Ann. For. Res. 65(1): 10336-10359, 2022
ISSN: 18448135, 20652445

ANNALS OF FOREST RESEARCH
https://www.e-afr.org/

REVIEW OF THE EFFECT OF VARIOUS BIOLOGICALLY ACTIVE SUBSTANCES ON THE EXPRESSION OF SOD-3 AND HSP-16.2 PROTEINS AND THE ACCUMULATION OF CARBONYLATED PROTEINS IN THE ORGANISM OF *CAENORHABDITIS ELEGANS*

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Abstract

The problem of aging today is an urgent problem that attracts the attention of scientists from all over the world. Aging is the cause of the appearance in living organisms of diseases such as Alzheimer's disease, Parkinson's disease, neurodegenerative, immune diseases, diabetes, etc. Recently, the attention of scientists has been attracted by medicinal plants, because they have a wide range of morphologically active substances that could be effective in the fight against diseases caused by aging. Polyphenols are recognized as the most promising biologically active substances due to their powerful antioxidant properties. The purpose of this work is to carry out an analytical review of scientific data aimed at searching for plant-derived polyphenols, which in the future will be used as means of ensuring a healthy long life. The review was carried out using databases: Elibrary, Elsiever, PubMed. The inclusion criteria were studies in which the effect of

BAS on the expression of proteins SOD-3, HSP-16.2 and carbonylated proteins was studied, since they are responsible for the antioxidant system of the human body. The nematode *Caenorhabditis elegans* was a model for studying the effect of BAS on the aging process due to a number of advantages, such as a fully sequenced genome, a transparent integument and ease of maintenance in laboratory conditions. As a result, it was found that such polyphenols as caffeic acid, chlorogenic acid, epigallocatechin gallate, genistein, naringenin exhibit antioxidant activity, and, therefore, they are promising compounds for increasing life expectancy. In the future, it is planned to isolate these BAS from plants of the Siberian Federal District in order to study their ability to influence the expression of proteins SOD-3, HSP-16.2 and carbonylated proteins.

Keywords: aging, *Caenorhabditis elegans*, SOD-3, HSP-16.2, protein carbonylation, medicinal plants, biologically active substances.

Introduction

Increasing life expectancy without maintaining a healthy state of the body is an important social health problem. By 2050, 16% of people will be over 65, in comparison with 9% in 2019, and the number of people aged 80 and older is projected to triple, from 143 million in 2019 to 426 million in 2050 [11]. The majority of elderly people will suffer from Alzheimer's disease [49], Parkinson's disease [92] and other neurodegenerative, immune, oncological diseases, diabetes [15, 84, 86]. With an increase in the proportion of elderly people in society and, consequently, with the growth of diseases associated with aging, it becomes urgent to search for natural nutraceuticals not only to increase life expectancy, but also to improve health and stress resistance of the body [87].

The free radical theory of aging is one of the theories leading to deterioration of health in old age [62]. According to this theory, the aging of organism occurs due to an increase in the number of free radicals, therefore, damage from them, and a decrease in the enzymes of the antioxidant defense of the body. [89]. The result of this is oxidative stress. A violation of the oxidative balance occurs due to many factors, which leads to oxidative stress. Subsequently, the number of substances that can neutralize free radicals becomes lower than the number of free radicals. As a result, it becomes important to support the endogenous defense system of the body with exogenous biologically active compounds with an antioxidant effect, which can have a significant impact on the work of various proteins, the cellular signaling process and a number of enzyme systems [125].

An important factor is the transcription factor of the DAF-16 protein, which is involved in increasing life expectancy, improving metabolism and increasing the stress resistance of the body [55]. Transcriptional target genes of DAF-16, including superoxide dismutase-3 (SOD-3) and heat shock protein-16.2 (HSP-16.2), are key factors that contribute to oxidative stress and heat shock response [100].

Superoxide dismutase (SOD) is an antioxidant enzyme that catalyzes the dismutation of superoxide into hydrogen peroxide and oxygen molecules [80]. There are three isoforms of SOD in mammals: SOD-1 (Cu, Zn-SOD) is located in the cytoplasm, SOD-2 (Mn-SOD) is in the mitochondria, and SOD-3 (EC-SOD) is an extracellular form [102]. In 1982 S.L. Marklund discovered SOD-3 as a superoxide dismutase due to its predominant form in extracellular fluids such as lymph, synovial fluid and plasma [71]. SOD-3 is a promising biopharmaceutical candidate

for the treatment of inflammatory diseases due to its ability to suppress inflammatory reactions not only by reducing the level of reactive oxygen species, but also by modulating cellular signals [64].

The main physiological role of SOD has been shown experimentally in knockout mice. Mice with SOD-1 knockout protein had a wide range of pathologies, including the development of carcinoma, cataracts, muscle dystrophy and shortened life expectancy [75]. Other mice with the knocked-out mitochondrial form of SOD-2 lived only a few days after birth, as they develop severe oxidative stress [124]. Mice lacking the SOD-3 extracellular form gene became more sensitive to hyperoxia [126]. Thus, some researchers suggest that the amount of SOD decreases with aging and, consequently, with an increase in the level of SOD, the body acquires a stable immunity and increases the life expectancy [1, 38, 99].

Heat shock proteins (HSP) belong to a family of proteins that can be produced by cells in response to stress [29]. The increase in intracellular synthesis of HSP occurs not only on the reaction of heat shock, but also on other stressful effects, for example, external - ultraviolet light, heavy metals, pathological - bacterial and parasitic infections, inflammation, autoimmune reactions, physiological - growth factors, hormonal stimulation, cellular differentiation [114]. Today, there are only three families of HSP. The first group includes HSP90 – these are high-molecular HSP, available in mammals with a molecular weight of 90 kDa. The second family includes HSP70, a group of proteins with a molecular weight of about 70 kDa. This group is the most common and studied in mammals. And the third group includes small HSPs, whose molecular weight ranges from 15 to 30 kDa [K.D. Nikitin: Heat shock proteins: biological functions and application prospects. 2008;2(1):125–130]. One of the main tasks of HSP is ensuring the survival of the cell under stress. The main functions of HSP vary from group to group under normal conditions and under stress [103].

Heat shock proteins form part of the cell's molecular chaperone system. The main function of HSP is to bind newly formed proteins and control the correct formation of their tertiary structure [78]. Heat shock proteins also have the property of binding mutant proteins or proteins that have an improperly formed tertiary structure, and thus are able to protect the cell from the effects of such proteins [97]. When a cell is stressed, HSP actively binds to denaturing proteins and contributes to the maintenance of damaged proteins until complete recovery [131]. Based on the above, Heat shock proteins are a unique biological phenomenon, a natural compound used to enhance the immune response.

In addition to the normal activity of proteins involved in the antioxidant defense system of the body, the regulation of protein carbonylation is important. Protein carbonylation is a reaction of addition of a carbonyl group (C =O) to amino acid residues of proteins. Carbonylation of proteins is the result of oxidative stress and leads to their irreversible functional and structural damage. These protein modifications accumulate during the life of all organisms [95]. Reactive carbonyls can be generated from endogenous (e.g., mitochondria, phagocytes) or exogenous (e.g., cigarette smoke, food additives) sources [16].

Promising BAS showing antioxidant activity, as well as anti-inflammatory, cytotoxic, antibacterial, antifungal and other properties are secondary metabolites of medicinal plants [120].

For example, plant polyphenols that exhibit not only antioxidant properties, but are not addictive, do not have a toxic effect on the body [13].

Some medicinal plants of the Siberian Federal District - *Medicago sativa L.* [36], *Panax ginseng* [28], *Pulmonaria officinalis L.* [27] and *Hedysarum neglectum* [26] are promising sources of antioxidants that affect the expression of SOD and HSP proteins.

Experiments on such animal models such as mice differ in duration, ethical problems and other burdensome conditions. The short-lived model organism Caenorhabditis elegans offers a wide range of opportunities to study the effect of biologically active compounds on the aging process. In addition, some physiological indicators associated with aging found in this species of worms are similar to those found in higher mammals [119]. The Caenorhabditis elegans organism is used for biomedical research and has a number of advantages over vertebrates, mainly such as small size, high productivity, transparency of integument, which is important for monitoring gene expression, and ease of maintenance in laboratory conditions [24]. Nematodes Caenorhabditis elegans are used as a model for the study of neurogenerative diseases, cancer, immune disorders, diabetes, as well as the study of biological and physiological processes that are common to all living organisms [40].

The purpose of this work is aimed at carrying out a literary review of scientific information devoted to the study of the effect of BAS, of plant origin, exhibiting antioxidant properties, on a model organism that is nematodes *Caenorhabditis elegans.*

1. Characteristics of the C. elegans nematode model

Caenorhabditis elegans is a eukaryotic multicellular organism with a complete sequenced genetic profile [123]. The organism *Caenorhabditis elegans* is used as a genetic model, which is mainly used to study the aging process [40]. The structure of the organism is quite simple (Figure 1). The length of an adult individual can reach up to 1 mm with a reproductive cycle of 2.5-4 days at room temperature and with an average lifespan of about 18-20 days at a cultivation temperature of 12 to 20 ℃ [1128].

Figure 1. - Model organism of *Caenorhabditis elegans*

There are a number of advantages of working with the model organism Caenorhabditis elegans to study aging mutations. Its main features are: simplicity in the maintenance of the organism in the laboratory, high genetic homology in the amount of 70-80% with a person, complete decoding of the genome, high fertility rates (within 2-3 days the body is able to produce about 250 eggs) and

suitable for anatomical observation (has a transparent body) [131]. As the advantages, there are also disadvantages in the form of some limitations as a model organism. Thus, the organism of Caenorhabditis elegans does not possess certain anatomical features of mammals, such as the presence of a blood transport system, a hemato-encephalic barrier, the process of metabolism of the first passage in the liver and blood filtration in the kidneys [72]. This may lead to a limited understanding of any tissue-specific signaling. [129].

As a model system, the nematode Caenorhabditis elegans can be used to study genetic approaches to understanding the aging process, age-related diseases, mechanisms of longevity and drug screening for biologically active compounds that can increase life expectancy. Studies of longevity in this lower organism helped to give an idea of the signaling pathways involved in aging and to predict their behavior in complex organisms [131].

Thanks to numerous studies, it has been established that there are 50 genes in the body of *C. elegans* that counteract the aging process [131]. One of the most widely studied pathways of longevity is the insulin/IGF-1 signaling pathway (IIS), which links the metabolism, growth, development and longevity of the *C. elegans* organism [43]. One of the key genes contained in this signaling pathway is the *daf-2*, *age-1* and *daf-16* gene. The increase in life expectancy and increased stress resistance of C. elegans depends on mutations in daf-2, age-1 [101]. The DAF-16 protein (fork head transcription factor) encoded by the daf-16 gene is responsible for the transcription of genes that are necessary to prolong life. DAF-16, heat shock transcription factor (HSF-1) and Skinhead-1 (SKN-1, erythroid-related nuclear factor (Nrf), similar to xenobiotic factor) significantly affect life expectancy by regulating various genes [121]. It was found that daf-16 mutants demonstrate increased sensitivity to several types of stress, and overexpression of DAF-16 leads to increased stress tolerance [103].

2. Characteristics of SOD-3 proteins

Superoxide dismutase is an enzyme encoded by the gene of the same name that exhibits antioxidant activity by catalyzing the dismutation of superoxide into oxygen and hydrogen peroxide [94].

Extracellular superoxide dismutase-3 (SOD-3) is a glycoprotein that makes up most of the extracellular matrix (ECM) of tissues and is anchored to heparin sulfate proteoglycans in the glycocalyx of cell surfaces. It is also an isoform of SOD, which absorbs superoxide radicals [66].

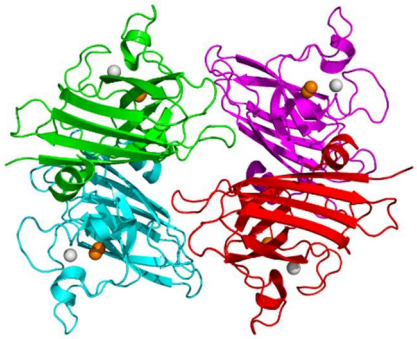


Figure 2. - Crystallographic structure of the tetrameric SOD-3 human fragment

There are several forms of this enzyme: SOD-1 (homodimer 32 kDa), SOD-2 (homotetramer 96 kDa) and SOD-3 (homotetramer 135 kDa). Consisting of two dimers bound to disulfide, SOD-3 is a secretory protein containing an imaginary 18-amino acid (aa) signaling peptide at the N-terminus, which directs this enzyme exclusively to extracellular spaces [53].

The distribution and activity of the protein depends on the missense mutations in SOD-3 [45]. There are 3 known mutations in this protein.

Replacement of glycine with arginine at position 231 of SOD-3 leads to inhibition of the ability of SOD-3 to bind to heparin and dramatically increases the expression of this protein in plasma.

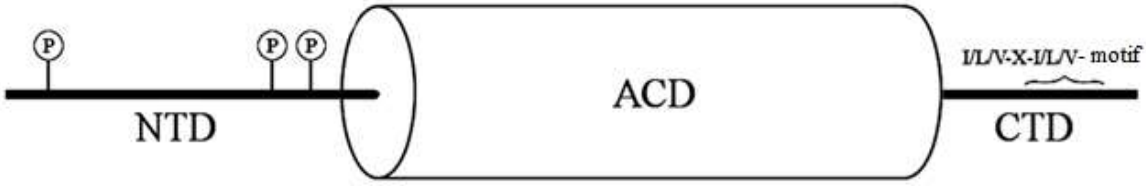
On the one hand, the consequence of this is a reduction in the risk of developing chronic obstructive pulmonary disease, and on the other hand, an increase in the severity of coronary heart disease and myocardial infarction. [44, 45]. Replacement of alanine with threonine at position 58 of SOD-3 is associated with an increased risk of hepatocellular carcinoma and glioma, but the functional effects of this mutation remain unclear and require further research. [45].

Replacement of alanine with threonine at position 91 of SOD-3 causes protein aggregation and it is associated with the development of amyotrophic lateral sclerosis [107, 104].

It has been proven that SOD-3 prevents skin inflammation, weakens inflammatory arthritis and other inflammatory diseases by eliminating ROS products, modulation of immune cells and regulation of cellular signaling cascades (TLRs, NF-KB, MAPKs and JAK-STAT) [79]. Therefore, SOD-3 is a potential candidate for the development of a drug for the treatment of inflammatory diseases.

3. Characteristics of HSP-16.2 proteins

The HSP-16.2 protein belongs to the class of small heat shock proteins. Heat shock proteins belong to the class of polypeptides whose molecular weight ranges from 12 to 43 kDa [14].



The primary structure of sHSP consists of three areas: a structured α-crystalline domain (ACD) with a length of 90-100 a.u., which is surrounded by an N-terminal region (NTR) of variable length and sequence and a short C-terminal region (CTR). By its structure, ACD is a β-sandwich consisting of two sheets. The first sheet contains 3, the second 4 folds, respectively. ACD sHsps in mammals and higher eukaryotes contain an extended β-strand (called the β6 + 7 strand) instead of a distinct β6-th chain. The C-terminal region of the primary structure of the protein does not exceed a length of 20-30 a.u., and it is also susceptible to the action of solvents due to the hydrophobic β-site [108]. The role of this motif is to oligomerize the protein due to the content of a characteristic motif with three residues IX(I/V).

The structure of the N-terminal domain is variable in sequence and length. Some sHSP contain the so-called WDPF-domain, some contain a large number of hydrophobic residues. This domain

plays an important role in the oligomerization of proteins and interaction with them by connecting neighboring sHsp dimers with peculiar bridges.

Their biological activity is based on a plastic quaternary structure, which is formed in an ensemble of oligomeric species [50]. This group of proteins has a high binding capacity, due to which they protect improperly folded proteins from uncontrolled aggregation [59]. A distinctive feature of sHsp is the isolation of improperly folded proteins into a separate sHsp/substrate complex, whereas monomeric species simply retain proteins in solution. This ability eliminates the interaction of damaged proteins with other macromolecules, and also protects the substrate from degradation. sHsp expression provoked by oxidative or thermal stress is at one of the highest levels among all HSP classes [105].

It was found that the genome of the nematode *C. elegans* contains 16 genes that encode 14 different sHsp [52]. In the process of studying the mutagenesis of the *hsp-16.2* promoter, it was found that HSF, as well as other transcription factors, are able to control the induction of *hsp-16.2* in response to heat shock [39].

C. elegans has two systems that control the magnitude of the reaction to heat stroke. The first, the neural system, is influenced by the action of thermosensory neurons [91]. The second, insulin-like signaling system also affects the magnitude of the autonomous heat shock reaction of the cell, [73] including the induction of HSP-16.2.[76]. In C. elegans, the transmission of insulin signals requires the organization of a ligand and antagonization of the insulin-like receptor product of the *daf-2 22* gene [60, 61], which suppresses or activates, respectively, the nuclear translocation of the main subsequent transcription factor, the mammalian FOXO3 homologue, a product of the *daf-16* gene. When insulin signaling is low (which occurs, for example, due to an increase in temperature), the DAF-2 receptor reduces intracellular signaling, allowing the transcription factor DAF-16 to translocate into the nucleus, induce the expression of stress response genes, including genes encoding heat shock proteins. [73].

The expression of human *β*-amyloid peptide (A*β*) in the transgenic model of *C. elegans* leads to the induction of HSP-16 proteins [34]. To investigate the molecular basis and biological function of this interaction between HSP-16 and A*β*, C. elegans transgenic animals with a high level of constitutive expression of HSP-16 were created.2. It was found that constitutive expression of wild type, but not mutant, HSP-16.2 partially suppresses Aß toxicity. It has been observed that the wild type A*β*-(1-42), but not the single-stranded dimer A*β*, is isolated in inclusions containing HSP-16.2, indicating a conformation-dependent interaction between HSP-16.2 and A*β* *in vivo.*

Constitutive expression of HSP-16.2 can reduce the formation of fibroid amyloid, but it does not reduce the total accumulation of the A*β* peptide and does not change the structure of the predominant oligomeric species. Studies with recombinant HSP-16.2 have shown that HSP-16.2 can bind directly to A*β* *in vitro*, with preferential affinity for oligomeric A*β* species. This interaction between A*β* and HSP-16.2 also affects the formation of A*β* oligomers in in vitro assays. These studies are consistent with a model in which small chaperone proteins reduce the toxicity of A*β* by interacting directly with the A*β* peptide and changing its oligomerization pathways, thereby reducing the formation of minor toxic species [35].

4. Characteristics of carbonylated proteins

Protein carbonylation is a reaction of addition of a carbonyl group (C=O) to amino acid residues of proteins. Carbonylation of proteins is the result of oxidative stress and leads to their irreversible functional and structural damage [31]. The formation of carbonylated proteins occurs under the influence of various mechanisms, such as metal-catalyzed oxidation, the inclusion of lipid peroxidation and glycoxidation [96]. Reactive carbonyls can be generated from endogenous (e.g., mitochondria, phagocytic) or exogenous (e.g., cigarette smoke, food additives) sources [97].

Protein carbonylation is one of the distinguishing features of various disorders, for example, Alzheimer's and Parkinson's diseases, chronic lung diseases, diabetes, cataractogenesis and other age-related diseases [63].

Protein carbonylation as a result of nucleophilic attack of lysine, histidine, and cysteine residues is the result of oxidative stress and functions as sensitive to redox signaling mechanisms that are involved in autophagy, cell proliferation, transcriptional control, and apoptosis [51]. In addition, protein carbonylation is involved as an initiating factor of mitochondrial dysfunction and endoplasmic reticulum stress, providing a mechanistic link between oxidative stress and metabolic diseases [122].

When oxidative stress increases, protein carbonylation accumulates and increases the hydrophobicity of the protein. This physicochemical modification, along with improper protein folding, is coordinated to generate aggregates that ultimately worsen the processes of protein degradation and lead to various pathologies and disorders, such as Alzheimer's disease, chronic lung diseases and atherosclerosis [17,22,23]. In view of this, the study of protein carbonylation is currently a growing field in general and in medical science.

The most common products formed as a result of carbonylation of amino acid residues are aminoadypical semialdehyde, obtained by carbonylation of lysine, and glutamic semialdehyde, obtained by carbonylation of arginine and proline [2]. Due to the oxidation of other amino acid residues, carbonylation products are also obtained. Thus, due to the oxidation of the hydroxyl groups of threonine, 2-amino-3-ketobutyric acid is formed, and the tryptophan residue is carbonylated to form kynurenine. The formation of N-Pyruvyl derivatives is the result of oxidation of glutamyl and aspartyl residues in the protein [69].

Aminoadipic and glutamic semialdehydes are responsible for 60% of total protein carbonylation in the liver [58]. As detection methods improved, the identification of specific proteins that become modified contributed to the discovery that protein carbonylation plays an active role in a wide range of cellular mechanisms, including oxidative stress response, autophagy, endoplasmic reticulum stress response, proliferation, mitochondrial function and apoptosis [51].

In obesity, for example, total protein carbonylation increases significantly in visceral adipose tissue [46] and in the heart [37]. Although the specific role of protein carbonylation remains complex, a number of studies show that protein carbonylation is a mechanistic link between obesity and the development of metabolic dysfunction, especially in adipose tissue [20].

Experimental data of plasma, sera and tissues indicate a positive correlation between the levels of carbonylated proteins and age [113]. In addition, the content of carbonylated protein increased dramatically in the late phase of life, and it was found in the heart, muscles, brain and plasma of elderly people [42, 33, 77].

Elevated levels of carbonylated proteins were observed in diabetes mellitus, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, cancer, cataractogenesis, Werner syndrome, cystic fibrosis and essential arterial hypertension [97]. However, carbonylated proteins have been observed in both healthy and diseased parts of the brain in patients with Parkinson's disease. In addition, brain regions in people with concomitant Levi's body disease (presymptomatic Parkinson's disease) did not show an increase in carbonyls in any brain regions. It can be assumed that oxidative protein damage occurs widely in the brain, but this phenomenon is manifested only in elderly patients.

In cases of Huntington 's disease, Túnez I. and others a close correlation was shown between global oxidative stress, protein carbonylation and disease severity. This correlation may indicate that oxidative stress accompanied by protein carbonylation is associated with the evolution of Huntington's disease [109].

In the context of cancer development, Aryal B. et al. specific carbonylation of filamin A, heat shock protein 90ß and bifunctional glutamate/proline-tRNA ligase was detected in breast tumor tissues [8].

Thus, it can be concluded that studies of carbonylated proteins play an important role in the study of diseases of old age from a geroprotective point of view.

5. Description of biologically active compounds

Since ancient times, various types of plants have been used in medicine because of their medicinal properties. However, it is impossible not to notice the increased interest of scientists in medicinal plants as sources of geroprotective biologically active compounds in recent years. Medicinal plants are distinguished by a wide range of biologically active substances that can affect microorganisms, animals and humans [9].

The substances contained in plant raw materials have an effect on the cardiovascular and nervous systems, are effective in the fight against cancer, diabetes, etc. A promising direction is to obtain biologically active compounds from callus, cell and tissue cultures of plants due to their low toxicity and commercial benefits [30]. Antioxidants have the ability to absorb free radicals, which is the reason for reducing the degree of damage to nerve cells due to oxidative stress [19]. Thanks to this, it is possible to maintain the body in a more active physiological state.

One of the most widely known and used antioxidants are polyphenols. This group of substances is widespread in plants [48]. Polyphenols are characterized by the presence of at least two phenolic groups and have different structures. This group of substances includes compounds such as simple phenols (they are also phenolic acids), coumarins, flavonoids, lignans, tannins and lignins [93].

The structure of flavonoids is characterized by the presence of two phenolic rings (rings A and B) and one heterocyclic ring (ring C). These compounds include substances such as quercetin, kaempferol, genistein, resveratrol [21].

Evidence that polyphenols such as resveratrol and quercetin extended the lifespan of various species was first described in yeast and then confirmed in many other model species such as *Caenorhabditis elegans*, *Drosophila melanogaster* and mice [10,54]. Yeast cells proved to be an excellent model for *in vivo* evaluation of the antioxidant capacity of polyphenols in the context of cellular oxidative stress [80, 116, 12, 41]. It is also an attractive and stable eukaryotic model, whose mechanisms of protection and adaptation to oxidative stress are well established and can be extrapolated to human cells.

In addition to the simple antioxidant activity, the question of the effect of polyphenols on health promotion is extensive. This issue has been discussed in several documents. In particular, in their review "Flavonoids and Other Phenolic Compounds from Medicinal Plants for Pharmaceutical and Medical Aspects: An Overview" Tungmunnithum et al. [110] give a comprehensive description of the biological activity of plant polyphenols (flavonoids and phenolic compounds) in relation to their applied or potential pharmaceutical and medicinal potential.

Currently, it is recognized that the health effects of polyphenols are broader than their main antioxidant function. The control of aging and degenerative diseases by polyphenols has also been associated with their ability to inhibit certain enzymes, such as cyclooxygenases and 15-lipoxygenase, involved in inflammation [18] or acetylcholinesterase [83], associated with some neurodegenerative diseases in which oxidative stress and cholinergic deficiency create favorable conditions for Alzheimer's disease or Parkinson's disease.

Research related to polyphenols is primarily based on their ability to affect critical regulatory molecules involved in various diseases [5].

Such biologically active substance as curcumin, together with resveratrol and quercetin, also have a significant effect on the aging process in various organisms [7]. These BAS are able to influence numerous aging-related diseases, such as cancer [6], neurodegenerative diseases [3], nephrosclerosis, arthritis and cardiovascular diseases [82] caused by a number of genetic and non-genetic factors.

Apigenin is a flavone with antioxidant properties. Studies have demonstrated the protective effect of apigenin on aging-related diseases such as colon cancer, skin cancer and many others. In a study by Y. Sang et al., the protective effects of apigenin were studied, where mice were injected with this compound continuously for 9 weeks with D-galactose subcutaneously. As a result, dietary treatment with apigenin led to an improvement in aging-related changes, such as deterioration of behavior, a decrease in the organic index, histopathological trauma, and an increase in the aging-related activity of β-galactosidase (SAβ-gal). In addition, apigenin treatment also caused an increase in the regulation of HO-1 and NQO-1, subsequent gene targets for the Nrf2 pathway, ultimately delaying the aging process [98].

In addition to apigenin, genistein is another polyphenol that is associated with aging. Genistein also has inhibitory properties, controlling the synthesis of glycosaminoglycans and increasing stability to UV radiation [115].

The administration of quercetin prolongs the life expectancy of the wild type *P. anserine*. Quercetin treatment also increased mitochondrial respiration and respiratory complexes along with

increased release of the superoxide anion [112]. Another study reported the effect of quercetin on a decrease in oocyte quality during postovulatory aging of mouse oocytes by modulating the expression of SIRT (a family of cellular proteins that are associated with an increase in life expectancy) and the activity of MPF (maturation factor).

As a result, quercetin exposure suppressed aging-related changes in spindle organization and mitochondrial distribution. In addition, treatment with quercetin prevented a general decrease in SIRT expression and MPF activity and a further delay in the onset of apoptosis during postovulatory aging. Moreover, treatment with quercetin during postovulatory aging also enhanced early embryo development [111]. These studies show that quercetin plays a key role in prolonging life expectancy in different organisms.

Quercetin protects cells from H2O2-inducing and increases mitochondrial biogenesis by increasing the regulation of PGC-1 and SIRT1, which affect mitochondrial activity and mtDNA, thus can prevent cellular aging [85].

Research by A. Kampkotter et al. showed that quercetin and kaempferol increase life expectancy in *C.elegans* by activating FOXO (a subfamily of transcription factors that act as key regulators of longevity after signaling insulin and insulin-like growth factors), which increases stress resistance to oxidative stress [56,57]. It is believed that kaempferol improves the diabetic condition by protecting the kidneys [Yang H. et al. Quercetin treatment improves renal function and protects the kidney in a rat model of adenine-induced chronic kidney disease //Medical science monitor: international medical journal of experimental and clinical research. – 2018. – Vol. 24. – p. 4760.]. It was reported that kaempferol protects against the expression of inflammatory cytokines induced by AGE NF-KB-dependent in an aging kidney rat [60]. Kaempferol also protects glucose-induced oxidative damage and cell death in pancreatic β cells [67].

It has been proven that genistein prevents Aβ-induced oxidative damage to mitochondria and increases SOD expression in both PC12 and rat cells and decreases learning and memory deficits in rats [117].

It was found that rosemary acid reduces the amount of reactive oxygen species and malondialdehyde, which, in turn, mitigates cellular oxidative stress and protects glial cells treated with hydrogen peroxide [32] by phosphorylation of protein kinase B (Akt), Ser9 glycogen synthase, kinase-3β (GSK-3β) and Fyn.

Reducing oxidative stress and inflammation by treating organisms with ursolic acid plays an important role in maintaining skeletal muscle mass and regulates protein turnover (synthesis and degradation) [93].

6. The effect of BAS of vegetable raw materials on the expression of proteins SOD-3, HSP-16.2 and carbonylated proteins

Numerous studies of scientists confirm that BAS of plant raw materials have an effect on the expression of proteins SOD-3, HSP-16.2 and carbonylated proteins.

Thus, S.M Gutierrez-Zetina et al. evaluated the effect of caffeic acid on life expectancy and the ability to counteract oxidative damage in *C. elegans*. [47]. During the experiment, worms were cultured together with caffeic acid in the amount of 200 μmol and 300 μmol.

As a result, data were obtained indicating an increase in the survival rate of worms on the 9th day of life compared with the control group due to a decrease in the level of reactive oxygen species and the formation of polyglutamine aggregates. Mechanistic studies have shown that caffeic acid activates the transcription factor DAF-16 and its subsequent targets SOD-3 to protect against beta-amyloid toxicity. By K. Pietsch et al. It was found that caffeic acid at a concentration of 200 μmol can increase the survival rate of worms exposed to heat shock (35 °C for 8 hours) by 12% compared to the control group [88].

Similar results were demonstrated by quercetin-3, an O-glucoside in concentrations from 10 to 100 μmol, which prolonged the life of nematodes in a dose-dependent manner [25]. Similar studies by other scientists with caffeic acid derivatives have also confirmed their ability to increase the lifespan of worms [88, 130]. However, during the experiments S.M. Gutierrez-Zetina et al. found that an increase in the expression of the genes *daf-16, daf-18*, *hsf-1*, *sod-3* and *sir-2.1* compared with the control group occurred only with the joint participation of caffeic and dihydrocopheic acids. Separately, the acids did not achieve such an effect. Treatment of nematodes with these acids led to a decrease in the concentration of ROS, albeit insignificant. In the work of H. Li and his colleagues [68] examined the effect of caffeic acid on Alzheimer's disease using *Caenorhabditis elegans* models. In this work, it was found that caffeic acid significantly reduces the toxicity caused by beta-amyloid oligomers, increases life expectancy, reduces body paralysis and improves reproductive effects.

N. Tawfeek et al. evaluated the effect of *P. alba* and *S. subserrata* extracts on the expression of heat shock proteins (hsp-16.2::GFP) in nematodes after treatment with juglone [106]. To assess the effect of extracts on the expression of the *sod-3* gene, mutant CF1553 (sod-3::GFP) strains were incubated with extracts for 72 hours, and then the emitted fluorescence was measured. The results showed significantly higher levels of sod-3 expression and higher fluorescence intensity among the strains compared to the untreated ones in the control group.

The results clearly indicated that the components of the extracts are absorbed by worms and play a vital role in improving resistance to oxidative stress in this animal model. To assess the effect of BAS isolated from extracts on the expression level of hsp-16.2::GFP, transgenic mutants TJ375 (hsp-16.2::GFP) were treated with compounds such as aromatendrin, tremuloidin, salicin, isorhamnetin 3-O-β-d-rutinoside, gallocatechin, chrysoeryol-7-O-glucuronide at concentrations of 50 mcg/ml for 72 hours, and then nonlethal a dose of juglone (20 μmol).

After this time, the level of expression of hsp-16.2::GFP was evaluated. The results showed that expression levels were significantly reduced compared to the control treated with juglone. When measuring the intensity of the emitted fluorescence, it was observed that among all the tested compounds, pretreatment with gallocatechin led to higher levels of *sod-3* gene expression compared to untreated worms.

S. Q. Zheng et al. studied the effect of chlorogenic acid on the lifespan of wild worms [133]. Scientists have found that a concentration of 50 μmol of chlorogenic acid can increase the average lifespan of adult worms by up to 20.1% at 20 °C and a maximum lifespan of 28 to 32 days. To assess whether the worms treated with chlorogenic acid were resistant to oxidative stress, they

were cultured on plates containing 5 mM of paraquat, an intracellular compound that generates free radicals, and treated with chlorogenic acid at 20 °C. The average life expectancy of worms treated with 50 μmol of chlorogenic acid increased by at least 20%. The survival rate of *C. elegans* treated with chlorogenic acid was significantly higher than that of untreated worms. These results showed that chlorogenic acid can improve the health of worms and increase their resistance to thermal and oxidative stress.

Studies by L. Zhang et al. confirmed that epigallocatechin gallate prolonged the longevity of *Caenorhabditis elegans* under stress [127]. The life-prolonging effect of epigallocatechin gallate on *C. elegans* was explained by its effects *in vitro* and *in vivo*, absorbing free radicals, and its regulatory effect on proteins associated with stress resistance, including superoxide dismutase-3 (SOD-3) and heat shock protein-16.2 (HSP-16.2).

Quantitative real-time PCR results have shown that the regulation of aging-related genes, such as *sod-3*, can also contribute to increased stress tolerance. The effect of epigallocatechin gallate on the expression of HSP-16.2 was studied to understand the role of this BAS on *C. elegans* under stress. Compared with the control group, the group receiving 0.1 mcg/ml of the compound showed a higher intensity of HSP-16.2. It was concluded that this compound regulates the expression of the HSP-16.2 GFP reporter gene in *C. elegans* under heat stress.

E. B. Lee et al. conducted experiments with wild-type N2 worms to determine whether genistein affects life expectancy [65]. As a result, there was a significant increase in the estimated long life (by 27.9%) when treating worms with 100 microns of genistein compared to the control group. At the same time, the average long life of the treated group was 24.0 ± 0.7 days (in control worms, the life expectancy was 21.0 ± 0.3 days). In order to test the effect of genistein on the lifespan and stress resistance of nematodes, the effect of genistein on the activity of antioxidant enzymes was investigated. The results showed that genistein was able to significantly increase SOD activity by 7.07% at 100 μmol. To find out whether the increase in stress resistance mediated by genistein was associated with the regulation of stress response genes, the expression of SOD-3 and HSP-16.2 was quantified using transgenic strains, including CF1553 and CL2070, respectively. According to the data obtained, CF1553 worms treated with genistein showed significantly higher SOD-3::GFP intensity (25.1% at 100 microns) compared to untreated control worms. CL2070 worms containing the reporter gene HSP-16.2::GFP. This expression of HSP-16.2::GFP caused by heat shock was additionally increased by 100 μmol of genistein by about 11.1%.

A study conducted by the scientist Al-Rejaie S.S. [4] describes the antioxidant and anti-inflammatory effects of naringenin, demonstrating protective properties in inflammatory bowel diseases. In this study, it was found that naringenin increases the antioxidant protein SOD. Other studies have examined the effect of another flavonoid compound myricetin on SOD proteins. Analysis presented by scientist Xia S.F. and his colleagues [118], described antioxidant enzymes, including SOD, which were fundamentally important in the development of therapeutic approaches to oxidative liver pathologies. He found that the antioxidant enzyme SOD was significantly normalized by the bioflavonoid myricetin.

Thus, plant-derived BAS, in particular polyphenols, have a direct effect on the lifespan of *C. elegans* nematodes under stress, which is important when conducting anti-aging studies.

Conclusion

The aging process is the cause of many diseases. Therefore, it is very important to study its mechanism, causes and ways to solve this problem. Scientists have found that aging is a consequence of the effects of oxidative stress on the body. As a result of exposure to oxidative stress on the body, the expression of SOD-3 and HSP-16.2 proteins changes, which is one of the main causes of aging of the body. By interacting with ROS, protein carbonylation also occurs, and, as a consequence, a violation of their modification and structure.

To study the aging process *in vivo*, scientists use an organism such as the nematode *Caenorhabditis elegans*. It has a number of advantages, thanks to which it has become the most widely used object for studying the mechanism of aging. In the course of the conducted literary research, it was found that medicinal plants contain many biologically active substances. One of the most common groups of plant origin are polyphenols. They are powerful antioxidant, which gives scientists the opportunity to use them as geroprotectors.

Thanks to many studies, it has been established those various polyphenols, the sources of which are medicinal plants, they are able to influence the expression levels of SOD-3 and HSP-16.2 proteins, thereby preventing or slowing down the aging process of living organisms. Thus, caffeic acid is able to influence the expression of the SOD-3 gene, chlorogenic acid affects the lifespan of wild worms by increasing resistance to thermal and oxidative stress, *P. alba* and *S. extracts*. subserrata, as well as genistein, have an effect on the expression of heat shock proteins (hsp-16.2::GFP), and naringenin and myricetin have an anti-inflammatory effect due to the effect on the SOD enzyme.

Conflict of interest statement

There is no conflict of interest.

Financing

The work was carried out with the financial support of the Ministry of Science and Higher Education of the Russian Federation (project FZSR-2020-0006 "Screening of biologically active substances of plant origin with geroprotective properties and development of technology for obtaining nutraceuticals that slow down aging".

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