Biological Forum – An International Journal **15(5): 906-911(2023)**

ISSN No. (Print): 0975-1130
ISSN No. (Online): 2249-3239

Potential Bioactive Compounds to Treat Alzheimer's Onset: A review

Mohan Kumar B.S.[1]*, Suresh Kumar C.[2] and Narasimha Murthy V.N.[3]
[1]Department of Zoology, Maharani Cluster University, Bangalore, (Karnataka), India.
[2]Department of Botany, Maharani Cluster University Bangalore, (Karnataka), India.
[3]Department of Physics, Maharani Cluster University Bangalore, (Karnataka), India.

(Corresponding author: Mohan Kumar B.S.)*
(Received: 03 March 2023; Revised: 16 April 2023; Accepted: 20 April 2023; Published: 20 May 2023)
(Published by Research Trend)

ABSTRACT: Neurological disorders affecting aging individuals are characterized by neurodegeneration, posing a severe health risk. With the aging population increasing globally, the incidence of such diseases is escalating, creating a growing public health concern. Alzheimer's disease (AD) is the most prevalent cause of age-related dementia, and currently, no effective therapies exist to prevent, delay, or reverse its course. However, various studies have indicated that lifestyle changes, including diet, could postpone or prevent the onset of AD. Food is increasingly recognized as a crucial component in maintaining good health, preventing oxidative stress and chronic inflammation, and avoiding chronic degenerative diseases. Preprobiotics, nutraceuticals containing bioactive compounds with antioxidant and anti-inflammatory properties, and anti-protein aggregation molecules are essential in preventing and treating cognitive impairment and AD. This study focuses on natural plant-derived compounds and their derivatives, demonstrating neuroprotective activity and providing promise for treating and preventing AD.

Keywords: Alzheimer's disease, galantamine, huperzines, berberine, aporphine, polyphenols, flavonoids, curcumin, terpenoids, resveratrol.

INTRODUCTION

Alzheimer's disease is a progressive neurological disorder that affects memory and cognitive function as people age. It is responsible for 60-80% of all dementia cases, making it the fifth leading cause of death. AD gradually and permanently reduces memory, cognition, and the ability to perform daily tasks, requiring full-time care. While the disease is most common in people over the age of 65, it can also affect younger individuals. One of the most significant risk factors for AD is age, with research showing that the likelihood of developing AD dementia increases with age. Specifically, 3% of people aged 65-74, 17% of people aged 75-84, and 32% of those aged 85 or older have AD dementia (Garre-Olmo, 2018). Both environmental and genetic factors affect the pathogenesis of AD. Amyloid deposition and neurofibrillary tangles are two prominent pathologic hallmarks of the disease (Lacosta *et al.*, 2017). The accumulation of amyloid causes cognitive decline, which can lead to clinical dementia. The formation of amyloid plaques and neurofibrillary tangles involves the amyloid precursor protein and presenilin (Nizzari *et al.*, 2012). Mutations in both the amyloid precursor protein (APP) and presenilin can result in different production levels of amyloid-beta (Aβ) peptides and neuronal death, both of which are associated with Alzheimer's disease (AD) development. Interestingly, recent research has revealed that neuroinflammation is also a critical pathological factor in AD. The accumulation of extracellular Aβ protein and intracellular neurofibrillary tangles (NFTs) are two prominent features of AD (Lacosta *et al.*, 2017). NFTs are generated due to hyperphosphorylation of tau proteins in neurons and lead to neuronal cell death, primarily in the cerebral cortex and hippocampus of the brain. The deposition of aggregated Aβ protein in the synapses of AD patients can cause inflammation and oxidative stress (OS). Additionally, AD is characterized by excessive glutamatergic neurotransmission (Bukke *et al.*, 2020) and a depletion of cholinergic neurotransmission (Herholz *et al*., 2008).

The main and earliest symptom of Alzheimer's disease is difficulty in recalling memories, especially short-term memory. However, memory that does not rely on the hippocampus is usually unaffected. As the disease progresses, patients lose the ability to communicate and move, resulting in significant memory loss and confusion about time and place, requiring additional care (Garre-Olmo, 2018). To reduce the number of AD cases over the next 50 years, it is expected that therapeutic interventions delaying the onset or progression of the disease will be developed. Natural products have been identified as promising sources of potential drug leads for treating AD. Extracts or mixtures of natural products containing natural bioactive molecules have been used to develop potential therapeutic strategies for preventing or treating AD in animal models and clinical trials (Sawikr *et al.*, 2017). This review highlights the neuroprotective properties of plant-based natural products and their

therapeutic potential for controlling and treating AD through various mechanisms.

PATHOLOGY OF AD

AD is characterized by the presence of amyloid plaques and NFTs, which are the major pathological markers of the disease. Other features, including neuropil threads, dystrophic neurites, and related changes in the brain's structure, are also seen in AD. The loss of neurons and synapses leads to macroscopic atrophy due to these pathological processes. Mixed pathology, which includes vascular disease and Lewy bodies, is also common in older people with neurodegenerative dementia (Kotzbauer *et al.,* 2001). Lewy body pathology often coexists with familial AD, although the underlying mechanism is unknown.

Amyloid plaques are a collection of Aβ proteins, which are formed from APP metabolism and are either 40 or 42 amino acids long (Zhang & Xu 2007). The rate of insolubility and fibrillation is higher in Aβ42 than in Aβ40, resulting in more Aβ42 being present in the plaques. Amyloid accumulation is not always sequential, but usually starts in the isocortex and eventually affects subcortical regions. Amyloid plaques have a smaller impact on the entorhinal cortex and hippocampal formations than NFTs. In contrast, NFTs are primarily made up of hyperphosphorylated tau paired helical filaments (PHFs) and often begin in the medial temporal lobes before spreading to other areas of the brain (Goedert *et al*., 2006). Since NFT pathology is typically accompanied by neuronal and synapse loss, it is more closely connected to the clinical symptoms and severity of AD. On the other hand, Aβ pathology reaches a plateau early on in the disease's clinical phase

PATHOPHYSIOLOGY OF AD

AD was first described by Aloise Alzheimer, a German doctor, more than a hundred years ago, but its underlying mechanisms are still unknown. AD is characterized by symptoms such as memory loss, dementia, hallucinations, mobility dysfunction, spatial awareness impairment, delusion, apathy, and anomic aphasia (Garre-Olmo, 2018). Patients in the advanced stages of AD become increasingly dependent and cannot perform basic daily tasks. The behavioural changes in AD are indications of CNS dysfunction. Despite ongoing research, the cause of AD remains elusive, but some pathways have been identified at the cellular and tissue levels. One of the common symptoms of AD is the build-up of Aβ, a short peptide that is synthesized from naturally occurring APP and produces senile plaque APP (Zhang & Xu 2007). Aβ plays a role in synaptic plasticity, axonal growth, and modulates axonal growth under physiological conditions.

The development of tau tangles, which disrupt the structure of pyramidal neurons, is often accompanied by other pathological alterations. Tau proteins are involved in the stabilization of microtubules, which provide proper neuron function and synaptic signalling. However, increased phosphorylation of tau proteins can induce microtubule disassembly and the formation of tau tangles, a hallmark of AD (Salvadores *et al.*, 2020). In addition, increased concentration of Ca^{2+} ions (Supnet & Bezprozvanny 2010) caused by the aggregation of Aβ inside nerve cells can trigger cyclin-dependent kinase five, leading to microtubule depolymerization and disruption of the cytoskeleton (Henriques *et al.,* 2015). This can result in reduced neuron function and intracellular transport, along with inflammation, neuronal damage, and cell death caused by toxic aggregates in tau tangles that activate microglia (McMurray, 2000).

NATURAL PRODUCTS

According to research, certain components of the diet have been found to reduce the occurrence of AD, which has led scientists to explore the properties of bioactive molecules found in plants. Bioactive molecules are referred to as "secondary metabolites" of plants and various chemicals extracted from different plant parts, such as roots, rhizomes, leaves, and seeds, have been found to inhibit the development of harmful plaques and enhance cholinergic signaling (Williams *et al*., 2011). Foods rich in antioxidants are known to decrease oxidative stress in the brain, and plant-derived products have been found to have a wide range of pharmacological effects, making them a focus of interest for scientists who aim to develop molecules to treat various ailments. These findings have revealed that certain natural bioactive compounds may be useful for managing AD, and more information about these compounds is presented below.

Alkaloids are a type of chemical compounds that contain nitrogen and are commonly found in certain flowering plant families. While some plant species only have a few alkaloids, others such as Solanaceae, Papaveraceae, Amaryllidaceae, and Ranunculaceae have a high concentration of these substances (Ng *et al*., 2015). Furthermore, alkaloids are not limited to plants and can also be found in other organisms such as amphibians like the poison dart frog, rodents like the new world beaver, and even fungi like ergot. It is worth noting that some alkaloids have been developed into pharmaceuticals such as rivastigmine and galantamine, which are both alkaloid-based acetylcholinesterase inhibitors (AChEIs) approved by the FDA in the United States (Kaushik *et al*., 2018).

Galantamine is an alkaloid that can be found in certain plants such as *Galanthus caucasicus*, *Galanthus sworonowii*, and *Leucojum aestivum*, which are part of the Amaryllidaceae family. Galantamine works as a modulator of nicotinic acetylcholine receptors and has been used as an AChEI (Prvulovic *et al.,* 2010). Scientists have synthesized galantamine derivatives by linking them to memantine with various linkers to test their inhibitory activity against AChE and selectivity toward NMDAR binders and NMDAR subunit 2B (NR2B) (Moriguchi *et al*., 2004). Some synthesized compounds showed potent inhibitory activity against AChE and affinity for NR2B. Researchers also tested the neuroprotective activity of the compounds using a cell-based assay and found that three of the compounds

showed remarkable neuroprotective activity, inhibiting NMDA-induced neurotoxicity at subnanomolar concentrations (Scott & Goa 2000). One of the prepared compounds had an IC_{50} value of 0.28 nM.

Huperzines A and B are alkaloids obtained from Huperzia serrata, a medicinal herb in China. Huperzine A is a potent and reversible inhibitor of AChE and BuChE, with IC_{50} values of 0.82 and 74.43 nM, respectively. Huperzine B is also a reversible AChE inhibitor, with an IC_{50} of 14.3 μM (Bai *et al*., 2000). These compounds are often used in the development of more effective AChEIs. Furthermore, novel AChE inhibitors based on the structures of huperzine A and tacrine have been proposed. Additionally, various heterodimers containing donepezil dimethoxyindanone and huperzine A pyridone connected via a different methylene linker have been considered as potential AChE inhibitors for the treatment of AD (Yang *et al.*, 2013). New huperzine A and imine derivatives with an additional small substituted aromatic ring have demonstrated remarkable efficacy as hAChE inhibitors in the nanomolar range. The aromatic rings of the huperzine derivatives interact with AChE amino acid residues via π-π stacking. Additionally, new huperzine B compounds have been cleverly designed, where the huperzine B moiety is connected to the terminal aromatic ring by a tether chain, favoring interaction with the peripheral anionic site (PAS). Moreover, novel multitarget rhein-huprin hybrids have been created by connecting the hydroxyanthraquinone system of rhein to a heparin Y unit using various linkers (Patil *et al.*, 2020). These hybrids interact with both the active catalytic site (CAS) and AChE's PAS, resulting in a dual-site inhibitor.

Berberine has been extensively studied for its potential therapeutic applications in various diseases. Its ability to inhibit AChE and BuChE makes it a potential candidate for the treatment of AD. In addition, its antioxidant, anti-inflammatory, and neuroprotective properties may also contribute to its efficacy in treating cognitive impairment in AD. Berberine has also been shown to inhibit the voltage-dependent potassium current and exhibit an antagonistic effect against the NMDA receptor, which could contribute to its neuroprotective effect (Imenshahidi & Hosseinzadeh 2020). Furthermore, novel derivatives of triazole and berberine moieties have been synthesized, which show promising dual-site binding activity with TcAChE, suggesting their potential as AD therapeutics (Cai *et al.*, 2016).

Aporphine alkaloids are a type of isoquinoline alkaloids that have a tetrahydroisoquinoline substructure and are derived from *Menispermum dauricum*. Among these alkaloids, oxoisoaporphine and oxoaporphine are known to have various biological activities such as inhibiting telomerase, cholinesterase, and Aβ aggregation, as well as antioxidant activity. Synthetic derivatives of oxoaporphine are less potent than oxoisoaporphine as AChE inhibitors (Nabavi *et al.*, 2019). Molecular modeling studies showed that the azabenzanthrone moiety of oxoisoaporphine alkaloids can bind to Trp279 residue of the PAS of AChE via π-π stacking interaction (Wei *et al*., 2016). By connecting an aminoalkyl tether to oxoisoaporphine-tacrine hybrids, anti-aggregating compounds were produced that were potent inhibitors of self-induced Aβ aggregation. Additionally, eight nuciferine derivatives were produced by dealkylation and ring aromatization processes, two of which were discovered to be AChE inhibitors with IC_{50} values of 28 and 25 μg/mL in 1,2-dihydroxyaporphine and dehydronuciferine products.

Polyphenols known as flavonoids can be found in fruits and vegetables, particularly in plant families such as Polygonaceae, Rutaceae, and Leguminosae. These compounds have neuroprotective properties due to their polyphenolic nature, which allows them to scavenge free radicals such as superoxide radicals and hydrogen peroxide. The location and number of hydroxyl groups present in polyphenols affect their ability to scavenge free radicals. To further enhance their antioxidant properties, a new series of flavonoid derivatives has been developed (Syarifah-Noratiqah *et al*., 2018). Flavonoids can be divided into different subgroups based on the position of the B ring, the degree of unsaturation, and the oxidation of the C ring. Isoflavones have a 3-phenylchromen-4-one structure, with the B ring connected to position 3 of the C ring. Neoflavonoids, on the other hand, have a 4-phenylcoumarine structure, with the B ring connected to position 4 of the C ring. Flavones, flavonols, flavanones, flavan-3-ol or flavanols or catechins, and chalcones have the B ring connected to position 2 of the C ring, with only variations in the structural properties of the C ring.

Flavonoids have gained popularity as phytochemicals with medicinal effects due to their ability to reduce neuroinflammation in Alzheimer's disease (AD) by inhibiting proinflammatory transcription factors and activating transcription factors of antioxidant and anti-inflammatory (Prasanna & Upadhyay 2021). However, their bioavailability is usually low, and the parent flavonoids' average bioavailability is also limited. Despite these limitations, flavonoids can pass through the blood-brain barrier (BBB) because of their intense polarization, making them a potential natural treatment for preclinical AD models (Youdim *et al.*, 2004)

Flavones are a group of compounds that are commonly found in medicinal plants and have been shown to provide several health benefits. These compounds have been found to inhibit advanced glycation products (AGEs) and possess various biological activities such as antioxidant, anti-inflammatory, and neuroprotective effects (Shi *et al.*, 2020). Therefore, they have potential as agents for treating and preventing AD.

Isoflavones are naturally occurring compounds that can be found in leguminous plants, such as soybeans, and can also be extracted from microorganisms. They serve as precursors for the production of phytoalexins during interactions between plants and microbes (Gleason *et al.*, 2015). Isoflavones are known to inhibit the activity of enzymes such as acetylcholinesterase (AChE) and monoamine oxidase-B (MAO-B).

Flavanones, including hesperetin, are a notable subgroup of flavonoids that are plentiful in citrus fruits

like oranges, grapefruit, tangerines, lemons, and limes. These flavanones have been shown to possess properties such as free radical scavenging, anti-inflammatory, and blood lipid-lowering effects. As a result, the use of flavanones in the production of multitarget-directed ligands (MTDL) has increased (Barreca *et al.,* 2017).

Chalcones, which belong to the open chain flavonoids subgroup, are important since their basic flavonoid skeleton structure does not have ring C. Several vegetables, such as tomatoes and ladies' fingers, have a certain amount of chalcones. Due to their diverse range of biological effects, chalcones and their derivatives have attracted researchers' attention as anti-Alzheimer's agents (Thapa *et al*., 2021).

Neoflavonoids are a class of natural products that belong to the polyphenolic compounds. They have a 4-phenylchromen backbone without hydroxyl group substitution at position 2, unlike flavonoids which have a 2-phenylchromen-4-one backbone. Coumarin is a neoflavonoid found in various plants and has a wide range of therapeutic functions (Yun *et al.,* 2020). Molecular modeling studies have shown that coumarin interacts with AChE's peripheral anionic site (PAS) and acts as a potent inhibitor of AChE and inhibits Aβ aggregation (Singh *et al*., 2013). Researchers have prepared derivatives of coumarin with piperazine-based alkyl spacers connected to a new tacrine-coumarin hybrid, which showed substantial inhibitory action against EeAChE and moderate activity against EqBuChE, as well as anti-aggregation capabilities. In coumarin-based multitarget-directed ligands (MTDL) derivatives, the 6 and 7 positions of coumarin are associated with alkyl spacers of various lengths with a terminal diethylamino group, resulting in human AChE inhibition at nanomolar concentrations. These compounds exhibit remarkable inhibitory activity against Aβ42 self-aggregation, providing a neuroprotective effect and making them a possible disease modifier (Bajda *et al.,* 2011; Shi *et al*., 2020).

The compound known as curcumin has been used for hundreds of years as a treatment for various diseases. Its ability to reduce inflammation and act as an antioxidant make it effective in protecting the brain from neurological illnesses. Research shows that when combined with the Aβ peptide, which is responsible for cognitive deficits and oxidative stress, curcumin can reduce these symptoms in rats. In vivo and in vitro experiments demonstrate that curcumin has the potential to prevent the formation of amyloid plaques, which are linked to Alzheimer's disease. Curcumin achieves this by modulating various signaling pathways, including metal chelation, low cholesterol levels, lipid peroxidation, facilitated transcription, and reduced production of β-secretase enzyme. Furthermore, curcumin can also prevent protein aggregation by influencing the production of heat shock proteins (HSP), which act as molecular chaperones that prevent the formation of protein aggregates (Maiti *et al.,* 2014). Curcumin has been found to increase the formation of HSP in both in vivo and in vitro experiments. Additionally, it can inhibit the formation of harmful amyloid aggregates and proinflammatory cytokines in the brain.

On the other hand, the intraneuronal tau protein's accumulation, which is another significant cause of Alzheimer's disease. The β-sheet in tau protein can cause aggregation, but drugs like curcumin can inhibit this process. Curcumin's broad range of systemic effects make it a versatile and cost-effective treatment for neuronal dysfunction. In studies, curcumin has been shown to suppress the accumulation of Aβ in PC12 cells and human umbilical vein endothelial cells. It has also been found to exhibit antioxidant and anti-inflammatory properties in a Tg2576 mouse model of AD. Additionally, curcumin has been shown to have neuroprotective effects in primary neuronal cell culture against quinolinic acid-induced neurotoxicity. Pre-treatment with curcumin resulted in a significant decrease in neuronal nitric oxide synthase

Terpenoids are a group of substances made up of 2-methyl-1 or 3-butadiene, which are produced through biosynthesis from a combination of two or more isoprene units. Tanacetum parthenium is a plant that contains parthenolide, a physiologically active sesquiterpene lactone that has been shown to improve cognitive performance and reduce TNF-α and IL-6 levels in the cortex and hippocampus regions of rats. Recent research has demonstrated that the reduction of TNF-α, IL-6, and IL-17 in the brain's ipsilateral hemispheres through TLR4/NF-κB-mediated mechanisms controls neuroinflammation in intracerebral hemorrhage, which causes brain damage in rats (Ng *et al.,* 2018). Parthenolide has various inhibitory effects in multiple neuropathologies involving inflammation, which seem to be due to its NF-κB inhibitory action. However, clinical studies are required to confirm the neuroprotective effects of this sesquiterpene lactone in Alzheimer's disease (Seca *et al.,* 2017).

Artemisinin, a sesquiterpene lactone found in Artemisia annua, has been used to treat drug-resistant malaria and has shown potential neuroprotective effects in AD due to its anti-inflammatory properties. Its synthetic derivatives have also been found to pass through the BBB due to their lipophilicity. Carnosic acid and carnosol, both found in Rosmarinus officinalis, are natural diterpenes that can penetrate the brain and exhibit significant neuroprotective activity (Zhao *et al.,* 2020). However, clinical trials of Ginkgo biloba extracts have yielded mixed results in treating AD. While one study showed improvement in cognitive performance and functional capacities in patients with mild to moderate AD or vascular dementia, another study found that long-term use of Ginkgo biloba extract did not reduce the progression of AD in older individuals with memory complaints when compared to placebo (Shi *et al.,* 2010).

Resveratrol has been shown to have various pharmacological activities and has demonstrated neuroprotective effects in both in vitro and in vivo models of AD. Its ability to enhance nonamyloidogenic APP division and aid in the elimination of neurotoxic Aβ peptides is considered essential in preventing and

slowing down AD pathology (Sawda *et al.*, 2017). In addition to its antioxidant and anti-inflammatory properties, resveratrol's ability to modulate multiple cellular pathways, such as sirtuins and AMP-activated protein kinase, makes it a promising candidate for AD treatment (Li *et al*., 2012). Resveratrol has been shown to have multiple mechanisms of action that contribute to its neuroprotective effects in AD, including enhancing nonamyloidogenic APP division, reducing neurotoxic Aβ peptides, reducing neuronal cell loss through sirtuin activity, inhibiting ROS generation, increasing GSH and intracellular Ca21 in neurons, altering calcium-dependent second messengers, binding to Aβ plaques, and inhibiting AChE activity in in vitro cells (Yan *et al.*, 2020). These effects make resveratrol a promising candidate for further study as a potential therapeutic agent for AD.

CONCLUSIONS

Natural compounds have gained significant attention as potential therapeutic agents for the treatment of Alzheimer's disease due to their diverse pharmacological activities and relatively fewer side effects. The various natural compounds discussed in the article, including curcumin, omega-3 fatty acids, flavonoids, terpenoids, and resveratrol, have shown promising results in preclinical studies and clinical trials. However, further research is necessary to determine their effectiveness, safety, and optimal dosage for the treatment of Alzheimer's disease. Overall, natural compounds provide a promising avenue for the development of novel therapeutics for Alzheimer's disease and other neurodegenerative disorders.

FUTURE SCOPE

The future scope of work in the field of Alzheimer's disease and natural compounds includes further research and development of novel compounds from natural sources that could potentially be used in the treatment and prevention of the disease. This includes exploring the mechanisms of action of these compounds, optimizing their pharmacological properties, and conducting preclinical and clinical studies to evaluate their efficacy and safety. Additionally, the development of multitarget-directed ligands (MTDL) that can simultaneously target multiple pathways involved in the pathogenesis of Alzheimer's disease is a promising area of research (Bajda *et al.*, 2011). The use of advanced technologies such as molecular modeling and computer-aided drug design can aid in the rational design and optimization of such compounds (Kumar *et al.*, 2022). Overall, continued research in this area holds significant potential for the development of effective therapies for Alzheimer's disease.

REFERENCES

Bai, D. L., Tang, X. C. & He, X. C. (2000). Huperzine A, a potential therapeutic agent for treatment of Alzheimer's disease. *Current Medicinal Chemistry*, *7*(3), 355–374.

Bajda, M., Guzior, N., Ignasik, M. & Malawska, B. (2011). Multi-target-directed ligands in Alzheimer's disease treatment. *Current Medicinal Chemistry*, *18*(32), 4949–4975.

Barreca, D., Gattuso, G., Bellocco, E., Calderaro, A., Trombetta, D., Smeriglio, A., Laganà, G., Daglia, M., Meneghini, S. & Nabavi, S. M. (2017). Flavanones: Citrus phytochemical with health promoting properties. *BioFactors*, *43*(4), 495–506.

Bukke, V. N., Archana, M., Villani, R., Romano, A. D., Wawrzyniak, A., Balawender, K., Orkisz, S., Beggiato, S., Serviddio, G. & Cassano, T. (2020). The dual role of glutamatergic neurotransmission in Alzheimer's disease: From pathophysiology to pharmacotherapy. *International Journal of Molecular Sciences*, *21*(20), 7452.

Cai, Z., Wang, C. & Yang, W. (2016). Role of berberine in Alzheimer's disease. *Neuropsychiatric Disease and Treatment*, 2509–2520.

Garre-Olmo, J. (2018). Epidemiology of Alzheimer's disease and other dementias. *Revista de Neurologia*, *66*(11), 377–386.

Gleason, C. E., Fischer, B. L., Dowling, N. M., Setchell, K. D. R., Atwood, C. S., Carlsson, C. M. & Asthana, S. (2015). Cognitive effects of soy isoflavones in patients with Alzheimer's disease. *Journal of Alzheimer's Disease*, *47*(4), 1009–1019.

Goedert, M., Klug, A. & Crowther, R. A. (2006). Tau protein, the paired helical filament and Alzheimer's disease. *Journal of Alzheimer's Disease*, *9*(s3), 195–207.

Henriques, A. G., Oliveira, J. M., Carvalho, L. P. & da Cruz e Silva, O. A. B. (2015). Aβ influences cytoskeletal signaling cascades with consequences to Alzheimer's disease. *Molecular Neurobiology*, *52*, 1391–1407.

Herholz, K., Weisenbach, S. & Kalbe, E. (2008). Deficits of the cholinergic system in early AD. *Neuropsychologia*, *46*(6), 1642–1647.

Imenshahidi, M. & Hosseinzadeh, H. (2020). Berberine neuroprotection and antioxidant activity. In *Oxidative Stress and Dietary Antioxidants in Neurological Diseases* (pp. 199–216). Elsevier.

Kaushik, V., Smith, S. T., Mikobi, E. & Raji, M. A. (2018). Acetylcholinesterase inhibitors: beneficial effects on comorbidities in patients with Alzheimer's disease. *American Journal of Alzheimer's Disease & Other Dementias*, *33*(2), 73–85.

Kotzbauer, P. T., Trojanowski, J. Q. & Lee, V. M. Y. (2001). Lewy body pathology in Alzheimer's disease. *Journal of Molecular Neuroscience*, *17*, 225–232.

Kumar, N., Kumar, V., Anand, P., Kumar, V., Dwivedi, A. R. & Kumar, V. (2022). Advancements in the development of multi-target directed ligands for the treatment of Alzheimer's disease. *Bioorganic & Medicinal Chemistry*, 116742.

Lacosta, A.-M., Insua, D., Badi, H., Pesini, P. & Sarasa, M. (2017). Neurofibrillary tangles of Aβ x-40 in Alzheimer's disease brains. *Journal of Alzheimer's Disease*, *58*(3), 661–667.

Li, F., Gong, Q., Dong, H. & Shi, J. (2012). Resveratrol, a neuroprotective supplement for Alzheimer's disease. *Current Pharmaceutical Design*, *18*(1), 27–33.

Maiti, P., Manna, J., Veleri, S. & Frautschy, S. (2014). Molecular chaperone dysfunction in neurodegenerative diseases and effects of curcumin. *BioMed Research International*, *2014*.

McMurray, C. T. (2000). Neurodegeneration: diseases of the cytoskeleton? *Cell Death & Differentiation*, *7*(10), 861–865.

Moriguchi, S., Marszalec, W., Zhao, X., Yeh, J. Z. & Narahashi, T. (2004). Mechanism of action of galantamine on N-methyl-D-aspartate receptors in rat cortical neurons. *Journal of Pharmacology and Experimental Therapeutics*, *310*(3), 933–942.

Nabavi, S. M., Uriarte, E., Rastrelli, L. & Sobarzo-Sánchez, E. (2019). Aporphines and Alzheimer's disease: Towards a medical approach facing the future. *Current Medicinal Chemistry*, *26*(18), 3253–3259.

Ng, A., Tam, W. W., Zhang, M. W., Ho, C. S., Husain, S. F., McIntyre, R. S. & Ho, R. C. (2018). IL-1β, IL-6, TNF-α and CRP in elderly patients with depression or Alzheimer's disease: systematic review and meta-analysis. *Scientific Reports*, *8*(1), 12050.

Ng, Y. P., Or, T. C. T. & Ip, N. Y. (2015). Plant alkaloids as drug leads for Alzheimer's disease. *Neurochemistry International*, *89*, 260–270.

Nizzari, M., Thellung, S., Corsaro, A., Villa, V., Pagano, A., Porcile, C., Russo, C. & Florio, T. (2012). Neurodegeneration in Alzheimer disease: role of amyloid precursor protein and presenilin 1 intracellular signaling. *Journal of Toxicology*, *2012*.

Patil, P., Thakur, A., Sharma, A., & Flora, S. J. S. (2020). Natural products and their derivatives as multifunctional ligands against Alzheimer's disease. *Drug Development Research*, *81*(2), 165–183.

Prasanna, P., & Upadhyay, A. (2021). Flavonoid-based nanomedicines in Alzheimer's disease therapeutics: Promises made, a long way to go. *ACS Pharmacology & Translational Science*, *4*(1), 74–95.

Prvulovic, D., Hampel, H. & Pantel, J. (2010). Galantamine for Alzheimer's disease. *Expert Opinion on Drug Metabolism & Toxicology*, *6*(3), 345–354.

Salvadores, N., Gerónimo-Olvera, C. & Court, F. A. (2020). Axonal degeneration in AD: the contribution of Aβ and Tau. *Frontiers in Aging Neuroscience*, *12*, 581767.

Sawda, C., Moussa, C. & Turner, R. S. (2017). Resveratrol for Alzheimer's disease. *Annals of the New York Academy of Sciences*, *1403*(1), 142–149.

Sawikr, Y., Yarla, N. S., Peluso, I., Kamal, M. A., Aliev, G. & Bishayee, A. (2017). Neuroinflammation in Alzheimer's disease: the preventive and therapeutic potential of polyphenolic nutraceuticals. *Advances in Protein Chemistry and Structural Biology*, *108*, 33–57.

Scott, L. J. & Goa, K. L. (2000). Galantamine: a review of its use in Alzheimer's disease. *Drugs*, *60*, 1095–1122.

Seca, A. M. L., Silva, A. M. S. & Pinto, D. C. G. A. (2017). Parthenolide and parthenolide-like sesquiterpene lactones as multiple targets drugs: current knowledge and new developments. *Studies in Natural Products Chemistry*, *52*, 337–372.

Shi, C., Liu, J., Wu, F. & Yew, D. T. (2010). Ginkgo biloba extract in Alzheimer's disease: from action mechanisms to medical practice. *International Journal of Molecular Sciences*, *11*(1), 107–123.

Shi, D. H., Min, W., Song, M., Si, X. X., Li, M. C., Zhang, Z., Liu, Y. W. & Liu, W. W. (2020). Synthesis, characterization, crystal structure and evaluation of four carbazole-coumarin hybrids as multifunctional agents for the treatment of Alzheimer's disease. *Journal of Molecular Structure*, *1209*, 127897.

Shi, S., Wang, H., Wang, J., Wang, Y., Xue, X., Hou, Z., Yao, G. D., Huang, X. X., Zhao, H. & Liu, Q. (2020). Semi-synthesis and biological evaluation of flavone hybrids as multifunctional agents for the potential treatment of Alzheimer's disease. *Bioorganic Chemistry*, *100*, 103917.

Singh, M., Kaur, M., Kukreja, H., Chugh, R., Silakari, O. & Singh, D. (2013). Acetylcholinesterase inhibitors as Alzheimer therapy: from nerve toxins to neuroprotection. *European Journal of Medicinal Chemistry*, *70*, 165–188.

Supnet, C. & Bezprozvanny, I. (2010). The dysregulation of intracellular calcium in Alzheimer disease. *Cell Calcium*, *47*(2), 183–189.

Syarifah-Noratiqah, S.-B., Naina-Mohamed, I., Zulfarina, M. S. & Qodriyah, H. M. S. (2018). Natural polyphenols in the treatment of Alzheimer's disease. *Current Drug Targets*, *19*(8), 927–937.

Thapa, P., Upadhyay, S. P., Suo, W. Z., Singh, V., Gurung, P., Lee, E. S., Sharma, R. & Sharma, M. (2021). Chalcone and its analogs: Therapeutic and diagnostic applications in Alzheimer's disease. *Bioorganic Chemistry*, *108*, 104681.

Wei, S., Chen, W., Qin, J., Huangli, Y., Wang, L., Shen, Y. & Tang, H. (2016). Multitarget-directed oxoisoaporphine derivatives: anti-acetylcholinesterase, anti-β-amyloid aggregation and enhanced autophagy activity against Alzheimer's disease. *Bioorganic & Medicinal Chemistry*, *24*(22), 6031–6039.

Williams, P., Sorribas, A. & Howes, M. J. R. (2011). Natural products as a source of Alzheimer's drug leads. *Natural Product Reports*, *28*(1), 48–77.

Yan, Y., Yang, H., Xie, Y., Ding, Y., Kong, D. & Yu, H. (2020). Research progress on Alzheimer's disease and resveratrol. *Neurochemical Research*, *45*, 989–1006.

Yang, G., Wang, Y., Tian, J. & Liu, J. P. (2013). Huperzine A for Alzheimer's disease: a systematic review and meta-analysis of randomized clinical trials. *PloS One*, *8*(9), e74916.

Youdim, K. A., Shukitt-Hale, B. & Joseph, J. A. (2004). Flavonoids and the brain: interactions at the blood–brain barrier and their physiological effects on the central nervous system. *Free Radical Biology and Medicine*, *37*(11), 1683–1693.

Yun, Y., Yang, J., Miao, Y., Wang, X. & Sun, J. (2020). Synthesis and biological evaluation of 4-arylcoumarins as potential anti-Alzheimer's disease agents. *Bioorganic & Medicinal Chemistry Letters*, *30*(4), 126900.

Zhang, Y. & Xu, H. (2007). Molecular and cellular mechanisms for Alzheimer's disease: understanding APP metabolism. *Current Molecular Medicine*, *7*(7), 687–696.

Zhao, X., Li, S., Gaur, U. & Zheng, W. (2020). Artemisinin improved neuronal functions in Alzheimer's disease animal model 3xtg mice and neuronal cells via stimulating the ERK/CREB signaling pathway. *Aging and Disease*, *11*(4), 801.

How to cite this article: Mohan Kumar B.S., Suresh Kumar C. and Narasimha Murthy V.N. (2023). Potential Bioactive Compounds to Treat Alzheimer's Onset: A review. *Biological Forum – An International Journal, 15*(5): 906-911.