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PHYTODRUGS COMBINED WITH PHARMACOTHERAPY AGENTS FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES (RESEARCH LITERATURE REVIEW)

Actuality. *In Ukraine and in the world as a whole, neurodegenerative diseases are widespread, the number of which is not decreasing, such as Parkinson's disease, Huntington's disease, Alzheimer's disease and amyotrophic lateral sclerosis, multiple sclerosis.*

Neurodegenerative diseases arise from the neurons of the cortex and spinal cord. Each of these diseases has its own pathogenesis and classification of recommended drugs. In recent years, a certain group of these drugs is occupied by medicinal products of plant origin or their combinations with approved drugs, which helps to increase medical care for patients and makes it more targeted.

The aim of the study. *Identify the main existing drugs for the treatment of neurodegenerative diseases, identify herbal drugs that can be included in complex pharmacotherapy.*

Materials and methods. *Based on the data of domestic and foreign studies on the use of medicinal products for the treatment of neurodegenerative diseases, as well as the possibility of their combination with herbal drugs according to the data of SCOPUS, "Web of Science", Google Scholar and others, the direction of activation of the use of herbal drugs in the treatment of these diseases is shown.*

Research results. *The pathogenesis and mechanisms of the occurrence of such diseases as Parkinson's disease, Huntington's disease, Alzheimer's disease and amyotrophic lateral sclerosis, multiple sclerosis have been determined. The main names of drugs prescribed for these diseases and their mechanisms of action are described. The main herbal drugs that can be used in neurodegenerative diseases in addition to the basic therapy in order to increase efficiency and improve the condition of patients are indicated.*

Conclusions. *Phytodrugs are recommended to be used as concomitant treatments for Parkinson's disease, Huntington's disease, Alzheimer's disease, amyotrophic lateral sclerosis, and multiple sclerosis. Focused attention on the mechanisms of action of these means. The herbal drugs that can be included in the pharmacotherapy of neurodegenerative diseases are listed.*

Key words: *neurodegenerative diseases, phytodrugs, efficiency enhancement.*

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ФІТОПРЕПАРАТИ ЯК ЗАСОБИ ДЛЯ ЛІКУВАННЯ НЕЙРОДЕГЕНЕРАТИВНИХ ЗАХВОРЮВАНЬ (ОГЛЯД ЛІТЕРАТУРИ)

Актуальність. *В Україні й у світі загалом поширені нейродегенеративні захворювання, як-от хвороба Паркінсона, хвороба Гентінгтона, хвороба Альцгеймера і бічний аміотрофічний склероз, розсіяний склероз, кількість яких не зменшується. Нейродегенеративні захворювання виникають унаслідок нейронів кори та спинного мозку. Кожне із цих захворювань має свій патогенез і класифікацію рекомендованих лікарських засобів. В останні роки певну групу цих препаратів займають лікарські засоби рослинного походження або їх комбінації із затвердженими препаратами, що допомагає збільшити медичну допомогу хворим і робить її більш цілеспрямованою.*

Мета роботи – *визначити головні сучасні лікарські засоби для лікування нейродегенеративних захворювань, виявити фітопрепарати, які можна включати в комплексну фармакотерапію.*

Матеріали та методи. *На підставі даних вітчизняних і зарубіжних досліджень щодо застосування лікарських засобів для лікування нейродегенеративних захворювань, а також можливість їх комбінації з фітопрепаратами за даними SCOPUS, «Web of Science», Google Scholar та інших показано спрямованість активізації використання фітопрепаратів під час лікування цих хвороб.*

Результати дослідження. *Визначено патогенез і механізми виникнення таких захворювань, як хвороба Паркінсона, хвороба Гентінгтона, хвороба Альцгеймера і бічний аміотрофічний склероз, розсіяний склероз. Надано головні назви лікарських препаратів, які призначають за цих хвороб, та описано механізми їх дії. Вказано основні фітопрепарати, які можливо використовувати за нейродегенеративних захворювань додатково до базової терапії з метою підвищення ефективності та покращення стану пацієнтів.*

Висновки. *Фітопрепарати доцільно використовувати як супутні засоби за хвороби Паркінсона, хвороби Гентінгтона, хвороби Альцгеймера і бічного аміотрофічного склерозу, розсіяного склерозу. Акцентовано увагу на механізмах дії цих засобів. Перелічено фітопрепарати, які можна включати до фармакотерапії нейродегенеративних захворювань.*

Ключові слова: *нейродегенеративні захворювання, фітопрепарати, посилення ефективності лікування.*

Introduction. Actuality. Neurodegenerative diseases are a group of hereditary or acquired diseases of the nervous system during life. An important effect of these diseases is the progressive death of nerve cells, which leads to various neurological symptoms, primarily dementia and movement disorders (Connors et al., 2020; Belenichev et al., 2023–2025).

Today, neurodegenerative diseases include a large group of central nervous system diseases, the pathogenesis of which is the irreversible death of neurons in certain parts of the brain or spinal cord. However, damage to neurons in neurodegenerative diseases occurs in different departments of the CNS and is typical for each disease:

– in Parkinson's disease and Huntington's disease, the death of neurons of the basal nuclei is observed, which leads to movement disorders;

– in Alzheimer's disease, the neurons of the cortex and hippocampus die, which leads to the appearance of cognitive disorders;

– in amyotrophic lateral sclerosis, the death of spinal, trunk, cortical motoneurons, characterized by muscle weakness, was determined;

– in multiple sclerosis, demyelination of nerve fibers is observed.

Despite the existence of active psychotropic drugs, the treatment of these conditions remains symptomatic and does not change the active course of the disease. Basic and herbal preparations are included in the treatment of these diseases, taking into account the mechanism of their action.

The purpose of the study is to determine the main existing drugs for the treatment of neurodegenerative diseases, to identify herbal preparations that can be included in complex pharmacotherapy.

Research methods. Based on the data of domestic and foreign studies on the use of medicinal products for the treatment of neurodegenerative diseases, as well as the possibility of their combination with herbal preparations according to the data of SCOPUS, "Web of Science", Google Scholar and others, the direction of activation of the use of herbal preparations in the treatment of these diseases is shown.

Research results and their discussion. Parkinson's disease is a chronic neurodegenerative disease that occurs as a result of neurophysiological lesions in the tissues of the central nervous system. During its development, the nuclei of the extrapyramidal system are affected, it is characterized by tremors of the hands, head, and muscles with general stiffness, bradykinesia, and brodyphrenia (slowing down of mental processes). It is important that non-motor symptoms also appear in patients with parkinsonism: neuralgic disorders due to stroke, brain injury, chemical poisoning, overdose of neuroleptics and others (I.N. Karaban et al., 2017).

The basis of the pathogenesis of parkinsonism is a violation of the balance of mediators in some structures of the central nervous system (basal nuclei, substantia nigra, etc.), which is characterized by a decrease in the amount of dopamine and an increase in the release of acetylcholine. The substantia nigra in parkinsonism gradually discolors, as the neurons containing the pigment neuromelanin die in it.

This pigment is formed from catecholamines – dioxyphenylalanine (DOPA), dopamine. Serotonergic, GABA-ergic and other systems can also participate in the pathogenesis of parkinsonism.

Most drugs for the treatment of parkinsonism affect either the formation of dopamine (levodone with carbide or benzperacid) or its accumulation (bromocriptine, pramipexole, ropinerol), MAO B inhibitors (selegiline, rasagiline, safinamide), KOMT inhibitors (entacapone). Accumulation of dopamine in the synaptic cleft of NMDA receptors, inhibition of glutamatergic influence, increased release of dopamine from presynaptic endings (I.N. Karaban et al., 2016).

Central m- and n-cholinoblockers (trihexyphenidyl, cyclodol, biperidine) are included in the means that suppress cholinergic influence.

Neuronal disorders in Parkinson's disease are explained by incorrect folding of α-synuclein, which leads to the formation of protein aggregates (Lewy bodies) in the brain.

According to the classification, antiparkinsonian drugs belong to:

– dopamine derivatives precursors of dopamine synthesis (levodopa+carbidopa, levodopa+benserazide), i.e. decarboxylase inhibitors are added to dopamine. It is also possible to add entacapone – a catechol-O-methyltransferase inhibitor;

– medicines that increase the content of dopamine in the synaptic cleft;

– dopamine receptor agents (bromocriptine, ropinirole, pramipexole, rotigotine, piribedil);

– monoamine oxidase type B inhibitors (selegiline, rasagiline);

– catechol-O-methyltransferase inhibitors (entacapone, tolcapone).

1. Means that increase the content of dopamine in the synaptic cleft: increase the extracellular concentration of dopamine by increasing its release and inhibiting its reuptake in presynaptic nerve tissues due to the effect on NMDA receptors (amantadine).

2. Acetylcholine antagonists (trihexyphenidyl, orphenadrine, procyclidine). Blockade of muscarinic receptors reduces the inhibitory effect on dopamine nerve endings, which compensates for the lack of endogenous dopamine.

Agonists of cannabinoid receptors (tetrahydrocannabinol, cannabinol) became the first herbal medicines for the treatment of Parkinson's disease. The activity of CB 1–2 receptors improves the survival of dopamine-producing neurons, exhibits an antioxidant effect (M.T. Kabir et al., 2022).

One of the main alkaloids that has anti-amyroid activity is myrecithin, which affects superoxide dismutase and causes depolymerization and destabilization of fibrils, so it is an important component in the treatment of neurodegenerative diseases (S. Sharma et al., 2023). A remedy obtained from bergamot with the use of nanotechnology showed activity in dementia (Scuteri, Sandrini et al., 2021). Bergamot extracts had a significant effect on the neuropathogenesis of pain, including in patients suffering from dementia. Extracts were prescribed in the form of aromatherapy. Successfully treated chronic, neuropathic pain (Scuteri, Sakurada et al., 2022).

Extracts of plants of the genus Bistoria have a wide range of applications – treatment of rheumatism, tuberculosis, inflammatory diseases, including respiratory tract. Recently, references to the presence of antitumor, anti-inflammatory, protoxic, antimicrobial effects appeared in the literature, and in recent years, their effectiveness in diabetes and neurodegenerative diseases was established (Javid et al., 2024).

Herbal remedies and preparations from algae are often prescribed for neurodegenerative diseases due to their antioxidant, anti-inflammatory activity, ability to influence protein metabolism, delay the development of amylosis. In addition, these agents can reduce the level of glucose in diabetes, prevent brain ischemia (Hannan et al., 2020; Li et al., 2020; Ding et al., 2019).

To enhance the effect of existing means for the treatment of Parkinson’s disease, Ayurveda collections are increasingly being consulted and the properties of herbal preparations are compared with synthetic ones, so turmeric, mucuna, and ginger preparations are often added to enhance antioxidant properties and anticholinesterase anti-inflammatory properties, which helps to increase the effectiveness of treatment (Deka et al., 2023).

Activation of CB-1 receptors can contribute to the release of dopamine, which is the basis for the use of cannabinoid drugs for the treatment of Parkinson’s disease. Activation of CB-2 receptors in Parkinson’s disease improves survival of dopamine-sensitive neurons (Ranieri et al., 2016; Lim et al., 2017) and dopamine-producing neurons due to stimulation of superoxide dismutase formation (Hill, 2015).

Currently, the search for phytodrugs that can increase the effectiveness of the treatment of Parkinson’s disease

continues. These phytoremedies were applied based on the works of Ayurveda and allow to increase the content of dopamine, have anti-inflammatory and anticholinesterase activity. Among them are well-known extracts of turmeric (Curcuma longa), mucuna pruriens, ginger (Zingiber officinale), Bacopa Monnieri (Bacopa Monnieri), Indian spikenard (Nardostachys jatamansi), ashwagandha (Withania somnifera), milk thistle (Silybum marianum). All these plants contain a complex of polyphenols and play a role in neurotransmission, pass through the blood-brain barrier, and affect the vascular system. All plant extracts have antiviral, bactericidal and anti-inflammatory activity. Some of these herbal remedies are included in antiparkinsonian therapy in some countries (Aijaz et al., 2024).

One of the main properties of these herbal remedies is the minimal amount of side effects when used. phytodrugs show anti-inflammatory, antioxidant, anticholinesterase effect at the same time. These effects are manifested in turmeric preparations. Special attention is paid to plants containing curcumin due to their immunomodulatory properties. Plant extracts that can be prescribed for Parkinson's disease have been identified. Due to the useful general pharmacological properties and effectiveness in neurodegenerative diseases, these extracts have been studied experimentally and in the clinic. All of them had anti-inflammatory effects, regulated apoptosis, mitochondrial dysfunction, affected GABA-ergic and glutamate systems, had effects on monoamine oxidase activity, serotonin depletion, and estrogen protection (Acero et al., 2023).

The pharmacological activity of these plants has been established in the experiment and in the clinic, which confirms their effectiveness in neurodegenerative diseases (N. Sharma et al., 2021).

It has been established that in Parkinson's disease, neurodegenerative disorders are associated with digestive tract activity disorders. Plants that contain polyphenols capable of affecting the cerebrovascular and immune systems may be used in neurodegenerative diseases (Chatterjee et al., 2024).

For Parkinson's disease, Ayurvedic plants were prescribed in the form of extracts. Extracts of these plants are prescribed in many countries for Parkinson's disease. These include: turmeric extract (Curcuma longa), mucuna pruriens, ginger (Zingiber officinale), Bacopa monnieri (Bacopa monnieri), spikenard (Nardostachys jatamansi), ashwagandha (Withania somnifera), milk thistle (Silybum marianum). These plant extracts were prescribed together with levodopa. Plant extracts were able to realize anti-inflammatory, antioxidant, anticholinesterase activity and had a negligible number of side effects (Deka et al., 2023).

All additional means contributed to the reduction of the manifestations of Parkinson's disease, possibly eliminating mitochondrial dysfunction. α-arbutin is thought to reverse mitochondrial dysfunction in Parkinson's disease. In addition, the level of ATP increased, motor functions were restored. Thus, α-arbutin protects against the manifestations of Parkinson's disease (Ding et al., 2019).

Curcuma longa, Mucuna pruriens, Zingiber officinale, Bacopa monnieri, Nardostachys jatamansi, Withania somnifera, Silybum marianum were studied in in vitro and in vivo experiments simulating the conditions of Parkinson's disease. It was established that the dopamine content of the experimental animals decreased. The above-mentioned plant extracts turned out to be dopamine agonists and restored the motor functions of animals. The appointment of herbal remedies made it possible to use them as auxiliary means for the treatment of the disease.

From herbal preparations, well-known, widely prescribed drugs in cardio-neurological practice, such as quercetin, curcumin, epigallocatechin, which pass well through the blood-brain barrier, are added to the treatment regimen for Parkinson's disease. They are effective in almost all neurodegenerative diseases (Madhubala et al., 2024).

Some of the herbal remedies can reduce the muscle pain observed in patients with parkinsonism. This is due to the effect on protein aggregation, regulation of mitochondrial dysfunction, cation transport, reduction of inflammation and oxidative stress. This is noted in the plants of alfinium, valerian, acorus calamus. All these data are obtained in experimental studies, clinical trials have not yet been conducted (Yin et al., 2021).

When treated with dopamine mimetics, especially levodopa, the drug most of all eliminates the manifestations of akinesia and restores the ability to concentrate. tremors and other hyperkinetic phenomena are less treatable. Trihexyphenidyl (Cyclodone) Reduces tremor to a greater extent, has less effect on bradykinesia.

Medicines with antioxidant and neuroprotective effects increase the effectiveness of the treatment of Parkinson's disease by preventing the oxidative stress of cytokines and cerebrolysin (Demchenko & Biriuk, 2021; Gonchar et al., 2022). The introduction of bone marrow mesenchymal stem cells has been proposed for the treatment of parkinsonism (Pyatikop et al., 2014). In recent years, scientists have been paying more and more attention to herbal preparations in the treatment of neurological diseases.

To increase the content of dopamine, it is also recommended to use antagonists of glutamate receptors (amantadine sulfate). It increases the dopamine content

by increasing the release of dopamine, blocking the reuptake mediated by NMDA receptors.

Amantadine stimulates the release of dopamine from drug endings, reduces the reuptake of dopamine in the synapse, inhibits the glutamatergic effects of the frontal cortex on the striatum and has a pronounced NMDA-blocking effect. As an antagonism of glutamate receptors, amantadine is able to realize its effect at the level of excitotoxicity.

Therefore, it is advisable to prescribe antagonists of central M-H cholinergic receptors (trihexyphenidyl, orphenadrine, rasagiline, procyclidine) to reduce the effect of cholinomimetics on dopaminergic nerve endings, compensating for the lack of endogenous dopamine (I. Karaban et al., 2013).

From herbal preparations, cannabinoid preparations (tetrahydrocannabinol, cannabidol) began to be recommended, which can activate CB-1 receptors, reduce the activity of, for example, glutathione and the function of mitochondria. Its effectiveness increases the ability to pass through the blood-brain barrier. To some extent, it can be considered as a reference plant antioxidant in neurodegenerative neurological diseases (Jiang et al., 2023).

Saffron and its derivatives (crocin, crocetin, picrocrocin, safranal) also have a protective effect in plants against neurodegenerative diseases. This active ingredient is very effective in amphotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease, Huntington's disease, and Alzheimer's disease. Later, greater activity of metabolites in Parkinson's disease was established, antioxidant, anti-inflammatory, immunomodulatory activity and practically no toxicity were determined (Abdian et al., 2024).

Most articles emphasize that it is carotenoids that, thanks to their antioxidant properties, have a protective effect against neurodegenerative diseases. They accumulate in certain areas of the brain, activate microglia, and have an anti-inflammatory antioxidant effect (Kabir et al., 2022).

Huntington's disease is a neuropsychiatric disorder with an autosomal dominant inheritance pattern. The results of genetic testing indicate an expansion of the CAG trinucleotide repeat in the gene located on the chromosome. The main symptom of the disease is the development of disorders of cognitive functions and the rapid appearance of disorders of executive function, i.e. the speed of information processing, the ability to organize and plan, but the inability to learn and remember. Cognitive impairment and associated behavioral abnormalities often precede the onset of characteristic motor disturbances such as bradykinesia and choreiform movements. Common symptoms include depression, irritability, anxiety, obsessive-compulsive symptoms, and apathy, and psychosis is less common.

On average, the age of patients at the time of detection of Hettington's disease is approximately 40 years, although it can significantly differ from the indicated figure. At the beginning of the disease, it is inversely proportional to the level of expansion of the CA6 space. Young-onset Hettington's disease (under 20 years) is often characterized by bradykinesia, dystonia, and rigidity, rather than the choreiform movements typical of adult-onset disease. This disease is progressive and inevitably ends in death. Disturbances in behavior may include pronounced apathy, disinhibition, impulsivity, and decreased criticality, with apathy often gradually increasing. Early motor disturbances may consist of the appearance of twitching of the limbs, as well as mild apraxia (difficulty in making purposeful movements), especially when performing actions that require the involvement of fine motor skills. With the further development of the disease, other motor symptoms appear, in particular, gait disturbances (ataxia) and postural instability. Motor disorders over time negatively affect speech (dysarthria), as a result of which it becomes very difficult to understand the patient, which causes him deep frustration. In the later stages, motor disorders significantly affect gait due to the progression of ataxia, and eventually the person loses the ability to walk. The terminal stage of the disease of the motor system significantly complicates the process of eating and swallowing, which is usually the main cause of death due to aspiration pneumonia.

Sometimes herbal remedies are included in the treatment regimens for Huntington's disease. So, for the treatment of neurodegenerative diseases, it is recommended to include quercetin, resveratrol, catechins, and genistein. All these agents can restore the activity of mitochondria, and polyphenols play a significant role in this (Hakeem et al., 2021). In addition, plant compounds have been identified that have a targeted effect in Huntington's disease, such as curcumin, quercetin, epigallocatechin, gallate, epigenin, and carotenoids. These compounds cross the blood-brain barrier well and reduce the manifestations of neurogenetic diseases (Madhubala et al., 2024).

In Hettington's disease, it is recommended to prescribe herbal preparations containing flavonoids, which are characterized by antiviral, antiallergic, antitumor, thrombolytic, antiapoptotic, and antioxidant effects (Faysal et al., 2024).

Alzheimer's disease is a progressive degenerative disease characterized by a decrease in cognitive abilities, the development of behavioral disorders that lead to disability, frequent development of dementia with Lewy

bodies or vascular dementia. The prevalence of dementia increases dramatically with age. Difficulty remembering and recalling recent events is typical of Alzheimer's disease. Changes in the metabolism of the structure of neurons are observed in many parts of the brain tissue, especially in the hippocampus, the main part of the midbrain. Currently, the standards of diagnosis and treatment of this disease have been established (Trufanov, 2018).

The mechanisms and etiology of Alzheimer's disease were first proposed in the form of the cholinergic hypothesis, according to which the disease is caused by a lack of acetylcholine. Subsequently, the amyloid hypothesis appeared, which suggests that the disease develops due to the deposition of β-amyloid (Aβ) aggregates in the brain – proteins with a molecular weight of 4200. In parallel, the tau hypothesis arose, according to which hyperphosphorylation of the tau protein leads to the disruption of neurofibrils in the neuron body and the development of the disease.

Inflammation can play the role of an activator and initiator of the disease, and β-amyloid is considered as its trigger. Different forms of the disease can be associated with gene mutations. Alzheimer's disease is accompanied by the loss of neurons in many areas of the brain, especially in the hippocampus and the main part of the forebrain. Loss of cholinergic neurons in the hippocampus and frontal cortex is a hallmark of the disease and underlies cognitive deficits and short-term memory loss.

Alzheimer's disease is characterized by two morphological features: the formation of extracellular amyloid plaques, consisting of amorphous β-amyloid deposits, and intracellular neurofibrillary tangles containing abnormally phosphorylated tau protein.

In addition to typical forms of Alzheimer's disease, atypical forms are distinguished. The following are considered diagnostic biomarkers of the disease:

– genetic biomarkers: apolipoprotein E4 (APOEε4), β-amyloid precursor (AβPP), presenilins 1 and 2 (PSEN1 and PSEN2), BIN1, CLU, PICALM and others.

– cerebrospinal fluid biomarkers: Aβ1-42, tau protein, phosphorylated tau amyloid.

– blood biomarkers: Aβ40, Aβ42, predictors of protein and lipid metabolism.

– structural neuroimaging: generalized brain atrophy, more pronounced in the medial temporal regions, including the hippocampus.

– functional neuroimaging: bilateral hypometabolism and hypoperfusion in the temporal cortex.

The main drugs for the treatment of Alzheimer's disease include cholinesterase inhibitors: donepezil, rivastigmine, galantamine (acetyl- and butyrylcholinesterase inhibitors), with the exception of donezepil, which is a selective acetylcholinesterase inhibitor. All acetylcholinesterase inhibitors promote cholinergic transmission, slowing down the degradation of acetylcholine, which leads to the improvement of cognitive functions caused by disturbances in cholinergic transmission. They have a different duration of pharmacological action (donezepil up to 24 hours, galantamine, rivastigmine up to 8 hours). There are also data on the possibility of using cholinesterase inhibitors in combination with the direct m- and n-cholinemimetic choline alfoscerate (Carotenuto et al., 2017).

In patients who are additionally prescribed choline alfoscerate microglia β-amyloid, neurotoxicity is reduced and cognitive functions are preserved. Of course, direct m- and n-cholinomimetics, in particular choline alfoscerate, are also prescribed for dementia (Chystyk, 2019; Gorbachenko & Lukyanetz, 2020). Significant severity of mood disorders (anxiety, depression, apathy) was observed, while in another group receiving donepezil, the frequency and degree of severity of these phenomena increased.

The NMDA receptor agonist memantine is more effective for the general treatment of Alzheimer's patients (Schneider, 2011). It has a longer half-life, and its side effects include headache, dizziness, drowsiness, constipation, shortness of breath, and hypertension. It is used for moderate and severe Alzheimer's disease.

Among herbal preparations, agonists of cannabinoid receptors (tetrahydrocannabiol, cannabidiol) are primarily noted. They stimulate CB1 and CB2 receptors, which leads to inhibition of microglial activation by β-amyloid, reduces neurotoxicity and helps preserve cognitive functions (Hill, 2015).

Many extracts from southern plants can be given to the elderly to slow the onset of Alzheimer's disease. They have an effect on consciousness, improve memory, so they can be used in neurodegenerative diseases.

Their mechanism of action is related to the blockade of acetylcholinesterase and the reduction of beta-amyloid formation, and also has a neurotrophic and antioxidant effect. Preclinical studies have established that these extracts can be taken in Alzheimer's disease.

These plants have an antioxidant effect, protect nerve cells, and increase mental abilities. St. John's wort is one of them (Suryawanshi et al., 2024).

Dementia development factors are considered to be:

1. Age – it is with age that the risk of developing both Alzheimer's disease and Parkinson's disease, atherosclerosis, stroke, arterial hypertension, heart disease, and diabetes increases. Changes occur in neurons and DNA.

2. Genetic factors – a number of genes have now been identified that increase the risk of developing dementia, for example, APOE.

3. Lifestyle – reduced mental, physical and emotional activity increases the risk of developing dementia.

4. Environmental factors – aluminum, iron, car exhaust gases can increase the risk of developing dementia.

In addition to standard drugs for the treatment of Alzheimer's disease, medicinal products of plant origin are also prescribed.

Alzheimer's disease is one of the indications for the use of medical cannabis and cannabinoids (Belendiuk et al., 2015).

This is due to the stimulation of CB1 receptors, which leads to inhibition of β-amyloid activation of microglia and reduction of neurotoxicity (Suryadevara et al., 2017).

In the treatment of Alzheimer's disease, liquid and dry extracts of plants cultivated in China, other Asian countries, and also in some regions of Europe are widely used.

Ginkgo biloba preparations, which have antitoxic, antitumor, neuroplastic, neurotransmitter and anti-inflammatory effects, are especially often used in the treatment of neurodegenerative and cardiovascular diseases.

Their effectiveness is explained by the content of flavonoids, terpenes, lactones, proanthocyanids, amino acids and other biologically active compounds, which determines their activity in neurodegenerative diseases (Peng et al., 2024; Xu & Cock, 2023).

Plants have been identified, the active substances of which can have an immunomodulatory effect and contribute to the elimination of symptoms of COVID-19, such as fever, cough, pneumonia, anxiety.

Overlying such plants are: Chenopodium quinoa, Chuquiraga spinosa, Croton lechleri, Lepidium meyenii, Mauritia flexuosa, Maytenus macrocarpa, Physalis peruviana (Choi et al., 2024).

Green tea extract had an anti-inflammatory effect in skin diseases and acts on mucous membrane warts. In some cases, phytoimmunotherapy can complement synthetic remedies (Tabolacci et al., 2023).

One of the dangerous diseases, in the treatment of which the use of herbal preparations is proposed, is melanoma, which is complicated by atypical transformation of the melanin pigment under the influence of radiation. Melanoma is characterized by heterogeneity and the ability to metastasize. At the same time, BRAF kinase is activated. The target on which the drugs vemurafenib (Vemurafenib), dabrafenib (Dabrafenib) and encorafenib (Encorafenib) acted was identified.

Trimetinib, binimetinib, and colometinib are proposed for targeted therapy, which prevent the progression of melanoma. Currently, it has been established that melanoma is an immunogenic disease that is amenable to immunotherapy, but this complicates treatment. Melanoma progresses through several mechanisms, so the use of immunotherapy is considered possible. This leads to the need to find non-toxic phytoremedies for the treatment of melanoma, in particular, those with immunomodulatory properties (Behl et al., 2021).

Indeed, a number of sources indicate the presence of immunomodulatory activity of plants and their metabolites. Green tea extract has a therapeutic effect on inflammatory markers (IL-6, IL-1β) of interest. Currently, there are no phytodrugs that have therapeutic properties for melanoma. However, their use may be able to reduce the dosage of chemotherapy drugs (Tabolacci et al., 2023).

Mini plant extracts proposed in Ayurveda are recommended for the prevention of severe dementia (Hanafy et al., 2020). There is information on the feasibility of combining melanin and donepencil with plant extracts that protect mitochondria (Imran et al., 2024).

Amyotrophic lateral sclerosis is a neurodegenerative disease, which is accompanied by the death of central and peripheral neurons, constant progression and lethality. In recent years, the progression of the disease has been observed in all age groups.

The disease is mainly diagnosed in people of mature and working age with high intellectual and professional potential, which leads to their disability and death.

The development of the disease is facilitated by genetic factors, oxidative stress, excitotoxicity, formation of protein aggregates, disruption of autophagy processes, neuroinflammation, disruption of post-transcriptional modification of RNA, as well as axonal transport and mitochondrial dysfunction (Bräuer et al., 2018; Ramesh & Pandey, 2017; De Vos & Hafezparast, 2017).

Amyotrophic lateral sclerosis is the most common form of neurodegenerative disease, leading to paralysis and eventual death. Dysfunction of motor neurons is a typical sign.

It has been established that already in the early stages of amyotrophic lateral sclerosis, there is a violation of the transmission of electrical impulses from one neuron to another, which is associated with the release of a significant amount of glutamate, which has a toxic effect. Suppression of antioxidant activity in neurons of the spinal cord and brain causes their damage by oxygen free radicals. In amyotrophic lateral sclerosis, a disturbance in upper neurons is associated with changes in the transmission of excitation to the spinal cord, motoneurons, and skeletal muscles. Also, with amyotrophic lateral sclerosis, the exchange of lipids and DNA is disturbed, and pro-inflammatory cytokines accelerate the further degradation of motor neurons.

A drug approved by the FDA for the treatment of amyotrophic lateral sclerosis is riluzole (Brizol) (Chy-

styk, 2019). Riluzole is a benzodiazole derivative that blocks the release of glutamate, i.e. reduces glutamate neurotoxicity. The drug inhibits the release of glutamate, inactivates voltage-dependent sodium channels, competitively blocks N-methyl-D-aspartic acid receptors. Riluzole also stimulates G-protein-dependent pathways of nerve impulse transmission. The drug protects motor neurons from the excitotoxic effect of glutamate and prevents the death of cerebral cortex neurons in hypoxia. Due to the blockade of glutamate neurotransmission, the muscle relaxant and sedative effect of the drug, as well as its anticonvulsant effect, were revealed in the experiments. It is believed that it increases life expectancy.

Sometimes it is also recommended to prescribe edaravone (Xavron). Edaravone inhibits lipid peroxidation by binding free radicals. Thanks to its action, it absorbs both water-soluble and fat-soluble peroxyl radicals, transferring an electron. The drug can absorb water-soluble peroxyl radicals that initiate chain chemical reactions, as well as fat-soluble peroxide radicals that support this chain. This drug is prescribed for amyotrophic lateral sclerosis and in the treatment of stroke. In the literature, there is information about the possibility of using the drug Dysport in amyotrophic lateral sclerosis. Dysport is a botulinum toxin of the A-hemagglutinin type.

Among herbal preparations for the treatment of amyotrophic lateral sclerosis, the addition of cannabinoids as part of complex pharmacotherapy is recommended (Whiting et al., 2015; Bonini et al., 2018). Among other herbal remedies for amyotrophic lateral sclerosis, those containing polyphenols such as genistein, resveratrol, and quercetin are noted for their antioxidant properties and antiapoptotic effect (Hakeem et al., 2021). Herbal preparations for the treatment of amyotrophic lateral sclerosis should contain antioxidant components that not only suppress oxidative stress, but also have an anti-inflammatory effect and reduce glutamate release (de Oliveira et al., 2023). In amyotrophic lateral sclerosis, the effectiveness of resveratrol and quercetin is emphasized, which, in addition to their antioxidant effect, also have anti-aging properties. This confirms the expediency of their appointment in this disease (Monteiro et al., 2023).

In amyotrophic lateral sclerosis, plant extracts containing carotenoids are recommended, which suppress oxidative stress, normalize the transmission of excitation in motoneurons, and have an anti-inflammatory effect (Kabir et al., 2022).

Taking flavonoids in amyotrophic lateral sclerosis prevents damage to neurons. Extracts of these plants have practically no side effects. In addition to normalizing nervous activity, flavonoids have anti-inflammatory, antiviral, anti-allergic, anti-apoptotic and anti-thrombotic effects, restore the content of cytochrome C (Faysal et al., 2024).

Multiple sclerosis is the most common demyelinating disease of the nervous system, which leads to the disability of people of young working age. After 10 years from the onset of the disease, approximately 50% of patients are able to move around only with the help of outsiders (Rommer & Zettl, 2018).

Multiple sclerosis affects women more often, but the adverse course of the disease is also noted in men. Timely and targeted treatment allows delaying the onset of disability. The latest scientific research is devoted to the study of the etiology, pathogenesis and clinical diagnosis of multiple sclerosis. Its development is associated with demyelination, due to which work capacity can be impaired already at the age of 20–30 years (Skliar et al., 2020).

Although the pathogenesis of the disease is not yet fully understood, among the main causes of the development of multiple sclerosis are:

1. Genetic predisposition – more than 200 genetic risk factors are known.
2. Implementation of hereditary predisposition under the influence of external factors.
3. Viral infections, including Epstein-Barr virus, herpes simplex viruses, herpes type 6, cytomegalovirus, chlamydial infections, endogenous retroviruses.
4. Vitamin D deficiency.
5. Smoking.
6. Changes in the gut microbiome and other factors

Some of the intestinal bacteria are triggers because they contribute to the launch of autoimmune processes in multiple sclerosis. Other bacteria, on the contrary, can be protectors, because they contribute to the formation of immune tolerance, which protects against excessive allergic reactions.

The composition of persistent viruses also has a certain genetic component. As a result of the interaction of these factors, an autoimmune response is initiated. The effector stage of the immunopathological response in multiple sclerosis has been studied quite fully, and the T-cell link of immunity plays a significant role in it (Ontaneda et al., 2015; Macaron & Ontaneda, 2019).

The initial step is the activation of $CD4^+$ T lymphocytes, called helper (Th) cells, outside the central nervous system. These cells are the main initiators of the pathological process in multiple sclerosis. Their activation occurs under the influence of pro-inflammatory cytokines, in particular tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). Molecular mimicry of viruses and double expression of T-cell receptors are the main triggering mechanisms for starting the pathological process. Many

bacterial and viral antigens, such as the Epstein-Barr virus, have amino acid sequences homologous to autoantigens of the nervous system. This leads to the initiation of a pathological autoimmune response of T-lymphocytes, subject to the appropriate immune status of the body.

The initial step is the activation of $CD4^+$ T-lymphocytes, called helper cells (Th), in the periphery outside the CNS. These cells are the main initiators of the pathological process in multiple sclerosis. Their activation occurs under the influence of pro-inflammatory cytokines – tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). The main triggering mechanisms of activation of the pathological process are molecular mimicry of viruses and double expression of T-cell receptors. Many bacterial and viral antigens, such as the Epstein-Barr virus, have amino acid sequences homologous to autoantigens of the nervous system. This is what causes the pathological autoimmune response of T-lymphocytes to be triggered, given the corresponding immune status of the organism. Another variant of activation is the presence of a part of T-lymphocytes with two receptors: one for a bacterial antigen, the other for an autoantigen. During a bacterial infection, their activation occurs, which triggers an autoimmune pathological process. While resting T cells have limited ability to enter the brain and spinal cord, activated T cells express many molecules, including chemokines, adhesion molecules, metalloproteinases, and reactive oxygen species, that facilitate their entry into the CNS. In parallel with the activation of T-lymphocytes on the periphery, CNS factors arise – persistent viral infection and metabolic stress, which increase the expression of adhesive molecules on endothelial cells. At the second stage, after interaction with adhesion molecules, the endotheliocytes of the vascular wall allow T-lymphocytes to penetrate through the blood-brain barrier into the brain. Activated astrocytes, secreting matrix metalloproteases, contribute to proteolysis of vascular wall proteins, damage to myelin-forming oligodendrocytes and myelin itself. At the third stage of immunopathogenesis, T cells are reactivated in the CNS by antigen-presenting cells, which are macrophages and microglia. CNS-infiltrating Th cells and secondarily activated macrophages and microglia secrete proinflammatory cytokines that cause B-cell activation with antibody production. This only increases inflammatory reactions and increases the permeability of the blood-brain barrier. Immune cells destroy myelin, and involved macrophages carry out phagocytosis of damaged areas of myelin. In recent years, it has been proven that the B-cell link of immunity plays a significant role in the maintenance of immunity in multiple sclerosis (Rae-Grant et al., 2013).

Clinical neurological symptoms in multiple sclerosis include:

1. Damage to the pyramidal tract – suppression or reduction of tendon reflexes, the appearance of pathological reflexes, central paresis.
2. Violations of sensitivity – paresthesias, decreased sensitivity.
3. Damage to the cerebellum – intentional tremor when performing coordination movements, ataxia, dysmetria.
4. Visual disorders – reduced vision, retrobulbar neuritis.
5. Ophthalmological disorders – eye movement disorders, nystagmus, diplopia.
6. Damage to the brain stem – dysarthria, dysphagia.
7. Dysfunction of the pelvic organs – urination disorders, constipation, erectile dysfunction.
8. Other symptoms are dizziness, chronic fatigue syndrome, pain syndromes, depression, cognitive impairment (reduced memory, impaired concentration).

For the treatment of multiple sclerosis, immunostimulators are prescribed – beta interferons, as well as immunosuppressants – teriflunomide, monoclonal antibodies (natalizumab, daclizumab, ocrelizumab).

To reduce spasticity, muscle relaxants of central action are used - baclofen, as well as its combinations with other muscle relaxants, for example, tolperisone (Odintsova & Kopchak, 2021).

Currently, for the treatment of multiple sclerosis, drugs of plant origin, in particular plant extracts of cannabis, are increasingly used. Among the cannabis drugs used in multiple sclerosis, nabiximols (Sativex) is noted. This drug contains standardized cannabinoids – tetrahydrocannabinol (THC) and cannabidiol (CBD). The mechanism of action of THC is related to the stimulation of cannabinoid receptors of the first (CB1) and second (CB2) types, which leads to increased appetite, reduced pain, and changes in emotional and cognitive processes. In contrast to the weak agonistic activity of THC, CBD acts as a negative allosteric modulator of CB1 receptors, the most abundant G protein-coupled receptor (GPCR) in the body. Cannabinoids exhibit immunosuppressive and neuroprotective effects, which is explained by inhibition of the secretion of interleukins 12 and 23 by microglial cells, as well as inhibition of the activity of COX-2 and tumor necrosis factor (TNF-α) upon stimulation of CB receptors (Lim et al., 2017).

Of the herbal preparations that are proposed to be included in multiple sclerosis treatment regimens, Ginkgo biloba leaf extract, which is available in capsules, is especially noteworthy. The drug normalizes metabolism in the cells of various organs, and also improves the rheological properties of blood, microcirculation, and mediator processes in the central nervous system. Ginkgo biloba

increases the resistance of brain tissues to hypoxia, prevents erythrocyte aggregation and inhibits the activity of platelet activating factor (PAF). Also, the drug contributes to the formation of an endothelium-dependent relaxing factor – nitric oxide (NO), which expands small arteries, increases the tone of veins and normalizes the blood supply of vessels. In addition, it prevents the formation of free radicals, showing antioxidant activity (Wang et al., 2007; Chan et al., 2007; Nash & Shah, 2015). It is also possible to prescribe plant extracts containing natural cardenolides, which can be useful in neurological diseases. Antioxidant and anti-inflammatory effects have been established for these compounds, which explains their promise in the therapy of multiple sclerosis (Kabir et al., 2022).

In scientific foreign literature, in particular in key publications devoted to the treatment of multiple sclerosis, plant extracts are recommended, the active substances of which are saffron metabolites – crocin, crocetin and picrotoxin. Saffron and its metabolites exhibit antioxidant and anti-inflammatory effects, and also affect apoptosis. Their mechanism of action is related to the modulation of signaling pathways of cell survival and death, playing a role in neuroprotection. These compounds have practically no toxic effect on the body, which makes them promising for inclusion in treatment regimens (Abdian et al., 2024).

Multiple sclerosis is one of the neurodegenerative diseases in which herbal remedies have a therapeutic effect due to the content of polyphenols. Many patients with neurodegenerative diseases suffer from disorders of the work of the small and large intestines, while ascertaining changes in their microbiological composition. On the one hand, metabolites of polyphenols normalize the activity and microbiological composition of the intestine, on the other hand, penetrating through the blood-brain barrier, they affect the nervous system, changing the activity of enzymes and components of signaling pathways (Chatterjee et al., 2024; Chatterjee et al., 2024).

Limonene is a widespread orange terpene, the main component of orange peel, a cyclic monoterpene. Has a wide spectrum of pharmacodynamics. It has an antioxidant effect in case of oxidative stress, anti-inflammatory, antimicrobial effect, regulates apoptosis processes. A neuroprotective effect in neurodegenerative diseases has been revealed. Obtained results of preclinical and clinical studies of limonene (Eddin et al., 2021).

Conclusions. Thus, despite the proposed and accepted drugs for the treatment of neurodegenerative diseases, which are quite effective, their combination with herbal preparations allows to increase the therapeutic effect, and in some cases to eliminate side effects.

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