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Alzheimer-Dementia: Drugs and Herbal preparations

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Abstract
Dementia is defined as the gradual decline of all acquired intellectual skills / abilities such as memory, ability to concentrate, learning etc. From the onset of human civilization, loss of mental capacity and function was observed and recorded. The disease affects the patient's behavior and personality, causing neglect of physical hygiene, withdrawal, indifference, arousal and paranoid ideation usually around the close relatives. Alzheimer's disease is characterized by the presence of senile or neurotic plaques in the extracellular space, consisting of nerve endings with central deposition of β-amyloid, protein glycans and other proteins, and end neuronal neurofibrillary tangles. The pathological findings of a brain patient with Alzheimer's contain abnormal masses and irregular bundles of brain cells. The goal of drug therapy is to stabilize mental disorders, improve behavioral disorders, and treat the depression that often accompanies dementia. Acetylcholinesterase Inhibitors (AchE): donepezil, rivastigmine and galantamine aim to stabilize the mental state of Alzheimer's patients. Additionally, there are plants that play cytoprotective role against the observed inflammation in dementia. Such plants include *Gingo biloba* L, *Galanthus nvalis* L *Melissa officinalis* L *Salvia officinalis* L and *Crocus sativus* L.

Keywords: Dementia, β-amyloid, anticholinesterases, cytoprotective plants

Introduction
Loss of mental capacity and function was observed from the onset of human civilization. Pythagoras refers to the seemingly inevitable reduction of mental abilities in the elderly, while Galen connects the loss of cognitive ability and mental skills with the progressive process of aging, and coined the term "Morosis" (Morosis = mental slowness) to describe the specific condition [1, 2]. Aretaeus the Cappadocian, referred to organic mental disorders, and is probably the first to introduce a distinction between acute and chronic neurological-psychiatric disorders. Specifically, he described acute disorders as reversible, which correspond to what is now called delirium.

Alzheimer-Dementia
Certain chronic disorders of CNS have been described as irreversible disabilities of higher mental functions, causing injuries like dementia [3, 4]. Dementia is defined as the gradual decline of all acquired intellectual skills / abilities such as memory, ability to concentrate, learning, attention, determination, spatial orientation and the ability to express desires in relation to an earlier level of functionality. There is also an inability to handle daily needs and functions such as attendance at work, and communication with the social environment. It is manifested by disturbance of the patient's relationships, loss of motivation, reduced control of emotions and generally differentiation in behavior. The person becomes dependent and distanced from his environment. According to the National Institute on Aging, dementia is a brain disorder that affects communication and performance of daily activities, and Alzheimer's disease is a form of dementia that affects specific parts of the brain that control thinking, memory and language. Alzheimer is a very specific form of dementia. Dementia results from a variety of diseases and injuries that primarily or secondarily affect the brain. It is caused by damage to brain cells which interferes with the ability of brain cells to communicate with each other.
Different types of dementia are associated with certain types of brain cell damage in particular regions of the brain. Alzheimer's is the most common form of dementia, contributing to 60%-80% of cases, with a huge social impact. Its incidence increases with age. It usually appears after the age of 65 (less often at younger ages).

In Alzheimer high levels of certain proteins inside and outside brain cells make it difficult for brain cells to communicate with each other and stay healthy. Brain cells in the hippocampus (center of learning and memory) are often the first to be affected.

Table 1: Dementia vs. Alzheimer

Dementia	Alzheimer's
Word for a group of Symptoms caused by disorders that affect the brain.	Progressive, degenerative disorder that attacks the brain's nerve cells and neurons.
Not a specific disease	Results in loss of memory, thinking and languages skills.
Affects the ability to remember how to execute certain daily tasks.	Often results in behavioral changes

Symptoms of Alzheimer's disease

Symptoms of Alzheimer's disease include impaired thinking, decreased speech, and confusion. There are a variety of tests to determine the cause of dementia, including blood tests, mental health assessments, and brain tests [1, 2]. The symptoms of Alzheimer's disease usually start and progress slowly, so that the patient and his family cannot pinpoint the exact time of onset of the disease. Sometimes the disease manifests itself after the onset of organic psychosis with acute cognitive impairment, intense agitation and confusion, usually after a fall, trauma, infection or surgery. The initial symptom of the disease is the progressive decline of recent memory. In advanced stages the disease affects the patient's behavior and personality, causing neglect of physical hygiene, withdrawal, indifference, arousal and paranoid ideation usually to close relatives (spouses, children). In the final stages of the disease, patients also show movement problems with particular difficulty in walking and swallowing. Death occurs 6-10 years after the onset of symptoms due to indirect complications from bed rest, infections, falls, injuries or pulmonary embolism.

It is a characteristic that the patient usually does not recognize or accept all these symptoms and the difficulties in his daily life and reacts to the interventions of his/her family.

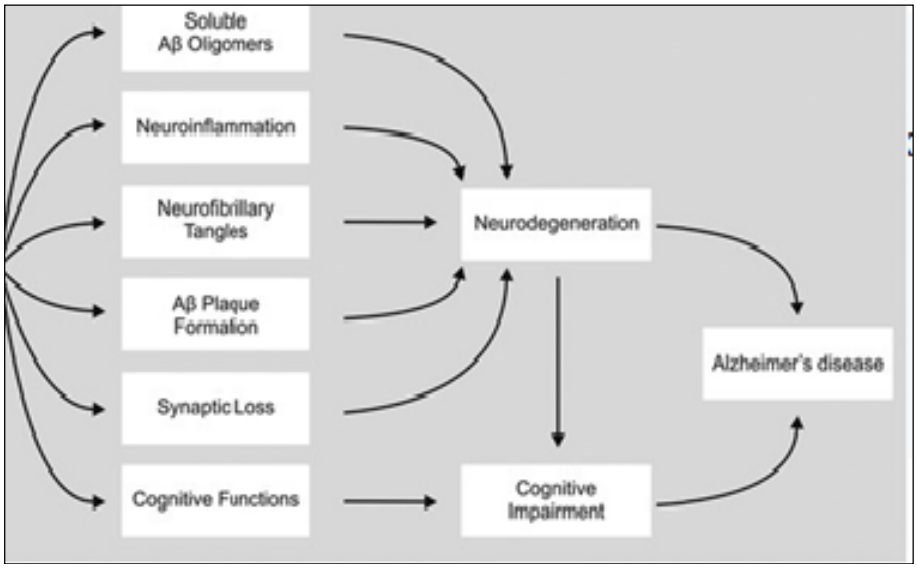

Fig 1: Mechanism of Alzheimer Disease

Diagnosis and treatment

Early and correct diagnosis of dementia is especially important for patients and their environment as they can significantly improve their quality of life and daily life. Proper prognosis depending on the type of dementia also offers the ability to properly plan the lives of patients and their families.

The treatments available for Alzheimer's disease, although they do not reverse the disease, they can slow down its progression and improve the cognitive functions of patients. They can address other behavioral symptoms, reduce arousal and help patients remain autonomous, functional and integrated into the social environment for longer. New drugs that reverse or slow the progression of the disease are also being investigated. Dementia is divided into primary Alzheimer's disease and secondary dementia due to cerebrovascular perfusion disorders. The causes of secondary dementia include depressive syndromes, as well as CNS-independent diseases, such as metabolic disorders, infections and autoimmune diseases [30].

Clinical evidence of dementia

Memory loss, confusion and disorder in the normal mental state including ability to form, combine and communicate thoughts and ideas.

Depression
Anxiety
Decreased learning ability
Dizziness and tinnitus
Emotional disorders
Inability to perform a project

Alzheimer's disease is characterized by the presence of senile or neurotic plaques in the extracellular space, consisting of nerve endings with central deposition of β-amyloid, protein glycans and other proteins, and endoneuronal neurofibrillary tangles. Hyperphosphorylation of the microtubule protein Tau is associated with their formation. Increased β-amyloid synthesis and deposition in neurons and vascular wall is considered to be the most likely cause of Alzheimer's disease pathogenesis. At the same time, within the neurons takes place a characteristic granulocytopenia degeneration. There is a concentration of proteins in the form of granules similar to tubulin. Decreased release of the neuroprotective sAPPa (soluble amyloid precursor protein-α) peptide has generally been observed. In addition, there is strong evidence that apoptosis plays an important role in the development of chronic degenerative diseases of the nervous system, such as Alzheimer's disease. Besides, β-amyloid deposition is accompanied by the death of the nerve cell with obvious apoptotic elements [27]. Severe forms of dementia of vascular origin, such as multiple infarcts* or atherosclerotic lesions in the brain at a frequency of 10-20%, or degenerative Alzheimer's dementia (50% of all other forms of dementia) lead to a complete change in the patient's personality with progressive mental retardation functions.
** "Multi-infarct" means that multiple areas of the brain have been injured due to a lack of blood from a series of small strokes.*

Image Credit: Lightspring / Shutterstock

Fig 2: Memory erasure

Phosphorylation of Tau microtubule protein plays an important role in the formation of microfibers. Normally, Tau protein is mainly involved in the transport of nutrients to the cell, regulates the orientation of the microtubules into nerve cells, astrocytes and oligodendrocytes. The β-amyloid is part of the amyloid precursor protein (APP), consisting of about 765 amino acids. In Alzheimer's disease, Tau-protein is phosphorylated, resulting in structural disorders of its molecule, and the appearance of toxicity in the cell. The accumulation of Tau protein leads to the formation of neurofibrillary tangles, which are homologous to many disorders known as Tau-diseases [5]. Hyperphosphorylation of the Tau protein results from disturbances in the balance of phosphate groups in the cell and is catalyzed by a kinase (which adds phosphate groups), while reduced degradation of the hyperphosphorylated Tau by proteolytic complexes leads to an increase in cell volume.

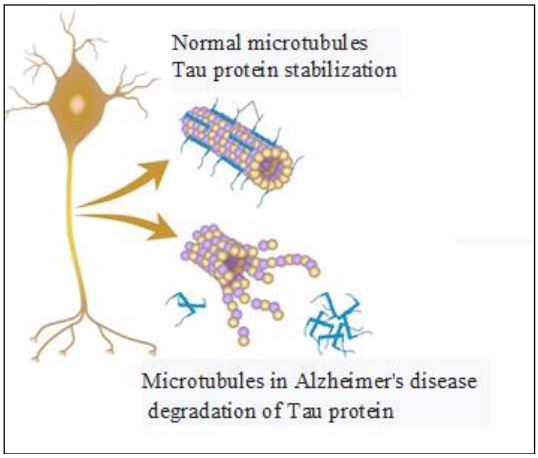

Fig 3: Normal Microtubules and degradation of Tau protein

Tau protein degradation (usually by rotating around itself) leads to the "death" of neurons in Alzheimer's.
The oldest hypothesis of the pathogenesis of Alzheimer's dementia is of cholinergic etiology, and is based on the reduced synthesis of acetylcholine. The cholinergic system innervates areas related to memory and learning, such as the hippocampus and temporal cortex. Despite the purely symptomatic nature of cholinergic therapy and the small improvement it offers to patients, modern clinically treatments offer a significant positive and beneficial action. In addition, it has been shown that different conditions as food restriction lead to autophagy. It is also accepted that suppression of autophagy is necessary for synaptic plasticity and memory improvement under conditions of nutritional stress.
Dementia can be divided into 4 stages based on the changes of various functions of the CNS and the corresponding functional examinations.

Initial dementia: Appears 2-3 years before the appearance of pathognomonic diagnostic criteria with the main feature being the loss of short-term memory and the inability to assimilate new information. Apathy and loss of motivation for previously important interests of the patient may coexist.

Early dementia: At this stage the memory as well as the ability to write and learn and possible shrinkage of the vocabulary are more widely affected. The patient can live independently with little help or supervision.
Moderate dementia: Worsening of speech difficulty and unpredictable outbursts of aggression, long-term memory loss, possibly urinary incontinence. Although patient's autonomy is limited, the patient refuses the help of his family. Professional nursing assistance is required.

Advanced dementia: It is the last stage and the change in behavior is radical. Complete loss of autonomy, inability to perform even the simplest tasks.
The age of the patient at the onset of the disease is important and there is often a decline in mental function before the age of 65. In addition, the reduction of the patient's functions is characteristic, with a clear difference every five years from

the onset of the phenomena. 25% of patients with dementia show both vascular and degenerative lesions. The incidence of dementia is constantly increasing as the average life expectancy has been extended. People 65 years of age develop dementia at a rate of 5%, while the incidence increases to 30% at the age of 80. The pathogenesis of dementia is multifactorial, there is increased vasoconstriction of the capillaries of the brain, reduction or lack of certain neurotransmitters, increased

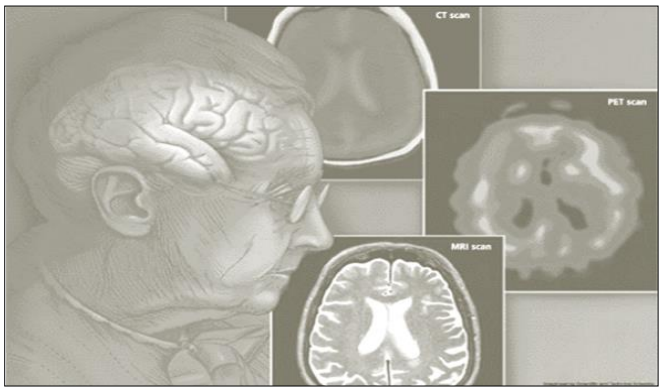

Fig 4: Various brain damages in Alzheimer disease

platelet, aggregation and blockage of blood vessels in the brain (due to a stroke), increased amounts of free radicals, cell membrane damage, metabolic disorders and progressive neuronal degeneration.

It has been observed an association of the disease with chronic microbial infections [24, 25]. Recent studies claim that bacteria or spirochetes are responsible for a number of events that lead to inflammatory processes in the CNS such as activation of proinflammatory cytokines and the presence of free radicals with cell apoptosis. Spirochetes and bacteria infections should be considered risk factors for Alzheimer's disease or cognitive impairment [22, 23].

The pathological findings of the brain

The pathological findings of the brain of an Alzheimer patient contain abnormal masses and irregular bundles of brain cells. These masses, plaques, and bundles, tangles, are considered features of the disease.

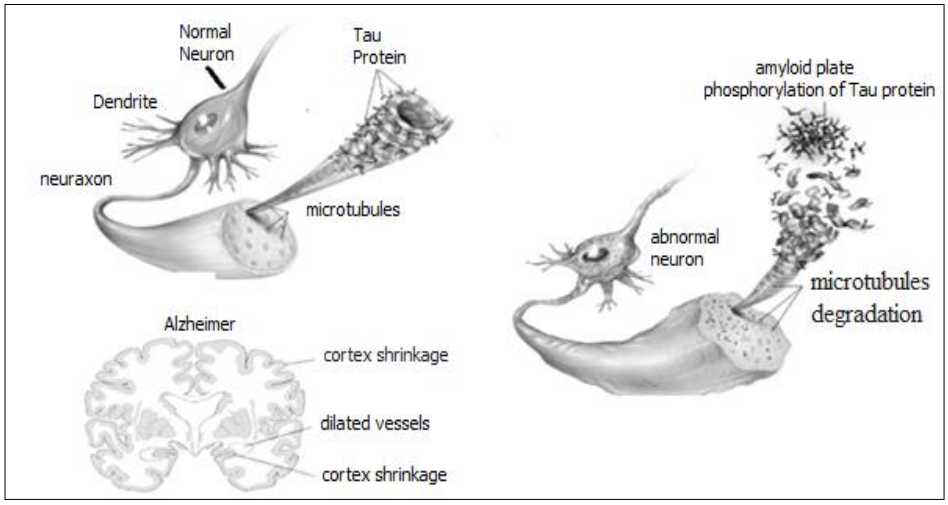

Fig 5: Degenerative brain damage

Plaques

Plaques are made up of normally harmless proteins called amyloid beta. Amyloid deposits are thought to form plaques between neurons early in the course of the disease, before neurons begin to die and before symptoms appear. Although the ultimate cause of neuronal necrosis in Alzheimer's is not known, much evidence suggests that amyloid beta proteins may be responsible. The plaques are located in the extracellular space and consist of degenerate nerve endings with central β-amyloid deposition and endoneuronal neurofibrillary tangles in the cytoplasm, forming helical bundles per pair of fibrils. Phosphorylation of the Tau microtubule protein plays an important role in the formation of microfibers. Normally, the Tau protein is involved in the transport of nutrients to the cell, regulating the orientation of the microtubules into astrocytes and oligodendrocytes. The β-amyloid is part of the amyloid precursor protein (APP), consisting of about 765 amino acids. In Alzheimer's disease, Tau-protein is phosphorylated resulting in:

a. the formation of neurofibrillary tulips,
b. the disturbance of the transport system of the nerve cells with alteration of the structure of the microtubules,
c. insufficient communication of nerve cells, and
d. cell death.

There are two types of lesions in the brain that affect its structure and function: a) amyloid plaques between nerve cells and b) neurofibrillary tangles [23, 24]. While these lesions occur during the normal aging process, in Alzheimer's disease they occur in high concentrations in the hippocampus and cerebral cortex.

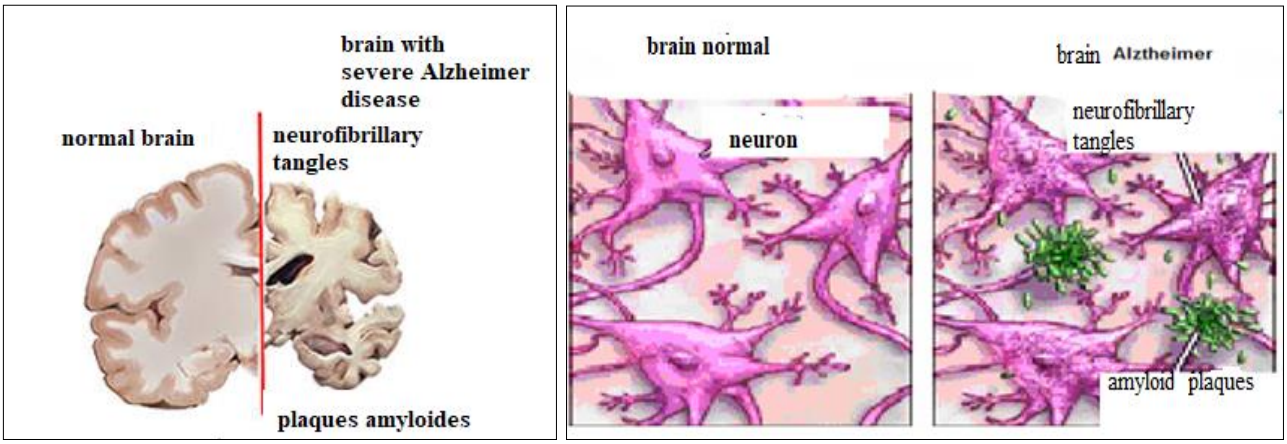

Fig 6: Normal brain vs. Alzheimer brain

Tau protein when degraded (usually by rotating around itself) leads to the "death" of neurons in Alzheimer's.

The oldest hypothesis of Alzheimer's dementia pathogenesis is cholinergic etiology, and is based on reduced acetylcholine synthesis. The cholinergic system innervates areas related to memory and learning, such as the hippocampus and temporal cortex. Despite the purely symptomatic nature of cholinergic therapy and the small-scale improvement it offers to patients, modern Alzheimer's medication has clinically significant positive and beneficial effects.

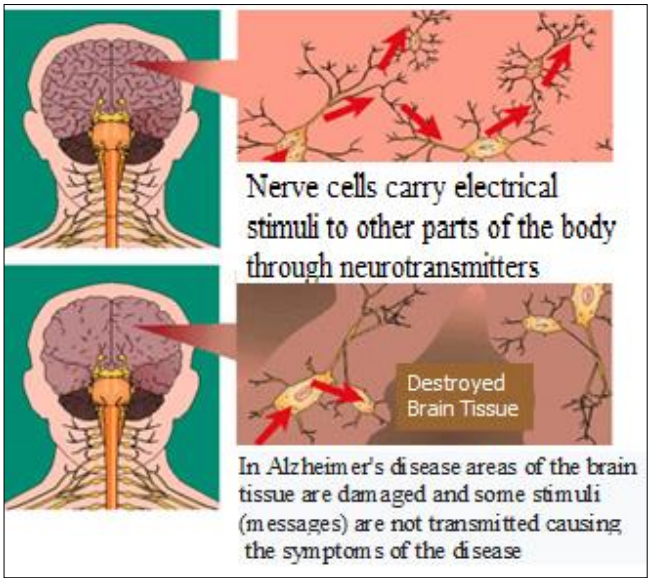

Fig 7: Brain tissue are damaged during Alzheimer's disease and some nerve stimuli are effected

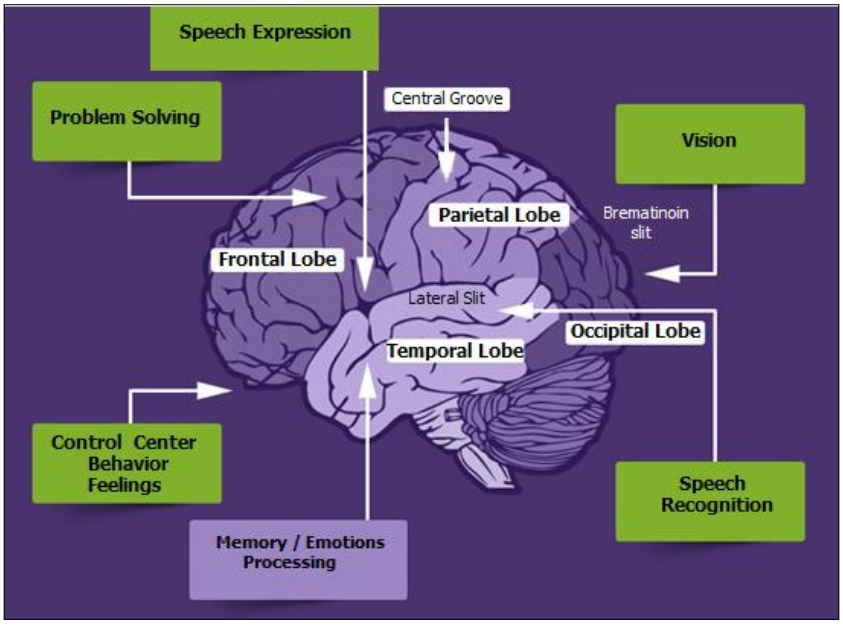

Fig 8: Memory / Emotions Processing: Lesions of regions of the brain caused by Alzheimer disease

The loss of synapses is what seems to be most associated with cognitive impairment. While the loss of synapses in Alzheimer's is not fully understood by the scientific community, studies suggest that this loss of synapses is one of the earliest events in the development of the disease. CNS small vessel disease (CSVD) causes 25% of strokes and contributes to 45% of dementia cases. CSVD can be asymptomatic; however, depending on location, lesions can cause mild cognitive dysfunction, dementia, mood and motor disorders [27].

Tangles

Although the main feature of Alzheimer's disease is the presence of neurofibrillary tangles and amyloid plaques in the brain. The internal structural support of brain neurons depends on the normal function of a protein called Tau. In people with Alzheimer's disease, the Tau protein undergoes changes that cause it to rotate. Many researchers believe that this can cause serious damage to neurons, and destroy them. The role of genetics in Alzheimer's disease is also being investigated. Certain rare forms of early-onset Alzheimer's disease before the age of 65 are caused by specific genetic mutations. But the number of people with these mutations is extremely small, about 200 families around the world. The sporadic form of Alzheimer's disease, which has no known cause, is responsible for the majority of cases. The presence of a gene known as apolipoprotein E (APOE 4) can also increase a person's risk of developing Alzheimer's, without guaranteeing that the disease will actually occur.

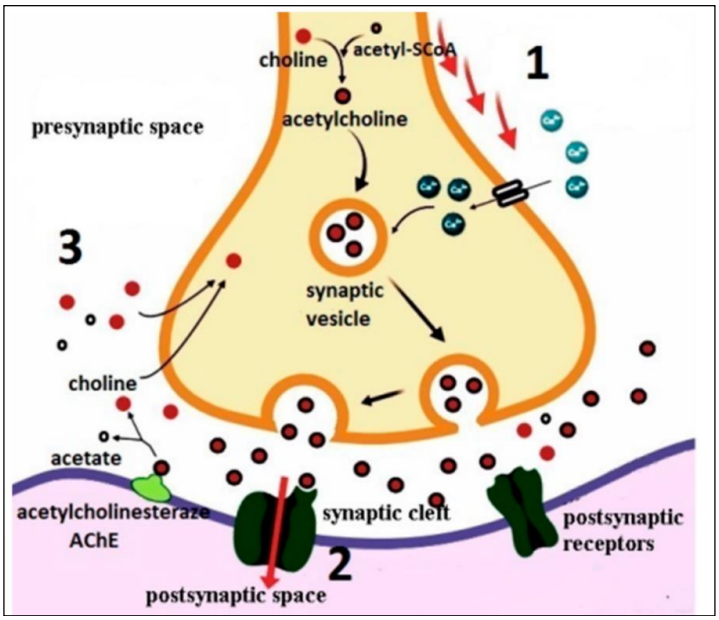

Fig 9: The role of acetylcholine (ACh) metabolism in Alzheimer's disease

Schematic representation of the acetylcholine release course and cholinergic hypothesis of AD. (1) Action potential causing influx of Ca2+ and subsequent membrane docking of synaptic vesicles; (2) acetylcholine binds to receptors initiating a graded depolarization in the post synaptic cell; (3) AChE catalyzes the breakdown of acetylcholine and choline molecules are reabsorbed by the presynaptic neuron. ACh, acetylcholine; AChE, Acetylcholinesterase; Acetyl-CoA, acetyl coenzyme A [34].

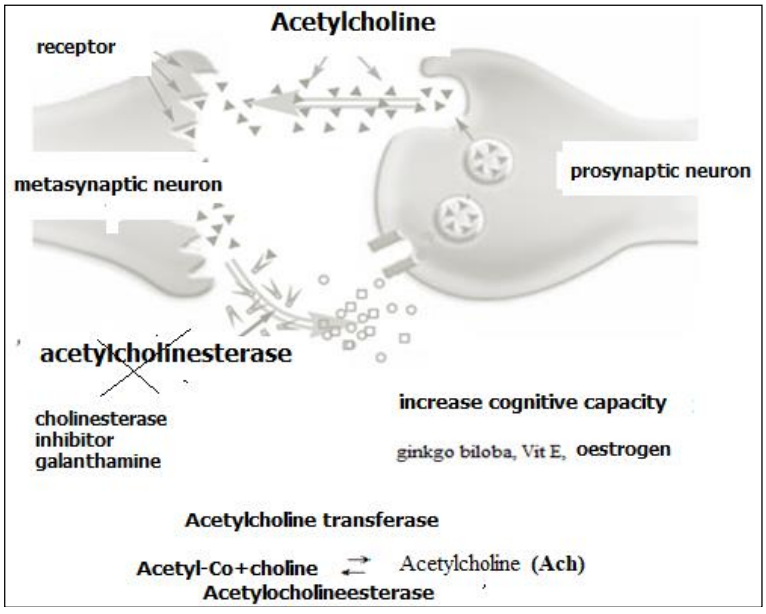

Fig 10: Schematic representation of the acetylcholine release course and cholinergic hypothesis of AD

The goal of drug therapy

The goal of drug therapy is to stabilize mental disorders, improve behavioral disorders, and treat the depression that often accompanies dementia. Before starting medication, the patient with dementia should undergo a complete examination for the existence of secondary, potentially treatable, causes, such as thyroid disease, taking drugs that adversely affect mental functions, (e.g. Anticholinergics, β-blockers), metabolic diseases (SD, B12 deficiency, folic acid), systemic diseases, intracranial invasive processes (e.g. benign and malignant neoplasms, chronic subdural hematoma) and chronic hypoxia (sleep apnea, heart failure) [33].

Acetylcholinesterase Inhibitors (AchE): donepezil, rivastigmine and galantamine aim to stabilize (sometimes improve over a short period of months) the mental state of Alzheimer's patients. Their approved indication is the treatment of mild to moderate Alzheimer's disease. Studies comparing 3 AchEs have not shown superiority over other regimens. However, about one-third of patients with Alzheimer's disease do not appear to benefit from cholinergic therapy. All 3 AchEs substances should be tested before actual usage in the therapeutic schema.

Side effects of cholinergic drugs are dose-dependent and are observed: abdominal pain, anorexia, nausea, vomiting, diarrhea, bradycardia, syncope, tremor, weight loss, abnormal dreams, dizziness and headache. In patients with a history of heart disease bradycardia, ECG should be monitored prior to administration. (Table.2.)

Glutamine antagonists: Memantine, a partial NMDA receptor antagonist, is officially indicated for the treatment of moderate to severe Alzheimer's disease. Its beneficial effects are found in the mental functions, behavioral disorders and daily functioning of patients. The dosage and titration of Memantine are shown in Table 3. Memantine is a generally well-tolerated drug and the rare side effects are irritability, confusion and flu-like syndrome.

Table 2: Anticholinesterases

Active substances	Formulations	Forms
Donepezil Side effects: nausea, diarrhea and fatigue, usually mild and short-lived.	Aricept/Pfizer	Tabs fc,10mg/tab, 5mg/tab Tabs oral disp 10mg/tab(blister) Tabs oral disp 5mg/tab(blister)
	Dementis/Elpen	Tabs fc,10mg/tab, 5mg/tab
	Donepezil/Genepharm	Tabs fc 10mg/tab, 5mg/tab
	Donepezil/Generics Pharma Hellas	Tabs fc 5mg/tab
	Covolos/Verisfield	Tabs fc,10mg/tab, 5mg/tab (blister)
Rivastigamine Reduces the symptoms of mild to moderate Alzheimer's with side effects nausea and vomiting. .	Exelon/Novartis Europharm	Capsules Caps 1,5mg/cap,3mg/cap, 4,5/cap, 6mg/cap (blister)
	Exelon/Novartis Europharm	Patches : Sachets 4,6mg/24h Sach. 9,5mg/24h, 13,5mg/24h
		Oral sol 2mg/ml x 50ml ;h 120ml
Galantamine Mild to moderate Alzheimer's. Improves cognitive function and behavior, well tolerated during clinical trials.	Galantamine/Generics Pharma Hellas	Caps 16mg/cap, 24mg/cap, 8mg/cap (Alu blister)
	Galantamine/Mylan	Caps 16mg/cap, 24mg/cap, 8mg/cap (Alu blister)
	Galantamine/Pharmaten ABEE	Caps 16mg/cap, 24mg/cap, 8mg/cap (Alu blister)
.	Galanyl/Viofar ΕΠΕ	Oral sol.4mg/ml x100ml
	Aneprosil/Verisfield UK	Oral sol.4mg/ml x100ml
	Memoton Life/Farmellas enterprises Ltd	Oral sol.4mg/ml x100ml
Tacrine Tacrine is the first drug approved for Alzheimer's disease but is now rarely used. It requires monitoring of liver function and should be given four times a day.	Cognex	10 mg orally 4 times/d (between meals if possible) for 6 weeks. Maintenance **dose**: May increase to 20 mg orally 4 times a day.
Gloutamic acid inhibitors		
Memantine It is the first drug approved for the treatment of moderate or severe Alzheimer's disease. Guidance from the National Institute for Clinics (NICE) does not recommend the use of Memantine in combination with cholinesterase inhibitors (Acetylcholinesterase inhibitor (AChEI)). The basic meta-analysis was challenged by clinicians. Interactions of Memantine with other drugs: **Anticholinergic therapy** (eg, atropine, Yoskinamine) **Dopamine agonists** (Bromocriptine, pergolide pramipexole Rominirol)	Almerzac/Pharmazac	Tabs oral disp 10mg/tab
	Ebixa/Lundbeck A/S	Tabs fc.10mg/tab
	Memantine/Radiopharm	Tabs 20mg/tab, Tabs oral disp10mg/tab
	Memantine/Mylan	Tabs fc.10mg/tab
	Memantine/Sandoz	Tabs fc 10mg/tab (Blister)

Memantine is licensed for moderate to severe Alzheimer's disease (AD). Guidence from the National Institute for Clinics (NICE) does not recommend the use of Memantine in combination with cholinesterase inhibitors

(Acetylcholinesterase inhibitor (AChEI).The basic meta-analysis was challenged by clinicians. Interactions of Memantine with other drugs [14].

Table 3: Dosage schedule for cholinesterase inhibitors [32]

Drugs	Starting dose	Titration period	Dose increase	Maximum dose	Metabolism
Donepezil	5 mg	4–6 weeks	5 mg increase	10 mg	Hepatic 24h CYP2D6, CYP3A4
Rivastigmine	1.5 mg b.i.d.	2–4 weeks	1.5 mg b.i.d. Increments	6 mg b.i.d.	Adhesive renal clearance
Rivastigmine Transdermal patch	4.6 mg/24 h	2-4 weeks	One-step Increase to 9.5 mg /24h	9.5 mg /24h	
Galantamine ER	8 mg	4–6 weeks	8 mg increments	24 mg	Hepatic CYP2D6, CYP3A4

(Adapted from Hsiung GYR, Loy- English l7)

Table 4: Memantine interactions with other drugs

Anticholinergic treatment (Atropine, yoscinamin)	Dopamine antagonist (bromocriptin, pergolide, pramipexole. rominirole)
Boupropion	Hydrochlorothiazide
Carbonic anhydrides (e.g., acetazolamide, topiramam acetazolamide	Ketamine
Ccimetidine	Levodopa
Dextromethorphan	Nicotine
Triamterene	Quinidine
Trimethoprim	Ranitidine
Warfarin	Sodium bicarbonate

In contrast, glutamic acid regulators (Memantine) reduce neurons' overexposure to glutamate (the ionic form is known as glutamate) and thus protect them from its neurotoxic action. It should be noted that glutamic acid in the brain is related to the process of recording information. Both cholinesterase inhibitors and glutamate regulators aim to treat the patient's cognitive loss. At the same time, however, behavioral disorders such as agitation, suspicion, aggression, and depression should be addressed [9].
Other medications used are selegiline, vitamin E, estrogen and anti-inflammatory drugs.

New possible treatments

Antiamyloid therapy: A better understanding of the mechanisms that contribute to the formation of amyloid plaques and their potentially toxic accumulation in the brains of people with Alzheimer's disease has led to the search for ways to remove protein accumulations or prevent their formation.

Anti-inflammatory agents. A number of anti-inflammatory agents are being investigated to prevent future neuronal degeneration by reducing the inflammatory response triggered in the brains of people with Alzheimer's. Some of the drugs being studied are prednisone, non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors [10].

Estrogens. Research shows that hormone replacement therapy after menopause can reduce a woman's risk of developing Alzheimer's disease by 40 to 50%. However, when estrogen was given experimentally as a form of treatment to women with Alzheimer's, the results were negative.
Because the effects of estrogen have not yet been proven, women should not start hormone replacement therapy just to prevent Alzheimer's disease.

Antioxidants: Vitamin E, seligillin and ginkgo biloba are antioxidants that can help prevent brain cell damage by destroying free radicals. Free radicals are waste products of normal cell function. Excess of these can disrupt the function of brain cells [10, 11].

Neurotrophic factors: Neurotransmitters are proteins that help neurons grow and survive. In the treatment of Alzheimer's disease, it seems that the introduction of these factors into the brain can help damaged neurons.
In addition, citalopram seems to have positive effects on stimulating hallucinations and sleep / nighttime disorders.

Herbal preparations and dementia

Clinical studies have shown beneficial effects from the use of herbal preparations [6, 7, 15, 16, 26, 29]. Herbal preparations can act as cytoprotectants against inflammation. Inflammation can stimulate neuroglobulins and lead to the release of free radical mediators (TNFα, IL-1β), (ROS), nitric oxide (NO), which are harmful stimuli to nerve tissue.

Fig 11: *Ginkgo biloba* L. (F-EMA)

A large number of clinical studies, double-blind randomized studies, show positive results with the use of Ginkgo biloba extract (especially Egb 761).
Extracts of the plant *Gingo biloba* L. may protect cell membranes and neurons from cell death and apoptosis, improve the metabolism of nerve cells in the brain, and protect cells from O_2 depletion and vascular occlusion. They reduce the swelling of the brain, bind to free radicals and improve blood circulation and viscosity, because they compete with PAF (Platelet Activator Factor = platelet activating factor) [10, 11, 12, 13].
They therefore inhibit platelet aggregation and the formation of edema in the brain, an action attributed to the active ingredients gingolide and vilovalid. However [he has been blamed for cerebral hemorrhage.

As already mentioned, the extract from the plant Ginkgo biloba L has a beneficial effect on obstructive vascular diseases, but also has a general multi-potency action. It also has antioxidant activity against lipoproteins, but also competes with the neurotoxicity caused by β-amyloid. Increasing the elasticity of erythrocytes and inhibiting their adhesion locally improves the microcirculation of the brain.
Increases the resistance of brain tissues to hypoxia, increasing ATP stores, mainly through vilovalide. It increases the thickness of α2 adrenergic, m-cholinergic and HT1A receptors in the hippocampus, thus promoting choline uptake into the CNS tissues. Clinical studies of 1975-77 proved the beneficial effect of extracts of the plant Ginkgo biloba (Ebb 761, LI1370) according to monographs of the European Union.

Fig 12: *Galanthus* (*Galanthus nivalis* L.)

The plant Galanthus (*Galanthus nivalis* L.) contains galanthamine hydrobromide, which belongs to the Acetylcholinesterase inhibitors, thus increasing the cholinergic activity [14, 16]. In addition it activates presynaptic acetylcholine receptors. Increases the release of glutamic acid, serotonin and GABA, thus improving feeling, reducing aggression and feeling anxious.

Fig 13: Medicinal bee (*Melissa officinalis* L. F-EMA)

The bee improves cognitive functions and reduces arousal in patients with mild to moderate disease. It has been shown to act on both nicotinic and muscarinic acetylcholine receptors in the CNS.
Sage the medicinal (Salvia officinalis L. folium C-EMA, Aetheroleum F-EMA) [7, 8]
Sage is also likely to have a cholinesterase inhibitory effect but has side effects such as cholinergic activity. It seems that their leaf extracts are rich in Monoterpene aldehydes, polyphenols (rosemary or rosmarinic acid) and Monoterpene glycosides. These compounds showed *in vitro* antioxidant activity and chemical affinity for nicotinic and muscarinic receptors in the human cerebral cortex. This action on the cortex may be attributed to the inhibition of the enzyme Acetylcholinesterase, so it can be an important aid in maintaining cognitive function [14, 16].

Fig 14: *Crocus sativus* L.

The plant *Crocus sativus* L is of particular interest among plants in Greece. It is cultivated in the village of Krokos in Kozani for its red poles, which are widely used in the diet as a seasoning (crocus or saffron). Crocus is also a herbal preparation with important properties, and has been used often in traditional medicine. Crocus poles contain unusual hydrophilic carotenoids, crocins, crocetin glycosides.
The neuroprotective mechanisms of the constituents of the stems of the plant Crocus sativus and other endemic species of Crocus with emphasis on Alzheimer's disease were studied. The extract of C. sativus (CSE) poles and its components, as well as other endemic Crocus species were used to evaluate: (a) their antioxidant properties and their effect on Aβ aggregation, both *in vitro* and in cell cultures (SH-SY5Y, HEK293, CHOAPP770) and (b) memory processes, brain oxidative state and Acetylcholinesterase (AChE) activity in adults [17, 18]. Balb-c muscles after intraperitoneal administration of CSE (7-day) (30 & 60 mg / Kg body weight) (n = 9 / group). One of the active ingredients is crocin.

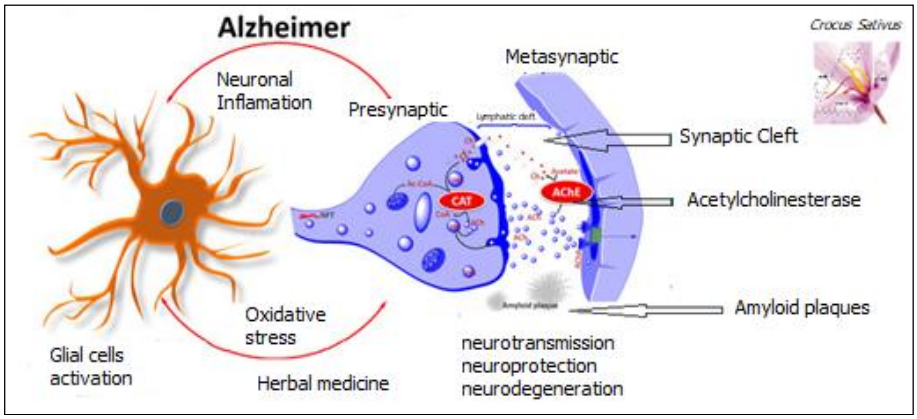

Fig 15: Crocin and Alzheimer's disease

Crocines are bright yellow pigments and are the most important pigments of the spots / pillars, i.e. the drug. They are mono-glycosidic or di-glycosidic esters of crocetin and are water-soluble carotenoids due to their high glycosidic content. Crocetin is esterified with two water-soluble gentiobioses (sugars). Hydrolysis products of crocin are gentiobiose and crocetin. Oxidative stress affects all macromolecule groups (glucose, lipids, proteins and DNA), resulting in neuronal dysfunction [15]. The administration of antioxidants (e.g. vitamins E and C, melatonin, flavonoids, carotenoids) that trap the free radicals created by oxidative stress, can have an improving effect, while in addition they do not show side effects [17, 18]. Experimental studies have shown that crocin administration improved cognitive impairment in experimental animals subjected to various tests such as intracranial (ICV) injection into the ventricles of the brain of streptozotocin, which contributes to increased glucose uptake stress. It should be noted that crocin reduced the levels of malondialdehyde (MDA) which is considered an indicator of oxidative stress and improved the activity of glutathione peroxidase (GPx). Crocin appears to act mostly as an antioxidant and does not interfere with the cholinergic component of dementia (i.e. changes in Acetylcholinesterase levels). Also trans-crocin-4, the major carotenoid, appears to inhibit Aβ amyloid aggregation at low concentrations [18, 19, 20, 21].

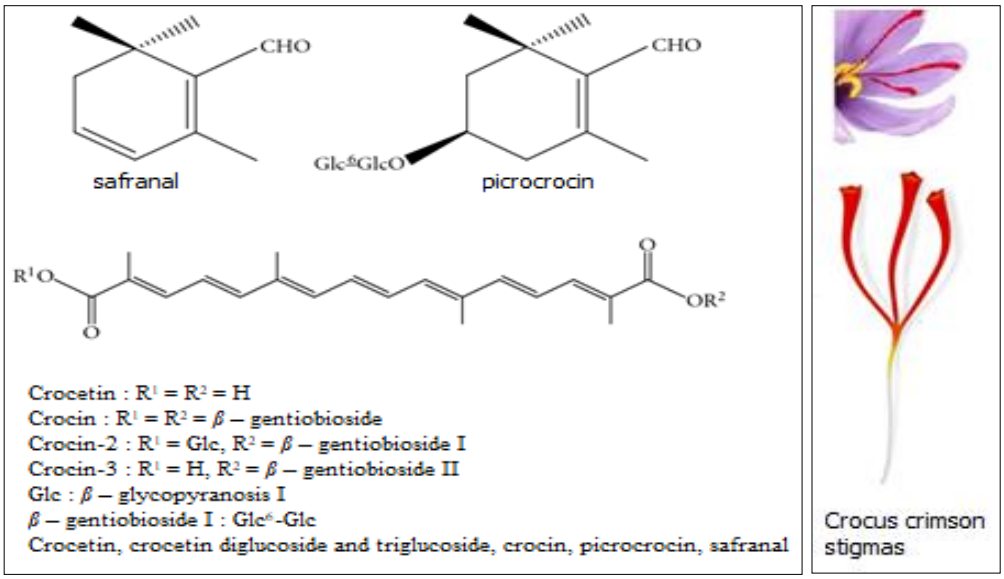

Fig 16: Monograph of Crocus Sativus– BGA / BfArM (Kommission E)

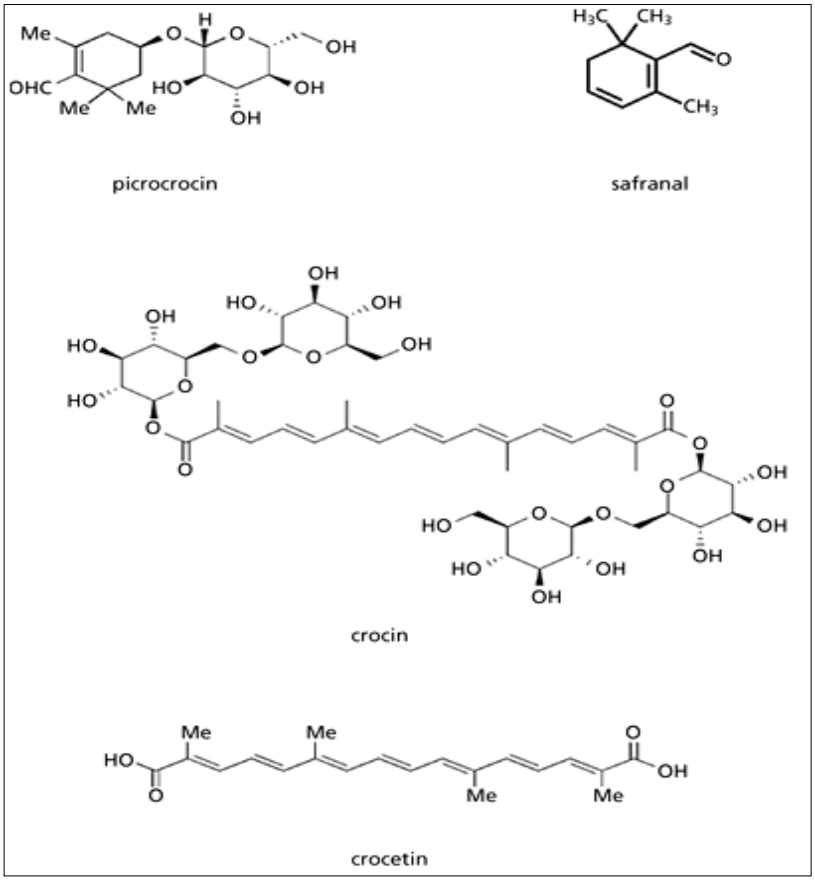

Fig 17: Crocines

Fig 18: Olive leaves (Olea Europaea folium F-EMA) Oleuropein

Drupe and oil, contain phenolic compounds and vitamin E. The most important of these compounds are oleuropein (oleuropein) and hydroxytyrosol (3,4-dihydroxy-phenyl). Oleuropein is a glucoside, the hydrolysis of which gives rise to various forms of aglycones. In nature, hydroxytyrosol is found in olive leaf and olive oil, in the form of its elenolic acid ester oleuropein these forms seem to exert the greatest beneficial effect as antioxidants [19, 20, 21, 22, 23, 26]. Oleuropein has been demonstrated in experimental studies that intracranial administration to Wistar rats in concomitant administration with Aβ42 peptide (Bachem) neutralizes amyloid accumulation and acts as a protective agent against further nerve degeneration. Cells and especially cholinergic neurons: It also reduced amyloid toxicity in the administered animals and exerted anti-inflammatory action.

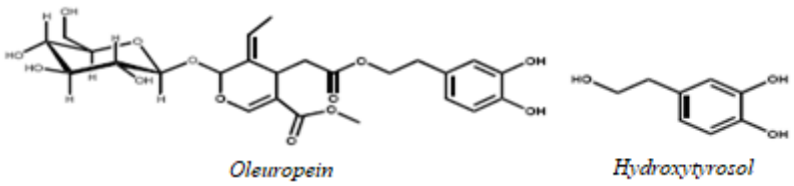

Fig 19: Oleuropein and Hydroxytyrosol: The most important compounds present in drupe and olive oil neutralize amyloid accumulation and act as protective agent against further nerve degeneration

Fig 20: *Hypericum Perforatum* L.

Perforated hyperforin, according to experimental data in rats, inhibits the polymerization of amyloid fibrils, reduces its deposition and improves neuropathic changes as well as behavioral disorders, while acting prophylactically on the neurotoxicity of β-chain amyloid. (as shown in the figure below). There is evidence that it acts preventively both in the onset / genesis of Alzheimer's disease and in its progression. [31].

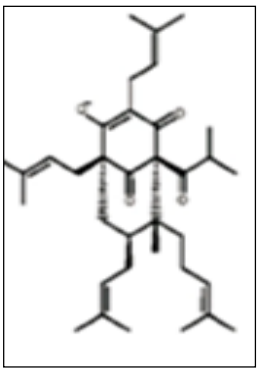

Fig 21: Schema of Hyperforin

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