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ALZHEIMER'S DISEASE: PHARMACOLOGICAL ASPECTS AND DRUG THERAPY

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disease in which there is a progressive loss in the structure and function of neurons. In a neuron, myelin sheath is highly affected in this disease. AD mainly affects the older people and is the fourth largest cause of death. In AD, because of overactivity of APP secretase, activation of β- and γ-pathways initiate that causes the overproduction of toxic amyloid species *i.e.* Aβ oligomers and amyloid plaques. The function of MAPs is to interact with tubulin and assemble them into microtubules to form a microtubule network. Dementia a chronic loss of cognition usually affecting memory and Alzheimer causes 50% to 80% of dementia causes. Molecular mechanisms underlying the pathophysiology of AD are still not known. Currently available drug therapies primarily consist of cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonist approved by the U.S. Food and Drug Administration (FDA) and some neuroprotective agents. Various target specific drugs from natural, organic and inorganic origins are studied which with the help of animal models can be evaluated to show a potential in the treatment of AD. All these available drugs show only symptomatic relief but not treating the cause of this disease.

KEYWORDS: Alzheimer's disease, Amyoid precursor protein, Amyloid β, Dementia, natural, organic, inorganic.

INTRODUCTION

Neurodegenerative diseases are a multifarious group of disorders that are characterised by the continuous disruption in the anatomy and functioning of central nervous system. In these disorders deterioration in the neuronal cells of brain and spinal cord occurs. Neurodegenerative diseases affect various body activities that include balance, movement, talking, breathing, and heart function.[1]

Alois Alzheimer discovered the AD in 1906.[2] It is a neurodegenerative disease that mainly affects the older people having an age above 65 years and one of the largest common causes of death. It impairs the memory and cognitive judgement of the person. The credit of the discovery of AD is given to Alois Alzheimer who firstly describes the dementic condition which thereafter became known as AD. [3] He described the case of 51 years old lady, named Auguste D, who was suffered with cerebral cortex disease; showed impairment in memory, language, orientation, behaviour.[4]

AD is the commonest origin of irreversible dementia that initiates neurodegeneration and vascular processes in brain.[5] Dementia is a clinical syndrome that causes progressive loss in the intellect, cognitive abilities, social behaviour, emotional state, person's ability to perform daily activities. Person's memory, language, decision making ability, attention, social activities, relationships, all get affected in the AD.[6] AD is characterised by accumulation of hyperphosphorylated Tau protein inside the neuronal cytoplasm that constitute neurofibrillary tangles (NFT's) and Aβ peptide that forms Aβ plaques outside the neuron of diseased person.[7]

Neuroinflammation, oxidative stress, genetic alterations, and environmental factors plays important role in the pathogenesis of AD. Various animal models are available which are used in the evaluation of drugs that shows their action on the particular targets to treat the complication occurs in the AD. Currently available drugs used in the treatment of AD are only show symptomatic relief but does not treat the underlying cause. So there is an urgent need to develop efficient therapies to treat the cause of AD. In the last years, various compounds were isolated from the natural sources that showed their effectiveness in treating the different pathological mechanism of AD.[8] In this review, we will focus on various natural, organic, inorganic compounds that are under different phases of clinical trials.[9-11] Natural compounds obtained a first position in the treatment of AD. In a current scenario, scientific community showing

lot of interest in choosing the naturals as they have neuroprotective effects in treating the cause of AD.[12] Natural compounds inhibit the pathological mechanisms in different ways such as; inhibiting Aβ production, reducing oxidative stress, stimulating the degradation of Aβ, decreasing neuroinflammation. In vitro and in vivo studies are done using naturals that shows their potential pharmacological activity in the treatment of AD.[13]

Organic and inorganic compound are formed by various substitution reactions. Redox chemistry has shown its prominent role in the development of various organic, inorganic compounds in AD pathogenesis. [14] Metal ions such as copper, ferrous, zinc have potential role in the pathogenesis of AD. These ions stimulate the oxidative stress in Aβ toxicity. Aβ plaques having complexes with copper and iron generate hydrogen peroxide free radical species that enhances oxidative stress in the neurons. On the basis of this, various antioxidants and metal coordinating compounds showing promising effects in clinical trial phases in the treatment of AD.[15]

Epidemiology of AD

AD is a multifactorial disease that is not defined with the help of a single known cause. For its development and progression several factors are associated which can be modifiable or nonmodifiable. [16] These factors include age is the largest risk factor for AD. More than 95% cases of AD are the people that are having an age of 65 or above this. [17] AD can occur due to mutation in the Presenillin *genes* present on chromosomes 1-14 or mutation in the Amyloid Precursor Protein (APP) *genes* present on chromosomes 21. People with Down's syndrome disorder may have early onset of AD. In this disorder abnormal cell division occurs that results in extra genetic material from chromosome 21. Due to which a distinct facial appearance, mental dysfunctioning, retardation of growth and various thyroid or heart related diseases may occur.[18] The E4 variant of Apolipoprotein E (APOE) *gene* which is located on a chromosome 19 is the largest risk factor for late onset AD. Nigerian blacks have higher levels of APO E4 allele in world populations. APOE is synthesized by astrocytes, and it helps in the transport of cholesterol to neurons by acting on their receptors. People with diabetes, hypertension, obesity, and smoking have high risk of AD.[19]

Pathological Mechanisms in AD

In AD, progressive neuron degeneration occurs because of formation of Aβ a plaque forming peptide and NFT's composed of hyperphosphorylated Tau proteins. Both these reasons results in the formation of Aβ toxic oligomers that ultimately cause imbalance between the formation, aggregation and excretion of Aβ plaques. [20] The overproduction and aggregation of Aβ peptides leads to the generation of neuritis plaques and hyperphosphorylation of Tau proteins results in the formation of NFT's that ultimately changes the cytoskeletal. Both these impair neuronal equilibrium and results in neuronal dysfunctioning and cell death in the AD .With the help of α-secretase (non-amyloidogenic) and β and γ-secretases (amyloidogenic) enzymes, APP cleaved into smaller peptides (Aβ1-40 and Aβ1-42). In AD, APP secretases are highly active that results in the activation of β and γ pathway. These pathways are responsible for the formation of reactive and toxic amyloid species i.e. Aβ oligomers (Aβ1-42 and Aβ1-40) and amyloid plaques. Aβ1-42 form insoluble aggregates and is more toxic than Aβ1-40. [21] Generation of signals because of cleavage of APP results in the formation of active oligomers involved in the pathogenesis of AD. β and γ-secretase enzymes act on the APP and initiate the process of proteolysis because of which Aβ1–42 monomer are formed, which in turn again converted into toxic oligomers. Neprilysin and insulin-degrading enzyme (IDE) are the two enzymes that are able to degrade the Aβ monomer. Accumulation of toxic oligomers cause inactivation of various signalling pathways like inactivation of cyclin dependent kinase 5 pathway because of which cell cycle get arrested (Fyn, FAK, GSK3β, CDK5) and changes in the structure of cell, proteins present in the synaptic cleft get altered. Matrix type metalloproteinase shows its emerging effects in pathogenesis of AD by progressing the intracellular neuronal inflammation and synaptic dysfunction. All these mechanisms ultimately results in the neuronal deterioration.[22-23]

Treatment of AD

Molecular pathways underlying the cause of AD are yet not completely understood. [24] USFDA approved some drug therapies that only able to produce a symptomatic relief but not treat the underlying cause. Presently available drug treatment includes; inhibitors of cholinesterase (ChE) enzyme that inhibits the cholinesterase enzyme and able to increase the level of Ach at the synaptic cleft. Other than this Memantine drug is available which is a competitive antagonist of glutamate receptor is. These drugs show their actions by one of the following mechanism: a) by increasing blood flow to cerebral region, b) by inhibit the metabolism of ACh, c) by enhancing the level of ACh at synaptic cleft, d) by enhancing the memory. Recently available new drug therapies are able to target the genetic variants and enzymes that are involved in the AD.[25]

Treatment is chosen on the basis of age, overall health, and medical history, severity of disease, effectiveness of drug, priority of patient and caregivers about what treatment have to be taken. Aβ protein cataract and hyperphosphorylation of Tau protein are the two major causes for the AD. Thus the drug therapy of AD mainly target on decreasing Aβ level and hyperphosphorylation of Tau protein. Drugs used in the AD are also known as cerebroactive drugs. [26] In a current scenario various drugs are available which are classified into AChE inhibitors (Tacrine, Rivastigmine, Donepezil, Galantamine), Glutamate Antagonist (Memantine) act on NMDA receptor. Others are (Piracetam, Pyritinol,

Dihydroergotoxine, Citicoline, Piribedil), NSAIDs, Estrogen, Melatonin, Antihypertensives, Insulin, Secretase Inhibitors, Immunization. [27] The available marketed drugs only treat the symptoms but not the cause so there is an urgent need to develop the drugs to treat the cause of AD. In this review, we have discussed the researches of scientific community on various natural, organic, inorganic compounds based on their potential efficacy in AD based preclinical and clinical models. This review focused on potential therapeutic effects of natural agents followed by organic and inorganic agents by inhibiting different the pathological mechanisms involved in AD.

Natural Agents

Maher P *et al* investigated the neuroprotective activity of *Eriodictyon* (Yerbasanta), a genus to treat respiratory and age-related complications. Investigator prepared Dichloromethane extracts from leaves of 14-Eriodictyontaxa and were preserved in the SD Herbarium for further research. The extracts were tested for neuroprotection in nerve cells against oxytosis and ferroptosis and for antinflammatory activity in brain microglial cells exposed to bacterial lipopolysaccharide. In parallel, the levels of the flavanones sterubin, *Eriodictyon* and homoeriodictyol were measured by mass spectrometry. *Eriodictyon* species presented strong neuroprotective and antinflammatory activities. The extract was co related with sterubin content for its protective properties, indicating that sterubin was the major active compound present.[28]

Kurt B *et al* investigated the antineuroinflammatory and glia/neuroprotective properties of GR24, making SLs promising Scaffolds for the development of novel anti AD candidates. A Subclasses was identified which was structurally different and biologically active compound as of apocarotenoids named strigolactone (SLs) was found to be novel phytohormones. SLs are mainly anti-cancer agents but, their effects on the brain need to be explored. Herein, the SIM-A9 Microglial cell line was used as a phenotypic screening tool to search for the representative SL, GR24, and demonstrating marked potency in the suppression of lipopolysaccharide induced neuroinflammatory / neurotoxic mediators by regulating NF-κB, Nrf2, and PPARγ signaling. GR24 also in the brain endothelial cell line bEnd3 mitigated the LPS-increased permeability as evidenced by reduced Evans blue extravasation through enhancing the expression of tight junction protein, occluding.[29]

Gao N *et al* synthesized and carried out the screening of inorganic metal compounds as multifunctional therapeutic agents against AD by Inhibitions of Aβ aggregation and Aβ haem peroxidase like activity have received much attention because polyoxometalate with a Wells Dawson structure can efficiently inhibit Aβ aggregation. However, the interaction between POMs and Aβ is robust, but still needs to improve Aβ binding affinity. The designed series of transition metal-functionalized POM derivatives with a defined histidine chelated binding site have much better Aβ inhibition and peroxidase like activity inhibition effects than the parent POM and these compounds can cross the BBB and are metabolized after 48h.[30]

Kumar H *et al* investigated the oxidative stress is the central component of chronic diseases. The cytoprotective genes help to up-regulate enzyme activity in response to oxidative stress and its treatment with certain dietary phytochemicals with respect to nuclear factor, erythroid 2-related factor and antioxidant response (Nrf2/ARE) pathway. Research work drafted natural product derived bioactive compounds to activate Nrf2/ARE pathway and recapitulated to induce Nrf2 molecular mechanisms for providing favorable condition in model for experiment of chronic diseases. Also, pharmacological barrier of Nrf2 signaling has arrived as a favorable strategy against multi-drug resistance by remodeling its treatment strength. Many natural product-derived inhibitors of Nrf2/ARE pathway were also enlisted by the researcher as oxidative stress is the main and basic component of all major chronic diseases. The Nrf2/ARE pathway was primarily thought to be a regulator of antioxidant enzymes but recent studies have proved its role in the regulation of many genes for stress-generated. Contrary Nrf2 production appears to decline with ageing. It is still unclear which target gene in the Nrf2 pathway contributes to these detrimental effects; hence, it is mandatory to evaluate the role of activating Nrf2 in in vitro and in vivo experimental models with the use of available Nrf2 inducers, Nrf2 overexpression, or Keap1 down-regulation. Epidemiological studies have shown that natural products provide beneficial effects by regulating Nrf2 levels.[31]

Murray AP *et al* investigated a total of 128 studies which correspond to the most relevant research work published during 2006-2012 on plant derived compounds, plant extracts and essential oils found to explore AChE inhibition as AChE inhibitors show useful therapeutic approach in AD, target is for new molecules with antiAChE activity. Many secondary metabolites are potential origin for new inhibitors and extracts derived from plants to inhibit ACh enzyme, as it, increases the levels of the acetylcholine neurotransmitter present in the brain, thereby correcting cholinergic functional activity in patients with AD and alleviating the symptoms of this neurological disorder.[32]

Gao J *et al* investigated that the efficacies and underlying mechanisms of flavonoids, alkaloids, phenylpropanoids, triterpenoid saponins, and polysaccharides have potential efficacies against AD *via* targeting multiple pathological changes of this disease. Research explained the evidence-based medicine principle to use medicines clinically for the treatment of AD, and also discovered its monomer compositions as promising lead molecule for drug design in treatment of AD. Some agents in categories of flavonoids and

phenylpropanoids exhibit multiple biological properties that aim to eradicate the root causes of AD onset and may represent the future direction of new drug development.[33]

Habtemariam S *et al* investigated the Aβ peptides, Aβ 1–40 and Aβ 1–42, represent major molecular targets to develop potential drugs and diagnostic tools for AD. Many oligomeric and fibrillar mixture derived from peptides are principal component for amyloid plaques which is seen in post mortem of patients suffering from AD. Rosmarinic acid was found to be efficient in blocking in vitro amyloid peptides aggregation and also hamper the growth of the disease in targeted animal models. They also demonstrated the possibility to exploit STD-NMR and trNOESY experiments to screen extracts from natural sources for the presence of Aβ peptide ligands. RA has been previously identified as the main molecule causing the neuroprotective effect of sage against Aβ peptide neurotoxicity, the characterization of Aβ oligomer recognition and binding processes is crucial for the rational design of new ligands with higher affinity for Aβ aggregates, suitable for the development of innovative tools for both therapy and diagnosis of AD. The significance of this result increases in the light of the recent discovery of the antidiabetic activity of methyl caffeate which fits with the accumulation of Aβ fibrils in type 2 diabetes.[34]

Choi DY *et al* investigated several factors contribute to oxidative stress in AD brains as it is a disease's hallmark. Mitochondrial dysfunction found in AD patients may exaggerate generation of ROS and oxidative stress. Second, Aβ peptide generates ROS in the presence of metal ions such as Fe^{2+} and Cu^{2+}. Third, activated glial cells in AD brains may produce excessive amount of superoxide and nitric oxide through NADPH oxidase and inducible nitric oxide synthetase, respectively. Increased concentrations of ROS damage the body protein, lipid and nucleic acids. Plant derived polyphenolic compounds act in vitro and in vivo against many neurotoxic problems found in AD models. Dietary polyphenolic compounds exhibit neuroprotective effects through scavenging free radicals and increasing antioxidant capacity. Furthermore, they could facilitate the endogenous antioxidant system by stimulating transcription as many epidemiological and clinical studies showed therapeutic potential in the treatment of AD. Antioxidant polyphenolic compounds have been considered as an alternative therapeutic strategy for AD, natural polyphenolic chemicals still hold potential for intervention of AD neurodegeneration due to their safety and neuroprotective capacity. Elucidation of their action mechanism may provide better insight for new targets for neuroprotective drugs.[35]

Ballatore C *et al* investigated the microtubule (MT) associated protein tau and is expressed in the axons of neurons. Protein tau is an endogenous MT stabilizing agent required for axonal transport. There are many factors responsible for the loss of MT stabilizing tau activity majorly caused by misfolding, hyper-phosphorylation, and sequestration of tau to insoluble form of aggregates, and this leads to deficiency in axonal transport along with Neuropathological disorder. MT stabilizing drugs can be utilized for in vitro and preclinical in vivo studies to compensate the loss of tau function and also help to maintain or restore transport of axon. According to this research MT stabilizing compounds help in the treatment of AD and related tauopathies. Research also demonstrates the therapeutic activity of MT stabilizing drugs with respect to neurodegenerative tauopathies, as well as an overview of the different classes of MT stabilizing compounds. These agents appear to be among the most compelling as potential treatments for neurodegenerative tauopathies. The promising results obtained from the epothilone D studies in tau animal models, summarized here, provide important validation of this therapeutic strategy and, notably, have resulted in the selection of epothilone D as a clinical candidate for the treatment of AD.[36]

Mancuso C *et al* investigated the study on curcumin obtained from *Ginkgo biloba* and acetyl-L-carnitine with the help of some preclinical studies suggested neuroprotective effects can be caused due to free radical scavenging activity or the inhibition of pro-inflammatory pathways or the potentiation of the cell stress response. A new drug-delivery strategy involving factors like improve systemic bioavailability, brain penetrance and administration of natural substances at low doses will help in the treatment of AD. This approach could also minimize the risk for adverse effects related to unwanted fluctuations in nutraceutical plasma concentrations.[37]

Essa MM *et al* investigated the effect of polyphenolic antioxidants present in fruits, vegetables, herbs and nuts, can effectively help hinder neurodegeneration effect by improving memory and cognitive behaviour. Walnut showed neuroprotective effect against AD, as mechanisms behind the curative effects depends on the activity of phytonutrients signalling pathways mainly associated with protein folding and neuroinflammation shown by resveratrol in grapes, curcumin in turmeric, gingerols in ginger, and epicatechin-3 gallate in tea since all the mentioned phytopeholics exhibit antiamyloidogenic activity in AD models. Furthermore, polyphenols can also exert protective effects by regulating signalling pathways such as NF-kB, JNK and MAPK. The neuroprotective effects of the natural compounds, withanoides, ginkolide, iridoid glycoside, and huperzine, these natural products act against Aβ formation and/or tau hyper phosphorylation. AChE inhibitory activity of herbs, marine sponges and other natural products can also play important role in the prevention of AD.[38]

Di Paolo *et al* investigated the lipid-mediated signal regulates physiological processes, and function of brain. This dysregulation of lipid pathways cause AD.

Similar to genome-wide and proteomics-based approaches, lipidomics can unmask crosstalk between biochemical pathways and provide essential mechanistic insights into the molecular basis of cellular or organismal changes. Additionally, lipidomics offers enormous potential for the identification of disease linked body fluid biomarkers, which can prove particularly helpful as diagnostic tools at early stages of dementia and in the diagnosis of AD specific mild cognitive impairment.[39]

Ji HF *et al* investigated a study on a natural isoquinoline alkaloid namely berberine possesses antioxidant activity, AChE and butyrylAChE inhibitory effect, monoamine oxidase inhibitory action, Aβ peptide level-reducing and cholesterol lowering action, showed multipotent activity of berberine to encounter AD since the compound is nontoxic at clinical use dose, show loss of genotoxic effect, cytotoxic effect or mutagenic activity. Berberine when orally administered it passes through the BBB and is multipotent agent to combat AD.[40]

Ferruzzi MG *et al* investigated a study on grape seed polyphenolic extract (GSPE) the bioavailability profile and its brain deposition in mouse model of AD. Plasma pharmacokinetic response of plasma in GSPE phenolic compound was measured by intragastric gavage of 50, 100, and 150 mg per kg body weight. Presence of gallic acid, catechin, and epicatechin in plasma of rats was identified using liquid chromatography mass spectrometry analysis as gavaged acutely with GSPE. Also found the presence of metabolites like 4-methylgallic acid, 3'-methylcatechin, and 3'-methylepicatechin. C_{max} for individual GSPE constituents and their metabolites increased with increasing GSPE oral dose. A Significant increase in bioavailability was found on daily exposure of GSPE of gallic acid, catechin, and epicatechin. Catechin, and epicatechin were not found active in brain tissues of rats on single GSPE dose.[41]

Adams M *et al* investigated a study on vietnamese medicine for treating age related dementia. *Acanthopanax trifoliatus* family Araliaceae useful for its stimulant and tonic activity also improve memory. Leaves of *Acanthopanax trifoliatus* contain 16-en-19-oic acid, taraxerol, taraxerol acetate, lupane-triterpene carboxylic acids, called acantrifoic acid and acantrifoside as major chemical constituents. *Dimocarpus longan* family Sapindaceae, source of longan fruits also useful as tonic and used to treat mental deficiency, neurasthenia, insomnia and amnesia. In Malaysia *Casuarina equisetifolia* (Casuarinaceae) a wide spreads herb or tree which somewhat resembles pine trees, is used as a sedative for the demented and to treat memory problems. In *Tibet Iris germanica* (Iridaceae) is believed to be a promoter of intellect and also useful in the treatment of insanity, epilepsy and against evil spirits. *Centella asiatica* already listed in the part on India is also used in Tibet as a promoter of memory and voice and is believed to be rejuvenating in general. Another remedy, believed to prevent aging is ghee, a form of melted butterfat which is said to promote complexion, beauty, voice, intellect, memory and give strength, virility and longevity Interestingly, a large study conducted with ginkgo extract EGb761 in France over 7 year suggested a preventive effect in an aged population cohort. The outcome of these long-term trials will be important in defining a possible role of natural product based preventive therapy in AD.[42]

Filho JMB *et al* investigated the species belonging to Amaryllidaceae, Apiaceae, Asteraceae, Fabaceae and Fumariaceae. Rich alkaloid amount present in extract increases activity because many of AChE inhibitors contain nitrogen. The alkaloids are the major compounds isolated from this species and shows inhibitory activity for the AChE.[43]

Akhondzadeh S *et al* investigated the *Savia officinalis* used in herbal medicine. In vitro cholinergic binding properties and modulation of mood and cognitive performance in humans suggested that the *Salvia officinalis* might potentially provide a novel natural treatment for AD. The efficacy and safety study obtained from extract of *Salvia officinalis* was explored using cognitive subscale of AD Assessment Scale (ADAS-cog) and Clinical Dementia Rating (CDR) with 60 drops/day dose over 4-month period using randomized studies. Results after 4 months of *Salvia officinalis* extract treatment produced a significant better outcome on cognitive functions than placebo. There were no significant differences in the two groups in terms of observed side effects except agitation that appears to be more frequent in the placebo group. The results of this study indicated that the efficacy of *Salvia officinalis* extract in the management AD. Moreover, *Salvia officinalis* may well reduce agitation of patients but these needs to be confirmed.[44]

Houghton PJ *et al* investigated the AChE inhibitors such as galantamine, huperzine A, physostigmine to increase ACh level than using cholinergic compounds, even nicotinic properties are of major interest PD treatment has relied on the increased level of DA levels using precursor and main drug L-DOPA, dopaminergic agonists obtained from ergot alkaloid derivatives upon its administration. Enzyme inhibitor causes breakdown of DA and is under research. Future trends could involve the use of a polyvalent 'cocktail' of drugs which act in different ways by mechanisms such as antioxidant and anti-inflammatory activity and the inhibition of the formation of fibrillary tangles and Aß plaques. Although the introduction of L-DOPA and other dopaminergic compounds over the last three decades has improved the condition of many sufferers of PD, the side effects and their unpredictability of occurrence highlight the fact that more work is needed. In this context also, the exploitation of compounds derived from plants with other mechanisms, such as monoamine oxidase

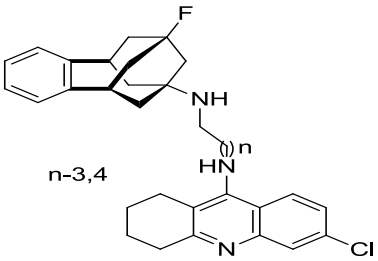
inhibition, may provide a better treatment experience in due course.[45]

Howes MJ *et al* investigated for their potential in AD therapy, and are now in clinical use of galantamine from *Galanthus nivalis* shown agreeable pharmacological effects in AD therapy. The majority of studies have focused on the antiChE alkaloids, such as physostigmine and galantamine. This is perhaps a reflection of the relative success of the use of AChE inhibitors in AD patients, and a lack of understanding of the pathological mechanisms that occur in AD and the subsequent targets for treatment. Although some plants, such as *Ginkgo biloba* and *Withania somnifera*, have shown beneficial effects on cognitive function, further studies regarding the compounds responsible for activity are necessary, to identify pharmacological activities of compound and was observed synergistically to increase activity.[46]

Auddy B *et al* investigated three such rasayana plants were tested for the first time for their toxicity and free radical scavenging activity both in vitro and ex vivo. Plant mixture infusions displayed no toxic effects on the viability of PC12 cell line when tested using MTT-test. The plant Extract of ethanol and water infusions were tested for their antioxidant activity in the 2,2-azinobis-3-ethyl-benzothiazoline-6-sulfonic acid radical cation decolourization assay; inhibition of lipid peroxidation by plant infusions was carried out using spontaneous lipid peroxidation of rat brain homogenate, and IC50 values were determined. The results showed that ethanolic extract obtained from *Sida cordifolia* was most potent followed by *Evolvulus alsinoides* and *Cynodon dactylon*. The antioxidant activity for the water infusions was observed using given order: *Evolvulus alsinoides* / *Cynodon dactylon* / *Sida cordifolia*. The results obtained for plant's water infusions on lipid peroxidation were high value of IC50 for Cynodon *dactylon followed by Sida cordifolia and Evolvulus alsinoides*.[47]

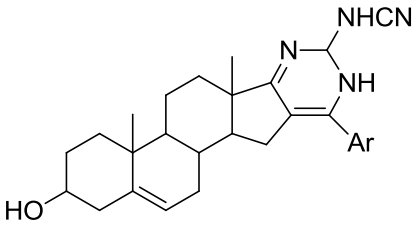
Organic Agents

Perez-Areales FJ *et al* investigated the synthesis of fluorobenzohomoadamantanamine with the potent AChE inhibitor 6-chlorotacrine by molecular hybridization of an NMDA receptor. The best hybrids **(1)** exhibit greater potencies than parent compounds against AChE IC50 44-fold increased potency over 6-chlorotacrin, IC50 44-fold increased potency over 6-chlorotacrine against butyrylAChE and 2-fold increased potency over the parent benzohomoadamantanamine and memantine against NMDA receptors, which suggests an additive effect of both pharmacophoric moieties in the interaction with the primary targets.[48]



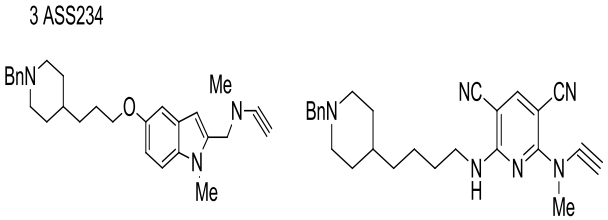
(1)

Abdallaa MM *et al* investigated the antiAD activity of some heterocyclic pyrimidine and thiopyrimidine derivatives fused with steroidal structure using Flurbiprofen as the reference drug. Some of these compounds were demonstrated to exhibit remarkable activity and their Aß lowering results as IC50 values reported. The tested derivatives represent the most populated set of compounds obtained during this study. One compound **(2)** has displayed the highest activity with IC50 value. Throughout this study, it has been noticed that no ulcerogencity or bleeding especially gastric ones cases, no effects on Notch intracellular domain responsive genes and no effects on cyclooxygenase 1 and cyclooxygenase 2.[49]



(2)

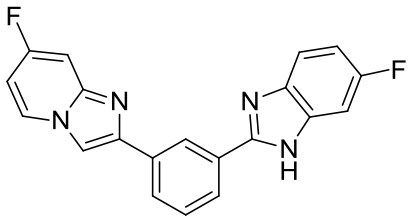
Aguilera OMB *et al* investigated the synthesis of donepezil-pyridyl hybrids and screened as multipotent ChE and monoamine oxidase inhibitors for the treatment of AD. One of the compound **(3)** was found as 318-fold more potent for AChE inhibition, and 1.3-fold less potent for ButyrylChE inhibition than the reference compound electrophorus electricus AChE.[50]



(3)

Al-Tel TH *et al* structured profoundly selective imidazopyridines with benzimidazolas well as arylimidazole as potent β-secretase inhibitors. As measured by FRET and cell-based enzyme linked immunosorbent assays some of the analogues demonstrated low nanomolar potency for the BACE1 enzyme and exhibited comparable affinity and high ligand efficiency. One of the compounds **(4)** displayed a

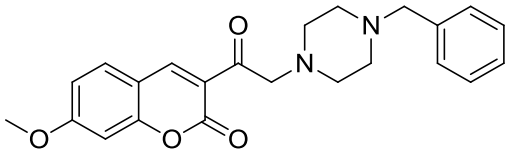
higher IC50 for BACE1 and exhibited cellular activity in the cell-based enzyme linked immunosorbent assay, high affinity and ligand efficiency. It has shown 204-fold more selectivity for BACE1 as compare to aspartyl protease BACE2.[51]



(4)

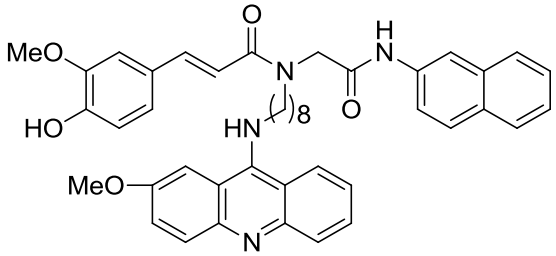
Annweiler C *et al* investigated the new drug regimen techniques dependent on Memantine joined with molecules having antioxidant effects, so as to make a multi-target therapy to increase neuronal protection and forestall AD progression. The Memantine and vitamin D combination enhanced protection against several degenerative processes linked to AD. This new pharmaceutical composition may give a viable answer for the issue of neuronal death and cognitive decline in AD.[52]

Bag S *et al* investigated the synthesis of compounds containing α, β-unsaturated carbonyl moiety (chalcones and coumarins) and evaluated as antiAD agents by means of inhibition of AChE, ButyrylAChE, Aβ self assembly and the disassembly of Aβ oligomers. Several compounds showed excellent potential as multifunctional compounds for AD. Docking studies performed well in all the assays gave a clear interpretation of various interactions in the gorge of AChE. Based on the results, the long chain coumarin **(5)** scaffold appears to be a promising structural template for further AD drug development.[53]



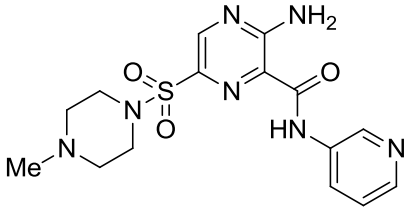
(5)

Benchekroun M *et al* investigated the synthesis of new tacrine ferulic acid hybrids and evaluated their biological and ADME studies and in vitro PAMPA-BBB analysis. (E)-3-(hydroxy3-methoxyphenyl)-*N*-{8[(7-methoxy-1,2,3,4-tetrahydroacridin-9-*yl*)amino]octyl}-*N*-[2-(naphthalen-2-ylamino)2-oxoethyl] acrylamide **(6)** identified as a multipotent that shows moderate and completely selective inhibition of human butyrylAChE, strong antioxidant activity and good Aβ aggregation properties. It is also able to permeate central nervous system (CNS) tissues, according to PAMPA-BBB assay.[54]



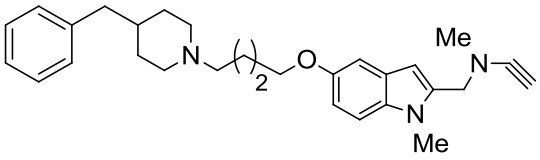
(6)

Berg S *et al* investigated the high throughput screening approach for new GSK3β inhibitors and co-crystallization of key analogues to guide the optimization and synthesis of pyrazine series. They developed highly potent and selective inhibitors showing cellular efficacy and BBB penetrance. The inhibitors are suitable for in vivo efficacy testing and may serve as a new treatment strategy for AD. The pyrazine containing compounds generated high potency and selective inhibition, good bioavailability and brain penetrance. Several pyrazine analogues were having potential as novel therapeutic agents for the neurodegenerative diseases. Potency for the para substituted sulfonamide analogue **(7)** increased 8 folds whereas potency for the meta and ortho isomers decreased to 79 and 30 folds respectively.[55]



(7)

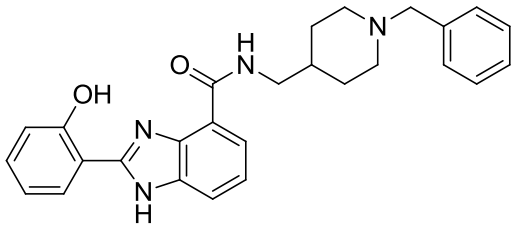
Bolea I *et al* investigated the multitarget molecules which are able to interact with AChE and butyrylAChE and also with monoamino oxidase A and monoamino oxidase B. Novel compounds have been designed using a conjunctive approach that combines the benzylpiperidine moiety of the AChE inhibitor donepezil and the indolylpropargylamino moiety of the MAO inhibitor *N*-[(5-benzyloxy-1-methyl-1*H*-indol-2-*yl*) methyl]-*N*-methylprop-2-yn-1-amine, connected through an oligomethylene linker. The most promising hybrid **(8)** is a potent inhibitor of both MAO-A and MAO-B and is a moderately potent inhibitor of AChE and butyrylAChE.[56]



(8)

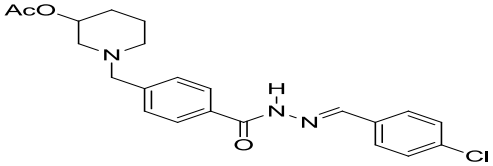
Chaves S *et al* investigated the series of multi target-directed ligands, obtained by attachment of a hydroxyphenylbenzimidazole unit to Donepezil active mimetic moiety benzylpiperidine/-piperazine and evaluated for inhibition of AChE and Aβ aggregation, metal chelation, and neuroprotection as potential antiAD

drugs. All the compounds are able to chelate Cu and Zn metal ions through their bidentate moieties, but below compound **(9)**, containing tridentate chelating unit, is the strongest Cu^{+2} chelator.[57]



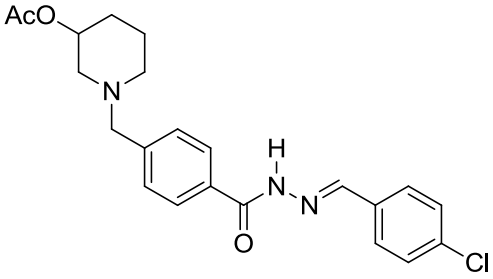
(9)

Costanzo P *et al* investigated the synthesis of donepezil precursors. For all products, characterized by an improved structural rigidity, the inhibitor activity on AChE selectivity *vs* butyrylAChE side activity on BACE-1, and tested for the effect on SHSY-5Y neuroblastoma cells. Two lead compounds were envisaged for a dual therapeutic strategy against AD. One of the compound **(10)** displayed better dual activity and lower IC50 values against both AChE and BACE-1 enzymes as compared reported literature for structurally similar molecules.[58]



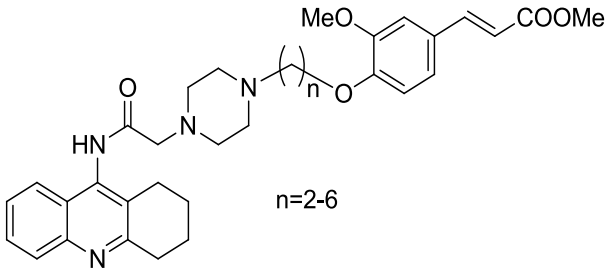
(10)

Viegas FPD *et al* investigated the series of multifunctional *N*-benzyl-piperidine-aryl-acylhydrazones hybrid derivatives and screened for multi target activities related to AD. Four compounds showed the best AChE inhibitory activities, but only two compounds presented concurrent antiinflammatory activity in vitro and in vivo, against Aβ oligomer induced neuroinflammation. One of the compounds **(11)** also showed the best neuroprotective effects against Aβ induced neurodegeneration.[59]



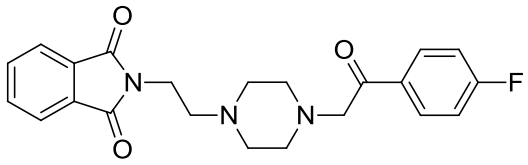
(11)

Fu Y *et al* investigated the synthesis of five novel tacrine ferulic acid hybrid compounds which were screened for inhibition of AChE and butyrylAChE, self-induced Aβ aggregation reduction and chelating Cu^{2+} in vitro. Two compounds displayed the higher selectivity in inhibiting AChE over butyrylAChE. One of them **(12)** also presented dramatic inhibition of self Aβ aggregation, activity of chelating Cu^{2+} and activity against Aβ induced neurotoxicity.[60]



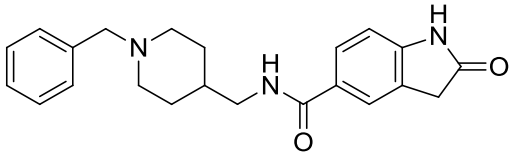
(12)

Aliabadi A *et al* investigated the new series of phthalimide based compounds and antiACh effect was assessed using Ellman's test. The more potent compound of this series was with 4-fluorophenyl moiety **(13)**. But, none of the compounds displayed superior inhibitory potency when compared to reference drug donepezil.[61]



(13)

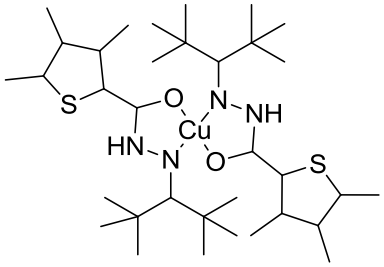
Guo Y *et al* investigated the series of novel compounds and evaluated for their inhibitory activities towards AChE and butyrylAChE in vitro by Ellman method. The results show that some compounds have good inhibitory activity against AChE and butyrylAChE. The compound **(14)** exhibited the strongest inhibitory effect on both AChE and butyrylAChE. Moreover, it also showed lower cytotoxicity than that of Tacrine, indicating its safety as antiAD agents.[62]



(14)

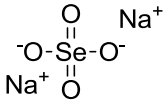
Inorganic Agents

Boulguemh IE *et al* synthesized and characterized two new $Copper^{+2}$ complexes with bidentate Schiff base ligand *N'*-(propan-2-ylidene) thiophene-2-carbohydrazide. To determine the antioxidant properties of both complexes, the ABTS radical scavenging and the reduction of $copper^{+2}$-neocuproine [Cu^{+2}-Nc] methods were used. AntiAChE activity method has been used to estimate in vitro antiAD effect of both and one of them **(15)** showed a potent AChE inhibition.[63]



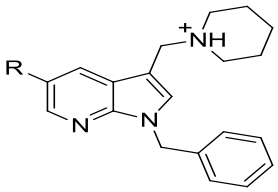
(15)

Cardoso BR *et al* investigated the tolerability and efficacy of selenate in modulating selenium concentration in the CNS by examining selenium and selenoproteins in serum and cerebrospinal fluid from a 2 fold-dose 24-week randomized controlled trial of sodium selenate in AD patients. Results of analysis have shown that CSF selenium can predict change in MMSE performance. Sodium selenate **(16)** supplementation is well tolerated in high dose and can control CNS selenium concentration while individual variation must be considered in selenium metabolism to improve potential benefits in AD.[64]



(16)

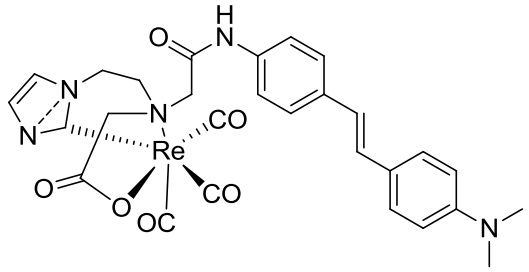
Garcia-Vazqueza R *et al* investigated and developed hybrid systems based on clay minerals and 7-azaindole derivatives **(17)** in order to facilitate the oral administration of drugs in the treatment of AD and provide a controlled release. Two 7-azaindole derivatives with different substitutions were synthesized and adsorbed on nanocarriers of different morphology, the lamellar clay montmorillonite and the halloysite nanotubes. The drugs intercalation in MMT was confirmed by X-ray diffraction. Studies carried out in cultures of human neuroblastoma cells confirmed the lack of toxicity of the hybrids and their neuroprotective effect against okadaic acid, the inhibitor of the protein phosphatase 2A, similarly to the nonencapsulated drugs.[65]



(17)

Hou R *et al* investigated and synthesized a novel 2-dimensional coordination polymer with chemical formula $[Zn_2(HL)(4,4'\text{-bipy})(H_2O)]$ (DMA) and evaluated the activity of the compound on the AD. AD mice model was established and treated with the compound. And then, AD mice brain tissues were weighted and the cognitive function of AD mice was determined. Then, the content of Aβ peptides in the hippocampus was measured with western blot; the inflammatory cytokines. The enzyme linked immunusorbent assay exhibited that compound could decrease the inflammatory cytokines level of TNF-α and IL-1β ease the inflammatory response in the body. The ROS results showed the compound also has the ability in reducing the oxidative stress level in the nerve cells.[66]

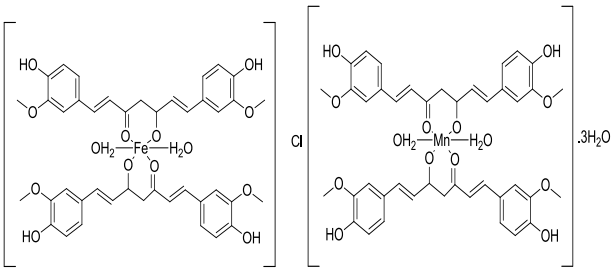
Wiratpruk N *et al* investigated the two tridentate ligand systems bearing *N*-heterocyclic carbene, amine and carboxylate donor groups coupled to benzothiazole or stilbene based Aβ binding moieties. Reaction of the imidazolium salt containing pro-ligands with $Re(CO)_5Cl$ yielded the corresponding rhenium metal complexes **(18)** which were characterized by NMR, and X-ray crystallography. These ligands are of interest for the potential preparation of technetium-99m imaging agents for AD and the capacity of these rhenium complexes bind to Aβ fibrils composed of Aβ peptide in human frontal cortex brain tissue was evaluated using fluorescence microscopy. These studies show that the complexes bound efficiently to Aβ fibrils and some evidence of binding to Aβ plaques.[67]



(18)

Zhao J *et al* synthesized a new coordination polymer, namely, $[Co_2(L)_2(H_2O)_4]_nnH_2O$; ($H_2L$= 5-(1*H*-1,2,4-triazol-1-*yl*)-1,3- benzenedicarboxylic acid). A technique of green hand grinding was carried out to decrease complex's particle size, resulting in the formation of nano scale ball-like morphology. Furthermore, the prevention and treatment ability of the compound on the AD was evaluated and the related mechanism was discussed.[68]

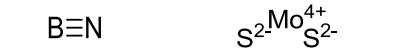
Bicer N *et al* investigated the metal complexes of the curcumin ligand with Mn^{2+} and Fe^{3+} salts **(19, 20)** and characterized by elemental analysis, magnetic susceptibility, FT-IR, AAS, TG, argentometry. In vivo studies of the synthesized metal complexes have been carried out on *Swiss Albino* male mice to reduce the accumulation of Aβ 25-35 protein which is the cause of AD. Latent period rates of Aβ25-35/curcumin and Aβ25-35/Fe^{3+}complex groups measured. Consequently, the synthesized curcumin iron complex reinforced the memory and it was more effective than curcumin according to latent period comparison.[69]



(19, 20)

Gorantla NV *et al* investigated the development of effective drugs against AD, to prevent Tau aggregation. They synthesized and screened metal based complexes to prevent Tau protein aggregation. The role of synthetic cobalt complexes in inhibiting Tau aggregation was proposed by ThS fluorescence and TEM. CD spectroscopy showed that these complexes prevented conformational changes in Tau to β -sheet. CBMCs were not toxic at lower concentration and formed nontoxic Tau species. L1 and L2 prevented membrane leakage; whereas, higher concentrations of L3 caused membrane leakage as observed by LDH release assay. It was concluded that the synthetic cobalt complexes will be a promising molecule against AD.[70]

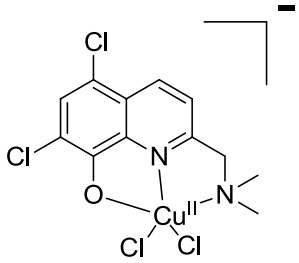
Pavuluru N *et al* investigated that the overabundance of certain metal ions in the brain may contribute to problem of formation of senile plaques which originate from the aggregation of the Aβ protein and that chelation therapy may be an effective tool to solve it. Due to copper strong affinity, binding energies were also evaluated for its interaction with potential chelators: monolayer boron nitride **(21)**, monolayer molybdenum disulphide **(22)**, and monolayer silicone. Silicene generated very high binding energies with copper, and the evidences demonstrated that there is a strong ionic bond existing between them. The minimal differences between the binding energies of the silicene binding sites and the Aβ binding sites evidencing that advance research in silicone chelators will expose doors for therapy in AD.[71]



boron nitride molybdenum disulfide

(21) **(22)**

Nguyen M *et al* investigated the structures of the copper^{2+} and zinc^{2+} complexes of PBT2 to treat the disruption of metal homeostasis in neurodegenerative diseases, especially AD. They are believed to reduce metal Aβ interactions and regulate redox homeostasis in AD brains. Different complexes can be formed with copper **(23)**, including ternary complexes PBT2–Cu–X due to bi or tridenticity of PBT2.[72]



Cu^{II}(PBT2)

(23)

Conclusion and Future Perspectives

AD is a medically and financially overwhelming condition which completely alters the structure and functions of neuronal and the incidence rates are expected to triple by 2050. Marketed conventional therapies treat the symptoms that are associated with the AD but are not be able to treat the cause of the disease. Despite decades of research in animal models of AD, the disease remains incompletely understood, with few treatment options. Nowadays researchers focused on various target specific drugs based on natural and synthetics sources that treat the underlying cause of AD. The Ontario Brain Institute took an initiative to improve the diagnosis and treatment of AD by which there will be an improvement in the person's cognitive abilities and memory. Moreover, epidemiological data and diverse traditional medicines, animal studies and the recent investigations about AD cellular and molecular aspects also provide strong starting points to develop new therapeutic approaches for AD. Preclinical and clinical studies on AD are under investigation and some have already shown promising results in patients.

Conflict of Interest

There is no conflict of interest.

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