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Pharmacological Role of Heterocyclic Compounds in the Treatment of Alzheimer's Disease: A Review

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ABSTRACT

Alzheimer's disease (AD) is a multifactorial neurological disease that mainly affects the old age people. Neuropathologically, AD is characterized by low level of acetylcholine, loss of synapses and neurons in certain brain regions, accumulation of extracellular amyloid beta peptide (Aβ) and phosphorylation of intracellular tau protein. Patients with AD are characterized by various symptoms such as memory deficits, depression, cognitive dysfunction and difficult to perform daily activities. Currently available drugs for the treatment of AD are used to treat symptomatic relief at an early stage, however the prolonged usage of the drugs may cause adverse side effects. To overcome this, development of drugs produced from natural products is considered as one of the promising alternatives for the treatment of AD. Among that heterocyclic compound play a major role in the development of therapeutic drugs against various disorders. An organic compound which is cyclic or non-cyclic consists of one or more atoms in their ring structure are known as heterocyclic compounds. These heterocyclic compounds occur both in natural and synthetic form and play a major role in the metabolism of all living cells. Most of the organic compounds used as drugs have a heterocyclic core in their skeleton. Nitrogenous bases such as purines and pyrimidines present in DNA, chlorophyll, vitamins contain heterocycle in their structure. Other compounds containing heterocycles are proline, morphine, furan, vinblastine, cephalosporin, penicillin etc. This review summarizes the nomenclature, classification, and the role of heterocyclic compounds in the treatment of Alzheimer's disease.

Keywords: Alzheimer's Disease (AD), AD Pathology, Heterocyclic Compounds, Classification of Heterocycle, Role of Heterocycles Against AD.

INTRODUCTION

In the universe, aging is a common biological mechanism that occurs in all living species. In humans, the process of aging is divided into two categories such as programmed and error or damage theories. The programmed theories emphasize that aging involves the prolongation of the sequential switching on and off of certain genes essential to follow a biological schedule, which regulates the growth and development of adolescence. This theory mainly affects the entire system responsible for repair, maintenance and defines mechanism due to the changes in gene expression. The error or damage theories of aging involves the ecological threats to living organisms which induces the cause of aging process in humans [1]. Moreover, aging is responsible for various types of cancer, cardiac diseases, inflammation and neurological disorder like Alzheimer's disease (AD). Among that AD is the most common form of dementia which affects most of the elderly people. AD is characterized by the aggregation of extracellular amyloid β-protein (Aβ) that primarily occur in a filamentous form known as plaques and intracellular hyperphosphorylated tau protein known as neurofibrillary tangles [2].

These changes in the brain cause synaptic loss and dysfunction of neurons leads to reduction in glucose metabolism and shrinkage of grey matter. Also, the formation of plaques affects communication between neurons at synapses and intracellular phosphorylated tau tangles blocks the nutrient transportation and other essential nutrients leads to cell death [3,4].

The symptoms of AD are cognitive dysfunction, issues in planning or problem-solving tasks, poor judgement, depression, confusion and behavioural changes which can disrupt the person's daily activities [5].

To date, the development of therapeutic drugs against AD is the promising strategy due to the poor diffusion of drugs across the blood brain barrier (BBB). Furthermore, there is a need for development of novel, safe, and efficient therapies for this neurodegenerative disease. Recent studies have focused on the development of novel drugs from natural sources to treat various disorders, including AD [6]. This review highlights the use of heterocyclic compounds in the treatment of AD.

Pathology of AD

The pathology of AD involves the formation of senile plaques due to the aggregation of amyloid beta (Aβ) peptides that induces the reactive oxygen species (ROS). Then the diminution of cholinergic neurons increased the activity of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) results in cognitive losses [7]. Additionally, a few other reports showed that an inflammatory mechanism is also responsible for the pathology of AD. Histopathological studies showed that the presence of Aβ peptides in AD patients is correlated with groups of activated microglia cells and inflammatory proteins such as complement proteins, acute-phase proteins and anti-inflammatory cytokines [8]. Some studies indicated that the genetic variation of cytokines, particularly over expression of interleukin-1 and acute phase proteins triggers the cause of AD [9]. Several studies reported that elevated serum level of high sensitivity C-reactive protein (hs-CRP) that are found in extracellular plaques and tangles, acute phase reactant like α_1-antichymotrypsin and interleukin-6 are associated with the cause of AD [10-12]. Based on the epidemiologic surveys suggested that the prolonged use of anti-inflammatory drugs may prevent or slow down the progression of AD [13,14].

The formation of amyloid peptides by APP (amyloid precursor protein) pathway is mainly involved in the pathology of AD [15]. The APP hypothesis involves the cleavage of α or β-secretase which releases APP. Although the products released by cleavage of α-secretase are considered as nontoxic, β-secretase involves the amyloidogenic and non-amyloidogenic division of APP pathway. Further the cleavage of β-secretase involves the formation of C-terminal APP (C-APP) by γ-secretase, based on the cleavage site, variable length of Aβ peptides are formed from the plasma membrane. Among these peptides, Aβ42 is considered as the main pathological cause of AD [16,17].

The oxidative stress is also a major impact in the pathogenesis of AD. The formation of reactive oxygen species (ROS) or free radicals such as hydrogen peroxide (H_2O_2, hydroxyl (OH) and superoxide (O_2) stimulate oxidative damage which leads to DNA strand breaks, destruction of nucleic acids and sugars in the cell membrane and finally induces cell death [18,19].

Based on the epidemiologic studies, it was indicated that Apolipoprotein E (ApoE) genotype is also responsible for the pathology of AD. Lipid metabolism is regulated by three ApoE isoforms such as apoE2, apoE3, and apoE4 which are encoded by different alleles (ε2, ε3, ε4). In US, based on the clinical studies showed that ε4 allele is responsible for 50% of AD and 95% of AD cases are due to the variation of ε2 allele in the gene encoding this protein. Additionally, several studies suggested that the fragments of ApoE are also responsible for the formation of plaques and tangles [20]. Based on these pathologies, the development of therapeutic drugs with less side effects against AD are the major task of this period. Although few drugs are approved by the U.S. Food and Drug Administration (FDA) for treating cognitive disorder like AD, but the efficiency varies among individuals [21].

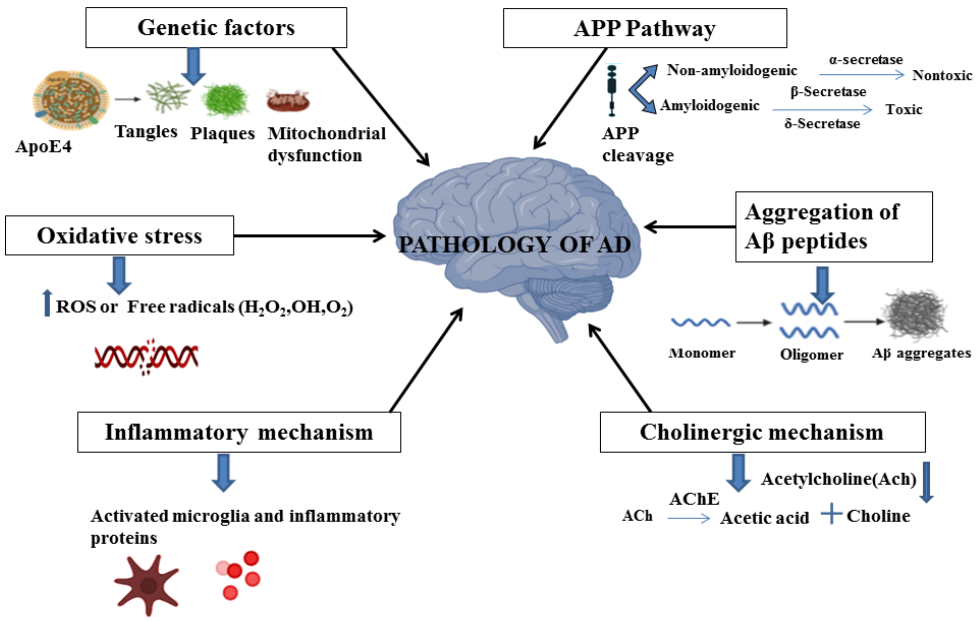


Figure 1: Pathology of AD (Figure sketched through biorender.com)

Currently Available Drugs Against AD

Currently, the drugs prescribed for the treatment of AD approved by FDA are tacrine, galantamine, donepezil and rivastigmine. However, each of these cholinesterase inhibitors has a different mode of action with some adverse side effects. The structure, source, trade name is given in the table 1 [22,23].

Tacrine (THA) is the first reversible acetylcholinesterase inhibitor approved by FDA that inhibits monoaminoxidases. THA is used to treat cognitive symptoms of AD related to increased binding of nicotine receptors and increased glucose metabolism in the frontal and temporal region of the brain [24]. Several studies involved in the synthesis of bifunctional THA to improve the selectivity of cholinesterase inhibitors, which binds to the peripheral and the catalytic site of AChE. Though it has positive results in the clinical trials, the usage of the drug is limited due to its hepatotoxicity [25,26].

Galantamine (GAL) is a reversible phenanthrene alkaloid used to treat cognitive dysfunction, which is active against AChE than BChE. Additionally, GAL stimulates the nicotinic receptors at different binding site of acetylcholine enhancing the acetylcholine production and neurotransmitters. Though numerous studies reported the significant clinical trials it remains uncertain [27].

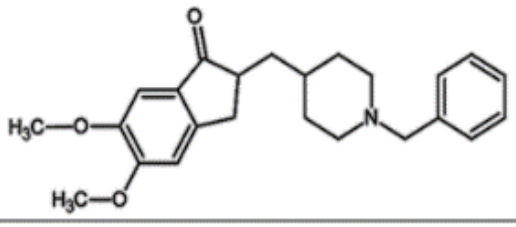
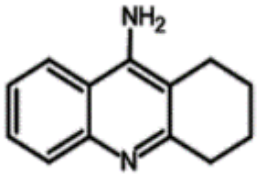
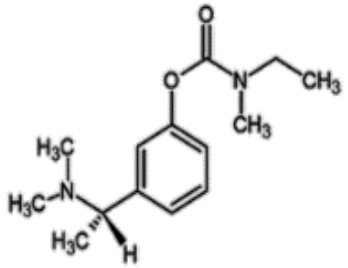
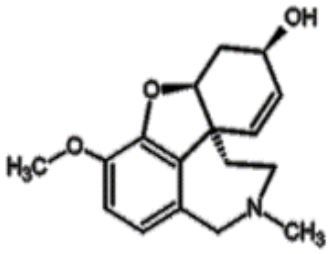
Donepezil is a reversible inhibitor and the derivative of piperidine which enhances the acetylcholine concentration for communication of synapses. Donepezil is highly selective with long plasma life and the

interaction of acetylcholinesterase involves at the bottom of the active site and top of the peripheral anionic site. several studies reported that donepezil related with dose and have mild adverse effects with best tolerability [28].

Rivastigmine is a pseudo-irreversible inhibitor form carbamate complex with a short plasma half-life which inhibits both acetylcholinesterase and butyl cholinesterase. Rivastigmine has a selective activity in the cortex and hippocampus and also effective

with less tolerability. Though the treatment with rivastigmine has clinical significance it slows down the progression of the disease but did not stop completely [29].

Table 1: Currently available drugs against AD [22,23]. Structures are constructed using ACD/Che sketch software

DRUGS	STRUCTURE	SOURCE	TRADE NAME	CLASS
Donepezil		Piperidine	Aricept	Heterocyclic compound
Tacrine		Aminoacridine	cognex	Tricyclic heterocycle
Rivastigmine		Carbamate	Exelon	Phenoxy compound
Galanthamine		Tertiary alkaloid	Reminyl	Amaryllidaceae alkaloids

Heterocyclic Compounds

Heterocycle derived from the Greek word haters – different or other denotes any atom other than carbon (heteroatom). Alloxan (2,4,5,6-pyrimidinetetrone) is the first heterocyclic compound developed by Luigi Brugnatellite in 1818. Heterocycles are a class of organic compounds that may be cyclic or noncyclic with the presence of one or more heteroatoms in their ring structure. A compound which contains at least one ring structure is said to be cyclic. If the cyclic structure contains atoms of the same element are called exocyclic compounds. In a cyclic system, Nitrogen, sulphur and oxygen is the commonly used heteroatom for the replacement of carbon atom [30].

Heterocycles play a major role in the medicinal chemistry and pharmaceutical industry. Diseases such as cancer, AIDS, circulatory diseases, central nervous system disorders and diabetics are considered as the major threats to the society. Most of the heterocyclic derivatives are used as drugs to combat these diseases which indicate the requirement of novel heterocycles. In 2013, some of the heterocyclic derivatives topped the best sellers in pharmaceutical industry are listed below (http://www.drugs.com/stats/top100/2013/sales) [30].

Table 2: Heterocyclic drugs and availability

S. No	Heterocyclic drugs (brand name)	Generic name	Pharmaceutical company	Rank
1.	Abilify	Aripiprazole	Otsuka	1
2.	Nexium	Esomeprazole	AstraZeneca	2
3.	Crestor	Rosuvastatin	AstraZeneca	4
4.	Cymbalta	Duloxetine	Eli Lilly And Company	5
5.	Spiriva	Tiotropium Bromide	Boehringer Ingelheim	12
6.	Atriplex	A Combination of Efavirenz, Emtricitabine and Tenofovir	Gilead Sciences	14
7.	Janu via	Sitagliptin	Merck & Co. Inc.	15
8.	Oxycontin	Oxycodone	Purdue Pharma	18
9.	Celebrex	Celecoxib	Pfizer Inc	21

Nomenclature of Heterocyclic Compounds

The nomenclature of heterocyclic compounds was introduced by The International Union of Pure and Applied Chemistry (IUPAC) that has framed certain considerations to schematize the name of heterocyclic compounds. Each heterocyclic compound has a trivial name based on the prefix, ring size and nature of the heteroatom [31]. (Ram *et al.*, 2019). Heteroatom with their prefix is given below:

O - Oxa P – Phosphor Pb - Plumb Th - Thala

S - Thai as – Arsan B - Bora Be - Beryllia

Se - Selena Si - Silla Al – Alumina Mg - Magnesia

TI – Tellural Ge – German Ga - Gala Zn - Zinc

N – Aza Sn – Stann In - India Hg - Mercure

Classification of Heterocyclic Compounds

To estimate the stability and reactivity of heterocyclic compounds, they are classified into four groups [32].

- Heterocycloalkanes - Fully saturated - sp3 hybridization
- Heterocycloalkanes - Partially saturated - sp3 hybridization except olefinic carbons which are sp2 hybridized
- Heteromannans - Fully unsaturated – sp2 hybridization
- Heteroaromatics – contains (4n+2) π electrons

Another classification is to determine the ring size, it is necessary to know the heterocyclic type of atoms and their total number present in the ring structure (Table 1). Based on the ring type and the increased number of heteroatoms, they are classified from three to ten membered heterocyclic compounds [33]. Among that three to six membered heterocyclic compounds are explained as below.

Three Membered Heterocyclic Compound

Three membered heterocyclic compounds are produced by the replacement of carbon atom with the addition of heteroatoms (oxygen, nitrogen, phosphorus and sulphur) in the cyclopropane and cyclopropane ring structure. Due to these alterations in the bond angle and ring structure affects the physical and chemical properties of newly formed heterocyclic compounds**.** Examples are aziridine, oxirane, thiirane, phosphorane, azirine, oxirene, thiirene, phosphorene. Aziridine and azirine are monocyclic, highly reactive, three membered saturated nitrogen heterocycles which plays an essential role in the synthesis of organic chemistry with significant pharmacological activities [34].

Oxiranes are very reactive, thermally labile, saturated three-membered oxygen heterocycles which are also known as ethylene oxide. Due to the contraction of bond angles, the oxirane ring is highly stretched, which is susceptible to ring opening by cleavage of C-O bond, that induces polymerization. Thiirane are unstable, unsaturated three membered sulphur heterocycle are also known as ethylene sulphide or this cyclopropane. In industries, thiirane is used in the synthesis of several intermediates like 2-mercaptoethylamines and also for the synthesis of adhesives, polymers etc. Additionally, thiirane act as a beneficial heterocyclic compound which possess anticancer, antibacterial activities [35].

Four Membered Heterocyclic Compounds

Four membered saturated and unsaturated heterocycles are replaced by the addition of heteroatoms such as oxygen, nitrogen and sulphur by replacing one or more carbons in cyclobutene or cyclobutene ring structure. Examples are azetidine, oxetanes, oxetane, thietanes etc. These heterocycles are varied from carbocycles due to the heteroatoms from carbon has different physical and chemical properties. The four membered heterocycles are commonly known as β-lactams which plays a crucial role among different pharmacophores due to their important therapeutic properties. The primary goal in the development of drugs is the production of β-lactamase due to its bacterial resistance and also the diversity of the core structure. In addition to that anti-infective properties, derivatives of β-lactam have various pharmacological activities such as anti-inflammatory, anti-diabetic [36]. For example, an antibiotic penicillin V contains four membered fused nitrogen heterocycles used to treat various bacterial infections. In biologically active compounds, the occurrence of the azetidine ring as a substructure is rare; but lactams are generally present in pen azetidine, calydaphninone and mutinied acid etc [37,38].

Five Membered Heterocyclic Compound

Five membered heterocyclic compounds are produced by the replacement of carbon atom with the addition of heteroatoms (oxygen, nitrogen, phosphorus and sulphur) in the cyclopentane or cyclopentadiene ring structure. Examples are such as pyrrolidine, tetrahydrofuran (THF), tetrahydrothiophene are saturated and pyrrole, furan, thiophene, etc. are unsaturated heterocycles. Five membered heterocycles containing heteroatoms (Nitrogen, Oxygen and Sulphur) are called π-rich or π-excessive heterocycles which is highly reactive in electrophilic substitution reactions. The rings attached with benzene are called indole, benzofuran, and pentathiophene, respectively [39]. Important natural products contain indole ring are indole 3-acetic acid (IAA) a plant hormone used as plant growth regulator and tryptophan an essential amino acid present in proteins.

Six Membered Heterocyclic Compound

Six membered unsaturated heterocyclic compounds are produced by the replacement of CH group with the addition of nitrogen in benzene known as pyridine. In living cells, NAD and NADP are the two important coenzymes play an essential role in the metabolic reactions and several alkaloids contain a pyridine structure. Additionally, Quinoxalines is an important six membered heterocycle containing two nitrogen atoms which initiates the central structural motifs in various classes of organic compounds. Several studies reported that quinoxalines act as an enzyme inhibitor and also found in various synthetic medications which includes antifungal, anti-inflammatory, antiviral, antibacterial [40].

Role of Heterocyclic Compounds Against AD

Currently, Alzheimer's disease is one of the major health issues which mostly affect the elderly people. Till date, FDA approved only five drugs to treat AD with lower outcomes, among that Tacrine is withdrawn from the market due to its hepatotoxic effect. Evidently, this devastating pathology of AD affects the old age people and its growth in the U.S is predicted from 5 million in 2014 up to 13.8 million in 2050, except the progression of modern technologies to combat AD [41]. Over the past decades, researchers have reviewed the activity on finding the novel phytocompounds to implement enhanced therapeutic drugs with minimal side effects. Several studies focussed on the importance of five and six membered heterocyclic compounds [42]. Currently, nitrogen, oxygen and sulphur containing heterocyclic compounds play a major role in medicinal chemistry due to their beneficial applications [43]. Several studies reported that triazole, pyrazole and benzimidazole compounds containing nitrogen heterocycle possess antimicrobial, anti-inflammatory and anticancer properties [44]. Also, benzofuran, benzopyran and pentathiophene compounds containing oxygen and sulphur heterocycle possess antibacterial, antioxidant and anticancer properties [45].

CONCLUSION

Alzheimer's disease is an irreversible neurological disorder that affects nerve cells in the brain. Currently there is no effective treatment for this disease and drugs available are used to slow down the progression of the disease. To compensate the rising demand of drugs, researchers synthesize potent naturally occurring phytocompounds with fewer side effects. Among that heterocyclic compounds play an essential role with beneficial pharmacological activities. Additionally, a huge number of phytocompounds used as drugs to treat various disorders have a core of heterocycle in its structure. Based on the literature survey, it may be concluded that the heterocyclic compounds act as a promising alternative for emerging novel neuroprotective approaches against AD.

Conflict of Interest

None declared.

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None declared.

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