitochondrial dysfunction, **gabaergic**~~**GABAergic**~~, glutamatergic and dopaminergic systems alterations, **monoamine oxidase** alterations, serotonin depletion and oestrogenic protection.

Conclusions: The potential therapeutic effect of the different medicinal plants depends on the type of neurodegenerative dementia and its stage of development, but more clinical and preclinical research is needed to find better, safer and more effective treatments.

Keywords: Phytotherapy, medicinal plants, **n**eurodegenerative **d**ementia, Alzheimer, Parkinson, antioxidants.

Annotated table of contents

Abbreviations

AChE, **a**cetylcholinesterase

AD, Alzheimer's disease

Aβ, amyloid β

BACE, β-site amyloid precursor protein-cleaving enzyme

BChE, **b**utyrylcholinesterase

CAG, cytosine-adenine-guanine

CBD, cannabidiol

CNS, central nervous system

COMT, catechol-O-methyltransferase

COX, cyclooxygenase

DA, dopamine agonists

DLB, **d**ementia with Lewy bodies

~~**EGCG, epigallocatechin gallate**~~

ERK1/2, extracellular signal-regulated protein kinase

~~**FDA, Food & Drug Administration**~~

GABA, gamma-aminobutyric acid

HD, Huntington's disease

IL, **i**nterleukin

IL-1β, interleukin-1β

IL-6, interleukin-6

iNOS, inducible nitric oxide synthase

JNK, c-Jun N-terminal kinase

MAO, monoamine oxidase

MAPK, mitogen-activated protein kinase

MCI, Mild cognitive impairment

ND, neurodegenerative diseases

NDs, neurodegenerative dementias

NFTs, neurofibrillary tangles

NF-κB, nuclear factor kappa B

NMDA, N-methyl-D-aspartate

PD, Parkinson’s disease

~~**PDE, phosphodiesterase**~~

PI3K/Akt, **phosphatidylinositol** -3 kinase/Akt

PGE, prostaglandin

PKC, protein kinase C

ROS, reactive oxygen species

~~SSIRs, selective serotonin reuptake inhibitors~~

TLRs, Toll-like receptors

TNF-α, tumor necrosis factor-α

1. Introduction.

Population ageing worldwide and, with it, a higher prevalence of neurodegenerative diseases (ND), including neurodegenerative dementias (NDs), pose a relevant problem for countries' health systems not only because of the economic cost, but also for human suffering. According to United Nations estimations, the number of people aged over 60 is set to double in the next 30 years. This ageing, which results from longer life expectancy, is evident in the brain because it shows characteristic changes associated with increasing neurodegeneration. Some of these changes can be highlighted, such as amyloid plaques, Lewy bodies, loss of neurons and brain volume, neurofibrillary tangles (NFTs), synaptic dystrophy, or protein abnormalities and inclusion bodies (Elobeid et al., 2016). Yet whether these lesions are the cause or effect of neurodegeneration is still not well-established (Wyss-Coray, 2016). Not only genetic factors are important in the development of NDs, environmental factors like lifestyle, diet, drug abuse and exposure to other toxins are also determining factors (Newman and Murabito, 2013). Cerebral degenerative disorders are often associated with sleep disorders. Disturbed sleep patterns and sleep deprivation accelerate the progression of NDs. Therefore, the treatment of these symptoms is a key therapeutic target for preventing such conditions (Malhotra, 2018).

However, ageing is the highest risk factor for NDs (Niccoli and Partridge, 2012). The link between aging and neurodegeneration **could** be related to loss of protein homeostasis, DNA damage, immune dysregulation, epigenetic changes, and lysosomal dysfunction (Wyss-Coray, 2016). **In this sense, aging also involves dysregulation of the immune system which also occurs in the central nervous system (CNS) (Chee and Solito, 2021). Microglia and astrocytes, components of the CNS innate immune system, release proinflammatory mediators (cytokines) in response to any damage. An excessive and prolongued inflammation can induce neurotoxicity and as a consequence dementia neurodegeneration development (Pasqualetti et al., 2015; Guo et al., 2022). There is evidence to suggest that neurodegeneration occurs in part due to processes collectively referred to as neuroinflammation (Ransohoff, 2016), which is common to neurodegenerative disorders such as multiple sclerosis (MS), Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), tauopathies and age-related macular degeneration (AMD) (Frank-Cannon et al., 2009). Neuroinflammatory responses may begin before significant loss of neuronal populations in the progression of these diseases, several of which always include the manifestation NDs.**

NDs can be classified according to clinical manifestations, and also to modifications and accumulation of proteins in neurons, glial cells and extracellular locations (Kovacs, 2016). The clinical symptoms that include cognitive decline, dementia and high-order brain function alterations, together with movement disorders (both hyper- and hypokinetic movement disorders), are especially helpful in early symptoms. Protein abnormalities can be detected only by immunohistochemistry (Kovacs, 2017). The most important proteins are tau, amyloid β (Aβ) and its precursor ~~**amyloid precursor protein**~~, α-synuclein, prion protein, transactive DNA-binding protein 43, and fused-in sarcoma

protein (Kovacs and Budja, 2010). The location of these proteins is also important for diagnostic approaches when differentiating among synaptic, intra- and extracellular protein accumulation. Apart from protein deposits, other processes cause neuronal dysfunction and death, and are, therefore, associated with these disorders. Oxidative stress, apoptosis, mitochondrial dysfunction, accumulation of interstitial lactate and glutamate, neuroinflammation, or ubiquitin-proteasomal and autophagosome/lysosomal abnormalities are normally related to neurodegeneration (Dugger and Dickinson, 2017).

Although NDs have no cure, prevention and palliative therapies can slow down the effects of ageing and help to prevent patients from becoming worse for a period of time (Solanki et al., 2016; **Di Meo et al., 2021**). Such illnesses remain asymptomatic in their early stages, which means that therapies usually commence in their more advanced stages and render them less effective. The enhancement of neuronal function or neuronal regeneration can contribute to prevent brain degenerative diseases. In line with this, evidence from many scientific research works supports the notion that plant extracts, and the secondary metabolites isolated from them like phenolics, terpenes, alkaloids, among others, are alternative sources for neurodegeneration therapy, mainly for prevention purposes (Pérez-Hernández et al., 2016). This has led to searches being made for novel treatments, which have also focused on traditional medicine and diets as alternative or complementary solutions. The ethnobotanical approach from Thai, Chinese and Ayurvedic traditional medicines, together with the traditional Mediterranean diet, are examples that provide numerous herbs used as medicinal plants, foods or spices with proven neuroprotective ability (Iriti et al., 2010).

The antioxidant and anti-inflammatory properties of the molecules isolated from plants, mainly phenolics, are well-known. The brain is especially sensitive to oxidative damage given its high oxygen demand, and the large amount of polyunsaturated fatty acids present

in neurons membranes, which are susceptible to peroxidation reactions (Uttara et al., 2009). Plant extracts are able to reduce oxidative stress by the direct uptake of free radicals, chelating divalent cations or modulating the enzymes associated with antioxidant cell strategies. Besides, their neuroinflammation suppression capacity is a consequence of their effect on the release of cytokines, and also on the down-regulation of proinflammatory transcription factors. The potential to modulate the cell-signalling pathways that affect gene expression, and to alter the phosphorylation state of target molecules, also confers neuroprotection. The blocking and activation of pathways is sometimes linked with these compounds' antioxidant activity. The **phosphatidylinositol** -3 kinase/Akt pathway (PI3K/Akt) has been found to be activated by some flavonoids to induce pro-survival and antiapoptotic genes, and to inhibit pro-apoptotic signals. Other pro-survival signalling pathways can also be activated, such as extracellular signal-regulated protein kinase (ERK1/2) **or** protein kinase C. ~~**and,**~~ **Conversely**, ~~**other inhibited**~~ cell death pathways **can be inhibited**, like c-Jun N-terminal kinase (JNK) and p38 (Solanki et al., 2016).

Phenolics have also been demonstrated to reverse neuroinflammation due to glial activation by reducing cytokine and chemokines production, such as tumour necrosis factor-α (TNF-α), IL-6 (interleukin-6) or IL-1β. They also decrease reactive oxygen species (ROS) generation and inducible nitric oxide synthase (iNOS) activity and, therefore, nitric oxide levels, and suppress cytochrome c oxidase activity through the inhibition of mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) in microglial cells (Hornedo-Ortega et al., 2018). Other neuroprotective mechanisms of phenolics involve binding to cell surface receptors, modifying cell membrane functions, modulation of enzymes in neurotransmission like acetylcholinesterase (AChE) (Pérez-Hernández et al., 2016), and anti-amyloidogenic capacity. In this sense, plants

with a wide range of ethnomedicinal uses have mitoprotective activity (Wong et al., 2021), and also have demonstrated their ability to counteract glutamate-induced neuronal damage (Prasansuklab et al., 2020), a potential mechanism underlying neuro-degeneration, and to attenuate homocysteine increases (Morillas-Ruiz et al., 2010).

Plants have been traditionally used worldwide in medicine since ancient times. Nowadays, the demand of phytotherapy is growing as an alternative and complementary approach for ND treatments. The aim of this article is to review the role of traditional plants and their components in the treatment of most NDs. With this objective, clinical and preclinical evidence is presented. Of the latter, aspects of relevance to clinical symptoms are highlighted. Finally, after discussing the background data, it proposes the plants and products considered to be the most promising ones for NDs.

2. Methodology.

A literature search was conducted in the Google Scholar, PubMed, ScienceDirect, SciFinder and **Web of science** databases, using the keywords "neurodegenerative dementias", **"neurodegeneration"** "Alzheimer's disease", "Parkinson's disease", "Huntington's disease", "~~**Dementia with**~~ Lewy bodies", **"dementia", "insomnia", "anxiety",** "aging" and "ageing", "ethnopharmacology", "ethnomedicine", "Traditional Medicine", “Natural products”, “Natural molecules”, “Phytotherapy”, “Herbal Medicine”, **and "Medicinal plants"**. Boolean operators "OR" and "AND" were used to narrow and target the search. Inclusion criteria were applied by filtering out those published 10 years ago or less, review articles, research articles, clinical trials, meta-analyses and case~~s~~ studies.

The results of the literature search for botanical species in traditional medicine are shown in Table 1.We pre-selected ND that often cause dementia associated with

ageing, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), dementia with Lewy bodies (DLB) and mild cognitive impairment (MCI). The results of the review are summarised in Tables 2-9. As the results of a first search on MCI and medicinal plants were scarce, we did not consider presenting a table.

3. Phytotherapy for neurodegenerative dementias.

The current landscape of social globalisation affects the use of medicinal plants from different traditional medicines, leading to globalisation in traditional medicine (Knöss and Wiesner, 2019). Table 1 lists the botanical names of the species and families, as well as the common name of the plants and the different traditional medicines that cite them for the amelioration of ageing-related disorders, mainly dementias, which materialise in loss of memory and attention and difficulty in learning. The species shown in table 1 are those presented as the most promising for the prevention and treatment of **NDs**, supported by scientific **background**.

3.1 Alzheimer's disease.

Alzheimer's disease (AD) occupies an important place for its high incidence in people aged over 65 years. It corresponds to 60-80% of dementia cases. Given its correlation with population ageing, AD is currently the commonest neurological disorder in the elderly and one of the most important health problems worldwide, but mainly in developed countries. This **health** problem will become more acute in forthcoming decades (Gregory et al., 2021). AD symptoms are the consequence of complex brain disorders, and include progressive memory loss, cognitive impairment, the inability to learn new information, mood swings, disorientation, executive and language dysfunctions and, therefore, the inability to carry out one's daily life. Neuropsychiatric symptoms, such

as anxiety and depression, agitation, apathy or hallucinations, may also be observed. In AD, the extracellular accumulation of Aβ aggregates in the brain's neocortex portion, and the intracellular accumulation of phosphorylated microtubule-associated tau proteins in NFTs, develop. Moreover, persistent neuroinflammation appears in the areas near these accumulations.

The activation of pro-inflammatory genes is observed, which promotes the release of IL-6, IL-1β and TNF-α. This release of pro-inflammatory mediators is accompanied by glia activation, which leads to an increase in NF-κB and toll-like receptors (TLRs) types TLR2 and TLR4 (Hampel et al., 2021; Uddin et al., 2020). In addition, the following alterations may be present: the blood-brain barrier (BBB) ~~mediated by the release of nitric oxide~~ **dysfunction related to the alteration of endothelial cells (De Bock et al., 2013)**; the cell cycle, with damage to *N*-methyl-D-aspartate (NMDA) receptors; glutamatergic transmission; different enzyme systems, as also observed in AD. All the described changes and alterations cause apoptosis dysregulation, and lack of oxidative stress control and calcium homeostasis. The resulting neurodegeneration causes a dramatic loss of synapses in the hippocampus, cortex and subcortical structures.

~~Despite considerable research efforts, the aetiology of AD still needs to be solved. It is considered that genetic factors can be determining factors in a low percentage of cases. More than 20 genes have been associated with AD. Of them, only three are related to early-onset familial forms of AD (APP, PS1, PS2) (Cuyvers and Sleegers, 2016; Gregory et al., 2021). Of other yet undescribed causes,~~ Inflammatory processes, oxidative stress, excitotoxicity~~, toxicity to metals or biotoxins, cellular autophagy impairment, insulin resistance, hypercholesterolaemia, alterations to the microbiota, hypertension, diabetes, depression, and even infections,~~ can be involved in AD onset and development (Livingston et al., 2020). As it is a chronic complex disease

of multifactorial origin, in which different pathological processes intervene whose aetiology has not yet been fully elucidated, there is no curative treatment available. Pharmacological treatment aims to alleviate symptoms. In June 2021, the Food and Drug Administration approved the use of aducanumab, a human monoclonal antibody, to prevent disease progression. Antidepressants, such as selective serotonin reuptake inhibitors and anxiolytics (benzodiazepines), are also employed to treat psychopathological states associated with moderate or severe AD. Moreover, AChE and butyryl cholinesterase inhibitor drugs (galantamine, donezepil and rivastigmine), monoamine oxidase inhibitors, anti-inflammatories, antioxidants, NMDA receptor antagonists (memantine), metal chelators and normalisers of metabolic processes are also applied. These drugs are effective in early disease stages, but not for moderate to severe processes. It can be assumed that plants might be a promising source of new bioactive compounds with anti-AChE activity, such as galantamine, an alkaloid isolated from several Amaryllidaceae members (*Galanthus* sp.pl., *Leucojum* sp.pl. and *Narcissus* sp.pl.) (Agatonovic-Kustrin et al., 2019). So it would seem reasonable to investigate the possible efficacy of medicinal plants and their active principles in which different pharmacological activities are combined because this could provide a multifactorial approach to the disease with a low incidence of adverse effects. Natural products can also act as a source of new effective molecules to be later utilised to treat AD if their low bioavailability is overcome (Daghe et al., 2021; Singh, et al., 2021a).

Many publications report the positive effects of medicinal plants and isolated active principles on AD-related cognitive decline in both clinical and preclinical studies with animal models of the disease. **It is important to highlight that different beneficial biological activities for this disease frequently converge in the same medicinal plant.** ~~**The combination of activities, such as anti-inflammatory, antioxidant,**~~

~~**neuroprotective, normalisation of metabolic processes, anti-infective, and even inhibition of Aβ protein accumulation, is attributed to most plants being effective in treating AD (Figure 1).**~~ All these activities seem to be the consequence of the synergistic action of active principles **(Figure 1)**.

3.1.1. Preclinical studies.

Several publications are available about observational and *in vitro* or *in vivo* studies, which indicate the possible efficacy of other medicinal plants like: Ginseng (*Panax ginseng* C.A.Mey.); Sage (*Salvia officinalis* L.); *Lippia origanoides* Kunth; and the mushroom *Hericium erinaceus* (Bull.) Persoon (Akhondzadeh et al., 2003; Gregory et al., 2021; Heo et al., 2008; Singh, et al., 2021a, 2021b). The active principles isolated from plants have pharmacological activities capable of counteracting some of the pathological processes involved in AD. The main targets on which they act are: AChE inhibition, Aβ peptides accumulation via the modulation of APP and β-secretase (transmembrane aspartic proteases β-site amyloid precursor protein-cleaving enzyme (BACE) 1 and BACE2); γ-secretase (presenilin proteins PS1 and PS2) activity, tau protein hyperphosphorolation; induced autophagy; control of oxidative processes in both neuronal or glial cells, or in inflammation or apoptosis (Ahmed et al., 2021; Hampel et al., 2021).

Apart from possessing marked antioxidant activity, many essential oils can inhibit AChE and BChE, and these activities are correlated with the presence of monoterpenes. Through *in vitro* and molecular docking tests, monoterpenes like 3-carene, α-pinene and β-pinene with IC_{50} values of 1.73, 2.66 and 14.75 µg/mL, respectively, exhibit more AChE inhibitory potency (Chen et al., 2021). Based on

these activities of this compounds, several essential oils from medicinal plants have been proposed to reduce AD symptoms (Table 2).

Other active principles of medicinal plants can also improve AD symptoms by acting as AChE inhibitors and, therefore, improving the cognitive functions of AD patients. The compounds with the highest inhibitory potency are those of a steroidal nature like saponins, and this activity can be reduced if a long carbon chain or two heterocyclic nitrogen methylation is introduced into the structure. Other compounds with only one benzene like ring showed also interesting IC_{50} (Ahmed et al., 2021).

Powerful antioxidants like isoflavones (genistein), chalcones like cardamonin and its derivatives, and flavonoids rutin, galangin, baicalein and myricetin, could be used to prevent the deleterious effects induced by oxidative stress. Phenolic acids like rosmarinic acid have protective effects against Aβ peptide-induced neurotoxicity, ROS generation, lipid peroxidation, DNA decomposition, tau protein hyperphosphorylation and protein kinase activation. Therefore, these substances could help to prevent the worsening of AD-related neuropsychiatric symptoms (Agatonovic-Kustrin et al., 2019; Noguchi-Shinohara et al., 2020; Subedi et al., 2021). Some of these compounds, e.g. myricetin for its hydrophobic nature and low molecular weight, can cross the BBB. Linalool, a monoterpene that is frequently present as a constituent in essential oils from aromatic plants, possesses a wide range of biological activities, including antioxidant and anti-inflammatory effects. In rat models of AD, linalool prevents Aβ neurotoxicity by inhibiting free radical production and inflammatory response (Yuan et al., 2021). Isoquinoline alkaloids like berberine (Figure 2) are capable of crossing the BBB by inhibiting Aβ production and lowering the levels of BACE1 protein and its accumulation by

promoting its clearance by autophagy through the class I PI3K/BecLin-1 pathway. This alkaloid also possesses antioxidant properties and normalising effects on blood glucose and lipidaemia (Noori et al., 2021).

However, as previously mentioned, these active principles often have a wide spectrum of actions, such as quinazolidine alkaloids that can act as modulators/inhibitors of Aβ, tau protein, AChE, BuChE, monoamine oxidase (MAO) and phosphodiesterase, as well as other protective effects that are useful in AD patients (Haghighijoo et al., 2021). In addition, numerous medicinal plants and natural products with sedative and/or anxiolytic activity can be used to treat AD-related neuropsychological effects. Aromatherapy with the essential oils of chamomile, lavender, marjoram and rosemary can significantly reduce agitated behaviour in AD patients (Agatonovic-Kustrin et al., 2019; Jimbo et al., 2009).

3.1.2. Clinical studies.

~~**Therefore, what has been believed to be a negative aspect for treating diseases with natural products to date ("dirty drugs") may now clearly represent an opportunity under multitarget conditions like AD.**~~ In most cases, the possible efficacy of applying natural products in AD has been studied ~~**as a consequence**~~ **because** of their use in traditional medicine to improve cognitive functions (Singh et al., 2021b). In quality clinical studies with AD patients, several plant species and drugs have been shown to be effective due to the active ingredients they contain **(Table 2)**.

However, although an immense effort has been made to study the efficacy of medicinal plants for treating AD, the common idea shared by both clinical and observational trials and many preclinical studies is the need for further research to

confirm the effects of plants and phytochemicals, and to establish an effective and safe dosage regimen.

Large multi-centre clinical trials are needed to validate the efficacy of both individual herbs and mixed formulations in the treatment of Alzheimer's disease and its earl. It is important that more rigorous research is conducted, with good study design, larger sample sizes and good outcome endpoints.

~~**Thus, Ashwagandha roots contain withanolides and alkaloids, Brahmi with saponins, Turmeric rhizome with phenolic compounds (curcuminoids), Ginkgo leaves have diterpenes (ginkgolides) and biflavonoids with antiplatelet and antioxidant activity, respectively (Nowak et al., 2021). Also of interest are *Centella asiatica* leaves with saponins (asiaticoside and madecassoside), and *Crocus sativus* stigmas with positive memantine-like effects on cognitive impairment (Farokhnia et al., 2014; Gregory et al., 2021). Likewise, an extract of grapes (*Vitis vinifera*) containing phenolic compounds with powerful antioxidant activity has been shown to reduce the cognitive decline associated with AD (Lee et al., 2017). Many other publications are available about observational and *in vitro* or *in vivo* studies, which indicate the possible efficacy of other medicinal plants: Ginseng (*Panax ginseng*); Sage (*Salvia officinalis*); *Lippia origanoides*; and the mushroom *Hericium erinaceus* (Akhondzadeh et al., 2003; Gregory et al., 2021; Heo et al., 2008; Singh, et al., 2021a, 2021b). The active principles isolated from plants have pharmacological activities capable of counteracting some of the pathological processes involved in AD. The main targets on which they act are: AChE inhibition, Aβ peptides accumulation via the modulation of APP and β-secretase (transmembrane aspartic proteases β-site amyloid precursor protein-cleaving enzyme (BACE) 1 and BACE2); γ-secretase (presenilin proteins PS1 and PS2) activity, tau protein hyperphosphorolation;**~~

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~~the structure. Other compounds with only one benzene like ring showed also interesting IC_{50} (Ahmed et al., 2021).~~

~~Powerful antioxidants like isoflavones (genistein), chalcones like cardamonin and its derivatives, and flavonoids rutin, galangin, baicalein and myricetin, can be used to prevent the deleterious effects induced by oxidative stress. Phenolic acids like rosmarinic acid have protective effects against Aβ peptide-induced neurotoxicity, ROS generation, lipid peroxidation, DNA decomposition, tau protein hyperphosphorylation and protein kinase activation. Therefore, these substances can help to prevent the worsening of AD-related neuropsychiatric symptoms (Agatonovic-Kustrin et al., 2019; Noguchi-Shinohara et al., 2020; Subedi et al., 2021). Some of these compounds, e.g. myricetin for its hydrophobic nature and low molecular weight, can cross the BBB. Linalool, a monoterpene that is frequently present as a constituent in essential oils from aromatic plants, possesses a wide range of biological activities, including antioxidant and anti-inflammatory effects. In rat models of AD, linalool prevents Aβ neurotoxicity by inhibiting free radical production and inflammatory response (Yuan et al., 2021). *Origanum majorana* essential oil, with monoterpenes (90.4%) and sesquiterpenes (7.9%) as minor components, promotes cognitive functions, reduces brain oxidative stress and enhances memory function in the AD Aβ1-42 rat model (Postu et al., 2020). For example, salvianolic acid B (Figure 2) obtained from the roots of *Salvia miltiorrhiza*, a water-soluble compound that could cross the blood-brain barrier, inhibits Aβ aggregation and fiber formation, contributing to decrease the neurotoxicity mediated by Aβ (Zhang et al., 2016). Isoquinoline alkaloids like berberine (Figure 2) are capable of crossing the BBB by inhibiting Aβ production and lowering the levels of BACE1 protein and its accumulation by promoting its clearance by~~

~~autophagy through the class I PI3K/BecLin-1 pathway. This alkaloid also possesses antioxidant properties and normalising effects on blood glucose and lipidaemia (Noori et al., 2021). Saponins, such as the ginsenosides from *P. ginseng*, prevent Aβ formation by the glycogen synthase kinase 3 beta (GSK3β)/tau signalling pathway, and decrease both BACE1 activity and BACE1 expression with no action on total APP and sAPPα levels (Dahge et al., 2021; Noori et al., 2021). Diterpenes like andrographolide (Figure 2) from *Andographis paniculata* are capable of reducing Aβ extracellular plaque maturation and tau protein phosphorylation by significantly reducing the oxidative stress and neuroinflammatory processes (astrogliosis and IL-6) associated with AD (Noori et al., 2021). However, as previously mentioned, these active principles often have a wide spectrum of actions, such as quinazolidine alkaloids that can act as modulators/inhibitors of Aβ, tau protein, AChE, BuChE, monoamine oxidase (MAO) and phosphodiesterase, as well as other protective effects that are useful in AD patients (Haghighijoo et al., 2021). In addition, numerous medicinal plants and natural products with sedative and/or anxiolytic activity can be used to treat AD-related neuropsychological effects. Aromatherapy with the essential oils of chamomile, lavender, marjoram and rosemary can significantly reduce agitated behaviour in AD patients (Agatonovic-Kustrin et al., 2019; Jimbo et al., 2009).~~

3.2 Parkinson's disease.

Parkinson's disease (PD) was first described in 1817 by British neurologist James Parkinson. It is the second commonest neurodegenerative disease, affects 1% of people over the age 65 years, and is more prevalent in men than in women (3:2 ratio) (Rabiei et al., 2019). PD has very characteristic symptoms, such as resting tremors, bradykinaesia, rigidity and postural instability, which usually begin gradually and worsen over time.

Other motor and non-motor (i.e. hyposmia, constipation, cognitive impairment, mood disturbances, sleep dysfunction, etc.) signs and symptoms may be related (Amstrong and Okum, 2020; Jankovic and Tan, 2020).

PD is considered to result from the interaction of many factors, such as ageing, genetic vulnerability and exposure to certain environmental factors. Currently, its aetiology remains unclear, but seems to be due to loss of pigmented dopaminergic neurons in the substantia nigra that, consequently, causes dopamine in the basal ganglia to drop, and also brings about the accumulation of intraneuronal aggregates, Lewy bodies ~~**containing α-synuclein**~~. Lack of neurotransmitter dopamine mainly affects PD patients' movement (Lee and Yankee, 2001). As in all NDs, PD has no cure. Thus treatments focus on managing symptoms with drugs (dopamine replacement, dopamine agonists with **catechol-O-methyltransferase (COMT)** inhibitors, MAO-B and COMT inhibitors, anticholinergic drugs, neurotrophic factors, etc.), surgical treatments, behavioural therapy, or a combination of different treatment options (Church, 2021; Jankovic and Tan, 2020; Rietdijk et al., 2017; Ríos et al., 2016).

Several mechanisms responsible for the degradation of dopaminergic neurons in molecular pathogenesis may be involved, such as oxidative stress, mitochondrial dysfunction, α-synuclein proteostasis, calcium homeostasis, axonal transport and neuroinflammation (Poewe et al., 2017; Rabiei et al., 2019). There is increasing evidence to link the brain-gut axis to the origin of PD. On this matter, Kochank et al. (2003) postulate that an unknown pathogen (virus or bacteria) in the gut may be responsible for sporadic PD onset. Braaks' hypothesis is that the pathology spreads through the olfactory tract and the vagus nerve, and triggers α-synuclein aggregation in the central nervous system (CNS) (Rietdijk et al., 2017). Other researchers conclude that some

microorganisms present in the faecal microbioma might be related to PD (Fernández-Espejo, 2020; Generoso et al., 2021).

As PD therapeutic strategies aim to reduce disease progression by delaying neurodegeneration, the tendency to prevent it by employing botanical-based medication with neuroprotective activity is growing (Rahman et al., 2021). Phytochemicals from medicinal plants can be a safe alternative to, or can complement, standard pharmacological treatments. According to different epidemiological studies, eating fruit, vegetables and whole grains with high contents of biologically active phytochemicals, such as flavonoids, anthocyanins, carotenoids, phytoestrogens, terpenoids, phytosterols, among others, reduces the risk of certain diseases, even in synucleinopathies like PD (Surguchov et al., 2021).

In this context, **we highlighted in Table 3 experimental and clinical studies about botanical species, and their bioactive substances, that have been reported for their therapeutic potential in PD. Some medicinal plants, such as *Ampelopsis grossedentata* (Hand.-Mazz.) W.T.Wang, *Apium graveolens* L., *Bacopa monnieri* L., *Capsicum annuum* L., *Crocus sativus* L., *Curcuma longa* L., *Garcinia indica* L., *Ginkgo biloba* L., *Hyoscyamus niger* L., *Paeonia* ×*suffruticosa* Andrews and *Sorbus alnifolia* (Siebold & Zucc.) K.Koch, have shown a remarkable neuroprotective effect. Its compounds might mitigate neurodegeneration by lowering ROS levels in the brain, preventing NO accumulation, and promoting the enhancement of α-synuclein clearance. They also act on the inhibition of MAOs and the modulation of the content of DA (Amro et al., 2018; Khazdair et al., 2021; Peterson, 2020).**

Other effective species, including *Asparagus racemosus* Willd., *Bacopa monnieri, C. sativus, C. longa, G. indica, G. biloba, Juglans regia* L., *Nigella sativa* L., *Peganum harmala* L., *Portulaca oleracea* L. *Valeriana officinalis* L., and *Vicia faba* L. have

been considered by their potent antioxidant and anti-inflammatory effects. Some in vivo and in vitro studies have proved their ability to increase the mRNA expression of stress responsive genes and reduce the expression of inflammatory mediators. (De Oliveria et al., 2009; Martins et al., 2016; Rahman et al., 2021; Yin et al., 2021).

The observed variability of therapeutic effects could be attributed to the different doses, routes of administration and origin of tested plants, extracts or active principles. Further clinical investigations to demonstrate their efficacy and to adequately explain mechanisms of action will be needed in the future to know how phytochemicals work in the brain.

~~**many medicinal plants and their active ingredients have been reported for their therapeutic potential in a variety of NDs, including PD (Rabiei et al., 2019; Rietdijk et al., 2017). Recent studies indicate that phytochemicals, such as baicalein, thymoquinone, crocin, curcumin, baicalein and other phenolics (i.e. resveratrol), have exerted considerable protective effects on the nervous system through the modulation of oxidative stress and inflammatory responses. These compounds might mitigate neurodegeneration by lowering ROS levels in the brain, preventing a drop in the dopamine levels in the basal ganglia and promoting the enhancement of α-synuclein clearance. Experimental and clinical data highlight the effect of medicinal plants, such as *Vicia faba*, *Nigella sativa*, *C. sativus*, *Bacopa monnieri*, *Peganum harmala*, *Juglans regia* and *Curcuma longa*. They act by reducing oxidative stress and neuroinflammation, also act on the inhibition of MAOs and the modulation of the content of neurotransmitters (Amro et al., 2018; Khazdair et al., 2021; Peterson, 2020).**~~

~~**Effective medicinal plants against PD also include *Mucuna pruriens* (Amro et al., 2018; Peterson, 2020), *Ginkgo biloba* (Ahmad et al, 2005; Amro et al., 2018),**~~

~~*Valeriana officinalis* (De Oliveria et al., 2009), *Paeonia suffructicosa* (Kim et al., 2014) and *Portulaca oleracea* (Martins et al., 2016). Many of these plant extracts have been studied in animal models of PD, such as *Mucuna pruriens*, a natural and important source of levodopa, and *G. biloba*, whose effects, among others, are reduced thiobarbituric acid reactive substances (TBARS) generation and more dopamine D2 receptors. As only some extracts have been tested in cell models, further studies are needed to demonstrate their efficacy and to adequately explain mechanisms of action. It should be noted that traditional medicine in both China and India has used herbs to treat NDs for thousands of years. Plenty of attention has been recently paid to this to develop promising drugs for PD. Thus, species from *Acanthopanax*, *Alpinia*, and *Astragalus*, traditional Chinese medicines such as Tianma Gouteng Yin, Chunghyuldan, Bushen Huoxue, Paeoniae alba radix, and other crude drugs and herbal formulations have been extensively investigated in both *in vitro* and *in vivo* PD models (Amro et al., 2018; Rahman et al., 2021; Yin et al., 2021). The authors note that clinical trials are essential prior to the clinical use of these medicinal plants given the observed variability of therapeutic effects, which could be attributed to the different doses, routes of administration and origin of tested plants, extracts or active principles. About the form of administration, Rahman et al. (2021) propose using nanotechnology to develop new forms of drug delivery to facilitate the access of neuroprotective phytochemicals to the brain.~~

3.3 Other neurodegenerative dementias.

3.3.1 Huntington's disease.

Huntington's disease (HD)~~, is~~ a ~~rare~~ ND of the CNS characterised by undesired choreatic movements, behavioural and psychiatric disturbances, and dementia~~. HD~~ is ~~entirely~~

~~determined genetically. It is caused by~~ an autosomal dominantly inherited mutation on chromosome 4, which results in an abnormal expansion of the **cytosine-adenine-guanine (CAG)** repeats in ~~the coding region of~~ the gene that encodes the huntingtin protein **(Jimenez-Sanchez et al., 2017)**.

The role of this protein in the neurodegeneration of striatal neurons is yet to be fully elucidated, but seems to be related to energetic defects, oxidative damage and excitotoxicity. Proteolytic production of the N-terminal fragments of the huntingtin protein ~~characterises HD and~~ results in the formation of ubiquitinated aggregates in both the nucleus and cytoplasm of neurons to induce cell death. It would seem that oxidative processes favour aggregates, and mitochondrial dysfunction and oxidative stress may play an important role in the aetiology of HD (Manoharan et al., 2016).

Currently, HD treatment is only symptomatic (Wyant et al., 2017). ~~Given the many mechanisms that converge in HD development, therapies must address different molecular targets. Indeed, plants and plant extracts are composed of many substances that can act on multiple molecular targets in an additive, or even, synergistic way (Tewari et al., 2018). Lots of studies have scientifically~~ **Scientific studies have** validated the beneficial effect of natural products against NDs, mainly those with neuroprotective, antioxidant and anti-inflammatory properties ~~(Kumar et al., 2021)~~, and other relevant pharmacological activities, like AChE, secretase inhibitory and metal chelating properties (Natarajan et al., 2013; **Tewari et al., 2018; Kumar et al., 2021**). ~~The scientific review by Lum et al. (2021) on the effect of natural products in HD shows~~ **In vitro and in vivo assays have shown** ~~14 promising~~ plants with **promising** therapeutic potential **in HD, (Table 4)**, whose mechanisms of action produce mainly ~~three effects:~~ anti-oxidant, anti-inflammatory **effects, preservation of mitochondrial function,** and neurotransmitter enhancement**, that ultimately result in neuroprotective**

activity (Lum et al., 2021). ~~These three effects ultimately result in neuroprotective activity, so the medicinal plants that Lum et al. mentioned could be potential therapeutic agents in HD.~~ However, ~~translation to clinical trials is lacking.~~ Further studies are required to elucidate the molecular mechanisms involved in the therapeutic effect of natural products in HD, and randomised controlled trials are required to confirm clinical efficacy. ~~Piwowar et al. (2020) tested *in vitro* the xanthone-enriched fraction of the ethanolic extract of *Anemarrhenae asphodeloides* rhizome in a cell culture exposed to a neurotoxic agent. The result was positive, showing a dose- and time-dependent neuroprotective effect. According to the authors, this effect could justify the traditional use of the rhizome of this species for neurological and cognitive disorders. Shivasharan et al. (2013) evaluated the neuroprotective effect of flower extract of *Calendula officinalis* in rat brain. They observed that the treatment significantly attenuated behavioral alterations, oxidative damage and striatal neuronal loss. *Celastrus paniculatus* is another species with a strong antioxidant effect and an important role against glutamate toxicity by inhibiting NMDA receptors (Malik et al., 2017). In the same vein, Shinomol et al. (2010) demonstrated that *C. asiatica* extract exhibits prophylactic protection against neurotoxicant exposure in the brain of prepubertal mice. This neuroprotective effect may be due to the enhancement of GSH, thiols and antioxidant defences. By the other hand, *Convolvulus pluricaulis* appears to have a neuroprotective effect on the brain of HD-induced rats by accelerating the brain's antioxidant defence mechanisms (Kaur et al., 2016; Malik et al., 2015). Similarly, Bhangale et al (2016) studied the effect of *Ficus religiosa* on induced HD animals. They found that high doses of ethyl acetate and ethanolic extracts (400 mg/kg) of *F. religiosa* prevented behavioural, biochemical and neurochemical alterations in neurotoxicant-treated rats, and lower~~

~~doses tested (100 and 200 mg/kg) of both extracts showed no significant activity. The authors concluded that treatment with *F. religiosa* protects the brain against oxidative stress and suggested that this plant could be of interest for the prevention of HD. Another study in HD-induced mice (Jang et al., 2013) suggests that *P. ginseng* can attenuate neurological deterioration and striatal cell death. Regarding the mechanisms of action, it inhibits microglial activation, the expression of proinflammatory cytokines (TNF-α, IL-1β and IL-6) and iNOS, and the activation of JNK, ERK, p38 MAPKs and NF-κB signalling pathways. *Luehea divaricata, Panax quinquefolius, Phoenix dactylifera, Cullen corylifolium, Punica granatum* and *Withania somnifera* are species with different mechanisms against oxidative stress, which are beneficial in HD due to their neuroprotective effect (Al-Sabahi et al., 2017; Courtes et al., 2015; Essa et al., 2019; Im et al., 2019; Kumar and Kumar, 2009; Lian et al., 2005; Mahdy et al., 2014). Finally, *Zingiber officinale* was tested in rats previously treated with a neurotoxicant inducing HD, and it was found to be neuroprotective, improving memory, locomotor strength and muscle grip in a dose-dependent manner. The results appear to be related not only to the plant's antioxidant properties, but also to its AChE capacity (Sharma et al., 2012).~~

3.3.2 Dementia with Lewy bodies.

Dementia with Lewy bodies (DLB) is a disease associated with the presence of Lewy bodies, **aggregates which contain α-synuclein associated with other proteins such as ubiquitin, neurofilament protein and αB-crystallin; Tau proteins may also be present. These protein aggregates** affect the brain´s biochemistry and functioning, and cause problems with thinking, movement, behaviour, sleep and mood (McKeith et al., 2017). Lewy bodies spread throughout the cerebral cortex and/or other brain regions. In addition to the protein abnormalities, other pharmacologically relevant biomarkers **such**

as cholinergic, dopaminergic and serotonergic systems are altered. ~~**The boundaries of DLB are unclear because it overlaps other NDs, especially AD and PD. However, DLB has its own clinical features (McKeith et al., 2017)**~~. **Although the boundaries of DLB are unclear and overlap with NDs such as AD and PD, this disorder has its own clinical features (McKeith et al., 2017).** A large body of evidence suggests that oxidative stress and neuroinflammation play a key role in disease progression ~~**and contribute to nigrostriatal degeneration**~~ (Grewal et al., 2021; Howes et al., 2020; Thapa et al., 2021). As in most NDs associated with ageing, pharmacological interventions are currently limited (Brem and Sensi, 2018), which makes medicinal plants and their extracts, plus nutraceuticals, worthy options to be investigated (Solfrizzi et al., 2018). ~~**As the presence of Lewy bodies is common in several dementias, the phytotherapeutic approach is similar for them all.**~~

In 2011, Perry and Howes conducted a comprehensive review of the scientific literature published **to date on the use of phytopharmaceuticals and nutraceuticals for brain ageing from medicinal and food plants cited in herbal and traditional medicine (Table 5).** They **commented** that galantamine (Figure 3) from ~~***Galanthus* and *Narcissus* species and other**~~ species of Amaryllidaceae **and yokukansan, a mixture of medicinal plants and mushrooms from traditional Japanese medicine,** may be useful for treating LBD, ~~**and vascular dementia,**~~ **mainly by improving psychiatric and psychological symptoms, such as irritability, agitation, aggressive behaviour, hallucinations, depression and anxiety.** ~~**As with Yokukansan, a mixture of medicinal plants and mushrooms from traditional Japanese medicine, it improves the symptoms of DLB, such as hallucinations, agitation, depression, anxiety and irritability. In the same article, the authors cited that some cannabinoids in *Cannabis sativa*, especially**~~

~~cannabidiol (Figure 3), have proven efficiency in alleviating psychotic symptoms in DLB cases, among other dementias~~.

In another review **(Table 5)**, Howes et al. (2020) offered scientific evidence for the activity of epigallocatechin gallate (Figure 3), green tea (*Camellia sinensis* **(L.) Kuntze**), cocoa (*Theobroma cacao* **L.**), coffee (*Coffea Arabica* **L.**), grape juice and wine (*Vitis vinifera* **L.**), blueberries (*Vaccinium sp pl*), citrus fruit, monoterpenes and rosmarinic acid (Figure 3) from Lamiaceae species, turmeric and soya beans. Based on this background **and despite positive results in vivo and in vitro experiments elucidating the mechanisms of action,** there is no clear correlation between using epigallocatechin gallate **or caffeine/coffee** and improving or delaying cognitive decline. However, following nutritional and medicinal guidelines, supplementation with cocoa or chocolate appears to decrease and/or delay cognitive decline and its associated symptoms. **Positive results are also cited for ~~caffeine from coffee~~, grape juice, wine,** resveratrol from grapes **with anti-Aβ-aggregates and anti-inflammatory properties; blueberries/cherries, anthocyanins and anthocyanidins from blueberries with anti-apoptotic, neuroprotective and antioxidant properties; flavanones, methoxyflavones and coumarin from citrus juice with antioxidant, anti-inflammatory and neuroprotective properties, similar to carotenoids from species containing especially crocin/crocetin, β-carotene, lutein and zeaxanthin. ~~flavonoids. from citrus juice and carotenes from saffron~~ ~~obtained from grapes~~ ~~are also cited~~. ~~In the same vein, anthocyanins and anthocyanidins from blueberries improve cognitive functions thanks to their antioxidant properties, and against Aβ induced deterioration and hyperphosphorylation~~. ~~Flavonoids from citrus juice or carotenes from saffron are also very helpful for maintaining and improving cognitive functions~~**. Other phytochemicals of interest for their activity include curcuminoids from turmeric,

especially curcumin (Figure 3) **with antioxidant, anti-inflamatory neuroprotective and neuroregenerative properties;** monoterpenes **from several aromatic species, some of them belonging to the Lamiaceae family, with anti-inflammatory, antioxidant and neurotransmitter-regulating properties;** ~~**and**~~ rosmarinic acid from Lamiaceae species, **which is antioxidant and neuroprotective; and** ~~**as well as**~~ isoflavones from soya beans **with strogenic and antioxidant effects**. Rice bran (*Oryza sativa*) may **also** be an interesting option against **NDs as** DLB for its antioxidant and anti-inflammatory properties **(Table 5)**~~**. It activates PGC-1-alpha-dependent pathways involved in the regulation of several mitochondrial proteins, increasing cardiolipin levels, citrate synthase activity, respiratory chain complexes I and II, ATP levels and mitochondrial membrane potential, resulting in decreased mitochondrial dysfunction and oxidative stress. In addition, it activates the M2 glial receptor, increasing levels of the anti-inflammatory marker IL-10, decreasing the release of COX-2 and PGE-2, resulting in decreased neuroinflammation**~~ (Behl et al., 2021).

3.3.3. Mild Cognitive Impairment.

Mild cognitive impairment (MCI) is characterised mainly by memory impairment beyond what is naturally expected for age and education, but it is not included in the dementia category. MCI is a disorder that can affect not only memory, but also other cognitive areas, which means that this disease presents different clinical patterns related to distinct aetiologies (neurodegenerative, vascular and metabolic disorders, psychiatric diseases, etc.). ~~**As in other dementias,**~~ **P**harmacological intervention is currently very limited (Brem and Sensi, 2018)**, t**hus, medicinal plants and their extracts may be an alternative to prevent or delay MCI and its transformation into other NDs like AD, whose early stage may be MCI. Although many authors still consider this disorder as the incipient phase of other age-related dementias, MCI is now classified as a distinct disease (Chandra et al.,

2019; Petersen, 2016), and specific phytotherapeutic proposals have been made. Rai et al. (2021) reported that the mushroom *Ganoderma lucidum* **(Curtis) P.Karst** is neuroprotective, reduces neuronal degeneration, regulates neurotrophin ageing-related genes and protects against MCI. The substances present in the fruiting body of this mushroom~~, responsible for the pharmacological activity,~~ include psilocybin, triterpenoids, nucleotides, sterols and steroids. Howes et al. (2020) mentioned that there is sufficient scientific evidence to conclude about the benefits of cocoa flavanols on cognitive functions in older people with MCI, but they caution that the conclusions of the consulted research works are heterogeneous ~~for the beneficial effect on cognitive functions of a flavonoid rich diet. In addition, many other studies on the effects of cocoa flavanols neither define the specific chemical profile nor identify the studied cocoa flavanols. Based on these two assumptions,~~. **Q**uantitative and qualitative variations in cocoa flavonols may partly explain the contradictory results obtained about cocoa benefits for cognitive functions. In addition, cocoa, tea and coffee are sources of caffeine with known effects on the CNS. Caffeine (Figure 4) has been shown to play a role in long-term neuroprotection against neurotoxicity and in improving cerebral blood flow, but its ability to modulate cognitive functions cannot be confirmed because no **clinical** studies ~~about this~~ are available (Howes et al., 2020). This substance is an adenosine A_{2A} receptor antagonist that inhibits glutamate release by favouring neuroprotection, and it reduces Aβ. All these findings suggest that caffeine may act through different mechanisms to preserve or improve cognitive functions. **Although no clinical trials are available, e**pidemiological evidence suggests that coffee or caffeine intake may preserve cognitive function with ageing**, and s**ome studies associate high serum caffeine levels with slower dementia progression in older people with MCI. For saffron, only a few human studies support its benefit in dementia. One clinical trial

concluded that 1-year saffron supplementation improves cognitive function in MCI patients, but the study included only 35 participants, the trial design was unclear and it provides no details on the administered saffron supplementation (Tsolaki et al., 2016). Another study has evaluated saffron in combination with *G. biloba* and *P. ginseng*, a formula known as Sailuotong, which has already obtained positive results in vascular dementia. However, the clinical trial in MCI patients is yet incomplete. Based on background, Howes et al. (2020) conclude that antioxidant-rich foods, such as walnuts, grapes and cherries, and supplementation with fatty acids, mainly n-3 polyunsaturated fatty acids (PUFA), improve specific cognitive domains in MCI. Unfortunately, there are no conclusive data for other promising foods like turmeric, grapes (red wine) and coffee. Lau et al. (2020) published the results of the double-blind, randomised and placebo-controlled trial conducted to evaluate MCI treatment with *Persicaria minor* **(Huds.) Opiz.** The extract of this species was used **(250 mg/day)** for 6 months in older adults with MCI. ~~**The trial included 36 people aged 60-75 years, all with MCI, of whom 18 were treated with 250 mg/day of *P. minor* extract and the rest with a placebo.**~~ After evaluating the study data, they reported an improvement in MCI symptoms ~~**and concluded that a 6-month supplementation with *P. minor* extract can significantly improve**~~ **such as** visuospatial memory, tension, anger, confusion, total negative subscales and even triglycerides. However, the authors are self-critical of their small study sample size. They concluded that the results should be considered preliminary and a study with more participants is necessary.

3.4. Insomnia and neurodegenerative diseases.

Sleep disorders are frequently related to many NDs (Bah et al., 2019), and there is clear evidence for an association between sleep disorders and cognitive impairment. However, insomnia is also associated with an increased risk for dementia in older adults (Almondes

et al., 2016; Shi et al., 2018). In addition, prospective studies identify female gender, depressed mood and physical illness as general risk factors for future sleep disturbances, but no specific physiological pathways have yet been established (Smagula et al., 2016).

Common sleep disorders include insomnia, hypersomnia, sleep apnea, restless legs syndrome, circadian rhythm disorders, rapid eye movement and sleep behaviour disorder NDs (Malhotra 2018; Chan et al., 2018). These disorders can be the consequence of NDs and act as primary symptoms, or may be generated by alterations in sleep-controlling centres in the brain by modifying the cellular clearance of misfolded neurotoxin proteins like Lewy bodies, α-synuclein, amyloid-β and tau, which are involved in different NDs (Bishir et al., 2020; Chan et al., 2018; Malhotra 2018). There is evidence that sleep deficiency in AD and PD affects the circadian physiology and negatively impacts brain and behavioural functions (Lim et al., 2014; Zhong et al., 2011). This process occurs in the dorsomedial hypothalamic nucleus, which transmits an excitatory glutamatergic projection to the wake-promoting neurons of the ascending arousal system, and inhibits **gamma-aminobutyric acid (GABA)** projection to the sleep-promoting neurons of the ventrolateral pre-optic nucleus (Zhong et al., 2011).

The pharmacological treatments of these events are the same as those used for treating primary sleep disorders, but need to be paid special attention because they can cause or increase sedation and falls in demented and older people. Other therapies, such as melatonin or bright light therapy, can serve as a possible treatment for sleep disorders in these people (Deschenes and McCurry, 2009; Ooms and Ju, 2016). Complementary medicine may also be a good way to treat insomnia (Sarris and Byrne, 2011), and the principal phytomedicines used for treating sleep disorders are lemon balm, neroli oil, lavender, valerian, hops and passionflower. Other medicinal plants**, such as goldshower (*Galphimia glauca*),** have been employed for the same purposes, but no relevant clinical

trials ~~performed~~ with patients suffering NDs have been performed **(Herrera-Arellano et al., 2007; Herrera-Arellano et al., 2012)**.

Therefore, in the NDs context, it is interesting to indicate phytotherapeutic alternatives for important symptoms in such diseases, such as insomnia and anxiety. Lemon balm (*Melissa officinalis* **L.**) is a widely used sedative-hypnotic that strengthens memory, relieves stress-induced headaches, among others (Moradkhani et al., 2010). Haybar et al. (2018) **conducted a clinical trial with patients suffering from cardiovascular diseases with high levels of depression, anxiety, stress and insomnia. The results were evaluated before and after treatment and the levels of depression, anxiety and stress, and total sleep disturbance, of the patients treated with lemon balm were lower than for the placebo group (Table 6). Besides, lemon balm can be used as protection in ischemia mediated by the inhibition of hypoxia-inducible factor 1-alpha (HIF-1α) and oxidative stress (Table 7) (Bayat et al. 2012).** ~~**performed a double-blind placebo-controlled clinical trial with 80 patients affected by cardiovascular diseases with high levels of depression, anxiety, stress and insomnia. The results were evaluated before and after treatment, using the short 21-item version of the Depression, Anxiety and Stress Scale (DASS-21) and the Pittsburgh Sleep Quality Index (PSQI). The levels of depression, anxiety and stress, and total sleep disturbance, of the patients treated with lemon balm (3 g daily for 8 weeks) were lower than for the placebo group. Besides, lemon balm can be used as protection for ischaemic damage mediated by the inhibition of hypoxia-inducible factor 1-alpha (HIF-1α) and oxidative stress. These effects have been demonstrated in animals, but could be interesting for humans.**~~

Neroli oil (*Citrus* × *aurantium* **L.**) is employed as a sedative to treat anxiety (Borrás et al., 2021). **Different properties have been proposed for neroli oil (Dosoky and Setzer,**

2018). Indeed, there are reports of it acting as an effective agent for reducing anxiety before colonoscopy and in postmenopausal women (Table 6) (Hu et al., 2010; Abbaspoor et al., 2021). Arabfirouzjaei et al. (2019) reported a clinical trial applied to elderly patients with heart failure. Sleep quality was assessed before and after intervention and it observed that enhanced the sleep quality (Table 6). These effects occur through the regulation of serotoninergic receptors (5-HT$_{1A}$) (Table 8) (Costa et al., 2013) whereas antioxidant effects are implicated in neuroprotection (Ammar et al. 2012; Stohs et al., 2017). ~~**Arabfirouzjaei et al. (2019) reported a randomised clinical trial applied to elderly patients with heart failure (N=80). Sleep quality was assessed before and after intervention by a standard measure with the Saint Mary Hospital Sleep Questionnaire (SMHSQ). Elderly patients were treated with 2 drops of 10% neroli oil (on cotton wool ball, 20 min. on 3 consecutive nights), which enhanced sleep quality *versus* a placebo (without treatment). Different properties and mechanisms have been proposed for neroli oil. Indeed, there are reports of it acting as an effective agent for reducing preoperative anxiety before minor operations and in postmenopausal women. These effects occur through the regulation of serotoninergic receptors (Ammar et al., 2012) whereas antioxidant effects are implicated in neuroprotection (Dosoky and Setzer, 2018).**~~

Lavender (*Lavandula angustifolia* Mill.) is helpful for treating insomnia and anxiety (Table 6) (Kasper et al., 2010). Dos Reis Lucena et al. (2021) carried out a clinical trial in that patients inhaled a lavender essential oil. It observed an improvement in lavender-treated patients: wake after sleep onset, sleep pattern, sleep quality and sleep efficiency (Table 6). In a meta-analysis, Von Känel et al. (2021) investigated the therapeutic effects of Silexan (80 mg) on the somatic symptoms, insomnia/fatigue and physical health of patients with anxiety disorders. Their results confirmed that

Silexan may be used for anxiety and for enhancing somatic symptoms, including pain and insomnia. Lavender is also cited as a neuroprotective agent (Koulivand et al., 2013). Hancianu et al. (2013) described that these effects are due to the antioxidant and antiapoptotic activities of lavender (Table 2). Another study suggests that lavender oil neuroprotection can be generated by the inhibition of protein oxidation and lipid peroxidation (Table 8) (Wang et al., 2012).

Passionflower (*Passiflora edulis* Sims) is used to treat anxiety and insomnia (Miroddi, 2013). Ngan and Conduit (2011) indicated that a low dose of passionflower yields short-term subjective sleep benefits for healthy subjects with mild fluctuations in sleep quality (Table 6). Another clinical trial demonstrates the positive effects of passionflower on objective sleep parameters in adult patients with insomnia disorder using a total sleep time by polysomnography (Table 6) (Lee et al., 2020). A systematic review by Janda et al. (2020) includes nine clinical trials and reports the lowering of anxiety levels in patients treated with passionflower preparations, with less evident effects in people with mild anxiety symptoms. These findings demonstrate its capacity to reduce symptoms of neuropsychiatric origin with no adverse effects. The anti-anxiety effect of passionflower is comparable to standard benzodiazepines, and its use can be safe and effective in diminishing stress reactivity, anxiety and depression-like behaviours and, consequently, to treat insomnia. The different compounds present in passionflower have been implicated in its sedative effects. For example, preclinical experiments demonstrate that flavonoid chrysin (Figure 5) has similar anxiolytic properties to midazolam, an effect that is due to the modulation of GABAA receptor activity (Table 8) (Brown et al., 2007). Recently, Zhang et al. (2021) studied the effects of chrysin nanoparticles on oxidative stress, neuronal apoptosis and nuclear factor erythroid (Nrf2) (Table 8). These authors

report that the flavonoid can counteract oxidative stress, reduce neuronal apoptosis and up-regulate Nrf2. All this can account for the role of this flavonoid in the pharmacological passionflower profile. Alkaloids harmine and harmaline (Figure 5) may be partly responsible for passionflower anxiolytic and sedative properties (Al-Mamoori et al., 2019).

Valerian (*V. officinalis*) is widely used as a sedative, hypnotic and anticonvulsant (Plushner., 2000). Ziegler et al. (2002) studied the hypnotic effect of valerian showing a similar effect when patients received valerian or oxazepam (Table 6). Stevinson and Ernst (2000) carried out a meta-analysis with nine clinical trials to determine the beneficial effects of valerian on patients with insomnia. Clear sedative effects and significant differences appear between the methodologies of the evaluated clinical trials. Fernández-San Martín et al. (2010) performed three meta-analyses and the outcomes indicate that valerian enhances sleep quality with the dichotomous variable. However, valerian does not improve the latency time in sleep quality according to visual analogical scales. On the valerian properties in neuroprotection, Malva et al. (2004) suggested them being due to its long-term effects against amyloid-β toxicity, and it possibly preventing neuronal degeneration in ageing or NDs.

Hops (*Humulus lupulus* L.) have been used for anxiety and mood disorders (Borrás et al., 2021). In a clinical trial, Kyrou et al. (2017) report enhanced symptoms in patients with anxiety, stress and depression, and reduced insomnia associated with these effects (Table 3). Hops contains the chalcone xanthohumol (Figure 5), which is cited as being responsible for different plant properties (Vázquez-Cervantes et al., 2021). For example, in a preclinical trial, Rancán et al., 2017 demonstrated that xanthohumol exerted a protective effect on damage induced by ageing and by reducing insomnia.

Ashwagandha (*Withania somnifera* (L.) Dunal) is a traditional herb used in Ayurvedic medicine. It has been used to treat neuropsychiatric effects, particularly stress, anxiety, depression, and insomnia. This species spreads widely due to is an adaptogen (Speers et al., 2021). Langade et al (2021) designed a clinical trial and showed an improvement of sleep quality in healthy subjects and in patients with insomnia (Table 6). Deshpande et al. (2020) demonstrated the enhancement of sleep quality in healthy patients (Table 6). Ashwagandha is also used for neurodegenerative diseases (Dar et al. 2020). Withanolide-A, can induce neuroprotective effects against glutamate-induced excitotoxicity by mitigating the neuronal dysfunction and oxidative stress through PI3K and Akt-dependent mechanism (Table 7) (Dar et al. 2018). In a preclinical trial, Kaur et al. (2017) showed the anxiolytic and anti-neuroinflammatory potential in diet-induced obesity (Table 8).

The principal combination of interest for treating insomnia is valerian/hops. Koetter et al. (2007) studied the efficacy of an extract composed of valerian/hops in patients with non-organic insomnia (Table 9). The outcomes show that the valerian/hops mixture is more effective than valerian alone. Nevertheless, no differences appear between the valerian and placebo groups. In another study, Dimpfel and Suter (2008) observed an enhancement in the patients who took a single valerian/hops fluid extract administration (Table 9). Morin et al. (2005) investigated the hypnotic effect of valerian/hops versus an antihistamine drug. The outcomes confirm that the valerian/hops mixture can be used to treat mild insomnia (Table 9).

After reviewing the limited clinical trials conducted with sedative and hypnotic species, these medicinal plants can be used to treat sleep disorders. They may also have neuroprotective effects on different NDs given their antioxidant and anti-

inflammatory properties, as several studies demonstrate. Although very few clinical trials have confirmed the sedative properties of these plants, numerous preclinical trials back their potential use (Hattesohl et al., 2008; Grundmann et al., 2008).

~~**Dos Reis Lucena et al. (2021) reported a double-blind randomised controlled trial with 35 postmenopausal women with insomnia who inhaled 0.12 mL of lavender essential oil or a placebo. The following were enhanced in the lavender-treated patients: wake after sleep onset, sleep pattern, sleep quality and sleep efficiency. In a meta-analysis, von Känel et al. (2021) studied five randomised placebo-controlled trials to investigate the therapeutic effects of Silexan (80 mg) on the somatic symptoms, insomnia/fatigue and physical health of patients with anxiety disorders. Their results confirm that Silexan may be used for anxiety and for enhancing somatic symptoms, including pain and insomnia. Lavender is also cited as a neuroprotective agent (Koulivand et al., 2013). By knowing this property, Hancianu et al. (2013) studied the neuroprotective effects of lavender oil on scopolamine-induced dementia in animals. These authors describe how these effects are due to the antioxidant and antiapoptotic activities of lavender. Another study suggests that lavender oil neuroprotection can be generated by the inhibition of protein oxidation and lipid peroxidation (Wang et al., 2012). Passionflower (*Passiflora edulis*) is used to treat anxiety and insomnia (Borrás et al., 2021). Ngan and Conduit (2011) indicated that a low dose of passionflower yields short-term subjective sleep benefits for healthy subjects with mild fluctuations in sleep quality. The double-blind placebo-controlled trial was performed for 1 week with 41 participants and was evaluated by the Spielberger's State-Trait Anxiety Inventory (STAI). Another clinical trial demonstrates the positive effects of passionflower on objective sleep parameters in adult patients with insomnia disorder (N=110) using a total sleep time**~~

~~by polysomnography (Lee et al., 2020). A systematic review by Janda et al. (2020) includes nine clinical trials, and reports the lowering of anxiety levels in patients treated with passionflower preparations, with less evident effects in people with mild anxiety symptoms. These findings demonstrate its capacity to reduce symptoms of neuropsychiatric origin with no adverse effects. The anti-anxiety effect of passionflower is comparable to standard benzodiazepines, and its use can be safe and effective in diminishing stress reactivity, anxiety and depression-like behaviours and, consequently, to treat insomnia. The different compounds present in passionflower have been implicated in its sedative effects. For example, preclinical experiments demonstrate that flavonoid chrysin (Figure 5) has similar anxiolytic properties to midazolam, an effect that is due to the modulation of $GABA_A$ receptor activity (Brown et al., 2007). Recently, Zhang et al. (2021) studied the effects of chrysin nanoparticles on oxidative stress, neuronal apoptosis and nuclear factor erythroid (Nrf2). These authors report that the flavonoid can counteract oxidative stress, reduce neuronal apoptosis and up-regulate Nrf2. All this can account for the role of this flavonoid in the pharmacological passionflower profile. Alkaloids harmine and harmaline (Figure 5) may be partly responsible for passionflower anxiolytic and sedative properties (Al-Kuraishy et al., 2020). Valerian (*Valeriana officinalis*) is widely used as a sedative, hypnotic and anticonvulsant (Borrás et al., 2021). Ziegler et al. (2002) studied the hypnotic effect of valerian on 202 subjects, who received an extract of valerian (LI156) or a standard drug for 6 weeks, with similar results in both groups. Stevinson and Ernst (2000) carried out a meta-analysis with nine clinical trials to determine the beneficial effects of valerian on patients with insomnia. Clear sedative effects and significant differences appear between the methodologies of the evaluated clinical trials. Fernández-San Martín et~~

al. (2010) performed three meta-analyses with 18 randomised, placebo-controlled and double-blind clinical trials to measure the latency time in minutes to fall to sleep, sleep-quality improvement and improvement in dichotomic sleep quality. The outcomes indicate that valerian enhances sleep quality with the dichotomous variable. However, valerian does not improve the latency time in sleep quality according to visual analogical scales. On the valerian properties in neuroprotection, Malva et al. (2004) suggest them being due to its long-term effects against amyloid-β toxicity, and it possibly preventing neuronal degeneration in ageing or NDs. Hops (*Humulus lupulus*) have been used for anxiety and mood disorders (Borrás et al., 2021). In a clinical trial, Kyrou et al. (2017) report enhanced symptoms in patients with anxiety, stress and depression, and reduced insomnia associated with these effects. In a preclinical trial, hops are interesting for treating the inflammation and apoptosis of aged brains by exerting a protective effect on damage induced by ageing and by reducing insomnia. Hops contain the chalcone xanthohumol (Figure 5), which is cited as being responsible for different plant properties (Rancán et al., 2017; Vazquez-Cervantes et al., 2021). References should also be made to relevant plant combinations to treat insomnia. The principal combination of interest for treating insomnia is valerian/hops. Koetter et al. (2007) studied the efficacy of a dry fixed extract combination (Ze 91019) composed of valerian/hops. This was administered to patients with non-organic insomnia. The outcomes show that the valerian/hops mixture is more effective than valerian alone. Nevertheless, no differences appear between the valerian and placebo groups. In another study, Dimpfel and Suter (2008) observed an enhancement in the patients who took a single valerian/hops fluid extract administration. In another clinical trial, Morin et al. (2005) investigated the hypnotic effect of valerian/hops *versus* an antihistamine drug. The outcomes confirm

~~that the valerian/hops mixture can be used to treat mild insomnia. After reviewing the limited clinical trials conducted with sedative and hypnotic species, these medicinal plants can be used to treat sleep disorders. They may also have neuroprotective effects on different NDs given their antioxidant and anti-inflammatory properties, as several studies demonstrate. Although very few clinical trials have confirmed the sedative properties of these plants, numerous preclinical trials back their potential use.~~

4. ~~Discussion and therapeutic proposals. Research perspectives and improvements.~~ Discussion and Therapeutic Proposals: Research Perspectives and Improvements.

In a normal population, some cognitive functions decline upon ageing with a certain degree of forgetfulness, the diminished ability to concentrate and solve problems, which are not considered pathological. Biomarkers of the normal brain ageing process have not been extensively investigated, but oxidative stress, mitochondrial dysfunction, apoptosis and telomeric DNA depletion are implicated (Van Ginneken, 2017), as are increased white matter lesions, Aβ plaques, NFTs and tau pathology, Lewy bodies, α-synucleinopathy, decreased neurotransmitter systems, including cholinergic ones, vascular lesions and cortex shrinkage, especially the hippocampus. All these changes increase in NDs (Howes et al., 2020), and each is associated with specific disorders. No curative treatment for NDs exists. Treatment is specific and personalised according dementia type, disease stage, and the characteristics of both the patient and drug. ~~For AD, MCI, DLB and PD, treatments are normally established on several fronts, and drugs are administered and improve cholinergic function, reduce oxidative stress, as well as anti-parkinsonian and anti-dementia drugs, and sometimes a miscellany of natural substances~~ **For AD, MCI and PD, treatments are often established on several fronts, with drugs that improve cholinergic function and reduce oxidative stress;**

anti-parkinsonian and anti-dementia drugs are also used, and sometimes a miscellany of natural substances (Martín, 2008). **Information is available from clinical and preclinical studies, especially the latter, on the potential of medicinal plants and their phytochemicals in the therapy of dementias, including NDs. However, we must comment that, despite this information, we cannot be sure that in all cases the improvement in cognition achieved in the elderly population with dementia is substantially greater than that achieved by the drugs currently used. It should also be noted that one of the points of agreement in clinical and observational trials and in many pre-clinical studies is the need for further research to confirm the effects of plants and phytochemicals, to obtain an effective and safe treatment regimen. What we can say, however, is that medicinal plants and their isolated active principles show promise in the treatment of NDs, especially given the limited pharmacological arsenal, the chronic nature of the treatments and the need for personalised treatments for optimal results.** ~~**Therefore, the treatment of NDs includes employing medicinal plant extracts, or better still, their active principles beyond a folk form.**~~ ~~**There is plenty of information available from clinical and preclinical studies about the potential of medicinal plants and their phytochemicals for the therapy of dementias, including NDs. However, we should state that, despite such information, we cannot generally argue that the improvement in cognition achieved in the elderly population with dementia is substantially greater than that accomplished by currently used drugs. We should also point out that one of the points of agreement in clinical and observational trials and many preclinical studies is the need for further research to confirm the effects of plants and phytochemicals, and to obtain a safe effective treatment regime.**

Folk medicine is a source of knowledge about the use of plants to treat dementia. In traditional European medicine (Perry and Howes 2011), the most frequently used plants include ***M.~~elisa~~*** *officinalis* and several *Salvia* species, as resources to treat memory problems in particular. Some clinical studies support the traditional use and preclinical studies explain the activity of plants. Except for one species, *Vinca minor* **L.**, whose activity relates more to cerebral blood flow, others contain several substances that act on not only AChE, but also as antioxidants through mechanisms that are not always known. In all cases, the effect noted in clinical trials is improved cognition maintenance at several levels, especially memory. In traditional Chinese medicine (Perry and Howes, 2011), the species used and scientifically proven to ameliorate the deterioration associated with ageing include *G. biloba* and *P. ginseng*. These plants have several active principles capable of acting via very different mechanisms on oxidative stress, AChE, Aβ and its toxicity, the protein profile, etc. In clinical trials, improvement in disease appears in all cases, although these studies are neither definitive nor comparable given their different designs, numbers of patients, etc. Of all these active ingredients, we highlight two as authorised drugs to treat the cognitive symptoms of dementia: galantamine and rivastigmine. This supports the interest shown in, and the need for, further research in the plant-derived substances field to treat NDs. Ayurvedic medicine also cites some botanical species used against dementia. They include ***~~Withania~~ W.*** *somnifera, C. longa, B. monnieri* and ***~~C.~~ Centella*** *asiatica* **(L.) Urb.**, which reduce brain ageing, induce anti-oxidative stress and memory-enhancing effects, and help to regenerate neural tissue. They also induce anti-inflammatory, anti-amyloidogenic nutritional and immune-supporting effects on humans. The extracts or some of the active ingredients from cited species are interesting as adjuvants for treating some NDs, e.g. AD (Farooqui et al., 2018). According to Wong et al. (2021), there is ample evidence for a potential role of *C. asiatica*

in treating brain ageing, PD and AD. These authors provide evidence for activity on mitochondrial dysfunction and an anti-neuroinflammatory effect, but provide neither detailed information about the chemical profile of extracts or plants, nor the mechanisms of action of active principles. These data are necessary to understand and manage pharmacological activity for possible treatment. Nevertheless, *C. asiatica* is still a promising alternative for NDs. Thai medicinal plants include some that are cited as possessing activity against glutamate degeneration and related toxicity (Prasansuklab et al., 2020), which might prove beneficial for many NDs. However, chemical tests and in-depth studies on their active principles and mechanisms of action are lacking. Although the information that derives from traditional medicine is incomplete and more research is necessary, we note that all the species (and substances) recommended in different folk medicines are the same as those we find in the clinical and preclinical background on phytotherapy with applications in different NDs. Once again, the richness of ethnobotany, ethnopharmacology and ethnomedicine is evidenced. These should be the starting point to search for active molecules to treat diseases when a poor pharmacological arsenal is available.

The problem with many phytochemicals, as with other types of substances, is that they do not always easily pass through the human BBB and are, therefore, not effective in patients, even if they come over in preclinical studies as promising candidates. Ovais et al. (2018) present encouraging work on future opportunities to treat NDs, mainly AD, based on the combined use of natural substances and nanoparticles. These authors report an exhaustive review of potential anti-AD substances, which coincides with those highlighted in our review and can be useful for treating several NDs with a similar aetiology. They mention the withanolides and withanamides from ~~***Withania W.***~~ *somnifera* and how they effectively inhibit the ~~**β-site amyloid precursor protein cleavage enzyme**~~

BACE1 and AChE. They also include curcumin from *C. longa* because it binds to the active motif of Aβ, protects neuronal cells from Aβ-induced cell damage, prevents fibril formation, effectively inhibits the formation of Aβ oligomers and fibrils in the brain, and reduces some astrocytic markers and plaque burden. Asiaticosides from *C. asiatica* also inhibit the Aβ level in the brain. Other substances from several plants that also act on Aβ and its toxic effects include crocin from *C. sativus*, bacosides and reserpine from *B. monnieri*, and *S*-allylcysteine from *Allium sativum* **L**. Another constant of the plant drugs cited by these authors is their effect on the cholinergic system, such as gingenosides from *P. ginseng* and the previously cited bacosides and reserpine. Activity on protein and enzyme profiles is also highlighted through either direct or indirect effects. The substances with this activity include cathequins, ginsenosides, caffeine, among others. These authors also highlight effects on neuroinflammation, especially of glycyrrhizin, and on neuronal maintenance and even regeneration, especially of bilobalides and ginkgolides. All these substances, their effects and properties, are the same as those that appear in the current literature. All the substances that are presented as plausible alternatives to treat NDs must have adequate pharmacokinetic properties to reach their target site, namely the brain. However, their pharmacokinetic characteristics do not always allow them easy access to the brain, and so, they do not show expected activity in clinical studies, whose results are heterogeneous and inconclusive. To avoid pharmacokinetic problems, employing nanoparticles can be very useful for administering the four essential types of phytochemicals for NDs: substances that modulate neurotransmitters; antiprotein aggregates; oxidative stress reducers; inhibitors of neuroinflammation. Based on the results of the experiments in Ovais et al. (2018), this system seems effective in crossing the BBB and gaining access to the brain, where active principles must exert their action. However, we note that further preclinical and clinical

research is necessary in this area. Perhaps an alternative to nanotechnology would be to redesign phytochemicals to improve their pharmacokinetic properties (pharmacomodulation) and to check that they have not lost their pharmacological activity. On the other hand, it would also be interesting to investigate the use of extracts instead of isolated active ingredients because the non-active compounds that accompany active ingredients can sometimes act as adjuvants to improve their bioavailability.

Despite pharmacokinetic problems with some phytochemicals, and as chemical profiles of the extracts of many botanical species, knowledge about specific mechanisms of action and, above all, clinical trials supporting the use of phytochemicals and/or plant extracts are lacking, we wish to put forward a proposal that can be the basis for future research. We consider that employing medicinal plants and their phytochemicals could follow a strategy, which should be based on the characteristics of each disease and its evolution, the properties and mechanisms of plant extracts or phytochemicals, and the characteristics of phytochemicals and existing data from clinical trials. To develop our proposal, Table **10** ~~**2CC**~~ summarises the actions of the medicinal plants tested in each reviewed ND. Protein abnormalities in NDs occur and lead to the formation of intra- or extra-neuronal aggregates. These aggregates differ in each disease, but are favoured by oxidative stress in all cases, and lead to neuroinflammation and apoptosis in many cases. Using plants or their phytochemicals with antioxidant properties can reduce or delay the formation of aggregates, neuroinflamation and apoptosis. This is particularly interesting in the early stages of AD and MCI, and of dementias characterised by the presence of Lewy bodies, such as DLB and PD. HD differs in aggregate formation terms because the huntintian protein is difficult to modulate as its origin lies in a genetic mutation, and not in the cellular ageing effect. However, antioxidants can counteract the effect of the aggregates of this protein. The species with antioxidant, anti-neuroinflammatory and anti-aggregate

properties, and backed by sufficient data to support its efficacy and safety, include ~~*Withania*~~ ***W.*** *somnifera*, *B. monnieri*, *C. longa*, *G. biloba*, *C. sativus*, *C. asiatica*, ~~*Vitis*~~ ***V.*** *vinifera* and ~~*Panax*~~ ***P.*** *ginseng*. In more advanced dementia stages, neuronal connections fail as synapses become less effective. Hence employing plants with AChE inhibitory activity, such as ~~*Panax*~~ ***P.****ginseng* and *Zingiber officinale* **Roscoe**, may be interesting, especially in AD. Other species are also effective in modulating different neurotransmitters. Then, *G. biloba*, *Panax quinquefolius* **L.**, ~~*Withania*~~ ***W.*** *somnifera* and *Z. officinale* act on the dopaminergic system by affecting movement and, therefore, have been investigated in PD and HD. ~~*Panax*~~ ***P.*** *quinquefolius* is a good option for glutaminergic system disturbances affecting memory and learning, and it could be explored for MCI. *C. aurantium* acts against serotonin depletion observed in some NDs; in addition, this species stands out in the treatment of insomnia and anxiety related to NDs, as well as ~~*Valeriana*~~ ***V.*** *officinalis*, *H. lupulus* and ~~*Passiflora*~~ ***P.*** *edulis*, due to the multiple effects that also improve other symptoms of the disease.

The main conclusions that can be drawn from the present work are, firstly, the importance of ethnopharmacological knowledge as a first source of information for research into future treatments for NDs; secondly, the therapeutic potential of plant species already investigated; and thirdly, the need to conduct clinical trials with homogeneous and compatible designs, as well as with sufficiently large population samples. In any case, once again, the importance of information derived from ethnopharmacological research and Traditional Medicine is highlighted. This information is necessary to open up new research lines in order to confirm the medicinal properties of plants and to search for active plant molecules. This is particularly interesting in the case of NDs, as there is currently no broad therapeutic arsenal available to meet the specific needs of each dementia and each patient.

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Figure captions.

Figure 1. Effects of natural products on **Alzheimer disease** (Based on Ahmed et al., 2021).

Figure 2. Active compounds of plants used in Alzheimer's disease.

Figure 3. Chemical structure of natural products from neuroprotective plants used for Dementia with Lewy bodies.

Figure 4. Structure of caffeine, potentially useful substance for Mild Cognitive Impairment.

Figure 5. Active plant compounds for insomnia in neurodegenerative dementias.

Table 1. Botanical species (scientific name, common name, botanical family) used in traditional medicine against the effects of ageing, including dementia and other age-related ailments, diseases and processes.

Scientific name	**Common name**	**Botanical family**	**Traditional Medicine**	**References**
Allium sativum L.	Garlic	Amaryllidaceae	TCM, TPM	Iranshahy and Javad, 2019; Shen et al., 2017
Andographis paniculata (Burm.F.) Nees.	Creat, green chireta	Acanthaceae	AM	Elaheebocus et al., 2017
Anemarrhenae asphodeloides Bunge	'Zhi mu'	Asparagaceae	TCM	Han et al., 2018; Lin et al., 2021
Artemisia annua L.	Sweet wormwood	Compositae	TCM, TM	Lu et al., 2019

Bacopa monnieri (L.) Wettst.	Brahmi, waterhyssop	Plantaginaceae	AM, TIM	Mehla et al., 2020
Calendula officinalis L.	Common marigold	Compositae	TCM	Ahmad et al., 2012; Shen et al., 2017
Camellia sinensis (L.) Kuntze	Green tea	Theaceae	HM, TCM	Roychoudhury et al., 2021; Shen et al., 2017
Celastrus paniculatus Willd.	black oil plant	Celastraceae	TIM, TCM	Shen et al., 2019
Centella asiatica (L.) Urb.	Gotu kola	Apiaceae	AM, TIM	Mehla et al., 2020
Citrus × *aurantium* L.	Bitter orange, Neroli oil	Rutaceae	AM, TM	Antara Banerjee et al., 2021

Coffea arabica L.	Coffee	Rubiaceae	TrM	Patay et al., 2016
Convolvulus prostratus Forssk. (syn: *Convolvulus pluricaulis* Choisy)	'Shankapushpi'	Convolvulaceae	AM, TAM, TCM	Semwal et al., 2021
Crocus sativus L.	Saffron	Iridaceae	AM, ITM, TCM, TM, TPM, UM	Abu-Izneid et al., 2020; Antara Banerjee et al., 2021; Iranshahy and Javad, 2019; Mehla et al.,

				2020; Shen et al., 2017
Curcuma longa L.	Turmeric	Zingiberaceae	AM, HM, TCM, TM	Antara Banerjee et al., 2021; Roychoudhury et al., 2021; Shen et al., 2017
Cullen corylifolium (L.) Medik. (syn.: *Psoralea corylifolia* L.)	Babchi	Leguminosae	TM	Im et al., 2014

Ficus religiosa L.	Sacred fig	Moraceae	TM	Bhangale et al., 2015; Tiwari et al., 2019
Ganoderma lucidum (Curtis) P.Karst.	Lingzhi, Reishi	Ganodermataceae	TCM, TM	Wachtel-Galor et al., 2004
Ginkgo biloba L.	Ginkgo	Ginkgoaceae	TIM, HM, TCM	Mehla et al, 2020; Roychoudhury et al., 2021; Shen et al., 2017
Glycyrrhiza glabra L.	Licorice	Leguminosae	AM, TCM, TM	El-Saber Batiha et al., 2020;

				Wahab et al., 2021
Hericium erinaceus (Bull.) Persoon	Lion's mane mushroom	Hericiaceae	TCM	Spelman et al., 2017
Humulus lupulus L.	Hops	Cannabaceae	TM	Astray et al., 2020
Juglans regia L.	Common walnut	Juglandaceae	TCM, TPM	Ahmad et al., 2012; Iranshahy and Javad, 2019
Lavandula angustifolia Mill.	Lavander	Lamiaceae	TEM, TM	Perry and Howes, 2011; Xu et al., 2017

Lavandula sp *(Lavandula pubescens* Decne.)	Downy lavender	Lamiaceae	TM	Paul et al., 2022
Lippia origanoides Kunth	'Orégano de México'	Verbenaceae	BTM, TM	Danilo et al-. 2014; Leyva-Jiménez et al., 2019
Luehea divaricata Mart.	'Açoita-cavalo', 'ibatingui'	Malvaceae	TCAM	Courtes et al., 2015
Melissa *officinalis* L.	Lemon balm	Lamiaceae	TEM, TPM	Iranshahy and Javad, 2019; Perry et al., 1996

Mucuna pruriens (L.) DC.	Velvet bean	Leguminosae	TM	Ogunmoyole et al., 2021
Nigella sativa L.	Black caraway	Ranunculaceae	AM, ITM, TEM, TIM, TJM, TMaM, UM	Dabeer et al., 2022
Origanum majorana L.	Sweet marjoram	Lamiaceae	TEM, TM	Mossa and Nawwar, 2011; Postu et al., 2020
Oryza sativa L.	Asian rice	Poaceae	PFM	Cabanting and Perez, 2016
Panax ginseng C.A. Mey.	Ginseng, Korean ginseng	Araliaceae	AM, TCM, TM	Antara Banerjee et al, 2021

Panax quinquefolius L.	American ginseng	Araliaceae	TNAM	Kochan and Chmiel, 2014
Passiflora edulis Sims. (syn: *Passiflora incarnata* L.)	Passionflower	Passifloraceae	TCAM, TEM, TNAM, TSAM,	Coleta et al., 2001; Deng et al., 2010; Dhawan et al., 2004
Peganum harmala L.	Wild rue	Nitrariaceae	ETM, TTuM, TItM, TCM	Ali et al., 2013; Leporatti and Ghedira, 2009; Liu et al., 2017
Persicaria minor (Huds.) Opiz	Pygmy smartweed	Polygonaceae	TMaM	Hussin et al., 2019

Phoenix dactylifera L.	Date palm	Arecaceae	TAM	Gruca et al., 2015
Pistacia	Wild pistachio	Anacardiaceae	TPM	Mahjoub et al., 2018
Punica granatum L.	Pomegranate	Lythraceae	TCM, TTM, TMoM	Ge et al., 2021
Salvia miltiorrhiza Bunge	Chinese sage	Lamiaceae	AM, TCM, TEM, TM	Perry et al., 1996
Salvia officinalis L.	Sage	Lamiaceae	TEM	Perry et al., 1996
Theobroma cacao L.	Cocoa tree	Malvaceae	TMM (Maya and Aztec civilizations)	Dillinger et al., 2000

Thymus sp	Thymes	Lamiaceae	TM	Aldosary et al., 2023; Komaki et al., 2016
Vaccinium sp pl		Ericaceae	Ethnopharmacological use Inupiat tribe (Alaska)	Kellogg et al., 2010
Valeriana officinalis L.	Valerian	Caprifoliaceae	TIM, TM	Malva et al., 2004; Nandhini et al., 2018
Vicia faba L.	Faba bean	Leguminosae	TIM	Ramírez-Moreno et al., 2015
Vitis vinifera L.	Common grape vine	Vitaceae	TPM (TIrM)	Ardid-Ruiz et al., 2020;

			TKM	Bakhtiyari et al., 2017; Chun et al., 2008; Mirheidary et al., 2020
Withania somnifera (L.) Dunal	Ashwagandha, Indian ginseng	Solanaceae	AM, TIM	Mehla et al., 2020; Sharma and Martins, 2020
Zingiber officinale Rosc.	Ginger	Zingiberaceae	TCM, TPM	Iranshahy and Javadi, 2019; Shen et al., 2017; Zhang et al., 2022

AM: Ayurvedic Medicine; **BTM**: Brasilian traditional medicine; **ETM**: Egyptian Traditional Medicine; **HM**: Herbal Medicine based on TM; **ITM**: Islamic traditional medicine; **PFM**: Philippine Folk Medicine; **TAM**: Traditional African Medicine; **TCAM**: Traditional Central America Medicine; **TCM**: Traditional Chinese Medicine; **TEM**: Traditional European Medicine; **TIM**: Traditional Indian medicine; **TIrM**: Traditional Iranian Medicine; **TItM**: Traditional Italian Medicine; **TJM**: Traditional Jewish Medicine; **TKM**: Traditional Korean Medicinal; **TM**: Traditional Medicine; **TMA**: Traditional Medicine in Asia; **TMM**: Traditional Mexican Medicine; **TMaM**: Traditional Malaysian Medicine; **TMoM**: Traditional Mongolian Medicine; **TNAM**: Traditional North America Medicine; **TPM**: Traditional Persian Medicine; **TrM**: Tropical Medicine based on TM; **TSAM**: Traditional South America Medicine; **TTM**: Traditional Tibetan Medicine; **TTuM**: Traditional Tunisian Medicine; **TUM**: Traditional Uygur medicine (Turkish); **UM**: Unani Medicine.

Table 2. Studies on medicinal plants for Alzheimer disease

SPECIES	BIOACTIVE SUBSTANCES	ACTIVITY/ MECHANISM	STUDY TYPE	REFERENCE
Allium sativum *Pistacia khinjuk*	phenols	anti-AChE activity	Preclinical study (*in vitro and in vivo*)	Chajarbeygi et al., 2019
Amaryllidaceae members: *Galanthus* sp.pl., *Leucojum* sp.pl. and *Narcissus* sp.pl.)	galantamine	anti-AChE	Preclinical study (*in vitro*)	Agatonovic-Kustrin S, et al., 2019
Andographis paniculata	andrographolide	reduces Aβ extracellular plaque maturation, tau protein phosphorylation and neuroinflammation	Preclinical study (*in vitro and in vivo*)	Lu et al., 2019 Souza et al, 2022
Artemisia annua *Glycyrrhiza glabra*	myrtenal	anti-AChE activity	Preclinical study (*in vitro*)	Kaufmann et al., 2011
Lavandula pubescens	carvacrol	anti-AChE and anti-BuChE activity	Preclinical study (in vitro)	Abd Rashed et al., 2021
Origanum majorana	monoterpenes, sesquiterpenes	antioxidant activity,	Preclinical study (*in vivo*)	Postu et al, 2020
Panax ginseng	ginsenosides	prevent Aβ formation and decrease both BACE1 activity and BACE1 expression	Preclinical study *(in vitro*)	Dahge et al., 2021; Noori et al., 2021
Rosmarinus officinalis	rosmarinic acid	Inhibits amyloid-beta oligomerization and deposition	Preclinical study (*in vitro and in vivo*)	Agatonovic-Kustrin S, et al., 2019 Noguchi-Shinohara et al., 2020 Subedi et al., 2021

Salvia sp.	α-thujone, camphor, 1,8-cineole and β-thujone	anti-AChE and anti-BuChE activity	Preclinical study (*in vitro*)	Abd Rashed et al., 2021
Salvia miltiorrhiza	salvianolic acid B	inhibits Aβ aggregation and fiber formation	Preclinical study (*in vitro and in vivo*)	Zhang et al., 2016 Abd Rashed et al., 2021
Thymus sp.	thymol, carvacrol and linalool	anti-AChE activity	Preclinical study (*in vitro*)	Agatonovic-Kustrin S, et al., 2019
Bacopa monnieri	saponins	antioxidant, anti-inflammatory, blocks Aβ production, inhibits neural cell death	Clinical study	Gregory et al., 2021
Crocus sativus	safranal	antioxidant, anti-amyloidogenic, anti-inflammatory, antidepressant, immunomodulation, neuroprotection	Clinical study	Farokhnia et al., 2014; Gregory et al., 2021
Curcuma longa	phenolic compounds (curcuminoids)	antioxidant, anti-inflammatory, antimicrobial, blocks Aβ production, inhibits neural cell death	Clinical study	Gregory et al., 2021
Ginkgo biloba	diterpenes (ginkgolides) and biflavonoids	antiplatelet and antioxidant activity	Clinical study	Nowak et al., 2021
Centella asiática	saponins (asiaticoside and madecassoside)	reduces oxidative stress, Aβ levels, and apoptosis, promotes dendritic growth and mitochondrial health	Clinical study	Gregory et al., 2021
Vitis vinifera	phenolic compounds	antioxidant activity,	Clinical study	Lee et al., 2017
Withania somnifera	withanolides and alkaloids	antioxidant, anti-inflammatory, blocks Aβ production, inhibits	Clinical study	Gregory et al., 2021

		neural cell death, dendrite extension, neurite outgrowth and restores synaptic function, neural regeneration, reverses mitocondrial dysfunction		

Table 3. Botanical species used against effects of Parkinson's disease.

Scientific name	Bioactive substances	Activity/mechanism	Study type Model of study	References
Ampelopsis grossedentata (Hand.-Mazz.) W.T.Wang	Dihydromyricetin	Potent neuroprotective agent: modulating the Akt/GSK-3β pathway	In vivo C57BL/6J Mice MES23.5 cells	Ren et al., 2016
Apium graveolens L.	Apigenin, Luteonin	Neuroprotective: improve oxidative stress, decrease the activity of MAO-A and B, and protect dopaminergic neurons.	In vivo C57BL/6J Mice	Chonpathompikunlert P et al., 2018
Asparagus racemosus Willd.	Shatavarin IV	Antioxidant (attenuation of oxidative stress) and promotes longevity: increasing the mRNA expression of stress responsive genes. Improved PD symptoms: reducing α-synuclein aggregation, lipid accumulation and enhancing dopamine level.	In vivo (*Caenorhabditis elegans* model system)	Smita et al., 2017
Bacopa monnieri	Bacosides, bacopasides, bacosaponins	Anti-inflammatory: suppressed the pro-inflammatory cytokines level, decreased α-synuclein levels, and reduced ROS generation.	In vivo Albino rats of Wistar strain	Singh et al, 2020
		Neuroprotective: decrease in GFAP immunostaining and expression of iNOS in the substantia nigra region; maintain dopamine concentrations; can inactivate the MAO-B. Improve behavioral parameters.	In vivo *MPTP-induced PD in mice* *In silico* study-AutoDock Tools	Singh et al, 2021

		Neuroprotective: reduction in the basal levels of oxidative markers such as ROS, MDA and HP; attenuating mitochondrial dysfunction.	In vivo PQ-treated mice	Hosamani et al., 2016
Capsicum annuum L.	Capsaicin	Neuroprotective: antioxidant, decrease the inflammatory response	In vivo Rotenone intoxicated mice	Abdel-Salam et al., 2018
	Quercetrin and others polyphenols	Neuroprotective: modulating DA metabolism and GSH redox status in rat brain.		Ogunruku OO et al, 2019
Crocus sativus	Crocin	Cytoprotective	In vitro (MPP^+)-injured PC12 cells	Zhang GF et al., 2015
	Crocetin	Antioxidant, cytoprotective	In vivo (fly model) Fly PD models	Inoue E et al., 2021
Curcuma longa	Curcumin	Neuroprotective: reduce apoptosis and the oxidative stress.	In vitro SH-SY5Y human neuroblastoma cells	Ma XW et al., 2017
	Aromatic-turmerone	Anti-inflammatory. Neuroprotective	In vitro Murine microglial BV2 cells Wistar rats - midbrain slice cultures	Hori Y et al., 2021
	Curcumin	Neuroprotective	In vitro/In vivo 6-hydroxydopamine lesioned rat model and PC12 cells	He HJ et al., 2022
		Antioxidant and neuroprotective	In vivo	Khatri et al., 2016

			Rotenone-treated mice	
		Neuroprotective		Darbinyan LV et al., 2017
	Curcuminoids	Anti-inflammatory. Neuroprotective	In vivo MPTP-induced PD in mice	Ojha RP et al., 2012
Garcinia indica	Garcinol	Neuroprotective: garcinol prevents NO accumulation in lipopolysaccharide-treated astrocytes. Garcinol significantly reduce the expression of inflammatory mediators (iNOS and COX-2).	In vivo (rat model) 6-hydroxydopamine lesioned rat model	Antala BV et al., 2012
Ginkgo biloba	Flavonoids, terpene lactones (ginkgolides A, B, and C)	Neuroprotective and neuromodulatory potential. Anti-oxidoinflammatory and anti-apoptotic effects. Potential gastroprotective property.	In vivo Rotenone-treated mice	Adebayo OG et al., 2022
Hyoscyamus niger	Methanolic extract of seeds: L-DOPA	Neuroprotective effect	In vivo (rat model) Wistar rats	Khatri et al., 2015
Juglans regia	Caffeic acid, polyphenols	Antioxidant: protection of dopaminergic neurons against induced neurotoxicity; prevent depletion of striatal DA and its metabolites. Improve motor symptoms.	In vitro/In vivo MPTP-induced PD in mice	Choi et al. 2016
Mucuna pruriens	L-DOPA	Efficacy and safety, noninferior to levodopa/benserazide.	Clinical trial	Cilia R et al, 2017.
		Antioxidant properties. Improves muscle rigidity compared to L-DOPA.	In vivo (mice model) Adult Balb/c mice	Jahromy et al, 2014
		Neuroprotection in early PD	In vivo (rat model)	Sedaghat R et al., 2014

Nigella sativa	Thymoquinone		Adult male Wistar rats	
		Anti-neuroinflammatory	In vitro LPS activated microglial murine cells	Taka E., 2015
		Antioxidant. Neuroprotection. Modulation of the Nrf2-ARE signalling cascade.	In vitro/In vivo Human neuroblastoma SH-SY5Y cells / C57/BL6 mice	Dong J., 2021
Paeonia x suffruticosa Andr.	Terpenes, phenols, flavonoids, tannins.	Neuroprotective	In vivo (mice model) MPTP-induced PD in mice	Kim et al. 2014
Peganum harmala	Harmaline	Antioxidant Neuroprotective	In vivo (rat model) Wistar rats	Rezaei M., 2016
Portulaca oleracea L.	Betacyanins, gallotannins, omega-3 fatty acids, ascorbic acid, α-tocopherols, kaempferol, quercetin, and apigenin. L-DOPA, DA	Antioxidant Neuroprotective	In vivo (rat model) 6-hydroxydopamine lesioned rat model	Martins et al., 2016
Sorbus alnifolia (Sieb. et Zucc.) K. Koch	Anthocyanins, flavanols, polyphenolics	Neuroprotection. *Sorbus alnifolia* protects dopaminergic neurodegeneration in *Caenorhabditis elegans* and show lifespan-extension effects in wildtype worms.	In vitro/In vivo PC12 cells / Caenorhabditis elegans	Cheon SM, 2017

Valeriana officinalis	Valeric acid (valerianic acid)	Anti-inflammatory Neuroprotective	In vivo Rotenone-treated mice	Jayaraj RL, 2020
			In vivo MPTP-induced PD in mice	Rodríguez-Cruz A, 2019
Vicia faba	Phenolic acids, saponins, aromatic amino acids, flavonoids	Anti-inflammatory, antioxidant and neuroprotective effects Improved motor activity and striatal DA level. Decrease the striatal malondialdehyde.	In vitro/In vivo In vivo Rotenone-treated mice	Abdel-Sattar E, 2022
Zizyphus spina-christi Mill.		Neuroprotection. Antioxidant. Reduce neurotoxicity.	In vitro SH-SY5Y cells	Singh et al., 2018

Abbreviations: COX-2, cyclooxygenase-2; DA, dopamine; GFAP, glial fibrillary acidic protein; GSH, oxidized glutathione; HP, hydroperoxides; iNOS, inducible nitric oxide synthase; L-DOPA, levodopa; MAO-A, monoamine oxidase-A; MAO-B, monoamine oxidase-B; MDA, malondialdehyde; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NO, nitric oxide; Nrf2-ARE, nuclear factor erythroid 2-related factor 2-antioxidant response element; PD, Parkinson's disease; PQ, paraquat; ROS, reactive oxygen species;

Table 4. Potentially useful botanical species for Huntintong's disease.

Species	Bioactive substances	Activity/mechanism	Study type	Ref
Anemarrhenae asphodeloides	Mangiferrin	↑ Antioxidant defense system	In vitro (PC-12 cells, 3 NP model)	Piwowae et al., 2020
Phoenix dactylifera		ROS scavenging, ↓ mitochondrial dysfunction	In vitro (PC-12 cells, 3-NP model)	Essa et al., 2019
Psoralea corylifolia		Restoration of mitochondrial dysfunction	In vitro (PC-12 cells, 3-NP model)	Im et al., 2014
Punica granatum	Unsaturated fatty acids (6,9-octadecadiynoic acid as 4,4-dimethyloxazoline derivative)	Neutralize ROS, ↑ antioxidant gene expression	In vitro (PC-12 cells, Genetically modified)	Al Sabahi et al., 2017
Calendula officinalis	Chlorogenic acid, rutin ferulic acid	Antioxidant, anti-inflammatory	In vivo (Wistar rats, female; 100, 200 mg/Kg; po, Toxin: 3-NP, ip)	Shivasharan et al., 2013
Celastrus paniculatus	Sesquiterpenoid polyalcohols and esters (malkanguniol, malkangunin, polyalcohol A–D, celapnin); alkaloids (paniculatine, celastrine); phenolic	↑ Antioxidant defense system, ↓ glutamate toxicity	In vivo (Wistar rats, male; 100[b], 200 mg/Kg; po, Toxin: 3-NP, ip)	Malik et al., 2017

	triterpenoids (celastrol, paniculatadiol); fatty acids (oleic, linoleic, linolenic, palmitic, stearic and lignoceric acid) and agarofuran derivatives			
Centella asiatica	Triterpene sapogenins, (madecassoside, asiaticoside), caffeic acid derivatives and flavonols	↑ antioxidant defense, preservation of mitochondrial integrity	In vivo (prepubertal mice, male, 5 mg/Kg, po, Toxin: 3-NP, ip)	Shinomol et al., 2010
Convolvulus pluricaulis	Scopoletin	↑ Antioxidant defense system	In vivo (Wistar rats, male; 10, 20[b] mg/Kg; po; Toxin: 3-NP, ip)	Kaur et al., 2016
Convolvulus pluricaulis	Scopoletin	↑ Antioxidant defense system	In vivo (Wistar rats, male; 100, 200[b] mg/Kg; po; Toxin: 3-NP, ip)	Malik et al., 2015
Gingko biloba L.	Flavoglycosides; terpene lactones	Improvement of energy metabolism, antioxidant, antiapoptotic	In vivo (Wistar rats, male; 100 mg/Kg; ip; Toxin: 3-NP, ip)	Mahdy et al., 2011
Ficus religiosa	Ethyl acetate extract: alkaloids, terpenoids and flavonoids; ethanolic extract: tannins, phenols,	↓ Oxidative stress	In vivo (Wistar rats, male; 100, 200, 400[b] mg/Kg; po; Toxin: 3-NP, ip)	Bhangale et al., 2016

	alkaloids, terpenoids, flavonoids and glycosides			
Luehea divaricata	Gallic acid, catechin,chlorogenic acid, caffeic acid, epicatechin, vitexin, rosmarinic acid, rutin, quercetin, and luteolin	↑ Antioxidant defense system, ↓ acetylcholinesterase activity	In vivo (Wistar rats, male; 500, 1000 mg/Kg; ig; Toxin: 3-NP, ip)	Courtes et al., 2015
Panax ginseng	Gingenosides	↓ Oxidative stress	In vivo (ICR mice, male; 50, 100, 250 mg/Kg[c]; po; Toxin: 3-NP, ip)	Jang et al., 2013
Panax quinquefolius	Panaxadiols (Rb1, Rb3, Rd)	Free radicals scavenger	In vivo (SD rats, male; 10 mg/Kg, po Toxin: 3-NP, ip)	Lian et al., 2005
Withania somnifera	Withanolides Withanolide A	↑ Antioxidant defense system, ↓ mitochondrial dysfunction	In vivo (Wistar rats, male) 100,200 mg/Kg;c po Toxin: 3-NP, ip)	Kumar and Kumar, 2009
Zingiber officinale		Anticholinesterase potency	In vivo (Wistar rats; 100, 200 mg/Kg[c]; po; Toxin: 3-NP, ip)	Sharma et al., 2012

Table 5. Studies on medicinal plants for Dementia with Lewy bodies.

Species	**Bioactive substances**	**Activity/Mechanism**	**Study type**	**Reference**
Species of Amaryllidaceae	galantamine	AChE inhibitor and a positive allosteric modulator of nicotinic receptors.	Review	Perry and Howes, 2011
-Yokukansan- (*Atractylodes* species; *Cnidium*; *Uncaria*; *Angelica*; *Bupleurum*; *Glycyrrhiza*; and the fungus *Poria cocos*		Partial agonist effect on 5HT1A receptors. ↑ Serotonergic and dopaminergic transmission in the prefrontal cortex. ↓Behavioural and psychological symptoms of dementia. No effect on cognitive functions.		
Camellia sinensis; *Theobroma cacao;*	Epigallocatechin gallate	↑ γ-glutamylcysteine ligase mRNA expression. ↑Cellular glutathione.	Review	Howes et al., 2020

Coffea species; *Vitis vinifera*		↑Protein kinases C activity. Suppress Bcl-2 down-regulation. Inhibits AChE and neuroinflammatory response. Modulates cerebral blood flow and electroencephalographic activity. No effect on cognitive functions.		
	Caffeine	Glutamate release inhibition. ↓Aβ aggregates. ↑Protein kinases C activity.		

		↑Phosphor- cAMP-response element binding protein levels. ↓Phosphor-JNK and –ERK expression. There is no clear clinical evidence on cognitive functions.		
Vitis vinifera; *Vaccinium corymbosum;* *Arachis* *Hypogaea;* *Pistacia vera*	Resveratrol	↓Aggregation and toxicity of amyloidogenic proteins. ↓Astrocyte and microglial activation. ↓NF-κB activation. ↓TNF-α production. ↓NO production.		

		↓MAPK phosphorylation. ↑Neurogenesis. Apparent ↓decline of cognitive functions.		
Citrus species	Flavanones	↓Cell death. ↓Excitotoxicity. ↓Oxidative stress. ↓Inflammation. ↓Mitochondrial dysfunction. ↓Lipid peroxidation.		

		↓TNF-α, TNF-β, IL-1, NF-κB activation ↓Caspase-3 activation. Improvement of cognitive functions.		
	Methoxyflavones	↓Tau hyperphosphorylation. ↓Oxidative stress. ↑BDNF production. Activation of the cAMP/ERK/CREB cell survival signalling pathway. ↓TNF-α levels.		
	Coumarins	Anti-inflammatory by inhibiting microglial activation and COX-2 expression.		

Crocus sativus; other species containing carotenoids as crocins/crocetin, β-carotene, lutein and zeaxanthin	Carotenoids	↓Aβ aggregates. Inhibition of NO, TNF-α and IL-1β. ↑Antioxidant enzymes. ↓lipid peroxidation. NO, TNF-α and IL-1β inhibition. AChE inhibition. Improvement of cognitive functions.		
Curcuma longa	Curcuminoids (curcumin)	↓NF-κB, TNF-α, and COX-2 signalling pathways.		

		Inhibition of IL-8, Il-6, IL-1β and IL-1α production. MAPK and NF-κB pathway inhibition. ↑GSH peroxidase. ↓Lipid peroxide levels. Inhibition of Aβ aggregates formation. β-secretase inhibition. ↓Microglial activation. Improvement of cognitive functions.		

Lamiaceae species; other aromatic species	Monoterpenes	AChE inhibition. ACh inhibition via nicotinic receptors. Suppresses pro-inflammatory cytokine production, via NF-κB, TNF-α, IL-1β and IL-6 and ERK pathways. ↓Oxidative stress. Improvement of cognitive functions.		
	Rosmarinic acid	AChE inhibition. Anti-Aβ. Antioxidant.		

		Enhances cognition, verbal learning, memory and attention.		
Glycine max	Isoflavones	Estrogenic effects. Improvement in cholinergic function. ↓Age-related neuronal loss. ↓Cognitive decline. ↑GSH peroxidase. ↓Lipid peroxidation. ↓Apoptosis. Improvement of memory.		

Oryza sativa	Rice bran extract; rice bran oil; γ-Oryzanol; Tocopherol and Tocotrienol	Activation of PGC-1-alpha-dependent pathways. ↑Cardiolipin levels. ↑Citrate synthase activity. ↑Respiratory chain complexes I and II. ↑ATP levels. ↑Mitochondrial membrane potential. ↓Mitochondrial dysfunction. Activation of the M2 glial receptor. ↑ IL-10.	Review	Behl et al., 2021

		↓ Release of COX-2 and PGE-2. ↓Oxidative stress. ↓Neuroinflamation. No clinical results.		

Table 6. Clinical trials of medicinal plants for insomnia and neurodegenerative diseases.

Species	Sample/extract	Activity/mechanism	Type of study/ Dose/ time/ administration via number of patients	Criteria	References
Citrus × *aurantium* (neroli oil)	Neroli oil	Decrease systolic blood pressure	Randomized controlled trail/ 1 drop/1 time/ inhalation N = 27	STAI-S, VAS, DBP, HR, RR, SBP	Hu et al. (2010)
	Essential oil (10%)	Improvement sleep quality	Double-blind randomized controlled trial/ 2 drop/2 time per day - 4d consecutives in a wk - 4-wk/ inhalation N = 80	PSQI	Abbaspoor et al. (2021)
	Essential oil (10%)	Enhancement sleep quality	Randomized, clinical trial 2 drop / 3-nights / inhalation N = 80	SMHSQ	ArabFirouzjaei et al. (2019)
Humulus lupulus (hops)	Melcalin (dry extract)	Least mild depression, anxiety and stress symptoms	Randomized, double-blind, placebo-controlled, crossover pilot study 400 mg / 4-wk / p.o. N = 36	ADSS, DASS-21	Kyrou et al. (2017)
Melissa officinalis (lemon balm)	Dry extract	Positive effects for depression, anxiety, stress, and sleep disorder in patients with chronic stable angina	Double-blind placebo-controlled, clinical trial 3000 mg/ 8-wk/ p.o. N = 80	DASS-21, PSQI	Haybar et al. (2018)
Lavandula angustifolia (lavender)	Silexan	Improving sleep disorders and anxiety	Randomized, double-blind, placebo-controlled trial 80 mg / 10-wk N = 221	CGI, HAM-A, PSWQ-PW, SAS	Kasper et al. (2010)

	Essential oil dilution of 6%	Improvement sleep quality	Double-blind randomized trial 0.12 mL / 29 day Silexan (essential oil) N = 35	PSQI	Dos Reis Lucena et al. (2021)
Passiflora edulis (passionflower)	Aqueous extract	Sedative effects	Double-blind, placebo-controlled trial 2000 / 1-wk N = 41	STAI	Ngan and Conduit (2011)
	EtOH extract	Sleep efficiency	Double-blind randomized placebo-controlled clinical 60 mg / 2-wk N = 110	TST, WASO, ISI, PSQI	Lee et al. (2020)
Valeriana officinalis (valerian)	Valerian extract LI 156 (Sedonium)	Decrease insomnia	Randomized, double-blind, multicenter, parallel, clinical study 600 mg / 6-wk / p.o. N = 202	GES, CGI, SF-B, PSYA, PSYE, PSS, TRME	Ziegler et al. (2002)
Withania somnifera (ashwagandha)	KSM-66 Ashwagandha extract	Increase sleep quality and it could be also used for patients with insomnia and anxiety	Randomized, double-blind, placebo controlled, parallel-group study 300 mg x 2/ 8-wk/ p.o. N= 80	HAM-A, PSQI, SE, SOL, TST, WASO Mental alertness, sleep quality	Langade et al. (2021)
	Shoden Ashwagandha extract	Improve sleep quality and it could be used to promote healthy sleep patterns and restful sleep	Randomized, double blind, prospective, parallel, placebo controlled, clinical study 120 / 6-wk/ p.o. N = 144	RSQ-W, SE, SOL, TBT, TST, WASO, WHOQOL-Bref,	Deshpande et al. (2020)

ADSS, Anxiety, Depression, and Stress Scores; CGI, clinical global impression; DASS, Depression Anxiety Stress Scale; DBP, diastolic blood pressure; GES, feeling of refreshment after sleep; HAM-A, Hamilton Anxiety Rating Scale; HR, heart rate; ISI, insomnia severity index; PSS, psychosomatic symptoms in the sleep phase; PSQI, Pittsburgh Sleep Quality Index; PSYA, psychic stability in the evening; PSYE, psychic exhaustion in the evening; RR, respiratory rate; RSQ-

W, Restorative sleep questionnaire; SBP, systolic blood pressure; SE, sleep efficiency; SF-B, sleep questionnaire B; SMHSQ, St. Mary's Hospital Sleep Questionnaire; SOL, sleep onset latenc; STAI, state trait anxiety inventory; STAI-S, State Trait Anxiety Inventory State; TST, total sleep time; TRME, dream recall; VAS, Visual Analogue Scale; WASO, wake after sleep onset.

d, day; m, month; p.o., per os (orally); wk, week.

Table 7. Studies *in vitro* of medicinal plants for insomnia and neurodegenerative diseases.

Species (common name)	Sample/extract	Bioactive substances	Activity/mechanism	Criteria	References
Citrus × *aurantium* (neroli oil)	Neroli oil	Limonene, (*E*)-nerolidol, α-terpineol, α-terpinyl acetate and (*E*,*E*)-farnesol	Antimicrobial and antioxidant (bitter orange flowers)	ABTS, GC-FID, GC-MS	Ammar et al. (2012)
Melissa officinalis (lemon balm)	Balm oil B4008 Sigma	Polyphenolics, such as rosmaric acid, trimeric compounds, flavonoids, phenolic compounds and tocopherols	Protection for ischaemic damage. Inhibition of hypoxia-inducible factor 1-alpha (HIF-1α) and oxidative stress in mouse embryos	Hypoxia *in vitro*, caspase-3 activity assay, *in situ* labeling of DNA fragmentation, RT-PCR, lipid peroxidation and antioxidant capacity	Bayat et al. (2012)
Valeriana officinalis (valerian)	Alcoholic extract	Valeneric acids	Neuroprotective mechanisms against Aβ toxicity tested in rat hippocampal neurons 10 ng/mL to 100 μg/mL	Intracellular free calcium ($[Ca^{2+}]i$	Malva et al. (2004)
Withania somnifera (ashwagandha)	*Withania somnifera* extract	Withanolide-A	Withanolide-A reduced the glutamate-induced influx of intracellular calcium and excessive ROS production	JNK/p-38/ERK (MAPK Family) Intracellular Signaling Pathway	Dar et al. (2018)

ABTS, 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) radical-scavenging; GC-FID, Gas Chromatography-Flame Ionization; GC-MS, Gas chromatography–mass spectrometry.

Table 8. Studies *in vivo* of medicinal plants for insomnia and neurodegenerative diseases.

Species (common name)	**Sample/extract**	**Bioactive substances**	**Activity/mechanism**	**Animal/ Dose: mg/kg Via**	**Criteria**	**References**
Citrus × *aurantium* (neroli oil)	Essential oil	Monoterpene limonene, β-pinene, β-myrcene	Anxiolytic-like activity mediated by 5-HT_{1A}-receptors	Adult Swiss male mice 10 mL/kg p.o.	LDB procedure	Costa et al. (2013)
Humulus lupulus (hops)	Xanthohumol	Xanthohumol	Modulated the inflammation and apoptosis of aged brains	Male senescence-accelerated prone mice (SAMP8) 1 mg/kg or 5 mg/kg day p.o.	RT-PCR and Western blotting	Rancán et al. (2017)
Melissa officinalis (lemon balm)	Plant material diluted with physiological saline to obtain a final concentration of 10%.	Polyphenolics, such as rosmaric acid, trimeric compounds, flavonoids, phenolic, and tocopherols	Protection for ischaemic damage. Inhibition of hypoxia-inducible factor 1-alpha (HIF-1α) and oxidative stress	Male Sprague–Dawley rats/ 100 mg/kg p.o	Caspase-3 activity assay, TUNEL	Bayat et al. (2012)
Lavandula angustifolia (lavender)	Lavender oil	Linalool, linalyl acetate, terpinen-4-ol, lavandulyl acetate	Neuroprotective effects: antioxidant and antiapoptotic activities	Male Wistar rats 200 µL inhalation	TTC staining, Histopathology (H&E) Staining, PCC, MDA formation, SOD, GPX, CAT, GSH,	Hancianu et al. (2013)

					DNA fragmentation	
	Lavender oil		Neuroprotection: inhibition of protein oxidation and lipid peroxidation	Mice/Kunnmig 50/100/200 mg/kg / Reperfusion - i.l.	TTC Staining, PCC, MDA and carbonyl formation, SOD, CAT, GSH/GSSG, GSH-Px	Wang et al. (2012)
Passiflora edulis (passionflower)	Flavonoid extract, chrysin	Chrysin (5,7 dihydroxy-flavone)	Chrysin may have anxiolytic properties	Sprague-Dawley rats. Each animal: DMSO 4%, 2 mg/kg chrysin, 1.5 mg/kg midazolam or 3 mg/kg flumazenil, and 2 mg/kg chrysin i.p.	EPM	Brown et al. (2007)
		Chrysin	Decreases epileptic seizures and alleviates the oxidative stress	Male adult Wistar rats 35 mg/kg of PTZ i.p. 5 and 10 µg/mL p.o.	Nick-end labeling assay, histopathology, and reverse transcription-polymerase chain reaction for messenger RNA expression	Zhang et al. (2021)

Withania somnifera (ashwagandha)	Dry leaf powder	No cited	Anxiolytic, anti-inflammatory, and anti-apoptotic properties. Reduction and normalization of GFAP, Iba1, PPARγ, and inflammatory cytokines	Young adult female rats 1 mg/g p.o.	PPARγ, iNOS, MCP-1, TNFα, IL-1β, and IL-6	Kaur et al. (2017)

Table 9. Clinical trials of combination of medicinal plants for insomnia and neurodegenerative diseases.

Species	**Sample/extract**	**Dose/ time/ via/ number of patients**	**Criteria**	**Reference**
Valerian and hops	Ze 91019 (valerian 500 mg) + hops extract siccum (120 mg)	Randomized, double blind, placebo-controlled, prospective clinical study 2 tablets / 28-d / p.o. N = 210	CGI, S3 + S4, SL-2	Koetter et al. (2007)
	Dormeasan: 25 drops contain: hydroalcoholic extracts of valerian (460 mg) +hops (460 mg)	Randomized, double blind, placebo-controlled study 2 mL / 2-nights / p.o. N= 42	SFx, 'sleep quantity', SF-A CIPS	Dimpfel and Suter (2008)
	One tablet contains 187 mg valerian/ 41.9 of hops native extracts	Randomized, multicenter, placebo-controlled, parallel-group study 2 tablets / 28-d / p.o. N = 210	CGI, ISI, PSG, SF-36	Morin et al. (2005)

CGI, clinical global impression; ISI, insomnia severity index; PSG, Polysomnography; SFx, Spectral Sleep Frequency Index; SF-A, sleep questionnaire; SL-2, sleep latency; S3 + S4, slow wave sleep;

p.o., per os (orally); wk, week.

Table 10. Medicinal plants with properties on neurodegenerative dementia disorders and associated anxiety, depression and sleep disturbances

Disturbances	Alzheimer's disease	Parkinson's disease	Huntington's disease	Dementia with Lewy bodies	Mild Cognitive Impairment	Dementia-associated depression/anxiety/sleep disturbance
Aggregates and/or their effects	*A. paniculata* *B. bonnieri* *C. longa* *G. biloba* *H. erinaceus* *L. origanoides* *P. ginseng* *S. miltiorrhiza*			*Vaccinium sp pl*		*V. officinalis*

	S. officinalis *W. somnifera*					
Neuroinflammation	*A. paniculata* *B. monnieri* *C. sativus* *C. longa* *J. regia* *N. sativa* *P. harmala* *V. faba*	*B. monnieri* *C. sativus* *C. longa* *J. regia* *N. sativa* *P. harmala* *V. faba*	*C. officinalis*	*O. sativa*		*H. lupulus*
Apoptosis dysregulation			*P. ginseng*		*G. lucidum*	*H. lupulus* *L. angustifolia*

						P. edulis
Oxidative stress Mitochondrial dysfunction	*B. bonnieri* *C. asiatica* *C. sativus* *C. longa* *G. biloba* *H. erinaceus* *J. regia* *L. origanoides* *N. sativa* *O. majorana* *P. ginseng*	*B. monnieri* *C. sativus* *C. longa* *J. regia* *N. sativa* *P. harmala* *V. faba*	*A. asphodeloides* *C. officinalis* *C. paniculatus* *C. asiatica* *C. pluricaulis* *F. religiosa* *L. divaricata* *P. quinquefolius* *P. dactylifera* *C. corylifolium* *P. granatum*	*C. sinensis* *Citrus sp pl* *C. arabica* *C. sativus* *O. sativa* *T. cacao* *V. vinifera* *Vaccinium sp pl*	*C. sativus* *J. regia* *T. cacao* *V. vinifera*	*C. aurantium* *L. angustifolia* *M. officinalis* *P. edulis*

	P. harmala *S. officinalis* *V. faba* *V. vinifera* *W. somnifera*		*W. somnifera* *Z. officinale*			
Disturbances of GABAergic system			*P. quinquefolius*			*P. edulis*
Disturbances of MAO		*B. monnieri* *C. longa* *C. sativus* *J. regia* *N. sativa*				

		P. harmala *V. faba*				
Sinapsis disturbances	*A. sativum* *A. annua* *G. glabra* *H. erinaceus* *L. pubescens* *L. origanoides* *P. ginseng* *P. khinjuk* *S. officinalis* *Thymus sp*		*L. divaricata* *Z. officinale*			

Disturbances of dopaminergic system, movements		*G. biloba* *M. pruriens*	*C. officinalis* *C. pluricaulis* *F. religiosa* *P. quinquefolius* *W. somnifera* *Z. officinale*			
Disturbances of glutaminergic system, memory and learning			*C. paniculatus* *P. quinquefolius*		*P. minor*	
Decrease in serotonin						*C. aurantium*
Disturbance of estrogenic protection			*C. officinalis*			

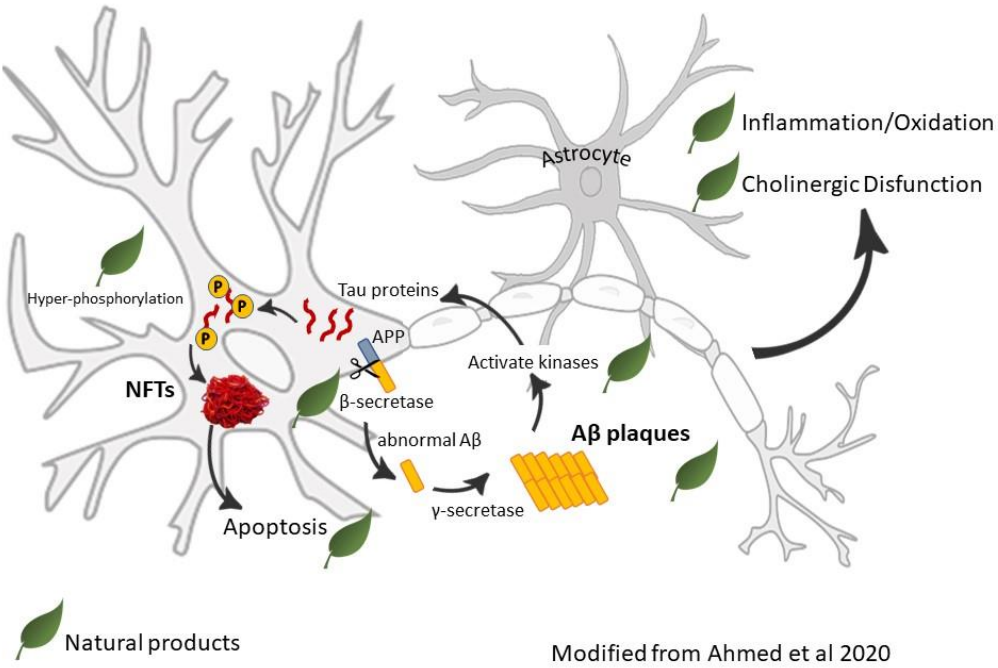


Figure 1. Effects of natural products on **Alzheimer disease** (Based on Ahmed et al., 2021).

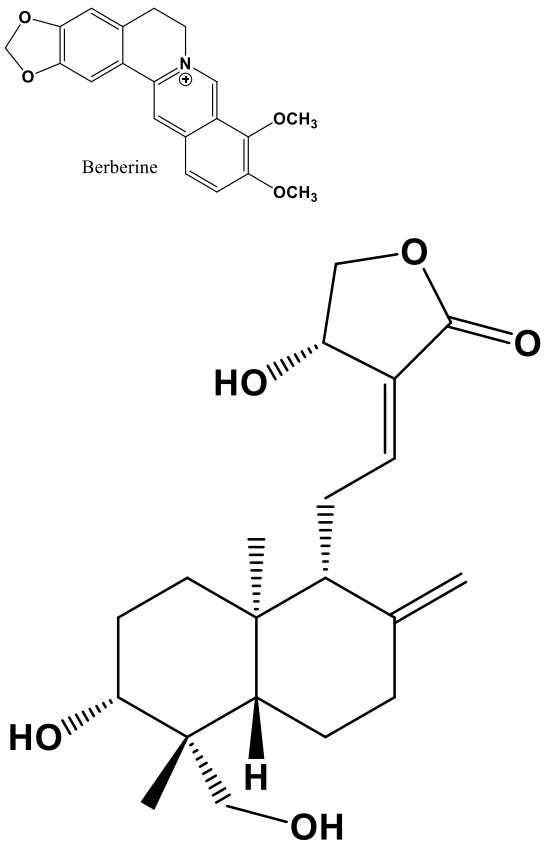
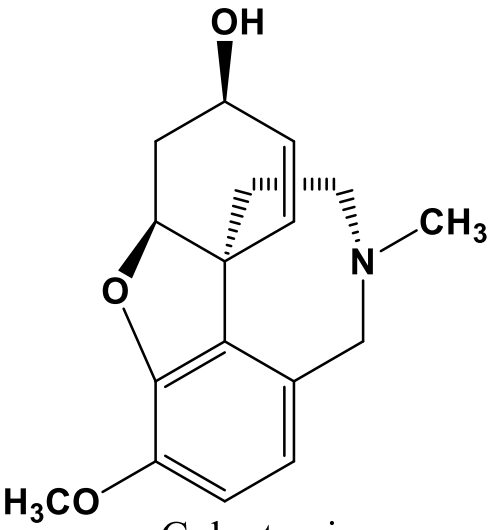
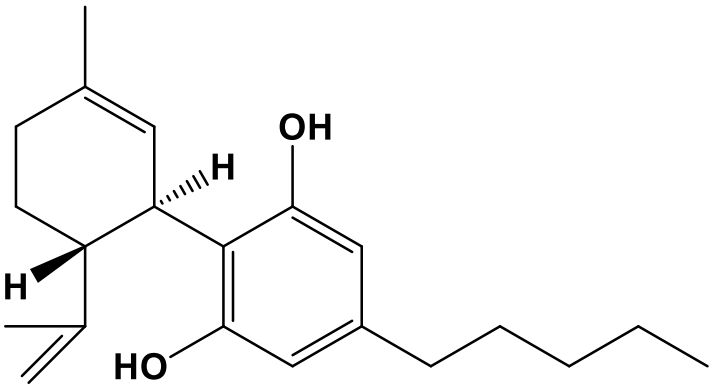


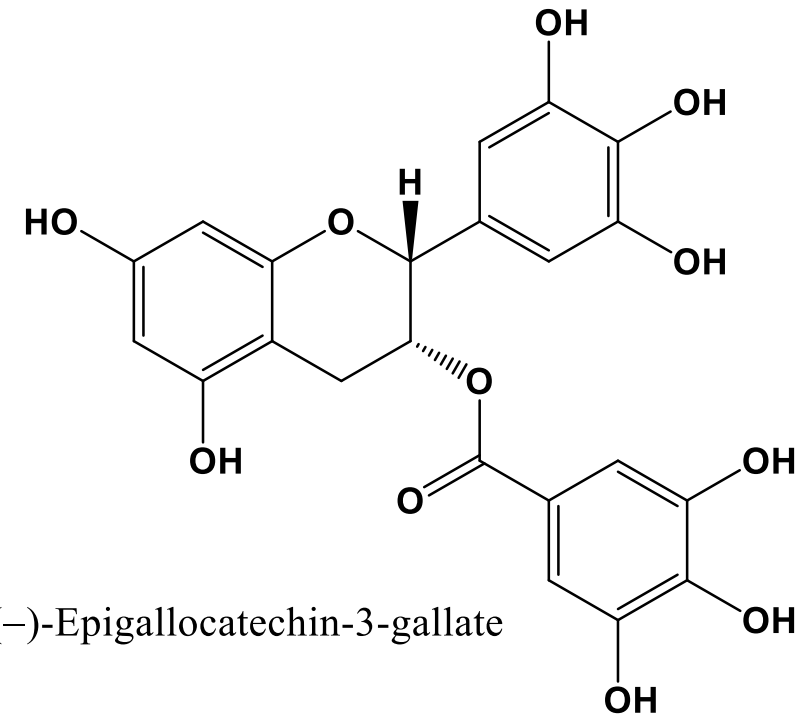
Figure 2. Active compounds of plants used in Alzheimer's disease.



Galantamine



Cannabidiol



(–)-Epigallocatechin-3-gallate

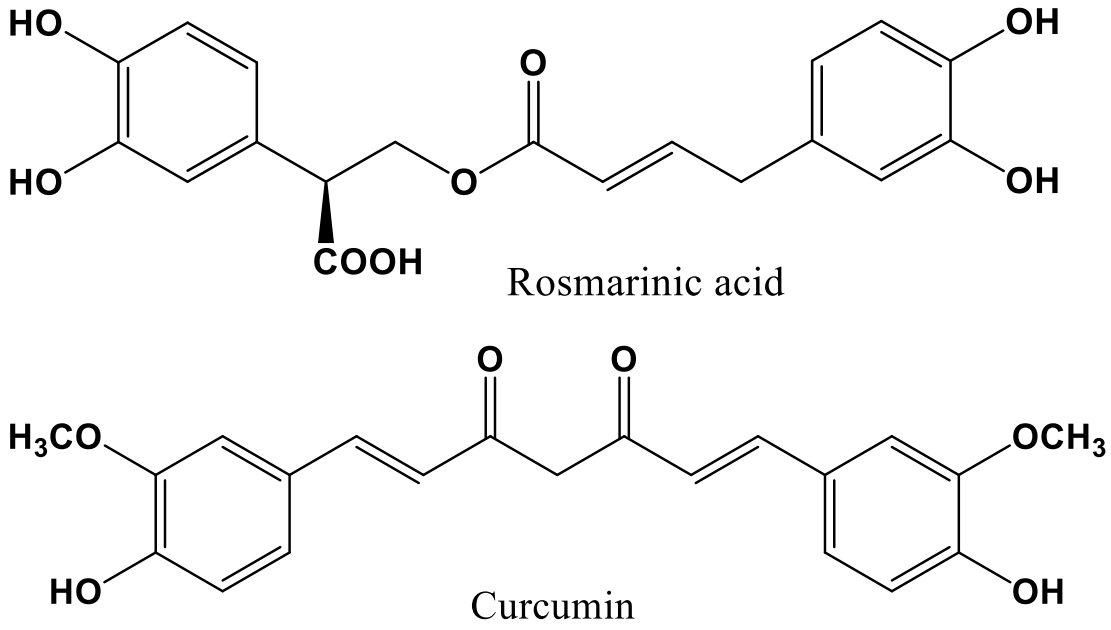
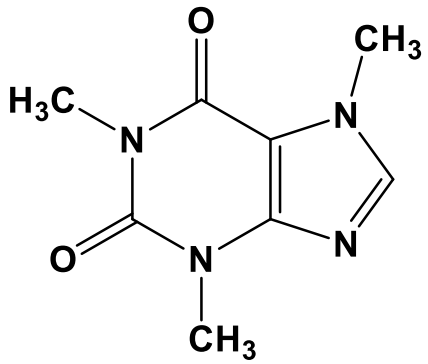
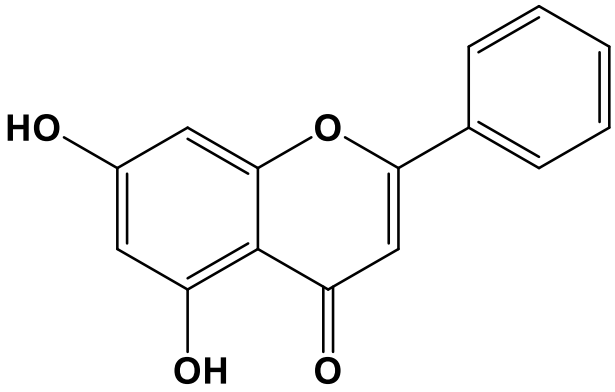


Figure 3. Chemical structure of natural products from neuroprotective plants used for Dementia with Lewy bodies.

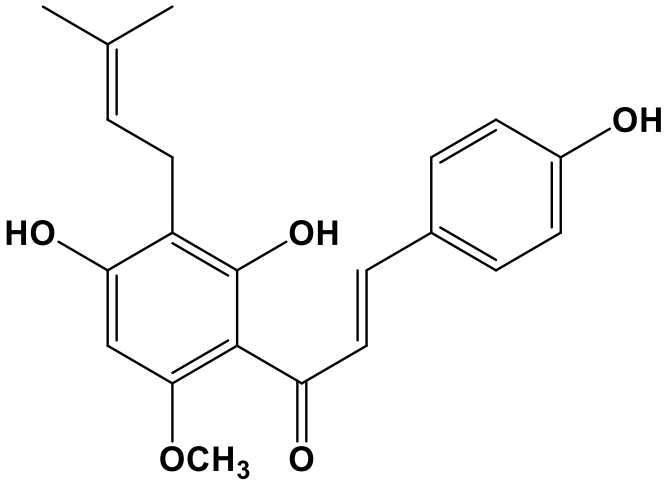


Caffeine

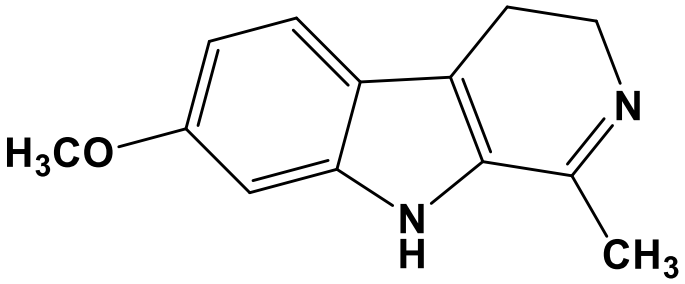
Figure 4. Structure of caffeine, potentially useful substance for Mild Cognitive Impairment.



Chrysin



Xanthohumol



Harmaline

Figure 5. Active plant compounds for insomnia in neurodegenerative dementias.