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Revisión / Review

Therapeutic potential of Zingiberaceae in Alzheimer's disease

[Potencial terapéutico de Zingiberaceae en la enfermedad de Alzheimer]

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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

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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 & Abbasi (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. (Apiaceae) (Gray *et al*., 2018), *Coriandrum sativum* L. (Apiaceae) (Cioanca *et al*., 2013), *Ilex paraguariensis* A.St.-Hil. (Aquifoliaceae) (Bortoli *et al*., 2018), *Panax ginseng* C.A.Mey. (Araliaceae) (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), *Convolvulus pluricaulis* Wall. ex Choisy (Convolvulaceae) (Kizhakke *et al*., 2019), *Evolvulus alsinoides* (L.) L. (Convolvulaceae) (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), *Punica 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.) Dun. (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 phytocomposites 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, antiemetic, antidiarrheal, antidiabetic, 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 (Sereniki & 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. katsumadae* 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 (Srividya *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 vulgare* 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. *Catimbium 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 katsumadae* Hayata *Alpinia katsumadai* Hayata (name probably misspelt) *Langas hainanensis* (K.Schum.) Merr. *Langas henryi* (K. Schum.) Merr. *Langas katsumadae* (Hayata) Merr.

Alpinia officinarum Hance	*Langas officinarum* (Hance) Farw.
Alpinia oxyphylla Miq.	*Amomum amarum* F.P.Sm. *Langas oxyphylla* (Miq.) Merr.
Alpinia rafflesiana Wall. ex Baker	*Langas rafflesiana* (Wall. ex Baker) Burkill

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-κβ) 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 $A\beta_{25–35}$, aiming to verify cognitive improvement. They induced neurotoxicity by intracerebroventricular injection of $A\beta_{25-35}$ and treated animals on the 14th to 21th 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 $A\beta_{25-35}$ 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'-acetoxyyeugenol acetate isolated from *A. galanga* on $A\beta_{25-35}$ 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'-acetoxyyeugenol 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'-acetoxyyeugenol acetate on neuroprotection (Table No. 2).

Table No. 2
***In vitro* and *in vivo* studies on *Alpinia* genus bioactivity**

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	Protocatechuic 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. katsumadae*) 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 $A\beta_{1-42}$, were identified. Kunming mice were treated with 5-(hydroxymethyl)furfural (15 and 150 μg/kg, intracerebroventricular) for five consecutive days after $A\beta_{1-42}$. 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 $A\beta_{1-42}$ 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)

(Liu *et al*., 2014).

Moreover, Shi *et al.* (2014) demonstrated neuroprotective effects of 5-(hydroxymethyl)furfural and three other small molecules compounds (protocatechuic acid, teuhetenone A, and tectochrysin) isolated from n-butanol *A. oxyphylla* extract on learning and memory impairments induced by $A\beta_{1–42}$ 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 $A\beta_{1–42}$ were also involved in the action mechanisms of 5-(hydroxymethyl)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, teuhetenone A, teuhetenone B, oxyphyllol B, nootkatone, and dibutyl phthalate (Table No. 2). ICR mice were injected with $A\beta_{1–42}$ 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 (H_2O_2)-induced apoptosis and oxidative stress in cultured PC12 cells were investigated by (Guan *et al*., 2006). It was demonstrated that H_2O_2-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 H_2O_2 in the presence or absence of Fe^{2+} 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 cardamonin (2′,4′-dihydroxy-6′-methoxychalcone), a compound isolated from *A. rafflesiana*. In interferon gamma (IFN-γ)/lipopolysaccharide (LPS)-stimulated microglial cell line BV2, cardamonin 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

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 antihisteric, 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_2O_2 oxidative stress-induced PC12 cell death after pretreatment for 6 h. This effect was mediated by the regulation of pkt-A, p38 mitogen-activated protein kinase kinase and oxidative status, 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. oxyphylla*. 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. oxyohylla*, *A. zerumbet*) or seeds or kernels (*A. hainanensis*, *A. oxyohylla*) 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'-acetoxyyeugenol acetate, 1'-1'-acetoxyyeugenol acetate, protocatechuic acid, 5-(hydroxymethyl)furfural, pinocembrin and (+)-catechin, kavalactones dihydro-5,6-dehydrokavain, and 5,6-dehydrokavain, cardamonin (2',4'-dihydroxy-6'-methoxychalcon), 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) Roscoe 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.

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* *Erndlia zerumbet* Giseke *Roscoea lutea* (Blanco) Hassk. *Roscoea nigrociliata* 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)

				function in Aβ peptide	
C. comosa	Rhizome	(3*S*)-1-(3,4-dihydroxyphenyl) -7-phenyl-(6*E*)-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 and ex vivo*	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 $A\beta_{1-42}$ using MTT reduction assay was investigated by Kim *et al*. (2007). The results indicated that the half maximal inhibitory concentration (IC_{50}) 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 H_2O_2-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_2O_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 $A\beta_{25-35}$ peptide dissolved in sterile saline and 3 μL aggregated $A\beta_{25-35}$ 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 $A\beta_{25-35}$ 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 (Kaewamatawong *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 (3*S*)-1-(3,4-dihydroxyphenyl)-7-phenyl-(6*E*)-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 $A\beta_{40}$ and $A\beta_{10}$, 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 IC_{50} 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 (IC_{50}) 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) (Kalaycıoğlu *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*.,

2013). 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 anticandidal, antibacterial, and antimetastatic 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-hydroxy-isogermafurenolide, α-curcumene, 3-hydroxy-6-methylacetophenone, 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-methylacetophenone 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 H_2O_2-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 H_2O_2 treatment condition than in an untreated H_2O_2 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-a, 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 H_2O_2-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, isoprocurcumenol, curcumenone, procurcumenol, 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 curcuminoids 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 curcuminoids, 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.

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 xanthorhiza* 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 missionis Wall. *Zingiber officinale* var. *cholmondeleyi* F.M. Bailey *Zingiber officinale* f. *macrorhizonum* (Makino) M.Hiroe *Zingiber officinale* var. *macrorhizonum* Makino *Zingiber officinale* f. *rubens* (Makino) M.Hiroe *Zingiber officinale* var. *rubens* Makino *Zingiber officinale* var. *rubrum* Theilade *Zingiber officinale* var. *sichuanense* (Z.Y.Zhu, S.L.Zhang & S.X.Chen) Z.Y.Zhu, S.L.Zhang & S.X.Chen *Zingiber sichuanense* Z.Y.Zhu, S.L.Zhang & S.X.Chen *Zingiber zingiber*
Zingiber ottensii Valeton	without synonym
Zingiber rubens Roxb.	without synonym
Zingiber zerumbet (L.) Roscoe ex Sm.	*Amomum sylvestre* *Amomum zerumbet* L. *Zingiber zingiber* T.Lestib. *Zingiber sylvestre*

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, galanal 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

	bud				
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

				decreasing in the levels of the amyloidogenic signals	
Z. officinale	Rhizome	Fermented extract with *Schizosaccharomyces pombe*	*In vivo*	Improvement in recognition memory and memory impairment	Huh *et al*., 2018
Z. officinale	Rhizome	Ethanolic extract	Clinical	Improvement of cognitive function	Saenghong *et al*., 2012
Z. ottensii	Rhizome	Crude extract	*In vitro*	AChE inhibition	Rungsaeng *et al*., 2013
Z. zerumbet	Rhizome	Zerumbone	*In vitro*	AChE inhibition	Bustamam *et al*., 2008

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

Cho *et al*. (2014) evaluated the effect of 70% ethanolic extract of *Z. mioga* flower buds on AChE enzyme by the bioautographic method. The authors compared it with the drug tacrine (used in Alzheimer's disease). *Z. mioga* extract showed an inhibition of 40% on AChE whereas tacrine *inhibited* 70%, making the anticholinesterase effect of this species evident (Table No. 6). The authors also investigated the effect of *Z. mioga* extract on memory using the novel object recognition test and Y-Maze test *in vivo*. The tests were performed in male ICR mice orally treated with the extract (200 mg/kg) 1 h prior to the beginning of the experiments. The results made evident that in novel object recognition test effects of *Z. mioga* extract were similar to those of donepezil (used in AD). In Y-maze test, the performances of treated mice were similar to control, suggesting that *Z. mioga* has potential to be a new functional food for cognition enhancement.

The suppressive effects of *Z. mioga* component, aframodial, on ROS generation and inducible proinflammatory gene expressions were investigated by Kim *et al.* (2005). Aframodial (20 μM) exhibited marked suppressive effects on 12-O-tetradecanoylphorbol-13-acetate-induced O_2-generation in HL-60 cells and LPS/IFN-γ-induced NO generation in RAW 264.7 cells (Table 6). Aframodial also strongly suppressed the stimulated HL-60 cell-induced mutagenicity in AS52 cells. The LPS-induced expression of inducible proinflammatory genes such as iNOS, NO synthase, IL-1β, IL-6, and granulocyte-macrophage colony-stimulating factor was abolished by aframodial.

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. montanun* 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.

The anti-inflammatory activity of *Z. montanun* was also evaluated by Han *et al.* (2005). The researchers isolated two compounds ((±)-*trans*-3-(3,4-dimethoxyphenyl)-4-[(E)-3,4-dimethoxysty-ryl]cyclohex-1-ene and (±)-*trans*-3-(4-hydroxy-3-methoxyphenyl)-4-[(E)-3,4-dimethoxy-styryl]cyclo-hex-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.

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 microemulsion 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-arthrosis, 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 astroglioma 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 astroglioma 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 $A\beta_{1-42}$-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 $A\beta_{1-42}$ 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 $A\beta_{1-42}$ 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).

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 that. The species 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. IC_{50} 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., 2011).

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 acute 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 LD_{50} 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. officinalis*, 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 $A\beta_{1-42}$, 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.

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