Possibilities of herbal medicine for Alzheimer's diseaseYu.A. Smirnov, T.A. Smirnova, Z.S. Plieva, V.G. Zhukhovitsky

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The potentialities of phytotherapy for Alzheimer's disease

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SUMMARY

Alzheimer's disease is a neurodegenerative brain disease that causes memory damage and impaired social behavior. Alzheimer's disease is currently an incurable disease, so the search for new treatments for this disease is very urgent. Along with the development of new synthetic preparations, research is being carried out for substances of plant origin. The review provides general information about Alzheimer's disease, summarizes scientific data on the activity of herbal medicines. The mechanisms of action of biologically active substances of medicinal plants are considered.

Key words: Alzheimer's disease, amyloid beta (Aβ), medicinal plants, biologically active substances.

RESUME

Alzheimer's disease is a progressive neurodegenerative disorder and the leading cause of cognitive and behavioral impairment in societies. The cause of Alzheimer's disease is unknown. Therefore, the search for new drugs is very important. Along with the search of new synthetic drugs surveys of substances of plant origin are conducted. Data on potentialities of phytotherapy for Alzheimer's disease and effective substances from medicinal plants are summarized in the overview with attention for their mechanisms of action.

Keywords: Alzheimer's disease, β-amyloid (Aβ), medicinal plants, biologically active substances.

INTRODUCTION

Neurodegenerative brain diseases have been known for a long time. Alzheimer's disease (AD) - senile dementia, was first described in 1907 by the German psychiatrist Alzheimer [12]. In 1977, this disease was singled out as an independent nosological unit due to the prevalence of the disease and the need to find the causes of its occurrence and methods of treatment. The incidence of asthma in the world in 2006 was 26.6 million people, and by 2050 the number of patients is predicted to quadruple [13]. AD is currently an incurable disease, therefore therapy is aimed at combating the symptoms and manifestations of the pathological process and, if possible, slowing it down. Herbal medicine, like BA drug therapy, is symptomatic. Herbal medicine is a complementary treatment. Therapy with herbal preparations for this disease is very common, since it rarely has side effects on the body, in contrast to chemical agents. Along with the search for new synthetic drugs, research is being carried out for substances of plant origin. It is known that biologically active substances (BAS) from medicinal plants have a wide range of pharmacological activity [3].

Alzheimer's disease pathogenesis

Currently, there is no complete understanding of the causes of AD. The features of the pathogenesis of the disease are the accumulation of amyloid plaques and neurofibrillary tangles of tau protein in the brain tissues [8]. There are several hypotheses about the mechanism of the onset of cerebral dysfunctions characteristic of this disease. According to the cholinergic hypothesis, the disease is caused by a decrease in the synthesis of the neurotransmitter acetylcholine. This hypothesis is considered

unlikely. However, anticholinergic drugs are used to suppress cholinergic effects, such as the initiation of amyloid aggregation, leading to a generalized neuroinflammatory process [64].

In 1991, the amyloid hypothesis was proposed, according to which the cause of the disease is deposition in the human brain of beta-amyloid (Aβ) (42 amino acids), which causes disruption of neural connections and cell death, which leads to degeneration of the brain substance [24]. The amyloid hypothesis is currently the main one. However, the reason for the accumulation of Aβ in brain tissues is unclear.

Along with the amyloid hypothesis, the tau hypothesis is being studied, according to which neurofibrillary tangles arising from disturbances in the structure of the tau protein are detected in the brain tissues. This assumption about the causes of AD development is recognized as relevant along with the hypothesis of amyloid deposits. The reasons for the violations have not been identified either [49].

Thus, the formation of amyloid plaques and neurofibrillary tangles of tau protein in the brain tissues is currently considered the main cause of AD. But even this hypothesis does not allow explaining all the variety of manifestations in AD. Amyloid plaques, which form first in the tissues of the hippocampus and then spread to the entire brain, prevent the organ from performing its functions. Aβ increases the concentration of calcium in brain cells, which causes damage. The second type of deposits, neurofibrillary tangles found by Alzheimer's in the brain of a deceased patient, are composed of insoluble tau protein, which also interferes with normal brain function.

Germs and Alzheimer's

More recently, the amyloid hypothesis of AD has been further developed. It has been suggested that changes in the composition of the intestinal microbiota may be associated with the appearance of certain human pathologies, such as AD, neurodegenerative syndrome associated with the cerebral accumulation of Aβ fibrils. Dysbacteriosis and disturbance in the composition of the intestinal microbiota contribute to this [26]. The gut microbiota plays a fundamental role in modulating the bidirectional signaling underlying the gut-brain axis [14]. The gut microbiota consists of 10^{14} microorganisms, mainly bacteria, as well as bacteriophages, viruses, fungi and archaea [50]. It has been shown that bacteria that make up the intestinal microbiota can secrete a significant amount of amyloids and lipopolysaccharides, which can play a role in modulating signaling pathways and producing proinflammatory cytokines associated with AD pathogenesis [57]. Indirectly, a strong innate immune response activated by bacterial amyloids can stimulate neuropathogenic signals that promote amyloid aggregation and inflammatory degeneration of brain cells [80]. The data of studies of the properties of amyloid proteins of the cell surface of microorganisms are summarized in detail, demonstrating the important role of pili, curley, tafi, and some other fibrillar proteins of bacteria in the colonization of the host organism [2].

Various strains of bacteria are capable of producing a unique class of functional amyloids called curli. They are essential for biofilm formation, bacterial adhesion to host cells, and colonization of inert surfaces. Curli have common biochemical and structural characteristics with amyloid plaques in the brain of patients with neurodegenerative diseases [9]. Curli is the main protein component of the complex extracellular matrix produced by many enterobacteria. Curli were first discovered in the late 1980s in strainsEscherichia coli. They were involvedin many physiological and pathological processes E. coli and Salmonella spp. Structure andthe biogenesis of kurli is unique among the bacterial outgrowths known to date. Structurally and biochemically, curli provides a unique system for studying the macromolecular aggregate of amyloid in bacteria and for studyingin vivo formation of amyloidplaques in the mammalian brain [10]. Microbial amyloids can be examined and manipulatedin vivo and in vitro with Congo red dye [60]. This simple method is useful for screening antiamyloid drugs.

Microbes can enter the brain [73]. Dysfunction of the blood-brain barrier (BBB) in AD leads to an increase in the amount of Aβ in the brain. In inflammatory processes, the capture of Aβ by pericytes increases, which leads to their death. Pericytes are part of the walls of small blood vessels [74].

Few pathogenic microorganisms are able to penetrate the BBB. These include meningococci (Neisseria meningitidis), streptococci (Streptococcus pneumoniae), Haemophilus influenzae, Listeria, Escherichia coli and others. The exact mechanism of penetration of these pathogens through the BBB is not fully understood, however, it has been shown that inflammatory processes affect this mechanism [19]. So, inflammation caused by Listeria can lead to the BBB becoming permeable to these bacteria. Having attached to the endothelial cells of the capillaries of the brain, Listeria secrete lipopolysaccharides and toxins that affect the BBB and make it permeable to leukocytes. Leukocytes that have penetrated into the brain tissue trigger an inflammatory process, as a result of which the BBB also allows bacteria to pass through [19]. Pneumococci secrete an enzyme of the hemolysin group, which forms pores in the endothelium through which bacteria penetrate [22]. Meningococci andE. Coli undergo BBB transendothelial [nineteen].

Thus, bacterial amyloids from the gastrointestinal tract through the BBB can also directly contribute to progressive neuroamyloidogenesis [80]. These data indicate how biofilm-forming bacteria can contribute to the progression of several immunological and neurological diseases and point to Aβ as a potential molecular target for their treatment.

Alzheimer's disease herbal medicine

As the prevalence of AD increases in the 21st century, there is an urgent need to develop effective pharmacotherapy. Currently, drug treatment of AD is aimed at the symptoms of the disease and does not stop the progression of the disease. Therefore, natural preparations of biologically active substances of medicinal plants are being actively investigated for use in BA therapy. Herbal medicine for AD uses the same medicinal plants as for any other diseases of the nervous system, since so far no BAS of medicinal plants have been found that would treat this particular disease. Herbal medicine is used as a treatment in addition to medication. Therapy with herbal preparations for this disease is very common, since it rarely has side effects on the body, in contrast to medications. Table 1 shows biologically active substances of medicinal plants used for the treatment of AD. Some of these plants help in the prevention of AD, while others improve memory, cognitive functions and general well-being of patients. But the main target of AD treatment at present is the accumulation of amyloid plaques and neurofibrillary tangles in the brain tissues.

Table 1

BAS of medicinal plants used in Alzhemer's disease

Plant name	Family	Connection class	BAS	Link
Sowing onion (Allium sativum)	Onion (Alliaceae)	Disulfides	S-allyl-L-cysteine	6
Angelica chinese (Angelica sinensis)	Umbrella (Umbelliferae)	Essential oils tannins	Z-ligustilide, Ferulic acid	16, 27, 79
Astragalus membranous (Astragalus membranaceus)	Legumes (Fabaceae)	Alkaloids	Cycloastragenol	44, 69, 79
Water hyssop (Bacopa monniera)	Amaryllidaceae (Scrophulariacea)	Alkaloids	Reserpine chloromazine	20, 72, 79

Arbor vitae (Biota orientalis)	Cypress (Cupressaceae)	Labdanoids	Pinusolides	51, 79
Chinese tea (Camellia sinensis)	Tea rooms (Theaceae)	Flavonoids	Epigallocatechin gallate	6
Centella asiatica (Centella asiatica)	Umbrella (Apiaceae)	Triterpene saponins	Hydrocotylin, Hersaponin	6, 71
Clitoria trifoliate (Clitoria ternatea)	Legumes (Fabaceae)	Squirrels (amino acids)	Histidine, threonine	59, 79
Coptis rhizome (Coptidis rhizoma)	Buttercup (Ranunculaceae)	Alkaloids	Berberine	7
Long turmeric (Curcuma longa)	Ginger (Zingiberaceae)	Polyphenols	Curcumin	6, 75
Teasel rough (Dipsacus asper Wall)	Teasers (Dipsacaceae)	Saponins	Saponins	58, 78, 79
Evodia rutoparny (Evodia rutaecarpa)	Root (Rutaceae)	Alkaloids	Dihydroephodiamine	56, 79
Snowdrop (Galanthus nivalis L.)	Amaryllidaceae (Amaryllidaceae)	Alkaloids	Galantamine	54
Gastrodia high (Gastrodia elata)	Orchid (Orchidaceae)	Glucosides, alcohols	Gastrodin, p-hydroxybenzyl alcohol	23, 36, 79
Ginkgo biloba (Ginkgo biloba)	Ginkgo (Ginkgoaceae)	Flavonoids	Kaempferol Quercetin	11, 40, 46, 53, 67
Serrated ram (Huperzia serrata)	Floating (Lycopodiaceae)	Alkaloids	Huperzine A	77
St. John's wort (Hypericum perforatum)	Hypericum (Hypericaceae)	Flavonoids	Hyperforin	35, 37, 39, 79
Indigo natural (Indigo naturalis)	Umbrella (Apiaceae)	Alkaloids	Indirubins	6, 41
Dereza Berber (Lycium barbarum)	Nightshade (Solanaceae)	Polysaccharides	Polysaccharides (LBP)	17, 28, 34, 76
Melissa officinalis (Melissa officinalis)	Lipocytes (Lamiaceae)	Polyphenols	Rosmarinic acid	4
Narcissus mixed (Narcissus confusus)	Amaryllidaceae (Amaryllidaceae)	Alkaloids	Galantamine	45, 54
Tobacco (Nicotiana tabaccum)	Nightshade (Solanaceae)	Alkaloids	Nicotine	6, 25–52
Real ginseng (Panax ginseng)	Aralievs (Araliaceae)	Terpenes	Ginsenosides Rg1, Rg2, Rg3	18, 28, 33
Istod thin-leaved (Polygala tenuifolia)	Source (Polygalaceae)	Saponins	Tenuifolin, tenuigenin	32, 55, 79
Calamus root (Rhizoma acori)	Aroid (Araceae)	Phenols	Eugenol, asarone	6, 30
Schisandra chinensis (Schizandrae chinensis)	Magnolia (Magnoliaceae)	Lignans	Schisandrin	65, 79

Fender Wilford (Tripterygium wilfordii)	Euonymus (Celastraceae)	Terpenes	Celastrol	5, 63
Uncaria gambir (Uncaria gambir)	Madder (Rubiaceae)	Terpenes	Uncarin E	48, 79
Cultural grapes (Vitis vinifera)	Grape (Vitaceae)	Phytoalexins	Resveratrol	31, 61
Vitania sleeping pills (Withania somnifera)	Nightshade (Solanaceae)	Alkaloids	Scopolamine	21, 79

One of the most effective remedies today is Ginkgo Biloba, or Ginkgo biloba (Ginkgo bilŏba). In clinical practice, various drugs are used forbased on Ginkgo Biloba, which regulate vascular tone, normalize blood circulation, improve memory, and also have a calming effect [1]. Ginkgo Biloba is found in other medicines. For example, EGb 761, which contains Ginkgo Biloba, has been shown to inhibit the aggregation of Aβin vitro and attenuates reactive oxidative processesin a model organism [46]. However, there are studies of several American medical institutes that indicate the absence of a noticeable effect of improving cognitive abilities in healthy people, and there was no positive effect on the manifestations of dementia in old age.

Ginseng (Pánax) is one of the most popular plants in herbal medicine. It containspowerful anti-inflammatory biologically active substances - ginsenosides [1]. Shown in a cellular model system, ginseng treatment significantly reduced Aβ levels. It was also shown that some ginsenosides reduce the concentration of Aβ in a dose-dependent manner. Ginsenosides Rg1, Rg3, and RE significantly reduce the amount of Aβ in animal brains. The authors believe that ginseng itself or purified ginsenosides can be used to treat AD [18].

Melissa (Melissa officinalis) is often used as a sedative forprevention and treatment of insomnia and improvement of brain function [1]. In 2003, scientists conducted a small but convincing experiment: 42 patients with mild to moderate asthma took either a placebo or lemon balm extract for 4 months. Lemon balm supplementation compared with placebo showed a clear improvement in cognitive function [4].

Ashwagandha (Withania somnifera) inhibits amyloid plaque formation and protects the brainfrom BA. According to studies in mice, ashwagandha alleviates the effects of oxidative stress [21]. This process of damage to brain cells makes a significant contribution to the development and progression of senile dementia. Therefore, the authors recommend: with age, you should increase your intake of foods rich in antioxidants.

Centella asiatica (Centélla asiática) of the Apiaceae family. In an alternativeIn medicine, Centella asiatica has long been used as a stimulant and tonic. In Ayurveda, it is considered an important anti-aging agent that strengthens brain cells, enhances intelligence, improves memory and even prolongs life [1]. In 2003, in experiments on rats, it was shown that Centella asiatica has a positive effect on oxidative stress and improves cognitive functions, slowing down the development of AD [39]. Also, this plant is a component of many drugs for rehabilitation after traumatic brain injury and the treatment of neuro-emotional disorders.

Turmeric (Cúrcuma) is a genus of monocotyledonous herbaceous plants of the ginger family (Zingiberaceae). These include turmeric longa (Curcuma longa), other names - turmeric home (Curcuma domestica), turmeric, which is cultivated as a spice andmedicinal plant. Turmeric has long been used in Ayurveda as a powerful analgesic, antiseptic, bactericidal and wound healing agent. Turmeric rhizomes and stems contain essential oils and yellow dyes (curcuminoids) [1]. The main curcuminoid is curcumin (polyphenol). Curcuminoids also include dimethoxycurcumin and

bis-dimethoxycurcumin. Curcumin possesses anti-cancer, antioxidant, anti-inflammatory and anti-amyloid action.

Curcumin is being extensively researched as a drug in both experimental animals and human volunteers. The molecular structure of curcumin suggests its potential for binding to Aβ. A 2005 study by American scientists on cell culture and two models (mouse and rat) showed that turmeric clears Aβ from the brain. In experimentsin vitro curcumin blocked aggregation Aβ and disaggregated its fibrils. Researchin vivo have shown that curcumin, administered peripherally in elderly animals,crossed the BBB and associated with Aβ plaques in the brain. These data show that low doses of curcumin effectively disaggregates Aβ and prevents the formation of Aβ fibrils and oligomers [75]. In addition, turmeric inhibits the breakdown of nerve cells, protecting the brain from the dangerous effects of chronic stress. It is assumed that the antidepressant effect of curcumin is realized through the inhibition of monoamine oxidase [38]. The other two curcuminoids also contribute significantly to the effectiveness of AD treatment. Turmeric has immunomodulatory properties. Was shownin vitro that one of the minor curcuminoids, bisdemethoxycurcumin, isan immunomodulator that stimulates phagocytosis of Aβ by monocytes [15]. The mixture of curcuminoids represents turmeric in its medicinal value better than curcumin alone, which makes this mixture more promising in the fight against AD [70].

Curcumin is an amyloid-specific dye similar to Congo red. Curcumin has been shown to bind to all cellsEscherichia coli and isolatedthey were smoked with amyloid fibers [47]. The ability of curcumin to stain Aβ made it possible to determine its localization and amount in the brain of patients using positron emission tomography (PET). Recently, American scientists conducted volunteer studies on the effects of long-term curcumin supplementation on cognitive performance in older people.in vivo. Vthe study involved 40 people aged 51 to 81 years. Half of the volunteers took curcumin (90 mg twice daily) for 18 months, and the other half took a placebo. At the beginning and end of the dosing period, urine curcumin and the presence of Aβ and tau proteins in the brain were measured by PET. Participants' cognitive ability (memory) was tested using a standardized test. Analysis of PET scans showed a decrease in the amount of both tau proteins and Aβ in the amygdala and hypothalamus of the participants who took curcumin. Researchers concluded that curcumin halts cognitive decline (improves mood) in old age by reducing the number of pathological forms of proteins associated with AD: this means

Thus, in experiments in vitro and in vivo, curcumin has been shown to inhibitformation and disaggregation of Aβ plaques, weakens hyperphosphorylation of tau protein and enhances its clearance, inhibits acetylcholinesterase and is an antioxidant. In conclusion, curcumin has great potential to be a more effective drug than current AD treatments. However, curcumin as a therapeutic agent has low bioavailability and is insoluble in water. If the problem of low bioavailability is overcome, curcumin preparations for AD can be actively used in clinical practice [68]. Many companies are trying to develop a modified version of turmeric with maximum absorption. Clinical trials are underway to measure plasma levels of turmeric in patients. Japanese scientists have partly solved this problem by reducing the particle size of turmeric to nano-size. Nanoparticles do not precipitate in a liquid for a long time. This turmeric is called teracurmin. This drug increased the effectiveness of the antiamyloid activity of turmeric by 30 times [62].

CONCLUSION

From the moment BA was described for a long time, it was terra incognita. Neither the reasons, nor the means, nor the methods of treatment of this serious disease, as a result of which a person turns into a meaningless, helpless creature, were known. The last 30 years have been

large-scale studies of BA in many laboratories around the world.

From the hypotheses put forward for the causes of AD, the "amyloid hypothesis" is being intensively developed by neuropathologists, biochemists, geneticists and other specialists. The main objects of research are the formation of amyloid plaques and neurofibrillary tangles of tau protein in brain tissues. Microbiologists have shown that the microflora of the gastrointestinal tract contributes to the progression of AD and indicates Aβ as a potential molecular target for its treatment.

Herbal medicine has made a significant contribution to the search and creation of effective drugs against AD. Several medicinal plants and their biologically active substances have been found with antiamyloid activity. Particular hopes are pinned on turmeric and its biologically active substances - curcuminoids. Turmeric is believed to help stop the active development of neurodegenerative diseases in old age. Residents of India, for example, who actively consume curry (a mixture of turmeric with coriander and caraway seeds), are much less likely to get AD.

Research is ongoing.

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Possibilities of herbal medicine for Alzheimer's disease / Yu.A. Smirnov, T.A. Smirnova, Z.S. Plieva, V.G. Zhukhovitsky // Traditional medicine. - 2018. - No. 4 (55). - S.20-28.