Review Article

Antioxidant activity of medicinal plant compounds and aminoacids for prevention of Alzheimer's disease

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ABSTRACT

The chronic progression of neurodegeneration is the main characteristic in the development of Alzheimer's disease. The prevention of brain from the neuronal damage by use of phytocompounds with antioxidant activity is an important therapeutic approach for the delay of the neuronal degeneration. The aim of current work is to summarize the data for types of plant compounds possessing antioxidant potential against Alzheimer's disease. From the results it is obvious that the more important phytocomponents with benefitial effect towards oxydative stress in Alzheimer's disease include: 1) flavonoids: quercetin, epigallocatechin-3-gallate, moringine, magnolol, honokiol, kaempferol, isorhamnetin, myricetine; 2) non-flavonoid compounds: Curcumine, Resveratrol, Caffeinc acid, Ferulic acid, Rosmarinic acid; 3) alkaloids: Arecoline, Caffeine, Galantamine, Huperzine A, Morphine, Nicotine, Piperine. Promising antioxidant effect against Alzheimer's disease exhibit the extracts from the different medicinal plants, such as *Acorus calamus L., Angelica sinensis L., Asparagus racemosus L., Azima tetracantha Lam, Berberis aquifolium Pursh, Berberis vulgaris L., Camelia sinensis (L.) Kuntze, Centella asiatica L., Citrus aurantium L., Coffea arabica L., Convolvulus pluricaulis Choisy, Coptis chinensis Franch, Curcuma longa L., Daucus carota L., Eryngium campestre L., Eryngium planum L., Galanthus caucasicus (Baker) Grossh., Galanthus nivalis L., Galanthus woronowii Losinsk, Huperzia serrata (Thumb. ex Murray) Trevis., Glycyrrhiza glabra L. Hydrastis canadensis L., Juglans regia L., Lavanduila angustifolia Mill, Leucojum aestivum L., Lycoris radiata (L'Her.) Herb, Narcissus tazetta L., Morus alba L., Panax notoginseng (Butkill) F.H.Chen, Phyllanthus emblica L., Piper longum L., Piper nigrum L., Vitis vinifera L., Zingiber officinalis L.* Antioxidant effects exert L-Arginine, L-Histidine, L-Isoleucine, L-Serine, L-Tryptophan, L-Tyrosine, L-Cysteine, L-Methionine.

Keywords: Alzheimer's disease, Phytocompounds, Plants, Antioxidants, Aminoacids

Introduction

Oxydative stress

One of the important pathogenetic hypotheses for the develpment of progressive neurodegenerative Alzheimer's disease is the oxidative stress hypotheses. It has been found that there is a dynamic balance between the free radical formation and the function of protective antioxidant systems (superoxid-dismutase, catalase, glutathione-peroxidase, glutathione-reductase). The increased levels of free radicals lead to oxidative stress, which is at the base of the pathogenesis of neurodegenerative diseases [1], such as Alzheimer [2], Parkinson [3], Huntington, Amyotrophic lateral sclerosis (Lou-Gerich's disease) [1], and for the development of the disorders, such as atherosclerosis, cancers, such as brain gliomas and meningiomas [4], chronic renal failure, Daun syndrome, diabetes type 1 and 2, hypertension, schizophrenia, vasculas diseases, psoriatic arthritis [5], brain aneurysm [6]. Under lipid peroxidation polyunsaturated fatty acids cause the formation of oxidation product malondialdeyhde in erythrocyte membrane [7]. Oxidative stress causes pathological changes in aging [8].

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The most important hallmarks of Alzheimer's disease are the beta-amyloid plaques, tau protein tangles and oxidative stress [2], that both with inflammation play an important role in the pathogenesis of early and late phase of Parkinson disease [3].

By the oxidation of lipids, proteins and DNA and RNA nucleic acids and because of the impairment of glucose metabolism, the free oxygen species [(superoxide (O2•−), hydroxyl (OH•), hydroperoxyl (HO_2•), peroxyl (ROO•), lipid peroxyl (LOO•), alkoxyl (RO•), nitric oxide (NO•)] generation causes the beginning of the inflammatory processes [9]. The observed dysfunction of cell membranes and the increased activation of programmed nerve cell death (apoptosis) are also results from the oxydative stress [10].

In the neuropathology of Alzheimer's disease the important markers of oxidative stress in the brain include [11]:

1. lipid peroxidation products: acrolein, peroxynitrite, 4-hydroxy-2-nonenal, hydroxyoctadecadienoic acid [9];
2. oxidized proteins and nucleic acids: nuclear DNA, mitochondrial DNA and ribosomal RNA;
3. elevated levels of γ-glutamyltransferase and of inflammatory factors: microglial Interleukin-1β, Interleukin--6, tumor necrosii factor (TNFα), reactive C-protein and α1-antichymotrypsin, synthesized in astrocytes;
4. glycosylation products [9];
5. decreased concentration of the Aβ-peptide-destruction enzyme sortryline 1.

Free radicals generate acroleine by oxidation of membrane unsaturated fatty acids [9]. It has been reported that lipid peroxidation leads to the formation of:

1. reactive acrolein, that by interacting with the proteins, forms carbonyl derivatives;
2. 4-hydroxy-2-nonenal, that stimulates the aggregation of Aβ-peptides via covalent attachment and induces neuronal apoptosis by attacking of the phospholipid bilayer membrane;
3. products that by disrupting the function of mitochondrial enzymes, increase the levels of free hydroxyl radicals, that oxidize cellular proteins, lipids and nucleic acids and form dityrosine-linked Aβ-peptides with high affinity to oligomerization and aggregation [10].

By oxidation, the toxic soluble $Aβ_{1-42}$ oligomers are converted into aggregates in senile plaques and cause oxidative modification, denaturation and inactivation of cellular proteins. Aggregates of $Aβ_{42}$-oligomers lead to the following cascade of pathological neurodegenerative changes [2]:

1. neurotransmitter disorders;
2. neuroinflammatory processes;
3. neuroimmune dysfunction;
4. damage of axones;
5. dysfunction of synapses and dendrites;
6. loss of synapses, dendrites and axones;
7. increased levels of superoxide radicals;
8. oxidation of proteins and DNA [9];
9. mitochondrial dysfunction;
10. microglial proliferation;
11. disruption of phospholipid bilayer;
12. amyloid angiopathy;
13. neuronal apoptosis.

This cascade of processes in brain, resultng by the influence of the increased oxidative stress, causes the cognitive degeneration, that further leads to the progression of Alzheimer's disease in the frontal cortex. Under the influence of oxidative stress, Aβ-aggregates elicit mitochondrial dysfunction, that by initiating of free radical formation, stimulates the oxidation of DNA, resulting in a change in the structure and function of synapses [2]. Factors stimulating tau-protein hyperphosphorylation and formation of neurofibrillary tangles [2] incluse:

1. increased production of Aβ-peptides;
2. mitochondrial oxidative stress;
3. reduced activity of antioxidant systems;
4. enhancement of inflammatory processes.

Currently one of the most promising trend is the use of non-toxic high-effective antioxidants. For the achievement of this aim two basic strategies can be implemented. One trend is the combination in one product of different functional components that can independently interact synergistically at different stages of the complex multi-stage lipid oxidation process. Other approach is the investigation of high effective, non-toxic and biologically active antioxidants. For the increase of antioxidant and biological activity, it is important to consider not only individual compounds, but also suitable antioxidant compositions, including extracts of natural products containing a very wide range of polyphenol antioxidants with synergistic effect. Plant-based dietary supplements containing antioxidants are important for prevention and treatment of age-related diseases [12].

Natural phytocompounds with antioxidant properties against Alzheimer's disease

One of the most promising approach for the prevention of Alzheimer's disease is an antioxidant therapy, that inhibits harmful free radical action by induction of endogenous antioxidant enzymes [13]. The natural phytocompounds [14] with antioxidant properties are new alternatives [15].

Antioxidants as nutritional supplements, improve thinking, memory and mental abilities. Food supplements with antioxidant activity include plant extracts containing flavonoids, polyphenols [16], phenolcarboxylic acids, aminoacids and vitamins.

Polyphenols

Polyphenols are natural antioxidants [16] and are classified as: flavonoids [17]: flavonols, flavones, flavanones, flavanols, isoflavones, chalcones, and anthocyanidins [18] **(Figure 1)** and non-flavonoids: phenolic acids, stilbenes and lignans [19].

Polyphenols posesses antioxidant, antiinflammatory and antiamyloidogenic functions [20].

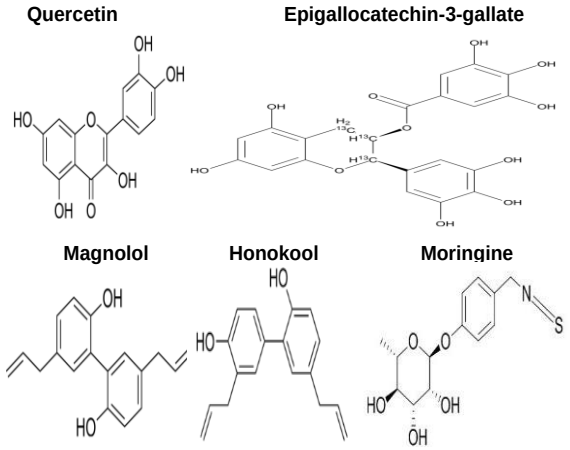

Figure 1. Chemical structures of flavonoids with antioxidant activity.

- *Quercetin*

Quercetin exerts antioxidant properties. The compound is an aglycone of flavonoid glycosides rutin and quercitrin, Quercetin is found in apples and citrus fruit [21] and prevents neurons from free radicals and suppresses the oxidative neurons damage, that leads to te development of Alzheimer's disease [22].

- *Epigallocatechin-3-gallate*

Flavanol Epigallocatechin-3-gallate is found in *Camelia sinensis (L.) Kuntze*. Because to its antioxidant properties, this phytoconpound suppresses cognitive impairment by reduction of the amyloid-induced mitochondrial dysfunction and neurotoxicity [23].

- *Moringine*

Isothyocyanate Moringine is isolated from *Moringa oleifera Lam.* (*Moringaceae*). This tropical plant is widely used in traditional medicines and as a food supplement. It is characterized by the presence of flavonoids, isothiocyanates, lignans and phenolic acids [24].

Moringine is sulfur-containing phytochemical with a protective effect on neurodegenerative diseases, because of antioxidant and antiinflammatory properties. Other biological activities of Moringine are antimicrobial, antifungal and antiviral [24].

- *Magnolol*

Magnolia officinalis Rehder & E.H.Wilson (*Magnoliaceae*) contains biphenolic lignans Magnolol and Honokiol, that exert neuroprotective effect against Alzheimer's disease by inhibition of reactive oxygen species. This process include mechanism, such as depletion of Glutatione inhibition of NADPH oxydase activation. The compounds protect nerve cell by suppression of neurotoxicity and by regulation of neuronal function. Magnolol has neuroprotective properties in cortical neuron-astrocyte cultures and protects against Aβ damage [25].

- *Honokiol*

Honokiol is isolated from *Magnolia officinalis Rehder & E.H.Wilson* (*Magnoliaceae*), Japan species *Magnolia grandiflora L.* and endemic species in Mexico *Magnolia dealbata Zucc* [25]. Honokiol is known to exert anxiolytic, analgesic, antidepressant, anti-tumorigenic, and neuroprotective properties in cortical neurons. It has been observed that Honokiol protects neurons against Aβ damage. The compound is reported to inhibit the reactive free radicals by improving mitochondrial function [25].

- *Hesperidin*

Hesperidin is a flavanone glycoside of aglycon hesperitin, and is found in *Citrus aurantium L., Citrus sinensis L. (Osbeck).*

The mechanisms of Hesperidin for the improvement of learning. memory and cognition are result of:

1. increasing the anti-oxidative defense systems;
2. correction of Aβ-induced mitochondrial abnormalities;
3. restoring of Glutation concentration;
4. normalization of the mitochondrial enzyme activities;
5. decreasing of Glycogen synthase kinase-3β, which deactivation can supprees the oxidative damage;
6. blockage of β- and γ-secretases;
7. suppression of $A\beta_{1-40}$ formation [26].

Extracts of *Ginkgo biloba L.* leaves contain flavonoids kaempferol, isorhamnetin, myricetin **(Figure 2)**, which protect neurons against oxidative stress.

- *Kaempferol*

Kaempferol (3,4′,5,7-tetrahydroxy-flavone) is a natural flavonol, which can be found in *Hypericum perforatum L., Moringa oleifera oleifera Lam., Rosmarinus officinalis L.* [27].

- *Myricetin*

Myricetin (3,3',4',5,5',7-hexahyfroxyflavone) is found in *Citrus aurantium L.*, *Fragaria vesca L, Rubus idaeus.* tea [28].

It has been described that mechanisms of neuroprotective effect of this polyphenol compound include:

1. scavenging of free oxygen species;
2. chelation of transition metal ions that produce free radicals;
3. increasing the effects of other antioxidants;
4. induction of the activity of enzyme glutathione S-transferase, which can protect cells towards free-radicals [28].

- *Ginkgolide B*

In Alzheimer's disease for reduction of oxidative stress are used natural antioxidants from *Gingko billoba L.* (Ginkgolide B) that

reveals neuroprotective potential by the inhibition of amyloid-beta aggregation [29].

Figure 2 illustrates the chemical structures of antioxidant flavonoids Kaempferol, Isorhamnetin and Myricetin.

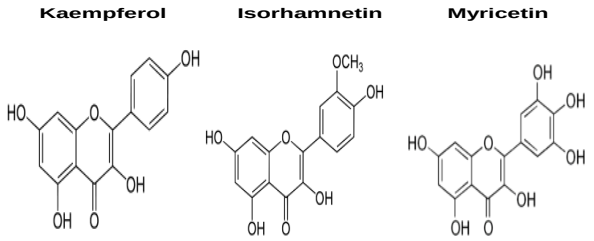

Figure 2. Chemical structures of antioxidant flavonoids Kaempferol, Isorhamnetin, Myricetin.

Non-flavonoids with antioxidant activity

Non-flavonoids with antioxidant activity and benefits against Alzheimer's disease are Curcumine, Resveratrol, Caffeic acid, Ferulic acid and Rosmarinic acid **(Figure 3)**.

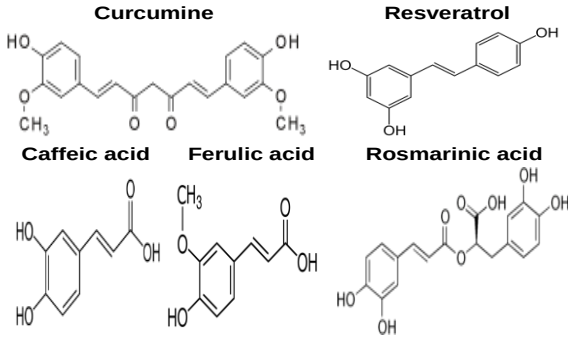

Figure 3. Chemical structures of non-flavonoids with antioxidant activity.

- ### Curcumine

Curcumine is a non-flavonoid compound isolated from *Curcuma longa L.,* that protects neurons against oxidative stress. It exerts a benefitial effect in Alzheimer's disease [30] due to antioxidant action, antiinflammatory effect and binding of redox-active metals iron and copper. The compound induces the antioxidant protective system glutathione transferase, lowers cholesterol levels, and binds ferric ions to complexes. Curcumine inhibits the aggregation and formation of Aβ42 oligomer and antiamyloid effects are the result of the increase in enzymes required for amyloid plaque degradation: insulin degradation enzyme and Neprilisine [21].

- ### Resveratrol

The very important natural polyphenol with a stilbene structure is Resveratrol (3,5,4′-trihydroxystilbene). It belongs to non-flavonoid class polyphenol compounds: stilbenes. Source of Resveratrol are *Arachis hypogaea L., Fragaria ananassa Duchesne ex Rozier (Rosaceae), Lycium chilense Bertero (Solanaceae),* roots of *Polygonum cuspidatum Siebold and Zucc., Rubus idaeus L. (Rosaceae),* leaves of *Veratrum grandiflorum (Maxim. ex Miq.) O. Loes*, roots and rhizomes of *Veratrum formosanum O. Loes, Helichrysum spp. (Compositae), Vaccinium spp. (Ericaceae)* [21].

The antioxidant properties of Resveratrol are related to its ability:

1. for stimulation of the endogenous antioxidant enzymes superoxide dismutase and catalase;
2. for reduction the ettect of malondialdehyde in the brain in models of Alzheimer's disease in mice.

Throught these mechanisms the compound acts neuroprotectively and reduces cognitive impairment. Resveratrol possesses anti-Aβ deposition action [31].

- ### Caffeic acid

The potentiral mechanisms of neuroprotective activity in Alzheimer's disease of antioxidant Caffeic acid include:

1. normalization of superoxide dismutase activity and glutathione concentration;
2. suppression glycogen synthase kinase 3β activity;
3. decreasing the level of β-amyloid and phosphorylated tau protein [32].

- ### Ferulic acid

Ferulic acid is a hydroxycinnamic acid, phenol derivative with antioxidant, neuroprotective, anti-Aβ aggregation, and anti-inflammatory effect [33].

- ### Rosmarinic acid

Rosmarinic acid is a natural polyphenol antioxidant. trat first was extracted found in *Rosmarinus officinalis L.* in 1958. It is found in about 160 plants, such as *Melissa officinalis L., Mentha arvensis L., Ocimum basilicum L., Ocimum tenuiflorum L., Origanum majorana L., Origanum vulgare L., Perilla frutescent (L.) Britton, Rosmarinus officinalis L., Salvia officinalis L., Salvia lavandulifolia Vahl*. Rosmarinic acid has powerful antioxidant and anti-inflammatory properties and reduces markers of oxidative stress while increasing levels of antioxidant enzymes. Rosmarinic acid can be beneficial in protection of cognitive deficits and may improve learning and memory [34].

Alkaloids with antioxidant activity

Plant derived alkaloids which exerts antioxidant activity [35], show a tendency for efficacy in the treatment of behavioral symptoms, with proven neuroprotective properties against Alzheimer's disease [36]. The more important antioxidant alkaloids wih potential benefit against Alzheimer's disease are: Arecoline (*Areca catechu L.*); Galantamine *(Galanthus caucasicus (Baker) Grossh., Galanthus nivalis L., Galanthus woronowii Losinsk*, *Leucojum aestivum L.*, *Narcissus tazetta L.*); Nicotine; Morphine, Caffeine (*Coffea arabica L,*), Berberine *(Berberis aquifolium Pursh, Berberis vulgaris L., Coptis chinensis Franch*, *Hydrastis Canadensis L.)*, Huperzine A (*Huperzia serrata (Thumb. ex*

Murray) Trevis., Piperine *(Piper longum L.*, *Piper nigrum L.)* [21, 35, 36] **(Figure 4)**.

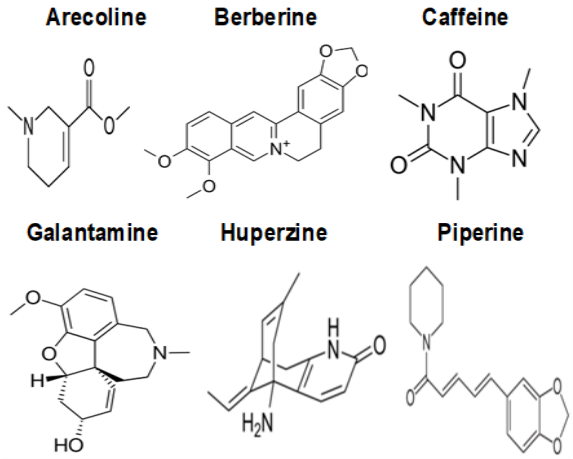

Figure 4. Chemical structures of alkaloids with antioxidant activity.

- *Nicotine*

Nicotine increases the expression of α7-nicotinic receptors and potentiates the cholinergic system, which causes a neuroprotective effect against amyloid toxicity [21].

- *Morphine*

Morphine from *Papaver somniferum L.* possesses an anti-amyloid effect by stimulating the release of estradiol from neurons [21].

- *Caffeine*

Caffeine is a xanthine alkaloid isolated from *Coffea arabica L.* In Alzheimer's models, Caffeine exhibits anti-oxidative effect, reduces the tau-proteine phosphorylation [37], decreases the β-amyloid levels in the hippocampus and induces inhibition of lipid peroxidation [21].

- *Berberine*

Berberine is isoquinoline alkaloid [38] found in *Berberis aquifolium Pursh, Berberis vulgaris L., Coptis chinensis Franch*, *Hydrastis canadensis L.* [21].

It has beeu reported that mechanisms of action of Berberine include:

1. exhibits antioxidant activity by increasing d superoxyd dismutase [38];
2. increases cholinergic transmission by inhibition of butyryl-cholinesterase [39];
3. stimulates α-secretase activity;
4. suppresses β- and γ-secretase [40];
5. blocks tau-proteine hyperphosphorylation [39].

- *Huperzine A*

Alkaloid Huperzine A is isolated from *Huperzia serrata (Thumb. ex Murray) Trevis*. The compound was approved in China for therapy of Alzheimer's disease in 1994, due to possesses neuroprotective effects by [41]:

1. increasing the concentration of antioxidant enzymes;
2. decreasing the level of free radicals (antioxidant and antiapoptotic activity);
3. reduction of the glutamate toxicity;
4. inhibition of acetylcholinesterase;
5. antiamilodogenic effect;
6. modulation of the amyloid precursor protein processing;
7. protection of mitochondria;
8. antiapoptotic effect.

- *Harmine*

Harmine harmine,harmaline is antioxidant isolated from *Peganum harmala L.* [35].

- *Galantamine*

Galantamine is the very important alkaloids for therapy of Alzheimer's disease as a centrally active reversible acetylcholinesterase inhibitor. It is a natural product which exerts beneficial activity, leading to the improvement of behavior and protection of brain functional activities. Galantamine inhibits β-amyloid aggregation. It has been reported that Galantamine enhances dopaminergic neurotransmission and possesses antioxidant [42] and neuroprotective properties by the inhibition of reactive oxygene species. The neuroprotective activity of Galantamine against oxidative stress, is mediated through positive allosteric modulatory stimulation of α7-subtype sites-binding [43].

Medicinal plants containing compounds with antioxidant activity against Alzheimer disease

For the prevention of oxidative stress an important approach is the investigation and application of plants against Alzheimer's disease [44].

The effect of plant extracts on aging and Alzheimer's disease has been investigated, and the results showed that higher antioxidant intake improves cognitive function and reduces the risk of development of the disease [7]. The mechanisms of these effects are associated with increased neural communication and decreased oxidative stress [45].

For Alzheimer's disease due to the content of different compounds, very promising antioxidant effect exhibit the extracts from the different medicinal plants **(Figures 5 and 6)** such as: *Acorus calamus L., Angelica sinensis L.*, *Asparagus racemosus L.*, *Azima tetracantha Lam*, *Berberis aquifolium Pursh, Berberis vulgaris L., Camelia sinensis (L.) Kuntze, Centella asiatica L., Citrus aurantium L., Coffea arabica L.*, *Convolvulus pluricaulis Choisy*, *Coptis chinensis Franch*, *Curcuma longa L.*, *Daucus carota L.*, *Eryngium campestre L., Eryngium planum L., Galanthus caucasicus (Baker) Grossh. Galanthus*

nivalis L., Galanthus woronowii Losinsk, Huperzia serrata (Thumb. ex Murray) Trevis., *Glycyrrhiza glabra L. Hydrastis canadensis L.*, *Juglans regia L.*, *Lavandula angustifolia Mill*, *Leucojum aestivum L., Lycoris radiata (L'Her.) Herb, Narcissus tazetta L., Morus alba L., Panax notoginseng (Butkill) F.H.Chen, Phyllanthus emblica L.*, *Piper longum L., Piper nigrum L.,Vitis vinifera L., Zingiber officinalis L.*) [21, 35, 36, 46].

Some of plants containing the more important phytocompounds with antioxydant activity include [21, 46]:

1. *Acorus calamus Linn.* (A-Asarone and B-Asarone);
2. *Angelica sinensis (Oliv.) Diels* (Ferulic acid);
3. *Berberis aquifolium Pursh, Berberis vulgaris L., Coptis chinensis Franch*, *Hydrastis canadensis L.* (Berberine);
4. *Camelia sinensis (L.) Kuntze* (Epicatechin, Epicatechingallate, Epigallocatechin, Epigallocatechin gallate, Catechin, Catechingallate, Gallocatechin, Gallocatechingallate, Quercetin, Kaempferol, Myricetin Caffeine, Theophylline, Theobromine [47]
5. *Citrus aurantium L.* (Nobiletin);
6. *Coffea arabica L.* (Caffeine);
7. *Curcuma longa L.* (Curcumin);
8. *Galanthus caucasicus (Baker) Grossh., Galanthus nivalis L,, Galanthus woronowii Losinsk*, *Leucojum aestivum L.*, *Lycoris radiata, Narcissus tazetta L.*) (Galantamine)
9. *Ginkgo biloba L.* (Ginkgolide B, Kaempferol, Isorhamnetin, Myricetin)
10. *Huperzia serrata (Thumb. ex Murray) Trevis*, (Huperzine A) [41];
11. *Hypericum perforatum L., Moringa oleifera Lam., Rosmarinus officinalis L.* (Kaempferol)
12. *Magnolia officinalis Rehder and E.H.Wilson* (Magnolol, Honokiol) [25];
13. *Magnolia dealbata Zucc., Magnolia grandiflora L, (*Honokiol) [25];
14. *Melissa officinalis L.* (Caffeic acid [32], Ferulic acid [33];
15. *Melissa officinalis L., Mentha arvensis L., Ocimum basilicum L., Ocimum tenuiflorum L., Origanum majorana L,, Origanum vulgare L., Perilla frutescent (L.) Britton, Rosmarinus officinalis L., Salvia officinalis L., Salvia lavandulifolia Vahl.* (Rosmarinic acid) [34];
16. *Moringa oleifera Lam.* (Moringine);
17. Morus *alba L.*(Quercetin);
18. *Piper longum L.*, *Piper nigrum L.* (Piperine) [36]
19. *Rosmarinus officinalis L.* (Carnosic acid [32], Ferulic acid [33], Hesperidin [26], Rosmarinic acid [34];
20. *Arachis hypogaea L., Fragaria ananassa Duchesne ex Rozier, Lycium chilense Bertero, Polygonum cuspidatum Siebold and Zucc. Rubus idaeus L.*, *Veratrum grandiflorum (Maxim. ex Miq.) O.Loes, Veratrum formosanum O. Loes, Vitis vinifera L.* (Resveratrol) [36].

Protective antioxidant effect in Alzheimer's disease is caused by extracts of the following different parts of plants [46]:

1. leaves of: *Azima tetracantha Lam.*, *Camellia sinensis (L.) Kuntze*, *Centella asiatica L., Coptis chinensis Franch*, *Hypericum perforatum L.*, *Melissa officinalis L., Ocimum basilicum L., Ocimum sanctum, Rosmarinus officinalis L., Salvia officinalis L.*;
2. seeds and fruits from *Ginkgo biloba L.*, *Juglans regia L.*;
3. fruits of *Phyllanthus emblica L.*;
4. roots of *Angelica sinensis L.*, *Asparagus racemosus L.*, *Glycyrrhiza glabra L., Withania somnifera (L.) Dunal. Panax notoginseng (Butkill) F.H.Chen.* [47];
5. rhizomes from: *Acorus calamus L.*, *Zingiber officinalis L.* [47]
6. roots and rhizomes from: *Acorus calamus L.*

Some of the more important mechanism of neuroprotective action of natural compound are [47]:

1. antioxidant activity;
2. stimulation of the activity of superoxide dismutase, catalase and glutathione peroxidase: *Withania somnifera (L.) Dunal;*
3. improvement of memory and learning due to inhibition of amyloid beta-peptide 1-42) deposition: *Angelica sinensis, Convolvulus pluricaulis Choisy*, *Ginkgo biloba L., Morus alba L.*, *Hypericum perforatum L, Centella asiatica L.* [46];
4. protection against lipid peroxidation) *Lavandula angustifolia.*

Morinda citrifolia L. (Rubiaceae) is spread in tropical countries such as Australia, Caribbean, Cuba, Dominican Republic, India, Jamaica, Malaysia, Puerto Rico [48].

It has been reported that the extracts of *Morinda citrifolia L.* fruit inhibits lipid oxidation. It has been described that found in *Morinda citrifolia L.* Proxeronine can be converted in the body by an enzyme proxeronase to the alkaloid Xeronine, that exerts the following effects:

1. modification of the proteins structure;
2. ability for changing the intra- or extracellular accumulated aggregated proteins into their original conformation and for revertimg their normal function [48].

Withania somnifera is named(as Ashwagandha, Indian ginseng and is from Solanaceae. The ability of steroidal lactone Withaferin A to induce changes in the activity of free-radical binfing scavenging enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase are expressed in the following properties:

1. normalizes the superoxide dismutase activities.
2. potential to enhance catalase and glutathione peroxidase activities
3. root extracts are reported to reduce the lipid peroxidation and to increase the decreased glutathione, superoxide dismutase and catalase levels [49].

Figures 5 and 6 illustrate some of the more applied plants with antioxidant activity against Alzheimer disease.

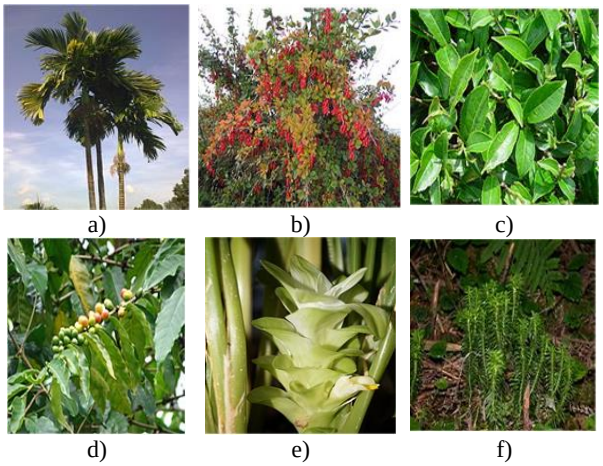

Figure 5. Medicinal plants containing compounds with antioxidant activity against Alzheimer disease.
a) *Areca catechu L.* b) *Berberis vulgaris L.* c) *Camelia sinensis L.* d) *Coffea arabica L.* e) *Curcuma longa L.* f) *Huperzia serrata (Thunb. ex Murray) Trevis*

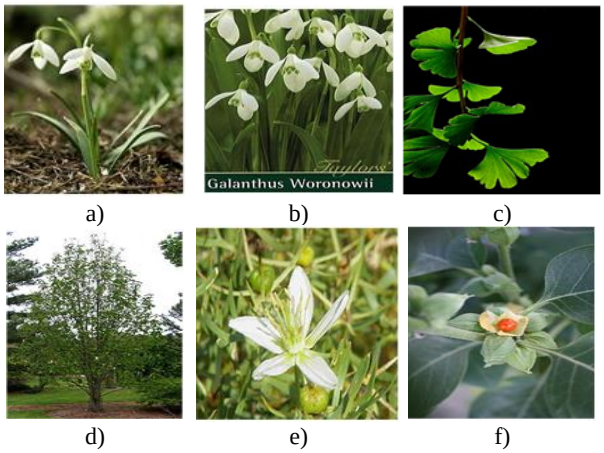

Figure 6. Medicinal plants containing compounds with antioxidant activity against Alzheimer disease.
a) Galanthus nivalis L. b) Galanthus Woronowii Losinsk. c) Ginkgo biloba L. d) Magnolia officinalis Rehder & *E.H.* Wilson e) Peganum harmals L. f) Withania somnifera (L.) Dunal

Aminoacids with antioxidant activity

Antioxidant effects exhibit the following aminoacids: L-Arginine, L-Histidine, L-Isoleucine L-Serine, L-Tryptophan and L-Tyrosine [50] **(Figure 7)**. *Camellia sinenensis (L.) Kuntze* contains L-Arginine, L-Serine, L-Tryptophan and L-Tyrosine and in *Morinda citrifolia L.* is found .L-Isoleucine.

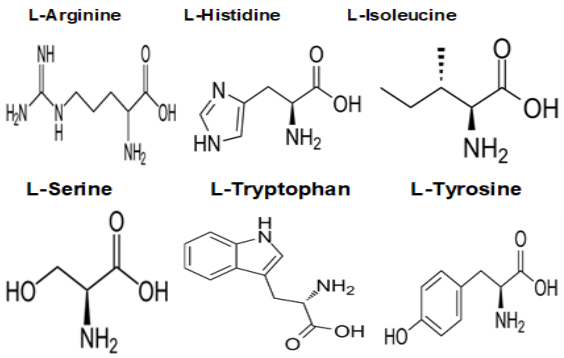

Figure 7. Chemical structures of aminoacids with antioxidant activity.

Antioxidant activity exhibit a sulfur amino acids: L-Cysteine, N-Acetylcysteine, L-Methionine, Taurine. N-Acetylcysteine has antioxidant properties that alleviate symptoms of depression, and improves activity of the brain and memory. Contained in garlic extract, S-Alyl-L-Cysteine inhibits pathological cascades associated with synaptic degeneration and neuroinflammation. Taurine is an antioxidant that provides access of magnesium and calcium in brain cells and stimulates nerve cells. Phosphatidylserine exhibits antioxidant activity against lipid peroxidation of the membranes of nerve cells and is particularly effective in combination with omega-3 unsaturated fatty acids. In Alzheimer's model in mice it has been shown that the decreasing of the levels of L-Arginine leads to amyloid deposition, hyperphosphorylation of tau-proteine, changes in behavior and loss of neurons. Treatment with L-Arginine improves cognitive function by reduction of oxidative stress [50].

Conclusion

The therapeutic approaches in Alzheimer's disease are connected with improvement of neuronal degeneration. Application of antioxidans, which inhibit free radicals effect and induce the activity of endogenous antioxidant enzymes, is one of the most promising approach for prevention of Alzheimer's disease. New perspective for the improvement of cognitive functions is the investigation of natural phytocompounds that exert synergistic antioxidant effects. For Alzheimer's disease due to the content of different compounds, very promising antioxidant effect exert the extracts from different medicinal plants. The more important antioxidant compounds with potential benefit against Alzheimer's disease include: 1) flavonoids Quercetin, Epigallocatechin-3-gallate, Moringine, Magnolol, Honokiol, Kaempferol, Isorhamnetin, Myricetin; 2) non-flavonoids: Curcumine, Resveratrol, Rosmarinic acid. 3) alkalolids: Arecoline, Berberine, Caffeine, Galantamine, Huperzine A, Nicotine; Morphine, Piperine. Antioxidant effects exhibit L-Arginine, L-Histidine, L-Isoleucine, L-Serine, L-Tryptophan. L-Tyrosine, L-Cysteine, L-Methionine.

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