Therapeutic potential of Zingiberaceae in Alzheimer's disease

[Potencial terapéutico de Zingiberaceae en la enfermedad de Alzheimer]

Wanessa de Campos Bortolucci¹, Jéssica Rezende Trette², Danilo Magnani Bernardi³, Marília Moraes Queiroz Souza⁴, Ana Daniela Lopes⁵, Evellyn Claudia Wietzikoski Lovato⁵, Francislaine Aparecida dos Reis Lívero⁴,⁶, Glacy Jaqueline da Silva⁴, Hélida Mara Magalhães², Silvia Graciela Hülse de Souza², Zilda Cristiani Gazim¹ & Nelson Barros Colauto⁴

¹Graduate Program in Biotechnology Applied to Agriculture, Universidade Paranaense, Umuarama, PR, Brazil
²Graduate Program in Biotechnology Applied to Agriculture, Universidade Paranaense, Umuarama, PR, Brazil
³Graduate Program in Medicinal Plants and Phytotherapeutics in Basic Attention, Universidade Paranaense, Umuarama, Brazil
⁴Graduate Program in Medicinal Plants and Phytotherapeutics in Basic Attention, Universidade Paranaense, Umuarama, PR, Brazil
⁵Graduate Program in Animal Science with Emphasis on Bioactive Products, Universidade Paranaense, Umuarama, PR, Brazil

Abstract: Alzheimer's disease is the most common form of dementia and is highly prevalent in old age. Unlike current drugs, medicinal plants can have preventive and protective effects with less side effects. Given the great number of bioactive substances, plants from the Zingiberaceae Family have medicinal potential and currently are widely studied regarding its anti-Alzheimer's disease effects. The objective of this study was to provide an overview of advances in phytochemical composition studies, in vitro and in vivo pharmacological studies, and toxicological effects of the Zingiberaceae Family on Alzheimer's disease. Information was obtained from relevant papers in electronic databases. Most of the studies of Zingiberaceae effects on Alzheimer's disease pathogenesis theory are related to cholinergic, β amyloid cascade, tau, inflammation, and oxidative stress hypothesis. Also, in vitro and in vivo preclinical studies on the effect of Alpinia, Curcuma, and Zingiber genera have been reported as harmless and safe, with potential for anti-Alzheimer treatment.

Keywords: Aging; Alpinia; Curcuma; Dementia; Herbal medicine; Zingiber.

Resumen: El Alzheimer es la forma más común de demencia y es altamente prevalente en la vejez. A diferencia de los medicamentos actuales, las plantas medicinales pueden tener efectos preventivos y protectores con menos efectos secundarios. Dada la gran cantidad de sustancias bioactivas, las plantas de la familia Zingiberaceae tienen potencial medicinal y actualmente se estudian ampliamente los efectos de la enfermedad anti-Alzheimer. El objetivo de este estudio fue proporcionar una visión general de los avances en los estudios de composición fitoquímica, estudios farmacológicos in vitro e in vivo, y los efectos toxicológicos de la familia Zingiberaceae sobre la enfermedad de Alzheimer. La información se obtuvo de documentos relevantes en bases de datos electrónicas. La mayoría de los estudios sobre los efectos de Zingiberaceae en la teoría de la patogénesis de la enfermedad de Alzheimer están relacionados con la hipótesis colinérgica, la cascada β amiloide, la tau, la inflamación y el estrés oxidativo. Además, los estudios preclínicos in vitro e in vivo sobre el efecto de los géneros Alpinia, Curcuma y Zingiber se han informado como inofensivos y seguros, con potencial para el tratamiento contra el Alzheimer.

Palabras clave: Envejecimiento; Alpinia; Cúrcuma; Demencia; Medicina herbaria; Zingiber

Recibido | Received: February 15, 2020
Aceptado | Accepted: March 20, 2020
Aceptado en versión corregida | Accepted in revised form: March 25, 2020
Publicado en línea | Published online: September 30, 2020

Este artículo puede ser citado como / This article must be cited as: WC Bortolucci, JR Trettel, DM Bernardi, MMQ Souza, ADLopes, ECW Lovato, FAR Livero, GJ da Silva, HM Magalhães, SGH de Souza, ZC Gazim, NB Colauto. 2020. Therapeutic potential of Zingiberaceae in Alzheimer's disease. Bol Latinoam Caribe Plant Med Aromat 19 (5): 428 - 465. https://doi.org/10.37360/blacpma.20.19.5.30
INTRODUCTION
The increase in population aging is a worldwide phenomenon, a consequence of the improvement of healthcare in the last century. However, this has increased the number of long-lived people and the number of non-communicable diseases in this group such as dementias, one of the major causes of disability in later life (Prince, 2004; Lunenfeld & Stratton, 2013; Park et al., 2013).

Dementia is a comprehensive term that encompasses a variety of diseases and conditions that develop when neurons die or cease to function normally, causing changes in memory, behavior, and the ability to think clearly (Sacuiu, 2016). About 2 to 10% of all dementia cases begin before age 65 and the prevalence doubles every five years from the age of 65, with a new case recorded every 4 s in the world (WHO, 2013). According to the latest estimate, the incidence of people affected with dementia will jump from 35.6 million cases in 2010 to 115.4 million people in 2050 (Prince et al., 2012).

The World Health Organization (WHO, 2012) states that Alzheimer’s disease (AD) is the most common form of dementia and possibly accounts for 60-70% of cases. AD is highly prevalent with old age, a scenario that occurs all over the world, with estimates pointing to 47 million people affected by dementia worldwide (Prince et al., 2015; Keene et al., 2020). AD has been affecting 46.8 million people throughout the world and this number is likely to double by 2030 due to the lack of effective treatment (Penumala et al., 2018). In the United States of America in 2011, there were 4.5 million individuals over 65 years old with AD; this included 0.7 million people between 65 and 74 years old; 2.3 million aged 75-84 years and 1.8 million aged 85 or over. There is a projected increase to 13.8 million people with dementia in the US and more than 130 million worldwide by 2050 (Keene et al., 2019). Most of these people will be living in developing countries (WHO, 2013). The disease is also responsible for a global annual cost of USD 818 billion and a substantial increase is expected in the coming decades (Shah et al., 2016).

Although awareness of “dementia diseases” as a public health problem has been increasing, in some countries, precisely where the number of cases will be greater, this awareness is low or absent (Thies & Bleiler, 2013). The basis of AD treatment is still symptomatic, there is no neuroprotective effect or changes in the trajectory of the disease. In addition, current drugs (acetylcholinesterase inhibitors and the NMDA receptor antagonist) present absolute contraindication for patients with bradycardia or altered cardiac conduction system (Howes, 2014). Another restriction to the use of current pharmacological therapy are its side effects, which may stand out for the modest beneficial impacts of these medications (Press & Alexander, 2019a).

Considering that none of the available treatments with memantine (NMDA antagonist) and acetylcholinesterase (AChE) inhibitors such as rivastigmine, galantamine, and donepezil cure or alter the progressive course of the disease (Press & Alexander, 2019b), it is necessary to diversify the therapeutic arsenal, a goal proposed by WHO at the first Ministerial Conference on Global Action Against Dementia in March, 2015 (Shah et al., 2016), which can be achieved and/or improved with the use of bioactive herbs (Akran & Nawaz, 2017).

Unlike the current “anti-dementia” drugs, plants can have preventive and protective effects with little or no side effects, as noted with traditional therapy for AD, including nausea, anorexia, diarrhea, vomiting, and mass loss (Delagarza, 2003; Santos-Neto et al., 2006; Nisar et al., 2017). Therefore, as revised by Santos-Neto et al. (2006), Akhondzadeh & Abbas (2006), Wu et al. (2015) and Yang et al. (2017) several medicinal plants have been used for decades in different cultures to improve memory and many of them have been scientifically studied regarding their anti-dementia activity such as the following ones that stand out Centella asiatica (L.) Urb. (Aipiacae) (Gray et al., 2018), Coriandrum sativum L. (Aipiacae) (Cioanca et al., 2013), Ilex paraguariensis A.St.-Hil. (Aquifoliaceae) (Bortoli et al., 2018), Panax ginseng C.A.Mey. (Araliacae) (Shin et al., 2019), Lepidium meyenii Walp. (Brassicaceae) (Rubio et al., 2007), Commiphora whighitti (misspelt name, probably Commiphora wightii (Arn.) Bhandari; (Burseraceae) (Saxena et al., 2007), Nardostachys jatamansi (D.Don) DC (Caprifoliaceae) (Liu et al., 2018), Celastrus paniculatus Willd. (Celastraceae) (Malik et al., 2017), Convulvulus pluricaulis Wall. ex Choisy (Convulvaceae) (Kizhakke et al., 2019), Evolvulus alsinoides (L.) L. (Convulvaceae) (Siripurapu et al., 2005), Glycyrrhiza glabra L. (Fabaceae) (Guo et al., 2016), Ginkgo biloba L. (Ginkgoaceae) (Liu et al., 2020), Crocus sativus L. (Iridaceae) (Wang et al., 2019), Melissa officinalis L. (Lamiaceae) (Watson et al., 2019), Salvia officinalis L. (Lamiaceae) (Miroddi et al., 2014), Panica granatum L. (Lythraceae) (Yuan et al., 2016), Magnolia officinalis Rehder &
E.H.Wilson (Magnoliaceae) (Lee et al., 2012), Cissampelos pareira L. (Menispermaceae) (Thukham-Mee & Wattanathorn, 2012), Tinospora cordifolia (Willd.) Miers (Menispermaceae) (Malve et al., 2014), Ficus carica L. (Moraceae) (Ashfaq et al., 2018), Ficus racemosa L. (Moraceae) (Ahmed et al., 2011), Moringa oleifera Lam. (Moringaceae) (Mahaman et al., 2018), Myristica fragrans Houtt. (Myristicaceae) (Parle et al., 2004), Emblica officinalis (current name Phyllanthus emblica L., Phyllanthaceae) (Uddin et al., 2016), Bacopa monnieri (L.) Pennell (Plantaginaceae) (Saini et al., 2019), Withania somnifera (L.) Dunal. (Solanaceae) (Sehgal et al., 2012), Curcuma longa L. (Zingiberaceae) (Giacomeli et al., 2019), and Zingiber officinale Roscoe (Zingiberaceae) (Cuya et al., 2018). In addition, medicinal plants may act through multi-target and pathways, at cellular and molecular levels, presenting potential beneficial effects on AD (Wu et al., 2015; Yang et al., 2017). A large number of plant extracts and phytoconstituents have been evaluated for their anti-Alzheimer’s effects and several bioactive compounds have been identified and correlated with anticholinesterase and anti-amyloidogenic activities. Among these main compounds are sterols, triterpenes, polyphenols, tannins, flavonoids, and lignins (Akran & Nawaz, 2017).

The Zingiberaceae Family, commonly known as the ginger Family, the largest Family of the Zingiberales order, has several bioactive substances and medicinal potential (Sharifi-Rad et al., 2017). It is a Family of flowering plants with 53 genera and more than 1,200 species worldwide, mainly in China and Asia. Most species of this Family are aromatic, presenting perineal with or without tuberous rhizomes, and most of them have medicinal properties (Larsen et al., 1998; Saensouk et al., 2016). Popularly, these plants are widely used as food, seasoning, and for the treatment of a wide range of diseases due to their antimicrobial, antioxidant (Chen et al., 2008), anti-inflammatory (Namsa et al., 2009), analgesic, nematicidal, vasorelaxant, sedative, antineoplastic, anti-allergic, healing (Umar et al., 2011), antitussive, anti-influenza, anti-inflammatory, anti-diarrhea, anti-diabetic, anti-urinary incontinence activities (Kumar et al., 2011; Victório, 2011), and widely studied regarding its AD pharmacological effects (Monroy et al., 2013; Roy, 2018).

In this review, an overview of AD (definition, pathogenesis, cardinal symptoms, diagnosis, treatment, and emerging therapies) and the relationship of Zingiberaceae in AD were presented. Also, a bibliographical survey about the phytochemical composition, in vitro and in vivo pharmacological studies, and toxicological effects of plants from this Family related to AD were revised and discussed. In addition, future perspectives and challenges regarding therapeutic use of the Zingiberaceae family in AD are discussed.

**ALZHEIMER’S DISEASE**

**Definition**

AD was first reported more than 100 years ago. However, advances in research involving risk factors, symptoms, pathophysiology, and treatment have only gained momentum in the past 30 years. Although the depth of research has revealed much about AD, the precise cerebellar mechanisms that trigger the development of the disease and the order in which these events occur are still not fully elucidated, except for rare inherited forms caused by known genetic mutations (Thies & Bleiler, 2013). The disease is a neurodegenerative disorder that primarily affects older adults’ brains. It has a chronic and progressive character, with disorders of multiple major cortical functions, including memory, thought, orientation, understanding, calculation, learning ability, language, and judgment (Apostolova, 2016). The level of consciousness is not altered, but its content is. Failure of the cognitive function is commonly accompanied and occasionally preceded by deterioration of emotional control, social behavior, or motivation (WHO, 2013).

**Pathogenesis**

Many hypotheses about AD have been developed, including amyloid-β (Aβ), tau, cholinergic neuron damage, involvement of oxidative stress, inflammation (Du et al., 2018; Gamba et al., 2019), mitochondrial dysfunction, defective insulin signaling, decreased glucose utilization, and unregulated cholesterol homeostasis (Gamba et al., 2019). Thus, many efforts have been made to develop anti-AD drugs based on these hypotheses. According to the cholinergic hypothesis, acetylcholinesterase enzyme (AChE) acts primarily as a regulatory enzyme at cholinergic synapses, while butyrylcholinesterase enzyme (BuChE), an enzyme closely related to AChE, serves as a co-regulator of cholinergic neurotransmission by hydrolyzing acetylcholine (ACh) (Stanciu et al., 2020). AChE and BuChE dual inhibition has been documented as critical targets for the effective management of AD.
by an increase in ACh availability in the brain regions (Penumala et al., 2018; Hampel et al., 2019).

The Aβ cascade hypothesis has evolved in the last 15 years. The Aβ peptide is generated by a metabolism of the amyloid precursor protein (APP) and results in the production, aggregation, and deposition of Aβ substance and senile plaques (Sereni & Vital, 2008; Reitz, 2012). The Aβ precursor cleavage enzyme (BACE-1) is a key enzyme responsible for the production of amyloid plaque, which involves AD progression and symptoms (Konno et al., 2014). The Aβ deposition in the AD brain happens in three phases: 1) Aβ deposits occur exclusively in the neocortex region; 2) allocortical brain, diencephalic nuclei, striatum, and cholinergic nuclei of the basal forebrain are the regions with Aβ deposition that also affects several brainstem nuclei as the deposition progress; and 3) Aβ deposition is found in cerebellar region (Panza et al., 2019). Extracellular deposits of Aβ peptides as senile plaques, intraneuronal neurofibrillary tangles, and large-scale neuronal loss were the main pathological features of AD. Thus, Aβ peptides have long been viewed as a potential target for AD which dominated new drug research in the past 20 years (Du et al., 2018; Keene et al., 2020).

According to tau hypothesis, neurofibrillary tangles, another intracellular hallmark of AD, are composed of tau. Tau is a microtubule-associated protein working as scaffolding proteins that are enriched in axons. In pathological conditions, tau aggregation will impair axons of neurons and, therefore, cause neurodegeneration (Du et al., 2018). The neurofibrillary tangles are also the primary pathology observed in related tauopathies, including frontotemporal lobar degeneration-tau, corticobasal degeneration, and progressive supranuclear palsy. The major compound of neurofibrillary tangles is the microtubule-associated protein tau which undergoes hyperphosphorylation and self-aggregation to form insoluble fibers known as straight and paired helical filaments (Brici et al., 2018). The neuropathological marker of AD is diffuse neuritic plaques, marked by extracellular deposition of Aβ proteins, and neurofibrillary tangles, secondary to the intracellular accumulation of hyperphosphorylated tau proteins (Gasparotto et al., 2018). Brain cells depend on an internal support and transport system to carry nutrients and other essential materials throughout their long extensions. This system requires the normal structure and functioning of a protein called tau. In AD, threads of tau protein twist into abnormal tangles inside brain cells, leading a transport system failure. This failure is also strongly implicated in the decline and death of brain cells (Agarwal et al., 2013).

Regarding the inflammation hypothesis, reactive gliosis and neuro-inflammation are hallmarks of AD. Microglia-related pathways were considered to be central to AD risk and pathogenesis, as supported by emerging genetic and transcriptomic studies. Neurodegeneration, comprising loss of synapses and neurons, occurs in brain regions with high tangle pathology, and an inflammatory response of glial cells appears in brain regions with pathological aggregates (Tzioras et al., 2018).

Finally, the oxidative stress hypothesis is considered to play an important role in the pathogenesis of AD. The brain specially utilizes more oxygen than other tissues and undergoes mitochondrial respiration, which increases the potential for reactive oxygen species (ROS) exposure (Du et al., 2018). Recent studies have confirmed that protein and lipid oxidation were observed in brain regions rich in Aβ peptides, where redox proteomics allowed identification of oxidized proteins in early stages of the disease. Moreover, mitochondrial dysfunction has also been involved in AD pathogenesis, via mitochondrial ROS generation (Cheignon et al., 2018) when ROS production by Aβ peptides occurred in the presence of metal ions. Besides ROS, reactive nitrogen species also play an important role in neurodegenerative disorders. Nitric oxide (NO) is a free radical generated by endothelial cells, macrophages, neurons, and involved in the regulation of various physiological processes. Oxygen reacts with NO excess to generate nitrite and peroxynitrite anions, which act as free radicals and potentially damage cells (Uttara et al., 2009).

**Cardinal symptoms**

Insidious memory loss is the most common symptom. Executive and visuospatial dysfunctions are present in the early stages of the disease, while deficits in language and behavioral symptoms usually manifest later. Other signs such as apraxia, olfactory dysfunctions, sleep disorders and seizures may also occur (Wolk & Dickerson, 2019).

**Diagnosis**

The definitive diagnosis of AD requires histopathological examination, which is rarely done in life. The diagnostic criteria for probable AD have been established by the National Institute on Aging.
and Alzheimer’s Association (NIA-AA); the disease should be suspected for any elderly with slow and progressive memory loss and alteration of at least another cognitive domain with functional failure as 1) interference in the ability to function at work or in usual activities; 2) functional decline compared to a previous level; 3) alteration not explained by delirium or major psychiatric disorder; 4) cognitive deficit established from the conversation with the patient and an informant, objective physical examination, and neuropsychological tests; and 5) cognitive deficit involving the following domains: a) loss of ability to acquire or recall new information, deficits in reasoning, handling of complex tasks, and poor judgment; b) lack of visuospatial skills; c) failure in language functions; and d) changes in personality or behavior (Wolk & Dickerson, 2019).

**Conventional treatment**

The main goal of treatment is to maximize the patient’s daily functional capacity, maintain quality of life, slow the progression of the disease and consequently progression of symptoms, and treat underlying diseases such as depression or disruptive behaviors (WHO, 2012). It is important to notice that such important indications were simplified and personalized for each patient, taking into account the clinical response and side effects. The treatment base is symptomatic, and there are no modifying drugs (Yiannopoulou & Papageorgiou, 2013; Press & Alexander, 2019a). The current pharmacological therapy for AD only results in short-term improvement for a short period of time, from six to eighteen months (Seltzer, 2005). Within the pharmacological scope, there are two groups: 1) cholinesterase inhibitors such as rivastigmine, galantamine, and donepezil, indicated for the mild to moderate phases; and 2) memantine, an N-metil D-aspartato (NMDA) receptor antagonist, indicated for the severe phase of the disease. These drugs do not act reversing AD damage, but allow brain compensation for the loss of neurons that communicate through ACh (Sastre et al., 2005; Birks, 2006).

**Emerging therapies**

Immunotherapy for AD with anti-Aβ antibodies has been studied by Panza et al. (2019), but without success. Thus, there are currently no treatments that promise to modify the course of the disease. Medicinal plants for the treatment of AD are a vast source of potential medications, such as the Zingiberaceae Family, which comprises nearly 53 genera and more than 1,200 species (Kress et al., 2002). Among the main genera of this Family that present in vitro and in vivo pharmacological studies related to AD are Alpinia, Curcuma, and Zingiber genera.

**Zingiberaceae in Alzheimer’s disease**

Zingiberaceae is a pantropical Family with the center of origin in South and Southeast Asia (Saensouk et al., 2016). The main genera of this Family with reports on AD and/or its symptoms are Alpinia, Curcuma, and Zingiber and they are presented as follows.

**Genus Alpinia**

*Alpinia* genus is diverse in Alzheimer’s studies and the main species found are *Alpinia galanga* (L.) Willd., *A. hainanensis* K.Schum., *A. officinarum* Hance, *A. oxyphylla* Miq., *A. rafflesiana* Wall. ex Baker, and *A. zerumbet* (Pers.) B.L.Burtt & R.M.Sm. However, for each species several names have been used incorrectly which could be confusing; therefore, the current name and its synonyms as well as eventual typing mistakes or misspellings must be clarified. Other species such as *A. katsumadai* Hayata is not registered in the most comprehensive and authoritative global species indexes, making its validation even more difficult; it is likely that it is misspelled, and the correct spelling is *A. katsumadai* Hayata, a synonym of the current name *A. hainanensis* K.Schum. Thus, the main species and its synonyms are presented in Table No. 1.

**Alpinia galanga (L.) Willd.**

*A. galanga*, used for medication, culinary and cosmetics, is a perennial, aromatic, rhizomatous herb, abundantly found in India and tropical Asia (Chudiwal et al., 2010; Hanish et al., 2019). Traditionally it is used as a nerve tonic, stimulant, revulsive, carminative, stomachic, disinfectant, aphrodisiac, and anti-inflammatory agent (Warrier et al., 1994). It has antibacterial (Miyazawa & Hashimoto, 2002), antifungal (Bin Jantan et al., 2003), anti-diabetic (Akhtar et al., 2002), and antioxidant activities (Srividy et al., 2010), besides having in vitro BuChE inhibitory activity (Khattak et al., 2005a).
Table No. 1
*Alpinia* genus: current scientific name and its synonyms (Hassler, 2020)

| Current scientific name                      | Synonyms                                                                 |
|---------------------------------------------|---------------------------------------------------------------------------|
| *Alpinia galanga* (L.) Willd                | *Alpinia alba* (Retz.) Roscoe                                             |
|                                             | *Alpinia bifida* Warb.                                                    |
|                                             | *Alpinia carnea* Griff.                                                   |
|                                             | *Alpinia galanga* var. *pyramidata* (Blume) K.Schum.                     |
|                                             | *Alpinia pyramidata* Blume                                                |
|                                             | *Alpinia rheedei* Wight                                                  |
|                                             | *Alpinia viridiflora* Griff.                                             |
|                                             | *Amomum galanga* (L.) Lour.                                               |
|                                             | *Amomum medium* Lour.                                                    |
|                                             | *Galanga major*                                                          |
|                                             | *Galanga officinalis* Salisb.                                             |
|                                             | *Hellenia alba* (Retz.) Willd.                                           |
|                                             | *Heritiera alba* Retz.                                                   |
|                                             | *Languas galanga* (L.) Stuntz                                             |
|                                             | *Langas pyramidata* (Blume) Merr.                                       |
|                                             | *Langas vulgar* J.Koenig                                                  |
|                                             | *Maranta galanga* L.                                                     |
|                                             | *Zingiber galanga* (L.) Stokes                                           |
|                                             | *Zingiber medium* Stokes                                                 |
|                                             | *Zingiber sylvestre* Gaertn.                                             |

| *Alpinia zerumbet* (Pers.) B.L.Burtt & R.M.Sm. | *Alpinia cristata* Griff.                                                 |
|                                               | *Alpinia fimbriata* Gagnep.                                               |
|                                               | *Alpinia fluvitialis* Hayata                                              |
|                                               | *Alpinia nutans* var. *longiramosa* Gagnep.                              |
|                                               | *Alpinia penicillata* Roscoe                                             |
|                                               | *Alpinia schumanniana* Valeton                                           |
|                                               | *Alpinia speciosa* (J.C.Wendl.) K.Schum.                                |
|                                               | *Alpinia speciosa* var. *longiramosa* Gagnep.                            |
|                                               | *Amonum nutans* (Andrews) Schult.                                        |
|                                               | *Catimbiun speciosum* (J.C.Wendl.) Holttum                              |
|                                               | *Costus zerumbet* Pers.                                                   |
|                                               | *Langas schumanniana* (Valeton) Sasaki                                   |
|                                               | *Langas speciosa* (J.C.Wendl.) Small                                    |
|                                               | *Renealmia nutans* Andrews                                               |
|                                               | *Renealmia spectabilis* Rusby                                            |
|                                               | *Zerumbet speciosum* J.C.Wendl.                                          |

| *Alpinia hainanensis* K.Schum.               | *Alpinia henryi* K.Schum.                                                 |
|                                               | *Alpinia henryi* var. *densihispida* H.Dong & G.J.Xu                     |
|                                               | *Alpinia kainantensis* Masam.                                             |
|                                               | *Alpinia katsumadai* Hayata                                              |
|                                               | *Alpinia katsumadai* Hayata (name probably misspelt)                      |
|                                               | *Langas hainanensis* (K.Schum.) Merr.                                    |
|                                               | *Langas henryi* (K. Schum.) Merr.                                        |
|                                               | *Langas katsumadai* (Hayata) Merr.                                       |
Previous studies have shown that *A. galanga* rhizomes promote protective effects on cognition presenting therapeutic potential for AD (Grzanna et al., 2004; Hanish et al., 2011; Hanish et al., 2019).

Phytochemical research showed that *A. galanga* rhizome has a variety of isolated compounds with biological activity for AD. Some active biomolecules, such as 8–9’ linked neolignans, galanganal, galanganols A, B and C, were isolated with other ten known screened compounds for NO production inhibitory activity (Morikawa et al., 2005). 1’δ-1’-acetoxyeugenol acetate was reported to possess inhibitory action on pro-inflammatory cytokine release and suppress the nuclear factor-kappa beta (NF-κB) activation (Matsuda et al., 2003, Ichikawa et al., 2006). Another study evaluated neuroimmune and neuroendocrine properties of 1’δ-1’-acetoxyeugenol acetate isolated from the chloroform fraction of *A. galanga* in neurodegeneration-induced mice (Hanish et al., 2019).

Khattak et al. (2005a) analyzed in vitro inhibition of AChE, BChE, and lipoxygenase enzymes of 22 ethanolic extracts from 14 indigenous medicinal plants, among them *A. galanga*. It was observed that *A. galanga* promoted in vitro inhibition only for BChE. However, the isolation, purification and investigation of active principles responsible for the enzymatic inhibition activity were not performed.

Preclinical studies reported that *A. galanga* rhizomes present protective effects on cognitive deficits by reducing ROS and regulating antioxidant modulators such as superoxide dismutase (SOD), catalase (CAT), and reduced glutathione in Aβ-induced AD mice (Hanish et al., 2011). Hanish et al. (2011) analyzed the effect of *A. galanga* fractions on Alzheimer’s-type amnesia in Swiss mice induced by Aβ25-35, aiming to verify cognitive improvement. They induced neurotoxicity by intracerebroventricular injection of Aβ25-35 and treated animals on the 14th to 21st day with *A. galanga* chloroform fraction (200 and 400 mg/kg, by oral route). The cognitive improvement (habituation memory and hippocampal memory) was evaluated through an open field test and Morris water maze. Na+/K+-ATPase, AChE, and antioxidant enzymes SOD, CAT, glutathione peroxidase (GPx), and vitamin C levels were determined to estimate the biochemical changes in the brain and its potential anti-amnesic action on oxidative stress. The results suggest that there is a potential therapeutic effect on Alzheimer’s-type amnesia. Another study from the same group investigated the effect of *A. galanga* ethanolic extract on the oxidative stress inducing Alzheimer’s-type amnesia in Swiss mice. Neurotoxicity was induced in animals by intracerebroventricular injection of Aβ25-35 and the treatment was carried out for 21 days (200 and 400 mg/kg, by oral route). Behavioral studies with open field, step-down inhibitory avoidance and a water maze after treatment indicated improvement of the cognitive function. The elevated levels of AChE and monoamine oxidase enzymes were attenuated by *A. galanga* treatment. Furthermore, a decrease in the generation of ROS and an increased activity of antioxidant enzymes in the animals treated with the extract were observed, suggesting that *A. galanga* ethanolic extract has an anti-amnesic effect on Aβ-induced neurodegeneration through an antioxidant property (Hanish et al., 2011).

Hanish et al. (2019) showed the effect of different doses (12.5, 25 and 50 mg/kg, by oral route) of 1’δ-1’-acetoxyeugenol acetate isolated from *A. galanga* on Aβ25-35 induced neurodegeneration in Swiss mice (injection on the 15th day of the 28-day treatment). Open field, water maze and step-down inhibitory tests were performed on the 27th day to determine the habituation memory, spatial learning, and short- and long-term memory, respectively. AChE, corticosterone, biogenic amines (serotonin and dopamine), tumor necrosis factor-α (TNF-α), and antioxidant parameters such as SOD, CAT, GPx, and vitamin C levels were evaluated in brain homogenates after behavioral tests to ascertain the cognitive improvement through neuro-immune-endocrine modulation. The 1’δ-1’-acetoxyeugenol acetate treatment (25 and 50 mg/kg) resulted in improvement of the habituation memory and step-
down inhibitory avoidance task. AChE reduction indicates pre- eminent neuroprotection. Corticosterone and TNF-α were significantly reduced and biogenic amines and antioxidant markers were increased, which indicates potential influence of 1′δ-1′-acetoxyeugenol acetate on neuroprotection (Table No. 2).

Table No. 2

| Species       | Plant part | Extract/Isolated compound                                      | Study     | Effect                                                                 | Source                                      |
|---------------|------------|----------------------------------------------------------------|-----------|----------------------------------------------------------------------|---------------------------------------------|
| A. galanga    | Rhizome    | 8′-9′ linked neolignans, galanganal, galanganols A, B and C     | *In vitro*| NO production inhibition                                              | (Morikawa et al., 2005)                    |
| A. galanga    | Rhizome    | Ethanolic extract                                              | *In vitro*| BuChE inhibition                                                      | (Khattak et al., 2005a)                     |
| A. galanga    | Rhizome    | 1′δ-1′-acetoxyeugenol acetate                                   | *In vitro*| Inhibition of pro-inflammatory cytokine release and suppress the nuclear factor kappa beta activation | (Matsuda et al., 2003, Ichikawa et al., 2006) |
| A. galanga    | Rhizome    | Ethanolic extract                                              | *In vivo* | Neuroprotective                                                       | (Hanish et al., 2011)                      |
| A. galanga    | ni         | Chloroform fraction                                            | *In vivo* | Anti-amnesic action on oxidative stress                               | (Hanish et al., 2011)                      |
| A. galanga    | Rhizome    | 1′δ-1′-acetoxyeugenol acetate                                   | *In vivo* | Neuroprotective                                                       | (Hanish et al., 2019).                     |
| A. hainanensis (A. katsumadai, A. katsumadae) | Seed       | Methanolic extract, pinocembrin and (+)-catechin               | *In vitro*| Neuroprotective                                                       | (Jeong et al., 2007)                       |
| A. officinarum| Rhizome    | Ethanolic extract and 7-(4-hydroxyphenyl)-1-phenyl-4E-hepten-3-one (AO-1) | *In vitro*| Neuronal differentiation and neurite outgrowth                        | (Huang et al., 2016).                     |
| A. officinarum| Rhizome    | 7-(4-hydroxyphenyl)-1-phenyl-4E-hepten-3-one (AO-1) and 7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-4E-hepten-3-one (AO-2) | *In vivo* | Neuronal differentiation and neurite outgrowth                        | (Tang et al., 2015)                       |
| A. oxyphylla  | Fruit      | Ethanolic extract                                              | *In vitro*| Neuroprotective                                                       | (Yu et al., 2003)                          |
| A. oxyphylla  | Kernel     | Protocatechic acid                                             | *In vitro*| Neuroprotective                                                       | (Guan et al., 2006)                        |
| A. oxyphylla  | Fruit      | Chloroform fraction of 95% ethanol extract                     | *In vivo* | Enhanced the cognitive performances                                   | (Shi et al., 2014)                         |
| A. oxyphylla  | ni         | 5-(hydroxymethyl)furfural                                      | *In vivo* | Neuroprotective                                                       | (Liu et al., 2014, Shi et al., 2014)       |
| A. oxyphylla  | Fruit      | Chloroform fraction of 95% ethanol extract                     | *In vivo* | Ameliorating                                                          | (Wang et al., 2018)                        |
| A. rafflesiana| ni         | Cardamonin (2′,4′-dihydroxy-6′-methoxychalcon)                   | *In vitro*| Anti-inflammatory                                                     | (Chow et al., 2012)                       |
| A. zerumbet   | Fruit      | Hexane extract, kavalactones dihydro-5,6-dehidrokavain and 5,6-dehidrokavain | *In vitro*| Neuroprotective                                                       | (Rao et al., 2014)                        |

ni = not informed. All information and terms were written according to the original source
Acute toxicity of A. galanga was performed according to OECD 423. For this, female Swiss mice were orally treated with 50, 300 and 2000 mg/kg, and mortality, behavioral changes, locomotion, convulsions were evaluated. Any signs of toxicity or clinical alterations were found in animals treated with A. galanga ethanol extract and the lethal dose 50 was 2000 mg/kg (Hanish et al., 2011).

**Alpinia hainanensis** K. Schum.

*A. hainanensis* (A. katsumadai, A. katsumadai) seeds were used to treat inflammatory and digestive diseases in traditional Chinese medicine (Yang et al., 2009). It is also reported as presenting potent antimicrobial, antioxidant, and anti-inflammatory activities (Jeong et al., 2007; Yang et al., 2009).

It is suggested that *A. hainanensis* seeds might be beneficial for AD treatment. In addition, in a bioassay-guided fraction of the methanolic extract of *A. hainanensis* seeds, three phenolic compounds were found: alpinetin, pinocembrin, and (+)-catechin. Of these, two compounds (pinocembrin and (+)-catechin) presented in vitro neuroprotective effects on glutamate-induced neurotoxicity and ROS generation in the mouse hippocampal HT22 cells (Table No. 2). The 2,2-diphenyl-1-picryl-hydrazyl (DPPH) assay also revealed the anti-oxidative effect of isolated compounds (Jeong et al., 2007).

**Alpinia officinarum** Hance

*A. officinarum* is a perennial plant that has been traditionally used to treat inflammation, pain, stomachache, cold, among others. Its biological effects are related to anti-inflammatory, cytotoxicity, homeostasis, lipid regulation, antioxidant, antiviral, antimicrobial, and anti-osteoporosis, among others well-described activities (Abubakar et al., 2018). Several phytochemical compounds have been identified and isolated from *A. officinarum* rhizome and the observed effect has been attributed to them (Table No. 2).

Huang et al. (2016) showed that the compound 7-(4-hydroxyphenyl)-1-phenyl-4E-hepten-3-one, a diarylheptanoid extracted from 95% ethanolic extract of *A. officinarum* rhizome, presents effects on neuronal differentiation and neurite outgrowth in vitro. 7-(4-hydroxyphenyl)-1-phenyl-4E-hepten-3-one (0.5–10 μM) had neuroprotective effects against the neurotoxicity caused by Aβ, attenuated the damage of Aβ oligomers, and reduced apoptotic levels and oxidative stress triggered by Aβ. The produced effects were dependent on the activation of phosphatidylinositol 3-kinase (PI3K)-mammalian target of rapamycin (mTOR) pathways (Table No. 2).

Previously, Tang et al. (2015) reported that the same compound, 7-(4-hydroxyphenyl)-1-phenyl-4E-hepten-3-one and 7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-4E-hepten-3-one (2 or 4 μM for 24 h), promoted differentiation and neurite outgrowth in both neuro-2a cells and cultured hippocampal neurons through activation of extracellular signal-regulated kinase and phosphatidylinositol 3-kinase pathways, and that 7-(4-hydroxyphenyl)-1-phenyl-4E-hepten-3-one accelerates differentiation of newborn neurons in vivo. Neuronal differentiation is a critical developmental process and circuit wiring, and may be impaired in AD. Therefore, the results of the both researchers pointed out that 7-(4-hydroxyphenyl)-1-phenyl-4E-hepten-3-one is a beneficial compound to improve the deleterious effects of Aβ on dendrite integrity and cell survival, presenting potential for AD treatment (Table No. 2) (Tang et al., 2015; Huang et al., 2016).

**Alpinia oxyphylla** Miq.

*A. oxyphylla* is used to treat ulcerations, gastralgia, diarrhea, dementia, tumors (Chang et al., 2017) and potential neuro-protective effects against oxidative damage or neurotoxicity (Shi et al., 2006, (Yu et al., 2003) with a therapeutic potential for AD treatment. 5-(hydroxymethyl)furfural is the main effective compound of 95% ethanolic extract of *A. oxyphylla*, and shows memory improvement activity against AD (Liu et al., 2014). In this in vivo study, a potential therapeutic agent, the neuroprotective effects of 5-(hydroxymethyl)furfural on cognition impairment and memory function, induced by intracerebroventricular injection of Aβ1–42, were identified. Kunming mice were treated with 5-(hydroxymethyl)furfural (15 and 150 μg/kg, intracerebroventricular) for five consecutive days after Aβ1–42. The results showed that 5-(hydroxymethyl)furfural improved learning and memory impairment evaluated by the locomotor activity, Y-maze test, and Morris water maze test. Also, it was observed that 5-(hydroxymethyl)furfural inhibited β-secretase activity, decreased the content of Aβ1–42 and malondialdehyde, and increased antioxidative enzyme activities, including superoxide SOD and GPx. Also, the degree of neuronal damage shown by hippocampus slices indicated that 5-(hydroxymethyl) furfural may serve as a potential therapeutic agent for AD treatment (Table No. 2).
Moreover, Shi et al. (2014) demonstrated neuroprotective effects of 5-(hydroxy methyl)furfural and three other small molecules compounds (protocatechuic acid, teuhenetone A, and tectochrysin) isolated from n-butanol A. oxyphylla extract on learning and memory impairments induced by Aβ1-42 in Y-maze test, active avoidance test and Morris water maze test. It was also demonstrated that the treatment with the extract (180 and 360 mg/kg by oral route) was able to decrease neuronal damage and apoptosis in the frontal cortex and hippocampus in ICR mice. In addition, the inhibition of β-secretase and the level of Aβ1-42 were also involved in the action mechanisms of 5-(hydroxy methyl)furfural compounds, suggesting that there is a potential clinical application in AD therapy (Table No. 2).

The improving effects of A. oxyphylla and Schisandra chinensis (Schisandraceae) fruit (1:1) extract (chloroform fraction of 95% ethanol extract, 1200 mg/kg, orally administered for 30 days) were evaluated using scopolamine (3 mg/kg for nine days) to induce learning and memory impairments in an AD mouse model (Wang et al., 2018). After, Y-maze test and Morris water maze test were carried out to observe the behavior of KM mice. Finally, the level of Ach and muscarinic (M1) receptors, and the activity of choline acetyltransferase and AChE were measured by commercial assay kits and an enzyme-linked immunosorbent assay (ELISA) kit. A significant protection against learning and memory impairments induced by scopolamine in Y-maze test and Morris water maze test was observed. In addition, the treatment with the extract was able to increase the level of ACh and M1 receptors, and decrease AChE activity, but it did not affect choline acetyltransferase activity. The authors hypothesized that the extract may interfere in the Aβ pathological mechanism, and then play a role in neuroprotective effects on AD (Wang et al., 2018).

Another study evaluated the effects of sesquiterpene-rich chloroform fraction of 95% A. oxyphylla fruit ethanol extract on Aβ-induced cognitive impairment and neuronal abnormalities in the cortex and hippocampus of ICR mice (Shi et al., 2014). Main compounds were oxyphyllanene A, protocatechuic acid, 11S-nootkatone-11,12-diol, 11R-nootkatone-11,12-diol, teuhenetone A, teuhenetone B, oxyphyllol B, nootkatone, and dibutyl phthalate (Table No. 2). ICR mice were injected with Aβ1-42 and later with chloroform extract from A. oxyphylla fruits (180 and 360 mg/kg for 20 days by intragastric infusion). The results showed that the treatment with the extract enhanced cognitive performances in behavior tests (Y-maze, active avoidance test, and Morris water maze test), increased activities of GPx, and decreased the levels of malondialdehyde, AChE, and Aβ, and reversed the activation of microglia, degeneration of neuronal acidophilia, and nuclear condensation in the cortex and hippocampus. The possible action mechanism is attributed to the oxidative stress attenuation, regulation of microglia activation, and degeneration of neuronal acidophilia to reinforce cholinergic functions (Shi et al., 2014).

Previous in vitro studies have shown that A. oxyphylla presents neuroprotective effects, suggesting that it could be a chemical candidate for AD treatment. Protocatechuic acid, a phenolic compound isolated from the A. oxyphylla kernels, on hydrogen peroxide (H2O2)-induced apoptosis and oxidative stress in cultured PC12 cells were investigated by (Guan et al., 2006). It was demonstrated that H2O2-induced apoptotic death via oxidative stress in cultured PC12 cells was reduced by protocatechuic acid (at a concentration over 0.3 mM). Also, it was observed that the increased lactate dehydrogenase leakage and decreased viability in differentiated PC12 cells exposed to H2O2 in the presence or absence of Fe2+ was significantly attenuated by the treatment with protocatechuic acid.

Another in vitro study evaluated the neuroprotective effect of 94% ethanolic extract from the fruits of A. oxyphylla on glutamate-induced neuronal apoptosis (exposure to 30 mM of glutamate for 24 h) in primary cultured mouse cortical neurons (Yu et al., 2003). The treatment with the extract (80 and 200 mg/mL) significantly elevated cell viability, reduced the number of apoptotic cells, and decreased the intensity of glutamate-induced DNA fragmentation, suggesting a neuroprotective effect.

Alpinia rafflesiana Wall. ex Baker
Chow et al. (2012) analyzed the in vitro anti-inflammatory effects of cardamomin (2′,4′-dihydroxy-6′-methoxy chalcone), a compound isolated from A. rafflesiana. In interferon gamma (IFN-γ)/lipopolysaccharide (LPS)-stimulated microglial cell line BV2, cardamomin inhibited the secretion of pro-inflammatory mediators including NO and prostaglandin E2 (PGE2), through a decrease in the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). The compound also suppressed TNF-α, interleukin (IL) IL-1β and IL-6.

Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas/437
levels, indicating the interference of upstream signal transduction pathways. In addition, it has been observed that cardamonin interrupts NF-κB signaling pathway via attenuation of NF-κB DNA binding activity, suggesting a possible application in neuro-inflammatory disorders (Table No. 2).

**Alpinia zerumbet (Pers.) B.L.Burtt & R.M.Sm.**
The hypotensive and diuretic effects of *A. zerumbet* leaves were reported (Mendonça et al., 1991; Albuquerque et al., 2008; Oliveira et al., 2015) and antimicrobial activities of their essential oils were presented. The leaves, flowers, and rhizome of this plant also have antiinflammatory, stomatal, and vermicide properties (Correa et al., 2010) and recently it has been reported to have potential use as anti-Alzheimer’s disease (Rao et al., 2014).

Rao et al. (2014) prepared a hexane fruit shell extract of *A. zerumbet* and isolated two compounds (kavalactones dihydro-5,6-dihydrokavain, and 5,6-dihydrokavain (1, 5, 10, and 50 mM) that had a protective effect against H$_2$O$_2$ oxidative stress-induced PC12 cell death after pretreatment for 6 h. This effect was mediated by the regulation of p38mitogen-activated protein kinase kinase and oxidative stress, suggesting that kavalactones dihydro-5,6-dihydrokavain and 5,6-dehidrokavaincould are a potential therapeutic agent for controlling and preventing neurodegenerative diseases such as AD (Table No. 2).

**Concluding remarks of genus Alpinia**
It was observed in the genus *Alpinia* that the majority of the studies were preclinical, mainly with *A. galanga* and *A. oxyphiilla*. AD studies with *A. hainanensis* (A. katsumadai, A. katsumadae), *A. zerumbet*, and *A. officinarum* were also reported. Several parts of the plants were used such as fruit, whole seed or kernel, and rhizome. For *A. galanga* and *A. officinarum*, rhizomes were the main utilized parts of the plant but for others fruits (*A. oxyphiilla*, *A. zerumbet*) or seeds or kernels (*A. hainanensis*, *A. oxyphiilla*) were used. Most of the in vitro and in vivo studies were carried out with several isolated compounds highlighting 8-9’ linked neolignans, galanganal, galanganols A, B and C, 1’d-1’-acetoxyxyugenol acetate, 1’-1’-acetoxyxyugenol acetate, protocatechuic acid, 5-(hydroxymethyl)furfural, pinocembrin and (+)-catechin, kavalactones dihydro-5,6-dehydrokavain, and 5,6-dehydrokavain, cardamonin (2’,4’-dihydroxy-6’-methoxyxalcon), 7-(4-hydroxyphenyl)-1-phenyl-4E-hepten-3-one (AO-1), 7-(4-hydroxy-3-methoxyphenyl)-1-phenyl-3-one (AO-2). In preclinical studies, the most widely used in vitro assays were those that measure the inhibitory potential of acetyltransferase, AChE, BChE, lipoxygenase enzyme activity, antioxidant enzymes SOD, CAT, glutathione peroxidase (GPx) and vitamin C levels, and oxidative stress in cultured PC12 cells. In vivo studies were performed mainly on the Aβ-induced AD model, and the main tests to evaluate the neuroprotective activity of the compounds were open field, Morris water maze, step-down inhibitory avoidance, active avoidance, and Y-maze test. Preclinical toxicity studies have been found only for *A. galanga* that is considered safe and with low toxicity. Thus, *Alpinia* genus is an alternative potential source of AD treatment; however, further studies on the mechanisms that mediate its bioactivities are still necessary as well as the potential toxicity and clinical studies. Other plants of the *Alpinia* genus are reported in the literature such as *Alpinia calcarata* (Andrews) Roscoce and *Alpinia macroura* K.Schum. Despite potential clinical studies, their effects on AD have not been evaluated yet (Arambewela et al., 2011; Huong et al., 2016).

**Genus Curcuma**
*Curcuma* genus is related to diverse Alzheimer’s studies. The main found species are *C. aromatica* Salisb, *C. comosa* Roxb., *C. longa* L., *C. zanthorrhiza* Roxb., and *C. zedoaria* (Christm.) Roscoe. However, several names have been used incorrectly for each species which could be confusing; therefore, the current name and its synonyms as well as eventual typing mistakes or misspellings must be clarified. Other species, such as *C. xanthorrhiza* Roxb., are not registered in the most comprehensive and authoritative global species indexes and they are likely to have a misspelled name. We assumed that the correct spelling is *C. zanthorrhiza* Roxb. without other synonyms, except *C. xanthorrhiza* Roxb. Thus, the main species and its synonyms are presented in Table No. 3.

**Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas**/438
Table No. 3

_Curcuma_ genus: current scientific name and its synonyms (Hassler, 2020)

| Current scientific name | Synonyms |
|-------------------------|----------|
| _Curcuma aromatica_ Salisb. | _Curcuma wenyujin_ Y.H.Chen & C.Ling  
_Curcuma zedoaria_ Roxb. |
| _Curcuma comosa_ Roxb. | without synonym |
| _Curcuma longa_ L. | _Amomum curcuma_ Jacq.  
_Curcuma brog_ Valeton  
_Curcuma domestica_ Valeton  
_Curcuma longa_ var. _vanaharidra_ Velay., Pandrav., J.K.George & Varapr.  
_Curcuma ochrorhiza_ Valeton  
_Curcuma soloensis_ Valeton  
_Curcuma tinctoria_ Guibourt  
_Kua domestica_  
_Stissera curcuma_ |
| _Curcuma zanthorrhiza_ Roxb. | _Curcuma xanthorrhiza_ Roxb. (name probably misspelt) |
| _Curcuma zedoaria_ (Christm.) Roscoe | _Amomum latifolium_ Lam.  
_Amomum latifolium_ Salisb.  
_Amomum zedoaria_ Christm.  
_Curcuma luteus_ Blanco  
_Curcuma nigricans_ Blanco  
_Curcuma malabarica_ Velay., Amalraj & Mural.  
_Curcuma pallida_ Lour.  
_Curcuma raktakanta_ Mangaly & M.Sabu  
_Curcuma speciosa_  
_Erindia zerumbet_ Giseke  
_Roscoea lutea_ (Blanco) Hassk.  
_Roscoea nigrociiliata_ Hassk. |

_Curcuma aromatica Salisb._

_C. aromatica_ is a perennial herb and its rhizomes are used by traditional Chinese medicine for the treatment of convulsions and fever (Li _et al._, 2017). Several _in vitro_ studies described the neuroprotective effects of _C. aromatica_, and researchers have tested the anticholinesterase action of biomolecules by the bioautographic method _in vitro_, as a way to complement AD treatment. Alkaloidal extracts obtained from _C. aromatica_ roots (at a concentration of 100 µg/mL) were tested in AChE by the bioautographic method and showed 35.8 ± 2.5% inhibitory activities (Yang _et al._, 2012). Jung _et al._ (2012) isolated curcumin from an ethanolic extract of _C. aromatica_ rhizomes. These compounds were evaluated for their anticholinesterase potential by the bioautographic method (at the concentration of 12.19 µg/mL) and presented 50.8 ± 3.6% of inhibition on the enzyme (Table No. 4).

Table No. 4

_In vitro and in vivo_ studies on _Curcuma_ genus bioactivity

| Species | Plant part | Extract/Isolated compound | Study | Effect | Source |
|---------|------------|---------------------------|-------|--------|--------|
| _C. aromatica_ | Rhizome | Alkaloidal extract | _In vitro_ | AChE inhibition | (Yang _et al._, 2012) |
| _C. aromatica_ | Rhizome | Curcumin | _In vitro_ | AChE inhibition | (Jung _et al._, 2012) |
| _C. aromatica_ | Rhizome | Methanol, dichloromethane and petroleum ether extract | _In vitro_ | Neuroprotective | (Liu _et al._, 2018) |
| _C. aromatica_ | Rhizome | Aqueous extract | _In vitro_ | Tau protein inhibition | (Li _et al._, 2017) |
| _C. aromatica_ | Rhizome | Aqueous extract | _In vivo_ | Improved the cognitive | (Yabin _et al._, 2016) |

Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas/439
| Species                            | Extract/Cat.          | Function in Aβ peptide                                                                 | Source                              |
|-----------------------------------|-----------------------|----------------------------------------------------------------------------------------|-------------------------------------|
| *C. comosa*                       | Rhizome               | (3S)-1-(3,4-dihydroxyphenyl)-7-phenyl-(6E)-6-hepten-3-ol                               | In vitro Pro-inflammatory and antioxidant (Jiamvoraphong et al., 2017) |
| *C. comosa*                       | Rhizome               | 1,7-diphenyl-(4E,6E)-4,6-heptadien-3-ol                                               | In vitro Antioxidant (Thampithak et al., 2009) |
| *C. comosa*                       | Rhizome               | *n*-hexane extract                                                                     | In vitro Anti-inflammatory (Jantaratnotai et al., 2006) |
| *C. longa*                        | ni                    | Curcumin                                                                               | In vitro Inhibition of Aβ (Xiong et al., 2011) |
| *C. longa*                        | ni                    | Curcumin                                                                               | In vitro Inhibition of Aβ (Konno et al., 2014) |
| *C. longa*                        | Rhizome               | Curcuminoid                                                                            | In vitro AChE and BuChE inhibition and antioxidant (Kalaycıoğlu et al., 2017) |
| *C. longa*                        | Rhizome               | Curcuminoid                                                                            | In vitro AChE inhibition (Ahmed & Gilani, 2009) |
| *C. longa*                        | ni                    | Curcumin                                                                               | In vivo Improvement of cognitive impairment (Wei et al., 2012) |
| *C. longa*                        | ni                    | Curcumin                                                                               | In vivo AChE inhibition (Wolkmer et al., 2013) |
| *C. longa*                        | Rhizome               | Methanolic extract                                                                     | In vitro and in vivo Neuroprotective, cognitive function, and inhibition of Aβ (Wang et al., 2014) |
| *C. longa*                        | ni                    | Curcumin                                                                               | In vivo Mitochondrial membrane potential, High-resolution respirometry, and ATP measurement in cultured cells (Hagl et al., 2015) |
| *C. longa*                        | ni                    | ni                                                                                     | In vitro AChE inhibition (Eun et al., 2017) |
| *C. longa*                        | ni                    | Curcumin                                                                               | In vivo Improvement of cognitive impairment (Chen et al., 2018) |
| *C. longa* (C. domestica)          | Dried leaves          | Ethyl acetate extract - phenolic compounds                                               | In vitro Antioxidant (Hincapié et al., 2011) |
| *C. zanthorrhiza* (C. xanthorrhiza) | Rhizome               | Zedoaraldehyde, 13-hydroxygermacrone, germacrone, and α-curcumene                        | In vitro AChE inhibition (Zhang et al., 2015) |
| *C. zanthorrhiza* (C. xanthorrhiza) | Rhizome               | Xanthorrhizol                                                                          | In vitro Antioxidant and anti-inflammatory (Lim et al., 2005) |
| *C. zedoaria*                     | Rhizome               | n-hexane extract and dichloromethane extract                                            | In vitro Antioxidant (Hamdi et al., 2015) |
| *C. zedoaria*                     | Rhizome               | Methanolic extract                                                                     | In vitro Anti-oxidative (Hong et al., 2002) |

ni = not informed. All information and terms were written according to the original source.

The ability of a chloroform and methanolic extract of *C. aromatica* to protect PC12 cells and primary cortical neurons from Aβ1-42 using MTT reduction assay was investigated by Kim et al. (2007). The results indicated that the half maximal inhibitory concentration (IC₅₀) of the chloroform extract for a PC12 was 23 ± 12 μg/mL, and for a primary neuron protection was 22 ± 4 μg/mL. For the methanolic extract, the results were PC12 (53 ± 11 μg/mL) and primary neuron protection (46 ± 18 μg/mL) but for chloroform extract in PC12 cells and primary neuron protection the results were better (Table No. 4).

Treatment of H₂O₂-damaged PC12 with 75 and 95% ethanolic, methanolic, dichloromethane, and petroleum ether extracts (at concentrations of 1, 10, and 50 μg/mL) of *C. aromatica* rhizomes considerably reduced ROS levels. PC12 cells
exposed to H$_2$O$_2$ for 24 h displayed a significant increase in the intracellular level of ROS. Intracellular ROS accumulation was determined using fluorescence probes. The results indicated that 75 and 95% ethanolic extracts increased the survival rate as well as the activity of SOD (Table No. 4) (Liu et al., 2018).

Preclinical studies conducted by Li et al. (2017) demonstrated that a prescription with C. aromatica as the main component is favorable for AD treatment. These authors used Aβ$_{25-35}$ peptide dissolved in sterile saline and 3 µL aggregated Aβ$_{25-35}$ and intracerebroventricularly injected it in male and female Kunming mice. The mice received an oral dose of C. aromatica aqueous extract (0.16-0.80 g/kg), and also donepezil (1.3 mg/kg) by gavage following the second day after Aβ$_{25-35}$ injection. The mice were dosed on a daily basis. Levels of tau protein on the serine (ser) 404 sites and threonine (thr) 231 sites were determined with an immunohistochemistry assay, and western blot was used to detect the expressions of tau protein on ser404, thr231, and thr181 sites, as well as the changes in the phosphorylation level of PI3K/Akt/GSK-3β signaling pathways. The results confirmed that the aqueous extract from C. aromatica rhizomes promotes neuroprotective effects, the extract inhibited the phosphorylation levels of tau (thr231, ser404, and thr181) and the phosphorylation of PI3K, AKT, and GSK-3β in the hippocampus of the animals (Table No. 4).

Curcuma comosa Roxb.
C. comosa is an herbal plant usually used as ingredient for Thai dishes and also used as traditional folk medicine for many decades, mainly for inflammation in the uterus (Boonmee et al., 2011), hemorrhoids, and promotion of lactation (Kaewamatawon et al., 2009). In the last few years, some studies revealed that C. comosa has great effects against bone loss induced by estrogen deficiency (Weerachayaphorn et al., 2011).

Prolonged activity of microglia has been associated with mental disorders such as AD. Jantaratnotai et al. (2006) investigated the anti-inflammatory effect of n-hexane extract of C. comosa rhizome on the responses in highly aggressively proliferating immortalized (HAPI) microglia cells. For that, the Griess assay was performed, followed by immunoblotting. It was demonstrated that, at a concentration of 10$^9$ to 10$^5$ g/mL, it significantly suppressed the levels of NO released from these cells.

In another study conducted by Thampithak et al. (2009), it was demonstrated that the compound 1,7-diphenyl-(4E,6E)-4,6-heptadien-3-ol obtained from C. comosa hexanic extract (0.1, 0.5, and 1 M) reduced NO production and suppressed iNOS mRNA in LPS-stimulated HAPI cells (Table No. 4).

Jiamvoraphong et al. (2017) used the isolated compound (3S)-1-(3,4-dihydroxyphenyl)-7-phenyl-(6E)-6-hepten-3-ol) dissolved with dimethyl sulfoxide at the final concentration of 0.01%. Aiming to investigate the molecular mechanisms involved in the production of pro-inflammatory mediator and oxidative stress in HAPI microglial cells, the authors reported that the compound suppressed NO production and iNOS expression in HAPI cells by attenuating p38 mitogen-activated protein kinases and NF-κB activation (Table No. 4).

Curcuma longa L.
C. longa is an herbaceous and perennial species from Asia, distributed among the tropics (Sasikumar, 2012). The plant is formed by one pseudo-stem of up to 1 m height and the leaf blade is usually large and lanceolate. The stem is a rhizome type (Sirirugsa et al., 2007), which has a wide use, especially as medicinal and pharmaceutical herb, and food (Kuddus et al., 2010; Sasikumar, 2012).

Of all four pathological features of AD, curcuminoids have shown potential to the immunotherapeutic process targeting Aβ peptide in animal models. Wang et al. (2014), in an assay performed in vitro at 0.75 µL methanolic extract obtained from rhizomes, reported that bisdemethoxycurcumin was 20 and 13 times more potent to inhibit BACE-1 when compared to curcumin and demethoxycurcumin. However, curcuminoids were not more efficient at inhibiting BACE-1 than the inhibitor (control). Similarly, Zheng et al. (2017) reported that transgenic 5 × FAD mice orally treated with curcumin (150 or 300 mg/kg for 60 days) dramatically reduced BACE-1 expression, preventing synaptic degradation, and improving spatial learning and memory impairment of mice. The quantity and area of amyloid plaques were decreased in the cortex and hippocampus of curcumin-treated groups, especially in the group treated with 300 mg/kg of curcumin (Table No. 4).

Other studies have evaluated that in vitro and in vivo studies with synthetic curcumin with phenolic hydroxyl groups and an alkenyl spacer on the inhibitory activity of rBACE-1 (at the concentration of 0.67 mM) are important structural factors for the
inhibition of beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1) (Konno et al., 2014). Xiong et al. (2011) reported that in SH-SY5Y neuroblastoma cells treated with 5 and 20 µM curcumin for 24 h, production of Aβ40 and Aβ42, was decreased by 39 and 51%, respectively. According to Xiong et al. (2011) curcuminoids have action on Aβ peptide because they act in a key step of the process mediated by secretases. This is an atypical multimeric membrane bound aspartyl protease consisting of presenilin 1 or 2, nicastrin, and presenilin enhancer 2. The activity of each of the components of the γ-secretase complex is tightly coordinated (Table No. 4).

There are some studies reporting AChE inhibitors that were found in C. longa rhizomes. Ahmed & Gilani (2009) verified the use of curcuminoid (a mixture of curcumin, bisdemethoxycurcumin, and demethoxycurcumin), combined and compared with the same individual components, for AChE inhibitory effect along with memory enhancing activities. For that, they utilized purified compounds, administered by injection, in vitro, in vivo, and an ex vivo assay performed with male Sprague–Dawley rats for seven consecutive days. The results showed that curcuminoids inhibited AChE in the in vitro assay with IC50 of 19.67 µM, bisdemethoxycurcumin of 16.84 µM, demethoxycurcumin of 33.14 µM and curcumin of 67.69 µM. When the assay was performed ex vivo, only curcumin did not show dose-dependent (3-10 mg/kg) inhibition in the frontal cortex and hippocampus. The in vivo assay was performed using a Morris water maze test that showed that all the curcuminoid compounds presented comparable memory enhancing effects, even curcumin that did not present good results with AChE inhibitory effect in the ex vivo model. According to this study, curcuminoids mixture might have better therapeutic profile, than the use of the individual components for its medicinal use in AD (Table No. 4).

In another in vitro study, the same curcuminoids were evaluated for antioxidant activity by reducing iron capacity and DPPH assay methods, and also for their drug potential against AD through the inhibition effects against AChE and BChE enzymes. The results revealed that the antioxidant activity was better with curcumin, followed by DMC, and BDMC. The results of AChE and BChE inhibitory activities (IC50) showed significant AChE inhibition activity and showed that curcumin presented less activity on AChE inhibitory, while curcumin and DMC presented no inhibitory activity against BChE. BDMC presented BChE and AChE enzyme activity inhibition (Table No. 4) (Kalaycıklı et al., 2017).

Another in vivo experiment conducted with rats infected with Trypanosoma evansi evaluated the effect of a pretreatment with curcumin in the modulation of AChE activity in whole blood. For this, they used male Wistar rats to which curcuma was administered by oral gavage (20 and 60 mg/kg, daily for 45 days) before the infection, and 15 and 30 days after the infection. The results showed that the pretreatment (injection before infection) reduced the enzyme activity when 60 mg/kg was administered at 15 and 30 days after infection (Wolkmer et al., 2013).

Some studies suggest that curcumin has the potential to improve cognitive impairment and that it is closely related with synaptic loss in the hippocampus in AD. Wei et al. (2012) carried out an in vivo study in double transgenic APP/PS1 mice. After three months of gavage with curcumin (400, 200, and 100 mg/kg), through immunohistochemistry and western blot techniques, it was possible to detect an increase in the expression of postsynaptic density protein 95 and SH3 domain and ankyrin repeat containing 1 protein (SHANK1), two important synapse-associated proteins, which are related to postsynaptic density (PSD) synapsis and improve their abilities of learning and memory (Table No. 4).

Chen et al. (2018) performed an in vivo study with APPswe/PS1dE9 mice. Synapsis ultra-structures in CA1 area of the hippocampus were observed, and also the expression levels of postsynaptic density protein 95 and SHANK1 were analyzed by immunohistochemical staining and western blot after three months of gavage with curcumin (100, 200 and 400 mg/kg per three months) (Table No. 4). It was demonstrated that curcumin increased the synapsis ultrastructure and upregulated the expression of these proteins.

Curcuma zanthorrhiza Roxb.
C. zanthorrhiza (C. xanthorrhiza), is an important and potential medicinal plant, commonly known as temu lawak or Javanese turmeric in Indonesia. It is commonly used in the local food industry and possesses a variety of therapeutic values (Cleason et al., 1993), among them anti-inflammatory (Ozaki, 1990) and anticancer (Park et al., 2008) activities as well as protective effects against liver damage (Lin et al., 1995) and AChE inhibitory activity (Zhang et al., 2018).
One of its components, xanthorrhizol, is a unique marker for *C. zanthorrhiza*; thus, its presence differentiates this plant from other *Curcuma* species. Xanthorrhizol has been reported to exhibit a wide range of biological activities such as antioxidant, antibacterial, and antitumour activities (Choi et al., 2005; Rukayadi et al., 2006). Zhang et al. (2015) evaluated AChE inhibition promoted by the following compounds isolated from *C. zanthorrhiza* rhizome ethanolic extract (95%): zedoaraldehyde, gweicurculactone, 13-hydroxygermacrone, germacrone, gelchomanolide, 8β-hydroxyisogermafurenole, α-curcumene, 3-hydroxy-6-methylacetoephone, and dehydro-6-gingerdione, using a thin layer chromatography bioautography assay modified from a previous method (Fan et al., 2008) and compared with the positive control galanthamine (minimum inhibitory quantity = 10 ng), an AChE inhibitor approved by the USA Food and Drug Administration. The isolated compounds zedoaraldehyde, 13-hydroxygermacrone, germacrone, and α-curcumene exhibited a moderate AChE inhibitory activity *in vitro* when compared with galanthamine, an AChE inhibitor. The compounds zedoaraldehyde, 13-hydroxygermacrone, germacrone, and 3-hydroxy-6-methylacetoephone were evaluated for their effects on SIR expression in HEK293 cells and, before the test, cytotoxicities of the compounds at different concentrations (12.5, 25.0, 50.0 and 100.0 mM) were first detected by 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) assays (Table No. 4). It was found no cytotoxicity to HEK293 cells of all compounds at final concentration of 100 mM.

The neuroprotective effects of xanthorrhizol, a compound isolated from the ethyl acetate fraction of 75% methanolic extract of *C. zanthorrhiza* rhizome against *H₂O₂*-induced apoptosis and lipid peroxidation in cultured HT22 cells, was evaluated by Lim et al. (2005). The lipid peroxidation was about 1.6 times higher in an *H₂O₂* treatment condition than in an untreated *H₂O₂* condition. Xanthorrhizol (10 μM) inhibited the lipid peroxidation entirely. The treatment with 1 and 10 μM of curcumin (another *C. zanthorrhiza* compound) also inhibited lipid peroxidation. Xanthorrhizol and curcumin also effectively suppressed glutamate-induced ROS generation in HT22 cells. In addition, xanthorrhizol presents anti-inflammatory effects on LPS-activated microglial cells. LPS induced robust increases in IL-6, TNF-α, and NO. Xanthorrhizol (10 μM) effectively suppressed the increase of these cytokines more effectively than curcumin. Finally, xanthorrhizol and curcumin potently reduced NO amount, iNOS expression, and COX-2 increased as well as curcumin. These results indicate the potential of sesquiterpenoids from *C. zanthorrhiza*, specially xanthorrhizol and curcumin for AD treatment and other neurological disease-related to ROS and inflammation (Table No. 4). However, it was not found *in vivo* studies for *C. zanthorrhiza* compounds.

**Curcuma zedoaria** (Christm.) Roscoe

*C. zedoaria* is a perennial herb, widely cultivated in China, Japan, Brazil, and Thailand, but it is native to India and Bangladesh (Lobo et al., 2009). It is an important medicinal plant, used in Asian medicine for many years, with several biological activities reported such as anti-inflammatory, antioxidant, against stomach disease, among others (Loc et al., 2005).

Hamdi et al. (2015) investigated the antioxidant effects of an air dried powder of *C. zedoaria* in *H₂O₂*-induced oxidative stress in mouse neuroblastoma-rat glioma hybridoma cells NG108. Ten compounds were identified in *C. zedoaria* rhizome powder extracted by maceration with n-hexane and dichloromethane such as germacrone, dehydrocurdione, curcumenol, isoprocurnenol, curumenone, procurnenol, zerumbone epoxide, zederone, gweicurculactone, and zerumin A. The neuroprotective activity was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay, and oxygen radical antioxidant capacity assay. The concentrations of evaluated extracts were 1, 4, 8, 15, and 30 μM. Among these, seven compounds presented 100 to 80% of protection against oxidative stress damage; and nine presented strong antioxidant activity. However, curcumenol and dehydrocurdione were the most active compounds with neuroprotective effects in NG108-15 cells (Table No. 4).

In a study conducted by Hong et al. (2002), 100% methanolic extract (50 mM) was used in a culture of RAW264.7 cells to measure NO formation by iNOS activity. It was observed that *C. zedoaria* showed great inhibition potential of iNOS activity with about 70% of inhibition at 10 mg/mL (Table No. 4).

**Concluding remarks of genus Curcuma**

Within the genus *Curcuma*, *C. longa* stands out in AD investigations. The main compounds evaluated in this genus were curcuminoids, highlighting curcumin...
in preclinical studies. These trials indicated AChE inhibition activity, improvement of cognitive impairment, neuroprotective, cognitive function, and inhibition of Aβ, mitochondrial membrane potential, high-resolution respirometry, and ATP measurement in cultured cells. *In vitro* investigations with the curcuminoïds found in *C. longa* demonstrated inhibition of Aβ effects, AChE and BuChE inhibition, and antioxidant activity. Also, *C. aromatica* has been used in *in vivo* tests with improvements at the cognitive function in Aβ peptide. The *in vitro* assays demonstrated AChE and tau protein inhibition and neuroprotective activity. However, there is a minor advance with *in vitro* assays of other species of this genus such as *C. zanthorrhiza* with xanthorrhizol, germacrone, alpha curcumene, and zedoaraldehyde extracts that provided antioxidant, anti-inflammatory, and AChE inhibition. In addition, *C. zedoaria*, *C. comosa*, and *C. zanthorrhiza* have been reported to present anti-inflammatory and antioxidant activities. Besides *C. longa* has been the most explored plant in the genus *Curcuma* due to the curcuminoïds, studies on its cytotoxicity or clinical assays have not been found, showing that further studies are needed to be used in the AD treatment.

**Genus Zingiber**

Many researchers have described the anti-Alzheimer’s effects of the *Zingiber* genus. The main found species are *Z. mioga* (Thunb.) Roscoe, *Z. montanum* (J.Koenig) Link ex A. Dietr., *Z. officinale* Roscoe, *Z. ottensii* Valeton, and *Z. zerumbet* (L.) Roscoe ex Sm.. *Z. bisectum* D. Fang and *Z. rubens* Roxb. have no reports on AD treatment but they were included because of their antioxidant activity. However, for each species, several names have been used incorrectly, making them confusing. Therefore, the current name and its synonyms as well as eventual typing mistakes or misspellings must be clarified. Thus, the main species and its synonyms are presented in Table No. 5.

| Zingiber genus: current scientific name and its synonyms (Hassler, 2020) |
|-----------------------------------------------|
| **Current scientific name** | **Synonyms** |
| *Zingiber bisectum* D.Fang | without synonym |
| *Zingiber mioga* (Thunb.) Roscoe | *Amomum mioga* Thunb.  
*Zingiber echuanense* Y.K.Yang  
*Zingiber mijooka* Siebold  
*Zingiber mioga* var. *variegatum* Makino  
*Zingiber sjooka* Siebold |
| *Zingiber montanum* (J.Koenig) Link ex A. Dietr. | *Amomum cassumunar* (Roxb.) Donn  
*Amomum montanum* J.Koenig  
*Amomum xanthorrhiza* Roxb. ex Steud.  
*Cassumunar roxburghii* Colla  
*Jaegera montana* (J.Koenig) Giseke  
*Zingiber anthorrhiza* Horan.  
*Zingiber cassumunar* Roxb.  
*Zingiber cassumunar* var. *palamauense* Haines  
*Zingiber cassumunar* var. *subglabrum* Thwaites  
*Zingiber cliffordiae* Andrews  
*Zingiber luridum* Salisb.  
*Zingiber purpureum* Roscoe  
*Zingiber purpureum* var. *palamauense* (Haines) K.K.Khanna  
*Zingiber xantorrhizon* Steud. |
| *Zingiber officinale* Roscoe | *Amomum angustifolium* Salisb.  
*Amomum zingiber* L.  
*Amomum zinziba* Hill  
*Zingiber aromaticum* Noronha  
*Zingiber cholmondeleyi* (F.M. Bailey) K.Schum. |
Zingiber bisectum D. Fang and Zingiber rubens Roxb.

There were no reports or studies with Z. bisectum and Z. rubens on AD. However, these two species have antioxidant activity (Kantayos & Paisooksantivatana, 2012) and, therefore, may be explored in future studies on AD treatment.

Zingiber mioga (Thunb.) Roscoe

Z. mioga is a rhizomatous perennial plant with short vegetative shoots. The most vigorous variants of Myoga plants are from central and Southeast China, Japan, and South Korea. The flower color also varies; buttercup-yellow in Southwest China, creamy white in Japan, and yellow to white corolla with lilac-pink staminodes in South Korea. In China there is a long tradition of utilizing it as a medicinal plant. However, in Japan, the young inflorescences are widely consumed as food. It is also widely grown in home gardens and commonly available in markets. Z. mioga is deeply rooted in Japanese culture and tradition (Gracie et al., 2004).

Kim et al. (2016) evaluated Z. mioga activity in brain cell cultures prepared from hippocampus of postnatal Sprague-Dawley rats at day 1, focusing especially on the nerve growth factor (NGF), which is believed to mediate synaptic plasticity, supporting learning and memory. In a rat primary hippocampal astrocyte culture system, treatment with Z. mioga extract for 24 h stimulated the production of NGF. In Swiss mice orally administered with water extract of dried Z. mioga flower buds (200 and 400 mg/kg for 14 days) an increase in NGF levels in the hippocampus was observed (Table No. 6). Z. mioga extract treatment also regulated the phosphorylation of extracellular signal-regulated kinases and cAMP response element-binding protein (CRE) in the rat’s hippocampus, leading to increased synaptic plasticity. In addition, it significantly increased novel object recognition time and spontaneous alternation, indicating improvement of learning and memory. These results suggest that Z. mioga helps regulate NGF and synaptic plasticity, increasing memory ability.

### Table No. 6

*In vitro and in vivo studies on Zingiber genus bioactivity*

| Species          | Plant part | Extract/Isolated compound          | Study    | Effect                              | Source                        |
|------------------|------------|------------------------------------|----------|------------------------------------|-------------------------------|
| Z. mioga         | Rhizome    | Ethyl acetate extracts, aframodial, galanalin B, [6]-gingerol, and galanolactone | *In vitro* | Oxidative stress by interferon-induced NO | Kim et al., 2005; Cho et al., 2014 |
| Z. mioga         | Flower     | Alcoholic extract                  | *In vitro* | AChE inhibition                    | Kim et al., 2016              |
| Plant            | Part                | Extract/Compound                        | Model       | Effect                                         | Reference                     |
|------------------|---------------------|-----------------------------------------|-------------|-----------------------------------------------|-------------------------------|
| Z. mioga         | Flower bud          | Water extract                           | *In vivo*   | Synaptic plasticity and memory ability       | Han *et al.*, 2005            |
| Z. montanum      | Rhizome             | Crude extract                           | *In vitro*  | Anti-inflammatory and antioxidant             | Rout *et al.*, 2011           |
| Z. montanum      | Rhizome             | Essential oil                           | *In vitro*  | AChE inhibition                               | Okonogi & Chaiyana, 2012      |
| Z. montanum      | Rhizome             | Hexane extract and phenylbutenoid dimmers | *In vitro*  | Anti-inflammatory by COX-2 inhibitory activity in a cell culture | Matsui *et al.*, 2012 |
| Z. montanum      | Rhizome             | Cassumunin A and B                       | *In vitro*  | Oxidative stress                              | Hassan *et al.*, 2019         |
| Z. montanum      | Rhizome             | Methanol extract and Phenylbutenoid dimmers | *In vivo*   | Neurotrophic                                  | Chaiyana *et al.*, 2010       |
| Z. officinale    | ni 6-gingerol       | In vitro                                |             | Neuroprotective and antioxidant               | Lee *et al.*, 2011            |
| Z. officinale    | ni 6-shogaol        | In vitro                                |             | Neuroprotective and anti-inflammatory         | Ha *et al.*, 2012             |
| Z. officinale    | Rhizome             | Aqueous extract                          | *In vitro*  | Antioxidant and AChE inhibition               | Oboh *et al.*, 2012           |
| Z. officinale    | ni 10-gingerol      | In vitro                                |             | Anti-inflammatory and antioxidant             | Ho *et al.*, 2013             |
| Z. officinale    | Rhizome             | Methanolic extract                       | *In vitro*  | Antioxidant and Aβ, BChE, and AChE inhibition | Mathew & Subramanian, 2014    |
| Z. officinale    | ni 6-gingerol       | In vitro                                |             | Phosphorylation of akt/GSK-3β pathway, antioxidant and anti-inflammatory | Tung *et al.*, 2017 |
| Z. officinale    | Rhizome             | Methanolic extract                       | *In vitro*  | Antioxidant and AChE inhibition               | Tung *et al.*, 2017           |
| Z. officinale    | ni 6-shogaol        | In vitro                                |             | SORL1 activation and decreasing in the levels of the amyloidogenic signals | Na *et al.*, 2017            |
| Z. officinale    | ni 6-gingerol       | In vitro                                |             | Neuroprotective, anti-inflammatory and antioxidant | Zhang *et al.*, 2018          |
| Z. officinale    | Rhizome             | Ethanolic extract                        | *In vivo*   | Improvement of cognitive function and antioxidant | Wattanathorn *et al.*, 2011   |
| Z. officinale    | ni Zingerone        | In vivo                                  |             | Antioxidant, antiapoptotic activity, and improvement in behavioral outputs | Vaibhav *et al.*, 2013        |
| Z. officinale    | Rhizome             | Powder                                  | *In vivo*   | Increasing the number of neurons and improvement of neuronal activity and behavioral dysfunction | Zeng *et al.*, 2013           |
| Z. officinale    | Rhizome             | Ethanolic extract                        | *In vivo*   | Improvement in spatial memory and inhibition of Aβ accumulation and neuroinflammation | Lim *et al.*, 2016           |
| Z. officinale    | ni 6-shogaol        | In vivo                                  |             | Increasing in the levels of SORL1 and         | Na *et al.*, 2017             |

Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas/446
The anti-inflammatory activity of *Z. montanum* was also evaluated by Han et al. (2005). The researchers isolated two compounds ((±)-trans-3-(3,4-dimethoxyphenyl)-4-[(E)-3,4-dimethoxystyryl]cyclohex-1-ene and (±)-trans-3-(4-hydroxy-3-methoxyphenyl)-4-[(E)-3,4-dimethoxy-styryl]cyclohex-1-ene from the chloroform extract of *Z. montanum* rhizome (Table No. 6). The compounds were evaluated for their inhibitory activity of PGE$_2$ production, through COX-2 inhibitory activity in a cell culture system, using LPS–activated murine macrophage RAW 264.7 cells. The compounds showed the most potent COX-2 inhibitor activity at half of the maximal inhibitory concentration (IC$_{50}$) values of 2.71 and 3.64 mM, respectively.

**Zingiber montanum (J.Koenig) Link ex A.Dietr.**

*Z. montanum* is an aromatic perennial herb, the species is probably native to India and is widely cultivated in Southeast Asia for medicinal uses (Acevedo-Rodríguez & Strong, 2012). The rhizomes are very popular for the treatment of gastric ulcer, inflammation, colic, diarrhea, verminosis, sprains, wounds, asthma (Al-Amin et al., 2012), allergy, pain, and for local anesthetic (Leelarungrayub et al., 2017). Phytochemical analysis of *Z. montanum* rhizomes showed that they have specific characteristics such as yellow rhizome and slim leaf. The yellow color of the rhizome is attributed to the presence of curcuminoids (Sanatombi & Sanatombi, 2017). A number of pure compounds isolated from *Z. montanum* have been shown to possess anti-inflammatory, antioxidant, and anti-cholinesterase activities which have become another focus of new treatment strategies against AD.

According to Hassan et al. (2019), the new curcuminoids cassumunin A and B, isolated from *Z. montanum* rhizomes, showed potent protective action against oxidative stress (Table No. 6). Nagano et al. (1997) carried out a study on thymocytes dissociated from thymus glands of 4-week-old Wistar rats. Pretreatment of rat thymocytes with cassumunins at concentrations ranging from 100 to 3 µM dose-dependently prevented hydrogen peroxide-induced decrease in cell viability. It is suggested that cassumunins A and B may possess a potent protective action on living cells suffering from oxidative stress.

**Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas/447**
Okonogi & Chaiyana (2012) evaluated the inhibitory potential of essential oil of fresh Z. montanum rhizomes on the AChE and BuChE enzymes by Ellman’s colorimetric assay. The concentration required to inhibit the enzymes was 0.35 ± 0.13 mg/mL and 5.57 ± 0.17 mg/mL, respectively. Chaiyana et al. (2010) also evaluated the effect of Z. montanum essential oil on BChE and AChE enzymes. The inhibitory effect was 47.5 ± 5.6% for BChE and 28.4 ± 4.4% for AChE activity. The loaded microemulsions of Z. montanum essential oil is an attractive formulation for further characterization and an in vivo study of an animal model with AD (Table No. 6).

Matsui et al. (2012) investigated the neurotrophic effects of Z. montanum by isolating two compounds from a methanolic extract of the rhizome. Compound-1 trans-3-(3,4-dimethoxyphenyl)-4-[(E)-3,4-dimethoxystyryl]cyclohex-1-ene and compound-2 cis-3-(3,4-dimethoxyphenyl)-4-[(E)-3,4-dimethoxystyryl]cyclohex-1-ene were evaluated in PC12 cells and primary cultured rat cortical neurons (Table No. 6). Both compounds presented in vitro neurotrophic effects characterized by neuritogenesis, neurite outgrowth promotion, and neuronal survival enhancement. Both compounds were also evaluated in OBX mice, an experimental depression, and dementia animal model. The oral treatment with compounds (50 mg/kg for 14 days) enhanced hippocampal neurogenesis in OBX mice. These results suggest that these compounds, isolated from Z. montanum, enhance hippocampal neurogenesis through their neurotrophic activity.

Zingiber officinale Roscoe
Z. officinale is the most common spice and fresh plant used worldwide (Choi et al., 2018). It is broadly known for its rhizomes, important sources of phytonutrients, with characteristic aroma and spicy taste, widely used in beverages and food (Mirmosayyeb et al., 2017). In addition, it is highly prized due to its aromatic and culinary properties. It is also widely and popularly utilized for the treatment of colds, headaches, nausea, and diarrhea with significant mention in Ancient Chinese, Indian, and Greek writings (Ahmad et al., 2015). It has well-described biological effects such as lipolytic, anti-inflammatory, anti-arthritis, antiemetic, antidiarrheal, immune stimulant, antioxidant, anticancer activity, and is a growth enhancer (Palatty et al., 2013; Vinothkumar et al., 2014; Ahmad et al., 2015; Oliveira et al., 2015). Most of these pharmacological effects are related to zingerone, a nonvolatile compound of Z. officinale found in a significant amount of 9.25% in the species (Table No. 6). This phenolic compound is primarily present in dry rhizome but cooking or drying can convert gingerol (another metabolite) into zingerone (Zhang et al., 2012). Due to its antioxidant and anti-inflammatory activities, Z. officinale is a potential candidate for research on its anti-Alzheimer’s effects, as demonstrated in in vitro and in vivo preclinical studies (Table No. 6).

Many in vitro studies described the effects of Z. officinale in pathways involved in AD. Mathew & Subramanian (2014) evaluated the anti-Alzheimer activity of Z. officinale methanolic extract. The extract presented antioxidant activity in DPPH and, reducing capacity of iron assays, it increased cell survival against Aβ induced toxicity in primary adult rat hippocampal cell culture, preventing the formation of Aβ oligomers, dissociating the preformed oligomers and inhibiting BuChE and AChE (Table No. 6). These results indicate that this extract, in vitro, acts on multiple molecular therapeutic targets of AD. The hydroethanolic extract of Z. officinale roots was also evaluated and presented a strong radical scavenger activity in DPPH assay, and inhibited AchE in a concentration-dependent manner (Tung et al., 2017).

Another possible action mechanism through which Z. officinale extracts present anti-Alzheimer’s effects was described by Oboh et al. (2012). Two aqueous extracts of red and white Z. officinale were evaluated regarding their AChE activities, and sodium nitroprusside and quinolinic acid-induced lipid peroxidation in the rat brain. White Z. officinale inhibited AChE activity more effectively than red Z. officinale, and the association of both extracts inhibited AChE activity synergistically (Table No. 6). Furthermore, the extracts decreased malondialdehyde contents in the brain, indicating that anti-Alzheimer’s properties of white and red Z. officinale could be utilized to prevent lipid peroxidation in the brain, besides inhibiting AChE activity.

Another action mechanism of Z. officinale against dementia was proposed by Ghayur et al. (2008) who evaluated a 70% methanolic extract of dried Z. officinale on isolated rat stomach fundus. The extract showed a stimulant effect that was sensitive to atropine, indicating activity via muscarinic receptors. The researchers also described an interaction between the extract and voltage-operated Ca++ channels, showing a possible Ca++...
antagonism by *Z. officinale*. These effects could justify *Z. officinale* benefit in dementia, including AD.

The involvement of sortilin-related receptor (SORL1), a neuronal sorting protein that reduces APP trafficking to secretases that generate Aβ, was evaluated *in vitro* in hippocampal neuronal cells treated with 6-shogaol, a metabolite of *Z. officinale*. SORL1 activation by 6-shogaol (10 and 20 µM) provides neuronal cell survival inhibiting Aβ production (Table No. 6). Furthermore, the expression levels of β-secretase APP cleaving enzyme (BACE), soluble APPβ and Aβ, amyloidogenic signals, normally induced by SORL1 blockade, were counteracted by 6-shogaol treatment (Na et al., 2017). 6-shogaol also presented neuroprotective and anti-inflammatory effects on LPS-stimulate primary microglial cell culture, by inhibiting the production of PGE2, IL-1β and TNF-α, and by downregulating COX-2, p38 mitogen-activated protein kinase, and NF-kB expression (Table No. 6) (Ha et al., 2012).

Another metabolite of *Z. officinale* (6-gingerol) presented neuroprotective, anti-inflammatory, and antioxidant effects in LPS-stimulated C6 astroglia cells. Cells stimulated with LPS released pro-inflammatory cytokines (TNF-α and IL-6) and increased intracellular ROS and NO, mediators related to AD. The treatment with gingerol (5 and 20 µM) blocked all these alterations (Zhang et al., 2018). These effects of 6-gingerol on astroglia cells were not observed in LPS-stimulated microglia culture cells. At the concentration of 20 µM, only 10-gingerol was effective in inhibiting the production of NO, IL-1β, IL-6 and TNF-α (Table No. 6) (Ho et al., 2013).

The mechanisms underlying 6-gingerol neuroprotective effects were also evaluated by Zeng et al. (2015). In Aβ1-42-induced neurotoxicity and apoptotic death in PC12 cells, 6-gingerol (80, 120 and 200 µM) up-regulated the phosphorylation levels of Akt/GSK-3β, a vital pathway that regulates tau hyperphosphorylation in cells (Table No. 6). Furthermore, 6-gingerol reduced the levels of NO and lipoperoxidation, besides decreasing the production of ROS and increasing the levels of SOD. The antioxidant effects of 6-gingerol is a key role on neuroprotective effects of 6-gingerol. In human neuroblastoma, SH-SY5Y cells and mouse hippocampal HT22 cells, 6-gingerol (10 µM) presented protective effects against Aβ-induced cytotoxicity, decreased intracellular peroxide, peroxynitrite, and malondialdehyde levels, and increased reduced glutathione levels. These antioxidant effects were mediated by the activation of NF-E2-related factor 2, a transcription factor that plays a key role in the expression of antioxidant enzymes (Lee et al., 2011).

There are several *in vivo* preclinical studies involving *Z. officinale* in AD. The 95% hydroethanolic extract of *Z. officinale* rhizomes was evaluated in focal cerebral ischemia in Wistar rats which received, by oral route, the extract (100, 200 and 300 mg/kg) for 14 days before, and 21 days after the occlusion of right middle cerebral artery. The cognitive function assessment was performed at 7, 14, and 21 days after the occlusion of the right middle cerebral artery. The brain infarct volume, density of neurons in the hippocampus, and antioxidant status were also evaluated. The treatment improved neuron density in the hippocampus and cognitive function (partly via the antioxidant activity), and decreased the brain infarct volume (Wattanathorn et al., 2011).

The same protective effects of *Z. officinale* on brain damage were also observed with isolated compounds. Zingerone (4-(4-hydroxy-3-methoxyphenyl)-2-butanone, a nontoxic and inexpensive compound isolated from *Z. officinale*, is also present in anti-Alzheimer’s activity (Table No. 6) (Ahmad et al., 2015). The oral administration of zingerone (50 and 100 mg/kg), at 5 h and 12 h from initiation of the middle cerebral artery occlusion in rats, reduced the infarct volume and mitochondrial injury, and improved behavioral outputs and histological architecture. These effects are attributed to the reduction of lipid peroxidation, increase in reduced glutathione levels, and normalization of Na+-K+ ATPase and SOD activities. Moreover, the treatment was efficient in reducing pro-apoptotic proteins and caspase-3 and -9 activities (Vaibhav et al., 2013).

The neuroprotective effects of *Z. officinale* fermented with *Schizosaccharomyces pombe* of Aβ1-42 plaque-induced Alzheimer in mice. The oral administration of the extract (100 and 200 mg/kg, for 14 days) improved recognition memory and memory impairment in Aβ1-42 plaque-injected mice via protecting neuronal cells in the mouse hippocampus, and reinstated the pre- and postsynaptic protein levels, suggesting that the extract attenuates memory impairment in this model through inhibition of neuronal cell loss and synaptic disruption (Table No. 6) (Huh et al., 2018).

Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas/449
Male AβPP/PS1 mice, a double-transgenic animal of Aβ protein precursor and presenilin 1, were used by Lim et al. (2016) to demonstrate the effects of a 95% ethanolic extract of *Z. officinale* and *Paeonia lactiflora* Pall. (Paeoniaceae) rhizome on memory impairment. The animals were orally treated (50 and 100 mg/kg, for 14 weeks) and the cognitive deficits were evaluated by novel object recognition and Y-maze tests. The treatment with 100 mg/kg significantly improved spatial memory. This effect occurred through the inhibition of Aβ accumulation and neuroinflammation, and demonstrated by an immunohistochemical study of the brain sections. Male AβPP/PS1 mice were also utilized to evaluate the effects of 6-shogaol (5 or 20 mg/kg, orally, for 2 months) on the expression levels of SORL1. The treatment with the two doses of 6-shogaol significantly increased SORL1 levels, and decrease the levels of amyloidogenic signals like BACE, soluble APPβ, and Aβ in the brains of mice compared with non-treated APP/PS1 mice, pointing out a possible potential beneficial effect of this compound for early intervention and prevention in AD patients (Table No. 6) (Na et al., 2017).

The effects of *Z. officinale* on behavioral dysfunction were also evaluated using an operated rat model of AD (intracerebroventricular injection of Aβ protein and continuous gavage of aluminum chloride for four weeks) on female Sprague-Dawley. To access spatial learning and memory of animals, the Morris water maze was used. The treatment with *Z. officinale* rhizome extract (4 g/kg, orally for 35 days) protected rats from behavioral dysfunctions induced by the model. The Nissl and hematoxylin and eosin staining showed that the treatment with the extract improved the number of neurons and neuronal activity in the hippocampus. The extract also presented antioxidant and anti-inflammatory activities, reflected by increased levels of SOD and CAT activities, decreased levels of malondialdehyde, and improved expression of NF-κB and IL-1β (Table No. 6) (Zeng et al., 2013).

Another operated rat model of cognitive impairment (intracerebroventricular microinjection of 10 μg LPS) was used to evaluate the neuroprotective effects of 6-gingerol. Adult male operated Sprague-Dawley rats were treated with 6-gingerol (0.5 and 2 mg/kg, i.p.) three days prior to LPS infusions, and once daily for two weeks (Table No. 6). The Morris water-maze was used to evaluate spatial learning and memory of animals. The treatment (2 mg/kg) attenuated LPS-induced impairment of special learning and memory of animals, and decreased LPS-induced astrocyte activation and TNF-α release in the rat brain, showing a potent neuroprotective effect of this compound via its anti-inflammatory activities (Zhang et al., 2018).

Preclinical studies also described harmless and safety of *Z. officinale*. Rong et al. (2009) conducted a 35-days toxicity study on *Z. officinale* in male and female Sprague-Dawley rats. The animals were orally daily treated with ginger powder (500, 1000 and 2000 mg/kg for 35 days). The treatment was not associated with any mortalities and abnormalities in general conditions, behavior, growth, food and water consumption, and hematological and blood biochemical parameters. Acute and subacute toxicity (14 and 30 days of treatment, respectively) evaluation of 95% hydroethanolic extract of *Z. officinale* were performed in male and female hamsters, orally treated with 1000, 3000 and 5000 mg/kg (Table No. 6). Body mass, food and water consumption, and histopathological analyses of vital organs (brain, heart, kidneys, liver, spleen, stomach, intestine, and lungs) indicated absence of any significant toxicity at the maximum dose (Plengsuriyakarn et al., 2012). A longer treatment with *Z. officinale* oil was conducted by Jeena et al. (2011) that treated male and female Wistar rats for 13 weeks (100, 250, and 500 mg/kg, orally). The treatment with oil did not produce any changes in the histopathology of the brain, kidney, spleen, liver, stomach, and intestine. No alterations in hematological and biochemical parameters were observed as well as mortality.

Regarding the reproductive toxicology of *Z. officinale*, the preclinical studies also revealed absence of maternal toxicity; however, the effects of this species on fetuses are controversial. Pregnant Sprague-Dawley rats were treated with *Z. officinale* tea (20 and 50 g/L, via drinking water) from gestational day 6 to 15. No maternal toxicity was observed but the embryonic losses in the treatment groups were twice as many than controls. Despite the fact that no morphologic malformations were found, fetuses exposed to *Z. officinale* tea were heavier and had more advanced skeletal development than controls, suggesting that in utero exposure to *Z. officinale* rhizome tea results in increased early embryo loss with increased growth in surviving fetuses (Wilkinson, 2000). Despite these fetal alterations induced by *Z. officinale* tea, the oral treatment of pregnant Wistar rats with a patented standardized ethanolic extract of *Z. officinale* (100,
333 and 1000 mg/kg) from gestational days 6 to 15 caused neither maternal nor developmental toxicity (Weidner & Sigwart, 2001). A clinical study was conducted with 60 healthy, middle-aged women (53.40 ± 3.57 years old) that received placebo or a standardized extract of Z. officinale (400 or 800 mg) for two months, and were assessed for cognitive performance after one and two months of treatment. The improvement of cognitive function was observed in all cognitive processing domains of Z. officinale-treated group, analyzed by computerized battery tests, with no related side effects, suggesting that Z. officinale is a potential cognitive enhancer and a potential brain tonic for these patients (Table No. 6) (Saenghong et al., 2012).

Clinical toxicological studies also demonstrated that Z. officinale is safe in moderate consumption. The therapeutic dosage is no more than 2 g per day, divided into doses of 250 mg, according to the USA Food and Drug Administration (Tiran, 2012, Thomson et al., 2014). To date, no adverse events have been reported that could compromise the course of pregnancy in humans (Portnoi et al., 2003; Viljoen et al., 2014). Reviewed the effectiveness and safety of Z. officinale consumption during early pregnancy described in 15 studies and three prospective clinical trials and concluded that fresh ginger root (1 g per day for 4 days) resulted in a significant decrease in nausea and vomiting, without risk to the mother and fetus (Stanisiere et al., 2018).

**Zingiber ottensii Valeton**

Z. ottensii is an herb characterized by its rhizome with dark-purple texture, pale yellow labellum, and mottled pink. This plant is spread abundantly in Southeastern Asia in Borneo, Java, Peninsular Malaysia, Sumatra, Thailand, and Vietnam (Ngoc-Sam et al., 2016). Its reddish stem gives it a ginger-like appearance and, therefore, this plant is used for ornamental purposes in some areas because of its attractive look. In addition to its use as an appetizer and spice, Z. ottensii has medical properties and its rhizome is the main utilized part for these medicinal actions. This rhizome is traditionally used as a sedative remedy for convulsion and as a lumbago treatment in Malaysia. In Thailand, Z. ottensii has been traditionally used to treat external bruises and gastrointestinal ulcers (Karnchanatat et al., 2011).

Rungsaeng et al. (2013) investigated the inhibitory potential of AChE of the rhizome aqueous extract (obtained from ammonium sulfate), and proteases isolated from Z. ottensii. These enzymes play an important role to regulate the biological processes in plants, such as stress responses, recognition of pathogens, induction of effective defense responses, mobilization of storage proteins during germination, and initiation of cell death or senescence. Moreover, plant proteases also exhibit broad substrate specificity and are active over a wide pH and temperature range in the presence of organic compounds as well as other additives. IC50 of protease and extract on AChE inhibition were 113.4 ± 0.10 and 33.9 ± 0.24 U/mg protein, respectively, showing an interesting effect of both protease and Z. ottensii extract (Table No. 6).

**Zingiber zerumbet (L.) Roscoe ex Sm.**

Z. zerumbet is a native herbal plant to India and the Malaysian Peninsula, and it has been cultivated for ages in several places throughout Southeast Asia, the Pacific, and Oceania (Yob et al., 2011). Z. zerumbet rhizome has been traditionally used as herbal medicine in Asian, Indian, Chinese, and Arabic folktales since ancient times with remarkable therapeutic effects for the treatment of inflammation, diarrhea, stomach cramps, bacterial infections, fever, flatulence, allergies, and poisoning (Koga et al., 2016). Studies have reported that rhizomes of this species have multipotential bioactives like anti-inflammatory, anti-cancer and anti-apoptogenic, antinociceptive, antimicrobial, antiplatelet aggregation, antipyretic and cytotoxic, antihyperglycemic, chondroprotective, anti-LPS-induced NO production, anti-AD, chemopreventive, antioxidant, hepatoprotective, immunomodulatory, anti-edema, antiepileptic and angiogenic seizures, anti-pancreatitis, antiallergic, enzyme activation cyclooxygenase 1 and 2 (COX-1 and COX-2), anti-oomycete, and anti-HIV activities (Nongalleima et al., 2013).

Abdelwahab et al. (2008) described the inhibitory effect of zerumbone, a Z. zerumbet compound, on AChE using bioautography method compared to tacrine (10 mM), a positive control (Table No. 6). The compound (1 mg/mL) had an inhibitory effect on AChE, suggesting that zerumbone might be a potential candidate for the development of anti-AD drugs.

The antioxidant effects of Z. zerumbet rhizome aqueous extracts exhibited NO scavenging activity at the concentrations of 20, 40, 100, 125, and 250 µg/ml, in a concentration-dependent way. IC50 value for NO scavenging by extracts was 112.45 µg/mL, while for rutin it was 77.99 µg/mL (Rout et al., 2012).
Nag et al. (2018) evaluated the in vitro cytotoxic effect of Z. zerumbet rhizome ethanolic extracts (2.5, 5.0, and 10.0 µg/mL) by 2,3,5-triphenyltetrazolium chloride and 2',7'-dichlorofluorescein diacetate (DCFDAH2) assays (Table No. 6). 2,3,5-triphenyltetrazolium chloride reduction assay revealed that the extracts had no cytotoxic effect on Allium cepa root cells. In vivo orally and subchronic toxicity of Z. zerumbet was also evaluated in female and male Wistar rats. In the acute toxicity study, Wistar rats were administered a single dose of 15 g/kg and were monitored for 14 days. The extract did not produce any toxic signs or deaths; thus, the LD50 must be higher than 15 g/kg. In the subchronic toxicity study, the rats were daily treated with the extract (1, 2, and 3 g/kg) for four weeks. The treatment did not alter the body mass gain or the food and water intake. The hematological and biochemical analyses did not show significant differences in any of the examined parameters. The same was observed regarding necropsy and histopathological examination, showing that this extract is safe under the evaluated conditions Chang et al. (2012).

Concluding remarks of genus Zingiber
In the genus Zingiber, Z. officinale stands out in AD studies, but studies with Z. montanum, Z. mioga, Z. zerumbet, and Z. ottensii have also been carried out. The most used part of the plant in AD studies were rhizomes extracted with solvents of different polarities such as water, ethanol, ethyl acetate, dichloromethane, and hexane. There are several studies about rhizome isolated compounds and essential oils for this genus. The most used isolated compounds were aframodial (Z. mioga), curcuminoids cassumunin A and B, and phenylbutenoid dimers (Z. montanum), 6-shogaol, 6-gingerol, 10-gingerol, zingerone (Z. officinale), and zerumbone (Z. zerumbet). Isolated compounds from this genus endorse the more advanced studies on anti-Alzheimer's activity, pointing out a diversity of potential metabolites in AD assays. In preclinical studies with Z. officinale, the most utilized in vitro assays were for AChE inhibition, but Aβ peptide and tau protein have been used as well. For other plants of this genus, the main assays were on oxidative stress and anti-inflammatory activities. Furthermore, several animal models have been used for evaluation of the rhizome activity on Aβ cascade and tau protein with Z. officinale aqueous and ethanolic extracts and its isolated compounds. Preclinical studies assure the low toxicity of the genus, opening up good prospects for AD treatment. However, there were very few clinical studies with this genus.

Future prospects
Although the first identification of AD occurred approximately 100 years ago with the German psychiatrist Alois Alzheimer, there is currently no effective drug to prevent and delay cognitive deterioration and dementia associated with Alzheimer’s disease (Ryan et al., 2015). Therefore, the currently used medications only improve the symptoms. In the last decade, there are some hypotheses such as cholinergic, β amyloid cascade, tau, inflammation, and oxidative stress hypothesis that are involved in AD pathogenesis (Du et al., 2018). The vast majority of the clinical trials for AD are treatments targeting only the Aβ peptide and tau protein (Dyck, 2018, Folcha et al., 2018). However, there is increasing evidence that many other pathways and questioning whether the hypotheses currently postulated for Alzheimer are causes or consequences of the disease (Strooper & Karran, 2016). There are still many points that need to be elucidated regarding this neurodegenerative disease and new theories have been emerging constantly. One of these emerging theories was recently published by Dominy et al. (2019) that identified Porphyromonas gingivalis in the brain of AD patients and that bacterium produces toxic proteases called gingipains. This bacterium is found in chronic periodontitis and its presence in brain tissue has been correlated with tau and ubiquitin pathology. Also, these authors reported that oral P. gingivalis infection in mice resulted in brain colonization and increased production of Aβ1-42, a component of amyloid plaques, a pathophysiological marker of AD.

Based on Dominy et al. (2019) findings, the search for herbal medicine extracts, essential oils, and isolated compounds that present antimicrobial activity against P. gingivalis may become valuable and potentially useful in the treatment of neurodegeneration of AD. Therefore, Zingiberaceae Family is a promising source of antimicrobial compounds obtained from extracts and essential oils of Alpinia, Curcuma and Zingiber genera that have been empirically applied and reported in several studies (Hwang et al., 2000; Khattak et al., 2005b; Naz et al., 2010; Rao et al., 2010; Sivasothy et al., 2011; Udomthanadech et al., 2015; Padalia et al., 2018). However, although Zingiberaceae herbal
medicines have been popularly used for centuries due to their antimicrobial, antioxidant, anti-inflammatory, analgesic, vasorelaxant, sedative, antineoplastic, antiallergic, antitussive, antiemetic, antidiarrheal, and antidiabetic activities (Chen et al., 2008; Namsa et al., 2009; Kumar et al., 2011; Umar et al., 2011; Victório, 2011), their effects on dementia-related alterations have been studied only in the last decades. Nevertheless, the future of AD treatment based on plants, mainly Zingiberaceae, may have a different approach after the findings about *P. gingivalis*. *In vitro* and *in vivo* preclinical studies have demonstrated that Zingiberaceae acts in many pathways involved in AD (Table No. 2, Table No. 4, and Table No. 6). There are descriptions of neuroprotective effects due to its antioxidant and anti-inflammatory activities, inhibition of AChE and BuChE activities, inhibition of Aβ production, and inhibition of tau phosphorylation, indicating a relationship among the effects of Zingiberaceae medicinal plants on AD and the current findings about *P. gingivalis*. However, despite these important findings and indicatives of potential anti-Alzheimer’s effects with medicinal plants, no clinical trials were conducted to validate it in humans with AD. Several studies with laboratory animals try to reproduce the disease most similarly to the disease in humans, however important differences still remain unresolved, such as the difference in the neuronal death profile, difference in the genetic involvement for the development of the disease, and slow course as the disease occurs in humans (LaFerla & Green, 2012). Thus, the validation of these studies in humans is necessary to confirm efficiency of animal assays (LaFerla & Green, 2012). In order to improve the development of novel diagnostics and therapeutic agents, translational medicine could be helpful to evolve studies of Zingiberaceae on AD.

**CONCLUSIONS**  
This review provided an updated overview of the Zingiberaceae Family in AD treatment. Many AD hypotheses have been proposed and several plants of this Family have shown biological activity for all of them. Studies have pointed out important effects on the cholinergic hypothesis of *A. galanga*, *Curcuma* spp. (*C. aromatica*, *C. longa*, and *C. zanthorrhiza*), and *Zingiber* spp. (*Z. mioga*, *Z. montanum*, *Z. officinale*, *Z. ottensii*, and *Z. zerumbet*). In the inflammatory hypothesis, there are descriptions of the positive effects for the genus *Alpinia* (*A. galanga* and *A. rafflesiana*), genus *Curcuma* (*C. comosa* and *C. zanthorrhiza*), and genus *Zingiber* (*Z. montanum* and *Z. officinale*). In pathways with oxidative stress involvement, only the genus *Curcuma* (*C. comosa*, *C. longa*, *C. zanthorrhiza*, and *C. zedoaria*) and *Zingiber* (*Z. mioga*, *Z. montanum*, and *Z. officinale*) were studied. The studies involving Aβ cascade were carried out only with *C. aromatica*, *C. longa*, and *Z. officinale*. Finally, regarding the tau hypothesis, only *C. aromatica* was evaluated. It is important to stress that most of the Zingiberaceae Family studies on AD were performed only *in vitro*; however, some studies have already crossed this barrier with *in vivo* studies for the main genera such as the genus *Alpinia* (*A. galanga*, *A. officinarum*, and *A. oxyphylla*), genus *Curcuma* (*C. longa* and *C. aromatica*), and genus *Zingiber* (*Z. officinale*). In view of the entire scientific arsenal listed in this review, it is concluded that the most promising species for AD treatment were *C. longa* and *Z. officinale*. Most evidence from *in vitro* studies with these species has been confirmed in several preclinical studies at different mechanisms of the pathogenesis of AD. In addition, preclinical safety studies have also shown satisfactory results for these species. However, there was only one clinical study with *Z. officinale* that stood out regarding cognitive performance. Thus, despite the promising preclinical results, studies on the bioactive compounds and the therapeutic application with plants of the Zingiberaceae Family in AD patients are still needed. Therefore, the great challenge for the Zingiberaceae Family in AD is to cross the bench-to-bedside by translational research that validates the promising preclinical effects of the medicinal plants from this Family.

**ACKNOWLEDGMENTS**  
The authors thank Universidade Paranaense, Graduate Program in Biotechnology Applied to Agriculture, Graduate Program in Medicinal Plants and Phytotherapeutics in Basic Attention, Graduate Program in Medicinal Plants and Phytotherapics in Basic Attention, Graduate Program in Animal Science with Emphasis on Bioactive Products and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brazil (CAPES)-finance code 001- for the financial the fellowship.

**REFERENCES**  
Abdelwahab S, Al-Zubairi AS, Mohan S. 2008. Zerumbone: a natural compound with anti-cholinesterase activity.
Am J Pharmaco Toxicol 3: 209 - 211. https://doi.org/10.1016/j.jep.2018.05.027
Abubakar IB, Malami I, Yahaya Y, Sule SM. 2018. A review on the ethnomedicinal uses, phytochemistry and pharmacology of Alpinia officinarum Hance. J Ethnopharmacol 224: 45 - 62.
Acevedo-Rodríguez P, Strong MT. 2012. Catalogue of the seed plants of the West Indies. Smithsonian Institution, Washington, USA. http://botany.si.edu/Antilles/WestIndies/catalog.htm
Agarwal P, Alok S, Fatima A, Singh PP. 2013. Herbal remedies for neurodegenerative disorder (Alzheimer's disease): a review. Int J Pharm Sci Res 4: 3328 - 3340.
Ahmad B, Rehman MU, Amin I, Arif A, Rasool S, Bhat SA, Afzal I, Hussain I, Bilal S, Mir MR. 2015. A review on pharmacological properties of zingerone (4-(4-Hydroxy-3-methoxyphenyl)-2-butanol). Sci World J 3: 1 - 6. https://doi.org/10.1155/2015/816364
Ahmed F, Chandra JN, Manjunath S. 2011. Acetylcholine and memory-enhancing activity of Ficus racemosa bark. Pharmacognosy Res 3: 246 - 249. https://doi.org/10.4103/0974-8490.89744
Ahmed T, Gilani AH. 2009. Inhibitory effect of curcuminoids on acetylcholinesterase activity and attenuation of scopolamine-induced amnesia may express medicinal use of turmeric in Alzheimer's disease. Pharmacol Biochem Behav 91: 554 - 559. https://doi.org/10.1016/j.pbb.2008.09.010
Akhondzadeh S, Abbasi SH. 2006. Herbal medicine in the treatment of Alzheimer's disease. Am J Alzheimer's Dis Other Dement 21: 113 - 118. https://doi.org/10.1177/153331750602100211
Akhtar MS, Khan MA, Malik MT. 2002. Hypoglycaemic activity of Alpinia galanga rhizome and its extracts in rabbits. Fitoterapia 73: 623 - 628. https://doi.org/10.1016/s0367-326x(02)00235-6
Akrán M, Nawaz A. 2017. Effects of medicinal plants on Alzheimer's disease and memory deficits. Neural Regen Res 12: 660 - 670. https://doi.org/10.4103/1673-5374.205108
Al-Amin M, Sultana GNN, Hossain CF. 2012. Antiulcer principle from Zingiber montanum. J Ethnopharmacol 141: 57 - 60. https://doi.org/10.1016/j.jep.2012.01.046
Albuquerque UP, Silva VA, Cabral MC, Alencar NL, Andrade LDHC. 2008. Comparisons between the use of medicinal plants in indigenous and rural caatinga (dryland) communities in NE Brazil. Bol Latinoam Caribe Plantas Med Aromat 7: 156 - 170.
Apostolova LG. 2016. Alzheimer disease. Continuum: Lifelong Learning in Neurology 22: 419 - 434. https://doi.org/10.1212/212.00000000000307
Arambewela L, Arambewela L, Ratnasooriya WD. 2011. Safety profile of Alpinia calcarata Roscoe, used in traditional medicine in Sri Lanka. Bol Latinoam Caribe Plantas Med Aromat 10: 435 - 442.
Ashfaq M, Iqbal S, Gillani AUQ, Iqbal F. 2018. Ethanolic Ficus carica leaf extract supplementation affects the behavior of male albino mice. Pak J Pharm Sci 31: 1417 - 1422. https://doi.org/10.2478/pjps-2017-00492-0
Bin Jantan I, Yassin MSM, Chin CB, Chen LL, Sim NL. 2003. Antifungal activity of the essential oils of nine Zingiberaceae species. Pharm Biol 41: 392 - 397. https://doi.org/10.1076/phbi.41.5.392.15941
Birks J. 2006. Cholinesterase inhibitors for Alzheimer’s disease. Cochrane Database Syst. Rev. Psychoneuro 32: 508. https://doi.org/10.1055/s-2006-956993
Boonmee A, Srisomsap C, Karnchanatat A, Sangvanicha P. 2011. An antioxidant protein in Curcuma comosa Roxb. rhizomes. Food Chem 124: 476 - 480. https://doi.org/10.1016/j.foodchem.2010.06.057
Bortoli PM, Alves C, Costa E, Vanin AP, Sofiatti JR, Siqueira DP, Dallago RM, Treichel H, Vargas GDL, Kaizer RR. 2018. Ilex paraguariensis: potential antioxidant on aluminium toxicity, in an experimental model of Alzheimer's disease. J Inorg Biochem 181: 104 - 110. https://doi.org/10.1016/j.jinorgbio.2017.11.001
Brici D, Götz J, Nisbet RM. 2018. A novel antibody targeting tau phosphorylated at serine 235 detects neurofibrillary tangles. J Alzheimers Dis 61: 899 - 905. https://doi.org/10.3233/jad-170610
Bustamam A, Ibrahim S, Al Zubairi AS, Manal MET, Syam MM. 2008. Zerumbone: a natural compound with anticholinesterase activity. Am J Pharmaco Toxicol 3: 209 - 211. https://doi.org/10.3844/ajptsp.2008.209.211
Chaiyana W, Saeio K, Hennink WE, Okonogi S. 2010. Characterization of potent anticholinesterase plant oil based microemulsion. Int J Pharm 401: 32 - 40. https://doi.org/10.1016/j.ijpharm.2010.09.005
Chang CJ, Tzeng TF, Liou SS, Chang YS, Liu IM. 2012. Acute and 28-day subchronic oral toxicity of an ethanolic extract of Zingiber zerumbet (L.) smith in rodents. Evid Based Complement Alternat Med 2012: 1 - 11.

Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas/454
Chang YM, Chang HH, Tsai CC, Lin HJ, Ho TJ, Ye CX, Chiu PL, Chen YS, Chen RJ, Huang CY, Lin CC. 2017. *Alpinia oxyphylla* Miq. fruit extract activates IGFR-PI3K/Akt signaling to induce schwann cell proliferation and sciatic nerve regeneration. **BMC Complement Altern Med** 17: 1 - 9.

Chen IN, Chang CC, Ng CC, Wang CY, Shyu YT, Chang TL. 2008. Antioxidant and antimicrobial activity of *Zingiberaceae* plants in Taiwan. **Plant Foods Hum Nutr** 63: 15 - 20.

Choi JS, Ryu J, Bae WY, Park A, Nam S, Kim JE, Jeong JW. 2018. Zingerone suppresses tumor development through decreasing cyclin D1 expression and inducing mitotic arrest. **Int J Mol Sci** 19: 1 - 15.

Cho KH, Oh MS, Kim HG, Lee SH, Chung KS, Kim AJ. 2014. Effects of Korean *Zingiber mioga* R. (flower buds and rhizome) extract on memory. **J Korean Soc Food Sci Nutr** 43: 1519 - 1526.

Chow YL, Lee KH, Vidyadaran S, Lajis NH, Akhtar MN, Israf DA, Syahida A. 2012. Cardamonin from *Alpinia rafflesiana* inhibits inflammatory responses in IFN-γ/LPS-stimulated BV2 microglia via NF-κB signalling pathway. **Int Immunopharmacol** 12: 657 - 665.

Chudiwal AK, Jain DP, Somani R. 2010. *Alpinia galanga* Willd. - an overview on phyto-pharmacological properties. **Indian J Nat Prod Resour** 1: 143 - 149.

Cho KH, Oh MS, Kim HG, Lee SH, Chung KS, Kim AJ. 2014. Effects of Korean *Zingiber mioga* R. (flower buds and rhizome) extract on memory. **J Korean Soc Food Sci Nutr** 43: 1519 - 1526.

Chow YL, Lee KH, Vidyadaran S, Lajis NH, Akhtar MN, Israf DA, Syahida A. 2012. Cardamonin from *Alpinia rafflesiana* inhibits inflammatory responses in IFN-γ/LPS-stimulated BV2 microglia via NF-κB signalling pathway. **Int Immunopharmacol** 12: 657 - 665.

Chudiwal AK, Jain DP, Somani R. 2010. *Alpinia galanga* Willd. - an overview on phyto-pharmacological properties. **Indian J Nat Prod Resour** 1: 143 - 149.

Cho KH, Oh MS, Kim HG, Lee SH, Chung KS, Kim AJ. 2014. Effects of Korean *Zingiber mioga* R. (flower buds and rhizome) extract on memory. **J Korean Soc Food Sci Nutr** 43: 1519 - 1526.

Chow YL, Lee KH, Vidyadaran S, Lajis NH, Akhtar MN, Israf DA, Syahida A. 2012. Cardamonin from *Alpinia rafflesiana* inhibits inflammatory responses in IFN-γ/LPS-stimulated BV2 microglia via NF-κB signalling pathway. **Int Immunopharmacol** 12: 657 - 665.

Chudiwal AK, Jain DP, Somani R. 2010. *Alpinia galanga* Willd. - an overview on phyto-pharmacological properties. **Indian J Nat Prod Resour** 1: 143 - 149.

Cho KH, Oh MS, Kim HG, Lee SH, Chung KS, Kim AJ. 2014. Effects of Korean *Zingiber mioga* R. (flower buds and rhizome) extract on memory. **J Korean Soc Food Sci Nutr** 43: 1519 - 1526.

Chow YL, Lee KH, Vidyadaran S, Lajis NH, Akhtar MN, Israf DA, Syahida A. 2012. Cardamonin from *Alpinia rafflesiana* inhibits inflammatory responses in IFN-γ/LPS-stimulated BV2 microglia via NF-κB signalling pathway. **Int Immunopharmacol** 12: 657 - 665.

Chudiwal AK, Jain DP, Somani R. 2010. *Alpinia galanga* Willd. - an overview on phyto-pharmacological properties. **Indian J Nat Prod Resour** 1: 143 - 149.

Cho KH, Oh MS, Kim HG, Lee SH, Chung KS, Kim AJ. 2014. Effects of Korean *Zingiber mioga* R. (flower buds and rhizome) extract on memory. **J Korean Soc Food Sci Nutr** 43: 1519 - 1526.
The rhizomes of *Zingiber cassumunar*. *Chem Pharm Bull* 53: 1466 - 1468. https://doi.org/10.1248/cpb.53.1466

Hanish Singh JC, Alagarsamy V, Kumar SS, Reddy YN. 2011. Neurotransmitter metabolic enzymes and antioxidant status on Alzheimer’s disease induced mice treated with *Alpinia galanga* (L.) Willd. *Phytother Res* 25: 1061 - 1067. https://doi.org/10.1002/ptr.3364

Hanish Singh JC, Alagarsamy V, Ramachandran D, Gummadi SB, Manana MM, Yellue NR. 2019. Neuroprotective effects of 1’δ-acetoxyeugenol acetate on Aβ(25-35) induced cognitive dysfunction in mice. *Biomed Pharmacother* 109: 1454 - 1461. https://doi.org/10.1016/j.biopharma.2018.10.189

Hassan M, Devkota AA, Imai T, Devkota HP. 2019. Zerumbone and Kaempferol derivatives from the rhizomes of *Zingiber montanum* (J. Koenig) Link ex A.Dietr. from Bangladesh. *Separations* 6: 1 - 8. https://doi.org/10.3390/separations6020031

Hassler M. 2020. World plants: synonymic checklists of the vascular plants of the world (version Nov 2018). In: Species 2000 & ITIS Catalogue of Life, (Roskov Y, Ower G, Orrell T, Nicolson D, Baill N, Kirk PM, Bourgoin T, DeWalt RE, Decock W, Nieuwerken Zarucchi J, Penev L. eds.). Species 2000: Naturalis, Leiden, the Netherlands. www.catalogueoflife.org

Hincapié CA, Monsalve ZL, Seigler D, Alarcón J, Cespedes CL. 2011. Antioxidant activity of *Blechnum chilense* (Kaulf.) Mett., *Curcuma domestica* Valeton and *Tagetes verticillata* Lag. & Rodriguez. *Bol Latinoam Caribe Plantas Med Aromat* 10: 315 - 324.

Ho SC, Chang KS, Lin CC. 2013. Anti-neuroinflammatory capacity of fresh ginger is attributed mainly to 10-gingerol. *Food Chem* 141: 3183 - 3191. https://doi.org/10.1016/j.foodchem.2013.06.010

Hong CH, Noh MS, Lee WY, Lee SK. 2002. Inhibitory effects of natural sesquiterpenoids isolated from the rhizomes of *Curcuma zedoaria* against amyloid β induced toxicity. *Biol Pharm Bull* 39: 1961 - 1967. https://doi.org/10.1248/bpb.b16-00411

Huh E, Lim S, Kim HG, Ha SK, Park HY, Huhe Y, Oh MS. 2018. Ginger fermented with *Schizosaccharomyces pombe* alleviates memory impairment via protecting hippocampal neuronal cells in amyloid beta1–42 plaque injected mice. *Food Funct* 9: 171 - 178. https://doi.org/10.1039/c7fo01149k

Huong LT, Dai DN, Chung MV, Doan DM, Ogunwande IA. 2016. Constituents of essential oils from the leaf, stem, root, fruit and flower of *Alpinia macroura* K. Schum. *Bol Latinoam Caribe Plantas Med Aromat* 16: 26 - 33.

Hwang JK, Shim JS, Pyun YR. 2000. Antibacterial activity of xanthorrhizol from *Curcuma xanthorrhiza* against oral pathogens. *Fitoterapia* 71: 321 - 323. https://doi.org/10.1016/s0367-326x(99)00170-7

Ichikawa H, Murakami, A. Aggarwal, BB. 2006. 1’-acetoxychavicol acetate inhibits RANKL-induced osteoclastic differentiation of RAW 264.7 monocytic cells by suppressing nuclear factor- B activation. *Mol Cancer Res* 4: 275 - 281. https://doi.org/10.1158/1541-7786.mcr-05-0227

Jantararatnotai N, Utaisincharoen P, Piayachaturawat P, Chongthammakun S, Sanvarinda Y. 2006. Inhibitory effect of *Curcuma comosa* on NO production and cytokine expression in LPS-activated microglia. *Life Sci* 78: 571 - 577. https://doi.org/10.1016/j.lfs.2005.04.065

Jeena K, Liju VB, Kuttan R. 2011. A Preliminary 13-week oral toxicity study of ginger oil in male and female Wistar rats. *Int J Toxicol* 30: 662 - 670. https://doi.org/10.1177/091581811419023

Jeong GS, Li B, Gogo G, Byun E, Dae GK, Ho SL, Kim YC. 2007. Cytoprotective constituents of *Alpinia katsumadai* seeds against glutamate-induced oxidative injury in HT22 cells. *Nat Prod Sci* 13: 268 - 271.

Jiamvoraphong N, Jantararatnotai N, Sanvarinda P, Tuchinda P, Piayachaturawat P, Thampithak A, Sanvarinda P. 2017. Concurrent suppression of NF-κB, p38 MAPK and reactive oxygen species formation underlies the effect of a novel compound isolated from *Curcuma comosa* Roxb. In LPS-activated microglia. *J Pharm Pharmacol* 69: 917 - 924. https://doi.org/10.1111/jphp.12723

Jung YS, Park SJ, Park JH, Jhee KH, Lee IS, Yang SA. 2012. Effects of ethanol extracts from *Zingiber officinale* rhizomes of *Zingiber cassumunar*. *Chem Pharm Bull* 53: 1466 - 1468. https://doi.org/10.1248/cpb.53.1466

Bortolucci et al. Therapeutic potential of Zingiberaceae in Alzheimer's disease

Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas/457
Rosco., Curcuma longa L., and Curcuma aromatica Salisb. on acetylcholinesterase and antioxidant activities as well as GABA contents. J Korean Soc Food Sci Nutr 41: 1395 - 1401.

https://doi.org/10.3746/jkfn.2012.41.10.1395

Kaewmatawong R, Boonchoong P, Teerawatanasuk N. 2009. Diarylheptanoids from Curcuma comosa. Phytochem Lett 2: 19 - 21. https://doi.org/10.1016/j.phytole.2008.10.004

Kalayc梭lu Z, Gazio梭lu I, Erim FB. 2017. Comparison of antioxidant, anticholinesterase, and antidiabetic activities of three curcuminoïds isolated from Curcuma longa L. Nat Prod Res 31: 2914 - 2917. https://doi.org/10.1080/14786419.2017.1299727

Kantayos V, Paisooksantivatana Y. 2012. Antioxidant activity and selected chemical components of 10 Zingiber spp. in Thailand. J Dev Sustain Agr 7: 89 - 96.

Karnchanatat A, Tiengburanatam N, Boonmee A, Puthong S, Sangvanich P. 2011. A cysteine protease from Zingiber officinale Valeton rhizomes with antiproliferative activities against fungi and human malignant cell lines. Prep Biochem Biotechnol 41: 138 - 153. https://doi.org/10.1080/10826068.2011.547347

Keene CD, Montine TJ, Kuller LH. 2020. Epidemiology, pathology, and pathogenesis of Alzheimer disease - UpToDate.

www.uptodate.com/contents/epidemiology-pathology-and-pathogenesis-of-alzheimer-disease/print

Khattak S, Rehman S, Ullah Shah H, Khan T, Ahmad M. 2005a. In vitro enzyme inhibition activities of crude Ethanolic extracts derived from medicinal plants of Pakistan. Nat Prod Res 19: 567 - 571. https://doi.org/10.1080/14786410410001721986

Khattak S, Rehman S, Ullah Shah H, Ahmad W, Ahmad M. 2005b. Biological effects of indigenous medicinal plants Curcuma longa and Alpinia galanga. Fitoterapia 76: 254 - 257. https://doi.org/10.1016/j.fitote.2004.12.012

Kim DSHL, Kim JY, Han YS. 2007. Alzheimer’s disease drug discovery from herbs: neuroprotectivity from β-Amyloid (1-42). Insult J Alt Complement Med 13: 333 - 340. https://doi.org/10.1089/acm.2006.6107

Kim HG, Lim S, Hong J, Kim AJ, Oh MS. 2016. Effects of myoga on memory and synaptic plasticity by regulating nerve growth factor mediated signaling. Phytother Res 30: 208 - 213. https://doi.org/10.1002/ptr.5511

Kim HW, Murakami A, Abe M, Ozawa Y, Morimitsu Y, Williams MW, Ohigashi H. 2005. Suppressive effects of mioga ginger and ginger constituents on reactive oxygen and nitrogen species generation, and the expression of inducible pro-inflammatory genes in macrophages. Antioxid Redox Signal 7: 1621 - 1629. https://doi.org/10.1089/ars.2005.7.1621

Kizhakke PA, Olakkaran S, Antony A, Tilagul KS, Hunasanahally PG. 2019. Convolvulus pluricaulis (shankhpushpi) ameliorates human microtubule-associated protein tau (hMAPr) induced neurotoxicity in Alzheimer's disease Drosophila model. J Chem Neuroanat 95: 115 - 122. https://doi.org/10.1016/j.jchemneu.2017.10.002

Koga AY, Beltrame FL, Pereira AV. 2016. Several aspects of Zingiber zerumbet: a review. Rev Bras Farmacogn 26: 385 - 391. https://doi.org/10.4021/rbf2016.01.006

Konno H, Endo H, Ise S, Miyazaki K, Aoki H, Sanjoh A, Kobayashi K, Hattori Y, Akaji K. 2014. Synthesis and evaluation of curcumin derivatives toward an inhibitor of beta-site amyloid precursor protein cleaving enzyme. Bioorg Med Chem Lett 24: 685 - 690. https://doi.org/10.1016/j.bmcl.2013.11.039

Kress WJ, Prince LM, Williams K. 2002. The phylogeny and a new classification of the gingers (Zingiberaceae): evidence from molecular data. Am J Bot 89: 1682 - 1696.

Kuddus R, Farhana R, Kaisar MA, Hasan CM, Rashid MA. 2010. Trans-Isoferulic acid from Curcuma longa. Bol Latinoam Caribe Plantas Med Aromat 9: 3019 - 2021.

Kumar G, Karthik L, Bhaskar RK. 2011. A Review on pharmacological and phytochemical properties of Zingiber officinale Roscoe (Zingiberaceae). J Pharm Res 4: 2963 - 2966.

LaFerla FM, Green KN. 2012. Animal models of Alzheimer disease. Cold Spring Harb Perspec Med 2: 1 - 13.

Larsen L, Adams J, Deal B, Kweon BS, Tyler E. 1998. Plants in the workplace: the effects of plant density on productivity, attitudes, and perceptions. Environ Behav 30: 261 - 281. https://doi.org/10.1177/001391659803000301

Lee C, Park GH, Kim CY, Jang JH. 2011. [6]-Gingerol attenuates β-amylloid-induced oxidative cell death via fortifying cellular antioxidant defense system. Food Chem Toxicol 49: 1261 - 1269. https://doi.org/10.1016/j.fct.2011.03.005

Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas/458
Lee YJ, Choi DY, Han SB, Kim YH, Kim KH, Hwang BY, Kang JK, Lee BJ, Oh KW, Hong JT. 2012. Inhibitory effect of ethanol extract of Magnolia officinalis on memory impairment and amyloidogenesis in a transgenic mouse model of Alzheimer's disease via regulating β-secretase activity. Phytother Res 26: 1884 - 1892. https://doi.org/10.1002/ptr.4463

Leelasungrayub J, Manorsoi J, Manorsoi A. 2017. Anti-inflammatory activity of niosomes entrapped with plai oil (Zingiber cassumunar Roxb.) by therapeutic ultrasound in a rat model. Int J Nanomedicine 12: 2469 - 2476. https://doi.org/10.2147/ijn.s129131

Li Z, Qi Y, Kang K, Jia D. 2017. The aqueous extract of Curcuma wenyujin rescues learning and memory deficits through PI3k/Akt/GSK-3β pathway in Aβ-induced AD mice. Biom Res 28: 7438 - 7442. https://doi.org/10.21055/s-0042-107471

Lim CS, Jin DQ, Mok H, Oh SJ, Lee JU, Hwang BY, Kang JK, Ha I, Han JS. 2005. Antioxidant and antiinflammatory activities of xanthorrhizol in hippocampal neurons and primary cultured microglia. J Neurosci 82: 831 - 838. https://doi.org/10.1002/jnr.20692

Lim S, Choi JG, Moon M, Kim HG, Lee W, Bak H, Sung H, Park CH, Kim SY, Oh MS. 2016. An optimized combination of ginger and peony root effectively inhibits amyloid-β accumulation and amyloid-β-mediated pathology in aβpp/p1 double-transgenic mice. J Alzheimers Dis 50: 189 - 200. https://doi.org/10.3233/jad-150839

Lin SC, Lin CC, Lin YH, Supriyatna S, Teng CW. 1995. Protective and therapeutic effects of Curcuma xanthorrhiza on hepatotoxin-induced liver damage. Am J Chin Med 23: 243 - 254. https://doi.org/10.1142/s0192415x95000298

Liu A, Zhao X, Li H, Liu Z, Liu B, Mao X, Guo L, Bi K, Jia Y. 2014. 5-hydroxymethylfurfural, an antioxidant agent from Alpinia oxyphylla Miq. improves cognitive impairment in Aβ1-42 mouse model of Alzheimer’s disease. Int Immunopharmacol 23: 719 - 725. https://doi.org/10.1016/j.intimp.2014.10.028

Liu H, Ye M, Guo H. 2020. An updated review of randomized clinical trials testing the improvement of cognitive function of Ginkgo biloba extract in healthy people and Alzheimer’s patients. Front Pharmacol 10: 1688. https://doi.org/10.3389/fphar.2019.01688

Liu J, Zhang L, Liu D, Li B, Zhang M. 2018. Neuroprotective effects of extracts from the radix Curcuma aromatica on H2O2-induced damage in PC12 cells. Comb. Chem. High. Throughput Screen 21: 571 - 582. https://doi.org/10.2174/1386207321666181005121457

Liu QF, Jeon Y, Sung YW, Lee JH, Jeong H, Kim YM, Yun HS, Chin YW, Jeon S, Cho KS, Koo BS. 2018. Nardostachys jatamansi ethanol extract ameliorates Aβ42 cytotoxicity. Biol Pharm Bull 41: 470 - 477. https://doi.org/10.1248/bpb.b17-00750

Lobo R, Prabhu KS, Shirwaikar A, Shirwaikar A. 2009. Curcuma zedoaria Rosc. (white turmeric): a review of its chemical, pharmacological and ethnomedicinal properties. J Pharma Pharmacol 61: 13 - 21. https://doi.org/10.1211/jpp.61.01.0003

Loc NH, Duc DT, Kwon TH, Yang MS. 2005. Micropropagation of zedoary (Curcuma zedoaria Roscoe) – a valuable medicinal plant. Plant Cell Tiss Organ Cult 81: 119 - 122. https://doi.org/10.1007/s11240-004-3308-2

Lunenfeld B, Stratton P. 2013. The clinical consequences of an ageing world and preventive strategies. Best Pract Res Clin Obstet Gynaecol 27: 643 - 659. https://doi.org/10.1016/j.bpobgyn.2013.02.005

Mahaman YAR, Huang F, Wu M, Wang Y, Wei Z, Bao J, Salissou MTM, Ke D, Wang Q, Liu R, Wang JZ, Zhang B, Chen D, Wang X. 2018. Moringa oleifera alleviates homocysteine-induced Alzheimer’s disease-like pathology and cognitive impairments. J Alzheimers Dis 63: 1141 - 1159. https://doi.org/10.3233/jad-180091

Malik J, Karan M, Dogra R. 2017. Ameliorating effect of Celastrus paniculatus standardized extract and its fractions on 3-nitropionic acid induced neuronal damage in rats: possible antioxidant mechanism. Pharm Biol 55: 980 - 990. https://doi.org/10.1080/13880297.2017.1285945

Malve HO, Raut SB, Marathe PA, Rege NN. 2014. Effect of combination of Phyllanthus emblica, Tinospora cordifolia, and Ocimum sanctum on spatial learning and memory in rats. J Ayurveda Integr Med 5: 209 - 215. https://doi.org/10.4103/0975-9476.146564

Mathew M, Subramanian S. 2014. In vitro evaluation of anti-Alzheimer effects of dry ginger (Zingiber officinale Roscoe) extract. Ind J Exp Biol 52: 606 - 612.
Matsuda H, Morikawa T, Managi H, Yoshikawa M. 2003. Antiallergic principles from Alpinia galanga: structural requirements of phenylpropanoids for inhibition of degranulation and release of TNF-α and IL-4 in RBL-2H3 cells. *Bioorganic Med Chem C Lett* 13: 3197 - 3202. https://doi.org/10.1016/s0960-894x(03)00710-8

Matsui N, Kido Y, Okada H, Kubo M, Nakai M, Fukushima N, Fukuyama Y, Akagi M. 2012. Phenybutenoid dimers isolated from Zingiber purpureum exert neurotrophic effects on cultured neurons and enhance hippocampal neurogenesis in olfactory bulbectomized mice. *Neurosci Lett* 513: 72 - 77. https://doi.org/10.1016/j.neulet.2012.02.010

Mendonça VLM, Oliveira CLAO, Craveiro AA, Rao VS, Fonteles MC. 1991. Pharmacological and toxicological evaluation of Alpinia speciosa. *Mem Inst Oswaldo Cruz* 86: 93 - 97. https://doi.org/10.1590/s0070-40991991000600023

Mirmosayyeb O, Tanhaei A, Sohrabi HR, Martins RN, Tanhaei M, Najafi MA, Safaei A, Meammar R. 2017. Comparison of medicinally important natural products versus synthetic drugs as new aroma chemicals. *Pharmacolieral*. 78(1): 1 - 24. https://doi.org/10.4103/2008-7802.199640

Miroddi M, Navarra M, Quattropani MC, Calapai F, Gangemi S, Calapai G. 2014. Systematic review of clinical trials assessing pharmacological properties of Salvia species on memory, cognitive impairment and Alzheimer’s disease. *CNS Neurosci Ther* 20: 485 - 495. https://doi.org/10.1111/cns.12270

Miyazawa M, Hashimoto Y. 2002. Antimicrobial and bactericidal activities of esters of 2-endo-hydroxy-1,8-cineole as new aroma chemicals. *J Agric Food Chem* 50: 3522 - 3526. https://doi.org/10.1021/jf011555w

Monroy A, Lithgow GJ, Alarcon-Rangel P, Cortes A, Bigelow A,真皮D. 2017. Comparison of medicinally important natural products versus synthetic drugs as new aroma chemicals. *Pharmacolieral*. 78(1): 1 - 24. https://doi.org/10.4103/2008-7802.199640

Miroddi M, Navarra M, Quattropani MC, Calapai F, Gangemi S, Calapai G. 2014. Systematic review of clinical trials assessing pharmacological properties of Salvia species on memory, cognitive impairment and Alzheimer’s disease. *CNS Neurosci Ther* 20: 485 - 495. https://doi.org/10.1111/cns.12270

Miyazawa M, Hashimoto Y. 2002. Antimicrobial and bactericidal activities of esters of 2-endo-hydroxy-1,8-cineole as new aroma chemicals. *J Agric Food Chem* 50: 3522 - 3526. https://doi.org/10.1021/jf011555w

Monroy A, Lithgow GJ, Alavrez S. 2013. Curcumina e doenças neurodegenerativas. *Biofactors* 39: 122 - 132.

Morikawa T, Ando S, Matsuda H, Kataoka S, Muraoka O, Yoshikawa M. 2005. Inhibitors of nitric oxide production from the rhizomes of Alpinia galanga: structures of new 8′-9′ linked neolignans and sesquineolignan. *Chem Pharm Bull* 53: 625 - 630. https://doi.org/10.1248/cpb.53.625

Na JY, Song K, Lee JW, Kim S, Kwon J. 2017. Sortilin-related receptor 1 interacts with amyloid precursor protein and is activated by 6-shogaol, leading to inhibition of the amyloidogenic pathway. *Biochem Biophys Res Commun* 484: 890 - 895. https://doi.org/10.1016/j.bbrc.2017.02.029

Nag A, Chakraborty M, Banerjee R, Mukherjee A. 2018. Evaluation of cytotoxicity and antioxidant properties of some Zingiberaceae plants. *Int J Green Pharm* 12: 1 - 6.

Nagano T, Oyama Y, Kajita N, Chikahisa L, Nakata M, Okazaki E, Masuda T. 1997. New curcuminoids isolated from Zingiber cassumunar protect cells suffering from oxidative stress: a flow-cytometric study using rat thymocytes and H2O2. *Jpn J Pharmacol* 75: 363 - 370. https://doi.org/10.1254/jjp.75.363

Namgaling ND, Tagc H, Mandalb M, Kalita P, Das AK. 2009. An ethnobotanical study of traditional anti-inflammatory plants used by the Lohit community of Arunachal Pradesh, India. *J Ethnopharmacol* 125: 234 - 245. https://doi.org/10.1016/j.jep.2009.07.004

Naj S, Jabeen S, Ilyas S, Manzoor F, Aslam F, Ali A. 2010. Antibacterial activity of Curcuma longa varieties against different strains of bacteria. *Pak J Bot* 42: 455 - 462.

Ngoc-Sam L, Ba-Vuong T, Huong L. 2016. Zingiber ottensii Valeton (Zingiberacea) - a newly recorded species for Vietnam. *Bio Disc* 7: 93 - 96.

Nisar B, Sultan A, Rubab SL. 2017. Comparison of medicinally important natural products versus synthetic drugs-a short commentary. *Nat Prod Chem Res* 6: 1 - 2. https://doi.org/10.4172/2329-6836.1000308

Nongalleima K, Dey A, Deb L, Singh CB, Thongam B, Devi HS, Devi SI. 2013. Endophytic fungus isolated from Zingiber zerumbet (L.) Sm. inhibits free radicals and cyclooxygenase activity. *Int J Pharm Tech Res* 5: 301 - 307.

Oboh G, Ademiluyi AO, Akinyemi AJ. 2012. Inhibition of acetylcholinesterase activities and some pro-oxidant induced lipid peroxidation in rat brain by two varieties of ginger (Zingiber officinale). *Exp Toxicol Pathol* 64: 315 - 319. https://doi.org/10.1016/j.etp.2010.09.004

Okonogi S, Chaiyana W. 2012. Enhancement of anti-cholinesterase activity of Zingiber cassumunar essential oil using a microemulsion technique. *Drug Discov Ther* 6: 249 - 255. https://doi.org/10.5582/ddt.2012.v6.5.249

Oliveira GL, Oliveira AFM, Andrade LHC. 2015. Medicinal and toxic plants from Muribeca alternative health center (Pernambuco, Brazil): an ethnopharmacology survey. *Bol Latinoam Caribe Plantas Med Aromat* 14: 470 - 483.
Ozaki Y. 1990. Antiinflammatory effect of *Curcuma xanthorrhiza* Roxb. and its active principles. *Chem Pharm Bull* 38: 1045 - 1048. https://doi.org/10.1248/cpb.38.1045

Padalia RC, Verma RS, Chauhan A, Singh VR, Goswami P, Singh S, Goswami P, Singh S, Verma SK, Luqman S, Chanotiya CS, Darokar MP. 2018. *Zingiber zerumbet* (L.) Roscoe ex Sm. from Northern India: potential source of zerumbone rich essential oil for antiproliferative and antibacterial applications. *Ind Crops Prod* 112: 749 - 754. https://doi.org/10.1016/j.indcrop.2018.01.006

Palatty PL, Haniadka R, Valder B, Arora R, Baliga MS. 2013. Ginger in the prevention of nausea and vomiting: a review. *Crit Rev Food Sci Nutr* 53: 659 - 669. https://doi.org/10.1080/10408398.2011.553751

Panza F, Lozupone M, Seripa D, Imbimbo B. 2019. Amyloid-β immunotherapy for Alzheimer disease: is it now a long shot? *Ann Neuroi* 85: 303 - 315. https://doi.org/10.1002/ana.25410

Park JH, Park KK, Kim MJ, Hwang JK, Park SK, Chung WY. 2008. Cancer chemoprotective effects of *Curcuma xanthorrhiza*. *Phytother Res* 22: 695 - 698. https://doi.org/10.1002/ptr.2418

Park JH, Eum JH, Bold B, Cheong HK. 2013. Burden of dementia due to dementia in the elderly population of Korea: present and future. *BMC Public Health* 13: 1 - 9. https://doi.org/10.1186/1471-2458-13-293

Parle M, Dhingra D, Kulkarni SK. 2004. Improvement of mouse memory by *Myristica fragrans* seeds. *J Med Food* 7: 57 - 161. https://doi.org/10.1089/1096620041224193

Penumala M, Zinka RB, Shaik JB, Mallepalli SKR, Valde R, Amoru DG. 2018. Phytochemical profiling and *in vitro* screening for anticholinesterase, antioxidant, antiglucosidase and neuroprotective effect of three traditional medicinal plants for Alzheimer’s disease and diabetes mellitus dual therapy. *BMC Complement Altern Med* 18: 1 - 13. https://doi.org/10.1186/s12906-018-2140-x

Plengsuriyakarn T, Vijanant V, Eursitthichai V, Tesana S, Chaijaroenkul W, Itharat A, Nare J. 2018. Cytotoxicity, toxicity, and anticancer activity of Zingiber officinal roscoe against cholangiocarcinoma. *Asian J Cancer Prev* 13: 4597 - 4606. https://doi.org/10.7314/ajcp.2012.13.9.4597

Portnoi G, Chng LA, Tabesh LK, Koren G, Tan MP, Einarson A. 2003. Prospective comparative study of the safety and effectiveness of ginger for the treatment of nausea and vomiting in pregnancy. *Am J Obstet Gynecol* 189: 1374 - 1377. https://doi.org/10.1067/s0002-9378(03)00649-5

Press D, Alexander M. 2019a. Treatment of dementia - UpToDate. www.uptodate.com/contents/treatment-of-dementia/print

Press D, Alexander M. 2019b. Cholinesterase inhibitors in the treatment of dementia-UpToDate. www.uptodate.com/contents/cholinesterase-inhibitors-in-the-treatment-of-dementia/print

Prince M. 2004. 10/66 Dementia Research Group. Care arrangements for people with dementia in developing countries. *Int J Geriatr Psychiatry* 19: 170 - 177. https://doi.org/10.1002/gps.1046

Prince M, Acosta D, Ferri CP, Guerra M, Huang Y, Rodriguez JLL, Salas A, Sosa AL, Williams JD, Dewey ME, Acosta I. Jotheeswaran, AT, Liu Z. 2012. Dementia incidence and mortality in middle income countries, and associations with indicators of cognitive reserve: a 10/66 dementia research group population-based cohort study. *Lancet* 380: 50 - 58. https://doi.org/10.1016/s0140-6736(12)60399-7

Prince M, Wimo AGM, Ali GC, Wu YT, Prina M. 2015. *World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends*. Published by Alzheimer’s Disease International, London, UK. https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf

Rao K, Ch B, Narasu LM, Giri A. 2010. Antibacterial activity of *Alpinia galanga* (L) willd crude extracts. *Appl Biochem Biotechnol* 162: 871 - 884. https://doi.org/10.1007/s12010-009-8900-9

Rao YK, Shih HN, Lee YC, Cheng WT, Hung HC, Wang HC, Chen CJ, Tzeng YM, Lee M J. 2014. Purification of kavalactones from *Alpinia zerumbet* and their protective actions against hydrogen peroxide-induced cytotoxicity in PC12 cells. *J Biosci Bioeng* 118: 679 - 688. https://doi.org/10.1016/j.jbiosc.2014.05.009

Reitz C. 2012. Alzheimer’s disease and the amyloid cascade hypothesis: a critical review. *Int J Alzheimers Dis* 2012: 1 - 11.

Rong X, Peng G, Suzuki T, Yang Q, Yamahara J, Li Y. 2009. A 35-day gavage safety assessment of ginger in rats. *Regul Toxicol Pharmacol* 54: 118 - 123. https://doi.org/10.1016/j.yrtph.2009.03.002

Rout OP, Acharya R, Mishra SK. 2011. *In-vitro* antioxidant potentials in leaves of *Coleus aromaticus* Benth and rhizomes of *Zingiber zerumbet* (L.) SM. *J Appl Pharm Sci* 1: 194 - 198.

Roy A. 2018. Role of medicinal plants against Alzheimer’s disease. *Int J Complement Alt Med* 11: 205 - 208.

Rubio J, Dang H, Gong M, Liu X, Chen SL, Gonzales GF. 2007. Aqueous and hydroalcoholic extracts of black
maca (Lepidium meyenii) improve scopolamine-induced memory impairment in mice. *Food Chem Toxicol* 45: 1882 - 1890. https://doi.org/10.1016/j.fct.2007.04.002

Rukayadi Y, Yong D, Hwang JK. 2006. *In vitro* antifungal activity of zanthorrhizol isolated from *Curcuma xanthorrhiza* Roxb. *J Antimicrob Chemother* 57: 1231 - 1234. https://doi.org/10.1093/jac/dkl132

Rungsaeng P, Sangvanich P, Karnchanatat A. 2013. Zingipain, a ginger protease with acetylcholinesterase inhibitory activity. *Appl Biochem Biotechnol* 170: 934 - 950. https://doi.org/10.1007/s12010-013-0243-x

Ryan NS, Rossor MN, Fox NC. 2015. Alzheimer’s disease in the 100 years since Alzheimer’s death. *Brain* 138: 3816 - 3821. https://doi.org/10.1093/brain/awv316

Saciu SF. 2016. Dementias. *Handb Clin Neurol* 138: 123 - 151.

Saenghong N, Wattanathorn J, Muchimapura S, Tongun T, Piyavhatkul N, Banchonglikitkul C, Kajsongkram T. 2013. Zingipain, a ginger protease with acetylcholinesterase inhibitory activity. *Evid Based Complement Altern Med* 2012: 1 - 9. https://doi.org/10.1155/2012/383062

Saensouk S, Saensouk P, Pasorn P, Chantaranothai P. 2016. Diversity and uses of Zingiberaceae in Nam Nao national park, Chaiyaphum and Phetchabun provinces, Thailand, with a new record for Thailand. *Agric Nat Res* 50: 445 - 453. https://doi.org/10.1016/j.janres.2016.08.002

Saini N, Singh D, Sandhir R. 2019. *Bacopa monnieri* prevents colchicine-induced dementia by anti-inflammatory action. *Metab Brain Dis* 34: 505 - 518. https://doi.org/10.1007/s11011-018-0332-1

Sanatombi R, Sanatombi K. 2017. Biotechnology of Zingiber montanum (Koenig) link ex A. Dietr.: a review. *J Appl Res Med Aromat Plants* 4: 1 - 4. https://doi.org/10.1016/j.jarmap.2016.09.001

Santos-Neto LL, de Vilhena Toledo MA, Medeiros Neto LL, de Vilhena Toledo MA, Medeiros Neto LL, de Vilhena Toledo MA, Medeiros Neto LL, de Vilhena Toledo MA, Medeiros Neto LL, de Vilhena Toledo MA, Medeiros Neto LL, de Vilhena Toledo MA, Medeiros Neto LL, de Vilhena Toledo MA. 2005. Donepezil in the treatment of dementia. *Santos-Neto LL, de Vilhena Toledo MA, Medeiros-Souza P, de Souza GA. 2006. The use of herbal medicine in Alzheimer's disease-a systematic review. Evid Based Complement Alternat Med 3: 441 - 445. https://doi.org/10.1093/ecam/nel071

Sasikumar B. 2012. *Turmeric*. In: Handbook of Herbs and Spices; Peter KV, Ed. Woodhead Publishing: Cambridge, England.

Sastre A, Sherriff F, McShane R. 2005. Memantine for dementia. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.cd003154.pub4

Saxena G, Singh SP, Pal R, Singh S, Pratap R, Nath C. 2007. Gugulipid, an extract of *Withania somnifera* Dunal. helps in cholesterol lowering and reduces oxidative stress in middle-aged healthy women. *Proc Natl Acad Sci U S A* 104: 17339 - 17344. https://doi.org/10.1073/pnas.0707407104

Sehgal N, Gupta A, Valli RK, Joshi SD, Mills JT, Hamel E, Khanna P, Jain SC, Thakur SS, Ravindranath V. 2012. *Withania somnifera* reverses Alzheimer’s disease pathology by enhancing low-density lipoprotein receptor-related protein in liver. *Proc Natl Acad Sci* 109: 3510 - 3515. https://doi.org/10.1073/pnas.1112209109

Seltzer B. 2005. Donepezil in the treatment of dementia. *Aging Health* 1: 7 - 17.

Serendik A, Vital MABF. 2008. Alzheimer's disease: pathophysiological and pharmacological features. *Rev Psiiquiatr* 30: 1 - 17.

Shah H, Almanese E, Duggan C, Rudan I, Langa KM, Carrillo MC, Chan KY, Joanette Y, Prince M, Rossor M, Saxena S, Snyder HM, Sperling R, Varghese M, Wang H, Wortmann M, Dua T. 2016. Research priorities to reduce the global burden of dementia by 2025. *Lancet Neurol* 15: 1285 - 1294. https://doi.org/10.1016/s1474-4422(16)30235-6

Sharifi-Rad M, Varoni EM, Salehi B, Sharifi-Rad J, Matthews KR, Ayatollahi SA, Kobarfard F, Ibrahim SA, Mnayer D, Zakaria ZA, Sharifi-Rad M, Yousaf Z, Iriti M, Basile A, Rigano D. 2017. Plants of the genus *Zingiber* as a source of bioactive phytochemicals: from tradition to pharmacy. *Molecules* 22: 2145. https://doi.org/10.3390/molecules22122145

Shi GF, An LJ, Jiang B, Guan S, Bao YM. 2006. *Alpinia* proteaceichuic acid protects against oxidative damage *in vitro* and reduces oxidative stress *in vivo*. *Neurosci Lett* 403: 206 - 210. https://doi.org/10.1016/j.neulet.2006.02.057

Shi SH, Zhao X, Liu B, Li H, Liu AJ, Wu B, Bi KS, Jia Y. 2014. The effects of sesquiterpenes-rich extract of *Alpinia oxyphylla* Miq. on amyloid-β-induced cognitive impairment and neuronal abnormalities in the cortex and hippocampus of mice. *Oxid Med Cell Longev* 2014: 1 - 11. https://doi.org/10.1155/2014/451802

Shin SJ, Jeon SG, Kim JI, Jeong YO, Kim S, Park YH, Lee SK, Park HH, Hong SB, Oh S, Hwang JY, Kim HS,
Park H, Nam Y, Lee YY, Kim JI, Park SH, Kim JS, Moon M. 2019. Red ginseng attenuates Aβ-induced mitochondrial dysfunction and Aβ-mediated pathology in an animal model of Alzheimer’s disease. *Int J Mol Sci* 2: E3030. [https://doi.org/10.3390/ijms20123030](https://doi.org/10.3390/ijms20123030)

Siripurapu KB, Gupta P, Bhatia G, Maurya R, Nath C, Palit G. 2005. Adaptogenic and anti-amnesic properties of *Evolvulus alsinoides* in rodents. *Pharmacol Biochem Behav* 81: 424 - 432.

[https://doi.org/10.1016/j.pbb.2005.03.003](https://doi.org/10.1016/j.pbb.2005.03.003)

Sirirugsa P, Larsen K, Maknoi C. 2007. The genus *Curcuma* L. (Zingiberaceae): distribution and classification with reference to species diversity in Thailand. *Gard Bull Singapore* 59: 203 - 219.

[https://doi.org/10.1016/j.jalg.2013.02.025](https://doi.org/10.1016/j.jalg.2013.02.025)

Sivasothy Y, Chong WK, Hamid A, Elddeen IM, Sulaiman SF, Awang K. 2011. Essential oils of *Zingerib officinalae* var. *rubrum* thclade and their antibacterial activities. *Food Chem* 124: 514 - 517.

[https://doi.org/10.1016/j.foodchem.2010.06.062](https://doi.org/10.1016/j.foodchem.2010.06.062)

Srividya AR, Dhanabal SP, Misra VK, Suja G. 2010. Antioxidant and antimicrobial activity of *Alpinia officinarum*. *Indian J Pharm Sci* 72: 145 - 148. [https://doi.org/10.4103/0250-474x.62233](https://doi.org/10.4103/0250-474x.62233)

Stanciu GD, Luca A, Rusu RN, Bild V, Beschea Chiriac SI, Solcan C, Bild W, Ababei DC. 2019. Alzheimer’s disease pharmacotherapy in relation to cholinergic system Involvement. *Biomolecules* 10: E40.

[https://doi.org/10.3390/biom10010040](https://doi.org/10.3390/biom10010040)

Stanisiere J, Mousset PY, Lafay S. 2018. How safe is ginger rhizome for decreasing nausea and vomiting in women during early pregnancy? *Foods* 7: 1 - 29. [https://doi.org/10.3390/foods7040050](https://doi.org/10.3390/foods7040050)

Strooper BD, Karran E. 2016. The cellular phase of Alzheimer’s disease. *Cell* 164: 603 - 615.

[https://doi.org/10.1016/j.cell.2015.12.056](https://doi.org/10.1016/j.cell.2015.12.056)

Tang G, Dong X, Huang X, Huang XJ, Liu H, Wang Y, Ye WC, Shi L. 2015. A natural diarylheptanoid promotes neuronal differentiation via activating ERK and PI3K-Akt dependent pathways. *Neuroscience* 303: 389 - 401. [https://doi.org/10.1016/j.neuroscience.2015.07.019](https://doi.org/10.1016/j.neuroscience.2015.07.019)

Thamppithak A, Jaisin Y, Meesarapee B, Chongthammakun S, Piyachaturawat P, Govitra var. [https://doi.org/10.1016/j.pbb.2005.03.003](https://doi.org/10.1016/j.pbb.2005.03.003)

Thiam J, Meew W, Wattanathorn J. 2012. Evaluation of safety and protective effect of combined extract of *Anethum graveolens* and *Evolvulus alsinoides* in lipopolysaccharide induced microglial activation. *Neurosci Lett* 462: 171 - 175. [https://doi.org/10.1016/j.neulet.2009.06.094](https://doi.org/10.1016/j.neulet.2009.06.094)

Thies W, Bleiler L. 2013. Alzheimer’s disease facts and figures. *Alzheimers Dement* 9: 208 - 245. [https://doi.org/10.1016/j.jalz.2013.02.003](https://doi.org/10.1016/j.jalz.2013.02.003)

Thomson M, Corbin R, Leung L. 2014. Effects of ginger for nausea and vomiting in early pregnancy: a meta-analysis. *J Am Board Fam Med* 27: 115 - 122. [https://doi.org/10.3122/jabfm.2014.01.130167](https://doi.org/10.3122/jabfm.2014.01.130167)

Thukham-Mee W, Wattanathorn J. 2012. Evaluation of safety and protective effect of combined extract of *Cissampelos pareira* and *Anethum graveolens* (PMS2) against age-related cognitive impairment. *Evid Based Complement Alt Med* 2012: 674101. [https://doi.org/10.1155/2012/674101](https://doi.org/10.1155/2012/674101)

Tiran D. 2012. Ginger to reduce nausea and vomiting during pregnancy: evidence of effectiveness is not the same as proof of safety. *Complement Ther Clin Pract* 18: 22 - 25. [https://doi.org/10.1016/j.ctcp.2011.08.007](https://doi.org/10.1016/j.ctcp.2011.08.007)

Tung BT, Thu DK, Thu NTK, Hai NT. 2017. Antioxidant and acetylcholinesterase inhibitory activities of ginger root (*Zingiber officinale* Roscoe) extract. *J Complement Integr Med* 14: 1 - 7. [https://doi.org/10.1016/j.jcim.2016-0116](https://doi.org/10.1016/j.jcim.2016-0116)

Tzioras M, Davies C, Newman A, Jackson R, Spires-Jones T. 2018. Invited Review: APOE at the interface of inflammation, neurodegeneration and pathological protein spread in Alzheimer’s disease. *Neuropathol Appl Neurobiol* 45: 327 - 346. [https://doi.org/10.1111/nan.12529](https://doi.org/10.1111/nan.12529)

Uddin MS, Mamun AA, Hossain MS, Akter F, Iqbal MA, Asaduzzaman M. 2016. Exploring the Effect of *Phyllanthus emblica* L. on cognitive performance, brain antioxidant markers and acetylcholinesterase activity in rats: promising natural gift for the mitigation of Alzheimer’s disease. *Ann Neurosci* 23: 218 - 229. [https://doi.org/10.1515/an.2015.004](https://doi.org/10.1515/an.2015.004)

Udomthanadech K, Vajrodaya S, Pairoonsantivatana Y. 2015. Antibacterial properties of the extracts from some Zingiberaceous species in Thailand against bacteria causing diarrhea and food poisoning in human. *Int Trans J Eng Manage Appl Sci Technol* 6: 203 - 213.

Umar MI, Asmawi MZB, Sadikun A, Altarf R, Iqbal MA. 2011. Phytochemistry and medicinal properties of *Kaempferia galanga* L. (Zingiberaceae) extracts. *Afr J Pharm Pharmacol* 5: 1638 - 1647.
https://doi.org/10.5897/ajpp11.388

Uttara B, Singh AV, Zamboni P, Mahajan RT. 2009. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Curr Neuropharmacol 7: 65 - 74.

https://doi.org/10.2174/157015909787602823

Vaibhav K, Shrivastava P, Tabassum R, Khan A, Javed H, Ahmed ME, Islam F, Safhi MM, Islam F. 2013. Delayed administration of zingerone mitigates the behavioral and histological alteration via repression of oxidative stress and intrinsic programmed cell death in focal transient ischemic rats. Pharmacol Biochem Behav 113: 53 - 62. https://doi.org/10.1016/j.pbb.2013.10.008

Victório CP. 2011. Therapeutic value of the genus Alpinia, Zingiberaceae. Rev Bras Farmacogn 21: 194 - 201.

https://doi.org/10.1590/s0102-695x2011005000025

Viljoen E, Visser J, Koen N, Musekiwa A. 2014. A systematic review and meta-analysis of the effect and safety of ginger in the treatment of pregnancy-associated nausea and vomiting. Nutr J 1: 1 - 14.

https://doi.org/10.1186/1475-2891-13-20

Vinothkumar R, Vinothkumar R, Sudha M, Nalini N. 2014. Chemopreventive effect of zingerone against colon carcinogenesis induced by 1,2-dimethylhydrazine in rats. Eur J Cancer Prev 23: 361 - 371.

https://doi.org/10.1097/cej.0b013e32836473ac

Wang C, Cai X, Hu W, Li Z, Kong F, Chen X, Wang D. 2019. Investigation of the neuroprotective effects of crocin via antioxidant activities in HT22 cells and in mice with Alzheimer's disease. Int J Mol Med 43: 956 - 966.

https://doi.org/10.3892/ijmm.2018.4032

Wang X, Kim JR, Lee SB, Kim YJ, Jung MY, Kwon HW, Ahn YJ. 2014. Effects of curcuminoids identified in rhizomes of Curcuma longa on BACE-1 inhibitory and behavioral activity and lifespan of Alzheimer’s disease Drosophila models. BMC Complement Alt Med 14: 1 - 14.

https://doi.org/10.1186/1472-6882-14-88

Wang X, Miao Y, Ni J, Wang Y, Qian T, Yu J, Liu Q, Wang P, Yi S. 2018. Peripheral nerve injury induces dynamic changes of tight junction components. Front Physiol 9: 1 - 10.

https://doi.org/10.3389/fphys.2018.01519

Warrier PK, Nambiar VPK, Ramankutty C. 1994. In Indian Medicinal Plants 2, Ed. 1rd, Longman, Orient: South Asia.

Watson K, Hatcher D, Good A. 2019. A randomised controlled trial of lavender (Lavandula angustifolia) and lemon balm (Melissa officinalis) essential oils for the treatment of agitated behaviour in older people with and without dementia. Complement Ther Med 42: 366 - 373.

https://doi.org/10.1016/j.ctim.2018.12.016

Wattanathorn J, Jittiwat J, Tongun T, Muchimapura S, Ingkaninan K. 2011. Zingiber officinale mitigates brain damage and improves memory impairment in focal cerebral ischemic rat. Evid Based Complement Alt Med 2011: 429505. https://doi.org/10.1155/2011/429505

Weerachayaphorn J, Chuncharunee A, Mahagita C, Lewchalermwongse B, Suksamrarn A, Piyachaturawat P. 2011. A protective effect of Curcuma comosa Roxb. on bone loss in estrogen deficient mice. J Ethnopharm 137: 956 - 962. https://doi.org/10.1016/j.jep.2011.06.040

Weidner M, Sigwart K. 2001. Investigation of the teratogenic potential of a Zingiber officinale extract in the rat. Reprod Toxicol 15: 75 - 80. https://doi.org/10.1016/s0890-6238(00)00116-7

Wei P, Li R, Wang H, Ren Y, Sun H, Yang J, Wang P. 2012. Effect of curcumin on synapse-related protein expression of APP/PS1 double transgenic mice. China J Chinese Mat Med 37: 1818 - 1821.

https://doi.org/10.4268/cjcm20121226

WHO. 2012. Dementia cases set to triple by 2050 but still largely ignored. News Release. World Health Organization, Geneva. www.who.int/mediacentre/news/releases/2012/dementia_20120411/em/

WHO. 2013. Priority Medicines for Europe and the World “A public health approach to innovation” Alzheimer disease and other dementias. World Health Organization, Geneva. https://www.who.int/medicines/areas/priority_medicines/BP6_11Alzheimer.pdf

Wilkinson JM. 2000. Effect of ginger tea on the fetal development of sprague-dawley rats. Reprod Toxicol 14: 507 - 512. https://doi.org/10.1016/s0890-6238(00)00106-4

Wolk DA, Dickerson BC. 2019. Clinical features and diagnosis of Alzheimer disease-UpToDate. www.uptodate.com/contents/clinical-features-and-diagnosis-of-alzheimer-disease/print.
Wolkmer P, Silva CB, Paim FC, Duarte MMMF, Castro V, Palma HE, França RT, Felin DV, Siqueira LC, Lopes ST, Schetinger MRC, Monteiro SG, Mazzanti CM. 2013. Pre-treatment with curcumin modulates acetylcholinesterase activity and proinflammatory cytokines in rats infected with Trypanosoma evansi. Parasitol Int 62: 144 - 149. https://doi.org/10.1016/j.parint.2012.11.004

Wu JG, Wang YY, Zhang ZL, Yu B. 2015. Herbal medicine in the treatment of Alzheimer's disease. Chin J Integr Med 21: 102 - 107.

Xiong Z, Hongmei Z, Lu S, Yu L. 2011. Curcumin mediates presenilin-1 activity to reduce β-amyloid production in a model of Alzheimer's disease. Pharmacol Rep 63: 1101 - 1108. https://doi.org/10.1016/j.s1734-1140(11)70629-6

Yabin W, Kai K, Yue Q, Bingbing Z, Dong J. 2016. Radix curcumae extract on Alzheimer's disease mice induced by β-amyloid (Aβ25-35). Chin Archiv Trad Chin Med 34: 2905 - 2909.

Yang J, Dai Y, Xia YF, Huang WZ, Wang ZT. 2009. Alpinia katsumadai Hayata prevents mouse sepsis induced by cecal ligation and puncture through promoting bacterial clearance and downregulating systemic inflammation. Phytother Res 23: 267 - 273. https://doi.org/10.1002/ptr.2610

Yang WT, Zheng XW, Chen S, Shan CS, Xu QQ, Zhu JZ, Bao XY, Lin Y, Zheng GQ, Wang Y. 2017. Chinese herbal medicine for Alzheimer's disease: clinical evidence and possible mechanism of neurogenesis. Biochem Pharmacol 141: 143 - 155. https://doi.org/10.1016/j.bcp.2017.07.002

Yang Z, Zhang D, Ren J, Yang M, Li S. 2012. Acetylcholinesterase inhibitory activity of the total alkaloid from Zingiber officinale Roxb. on inhibiting amyloid β protein-induced apoptosis in PC12 Cells. Rejuvenation Res 15: 431 - 441. https://doi.org/10.1089/rej.2012.1389

Zhang C, Ji J, Ji M, Fan P. 2015. Acetylcholinesterase inhibitors and compounds promoting SIRT1 expression from Curcuma xanthorrhiza. Phytochem Lett 12: 215 - 219. https://doi.org/10.1016/j.phytol.2015.04.007

Zhang CM, Wang JD, Zhang YR, Fan PH. 2013. Chemical constituents of Curcuma xanthorrhiza Roxb. and their acetylcholinesterase inhibitory activity. J Shandong Uni 48: 20 - 23.

Zheng K, Dai X, Xiao N, Wu X, Wei Z, Fang W, Zhu Y, Zhang J, Chen X. 2017. Curcumin ameliorates memory decline via inhibiting BACE1 expression and β-amyloid pathology in 5x FAD transgenic mice. Mol Neurobiol 54: 1967 - 1977. https://doi.org/10.1007/s12035-016-9802-9