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NATURAL BIOLOGICALLY ACTIVE COMPOUNDS - PERSPECTIVE AGENTS FOR LONGEVITY

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Abstract. Aging is the most prominent risk factor for many diseases, which is considered to be a complicated biological process. The rate of aging depends on the effectiveness of important mechanisms such as the protection of DNA from free radicals, which protects the structural and functional integrity of cells and tissues. In any organism, not all organs may age at the same rate. Slowing down primary aging and reaching maximum lifespan is the most basic necessity. In this process, it may be possible to slow down or stabilise some diseases by using the compounds for both dietary and pharmacological purposes. Natural compounds with antioxidant and anti-inflammatory effects, mostly plant-based nutraceuticals, are preferred in the treatment of age-related chronic diseases and can also be used for other diseases. An increasing number of long-term studies on synthetic and natural compounds aim to elucidate preclinically and clinically the mechanisms underlying being healthy and prolongation of life. To delay age-related diseases and prolong the lifespan, it is necessary to take these compounds with diet or pharmaceuticals, along with detailed toxicological results.

Keywords: anti-aging compounds, caffeine, curcumin, fucoxanthin, metformin, resveratrol, spermidine, α-lipoic acid.

Introduction. Aging can be defined as the accumulation of damage over time, a loss in functional ability, adaptation difficulties to the environment and an increase in illness and mortality. The aging of the global population is posing significant issues for both industrialised and developing countries due to changes in the population pyramid [1, 2]. The percentage of persons over the age of 60 is increasing globally, and it is predicted that by 2050, it would nearly double, rising from 12 per cent in 2015 to 22 percent [3-5]. Despite the continued predicted increase in the aging population, the geriatric population's life expectancy and survival are improving significantly [4].

According to several studies, aging is one of the most important risk factors for chronic diseases including cancer, atherosclerosis, cardiovascular disease, stroke, diabetes, renal failure, chronic lung disease, osteoporosis, rheumatoid arthritis, blindness, dementia and neurological pathologies that cause the greatest global morbidity, mortality and use of medical resources. Additionally, aging increases a person's risk for the geriatric syndrome, a reduction in immunity and slower physical recovery [5-8].

Due to its significant role as a risk factor for morbidity and age-related diseases, the biology of aging has considerable interest among researchers.

Many hypotheses have been developed to expand our comprehension of the aging process and to help us develop methods for extending life. Based on the level at which the aging mechanism is targeted, the theories of aging are divided into categories including evolutionary, systemic, molecular and cellular theories [9].

In aging research, several natural products and dietary supplements continue to be studied extensively for their antiaging properties or are used as research materials to discover molecular mechanisms of biological aging [10, 11]. Using natural resources may be an effective way to delay physiological and pathological aging and, in turn, avoid the development of these disorders, according to recent research [12-14]. Natural compounds that are separated or obtained from plants are distinguished by the synthesis of secondary metabolites and are abundant in nature. Numerous chemical families, primarily flavonoids, phenolic acids and terpenoids, are included in secondary metabolites. Other compounds that are part of the primary metabolites have also demonstrated important anti-aging benefits.

The aim of the study. To analyze the data confirming the anti-aging properties of some of the most promising natural substances, summarizing their pharmacological and toxicological properties.

Materials and Methods. A literature analysis was carried out to study a number of potent natural compounds that inhibit the aging process according to scientific and metric data.

Results and Discussion. Caffeine, a methylxanthine derivative (13,7-trimethylxanthine) is a secondary metabolite classified as a purine alkaloid and synthesised majorly in various plants such as *Coffea arabica L.*, *Camellia sinensis*, *Paullinia cupana* Kunth and *Cola sp.* [15]. Psychomotor stimulant properties of caffeine are primarily associated with its reducing properties on adenosine transmission via the blockade of adenosine in the brain [16]. Other mechanisms of action proposed for caffeine, inhibition of phosphodiesterase and mobilisation of intracellular calcium,

require high concentrations of caffeine than likely to be taken in daily consumption [17]. It has been suggested that age-related neurodegenerative diseases are reduced by chronic, moderate caffeine consumption as well as habitual consumption was correlated with reduced mortality and positively affected healthspan features. In addition, its lifespan extending effect on the worm model was reported [18]. However, National Health and Nutrition Examination Survey on 5826 adults from two genders, investigating the relationships between caffeine and coffee intakes, and telomere length, presented that caffeine consumption caused a tendency to shorten telomeres in US adults. However, telomere lengths were positively affected by coffee consumption [19].

Metformin (MET) is a biguanide used as a first-line treatment for type-2 diabetes mellitus [20]. The discovery of MET (dimethylbiguanide) is linked to a plant *Galega officinalis L.*, which was traditionally used in Europe to treat the symptoms of diabetes and was later found to be rich in guanidine with blood sugar-lowering effects. The synthesised guanidine derivative MET was introduced as an antidiabetic agent in the 1990s in the USA [21]. It is a potent antihyperglycemic agent, which counters insulin resistance, reduces hepatic gluconeogenesis and increases glucose uptake, without causing weight gain and overt hypoglycemia [22]. The drug also has beneficial features for diabetes-related polycystic ovary disease, fatty liver disease and cardiovascular complications, alongside being suggested as an adjuvant treatment for cancer or gestational diabetes in the pre-diabetic population

The enhancing effects of MET on insulin sensitivity are assigned to its stimulation of the tyrosine kinase activity of the β subunit of the insulin receptor [22]. At the molecular level, MET blocks the mitochondrial respiratory chain, which leads to the activation of AMPK resulting in suppression the production of gluconeogenic enzymes [23]. MET's potential as an anti-aging candidate was shown in several studies. In the context of telomere length, telomere shortening was reduced by metformin in the mild age-related diabetes (MARD) group. The telomere length of MARD group was significantly shorter than the NON-MARD group, however, was disappeared after MET [24].

Fucoxanthin is a naturally occurring marine carotenoid, which was found in algae such as *Undaria pinnatifida*, *Laminaria japonica*, *Phaeodactylum tricornutum and Cylindrotheca closterium*, and has a unique structure. The molecular structure, which was composed of a conjugated carbonyl group with an unusual allenic bond, a 5,6-monoepoxide and some oxygenic functional groups, is unstable and easily degradable by oxygen, heat, light, etc [25]. Trans-fucoxanthin, which is responsible for its biological activities, is shown to produce its two minor cis-isomers according to storage conditions [26, 27]. Fucoxanthin has been shown to have potential health

benefits for lifestyle-related diseases by the evidence of hepatoprotective, anti-inflammatory, antioxidant, antidiabetic, antitumoural and anti-obesity activities [28] along with anti-aging properties. Especially with its enhanced antioxidant capacity, fucoxanthin inhibits the ROS which increases in some diseases like ischaemic stroke and acute lung injury [29].

Spermidine is a natural aliphatic polyamine and is found in all living cells of plants, animals and microorganisms, as well as can also be found in plant- and animal-originated foods [30]. For several organisms, the proportion of polyamines like spermidine is due to either administration via dietary sources or synthesised by the gut microbiota [31]. Spermidine is found high in foods such as wheat germ, fermented soybeans, mushrooms, nuts and some fruits and vegetables. It is absorbed mainly in the duodenum and proximal jejunum parts of the small intestine [32]. The nutritional intake of foods that contain arginine (precursor of polyamines) helps polyamine-producing bacteria produce spermin and spermidine in the microbiota of mammals [33]. The studies suggest that a polyamine rich diet including spermidine helps humans reach older ages healthy, recover especially after surgery and wound healing because of its antioxidant properties [30, 31]. It has antitumour, cardiovascular protective, neuromodulator, anti-obesity and anti-inflammatory features, and is an autophagy-inducing agent, as well [30, 32]. Besides, spermidine treatment induced a reduced percentage of the nuclei with short telomeres [33].

α-Lipoic acid is a caprylic acid-derived fatty acid found in several dietary sources such as red meats, heart, kidney, liver, wheat germ and to a lesser degree, fruits and vegetables. The compound has a dithiol functional group, which reacts with free radicals [34]. The studies reveal that it provides detoxification and promotes some biochemical reactions, especially the renewal of damaged detoxification enzymes that helps to treat chronic diseases associated with oxidative stress. Both in vitro and in vivo studies have shown α-lipoic acid demonstrating very high radical scavenging activity, the main reason for which has been added as an ingredient in several dietary supplements such as multivitamins also used by intravenous injection. Especially its reduced metabolite dihydrolipoic acid (DHLA) showed quite high radical scavenging activity [35]. PGC-1α (peroxisome proliferator-activated receptor γ coactivator-1α) is a receptor, plays a role in protecting from age-related chronic diseases. Xiong et.al. 2005 indicates that α-LA, as a cofactor, upregulated PGC-1α-dependent-TERT (telomerase reverse transcriptase), therefore modulating age-dependent arteriopathy which helps reducing vascular aging [36]. Studies also indicate that it is not possible to keep enough levels of α-LA only from natural sources to see its anti-aging effect, so

to have significant antioxidant activity it is needed to take α-LA as a supplement in higher doses. Therefore, the need of assessing its daily dose for humans occurred in the light of acute and subchronic toxicity, and potential mutagenic/genotoxic activity. Studies currently have found no adverse effects in the acute toxicity studies when given 175–550 mg/kg BW α-LA by oral gavage for 14-days to female CD Sprague-Dawley rats. At 2000 mg/kg BW, some rats 'were reported to show signs of reduced well-being, including sedation, apathy, piloerection, hunched posture and/or eye closure. There was no effect of treatment observable on body weight gain or gross pathological examination. As a result of the study, the acute oral LD50 of α-LA was concluded to exceed 2000 mg/kg, the highest dose tested in the study which indicates a very low order of acute toxicity. A 4-week sub-chronic toxicity study on both male and female Wistar rats was performed with the determined doses from low (31.6 mg/kg BW/day) to high (121 mg/kg BW/day). The no-observed-adverse-effect level (NOAEL) is considered to be 61.9 mg/kg BW/day. The results of these studies support the safety of α-LA. The experimental safety dosage values were found 400 to 500 mg/kg for dogs, 30 mg/kg for cats and 500 mg/kg for mice [35].

Resveratrol is a plant-specific polyphenolic compound produced by numerous plant species generally synthesised in terms of some stress conditions in fruits (especially grapes and several berries), nuts and table wines. The fruits of Vitis vinifera (grape) are dedicated as the most important dietary source of resveratrol [37]. It also belongs to the phytoalexin group because it has occurred under some stress conditions such as microbial infections, intense radiation and heavy metals [38]. The importance of resveratrol as a supplement for human health comes from several study results showing antioxidant, anticarcinogenic and antitumour activity [39]. The radical scavenging mechanism of resveratrol can be explained as acting as a pro-oxidant first, stimulating the free radical generation and then eliminating the ROS. This phenomenon is called 'hormesis' [40]. Besides its high antioxidant capacity studies showed that resveratrol activates proteins such as Sir2/SIRT1 and AMPK, which modulate lifespan in organisms [41]. Resveratrol could be a potential therapeutic supplement in preventing long-term cardiovascular morbidity and mortality [42]. Studies claim that resveratrol also significantly increased telomerase activity in vitro. Resveratrol has been shown to delay endothelial progenitor cells senescence by increasing the number of the cells, which may be dependent on telomerase activation [43]. Resveratrol was proven to prolong the lifetime with a range of 10 to 72% in several study models. Resveratrol has cis- and trans- isomeric forms, of which numerous studies have focused on the biological activities and safety studies of trans-form [44, 45] trans-Resveratrol

has been found more stable with high bioactive effects. According to the studies, resveratrol increases longevity and provides recovery for age-related diseases via scavenging free radicals [46]. Together with rapamycin and curcumin, resveratrol is in the preclinical test phase of the 'Interventions Testing Program of the National Institute on Aging' to be a candidate for phytomedicinal drug.

Curcumin, has been reported to exert several health effects as the main natural polyphenol found in the rhizome of *Curcuma longa L*. Most of the benefits of curcumin are attributed to its antioxidant and anti-inflammatory effects. It is stated that the high free radical scavenging activity and inhibitory effect on acute and chronic inflammation are due to the electron-donating group on the phenolic rings of curcumin [47]. In a study performed on human brain tumor cells, curcumin inhibited telomerase activity in all the telomerase-positive cell lines. Long-term curcumin treatment has also resulted in significant telomere shortening in cancer cell lines, which explains its potent anti-tumorigenic and antiproliferative activity [48]. Curcumin is now one of the most consumed food supplements in several countries. It is also accepted as a yellow pigment being used as a food additive [49]. In some acute toxicity studies with a single dose of 5.000 mg/kg body weight curcumin given orally to Swiss albino mice or albino Wistar rats, no toxic effects or adverse signs were observed for 14 days [50].

Conclusions. Aging is the most prominent risk factor for many diseases, which is considered to be a complicated biological process. The biology of aging has only lately been thoroughly explored by scientists, who have focused on the evolutionarily conserved mechanisms of aging available to control functional decreases and the onset of disorders associated with aging processes. Regulatory hallmark methodologies that describe how aging is connected to physiological processes and lifestyle choices have provided a path for possible medication development.

Natural products are connected to age-associated chronic diseases, according to the combined findings from in vitro, animal, and clinical investigations over the past few decades. The body contains more plant-based nutraceuticals, such as antioxidants and anti-inflammatory compounds, when it consumes diets high in natural foods. Furthermore, plants and botanicals, medicinally derived substances from nature have been shown to have anti-aging characteristics and are utilised as a springboard for developing effective anti-aging medications. The scientific community now makes considerable use of dietary supplements and small-molecule natural products to find aging mechanisms that have been preserved throughout evolution. Additionally, they have been shown to affect senescence, nutrient-sensing metabolic signalling and

mitochondrial function to slow down cellular aging and diseases associated with aging, including metabolic, cardiovascular, neurological and degenerative joint conditions.

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IRON AND FERRITIN CONCENTRATIONS FOR MONITORING THE HEALTH OF THE BLOOD DONORS

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Abstract. Iron and ferritin concentrations are essential parameters for monitoring the health of blood donors and ensuring the safety and effectiveness of blood donation programmes. This article highlights their importance in the assessment of donor health. We review the clinical correlates of low iron levels in blood donors, including fatigue, cognitive deficits, pica and restless legs syndrome (RLS), and highlight the importance of early detection and intervention to prevent adverse health outcomes. Mitigation approaches such as iron supplementation, dietary advice, individualised donation frequency and education are discussed as key strategies to maintain donor health and minimise the risk of iron depletion. The determination of iron and ferritin concentrations is an integral part of donor health monitoring and the promotion of safe and sustainable blood donation programmes. By implementing evidence-based practices for iron monitoring and management, blood centres can improve donor health and contribute to the well-being of both donors and transfusion recipients.

Keywords: iron, ferritin, blood donation, donor health, iron deficiency, iron depletion, monitoring, risk reduction strategies.