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Pre-Dominance Herbs Medicine against Alzheimer's Disease, In Vivo Studies: A Literature Review

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A B S T R A C T

Objective: Alzheimer's disease is a progressive, unremitting, neurodegenerative disorder that affects wide areas of the cerebral cortex and hippocampus. Abnormalities are usually first detected in the brain tissue involving the frontal and temporal lobes, then slowly progressing to other areas of the neocortex. The study aimed: to summarise pre-dominance herbs medicine with neuroprotective effects for Alzheimer's disease. Method: Searching at PubMed (during 2001-2021), the last research was performed in December 2001; relevant websites; and scanning of reference list of relevant articles. There were no language or publication restrictions. Search for keywords in MeSH (medical subject heading) with the words 'Alzheimer's disease, dementia, cognitive impairment, in vivo. Results: six plants medicine In vivo preclinical studies founds the medicinal plants have promising potential to prevent Alzheimer's disease.

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A B S T R A K

Objektif: Alzheimer yaitu penyakit degeneratif yang berhubungan dengan kerusakan saraf pada area *cerebral cortex* dan *hippocampus.* Gangguan ini dapat diketahui atau terdeteksi dari adanya perubahan pada lobus frontal dan temporal serta berkembang menuju *neocortex*. Tujuan: merangkum keunggulan tanaman obat herbal yang memiliki aktivitas neuroprotektif pada Alzheimer. Metode: pencarian data melalui PubMed (pada rentang tahun 2001-2021), pencarian dilakukan juga terkait penelitian yang relevan. Tidak ada batasan dalam pemilihan Bahasa. Pencarian dilakukan dengan memasukkan kata kunci pada MeSH (medical subject heading) berupa Alzheimer, dementia, gangguan kognitif, in vivo. Hasil: terdapat 6 tanaman herbal yang sudah dilakukan uji prekilins in vivo yang memiliki potensi menjanjika dalam pencegahan terjadinya Alzheimer.

INTRODUCTION

Alzheimer's disease is a progressive, unremitting, neurodegenerative disorder that affects wide areas of the cerebral cortex and hippocampus. Abnormalities are usually first detected in the brain tissue involving the frontal and temporal lobes, then slowly progressing to other areas of the neocortex at rates that vary considerably between individuals [1]. Alzheimer's is a condition whose pathogenesis can be caused by free radicals and neurotransmitter disturbances [2]. Alzheimer's can be caused by xenobiotic compounds (free radicals), which can reduce levels of glutathione (GSH), as well as disruption of communication between cells, which is the job of neurotransmitters, such as acetylcholine (Ach), gamma-aminobutyric acid (GABA), N-methyl-D -aspartate (NMDA), serotonin and histaminergic [2]. GSH plays a role in efforts to reduce the number of free radicals [3], free radicals will increase the occurrence of oxidative stress and can be determined by measuring the amount of lipid peroxidation results such as malondialdehyde (MDA) [4]. Apart from free radicals, there are other risk factors that cause Alzheimer's, such as age, gender, consumption of artificial sweeteners, reduced physical activity, genetics, stroke, vascular disease, smoking, alcohol, sleep disorders, depression and epilepsy [5]–[7].

The brain is an organ that can control the desire to understand, describe, imagine and even feel about what it was like from the past to the future. One part of the brain that plays a role in memory, learning, behaviour and controlling cognitive function is the hippocampus (HC) [8]. Memory is a process of remembering and then building or reconstructing every detail of an event, from when humans were kids to adults [9], [10]. here are two types of memory in the brain: explicit (declarative) and implicit (non-declarative). Explicit memory is used and linked to an object, for example, an event, place of occurrence and the people who were at the time of the incident; this memory involves parts of the hippocampus and cortex, while implicit memory is memory used in motor activity and a perception that involves cerebellum, striatum, and amygdala [9], [11]. Memory is divided into 3 (three): short-term, long-term, and working. Short-term memory reflects the ability of the human mind to store a certain amount of information temporarily. Long-term memory is stored for a long time, for example, memory and knowledge. Working memory (working memory) is used in terms of doing a plan [12].

Alzheimer's pathophysiology can be caused by the presence of Amyloid β (Aβ) plaques, formation of tau protein, oxidative stress [13], calcium homeostasis, exposure to heavy metals, disturbances in neurotransmitters [14].

a. Aβ plaques

Aβ plaque is a neurotoxic nerve protein that causes atrophy in dendrites and axons, impacting cell death. This protein is formed due to abnormalities in the proteolytic breakdown of amyloid precursor protein (APP) which plays a role in the pathogenesis of Alzheimer's. APP is a type 1 membrane protein with a cytoplasmic moiety. APP is synthesized in the endoplasmic reticulum (RE), transported through the secretary vesicles and broken down in the Golgi complex on the N and O glycosylation pathways. Within the Golgi complex, ɣ secretase and β secretase will be broken down through two metabolic pathways. The first pathway in the α pathway, APP, is hydrolyzed via α secretase, then proceeds through ɣ secretase; this process produces insoluble Aβ. The second pathway is through the β pathway. APP is hydrolyzed via β secretase (BACE1), then continues through ɣ secretase and produces insoluble Aβ. Under normal conditions, Aβ protein is not produced until APP is hydrolyzed in the α pathway. Some APP is hydrolyzed via the second pathway. Then the Aβ protein is released by the immune system. When mutations occur, such as in Lys670Asn/Met671Leu and Ala673Val, there will be interference with BACE1, causing APP to be hydrolyzed via the β pathway in the accumulation of insoluble Aβ and the development of Alzheimer's progression [1], [14].

b. Tau Protein

Tau protein contains NFT and plays a role in the occurrence of Alzheimer's pathological conditions. NFTs are formed from the aggregation of double-stranded filaments. Tau protein is a group of microtubule-binding proteins that function in stabilizing microtubules that play a role in innervation pathways in dendrites and axons [14]. Under normal conditions, the balance between microtubule phosphatase and kinase plays a role in maintaining the phosphorylation and dephosphorylation of tau. Under pathological conditions, an increase in kinase and a decrease in phosphatase results in hyperphosphorylation of tau protein in the form of NFT double-stranded filaments, which causes nerve degeneration and synapse dysfunction. NFTs are found in the HC, entorhinal cortex, amygdala, dorsal raphae, and Meynert's basal nucleus [15].

c. Oxidative Stress

Oxidative stress can cause damage to biomolecules, such as proteins, lipids, and deoxyribose nucleic acid (DNA). Oxidative damage to lipids is caused by the presence of reactive oxygen species (ROS) which produce lipid peroxides [16].

d. Calcium Homeostasis

Mattson et al., (1992) [17] first discovered calcium homeostasis on the pathogenesis of Alzheimer's and found that Aβ can increase the amount of intracellular calcium. There is a change in regulation of Ca^{2+}, allowing to increase the activity of calmodulin (CaM), then activate calcineurin (CaN), calmodulin dependent protein kinase II (CaMKII) and Ca^{2+} / calmodulin dependent protein kinase IV (CaMKIV) in the astrocyte inflammatory process, which will increase the risk of developing Alzheimer's . CaMKIV plays a role in the regulation of transcription of cAMP response element binding protein (CREB) in memory formation [18]. CaN can also increase the activation of T-cell signalling, which controls Aβ mediation in cognitive decline [19].

e. Metal Ion

Metal ions have a role in body functions, and some metal ions play a role in the central nervous system (CNS), nerve function, enzymatic activity and mitochondrial function, including zinc (Z), iron (Fe), copper (Cu) [14] and aluminium (Al) [20]. Zinc can cause tau hyperphosphorylation by activating kinases such as Raf/mitogen protein kinase kinase and inhibiting phosphatases such as PP2A, which will impact the formation of NFTs, resulting in nerve degeneration and synaptic disorders [21].

f. Acetylcholine (Ach)

Acetylcholine is the first neurotransmitter that was discovered. This neurotransmitter is used by all cholinergic neurons, which play a role in the peripheral and central nervous systems [22]. Acetyl-CoA is synthesized in the mitochondria. Choline is transported from the extracellular fluid into the neuron terminals via the membrane sodium-dependent choline transporter (CHT). Synthesized acetylcholine is transported from the vesicle cytoplasm via the vesicle-associated transporter (VAT), which is controlled by proton efflux. Release of the transmitter will occur if calcium channels in the membrane of the nerve end open, allowing an influx of calcium. At the moments intracellular calcium levels increase, the vesicle-associated membrane protein (VAMP) will interact with the synaptosome-associated protein (SNAP) so that VAMP can carry out its function, namely bringing the vesicles closer to the release area and interact with calcium ions so that fusion occurs between the vesicles and the cell membrane so that exocytosis can occur. And acetylcholine is released [23]. Cholinergic receptors are classified into nicotinic and muscarinic receptors. Nicotinic receptors play a role in learning and memory functions, located in the striatum, cortex, superior colliculus, lateral geniculate nucleus and cerebellum [15], [24]. Nicotinic transmission occurs at the neuromuscular junction. ACh released from motor nerve endings interacts with pentamer nicotinic receptor subunits to open channels so that Na+ can form an excitatory postsynaptic potential (EPSP). EPSP depolarizes the membrane, resulting in an increase in $Ca2^{+}$, which will cause an increase in CaN activity in the astrocyte inflammatory process [23].

Muscarinic receptors play a role in cognitive function, learning and memory, located in the HC, cortex and thalamus [15], [24]. Muscarinic receptors are GPCRs. The Gq protein will pair on the M1 and M3 muscarinic receptors to phospholipase C (PLC) and release the second messengers diacylglycerol (DAG) and inositol-1,4,5 triphosphate (IP3). DAG will modulate protein kinase C (PKC), an enzyme that plays a role in secretion where IP3 will trigger the release of $Ca2^{+}$ from intracells which affects the homeostasis of calcium $Ca2^{+}$ in the pathogenesis of Alzheimer's [23], [25].

g. Gamma-aminobutyric acid (GABA)

GABA is the primary inhibitory neurotransmitter in the CNS due to potential changes in the transmembranes that play a role in regulating responses and connecting communication signal activity in cortical nerves. The presence of GABAergic will control the process of regulating cognitive, memory, learning, and motor functions [26], [27]. Quevenco et al., (2019) [28] ABA imbalance is associated with increased Aβ accumulation and increased astrocyte reactivity in the brain through the GABA-permeable bestrophin 1 (BEST1) channel, which increases $Ca2^{+}$ activation from glia in the cerebellum which further disrupts synaptic transmission, thereby reducing LTP [29].

GABA transport is mediated by four GABA transporters, namely GABA transporter 1 (GAT1), GABA transporter 2 (GAT2), GABA transporter 3 (GAT3), and betaine-GABA transporter (BGT1). Within the neuron, the movement of GABA to the synaptic vesicles is mediated by the vesicle GABA transporter (vGAT). The GABA transporter is responsible for terminating GABAergic action at the GABA terminals, which play a role in the postsynaptic response by inhibiting presynaptic neurotransmitter release [30]. GAT1 and GAT3 are the two main transporters responsible for regulating GABA concentration in the central nervous system. GAT1 plays a role in the process of uptake of GABA and the process of regulation of GABA concentration in pyramidal cells, while GAT3 is present in astrocytes which plays a role in the regulation of GABA in extracellular; if there is increased activity, GAT3 will result in the accumulation of $Ca2^{+}$ astrocytes through $Na^{+}/Ca2^{+}$ exchange [31], increased $Ca2^{+}$ will cause a decrease in cognitive function through the CaMKII/IV pathway, external signal-regulated kinase/mitogen activated protein kinase (ERK/MAPK) and CREB [24]. Increased GAT3 also causes astrocytes to release ATP/adenosine [31], ATP and its reaction products adenosine, ADP and AMP (purinergic receptors) are released from synaptic vesicles [32]. In Alzheimer's there is a disturbance in the balance of converting ATP into energy in the nerves carried out by the mitochondria, causing an increase in ROS accumulation and inflammation and apoptosis occur, the inflammatory process is stimulated by activation of A1-3 adenosine receptors and activation of P2X7 receptors which will modulate the activity of PKC, MAPKs or glycogen synthase kinase 3 (GSK3) which can trigger the formation of Aβ and APP [33].

The hippocampus is a structure of the brain located in the cerebral cortex's temporal lobe and plays a role in learning and memory. The anatomy of the hippocampus consists of several parts, namely the cornu ammonis (CA) and dentate gyrus (DG), subiculum (SUB), and entorhinal area (EC); these arrangements are then called the hippocampal [34]. CA has four parts, namely CA1, CA2, CA3 and CA4 [35]. In humans and animals, the hippocampus plays an important role in the preparation of spatial memory, not as a place to store long-term memory but as an organizer so that the information obtained can be stored into long-term memory. Memory formation is based on the presence of long term potentiation (LTP). The formation of LTP is influenced by the presence of cells in the area of cornu ammonis 1 (CA1) and cornu ammonis 3 (CA3) [36]. The hippocampus also plays a role in transferring memory to be stored into long-term memory, called the consolidation process, and the memory will be in the neocortex [37].

Considering the etiologies of Alzheimer's, the use of combination therapy is expected to increase the effectiveness of treatment. One of the combination therapies used in the clinical stage of Alzheimer's treatment is the use of acetylcholinesterase inhibitors with antioxidants aimed at preventing the progression of Alzheimer's. The pharmacological intervention can use natural ingredients and must focus on biological activity on molecular targets [38], pathways of disease pathology development, cellular processes and individual responses.

METHOD

Searching at PubMed (during 2001-2021), the last research was performed in December 2001; relevant websites; and scanning of reference list of relevant articles. There were no language or publication restrictions. Search for keywords in MeSH (medical subject heading) with the words 'Alzheimer's disease, dementia, cognitive impairment, in vivo' was performed first. In the second part, the keywords were 'Herbal' and 'Phytotherapy'. Then, we tried to classify all data pertaining to the pharmacological effects on memory in different animal models, methods, mechanisms, etc. The summarized results comprised a total

of 6 plant species, herbs resources with anti Alzheimer's disease activities exhibited in various preclinical.

RESULTS AND DISCUSSION

Six herbs were identified to have effectiveness in the treatment of cognitive disturbance of AD. The main characteristics of the study are described in Table 1.

Turmeric

Turmeric is empirically used as hepatoprotection, anti-inflammatory, anticancer, antidiabetic, antimicrobial, antihyperlipidemic, cholera prevention, and antioxidant [39], [40]. The active compounds contained in turmeric are curcumin (77%), demethoxycurcumin (DMC 17%), and bisdemethoxycurcumin (BDMC; 3%) [41] besides that there are also carbohydrates (69.4%), protein (6.3%), fat (5.1%), minerals (3.5%), water (13.1%) [42]. Pre-clinical studies have shown that orally delivered curcumin has neuroprotective effects and has been found to reduce lipid peroxidation by maintaining the activities of antioxidant enzymes such as CAT, SOD, GPx, and GSH levels in rats exposed with neurotoxic compounds [43]. The ability of curcumin to increase the GSH levels is due to its affinity to induce the transcription of the mRNAs for the GSH biosynthetic genes [44]

Extract	*Dose (In vivo)*	Control (Positive)	Control (Negative)		Mechanism	Animal	Reference
Turmeric (*Curcuma longa* L.)	200 mg/kgBW	Citicoline	Trimethyltin	↕	SOD, CAT,GPx, GSH MDA	Rats Sprague Dawley	[43]
Greean tea (*Camellia sinensis*)	3,7x10^{-4}g/kgBW	Saline	$AlCl_3$	↕	SOD, CAT,GPx, GSH MDA	Rats Wistar	[45]
Bitter melon (*Momordica charantia*)	400 mg/kgBW	Donepezile	Scopolamine	↕	CAT,GPx, GSH AchE	Mice Swiss	[46]
Ginger root (*Zingiber officinale*)	1, 2, 4 g/kgBW	Saline	Aβ+$AlCl_3$	↕	CAT,SOD MDA, NF-Kb, IL-1β	Rats Sprague Dawley	[47]
Black paper (*Paper nigrum*)	100 mg/kgBW	Donepezile	Scopolamine	↕	CAT,SOD MDA	Rats Sprague Dawley	[48]
Ginkgo biloba	300 mg/kgBW 10 mg/kgBW, 20 mg/kgBW and 40 mg/kgBW		BCAA	↑	SOD, CAT, GSH, TNF-α, IL-1β, IL-6	Rats Wistar, Mice	[49], [50],[51]

Notes. Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx), Acetylcholinesterase (AchE), Nuclear factor kappa b (NF-Kb), Interleukin 1β (IL-1β), Alumunium chloride ($AlCl_3$), Body weight (BW).

Green tea

Active compounds in tea Green a flavonoid epigallocatechin-3-gallate (EGCG) 65%, epigallocatechin (EGC), epicatechin-3-gallate (ECG), epicatechin (EC), epigallocatechin-3(3'methyl)-gallate (EGCMG), catechin (C), gallocatechin-3-gallate (GTG). The phenolic group of catechins has a high antioxidant ability because it can react with reactive oxygen species (ROS), such as superoxide radicals, hydroxyl radicals, peroxyl radicals, nitric oxide, nitrogen dioxide, peroxynitrite, and free radicals lipids [52].

Another mechanism of antioxidant activity of tea catechins is as a chelator metal ions (such as copper(II) and iron(III)) by dihydroxyl and trihydroxyl groups form an inactive complex to prevent the generation of free radicals potentially damaging. In addition, catechins can scavenge free radicals by stable semiquinone free radicals, thus preventing deamination ability by free radicals [53], [54]

Bitter melon

Bitter melon grows in tropical and sub tropical regions of the world belonging to the family Cucurbitaceae. The active compounds in bitter melon consist of heteropolysaccharides (galactose, glucose, arabinose, ramnose, and mannose), proteins and peptides (momordin, momorcarins, MAP30 and lectins), terpenes and saponins, flavonoids (quercetin, kaempferol and isoramnetin) and phenolic compounds, as well as other components such as amino acids, sterols, essential oils, fatty acids, charantin, vitamin C, nicotinic acid, P alanine, gamma-aminobutyric acid [55], [56] . Active compounds that have neuroprotective activity are charantin [57] and flavonoids [58]. Tamilanban et al., (2018) [57] charantin compounds in bitter gourd can inhibit the activity of AChE, increase antioxidant levels in GSH, SOD, reduce MDA levels induced by scopolamine, besides that the use of bitter gourd can also improve spatial memory in rats induced with high fat diet . Flavonoid compounds (quercetin) act as antioxidants with parameters of oxidative stress (MDA, GPx, GSH, SOD and CAT) and inhibition of AChE in rat brains induced by oxaliplatin or using radiation [59].

Quercetin compound which is also a polyphenol, in in vitro and in silico studies conducted by Shimmyo, Kihara, Akaike, Niidome, & Sugimoto, (2008) [60] The OH group at position C-3 was significantly able to inhibit the activity of the BACE-1 enzyme, which is an enzyme in the formation of

Aβ; in vivo tests showed that quercetin can inhibit tau phosphorylation and inhibit NFT formation in mice [61]; in addition to the presence of a catechol group in ring B and an OH group at position three which can act as a free radical barrier [62], this antioxidant effect was demonstrated through nuclear modulation factors such as E2-related factor 2 (Nrf2), increase paraoxonase 2 (PON2) through the JNK/AP-1 pathway which indirectly inhibits the release of radicals superoxide [63].

Ginger

6-Gingerol, a phenolic compound, is the major pharmacologically active component in ginger rhizomes with diverse pharmacological activities, such as antitumor, anti-inflammatory, and antioxidant effects, etc [64] . Accumulated investigations have demonstrated that ginger positively affects memory function by anti-inflammatory effects in the treatment of Alzheimer's disease. The results from the Sprague Dawley rat model revealed that the operation + high dose (4 g/kg) groups of ginger root extract had lower levels of the nuclear factor-κB (NF-κB) and interleukin-1β (IL-1β) expression than the operation + moderate dose (2 g/kg) and operation + low dose groups (1 g/kg) . Further experiments in the hippocampus of Wistar rats revealed that *Zingiber officinale* extracts at a dose of 200 mg/kg significantly suppressed the inflammatory response of GFAP and IL-1β expression [47].

Black paper

Modern pharmacological research has been founded on broad biological activities, including antioxidant, antimicrobial, and insecticidal activities. Mahdy K et al. revealed that the total plant extracts of P. nigrum reduced oxidative stress and ameliorated neurodegeneration characteristics by significantly increasing Ach and serum total antioxidant capacity (TAC) and SOD and significantly decreasing AchE, MDA, and NO in AD-induced rats. The methanolic extract of P. nigrum (50 and 100 mg/kg) restored the activities of SOD and Catalase (CAT) and increased GPX activity in the hippocampus of a treated rats. β-caryophyllene can alleviate the Alzheimer-like phenotype by inhibiting inflammation and reducing the β-amyloid burden. Their research showed that β-caryophyllene prevented cognitive impairment in APP/PS1 mice by reducing the β-amyloid burden in both the hippocampus and the cerebral cortex. In addition, β-caryophyllene reduced the protein levels of COX-2 and the mRNA levels of the proinflammatory cytokines TNF-α and IL-1 in the cerebral cortex [65].

Ginkgo biloba

The extract of Ginkgo biloba leaves has been standardized to contain 24% flavonoid glycosides (containing quercetin, kaempferol, isorhamnetin ect.), 6% terpenoids and 5–10% organic acids [49]. Ginkgo biloba plays a role in neuroprotective, anti-inflammatory by increase expression of TNF-α, IL-1β, and IL-6 which is hippocampal proinflammatory [51], and Ginkgo biloba enhance antioxidant capacity [66]

REFERENCES

C. L. Masters, R. Bateman, K. Blennow, C. C. Rowe, R. A. Sperling, and J. L. Cummings, "Alzheimer's disease," *Nat. Rev. Dis. Prim.*, vol. 1, pp. 1–18, 2015, doi: 10.1038/nrdp.2015.56.

S. I. Ahmad, *Reactive oxygen species in biology and human health*. 2017.

H. J. Fan *et al.*, "The role of ginsenoside Rb1, a potential natural glutathione reductase agonist, in preventing oxidative stress-induced apoptosis of H9C2 cells," *J. Ginseng Res.*, no. xxxx, pp. 1–9, 2019, doi: 10.1016/j.jgr.2018.12.004.

M. Sinha, P. Bhowmick, A. Banerjee, and S. Chakrabarti, "Antioxidant role of amyloid β protein in cell-free and biological systems: Implication for the pathogenesis of Alzheimerdisease," *Free Radic. Biol. Med.*, vol. 56, pp. 184–192, 2013, doi: 10.1016/j.freeradbiomed.2012.09.036.

G. A. Edwards III, N. Gamez, G. Escobedo Jr., O. Calderon, and I. Moreno-Gonzalez, "Modifiable Risk Factors for Alzheimer's Disease," *Front. Aging Neurosci.*, vol. 11, no. June, pp. 1–18, 2019, doi: 10.3389/fnagi.2019.00146.

R. N. Kalaria *et al.*, "Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors," *Lancet Neurol.*, vol. 7, no. 9, pp. 812–826, 2008, doi: 10.1016/S1474-4422(08)70169-8.

M. P. Pase *et al.*, "Sugar- and artificially-sweetened beverages and the risks of incident stroke and dementia: A prospective cohort study Matthew," vol. 48, no. 5, pp. 1139–1146, 2017, doi: 10.1161/STROKEAHA.116.016027.Sugar-.

P. Zeidman and E. A. Maguire, "Anterior hippocampus: The anatomy of perception, imagination and episodic memory," *Nat. Rev. Neurosci.*, vol. 17, no. 3, pp. 173–182, 2016, doi: 10.1038/nrn.2015.24.

E. R. Kandel, Y. Dudai, and M. R. Mayford, "The molecular and systems biology of memory," *Cell*, vol. 157, no. 1, pp. 163–186, 2014, doi: 10.1016/j.cell.2014.03.001.

N. Ofen, L. Tang, Q. Yu, and E. L. Johnson, "Memory and the developing brain: From description to explanation with innovation in methods," *Dev. Cogn. Neurosci.*, vol. 36, no. June 2018, p. 100613, 2019, doi: 10.1016/j.dcn.2018.12.011.

A. I. Christou, R. C. Miall, F. McNab, and J. M. Galea, "Individual differences in explicit and implicit visuomotor learning and working memory capacity," *Sci. Rep.*, vol. 6, no. November, pp. 1–13, 2016, doi: 10.1038/srep36633.

N. Cowan, "What are the differences between long-term, short-term, and working memory? Nelson," *NIH Public Access*, vol. 6123, no. 07, pp. 323–338, 2009, doi: 10.1016/S0079-6123(07)00020-9.What.

K. Kumar, A. Kumar, R. M. Keegan, and R. Deshmukh, "Recent advances in the neurobiology and neuropharmacology of Alzheimer's disease," *Biomed. Pharmacother.*, vol. 98, no. December 2017, pp. 297–307, 2018, doi: 10.1016/j.biopha.2017.12.053.

P.-P. Liu, Y. Xie, X.-Y. Meng, and J.-S. Kang, "History and progress of hypotheses and clinical trials for Alzheimer's disease," *Signal Transduct. Target. Ther.*, vol. 4, no. 1, 2019, doi: 10.1038/s41392-019-0063-8.

A. Kumar, A. Aggarwal, A. Singh, and P. S. Naidu, "Animal Models in Drug Discovery of Alzheimer's Disease: A Mini Review," *EC Pharmacol. Toxicol.*, vol. 21, pp. 60–79, 2016.

[16] C. Peña-Bautista, M. Baquero, M. Vento, and C. Cháfer-Pericás, "Free radicals in Alzheimer's disease: Lipid peroxidation biomarkers," *Clin. Chim. Acta*, vol. 491, no. January, pp. 85–90, 2019, doi: 10.1016/j.cca.2019.01.021.

M. P. Mattson, B. Cheng, D. Davis, K. Bryant, I. Lieberburg, and R. E. Rydel, "β-Amyloid peptides destabilize calcium homeostasis and render human cortical neurons vulnerable to excitotoxicity," *J. Neurosci.*, vol. 12, no. 2, pp. 376–389, 1992, doi: 10.1523/jneurosci.12-02-00376.1992.

A. C. Mondal, "Molecular and Cellular Neuroscience Role of GPCR signaling and calcium dysregulation in Alzheimer ' s disease," *Mol. Cell. Neurosci.*, vol. 101, no. July, p. 103414, 2019, doi: 10.1016/j.mcn.2019.103414.

H. M. Abdul *et al.*, "Cognitive decline in Alzheimer's disease is associated with selective changes in calcineurin/NFAT signaling," *J. Neurosci.*, vol. 29, no. 41, pp. 12957–12969, 2009, doi: 10.1523/JNEUROSCI.1064-09.2009.

M. H. Yang *et al.*, "Reduction of aluminum ion neurotoxicity through a small peptide application – NAP treatment of Alzheimer's disease," *J. Food Drug Anal.*, vol. 27, no. 2, pp. 551–564, 2019, doi: 10.1016/j.jfda.2018.11.009.

Y. Huang, Z. Wu, Y. Cao, M. Lang, B. Lu, and B. Zhou, "Zinc binding directly regulates tau toxicity independent of tau hyperphosphorylation," *Cell Rep.*, vol. 8, no. 3, pp. 831–842, 2014, doi: 10.1016/j.celrep.2014.06.047.

T. H. Ferreira-Vieira, I. M. Guimaraes, F. R. Silva, and F. M. Ribeiro, "Alzheimer's disease: Targeting the Cholinergic System," *Curr. Neuropharmacol.*, vol. 14, no. 1, pp. 101–115, 2016, doi: 10.2174/1570159x13666150716165726.

J. A. Trevor, G. katzung Bertram, and K.-H. Marieke, *Examination & Board Review Pharmacology*, 11th ed. Lange Medical Book, 2015.

Y. Xu *et al.*, "Neurotransmitter receptors and cognitive dysfunction in Alzheimer's disease and Parkinson's disease," *Prog. Neurobiol.*, vol. 97, no. 1, pp. 1–13, 2012, doi: 10.1016/j.pneurobio.2012.02.002.

C. M. Norris *et al.*, "Calcineurin triggers reactive/inflammatory processes in astrocytes and is upregulated in aging and Alzheimer's models," *J. Neurosci.*, vol. 25, no. 18, pp. 4649–4658, 2005, doi: 10.1523/JNEUROSCI.0365-05.2005.

S. K. S. Bengtsson *et al.*, "GABA-A receptor modulating steroids in acute and chronic stress; relevance for cognition and dementia?," *Neurobiol. Stress*, vol. 12, no. September 2019, p. 100206, 2020, doi: 10.1016/j.ynstr.2019.100206.

V. Rodwell, W, B. David, A, B. Kathleen, M, K. Peter, J, and W. Anthony, P, *Harper's Illustrated Biochemistry*, 31st ed. McGraw-Hill Education, 2018.

F. C. Quevenco *et al.*, "GABA and glutamate moderate beta-amyloid related functional connectivity in cognitively unimpaired old-aged adults," *NeuroImage Clin.*, vol. 22, no. February, p. 101776, 2019, doi: 10.1016/j.nicl.2019.101776.

S. Jo *et al.*, "GABA from reactive astrocytes impairs memory in mouse models of Alzheimer's disease," *Nat. Med.*, vol. 20, no. 8, pp. 886–896, 2014, doi: 10.1038/nm.3639.

K. Govindpani, B. C. F. Guzmán, C. Vinnakota, H. J. Waldvogel, R. L. Faull, and A. Kwakowsky, "Towards a better understanding of GABAergic remodeling in alzheimer's disease," *Int. J. Mol. Sci.*, vol. 18, no. 8, 2017, doi: 10.3390/ijms18081813.

K. Boddum *et al.*, "Astrocytic GABA transporter activity modulates excitatory neurotransmission," *Nat. Commun.*, vol. 7, pp. 1–10, 2016, doi: 10.1038/ncomms13572.

I. D. Vainchtein and A. V. Molofsky, "Astrocytes and Microglia: In Sickness and in Health," *Trends Neurosci.*, vol. 43, no. 3, pp. 144–154, 2020, doi: 10.1016/j.tins.2020.01.003.

M. Cieślak and A. Wojtczak, "Role of purinergic receptors in the Alzheimer's disease," *Purinergic Signal.*, vol. 14, no. 4, pp. 331–344, 2018, doi: 10.1007/s11302-018-9629-0.

C. Destrieux, D. Bourry, and S. Velut, "Surgical anatomy of the hippocampus," *Neurochirurgie*, vol. 59, no. 4–5, pp. 149–158, 2013, doi: 10.1016/j.neuchi.2013.08.003.

R. L. Spencer and S. T. Bland, "Hippocampus and Hippocampal Neurons," *Stress Physiol. Biochem. Pathol.*, pp. 57–68, 2019, doi: 10.1016/b978-0-12-813146-6.00005-9.

M. A. Lynch, "Long-Term Potentiation and Memory," *Physiol. Rev.*, vol. 84, no. 1, pp. 87–136, 2004, doi: 10.1152/physrev.00014.2003.

B. J. Wiltgen *et al.*, "The hippocampus plays a selective role in the retrieval of detailed contextual memories," *Curr. Biol.*, vol. 20, no. 15, pp. 1336–1344, 2010, doi: 10.1016/j.cub.2010.06.068.

L. K. Caesar and N. B. Cech, "Synergy and antagonism in natural product extracts: When 1 + 1 does not equal 2," *Nat. Prod. Rep.*, vol. 36, no. 6, pp. 869–888, 2019, doi: 10.1039/c9np00011a.

A. Amalraj, A. Pius, S. Gopi, and S. Gopi, "Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives – A review," *J. Tradit. Complement. Med.*, vol. 7, no. 2, pp. 205–233, 2017, doi: 10.1016/j.jtcme.2016.05.005.

L. Shen, C. C. Liu, C. Y. An, and H. F. Ji, "How does curcumin work with poor bioavailability? Clues from experimental and theoretical studies," *Sci. Rep.*, vol. 6, no. February, pp. 1–10, 2016, doi: 10.1038/srep20872.

P. S. Chakraborty *et al.*, "Cassia fistula - A multicentric clinical verification study," vol. 5, no. 2, pp. 20–29, 2011.

S. Prasad, S. C. Gupta, A. K. Tyagi, and B. B. Aggarwal, "Curcumin, a component of golden spice: From bedside to bench and back," *Biotechnol. Adv.*, vol. 32, no. 6, pp. 1053–1064, 2014, doi: 10.1016/j.biotechadv.2014.04.004.

S. Yuliani, Mustofa, and G. Partadiredja, "The neuroprotective effects of an ethanolic turmeric (Curcuma longa L.) extract against trimethyltin-induced oxidative stress in rats," *Nutr. Neurosci.*, vol. 0, no. 0, pp. 1–8, 2018, doi: 10.1080/1028415X.2018.1447267.

D. A. Dickinson, K. E. Iles, H. Zhang, V. Blank, and H. J. Forman, "Curcumin alters EpRE and AP-1 binding complexes and elevates glutamate-cysteine ligase gene expression.," *FASEB J.*, vol. 17, no. 3, pp. 473–475, 2003, doi: 10.1096/fj.02-0566fje.

A. Jelenković *et al.*, "Influence of the green tea leaf extract on neurotoxicity of aluminium chloride in rats," *Phyther. Res.*, vol. 28, no. 1, pp. 82–87, 2014, doi: 10.1002/ptr.4962.

R. Pathakota, "Neuroprotective Effects of Momordica Charantia on Scopolamine Induced Alzheimer'S Disease," *World J. Pharm. Pharm. Sci.*, vol. 6, no. 04, pp. 2141–2155, 2017, doi: 10.20959/wjpps201704-9025.

G. F. Zeng, Z. Y. Zhang, L. Lu, D. Q. Xiao, S. H. Zong, and J. M. He, "Protective effects of ginger root extract on Alzheimer disease-induced behavioral dysfunction in rats,"

Rejuvenation Res., vol. 16, no. 2, pp. 124–133, 2013, doi: 10.1089/rej.2012.1389.

N. M. Mostafa, A. M. Mostafa, M. L. Ashour, and S. S. Elhady, "Neuroprotective effects of black pepper cold-pressed oil on scopolamine-induced oxidative stress and memory impairment in rats," *Antioxidants*, vol. 10, no. 12, pp. 1–15, 2021, doi: 10.3390/antiox10121993.

C. Shi, J. Liu, F. Wu, and D. T. Yew, "Ginkgo biloba extract in Alzheimer's disease: From action mechanisms to medical practice," *Int. J. Mol. Sci.*, vol. 11, no. 1, pp. 107–123, 2010, doi: 10.3390/ijms11010107.

C. M. H. Watanabe *et al.*, "The in vivo neuromodulatory effects of the herbal medicine Ginkgo biloba," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 98, no. 12, pp. 6577–6580, 2001, doi: 10.1073/pnas.111126298.

M. Kim, J. Hye, J. Lee, J. Han, T. Gon, and W. Kyung, "Phytomedicine Ginkgo biloba L . extract protects against chronic cerebral hypoperfusion by modulating neuroinflammation and the cholinergic system," *Phytomedicine*, vol. 23, no. 12, pp. 1356–1364, 2016, doi: 10.1016/j.phymed.2016.07.013.

O. Afzal *et al.*, "Green Tea Catechins Attenuate Neurodegenerative Diseases and Cognitive Deficits Obaid," 2022.

B. A. Sutherland, R. M. A. Rahman, and I. Appleton, "Mechanisms of action of green tea catechins, with a focus on ischemia-induced neurodegeneration," *J. Nutr. Biochem.*, vol. 17, no. 5, pp. 291–306, 2006, doi: 10.1016/j.jnutbio.2005.10.005.

C. s Yang, J. D. Lambert, and Sheming Sang, "Antioxidative and anti-carcinogenic activities of tea polyphenols," *Arch Toxicol*, vol. 83, no. 1, 2009, doi: 10.1007/s00204-008-0372-0.Antioxidative.

M. Bortolotti, D. Mercatelli, and L. Polito, "Momordica charantia, a nutraceutical approach for inflammatory related diseases," *Front. Pharmacol.*, vol. 10, no. MAY, 2019, doi: 10.3389/fphar.2019.00486.

S. S. Desai, "Development and validation of HPLC method for charantin from Momordica charantia Linn in development and validation of HPLC methods for marker compounds and bioactive as per ICH guideline," no. 12, pp. 70–98, 2014, [Online]. Available: http://shodhganga.inflibnet.ac.in/bitstream/10603/109888/12/12_chapter 6.pdf.

T. Tamilanban, V. Chitra, and K. Chitra, "Isolation, characterization, and memory enhancing activity of charantin using zebrafish model," *J. Pharm. Res.*, vol. 12, no. 4, pp. 648–655, 2018, [Online]. Available: http://jprsolutions.info/files/final-file-5ad557bc8b9b00.37082530.pdf.

A. Kale *et al.*, "Neuroprotective effects of Quercetin on radiation-induced brain injury in rats," *J. Radiat. Res.*, vol. 59, no. 4, pp. 404–410, 2018, doi: 10.1093/jrr/rry032.

M. Waseem and S. Parvez, "Neuroprotective activities of curcumin and quercetin with potential relevance to mitochondrial dysfunction induced by oxaliplatin," *Protoplasma*, vol. 253, no. 2, pp. 417–430, 2016, doi: 10.1007/s00709-015-0821-6.

Y. Shimmyo, T. Kihara, A. Akaike, T. Niidome, and H. Sugimoto, "Flavonols and flavones as BACE-1 inhibitors: Structure-activity relationship in cell-free, cell-based and in silico studies reveal novel pharmacophore features," *Biochim. Biophys. Acta - Gen. Subj.*, vol. 1780, no. 5, pp. 819–825, 2008, doi: 10.1016/j.bbagen.2008.01.017.

A. M. Sabogal-Guáqueta, J. I. Muñoz-Manco, J. R. Ramírez-Pineda, M. Lamprea-Rodriguez, E. Osorio, and G. P. Cardona-Gómez, *The flavonoid quercetin ameliorates Alzheimer's disease pathology and protects cognitive and emotional function in aged triple transgenic Alzheimer's disease model mice*, vol. 93. Elsevier Ltd, 2015.

A. W. Boots, G. R. M. M. Haenen, and A. Bast, "Health effects of quercetin: From antioxidant to nutraceutical," *Eur. J. Pharmacol.*, vol. 585, no. 2–3, pp. 325–337, 2008, doi: 10.1016/j.ejphar.2008.03.008.

L. G. Costa, J. M. Garrick, P. J. Roquè, and C. Pellacani, "Mechanisms of Neuroprotection by Quercetin: Counteracting Oxidative Stress and More," *Oxid. Med. Cell. Longev.*, vol. 2016, 2016, doi: 10.1155/2016/2986796.

P. Guo *et al.*, "Medicine-Food Herbs against Alzheimer's Disease: A Review of Their Traditional Functional Features, Substance Basis, Clinical Practices and Mechanisms of Action," *Molecules*, vol. 27, no. 3, 2022, doi: 10.3390/molecules27030901.

K. Mahdy, O. Shaker, H. Wafay, Y. Nassar, H. Hassan, and A. Hussein, "Effect of some medicinal plant extracts on the oxidative stress status in Alzheimer's disease induced in rats," *Eur. Rev. Med. Pharmacol. Sci.*, vol. 16, no. SUPPL. 3, pp. 31–42, 2012.

C. Ban *et al.*, "Characterization of Ginkgo biloba Leaf Flavonoids as Neuroexocytosis Regulators," pp. 1–15, 2020.

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