

UDC: 612.67:615.35:547.56.1

## GEROPROTECTIVE PROPERTIES OF POLYPHENOLIC COMPOUNDS OF FOOD PLANTS

DOI: <https://doi.org/10.15673/fst.v15i3.2115>

### Article history

Received 2.02.2021  
Reviewed 14.04.2021  
Revised 25.06.2021  
Approved 31.08.2021

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### Cite as Vancouver style citation

Oliinyk P, Voronenko D, Lysiuk R, Oliinyk A, Oliinyk S. Geroprotective properties of polyphenolic compounds of food plants. *Food science and technology*. 2021;15(3):4-14. DOI: <https://doi.org/10.15673/fst.v15i3.2115>

### Цитування згідно ДСТУ 8302:2015

Geroprotective properties of polyphenolic compounds of food plants. / Oliinyk P. et al // *Food science and technology*. 2021. Vol. 15, Issue 3. P. 4-14 DOI: <https://doi.org/10.15673/fst.v15i3.2115>

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### Introduction. Formulation of the problem

People's ageing causes economic and social problems all over the world. According to UN calculations, the world population will reach 8.5 billion by 2030, and the population of most countries is expected to grow old. This applies to many high-developed countries, including Australia, the United Kingdom, Canada, the United States of America, and the Member Countries of the European

Union [1]. According to the WHO, in 2050, the elderly are expected to make up 22% of the world's population [2]. The elderly bear the brunt of morbidity and disability, of merely a weak condition that needs care. Despite a significant number of theories of ageing, the final cause of ageing has not been established so far [3]. Most researchers believe that the ageing process of the human body is a disease that can be treated. There is an urgent need of finding ways and means that will eliminate the

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**Abstract.** People's ageing causes economic and social problems all over the world. The article presents the results of the analysis of modern research on ways and means that can eliminate the causes of ageing, prolong the active longevity and working ability of the elderly. It has been established that human health and longevity depend on the specific features of a person's nutrition and are affected by micronutrient deficiency in the body caused by unbalanced diet. Considering the free radical theory of ageing, which is based on the chemical nature and ubiquity of free radicals, it has been found that consumption of plant foods rich in antioxidants prevents oxidative damage to cellular structures, which is caused by reactive oxygen species. It has been demonstrated that well-known plant antioxidants, such as flavonoids and other polyphenolic compounds, have a protective effect. They modulate energy metabolism in a way conducive to well-being and longevity, and reduce the risk of chronic diseases and ageing. It has been established that the antioxidant effect of flavonoids involves scavenging of free lipoperoxide radicals, inhibition of nitric oxide production, inactivation of peroxynitrite and other oxidants, inhibition of xanthine oxidase and other radical-producing enzymes, chelation of metals. Neuroprotective and radioprotective properties of flavonoids have been revealed. Flavonoids can inhibit regulatory enzymes or transcription factors that are important for the control of inflammatory mediators, affect oxidative stress through DNA interactions, and enhance genomic stability. Combinations of polyphenols can exhibit synergistic or additive beneficial effects. It has been shown that the rational use of plant-based diets rich in polyphenolic compounds helps to reduce the total mortality rate and, in particular, mortality from coronary heart disease, to maintain sustainable weight management, to decrease the frequency and severity of high-risk conditions such as obesity, hyperglycaemia, hypertension, hyperlipidemia, and improve the general condition in cases of long-neglected cardiovascular diseases and diabetes.

**Key words:** ageing, edible plants, antioxidants, polyphenols, flavonoids, geroprotectors.

cause of ageing, maintain active longevity, and efficiency of the elderly.

Today, researchers on the ageing problem focus on attempting to increase the duration of people's active longevity and efficiency by means of a variety of food additives and pharmaceuticals. Much attention is paid to how human health and longevity correlate with the peculiarities of a person's nutrition. An important problem is the deficiency of micronutrients in the human body due to the unbalanced diet [4,5]. That is why nowadays, scientists pay attention to the pharmaceutical aspects of the use of bioactive substances of various food plants. It is established that the consumption of food products of plant origin rich in antioxidants prevents oxidative damage to cellular structures caused by reactive oxygen species (ROS). It has been demonstrated that well-known plant antioxidants, such as flavonoids and other phenolic compounds, have a protective effect [6-8]. The low bioavailability of flavonoids, which is largely due to their chemical structure, can be improved by consuming food appropriately processed. This processing can modify food products chemically or physically and increase their bioavailability [9].

The **purpose** of this review is to analyse the available scientific information and generalise data on polyphenolic compounds of edible plants, since these compounds have a wide range of pharmacological properties and can produce a geroprotective effect. The main **objectives** of this study are:

- to determine the main directions of increasing the body's natural defences and prolonging healthy life due to the geroprotective properties of polyphenolic compounds of food plants;

- to establish the potential functions of polyphenols of edible plants and the possibility of their use as geroprotective agents.

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### **Analysis of recent research and publications**

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#### **Theories of ageing**

At the end of the second millennium, there were more than 300 theories explaining the phenomenon of ageing [10-11]. The most widespread are the Theory of reliability, the Immune theory of ageing, the Theory of cross-linkage, the Free radical theory of ageing, and the Molecular genetic theories of ageing.

The Reliability theory is a general theory of failures of the body's systems. The authors of the theory view the human organism as a system with certain architecture (reliability structure) and predetermined reliability of its components. This theory assumes that even the systems that consist entirely of ageless elements (with constant failure intensity) will nevertheless deteriorate (fail more often) with age if these systems have excess irreplaceable elements. It is considered that ageing is a direct consequence of the excess of the system. The Reliability theory also predicts a slowdown in mortality at a later age with subsequent equalisation at a later age as an inevitable consequence of the

depletion of excess in old age. The theory explains why the relative differences in mortality rates of the populations compared (within a species) disappear with age, and why there is a convergence of mortality due to the exhaustion of the initial differences in excess levels. Thus, the Theory of reliability is a promising approach to developing a comprehensive theory of ageing and longevity, which combines mathematical methods with specific biological knowledge [12].

At the heart of the Immune theory of ageing are age-related changes in almost all physiological functions, including immunity. The human immune system must cope with the lifelong and evolutionarily unpredictable effect of various factors that underlie profound age-related changes, which are referred to worldwide as immune ageing. The main changes that occur during the ageing of the immune system result from accumulation of cellular, molecular defects and involutive phenomena that occur simultaneously with the hyperstimulation of both innate and adaptive immunity. A lot of data confirm the view that age-related immune dysfunction may at least partially explain the ageing process. Further research is needed to confirm the Immune theory of ageing [13-15].

The Molecular genetic theories of ageing are based on the hypothesis that ageing is caused by the primary changes in the apparatus of the cell. There are two opinions about the processes in the primary changes of the cell apparatus: the mechanism of ageing is genetically determined in the cell, the manifestations of the old age are a pattern established by nature; or they result from errors accumulated in the genetic memory during the evolution of living beings, from violation of genes regulating repair systems that develop under the influence of endogenous factors. Life expectancy is reduced by ionising radiation and chemical mutagens, by defects of DNA repair that accelerate the accumulation of damage in the genome. Thus, ageing can be a programmed natural process, a logical consequence of growth and maturation, or the result of the accumulation of random errors in the system of storage and transmission of genetic information [16-18].

Among a number of theories explaining the phenomenon of ageing, much of the modern scientific world's attention is drawn by the Telomeric theory, a variation of the Molecular genetic theory of ageing. From its point of view, ageing is the result of damage to the genetic apparatus. The process is programmed and associated with the expression of "old age" genes at a certain stage of ontogenesis, which are the cause of irreversible destructive changes in the cell. This theory is confirmed by the presence of a Hayflick limit and a telomeric cell division counter. A key point in the Telomeric theory of ageing is studying the relationship between the cell type, the presence of functionally active telomerase, and the cell cycle arrest. The mechanism of telomerase action is the completion of nucleotide sequences in telomeric regions of DNA, which are lost with each cell division [19-20].

From the 1940s, the Cross-linkage theory, as a variety of the Molecular genetic theory of ageing, has been seen as the primary reaction underlying age-related changes. Crosslinking (bonding of two or more large molecules together side by side) damages body tissues, causes loss of elasticity, reduces swellability, increases resistance to hydrolases and, possibly, to enzymes in general. Crosslinking agents present in a living organism include aldehydes, lipid oxidation products, sulphur, alkylating agents, quinones, ionising radiation-induced free radicals, polybasic acids, polyhalide derivatives and polyvalent metals. The latter four types of compounds act slowly, but also can accumulate in the organism, forming a metabolic pool. During a certain period of life, the organism accumulates enough of all these potential crosslinking agents to start the ageing process [21].

Of all theories, the Free radical theory of ageing, which is based on the chemical nature and ubiquity of free radicals, is the most popular and widely tested. It proves that damage by reactive oxygen species is crucial in determining life expectancy [10,22,23]. The Free radical theory put forward by D. Harman in 1956 explains not only the mechanism of ageing, but also a wide range of related pathological processes (cardiovascular disease, weakened immunity, brain dysfunction, cataracts, cancer, and some others). According to this theory, cell dysfunction is caused by free radicals necessary for many biochemical processes. They are reactive oxygen species (ROS) synthesised mainly in mitochondria, which can be called energy factories of cells [23]. This theory is based on the hypothesis that with age, mutations in mitochondrial DNA will accumulate and lead to loss of function with subsequent acceleration of cell death. However, mitochondrial DNA mutations caused by ROS, mitochondrial DNA accumulation, and the role of antioxidants have not been fully studied [24].

To date, the final cause of ageing has not been established. But, there is hope that the cause of ageing will be discovered soon. Despite a significant number of theories of ageing, most researchers believe that old age is a disease that can and should be treated, that the ageing program of the organism can be disabled, thus turning off the mechanism that shortens human life [25]. There is an urgent need to find ways and means that will eliminate the cause of ageing.

**Modern views on the problem of retardation of ageing.** The problem of how to delay ageing stimulates scientific research in gerontology. Animal studies have led to the discovery of several potential methods to slow ageing, and some are already being tested in human clinical trials. However, there remain many uncertain aspects about the ethical framework for conducting these studies and the implications of such rejuvenation methods.

S. I. S. Rattan (2020) believes that of all theories of ageing, only the physiological significance of gradually accumulating molecular damage remains

fully understandable. As for interventions in the ageing process, there are three main areas: food, physical activity, and social and mental activities, which actually demonstrate the healing effect and retardation of ageing. The dynamic nature of living systems with the properties of interaction, interdependence, adaptation, and constant restructuring requires holistic and interactive modes of understanding and maintaining health in order to slow down the ageing process and extend the age limits of active life [26]. However, as J. Sholl notes (2020), discussions on various aspects of ageing and longevity in biogerontology often differ in approaches that focus primarily on treating disease or on maintaining and promoting health. However, there is still no health theory in the health-related or ageing-related sciences that could provide an integrative explanatory base similar to other scientific theories [27].

It is known that the level of age-related methylation of a set of cytosine-guanine dinucleotides located at certain positions of DNA throughout the genome is a highly reliable biomarker of ageing. In a number of studies, ageing is seen as an epigenetic mechanism, and it is suggested that biological age can be reversed by reprogramming the genome [28-31]. A. Ocampo et al (2016) and Y. Lu et al (2020) suggest that rejuvenation of an ageing organism can be achieved by gaining access to young epigenetic information, partially encoded by DNA methylation, in mammalian tissues. Partial reprogramming by short-term cyclic expression of Oct4, Sox2, Klf4, and c-Myc has been shown to improve cellular and physiological signs of ageing and prolong life in a mouse model of premature ageing [32,33].

It has been experimentally established that blood transfusion in young mice (parabiosis) has a rejuvenating effect on cells, tissues, organs, and functions of older mice. Determining the factors of human blood rejuvenation has led to considerable optimism about finding affordable treatments for age-related diseases. The first studies on blood rejuvenation in people with Alzheimer's disease have been launched. However, no convincing results have been presented so far, and there is no common opinion on the mechanisms or implications. Transfusion data from young donors do not show results regarding the survival rate of older patients. Besides, the use of parabiosis to slow down ageing creates certain ethical challenges regarding the distribution of health care, the avoidance of imbalances, and equal access to health care resources. The use of internal substances in some people as a means to rejuvenate others creates a serious ethical problem, because this method can create a constant demand for certain types of blood. Rejuvenation methods, which are only available to a certain part of the society, significantly increase social inequality and lead to undesirable consequences [34-36].

**Flavonoids of food plants as anti-ageing agents.** For many years, a diet rich in fruits and vegetables has been considered healthy, increasing life expectancy

and reducing morbidity. Numerous studies have shown that the beneficial effects of plant foods are mainly due to the large number of bioactive polyphenolic compounds they contain, mainly flavonoids. Human studies of dietary nutrition have confirmed that polyphenol supplements have positive effects on health, especially in the elderly [37]. It has been reported that dietary intake of polyphenols far exceeds daily intake of vitamin C, vitamin E, and carotenoids. Over the last two decades, polyphenolic compounds have attracted much attention due to their wide distribution in various foods and powerful antioxidant properties [38]. Besides, polyphenols have been reported to modulate energy metabolism in a way conducive to well-being and longevity, and reduce the risk of chronic disease and ageing [39-42].

Flavonoids belong to one of the most diverse and widespread groups of polyphenolic compounds. More than 9,000 names of flavonoids have been identified in various species of many plants [43]. Flavonoids include compounds with a C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub> structure of the carbon skeleton. These compounds are usually distributed as secondary metabolites of plants and are found in stems or trunks, and in fruit, too. The structure of flavonoid molecules is based on the structure of flavan, which consists of two benzene rings and one heterocyclic (pyran) ring. Flavonoids are classified according to the chemical characteristics of carbon bonds and by the number and position of hydroxyl groups in more than 10 different categories, including flavones, flavonones, flavonols, flavonols, isoflavones, flavanols (catechins), and anthocyanidins [44-46].

The biosynthesis of flavonoids is carried out by the shikimate and acetate pathways. The hydrocarbon skeleton of flavonoids (two benzene rings), unlike other phenolic compounds, has a double biogenetic origin. One of the rings is a product of secondary transformations of L-phenylalanine amino acid (shikimate pathway). The synthesis of the second benzene ring goes on in a complex of transformations of p-coumaric acid. P-coumaric acid is pre-activated with CoA, reacts with three molecules of activated malonic acid, the side aliphatic chain is joined by three acetate fragments, and after their intramolecular closure, with the participation of the enzyme chalconesynthase, the second benzene ring is formed. It should be noted that it is chalcone with an open second ring that is formed first. Then, with the participation of the corresponding isomerase, it is converted into an isomeric form, flavanone [47]. The plants of the families *Fabaceae*, *Rutaceae*, *Polygonaceae*, *Rosaceae*, and *Asteraceae* are the richest in flavonoids.

Flavonoids contain reactive phenolic radicals and a carbonyl group in the molecule. Due to this, they are involved in various metabolic processes, which determines their biological activity. Recent studies have shown that flavonoids have anti-inflammatory properties and can inhibit regulatory enzymes or transcription factors important for the control of

mediators involved in inflammation. Flavonoids are also known as powerful antioxidants that can reduce tissue damage or fibrosis [48].

The antioxidant effect of flavonoids includes scavenging free lipoperoxide radicals, inhibiting NO production, inactivating peroxynitrite and other oxidants, inhibiting xanthine oxidase and other radical-producing enzymes, chelating metals, especially Fe (II) and Cu (II) [49]. Besides, flavonoids show neuroprotective and radioprotective properties. They can inhibit regulatory enzymes or transcription factors that are important for the control of inflammatory mediators, affect oxidative stress through interactions with DNA, and enhance genomic stability. Treatment with flavonoids can be a promising adjunctive therapy to prevent pathophysiological brain damage [50,51]. The use of polyphenols to prevent disorders associated with ageing has appeared promising in various model organisms [37].

However, the safety and potential health benefits of long-term human use of polyphenols in their pure form are still uncertain [37]. It should be noted that plant foods can contain at least a few or even hundreds of polyphenols [52], and some diets, such as the Mediterranean diet, include many foods rich in polyphenols, which together contain 290 different polyphenols [53,54]. So, it can be a mistake to attribute the benefits of consuming certain polyphenol-containing products to certain polyphenols, which are often administered in much higher doses, especially in animal and in vitro studies, than polyphenols that people can consume with appropriate food or dietary supplements [55]. In future, it can be more appropriate to investigate the beneficial effects of combining several polyphenols or products rich in polyphenols. Combinations of polyphenols can reveal synergistic or additive beneficial effects [54,56].

A. Yashin et al. (2017) report that the antioxidant activity of polyphenolic compounds is mainly due to their redox properties, such as adsorption and neutralisation of free radicals, singlet and triplet oxygen quenching, or decomposition of peroxides. Typically, flavonoids have higher antioxidant activity against peroxyl radicals than phenolic acids do due to the presence of several hydroxyl groups [57]. Studies by N.C. Cook and S. Samman (1996) showed that quercetin was the main dietary flavonoid in the Netherlands, followed by kaempferol, luteolin, and apigenin. The most common dietary source of flavonoids is onion (*Allium cepa L.*), which accounts for 29% of total consumption (approximately 23 mg/day as aglycones) [58].

Wojdylo et al. (2007) measured antioxidant activity and identified polyphenolic compounds in 32 plants. It was found that quercetin, luteolin, apigenin were the predominant flavonoids in these plants in addition to phenolic acids [1]. Yao et al. (2004) studied flavonoids in plant foods and the health effects of flavonoids. It was noted that cumin (*Carum*

*carvi* L.) and peppermint (*Mentha piperita* L.) were good sources of flavonoids (naringenin, eriodictiol), parsley (*Petroselinum crispum* L.) and thyme (*Thymus vulgaris* L.) were sources of flavones (apigenin, chrysin, luteolin, diosmetin), and onions (*Allium cepa* L.) were sources of flavanols (isoramnetin, kaempferol, quercetin, myricetin, rutin) [59]. The study by W. Zheng and S. Y. Wang (2001) showed that Greek mountain oregano (*Origanum vulgare* L. ssp. *Hirtum*), fragrant marjoram (*Origanum majorana* L.), Mexican oregano (*Lippia graveolens* L.) had a higher total content of polyphenols in various herbal extracts studied, with the total polyphenol content 11.8±0.60, 11.65±0.29, 17.51±0.22 mg/g respectively (the results were expressed in milligrams of gallic acid equivalent (GAE) per gram of raw weight) [60].

Shan et al. found that cloves (*Syzygium aromaticum* L.) contained the largest quantities of flavonoids (366.5 mg per 100 g), followed by dill (*Anethum graveolens* L.) (241.2), cumin (*Carum carvi* L.) (171.9), coriander (*Coriandrum sativum* L.) (167.2), rosemary (*Rosmarinus officinalis* L.) (37.8), mint (*Mentha piperita* L.) (23.2), basil (*Ocimum basilicum* L.) (21.0) and sage (*Salvia officinalis* L.) (20.5) [61, 62]. Not surprisingly, spices and herbs top the list of 100 products with the highest content of antioxidants. Their antioxidant activity is ten times higher than that of fruit and vegetables. Antioxidant properties of some spices showed a positive correlation with their corresponding total concentrations of polyphenols [63,64].

**Effect of the diet on life expectancy and reduction of morbidity.** The nutritional composition of the diet and the metabolic state of the human organism are closely related. Any prolonged violation of this connection leads to functional and organic disorders in the digestive system, blood circulation, bone tissue, immune system. Rationally constructed nutrition of older people helps to optimize the metabolic state of the organism and increases the level of the body's protective response to adverse environmental factors. Of particular importance is the factor of nutrition during the progress of age-related pathologies. Recently, a lot of experimental and clinical materials have been accumulated by gerontologists and geriatricians. These materials suggest that nutrition that lacks balance of essential nutrients and energy is the cause of major pathologies in old age [65].

Rational nutrition is one of the mechanisms of protection against ageing. Food contains substances, some of which accelerate ageing and others slow it down. By regulating the amount and frequency of the intake of this or that substance, eating more of one food and less of another, you can create a geroprotective effect for the organism. One of the theories of retardation of ageing views the limited caloric intake, with the need in other necessary nutrients satisfied, as a non-genetic intervention that slows down the internal rate of ageing of mammals [66,67]. According to experimental models of caloric restriction in mammals,

reducing the caloric intake by ~40% of the diet throughout an animal's life increases the maximum life expectancy by 30–40% [68]. Limiting the caloric intake can promote longevity by reprogramming the metabolism with a transcriptional shift towards lower energy metabolism and increased protein biosynthesis and turnover. It is shown that not only does life expectancy increase, but immune processes, too, intensify significantly (e. g., increased protection against stress, infections, cancer) [69]. However, long-term studies are difficult enough to perform in humans. The lack of data from human models is mainly because this intervention is too rigorous to be easily maintained. Another limitation is the length of human life [67].

C. J. Murray et al. (2013) note that the most serious dietary risks are diets low in fruit, nuts, seeds, and vegetables, but high in sodium, processed meat, and trans fats. [70,71]. Plant-based diets are associated with a reduction in overall mortality and mortality from coronary heart disease [72,73], reduced need for medication [74], sustainable weight management [76], lower frequency and severity of high-risk conditions such as obesity, hyperglycaemia, hypertension, hyperlipidaemia, and improved condition in advanced cases of cardiovascular disease and type 2 diabetes [71].

It has been shown that the population of Okinawa is characterised by reduced morbidity and mortality, and the world's largest percentage of people over the age of 100 live on this island. There is a hypothesis that the life expectancy of this category of people without disabilities may be due to a diet based on vegetables, grains, soya, fruit, fish, and seaweed and is characterised by low caloric intake (less by about 20% than in the rest of Japan, and less by 40% than in the US) [67]. However, A. J. Dirks and C. Leeuwenburgh (2006) believe that despite a lot of data on the health benefits and reduction of the ageing rate resulting from a reduced caloric intake in animal models, it is quite likely that these beneficial effects will be lost with caloric restriction of people's nutrition [66].

M. E. Walsh et al. (2014) indicate that dietary restriction prevents a number of age-related pathologies, including loss of myenteric neurons, hearing loss, cataracts, insulin resistance, and loss of skeletal muscles. However, although dietary restrictions are thought to reduce oxidative stress, these data are ambiguous and have not been comprehensively revised. Three mechanisms may be responsible for the antioxidant effect of dietary restriction. In particular, dietary restrictions can reduce the production of reactive oxygen species, increase the activity of antioxidant enzymes or the circulation of oxidised macromolecules. These mechanisms are interrelated and often lead to unclear results. For example, dietary restrictions can lead to decreased expression of antioxidant enzymes, but this may be due to reduced production of reactive oxygen species [77]. Besides, in case of ageing and diseases, the protective effects of dietary restriction are possibly mediated by a number of mechanisms, including the

prevention of apoptosis in postmitotic cells [78], preservation of stem cell function [79], reduction of inflammation [80] and reduction of senile cells [77,81]. It has been proved that many flavonoids, which are part of food diets, affect the process of cellular ageing and prolong the life of invertebrates. Cellular ageing is characterised by cellular hypertrophy (cell growth in the absence of cell division). Resveratrol, quercetin, butein, fistein, piceatanol, curcumin, and other flavonoids affect the process of cellular ageing by activating or inactivating the genes that regulate this process [82].

The impact of food diets on the health of people of all ages is complex and multifactorial. It depends on the environment, culture, religion, eating habits of people in one or another country. Obviously, food should be attractive to the elderly in appearance, texture, colour, taste, and aroma. The food industry and catering establishments could develop dishes for the diets of senior age and elderly people [83-85].

### **Conclusion**

People's ageing makes researchers think how to prolong people's lives and reduce their dependence on the health and social care system. There is a need to improve the body's defence mechanism with the fewest side effects. Further research is needed to solve a number of problems. In particular, it is important to clarify whether the ageing process can be slowed down, limited, stopped, or reversed. The purpose of research into the ageing process should not be to increase human longevity regardless of the consequences, but to increase

active longevity, devoid of disability and functional dependence.

The potential function of polyphenols as anti-ageing compounds in humans has been well confirmed by different studies indicating their possible role in both preventing age-related diseases and slowing ageing down. Animal studies demonstrate that healthy life expectancy can be extended by changing eating habits and using diets that contain flavonoids and other polyphenolic compounds of plant origin. However, the mechanisms associated with the anti-ageing process in people still require detailed study and understanding of the effects of polyphenolic compounds in plant foods.

In order to increase the body's natural protection and prolong healthy life expectancy due to the geroprotective properties of bioactive substances of food plants, some future directions of research have been suggested. These include: accurate identification of certain bioactive substances of food plants that have an impact on prolonging healthy life expectancy, establishing their synergistic interactions among different plant compounds, their bioavailability and bioefficiency, conducting well-controlled clinical trials in humans to determine the actual effects of bioactive substances in food plants (both well-known plants and the ones studied insufficiently) for all age groups, as it is already known that different people grow old differently. Only on the basis of the results of well-controlled clinical trials, can it be recommended how to consume certain bioactive substances of food plants, whether in the form of food and pharmaceutical additives or as components of industrial or individually made food products.

### **References:**

1. Wojdylo A, Oszmiański J, Czemerys R. Antioxidant activity and phenolic compounds in 32 selected herbs. *Food Chem.* 2007;105(3):940-949. DOI: <https://doi.org/10.1016/j.foodchem.2007.04.038>
2. Mori MA. Aging: a New Perspective on an Old Issue. *An Acad Bras Cienc.* 2020;92(2):e20200437. DOI: <https://doi.org/10.1590/0001-37652020200437>
3. Flatt T, Partridge L. Horizons in the evolution of aging. *BMC Biol.* 2018;16(1):1-13. DOI: <https://doi.org/10.1186/s12915-018-0562-z>
4. Vidacek NŠ, Nanic L, Ravlic S, Sopta M, Gerić M, Gajski G, et al. Telomeres, Nutrition, and Longevity: Can We Really Navigate Our Aging? *J Gerontol A Biol Sci Med Sci.* 2017 Dec 12;73(1):39-47. DOI: <https://doi.org/10.1093/gerona/glx082>
5. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell.* 2013;153(6):1194-1217. DOI: <https://doi.org/10.1016/j.cell.2013.05.039>
6. Bayliak MM, Burdyliuk NI, Lushchak VI. Effects of pH on antioxidant and prooxidant properties of common medicinal herbs. *Open Life Sci.* 2016;11(1):298-307. DOI: <https://doi.org/10.1515/biol-2016-0040>
7. Halliwell B. Are polyphenols antioxidants or pro-oxidants? What do we learn from cell culture and in vivo studies? *Arch. Biochem. Biophys.* 2008;476(2):107-112. DOI: <https://doi.org/10.1016/j.abb.2008.01.028>
8. Sies H. Polyphenols and health: update and perspectives. *Arch Biochem Biophys.* 2010 Sep 1;501(1):2-5. DOI: <https://doi.org/10.1016/j.abb.2010.04.006>
9. Karasawa MMG, Mohan C. Fruits as Prospective Reserves of bioactive Compounds: A Review. *Nat. Prod. Bioprospect.* 2018;8:335-346. DOI: <https://doi.org/10.1007/s13659-018-0186-6>
10. Badithe T, Ashok RA. The aging paradox: free radical theory of aging. *Experimental Gerontology* 1999;34(3):293-303. DOI: [https://doi.org/10.1016/S0531-5565\(99\)00005-4](https://doi.org/10.1016/S0531-5565(99)00005-4)
11. Medvedev ZA. An attempt at a rational classification of theories of aging. *Biol. Rev.* 1990;65:375-398. DOI: <https://doi.org/10.1111/j.1469-185x.1990.tb01428.x>
12. Gavrilov LA, Gavrilova NS. Reliability Theory of Aging and Longevity. *Journ. of Theoret. Biology.* 2001;213(4):527-545. DOI: <https://doi.org/10.1016/B978-012088387-5/50004-2>
13. Robert L, Fulop T. Aging: Facts and Theories. *Interdiscipl Top Gerontol.* Basel, Karger. 2014;39:163-176. DOI: <https://doi.org/10.1159/000358904>
14. Ostan R, Bucci L, Capri M, Salvioi S, Scurti M, Pini E, et al. Immunosenescence and Immunogenetics of Human Longevity. *Neuroimmunomodulation* 2008;15:224-240. DOI: <https://doi.org/10.1159/000156466>
15. Pinti M, Appay V, Campisi J, Frasca D, Fülöp T, Sauce D, et al. Aging of the immune system: Focus on inflammation and vaccination. *Eur J Immunol.* 2016;46(10):2286-2301. DOI: <https://doi.org/10.1002/eji.201546178>
16. Jin K. Modern biological theories of aging. *Aging Dis.* 2010;1(2):72-74.

17. Wang X, Ma Z, Cheng J, Ly Z. A genetic program theory of aging using an RNA population model. *Ageing Res Rev.* 2014 Jan;13:46-54. DOI: <https://doi.org/10.1016/j.arr.2013.11.001>
18. Sinclair AD, LaPlante MD. *Lifespan: Why We Age and Why We Don't Have To.* Simon & Schuster, 2019.
19. Fathi E, Charoudeh HN, Sanaat Z, Farahzadi R. Telomere shortening as a hallmark of stem cell senescence. *Stem Cell Investig.* 2019;6:1-7. DOI: <https://doi.org/10.21037/sci.2019.02.04>
20. Zhu Y, Liu X, Ding X, Wang F, Geng X. Telomere and its role in the aging pathways: telomere shortening, cell senescence and mitochondria dysfunction. *Biogerontology* 2019;20(1):1-16. DOI: <https://doi.org/10.1007/s10522-018-9769-1>
21. Bjorksten J. The crosslinkage theory of aging. *J Am Geriatr Soc.* 1968;16(4):408-427. DOI: <https://doi.org/10.1111/j.1532-5415.1968.tb02821.x>
22. Beckman KB, Ames BN. The free radical theory of aging matures. *Physiol Rev.* 1998;78(2):547-581. DOI: <https://doi.org/10.1152/physrev.1998.78.2.547>
23. Harman D. Free radical theory of aging. *Mutation Research/DNaging.* 1992;275(3,6):257-266. DOI: [https://doi.org/10.1016/0921-8734\(92\)90030-S](https://doi.org/10.1016/0921-8734(92)90030-S)
24. Biesalski HK. Free radical theory of aging. *Current Opinion in Clinical Nutrition and Metabolic Care.* 2002; 5(1):5-10. DOI: <https://doi.org/10.1097/00075197-200201000-00002>
25. Wray B. The ambitious quest to cure ageing like a disease [Internet]. BBC Future [online]: 5th February 2018 [cited 2021 Sich 4]. Available from: <https://www.bbc.com/future/article/20180203-the-ambitious-quest-to-cure-ageing-like-a-disease>
26. Rattan SIS. Naive extrapolations, overhyped claims and empty promises in ageing research and interventions need avoidance. *Biogerontology* 2020;21(4):415-421. DOI: <https://doi.org/10.1007/s10522-019-09851-0>
27. Sholl J. The sciences of healthy aging await a theory of health. *Biogerontology* 2020;21(3):399-409. DOI: <https://doi.org/10.1007/s10522-020-09872-0>
28. Chiavellini P, Canatelli-Mallat M, Lehmann M, Gallardo MD, Herenu CB, Cordeiro JL, et al. Aging and rejuvenation - a modular epigenome model. *Aging (Albany NY).* 2021;13(4):4734-4746. DOI: <https://doi.org/10.18632/aging.202712>
29. Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol* 2013;14(10):R115. DOI: <https://doi.org/10.1186/gb-2013-14-10-r115>
30. Bocklandt S, Lin W, Sehl ME, Sánchez FJ, Sinsheimer JS, Horvath S, et al. Epigenetic predictor of age. *PLoS One.* 2011; 6(6):e14821. DOI: <https://doi.org/10.1371/journal.pone.0014821>
31. Hannum G, Guinney J, Zhao L, Zhang Li, Hughes G, Sada SV, et al. Genome-wide methylation profiles reveal quantitative views of human aging rates. *Mol Cell.* 2013; 49(2):359-367. DOI: <https://doi.org/10.1016/j.molcel.2012.10.016>
32. Ocampo A, Redondo PM, Guillen I, Guillen P, Izpisua Belmonte JC, et al. In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming. *Cell.* 2016. 167(7):1719-1733. DOI: <https://doi.org/10.1016/j.cell.2016.11.052>
33. Lu Y, Bromme B, Tian X, Krishnan A, Meer M, Wang C, et al. Reprogramming to recover youthful epigenetic information and restore vision. *Nature* 2020;588(7836):124-129. DOI: <https://doi.org/10.1038/s41586-020-2975-4>
34. Lavazza A, Garasic M. Vampires 2.0? The ethical quandaries of young blood infusion in the quest for eternal life. *Med Health Care and Philos* 2020;23:421-432. DOI: <https://doi.org/10.1007/s11019-020-09952-5>
35. Hofmann B. Young Blood Rejuvenates Old Bodies: A Call for Reflection when Moving from Mice to Men. *Transfus Med Hemother* 2018;45(1):67-71. DOI: <https://doi.org/10.1159/000481828>
36. Edgren G, Ullum H, Rostgaard K, Erikstrup C, Sartipy U, Holmstrom MJ, Hjalgrim H, et al. Association of donor age and sex with survival of patients receiving transfusions. *JAMA Intern Med* 2017;177(6):854-860. DOI: <https://doi.org/10.1001/jamainternmed.2017.0890>
37. Luo J, Si H, Jia Z, Liu D. Dietary Anti-Aging Polyphenols and Potential Mechanisms. *Antioxidants.* 2021;10(2):283. DOI: <https://doi.org/10.3390/antiox10020283>
38. Scalbert A, Johnson IT, Saltmarsh M. Polyphenols: antioxidants and beyond. *Am J Clin Nutr.* 2005;81(1):215-217. DOI: <https://doi.org/10.1093/ajcn/81.1.215S>
39. Sandoval V, Sanz-Lamora H, Arias G, Marrero PF, Haro D, Relat J. Metabolic Impact of Flavonoids Consumption in Obesity: From Central to Peripheral. *Nutrients.* 2020;12(8):2393. DOI: <https://doi.org/10.3390/nu12082393>
40. Ebrahimpour S, Zakeri M, Esmaeili A. Crosstalk between obesity, diabetes, and alzheimer's disease: Introducing quercetin as an effective triple herbal medicine. *Ageing Res Rev.* 2020;62:101095. DOI: <https://doi.org/10.1016/j.arr.2020.101095>
41. Singh A, Yau YF, Leung KS, El-Nezami H, Lee JC. Interaction of Polyphenols as Antioxidant and Anti-Inflammatory Compounds in Brain-Liver-Gut Axis. *Antioxidants (Basel).* 2020;9(8):669. DOI: <https://doi.org/10.3390/antiox9080669>
42. Si H, Liu D. Dietary antiaging phytochemicals and mechanisms associated with prolonged survival. *J Nutr Biochem.* 2014;25(6):581-591. DOI: <https://doi.org/10.1016/j.jnutbio.2014.02.001>
43. Boojar MMA. An Overview of the Cellular Mechanisms of Flavonoids Radioprotective Effects. *Adv Pharm Bull.* 2020;10(1):13-19. DOI: <https://doi.org/10.15171/apb.2020.002>
44. Williams CA, Grayer RJ. Anthocyanins and other flavonoids. *Nat Prod Rep.* 2004;21(4):539-573. DOI: <https://doi.org/10.1039/b311404j>
45. Ghasemzadeh A, Ghasemzadeh N. Flavonoids and phenolic acids: role and biochemical activity in plants and human. *J Med Plant Res.* 2011;5(31):6697-6703. DOI: <https://doi.org/10.5897/JMPR11.1404>
46. Brodowska KM. Natural flavonoids: classification, potential role, and application of flavonoid analogues. *Eur J Biol Res.* 2017;7(2):108-123. DOI: <http://doi.org/10.5281/zenodo.545778>
47. Keller RB. *Flavonoids: Biosynthesis, Biological Effects and Dietary Sources (Nutrition and Diet Research Progress).* Nova Science Publishers Inc. 2009.
48. Maleki SJ, Crespo JF, Cabanillas B. Anti-inflammatory effects of flavonoids. *Journal of Food Chemistry.* 2019;299:125124. DOI: <https://doi.org/10.1016/j.foodchem.2019.125124>
49. Baraboy V. A. Izoflavony soi: biologichna aktyvnist' i zastosuvannia. *Biotekhnologiya,* 2009;2(3):44-54.
50. Wang Q, Xie C, Xi S, Qian F, Peng X, Huang J, et al. Radioprotective Effect of Flavonoids on Ionizing Radiation-Induced Brain Damage. *Molecules* 2020;25(23):5719. DOI: <https://doi.org/10.3390/molecules25235719>
51. Tiwari P, Mishra KP. Flavonoids sensitize tumor cells to radiation: molecular mechanisms and relevance to cancer radiotherapy. *International Journal of Radiation Biology* 2020;96(3):360-369. DOI: <https://doi.org/10.1080/09553002.2020.1694193>
52. Wu S, Tian L. Diverse Phytochemicals and Bioactivities in the Ancient Fruit and Modern Functional Food Pomegranate (*Punica granatum*). *Molecules* 2020;25(23):5719. DOI: <https://doi.org/10.3390/molecules25235719>
53. Tresserra-Rimbau A, Medina-Remón A, Pérez-Jiménez J, Martínez-González MA, Covas MI, Corella D, et al. Dietary intake and major food sources of polyphenols in a Spanish population at high cardiovascular risk: the PREDIMED study. *Nutr Metab Cardiovasc Dis.* 2013;23(10):953-959. DOI: <https://doi.org/10.1016/j.numecd.2012.10.008>

54. Schaffer S, Asseburg H, Kuntz S, Muller WE, Eckert GP. Effects of polyphenols on brain ageing and Alzheimer's disease: focus on mitochondria. *Mol Neurobiol.* 2012;46(1):161-178. DOI: <https://doi.org/10.1007/s12035-012-8282-9>.
55. Rein MJ, Renouf M, Cruz-Hernandez C, Actis-Goretta L, Thakkar SK, da Silva Pinto M. Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. *Br J Clin Pharmacol.* 2013;75(3):588-602. DOI: <https://doi.org/10.1111/j.1365-2125.2012.04425.x>
56. Zhang L, Virgous C, Si H. Synergistic anti-inflammatory effects and mechanisms of combined phytochemicals. *J Nutr Biochem.* 2019;69:19-30. DOI: <https://doi.org/10.1016/j.jnutbio.2019.03.009>
57. Yashin A, Yashin Y, Xia X, Nemzer B. Antioxidant Activity of Spices and Their Impact on Human Health: A Review. *Antioxidants.* 2017;6(3):70. DOI: <https://doi.org/10.3390/antiox6030070>
58. Cook NC, Samman S. Flavonoids-Chemistry, metabolism, cardioprotective effects and dietary sources. *J. Nutr. Biochem.* 1996;7:66-76. DOI: [https://doi.org/10.1016/0955-2863\(95\)00168-9](https://doi.org/10.1016/0955-2863(95)00168-9).
59. Yao LH, Jiang YM, Shi J, Tomas-Barberan FA, Datta N, Singanusong R, et al. Flavonoids in food and their health benefits, Flavanones in cumin, peppermint, Flavones in parsley, thyme and Flavonols in onions. *Plant Foods Hum. Nutr.* 2004;59(3):113-122. DOI: <https://doi.org/10.1007/s11130-004-0049-7>
60. Zheng W, Wang SY. Antioxidant activity and phenolic compounds in selected herbs. *J. Agric. Food Chem.* 2001;49(10):5165-5170. DOI: <https://doi.org/10.1021/jf010697n>
61. USDA Database for the Flavonoid Content of Selected Foods[Internet]. Release 3.1 [cited 2020 Gru 28]. Available from: [https://www.ars.usda.gov/ARSEUserFiles/80400525/Data/Flav/Flav\\_R03-1.pdf](https://www.ars.usda.gov/ARSEUserFiles/80400525/Data/Flav/Flav_R03-1.pdf)
62. Shan B, Cai YZ, Sun M, Corke H. Antioxidant capacity of 26 extracts of spices and characterization their phenolic components. *J. Agric. Food Chem.* 2005;53:7749-7759. DOI: <https://doi.org/10.1021/jf051513y>
63. Jorgustin K. Top 100 High ORAC Value Antioxidant Foods. [Internet]. 2014 [cited 2020 Gru 20]. Available from: <http://modernsurvivalblog.com/health/high-orac-value-antioxidant-foods-top-100/>
64. Haytowitz DB, Bhagwat S. USDA Database for the Oxygen Radical Absorbance Capacity (ORAC) of Selected Foods, Release 2. [Internet]. 2017 [cited 2020 Gru 5]. Available from: [http://www.orac-info-portal.de/download/ORAC\\_R2.pdf](http://www.orac-info-portal.de/download/ORAC_R2.pdf)
65. Korzun VN, Svidlo KV. Kharchovi ratsiony herodiietychnoho pryznachennia z vykorystanniam diietychnykh dobavok roslynnoho pokhodzhennia. *Problemy starenia y dolholetia.* 2016;25(2):235-252.
66. Dirks AJ, Leeuwenburgh C. Caloric restriction in humans: potential pitfalls and health concerns. *Mech Ageing Dev.* 2006;127(1):1-7. DOI: <https://doi.org/10.1016/j.mad.2005.09.001>
67. Tosato M, Zamboni V, Ferrini A, Cesari M. The aging process and potential interventions to extend life expectancy. *Clin Interv Aging.* 2007;2(3):401-412.
68. Weindruch R, Walford RL, Fligiel S, Guthrie D. The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake. *J Nutr.* 1986;116(4):641-654. DOI: <https://doi.org/10.1093/jn/116.4.641>
69. Mobbs CV, Bray GA, Atkinson RL, Bartke A, Finch CE, Maratos-Flier E, et al. Neuroendocrine and pharmacological manipulations to assess how caloric restriction increases life span. *J Gerontol A Biol Sci Med Sci.* 2001;56(1):34-44. DOI: [https://doi.org/10.1093/gerona/56.suppl\\_1.34](https://doi.org/10.1093/gerona/56.suppl_1.34)
70. Murray CJ, Abraham J, Ali MK, Alvarado M, Atkinson C, Baddour LM, et al. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. *JAMA.* 2013;310(6):591-606. DOI: <https://doi.org/10.1001/jama.2013.13805>
71. Hever J, Cronise RJ. Plant-based nutrition for healthcare professionals: implementing diet as a primary modality in the prevention and treatment of chronic disease. *J Geriatr Cardiol.* 2017;14(5):355-368. DOI: <https://doi.org/10.11909/j.issn.1671-5411.2017.05.012>
72. Orlich MJ, Singh PN, Sabaté J, Jaceldo-Siegl K, Fan J, Knutsen S, Beeson WL, et al. Vegetarian dietary patterns and mortality in Adventist Health Study 2. *JAMA Intern Med.* 2013;173(13):1230-1238. DOI: <https://doi.org/10.1001/jamainternmed.2013.6473>
73. Crowe FL, Appleby PN, Travis RC, Key TJ. Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study. *Am J Clin Nutr.* 2013;97(3):597-603. DOI: <https://doi.org/10.3945/ajcn.112.044073>
74. Barnard ND, Cohen J, Jenkins DJ, Turner-McGrievy G, Gloede L, Green A, et al. A low-fat vegan diet and a conventional diabetes diet in the treatment of type 2 diabetes: a randomized, controlled, 74-wk clinical trial. *Am J Clin Nutr.* 2009;89(5):1588-1596. DOI: <https://doi.org/10.3945/ajcn.2009.26736H>
75. Huang RY, Huang CC, Hu FB, Chavarro JE. Vegetarian Diets and Weight Reduction: a Meta-Analysis of Randomized Controlled Trials. *J Gen Intern Med.* 2016;31(1):109-116. DOI: <https://doi.org/10.1007/s11606-015-3390-7>
76. Barnard ND, Levin SM, Yokoyama Y. A systematic review and meta-analysis of changes in body weight in clinical trials of vegetarian diets. *J Acad Nutr Diet.* 2015;115(6):954-969. DOI: <https://doi.org/10.1016/j.jand.2014.11.016>
77. Walsh ME, Shi Y, Van Remmen H. The effects of dietary restriction on oxidative stress in rodents. *Free Radic Biol Med.* 2014;66:88-99. DOI: <https://doi.org/10.1016/j.freeradbiomed.2013.05.037>
78. Loncarevic-Vasiljkovic N, Pesic V, Todorovic S, Popic J, Smiljanic K, Milanovic D, et al. Caloric Restriction Suppresses Microglial Activation and Prevents Neuroapoptosis Following Cortical Injury in Rats. *PLoS ONE.* 2012;7(5):e37215. DOI: <https://doi.org/10.1371/journal.pone.0037215>
79. Cerletti M, Jang Y, Finley L, Haigis M, Wagers A. Short-term calorie restriction enhances skeletal muscle stem cell function. *Cell stem cell.* 2012;10:515-519. DOI: <https://doi.org/10.1016/j.stem.2012.04.002>
80. Johnson J, Summer W, Cutler R, Martin B, Hyun DH, Dixit VD, et al. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. *Free Radical Biology and Medicine.* 2007;42(5):665-674. DOI: <https://doi.org/10.1016/j.freeradbiomed.2006.12.005>
81. Wang C, Maddick M, Miwa S, Jurk D, Czapiewski R, Saretzki G, et al. Adult-onset, short-term dietary restriction reduces cell senescence in mice. *Aging (Albany NY).* 2010;2(9):555-566. DOI: <https://doi.org/10.18632/aging.100196>
82. Cherniack EP. The potential influence of plant polyphenols on the aging process. *Forsch Komplementmed.* 2010;17(4):181-187. DOI: <https://doi.org/10.1159/000319143>
83. Wilson DW, Nash P, Buttar HS, Griffiths K, Singh R, De Meester F, et al. The Role of Food Antioxidants, Benefits of Functional Foods, and Influence of Feeding Habits on the Health of the Older Person: An Overview. *Antioxidants (Basel).* 2017;6(4):81. DOI: <https://doi.org/10.3390/antiox6040081>
84. Dunne TE, Nearing SA, Cipolloni PB, Cronin-Golomb A. Visual contrast enhances food and liquid intake in advanced Alzheimer's disease. *Clin. Nutr.* 2004;23:533-538. DOI: <https://doi.org/10.1016/j.clnu.2003.09.015>
85. Bonfils P, Malinvaud D, Bozec H, Halimi M. Les troubles de l'olfaction [Olfactory disorders]. *Ann Otolaryngol Chir Cervicofac.* 2004;121(2):67-74. DOI: [https://doi.org/10.1016/s0003-438x\(04\)95492-8](https://doi.org/10.1016/s0003-438x(04)95492-8)

## ГЕРОПРОТЕКТОРНІ ВЛАСТИВОСТІ ПОЛІФЕНОЛЬНИХ СПОЛУК ХАРЧОВИХ РОСЛИН

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**Анотація.** Старіння населення створює економічні та соціальні проблеми для суспільства у всьому світі. У статті показані результати аналізу сучасних досліджень щодо способів і засобів, які можуть усувати причини старіння, продовжувати активне довголіття і працездатність людей похилого віку. Встановлено взаємозв'язок здоров'я і довголіття людини з особливостями її харчування, дефіцитом мікронутрієнтів в організмі через незбалансованість харчового раціону. На основі вільнорадикальної теорії старіння, яка заснована на хімічній природі і повсюдній присутності вільних радикалів, виявлено, що споживання харчових продуктів рослинного походження, багатих антиоксидантами, запобігає окислювальним пошкодженням клітинних структур, спричинених активними формами кисню. Захисний ефект продемонстровано для добре відомих рослинних антиоксидантів, таких як флавоноїди та інші поліфенольні сполуки, які модулюють енергетичний метаболізм способом, сприятливим для самопочуття та довголіття, та зменшують ризик хронічних захворювань і старіння. Встановлено, що антиокислювальний ефект флавоноїдів включає перехоплення вільних ліпопероксидних радикалів, пригнічення продукції оксиду азоту, дезактивацію пероксинітриду і інших окислювачів, інгібування ксантинооксидази та інших радикалпродуруючих ензимів, хелатування металів. Виявлено нейропротекторні та радіозахисні властивості флавоноїдів. Вони можуть інгібувати регуляторні ферменти або фактори транскрипції, які важливі для контролю медіаторів запалення, впливають на окислювальний стрес через взаємодію з ДНК та посилюють геномну стабільність. Комбінації поліфенолів можуть виявляти синергічні або адитивні сприятливі ефекти. Показано, що раціональне застосування рослинних дієт, багатих поліфенольними сполуками, сприяє зниженню загальної смертності і смертності від ішемічної хвороби серця, підтримці сталого управління вагою тіла, зниженню частоти і тяжкості станів високого ризику, таких як ожиріння, гіперглікемія, гіпертензія, гіперліпідемія і покращенню стану при запущених серцево-судинних захворюваннях і діабеті.

**Ключові слова:** старіння, харчові рослини, антиоксиданти, поліфеноли, флавоноїди, геропротектори.

### Список літератури:

1. Wojdylo A., Oszmiański J., Czemerys R. Antioxidant activity and phenolic compounds in 32 selected herbs // *Food Chem.* 2007. Vol. 105, Issue 3. P.940–949. DOI: <https://doi.org/10.1016/j.foodchem.2007.04.038>
2. Mori M.A. Aging: a New Perspective on an Old Issue // *An Acad Bras Cienc.* 2020. Vol. 92, Issue 2. P. e20200437. DOI: <https://doi.org/10.1590/0001-3765202020200437>
3. Flatt T., Partridge L. Horizons in the evolution of aging // *BMC Biol.* 2018. Vol. 16, Issue 1. P.1-13. <https://doi.org/10.1186/s12915-018-0562-z>
4. Telomeres, Nutrition, and Longevity: Can We Really Navigate Our Aging? / Vidacek N.Š. et al // *J Gerontol A Biol Sci Med Sci.* 2017. Vol. 73, Issue 1. P.39-47. doi: 10.1093/gerona/glx082
5. The hallmarks of aging / López-Otín C. et al // *Cell.* 2013. Vol. 153, Issue 1. P. 1194-1217. DOI: <https://doi.org/10.1016/j.cell.2013.05.039>
6. Bayliak M.M., Burdyliuk N.I., Lushchak V.I. Effects of pH on antioxidant and prooxidant properties of common medicinal herbs // *Open Life Sci.* 2016. Vol. 11. P. 298-307 DOI: <https://doi.org/10.1515/biol-2016-0040>
7. Halliwell B. Are polyphenols antioxidants or pro-oxidants? What do we learn from cell culture and in vivo studies? // *Arch. Biochem. Biophys.*, 2008. Vol. 476, Issue 2. P. 107-112. DOI: <https://doi.org/10.1016/j.abb.2008.01.028>
8. Sies H. Polyphenols and health: update and perspectives // *Arch Biochem Biophys.* 2010. Vol.501, Issue 1. P. 2-5. DOI: <https://doi.org/10.1016/j.abb.2010.04.006>
9. Karasawa M.M.G., Mohan, C. Fruits as Prospective Reserves of bioactive Compounds: A Review // *Nat. Prod. Bioprospect.* 2018. Vol. 8. P. 335-346. DOI: <https://doi.org/10.1007/s13659-018-0186-6>
10. Badithe T., Ashok R. A. The aging paradox: free radical theory of aging // *Experimental Gerontology* 1999. Vol. 34, Issue 3. P. 293-303. DOI: [https://doi.org/10.1016/S0531-5565\(99\)00005-4](https://doi.org/10.1016/S0531-5565(99)00005-4)
11. Medvedev Z. A. An attempt at a rational classification of theories of aging // *Biol. Rev.* 1990. Vol. 65. P. 375-398 DOI: <https://doi.org/10.1111/j.1469-185x.1990.tb01428.x>
12. Gavrilov L. A., Gavrilova N. S. Reliability Theory of Aging and Longevity // *Journ. of Theoret. Biology.* 2001. Vol. 213, Issue 4. P. 527-545. <https://doi.org/10.1016/B978-012088387-5/50004-2>
13. Robert L., Fulop T. Aging: Facts and Theories. *Interdiscipl Top Gerontol* // Basel, Karger. 2014. Vol. 39. P. 163-176. DOI: <https://doi.org/10.1159/000358904>
14. Immunosenescence and Immunogenetics of Human Longevity / Ostan R. et al // *Neuroimmunomodulation* 2008. Vol.15. P. 224-240. DOI: <https://doi.org/10.1159/000156466>
15. Aging of the immune system: Focus on inflammation and vaccination / Pinti M. et al // *Eur J Immunol.* 2016. Vol.46, Issue 10. P.2286-2301. DOI: <https://doi.org/10.1002/eji.201546178>
16. Jin K. Modern biological theories of aging // *Aging Dis.* 2010. Vol.1, Issue 2.P. 72-74.

17. Wang X, Ma Z, Cheng J, Lv Z. A genetic program theory of aging using an RNA population model // *Ageing Res Rev.* 2014. Vol. 13. P. 46-54. DOI: <https://doi.org/10.1016/j.arr.2013.11.001>
18. Sinclair A.D., LaPlante M. D. *Lifespan: Why We Age—and Why We Don't Have To.* Simon & Schuster, 2019. 432 p.
19. Telomere shortening as a hallmark of stem cell senescence / Fathi E. et al // *Stem Cell Investig.* 2019. Vol.6. P.1-7. DOI: <https://doi.org/10.21037/sci.2019.02.04>
20. Telomere and its role in the aging pathways: telomere shortening, cell senescence and mitochondria dysfunction / Zhu Y. et al // *Biogerontology.* 2019. Vol. 20, Issue 1. P. 1-16. DOI: <https://doi.org/10.1007/s10522-018-9769-1>
21. Bjorksten J. The crosslinkage theory of aging // *J Am Geriatr Soc.* 1968. Vol.16, Issue 4. P.408-427. DOI: <https://doi.org/10.1111/j.1532-5415.1968.tb02821.x>.
22. Beckman K.B., Ames B.N. The free radical theory of aging matures // *Physiol Rev.* 1998. Vol. 78, Issue 2. P. 547-81. DOI: <https://doi.org/10.1152/physrev.1998.78.2.547>
23. Harman D. Free radical theory of aging // *Mutation Research/DNAging.* 1992. Vol. 275, Issues 3(6). P. 257-266. DOI: [https://doi.org/10.1016/0921-8734\(92\)90030-S](https://doi.org/10.1016/0921-8734(92)90030-S)
24. Biesalski H. K. Free radical theory of aging // *Current Opinion in Clinical Nutrition and Metabolic Care.* 2002. Vol. 5, Issue 1. P. 5-10. DOI: <https://doi.org/10.1097/00075197-200201000-00002>
25. Wray B. The ambitious quest to cure ageing like a disease // *BBC Future: 5th February 2018.* URL: <https://www.bbc.com/future/article/20180203-the-ambitious-quest-to-cure-ageing-like-a-disease> (viewed on: 04.01.2021)
26. Rattan S.I.S. Naive extrapolations, overhyped claims and empty promises in ageing research and interventions need avoidance // *Biogerontology.* 2020. Vol. 21, Issue 4. P. 415-421. DOI: <https://doi.org/10.1007/s10522-019-09851-0>
27. Sholl J. The sciences of healthy aging await a theory of health // *Biogerontology.* 2020. Vol.21, Issue 3. P.399-409. DOI: <https://doi.org/10.1007/s10522-020-09872-0>
28. Aging and rejuvenation - a modular epigenome model / Chiavellini P. et al // *Aging (Albany NY).* 2021. Vol. 13, Issue 4. P.4734-4746. DOI: <https://doi.org/10.18632/aging.202712>
29. Horvath S. DNA methylation age of human tissues and cell types // *Genome Biol.* 2013. Vol. 14, Issue 10. 20 p. DOI: <https://doi.org/10.1186/gb-2013-14-10-r115>
30. Epigenetic predictor of age / Bocklandt S. et al // *PLoS One.* 2011. Vol. 6, Issue 6. P. e14821 DOI: <https://doi.org/10.1371/journal.pone.0014821>.
31. Genome-wide methylation profiles reveal quantitative views of human aging rates / Hannum G. et al. // *Mol Cell.* 2013. Vol. 49, Issue 2. P. 359–367. DOI: <https://doi.org/10.1016/j.molcel.2012.10.016>
32. In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming / Ocampo A. et al // *Cell.* 2016. Vol. 167, Issue 7. P. 1719-1733. DOI: <https://doi.org/10.1016/j.cell.2016.11.052>
33. Reprogramming to recover youthful epigenetic information and restore vision / Lu Y. et al // *Nature.* 2020. Vol. 588, Issue 7836. P. 124-129. DOI: <https://doi.org/10.1038/s41586-020-2975-4>
34. Lavazza A., Garasic M. Vampires 2.0? The ethical quandaries of young blood infusion in the quest for eternal life // *Med Health Care and Philos.* 2020. Vol. 23. P. 421-432. DOI: <https://doi.org/10.1007/s11019-020-09952-5>
35. Hofmann B. Young Blood Rejuvenates Old Bodies: A Call for Reflection when Moving from Mice to Men // *Transfus Med Hemother.* 2018. Vol. 45, Issue 1. P. 67-71. DOI: <https://doi.org/10.1159/000481828>
36. Association of donor age and sex with survival of patients receiving transfusions / Edgren G. et al // *JAMA Intern Med.*, 2017. Vol. 177, Issue 6. P. 854-860. DOI: <https://doi.org/10.1001/jamainternmed.2017.0890>
37. Dietary Anti-Aging Polyphenols and Potential Mechanisms / Luo J. et al // *Antioxidants.* 2021. Vol. 10, Issue 2. P. 283. DOI: <https://doi.org/10.3390/antiox10020283>
38. Scalbert A., Johnson I.T., Saltmarsh M. Polyphenols: antioxidants and beyond // *Am J Clin Nutr.* 2005. Vol. 81, Issue 1. P. 215-217. DOI: <https://doi.org/10.1093/ajcn/81.1.215S>
39. Metabolic Impact of Flavonoids Consumption in Obesity: From Central to Peripheral / Sandoval V. et al // *Nutrients.* 2020. Vol. 12, Issue 8. P. 2393. DOI: <https://doi.org/10.3390/nu12082393>
40. Ebrahimipour S., Zakeri M., Esmaeili A. Crosstalk between obesity, diabetes, and alzheimer's disease: Introducing quercetin as an effective triple herbal medicine // *Ageing Res Rev.* 2020. Vol. 62. P. 101095. DOI: <https://doi.org/10.1016/j.arr.2020.101095>
41. Interaction of Polyphenols as Antioxidant and Anti-Inflammatory Compounds in Brain-Liver-Gut Axis / Singh A. et al // *Antioxidants (Basel).* 2020. Vol. 9, Issue 8. P.669. DOI: <https://doi.org/10.3390/antiox9080669>
42. Si H., Liu D. Dietary antiaging phytochemicals and mechanisms associated with prolonged survival // *J Nutr Biochem.* 2014. Vol. 25, Issue 6. P.581-591. DOI: <https://doi.org/10.1016/j.jnutbio.2014.02.001>
43. Boojar M.M.A. An Overview of the Cellular Mechanisms of Flavonoids Radioprotective Effects // *Adv Pharm Bull.* 2020. Vol. 10, Issue 1. P. 13-19. DOI: <https://doi.org/10.15171/apb.2020.002>
44. Williams C.A., Grayer R.J. Anthocyanins and other flavonoids // *Nat Prod Rep.* 2004. Vol. 21, Issue 4. P. 539-573. DOI: <https://doi.org/10.1039/b311404j>
45. Ghasemzadeh A., Ghasemzadeh N. Flavonoids and phenolic acids: role and biochemical activity in plants and human // *J Med Plant Res.* 2011. Vol. 5. Issue 31. P. 6697-6703. DOI: <https://doi.org/10.5897/JMPR11.1404>
46. Brodowska K.M. Natural flavonoids: classification, potential role, and application of flavonoid analogues // *Eur J Biol Res.* 2017. Vol.7, Issue 2. P. 108-123. DOI: <http://doi.org/10.5281/zenodo.545778>
47. Keller R.B. *Flavonoids: Biosynthesis, Biological Effects and Dietary Sources (Nutrition and Diet Research Progress).* Nova Science Publishers Inc. 2009. 388 p.
48. Maleki S.J., Crespo J.F., Cabanillas B. Anti-inflammatory effects of flavonoids // *Journal of Food Chemistry.* 2019. Vol. 299. P.125124. DOI: <https://doi.org/10.1016/j.foodchem.2019.125124>
49. Барабой В.А. Изофлавононі сої: біологічна активність та застосування // *Біотехнологія.* 2009. Т.2, №3. С. 44-54.
50. Radioprotective Effect of Flavonoids on Ionizing Radiation-Induced Brain Damage / Wang Q. et al // *Molecules* 2020. Vol.25, Issue 23. 20 p. DOI: <https://doi.org/10.3390/molecules25235719>
51. Tiwari P., Mishra K.P. Flavonoids sensitize tumor cells to radiation: molecular mechanisms and relevance to cancer radiotherapy // *International Journal of Radiation Biology* 2020. Vol. 96, Issue 3. P. 360-369. DOI: <https://doi.org/10.1080/09553002.2020.1694193>
52. Wu S., Tian L. Diverse Phytochemicals and Bioactivities in the Ancient Fruit and Modern Functional Food Pomegranate (*Punica granatum*) // *Molecules.* 2017. Vol. 22, Issue 10. P.1606. DOI: <https://doi.org/10.3390/molecules22101606>.
53. Dietary intake and major food sources of polyphenols in a Spanish population at high cardiovascular risk: the PREDIMED study / Tresserra-Rimbau A. et al // *Nutr Metab Cardiovasc Dis.* 2013. Vol. 23, Issue 10. P. 953-959. DOI: <https://doi.org/10.1016/j.numecd.2012.10.008>.

54. Effects of polyphenols on brain ageing and Alzheimer's disease: focus on mitochondria / Schaffer S. et al // *Mol Neurobiol.* 2012. Vol. 46, Issue 1. P. 161-178. DOI: <https://doi.org/10.1007/s12035-012-8282-9>
55. Bioavailability of bioactive food compounds: a challenging journey to bioefficacy / Rein M.J. et al // *Br J Clin Pharmacol.* 2013. Vol.75, Issue 3. P. 588-602. DOI: <https://doi.org/10.1111/j.1365-2125.2012.04425.x>
56. Zhang L., Virgous C., Si H. Synergistic anti-inflammatory effects and mechanisms of combined phytochemicals // *J Nutr Biochem.* 2019. Vol. 69. P. 19-30. DOI: <https://doi.org/10.1016/j.jnutbio.2019.03.009>
57. Antioxidant Activity of Spices and Their Impact on Human Health: A Review / Yashin A. et al // *Antioxidants.* 2017. Vol. 6, Issue 3. 18 p. DOI: <https://doi.org/10.3390/antiox6030070>
58. Cook N.C., Samman S. Flavonoids-Chemistry, metabolism, cardioprotective effects and dietary sources // *J. Nutr. Biochem.* 1996. Vol. 7. P. 66-76. DOI: [https://doi.org/10.1016/0955-2863\(95\)00168-9](https://doi.org/10.1016/0955-2863(95)00168-9)
59. Flavonoids in food and their health benefits, Flavanones in cumin, peppermint, Flavones in parsley, thyme and Flavonols in onions / Yao L.H. et al // *Plant Foods Hum. Nutr.* 2004. Vol. 59, Issue 3. P.113-122. DOI: <https://doi.org/10.1007/s11130-004-0049-7>
60. Zheng W., Wang S.Y. Antioxidant activity and phenolic compounds in selected herbs // *J. Agric. Food Chem.* 2001. Vol. 49, Issue 10. P. 5165-5170. DOI: <https://doi.org/10.1021/jf010697n>
61. USDA Database for the Flavonoid Content of Selected Foods [Web-site]. Release 3.1. (May 2014) URL: [https://www.ars.usda.gov/ARSEUserFiles/80400525/Data/Flav/Flav\\_R03-1.pdf](https://www.ars.usda.gov/ARSEUserFiles/80400525/Data/Flav/Flav_R03-1.pdf) (viewed 28.12.2020).
62. Antioxidant capacity of 26 extracts of spices and characterization their phenolic components / Shan B. et al // *J. Agric. Food Chem.* 2005. Vol.53. P.7749-7759. DOI: <https://doi.org/10.1021/jf051513y>
63. Jorgustin K. Top 100 High ORAC Value Antioxidant Foods. 2014. URL: <http://modernsurvivalblog.com/health/high-orac-value-antioxidant-foods-top-100/> (viewed 20.12.2020)
64. Haytowitz D.B., Bhagwat S. USDA Database for the Oxygen Radical Absorbance Capacity (ORAC) of Selected Foods, Release 2. 2010. URL: [http://www.ars.usda.gov/ARSUserFiles/80400525/Data/ORAC/ORAC\\_R2.pdf](http://www.ars.usda.gov/ARSUserFiles/80400525/Data/ORAC/ORAC_R2.pdf) (viewed 5.12.2020)
65. Корзун В. Н., Свідло К. В. Харчові раціони геродієтичного призначення з використанням дієтичних добавок рослинного походження // *Проблеми старіння і довголіття.* 2016. Т. 25, № 2. С. 235-252.
66. Dirks A.J., Leeuwenburgh C. Caloric restriction in humans: potential pitfalls and health concerns // *Mech Ageing Dev.* 2006. Vol.127, Issue 1. P.1-7. DOI: <https://doi.org/10.1016/j.mad.2005.09.001>
67. The aging process and potential interventions to extend life expectancy / Tosato M. et al // *Clin Interv Aging.* 2007. Vol.2, Issue 3. P.401-412.
68. The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake / Weindruch R. et al. // *J Nutr.* 1986. Vol. 116, Issue 4. P. 641-654. DOI: <https://doi.org/10.1093/jn/116.4.641>
69. Neuroendocrine and pharmacological manipulations to assess how caloric restriction increases life span / Mobbs C.V. et al. // *J Gerontol A Biol Sci Med Sci.* 2001. Vol.56, Issue 1. P. 34-44. DOI: [https://doi.org/10.1093/gerona/56.suppl\\_1.34](https://doi.org/10.1093/gerona/56.suppl_1.34)
70. The state of US health, 1990-2010: burden of diseases, injuries, and risk factors / Murray C.J. et al. // *JAMA.* 2013. Vol. 310, Issue 6. P. 591-606. DOI: <https://doi.org/10.1001/jama.2013.13805>
71. Hever J., Cronise R.J. Plant-based nutrition for healthcare professionals: implementing diet as a primary modality in the prevention and treatment of chronic disease // *J Geriatr Cardiol.* 2017. Vol. 14, Issue 5. P. 355-368. DOI: <https://doi.org/10.11909/j.issn.1671-5411.2017.05.012>
72. Vegetarian dietary patterns and mortality in Adventist Health Study 2 / Orlich M.J. et al // *JAMA Intern Med.* 2013. Vol.173, Issue 13. P.1230-1238. DOI: <https://doi.org/10.1001/jamainternmed.2013.6473>
73. Risk of hospitalization or death from ischemic heart disease among British vegetarians and nonvegetarians: results from the EPIC-Oxford cohort study / Crowe F.L. et al // *Am J Clin Nutr.* 2013. Vol. 97, Issue 3. P. 597-603. DOI: <https://doi.org/10.3945/ajcn.112.044073>
74. A low-fat vegan diet and a conventional diabetes diet in the treatment of type 2 diabetes: a randomized, controlled, 74-wk clinical trial / Barnard N.D. et al // *Am J Clin Nutr.* 2009. Vol. 89, Issue 5. P.1588-1596. DOI: <https://doi.org/10.3945/ajcn.2009.26736H>
75. Vegetarian Diets and Weight Reduction: a Meta-Analysis of Randomized Controlled Trials / Huang R.Y. et al // *J Gen Intern Med.* 2016. Vol. 31, Issue 1. P.109-116. DOI: <https://doi.org/10.1007/s11606-015-3390-7>
76. Barnard N.D., Levin S.M., Yokoyama Y. A systematic review and meta-analysis of changes in body weight in clinical trials of vegetarian diets // *J Acad Nutr Diet.* 2015. Vol. 115, Issue 6. P. 954-969. DOI: <https://doi.org/10.1016/j.jand.2014.11.016>
77. Walsh M.E., Shi Y., Van Remmen H. The effects of dietary restriction on oxidative stress in rodents // *Free Radic Biol Med.* 2014. Vol. 66.P. 88-99. DOI: <https://doi.org/10.1016/j.freeradbiomed.2013.05.037>
78. Caloric Restriction Suppresses Microglial Activation and Prevents Neuroapoptosis Following Cortical Injury in Rats / Loncarevic-Vasiljkovic N. et al // *PLoS ONE.* 2012. Vol.7, Issue5. P. e37215. DOI: <https://doi.org/10.1371/journal.pone.0037215>
79. Short-term calorie restriction enhances skeletal muscle stem cell function / Cerletti M. et al // *Cell stem cell.* 2012. Vol. 10. P. 515-519. DOI: <https://doi.org/10.1016/j.stem.2012.04.002>
80. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma / Johnson J. et al // *Free Radical Biology and Medicine.* 2007. Vol. 42, Issue 5. P. 665-674. DOI: <https://doi.org/10.1016/j.freeradbiomed.2006.12.005>
81. Adult-onset, short-term dietary restriction reduces cell senescence in mice / Wang C. et al // *Aging (Albany NY).* 2010. Vol. 2, Issue 9. P. 555-566. DOI: <https://doi.org/10.18632/aging.100196>
82. Cherniack E.P. The potential influence of plant polyphenols on the aging process // *Forsch Komplementmed.* 2010. Vol. 17, Issue 4. P. 181-187. DOI: <https://doi.org/10.1159/000319143>
83. The Role of Food Antioxidants, Benefits of Functional Foods, and Influence of Feeding Habits on the Health of the Older Person: An Overview / Wilson D.W. et al // *Antioxidants (Basel).* 2017. Vol. 6, Issue 4. P. 81. DOI: <https://doi.org/10.3390/antiox6040081>
84. Visual contrast enhances food and liquid intake in advanced Alzheimer's disease / Dunne T.E. et al // *Clin. Nutr.* 2004. Vol. 23. P. 533-538. DOI: <https://doi.org/10.1016/j.clnu.2003.09.015>
85. Les troubles de l'olfaction / Bonfils P. et al // *Ann Otolaryngol Chir Cervicofac.* 2004. Vol. 121, Issue 2. P. 67-74. DOI: [https://doi.org/10.1016/s0003-438x\(04\)95492-8](https://doi.org/10.1016/s0003-438x(04)95492-8)