Pharmacogn J. 2021; 13(5): 1312-1322
A Multifaceted Journal in the field of Natural Products and Pharmacognosy
www.phcogj.com

Review Article

Potential Neuroprotective Activity of Essential Oils in Memory and Learning Impairment

Carmen R. Silva-Correa[1,*], Jorge L. Campos-Reyna[2], Víctor E. Villarreal-La Torre[1], Abhel A. Calderón-Peña[3], William Antonio Sagástegui-Guarniz[1], Luz M. Guerrero-Espino[2], Anabel D. González-Siccha[1], Cinthya L. Aspajo-Villalaz[3], María V. González-Blas[1], José L. Cruzado-Razco[1], Julio Hilario-Vargas[2]

ABSTRACT

Memory and learning is negatively affected by many factors. Alzheimer's disease is a progressive and irreversible neurological disorder that occurs gradually, a sickness that is increasingly common, and multiple scientific articles suggest that essential oils improve memory and learning and are useful in the treatment of various neurodegenerative diseases, including Alzheimer's disease. This review aims to conduct a critical collection of current information on research into both memory and learning impairment, as well as essential oils that are able to avoid this neurodegenerative disease. Currently, different animal models have been useful for the study of neurodegenerative problems that alter memory and learning, experimental pharmacological, genetic and toxicological models that can simulate specific cognitive deficit syndromes. In addition, research in this review show several essential oil compounds that present positive results in animal studies, but still lack human clinical trials. Therefore, the assessment of the safety and efficacy of these phytochemical compounds in diseases that cause memory impairment and learning, remain a promising area for future research.

Key words: Essential oil, Alzheimer disease, Neurodegenerative diseases, Animal model, Memory, Learning.

Carmen R. Silva-Correa[1,*], Jorge L. Campos-Reyna[2], Víctor E. Villarreal-La Torre[1], Abhel A. Calderón-Peña[3], William Antonio Sagástegui-Guarniz[1], Luz M. Guerrero-Espino[2], Anabel D. González-Siccha[1], Cinthya L. Aspajo-Villalaz[3], María V. González-Blas[1], José L. Cruzado-Razco[1], Julio Hilario-Vargas[2]

[1]Facultad de Farmacia y Bioquímica, Universidad Nacional de Trujillo, PERÚ.
[2]Facultad de Medicina, Universidad Nacional de Trujillo, PERÚ.
[3]Facultad de Ciencias Biológicas, Universidad Nacional de Trujillo, PERÚ.

Correspondence
Carmen R. Silva-Correa
Facultad de Farmacia y Bioquímica, Universidad Nacional de Trujillo, PERÚ.
E-mail: csilva@unitru.edu.pe

History
- Submission Date: 06-05-2021;
- Review completed: 11-06-2021;
- Accepted Date: 23-06-2021.

DOI : 10.5530/pj.2021.13.166

Article Available online
http://www.phcogj.com/v13/i5

INTRODUCTION

Memory and learning is negatively affected by many factors, and cases of attention deficit hyperactivity disorders in children and Alzheimer's disease are increasingly common in adults.[1] Alzheimer's disease (AD) is a progressive and irreversible neurological disorder that occurs gradually, begins with the accumulation, oligomerization and aggregation of amyloid beta peptide in extracellular deposits called senile plaques, subsequently, this accumulation promotes hyperphosphorylation of the tau protein, leading to neurofibrillary tangles and neurodegeneration, which leads to memory loss, unusual behavior, personality changes and loss of thinking ability.[2]

The brain areas associated with cognitive functions, in particular neocortex and hippocampus, are the most affected regions in AD.[3] Impairment of learning and memory can be chemically induced in laboratory animals and one of the most commonly used models is scopolamine-induced amnesia, an acetylcholine antagonist of central nervous system (CNS).[3-4] The acetylcholine is involved in improving long-term potentiation memory, but this cholinergic transmission is mainly interrupted by hydrolysis of acetylcholine by the enzyme acetylcholinesterase (AChE), which is responsible for the degradation of acetylcholine to acetate and choline in the synaptic cleft.[5] Good nutrition, physical activity and social participation are known to be beneficial in active aging to avoid the risk of cognitive decline and Alzheimer's.[6]

Nootropic agents like piracetam, pramiracetam, aniracetam and choline ester inhibitors are mainly used to improve memory, mood and behavior; however, its associated side effects have limited its use. Therefore, it is necessary to explore the usefulness of alternative medicines for the treatment of various cognitive disorders.[7] This includes the use of therapies such as aromatherapy, which is very popular and reliable among health professionals, because natural products have a lower risk of producing secondary damages compared to conventional drugs.[1]

Essential oils obtained from medicinal plants show high therapeutic potential against various types of pathologies, including CNS disorder.[8] The study of essential oils has many advantages such as easy use, safety and relatively low costs.[9]

NEUROPHYSIOLOGICAL BASES

Learning and memory are linked, but they are different. Learning is a process by which knowledge about the environment is acquired and memory is the process by which knowledge is encoded, consolidated, stored and then retrieved.[10-11] Coding involves processes by which newly learned information is received when it is for the first time.

Consolidation is a process that modifies newly stored and still labile information to make it more stable for long-term storage. Consolidation involves the expression of genes and the synthesis of new proteins, resulting in structural changes that store memory in a stable way over time. Storage refers to mechanisms and places that retain information over time. Recovery are processes that enable the retrieval and use of stored information.[12-14] Various types of memory have been proposed over the years,

Cite this article: Silva-Correa CR, Campos-Reyna JL, Villarreal-La Torre VE, Calderón-Peña AA, Sagástegui-Guarniz WA, Guerrero-Espino LM, et al. Potential Neuroprotective Activity of Essential Oils in Memory and Learning Impairment. Pharmacogn J. 2021;13(5): 1312-1322.

including Atkinson and Shiffrin in 1968,[15] Baddeley and Hitch in 1974,[16] Tulving in 1995 and Squire in 1994.[17]

The Squire taxonomy proposes a declarative or explicit memory and a non-declarative or implicit memory. Declarative memory is expressed verbally and includes facts and events; involves centers such as the temporal lobe, diencephalon and medial. Non-declarative is not expressed verbally and includes skills, habits, classical conditioning, perceptual and non-associative learning, involves amygdala, neocortex, cerebellum and reflex pathways.[10,17,18]

Medial temporal lobe is divided into left and right and includes the hippocampus and entorhinal, perirhinal and parahippocampal cortices. Primary sensory areas are those that receive the first cognitive stimuli, such as shape, color and temperature. These are processed at more complex levels such as unimodal or multimodal stimuli through the entorhinal cortex. This information enters the hippocampus through the perforant path to the Gyrus dentatus, where neurogenesis occurs. From there via mossy fibers to CA3 hippocampus; after Schaffer collateral pathways to CA1 hippocampus, where pyramidal cells interpret and modulate information using various neurotransmitters and receptors, such as monosodium glutamate and others.[19-22]

Glutamate is a neurotransmitter that acts by two types of superfamilies: (a) Receptors bound to ion channels (iGluRs): α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA), kainic acid (KA) and N-methyl-D-aspartate (NMDA). They are permeable to Ca^{2+}, Na^{+} and K^{+}. (b) Metabotropic receptors that are bound to G protein and coupled to second messengers (mGluRs): inositol 3-phosphate, diacylglycerol and cyclic AMP. Acetylcholine, by a pentameric nicotinic receptor alpha-7, is involved in cognitive functions and its modulation is important in diseases such as schizophrenia and Alzheimer's; other types of acetylcholine receptors are also involved. Gamma-aminobutyric acid (GABA) is an amino acid that acts as an inhibitory neurotransmitter; acts by two types of GABAA receptors using ion channel and metabotropic GABAB using G proteins.[23-27]

EXPERIMENTAL MODELS IN MEMORY AND LEARNING IMPAIRMENT

Over the past few decades, various animal models have been described that simulate the mechanisms of action and clinical picture of diseases with memory and learning alteration. Animal models of cognitive disorders have been mostly based on primates, rats and mice, whose neural processes are similar to those of human cognitive function. Several types of experimental models can be distinguished: pharmacological models which allow the evaluation of drugs; genetic models based on genetically manipulated animals (transgenic and knock-out),[28-29] and toxicological models to determine the toxicity of heavy metals, toxics and neurotoxins.[30]

Animal models simulate specific cognitive deficit syndromes in which the trigger is aging,[31-32] or head trauma.[33-34] Recently, other complementary models made with non-mammal animals, such as zebrafish (*Danio reiro*), vinegar flies (*Drosophila melanogaster*) and worms (*Caenorhabditis elegans*), have also been used to screen potentially toxic or therapeutic compounds, and determine some of the neuromolecular bases of cognitive function. It is highly relevant to emphasize that, from an experimental point of view, work with animals must be carried out under controlled conditions, making the greatest efforts and planning to minimize the suffering and the number of animals used. If this is not the case, the damage mechanisms and potential protection mechanisms generated are valid only for the model, but not for pathology (Figure 1).[35]

Aluminium-chloride induced cognitive impairments model

Aluminium-chloride induced cognitive impairments model in rodents is commonly used to evaluate nootropic activity by evaluating cognitive enhancement resulting from increased acetylcholine, however, AD is primarily caused by neurodegeneration, for this purpose, this model

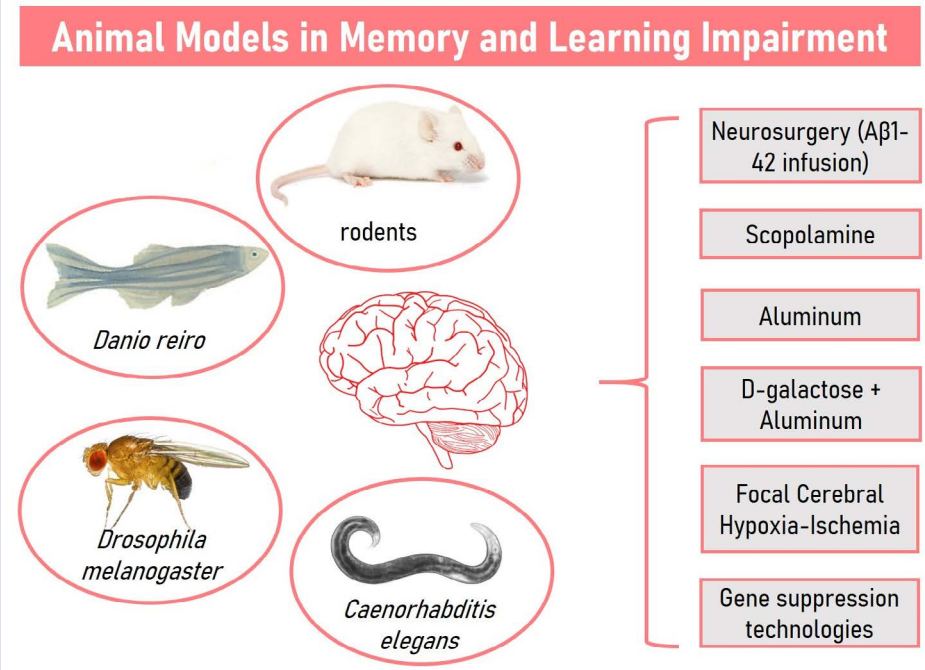


Figure 1: Experimental Models in Memory and Learning Impairment.

causes memory impairment learning and cognitive impairment in mice, but also produces neurodegeneration.[36]

Aluminium is a non-redox trivalent cation and has been recognized as a factor causing various neurological disorders due to its neurotoxicity; the accumulation of aluminium in the brain is one of the contributing factors in AD, causing a stroke neural loss that leads to neurodegeneration. Aluminium affects the integrity and permeability of the blood brain barrier (BBB) by altering the lipophilic characteristics of it, produces accumulation of amyloid beta (Aβ), hyperphosphorylation of tau protein, increased AChE activity, increased inflammatory cytokines and memory and learning deficits that are important manifestations in AD etiology.[37]

D-galactose and Aluminium-chloride induced cognitive impairments model

Combined administration of chronic D-galactose (D-gal) and $AlCl_3$ has induced cognitive alterations, producing mitochondrial dysfunction, apoptosis, amyloid peptide buildup β oxidative stress. D-gal is a reducing sugar and that in animals oxidizes in hydrogen peroxide (H_2O_2) and aldehydes when the intracellular level of D-gal is excessive. Long-term administration of D-gal induces behavioral and neurobiological changes similar to natural aging, coupled with aluminium possessing neurotoxicity, which accelerates the pathogenic course of AD.[38]

Scopolamine-induced Alzheimer's Disease (AD) model

Scopolamine is a competitive muscarinic receptor blocker and this drug is widely used to induce memory impairment in rodent models.[37] In addition, the zebrafish model (*Danio rerio*) shows high sensitivity to clinically active neurotropic drugs in a similar way to humans. Evidence suggests that in zebrafish, scopolamine exhibits memory-reducing effects without causing locomotive deficits.[39]

Model of permanent occlusion of common carotid arteries (OPACC's) in rats

This model reproduces ischemic event, early stages, and oligoemia, when cerebral hypoperfusion is chronic. The hippocampus is the brain area that has received the most attention for the study of neuropathological alterations induced by OPACC. Brain hypoperfusion has been associated with memory and learning alterations, a process involving the hippocampus, by modifying oxidative metabolic mechanisms.[40]

It is performed with a surgical procedure, which involves intraperitoneal anesthesia (chloral hydrate 350 mg/kg), (ketamine 50 mg/kg), then an incision is made in the neck and the common carotid arteries are ligated with 3.0 silk suture thread, permanently.[41-42]

Various techniques have been developed to find the right animal model to assess deficiencies in memory and learning, considering the models of focal or incomplete cerebral ischemia the most efficient, since one of the areas affected in hypoxia is the hippocampus (Table 1).[43-45]

Gene suppression technologies

Allow to generate models of mice with specific discontinuation of the nNOS gene (nNOS KO), which show > 95% loss of production of NO in C57BL/6J animals of the CNS, showing these specimens a poor cognitive performance. NO's participation in learning and memory is from a retrograde messenger during long-term empowerment (LTP) an important process for memory formation.[45-49]

The base stock of these animals was initially established at Massachusetts General Hospital (Boston, MA).[50] The nNOS gene mutation is generated by homologous recombination. The genetic background is based on a combination of the 129X1/SvJ and C57BL/6J strains with a predominance of C57BL/6J, because the mice are crossed for three generations in C57BL/6J and then crossed to obtain knockout mice and wild-type bedmates.[50-52]

Table 1: Experimental Models of Focal Cerebral Hypoxia-Ischemia.

In vivo	Methodology
Common carotid artery occlusion	Common carotid artery occlusion
	Common carotid artery occlusion and anoxia / hypoxia
Oclusión de la arteria cerebral media	Transorbital occlusion
	Transcranial occlusion
	Intraluminal occlusion
	by clot embolism
	autologous or heterologous blood
Occlusion of the microvasculature of the middle cerebral artery	
	Photothrombotic occlusion
	Microembolization
	Intracerebral endothelin injection (type 1 and 3)
Cortical devascularization	
Hypoxia Chemical ischemia due to cobalt chloride ($CoCl_2$)	
In vitro	
Primary neuronal cultures	
Organotypic cultures	
Brain slices (hippocampus)	

TESTS FOR MEMORY AND LEARNING ASSESSMENT

Among the tests used as part of neurological evaluation in experimental animals, there is the Y-maze test that evaluates short-term memory and is used to evaluate spatial recognition memory deficits based on your tendency to explore a new environment, the Radial Arm-Maze (RAM) test that evaluates working and reference memory[46] and the Morris Water Maze (MWM) test that allows evaluate spatial learning and memory.[47-48]

Likewise, the Object Recognition Test, which evaluates non-spatial learning, short-term memory, the Social Recognition Test that focuses on the degree of familiarity, the Barnes Maze that allows to study learning and spatial memory, working and reference memory, and short- and long-term memory, as well as other more complex tasks in rats and mice and the Passive Avoidance Test is a one-way test that allows you to study acquired learning and memory and the winter conditioning model that evaluates emotional memory.[53]

ESSENTIAL OIL STUDIES IN MEMORY AND LEARNING

Approximately 400 types of essential oils are currently available for therapeutic and clinical uses. Aromatic plants have been used for many centuries by different cultures around the world, with aromatherapy being one of the most widely used therapies in traditional and complementary medicine. Many scientific articles suggest that essential oils are useful in the treatment of various diseases, including AD (Table 2).[54]

MECHANISMS OF ACTION OF ESSENTIAL OILS

Essential oils are complex blends of hydrocarbons and arise from two different isoprenoid pathways; they are a complex mixture of molecules, which usually contains more than 20 different components of low molecular weight with very variable concentrations, so they have different mechanisms of action in the animal organism (Figure 2).[70-71]

Table 2: Essential Oil Research on Memory Impairment and Learning.

Medicinal plant source of essential oil	Main compounds	Model of study	Evaluation tests	Positive Control	Proposed mechanism of action	Ref.
Pinus halepensis	β-caryophyllene (29.45%), α-pinene (11.14%), myrcene (7.85%), terpinolene (3.90%)	Neurosurgery (Aβ1-42 infusion)	Y-maze test, Radial Arm-Maze test	Donepezil (5 mg/kg)	Inhibition of AChE activity and decrease oxidative damage in the rat hippocampus.	55
Nigella sativa	Thymoquinone (30-48%), p-cymene, carvacrol, thymohydroquinone, dihydrothymoquinone, α-thujene, thymol, β-pinene, α-pinene, and γ-terpinene.	Chronic administration under normal conditions	Radial Arm-Maze test	Corn oil (0.1 mL/100 g body weight)	Inhibition of AChE activity	56-57
Zataria multiflora	Thymol (34%), Carvacrol (32%), p-cymene (9.5%)	Neurosurgery (Aβ1-42 infusion)	Morris water maze test	-	Inhibition of AChE activity and enhancement of BDNF levels	58
Pelargonium graveolens	β-citronellol (26%), Geraniol (9%), Linalool (9%)	MET-induced Spatial Working Memory (SWM) déficits	Y-maze test	-	Inhibition of the AChE activity	59
Eugenia caryophyllata	Eugenol, beta-caryophyllene, eugenol acetate,	Scopolamine Model	Transfer latency (TL) in elevated plus-maze, Step-down passive avoidance task	Piracetam (200 mg/kg, i. p.)	Modulate oxidative stress	60
Lavandula angustifolia Lavandula hybrida	Linalool, linalyl acetate	Scopolamine Model	Y-maze test, Elevated Plus-Maze, Radial Arm-Maze test, Forced swimming test	Silexan®	Anxiolytic and antidepressant agent and improve spatial memory deficits	61
Ferulago angulata	α-pinene (24%), β-pinene (22%), α-phellandrene (12%), β-phellandrene (20%)	Scopolamine Model	Y-maze test, Radial Arm-Maze test	-	Inhibition of AChE activity	62
Salvia miltiorrhiza	β-caryophyllene (8%), 6,10,14-trimethyl-2-pentadecanone (7%), dihydro-neoproene (7%), germacrene D (6%) and caryophyllene (4%)	$AlCl_3$ and D-gal Model	Morris water maze test, a probe test	-	Reduce the accumulation of Aβ in the hippocampus and cerebral cortex	63
Albizia julibrissin	eugenol, linalool	Scopolamine Model	Elevated Plus-Maze	Piracetam (400 mg/kg i.p)	Inhibition of AChE activity	64
Dennettia tripetala	β-Phenylnitroethane, linalool	Scopolamine Model	Y-maze test	-	Inhibition of AChE activity	65
Origanum majorana	Terpinen-4-ol (23.52%), sabinene (12.59%), terpinolene (8.72%), linalool (5.94%)	Neurosurgery (Aβ1-42 infusion)	Y-maze test, Radial Arm-Maze test	-	Reduce brain oxidative stress	66
Hyssopus officinalis	β-pinene, limonene, eucalyptol, berbenone, pinocamphone, Linalool	Chronic Stress-Induced Model	Avoidance memory (shuttle box) test	-	Reduce brain oxidative stress	67
Schinus terebinthifolius	β-phellandrene (32.40%), α-pinene (16.68%), terpinen-4-ol (11.01%), α-phellandrene (10.56%), β-pinene, limonene, α-terpineol and α-terpinene	Scopolamine Zebrafish model.	Novel tank diving test (NTT), Y-maze test	Imipramin (20 mg/L), donepezil (10 mg/L)	Inhibition of AChE activity and decreased oxidative stress	39
Zingiber officinale	Gingerols and volatile oil	Morphine	Passive avoidance task	-	Inhibition of the AChE activity	68
Rosmarinus officinalis	1.8-cineole (32.7%), alfa-pinen (9.72%), camphor (7.91%), camphene (2.41%), beta-pinene	Scopolamine Model	Passive avoidance task	Huperzine A (0.5 mg/kg p.o.)	Inhibition of AChE and BuChE activity	69

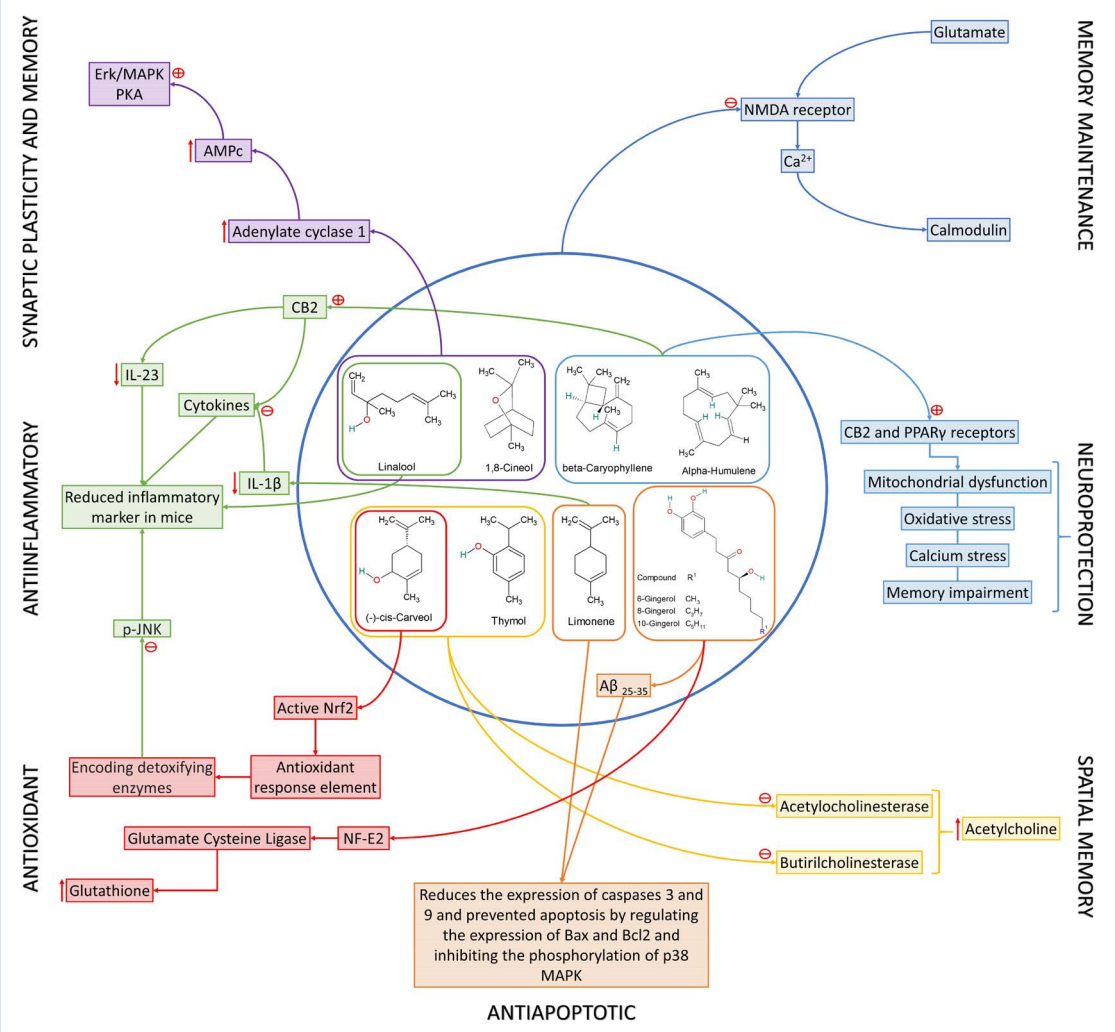


Figure 2: Mechanisms of action of essential oils on memory and learning.

Monoterpenes have marked effects on memory formation by modulating the activation of glutamate *in vitro* and *in vivo* by competitive antagonism of ionotropic receptors of type N-methyl-D-aspartate (NMDA). Glutamate is an excitatory neurotransmitter that drives changes in synaptic activity associated with the mechanisms responsible for memory formation.[72] Thymol, whose chemical name is 2-isopropyl-5-methylphenol is a dietary phenol monoterpene found abundantly in certain plants.[73] Thymol acts as an acetylcholinesterase inhibitor (AchE), this enzyme is used for Ach hydrolysis in the human body, a decrease in AchE content could be beneficial for increasing Ach levels in the brain.[74] Thymol also inhibited butyryl-cholinesterase (BuChE) in a dose-dependent manner.[75]

Dietary supplementation with thymol improved brain state by induction of antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) respectively and the proportion of phospholipids in the brain of aging rat.[76]

In addition, thymol inhibits cognitive decline caused by increased levels of Aβ peptide or cholinergic hypofunction in rats treated with Aβ(25-35) or scopolamine, these effects are attributed to its antioxidant, anti-inflammatory and anticholinergic esterase properties.[77] Also, it improves spatial memory in Morris' maze test in a rat-induced AD model that received consumption of a high-fat diet.[78]

Carveol is a monoterpene phenol that is isolated from essential oils extracted from plants of the Lamiaceae Family, which include the genera *Oreganum*, *Thymbra* and *Corydothmus*. (79) The (-)-cis-carveol, is considered an anti-AChE agent that attenuates cholinergic deficits produced after injection of Aβ. Therefore, this can be one of the mechanisms of (-)-cis-carveol that improves memory performance in the Y-maze test and Radial arm-maze test. While, linalool improves learning and memory in an DA transgenic mouse model by reducing the level of inflammation markers.[8] Carveol could be a powerful antioxidant and anti-inflammatory agent, activating the master endogenous protein Nrf2 which is an integral part of the cellular defense mechanism against oxidative stress and electrophilic aggression. Nrf2 joins the antioxidant response elements at the promoter site, which in turn encodes various phase II detoxifying and antioxidant enzymes and other important stress response factors,[80-81] and may be associated with negative modulation of p-JNK and other neuro-inflammatory mediators. Therefore, it may offer a new therapeutic option to prevent and control oxidative stress and inflammation in degenerative disorders.[80] It is obtained from plants belonging to different species such as cloves (*Eugenia caryophyllata, E. aromatica, E. caryophyllus, Syzygium aromaticum*),[82-83] oregano (*Origanum vulgare* L.), cinnamon (*Cinnamomum spp.*) and black pepper (*Piper nigrum* L.),[84-86] *Cannabis sativa*.[87] β-caryophyllene or (E)-β-caryophyllene is usually found in nature along with small amounts of its isomers (Z)-β-caryophyllene, α-humulene or in a mixture with β-caryophyllene oxide.[88] It is a phytocannabinoid, and a selective agonist of the CB2 cannabinoid receptor.[87] CB2 receptors are known to be expressed in

phagocytic cells and modulate the release of cytokines.[88] At the brain level, β-caryophyllene decreases circulating levels of IL-23, which together with IL-12 has been associated with the pathogenesis of multiple sclerosis.[89]

El β-caryophyllene prevents cognitive impairment in APP/PS1 mice, and this positive cognitive effect is associated with a reduction in the accumulation of Aβ in the hippocampus and cerebral cortex, relieves the glialization of neurons in the cerebral cortex and inhibits microglia activity by directly activating CB2 receptors and PPAR receptors. So, the β-caryophyllene is an interesting molecule for the development of new drugs with therapeutic potential for the treatment of AD.[63,90]

4-isoprenil-1-methyl-cyclohexene (D-limonene), is a cycloolefin classified as a monoterpene monocyclic that is commonly found in citrus fruits such as lemon, orange, tangerine and grapefruit.[91-92] D-limonene shows effects on the synthesis and changes of neurotransmitters such as dopamine, serotonin and GABA.[93] Mice treated with acute D-limonene showed a decrease in GABA levels in the hippocampus.[94] Administration of limonene results in a significant reduction in the expression of the Il-1 gene, related to inflammatory cytokine;[95] it also exerts anxiolytic effects, regulatory effects on neurotransmitters and anti-contraceptive effects.[93,96,97]

Likewise, consumption of D-limonene in stress-exposed rats improved memory and learning and decreased neuronal loss in the CA1 hippocampus region in these animals. D-limonene also reduced the expression of caspases 3 and 9 and prevented apoptosis by regulating the expression of Bax and Bcl_2 and inhibiting the phosphorylation of p38 MAPK. D-limonene prevents memory impairment in stress-exposed rats by strengthening the brain antioxidant system, reducing inflammation and preventing neuronal death.[36] D-limonene greatly mitigated the decrease in cognitive function, memory and behavior and ischemic injury in SHRsp rats, this may be due to inhibition of brain inflammation, vascular remodeling and antioxidant activities (increased activity of superoxide dismutase and catalase, decreased level of malondialdehyde, increased glutathione content).[98]

Zingiber officinale (ginger) has been commonly consumed as a spice and herbal medicine for a long time.[99] Its main components are gingerols such as 6-gingerol, 8-gingerol and 10-gingerol).[100] 6-Gingerol pretreatment protected against Aβ(25-35)-induced cytotoxicity and apoptotic cell death such as DNA fragmentation, disruption of mitochondrial membrane potential, elevated Bax/Bcl-2 ratio, and activation of caspase-3.[101]

The neuroprotective mechanism of 6-gingerol is mediated by the intracellular suppression Aβ(25-35)-induced accumulation of reactive oxygen species and reactive nitrogen species; 6-gingerol restored Aβ(25-35)-depleted endogenous antioxidant glutathione level of the immune system. In addition, it positively regulates the expression of mRNA and proteins responsible for the synthesis of key enzymes such as c-glutamylcysteine ligase (GCL), involved in glutathione biosynthesis and mediated by activation of NF-E2-related factor 2 (Nrf2). 6-Gingerol can be used effectively in the Alzheimer disease's prevention and/or treatment by improving the antioxidant capacity of the immune system.[101]

Lavandula angustifolia (lavender) is an aromatic plant recommended in the treatment of various neurological disorders.[102] Linalool, camphor, terpinen-4-ol, linalyl acetate, (Z)-β-ocimene and 1,8-cineole are the main components of lavender essential oil.[103] Essential oil showed significant antioxidant and anti-poptotic potential in rat models with scopolamine-induced dementia. Subacute inhalation exposure to essential oil significantly increased the level of antioxidant enzymes in the immune system, including superoxide dismutase, glutathione peroxidase and catalase. In addition, the total amount of GSH and lipid oxidation were reduced in homogenized from specific brain tissues. Therefore, the protective actions of lavender essential oil may be mediated by strong antioxidant and anti-poptotic activities that contribute to neuroprotective action.[104] Linalool and 1,8-cineole influence the expression of adenylate cyclase 1 (ADCY1). ADCY1 plays a crucial role in CNS, so synaptic plasticity and memory formation depend on optimal AMPc levels. Adenylyl cyclase activates several signal transduction pathways, including Erk/MAPK and PKA.[105-106]

The essential oils of *Eucalyptus globulus* (eucalyptus) and lavender have an effect on sustained attention in a monitoring task (attentive over a long period of time). In treatment with lavender essential oil reaction time was significantly reduced compared to the control group. Subjects treated with lavender essential oil kept their attention during prolonged and demanding exercises. In addition, sedative odors such as lavender are reported to be more useful than stimulating odors in arduous physical exercise situations. Stimulating odors were also reported to be more useful with less harsh tasks, as they keep subjects alert.[107]

Rosmarinus officinalis essential oil (rosemary) produces a stimulation of the nervous system; therefore, it increases memory capacity and concentration capacity. Improved performance is reported in a task due to the olfactory impact of rosemary essential oil with increased overall memory quality. In addition, it was reported that the combination of *Rosmarinus officinalis* essential oil and *Menta piperita* produces increased memory and activity level of mice and dogs. Of the isolated compounds, raw rosemary extract has been shown to improve memory impairment when tested *in vivo* using the scopolamine-induced dementia model,[108] increase locomotive activity, motivate vigor, stimulate brain cortex, cause mood relaxation and increase alertness.[109]

FUTURE PERSPECTIVES

There are numerous medicinal plants that have been shown to improve memory impairment and learning, and in different studies such as the Alzheimer's disease model, conducting preclinical studies with significant effects on disease modulation through antiamiloid, antioxidant and anti-AChE activity.[110]

Studies reported in this review show several compounds obtained from essential oils that present positive results in animal studies but still lack human clinical trials, as well as toxicological trials in several cases. Therefore, the evaluation of the safety and efficacy of these phytochemical compounds in degenerative diseases that cause memory impairment and learning such as Alzheimer's disease, remain a promising area for future research.

CONCLUSIONS

The use of essential oils obtained from various medicinal plants are a powerful alternative to the treatment of neurodegenerative diseases such as Alzheimer's disease, which is characterized by memory and learning disorders. Therefore, future studies of mixtures of these essential oils are recommended, evaluating dosages and likely side effects.

REFERENCES

1. Filiptsova OV, Gazzavi-Rogozina LV, Timoshyna IA, Naboka OI, Dyomina YV, Ochkur AV. The essential oil of rosemary and its effect on the human image and numerical short-term memory. Egypt J Basic Appl Sci. 2017;4(2):107-11.
2. Castello MA, Soriano S. On the origin of Alzheimer's disease. Trials and tribulations of the amyloid hypothesis. Ageing Res Rev. 2014;13(1):10-2.
3. Jivad N, Rabiei Z. A review study on medicinal plants used in the treatment of learning and memory impairments. Asian Pac J Trop Biomed. 2014;4(10):780-9.

4. Kim MS, Jeon WK, Lee KW, Park YH, Han JS. Ameliorating effects of ethanol extract of fructus mume on scopolamine-induced memory impairment in mice. Evidence-based Complement Altern Med. 2015;2015.
5. Sobhani R, Pal AK, Bhattacharjee A, Mitra S, Aguan K. Screening indigenous medicinal plants of northeast India for their anti-Alzheimer's properties. Pharmacogn J. 2017;9(1):46-54.
6. Bonetti F, Brombo G, Zuliani G. Nootropics, Functional Foods, and Dietary Patterns for Prevention of Cognitive Decline. Nutrition and Functional Foods for Healthy Aging: Elsevier; 2017. p. 211-232.
7. Patel SJ, Patel KK, Patel MS, Md Rupak A, Patel YB, Sanyal AP, *et al.* Neuro stimulants cognitive enhancers as nootropics in multitask hectic schedule. World Journal of Pharmaceutical Research. 2016;3(5):570-590.
8. Hritcu L, Boiangiu RS, De Morais MC, De Sousa DP. (-)-cis-Carveol, a Natural Compound, Improves β-Amyloid-Peptide 1-42-Induced Memory Impairment and Oxidative Stress in the Rat Hippocampus. Biomed Res Int. 2020;2020.
9. Filiptsova OV, Gazzavi-Rogozina LV, Timoshyna IA, Naboka OI, Dyomina YV, Ochkur AV. The effect of the essential oils of lavender and rosemary on the human short-term memory. Alexandria J Med. 2018;54(1):41-4.
10. Kandel ER, Schwartz JH, Jessell TM. Principles of Neural Science, 5th ed. The McGraw Hill Companies. 2015.
11. Hegde AN, Smith SG. Recent developments in transcriptional and translational regulation underlying long-term synaptic plasticity and memory. Learn Mem. 2019;26(9):307-17.
12. Amtul Z, Atta-Ur-Rahman. Neural plasticity and memory: Molecular mechanism. Rev Neurosci. 2015;26(3):253-68.
13. Asok A, Leroy F, Rayman JB, Kandel ER. Molecular Mechanisms of the Memory Trace. Trends Neurosci. 2019;42(1):14-22.
14. Yates D. Learning and memory: Consolidation circuitry. Nat Rev Neurosci. 2017;18(6):321.
15. Atkinson RC, Shiffrin RM. Human Memory: A proposed system and its control processes BT - The Psychology of Learning and Motivation. Psychol Learn Motiv. 1968;2(5):89-195.
16. Baddeley, A. D., & Hitch GJ. Working memory. En: The psychology of learning and motivation New York: Academic Press. 1974. p. 47–89.
17. Squire LR, Zola SM. Structure and function of declarative and nondeclarative memory systems. Proc Natl Acad Sci U S A. 1996;93(24):13515-22.
18. Riedel WJ, Blokland A. Declarative Memory. Handb Exp Pharmacol. 2015; 228:215-36.
19. Hou Q, Gao X, Zhang X, Kong L, Wang X, Bian W, *et al.* SNAP-25 in hippocampal CA1 region is involved in memory consolidation. Eur J Neurosci. 2004;20(6):1593-603.
20. Ocampo AC, Squire LR, Clark RE. Hippocampal area CA1 and remote memory in rats. Learn Mem. 2017;24(11):563-8.
21. Hainmueller T, Bartos M. Dentate gyrus circuits for encoding, retrieval and discrimination of episodic memories. Nat Rev Neurosci. 2020;21(3):153-68.
22. Urgolites ZJ, Hopkins RO, Squire LR. Medial temporal lobe and topographical memory. Proc Natl Acad Sci USA. 2017;114(32):8626-30.
23. Nakanishi S, Nakajima Y, Masu M, Yoshiki Ueda, Nakahara K, Watanabe D, et al. Glutamate receptors: Brain function and signal transduction. Brain Res Rev. 1998;26(2-3):230-5.
24. Reiner A, Levitz J. Glutamatergic Signaling in the Central Nervous System: Ionotropic and Metabotropic Receptors in Concert. Neuron. 2018;98(6):1080-98.
25. Vallés AS, Borroni MV, Barrantes FJ. Targeting brain α7 nicotinic acetylcholine receptors in Alzheimer's disease: Rationale and current status. CNS Drugs. 2014;28(11):975-87.
26. Hogg RC, Raggenbass M, Bertrand D. Nicotinic acetylcholine receptors: from structure to brain function. Rev Physiol Biochem Pharmacol. 2003;147:1-46.
27. Heaney CF, Kinney JW. Role of GABAB receptors in learning and memory and neurological disorders. Neurosci Biobehav Rev. 2016;63:1-28.
28. Iv S. Knockout and knockin mice to investigate the role of nicotinic receptors in the central nervous system Nicolas. Prog Brain Res. 2004;145:235-51.
29. Tzavara ET, Bymaster FP, Felder CC, Wade M, Gomeza J, Wess J, *et al.* Dysregulated hippocampal acetylcholine neurotransmission and impaired cognition in M2, M4 and M2/M4 muscarinic receptor knockout mice. Mol Psychiatry. 2003;8(7):673-9.
30. Luquin Piudo MR. Modelos experimentales de enfermedad de Parkinson. Rev Neurol. 2000;31(01):60.
31. Gower AJ, Lamberty Y. The aged mouse as a model of cognitive decline with special emphasis on studies in NMRI mice. Behav Brain Res. 1993;57(2):163-73.
32. Ingram DK, Spangler EL, Iijima S, Ikari H, Kuo H, Greig NH, *et al.* Rodent models of memory dysfunction in Alzheimer's disease and normal aging: Moving beyond the cholinergic hypothesis. Life Sci. 1994;55(25-26):2037-49.
33. Fox GB, Levasseur RA, Faden AI. Behavioral responses of C57BL/6, FVB/N, and 129/SvEMS mouse strains to traumatic brain injury: Implications for gene targeting approaches to neurotrauma. J Neurotrauma. 1999;16(5):377-89.
34. Sarti C, Pantoni L, Bartolini L, Inzitari D. Cognitive impairment and chronic cerebral hypoperfusion: What can be learned from experimental models. J Neurol Sci. 2002;203-204:263-6.
35. Sempere L, Rodríguez-Rodríguez A, Boyero L, Egea-Guerrero JJ. Principales modelos experimentales de traumatismo craneoencefálico: de la preclínica a los modelos *in vitro*. Med Intensiva. 2019;43(6):362-72.
36. Bigdeli Y, Asle-Rousta M, Rahnema M. Effects of Limonene on Chronic Restraint Stress-Induced Memory Impairment and Anxiety in Male Rats. Neurophysiology. 2019;51(2):107-13.
37. Lee GY, Lee C, Park GH, Jang JH. Amelioration of Scopolamine-Induced Learning and Memory Impairment by α -Pinene in C57BL/6 Mice. Evidence-based Complement Altern Med. 2017;2017.
38. Xu P, Wang K, Lu C, Dong L, Gao L, Yan M, *et al.* The Protective Effect of Lavender Essential Oil and Its Main Component Linalool against the Cognitive Deficits Induced by D-Galactose and Aluminum Trichloride in Mice. Evidence-based Complement Altern Med. 2017;2017.
39. Todirascu-Ciornea E, El-Nashar HAS, Mostafa NM, Eldahshan OA, Boiangiu RS, Dumitru G, *et al. Schinus terebinthifolius* Essential Oil Attenuates Scopolamine-Induced Memory Deficits via Cholinergic Modulation and Antioxidant Properties in a Zebrafish Model. Evidence-based Complement Altern Med. 2019;2019.
40. Ramos AJ, Merelli A, Avilés Reyes RX LA. Modelos experimentales de hipoxia - isquemia cerebral. TÓPICOS Actual EN Neurobiol secuencia. 2010;117-36.
41. Castaño Guerrero Y, González Fraguela ME, Fernández Verdecia I, Horruitiner Gutiérrez I, Piedras Carpio S. Alteraciones del metabolismo oxidativo y de la memoria y el aprendizaje en un modelo de hipoperfusión cerebral en ratas. Neurología. 2013;28(1):1-8.
42. Guerrero-Espino LM. Ligadura de arteria carótida común y exanguinación como modelo experimental de isquemia cerebral focal en ratas. Rev ECIPeru. 2018;126-31.

43. Farkas E, Luiten PGM, Bari F. Permanent, bilateral common carotid artery occlusion in the rat: A model for chronic cerebral hypoperfusion-related neurodegenerative diseases. Brain Res Rev. 2007;54(1):162-80.

44. Shang Y, Cheng J, Qi J, Miao H. Scutellaria flavonoid reduced memory dysfunction and neuronal injury caused by permanent global ischemia in rats. Pharmacol Biochem Behav. 2005;82(1):67-73.

45. Prieto Arribas R, Moreno Gutiérrez Á, Simal Hernández P, Pascual Garvi JM, Matías-Guiu Guía J, Roda Frade JM, *et al.* Modelos experimentales de isquemia cerebral. Rev Neurol. 2008;47(08):414.

46. O'Dell TJ, Hawkins RD, Kandel ER, Arancio O. Tests of the roles of two diffusible substances in long-term potentiation: Evidence for nitric oxide as a possible early retrograde messenger. Proc Natl Acad Sci USA. 1991;88(24):11285-9.

47. Schuman EM, Madison D V. A requirement for the intercellular messenger nitric oxide in long-term potentiation. 1989;(17):2-5.

48. Madison D V., Malenka RC, Nicoll RA. Mechanisms underlying long-term potentiation of synaptic transmission. Annu Rev Neurosci. 1991;14:379-97.

49. Bear MF, Malenka RC. Synaptic plasticity: LTP and LTD. Curr Opin Neurobiol. 1994;4(3):389-99.

50. Huang PL, Dawson TM, Bredt DS, Snyder SH, Fishman MC. Targeted disruption of the neuronal nitric oxide synthase gene. Cell. 1993;75(7):1273-86.

51. Gammie SC, Nelson RJ. Maternal aggression is reduced in neuronal nitric oxide synthase- deficient mice. J Neurosci. 1999;19(18):8027-35.

52. Contet C, Rawlins JNP, Deacon RMJ. A comparison of 129S2/SvHsd and C57BL/6JOlaHsd mice on a test battery assessing sensorimotor, affective and cognitive behaviours: Implications for the study of genetically modified mice. Behav Brain Res. 2001;124(1):33-46.

53. Navarrete Rueda F, Pérez Ortiz JM, Femenía Cantó T, García Gutiérrez MS, García Payá ME, Leiva Santana C, *et al.* Métodos de evaluación de trastornos cognitivos en modelos animales. Rev Neurol. 2008;47(03):137.

54. Akbaba E, Hassan S, Mohammed Sur T, Bagci E. Memory Enhancing, Anxiolytic and Antidepressant Effects of *Achillea biebersteinii* (Asteraceae) Essential Oil on Scopolamine-Induced Rats. J Essent Oil-Bearing Plants. 2018;21(3):825-39.

55. Postu PA, Sadiki FZ, El Idrissi M, Cioanca O, Trifan A, Hancianu M, et al. Pinus halepensis essential oil attenuates the toxic Alzheimer's amyloid beta (1-42)-induced memory impairment and oxidative stress in the rat hippocampus. Biomed Pharmacother. 2019;112(11):108673.

56. Sahak MKA, Mohamed AM, Hashim NH, Hasan Adli DS. Nigella sativa oil enhances the spatial working memory performance of rats on a radial arm maze. Evidence-based Complement Altern Med. 2013;2013.

57. Sahak MKA, Kabir N, Abbas G, Draman S, Hashim NH, Hasan Adli DS. The role of *Nigella sativa* and its active constituents in learning and memory. Evidence-based Complement Altern Med. 2016;2016.

58. Eskandari-Roozbahani N, Shomali T, Taherianfard M. Research paper: Neuroprotective effect of Zataria multiflora essential oil on rats with Alzheimer disease: A mechanistic study. Basic Clin Neurosci. 2019;10(1):85-97.

59. Kahina C, Nawel H, Faiza Z, Jean G, Mohamed T, Ahsene B. Protective Effects of *Pelargonium graveolens* Essential Oil on Methomyl-Induced Oxidative Stress and Spatial Working Memory Impairment in Association with Histopathological Changes in the Hippocampus of Male Wistar Rats. Basic Clin Neurosci. 2020;11(4):433-46.

60. Halder S, Mehta AK, Kar R, Mustafa M, Mediratta PK, Sharma KK. Clove oil reverses learning and memory deficits in scopolamine-treated mice. Planta Med. 2011;77(8):830-4.

61. Hritcu L, Cioanca O, Hancianu M. Effects of lavender oil inhalation on improving scopolamine-induced spatial memory impairment in laboratory rats. Phytomedicine. 2012;19(6):529-34.

62. Hritcu L, Bagci E, Aydin E, Mihasan M. Antiamnesic and Antioxidants Effects of *Ferulago angulata* Essential Oil Against Scopolamine-Induced Memory Impairment in Laboratory Rats. Neurochem Res. 2015;40(9):1799-809.

63. Chen Y, Hu J, Zhang Y, Han C, Li J. Anti-Alzheimer's disease effect of essential oil from aerial parts of *Salvia miltiorrhiza* Bge. Int J Clin Exp Med. 2018;11(2):641-52.

64. Dhanya K, Satish S, Karunakar Hegde SA. Investigation on Learning and Memory Enhancing activity of Essential Oil in *Albizia julibrissin* Flowers in Experimental Mice. Asian J Biomed Pharm Sci. 2016;6(55):11-5.

65. Oyemitan IA, Elusiyan CA, Akinkunmi EO, Obuotor EM, Akanmu MA, Olugbade TA. Memory enhancing, anticholinesterase and antimicrobial activities of β-phenylnitroethane and essential oil of *Dennettia tripetala* Baker f. J Ethnopharmacol. 2019;229:256-61.

66. Postu PA, Gorgan DL, Cioanca O, Russ M, Mikkat S, Glocker MO, *et al.* Memory-enhancing effects of *Origanum majorana* essential oil in an Alzheimer's amyloid beta1-42 rat model: A molecular and behavioral study. Antioxidants. 2020;9(10):1-20.

67. Salehi A, Setorki M. Effect of hyssopus officinalis essential oil on chronic stress-induced memory and learning impairment in male mice. Bangladesh J Pharmacol. 2017;12(4):448-54.

68. Gomar A, Hosseini A, Mirazi N. Memory enhancement by administration of ginger (*Zingiber officinale*) extract on morphine-induced memory impairment in male rats. J Acute Dis. 2014;3(3):212-7.

69. Ozarowski M, Mikolajczak PL, Bogacz A, Gryszczynska A, Kujawska M, Jodynis-Liebert J, *et al. Rosmarinus officinalis* L. leaf extract improves memory impairment and affects acetylcholinesterase and butyrylcholinesterase activities in rat brain. Fitoterapia. 2013;91:261-71.

70. Sharifi-Rad J, Sureda A, Tenore GC, Daglia M, Sharifi-Rad M, Valussi M, *et al.* Biological activities of essential oils: From plant chemoecology to traditional healing systems. Molecules. 2017;22.

71. Zitzelsberger C, Buchbauer G. Essential Oils as "A Cry for Help". A Review. Nat Prod Commun. 2015;10(6).

72. Aydin E, Hritcu L, Dogan G, Hayta S, Bagci E. The Effects of Inhaled Pimpinella peregrina Essential Oil on Scopolamine-Induced Memory Impairment, Anxiety, and Depression in Laboratory Rats. Mol Neurobiol. 2016;53(9):6557-67.

73. Nagoor Meeran MF, Javed H, Taee H Al, Azimullah S, Ojha SK. Pharmacological properties and molecular mechanisms of thymol: Prospects for its therapeutic potential and pharmaceutical development. Front Pharmacol. 2017;8:1-34.

74. Zhang Z, Chen W, Luan J, Chen D, Liu L, Feng X. Ameliorative effects of olibanum essential oil on learning and memory in Aβ1-42-induced Alzheimer's disease mouse model. Trop J Pharm Res. 2020;19(8):1643-51.

75. Lee BH, Nam TG, Park WJ, Kang H, Heo HJ, Chung DK, *et al.* Antioxidative and neuroprotective effects of volatile components in essential oils from *Chrysanthemum indicum* Linné flowers. Food Sci Biotechnol. 2015;24(2):717-23.

76. Youdim KA, Deans SG. Beneficial effects of thyme oil on age-related changes in the phospholipid C20 and C22 polyunsaturated fatty acid composition of various rat tissues. Biochim Biophys Acta - Mol Cell Biol Lipids. 1999;1438(1):140-6.

77. Azizi Z, Ebrahimi S, Saadatfar E, Kamalinejad M, Majlessi N. Cognitive-enhancing activity of thymol and carvacrol in two rat models of dementia. Behav Pharmacol. 2012;23(3):241-9.

78. Asadbegi M, Yaghmaei P, Salehi I, Komaki A, Ebrahim-Habibi A. Investigation of thymol effect on learning and memory impairment induced by intrahippocampal injection of amyloid beta peptide in high fat diet-fed rats. Metab Brain Dis. 2017;32(3):827-39.

79. Pastore A, Federici G, Bertini E, Piemonte F. Analysis of glutathione: Implication in redox and detoxification. Clin Chim Acta. 2003;333(1-2):19-39.

80. Rahman ZU, Al Kury LT, Alattar A, Tan Z, Alshaman R, Malik I, *et al.* Carveol a Naturally-Derived Potent and Emerging Nrf2 Activator Protects Against Acetaminophen-Induced Hepatotoxicity. Front Pharmacol. 2021;11:1-15.

81. Coon JT, Ernst E. Systematic review: Herbal medicinal products for non-ulcer dyspepsia. Aliment Pharmacol Ther. 2002;16(10):1689-99.

82. Kaur K, Kaushal S. Phytochemistry and pharmacological aspects of *Syzygium aromaticum* : A review. J Pharmacogn Phytochem. 2019;8(1):398-406.

83. Wińska K, Mączka W, Łyczko J, Grabarczyk M, Czubaszek A, Szumny A. Essential oils as antimicrobial agents—myth or real alternative? Molecules. 2019;24(11):1-21.

84. Orav A, Stulova I, Kailas T, Müürisepp M. Effect of Storage on the Essential Oil Composition of *Piper nigrum* L. Fruits of Different Ripening States. J Agric Food Chem. 2004;52(9):2582-6.

85. Jayaprakasha GK, Mohan Rao LJ, Sakariah KK. Volatile constituents from *Cinnamomum zeylanicum* fruit stalks and their antioxidant activities. J Agric Food Chem. 2003;51(15):4344-8.

86. Mockute D, Bernotiene G, Judzentiene A. The essential oil of *Origanum vulgare* L. ssp. vulgare growing wild in Vilnius district (Lithuania). Phytochemistry. 2001;57(1):65-9.

87. Gertsch J, Leonti M, Raduner S, Racz I, Chen JZ, Xie XQ, *et al.* Beta-caryophyllene is a dietary cannabinoid. Proc Natl Acad Sci USA. 2008;105(26):9099-104.

88. Sköld M, Karlberg AT, Matura M, Börje A. The fragrance chemical β-caryophyllene - Air oxidation and skin sensitization. Food Chem Toxicol. 2006;44(4):538-45.

89. Lindsey LP, Daphney CM, Oppong-Damoah A, Uchakin PN, Abney SE, Uchakina ON, *et al.* The cannabinoid receptor 2 agonist, β-caryophyllene, improves working memory and reduces circulating levels of specific proinflammatory cytokines in aged male mice. Behav Brain Res. 2019;372:112012.

90. Bagci E, Aydin E, Ungureanu E, Hritcu L. Anthriscus nemorosa essential oil inhalation prevents memory impairment, anxiety and depression in scopolamine-treated rats. Biomed Pharmacother. 2016;84:1313-20.

91. Maróstica MR, Pastore GM. Biotransformação de limoneno: Uma revisão das principais rotas metabólicas. Quim Nova. 2007;30(2):382-7.

92. Yoo ZW, Kim NS, Lee DS. Comparative Analyses of the Flavors from Hallabong (*Citrus sphaerocarpa*) with Lemon, Orange and Grapefruit by SPTE and HS-SPME Combined with GC-MS. Bull Korean Chem Soc. 2004;25(2):271-9.

93. Zhou W, Yoshioka M, Yokogoshi H. Sub-chronic effects of s-limonene on brain neurotransmitter levels and behavior of rats. J Nutr Sci Vitaminol. 2009;55(4):367-73.

94. Seo S, Song Y, Gu SM, Min HK, Hong JT, Cha HJ, *et al.* D-limonene inhibits pentylenetetrazole-induced seizure via adenosine A2A receptor modulation on gabaergic neuronal activity. Int J Mol Sci. 2020;21(23):1-11.

95. Lorigooini Z, Boroujeni SN, Sayyadi-Shahraki M, Rahimi-Madiseh M, Bijad E, Amini-Khoei H. Limonene through Attenuation of Neuroinflammation and Nitrite Level Exerts Antidepressant-Like Effect on Mouse Model of Maternal Separation Stress. Behav Neurol. 2021;2021.

96. De Almeida AAC, Costa JP, De Carvalho RBF, De Sousa DP, De Freitas RM. Evaluation of acute toxicity of a natural compound (+)-limonene epoxide and its anxiolytic-like action. Brain Res. 2012;1448:56-62.

97. Lima NGPB, De Sousa DP, Pimenta FCF, Alves MF, De Souza FS, MacEdo RO, *et al.* Anxiolytic-like activity and GC-MS analysis of (R)-(+)-limonene fragrance, a natural compound found in foods and plants. Pharmacol Biochem Behav. 2013;103(3):450-4.

98. Wang X, Li G, Shen W. Protective effects of D-limonene against transient cerebral ischemia in stroke-prone spontaneously hypertensive rats. Exp Ther Med. 2018;15(1):699-706.

99. Han Y, Song C, Koh W, Yon G, Kim Y. Anti-inflammatory Effects of the Zingiber of fi cinale roscoe Constituent 12-Dehydrogingerdione in. Phyther Res. 2013;1205:1200-5.

100. Stoner GD. Ginger: Is it ready for prime time? Cancer Prev Res. 2013;6(4):257-62.

101. Lee C, Park GH, Kim CY, Jang JH. [6]-Gingerol attenuates β-amyloid-induced oxidative cell death via fortifying cellular antioxidant defense system. Food Chem Toxicol. 2011;49(6):1261-9.

102. Ali B, Al-Wabel NA, Shams S, Ahamad A, Khan SA, Anwar F. Essential oils used in aromatherapy: A systemic review. Asian Pac J Trop Biomed. 2015;5(8):601-11.

103. Koulivand PH, Khaleghi Ghadiri M, Gorji A. Lavender and the nervous system. Evidence-based Complement Altern Med. 2013;2013.

104. Hancianu M, Cioanca O, Mihasan M, Hritcu L. Neuroprotective effects of inhaled lavender oil on scopolamine-induced dementia via anti-oxidative activities in rats. Phytomedicine. 2013;20(5):446-52.

105. Caputo L, Nazzaro F, Souza LF, Aliberti L, De Martino L, Fratianni F, *et al.* Laurus nobilis: Composition of essential oil and its biological activities. Molecules. 2017;22(6):1-11.

106. Ferguson GD, Storm DR, Ca T. Why Calcium-Stimulated Adenylyl Cyclases ? 2021;271-6.

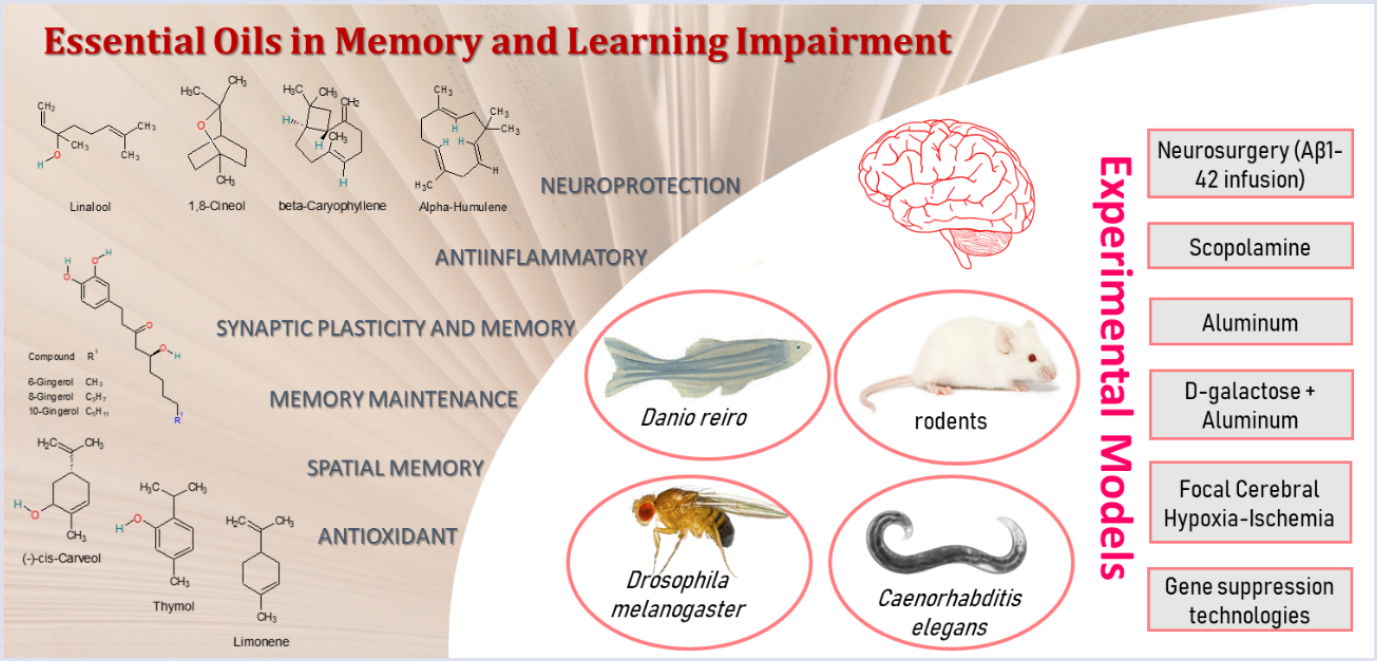
107. Shimizu K, Gyokusen M, Kitamura S, Kawabe T, Kozaki T, Ishibashi K, *et al.* Essential oil of lavender inhibited the decreased attention during a long-term task in humans. Biosci Biotechnol Biochem. 2008;72(7):1944-7.

108. Habtemariam S. The Therapeutic Potential of Rosemary (*Rosmarinus officinalis*) Diterpenes for Alzheimer's Disease. Evidence-based Complement Altern Med. 2016;2016.

109. Hongratanaworakit T. Simultaneous aromatherapy massage with rosemary oil on humans. Sci Pharm. 2009;77(2):375-87.

110. Benny A, Thomas J. Essential Oils as Treatment Strategy for Alzheimer's Disease: Current and Future Perspectives. Planta Med. 2019;85(3):239-48.

GRAPHICAL ABSTRACT



ABOUT AUTHORS

Silva–Correa Carmen R. Department of Pharmacology professor at Universidad Nacional de Trujillo, holds a degree in Pharmacy and Biochemistry (2011), Master of Chemical Sciences (2017), graduate student at Doctoral program in Biomedical Sciences since 2019. Currently participates in research projects on toxicological and pharmacological evaluation of medicinal plants, focusing in the evaluation of the wound healing activity of traditional medicinal plants from Peru

Campos-Reyna Jorge Luis. MD, Physician graduated in Universidad Nacional de Cordoba, , Master In Physiology and Medicine Doctor in Universidad Nacional de Trujillo, , Winner of 2 internationals research awards in line of research: calcium and heart. Internist in Universidad Nacional Federico Villarreal (Hospital Nacional Hipolito Unanue), Professor of physiology at "Universidad Nacional de Trujillo", former internist of internal medicine women's service at "Hospital Belen de Trujillo", Director of "Hospital Metropolitano de Trujillo", former editor of Medicine Magazine of Trujillo, founder of the physiology and physiopathology Peruvian society.

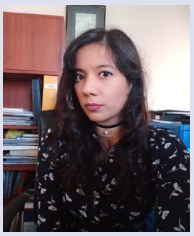
Villarreal–La Torre Víctor E. Master of Chemical Sciences, holds a degree in Pharmacy from Universidad Nacional de Trujillo (2011). Professor in the Medicinal Chemistry undergraduate program and the Molecular basis of the Action of Xenobiotics postgraduate program at the Universidad Nacional de Trujillo. He currently executes research projects aimed at the discovery of antimicrobial compounds in medicinal plants. Graduate student at Doctoral program in Pharmacy and Biochemistry since 2019.

Calderón-Peña Abhel A. Master of Physiology and Biophysic, holds a degree in Biological Science from Universidad Nacional de Trujillo. Animal Physiology, Human Anatomy, Histology and Biochemistry Professor of undergraduate program at the Universidad Nacional de Trujillo. He is currently conducting research on oxidative stress and the discovery of antioxidant compounds in medicinal plants. Graduate student at Doctoral in the Biological Sciences program.

Sagástegui-Guarniz William Antonio. Department of Pharmacology professor at Universidad Nacional de Trujillo, Perú since 1993 – to date. I am a graduated in Pharmacy and Biochemistry. Speaker at the graduate program of Universidad Nacional de Trujillo. Has bachelor in pharmaceutical chemistry 1988. Master's in chemical sciences, 1999. Doctorate in Biomedical Sciences, graduate program of the Universidad Nacional de Trujillo, 2010. Doctorate studies at Universidade Federal Do Ceará, Brazil, 2015-2018. Currently participates in research projects aimed at the phytochemical characterization of medicinal plants, focusing on antimicrobial activity, resistance to antimicrobials, and antimalarial.

Guerrero-Espino Luz M. Professor. Department of Physiology. School of Medicine - Universidad Nacional de Trujillo, PhD in Biomedical Sciences, Master's Degree in Physiology. Researcher in neuroscience, altitude and exercise.

González-Siccha Anabel D. Doctor in Pharmacy and Biochemistry. Master of science in Biochemistry. Magister in Physiology. Pharmacy degree in Spain. Second degree in Clinical and Biological Analysis. Principal Professor of Biochemistry and Molecular Biology undergraduate program of the Department of Biochemistry, Pharmacy and Biochemistry Faculty at the Universidad Nacional de Trujillo. Research Fellow in the Laboratory of Biochemistry and Molecular Biology at the Faculty of Medicine from Albacete, Universidad de Castilla-La Mancha from Spain. Research on Nutritional assessment and anemia in vulnerable populations. Research on medicinal plants on immunomodulatory, antitumor and tumor marker activity. Research on DLK1 and DLK2 proteins and differentiation on mouse tissues through immunohistochemistry.



Aspajo-Villalaz Cinthya L. Master of Food Technology holds a degree in Biological Science from Universidad Nacional de Trujillo. Bromatology and Biochemistry Professor of undergraduate program at the Universidad Nacional de Trujillo. She is currently conducting research on microbiological control of pharmaceutical products, functional foods design and evaluation. Graduate student at Doctoral in the Biological Sciences program.

González-Blas María V. Master of Chemical Sciences holds a degree in Pharmacy and Biochemistry from Universidad Nacional de Trujillo, Doctorate studies in Biomedical Sciences. She has participated in research projects of hypoglycemic, diuretic and antileishmanicidal activity of compounds in medicinal plants.

Cruzado–Razco José L. Department of Pharmacology professor at the Universidad Nacional de Trujillo, holds a degree in Pharmacy and Biochemistry, Master of Physiology and Biophysics, Doctorate studies in Biomedical Sciences. He has participated in research projects on epidemiology of tropical diseases and currently, in research on antimalarial, leishmanicidal and anti-trypanosomal activity of medicinal plants.

Hilario-Vargas, Julio S. Professor. Departamento de Fisiología, Facultad de Medicina. Universidad Nacional de Trujillo. Master in Physiology and Doctor in Biomedical Science. Research and publishes works on pemphigus, evaluation of medicinal plant extracts, and physiological function in special environments.

Cite this article: Silva-Correa CR, Campos-Reyna JL, Villarreal-La Torre VE, Calderón-Peña AA, Sagástegui-Guarniz WA, Guerrero-Espino LM, et al. Potential Neuroprotective Activity of Essential Oils in Memory and Learning Impairment. Pharmacogn J. 2021;13(5): 1312-1322.