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Natural acetylcholinesterase inhibitors: A multi-targeted therapeutic potential in Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD), the main dementia type accounting for over 70 % of the entire dementia population and exhibits progressive decline in memory and executive function. AD pathology is characterized by amyloid fibrils and neurofibrillary tangles. Acetylcholinesterase (AChE), an enzyme involved in the hydrolysis of the neurotransmitter acetylcholine, consistently colocalizes with the amyloid deposits is characteristic of Alzheimer's disease and may contribute to the generation of amyloid proteins. AChE is a potent amyloid-promoting factor as compared with other associated proteins. AChE inhibitors play a vital role to prevent the formation of toxic oligomeric form of amyloid peptide. Recent studies have reported that acetylcholinesterase inhibitors (ChE-Is) are present in plants, fungi, and marine products. Some cholinesterase inhibitors, obtained from plant source such as rivastigmine, donepezil, and galantamine, used in the treatment of AD, offer an alternative approach to alleviate its symptoms by reducing Aβ.

Due to limited efficacy of currently available drugs for AD, there is huge potential of phytomedicines for the treatment of AD. Medicinal herbs and herbal drug preparations have traditionally been used to treat neurological disorders such as AD by exhibiting its anti-inflammatory and neuroprotective properties. Phytomedicines containing flavonoids, polyphenols, and other naturally occurring antioxidants crosses the blood-brain barrier and protect neurons from oxidative stress. As compared to synthetic drugs, phytomedicines have fewer side effects. Therefore, recent research is focused to explore the potential of phytomedicines and develop it as effective treatment for AD. In our review, we summarized the pathology of AD, amyloid-deposition, role of Acetylcholinesterase, potential of phytoconstituents with acetylcholinesterase inhibitory activity for AD treatment.

1. Introduction

Alzheimer's disease (AD) is a neurodegenerative condition caused by ageing and selective loss of neurons leading to impairment of learning and memory [1]. The presence of neurofibrillary tangles, senile plaques, and amyloid-beta peptide deposition around dystrophic reactive glial cells are neuropathological hallmarks in AD patients [2]. The primary component of senile plaques and significantly increased neurotoxin (amyloid-beta peptide) are linked to dysfunction of laminin, apolipoprotein E, and acetylcholinesterase (AChE) [3,4]. Co-localization of Aβ deposits with AChE has been observed in mature senile plaques, pre-amyloid diffused deposits, and cerebral blood vessels [5,6]. AChE activity in the AD brain is linked to the amyloid core of senile plaques, rather than the neuritic (senile plaques) [7]. Amyloidoses is a protein-misfolding disorders characterized by accumulation of insoluble fibrillar protein complexes in the extracellular component. There are 25

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forms of human proteins and polypeptides as amyloid deposits, including the prion protein (PrP) and 39-43-residue amyloid peptide in AD [8]. Choline acetyltransferase is a single-strand globular protein that catalyzes the biosynthetic reaction of the acetylcholine neurotransmitter, while acetylcholinesterase hydrolyzes acetylcholine into acetic acid and choline in the central nervous system (CNS) [[5,9–11]]. Majority of AChE molecules are present in tetrameric form AChE to neuronal cell membranes and involved in both cholinergic and non-cholinergic function in the central and peripheral nervous systems. Biochemical studies showed that neurotoxicity accelerated by AChE-Aβ complexes increases neurodegeneration as compared to amyloid-β peptides alone [11]. AChE catalytic activity is crucial for cholinergic neuron to return to its resting state after activation [12]. Inhibiting the activity of the AChE enzyme increases acetylcholine level, which is essential for transmission between brain cells by breaking it down into acetylcholine in the brain [13]. In AD patients, cortical cholinergic function is compromised due to decreased cerebral choline acetyltransferase production, which decrease the acetylcholine synthesis [14]. Several types of neurons deteriorate as AD progresses, however, forebrain cholinergic neurons suffer a profound loss and accompanied by steady decline of acetylcholine. ChAT, the acetylcholine-synthesizing enzyme, and AChE activity are vastly affected in AD [15]. Despite the overall decrease in the activity of AChE in the AD patient, current AD therapy mostly targets the inhibitors of AChE (AChE-I), which enhance cholinergic transmission, but have modest and transient therapeutic effects [16]. Although the distribution of AChE molecular forms specifically affects the AD brain, the pathophysiological relevance and subsequent ramifications of these alterations in AChE enzyme remain unknown even though it has been known for almost 50 years.

An increase in AChE enzyme levels is a hallmark of AD [17]. For Alzheimer's disease treatment, only a few synthetic medications are approved by the FDA, and it provides only symptomatic relief and have more side effects. Phytomedicine has been explored as an alternative approach to alleviate Alzheimer's symptoms [18,19]. Some plants contain phytochemicals (Curcumin, Resveratrol, Epigallocate chin-3-gallate, Morin, Delphinidins, Quercetin, Luteolin) that enhances brain function and counteract oxidative stress. The therapeutic potential of herbal remedies, including *Lavandula angustifolia, Ginkgo biloba*, and *Salvia officinalis* has been shown to improve cognitive performance in mild to moderate AD [20,21].

Certain plants contain natural compounds that improve brain function and fight oxidative stress. Herbal remedies like lavender, ginkgo biloba, and sage have been found to enhance cognitive abilities in people with mild to moderate Alzheimer's disease (AD) [22]. These natural compounds may offer a new and effective strategy to treat AD and delay its onset. Some promising plant-based treatments are currently undergoing trials for AD. Bacterial extracellular vesicles (BEVs) show promise for delivering therapies for neurodegenerative diseases worldwide because they can interact with cells effectively [23]. Researchers are also exploring vaccines as a new approach to treating AD [24], targeting key factors like tau protein and beta-amyloid plaques. Developing drugs that can target multiple aspects of the disease simultaneously is becoming more important. Exosomes, tiny vesicles that can cross the blood-brain barrier, are being investigated for their potential to deliver treatments directly to the brain for conditions like AD [25].

Our review article provides an overview of Alzheimer's disease, including its pathology, amyloid-deposition, and the role of acetylcholinesterase. It also highlights the potential of phytoconstituents with acetylcholinesterase inhibitory activity for the treatment of AD.

2. Materials and methods

Our study includes research and review articles published between 1986 and 2023. Web of Science, PubMed, Science Direct, Springer, Google Scholar, Taylor and Francis imprints, ChemSpider, Wiley, and NCBI (National Centre for Biotechnology Information) were used for retrieving the articles. Keywords for literature search were acetylcholinesterase inhibitors, phytocompounds, and Alzheimer disease. It was used alone or in various combinations during search. A total of 250+ original studies were selected, of which 181 were taken into consideration for the final summary Fig. 1. For all the species, Latin names were validated at The Plant List (2023); version 1.1.; http://www.theplantlist.org/.

3. Metabolic disease and Alzheimer's disease

The relationship between Diabetes Mellitus (DM) and Alzheimer's Disease (AD) is complex and involves various factors such as insulin resistance, abnormal glucose metabolism, lipid imbalances, obesity-related inflammation, and impaired insulin signaling [27]. While the exact role of these factors in cognitive impairment is not fully understood, they are believed to contribute to the progression of AD. Type-2 diabetes mellitus, in particular, has a strong correlation with AD, and individuals with diabetes have a higher risk of developing AD compared to non-diabetics [[28–31]]. Obesity is also a significant risk factor for AD, as it impairs brain function and increases the risk of cognitive decline [32,33]. Additionally, vascular pathology [16,34], genetic factors [[35–37]], and inflammatory processes are involved in the development of AD. The vascular system, including cerebral blood flow and endothelial function, plays a crucial role in AD pathology. Genetic variations, such as the APOE ε4 allele, are associated with an increased risk of developing AD. Inflammatory processes involving cytokines and microglia contribute to the progression of AD [[38–40]]. Furthermore, the amylin signaling pathway [41,42], Wnt signaling pathway [43,44], and chemokine receptors are implicated in AD pathogenesis. Overall, these factors collectively contribute to the development and progression of AD, highlighting the multifaceted nature of the disease.

3.1. AD pathology and signaling pathways

AD is multifactorial, complex, and prevalent neurological disorders worldwide. There has been extensive research in this field for the past five decades, however the exact mechanism of pathogenesis is still unknown. Obesity, dyslipidaemia, diabetes mellitus, cholinergic pathways, Interleukin Receptor-Associated Kinase 4 Signaling pathway, cholinergic system, and Wnt signaling pathways are associated with AD [45]. The current review aims to provide a comprehensive and descriptive explanation of these pathways to generate in-depth knowledge of their role in AD. Understanding the pathology of AD and its related alterations on various metabolic, hormonal, and molecular pathways, as well as targeted interventions, could be correlated with age-related cognitive decline [46].

Acetylcholinesterase (AChE) is primarily known for its role in breaking down the neurotransmitter acetylcholine, but it can also influence various cellular processes beyond cholinergic neuro transmission.

3.1.1. Interleukin Receptor-Associated Kinase-4 (IRAK-4) and microglia

AChE has been implicated in modulating the immune response and inflammation, which are relevant to microglia and IRAK-4 signaling [[47–49]]. AChE can affect the production and release of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and IL-6 [50,51]. In conditions involving microglial activation and neuroinflammation, AChE activity can influence the extent of the inflammatory response mediated by IRAK-4 and other signaling pathways Fig. 2 [52].

3.1.2. Mononuclear phagocyte system

The mononuclear phagocyte system consists of immune cells, including microglia and peripheral monocytes/macrophages, which play a role in immune surveillance and phagocytosis in the brain [54]. AChE activity can impact the function and behavior of microglia and

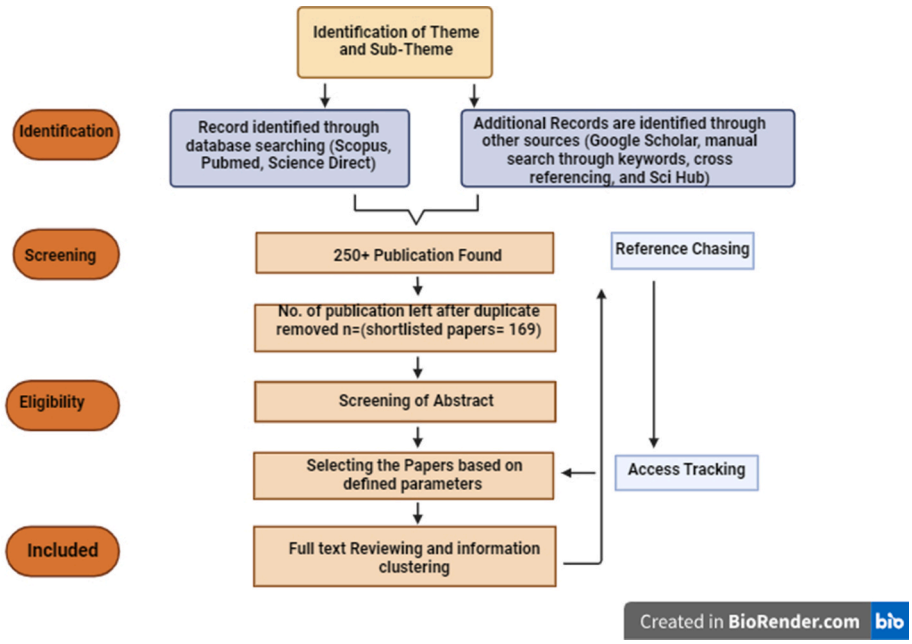

Fig. 1. Flow chart of the literature survey [26].

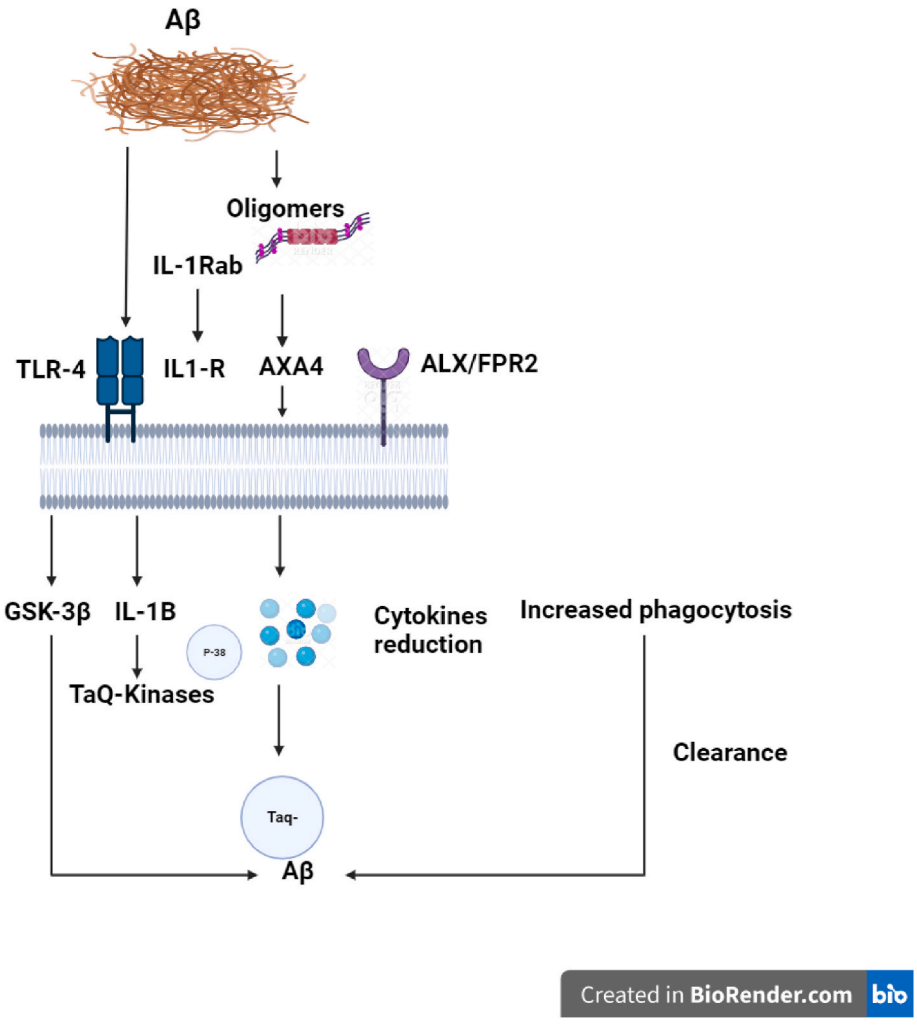

Fig. 2. Alzheimer's disease (AD) and inflammatory processes [53].

other phagocytic cells within this system [55]. By modulating AChE levels or activity, it may be possible to influence the immune response mediated by microglia and other mononuclear phagocytes [49].

3.1.3. Wnt signaling pathway

The Wnt signaling pathway is involved in various cellular processes, including neuronal development, synaptic plasticity, and neuroprotection Fig. 3 [56]. AChE can interact with the Wnt signaling pathway through its influence on acetylcholine levels. Acetylcholine can activate the Wnt pathway and promote neuroprotective effects [57]. Therefore, by regulating acetylcholine breakdown, AChE may indirectly impact Wnt signaling and its downstream effects on neuronal function and synaptic plasticity [58].

3.1.4. Amylin signaling dichotomy

The exact role of AChE in the amylin signaling dichotomy is not well-established. Amylin is primarily associated with metabolic processes and appetite regulation, although it has also been implicated in neuroprotection and neurotoxicity [60,61]. AChE's involvement in the amylin signaling dichotomy would likely depend on its interaction with acetylcholine and the downstream effects on amylin signaling pathways. However, the specific mechanisms of AChE's influence on amylin signaling in the context of neurodegenerative diseases like Alzheimer's disease are still being investigated.

AChE can influence the functioning of microglia, chemokine receptors, the mononuclear phagocyte system, and the Wnt signaling pathway through its impact on neurotransmission, immune response modulation, and cellular signaling. However, the precise mechanisms and interactions between AChE and these pathways are complex and require further research for a comprehensive understanding [61].

3.1.5. Autophagy, chaperone-mediated autophagy and ubiquitin/proteasome and/lysosome pathways in AD

The term "autophagy" encompasses a set of pathways that transfer cytoplasmic waste to lysosomes for degradation, including macroautophagy, chaperone-mediated autophagy, and microautophagy. These pathways play a vital role in maintaining cellular homeostasis by degrading aggregate-prone proteins and dysfunctional organelles like mitochondria. The nervous system primarily relies on autophagic pathways since post-mitotic neurons are unable to reduce the accumulation of undesirable proteins and organelles during cell division. However, as people become older and the brain's ability to do the functions decreases, this dependence could become vulnerable. It has been suggested that autophagic mechanisms protect against neurodegeneration [62].

The production and clearance of Aβ are significantly regulated by autophagy. Amyloid precursor protein (APP) is cleaved in autophagosomes during the autophagic turnover of APP-rich organelles, resulting in the production of Aβ peptides. Autophagolysosomes, or autophagosomes that have fused with lysosomes, are impeded in their maturation and retrograde movement towards the neuronal body in Alzheimer's disease (AD) [63]. As a result, there is a considerable accumulation of autophagic vacuoles in the neurons, which may be related to the dysfunction of ESCRT-III complex, and associated neurodegeneration [63,64].

Chaperone-mediated autophagy (CMA) is another proteolytic mechanism that facilitates the disintegration of intracellular proteins in lysosomes. CMA selectively targets substrate proteins to lysosomes and translocate them into the lysosomal lumen with the aid of chaperones and a particular protein translocation complex. The modulatory role of CMA in enzymatic metabolic processes and subsets of the cellular transcriptional programme is supported by its selectivity, which enables the timed degradation of certain proteins with regulatory objectives. Dysfunctional CMA has been implicated in severe human disorders such as neurodegeneration and AD [65].

Chaperone-mediated autophagy is a critical process in the degradation of certain proteins in neurodegenerative diseases (NDs), such as Parkinson's disease and Alzheimer's disease. The pathogenic process is aggravated by the formation of toxic protein aggregates in the central nervous system, which is a result of CMA dysfunction in NDs [66]. In

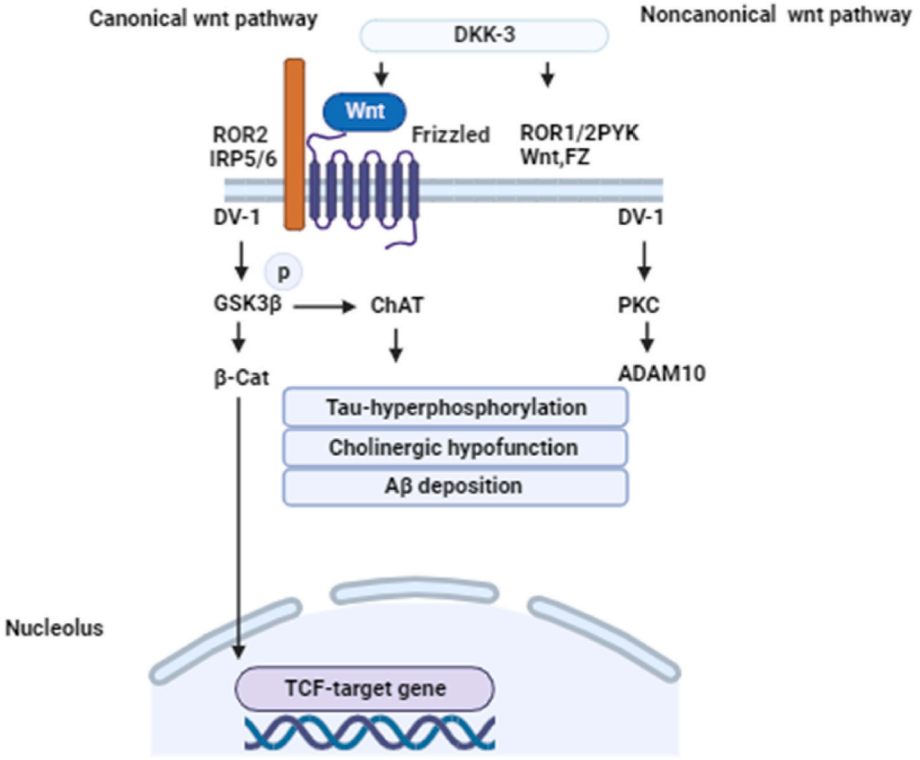

Fig. 3. Illustration of the Dickkopf 3 (Dkk3) defence against AD by the *Wnt* signaling pathway [59].

numerous models, strategies to increase CMA activity have demonstrated promise in promoting the degradation of ND-associated proteins and reducing ND phenotypes [67,68].

Reduced activity of the ubiquitin-proteasome system (UPS) is linked to Alzheimer's disease (AD). The accumulation of harmful substances linked to long-term memory impairment and synaptic plasticity is facilitated by this decline. Intracellular C-terminal membrane fragment b (CTFb) of the amyloid precursor protein (APP) has been identified as an early initiator of these disruptions, acting as a major toxic agent that negatively impacts neuronal function and grows to be a significant pathogenic factor for AD as well as a possible biomarker for AD patients [69].

3.2. Role AChE in metabolic syndrome X and AD pathogenesis

Insulin resistance, obesity, type 2 diabetes mellitus, hypertension, hyperlipidemias, metabolic syndrome X, and Alzheimer's disease are considered low-grade systemic inflammatory conditions. While some studies have shown elevated levels of inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and lipid peroxides, along with decreased levels of nitric oxide (NO), in the plasma of affected patients, other studies have not consistently confirmed these findings Fig. 4 [70,71]. This suggests the need for more reliable and straightforward markers of low-grade systemic inflammation. In this context, the observation that the activities of acetylcholinesterase enzymes are increased in the plasma and red blood cells of patients with insulin resistance, obesity, type 2 diabetes mellitus, hypertension, hyperlipidemias, metabolic syndrome X, and Alzheimer's disease is intriguing [[72–74]]. This finding suggests that these enzyme activities could potentially serve as markers of low-grade systemic inflammation present in these conditions. Acetylcholine (ACh), the substrate for these enzymes, has anti-inflammatory properties and serves as an important neurotransmitter [75]. Therefore, measuring the activities of acetylcholinesterase may indirectly provide insights into ACh concentrations in the brain, particularly in Alzheimer's disease [76]. Moreover, there is growing recognition of the potential involvement of the hypothalamus and other brain centers in the pathogenesis of insulin resistance, obesity, type 2 diabetes mellitus, hypertension, and metabolic syndrome X. Hence, measuring the activities of acetylcholinesterase may also reflect the role of the hypothalamus and other brain centers in the development of these diseases [73,74]. If acetylcholinesterase activities prove to be reliable and robust markers of inflammation, they could potentially be used to predict the development, prognosis, and response to treatment not only for insulin resistance, obesity, type 2 diabetes mellitus [71], hypertension, metabolic syndrome X, and Alzheimer's disease but also for other low-grade systemic inflammatory conditions such as schizophrenia, depression, cancer, atherosclerosis, and coronary heart disease [77].

Insulin Regulation: Acetylcholine, through its action on muscarinic receptors, can stimulate insulin secretion from pancreatic beta cells. Insulin is a hormone that helps regulate blood sugar levels, and dysfunction in insulin production or action is a characteristic feature of type 2 diabetes [78]. Disruptions in the cholinergic system or alterations in AChE activity may impact acetylcholine levels and subsequently influence insulin regulation [79]. Inflammation is a contributing factor to the development of insulin resistance, a condition in which cells become less responsive to the effects of insulin. While AChE is not directly involved in this pathway, alterations in acetylcholine levels, influenced by AChE activity, may impact the inflammatory processes involved in insulin resistance [80].

Autonomic Nervous System Dysfunction: Type 2 diabetes is associated with autonomic nervous system dysfunction, which affects the regulation of various bodily functions, including digestion, metabolism, and glucose homeostasis. Acetylcholine is a key neurotransmitter involved in the parasympathetic branch of the autonomic nervous system, which regulates resting and digestive functions. Changes in AChE activity or acetylcholine levels may contribute to autonomic dysfunction observed in type 2 diabetes [81].

While these potential links exist, it's important to note that type 2 diabetes is a complex metabolic disorder influenced by multiple factors, including genetics, lifestyle choices, AD, obesity, and insulin resistance. The specific role of AChE in the development or progression of type 2 diabetes requires further research to establish a clear and direct relationship [82].

Obesity is a chronic disease characterized by the excessive accumulation of body fat, which is associated with metabolic disorders such as low-grade chronic inflammation and insulin resistance. Detecting low-grade tissue-specific inflammation can be challenging, and therefore, the enzymatic activities of acetylcholinesterase (AChE) have been proposed as surrogate markers of systemic inflammation in obesity and other metabolic disorders. Acetylcholine (ACh), a neurotransmitter, plays a role in regulating neuropeptides and immune responses [77,83].

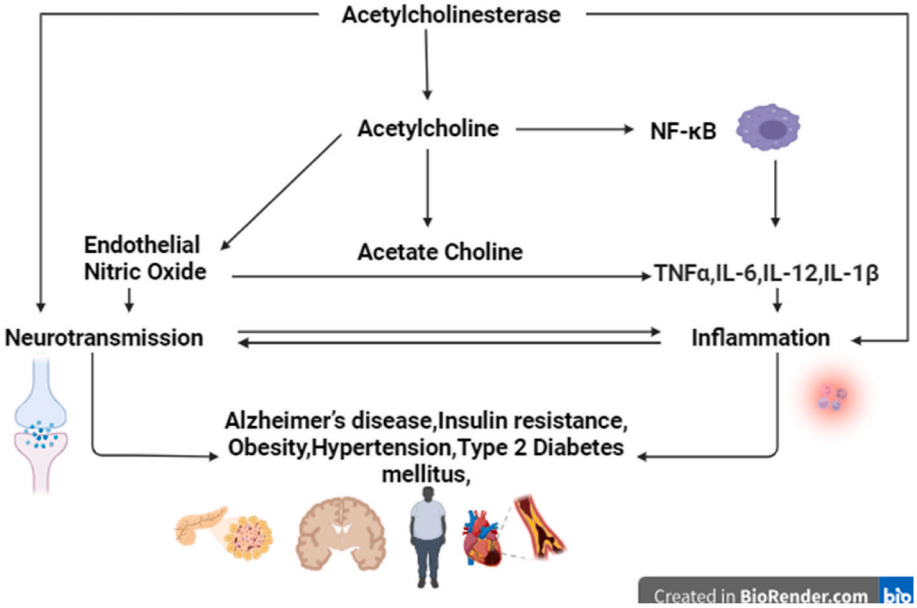

Fig. 4. The relationship between Acetylcholinesterase and inflammatory, cytokines, and various diseases [77].

AChE, by inactivating ACh, may contribute to inflammation. Studies indicate that visceral obesity and the metabolic syndrome are linked to increased sympathetic neural drive and impaired vagal signaling [77, 83]. The mechanisms connecting the metabolic syndrome with sympathetic activation involve various factors such as pro-inflammatory cytokines, leptin, hyperinsulinemia, non-esterified fatty acids, angiotensinogen, baroreflex impairment, and obstructive sleep apnea [84].

Alterations in AChE activity: Obesity has been associated with changes in AChE activity. Some studies suggest that obesity may lead to increased AChE activity, potentially resulting in higher breakdown of acetylcholine, a neurotransmitter involved in various functions, including memory and cognitive processes [85].

Acetylcholinesterase (AChE) is primarily associated with the breakdown of acetylcholine, a neurotransmitter involved in various physiological processes, including muscle contraction, cognition, and memory. While the direct link between AChE and T2D, obesity is not well-established, there are some potential connections worth mentioning.

3.3. Neurotoxicity induced by Aβ-AChE complex

Alzheimer's disease is characterized by the selective death of neurons, possibly caused by the accumulation of Aβ peptide and fibrils. AChE, a component of senile plaques, increases the formation of amyloid fibrils in the brain and Aβ-AChE complex is highly toxic [86,87]. Studies have shown that the Aβ-AChE complex induces neurotoxic effects in both in-vivo and in-vitro experiments. The brain of AD patients with excessive Aβ accumulates and precipitates in the form of insoluble amyloids, which cause neurotoxicity [88]. There is evidence of link between the Aβ-AChE complex and AD. The synaptic form of hAChE-S has been shown to be associated with plaques in AD brains. Only hAChE-S among human acetylcholinesterase variants has been reported to enhance Aβ fibrilization and deposition, as well as toxicity in in-vivo studies [89]. Transgenic mice models of hAChE-S/hAPPs have been used to study in-vivo implications of hAChE-S in AD pathology, and changes in cholinergic imbalance and neurotransmission have been observed in the presence of hAChE-S (double transgenic) [90]. Overexpression of hAChE-S in transgenic mice has been reported to cause senile dementia symptoms, such as dendritic branching, reduced cortical neuron numbers, learning and memory impairment, and increased uptake of high-affinity choline. Mature plaques in the cerebral cortex and Aβ were observed in hAChE-S, like AD. The presence of beta-helical forms and hAChE-S beta-sheet species in plaque cores was an important finding, and studies in animals have shown that hAChE-S is present in the brain's senile plaques [91,92].

3.4. Cholinergic system and AD

The cholinergic hypothesis of AD has led to the development of acetylcholinesterase inhibitors as a treatment for AD. These drugs prevent the breakdown of acetylcholine, which increases the amount of available acetylcholine in the brain, thereby improving cholinergic neurotransmission and cognitive function. However, these drugs only provide symptomatic relief and do not modify the underlying disease process. Galantamine is an acetylcholinesterase inhibitor acting as a modulator of nicotinic acetylcholine receptors, enhancing cholinergic neurotransmission, and reducing amyloid beta levels [140]. It has been shown to improve cognition and activities of daily living in patients with mild to moderate AD [93].

Other potential targets for the treatment of AD include butyrylcholinesterase, a cholinesterase enzyme that also breaks down acetylcholine, and muscarinic acetylcholine receptors. In addition, there is increasing interest in targeting the alpha 7 nicotinic acetylcholine receptor, which has neuroprotective effects by modulating inflammation and synaptic plasticity in the brain [110].

Natural products such as curcumin, resveratrol, and green tea extract have also been investigated for their potential to modulate cholinergic neurotransmission and reduce amyloid beta levels [95]. These compounds have antioxidant and anti-inflammatory effects, as well as it improves cognitive function in preclinical models of AD. However, clinical trials have not yet provided conclusive evidence of their efficacy in humans. Overall, the cholinergic system remains an important target for the development of new therapies for AD, both for its role in the pathogenesis of the disease and potential to improve cognitive function [96].

Several plant-based drugs like hyperforin and galantamine modulate ACh (acetylcholine) release in the central nervous system [136]. *In-vivo* studies showed the attenuation of amyloidal beta-induced spatial memory impairments and amyloidal beta neurotoxicity [138]. A derivative of hyperforin is tetrahydrohyperforin (THH). In a double transgenic mouse model of AD, it increases the brain's acetylcholinesterase activity, lowers the levels of cholinergic indicators that are associated with oxidative stress, amyloid plaques, and death, and protects cholinergic neurons Fig. 5 [97,98].

3.5. Cholinergic system and Wnt signaling pathway in AD

Wnt signaling pathway has been reported to play a critical role in the modulation of synaptic plasticity. Studies have shown that Wnt signaling regulates the clustering of ACh receptors (AChRs) at the neuromuscular junction, which is important for maintaining synaptic strength [93]. In addition, mutations in several components of the Wnt signaling pathway have been shown to induce impaired synaptic function, deficits in learning and memory, and accumulation of AChRs in *C. elegans* models [93]. These findings suggest that Wnt signaling is involved in regulating synaptic plasticity and the development of cognitive functions. Further research is required to fully understand the mechanisms of Wnt signaling pathway influencing synaptic plasticity and cognitive functions in AD [[26,94,95]].

3.6. Location of human AChE gene at chromosome number 7

Acetylcholinesterase (AChE) is a protein that plays a critical role in the cholinergic system by breaking down the neurotransmitter acetylcholine Fig. 6. In addition to its role in cholinergic neurotransmission [100,101], AChE has non-cholinergic roles, including tumorigenesis, amyloid fibril assembly, hematopoiesis, and thrombopoiesis. AChE is encoded by a gene located on chromosome 7 in humans [15,101], and abnormalities in this gene have been associated with several diseases, including Alzheimer's disease (AD). The loss of cholinergic neurons and the accumulation of amyloid plaques containing AChE have been observed in AD patients, leading to the development of cholinesterase inhibitors as a pharmacological approach to treat AD by raising the level of acetylcholine. Ongoing research is exploring the role of AChE in modulation of cholinergic function in various neurodegenerative and neurodevelopmental pathologies [102].

4. Amyloid precursor protein (APP) gene

The amyloid precursor protein is encoded by the APP gene, present in brain and spinal cord as well as other tissues. Its exact function is not well understood, but during the early stages of development, it plays a significant role to direct the migration of nerve cells. Enzymes break down the amyloid precursor protein into smaller peptides, including soluble amyloid precursor protein (sAPP) and amyloid-beta (Aβ) peptide, which are released outside the cell. Recent studies suggest that sAPP has growth-promoting properties and involve in the development of neurons in the brain, both pre- and post-birth. Additionally, the sAPP peptide has the potential to regulate other proteins by inhibiting their activity. The amyloid β peptide may also influence the capacity of neurons to change and adapt over time. Mutations in the APP gene, which has over 50 distinct variants, can lead to early-onset of

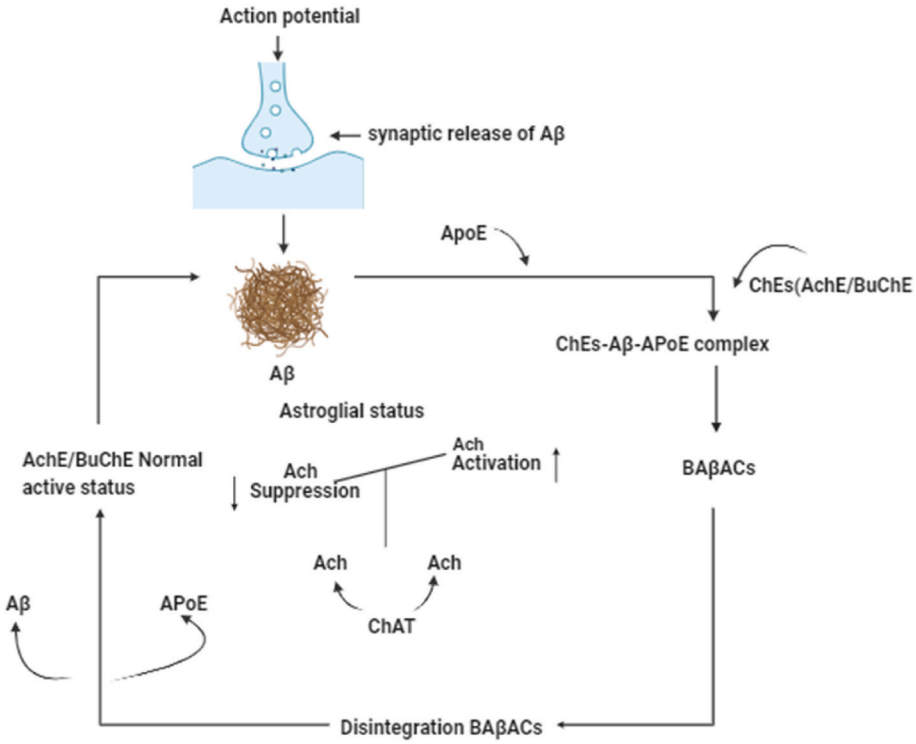

Fig. 5. A potential regulatory mechanism for cholinergic signaling by amyloid-β peptides [99].

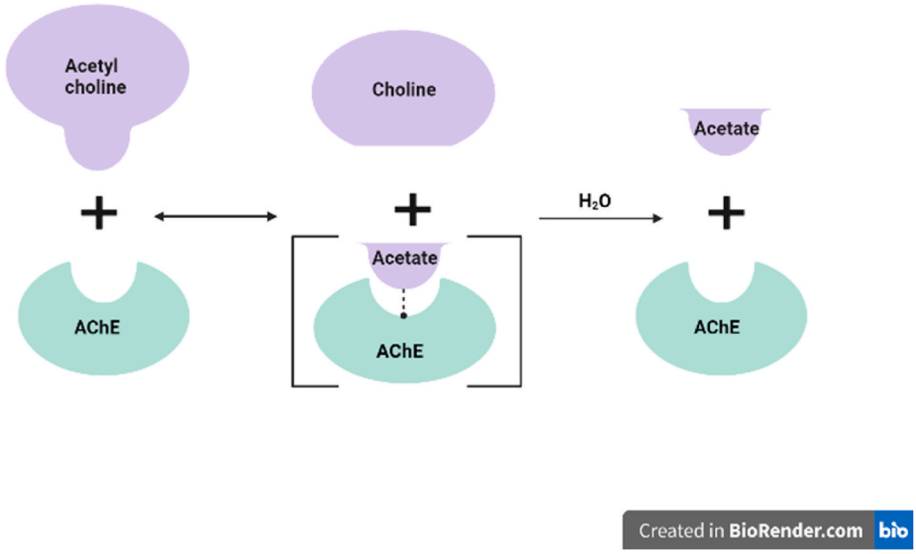

Fig. 6. The reaction of acetylcholinesterase hydrolysing acetylcholine into choline and acetate [26].

Alzheimer's disease, which occurs before the age of 65 [103]. However, less than 10 % of early-onset AD cases are caused by these mutations. Mutations in the APP gene can lead to the amplification of the amyloid β peptide or the production of a slightly longer and stickier version of the peptide, both of which can accumulate in the brain and form amyloid plaques, a hallmark of AD [59,104].

4.1. *Amyloidosis*

Amyloidosis is a pathological condition characterized by abnormal accumulation of amyloid in different tissues or organs. These proteins are typically stable, fibrous-like, insoluble and proteolytically resistant cross-beta super-20 structure. Amyloidosis can affect the normal functioning of tissues and cause changes in the body's organs [105]. It can be inherited or acquired, and amyloid fibrils can accumulate throughout the body or in specific regions of a single tissue. Different types of amyloidosis are categorized based on the primary peptide or protein that makes up the amyloid fibrils and the clinical symptoms. In addition to the main fibrillar component, amyloidosis deposits may also contain minor non-fibrillar components such as glycosaminoglycans (GAGs), apolipoprotein E (ApoE) and serum amyloid P components [106]. To date, 28 distinct human proteins have been identified as amyloids, with AD being one such example [107].

The "cholinergic hypothesis" of AD was developed based on initial neurochemical findings in AD brains, suggesting the impairment of acetylcholine metabolism. This theory proposes that individuals with

AD may have a reduction in cholinergic neurons in their brain or basal ganglia [108]. The accumulation of tau protein and amyloid-beta (Aβ) has been linked to cholinergic projection deficits in AD patients. Compensatory mechanisms may lead to an increase in Na + -dependent high-affinity choline absorption, as AChE and choline acetyltransferase activities decrease. Pre-synaptic α7 nicotinic acetylcholine receptors are critical for cognitive functions, and their levels increase and then decrease as AD progresses. Individuals with AD have lower levels of muscarinic acetylcholine receptors in their brains.

4.2. Amyloid plaque formation in AD

Amyloid plaques are composed of oligomers of a peptide containing approximately 40 amino acids, known as Aβ, which is generated from the amyloid-beta precursor protein. This protein contains 695 amino acids and is a cell membrane-bound receptor that has the amyloid-beta sequence in its extracellular domain [109]. The production of Aβ involves proteolytic cleavage of the amyloid-beta precursor protein by various secretases, leading to either an amyloidogenic or non-amyloidogenic pathway. Sorting nexin 17 (SNX17), an intracellular adaptor protein, chaperones Aβ as it travels to the membrane via endosomes, making it available for secretases to digest [110]. The initial proteolytic cleavage in the extracellular space by α-secretase produces soluble fragments, while β-secretase produces an insoluble fragment, determining the amyloidogenic pathway [111]. Cleavage of the β-amyloid precursor protein by α-secretase releases a soluble APP beta-protein (sAPPα) into the extracellular space [112]. This creates two subsequent fragments of the β-amyloid precursor protein, intracellular domain (AICD) which are released into the cytosol and subsequently into the extracellular space [113,114].

4.3. Amyloidogenic pathway

In the amyloidogenic pathway Fig. 7 β-site APP-converting enzyme 1 (BACE1) cleaves β-amyloid precursor protein (APP) at β-site, producing a shorter soluble amyloid precursor protein-β (sAPPβ) fragment and a remaining C-terminal fragment of 99 amino acids. The C-terminal fragment is then cleaved by γ-secretase, releasing two fragments of AICD and Aβ. The Aβ peptide aggregates into oligomers and fibrils, leading to the formation of amyloid plaques in the brain, a hallmark of Alzheimer's disease [114].

4.4. Non-amyloidogenic pathway

In the non-amyloidogenic pathway [115], APP is cleaved by α-secretase before β-secretase, resulting in the release of sAPPα and the p3 fragment, which is not involved in the formation of amyloid plaques. In contrast, in the amyloidogenic pathway, APP is first cleaved by β-secretase, followed by γ-secretase, resulting in the release of the Aβ peptide, which can aggregate to form amyloid plaques [110]. The longer Aβ peptide is considered to be the major neurotoxic component, while the sAPPα released in the non-amyloidogenic pathway is believed to have neuroprotective and neurotrophic effects. The balance between these pathways is crucial to maintain neuronal development and function. Any imbalance leads to the development of neurodegenerative disorders such as Alzheimer's disease [[105,112,114]].

5. Altered Aβ-AChE complexes induce neuronal loss in AD

Different molecular forms of AChE can exist, each with a unique expression pattern in various cell types and a distinct subcellular distribution, which likely reflects a specific physiological function of each form. There may be novel applications for AChE that are unrelated to cholinergic neurotransmission [115]. Both cholinergic and non-cholinergic brain regions contain AChE, but the functional importance of the non-cholinergic AChE is still unknown. The AChE species present in non-pathological and AD brains exhibit various characteristics. Even in pathological areas, the decline of AChE activity in the AD brain is not solely due to cholinergic reduction, as the density of AChE-rich fibers decreases in cortical areas of AD patients but is not correlated with the number of AChE-rich neurons [116,117]. Thus, an alteration in AChE levels may not reflect a change in cholinergic neurotransmission in the brain region. Not all molecular forms of AChE are equally affected in the AD brain. While most studies on the two main AChE subtypes in the mammalian brain, tetrameric and monomeric species with altered G4/G1 molecular form ratios, focus on neurochemical and neuroanatomical characteristics, the lighter species are conserved or even augmented in severely damaged cases of AD, whereas the G4 form is selectively lost in the AD brain. The AChE species that make up the majority of plasma forms are also more prevalent in AD plasma. Recent human investigations have demonstrated that AChE monomeric species are increased in the brains of transgenic mice (Tg2576) and the APPC100 mouse strain, which overproduces human Aβ in the brain. It has also been reported that amyloid-beta may have an impact on AChE [117]. AChE's action on Aβ aggregation leads to the creation of amyloid fibrils. AChE serves as a seed or nucleation factor, and it is absorbed into the process of Aβ aggregation at every stage. It also contributes to the elongation of the amyloid fibrils.

AChE act as a chaperone to facilitate the assembly of Aβ into oligomers with more structural complexity, such as amyloid fibrils, by shortening the lag phase of peptide aggregation Fig. 8 [117]. There are two possible mechanisms by which AChE may function in this process:

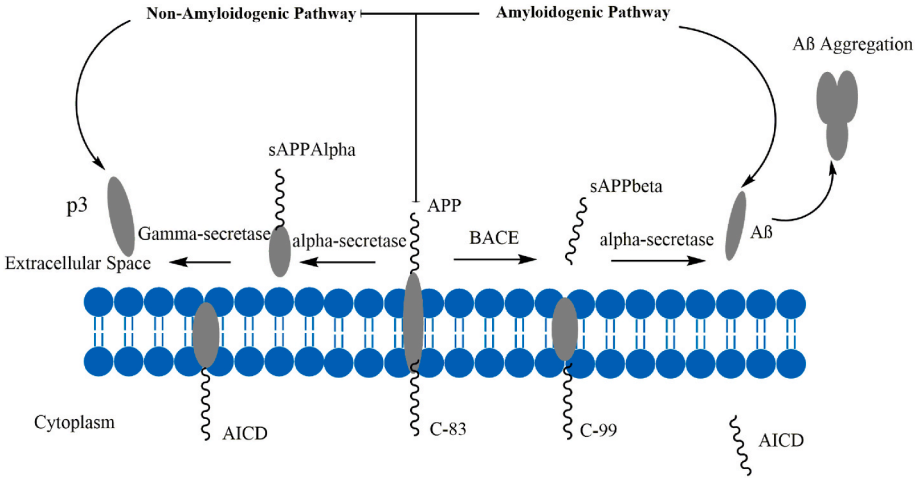

Fig. 7. Amyloidogenic and non-amyloidogenic pathways [105,153].

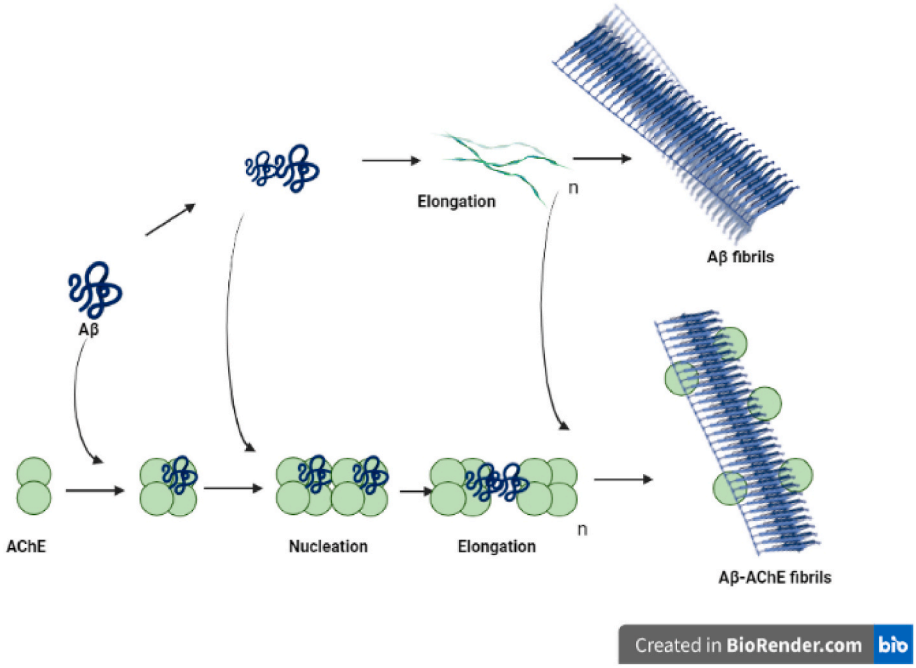

Fig. 8. AChE influences Aβ aggregation, which leads to the development of amyloid fibrils [108].

firstly, by increasing the seeds needed for the nucleation step, and secondly, by inducing fibril elongation [87]. AChE activity becomes evident when the enzyme is closely associated with amyloid deposits. Senile plaques in the brain of AD patients were described by Mesulam and Geula [170]. Using electron microscopy and a monoclonal antibody coated with gold particles have shown the growing amyloid fibrils in the AD patient. It demonstrated, how a small portion of the enzyme becomes closely associated with the amyloid fibril [118].

5.1. Evidence showing AChE involvement in amyloid deposition

The process of converting soluble Aβ into amyloid fibrils is nucleation-dependent and associated with the structural conversion of Aβ [[4,12,119]]. In vivo studies have demonstrated the binding of AChE to Aβ, with AChE binding to Aβ-coated wells at levels five to six times higher than that observed with BSA-coated wells, as determined by ELISA testing [120]. Several in vivo investigations have shown that AChE promotes Aβ aggregation and amyloid fibril production. AChE also accelerates the deposition of Aβ [121]. Double-transgenic mouse model that overexpresses human APP and human AChE has shown the accumulation of larger plaques in transgenic mice compared to control animals, as well as cognitive impairment [122].

5.2. Modification in the expression and distribution of AChE in the AD brain

Expression and distribution of AChE are altered in the brains with AD lesions [4]. Decreased AChE activity has been observed in the cortex, amygdala, hippocampus, and nucleus basalis of Meynert, which are associated AD. Ratios of the altered forms of AChE changes with a decreased tetrameric globular G4 AChE form. Simultaneously monomeric Gi and asymmetric AChE forms are increased, although the latter typically make up a small portion of the total enzyme in the human brain. AChE co-localize with Aβ deposits in cerebral blood vessels, pre-amyloid diffuse deposits, and mature senile plaques [123]. The deposition of Aβ is a critical stage in AD-related neurodegenerative processes, and elements of senile plaques, including AChE, are likely to cause selective neuronal cell death, indicating a significant involvement in AD pathogenesis. In fact, the expression of AD is the primary distinguishing hallmark of degenerating neurons, and groups of neurons that do not possess choline acetyltransferase exhibit AD. The majority of cortical AD activity in the AD brain has likely accelerated Aβ's accumulation into amyloid fibrils, enhancing its toxicity [124].

5.3. The role of AChE in amyloid deposition in the AD brain

Reduction of ACh production and alterations of Aβ-AChE complexes leads to neuronal death in AD, which is a major contributor to cholinergic deficits in the brain [1]. These deficits, in turn affects AChR levels and lead to further downstream effects, including the synthesis of Aβ. It is believed that amyloidogenic process results from soluble Aβ-isoforms is relatively benign nucleation-dependent process as compared to Aβ aggregation into amyloid fibrils. This complex process involves multiple factors and pathways, and the understanding of its underlying mechanisms remains an active area of research in AD [57].

5.4. Structural motifs of AChE in amyloid formation in AD patients

Molecular dynamic methods have been used to simulate the binding of Aβ to catalytic subunit of AChE to identify the AChE motif that promotes Aβ fibril production. This investigation identified four possible sites. Site I covering the primary hydrophobic sequence exposed on the surface of AChE. H peptide, a 3.4 kDa polypeptide [116], has been shown by turbidity data to accelerate the production of Aβ fibrils. This location's ability to interact with cell membranes correlates with a hydrophobic AChE sequence. The AChE motif promoting Aβ fibril production is located at the tryptophan, a conserved amino acid residue in the PAS (peripheral anionic site) of the catalytic subunit of AChE. The active site at the bottom should be accessible to both PAS and effective therapeutic AChE inhibitors. The latter site enhances catalytic efficiency by temporarily binding ACh until it AChEs the acylation site and serve as connections between AChE and Aβ. Ligands that bind to PAS show efficacy by speeding up processes towards the acylation site. The polyamine caproctamine, binding to the peripheral anionic site of AChE has been developed as a non-covalent inhibitor of AChE [116].

5.5. AChE-Aβ complexes increase the neurotoxicity of Alzheimer's fibrils in vitro and in vivo

AChE-Aβ complex fibrils is neurotoxic, similar to amyloid fibrils is toxic to neuronal cells in culture. To explore this, studies have been conducted in cell cultures and in vivo with AChE-Aβ complexes and Aβ aggregates [125]. AChE-Aβ complexes significantly affects the behavior of cells as compared to Aβ aggregates. Recent in vivo comparisons of the neuropathological changes caused by human Aβ fibrils and AChE-Aβ complexes in rat hippocampus indicates that AChE-Aβ complexes cause a more severe response than Aβ fibrils alone. In vitro research reports that AChE substantially increases rat Aβ aggregation, and in vivo investigations reports AChE-Aβ deposits, which attracted endogenous Aβ peptide [126]. Furthermore, the presence of neurons expressing laminin around the AChE-Aβ deposits in vivo suggests that these deposits recruit endogenous Aβ peptide. Recent study supports the idea that AChE-Aβ complexes are more toxic than Aβ fibrils and AChE is responsible for some of the neurodegenerative changes observed in AD brains by increasing Aβ deposition. These findings are supported by various in vivo and *in vitro* investigations [116,126–128].

5.6. Role of phytomedicine in AD

Alzheimer's disease (AD) is a common form of dementia characterized by memory impairment and neurological symptoms. The Food and Drug Administration has approved (synthetic medications) only a limited number of treatments for Alzheimer's disease, which include angiotensin-converting enzyme inhibitors (donepezil, galantamine, and rivastigmine) and *N*-methyl D-aspartate receptor blockers (memantine). However, these treatments are focused on a single target and only provide relief from symptoms rather than modifying the disease [18,129]. They are also known to have negative effects, including nausea, vomiting, diarrhea, headAChE, dizziness, fatigue, muscle spasms, and insomnia. However Herbal medicine is being increasingly explored as an alternative approach to alleviate symptoms of Alzheimer's disease [129]. Certain plants contain phytochemicals that can enhance brain function, and their antioxidant properties (including flavonoids, beta-carotene, vitamin C, and vitamin E) can potentially counteract oxidative stress, which is believed to contribute to the pathophysiology of neurodegenerative diseases such as Alzheimer's. New effective therapeutic agents with fewer side effects are needed [129]. Although synthetic medications are routinely used, herbal medicines have gained attention for their benefits and minimal side effects. This article reviews the therapeutic effects of phytomedicines in the prevention and treatment of AD, with a focus on herbal remedies such as *Lavandula angustifolia, Ginkgo biloba, Melissa officinalis, Crocus sativus, Ginseng, Salvia miltiorrhiza*, and *Magnolia officinalis* [[18,129–131]]. The paper also discusses recent research on the protective and therapeutic effects of these herbal remedies on AD, and evaluates their potential as alternative treatments for the disease.

6. Acetylcholinesterase inhibitor drugs

Currently, the most commonly drugs used to treat Alzheimer's disease are acetylcholinesterase/cholinesterase inhibitors (ChE-Is). The first ChE-I to be approved for the symptomatic therapy of AD was tacrine, but it is no longer used due to hepatotoxicity. Currently available ChE-Is are donepezil, rivastigmine, and galantamine [130,131]. In addition, some natural phytocompounds such as Curcumin, Varenicline, Huperrtzine, Resveratrol, and Cycloastrageno have received FDA approval to treat Alzheimer's disease (Table 1).

6.1. Acetyl cholinesterase inhibitors from plants

The prevalence of Alzheimer's disease (AD) is increasing due to aging population, posing a significant threat to the health of elderly individuals. Despite the absence of an effective treatment for AD, pathophysiology of AD and potential therapeutic agents have been explored extensively. Natural products have gained significant attention due to their unique advantages. One such compound has the potential to become a multi-target drug by interacting with various targets related to AD [130,137]. Structural modifications can be made to enhance interaction and decrease toxicity. Hence, research on natural products and their derivatives for treating pathological changes in AD is crucial. The focus of most of the research discussed in this review is on natural compounds and their derivatives for AD treatment [88]. Natural products have been a focus of research for their potential as acetyl cholinesterase inhibitors (AChEIs), with several plant-derived compounds being identified as having AChEI activity [138]. Alkaloids are one of the most common groups of AChEIs found in plants, but other groups of compounds like sterols, flavonoids, terpenes, and glycosides have also been shown to inhibit AChE [139]. Some examples of natural products with AChEI activity include huperzine A, galantamine, physostigmine, and rivastigmine (Table 2).

6.2. Clinical study

Huperzine A and Galantamine have been used clinically to treat Alzheimer's disease (AD). Both drugs are effective to treat age-related memory impairment or dementia, but its cognitive effects on patients with moderate AD are inconclusive [140,141]. Salvia officinalis L. has shown to improve cognitive performance in patients with mild to moderate AD and attenuate cognitive impairment in patients with moderate to severe AD [142]. However, long-term efficacy, safety, and

Table 1
FDA approved plant based anti-Alzheimer's drugs
It has been reported that the AChE inhibitor drugs, physostigmine and donepezil inhibit AChE and induce Aβ polymerisation in AD [121]. The AChE present in the AChE-Aβ complexes has shown properties similar to those of senile-plaque-associated AChE. In fact, the enzyme associated with Aβ peptide has demonstrated higher Km and Vmax values than those observed by free enzyme [132,133].

Sl. no	Plant Name	Active Compound	Biological Activity	Clinical trails	FDA Approval (year)	Reference
1.	*Physostigma venenosum*	Rivastigmine	Inhibiting AChE in the cortex and hippocampus region	–	2000	[131, 134]
2.	*Lycoris radiata*	Galantamine	Reversible inhibition of AChE and allosteric potential of nicotinic Ach receptors	–	2001	[135]
3.	*Cytisus laburnum*	Varenicline	Acetylcholine receptor	Phase 3	2006	[131,
4.	*Huperzia Spp*	Huperrtzine	AChE inhibitor commercialized as a dietary supplement for memory support, used to treat AD symptoms in China.	Phase 3	–	136]
5.	*Curcuma longa*	Curcumin	*Anti*-amyloidogenic, anti-inflammatory, *anti*-ChE, anti – secretase	Phase 3	–	
6.	*Vatis vinifera*	Resveratrol	Prevent cognitive impairment and associated oxidative stress by reducing plaque formation	Phase 3	–	
7.	*Astrogalus membranaceus*	Cycloastragenol	Anti-aging	–	2014	

Table 2
Examples of natural products with AChEI activity, class it belongs, plant source, family and IC 50 value.

Compound Name	Class Of Compound	Isolated from	Family	IC $_{50}$ (μM)	Reference
Ribalinine	Quinoline alkaloid	*Skimmia laureola*	Rutaceae	30.0	[149]
Methyl isoplatydesmine	Quinoline alkaloid	*Skimmia laureola*	Rutaceae	30.0	[149]
Leptomerine	Alkaloid	*Esenbeckia leiocarpa*	Rutaceae	2.5	[149]
Kokusaginine	Alkaloid	*Esenbeckia leiocarpa*	Rutaceae	46	[150]
Skimmianine	Furoquinoline alkaloid	*Zanthoxylum nitidum*	Rutaceae	8.6	[151]
N-methylasimilobine	Aporphine alkaloid	*Nelumbo nucifera*	Nelumbonaceae	1.5	[152]
Laurotetanine	Isoquinoline alkaloid	*Beilschmiedia alloiophylla & Beilschmiedia kunstleri*	Lauraceae	2.0–5.0	[153]
2-hydroxy-9-methoxyaporphine	Alkaloid	*Beilschmiedia alloiophylla & Beilschmiedia kunstleri*	Lauraceae	2.0–5.0	[151]
Liriodenine	Oxoaporphine alkaloid	*Beilschmiedia alloiophylla & Beilschmiedia kunstleri*	Lauraceae	2.0–5.0	[151]
Stylopine	Isoquinoline alkaloid	*Corydalis turtschaninovii*	Papaveraceae	15.8	[154]
Epiberberine	Isoquinoline alkaloid	*Corydalis turtschaninovii*	Papaveraceae	6.5	[155]
Pseudodehydrocorydaline	Isoquinoline alkaloid	*Corydalis turtschaninovii*	Papaveraceae	8.4	[154]
Pseudocopsitine	Isoquinoline alkaloid	*Corydalis turtschaninovii*	Papaveraceae	4.3	
Pseudoberberine	Isoquinoline alkaloid	*Corydalis turtschaninovii*	Papaveraceae	4.5	
Berberine	Benzylisoquinoline alkaloid	*Berberis darwinii*	Berberidaceae	0.44–0.80	[155]
(+)-Canadaline	Alkaloid	*Corydalis cava*		20.1	[151]
(+)-Canadine	Alkaloid	*Corydalis cava*		12.4	
Stepharanine	Protoberberine alkaloids	*Stephania venosa*	Menispermaceae	14.10	[198]
Cyclanoline	Protoberberine alkaloids	*Stephania venosa*	Menispermaceae	9.23	[156]
N-methyl stepholidine	Protoberberine alkaloid	*Stephania venosa*	Menispermaceae	31.30	
Taspine	Benzylisoquinoline alkaloids	*Magnolia x soulangiana*	Magnoliaceae	0.33	[157]
Galanthamine	Alkaloid	*Magnolia x soulangiana*	Magnoliaceae	3.2	[158]
Tacrine	Alkaloid	*Magnolia x soulangiana*	Magnoliaceae	0.22	[159]
Serpentine	Indole Alkaloid	*Catharanthus roseus*	Apocynaceae	0.775	[153]
Coronaridine	Indole alkaloid	*Ervatamia hainanensis*	Apocynaceae	8.6	[160]
Voacangine	Indole alkaloid	*Ervatamia hainanensis*	Apocynaceae	4.4	[160]
Xycoronaridine	Indole alkaloid	*Ervatamia hainanensis*	Apocynaceae	29	
19,20-dihydrotabernamine	Bisindole alkaloid	*Tabernaemontana divaricata*	Apocynaceae	0.227	[161]
19,20-dihydroervahanine A	Bisindole alkaloid	*Tabernaemontana divaricata*	Apocynaceae	0.071	[161]
Geissoschizine methyl ether	Alkaloid	*Uncaria rhynchophylla*	Rubiaceae	3.7	[162]
Uleine	Indole alkaloid	*Himatanthus lancifolius*	apocynacea	0.45	[163]
N-allylnorgalanthamine	Alkaloid	*Leucojum aestivum*	Amaryllidaceae	0.18	[158]
N-(14methylallyl)norgalanthamine	Alkaloid	*Leucojum aestivum*	Amaryllidaceae	0.16	
Lycoparin C	Alkaloid	*Lycopodium casuarinoides*	Lycopodiaceae	25	[164]
Salignarine C	Alkaloid	*Sarcococca saligna*	Buxaceae	19.7	[151]
Buxrugulosamine	Steroidal alkaloid	*Buxus hyrcana*	Buxaceae	24.8	[139]
Alkaloid-C	Steroidal alkaloid	*Sarcococca saligna*	Buxaceae	45.5	[165]
Cycloprotobuxine-C	Triterpenoid alkaloid	*Buxus papillosa*	Buxaceae	38.8	[166]
Papillozine C	Triterpenoidal alkaloid	*Buxus hyrcana*	Buxaceae	47.8	[166]
24-ethylcholest6-ene-3,5-diol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	3.5	[167]
24-ethyl-cholest-7-ene-3,5,6-trio	Sterol	*Haloxylon recurvum*	Chenopodiaceae	13.7	
Lawsarito	Sterol	*Haloxylon recurvum*	Chenopodiaceae	15.2	
5a, 8a-epidioxy-(24 S)-ethylcholesta6,9 (11), 22 (E)-triene-3b-ol	Sterol	*Haloxylon recurvum*	Chenopodiaceae	26.4	
Osajin	Isoflavonoid	*Maclura pomifera*	Moraceae	2.239	[139]
Pomiferin	Isoflavonoid	*Maclura pomifera*	Moraceae	0.096	[139]
Isothymonin 40-methyl ether	Flavonoid	*Micromeria cilicica*	Lamiaceae	>200	[168]
3-Methoxy quercetin	Flavonoid	*Agrimonia pilosa*	Rosaceae	37.9	[169]
Rutin	Flavonoid	*Micromeria cilicica*	Lamiaceae	>200	[168]
Quercitrin	Flavonoid	*Agrimonia pilosa*	Rosaceae	66.9	[169]
α-pinene	Monoterpene	*Salvia lavandulaefolia*	Lamiaceae	81.7	[139]
α-pinen	Monoterpene	*Salvia lavandulaefolia*	Lamiaceae	0.63	[170]
(+)-limonene	Terpene	*Pimpinella anisoides*	Apiaceae	225.9	[171]
Ursolic acid	Pentacyclic triterpene acid	*Micromeria cilicica*	Lamiaceae	93.8	[139]
(+)-sabinene	Terpene	*Pimpinella anisoides*	Apiaceae	176.5	[139]
Trans-anethole	Terpene	*Pimpinella anisoides*	Apiaceae	134.7	[223]
Piperitone 7-*O*-b-D-glucoside	Glycoside	*Micromeria cilicica*	Lamiaceae	>200	[139]
MS-1 compound	Triterpenoidal	*Curculigo orchioides*	Hypoxidaceae	–	[172]

administration strategy require further investigation. Crocus sativus L. dried extract has also shown significant improvement in cognitive capacity in individuals suffering from mild-to-moderate AD, comparable to that observed in donepezil-treated patients [143].

6.3. Clinical trial of phytomedicines

Phytomedicines have been used for medicinal purposes for centuries and are divided into four categories based on their origin and evolution. These medicines contain phytoconstituents that are known for their pharmacological effects on the body and are used globally. However, the lack of data on the safety and efficacy of phytomedicines has led to insufficient regulation. Critics of phytomedicines have called for more clinical trials to determine their safety and efficacy before they are accepted as evidence-based medicines. Clinical trials can only begin after the collection of relevant preclinical data and approval from relevant health authorities/ethics committees [144].

The drug development process is a long, costly, and high-risk endeavour due to lack of clinical efficacy, unmanageable toxicity, poor drug-like properties, and lack of commercial needs. The complexity of biological systems, the narrow focus on drug targets, and the lack of robust biomarkers can all contribute to the high failure rate. To improve

the success rate, a more holistic understanding of disease biology, the development of more reliable biomarkers, collaborations between stakeholders, and the use of new technologies like artificial intelligence can all play a crucial role [145].

There have been several instances of phytomedicines showing moderate efficacy in clinical trials. One example is the herbal drug St John's wort, which has been traditionally used to treat depression. However, a large-scale clinical trial conducted in 2002 found that St John's wort did not show significant efficacy [146]. Another example is the herbal drug Echinacea, which is commonly used as a natural remedy for the common cold. However, a clinical trial conducted in 2005 found that echinacea was less effective in preventing or treating the common cold [147]. A third example is the herbal drug ginkgo biloba, which is commonly used to improve memory and cognitive function. However, a large-scale clinical trial conducted in 2008 found that ginkgo biloba was not significantly effective than a placebo in preventing cognitive decline in older adults [148]. Therefore, it is imperative to conduct non-clinical study and proceed with multi-centric double-blind place-control clinical trial to evaluate the efficacy.

7. Recent developments and future perspectives

Alzheimer's disease (AD) is a complex disorder with multifactorial pathogenesis. Various mechanisms have been linked to the development of AD, including inflammation, amyloid-beta, oxidative stress, dyslipidemia, diabetes mellitus, cholinergic pathways, Interleukin receptor-associated kinase 4 signaling pathway, and Wnt signaling pathways [173]. Nutritional changes and healthy lifestyles can reduce the risk of AD by reducing the risk of cardiovascular disease, dyslipidemia, type 2 diabetes, insulin resistance, and chronic inflammation [174].

The cholinergic theory is based on the presynaptic deficits reported in AD patients, and few cholinomimetic medications might enhance cognitive performance. However, patient selection and consideration of side effects are crucial to determine the effectiveness of cholinomimetic therapy. FDA-approved medications like donepezil, galantamine, and rivastigmine are used to treat AD, but they only have improve the symptoms and do not prevent its progression [175].

Novel therapeutic drugs for AD must be thoroughly analysed for exact mechanisms before development. Effective AD medications require an understanding of how tau protein, AChE, and amyloid beta protein interact. Biomarkers such as Aβ1-42 and Aβ1-40 are effective biomarker for early AD prediction, and various diagnostic techniques such as MRI scanning, PET, and amyloid positron emission tomography are available for early AD diagnosis [176-178].

Drug designs must take into account for interaction of numerous pathways due to AD's complex pathophysiology [179]. Immunotherapy is a potential treatment approach for Aβ clearance in the brain, but it is expensive, and there are several serious side effects, including stability, poor BBB permeability, and autoimmune response in the AD brain. Molecular clamps that bind to target sites like APP and phosphorylation sites in tau could lead to potential therapeutic medications to reduce enzymatic activity without impairing the enzymes' other biological functions [180,181].

Overall, despite the complexity of AD, it is hopeful that new multi-targeted therapeutic medications will emerge to address the pathophysiology of AD and provide effective diagnosis and treatment strategy for AD patients.

8. Conclusions

To summarize, there are differences in the response of acetylcholinesterase species to AD and their interactions with amyloid-β protein, and they also interact with different amyloid β-peptide fragments. Accelerating the fibrilization of amyloid-beta protein and exploring the alternative functions of acetylcholinesterase, it is important to study their association with different AChE species and variants, and their role in the pathogenesis of AD. Recent studies suggest that acetylcholinesterase may play a role in the production of Aβ protein in the brain. To understand the physiological and clinical significance of altered AChE expression in the AD brain and the use of AChE inhibitor pharmaceutical treatments, it is important to elucidate the mechanisms.

Currently, herbal and synthetic medications such as rivastigmine, donepezil, and galantamine are used as AChE inhibitors to treat AD, providing an alternative approach to alleviate symptoms. However, due to the lack of a cure for AD and the limited effectiveness of current drugs, there is potential in using phytomedicines or medicinal plant products to treat AD. Medicinal herbs and herbal drug preparations have been used to treat neurological disorders like AD, and research supports their use due to their anti-inflammatory and neuroprotective properties. Phytomedicines containing flavonoids, polyphenols, and other naturally occurring antioxidants can cross the blood-brain barrier and protect neurons from oxidative stress associated with neurodegenerative diseases. Moreover, compared to synthetic drugs, phytomedicines have fewer side effects and are more compatible with the human system. As a result, research has been increased significantly to exploring the potential of phytomedicines to develop effective treatments for AD.

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Abbreviation

Ach	Acetylcholine
AChE	Acetylcholinesterase
AChE-I	Acetylcholinesterase inhibitor

AD Alzheimer's disease
AICD APP Intracellular domain
APOE apolipoprotein E
APP amyloid precursor protein
APPL amyloid precursor-like protein
Aβ Amyloid Beta
$Aβ_{1-40}$ Amyloid Beta Peptide1-40
Aβ-AChE Amyloid Beta- Acetylcholinesterase
BACE-1 Beta-secretase 1
BBB Blood-brain barrier

References

[1] J. Hardy, D.J. Selkoe, The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics, Science 297 (2002) 353–356, https://doi.org/10.1126/science.1072994.
[2] L. Agustín, Introducing sex at the margins, Development 50 (2007) 39–43, https://doi.org/10.1057/palgrave.development.1100421.
[3] C. Morgan, M.P. Bugueño, J. Garrido, N.C. Inestrosa, Laminin affects polymerization, depolymerization and neurotoxicity of Aβ peptide, Peptides 23 (2002) 1229–1240, https://doi.org/10.1016/S0196-9781(02)00058-X.
[4] N.C. Inestrosa, M.C. Dinamarca, A. Alvarez, Amyloid – Cholinesterase Interactions Implications for Alzheimer ' S Disease, vol. 275, 2008, pp. 625–632, https://doi.org/10.1111/j.1742-4658.2007.06238.x.
[5] K.A. Carson, C. Geula, M.M. Mesulam, Electron microscopic localization of cholinesterase activity in Alzheimer brain tissue, Brain Res. 540 (1991) 204–208, https://doi.org/10.1016/0006-8993(91)90508-S.
[6] M.A. Mordn, E.J. Mufson, P. Gomez-Ramos, A. Morcillo, Acta Neuropathologlca Regular papers Colocalization of cholinesterases with [5 amyloid protein in aged and Alzheimer's brains, Acta Neuropathol. 85 (1993) 362–369.
[7] A. Alvarez, C. Opazo, R. Alarcón, J. Garrido, N.C. Inestrosa, Acetylcholinesterase promotes the aggregation of amyloid-β-peptide fragments by forming a complex with the growing fibrils, J. Mol. Biol. 272 (1997) 348–361, https://doi.org/10.1006/jmbi.1997.1245.
[8] E.H. Koo, J. Lansbury, J.W. Kelly, Amyloid diseases: abnormal protein aggregation in neurodegeneration, Proc. Natl. Acad. Sci. U.S.A. 96 (1999) 9989–9990, https://doi.org/10.1073/pnas.96.18.9989.
[9] A. Berson, M. Knobloch, M. Hanan, S. Diamant, M. Sharoni, D. Schuppli, B. C. Geyer, R. Ravid, T.S. Mor, R.M. Nitsch, H. Soreq, Changes in readthrough acetylcholinesterase expression modulate amyloid-beta pathology, Brain 131 (2008) 109–119, https://doi.org/10.1093/brain/awm276.
[10] Y. Abreu-Villaça, C.C. Filgueiras, A.C. Manhães, Developmental aspects of the cholinergic system, Behav. Brain Res. 221 (2011) 367–378, https://doi.org/10.1016/j.bbr.2009.12.049.
[11] A. Trang, P.B. Khandhar, Physiology, acetylcholinesterase, Treasure Island (FL)01 (2023).
[12] M.B. Colovic, D.Z. Krstic, T.D. Lazarevic-Pasti, A.M. Bondzic, V.M. Vasic, Acetylcholinesterase inhibitors: pharmacology and toxicology, Curr. Neuropharmacol. 11 (2013) 315–335, https://doi.org/10.2174/1570159x11311030006.
[13] B. Aslan, B. Ozpolat, A.K. Sood, G. Lopez-Berestein, Nanotechnology in cancer therapy, J. Drug Target. 21 (2013) 904–913, https://doi.org/10.3109/1061186X.2013.837469.
[14] M. Mehrpouya, S. Ataei, A. Nili-Ahmadabadi, Potential drug interactions with cholinesterase inhibitors in alzheimer patients: a guideline for neurologists, J. Appl. Pharmaceut. Sci. 7 (2017) 223–226, https://doi.org/10.7324/JAPS.2017.70134.
[15] G.V. De Ferrari, M.A. Canales, I. Shin, L.M. Weiner, I. Silman, N.C. Inestrosa, A Structural Motif of Acetylcholinesterase that Promotes Amyloid -Peptide Fibril, 2001, pp. 10447–10457.
[16] D.A. Greenberg, K. Jin, From Angiogenesis to Neuropathology, vol. 438, 2005, https://doi.org/10.1038/nature04481.
[17] M.C. Dinamarca, J.P. Sagal, R.A. Quintanilla, J.A. Godoy, M.S. Arrzola, N. C. Inestrosa, Amyloid-β-Acetylcholinesterase complexes potentiate neurodegenerative changes induced by the A peptide. Implications for the pathogenesis of Alzheimer's disease, Mol. Neurodegener. 5 (2010) 1–15, https://doi.org/10.1186/1750-1326-5-4.
[18] J. Lee, C. Jin, S.-Y. Cho, S.-U. Park, W.-S. Jung, S.-K. Moon, et al., Herbal medicine treatment for Alzheimer disease, Medicine (Baltim.) 99 (2020) e21745, https://doi.org/10.1097/md.0000000000021745.
[19] F. Valéria Soares De Araújo Pinho, G. Felipe Da Silva, G. Echeverria Macedo, K. Raquel Muller, I. Kemmerich Martins, A.P. Lausmann Ternes, et al., Phytochemical constituents and toxicity of duguetia furfuracea hydroalcoholic extract in drosophila melanogaster, Evidence-Based Complement. Altern. Med. 2014 (2014), https://doi.org/10.1155/2014/838101.
[20] M. Soheili, M. Karimian, G. Hamidi, M. Salami, Alzheimer's disease treatment: the share of herbal medicines, Iran, J. Basic Med. Sci. 24 (2021) 123–135, https://doi.org/10.22038/IJBMS.2020.50536.11512.
[21] J. Sheng, S. Zhang, L. Wu, G. Kumar, Y. Liao, P. Gk, H. Fan, Inhibition of phosphodiesterase: a novel therapeutic target for the treatment of mild cognitive impairment and Alzheimer's disease, Front. Aging Neurosci. 14 (2022) 1019187.
[22] K. Nagori, K.T. Nakhate, K. Yadav, Ajazuddin, M. Pradhan, Unlocking the therapeutic potential of medicinal plants for alzheimer's disease: preclinical to clinical trial insights, Futur. Pharmacol. 3 (2023) 877–907, https://doi.org/10.3390/futurepharmacol3040053.
[23] A. Iyaswamy, K. Lu, X.J. Guan, Y. Kan, C. Su, J. Liu, R. Jaganathan, K. Vasudevan, J. Paul, Impact and advances in the role of bacterial extracellular vesicles in neurodegenerative disease and its therapeutics, Biomedicines 11 (2023) 1–13, https://doi.org/10.3390/biomedicines11072056.
[24] A.V. Atoki, P.M. Aja, E.N. Ondari, T.S. Shinkafi, Advances in Alzheimer's disease therapeutics: biochemistry, exploring bioactive compounds and novel approaches, Int. J. Food Prop. 26 (2023) 2091–2127, https://doi.org/10.1080/10942912.2023.2243050.
[25] A. Iyaswamy, A. Thakur, X.J. Guan, S. Krishnamoorthi, T.Y. Fung, K. Lu, I. Gaurav, Z. Yang, et al., Fe65-engineered neuronal exosomes encapsulating corynoxine-B ameliorate cognition and pathology of Alzheimer's disease, Signal Transduct. Targeted Ther. 8 (2023), https://doi.org/10.1038/s41392-023-01657-4.
[26] R. Taqui, M. Debnath, S. Ahmed, A. Ghosh, Advances on plant extracts and phytocompounds with acetylcholinesterase inhibition activity for possible treatment of Alzheimer's disease, Phytomedicine 2 (2022) 100184, https://doi.org/10.1016/j.phyplu.2021.100184.
[27] V. Ormazabal, S. Nair, O. Elfeky, C. Aguayo, C. Salomon, F.A. Zuñiga, Association between insulin resistance and the development of cardiovascular disease, Cardiovasc. Diabetol. 17 (2018) 1–14, https://doi.org/10.1186/s12933-018-0762-4.
[28] M. Care, Standards of medical care in diabetes - 2013, Diabetes Care 36 (2013), https://doi.org/10.2337/dc13-S011.
[29] M. Agrawal, A.K. Agrawal, Pathophysiological association between diabetes mellitus and alzheimer's disease, Cureus 14 (2022), https://doi.org/10.7759/cureus.29120.
[30] D. Bosco, A. Fava, M. Plastino, T. Montalcini, A. Pujia, Possible implications of insulin resistance and glucose metabolism in Alzheimer's disease pathogenesis, J. Cell Mol. Med. 15 (2011) 1807–1821, https://doi.org/10.1111/j.1582-4934.2011.01318.x.
[31] Y. Chung, H. Lee, M.W. Weiner, P. Aisen, R. Petersen, C.R. Jack, W. Jagust, J. Q, Correlation between Alzheimer's disease and type 2 diabetes using non-negative matrix factorization, Sci. Rep. 11 (2021) 1–14, https://doi.org/10.1038/s41598-021-94048-0.
[32] B. Antuna-Puente, B. Feve, S. Fellahi, J.P. Bastard, Adipokines: the missing link between insulin resistance and obesity, Diabetes Metab. 34 (2008) 2–11, https://doi.org/10.1016/j.diabet.2007.09.004.
[33] J.A. Flores-Cordero, A. Pérez-Pérez, C. Jiménez-Cortegana, G. Alba, A. Flores-Barragán, V. Sánchez-Margalet, Obesity as a risk factor for dementia and alzheimer's disease: the role of leptin, Int. J. Mol. Sci. 23 (2022), https://doi.org/10.3390/ijms23095202.
[34] C.R. De Almodovar, D. Lambrechts, M. Mazzone, P. Carmeliet, Role and therapeutic potential of VEGF in the nervous system, Physiol. Rev. 89 (2009) 607–648, https://doi.org/10.1152/physrev.00031.2008.
[35] R. Sims, M. Hill, J. Williams, The multiplex model of the genetics of Alzheimer's disease, Nat. Neurosci. 23 (2020) 311–322, https://doi.org/10.1038/s41593-020-0599-5.
[36] J. Lambert, ScienceDirect genetics of alzheimer ' s disease, where we are , and where we are going (2020) 40–48, https://doi.org/10.1016/j.conb.2019.11.024.
[37] C. Reitz, M.A. Pericak-Vance, T. Foroud, R. Mayeux, A global view of the genetic basis of Alzheimer disease, Nat. Rev. Neurol. (2023), https://doi.org/10.1038/s41582-023-00789-z.
[38] C.A. Hawkes, J. McLaurin, Selective targeting of perivascular macrophages for clearance of β-amyloid in cerebral amyloid angiopathy, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 1261–1266, https://doi.org/10.1073/pnas.0805453106.
[39] W.C. Huang, F.C. Yen, F.S. Shie, C.M. Pan, Y.J. Shiao, C.N. Yang, F.L. Huang, Y. J. Sung, H.J. Tsay, TGF-β1 blockade of microglial chemotaxis toward Aβ aggregates involves SMAD signaling and down-regulation of CCL5, J. Neuroinflammation 7 (2010) 1–11, https://doi.org/10.1186/1742-2094-7-28.
[40] J.K. Lee, E.H. Schuchman, H.K. Jin, J.S. Bae, Soluble CCL5 derived from bone marrow-derived mesenchymal stem cells and activated by amyloid β ameliorates Alzheimer's disease in mice by recruiting bone marrow-induced microglia immune responses, Stem Cell. 30 (2012) 1544–1555, https://doi.org/10.1002/stem.1125.
[41] B. De Strooper, R. Vassar, T. Golde, The secretases: enzymes with therapeutic potential in Alzheimer disease, Nat. Rev. Neurol. 6 (2010) 99–107, https://doi.org/10.1038/nrneurol.2009.218.
[42] C. Parr, N. Mirzaei, M. Christian, M. Sastre, Activation of the Wnt/β-catenin pathway represses the transcription of the β-amyloid precursor protein cleaving enzyme (BACE1) via binding of T-cell factor-4 to BACE1 promoter, Faseb. J. 29 (2015) 623–635, https://doi.org/10.1096/fj.14-253211.
[43] W.Q.Q. Erming Wanga, Haihao Zhua, Xiaofan Wanga, Adam C. Gowerb, Max Wallacka, et al., Amylin treatment reduces neuroinflammation and ameliorates abnormal patterns of gene expression in the cerebral cortex of an alzheimer's disease mouse model erming, Physiol. Behav. 176 (2017) 139–148, https://doi.org/10.1053/j.gastro.2016.08.014.CagY.
[44] J. Grizzanti, R. Corrigan, S. Servizi, G. Casadesus, Amylin signaling in diabetes and alzheimer's disease: therapy or pathology? J. Neurol. Neuromed. 4 (2019) 12–16, https://doi.org/10.29245/2572.942x/2019/1.1212.
[45] C.M. Nday, D. Eleftheriadou, G. Jackson, Shared pathological pathways of Alzheimer's disease with specific comorbidities: current perspectives and

interventions, J. Neurochem. 144 (2018) 360–389, https://doi.org/10.1111/jnc.14256.
[46] M. Calabrò, C. Rinaldi, G. Santoro, C. Crisafulli, The biological pathways of Alzheimer disease: a review, AIMS Neurosci. 8 (2021) 86–132, https://doi.org/10.3934/Neuroscience.2021005.
[47] C. Cunningham, Microglia and neurodegeneration: the role of systemic inflammation, Glia 61 (2013) 71–90, https://doi.org/10.1002/glia.22350.
[48] T. Zorbaz, N. Madrer, H. Soreq, Cholinergic blockade of neuroinflammation: from tissue to RNA regulators, Neuronal Signal 6 (2022) 1–15, https://doi.org/10.1042/NS20210035.
[49] M. Reale, E. Costantini, Cholinergic modulation of the immune system in neuroinflammatory diseases, Diseases 9 (2021) 29, https://doi.org/10.3390/diseases9020029.
[50] M. Reale, C. Iarlori, F. Gambi, C. Feliciani, A. Salone, L. Toma, et al., Treatment with an acetylcholinesterase inhibitor in Alzheimer patients modulates the expression and production of the pro-inflammatory and anti-inflammatory cytokines, J. Neuroimmunol. 148 (2004) 162–171, https://doi.org/10.1016/j.jneuroim.2003.11.003.
[51] K. Sadia, M.N. Leonel Javeres, F. Tahir, S.T.A. Shah, R. Habib, Z. Muneer, S. Hussain, S.M. Nurulain, Acetylcholinesterase, pro-inflammatory cytokines, and association of ACHE SNP rs 17228602 with male infertility, PLoS One 18 (2023) e0282579, https://doi.org/10.1371/journal.pone.0282579.
[52] J.S. Wu, Q.Y. Meng, X.H. Shi, L.X. Liu, Z.K. Zhang, H.S. Guan, C.L. Shao, C. Y. Wang, The oxygenated products of cryptotanshinone by biotransformation with Cunninghamella elegans exerting anti-neuroinflammatory effects by inhibiting TLR 4-mediated MAPK signaling pathway, Bioorg. Chem. 104 (2020) 104246, https://doi.org/10.1016/j.bioorg.2020.104246.
[53] A.C. Martini, S. Forner, L. Trujillo-Estrada, D. Baglietto-Vargas, F.M. Laferla, Past to future: what animal models have taught us about alzheimer's disease, J. Alzheim. Dis. 64 (2018) S365–S378, https://doi.org/10.3233/JAD-179917.
[54] E. Kim, S. Cho, Microglia and monocyte-derived macrophages in stroke, Neurotherapeutics 13 (2016) 702–718, https://doi.org/10.1007/s13311-016-0463-1.
[55] J.S. Cho, J. Lee, D.U. Jeong, H.W. Kim, W.S. Chang, J. Moon, J.W. Chang, Effect of placenta-derived mesenchymal stem cells in a dementia rat model via microglial mediation: a comparison between stem cell transplant methods, Yonsei Med. J. 59 (2018) 406–415, https://doi.org/10.3349/ymj.2018.59.3.406.
[56] M. Baudry, X. Bi, Calpain-1 and calpain-2: the yin and yang of synaptic plasticity and neurodegeneration, Trends Neurosci. 39 (2016) 235–245, https://doi.org/10.1016/j.tins.2016.01.007.
[57] N. Inestrosa, A. Alvarez, M. Dinamarca, T. Perez-Acle, M. Colombres, Acetylcholinesterase-Amyloid-β-peptide interaction: effect of Congo red and the role of the Wnt pathway, Curr. Alzheimer Res. 2 (2005) 301–306, https://doi.org/10.2174/1567205054367928.
[58] W. Wan, S. Xia, B. Kalionis, L. Liu, Y. Li, The role of Wnt signaling in the development of alzheimer's disease: a potential therapeutic target? BioMed Res. Int. 2014 (2014) 1–9, https://doi.org/10.1155/2014/301575.
[59] L. Zhang, C. Sun, Y. Jin, K. Gao, X. Shi, W. Qiu, C. Ma, L. Zhang, Dickkopf 3 (Dkk3) improves amyloid-β pathology, cognitive dysfunction, and cerebral glucose metabolism in a transgenic mouse model of alzheimer's disease, J. Alzheim. Dis. 60 (2017) 733–746, https://doi.org/10.3233/JAD-161254.
[60] H. Soreq, Checks and balances on cholinergic signaling in brain and body function, Trends Neurosci. 38 (2015) 448–458, https://doi.org/10.1016/j.tins.2015.05.007.
[61] J. Folch, I. Patraca, N. Martínez, I. Pedrós, D. Petrov, M. Ettcheto, et al., The role of leptin in the sporadic form of Alzheimer's disease. Interactions with the adipokines amylin, ghrelin and the pituitary hormone prolactin, Life Sci. 140 (2015) 19–28, https://doi.org/10.1016/j.lfs.2015.05.002.
[62] A. Fleming, M. Bourdenx, M. Fujimaki, C. Karabiyik, G.J. Krause, A. Lopez, et al., Rubinsztein, the different autophagy degradation pathways and neurodegeneration, Neuron 110 (2022) 935–966, https://doi.org/10.1016/j.neuron.2022.01.017.
[63] M.S. Uddin, A. Stachowiak, A. Al Mamun, N.T. Tzvetkov, S. Takeda, A. G. Atanasov, et al., Stankiewicz, Autophagy and Alzheimer's disease: from molecular mechanisms to therapeutic implications, Front. Aging Neurosci. 10 (2018) 1–18, https://doi.org/10.3389/fnagi.2018.00004.
[64] H. Barmaki, A. Nourazarian, F. Khaki-Khatibi, Proteostasis and neurodegeneration: a closer look at autophagy in Alzheimer's disease, Front. Aging Neurosci. 15 (2023), https://doi.org/10.3389/fnagi.2023.1281338.
[65] A.M. Cuervo, E. Wong, Chaperone-mediated autophagy: roles in disease and aging, Cell Res. 24 (2014) 92–104, https://doi.org/10.1038/cr.2013.153.
[66] Y.T. Wang, J.H. Lu, Chaperone-mediated autophagy in neurodegenerative diseases: molecular mechanisms and pharmacological opportunities, Cells 11 (2022), https://doi.org/10.3390/cells11142250.
[67] H. Kanno, K. Handa, T. Murakami, T. Aizawa, H. Ozawa, Chaperone-mediated autophagy in neurodegenerative diseases and acute neurological insults in the central nervous system, Cells 11 (2022), https://doi.org/10.3390/cells11071205.
[68] M.A. Assaye, S.T. Gizaw, Chaperone-mediated autophagy and its implications for neurodegeneration and cancer, Int. J. Gen. Med. 15 (2022) 5635–5649, https://doi.org/10.2147/IJGM.S368364.
[69] H.A. Bustamante, A.E. González, C. Cerda-Troncoso, R. Shaughnessy, C. Otth, A. Soza, P.V. Burgos, Interplay between the autophagy-lysosomal pathway and the ubiquitin-proteasome system: a target for therapeutic development in alzheimer's disease, Front. Cell. Neurosci. 12 (2018) 1–18, https://doi.org/10.3389/fncel.2018.00126.
[70] U.N. Das, Clinical laboratory tools to diagnose inflammation, Adv. Clin. Chem. 41 (2006) 189–229, https://doi.org/10.1016/s0065-2423(05)41006-9.
[71] A.A. Rao, G.R. Sridhar, U.N. Das, Elevated butyrylcholinesterase and acetylcholinesterase may predict the development of type 2 diabetes mellitus and Alzheimer's disease, Med. Hypotheses 69 (2007) 1272–1276, https://doi.org/10.1016/j.mehy.2007.03.032.
[72] U.N. Das, Hypertension as a low-grade systemic inflammatory condition that has its origins in the perinatal period, J. Assoc. Phys. India 54 (2006) 133–142.
[73] M.J. Ramírez, E. Cenarruzabeitia, B. Lasheras, J. Del Rio, 5-HT2 receptor regulation of acetylcholine release induced by dopaminergic stimulation in rat striatal slices, Brain Res. 757 (1997) 17–23, https://doi.org/10.1016/S0006-8993(96)01434-5.
[74] U.N. Das, Is type 2 diabetes mellitus a disorder of the brain? Nutrition 18 (2002) 667–672, https://doi.org/10.1016/S0899-9007(02)00746-3.
[75] L. V Borovikova, S. Ivanova, M. Zhang, H. Yang, G.I. Botchkina, L.R. Watkins, et al., Vagus nerve stimulation attenuates the systemic in¯ammatory response to endotoxin, Macmillan Mag. Ltd Nat. 405 (2000) 458–462.
[76] N. Waiskopf, S. Shenhar-Tsarfaty, H. Soreq, Serum cholinesterase activities as biomarkers of cardiac malfunctioning, Biomarkers Cardiovasc. Dis. (2015) 1–22, https://doi.org/10.1007/978-94-007-7741-5_10-1.
[77] U. Das, Acetylcholinesterase and butyrylcholinesterase as possible markers of low- grade systemic inflammatio, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. (2015) 214–221.
[78] G. Mushtaq, N. Greig, J. Khan, M. Kamal, Status of acetylcholinesterase and butyrylcholinesterase in Alzheimer's disease and type 2 diabetes mellitus, CNS neurol. Disord, - Drug Targets 13 (2014) 1432–1439, https://doi.org/10.2174/1871527313666141023141545.
[79] A.M. Stranahan, M.P. Mattson, Bidirectional metabolic regulation of neurocognitive function, Neurobiol. Learn. Mem. 96 (2011) 507–516, https://doi.org/10.1016/j.nlm.2011.01.004.
[80] K. Dayanand, R.W.R. Olivia E. Atherton, Jennifer L. Tackett, Emilio Ferrer, Status of acetylcholinesterase and butyrylcholinesterase in alzheimer's disease and type 2 diabetes mellitus, Physiol. Behav. 176 (2018) 139–148.
[81] S. Sucharita, G. Bantwal, J. Idiculla, V. Ayyar, M. Vaz, Autonomic nervous system function in type 2 diabetes using conventional clinical autonomic tests, heart rate and blood pressure variability measures, Indian J. Endocrinol. Metab. 15 (2011) 198, https://doi.org/10.4103/2230-8210.83406.
[82] G.R. Sridhar, H. Thota, A.R. Allam, C.S. Babu, A.S. Prasad, C. Divakar, Alzheimer's disease and Type 2 diabetes mellitus: the cholinesterase connection? Lipids Health Dis. 5 (2006) 1–5, https://doi.org/10.1186/1476-511X-5-28.
[83] K.J.C. Cruz, A.R.S. de Oliveira, J.B.S. Morais, J.S. Severo, D. do N. Marreiro, PhD, Role of microRNAs on adipogenesis, chronic low-grade inflammation, and insulin resistance in obesity, Nutrition 35 (2017) 28–35, https://doi.org/10.1016/j.nut.2016.10.003.
[84] S. Shenhar-Tsarfaty, S. Sherf-Dagan, G. Berman, M. Webb, A. Raziel, A. Keidar, D, et al., Obesity-related acetylcholinesterase elevation is reversed following laparoscopic sleeve gastrectomy, Int. J. Obes. 43 (2019) 297–305, https://doi.org/10.1038/s41366-018-0014-4.
[85] A. Fathi Hamouda, I. Abdu Khardali, I. Mohammed Attafi, M. Essa Oraiby, M. Ahmad Attafi, A. Mousa Sulaiman Muyidi, H. Abdu Ahmed Dohali, Study the relation between acetylcholinesterase and obesity in university students, Int. J. Nutr. Food Sci. 8 (2019) 46, https://doi.org/10.11648/j.ijnfs.20190803.11.
[86] Z. Breijyeh, R. Karaman, Comprehensive Review on Alzheimer ' S Disease, 2020.
[87] N.C. Inestrosa, A. Alvarez, R.D. Moreno, M. Vicente, C. Linker, O.I. Casanueva, C. Soto, J. Garrido, Acetylcholinesterase Accelerates Assembly of Amyloid- ␣ -Peptides into Alzheimer ' S Fibrils : Possible Role of the Peripheral Site of the Enzyme, vol. 16, 1996, pp. 881–891.
[88] J. Liu, H. Guo, Z. Quan, Q. Shen, H. Cui, Research progress of natural products and their derivatives against Alzheimer ' s disease, J. Enzym. Inhib. Med. Chem. 38 (2023), https://doi.org/10.1080/14756366.2023.2171026.
[89] M. Sternfeld, S. Shoham, O. Klein, C. Flores-flores, T. Evron, G.H. Idelson, et al., "read-through"' Acetylcholinesterase Attenuates but the "' Synaptic "' Variant Intensifies Neurodeterioration Correlates, vol. 97, 2000.
[90] T. Rees, P.I. Hammond, H. Soreq, S. Younkin, S. Brimijoin, Acetylcholinesterase promotes beta-amyloid plaques in cerebral cortex, Neurobiol. Aging 24 (2003) 777–787, https://doi.org/10.1016/S0197-4580(02)00230-0.
[91] R. Beeri, C. Andres, E. Lev-lehmant, R. Timberg, T. Hubermant, M. Shani, H. Soreq, Transgenic Expression of Human Acetylcholinesterase Induces Progressive Cognitive Deterioration in Mice, vol. 5, 1995.
[92] L. Jean, S. Brimijoin, D.J. Vaux, In vivo localization of human acetylcholinesterase-derived species in a β-sheet conformation at the core of senile plaques in Alzheimer's disease, J. Biol. Chem. 294 (2019) 6253–6272, https://doi.org/10.1074/jbc.RA118.006230.
[93] M. Jensen, F.J. Hoerndli, P.J. Brockie, R. Wang, E. Johnson, D. Maxfield, M. M. Francis, et al., Wnt signaling regulates acetylcholine receptor translocation and synaptic plasticity in the adult nervous system, Cell 149 (2012) 173–187, https://doi.org/10.1016/j.cell.2011.12.038.
[94] O. Isacson, H. Seo, L. Lin, D. Albeck, A.C. Granholm, Alzheimer's disease and Down's syndrome: roles of APP, trophic factors and ACh, Trends Neurosci. 25 (2002) 79–84, https://doi.org/10.1016/S0166-2236(02)02037-4.
[95] J.A. Godoy, J.A. Rios, J.M. Zolezzi, N. Braidy, N.C. Inestrosa, Signaling pathway cross talk in Alzheimer's disease, Cell Commun. Signal. 12 (2014) 1–12, https://doi.org/10.1186/1478-811X-12-23.
[96] F.J. Muñoz, N.C. Inestrosa, Neurotoxicity of acetylcholinesterase amyloid β-peptide aggregates is dependent on the type of Aβ peptide and the AChE

concentration present in the complexes, FEBS Lett. 450 (1999) 205–209, https://doi.org/10.1016/S0014-5793(99)00468-8.
[97] M.C. Dinamarca, M. Arrázola, E. Toledo, W.F. Cerpa, J. Hancke, N.C. Inestrosa, Release of acetylcholinesterase (AChE) from β-amyloid plaques assemblies improves the spatial memory impairments in APP-transgenic mice, Chem. Biol. Interact. 175 (2008) 142–149, https://doi.org/10.1016/j.cbi.2008.05.026.
[98] F.J. Carvajal, J.M. Zolezzi, C. Tapia-Rojas, J.A. Godoy, N.C. Inestrosa, Tetrahydrohyperforin decreases cholinergic markers associated with amyloid-β plaques, 4-hydroxynonenal formation, and caspase-3 activation in aβpp/ps1 mice, J. Alzheim. Dis. 36 (2013) 99–118, https://doi.org/10.3233/JAD-130230.
[99] R. Kumar, A. Nordberg, T. Darreh-Shori, Amyloid-β peptides act as allosteric modulators of cholinergic signalling through formation of soluble BAβACs, Brain 139 (2016) 174–192, https://doi.org/10.1093/brain/awv318.
[100] W.L. Roberts, B.H. Kim, T.L. Rosenberry, Difference in the glycolipid membrane anchors of bovine and human erythrocyte acetylcholinesterases, Proc. Natl. Acad. Sci. U.S.A. 84 (1987) 7817–7821, https://doi.org/10.1073/pnas.84.22.7817.
[101] I. Silman, J.L. Sussman, Acetylcholinesterase: how is structure related to function? Chem. Biol. Interact. 175 (2008) 3–10, https://doi.org/10.1016/j.cbi.2008.05.035.
[102] A.T. Schliebs R, The cholinergic system in aging and neuronal degeneration. Behavioural No Title, Behav. Brain Res. 2021 (2011) 555–563.
[103] M.S. Wolfe, S.Y. Guénette, APP at a glance, J. Cell Sci. 120 (2007) 3157–3161, https://doi.org/10.1242/jcs.03481.
[104] P. Westermark, M.D. Benson, J.N. Buxbaum, A.S. Cohen, B. Frangione, S.I. Ikeda, C.L. Masters, G. Merlini, M.J. Saraiva, J.D. Sipe, A primer of amyloid nomenclature, Amyloid 14 (2007) 179–183, https://doi.org/10.1080/13506120701460923.
[105] Mark B. . Pepys, Pepys (2006), https://doi.org/10.1146/annurev.med.57.121304.131243.
[106] G. Merlini, V. Bellotti, Molecular Mechanisms of Amyloidosis, 2003, pp. 583–596.
[107] A. Prasansuklab, T. Tewin, Amyloidosis in alzheimer's disease: the toxicity of amyloid beta, evidence-based complement, Alternative Med. 2013 (2013) 10.
[108] F.J. Carvajal, N.C. Inestrosa, Interactions of AChE with A? Aggregates in Alzheimer?s brain: therapeutic relevance of IDN 5706, Front. Mol. Neurosci. 4 (2011) 1–10, https://doi.org/10.3389/fnmol.2011.00019.
[109] E. Jorissen, J. Prox, C. Bernreuther, S. Weber, R. Schwanbeck, L. Serneels, et al., The disintegrin/metalloproteinase ADAM10 is essential for the establishment of the brain cortex, J. Neurosci. 30 (2010) 4833–4844, https://doi.org/10.1523/JNEUROSCI.5221-09.2010.
[110] D.J. Selkoe, The molecular pathology of Alzheimer's disease, Neuron 6 (1991) 487–498, https://doi.org/10.1016/0896-6273(91)90052-2.
[111] Z. Alraawi, N. Banerjee, S. Mohanty, T.K.S. Kumar, Amyloidogenesis: what do we know so far? Int. J. Mol. Sci. 23 (2022) https://doi.org/10.3390/ijms232213970.
[112] R. Vassar, B.D. Bennett, S. Babu-Khan, S. Kahn, E.A. Mendiaz, P. Denis, D. B. Teplow, S. Ross, et al., β-Secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE, Science 286 (1999) 735–741, https://doi.org/10.1126/science.286.5440.735.
[113] J. El Khoury, Neurodegeneration and the neuroimmune system, Nat. Med. 16 (2010) 1369–1370, https://doi.org/10.1038/nm1210-1369.
[114] J. Read, C. Suphioglu, Dropping the BACE: beta secretase (BACE1) as an alzheimer's disease intervention target, Neurodegener. Dis. (2013), https://doi.org/10.5772/53603.
[115] M.M. Mesulam, The cholinergic innervation of the human cerebral cortex, Prog. Brain Res. 145 (2004) 67–78, https://doi.org/10.1016/S0079-6123(03)45004-8.
[116] A. Alvarez, R. Alarco, C. Opazo, E.O. Campos, F. Jose, F.H. Caldero, et al., Stable complexes involving acetylcholinesterase and amyloid- ␣ peptide change the biochemical properties of the enzyme and increase the neurotoxicity of, Alzheimer ' s Fibrils 18 (1998) 3213–3223.
[117] M.S. García-Ayllón, I. Riba-Llena, C. Serra-Basante, J. Alom, R. Boopathy, J. Sáez-Valero, Altered levels of acetylcholinesterase in Alzheimer plasma, PLoS One 5 (2010), https://doi.org/10.1371/journal.pone.0008701.
[118] C. Geula, M. Mesulam, Special properties of cholinesterases in the cerebral cortex of Alzheimer's disease, Brain Res. 498 (1989) 185–189, https://doi.org/10.1016/0006-8993(89)90419-8.
[119] N.C. Inestrosa, J.A. Godoy, R.A. Quintanilla, C.S. Koenig, M. Bronfman, Peroxisome proliferator-activated receptor γ is expressed in hippocampal neurons and its activation prevents β-amyloid neurodegeneration: role of Wnt signaling, Exp. Cell Res. 304 (2005) 91–104, https://doi.org/10.1016/j.yexcr.2004.09.032.
[120] J.D. Harper, P.T. Lansbury, Models of amyloid seeding in Alzheimer's disease and scrapie: mechanistic truths and physiological consequences of the time-dependent solubility of amyloid proteins, Annu. Rev. Biochem. 66 (1997) 385–407, https://doi.org/10.1146/annurev.biochem.66.1.385.
[121] N.C. Inestrosa, A. Alvarez, C.A. Pérez, R.D. Moreno, M. Vicente, C. Linker, Acetylcholinesterase accelerates assembly of amyloid-β-peptides into Alzheimer's fibrils: possible role of the peripheral site of the enzyme, Neuron 16 (1996) 881–891, https://doi.org/10.1016/S0896-6273(00)80108-7.
[122] C. Soto, E.M. Castaño, R. Asok Kumar, R.C. Beavis, B. Frangione, Fibrillogenesis of synthetic amyloid-β peptides is dependent on their initial secondary structure, Neurosci. Lett. 200 (1995) 105–108, https://doi.org/10.1016/0304-3940(95)12089-M.
[123] R.N. Kalaria, S.N. Kroon, I. Grahovac, G. Perry, Acetylcholinesterase and its association with heparan sulphate proteoglycans in cortical amyloid deposits of Alzheimer's disease, Neuroscience 51 (1992) 177–184, https://doi.org/10.1016/0306-4522(92)90482-H.
[124] G.K. Kasa*$ P, Z. Rakonczay, The cholinergic system in ALZHEIMER'S disease, Prog. Neurobiol. 52 (1997) 511–535.
[125] A.E. Reyes, D.R. Perez, A. Alvarez, J. Garrido, M.K. Gentry, B.P. Doctor, N. C. Inestrosa, A monoclonal antibody against acetylcholinesterase inhibits the formation of amyloid fibrils induced by the enzyme, Biochem. Biophys. Res. Commun. 232 (1997) 652–655, https://doi.org/10.1006/bbrc.1997.6357.
[126] A. Roher, D. Wolfe, M. Palutke, D. KuKuruga, Purification, ultrastructure, and chemical analysis of Alzheimer disease amyloid plaque core protein, Proc. Natl. Acad. Sci. U.S.A. 83 (1986) 2662–2666, https://doi.org/10.1073/pnas.83.8.2662.
[127] N.C. Inestrosa, A. Alvarez, J. Godoy, A. Reyes, G.V. De Ferrari, Acetylcholinesterase-amyloid-β-peptide interaction and Wnt signaling involvement in Aβ neurotoxicity, Acta Neurol. Scand. Suppl. 102 (2000) 53–59, https://doi.org/10.1034/j.1600-0404.2000.00308.x.
[128] R. Randino, M. Grimaldi, M. Persico, A. De Santis, E. Cini, W. Cabri, et al., Investigating the neuroprotective effects of turmeric extract: structural interactions of β-amyloid peptide with single curcuminoids, Sci. Rep. 6 (2016) 1–17, https://doi.org/10.1038/srep38846.
[129] O.O. John, I.S. Amarachi, A.P. Chinazom, E. Adaeze, M.B. Kale, M.D. Umare, A. B. Upaganlawar, Phytotherapy: a promising approach for the treatment of Alzheimer's disease, Pharmacol. Res. - Mod. Chinese Med. 2 (2022) 100030, https://doi.org/10.1016/j.prmcm.2021.100030.
[130] G.K. Pratap, S. Ashwini, M. Shantaram, ALZHEIMER'S disease: a challenge inits management with certain medicinal plants-a review, Int. J. Pharma Sci. Res. 8 (2017) 4960–4972, https://doi.org/10.13040/IJPSR.0975-8232.8(12).4960-72.
[131] G.K. Pratap, M. Shantaram, An alternative approach for anti-alzheimer's compounds from plant extracts, Tyler Fr 1 (2020) 15–42.
[132] M.A. Chacón, A.E. Reyes, N.C. Inestrosa, Acetylcholinesterase induces neuronal cell loss, astrocyte hypertrophy and behavioral deficits in mammalian hippocampus, J. Neurochem. 87 (2003) 195–204, https://doi.org/10.1046/j.1471-4159.2003.01985.x.
[133] T. Rees, A. Berson, E. Sklan, L. Younkin, S. Younkin, S. Brimijoin, H. Soreq, Memory deficits correlating with acetylcholinesterase splice shift and amyloid burden in doubly transgenic mice, Curr. Alzheimer Res. 2 (2005) 291–300, https://doi.org/10.2174/1567205054367847.
[134] A. Castro, A. Martinez, Targeting beta-amyloid pathogenesis through acetylcholinesterase inhibitors, Curr. Pharmaceut. Des. 12 (2006) 4377–4387, https://doi.org/10.2174/138161206778792985.
[135] G. Brahmachari, Natural products in the drug discovery programmes in alzheimer ' s : impacts and prospects, Asia. Pac. Biotech News 15 (2011) 14.
[136] A. Kumar, A. Singh, A. Aggarwal, Therapeutic potentials of herbal drugs for Alzheimer's disease—an overview, Indian J. Exp. Biol. 55 (2017) 63–73.
[137] G.K. Pratap, V. Jayakar, V. Lokapur, M. Shantaram, Role of functional foods in the amelioration of chronic and neurodegenerative diseases, Bentham Publ. 1 (2021) 1–20.
[138] I. Erdogan Orhan, Current concepts on selected plant secondary metabolites with promising inhibitory effects against enzymes linked to alzheimer's disease, Curr. Med. Chem. 19 (2012) 2252–2261, https://doi.org/10.2174/092986712800229032.
[139] F. Ahmed, R. Ghalib, P. Sasikala, K. Mueen Ahmed, Cholinesterase inhibitors from botanicals, Phcog. Rev. 7 (2013) 121–130, https://doi.org/10.4103/0973-7847.120511.
[140] B. Koul, U. Farooq, D. Yadav, Phytochemicals : A Promising Alternative for the Prevention of Alzheimer ' S Disease, 2023.
[141] Z.M. Qian, Y. Ke, Huperzine A: is it an effective disease-modifying drug for Alzheimer's disease? Front. Aging Neurosci. 6 (2014) 1–6, https://doi.org/10.3389/fnagi.2014.00216.
[142] A. Ertas, S. Yigitkan, I.E. Orhan, A focused review on cognitive improvement by the genus Salvia L. (Sage)—from ethnopharmacology to clinical evidence, Pharmaceuticals 16 (2023), https://doi.org/10.3390/ph16020171.
[143] A. Mokhtari-Zaer, S. Saadat, V. Ghorani, A. Memarzia, M.H. Boskabady, The effects of saffron (Crocus sativus) and its constituents on immune system, Saffron 5 (2020) 193–217, https://doi.org/10.1016/b978-0-12-818462-2.00016-4.
[144] 1 and Sayeed Ahmad1 Abida Parveen, Bushra Parveen, Rabea Parveen, Challenges and guidelines for clinical trial of herbal drugs, J. Pharm. BioAllied Sci. 7 (2015) 329–333.
[145] D. Sun, W. Gao, H. Hu, S. Zhou, Why 90% of clinical drug development fails and how to improve it? Acta Pharm. Sin. B 12 (2022) 3049–3062, https://doi.org/10.1016/j.apsb.2022.02.002.
[146] M. Jonathan, R.T. Davidson, Effect of Hypericum perforatum (St john's wort) in major depressive disorder, Am. Med. Assoc. 287 (2015) 1807–1814.
[147] J.D.G. Ronald B. Turner, Bauer Rudolf, Karin Woelkart, Thomas C. Hulsey, An evaluation of echinacea angustifolia in experimental rhinovirus infections ronald, N. Engl. J. Med. 365 (2011) 687–696.
[148] B.E. Snitz, E.S. O'Meara, M.C. Carlson, A.M. Arnold, D.G. Ives, S.R. Rapp, J. Saxton, O.L. Lopez, L.O. Dunn, K.M. Sink, S.T. DeKosky, Ginkgo biloba for preventing cognitive decline in older adults a randomized trial, JAMA 302 (2009) 2663–2670, https://doi.org/10.1001/jama.2009.1913.
[149] A.U. Rahman, A. Khalid, N. Sultana, M. Nabeel Ghayur, M. Ahmed Mesaik, M. Riaz Khan, A.H. Gilani, M. Iqbal Choudhary, New natural cholinesterase inhibiting and calcium channel blocking quinoline alkaloids, J. Enzym. Inhib. Med. Chem. 21 (2006) 703–710, https://doi.org/10.1080/14756360600889708.
[150] E.M. Cardoso-Lopes, J.A. Maier, M.R. Da Silva, L.O. Regasini, S.Y. Simote, N. P. Lopes, J.R. Pirani, V. Da Silva Bolzani, M.C.M. Young, Alkaloids from stems of esenbeckia leiocarpa Engl. (Rutaceae) as potential treatment for alzheimer disease, Molecules 15 (2010) 9205–9213, https://doi.org/10.3390/molecules15129205.

[151] A. Murray, M. Faraoni, M. Castro, N. Alza, V. Cavallaro, Natural AChE inhibitors from plants and their contribution to alzheimer's disease therapy, Curr. Neuropharmacol. 11 (2013) 388–413, https://doi.org/10.2174/1570159x11311040004.
[152] Z.D. Yang, X. Zhang, J. Du, Z.J. Ma, F. Guo, S. Li, X.J. Yao, An aporphine alkaloid from Nelumbo nucifera as an acetylcholinesterase inhibitor and the primary investigation for structure-activity correlations, Nat. Prod. Res. 26 (2012) 387–392, https://doi.org/10.1080/14786419.2010.487188.
[153] P.K. Mukherjee, V. Kumar, M. Mal, P.J. Houghton, Acetylcholinesterase inhibitors from plants, Phytomedicine 14 (2007) 289–300, https://doi.org/10.1016/j.phymed.2007.02.002.
[154] T.M. Hung, M.K. Na, N.T. Dat, T.M. Ngoc, U.J. Youn, et al., Cholinesterase inhibitory and anti-amnesic activity of alkaloids from Corydalis turtschaninovii, J. Ethnopharmacol. 119 (2008) 74–80, https://doi.org/10.1016/j.jep.2008.05.041.
[155] H.A. Jung, B.S. Min, T. Yokozawa, J.H. Lee, Y.S. Kim, J.S. Choi, Anti-Alzheimer and antioxidant activities of coptidis rhizoma alkaloids, Biol. Pharm. Bull. 32 (2009) 1433–1438, https://doi.org/10.1248/bpb.32.1433.
[156] K.M. Cho, I.D. Yoo, W.G. Kim, 8-Hydroxydihydrochelerythrine and 8-hydroxydihydrosanguinarine with a potent acetylcholinesterase inhibitory activity from Chelidonium majus L, Biol. Pharm. Bull. 29 (2006) 2317–2320, https://doi.org/10.1248/bpb.29.2317.
[157] J.M. Rollinger, D. Schuster, E. Baier, E.P. Ellmerer, Europe PMC Funders Group Taspine : Bioactivity-Guided Isolation and Molecular Ligand – Target Insight of a Potent Acetylcholinesterase Inhibitor from Magnolia X Soulangiana, vol. 69, 2012, pp. 1341–1346, https://doi.org/10.1021/np060268p.Taspine.
[158] S. Berkov, C. Codina, F. Viladomat, J. Bastida, N-Alkylated galanthamine derivatives: potent acetylcholinesterase inhibitors from Leucojum aestivum, Bioorg. Med. Chem. Lett 18 (2008) 2263–2266, https://doi.org/10.1016/j.bmcl.2008.03.008.
[159] K. Chopra, S. Misra, A. Kuhad, Current perspectives on pharmacotherapy of Alzheimer's disease, Expet Opin. Pharmacother. 12 (2011) 335–350, https://doi.org/10.1517/14656566.2011.520702.
[160] M.T. Andrade, J.A. Lima, A.C. Pinto, C.M. Rezende, M.P. Carvalho, R.A. Epifanio, Indole alkaloids from Tabernaemontana australis (Müell. Arg) Miers that inhibit acetylcholinesterase enzyme, Bioorg. Med. Chem. 13 (2005) 4092–4095, https://doi.org/10.1016/j.bmc.2005.03.045.
[161] K. Ingkaninan, K. Changwijit, K. Suwanborirux, Vobasinyl-iboga bisindole alkaloids, potent acetylcholinesterase inhibitors from Tabernaemontana divaricata root, J. Pharm. Pharmacol. 58 (2010) 847–852, https://doi.org/10.1211/jpp.58.6.0015.
[162] M. Fiala, J. Lin, J. Ringman, V. Kermani-Arab, G. Tsao, A. Patel, et al., Ineffective phagocytosis of amyloid-β by macrophages of Alzheimer's disease patients, J. Alzheim. Dis. 7 (2005) 221–232, https://doi.org/10.3233/JAD-2005-7304.
[163] C. Seidl, B.L. Correia, A.E.M. Stinghen, C.A.M. Santos, Acetylcholinesterase inhibitory activity of uleine from Himatanthus lancifolius, Zeitschrift Fur Naturforsch. - Sect. C J. Biosci. 65 C (2010) 440–444, https://doi.org/10.1515/znc-2010-7-804.
[164] D.B. Zhang, J.J. Chen, Q.Y. Song, L. Zhang, K. Gao, Lycodine- Type alkaloids from lycopodiastrum casuarinoides and their acetylcholinesterase inhibitory activity, Molecules 19 (2014) 9999–10010, https://doi.org/10.3390/molecules19079999.
[165] A. Khalid, Zaheer Ul-Haq, M.N. Ghayur, F. Feroz, Atta Ur-Rahman, A.H. Gilani, M. I. Choudhary, Cholinesterase inhibitory and spasmolytic potential of steroidal alkaloids, J. Steroid Biochem. Mol. Biol. 92 (2004) 477–484, https://doi.org/10.1016/j.jsbmb.2004.08.003.
[166] Atta ur-Rahman, S. Parveen, A. Khalid, A. Farooq, M.I. Choudhary, Acetyl and butyrylcholinesterase-inhibiting triterpenoid alkaloids from Buxus papillosa, Phytochemistry 58 (2001) 963–968, https://doi.org/10.1016/S0031-9422(01)00332-6.
[167] E. Ahmed, S.A. Nawaz, A. Malik, M.I. Choudhary, Isolation and cholinesterase-inhibition studies of sterols from Haloxylon recurvum, Bioorg. Med. Chem. Lett 16 (2006) 573–580, https://doi.org/10.1016/j.bmcl.2005.10.042.
[168] M. Öztürk, U. Kolak, G. Topu, S. Öksüz, M.I. Choudhary, Antioxidant and anticholinesterase active constituents from Micromeria cilicica by radical-scavenging activity-guided fractionation, Food Chem. 126 (2011) 31–38, https://doi.org/10.1016/j.foodchem.2010.10.050.
[169] M. Jung, M. Park, Acetylcholinesterase inhibition by flavonoids from Agrimonia pilosa, Molecules 12 (2007) 2130–2139, https://doi.org/10.3390/12092130.
[170] N.S.L. Perry, P.J. Houghton, A. Theobald, P. Jenner, E.K. Perry, In-vitro inhibition of human erythrocyte acetylcholinesterase by Salvia lavandulaefolia essential oil and constituent terpenes, J. Pharm. Pharmacol. 52 (2010) 895–902, https://doi.org/10.1211/0022357001774598.
[171] F. Menichini, R. Tundis, M.R. Loizzo, M. Bonesi, M. Marrelli, G.A. Statti, F. Menichini, F. Conforti, Acetylcholinesterase and butyrylcholinesterase inhibition of ethanolic extract and monoterpenes from Pimpinella anisoides V Brig. (Apiaceae), Fitoterapia 80 (2009) 297–300, https://doi.org/10.1016/j.fitote.2009.03.008.
[172] P. Gk, P.G. Nagaraju, A. Danagoudar, C.G. Joshi, P. Priyadarshini, Y. Hussein, I. Mohammed, L. Kumar, M. Shantaram, Neuroprotective , lifespan , memory enhancing potential , and molecular docking studies of natural compound from Curculigo orchioides Gaertn .,: a study on Alzheimer ' s disease model of Appl-GAL4 Drosophila melanogaster, South Afr. J. Bot. 149 (2022) 60–66, https://doi.org/10.1016/j.sajb.2022.05.047.
[173] E. Hone, F. Lim, I.J. Martins, Fat and Lipid Metabolism and the Involvement of Apolipoprotein E in Alzheimer ' S Disease, 2019, pp. 189–231.
[174] M.J. Sharman, G. Verdile, S. Kirubakaran, C. Parenti, A. Singh, G. Watt, T. Karl, D. Chang, C. Guang, L. Gerald, Targeting inflammatory pathways in alzheimer ' s disease : a focus on natural products and phytomedicines, CNS Drugs (2019), https://doi.org/10.1007/s40263-019-00619-1.
[175] D. Kaufmann, A.K. Dogra, A. Tahrani, F. Herrmann, M. Wink, Extracts from traditional Chinese medicinal plants inhibit acetylcholinesterase, a known Alzheimer's Disease target, Molecules 21 (2016), https://doi.org/10.3390/molecules21091161.
[176] F.T. Hane, M. Robinson, B.Y. Lee, O. Bai, Z. Leonenko, M.S. Albert, Recent progress in alzheimer's disease research, Part 3: diagnosis and treatment, J. Alzheim. Dis. 57 (2017) 645–665, https://doi.org/10.3233/JAD-160907.
[177] E. Jack Jr, C.R., D.A. Bennett, K. Blennow, M.C. Carrillo, B. Dunn, S.B. Haeberlein, D.M. Holtzman, W. Jagust, F. Jessen, J. Karlawish, Liu, Development of novel phosphodiesterase 5 inhibitors for the therapy of Alzheimer's disease, Alzheimer's Dementia 14 (2018) 535–562, https://doi.org/10.1016/j.bcp.2020.113818.DEVELOPMENT.
[178] H. Hampel, S.E. O'Bryant, J.L. Molinuevo, H. Zetterberg, C.L. Masters, S. Lista, S. J. Kiddle, R. Batrla, K. Blennow, Blood-based biomarkers for Alzheimer disease: mapping the road to the clinic, Nat. Rev. Neurol. 14 (2018) 639–652, https://doi.org/10.1038/s41582-018-0079-7.
[179] E.V. Rao, Drug discovery from plants, Curr. Sci. 93 (2007) 1060, https://doi.org/10.1007/978-3-540-74603-4_1.
[180] E. Lien, J. Adams, L. Lien, M. Law, Alternative Approaches to the Search for Alzheimer's Disease Treatments, J, vol. 1, 2018, pp. 2–7, https://doi.org/10.3390/j1010002.
[181] J.J. Mo, J.Y. Li, Z. Yang, Z. Liu, J.S. Feng, Efficacy and safety of anti-amyloid-β immunotherapy for Alzheimer's disease: a systematic review and network meta-analysis, Ann. Clin. Transl. Neurol. 4 (2017) 931–942, https://doi.org/10.1002/acn3.469.