ejpmr, 2020,7(8), 230-237

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

A REVIEW ARTICLE ON ISOQUINOLINE ALKALOIDS WITH ANTI-ALZHEIMER'S ACTIVITY

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Article Received on 02/06/2020 **Article Revised on 23/06/2020** **Article Accepted on 13/07/2020**

ABSTRACT

Alzheimer's disease, a neurodegenerative disorder, is one of the severe age related health problem. Alkaloids of natural origin and their synthetic derivative form exhibit promising results with minimum side effects. Isoquinoline alkaloids and their derivatives are approved for the pharmacological treatment of AD by targeting multiple pathogenic factors. many therapeutic approaches have been taken.

KEYWORDS: Alzheimer's disease ,alkaloids-isoquinoline alkaloids.

INTRODUCTION

Alzheimer disease (AD) is an irreversible and progressive age- related neuro- degenerative disorder and is the most common form of dementia among the elderly, generally diagnosed in individuals over the age of 65 years. The disease affecting 28 million of the people around the world.[1, 2, 3] During the 37th Conference of German psychiatrists in Tübingen(1906), the Bavarian neuropsychiatries Alois Alzheimer described for the first time the symptoms of "a particular disease of the cerebral cortex", characterized by a gradual and irreversible degeneration of the intellectual functions such as memory, orientation, judgment, language and the capacity to acquire knowledge.[4,5]

AD is clinically characterized by progressive deterioration of cognition, behavior, functionality that impairs ctivities of daily living significantly. Morphologically, the disease is characterized by brain atrophy and by enlarged cerebral ventricles. From a biochemical point of view, the decreased levels of choline acetyl transferase and other cholinergic markers in cholinergic system. AD is characterized histologically by extracellular deposits, called cerebral plaques, composed of a dense proteinaceous core containing the Aβ peptide surrounded by dead and damaged neurons. The other typical histo-pathologic hallmarks of AD are the neuro fibrillar tangles within neurons, formed by a filamentous, hyper phosphorylated form of the microtubule- associated protein τ. whereas most cases of AD occur sporadically, approximately 5% of patients develop the disease early as a result of autosomal dominant gene mutations.

The main symptoms associated with AD involve a decline in cognitive dysfunction, primarily memory loss and in the later stages of the disease language deficits, depression, psychosis agitation, hallucination, delusion, anxiety, euphoria/ elation, apathy/ indifference, disinhibit ion, irritability/ liability, aberrant motor behavior and mood distunbenses.it is major health concern of present world.[6,7,8]

Epidemiology of Alzheimer's disease

The incidence and prevalence of AD rise with increasing age and are higher in women because of their increased longevity. The incidence of AD ranges from 1% at ages 65 to 70 to approximately 4% over age 85. In the United States, the number of people affected per year is expected to triple from approximately420,000 in 2000 to more than 1.3 million in 2050.[9] Estimates of prevalence of AD range from the lowest figure of 3% of the population at 65 years to the highest reported estimate of 47% of people over age 85.[10] This number will increase by almost three fold, to 13.2 million by 2050. In the United States, AD is the eighth leading cause of death, with approximately 63,000 deaths per year and a death rate of 21.8 deaths per 100,000 populations.[11] The death rate of AD is increasing by approximately 6% per year. The median survival from initial diagnosis recently was estimated to be 5.7 years for women and 4.7 years for men.[12]

Pathophysiology of AD

Genetics of AD

The presence of AD in individual in some families, who have an autosomal dominant inheritance pattern, due to the presence of disease genes. Also known as causative

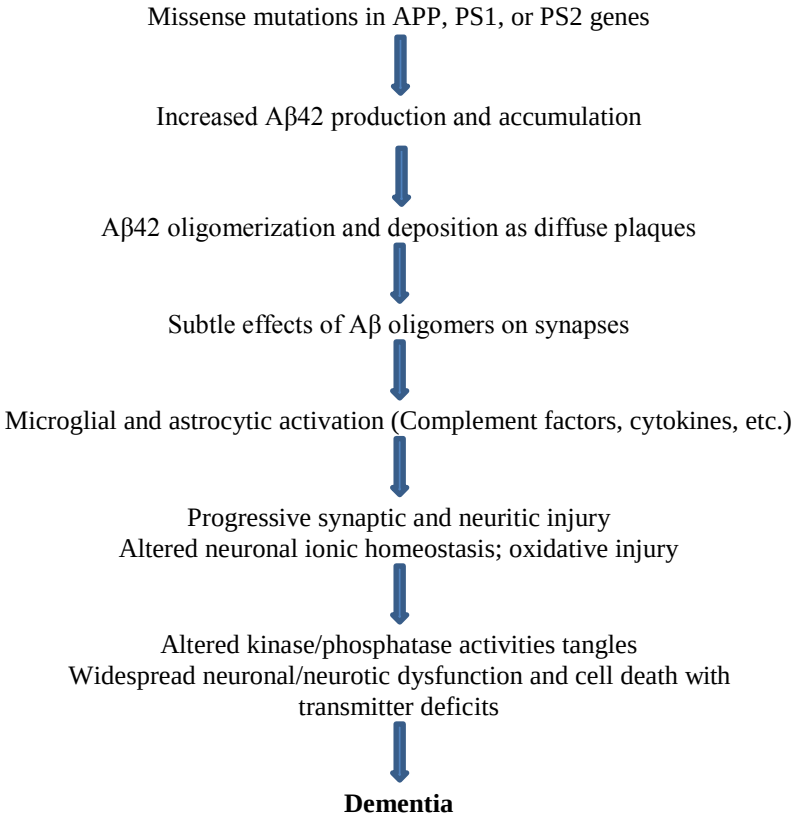
genes, mutation on this genes cause aggressive form of early-onset. The causative genes are encoding amyloid precursor protein on chromosome 21q21 (APP), presenilin 1 on chromosome 14q24 (PSEN1), and presenilin 2 on chromosome 1q42 (PSEN2). Mutations in these genes account for approximately 5% of the total number of AD cases.[13] There also are other genes, known as susceptibility genes, believed to be involved in the pathogenesis of AD via complex interactions with environmental factors.

Hypothesis for AD

Hyper-phosphorylated tau protein and β amyloid hypothesis

The major pathological features of AD the formation of senile plaques (SP), which is caused by amyloid beta (Aβ) deposition(a peptide with 40 or 42 amino acids). Which are produced by the splitting of the precursor protein of amyloid (APP) by the action of α- secretase, β-secretase and γ- secretase. The imbalance between β-amyloid (Aβ) production and clearance leads to various types of toxic oligomeric, namely fibrils, protofibrils and plaques depending upon the extent of oligomerization.[14,15]

The sequence of pathogenic events leading to AD proposed by the amyloid cascade hypothesis. The curved violet arrow indicates that Aβ oligomers may injure the synapses and neuritis of brain neurons directly, in addition to activating microglia and astrocytes. (From[16] Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science2002; 297:354;):



Cholinergic hypothesis

There are so many evidence to suggest a possible association between the memory deficits described in AD patients and impairment of cholinergic neurotransmission in the central nervous system (CNS), in an attempt to characterize the cognitive and behavioral abnormalities observed.[17,18,19,20] The effects of apo-lipoprotein E (APOE) genotype on the useful effect of acetyl- cholinesterase inhibitors (AChEIs) in Alzheimer's patient. AchEI medications are the currently approved treatment for AD.[21] APOE genotype is the most important factor associated with AD. This lack of major effect of APOE is analyzed with respect to the "Cholinergic Hypothesis" of AD, dating from 1976, through the recognition that cholinergic neurons are not the main target of AD.

The inhibition of acetyl cholinesterase (Ache), the enzyme in the breakdown of acetylcholine, is currently the main pharmacological strategy available for Alzheimer's disease (AD). The blockade of this catabolic process results in increased levels of the neurotransmitter, which may partially correct the cholinergic deficiency seen in AD.[21, 22, and 23]

Oxidative stress hypothesis

Reactive oxygen species (ROS) and reactive nitrogen species (RNO -Example: nitric oxide, NO) are produced in many normal and abnormal processes in humans, they play dual role as both have beneficial functions in

cellular signaling pathways and venomous processes that can lead to damage of cellular structures (including cell membrane, lipid, protein, and DNA). The brain, which utilizes 20% more oxygen than other mitochondrial respiratory tissues, means that the brain is more vulnerable to oxidative stress. The neuron is the basic functional unit of the brain, which contains a large number of polyunsaturated fatty acids, which can interact with ROS, leading to the lipid peroxidation reaction and molecular apoptosis, in addition, less glutathione in neurons is also one of the causes of oxidative stress.[14]

Metal ion hypothesis

Metal dyshomeostasis is involved in the progression and pathogenesis of neurodegenerative diseases and also in cancer. Ionosphere and metal chelators are modulators of transition metal homeostasis, and a number of these molecules are used in clinical trials. Metal-binding compounds are not the only drugs capable of targeting transition metal homeostasis. Current evidence indicates changes in the equilibrium of redox transition metals; mainly copper (Cu), iron (Fe), zinc (Zn) and other trace metals. Their levels in the brain are found to be high in AD. In other neurodegenerative disorders, Cu, manganese, aluminum and zinc are involved.[26, 27]

Diagnosis

- usually diagnoside based on the family and medical history
- Genetic test, eye drop test, spinal fluid test, various types of neuro -psychiatric or cognitive tests ,and brain imaging test
- Advanced medical imaging with computed tomography and with single –photon emission computed tomography (SPECT).

Current treatment strategies for AD

Existing pharmacological treatments for AD act by relieving symptoms rather than targeting the etiological mechanisms. The US FDA-approved medications for AD include acetyl cholinesterase. AChE inhibitors can enhance cholinergic transmission by limiting degradation of Ach.[28, 29] (AChE) inhibitors and NMDAR antagonist. The three most commonly prescribed AChE inhibitors are donepezil (Aricept™), rivastigmine (Exelon™), and glutamine (Reminyl™), which were approved in 1996, 2000,and 2001, respectively. Donepezil is the only AChE inhibitor approved for the treatment of all stages of AD. The second class of FDA-approved medications acts by blocking NMDAR. Memantine (Namenda™), a neuro-protective agent that blocks NMDAR, was approved for the treatment of moderate to severe AD in 2003. Memantine can be used alone or in combination with other AChE inhibitors such as donepezil.[29]

Prevention

- Avoid saturated fats and trans fat
- Eat a healthy diet
- Go nuts for nuts
- Make vitamin B12 a priority
- Choose your multivitamin wisely
- Cook with caution
- Keep moving

ALKALOIDS

Alkaloids are a class of naturally occurring organic nitrogen containing Compounds.[30] In modern medicine, alkaloids have a wide range of pharmacological applications because of their effects.[31] Large numbers of natural alkaloids and their synthetic derivatives have been reported to show neuro-protective effects. We have further grouped these alkaloids into different sub groups like Indoles, steroidal, piperidine, pyridine, and isoquinolines, from which certain compound can be used in AD management.[32]

REVIEW

Isoquinoline alkaloids are probably the largest single group of alkaloids from plants. Their basic structure is derived from tetra hydro isoquinoline, which can be modified in complex structures that are can be biosynthetically derived from phe- nylalanine and tyrosine. These alkaloids are aromatic bases; the majority of the natural derivatives present tetracyclic structures. But penta cyclic compounds (such as aporphine and emetines) are also present. The most widely distributed isoquinoline alkaloids are the aporphines and protoberberin types.[32] Isoquinoline and their derivatives have great therapeutic value for AD treatment[32,33] Previous phytochemical studies on different plant species have resulted in the isolation of alkaloids of different structural types, such as simple lsoquinoline, (seco) phthalides isoquinolines, aporphines, ptotopines, pritoberiberines, spirobenzylisoquinolines, benzophenanthridines, and indenobenzazepines.[34, 35, 36]

S.L NO	COMPOUND	PLANT	FAMILY	REFERENCE
1	(-)-fumaricine	*Fumaria officinalis*	Papaveraceae	[37]
2	(+)-dihydrofumariline	*Fumaria officinalis*	Papaveraceae	[37]
3	(-)-fumaritin	*Fumaria officinalis*	Papaveraceae	[37]
4	(-)-O-methylfumarophycine	*Fumaria officinalis*	Papaveraceae	[37]
5	(-)-fumarophycine	*Fumaria officinalis*	Papaveraceae	[37]
6	(+)-fumariline	*Fumaria officinalis*	Papaveraceae	[37]
7	(+)-parfumidine	*Fumaria officinalis*	Papaveraceae	[37]
8	(+)-parfumine	*Fumaria officinalis*	Papaveraceae	[37]
9	(±)-O-methylfumarofine	*Fumaria officinalis*	Papaveraceae	[37]
10	(+)-bicuculline	*Fumaria officinalis*	Papaveraceae	[37]
11	(+)-corlumine	*Fumariaofficinalis*	Papaveraceae	[37]
12	(-)-stylopine	*Fumaria officinalis*	Papaveraceae	[37]
13	(-)-sinactine	*Fumaria officinalis*	Papaveraceae	[37]
14	(-)-cheilanthifoline	*Fumaria officinalis*	Papaveraceae	[37]
15	N-methylcorydaldine	*Fumaria officinalis*	Papaveraceae	[37]
16	corydamine	*Fumaria officinalis*	Papaveraceae	[37]
17	protopine	*Fumaria officinalis*	Papaveraceae	[37]
18	cryptopine	*Fumaria officinalis*	Papaveraceae	[37]
19	9- methyldecumbenine	*Fumaria officinalis*	Papaveraceae	[37]
20	mucroniferanine H-M	*Corydalis mucronifera*	Corydalis mucronifera	[38]
21	5,6,7,8-tetrahydro-1,3-dioxolo[4,5-g]isoquinoline	*Corydalis mucronifera*	Papaveraceae	[38]
22	hydrohydrastinine	*Corydalis mucronifera*	Papaveraceae	[38]
23	6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin	*Corydalis mucronifera*	Papaveraceae	[38]
24	1-(1,3-dioxolo[4,5-g]isoquinolin-5-yl)- ethanone	*Corydalis mucronifera*	Papaveraceae	[38]
25	1R,9S,7′S-methylegenine	*Corydalis mucronifera*	Papaveraceae	[38]
26	(+)-adlumine	*Corydalis mucronifera*	Papaveraceae	[38]
27	orientaline	*Corydalis mucronifera*	Papaveraceae	[38]
28	hendersine	*Corydalis mucronifera*	Papaveraceae	[38]
29	(−)-corydalisol	*Corydalis mucronifera*	Papaveraceae	[38]
30	epi-coryximine	*Corydalis mucronifera*	Papaveraceae	[38]
31	demethylcorydalmine	*Corydalis mucronifera*	Papaveraceae	[38]
32	bicucullinine	*Corydalis mucronifera*	Papaveraceae	[38]
33	(−)-ochrobirine	*Corydalis mucronifera*	Papaveraceae	[38]
34	(+)-ochotensine	*Corydalis mucronifera*	Papaveraceae	[38]
35	Sanguinine	*Electrophorus electricus*	Electrophorus electricus	[39]
36	Galantamine	*Galanthus caucasicus*	Amaryllidace	[39]
37	11α-Hydroxygalantamine	*Galanthus caucasicus*	Amaryllidaceae.	[39]
38	Epinorgalantamine	*Galanthus caucasicus*	Amaryllidaceae.	[39]
39	Assoanine	*Narcissus assoanus*	Amaryllidaceae.	[39]
40	Oxoassoanine	*Narcissus assoanus*	Amaryllidaceae.	[39]
41	Pseudolycorine	*Hippeasrum equestre*	Amaryllidaceae.	[39]
42	Chlidanthine	*Galanthus caucasicus*	Amaryllidaceae.	[39]
43	1-O-Acetyllycorine	*Narcissus assoanus*	Amaryllidaceae.	[39]
44	Ungeremine	*Pancratium maritimum*	Amaryllidaceae.	[39]
45	Berberine	*Hydrastis Canadensis, Coptis Chinensis, Berberis aquifolium, Berberis vulgaris, Berberis aristata*	Amaryllidaceae.	[39]
46	Incartin	*Galanthus elwesii*	Amaryllidaceae	[39]
58	Dehydrocorydaline	*Corydalis saxicola*	Papaveraceae	[39]
59	Pseudocolumbamine	*Corydalis saxicola*	Papaveraceae	[39]
60	Pseudopalmatine	*Corydalis saxicola*	Papaveraceae	[39]

61	Coptisine	*Corydalis saxicola*	Papaveraceae	[39]
62	Bulbocapnine	*Corydalis cava*	Papaveraceae	[39]
63	Corydaline	*Corydalis cava*	Papaveraceae	[39]
64	Corydine	*Corydalis cava*	Papaveraceae	[39]
66	(R,S)-2-N-Norberbamunine	*Abuta grandifolia*	Menispermaceae	[39]
65	2-Hydroxy-9-Methoxyaporphine	*B. alloiophylla*	Lauraceae	[39]
67	(R,R)-Isochondodendrine	*Abuta grandifolia*	Menispermaceae	[39]
68	(S-S)-O4”-Methyl,O6’-Demethyl–(+)-Curine	*Abuta grandifolia*	Menispermaceae	[39]
69	Columbamine	*Berberis bealei*	Berberidacea	[39]
70	Epiberberine	*Berberis bealei*	Berberidacea	[40]
71	Tetrahydrocheilanthifolinium	*Berberis bealei*	Berberidacea	[40]
72	Tetradehydroscoulerine	*Berberis bealei*	Berberidacea	[40]
73	Hippeastrin	*Hippeastrum vitatum*	Amaryllidaceae.	[41]
74	Pretazine	*Hippeastrum vitatum*	Amaryllidaceae.	[41]
75	Salosine	*Sasola oppositofolia. salsola soda. s.tragus.*	Chenopodiaceae	[42]
76	Aalosidine	*Sasola oppositofolia. salsola soda. s.tragus*	Chenopodiaceae	[42]
77	N-methylisosalosine	*Sasola oppositofolia. salsola soda. s.tragus.*	Chenopodiaceae	[42]
78	Carnegine	*Sasola oppositofolia. salsola soda. s.tragus.*	Chenopodiaceae	[42]
79	fangchinoline	*Stephania Tetrandra S. Moore,*	Menispermaceae	[43]
80	Atherospermoline	*Stephania tetrandra S. Moore,*	Menispermaceae	[43]
81	Fenfangjine	*Stephania tetrandra S. Moore,*	Menispermaceae	[43]

DISCUSSION

The genus Fumaria L. *(Fumariaceae*) consists of 60 species and is a rich source of different structural types of isoquinoline alkaloids. Previous phytochemical studies on Fumaria species have resulted in the isolation of 80 alkaloids of different structural types, such as simple isoquinolines, (seco-) phthalide isoquinolines, aporphines, protopines, protoberberines, spiro benzyl isoquinolines, benzophenanthridines, and indenobenzazepines. F. officinalis, the most common species of Fumaria in Europe and Asia, has played a traditional role in empirical medicine over the centuries. The biological activities of Fumaria herbs are mainly associated with the presence of isoquinoline alkaloids. The important biological activities of Fumaria alkaloids and our ongoing search for new bioactive substances of plant origin for the treatment of Alzheimers disease (AD), encouraged us to examine the species F.officinalis. Two new alkaloids, (+)fumaranine and (-) fumarostrejdine, along with another 18 known isoquinoline alkaloids, were isolated. All structures were elucidated based on HRESI- MS, EI-MS, 1D- and 2D-NMR analysis, and circular dichroism (CD) data, supplemented with the values of optical rotations and melting points. The isolated alkaloids were investigated for their acetylcholinesterase (AChE), butyrylcholinesterase (BuChE), prolyl oligopeptidase(POP), and glycogen synthase kinase-3β (GSK-3b)inhibitory activities. Purification of the extract of F. officinalis afforded 20 compounds, including two new, 2 and 10, and 18 known compounds. The structures of the known compounds were elucidated as (-)-fumaricine,(+)-dihydrofumariline, (-)-fumaritine, (-)-O-methylfumarophycine, (-)-fumarophycine (+)-fumariline,(+)-parfumidine, (+)-parfumine,(+)-O-methylfumarofine, (+)-bicuculline,(+)-corlumine, (-) -stylopine, (-)-sinactine, (-)- cheilanthifoline, N-methylcorydaldine, corydamine, protopine, and cryptopine.

Isoquinoline alkaloids from *Corydalis mucronifera* like mucroniferanines H-M, and 16 known ones, identified as 9-methyldecumbenine C 5,6,7,8-tetrahydro-1,3-dioxolo[4,5-g]isoquinoline, hydrohydrastinine, 6,7-dimethoxy-2-methyl-1,2,3,4- tetrahydroisoquinoline, 1-(1,3-dioxolo[4,5-g]isoquinolin-5-yl)- ethanone (11), 1R,9S,7′S- methylegenine, (+)-adlumine (13) ,orientaline, hendersine, (−)-corydalisol, epi- coryximine, demethylcorydalmine, bicucullinine), (−)-ochrobirine, (+)-ochotensine.

The presence of *Amaryllidaceae* alkaloids, as their name suggests, is restricted to the Amaryllidaceae family and no other classes of alkaloids were reported from this source. The daffodil family includes narcissus, snowdrops, and amaryllis and is formed by 75 genera

and about 1100 species. All these alkaloids share a C-15 skeleton and their biosynthesis involves the phenolic coupling of two aromatic amino acids with one of the two nitrogen atoms retained in the process. These two classes of alkaloids are considered very important AChE-Is. Alkaloids from Colchicum speciosum Steven (Colchicaceae), Coptis spp. (Ranunculaceae) and Corydalis spp. (Papaveraceae) act as AChE-Is. Epiberberine, pseudoberberine, and pseudocoptisine are examples of such compounds. Berberin was recently considered as an attractive compound for AD treatment not only due to its AChE-I, but also for BuChE, antioxidant, monoamine oxidase inhibitory, amyloid-β peptide level-reducing and cholesterol-lowering activities which suggest a multi targeted approach for the disease's treatment. Berberin-based derivatives are more potent AChE-Is. Pseudoberberine and pseudocoptisine are also able to alleviate scopolamine-induced memory impairment in vivo models.

A methanolic extract of Corydalis saxicola (*Papaveraceae*) showed a significant inhibitory effect on AChE activity which led to the isolation of a reversible and competitive inhibitor, protopine .In vivo, mice treated with protopine exhibited a diminished scopolamine-induced dementia .Another species of the genus Corydalis, Corydalisspeciosa (Papaveraceae), was studied. Four isoquinoline alkaloids with anti- AChE activity were isolated; berberine and protopine, palmitine and corynoxidine.

The alkaloid galantamine is one of the most important derivatives with great therapeutic value for AD treatment, and it is isolated from Galanthusworonowii and G.nivalis and some Narcissus and Leucojum spp. of Amaryllidaceae. This compound is reported to be more selective to AChE than BuChE. Of particular importance are the inhibitory effects of galantamine on AChE in the frontal cortex and hippocampal regions of the brain, the two areas in which cholinergic neurotransmission is most affected in patients with AD. In addition galantamine has a peculiar mechanism of action because it both acts as competitive inhibitor of the enzyme and as a positive allosteric modulator of nAChRs. Galantamine is actually used in therapy (as Reminyl® (Janssen-Cilag SpA,) and its use is associated with a preservation of cognitive function in patients with AD. Galantamine is considered a well-tolerated treatment for the control of AD progression.

Sanguinine, galantamine, 11a-hydroxygalantamine, and epinorgalantamine inhibited AChE from the electric eel, Electrophoruselectricus (EeAChE). Assoanine, oxoassonine and 1-O-acetyllycorine are the most potent AChE inhibitors. Chlidanthine,a positional isomer of galantamine. Ungeremine, jatrorrhizine, incartine and incartine N- oxide also favour AChE inhibition. Palmatine, cyclanoline and N-methylstepholidine were about five-fold more potent for EeAChE inhibition. The benzophenanthridine alkaloid chelerythrine hasbeen shown to inhibit AChE (from Electrophorus electricus and humans) and BChE (from equine serum and humans) in an equipotent way. (-)-2,9- dihydroxyl-3,11-dimethoxy-1,10-dinitrotetrahydroprotoberberine,(+)-nitroapocavidine, dehydrocavidine and sanguinarine are inhibit AChE.

AChE inhibition was also observed for other protoberberine alkaloids, such as jatrorrhizine, dehydrocorydaline, pseudocolumbamine, pseudopalmatine and coptisine. The activity-guided fractionation of Corydaliscava led to the identification of three benzylisoquinolinealkaloids inhibiting EeAChE and equine BChE (eqBChE): bulbocapnine, corydaline, corydine. 2-Hydroxy-9-methoxyaporphine, an alkaloid obtained from B.alloiophylla, the bisbenzylisoquinoline alkaloids (R,S) N- norberbamunine, (R,R)-isochondodendrine and (S,S)-O4″-methyl,O6′-demethyl-(+)- curine, isolated from Abutagrandifolia (Menispermaceae), were able to inhibit AChE Salsoline is an isoquinoline alkaloid belonging to Chenopodiaceae family. Salsoline possesses the property of inhibiting the AChE enzyme. It has been demonstrated that the AChE and BuChE inhibitors are beneficial in the treatment of AD.

A number of bisbenzylisoquinoline (BBIQ) alkaloids; such as fangchinoline, atherospermoline, and fenfangjineE, isolated from root of Stephania tetrandraS. Moore, *Menispermaceae* family, was found to inhibit acetyl cholinesterase enzyme in micromolar range.

CONCLUSION

Alzheimer's disease (AD), a neuro degenerative disorder, is one of the most threatening problems of aged population. However, there is no efficient therapeutic agent to treat AD. Neuro protective compounds of natural origin and their synthetic derivatives form exhibit promising results with minimal side effects and some of them are in their different phases of clinical trials. Alkaloids and their synthetic derivatives form one of the groups which have been used in treatment of neurodegenerative diseases like AD. Isoquinoline and their derivatives possess potential to treat AD by targeting multiple pathogenic factors. Many therapeutic approaches have been taken. The first involves the re-establishment of neurotransmitters levels, by inhibiting the cholinesterases enzymes, acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), and also monoamine oxidase (MAO) enzymes. The second concerns decrease in the production or aggregation of a β peptide, and inhibition of γ- and β-secretase enzymes, which play a critical role in the amyloidogenic pathway, t-protein, among others. The third approach neuroprotection, where in oxidative stress is considered to be an early event in the pathological cascade for the disease, thus suggesting the potential use of antioxidants to limit the effects of free radicals on nerve cells. The therapeutic potential of isoqiunoline drugs raised new hope in the field of a neuro degenerative disorder

including AD.

BIBLIOGRAPHY

1. Jeffrey L Cummings. Alzheimer's disease. NEngl J Med, 2004; 351(1): 56–67.
2. Brookmeyer R ,Jhonson E, Ziegler-graham K,Arrighi HM. Forecasting the global burden of Alzheimer's disease. Alzheimers dement. Alzheimer's and amp;dementia, 2007; 3(3): 186–191.
3. Ballard C, Guuther S, Corbett A, Brayne C, Aarsland,Jones E. Alzheimer's disease. Lancet, 2011; 377(9770): 1019–103.
4. K.Hostettmann, A.Borloz, A.Urbain and A.Marston. Natural product of Acetylcholinesterase, Current organic chemistry, 2006; 10(23): 825-847.
5. Bruno P. Imbimbo, PhD, Jay Lombard, DO, Nunzio Pomara, MD, Pathophysiology of Alzheimer's Disease, Elsevier saunders, 2005; 15: 7727-753.
6. Ranges, B. Baron, J; de la Sayette, V. The neural substrates of memory systems impairment in Alzheimer's disease. Brain, 1998; 121(Pt 4): 611-631.
7. Forstl, H; Hentschel, F; Sattel, H. Age-associated memory impairment and early Alzheimer' disease. Drug Res, 1995; 45(3*A)*: 394-397.
8. McGuffey, E.C. Alzheimer's disease: An overview for the pharmacist. JAMA, 1997; NS37(3): 347-352.
9. Hebert LE, Beckett LA, Scherr PA, Beckett LA, Sch, Evans DA. Annual incidence of Alzheimer disease in the United States projected to the years 2000 through 2050. Alzheimer Dis Assoc Disord, 2001; 15(4): 169– 73.
10. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimerdisease in the US population: prevalence estimates using the 2000 census. Arch Neurol, 2003; 60(8): 1119–22.
11. Hoyert DL, Kung HC, Smith BL. Deaths: preliminary data for 2003. Natl Vital Stat Rep 2005; 53(15): 1– 48.
12. Larson EB, Shadlen MF, Wang L, Li Wang, Wayne C Mc Cormick, James Bowen, Linda Teri, Walter A Kukull. Survival after initial diagnosis of Alzheimer disease. Ann Intern Med, 2004; 140(7): 501–9.
13. Bird TD.Genetic factors in Alzheimer's disease. N Engl J Med, 2005; 352(9): 862-4.
14. Liu Z, Zhang A, Sun H, Ai Hua Zhang, Ying Han, Ling Kong, Xi-Jun Wang. Two decades of new drug discovery and development for Alzheimer's disease. RSC Advances, 2017; 7(10): 6046–6058.
15. Gandy S. The role of cerebral amyloid b accumulation in common forms of Alzheimer disease. J Clin Invest 2005; 1159(5): 1122.
16. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. Science, 2002; 297(5580): 353-356.
17. Schliebs R, Arendt T. The significance of the cholinergic system in the brain during aging and in Alzheimer's disease. J Neural Transm, 2006; 113(11): 1625–1644.
18. Cummings JL. Treatment of Alzheimer'sdisease: current and future therapeutic approaches. Rev Neurol Dis, 2004; 1(2): 60–69.
19. Cummings JL. The role of cholinergic agents in the management of behavioural disturbances in Alzheimer's disease. Int J Neuropsychopharmacol, 2000; 3(7): S21–S29.
20. Lahiri DK, Matrin R.Farlow, Nigel H.Greig, Kumar, Sambamurti. Current drug targets for Alzheimer's disease treatment. Drug Dev Res, 2002; 56(3): 267–281.
21. Martinez A, Castro, A Novel cholinesterase inhibitors as future effective drugs for the treatment of Alzheimer's disease. Expert Opin Investig Drugs, 2006; 15(10): 112.
22. Sultzer DL, Marder SR. Older Brains are Different: Brain–Behavior Studies and Their Clinical Utility. Am J Geriatr Psychiatry, 2017; 25(1): 11–12.
23. Munoz-Torrero D. Acetylcholinesterase inhibitors as disease-modifying therapies for Alzheimer's disease. Curr Med Chem, 2008; 15(23): 2433-2455.
24. Martinez A, Castro A. Novel cholinesterase inhibitors as future effective drugs for the treatment of Alzheimer's disease. Expert Opin Investig Drugs, 2006; 15(1): 1-12.
25. Orhan IE, Erdogan Orhani; Orhan G, bdulG; Grkas, E. An overview onnatural cholinesterase inhibitors – a multi-targeted drug class – and theirmass production. Mini-Rev MedChem, 2011; 11(10): 836–842.
26. Weekley CM, He C. Developing drugs targeting transition metal homeostasis. Curr Opin Chem Biol, 2017; 37(1): 26–32.
27. Prakash A, Dhaliwal GK, Kumar P, Puneet Kumar and Abu Bakar Abdul Majeed. Brain biometals and Alzheimer's disease – boon or bane Int J Neurosci, 2017; 127(2): 99–d108.
28. Allgaier, M., Allgaier, C., 2014. An update on drug treatment options of Alzheimer's disease. Front. Biosci (Landmark Ed.), 2014; 19(1): 1345-354.
29. National Institute on Aging, 2015. Alzheimer's Disease Medications Fact Sheet Alzheimer's disease Medications Fact Sheet National Institutes of Health.
30. Ng, Y.P, Terry Cho T sun Or, Nancy Y.Ip.Plant alkaloids as drug leads for Alzheimer's disease, Neurochemistry International, 2015; 89(1): 260–270.
31. Amirkia, V, Heinrich, M, 2014. Alkaloid as drug leads e a predictive structural and biodiversity-based analysis. Phytochem. Lett, 2014; 10(0), xlviiieliii.
32. Mukherjee PK, Kumar V, Mal M, Houghton PJ. Acetylcholinesterase inhibitors from plants. Phytomedicine, 2007; 14(4): 289–300.
33. Harborne JB, Baxter H, Moss GP. Phytochemical Dictionary. London, UK: Taylor and Francis, 1999.
34. A. Shakya, S. Chatterjee, V. Kumar, Holistic Psychopharmacology of Fumaria indica (Fumitory) Chin. Med, 2012; 3(4): 182., Article ID:26043).
35. Atta-ur-Rahman, M. K. Bhatti, F. Akhtar, M. I.

Choudhary, Alkaloids of *Fumaria indica*, Phytochemistry, 1992; 31(8): 2869-2872.
36. Z. H. Mardirossian, H. G. Kiryakovt, J. P. Ruder, D. B. MacLean, Alkaloids of *fumaria officinalis.* Phytochemistry, 1983; 22(3): 759-761.
37. Jakub Chlebeka, Zdenek Novak, Dominika Kassemova, Marcela Safratova, Jan Kostelnika, Lukas Maly, Miroslav Locareka, Lubomir Opletala, Anna HoDtI.lkova, Martina Hrabinova, Jiri. KuneDb, Pavl.na Novotn.d, Marie Urbanova,Lucie Novkova, Katerina Macakova, Daniela Hulcova, Petr Solichd, Concepciyn Perez Martinf, Daniel Junc, andLucie Cahlikova. Isoquinoline Alkaloids from *Fumaria officinalis L*. and Their Biological Activities Related to Alzheimer ’s disease. Chem. Biodiversity, 2016; 13(1): 91– 99.
38. Jun Zhanga, Chen Zhanga, Fu-Chun Xub, Queshengc, Qing-Ying Zhanga, Peng- Fei Tua, Hong Lianga. Cholinesterase inhibitory isoquinoline alkaloids from *Corydalis mucronifera*. Phytochemistry, 2019; 159(1): 199–207.
39. Eduardo Luis Konrath, Carolina dos Santos Passos, Luiz Carlos Klein-Júnior and Amélia T. Henriques. Alkaloids as a source of potential anticholinesterase inhibitors for the treatment of Alzheimer’s disease. Royal Pharmaceutical Society, *Journal of Pharmacy and Pharmacology*, 65(1): 1701–1725.
40. Dorothea Kaufmann, Anudeep Kaur Dogra , Ahmad Tahrani, Florian Herrmann and Michael Wink. Extracts from Traditional Chinese Medicinal PlantsInhibit Acetylcholinesterase, a Known Alzheimer’s Disease Target. Molecules, 2016; 21(1): 1161.
41. L.B.Pagolisa,S,C.Moneiro,M.Cammorata.K.B.Silva, J.P.Bastida, J.A.S.Zuanezzi.Eff ect of isoquinoline alkaloid from two Hippeastrum species on in vivo acetylcholinesterse activity, phyttomadicin, Elsevier GmbH, 2010; 17(1): 698-701.
42. Rosa tundis, Fedrica menichini, Filomena conforti,monica R Loizzo, Marco bonesi, Gincarlo statti,and Francesco menichen, Apotential role of alkaloid extract from *salsola* secies(Cinopodiacea) in the treatment of Alzheimer’s disease. Journal of enzyme inhibition and medicinal chemistry, 2019; 24(3): 818-824.
43. Sutthatip Markmee, Somsak Ruchirawat, Vilailak Prachyawarakorn, Kornkanok Ingkaninan and Nantaka Khorana. Isoquinoline derivatives as potential acetylcholinesterase inhibitors. Bioorganic & Medicinal Chemistry Letters, 2006; 16: 2170–2172.