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RESEARCH ARTICLE

BENEFITS OF ACETHYLCHOLINESTERASE INHIBITOR GALANTAMINE IN TREATMENT OF ALZHEIMER'S DISEASE AND INSTRUMENTAL METHODS FOR ITS ANALYSIS IN MEDICINAL PLANTS

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ABSTRACT

Alzheimer disease is a chronic progressive neurodegenerative disease, leading to memery loss as a result of the formation of amyloid plaques and neurofibrillary tangles.

Galantamine possesses dual mechaunism of action as a reversible blocker of enzyme acetylcholinesterase and an allosterically potentiator of α7 nicotinic acetylcholine receptors, leading to neuroprotection, increased dopaminergic neurotransmission, improved behavioral functions and enhanced concentration.

In Alzheimer's disease with vascular dementia or with cerebrovascular disorders as a result of its antioxidant effect, Galantamine decreases neurodegeneration and cognitive decline by improving the processes of learning, memory and attention.

By inhibition of β-amyloid aggregation and by increasing of Aβ clearance throught an activation of microglia, the drug protects against β-amyloid toxicity and exerts in anti-apoptotic action in cells.

For identification of Galantamine in plant extracts are described thin layer chromatographic methods in stationary phases: Silicagel G60F254 or aluminium and displaying the spots through different approaches: quenching the fluorescence at λ = 254 nm, spraying with Dragendorf reagent or iodine vapour.

For determination of Galantamine in plant extracts are reported the followingo mmethods: 1) thin layer chromatography-densitometry; 2) extraction-thin layer chromatography-spectrophotometry; 3) High Performance Thin Layer Chromatography; 4) High Performance Liquid Chromatography (HPLC) with UV-detection; 5) HPLC-radioimmunoassay; 6) gas chromatogram-phy with mass-spectrometric detection (GC-MS), capillary electrophoresis and polarography.

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INTRODUCTION

I. Alzheimer disease.

Alzheimer's disease is a chronic progressive neurodegenerative disorder, wherein the loss of cholinergic neurons in the basal ganglia of the cerebrum cause higher cortical disfunctions and leads to a deficiency in memory, learning, behavioral and functional disorders and total collapse of the intelligence and mental activity [1]. Synaptic dysfunction is mediated [1, 2] from increased accumulation of the peptide ß-amyloid [3] in senile plaques and the formation of neurofibrillary tangles, composed of aggregates of hyperphosphorylated microtubule associated tau-protein [4].

Risk factors for Alzheimer's disease include genetic predisposition, history of Alzhei-mer's and Down syndrome in a relatives, oxidative stress, depression, epilepsy, Parkinson's disease, migraine, hypothyroidism, brain injury [5], brain inflammation [6], high levels of diastolic pressure [7] and cholesterol, atherosclerosis [8], type 2 diabetes, obesity [9], tumor processes, female, pregnancy in old age, increased content of iron in the body, reduced levels of glutathione presence of aluminum in drinking water, alcohol abuse [10] and smoking [11].

According to the amyloid hypothesis the process of amyloidogenesis – synthesis of neurotoxic Aβ aggregates of extracellular proteins [12] is determined by: 1) E693 δ mutation of the gene for apolipoprotein E on chromosome 19 [13]; 2) mutations in the gene for amyloid- precursor protein in chromosome 21 [14, 15]; 3) 30 mutations in presenilin 1 gene in chromosome 14 and the presenilin gene in chromosome 2 [16].

It was found that in the body there is a dynamic equilibrium between formation of free radicals and function of the protective antioxidant systems (superoxidedismutase, catalase, glu-tathioneperoxidase, glutathione reductase, glucose-6-phosphate dehydrogenase) [17].

Oxidative stress is the basis of the pathogenesis of aging [17, 18] and a number of diseases [19]: neurodegenerative [20] as Alzheimer [18, 21, 22, 23], Parkinson [24], Huntington [18], amyotrophic lateral sclerosis, Lou Gehrig syndrome [20]; Down [18]; autism [25]; schizophrenia [26]; atherosclerosis [24]; vascular diseases [27], hypertension [28], chronic renal failure [29], diabetes mellitus type 1 and 2 [30], cancer diseases [31], macular degeneration [32] and psoriatic arthritis [33].

The brain is especially sensitive to the effects of free radicals due to high consumption of oxygen, the presence of unsaturated fatty acids and [14, 34], reducing the activity of

sensitive oxidation endogenous antioxidant systems [35].

In Alzheimer's disease oxidative stress [14, 34, 35, 36] arises as a result of violation of the balance between endogenous or exogenous overproduction of reactive free radicals [36] and the decrease in antioxidant defense mechanisms [22, 23]. Oxidative disorders are among the early neurologic abnormalities in Alzheimer's disease [18, 21, 23] and selectively occur in areas of the brain responsible for the regulation of memory functions [37].

Oxidative stress plays an important role in the pathogenesis of neuronal degeneraton [22, 38], because the formation of free radicals determines the inflammatory processes [39], dysfunction of cell membranes [40] and activation of programmed death of nerve cells (apoptosis) [41] by oxidation of proteins, lipids and nucleic acids (DNA, RNA) [42] and disruption of glucose metabolism [43].

In the neuropathology of Alzheimer's disease important markers of oxidative stress in the brain [44, 45, 46] are:

1) extracellular senile plaques [21, 47] and intracellular β-amyloid peptides Aβ1-42 [48]

2) intracellular neurofibrillary tangles [49, 50], composed of aggregated paired filaments connected [21, 35, 51] hyperphosphorylated microtubule associated tau-protein [4, 52] and surrounded by activated microglia and astrocyte cells and cells of Hirano

3) products of glycosylation [14, 42, 43]

4) oxidized proteins [14, 21, 42, 37, 53] and nucleic acid [42, 54]: nuclear DNA [14, 42, 55, 56], mitochondrial DNA [56] and ribosomal RNA [57, 58]

5) products of lipid peroxidation [14, 42, 53, 59]: acrolein [60], 4-hydroxy-2-nonenal [60, 61], hidroxyoktadekadienic acid [62] and peroxynitrite [63]

6) elevated levels of gamma-glutamyltransferase [64] and the factors of inflammation [65]: microglial interleukin 1 [65], α-1-antichymotrypsin synthesis in astrocytes [66], reactive C-protein [67]

7) decreased concentration of enzymes hydrolysed β-amyloid [68] (neprilysin) [69] and sortrilin 1 [70] (intracellular amyloid part suppresses the expression of neprilysin) [71].

The basis of the pathogenesis of Alzheimer's disease are two main mechanisms [72]: progressive accumulation of intraneuronal Aβ peptides [73] and extraneuronal Aβ oligomers [74, [75, 76] into amyloid plaques [21, 77, 78, 79] and the formation of intracellular neurofibrillary tangles of hyperphosphorylated tau (τ)-protein [75, 78].

Amyloid plaques and neurofibrillary tangles are the most important markers of oxidative stress [46]. As the disease progresses

neurodegenerative changes are extended in a natural way in discrete regions of cortical and subcortical structures, as the often affected are cortex and hippocampus and this correlated with the progressive development of cognitive disorders [80, 81].

II. Galantamine in therapy of Alzheimer's disease.

The actuality and the growing importance of developiment of new effective drugs for prevention and reduction of the progression of Alzheimer's disease is due to the following rea-sons:

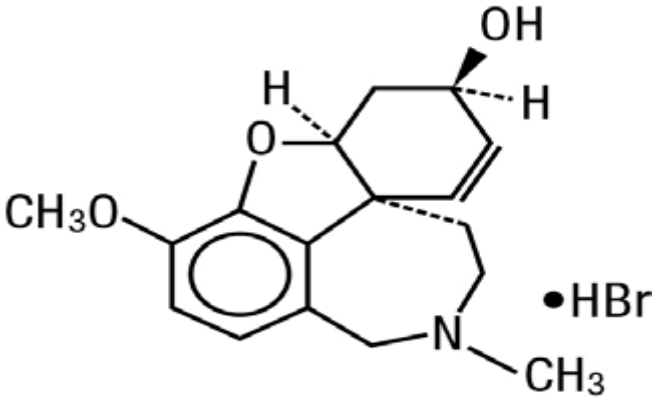
1) continuous increase of the incidence of disease
2) a large number of risk factors
3) involvement of many different areas in the cortex, hippocampus, temporal, parietal, frontal lobe and amygdale
4) a variety of pathogenetic mechanisms of neuronal degeneration
5) heterogeneous clinical picture, characterized by cognitive deficits, reduced learning ability, behavioral and functional impairment and total decay of intellect and mental activity
6) long duration of the disease (8-10 years).

The classical therapeutic approach for Alzheimer's disease is a compensatory therapy, through which is achieved the restoration of the cholinergic deficit. Medications are reversible inhibitors of enzyme acetylcholinesterase: Galantamine, Donepezil, Rivastigmine, which by suppressing the collapse of intrasinaptic acetylcholine, increase the possibility of holding a signal to postsynaptic cholinergic neurons.

Galantamine is 4aS, 6R, 8aS)-3-Methoxy-11-methyl-5,6,9,10,11,12-hexa-hydro-4aH-[1] benzofuro[3a,3,2-ef][2]benzazepin-6-ol hydrobromide.

On Fig. 1. is illustrated chemical structure of Galanthamine hydrobromide.

Fig. 1. Chemical structure of Galanthamine hydrobromide.



Galantamine possesse the following activities:

1) blocks reversibly enzyme acetylcholinesterase, leading to accumulation of endogenous acetylcholine and indirect cholinomimetic effects [82, 83]

2) allosterically potentiates α7 nicotinic acetylcholine receptors [83, 84, 85, 86, 87].

The activation of nicotinic receptors is associated with:

1) protection of protein Bcl-2 and prevention of the induced by β-amyloid apoptosis [88]

2) increase of dopamine neurotransmission [89]

3) improvement of the processes of learning, memory [90] and attention [91]

4) facilitation of the conduct nerve impulses at the level of neuromuscular synapses.

Galantamine is applied in Alzheimer's disease with vascular dementia [92], or with cerebrovascular disorders [93]. It has been found that in Alzheimer with cerebrovascular disease, vascular dementia [93] and ischemia due to its antioxidant effect, Galantamine leads to neuro-protection [94], improvement of memory [95] and behavioral functions, enhancement of concentration [96] and dopaminergic neurotransmission [97].

Galantamine decreases neurodegeneration and protects against β-amyloid toxicity [98], due its action as a reversible acethylcholinesterase inhibitor [99] and as an allosteric modulator of nicotinic receptors [100].

By modulation of amyloid precursor processing [101] and by inhibition of β-amyloid aggregation and cytotoxicity [102] exerts in cell anti-apoptotic action [103]. Galantamine increases Aβ clearance by activation of microglia [104]. Long-term therapy with galantamines decrease cognitive decline [105]

and behavioral symptoms, most strongly in patients with advanced forms of the disease [106].

III. Distribution of Galantamine in nature.

Galantamine is an alkaliod isolated for the first time from Proskurnina and Yakovleva and in 1952 from the tubers and aerial parts of Caucasian snowdrop (*Galanthus woronowii Losinsk*, *Amaryllidaceae*) (Fig. 2.).

Fig. 2. Distribution of Galantamine in natural plants.

In 1956 from Paskov and Ivanova-Bubeva the alkaloid is obtained from the tubers of winter snowdrop (*Galanthus nivalis L.*) (Fig. 2,) [107]. In Bulgaria genus *Galanthus* is represented by three species: *Galanthus nivalis L. var. grac*ilis, *Galanthus elwesii Hook.* fil (Figure 1) and *Galanthus graecus Orph. ex Boiss* [108].

Later Galantamine is found in 20 species, more important from which are: summer snowflake (*Leucojum aestivum L.*) (Fig. 2.) [109], *Lycoris aurea L.*, *Lycoris radiata L.*, yellow daffodil (*Narcissus pseudonarcissus L.*, *Narcissus tazetta L.* (Fig. 1) [107], *Narcissus jonquilla Pipit* [110], *Ungernia victoris L.*, *Ungernia severtzovii*, *Ungernia trisphera*, *Hippeastrum equestre*, *Eucharis subentana*, *Vallota speciosa* [107].

From *Leucojum aestivum L.* are isolated 20 alkaloids: Galantamine, Dihydrogalantamine, Apogalantamine, Epigalantamine, Epinorgalanta-mine, Lycorine, Homolycorine, Lycorenine, Narwedine, N-desmethylgalantamine, Nivalidine, Aestivine, Tacetine, Isotacetine, Ungerine [109, 111]. In *Leucojum aestivum L.* three of alkaloids

possesses a higher acethylcholinesterase inhibitory activity than Galanthamine: Sanguinine, N-allylnorgalanthamine and N-(14-methylallyl)-norgalanthamine [112]. The percentage of Galanthamine in the alkaloid mixture of leaves is 12 %. The main source of Galanthamine is *Narcissus pseudonarcissus L.*: 0.13 %. In *Ungernia victoris L.* the proportion of Galanthamine in the alkaloid mixtures is 57 % in the foliage and 48 % in the bulbs [113].

IV. Methods for analysis of Galantamine in plant extracts.

For identification of Galantamine in plant extracts are described thin layer chromatographic methods (TLC) [107] on stationary phases: Silicagel $G_{60}F_{254}$ or aluminium and displaying the spots through different approaches: quenching the fluorescence at λ = 254 nm, or spraying with Dragendorf reagent or iodine vapour [107].

High Performance Thin Layer Chromatography (HPTLC) is applied for analysis in extracts of *Narcissus jonquilla Pipit* [110]. Thin layer chromatographic method in combination with densitometry is applied for quantification of Galantamine in extracts of *Ungernia victoris L.* [107], *Galanthus elwesii Hook* and *Galanthus nivalis L.* [108].

Thin layer chromatographic extraction-spectrophotometric analysis is developed for Galantamine in extracts of *Galanthus nivalis L. subsp. cilicicus Baker* [114] or in extracts of leaves of *Narcissus* after derivatizatsion reaction with tropeolin 00 [107].

The most often method for quantification of Galanthamine in Amaryllidaceae plants is HPLC [115]. High Performance Liquid Chromatography (HPLC) [116] with UV-detection is used for determination of Galantamine in extracts of *Leucojum aestivum L.* [107] at λ = 280 nm, *Narcissus jonquilla Pipit* at λ = 290 nm [107] and in traditional Chinese medicine *Lycoris radiata L.*: column RP C_{18} Octadecylsilyl silicagel (4.6 mm x 150 mm x 5 μm), mobile phase: fosfaten bufer (pH = 4) : methanol = 93 : 7 v/v, injection volume: 20 μl, flow rate: 1.0 ml/min., UV-detection at λ = 289 nm [117].

RP-HPLC method is developed for the simultaneous determination of Galantamine, Lycorine and Lycoramine in *Lycoris radiata L.* The chromatographic separation of the three compounds is performed on an Intertsil ODS-SP column, mobile phase: 15 mM potassium dihydrogen phosphate solution (pH = 6.35) : methanol = 50 : 50 v/v, flow rate: 0.8 ml/min, fluorescent detection at λ excitation = 285 nm and λemission = 320 nm [118].

For analysis of Galantamine in flower and bulb of *Lycoris radiate L.* is described HPLC with RP C_{18} column, column oven temperature of 40˚C, mobile phases: A: 10 mM ammonium carbonate; B: 10 % 10 mM ammonium carbonate in acetonitrile, flow rate: 1.0 ml/min., UV-dtection at λ = 292 nm. The solvent program used is as follows: 0-13 min. (B = 0 %), 13-17 min. (B = 7 %), 23-35 min. (B = 10 %), 35-50 min. (B = 20 %), 50-55 min. (B = 70 %). MS analysis is carried out with an electrospray interface operating in the positive ion mode [M+H]+ with ion spray voltage: 5.5 kV, nebulizing and heating gas: N_2, heating gas temperature, 550˚C [119].

For simultaneous determination of Galanthamine and Lycorine in aerial parts and bulbs of *Galanthus cilicicus* and *Galanthus trojanus* is developed HPLC method coupled with UV- detection. The chromatographic separation is performed using an isocratic system with a mobile phase: trifluoroacetic acid : water : acetonitrile = 0.01 : 92.5 : 7.5 v/v, flow rate: 1 ml/min. [120]. For chromatographic separation of Galanthamine and Lycorine in *Galanthus elwesii Hook* is described an isocratic HPLC with Hichrom C column (250 mm, 4.6 mm x 5 μm), mobile phase: trifuoroacetic acid : water : acetonitrile = 0.01 : 90 : 10 v/v, flow rate: 1 ml/min. and UV-detection at λ = 290 nm [121].

Other natural sources of Galantamine [122] are *Daffodils* [123] and *Crinum* species [124]. Determination of Galanthamine content in the bulbs of *Crinum malabaricum Lekhak S.R. Yadav*, *Crinum viviparum*, *Crinum brachynema* and *Crinum pretense* is performed using an isocratic system with a mobile phase: methanol : 5 mM ammonium phaosphate = 55 : 45 v/v, flow rate: 0.8 ml/min, and UV-detection at λ = 288 nm [124].

For analysis Galantamine in extracts of *Leucojum aestivum L* is reported HPLC-radioimmunoassay method [125], based on the reaction between the antisera and conjugate of Galanthamine-2-O-hemisuccinate with bovine serum albumine [107].

Gas chromatographic method with mass-spectrometric detection (GC-MS) is developed for determination of Galantamine in extracts of *Eucojum aestivum L.* [126], *Narcissus* [126, 127] and *Galanthus* [128].

In *Galanthus elwesii Hook* and *Galanthus nivalis L.* [129] for GC-MS analysis is used the following chromatographic conditions: column HP-5 MS (30 m x 0.25 mm), injector temperature 280 °C, speed of gas carrier (helium): 0.8 ml/min. [108].

Other methods for determination of Galantamine extracts are capillary electrophoresis (in extracts of representatives of

the genus *Narcissus*) [126] and polarography (in extracts of *Ungernia victoris L.*) [107].

Galanthamine in bulbus *Lycoridis radiatae L.* is analysed by capillary electrophoresis and an electrochemiluminescence detection endusing tris(2,2'-bipyridyl)ruthenium(II) under optimized conditions: 18 mmol/l phosphate running buffer at pH = 9.0. and 12 kVseparation voltage [130].

Chromatographic systems for analysis of Galantamine in plant extracts are shown in Table 1. (HPLC) and Table 2. (TLC).

Table 1. HPLC systems for analysis of Galantamine in plant extracts [107].

1.	*Leucojum aestivum L.*	column Synchropack RP C_8 mobile phase: methanol : water = 90 : 10 v/v detection at λ = 280 nm
2.	*Narcissus jonquilla Pipit*	gradient mode column Xterra RP C_{18} (150 mm x 4.6 mm x 3.5 μm) column temperature: 25 ^{o}C mobile phase: acetonitrile : 15 mM ammonia flow rate: 0.3 ml/min. UV-detection at λ = 290 nm
3.	*Pancratium maritimum*	column LiChroprep SiO_2, mobile phase: chloroform : methanol = 8 : 2 v/v flow rate: 1 ml/min.

Table 2. TLC systems for analysis of Galantamine in plant extracts.

Silicagel $G_{60}F_{254}$ plate		
1.	*Galanthus nivalis L.* [107]	ether : acetone : diethylamine = 80 : 20 : 5 v/v ether : methanol : diethylamine = 90 : 5 : 5 v/v n-hexane : chloroform : diethylamine = 50 : 40 : 10 v/v benzene : chloroform : acetone : diethylamine = 80 : 25 : 30 : 5 v/v
Silicagel G_{60} plate; spraying with Dragendorf reagent		
1.	*Galanthus. nivalis L.* *Galanthus. Elwesii Hook fil.* [108]	chloroform : methanol : 25 % ammonia = 11 : 1 : 0.6 v/v chloroform : methanol : 25 % ammonia 12 : 1 : 0.5 v/v chloroform: ethylacetate : methanol = 2 : 2 : 1 v/v
2.	*Leucojum aestivum L.* [107]	diethyether : diethylamine = 80 : 15 : 5 v/v
3.	*Narcissus* [107]	chloroform : ethylacetate : methanol = 2 : 2 : 1 v/v
Silicagel G_{60} plate; spraying with iodine vapour		
1.	*Gananthus nivalis L.* [107]	chloroform : ethylacetate : methanol = 2 : 2 : 1 v/v
Aluminium $G_{60}F_{254}$ plate		
1.	*Galanthus nivalis L.* [107]	chloroform : methanol = 9.75 : 0.25 v/v chloroform : methanol = 24 : 1 v/v
2.	*Ungernia severtzovii* *Ungernia trisphera* [107]	chloroform : ethanol : acetone = 8 : 1 : 4 v/v
Aluminium G_{60} plate; spraying with Dragendorf reagent		
1.	*Lycoris guangxiensis* [107]	chloroform : methanol = 12 : 1 v/v chloroform : methanol = 4 : 1 v/v chloroform : methanol : ammonium = 12 : 1 : 0.05 v/v
2.	*Ungernia victoris* [107]	chloroform : methanol = 2 : 1 v/v chloroform : methanol : acetic acid = 90 : 80 : 2 v/v

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