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PHYTOTHERAPEUTIC STRATEGY AS A POWERFUL APPROACH FOR THE PREVENTION AND THERAPY OF ALZHEIMER'S DISEASE

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Abstract

According to the World Health Organization and Alzheimer's Disease International there were about 35.6 million people suffering from dementia in 2010 with an estimated double increase in 2030, triple in 2050, with 7.7 million new cases. per year (1 every 4 seconds) and with an average survival, after diagnosis, of 4-8 years. Alzheimer's disease is generally associated with the elderly and with aging, which is why the symptoms of this disease are often ignored. In reality, Alzheimer's seems to affect people between the ages of 65 and 70, while more precocious and severe cases occur before the age of 65 and aging and stress can only worsen the symptoms. The sex most affected is female. It has been noted that dementia in industrialized countries affects about 8% of people over 65 and rises to over 20% after the age of eighty. This suggests that, very often, different factors such as lifestyle, stress and nutrition influence the speed and onset of this disease. To date, it is now known that the affected organ is the brain, such a complex and fascinating organ, but above all difficult to study and treat due to its complicated structure and organization. In fact, the treatment is based on pharmacological therapies, but although numerous research studies are underway to identify effective therapies in the treatment of dementia, the available interventions have not given definitive solutions to treat 6 this pathology. The therapeutic strategies available for dementias in addition to those of a pharmacological type are: psychosocial and integrated management for continuity of care and also psychotherapeutic support for families. In recent decades, however, we have focused on another aspect of this disease: how to prevent it? And this is where the use of medicinal plants comes into play to prevent and mitigate the onset of this disease. This type of approach is based on the use of medicinal plants; in particular the phytocomplex, contained in them, owes its activity to the synergy between its components. Plants produce secondary metabolites, organic compounds, which unlike the primary ones such as carbohydrates, proteins and fats, do not participate in the normal development and growth of the plant, but are developed by the plant to mediate the relationship with the external environment, carrying out important activities such as facilitate reproduction and therefore attract pollinating insects or act as a deterrent to the external environment. These compounds have very complex chemical structures that can be used as guiding compounds for the discovery of new drugs or for the development of nutraceutical or cosmeceutical remedies. In phytotherapy, medicinal plants that can be used for preventive purposes or as adjuvants in the treatment of Alzheimer's, are identified essentially starting from their antioxidant, anticholinesterase and anti-inflammatory properties, or as very often happens from all three. This paper reviews the plant species used in the prevention of Alzheimer's disease and as adjuvants in the treatment of Alzheimer's.

Keywords: *Alzheimer's disease, phytotherapy approach, ginsenosides, eleuterosides, polyphenols.*

Introduction

Alzheimer's Disease: Various neurological disorders cause dementia, a deterioration of intellectual skills resulting from an organic brain disorder. A common form of dementia is called Alzheimer's disease. It affects 10% of the population over the age of 65 and nearly 50% of people over the age of 85.

Alzheimer's disease was first described by neuropathologist Alois Alzheimer's in an article entitled "A characteristic disease of the cerebral cortex". He studied the case of a fifty-year-old woman suffering from this pathology: one of the first symptoms she presented was a strong jealousy of her husband.

Very soon the symptoms worsened, the neuropathologist realized that the patient was not inable to find her way home, dragging objects back and forth, was disoriented both in time and space, it was confused and lost. The patient died after about 4 years of illness; in the last period the woman was completely apathetic, without stimuli and confined to bed.

Alzheimer's, after his death examined the old woman's brain and noticed some changes in the neurofibrils.

The severity of Alzheimer's disease dementia is closely related to the number and the distribution of what are now called neurofibrillary tangles, the "tombstones" of the gods dead and dying neurons. Indeed, as Alzheimer's has speculated, it is very likely that the tangle formation in the cerebral cortex is the cause of the symptoms of the disease. Electron microscopy indicates that the main components of tangles are a filaments helix coupled, long fibrous proteins twisted together like the strands of a rope. Today, it is understood that these filaments consist of the microtubule-associated protein tau [1].

Over the years, various theories concerning the mechanism of action have been developed basis of this disease, those that seem to have a justification are the hypothesis of *β*- amyloid and that of oxidative stress and it is on the latter that the preventive treatments carried out by phytotherapy.

Hypothesis of the amyloid *β* peptide: Alzheimer's disease, as mentioned above, derives from the production and accumulation of amyloid *β* (Aβ) proteins and from neurofibrillary tangles of the Tau protein. Amyloid *β* peptide originates from another protein called APP, a protein of membrane. The amyloid *β* protein accumulates forming plaques with one size between 10 and 200 µm. At the level of these plates, the neurons present mutations and alterations with dendritic and axonal damage, while astrocytes and glial cells.

They express antigens related to cell activation. The senile plaques however, do come to also create due to large clusters of abnormal fibers occupying the perinuclear space with globular shape. These fibers are made up of an additional protein called Tau, this protein stabilizes the cytoskeleton and modulates the stability of axonal microtubules interacting with tubulin, promoting its assembly into microtubules and stabilizing pre-established microtubule structures. Tau's ability to assemble and stabilize tubulin it is regulated by its degree of phosphorylation. Hyperphosphorylation of tau (P-tau) suppresses this activity, detaching it from the microtubules and secondarily promoting the self-assembly of tau into larger aggregate structures. These structures and their formation are closely associated with diseases related to the tau protein, called tauopathies, such as Alzheimer's. The spherical bodies of healthy neurons are covered by the neurites that form links with other cells. The tau molecules are tightly bound to the sides of the microtubules and there strengthen; but when Alzheimer's disease intervenes, the tau molecules detach from microtubules and join together to form tangles. At the same time, the microtubules became break up and neurons die.

In patients with this disease the Tau protein is phosphorylated and is believed to be responsible principal is A*β* 42.

Biology of the amyloid *beta* protein: The protein *β* amyloid is synthesized from its precursor APP, this is usually cut by two enzymes: α-secretase and γ-secretase, obtaining a product, called P3, harmless. Various functions of these APP isoforms have been identified, in particular the α-secretase cleavage not only precludes the formation of the A*β* peptide, but also causes the release of the large ectodomain of

APP (sAPPa) which has neuroprotective and memory improvement.

The action of α-secretase is regulated by the action of protein kinase C (PKC) and others reporting mechanisms. Inhibition of the α-TNF converting enzyme (TACE) in moles primary neurons leads to the suppression of the regulated activity of α-secretase but not of the constitutive activity of the same. In the immunohistochemical analysis of the human brain, the TACE has been localized in neurons and the localization of TACE has also been described with amyloid plaques in the brains of patients with the disease [2].

The *β*- secretase, of which the most important is an aspartic-protease, called BACE 1, is mainly located at the neuronal level, in the Golgi apparatus. The *β*-secretase is known since 1999, when it was classified as a member of the aspartyl protease family, enzymes which use two residues of aspartic acid and water for their action. Recently, it is it has been reported [2] that BACE 1 is required for the myelination of peripheral nerves and the correct grouping of axons by Schwann cells. In addition to this, it also deals with the cutting of the APP, during which it can give rise to two isoforms, consisting of 40 and 42 amino acids each; At *β* 40 makes up the majority of *β*- amyloids present in a normal brain, while the excess of A*β* 42 accumulates predominantly in amyloids [3]. Aggregation of both peptides can induce cytotoxicity, but this has been shown to be so effect is given mainly by A*β* 42. Peptide A *β* is characterized by a high tendency to aggregate forming insoluble oligomers and fibrils which, accumulating at the level extracellular, give rise to the well-known senile plaques. The extracellular deposits of A*β* they trigger a progressive synaptic damage and the activation of an inflammatory response. To elucidate the molecular mechanism underlying assembly and deposition in the brain of the *β*-amyloid, an immunochemical analysis of the obtained cortices was performed from autopsy of patients with AD 1 and of people who died without evidence of dementia.

These barks were centrifuged by the density gradient of sucrose, the amyloid nuclei formed by A*β* were recovered in the amyloid fraction, while the cell membranes are were recovered in the membrane fraction. Strong was observed in the barks reactivity of A*β* of the amyloid fraction and this led to the supposition that there was one strong formation of senile plaques. However, the scientists noted that strong immunoreactivity of A*β* was predominant in the membrane fraction, but not in the amyloid, this immunoreactivity was positively linked to the abundance of senile plaques present and negatively in the presence of neurofibrillary tangles. It was subsequently shown that α-amylase was bound to a ganglioside because, following a sodium dodecyl sulphate and sodium dodecyl sulfate (SDS) treatment-polyacrylamide gel electrophoresis (SDS) has shown delayed mobility [3]. Obviously, as a result, the researchers showed that the action of A *β* is influenced by GM1, increasing the production of monoclonal antibodies specific for altered conformation of A*β*. The experiment was conducted using 3 laboratory mice and finally a specific antibody was identified for the amino terminal of A*β* capable of recognize GA *β* [4]. Studies carried out on amyloid *β* have highlighted a correlation between the accumulation of *β* amyloid plaques and Alzheimer's disease.

Hypothesis of oxidative stress and apoptosis in Alzheimer's disease: Oxidative stress, also called redox imbalance, is characterized by alterations that occur they produce in biological tissues, cells and macromolecules when these are exposed to an excess of oxidizing agents, with the creation of free radicals. The effect is consisting of metabolic alterations, cell damage and cell death. It originates when there is no longer a balance between oxidizing agents and those antioxidants, in fact, in non-pathological conditions, the body defends itself through actions and enzymatic and non-enzymatic mechanisms. Among the first we remember the superoxide enzyme dismutase, catalase and glutathione peroxidase; there are, however, also substances of course present in foods that perform a similar action, namely vitamins, among which they cover a fundamental role in this process is vitamin A, C and E [5]. Under unfavorable conditions, or of excessive psycho-physical stress, you can have a surplus of free radicals that is not possible cope with the mechanisms mentioned above. Oxidative stress particularly affects the nerve tissue due to its high oxygen requirement, its ability to deposit iron, its

high content of polyunsaturated fatty acids and its reduced capacity of biosynthesis of endogenous antioxidants. ROS particularly affect membranes neuronal, formed by lipids and proteins, the latter in fact undergo oxidation reactions at the level of the side chains with the loss of functionality. Oxidative stress and inflammation are linked to our immune system, in fact, when cells they suffer damage, they produce antibodies that migrate into "diseased" cells triggering one reaction with the production of free radicals, which deal with the elimination of bacteria [6].

Closely related to Alzheimer's disease is apoptosis and autophagy of neuronal cells, apoptosis is a highly regulated process by which cells initiate an autonomous death program. It is a strategy to eliminate cells through a process of relatively rapid autolysis consisting of a leading mitochondrial dysfunction to the activation of caspases, which in turn mediate the proteolytic degradation of cytoplasmic and nuclear proteins, condensation, DNA degradation and, finally, the cell death. In particular, apoptosis is triggered by a family of defined proteins BCL2 (belonging to the caspase family) which regulate mitochondrial integrity [7].

Apoptosis is usually a mechanism activated by the combined action of receptors and more genes. Among the latter, the importance of p53, which controls the replication of DNA, cell proliferation and death, preventing cell propagation genetically damaged. When in this state, p53 induces the activation of the gene that it expresses another protein, p21, which interacts with cyclin-dependent protein kinase (cdk2), complexing with the latter and, in so doing, preventing the transition to phase M (mitotic) of the cell cycle, thus stopping the cycle in the G1 phase. This mechanism is advantageous, as it allows the activation of DNA-repair mechanisms; in case of failure of the latter, p53 initiates death by apoptosis of the mutated cell [8-10].

There is an extensive literature documenting that the exposure of neurons to fibrillar forms of A*β in vitro* causes apoptotic cell death. It is believed, in fact, that the fibrillar peptide A*β* binds to cell surface proteins, leading to the activation of proapoptotic cascades of intracellular signaling. Furthermore, A*β* peptides stimulate an increase in calcium levels intracellular and concealment of calcium homeostasis was the postulate to support the susceptibility of neurons to apoptotic death. Neurons exposed to Aβ peptides *in vitro* have shown to have signs of oxidative damage and increased peroxide levels, caused precisely from these A *β* peptides. Oxidative stress elicits JNK activation (c-Jun NH2-terminal kinase), stress-activated protein kinases. Tumor necrosis factors (TNF) mediate the JNKs, responsible for the transmission of stress signals to the nucleus, for regulation of gene expression and the induction of apoptosis [7].

Inflammation in Alzheimer's disease: In recent decades, by studying and observing the brain, researchers have noticed a tightening relationship between disease and inflammation, in fact this pathology can be caused by a uncured inflammation. Upon examining the brain, abundant pro-inflammatory caused by reactive microglia, the latter derive from a myeloid lineage and they are the primary immune cells of the brain. Active microglia in the brain of AD are associated with amyloid plaques and it has been shown that the interaction of microglia with amyloid fibrils, causes the phenotypic activation of these cells. Activation of the microglia is accompanied by the increase in the expression of a number of molecules of cell surface, as well as from the production and secretion of a wide range of molecules pro-inflammatory, including cytokines and acute phase proteins such as CD45 leukocytes, *β* 2 integrins (LFA-1, CR3 and CR4), MHC II surface antigens and immunoglobulins FcγRI, FcγRII and FcγRIII. Also, acute phase reagents such as inhibitors protease α 1-antichymotrypsin, α 1-antitrypsin, α 2-macroglobulin, pentraxins serum amyloid P and C-reactive protein are upregulated during inflammation and present in senile plaques [4]. In the death of neurons, due of inflammation, multiple mechanisms and molecules seem to be involved, for example cytokines such as TNF-α whose high concentrations can cause shock and apoptosis. TNF-α is the first factor to be produced by microglia and its toxic action is induced from low levels of insulin-like growth factor (IGF-I) and presumably from other factors of growth that operate in a similar way [4]. As has already been addressed in the previous chapter, oxidative stress can also be considered a causative agent of the

disease, in fact there is evidence regarding degeneration of this disease following the production of oxygen and free radicals by microglia. Aβ fibrils stimulate the activation of microglial and subsequent NADPH oxidase respiratory explosion, resulting in the production of toxic reactive oxygen (ROS), derived from the superoxide anion (O_2^-). The generation of ROS results in the direct oxidation of proteins and lipids and the consequent neurotoxicity and this explains the oxidative damage observed in the brains of patients [4]. In addition, oxidative damage leads to the formation of nitrogen monoxide (NO). Aβ stimulation of microglia cells activates the inducible form of nitric oxide synthase (iNOS) and subsequent production and secretion of NO.

Furthermore, iNOS neuronal expression is induced by microglial-derived TNF-α, with consequent stimulation of NO production by the neurons themselves, causing NO-mediated neuronal apoptosis.

The stages of the disease: Alzheimer's syndrome is a progressive disease that tends to get worse as it progresses some years. Symptoms are never the same for everyone, but generally it is divided into four stages:

- Phase 1: No disability (normal function), in this phase, the person experiences mild memory disturbances, especially for recent events, names and telephone numbers, with difficulty to learn new concepts or procedures. In addition, there may be difficulties in orientation in space and time, for example finding the way home or recalling the current date. On the linguistic level, problems appear in producing adequate sentences to support the thought and they come use frequent pauses due to inability to "find the right word". The person finds more difficult to perform tasks that require more planning, such as organizing a family lunch, managing the house or finances. The progressive loss of these cognitive abilities interferes with the normal development of daily activities. The sick person is aware of their own difficulties and their own failures and his mood may become more deflated, so much so that he may withdraw from social activities or reacting with aggressive and anxious manifestations. This phase lasts generally two to four years.
- Phase 2: very mild cognitive decline, lasting from two to ten years.

The forgetfulness gets worse and worse, the patient may have difficulty in normal daily activities, such as personal hygiene, nutrition.

In this phase the patient could have outbursts of anger and obsessive behaviors.

- Phase 3: usually lasts three years and is the most advanced stage of the disease during which the sick person is completely dependent and requires continuous and total assistance. It is characterized by an almost complete loss of production and understanding skills linguistics; however, the person can retain the ability to communicate through the body (facial expression, posture and gestures). The subject becomes totally incapable of recognize their family members, to perform the daily acts of life such as dressing, eat, wash, recognize your personal items and your home. Movement is increasingly compromised.
- Phase 4: it is the shortest phase, lasts a maximum of 12 months and is characterized by the complete insufficiency, incontinence and difficulty in swallowing and eating.

Symptoms: The symptoms of this pathology are initially mild, in fact it is not easy to diagnose this on the contrary, they are often confused with the ailments associated with old age.

There are some initial symptoms that, however, should not be underestimated:

- Amnesia: memory loss or forgetfulness concerning recent and remote facts. The patient has difficulty remembering the names of family members, events, the way home. Over time the symptoms worsen and the difficulty of washing, dressing and also occurs perform normal daily functions;
- Apraxia: is the term that defines the alteration or inability to speak or understand the language;
- Agnosia: is a perception disorder characterized by the lack of recognition of objects, people, sounds, shapes, smells already known, in

the absence of memory disorders and in the absence of lesions of the sensory systems;

- Difficulty in communication;
- Change of personality: initially the patient, aware of his difficulties, forgetfulness and problems, manifesting feelings of sadness, anxiety and depression.

Behavior change: the patient may manifest outbursts of anger, obsessive disorders towards people and objects, delusions, violence and incontinence.

The hippocampus and its role in Alzheimer's disease: The cerebral cortex is present in all vertebrate organisms, but it has characteristics different, in major mammals, such as humans, whose surface of the cortex brain has a large number of grooves, called 'sulci'. The oldest part of the cerebral cortex, the hippocampus, differs into three layers (alloortex), while the most recent neocortex (or isocortex) in six. Specifically, the cerebral cortex contains at least one layer of cells containing pyramidal cells that emit large apical dendrites, which extend up to the first layer where they form multiple branches.

The hippocampus is a region of the temporal lobe, along with the amygdala and septal area and goes to constitute the limbic system. The latter is made up of a set of regions belonging to the central nervous system, connected to each other and acts in the integration of the sense of smell and

short-term memory; performs important functions in relation to emotions, mood and to the sense of self-awareness. The limbic system also performs elementary functions such as integration between the vegetative and neuroendocrine nervous systems. In addition, some parts of the limbic system are involved in memory, visceral, defense and reproduction processes [11].

The hippocampus has a "C" shape and is made up of two thin folded neuronal layers one into the other: an Ammon horn layer, which is characterized by 4 parts CA 1, CA 2, CA 3,CA 4, the other dentate gyrus. The latter consists of pyramidal cells that have processes afferent processes (dendrites) and efferent processes (axons). It should be noted that the dendrites of a cell pyramidal extend from both the apex and the base. The basal dendrites extend towards the surface of the lateral ventricles, while the apical dendrites extend away from the ventricles lateral and towards the dentate gyrus [11].

The dendrites of the major neurons of the brain are covered with small protrusions known as dendritic spines, involved in the signaling mechanism in reception and in the processing of synaptic information. Dendritic spines exist in a variety of forms, but typically consist of a bulbous thorn head at the end of a thin tube, or neck. Each spine head contains one or more synapses and is located very close to an axon coming from another neuron.

Scientists have better understood the chemical properties of dendritic spines - the receptors of their surface are known to respond to a number of neurotransmitters, such as glutamate and glycine, released by other neurons. But, due to the extremely size reduced thorns (about 1/100 of the diameter of a human hair), their electrical properties they have always been difficult to study.

Regarding the hippocampus, the dendritic spines have been shown to be the site predominant excitatory synapses on CA1 pyramidal neurons in the hippocampus. The density of the spines is related to the amount of connectivity between neurons and the dendritic spines themselves and the axons of other neurons that have accumulated in synaptic contacts. Hence, a task of the dendrites is to establish and maintain these links and regulate neuronal plasticity. Alterations of the hippocampus during aging are linked to deficits behavioral and functional, in fact the hippocampus is involved in learning and in memory. However, the cognitive decline that occurs during aging does not appear be related to a loss of neurons, so it has been speculated that the spines may be altered in the course of aging throughout the hippocampus within a sub-region hippocampus. In the brains of individuals suffering from a variety of diseases or disorders in the shape or number of dendritic spines, many of these pathologies lead to one decrease of dendritic spines.

Prevention and Phytotherapy Approach

With the progressive aging of the global population, it is estimated that the number of people with dementia will double over the next 15 years, resulting in huge costs welfare and social. Therefore, the reduction in the risk of this disease is entering everyone the effects among the priorities of the World Health Organization. It is estimated that about one third of Alzheimer's disease cases can be attributed to modifiable risk factors and it is precisely in this case that the approach is recommended price quotation. Currently, the treatments approved by the Food and Drug Administration (FDA) of the states United include acetylcholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists (NMDA) that are involved in the symptomatic treatment of the disease.

These are forms of palliative care that slow the progression of cognitive symptoms as well prevent any worsening of the patient's symptoms. The phytotherapeutic products used in this field are divided into various categories, based on to their mechanism of action and three classes have been identified: antioxidant drugs, drugs anticholinesterase and anti-inflammatory drugs, but as often happens the ability of a phytocomplex to prevent or alleviate the symptoms of a disease is due to the synergism of various actions.

Adaptogens: The term adaptogen was first proposed in 1940 by a USSR scholar called N. Lazarev, when he studied and examined *Schisandra chinensis* [12].

According to this definition, adaptogens must meet three criteria:

- annihilate the body's resistance to harmful stimuli of various kinds (physical, biological, psychic), also carrying out an immunostimulating activity;

- maintain body homeostasis, ensuring a normalizing effect, able to counteract emotional or tense events, often perceived with much intensity, inducing, from the point of psychological view, feelings of self-control, calm and tranquility;

- not to create addiction and not to cause addiction, but above all not to harm the human body [12].

Consequently, adaptogens are referred to as natural bio-regulatory molecules they increase the ability to adapt to environmental factors and avoid the damage caused by these factors. Indeed, the advantage of adaptogens lies in increasing resistance to stress, reducing the negative reactions that may develop during the period of the alarm phase and eliminating, or at least decreasing, the beginning of the exhaustion phase [13].

This type of plants are indicated by geriatricians as they increase resistance to stress and fatigue, primary factors responsible for inflammation, which as we know is at the basis of this pathology [14, 15].

Activity and classification of adaptogens: Adaptogens are classified into different categories based on their function and theirs mechanism of action.

In general they act on the hypothalamus-pituitary-adrenal axis (HPA AXIS).

Primary adaptogens are those that can not only maintain or recover homeostasis and allostasis, but they can also promote anabolic recovery, plus they can produce a positive response to stress.

Secondary adaptogens do not directly affect the HPA axis, but act and improve anabolism, affecting the nervous, endocrine and immune systems. Not by chance fats, sterols and phenols belong to this category.

The last class of adaptogens is composed of plants that act on the HPA axis and on anabolism by acting synergistically with the other adaptogens belonging to the categories mentioned above.

In case of strong stress, adaptogens can activate different responses by the systems human stress response. The human stress response system is composed of the neurons of the hypothalamic paraventricular nucleus and includes distal ends of the brainstem, the axis HPA and the peripheral nervous system [16].The hormones involved in this system are arginine vasopressin (AVP) and corticotropin hormone (CRH) [16].

The sympathetic nervous system and the HPA system interact in terms of functions and anatomy systematic. When responding to the external environment, these systems can interact with different levels: for example, catecholamine can stimulate the HPA axis by releasing the hormone corticotropin (CRH) and the hormone produced by the HPA axis can act on the nervous system. When the hormone secretion corticotropin (CRH) and arginine vasopressin (AVP) increases following external stimuli, two hormones are released, cortisol and adrenocorticotropic hormone and the response of cytokines and metabolites of arachidonic acid to stress. The SNS system provides the human body with a rapid response mechanism to external stresses. In addition to catecholamine, the sympathetic and parasympathetic nervous systems they can also secrete a large variety of neuropeptides, ATP and nitric oxide (NO) with consequent regulation and production of energy, reduction of the sensation of pressure resistance, increase of resistance, improvement of mental concentration, facilitation of period of deep sleep.

These functions can be linked to the use of primary adaptogens which stimulate a greater release of nitric oxide and cortisol in the plasma and in the saliva allowing the body to adapt to too heavy stress levels.

***Panax ginseng* L.**: Ginseng is one of the main representatives of traditional Chinese medicine and presents a wide range of pharmacological actions. È a perennial herbaceous plant, belonging to the family of the Araliaceae, with well-developed tuberized root, erect branches of about 30-50 cm long, bearing palmate-lobed leaves with 5 leaflets. The flowers are white, gathered in umbels and the fruit is a red berry.

The drug consists of a cylindrical, large and spindle-shaped root and is considered by the Chinese to be one universal panacea, containing numerous constituents.

The main active molecules of ginseng are triterpene glycosides, that is ginsenosides, too if in the past they were more commonly known as panaxosides.

The panaxosides are nothing more than saponins, heterosides of tetracyclic genines of the series of dammarano. The differences between the various ginsenosides depend on the different sugar chains. The main aglycones of ginsenosides are 20(S)-protopanaxadiol and 20(S)-protopanaxatriol (Figure 1): the glycosides of the protopanaxatriol group are called panaxosides A, B and C and the glycosides of the protopanaxadiol group are called panaxosides D, E and F [17-21].

Clinical studies: Ginseng extract is used in the treatment of Alzheimer's disease (AD) for the purpose preventive and palliative treatment in the early stages of the disease.

Ginseng and the reduction of *β*-amyloid (Aβ) plaque levels : ginseng can have effects benefits by reducing the formation of senile plaques [17]. The saponins reduce mRNA levels for brain APP and improve learning and memory in mice. Indeed, elderly transgenic mice with AD treated with Rg1 ginsenoside (10mg / kg), showed a marked decrease in brain *Aβ* levels , inversion neuropathological changes and some protection of learning skills and of memory.

It has also been previously shown that an extract of a root of *Panax ginseng* of 4 years, inhibited the neurotoxicity of A *β* . The effect of dry white ginseng extract (WGE) on cell damage was examined neuronal and memory loss in mice injected with β-amyloid proteins (AβO) in the hippocampus. Mice were treated with 100 and 500 mg / kg / day of extract for 12 days after surgery. The results were an improvement in the loss of memory and inhibition of cell death induced by A*β*O [17].

- Ginsenosides and calcium levels in neurons: the mechanism of neuronal damage can be caused by an increase in the intracellular level of calcium ions (Ca^{2+}), in turn induced by glutamate. An increase in calcium levels leads to excessive stimulation of enzymes proteolytic, an increase in lipid peroxidation and an increase in the generation of ROS and nitrogen, thus contributing to the cytotoxic process. The A*β* not only leads to an increase of calcium channels in the cell membrane, but also promotes the phosphorylation of the channels of existing calcium, thereby increasing calcium flow and initiating neurodegeneration. In one study, it

was found that ginsenoside Rg2 not only reduces the level of Ca^{2+}, but also the lipid peroxidation caused by glutamate, while Rg1 suppresses the sensitivity of the activation of calcium channels to high values of membrane potential, also reducing the calcium currents induced by the administration of Aβ. The reduced influx calcium can reduce the level of calcium ions in neurons and attenuate the neurotoxicity of A*β* [17].

- Effect on the phosphorylation of the tau protein: an abnormal hyperphosphorylation renders the protein τ resistant to proteolytic degradation, which leads to the gradual accumulation of p-Tau in the cell. Inhibition of p-Tau may, therefore, be a potential therapeutic strategy for the prevention of the disease, by inhibiting the formation of the fibrillar tangle [17]. In a study conducted by Razgonova *et al.* [17] okadaic acid (OKA), a potent phosphatase inhibitor, it was used to examine the effects of ginsenoside Rg1 on the improvement of memory and related mechanisms in rats. In this study it is since ginsenoside Rg1 (10 mg/kg), administered for 7 days, protects rats from neurotoxicity induced by okadaic acid (OKA), as Rg1 reduces the loss of memory induced by okadaic acid (OKA), through the signaling pathway of the glycogen synthetase kinase 3 (GSK3)*β*/Tau, attenuating the formation of A*β* . Total ginsenoside extracts from *Panax ginseng* stems and leaves increased the activity phosphatase of purified calcineurin. This could be useful in AD, since inhibition of calcineurin leads to hyperphosphorylation of the tau protein at multiple sites in brains of the sick. Treatment with ginsenoside Rg1 in cortical neurons or in rats with AD (10 mg/kg for 7 days) reduced okadaic acid-induced neurotoxicity and hyperphosphorylation of the tau protein by improving the activity of the protein phosphatase 2.

- Antioxidant effect of ginsenosides: the effect of ginsenosides on the levels of acetylcholine (Ach), the main neurotransmitter of the destroyed parasympathetic nervous system by specific enzymes, the cholinesterases: acetylcholinesterase (AChE) and butylcholinesterase (BChE).

A decrease in concentration has been observed in the brains of Alzheimer's patients of Ach during the early stages of the disease.

The decrease in Ach is due to increased activation of AChE and inhibition of choline acetyltransferase (ChAT), the enzyme responsible for the biosynthesis of Ach. The analyzes *in vitro* have shown that some of the ginsenosides are AChE and BChE inhibitors, in particular ginsenoside Rg5 dose-dependently inhibits AChE and activates ChAT in another AD model.

Dosage and contraindications: The use of ginseng is safe, a LD 50 of *P. Ginseng* root in mice has been reported equal to 10-30 mg/kg. The German commission recommends the use of about 1-2 grams of raw drug per day, for no more than three months, or 200 mg of a standardized concentrated aqueous extract.

***Eleutherococcus senticosus* L.**: Eleutherococcus has received particular attention as a new plant in recent years medicine and also, in the United States, has taken on a very important role as dietary supplement.

Eleutherococcus or *Siberian Ginseng* is a shrub of the Araliaceae family, native to of Siberia or Mongolia. The root is used a lot in the Chinese Pharmacopoeia and Japanese for the treatment of heart, neurological and hypertension disorders.

The drug consists of the root which, like *Panax ginseng*, is a source of saponins triterpene and polysaccharides [22, 23].

The main constituents are represented by the A-M eleutherosides (heterogeneous group of compounds including sterols, phenylpropanoids, coumarins, monosaccharides and lignans) and caffeic acid derivatives (including chlorogenic acid) [24-30].

In general, the components that appear to be involved in the treatment of disorders age-related neurodegeneratives are eleutheroside B and E (Figure 2).

To study the effect of *E. senticosus* leaf extract on cognitive function in mice juveniles, the vehicle extract or solution was administered to the mice for 17 days. There used dose of the leaf extract was 500 mg/kg/day.

Clinical studies: Eleutherococcus is used in the treatment of Alzheimer's disease as:

- Increases neurotransmitters in the hippocampus.

Pathological changes in Alzheimer's disease manifest as degeneration and loss of cholinergic neurotransmission in the hippocampus and limbic system, decrease metabolism linked to the loss of neurotransmission and proteins.

During this study [31], following injections of eleutherosides E and B and quinolic acid in the hippocampus, there were no results on the cholinesterase enzyme in the blood plasma, an inhibitory effect occurred in the hippocampal homogenate.

Eleuteroside B and E at high doses (500 mg/kg/day), have attenuated the cholinesterase activity [31]. This indicates that eleutheroside B or E can regulate cholinesterase activity by an indirect mechanism. The determination of the content of acetylcholine and choline in blood plasma and hippocampal homogenate indicates that, injecting quinolinic acid into the hippocampus, had minimal effects on them levels in the blood plasma, but significantly reduced the acetylcholine content in the homogenate of the hippocampus. This indicates that quinolinic acid greatly damages the cholinergic neurons of the hippocampus and reduces their function, affecting learning and memory. In summary, eleutheroside B or E effectively improve learning and memory in elderly rats and the effects of β eleutheroside, at high, doses are stronger than those of eleutheroside E in high doses.

- Antioxidant activity

Antioxidant activity was evaluated using three methods: determination of free radicals, oxidation of oleic acid and chelating activity.

Both the fruits and the leaves have good antioxidant activity. Caffeic acid, present in the plant species, it is able to donate hydrogen atoms or electrons thanks to the presence of phenolic functions [24].

- Anti-peroxidation activity of lipids

Lipids are a major constituent of cell membranes and are very sensitive oxidation, generating lipid peroxidation with the production of ROS, which are the basis of Alzheimer's disease. The polarity of the phenolic component is a key factor in that confers the solubility and the ability to access the lipid chain and intervene in oxidation [32, 33].

- Anti-hyaluronidase and anti-cholinesterase activity

Eleutherococcus is also known for its influence on much faster degradation of the beta 1-4 bond of hyaluronic acid (HA). In addition, it is also known for its direct action to inhibit acetylcholine in nerve transmission; this action is related to flavonoids and triterpenes present in the plant. The mechanism of action is based on the chelation of calcium, involved in transmission and reactions.

Dosage and side effects: Eleutherococcus is traditionally used as a tonic to invigorate or fortify in case of tiredness and debilitation, or in the reduction of working capacity and concentration and during convalescence. It is usually used as a substitute for ginseng, because it is less expensive, albeit the mechanisms of action are not yet fully known.

The German commission recommends the same doses of *Panax ginseng* , so about 3 grams per day. No side effects were found.

***Withania somnifera* L.**: *W. somnifera*, known as Ashwagandha, is a medicinal plant belonging to the Solanaceae family used for about 3000 years in Ayurvedic and indigenous medicine.

The Solanaceae are live plants, they have simple, alternate or opposite leaves. The flowers they are generally carried in inflorescences, have rotated or tubular corolla, the stamens are welded together and the fruit is a berry, drupe or capsule.

W. somnifera is an erect, greyish shrub, 30-75 cm tall with long tuberous roots. The leaves are alternate or sub opposite, from widely ovate to oblong, petiolate. The flowers are small, greenish, axillary, solitary or in low flowering and bisexual buds. The fruit is a berry globose, red-orange when ripe and is enclosed in the enlarged calyx.

About 23 species of this plant are widespread in Southeast Asia, in tropical areas and subtropics and in Asia. There are many properties of this plant, in fact it used to be in ancient times used to promote

youthful vigor, stamina, strength and health by nourishing elements of the body and increasing the production of vital fluids, muscle fat, blood, lymph, sperm and cells. The similarity between these reconstructive properties and those of the roots of ginseng caused Ashwagandha roots to be called Indian ginseng. After numerous studies have shown the plant to have powerful aphrodisiac, sedative, calming, rejuvenating and life prolonging. It is also used as an energy tonic

known as Medharasayana, which means "that which promotes learning and a good memory [34].

The drug consists of the root, but the others are also used in Ayurvedic medicine parts of the plant.

The chemistry of this plant species has been extensively studied and several have been identified groups of compounds such as steroidal lactones, alkaloids (withanin), flavonoids and tannins, withaferina A. The main chemical constituents of these plants, the withanolides, are mainly localized in the leaves and their concentration usually varies from 0.001 to 0.5% dry weight [35-36].

The withanolides belong to the group of C-28 steroidal lactones and are generally polyoxygenates, it is believed, in fact, that the plants that process them have a system enzymatic capable of oxidizing all carbon atoms.

The characteristic of withanolides is a C8 or C9 chain with a lactone or lactol ring, but the lactone ring can have six or five members and can be fused with the carbocyclic part of the molecule through a carbon-carbon bond or through an oxygen bridge (Figure 3) [35].

Clinical studies: Historically, *W. somnifera* has been used as an antioxidant, adaptogen, aphrodisiac, liver tonic, anti-inflammatory and astringent and more recently as an antibacterial and anticancer, as well as for the treatment of ulcers and senile dementia.

- Clearance of *β*- amyloid plaques

In particular, as has already been reiterated in the previous pages, one of the main causes of dementia and Alzheimer's disease is the accumulation of A *β* proteins . It has been noted that active ingredients of the plant are effective in axonal and synaptic regeneration, this could therefore lead to the regeneration of neuronal tissue [37].

Therefore, the effects of Ashwagandha extracts on neurite growth were investigated using an *in vitro* culture system [37]: the extract of Ashwagandha (130-150 g in methanol) showed growth stimulating activity of neurites in human SK-N-SH neuroblastoma cells. Conanolide A, withanoside IV and withanolides VI have been identified as active constituents of the methanol extract it has induced neurite growth in human neuroblastoma SH-SY5Y cells and in neurons of rat. The effects of siteindosides VII-X, isolated from aqueous extracts of methanol by *W. Somnifera,* were studied on brain cholinergic, glutaminergic and GABAergic receptors in rats. The cognition and memory enhancing effects of *W. somnifera* extracts they may be partly explained by the increased capacity of muscarinic cortical receptors acetylcholine.

Furthermore, it has been noted that this plant promotes the cleansing of the amyloid *β* plaques form in the premature stages of the disease. The administration of the extract of Ashwagandha (15g in 300ml of solvent) led to an increase in the low coreceptor density lipoprotein (LRP) in the liver and the soluble form of LRP (sLRP) in the plasma. LRP mediates the outflow of A*β* from the brain to the periphery. The hepatic decrease in LRP blocked both the increase of sLRP and A*β* in plasma and the reduction of A *β* in brain after administration of the extract [38]. Therefore, the Ashwagandha extract promotes clearance of *Aβ* in the brain through liver up-regulation LRP.

- Neuroprotective effect: the scopolamine, hallucinogenic alkaloid obtained from plants of the Solanaceae family used as a cholinergic blocker.

Scopolamine is a muscarinic receptor antagonist that induces amnesia in rodents, it also influences the expression of genes related to receptor signaling pathways muscarinics, apoptosis and cell differentiation in the rat brain. Has been shown that scopolamine treatment induced cell death in the cells of the human neuroblastoma IMR-32 and in rat glioma C-6 cells, while the administration of Ashwagandha extract, prior to scopolamine treatment, has protected cells from death.

Withaferina A and withanone were identified as main components of the extract and perform the function of protection against damage induced by scopolamine, probably through antioxidant effects.

Other uses and side effects: Ashwagandha has almost the same properties as common ginseng, which is why it comes called Siberian ginseng.

In fact, like the latter, numerous are the other uses of Ashwagandha, the leaves of the plant they have a bitter taste and are used as an anthelmintic. The infusion is used in case of fever, the bruised leaves and fruits are applied locally on the tuberculous glands, carbuncles and ulcers [34]. The roots are used as nutrients in pregnant women and prevent infertility in the same. The roots are also used in constipation, senile weakness, rheumatism, general weakness, nervous exhaustion, memory loss, loss of muscle energy and spermatorrea [35].

The fruits are used as sedatives, emetics and stomachics, febrifuges, diuretics and bitter tonics in dyspepsia and growth promoters in newborns. The twigs are chewed for clean your teeth and smoke from the plant is inhaled to relieve toothache. There are no reported health risks or side effects in association with management adequate therapeutic dosages indicated.

However, high doses of the root in mice (750 mg/kg per day for 15 days) caused it serious side effects, such as diarrhea and severe weight loss. It is recommended to take 3-6 grams of pulverized root.

***Vitis vinifera* L.:** *Vitis vinifera*, or common vine, is a shrub belonging to the Vitaceae family. It presents as a sarmentoso shrub, of which numerous varieties are cultivated, to obtain the wine. Grape juice is used in dietetics because it is rich in organic acids and sugars. The leaves are characterized by a black cluster and red pulp and turn red in autumn as well they contain numerous quantities of anthocyanins, cyanidiol and peonidol glycosides [39]. The flowers are gathered in panicle inflorescences, first erect, then pendulous (cluster compound). A cluster is formed by a main axis, called the rachis, which branches into axes lateral in tum branched. Branches of II, III and IV order, generally decreasing from the base towards the apex. The branches of higher order they are called pedicels and carry the floral receptacle at the distal end.

The fruit is a berry, called grape; the color of the ripe berry varies, according to the grape variety, from green to yellow, pink to purplish-red, black or bluish-black, but the intensity and color tone may also vary according to environmental conditions, in particular lighting. The epicarp (skin or cuticle) is hairless and often pruinose. The shape of the berries it is generally spherical, subspherical, elliptical or ovoid, but, in some grape varieties, it can also be markedly elongated until it assumes a cylindrical or arched shape.

Polyphenols extracted from grape leaves have shown antioxidant, antidiabetic, anti-inflammatory, anti-aging and antilipid potentials. The polyphenolic preparation Bioactive Dietary (BDPP), according to a study [40], is a combination therapeutic nutraceutical consisting of three bioactive and bioavailable polyphenolic preparations derived from grapes.

This preparation was designed to delay the conversion of MCI into disease and as a multi-target for the pathogenetic pathways of AD progression; each component exerts its unique mechanism of action. BDPP targets the amyloid protein, the synaptic plasticity, metabolic syndrome and neurocognition.

***Camellia sinensis* L.:** The *Camellia sinensis* is part of the Theaceae family, woody plants with simple leaves, with whole or toothed margin, more or less leathery. In the leaves, cauli and pith, they are present of the sclereids.

The *Camellia sinensis* is a small evergreen tree, 10-50 cm, leaves from ovato-sharp, with toothed margin and light green color, they are also velvety due to the presence of unicellular hairs. The flowers, with 6-9 petals, white in color, are solitary or grouped in 2-3 all axilla of the leaves, while the fruit is a capsule. In cultivation the plants are kept at a height of one meter to facilitate collection, which is almost always done by hand.

The tea plant which was first grown in China and is native to the forests Asian downpipes, it is widely cultivated in India [41]. Chinese monks and European traders introduced the plant to Japan, Srilanka and other countries. Today there are more than 3000 varieties of tea, each with its own distinct character and the varieties depend on the type of

leaves, the treatment and any fragrance. Commercially they divide into various types of green teas, in which the leaves are stabilized by jets of steam and rolled up. In this way the chlorophyll remains more or less intact and the color can be reinforced with the addition of indigo and turmeric. Black tea is produced by allowing the tea leaves collections to ferment completely before cooking. Depending on the treatment that the leaves undergo, the caffeine content does not change, but only the appearance and the fragrance.

The drug consists of the leaves which contain proteins, amino acids, carbohydrates, acid ascorbic and vitamins of group B. The most abundant components are caffeine, theobromine and theophylline and purine alkaloids. Heterosides of terpenic, aliphatic and aromatic alcohols, help to give the aroma to the tea, the phenols they are very abundant and vary according to the age of the plant. Acid is present chlorogenic and caffeic, epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECG) and epigallocatechin-3-gallate (EGCG), where EGCG accounts for approximately 10% by weight dry extract and it is this class that is used in prevention and in treatment of neurodegenerative diseases. The catechins differ structurally from other flavonoids for:

- lack of the double bond between positions 2 and 3 of the C ring;
- absence of the carbonyl group in position 4;
- presence of a hydroxyl group in position 3, which allows the flavanols to have two centers chiral on the molecule (on C2 and C3), therefore four possible diastereomers.

This plant is widely used in the treatment and prevention of this disease, in fact numerous studies have shown advantages in the use of epigallocatechin gallate (EGCG) in Alzheimer's disease, this catechin in particular should be avoided accumulation of amyloid proteins, oxidative stress and inflammation [42].

***Ginkgo biloba* L.:** The *Ginkgo biloba* is a plant belonging to the family Ginkgoaceae, constituted for the mostly from fossils. Not surprisingly, ginkgo is defined as a "living fossil", it is a dioecious tree, originally from China. In Japan it is considered a sacred tree and is planted near the temples, it reaches a height of about 40 cm and a trunk diameter of 1 meter. It has long branches with scattered leaves and short branches, the leaves are fan-shaped and traversed by dichotomous ribs without anastomosis.

The drug consists of the leaves, while the inner part of the seed contains 4'-methyl-pyridoxine, potentially toxic. The external part, strongly irritating, contains some toxic phenolic substances which, by simple contact, cause violent dermatitis and, by ingestion, digestive, circulatory and respiratory disorders. The leaves constitute the drug and contain two main types of substances endowed with interesting pharmacological properties of flavonoids and terpenes: diterpenes and sesquiterpenes in lactone form [43, 44].

Leaf extracts of *G. biloba* contain a number of bioactive components, including diterpenes, ginkgolides A, B, C, J and M, sesquiterpene bilobalide and a series of flavonoids (Figure 4). The effects synergists of these phytochemicals result in interactions with the nervous system central, which should attenuate the neurocognitive decline. In particular, the action of terpenes seems to aim at the regulation of synaptic transmission, through the vasodilation induced by nitric oxide, with a consequent increase in the blood, the elimination and cleaning of free radicals.

The *G. biloba* appears to intervene in oxidative stress processes that affect the fabric cerebral and, in particular, the content of glutathione, superoxide dismutase in patients with occluded cerebral artery, decreases with increasing age, but the pretreatment of such patients with Ginkgo extract, leads to an increase in superoxide and glutathione. Furthermore, this plant is able to prevent oxidative stress, increasing the PUFAs (polyunsaturated fatty acids in the erythrocyte membranes).

Clinical studies: The *G. biloba* is a plant with proven efficacy and venous insufficiency, for its marked action on the venous tone is, in fact, used in the treatment of varicose veins, venous insufficiency, thrombophlebitis and hemorrhoids. In this field the effects would be due to the action of vitamin P-similar to bioflavonoids at the level of the capillary walls, ginkgo seems to increase the blood flow in

order to protect neuronal tissue from ischemia and hypoxic damage. *Ginkgo biloba* plays an important role in the treatment of pathology, in particular the its effect is given by a synergy of various actions. The *G. biloba* has been shown to be a potent antioxidant, as it goes to eliminate and reduce the free radicals present in the blood, or oxygen free radicals, oxygen singlet and the hydroxyl radical. Recent studies have shown that treatment with Ginkgo extract could inhibit free radicals in cardiovascular ischemia [45].

- *G. biloba* and apoptosis: the increase in apoptosis, induced by reactive oxygen species (ROS) in mitochondria, plays a key role in aging. Recent studies have tried to demonstrate how apoptosis, induced by an excess of ROS, could be inhibited with a *Ginkgo biloba* based treatment . Free radicals were given to elderly rats to induce apoptosis in spleen cells. After approximately 14 days of treatment, the Ginkgo appears to have halved deoxyribose (dRib 4) in apoptotic cells, unfortunately no effect was seen with the same treatment in young mice.

In particular, the active component, which had this effect, was the bilobalide, used to prevent H_2O_2 induced cell apoptosis by inhibiting the activation of caspases mediated by mitochondria.

The *G. biloba* going to also act on caspases, enzymes that play a key role in regulate apoptosis. It is interesting to note that a reduced caspasic activity was 3/7 observed only in the short-term (4 months) treated groups with it, but not in the treated group long-term (12 months), indicating that Ginkgo treatment at a young age is more advantageous compared to when the treatment is given halfway. The results have demonstrated that pretreatment with flavonoids could improve cell viability e decrease the levels of Caspase-3, Caspase-6, Caspase-8, Caspase-9, Bcl-2 and Bax [45].

- Effects on circulation: the increase in blood flow produced by Ginkgo would appear be due to the latter's ability to increase calcium within the cell and produce vasodilation. The effect of EGB on calcium level was examined intracellular in rat aortic endothelial cells, using D-Galactose to induce an aging phenotype in cardiocytes and treatment with EGb could reduce diastolic Ca^{2+} and increase its reuptake [45]. Their research has shown that the sarco-endoplasmic reticulum (SERCA) played a role important in improving diastolic dysfunction of aged rats.

The main interest of *G. biloba* 's research was to improve memory as well such as antioxidant, anti-ischemic and anti-cancer effects. Other researches [46] focused on the prevention or treatment of ischemia and injuries from reperfusion by the extract and its terpenoid constituents, particularly in stroke and in myocardial infarction, in fact it has been noted that ginkgolide B is antagonist of the receptor PAFR [47]. PAF is a chemical mediator of inflammation, derived from a phospholipid, the plasmalogen and is released into the blood by basophils. It is a powerful stimulator of platelet aggregation, also exerts a series of effects on the cardiovascular system (induces vasodilation) and on smooth muscle (contraction of smooth muscle gastrointestinal, uterine and pulmonary). Ginkgolide B is widely used as an antagonist PAFR coupled with G proteins, which is present on major target cells of the inflammatory, immune and hemostatic system. Its ligands, the PAF lipids, by binding to the PAFR, trigger a series of intracellular signaling cascades and induce responses, they amplify inflammatory, thrombotic or apoptotic events [47]. Has been demonstrated that bilobalide inhibits the activation of phospholipase A2 and the breakdown of phospholipids in the rat hippocampus. Phospholipase A2 is responsible for the inflammatory process, as it recognizes the sn-2 acyl bond of phospholipids and induces its hydrolytic catalysis, releasing arachidonic acid and lysophospholipids, thus allowing the initiation of the arachidonic acid cascade [48].

- Action on amyloid β proteins : it has been observed that *G. biloba* may increase neuronal excitability and synaptic plasticity in the hippocampus of elderly rats, but not in the young rats. The β- amyloid precursor protein is known to play a key role in AD development. Ginkgo is able to decrease the level of the precursor protein of β - amyloid in PC12 cells, leading to an Alzheimer's disease-related mutation.

The experiments reported a reduction in the levels of insoluble Aβ and nitric oxide [47]. Ginkgo is also capable of suppressing the induced toxic

effects by Aβ peptides in hippocampal cells of rats, inhibiting the activation of protein kinase C (PKC), which blocks sodium nitroprusside (SNP). Some experiments have also been conducted on human patients, in the clinical trial 66 healthy volunteers, aged between 50 and 65 years, were subjected to treatment with ginkgo and placebo for 4 weeks. They found that Ginkgo could get better significant mental health and quality of life, neuropsychological processes, and mnemonics cognitive [47].

Dosage and contraindications: Over the past 20 years, about 2 billion daily doses (120 mg) of ginkgo; ginkgo's most important potential clinical problem is caused by its inhibition of platelet activating factor, consequently *G. biloba* cannot be taken in combination with warfarin (coumadin), aspirin or other anti-platelet agents. Also, this one feature prevents the plant from being administered together with other plants medicines such as ginseng, garlic, red clover and other coumarins of natural origin, as the latter interfere with coagulation, inhibiting vitamin K, that is deals with the synthesis of factors such as prothrombin and factors VII, IX, X. Rare side effects such as nausea, vomiting, headache and palpitations have been noted, but with the recommended dose these effects should not occur.

In particular, 120 to 240 mg per day in 2-3 doses are recommended for those suffering from dementia and neuronal problems, while for those who have peripheral vascular problems advise not to exceed 160 mg per day always divided into 2-3 doses [49].

Polyphenols and Alzheimer's disease

Polyphenols are naturally occurring secondary metabolites found in large quantities in fruits, vegetables, seeds, oils and other foods. They play an essential role in the protection of plants from ultraviolet light and against the aggression of pathogens or predators, contribute to pigmentation and facilitate growth and reproduction.

This class of molecules, which has more than 8000 structural variants, includes several secondary metabolites of plants characterized by the presence of aromatic rings with one or more phenolic functionalities. Polyphenols have been classified according to their source of origin, biological activity and chemical structure. In addition, most of the polyphenols found in plants exist as glycosides with different sugar units and acylated sugars in different locations of the polyphenolic skeleton [39, 50].

They are classified into:

1) phenolic acids, which include benzoic acids such as gallic acid and acids hydroxycinnamic acids such as caffeic, ferulic or coumaric acid [51-55];

2) flavonoids with general formula C3-C6-C3 [56];

Flavonoids can be further divided into different subgroups such as anthocyanins, flavan-3-oils, flavones, flavones, flavanones and flavonols. Generally flavonoids have the B ring connected to the C2 position of the C ring, however there are some flavonoids, such as isoflavones and neoflavonoids, which have the B ring connected in place C3 and C4 of the C ring [50]. Flavanols or flavan-3-oils are often commonly called catechins.

3) polyphenols with a non-flavonic structure such as stilbenes, the best known representative of which it is definitely trans-resveratrol [57-59].

Studies carried out on molecules belonging to this class have highlighted an activity beneficial on the prevention of diseases associated with oxidative stress such as cancer, atherosclerosis, inflammation and neurodegenerative diseases [60]. We could define polyphenols as free radical scavengers because they are able to give electrons to reactive radicals, making them more stable and non-reactive species. This anti-oxidative potential could be related to their complex chemical structure and phenolic content as compounds phenolics can indirectly prevent the chelation of transition metal ions, thus inhibiting the generation of reactive hydroxyl radicals (·OH) [40].

Plaque-inhibiting effects of Aβ were found in approximately polyphenols related to wine (myrectin, morine, quercetin). Similar effects were found in curcumin, rosmarinic acid, tannic acids, epigallocatechin gallate [50].

Resveratrol and clinical studies: Resveratrol is the most abundant component, it belongs to the

stilbenes class, that is found mainly in the skins of mulberries, vines and pomegranate. One is attributed to resveratrol possible antitumor, anti-inflammatory and blood thinning action, which can limit the onset of thrombotic plaques. Chemically it contains two phenolic rings linked by a double bond, which can undergo "cis- or trans isomerization" upon exposure to UV rays (Figure 5). It is referred to as a pleiotropic (multi-target) polyphenol because it exerts activity neuroprotective through the up-regulation of cerebral imbalance, of interaction with the pathways of signaling related to neuronal function and survival, of Aβ inhibition oligomerization, suppression of cholinesterase activity and finally inhibition of neurodegeneration.

Resveratrol has shown antioxidant power *in vitro* and *in vivo by* decreasing the generation of free radicals and superoxide ions. Therefore, its consumption can stop or prevent neurodegeneration and limit age-dependent neurocognitive decline [61-62].

- Resveratrol and accumulation of amyloid plaques

It was recently discovered that resveratrol controls the accumulation of Aβ *by* facilitating its proteolytic clearance in neuronal cells and reduces cerebral amyloid deposition *in live* in APP transgenic mice. This effect is given by the activation of AMPK, it is one Ser/Thr proteinase heterotrimeric kinase activated by several upstream kinases such as hepatic kinase B1. It is an enzyme that plays a critical role in cellular homeostasis, regulates cellular functions such as glucose uptake, fat oxidation, and formation of new mitochondria. Decreases with aging. The studies [61] found that resveratrol can activate AMPK and lead to the inhibition of mTOR, autophagy induction and proteolytic clearance of Aβ, reducing the levels of Aβ and the deposition of the amyloid protein in the cerebral cortex.

A further hypothesis concerning the anti-amyloid activity of resveratrol is attributed mainly to their ability to bind directly to the A β fibers , preventing further hybridization of Aβ and compromising their stability through metal-chelating activity, or the formation of non-toxic oligomers. This could be related to the direct effect of the polyphenols on amyloid precursor protein (APP) through inhibition of β -secretase (amyloidogenic) and / or activation of α-secretase pathways (non-amyloidogenic).

Resveratrol interacts with Aβ proteins and the two form a protein interaction polyphenol-Aβ which blocks the self-association of monomers Aβ 42 to form oligomers a low molecular weight. In this way the polyphenols could function as inhibitors A β 42 ; therefore, by modifying the polyphenolic structures, the pharmacokinetics will be improved effectiveness. The mechanism of inhibition of Aβ [40] is driven by hydrophobic interactions, involving the π-π bond between the planar faces of the structure polyphenolic and aromatic residues of Aβ 42 .

- Anti-inflammatory activity

Polyphenols also have anti-inflammatory activity, that is, they are able to suppress the release of pro-inflammatory cytokines, production of nitric oxide (NO) and prostaglandins (PGE2), as well as the generation of ROS.

This could be through the interaction of polyphenols with signaling cascades molecular and related processes that regulate inflammation.

Resveratrol is a potent NF-κB inhibitor with therapeutic potential against neuroinflammation. Administration of resveratrol (RESV) to rats led to reduction of hippocampal NF-κB, in addition, oral supplementation of RESV in healthy subjects for 6 weeks showed a suppressive effect on oxidative stress. Inhibition of NF-κB by RESV and its analogs [63] can reduce associated inflammation to AD through the increase of the erythroid nuclear factor 2, the reduction of enzymes apoptotic such as caspase-3 and metal peptidase.

However, the effective concentration of polyphenols to exert *in vivo* a potential of anti-oxidative scavenging is unattainable due to their very limited bioavailability.

It has therefore been suggested that, in lower quantities, typical of those achieved in the diet, polyphenols can exert a pharmacological activity [40].

- Anti-acetylcholinesterase activity

Acetylcholine (Ach) deficiency is one of the main pathological features of AD.

Vitis-derived polyphenolic extracts inhibit brain and serum AChE in AD rats. Rats given the extract, containing 1g of polyphenols, showed a cognitive recovery, increasing ACh and IL-6, inhibiting AChE, increasing the level of BDNF (the classic neurotrophic factor) and finally improving survival and plasticity neuronal [40].

- Polyphenols and Tau protein assembly

Recent studies [64] have demonstrated the ability of some polyphenols to intervene significantly in the assembly of the Tau protein. They have been used mice that contained the P301L mutant gene within their chromosome structure Tau protein. These mice were fed polyphenols and resveratrol and the results are been very positive, reducing the abnormal aggregation of the protein [65].

Quercetin: Another active ingredient present inside the red vine, but also in the blueberry and in the Red fruits in general is quercetin (Figure 5). It is also widespread in the species *Camellia sinensis* and in *Ginkgo biloba*. It is considered one of the most used bioflavonoids for the treatment of metabolic and inflammatory disorders [60].

It is considered a natural inhibitor of various intracellular enzymes:

- the 5α-reductase (type I) responsible for the conversion of testosterone into dihydrotestosterone (DHT);
- aromatase involved in the transformation of androgens into estrogens;
- some tyrosine kinases (TKs), including the epidermal growth factor receptor (EGFR);
- some calcium-phospholipid dependent protein kinases (PKCs);
- 5-lipoxygenase (produces leukotrienes, mediators of asthma inflammation);
- phospholipase A2, which degrades membrane lipids by generating arachidonic acid, which comes then transformed into prostaglandins, involved in inflammation;
- ornithine decarboxylase (ODC) which produces polyamines, known to be involved in cell proliferation.

Clinical studies: Quercetin has numerous properties:

- anti-inflammatory action: a cause linked to neurodegenerative diseases is inflammation constant nerve tissue. Numerous studies [66] have shown that quercetin can act as a neuroprotector of inflammation. Has been noticed that a quantity of about 10 - 30 μM of quercetin reduces the action of lipopolysaccharides induced by the release of NO.

This effect appears to be related to quercetin's ability to inhibit cyclooxygenase, reducing the action of NO synthase, involved in the production of NO in inflammatory process.

Quercetin showed a significant reduction in the levels of inflammatory mediators such as NO synthase, COX-2 and CRP in human hepatocytes [66]. In the rats, quercetin (80 mg equivalent dose) inhibited both acute and chronic and also showed significant anti-arthritic activity [66].

- Direct action on neurons: quercetin together with ascorbic acid reduces the incidence of oxidative damage to human lymphocytes and neurovascular structures. Flavonoids play a role crucial in the protection against neuronal lesions and exert neuroprotective actions within the brain, including the ability to protect neurons from induced injury from neurotoxins.

Several studies [66] have demonstrated the protection of quercetin (25 - 100 μM) in PC12 cells (rat pheochromocytoma) against various types of oxidative stress such as that induced by hydrogen peroxide.

Quercetin was shown to increase cell survival by reducing cell survival quantity of reactive oxygen, developed during oxidative reactions. In a study [66], 100 μM of quercetin reduced the production of free radicals caused by juglone, a quinone that generates a superoxide anion, in N2a cells (mouse neuroblastoma). Additionally, quercetin reduced plaque formation Aβ and protected the system against the neurotoxicity of Aβ 25-35 plaques .

There have actually been various conflicting results, in fact quercetin has given negative results on the protection of some stressed human PC12 and SH-SY5Y (human neuroblastoma) cells from hydrogen peroxide. These conflicting data may arise

because most of the studies were supported in a short and not prolonged time [66].

Dosage and side effects of flavonoids: Flavonoids are included in the list of the Ministry of Health "Other nutrients and other substances nutritional or physiological effect ". The recommended daily dose relative to the intake of flavonoids as a complex is 1 gram (1000 mg) per day, while for individual flavonoids present in the same list the recommended daily doses are:

quercetin 200 mg; quercitrin 300 mg; rutin 300 mg; spireoside or spirein 300 mg;

hesperidin 600 mg; hesperitin 300 mg.

Flavonoids also have other properties: they promote the protection of small vessels blood and improve circulation; strengthen the immune system; play a role in the loss of visceral fat and in maintaining good physical shape; they are involved in the prevention of various diseases, especially cardiovascular, inflammatory and neoplastic.

Flavonoids taken in high quantities can give rise to harmful effects, as they go to inhibit the action of some enzymes involved in metabolism. They are in fact not recommended in pregnancy because they cross the placenta.

Epigallocatechin gallate (EGCG): EGCG has many properties, in fact it is attributed to:

- Antioxidant and anti-inflammatory action: it has been reported [67] as the catechin is effective against free radicals and even stronger than vitamin E and C. In particular [68], the active ingredients have been classified according to their scavenger action (ECG> EGCG> EC> EC> EGC> EGC) and their order of potential antioxidant (EGCG≥ ECG> EGC> EGC> EC) [69]. With the increase in number of hydroxyls, the radical scavenging property becomes stronger, which implies that EGCG has greater scavenging activity, as it possesses a hydroxyl group in the B ring a portion of galloyl with three hydroxyl groups in the C ring [69]. EGCG increased SOD 3 activity [70] showing an effect protective against neurotoxicity, decreasing ROS and MDA. Oral administration of EGCG (2/3 cups per day) reported a significant reduction in the product levels of lipid peroxidation with high levels of enzymatic and non-enzymatic antioxidants. It was a complete reversal of the harmful effects of AlCl 3 was observed [69] on the activity of superoxide dismutase and a marked improvement in the activity of glutathione peroxidase, cytochrome C oxidase and acetylcholinesterase.

In addition to reducing oxidative stress, EGCG has an anti-inflammatory action. It is a potent inhibitor of leukocyte elastase which mediates the activation of metalloproteases of MMP-2 and MMP9 matrix (MMP), which further trigger inflammation [69]. Oral administration of EGCG *in vivo* has been shown to reduce significantly inflammation in pulmonary fibrosis, to block mediated angiogenesis 3 SOD is an extremely efficient enzyme that catalyzes the neutralization of superoxide from neutrophils in inflammatory models and to inhibit proinflammatory mediators such as myeloperoxidase in a dose-dependent manner [69].

- Chelating action [71]: EGCG acts as an antioxidant protecting the rat hippocampal neurons from stress-induced neuronal damage, performing an activity antioxidant on peroxynitrate/peroxynitrite produced after ischemia. Recently, it was established the central role of iron in neurodegeneration and recent studies have examined it the action of EGCG in the Fe 2 chelation process [69]. The accumulation of iron leads to the generation of reactive oxidative species that trigger oxidative stress and activate the inflammatory cascade; in the brain the accumulation of iron induces oxidative stress e reduction of neuromelanin levels, visible well before the clinical manifestation of disease, *in vivo* [69].

Dosage and side effects: The intake of catechins carried out appropriately and according to the recommended doses it is well tolerated by most people. Since the catechins represent a set of substances different from each other, with regard to any side effects and any drug interactions, it is good to seek the advice of the doctor. The main action of the catechins is to fight free radicals, which are highly reactive substances implicated in a slow chain reaction of damage leading to heart disease and cancer. The best known antioxidants are vitamins C, E and beta-carotene found in fruit, vegetables, grains and vegetable oils. Antioxidant compounds are also found in green and black tea as well there is growing evidence that these can help

protect us against cancer and the heart disease [41]. Catechins have therapeutic potential in against neoplastic and cardiovascular diseases as they are able to inhibit the action of free radicals, to protect the body from the development of tumors (which in part depends precisely from the damage caused to cellular DNA) and from their diffusion. They would have the capacity also to prevent the formation, inflammation and rupture of atheromas or plaques cholesterol involved in the neurodegenerative process.

Omega 3 and inflammation

The brain is able to change plastically in response to environmental stimuli. In particular, the hippocampus, a region involved in the modulation of learning, memory and status mood, is easily influenced by external stimuli.

It has been shown [72] that omega 3s can influence plasticity of the brain, it is no coincidence that aging is associated with decreasing brain levels of polyunsaturated fatty acids (PUFA) due to their reduced absorption. In fact, PUFAs have the ability to cross the blood-brain barrier and convert multiple chain fatty acids short into longer fatty acids.

Not surprisingly, several studies, based on the evaluation of regular consumption of fish or on blood biomarkers of n-3 PUFA suggested the potential preventive role of n-3 PUFA against age-related cognitive decline.

Omega 3 are defined fatty acids, these in general are monocarboxylic acids, a linear structure with even number of carbon atoms (Figure 6).

They usually have 4 to 28 carbon atoms, however, a lot of them, especially those that found in the brain, retina and spermatozoa, they have one more carbon chain long. According to the length of the chain they are classified into:

• Short-chain fatty acids (SCFA), also called volatile fatty acids (VFA), contain

from one to six carbon atoms;

• Medium-chain fatty acids (MCFA) have from seven to 12 carbon atoms (C7-12);

• Long chain fatty acids (LCFA) have 14 to 18 carbon atoms (C14-18) and they make up most of the fatty acids ingested with food (diet);

• Very long chain fatty acids (VLCFA) contain more than 20 carbon atoms(C> 20).

Omega 3 are fatty acids, defined as essential, in which the first double bond occupies the position 3. They are defined as essential because our body is unable to synthesize these fatty acids, in particular because it has enzymes that operate only in position 9 and 10.

Omega 3 or α-linolenic acid is synthesized from linoleic in algae and from these, through fish, comes to man. In general, monounsaturated fatty acids are distinguished from each other (MUFA) with a double bond in the carbon chain and polyunsaturated fatty acids (PUFA) with more than one double bond in the carbon chain.

Essential fatty acids perform two main functions:

- structural role: constituting the membrane phospholipids, they influence the permeability, the membrane fluidity and functionality;

- functional role: they are the precursors of prostaglandins, therefore, they influence the pressure arterial, cardiac function and platelet aggregation.

Proper supplementation of essential fatty acids is important, otherwise it could be run into serious problems, not surprisingly insufficient integration, especially in people elderly, it can lead to skin abnormalities, susceptibility to infections, capillary fragility, reduction of oxidative phosphorylation and mitochondrial damage, alteration in the biosynthesis of prostaglandins and slowed cholesterol metabolism with the formation of plaques arteriosclerotic.

Omega 3 and their role in neuronal plasticity and function: Omega-3 acids are incorporated into the cell membrane of many organs and tissues, especially the heart, nerve tissue and retina. Levels of eicosapentaenoic acid (EPA) acid docosahexaenoic (DHA) and polyunsaturated fatty acids (PUFA) are significantly decreased in the peripheral blood tissues of patients with dementia. DHA, which is present abundantly in the brain, it is

neuroprotective and contributes to normal functions cerebral. Furthermore, the oxidative products of PUFAs act as cell mediators and can be involved in improving neuronal health, neurogenesis and function neuronal through different mechanisms, resulting in reduction and resolution inflammation.

In vitro experiments have shown that EPA and / or DHA administration decreases the expression of proinflammatory factors such as inducible NO synthase (iNOS), cyclooxygenase (COX) 2, IL-1b, IL-6, TNFa and NF-kB, and regulates the cell-surface expression of the protein CD14 and Toll-like 4 receptors, involved in initiating the inflammatory response [73]. In humans, however, epidemiological and observational studies have established that higher concentrations of n-3 (2-4 g) imply a lower production of cytokines inflammatory. In elderly patients with chronic heart failure, n-3 supplementation PUFA led to reductions in plasma concentrations of TNF, IL-6 and the molecule of intercellular adhesion 1 (ICAM-1), suggesting that similar effects may be observed in the brain [73].

Omega 3s play an important role in maintaining the structure and function of the brain during aging. Many studies have shown their effectiveness in prevention hippocampal neuronal loss in AD-like neurodegenerative models. About recent interventional studies in mice have shown that n-3 PUFA in old age is able to counteract atrophy in specific brain regions age [72].

A recent retrospective cohort study in patients with mild cognitive impairment and AD showed improvements in cognition and less atrophy with long-term use (6-48 months) of fish oil supplements [72]. It should be noted that some of the benefits observed in the consumption of fish, could derive from other ingredients of the fish, such as vitamin D, as vitamin D deficiency has been linked to an increase in risk of dementia and AD.

Dosage and other benefits of fatty acids: Essential fatty acids have a positive effect on lipemia. Omega 3s reduce especially the triglycerides, while the omega 6 mainly improve the profile of cholesterol. Omega 3s have a very positive role in triggered dyslipidemias or aggravated by type 2 diabetes mellitus, they also reduce blood pressure in both subjects healthy, both in subjects with primary arterial hypertension. In addition to dyslipidemias, the Omega 3 also exert a beneficial role on certain lesions due to chronic hyperglycemia. In the right ratio and quantity, omega 3 and certain omega 6 are anti-inflammatory and lower the condition of systemic inflammation. Omega 3s have a protective function on the endothelium, improve venous circulation and promote the elasticity of the capillaries. In addition, they prevent atherosclerosis, thin the plasma and reduce aggregation platelet.

All these effects, combined with the impact on metabolic parameters, should reduce the possibility of cardio-cerebro-circulatory events such as heart attack and stroke. In the fetus and child, omega 3 they are necessary (in quantities exceeding the norm) to allow the development of the nervous system and the eyes. In pregnant women we recommend about 450 mg of omega 3 per day, this dosage ensures a right amount of omega 3 for the development of the fetus, as ours brain is made up of 60% fat and 20% Omega 3 fatty acids pregnancy and childhood, in many studies, it was found an insufficient intake of DHA, which it has a significant impact on the development of children's brains. Research shows that in children with Omega 3/DHA deficient diets have 50% fewer synapses and one study about the diet of 12,000 pregnant women showed that the children of those who consumed the lowest Omega 3 they had a higher chance of getting the lowest score on IQ test. The integration of this fatty acid is also recommended during breastfeeding, in fact, in a study that assigned 89 breastfeeding women 200 or 400 mg of DHA per day for 6 weeks, it was observed that the levels of DHA in maternal plasma and breast milk are increased, thus improving the ratio of fatty acids available to infants for infant brain development [74]. According to the Lams (Reference Intake Levels of Nutrients and Energy for Italian population), the adequate Omega 3 intake level for adults and the elderly is 250 mg of EPA + DHA per day, while adequate intake for children and adolescents is 250 mg per day of EPA + DHA, plus 100 mg of DHA up to 2 years of age. These doses have been shown to be helpful in proper memory functioning as well in the increase of psychic concentration. Omega 3 based supplements are

generally well tolerated, the adverse effects are usually related to the system gastrointestinal (diarrhea, stomach pain, belching and indigestion). Omega 3 supplements can have contraindications because they can increase the time it takes for blood to clot; for this they could be contraindicated in case of taking medications which can, in turn, affect it. In general, it is good to tell your doctor or pharmacist about all medications, supplements and herbal medicines that are taken, in particular: anticoagulants, antiplatelet agents, beta-blockers, diuretics, estrogen-based contraceptives, hormone replacement therapy and NSAIDs.

Other active ingredients used in the treatment of Alzheimer's disease

There are many active ingredients that are used for preventive purposes, among them we have homotaurine (3-aminopropansulfonate), a small natural compound identified in different species of red marine algae, originally extracted from the latter [75]. This compound appears to be very similar to taurine (2-aminoethanesulfonate), which is one of the most abundant free amino acids in the brain. The two molecules share one similar chemical structure, but homotaurine has an additional carbon which modifies the properties of the molecule. Furthermore, it is very similar to GABA, it is in fact an agonist of this receptor, especially the type A receptor. Homotaurine has been studied as a principle active adjuvant in the treatment of Alzheimer's disease (AD) and to counteract the progressive cognitive decline. Amyloid *β*-peptide is an important constituent of plaques senile in Alzheimer's disease; whose presence is associated with neuronal death. For its part, homotaurine binds to the soluble fraction of *β*- amyloid, inhibiting the formation of those neurotoxic aggregates that lead to the deposition of amyloid plaques in the brain and, thus, preventing the protein from taking a fibrillar form, consequently not soluble, thus avoiding its accumulation. Seeing as homotaurine and GAG share similar binding properties to amyloid, it can be hypothesized that homotaurine may also influence the processing of the APP protein, as already shown for some proteoglycans [75].

The *Curcuma longa* is another plant species widely used in the treatment of disease Alzheimer's, especially in recent decades, is a herbaceous, perennial, rhizomatous plant of the family of the Zingiberacee (one of the many species of the genus Curcuma), native to Asia south-eastern and widely used as a spice especially in Indian cuisine, medium-Eastern, Thai and other areas of Asia.

The roots that contain curcuminoids are used, the main of which is curcumin. There volatile fraction (3-5%) mainly contains terpene compounds, such as curcumol, *β* -turmerone and zingiberene. Minor constituents are arabinogalactans, ukonan acids A, B, C, D and some polyphenols, such as diferuloylmethane [6]. It has numerous properties, is used as an antiviral, anti-inflammatory, antioxidant, eupeptic and choleretic. Another fundamental action attributable to *Curcuma longa* , described extensively in the medical-scientific literature, is its use in the field oncological. It helps inhibit angiogenesis, a process implicated in development and in the proliferation of neoplastic cells and is a potent inhibitor of NF-kB because predominantly leads to a cellular apoptotic response [76]. Recent studies have shown that curcuminoids appear to be useful in treating such disease, as it hinders the formation and aggregation of the *β*-amyloid protein , implicated in the progressive degeneration of brain cells that characterizes this form of dementia.

A critical observation about the use of *Curcuma longa* in neurodegenerative diseases it is linked to its reduced overall bioavailability. In fact, if on the one hand the hydrophobicity of curcumin promotes the passage of the blood brain barrier and subsequent accumulation in the brain, on the other hand curcumin shows extremely low bioavailability, mainly due to its poor solubility in water, its poor stability in solution and intestinal first pass and rapid hepatic metabolism. The Recommended daily dosage ranges from 400 to 1,500 mg, divided into two to three administrations. A cyclical use is always indicated, for example, 3 months of recruitment followed by a month of wash-out and, therefore, by a possible resumption of the protocol.

Bacopa monnieri (BM) belongs to the family of adaptogens , which is also called brahmi and is widely used in Ayurvedic medicine.

The part used is made up of leaves and stem, which contain alkaloids, saponins, sterols. Some components (brahmin and herpestine alkaloids, saponins, D-mannitol, acid A, la monnierina) were isolated in India more than 40 years ago. Other active constituents were subsequently identified and include birch acid, stigmasterol, beta-sitosterol and some bacosides and bacosaponins.

The components responsible for the neuroprotective action are bacosides, in particular have an antioxidant action (via redox and enzymatic induction), inhibit acetylcholinesterase and activate choline acetyltransferase, reducing and preventing the accumulation of the β protein amyloid. *Taken* together, these mechanisms of action would allow *B.monnieri* to increase the transmissibility of the nerve impulse, contributing to the restoration of activity synaptic, to carry out a neuroprotective and neuroreparative action and to carry out an action antioxidant [6]. The dosage range for the dry extract titrated at 20% in bacosides A and B is between 100 and 400 mg per day.

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Figure 1. The main aglycones of ginsenosides present within *Panax ginseng*: 20S-protopanaxadiol (left) and panaxadiol (right).

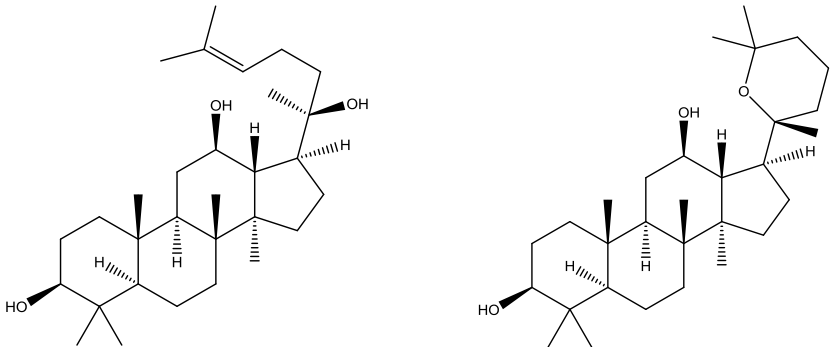


Figure 2. Structure of eleuteroside A (left) and eleutheroside B (right) in *Eleutherococcus senticosus.*

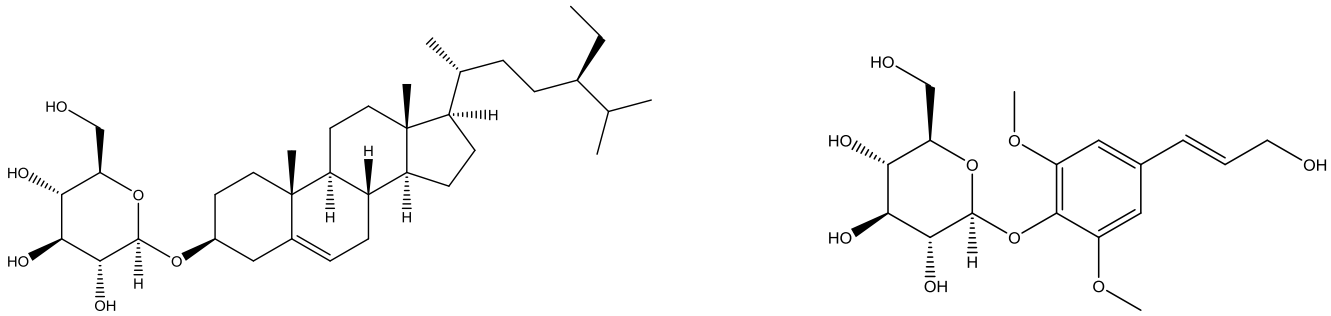


Figure 3. Some withanolides present *Withania somnifera*

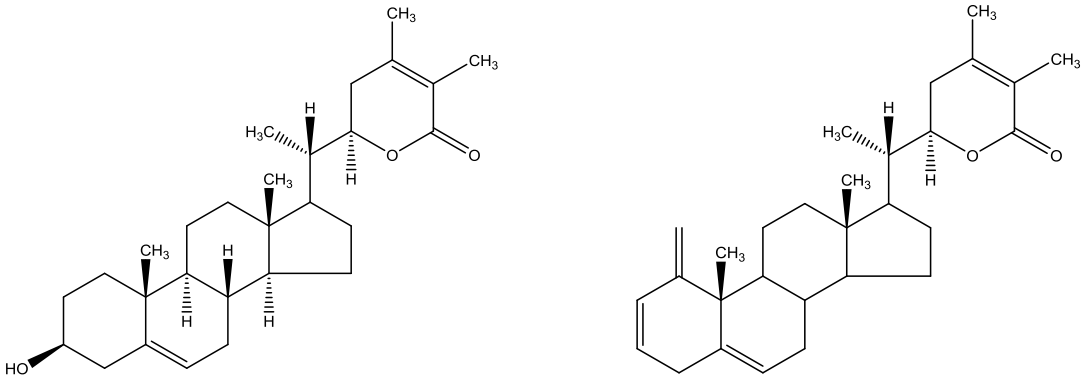
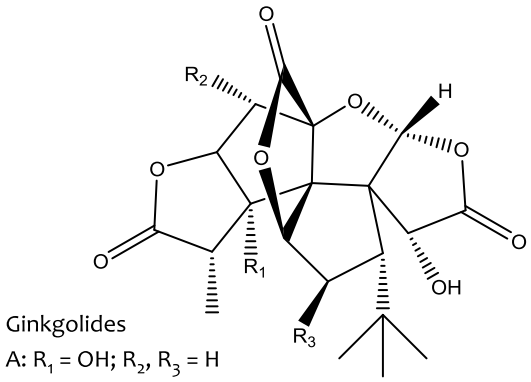
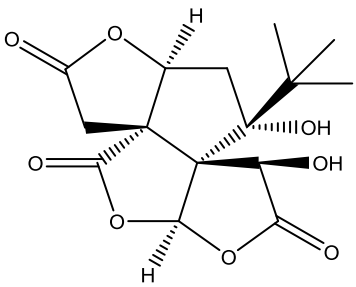


Figure 4. Ginkgolides (A, B and C) and bilobalide present within *Ginkgo biloba*



Ginkgolides
A: R_1 = OH; R_2, R_3 = H
B: R_1, R_2 = OH; R_3 = H
C: R_1, R_2, R_3 = OH



Bilobalide

Figure 5. Structure of resveratrol (left), quercetin (middle) and epigallocatechin-3-gallate (EGCG, right).

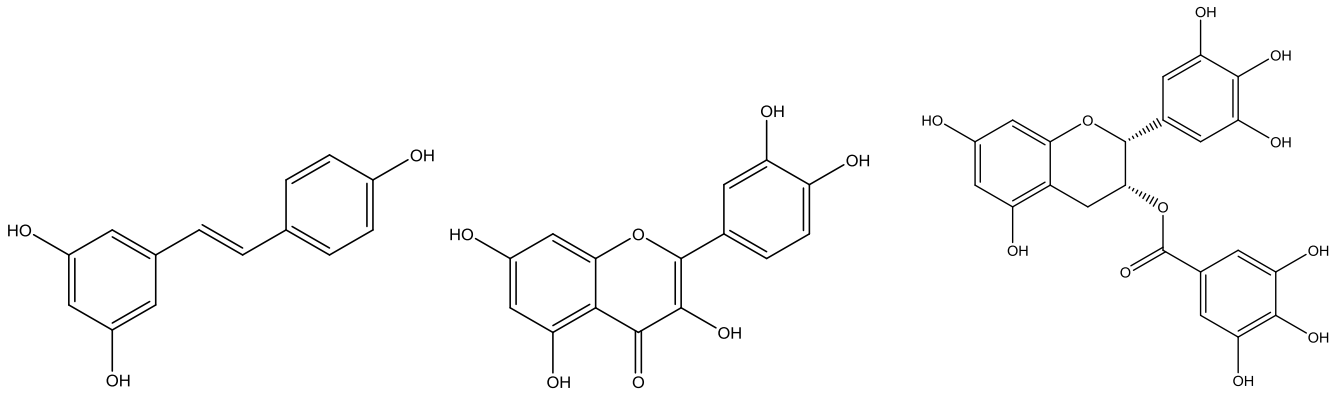
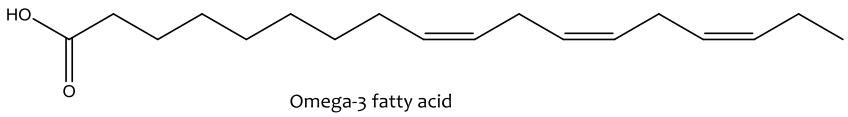
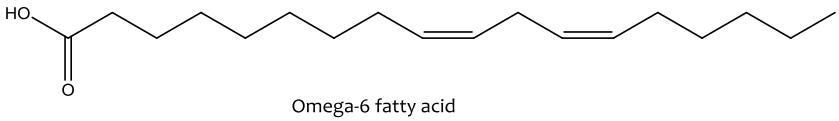


Figure 6. Structure of Omega 3 and Omega 6 fatty acids



Omega-3 fatty acid



Omega-6 fatty acid