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Студент	Доника Хоџа
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Тема	Истражување на избрани растенија Lamiaceae со традиционална употреба релевантни за управување со Алцхајмерова болест и други когнитивни нарушувања
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Растенија-хербални супстанци за третман на Алцхајмерова болест

Апстракт

Алцхајмеровата болест е дел од невродегенеративни нарушувања кои вклучуваат прогресивно оштетување на когнитивната функција што резултира со губење на меморијата што сериозно влијае на секојдневниот живот. Неколку хипотези се поставени за патофизиологија на Алцхајмерова болест и врз основа на тие хипотези истражувачите се фокусирани на различни патолошки цели за да најдат лек или симптоматски третман за Алцхајмерова болест. Во моментов, само неколку лекови се достапни за управување со Алцхајмерова болест и овој достапен третман дава само симптоматско олеснување.
Растенијата се користат во третманот на деменција, амнезија, како и Алцхајмерова болест одамна, а исто така и денешните лекови од растителна база во претклиничките и клиничките студии покажаа ветувачки резултати во третманот на Алцхајмеровата болест.
Во овој преглед, имаме за цел да покажеме релевантни in vitro, in vivo студии фокусирани на потенцијалните употреби на различни фитохемикалии добиени од растенијата во третманот на Алцхајмерова болест.[11]

Plants-herbal substances for treatment of Alzheimer condition

Abstract
Alzheimer's disease is part of neurodegenerative disorders that involves progressive impairment of cognitive function resulting in memory loss that severely affects daily life. Several hypotheses have been postulated for the pathophysiology of Alzheimer's disease and based on those hypotheses researchers are focused on different pathologic targets to find a cure or symptomatic treatment for Alzheimer's disease. Currently, only a few drugs are available for the management of Alzheimer's disease and this available treatment delivers only symptomatic relief.
Plants are used in the treatment of dementia, amnesia, as well as Alzheimer's disease a long time ago, and also now day's plant base drugs in preclinical and clinical studies have shown promising results in the treatment of Alzheimer's.
In this review, we aim to show relevant in vitro, in vivo studies focused on the potential uses of different phytochemicals obtained by plants in the treatment of Alzheimer's disease.[11]

Introduction

History of Alzheimer's disease

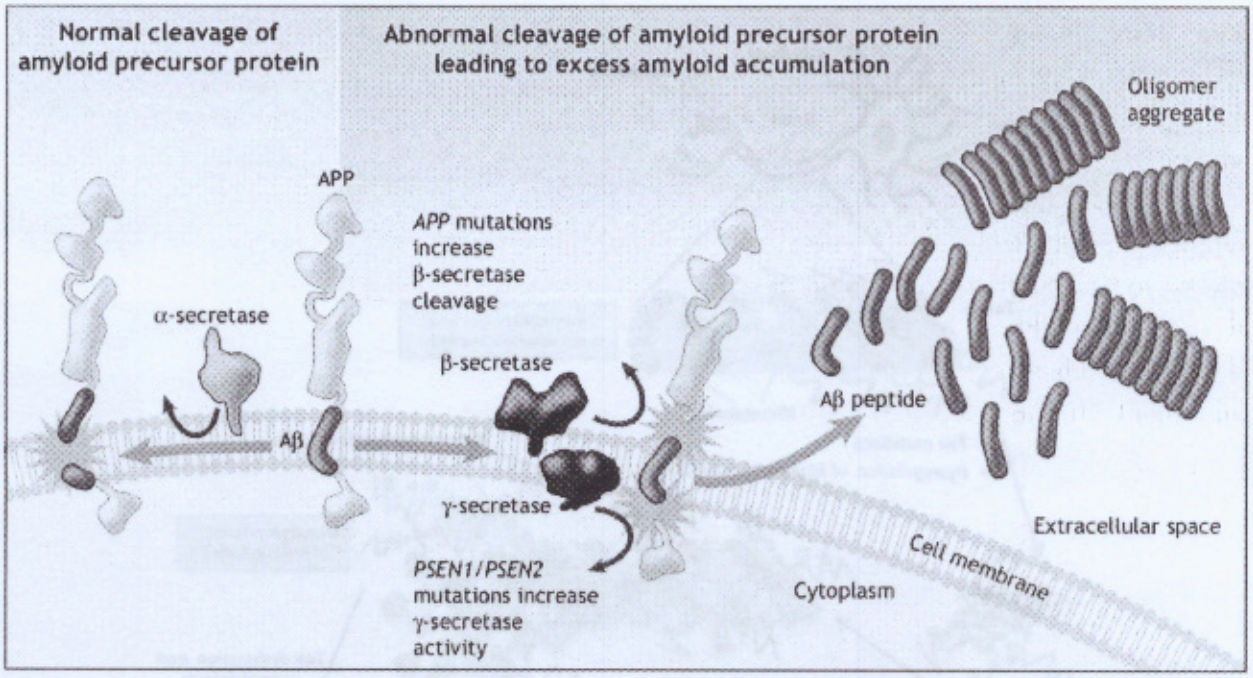


Figure 1: Normal and abnormal cleavage of APP and formation of Aβ peptides [21]

Another major pathological hallmark of Alzheimer's disease is the presence of intracellular neurofibrillary tangles (nFT), which consist mainly of the hyperphosphorylated tau protein (MaP-tau). [54]

Normally located at the axons, tau is important for neuronal differentiation and development, maintenance of cellular morphology and polarity, as well as axonal transport of organelles, vesicles or, molecules. [13] Although is not completely understood but it's thought Aβ plaque buildup outside the neuron, initiates pathways inside the neuron that leads to activation of kinase, an enzyme that transfers phosphate groups to the tau protein. Phosphorylation of tau in Alzheimer's disease leads to its dissociation from microtubules, microtubule destabilization, loss of dendritic microtubules and synapses, interruption of axonal transport, plasma membrane degeneration, and eventually neuronal loss. [13]

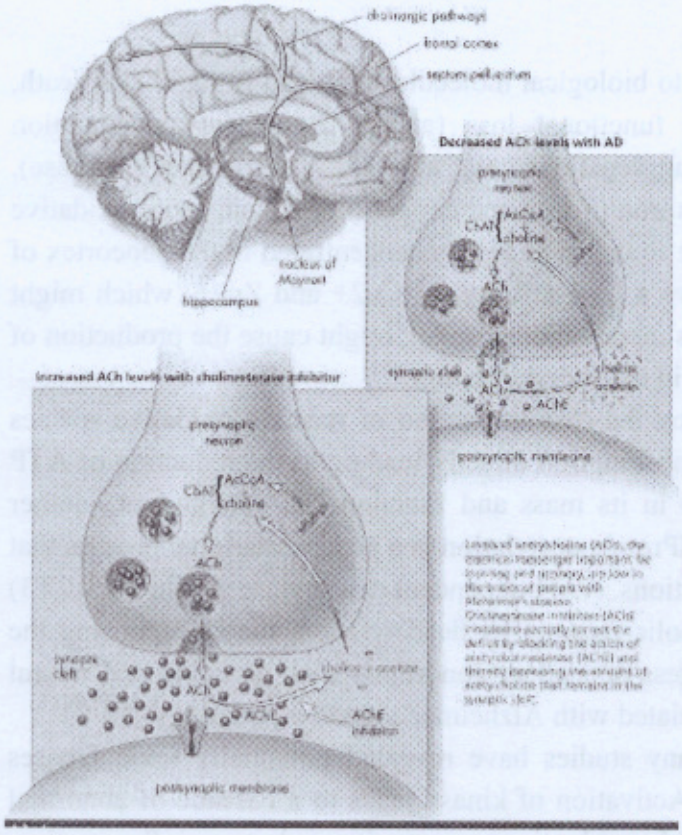


Figure 3: Ach levels in Alzheimer's disease brain and with AchE inhibitors [4]

In Alzheimer's disease, neurotoxicity is caused by mitochondrial dysfunction and oxidative stress.[70] [48] Oxidative stress is an imbalance between free radicals and antioxidant systems. Reactive oxygen species (ROS), such as superoxide (O2-), hydrogen peroxide (H2O2), and hydroxyl radical (OH), and reactive nitrogen species (RNS) are products of normal cellular metabolism and in normal concentrations, they possess various physiological roles ranging from cellular signal to defense against pathogens and are generated during normal aerobic respiration of the cells. [14][57] Sources of oxidants might be also bacteria or virus-infected cells that are demolished by phagocytosis, lipid and fatty acid degradation, and end products generated by cytochrome P450. If the balance between ROS and antioxidants is disrupted, the immoderate amounts of ROS will damage cells by protein oxidation, DNA/RNA strand breakage, lipid peroxidation, or the formation of advanced glycosylation end-products. Under normal circumstances, a slightly balance on the oxidant side is optimal for essential cell processes, such as cell signaling and redox regulation. Antioxidant protection should lower the levels of harmful ROS while keeping the balance of the ROS that should remain in the cell.

to perform logic, increased irritability, and increased inability to organize thoughts but are not severe enough to significantly interfere with daily routine activities.

Stage three or dementia generally lasts one to three years and diagnosis requires significant functional impairment to be present in addition to cognitive impairment and most often symptoms involve incontinence, swallowing difficulty, development of skin infections, and seizures. [65] [7]

Research on new strategies for earlier diagnosis is among the most active areas in Alzheimer's science with the hope that future treatments could target the disease in its earliest stages, before irreversible brain damage or mental decline has occurred because therapy in the late stages of Alzheimer's is not very effective and this is most likely due to massive neuronal death, which precedes symptoms of dementia. [66]

Statistical studies have shown that if scientists today can delay Alzheimer's disease onset by five years, the number of current affected patients this number will be reduced by nearly half in less than a generation. Better still, if Alzheimer's disease onset can be delayed by a decade or so, over 90 percent of current patients might die of old age rather than from this disease.[24]

Until now only five drugs are available for the management of Alzheimer's disease which is approved by the US Food and Drug Administration (FDA) and they are drugs used only symptomatic treatments that may help to stabilize temporary cognitive symptoms such as loss of memory and disorientation. [7]

From cholinesterase inhibitors group are three of the five available medications and they are donepezil, galantamine, and rivastigmine. The fourth medication is memantine and works by regulating the activity of a different chemical messenger in the brain that plays role in memory and learning. Both groups of drugs can help the management of symptoms in Alzheimer's disease but work in different pathways. The fifth medication is a combination of one of the cholinesterase inhibitors (donepezil) with memantine, Namzaric, and was approved in 2014 and it is the only advancement since 2003. [57] [6]

Since neurodegenerative diseases are multifactorial disease combination therapy using a mixture of compounds in acting on several disease targets, could have promising results. [57]

However, these drugs have emphasized side effects like nausea, vomiting, food aversion, headache, constipation, and dizziness and the need for new and improved therapy with fewer side effects and better outcomes is enormous. [7]

Some drugs used in other conditions showed a reduction in the risk of development or improvement of Alzheimer's disease, like selegiline which is normally used for the treatment of Parkinson's disease. Also some non-steroids anti-inflammatory drugs such as ibuprofen and long-term aspirin usage has shown a reduction in the risk of developing Alzheimer's and decreased inflammation or estrogen therapy shown to improve memory because of its antioxidant activity and decreased the risk of developing Alzheimer's.[35]

Also, probiotics are reported to have a role in increasing memory and are used as an antidepressant in Alzheimer's disease and it weakens psychological stress and lowers anxiety-like behaviors.[4]

Alkaloids

Alkaloids are natural secondary metabolites that contains nitrogen in the structure and are mostly derived from amino acids. [35] Alkaloids are a broad family and are classified using different techniques. Classification can be based on pharmacological properties (is based on the clinical use or pharmacological activity), taxonomic classification (is based on the family or genus), biosynthetic classification (based on the type of precursors used by plants to synthesize alkaloids), chemical classification (based on the chemical structure of the alkaloid).

Alkaloids classified biased on the chemical structure are described in the table 2. [68]

ALKALOIDS		
TRUE ALKALOIDS Inculde heterocyclic nitrogen (derived from amino acids)	**PROTO/AMINO ALKALOIDS** Simple amines (derived from amino acids)	**PSEUDO ALKALOIDS** Not derived from amino acids, but from Acyl CoA units

Table 2: Chemical classification of alkaloids [68]

There are many examples of drugs with CNS activity that are derived from plants that contain alkaloids as secondary metabolites and have shown promising results in many clinical trials for the management of Alzheimer's disease. [32] Various plant-derived compounds are already used for the treatment of Alzheimer's disease. The most prominent examples are galantamine, huperzine A and physostigmine.[34] *Galanthamine* isolated from several members of the Amaryllidaceae family like *Leucojum* spp. (especially from plant *Leucojum aestivum*), *Narcissus* spp. (especially from *Narcissus tazetta*), *Galanthus* spp. (especially from *Galanthus nivalis*) is one of the main therapeutic alternatives used to weaken the progression of neurological degeneration in Alzheimer's disease.[75]

Galantamine is shown to have a dual mechanism of action, modulates the nicotinic ACh receptors, and inhibits acetylcholinesterase.[12] Galantamine amplifies the effects of ACh by activating nicotine receptors which are responsible for learning and memory and also elevates the levels of glutamine, GABA, and seratoine due to its allosteric effect. [65] Studies have shown that galantamine except AChE has an anti-oxidant effect against reactive oxygen species those promoting neuroprotective effect by inhibiting oxidative stress-induced DNA damage and anti-genotoxic effects. Synthetic galantamine was first recognized in Sweden in 2000 and the drug also modulates nonamyloidogenic processing of APP by inhibiting β-site amyloid cleaving enzyme (BACE1) expression.[12][16][20]

Galanthus nivalis and *Narcissus spp* were also rich in *tazettine* and *pretazettine* isoquinoline alkaloids which has shown to possess acetylcholinesterase activity.[65] [73]

improvement in short-term memory. Vinpocetine also protects against NMDA-induced neurotoxicity whereas *vincamine* and *vincanol* also blocked voltage-gated Na+ channels. Alkaloid fractions from Vinca minor are associated with cytotoxicity and to assess their safety further trials are needed to provide more evidence for the therapeutic potential of Vinca-derived alkaloids in dementia. [32]

Celastress panicultus contains alkaloids *paniculatine, celapagine, celpanigine, celapanin*e and the extract exhibit neuroprotective properties by protecting neuronal cells against hydrogen peroxide-induced cell death also aqueous extracts of Celastress panicultus exhibited cholinergic activity thereby improving memory performance.[65]

Caragana chamlague steroidal alkaloids *α-viniferin* and *kobophenol A* has AChE activity due to structure-activity relationships. Studies suggest that the hydrophobic characteristics of the pregnane skeleton and the nitrogen substituent in the third position of carbon and/or in the twentieth position of the steroidal skeleton are the key structural features contributing to the inhibitory potency of pregnane-type steroidal alkaloids against AChE.

Buxus hyrcana steroidal alkaloids homomoenjodaramine and moenjodaramine are the bioactive compounds responsible for the AChE inhibitory activity. [51]

Protoberberine alkaloids like *stepharanine, cyclanoline and N-methyl stepholidine* which are found in *Stephania venosa* are accountable for AChE inhibitory activity.

In *Coptis spp* extract are found alkaloids *coptisine, berberine, groenlandicine, jateorrhizine, palmatine* (classified as protoberberine alkaloids) that has shown to inhibit the enzyme responsible for cleaving amyloid precursor protein on the β-site those adding an important attribution against Alzheimer's disease pathogenesis. Coptis spp. alkaloids also have AChE inhibitory properties. [16]

Coptis chinensis from traditional Chinese Medicine is another promising plant in the treatment of Alzheimer's disease due to having an up to hundredfold stronger AChE inhibitory activity than galantamine. Alkaloids obtained from extracts of Coptis chinensis are *berberine, epiberberine, coptisine, columbamine, palmatine, tetrahydrocheilanthifolinium, tetradehydroscoulerine*.

Some other plants with AChE inhibitory activity that can contribute to the treatment of Alzheimer's disease are *Fumaria vaillantii* (isoquinoline alkaloids like *ophiocarpine, β-allocryptopine, berberine* and *protopine), Zephyranthes carinata* (alkaloids lycoramine, 3-epimacronine), Berberis *aetnensis* (alkaloid *berberin*), *Holarrhena antidysenterica* (conarrhimin, conessimin, isoconessimine,conimin, conessine), *Phellodendron chinense* rich in isoquinoline alkaloids such as *berberine, palmatine, jatrorrhizine*, *Berberis bealei* with bioactive metabolites such as *columbamine, jatrorrhizine, and palmatine*. [51] [16] [63][65] [35] [4] [34]

When combined crude extracts of Coptis chinensis, Berberis bealei, and Phellodendron chinense probably due to of this synergism of isoquinoline alkaloids (*berberine, coptisine, and palmatine)* the mode of AChE inhibition results increased. [34]

Terpenoids

Alzheimer's disease in many ways like Aβ activity, AChE activity, antioxidant and anti-inflammatory properties. Some various types of diterpenes isolated from rosemary are *carnosic acid, carnosol, rosmadial, isorosmanol, royleanonic acid, rosmariquinone, epirosmanol.* Carnosic acid and carnsol are the main and most important secondary metabolites found in Rosmarinus officinalis and has shown to have an antioxidant effect by protecting neuronal cells from ischemic injury by scavenging ROS. Also, carnosol and rosemary essential oils have anti-inflammatory effects *via* inhibition of the TNF-α-induced protein and suppressing the expression of intercellular adhesion molecule. *Carnosic acid* has shown to possess very potent AChE inhibitory activity and the memory-enhancing effect of rosemary extract in the scopolamine-induced dementia model of Alzheimer's disease showed to be associated with a direct effect on AChE inhibitory activity.

A study done in SHSY5Y human neuroblastoma cells has shown the promising result of carnosic acid at α-secretase. This study showed 61% suppression of β42 secretion when the teste is performed at the concentration of 30 μM. Carnosic acid also plays a role in the inhibition of APP through the promotion of the normal non-amyloidogenic-dependent pathway.[27]

Rosmarinus officinalis is comprised of monoterpenes like *pinene, myrcene, camphene, limonine, 1,8 cineol,* and monoterpenols like *broneol.* The essential oil extracted from this plant contain *1,8-cineole* therefore is used in aromatherapy as body and brain stimulator therefore improves cognitive performance in terms of speed and accuracy. [65]

The methanol extract of *R. officinalis* has shown to have inhibitory activity in vitro due to the presence of essential oil *1,8-cineol and α-pinene.* [51]

Salvia officinalis is characterized by a high number of monoterpenes *α- and β-thujone, camphor, 1,8-cineole* and *borneol,* diterpenes like *carnosic acid* and triterpenes *oleanoic and ursolic acids.* Essential oils of *sage* are composed of larger amounts sesquiterpenes such as *α-humulene and β-caryophyllene. β-caryophyllene* has shown anti-inflammatory activity by inhibiting the main inflammatory mediators, such as inducible nitric oxide synthase, COX-1, COX-2, TNF-α, NF-κB, and interleukins 6 and 1 β. [28] [72] [20] The anti-inflammatory action of *Salvia officinalis* also it is thought to be related to the presence of manool, carnosol, and ursolic acid. *Salvia officinalis* and *Salvia lavandulifolia* may exert inhibition of AChE in vitro due to the presence of monoterpenoids *1,8-cineole* and *α -pinene.* [60] [28]

When essential oil of *Salvia lavandulaefolia* was administrated per-os into rats has shown to decrease striatal AChE activity in the striatum and the hippocampus in comparison with the control group and the effects of essential oils were better as a mixture of monoterpenes rather than those of individual isolated monoterpenes compounds. [51]

Due to the presence of diterpenes *tanshinones, dihydrotanshinone, cryptotanshinone, Salvia miltiorrhiza,* has shown to possess AChE inhibitory effect and also anti-inflammatory effects. Anti-inflammatory effect is exerted due to inhibition on leukotriene and prostaglandin production. [60] [51]

The volatile oil of *Melissa officinalis* exerted antioxidant and anti-inflammatory activities which is thought to be due to the presence of triterpenes like *oleanolic acid* and *ursolic acid.* Also,

sesquiterpene *α-bisabolol oxide A* reduced H2O2 in induced cell death and decreased free radical concentrations.

Zerumbone is a sesquiterpene found in *Zingiber zerumbet* and is known to possess an enzymolytic effect towards AChE. [51]

Asiatic acid triterpenoid in *Centella asiatica* extracts improved learning and memory *in vivo* with several studies suggesting that antioxidant mechanisms explain cognitive benefits. [60][65]

Phenolic Phytochemicals

Phenolic phytochemicals are the largest category of phytochemicals and the most widely distributed. [39] Based on their chemical structure, phytochemicals can be classified into the three main classes of polyphenols: (1) **phenolic acids** (i.e., hydroxybenzoic and hydoxycinnamic acids), (2) **flavonoids** (e.g., flavones, flavonols, flavan-3-ols, isoflavones, flavanones, and anthocyanidins or anthocyanins), and (3) **other phenolics** (e.g., stibenes, lignans, tannins, xanthones, lignins, chromones, and anthraquinones). [47]

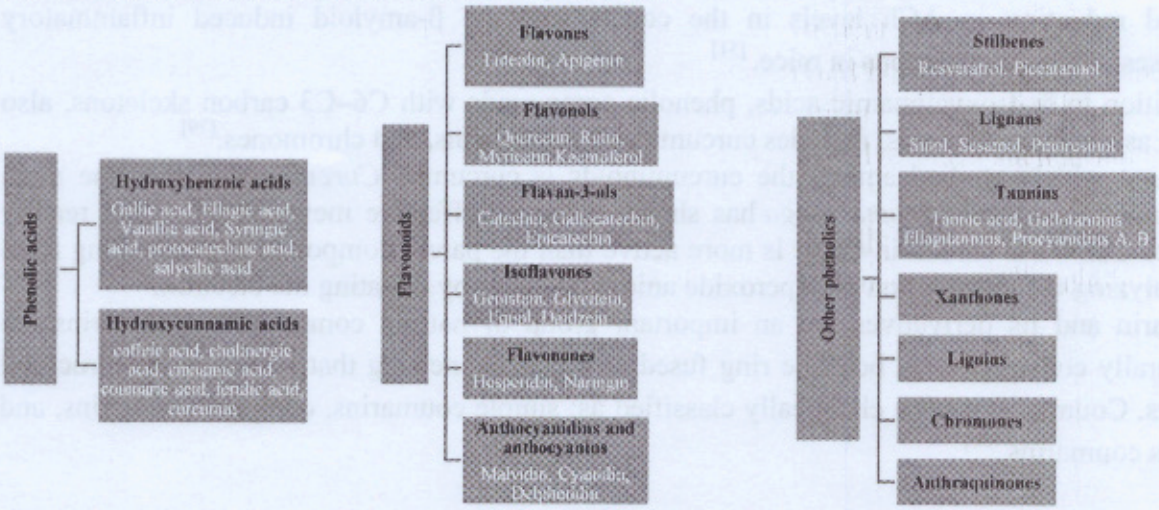


Table 4. Three main classes of polyphenols [47]

Several scientific studies have shown the beneficial activities of the polyphenols against Alzheimer's disease-like decreasing the cell damage caused by free radicals, neuroprotective effects (example polyphenols *resveratrol and tiron* has shown neuroprotective effects through inactivation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) induced by superoxide anion radical, AChE inhibitory activity (example *Rosmarinic acid* exhibited inhibitory activity towards AChE 85.8%) and β-amyloid aggregation (polyphenolic glycosides such as *naringenin, rutin, and apigenin*). [63][51]

Polyphenols like quercetin, resveratrol, curcumin, and (-)-epigallocatechin gallate etc., have shown to exhibit multiple pharmacological effects like anti-inflammatory activity, cholinesterase inhibition, blocking of Aβ, and tau aggregation. [51]

scoparone, scopolin, and esculetin and they were evaluated for their inhibitory activity against AChE, BChE, and BACE1 enzyme activity

As a result of the study umbelliferone 6-carboxylic acid and esculetin have shown the best potency to inhibit AChE, BChE, and BACE1. This study has shown that the catechol group, found in esculetin, exhibited significant activity against AChE and BChE also the presence of carboxyl

or catechol groups found in umbelliferone 6-carboxylic acid and esculetin is shown to increase the BACE1 inhibition, on the contrary, the presence of a sugar moiety and methoxylation has shown to reduce AChE and BChE activity of the coumarins investigated.[1]

From *Mutellina purpurea* was obtained dihydropyranocoumarin derivative pteryxin and studies have shown to be effective in AChE and BChE inhibition. Pteryxin was found to be more potent in the inhibition of BChE than galanthamine and can be a promising compound as BChE inhibition therapy in the treatment of Alzheimer's disease. [52]

From *Toddalia asiatica* were isolated nine coumarins phellopterin, isopimpinellin, artanin, fraxinol, toddalolactone, toddaculin, toddacoumaquinone, toddanone, and toddalenone and were tested for AChE activity, protect neuronal cell damage induced by H2O2 and anti-Aβ aggregation. Seven out of nine coumarins were shown to have a multifunctional effect in inhibiting the pathogenesis of Alzheimer's disease. The highest AChE inhibitory activity was shown by fraxinol due to the presence of hydroxyl group at position 6 while toddanone, toddaculin, and toddalolactone, have lower AChE inhibitory activity due to presence of longer side chain. Phellopterin has shown to have better AChE activity due to the presence of furan ring were as artanin was weaker in inhibition due to lack of furan ring in the composition. Those we can conclude that the presence of furan ring at position 6–7 showed an improved inhibitory activity because the furan ring possessing high electron density might influence the increase in binding affinity. The highest -Aβ aggregation induced by AChE has shown to possess toddacoumaquinone were as isopimpinellin and fraxinol did not have inhibitory effects. The substitution at position 6 of the coumarin ring played an important role in inhibition, for example, fraxinol, which has a small hydroxyl group, did not have an inhibitory activity while coumarin, which has a longer side chain like todaculin, toddalolactone, and toddanone was active. The attendance of di-hydroxyl or carbonyl groups at position 6 in the long alkyl chain, resulted in enhanced activity at toddalolactone and toddanone, comparable to toddaculin. Toddanone, phellopterin, and todalenone are the most active in the inhibition of self-induced Aβ aggregation and this is due to lipophilicity and also the presence of the furan ring might increase the binding activity. According to this study substituents on positions 6, 7, and 8 of coumarin ring influenced anti-AChE function and anti- Aβ aggregation. Phellopterin has shown to be the most potent compound in neuroprotective activity against H2O2 and Aβ 1–42-induced neuronal cell death. [71]

Flavonoids

Flavonoids are the largest group of plant phenols and great variability of structural basis make it possible to further sub-divided them into isoflavones, flavones, flavanones, flavanols, flavan-3-

From *Zizyphus jujube* has been extracted different types of flavonoids like *rutin, quercetin, kaempferol*, and the medicinal properties of jujube are attributed to the antioxidant properties of these compounds. [33] [35][65]

Icariin, a flavonoid isolated from *Epimedium species* has been shown to poses antioxidant effect dose-dependently those resulting in a protective effect on neurons damaged by ischemia.

Also, some recent studies using rats and 5xFAD mouse showed that icariin when given subcutaneously in rats and when in 5xFAD mouse was administrated icariin, resulted in less neuron damage compared to untreated groups and is suggested that the underlying mechanism is inhibition of tau protein hyperphosphorylation. Also AChE inhibitory effects, associated with alleviation of memory impairment in Alzheimer's, have been noted with an ethanolic extract *of E. koreanum*, but no studies have yet been conducted to determine the nature of the compounds responsible. [60]

Isoflavonoid and flavonoid constituents *in Glycyrrhiza* genus include *2,2'-4' trihydroxychalcone* (TDC), *glabridin, shinpterocarpin, glabrone, licoisoflavones A and B, galbrene* and due to their antioxidative, antiinflammatory properties, several species of Glycyrrhiza were investigated for possible therapeutic effects against neurodegenerative disorders. For example, *Glycyrrhiza glabra*s flavonoid TDC exhibited antioxidant, anti-inflammatory effect, and on the other hand extract from Glycyrrhiza inflata prevents tau misfolding in vitro. Thus, the extract of this genus may be effective against Alzheimer's disease. [70] [51]

Luteolin flavonoid found in *Lavandula officinalis*, increased plant effects on the central nervous system area by causing calming and soothing effects through GABA receptor. [33]

In *Cannabis sativa* have been identified more than 20 flavonoids that belong mainly in two classes, flavones and flavonols, and three prenylated aglycone flavanones named cannflavin A, B and C. Studies have shown that Cannflavin A has a neuroprotective role against Aβ-mediated neurotoxicity, associated with an inhibition of Aβ fibrillization.[55][19]

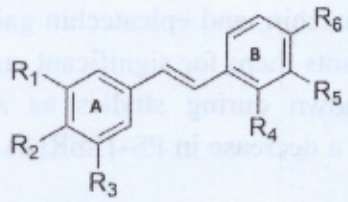
Free radical scavenging and antioxidant activity of *Hypericum perforatum* extract are mainly due to the presence of flavonoids such as quercetin and quercitrin and also from phytochemicals like hypericin and hyperforin. In a study testing for learning and memory impairment, associated with a change in brain due to oxidative stress caused in the rat by acute injection of scopolamine when Hypericum and its active ingredient, hyperforin was frequent administrated resulted in improvement of passive avoidance memory in mice via shuttle box. [51]

Convolvulus pluricaulis constituents like flavonol glycosides, anthocyanins, and triterpenoids have been effective for memory enhancing and nootropic attribution.[4]

A study has shown that aqueous extract, ethyl acetate and also ethanolic extract of *Convolvulus pluricaulis* increased memory functions and learning abilities including increasing in acetylcholinesterase activity. [59]

As we stated earlier in this article many poliphenols and terpene phytochemicals have exhibited effectiveness against cholinergic inhibition and many of the other factors contributing to Alzheimer's disease which the current alkaloid-based drugs do not. [73] For example, *galangin*, a

each carbon atom of the double bond substituted with phenyl rings, and compounds within the group differ from each other by phenyl ring R groups. [74]



R1	R2	R3	R4	R5	R6	
OH	H	OH	H	H	OH	resveratrol
OH	H	OH	H	OH	OH	piceatannol
OH	H	OH	OH	H	OH	oxyresveratrol
OGlc	H	OH	H	H	OH	piceid
OH	H	OH	H	OH	O-CH_3	rhapontigenin
OH	H	OH	H	O-CH_3	OH	isorhapontigenin
O-CH_3	H	O-CH_3	H	O-CH_3	O-CH_3	tetramethoxystilebne

Figure 6. Stilbenes structures [74]

Resveratrol, found in plants like *Polygonum cuspidatum* and *Vitis vinifera*, is the most common natural stilbene, widely studied, and has shown to have multiply pharmacological effects in different diseases including neurodegenerative diseases. Studies have shown that administration of *resveratrol* decreased plaque deposits, especially in the medial cortex, striatum, and hypothalamus, *resveratrol* has also exhibited neuroprotective effect by decreasing the amyloid burden and reducing tau hyperphosphorylation, reduced amyloid-β-induced cell death, and also decreased oxidative stress resulting in protection against spatial memory impairment.[58] [73]
Polygonum multiflorum, the main active ingredient, tetrahydroxy stilbene glucoside, can help to improve learning and memory abilities at mice with Alzheimer's disease and has been shown to reduce the expression level of the amyloid precursor protein. [64]
Resveratrol and its glucoside derivative *piceid* that can be found in barks of *Picea sitchensis*, could also suppress Aβ aggregation.[56]

Tannins

Tannins are water-soluble polyphenols, with many health-related beneficial effects and they are classified in two major groups: pseudo tannins and true tannins.

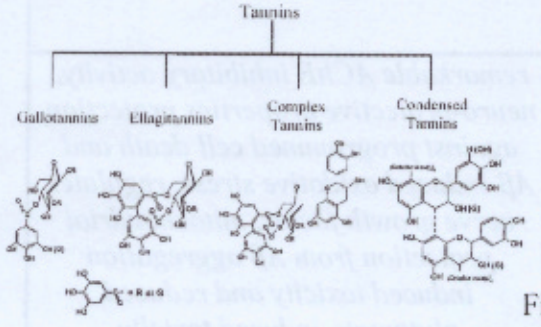


Figure 7. Main chemical structures of true tannins [5]

5	*Lycopodium serratum*			
6	*Physostigma venenosum*	*physostigmine*	*indole alkaloid*	*improved cognitive functions in rats with scopolamine-induced cognitive impairment, reversible inhibition of AChE*
7	*Zephyranthes carinata*	*lycoramine* and 3-*epimacronine*	*isoquinolone alkaloids*	*AChE and BChE inhibition activity*
8	*Vernonia amygdalina*	*nitrosodimethylamine, oxoassoanine, dihydro-oxo demethoxyhaemanthamine, and crinane-3alphaol*	*alkaloids*	*antioxidant properties and inhibit activities of AChE, BChE, MAO, BACE-1,*
9	*Rauwolfia serpentina*	*ajmalicine, serpentine, rauwolfine, sarpagine, ajmaline, yohimbine and reserpine*	*indole alkaloids*	*neuroprotective effect against Aß toxicity and anti-oxidative stress, AChE and BACE-1 inhibition, MAO-B nhibition.*
10	*Corydalis solida*	*protopine, berberine, palmatine, galantamine, corynoxidine*	*isoquinoline alkaloids*	*AChE inhibitory activities*
		physostigmine	*indole alkaloid*	
11	*Vinca minor*	*Vincamine* synthetic derivative vinpocetine vincamine and vincanol	*indole alkaloid*	*neuroprotective properties and also modulate neurotransmitter release, protects against NMDA-induced neurotoxicity*
12	*Celastress panicultus*	*paniculatine A,*	*lycopodium alkaloid*	*neuroprotective properties by protecting neuronal cells against hydrogen peroxide induced cell death, AChE inhibitory activity*
		celapagine, celpanigine, celapanine	*steroidal alkaloids*	
13	*Caragana chamlague*	*α-viniferin* and *kobophenol A*	*steroidal alkaloids*	*AChE inhibitory activity*

	Terpenoids			
24	*Rosmarinus officinalis*	*carnosic acid, carnosol, rosmadial, isorosmanol,royleanonic acid, rosmariquinone, epirosmanol*	*diterpene*	*AChE activity, antioxidant and anti-inflammatory properties*
		pinene, myrcene, camphene, limonine, 1,8 cineol	*monoterpenes*	
25	*Salvia officinalis*	*α- and β-thujone, camphor, 1,8-cineole* and *borneol, α -pinene*	*monoterpenes*	*inhibit AChE in vitro*
		carnosic acid, manool, carnosol	*diterpene*	*anti-inflammatory action*
		oleanoic and ursolic acids	*triterpenes*	
		α-humulene and β-caryophyllene	*sesquiterpenes*	
26	*Salvia lavandulaefolia*	*1,8-cineole* and *α -pinene.*	*monoterpenes*	*inhibit AChE in vitro*
27	*Salvia miltiorrhiza*	*tanshinones, dihydrotanshinone, cryptotanshinone*	*diterpenes*	*anti-inflammatory*
28	*Melissa officinalis*	*oleanolic acid* and *ursolic acid*	*triterpenes*	*antioxidant and anti-inflammatory*
29	*Ginkgo biloba*	*citral*	*monoterpenes*	*anti-AChE*
		ginkgolides A, B and C	*diterpene*	*antioxidant and anti-inflammatory*
		Bilobalide	*sesquiterpenes*	*strong antioxidant activity and possibly causing extra neural*

		isorhamnetin		
		quercetin	*flavonols*	*inhibit A β -induced cell apoptosis, inhibit COX*
		ginkgetin	*flavon*	
38	*Curcuma longa*	*curcumin*	*phenolic acids*	*metal chelator, ROS scavenging,*
39	*Salvia officinalis*	*ellagic acid,rosmarinic acid*	*phenolic acids*	*antioxidant*
		quercetin, and rutin	*flavonols*	
		apigenin, cirsimaritin, genkwanin, hispidulin, luteolin,	*flavon*	
40	*Silybum marianum*	*silibinin*	*flavon*	*inhibit AChE and aβ peptide aggregation*
41	*Nepeta sp*	*ferulic acid*	*phenolic acids*	*ameliorate β-amyloid-induced reduction in ACh levels*
42	*Prunella vulgaris*		*flavonoids*	*increase of cholinergic neurotransmitters, antioxidant activities*
43	*Camellia sinensis*	*quercetin, gossypetin, myricetin, quercitrin, isoquercitrin, and rutin gallocatechin gallate and theaflavin*	*flavonol*	*antioxidant properties, inhibit Aβ aggregation*
44	*Zizyphus jujube*	*rutin, quercetin, kaempferol*	*flavonols*	*antioxidant*
45	*Paeonia suffruticosa*	*quercetin, kaempferol,catechin*	*flavonols*	*aggregation inhibitory property*
46	*Caesalpinia crista*	*protocatechuic acid, chlorogenic acid, caffeic acid, p-coumaric*	*phenolic acids*	*aggregation inhibitory property in addition to the cholinergic activity*

	pilosa	*quercitrin*		
		Tiliroside, 3-methoxy	*flavonoid*	
57	*Peumus boldus*	*quercetin*	*flavonol*	*AChE inhibitory activity and antioxidant activity*
		boldine, aporphine derivatives	*alkaloid*	
58	*Zosima absinthifolia*	*bergapten, imperatorin, pimpinellin and umbelliferone*	*coumarins*	*remarkable antioxidant and anti BChE AChE activities*
59	*Angelica decursiva Artemisia capillaries*	*2'-isopropyl psoralene, 7-methoxy coumarin umbelliferone , umbelliferone 6-carboxylic acid, scopoletin, isoscopoletin, scoparone, scopolin, and esculetin*	*coumarins*	*inhibit AChE, BChE and BACE1*
60				
61	*Mutellina purpurea*	*pteryxin*	*coumarins*	*in AChE and BChE inhibiton*
62	*Toddalia asiatica*	*phellopterin, isopimpinellin , artanin, fraxinol, toddalolactone, toddaculin, toddacoumaquinone, toddanone and toddalenone*	*coumarins*	*AChE activity, protect neuronal cell damage induced by H2O2 and anti-Aβ aggregation*
	Other phenolics			
63	*Cannabis sativa*	*cannabisin-M,*	*lignan*	*powerful radical-scavenging activity*
		cannabisin- N	*lignan*	*weak acetylcholinesterase inhibitory*

CONCLUSION

Alzheimer's disease is a neurodegenerative disorder that involves progressive impairment of cognitive function resulting in memory loss that severely affects daily life.

Until now only five drugs are available for the management of Alzheimer's disease and cholinesterase inhibitors class of drug are three of the five available medications approved (donepezil, galantamine, and rivastigmine), the fourth medication is memantine and the fifth medication is a combination of one of the cholinesterase inhibitors (donepezil) with memantine, Namzaric, that was approved in 2014 and it is the only advancement since 2003.

The available treatments can treat it symptomatically but this is not enough and the need for a new drug with fewer side effects and more effective is a must.

Several scientific studies have shown the beneficial activities of the phytochemicals obtained by plants for treatment and prevention of Alzheimer's disease, like decreasing the cell damage caused by free radicals, neuroprotective effects, AchE, BchE, BACE-1 inhibitory activity, and β-amyloid aggregation and the side effect is much lower.

Many natural molecules obtained from plants showed properties that are important in alleviating Alzheimer's disease and these include crossing the blood-brain barrier (BBB) exhibit a hydrophobic functional character, and associate with protein and this is due to physicochemical characteristics like hydrogen bonding, hydrophobicity, and aromaticity.

In this review, we have gathered plants rich in phytochemicals like alkaloids, terpenes, flavonoids, phenolic acids, lignans, stilbenes, tannins, and coumarins.

Alkaloids mainly due to AChE inhibitory activity are important in the treatment of Alzheimer's disease. Huperzine A was widely studied and the activity of this quinolizidine alkaloid is as high as or even greater than physostigmine, galanthamine, donepezil, and tacrine, the commercial drugs already used against Alzheimer's disease. Also, isoquinoline alkaloids seem to be promising phytochemicals in the treatment of Alzheimer's disease, and especially when combined extracts probably due to of this synergism can the mode of AChE inhibition can result in increasement for example Coptis chinensis, Berberis bealei, and Phellodendron chinense due to this synergism of isoquinoline alkaloids (berberine, coptisine and palmatine) shown higher AchE inhibitory activity.

The benefit of terpenes in Alzheimer's disease more commonly is due to antioxidant and anti-inflammatory activity especially from plants rich in monoterpenes, diterpenes, triterpenes, and sesquiterpenes. The most promising phytochemicals in the terpene group we can mention carnosic acid, oleanoic and ursolic acids, 1,8-cineole and α –pinene, ginkgolides A, bilobalide.

Most polyphenols have shown good inhibit of Aβ aggregation, BACE1 inhibition, antioxidant and anti-inflammatory activity, and more rarely AchE and BchE activity. We can mention quercetin, curcumin, and ginkgetin from the group of polyphenols as promising phytochemicals.

Fewer studies were found regarding stilbenes, tannins, lignans, but these phytochemicals have shown powerful radical-scavenging activity which makes them strong antioxidants, inhibition of Aβ peptides accumulation, BACE-1, and also AchE and Bche activity and can be seen as

PKR-protein kinase R

CK-1δ-casein kinase 1δ

AChE- acetylcholinesterase and

BChE-butyrylcholinesterase

TNF-α- Tumor necrosis factor

COX-1- Cyclooxygenase 1

COX-2- Cyclooxygenase 2

LOX- Lipoxygenase

NF-Kb- nuclear factor kappa-light-chain-enhancer of activated B cells

IL-1β-_Interleukin 1 beta

CXCR2-Interleukin 8 receptor, beta

GAPDH-glyceraldehyde-3-phosphate dehydrogenase

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УНИВЕРЗИТЕТ „СВ. КИРИЛ И МЕТОДИЈ“ ВО СКОПЈЕ
ШКОЛА ЗА ДОКТОРСКИ СТУДИИ
ФАРМАЦЕВТСКИ ФАКУЛТЕТ

Студиска програма: Трет циклус за докторски студии од областа фармација

РЕЦЕНЗИЈА

на семинарски труд од III семестар под наслов „ Растенија-хербални супстанци за третман на Алцхајмерова состојба “ на докторандот, магистер по фармација Доника Хоџа

Со одлука на Советот на докторски студии на Фармацевтскиот факултет во Скопје, определена е рецензентска комисија за оцена на семинарскиот труд од трет циклус на докторски студии во состав: проф. д-р Ѓоше Стефков, проф. д-р Светлана Кулеванова и проф. д-р Марија Карапанџова. По прегледот на доставениот семинарски труд, Рецензентската комисија го доставува следниот

ИЗВЕШТАЈ

Семинарскиот труд под наслов „**Растенија-хербални супстанци за третман на Алцхајмерова состојба**“ претставува самостојно изработен прегледен труд со вкупно обработенени 79 референци, структуриран во следните поглавја: вовед, специјален дел и заклучок. Систематизацијата на деловите во наслови и поднаслови обезбедува соодветно следење на материјата која е обработена во трудот.

Во „**Воведот**”, докторандот дава осврт на Алцхајмеровата болест како дел од невродегенеративни нарушувања кои вклучуваат прогресивно оштетување на когнитивната функција што резултира со губење на меморијата што сериозно влијае на секојдневниот живот. Дава неколку поставени хипотези за патофизиологија на Алцхајмерова болест и врз основа на тие хипотези се фокусира на различни патолошки цели за се најде лек или симптоматски третман за Алцхајмерова болест. Во третманот на деменција, амнезија, како и Алцхајмерова болест одамна се користат растителни препарати, а исто така и денес постојат кандидат-лекови од растителна база во претклиничките и клиничките студии покажаа ветувачки резултати во третманот на Алцхајмеровата болест. Така да во овој преглед, докторандот има за цел да прикаже релевантни студии фокусирани на потенцијалните употреби на различни фитохемикалии во третманот на Алцхајмерова болест.

Во специјалниот дел „**Растенија и нивни фитохемикалии во третманот на Алцхајмерова болест“,** докторандот најнапред дава една генерална поделба на фитокомпонентите според биосинтетското потекло, делејќи ги во 3 поголеми групи и тоа терпени, феноли и алкалоиди. Потоа докторандот се осврнува на значењето различни соединенија, од пооделните групи, во третманот на Алцхајмерова болест, започнувајќи со кандидат-компоненти од групата на алкалоидите, потоа следат терпеноидите, за да заврши со фенолните фитокомпоненти, расчленети на фенолни киселини, флавоноиди, лигнани, стилбени и танини притоа изложува резултати од предклинички *in vivo* и *in vitro* истражувања (тестови за инхибиција на AChE, BChE, α glycosidase, α-amylase и др.)

Потоа следи табеларен приказ на сите растенија и нивните компоненти што ги обработил докторандот а за кои се објавени резултати дека имаат анти-Алцхајмер ефекти. Во оваа табела се излистани 75 растенија со нивни различни фитокомпоненти, како и тестовите и разултатите како е потврден нивниот ефект.

Во **заклучните согледувања**, докторандот ја нагласува потребата од нови истражувања на растенија во потрага за фитокомпоненти – кандидати за борба против Алцхајмерова болести наведува некои актуелни и ветувачки фитосоединенија, за да на крајот даде предлог дека во борбата со оваа мултифакторијална болест, пристапот за комбинирана терапија со различни фитоагенси што би таргетирале различни механизми по и бе делувале истовремено, најверојатно би можел да даде добри резултати во третманот на Алцхајмерова болест.

ЗАКЛУЧОК

По прегледот на семинарскиот труд под наслов „ Растенија-хербални супстанци за третман на Алцхајмерова состојба " на докторандот Доника Хоџа, Рецензентската комисија констатира дека станува збор за значаен прегледен труд кој има за цел да прикаже релевантни студии фокусирани на потенцијалните употреби на различни фитохемикалии во третманот на Алцхајмерова болест.

ОЦЕНКА И ПРЕДЛОГ

Врз основа на горенаведеното, Рецензентската комисија позитивно го оценува доставениот семинарски труд под наслов „ Растенија-хербални супстанци за третман на Алцхајмерова болест" на докторандот Доника Хоџа и му предлага на Советот на докторски студии на Фармацевтскиот факултет при УКИМ во Скопје да го прифати и закаже негова презентација.

Рецензентска комисија:

Проф. д-р Ѓоше Стефков

Проф. д-р Светлана Кулеванова

Проф. д-р Марија Карапанџова