Acta Clin Croat 2010; 49:537-544

Original Scientific Papers

THE ROLE OF NUTRACEUTICALS IN ANTI-AGING MEDICINE

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SUMMARY – 'Nutraceuticals' is a wide term including all kinds of food with health or medical effect. Regulations in the world on functional food and nutraceuticals are developed along with the development of new products. This nomenclature is not aligned across legal regulations in different countries. There are several theories trying to interpret the phenomenon of aging and the most interesting theory in terms of nutrition is free radical theory and the possible role of antioxidants in aging process. A large group of substances including vitamins, carotenoids, flavonoids and minerals have *in vitro* or *in vivo* clinically significant antioxidant characteristics. There is great interest in anti-aging substances derived from food, and the most popular ingredients are antioxidants, especially coenzyme Q10, phytoestrogens, probiotics and omega-3 fatty acids. These substances have beneficial effect on digestive and immune systems, and modulate inflammatory and degenerative processes in the body. The challenge in the future will be strategic combining of cosmeceuticals and nutraceuticals in order to intervene in biological aging processes and degenerative skin changes.

Key words: *aging, antioxidants, dietary supplements, nutraceuticals*

Introduction

Severe oxidative stress progressively leads to cell dysfunction and ultimately cell death. Oxidative stress is defined as an imbalance between pro-oxidants and/or free radicals on the one hand, and anti-oxidizing systems on the other. Epidemiological data suggest that antioxidants may have a beneficial effect on many age-related diseases: atherosclerosis, cancer, some neurodegenerative and ocular diseases. However, the widespread use of supplements is hampered by several factors: the lack of prospective and controlled studies; insufficient knowledge on the pro-oxidant, oxidant and antioxidant properties of the various supplements; growing evidence that free radicals are not only by-products, but also play an important role in cell signal transduction, apoptosis and infection control. Although current data indicate that antioxidants cannot prolong maximal life span, the beneficial impact of antioxidants on various age-related degenerative diseases may forecast an improvement in life span and enhance the quality of life. The current lack of sufficient data does not permit systematic recommendation of high-dosage antioxidants. Nevertheless, antioxidant-rich diets should be recommended.

Nutraceuticals have been proven to offer physiologic benefits or to reduce the risk of chronic disease, or both, beyond their basic nutritional functions. Some of the raw materials are derived from unusual sources and have, in fact, new applications, provide unusual mechanisms of action, or use the latest testing methods, making them on the leading edge of the wave of the future.

As a result, the combination of effective cosmetics and food supplements is the new multiple approach for providing the best skin care treatment that includes beauty, pleasure, and the pride to obtain total wellness one might desire.

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Nutraceuticals

Definitions of food related terms are given in the Croatian Act on Food[1]. According to the Act, a new food is a "food or food ingredients which have not yet been used for human nutrition, and which is not a result of genetic modification, while its composition, characteristics, and effects can have an impact on selection of diet and/or human health"[1].Some of the terms related to 'new' food products include: food for special dietary needs, dietary supplements, aforementioned functional food, nutraceuticals, pharmaconutrients, phytochemicals, zoochemicals, etc. According to the Regulations on Food for Special Dietary Requirements[2], the food for special dietary needs or dietary food refers to "food with special composition, or food manufactured in a special way, or food different from the usual food due to its nutritional characteristics and purpose"[2].

One of the terms that could not be included in those defined in the Regulations is nutraceutical (*nutra* = food; *ceutical* = refers to medical products properties), which is the term differently interpreted by scientists, food manufacturers and governmental organizations.

Regulations in the world on functional food and nutraceuticals are developed along with the development of new products. This nomenclature is not aligned across legal regulations in different countries. According to the 1996 definition by The Foundation for Innovation in Medicine (FIM), the nutraceuticals are "food or food ingredients providing medical and health benefits, including prevention and/or treatment of diseases. Such products include: isolated nutrients, dietary supplements, genetically engineered 'designer' foods, functional foods and herbal extracts"[3]. According to the above definition, all foods or food supplements can be defined as nutraceuticals. 'Health benefits' refer to long-term health improvement or decreasing the risk of development of chronic diseases. Nutraceuticals differ from functional foods as they are used in prevention and treatment of illnesses and they include supplements as well, while functional food is in the form of regular food[3]. Nutraceuticals is a wide term including all kinds of food with health or medical effect. It is closely connected to medical claim term, which is a sensitive matter in the field of regulations of functional foods. The meaning of nutraceuticals is in many aspects very close to the term 'healthy food'[3].

Theories of Aging

There are several theories trying to interpret the phenomenon of aging. Those theories are intervened, based on common assumptions, but none of them gives a completely satisfying explanation. There are three main aging groups: genetic theories group, physiological theories group, and a group of changed organ functions. The physiological theories group contains free radicals theory, cross-linking theory, and theory of waste material accumulation[4].

In the 1950s, Denham Harman (the author of the free radicals theory) assumed that aging is a consequence of excessive production of free radicals[5]. Free radicals are molecules or atoms containing one unpaired electron. That unpaired electron has a tendency to create an electronic couple. This is what makes the free radicals highly reactive but they have a short life. They are produced in regular conditions during metabolic reactions like chemical reactions including enzyme chains. Free radicals are also generated by emotional stress, UV rays, toxic substances, cigarette smoke and other factors. Even though they are included in regular metabolism processes, free radicals do not penetrate in the cells. Those free radicals that penetrate into cells have a detrimental effect on the human body. Those radicals are either created in the environment, consumed through food, or created by UV rays[4].

Free radicals are needed in the production of cell energy, which is released from food, they protect the body from opportunistic infections and participate in the creation of hormones needed for adequate communication in the body.

It is considered that excessive production of free radicals can cause many damages to human body, including collagen, elastin, DNA and fibrosis changes of blood vessels[4].

Oxidative damage to DNA molecule, proteins and other macromolecules is accumulated over years and it is considered a significant but not the only type of endogenous damages that contribute to aging. Basically, oxygen has a double function in the body; it is definitely necessary for life, but it is also a source of potentially harmful compounds, free radicals. Free oxygen radicals are formed during creation of energy in aerobic metabolism, and there are several types of the following reactive oxygen species:

Superoxide anion radical:	$-O_2^-$
Hydroperoxyl radical	$-HO_2$
Hydrogen peroxide	$-H_2O_2$
Hydroxyl radical	$-OH^-$
Peroxide radical (R=lipid)	$-ROO^-$
Singlet oxygen	$-{}^1O_2$

If a free radical attacks a part of the DNA molecule, then a genetic mutation, in case that it has not been corrected by a correction mechanism, causes a continually defected protein synthesis in the next replication cycle. It was already mentioned that free radicals are formed in aerobic metabolism during creation of energy, i.e. the ATP molecule. 'Cell factories' of the ATP are mitochondria. As the human body ages, the efficiency of mitochondria in the production of ATP is decreased, meaning that free radicals, which are needed in the ATP production, are accumulated, passing through the mitochondrial membrane and damaging other parts of the cell. We can identify two factors operating in favor of aging: decreased production of energy and increased oxidative damage. Scientific studies show that there are more mutations in mitochondrial DNA than in the core DNA[5].

Decrease of energy intake (restriction of calories) slows down the aging process and extends the life of mammals (rats, mice), fish, spiders and flies. It is considered that the decrease of oxidative load as a result of calorie restriction is responsible for decreased formation of free radicals in mitochondria, which results in a decreased number of oxidized lipid, proteins and mutations on the mitochondrial DNA. The studies are mostly carried out on older rodents, fed according to controlled diets enriched with vitamins and minerals. The results of calorie restriction studies, if applicable to humans, can be considered due to the smaller impact of high antioxidant intake on longevity[6,7].

Mechanism of Action and Classification of Antioxidants

Oxidant load or oxidative stress is a phenomenon included in many pathological processes incurred by imbalance of prooxidants and antioxidants. Human body has endogenous antioxidative systems protecting it from damaging influence of the free radicals, but an important segment of the antioxidative protection are the antioxidants, which should be taken with food in adequate doses. Stable molecules have paired electrons, but metabolic processes, stress and pollution may remove an electron from the molecule by creating a free radical, which is searching for a new electron. A free radical 'steals' an electron from a stable molecule, creating a new free radical along the way. Chain reaction of electron transfer can seriously damage membranes, scramble cellular genetic code and diminish natural cell defensive strength. The molecular structure of an antioxidant is a unique property, which enables the antioxidant to give the electron to a free radical and so stabilize it.

Telomeres, DNA sequences on the ends of chromosomes, are shortened as the cells replicate and age. A cell has a limited number of possible replications and the length of a telomere is an indicator of biological aging. A recent study has shown that the intake of multivitamins influences the length of telomeres by modulating oxidative stress and inflammatory processes. The goal of the study conducted by Xu *et al.* in 2009 was to explore the connection between the usage of multivitamins by women aged 35 to 74 with longer telomeres. The results showed that the telomeres where by 5.1% longer in women regularly taking multivitamins compared to women not taking them[8].

Antioxidants represent a very large category of products since many chemical compounds (substances) have a direct or indirect antioxidant activity[9]. The most important systems consist of several enzymes and low molecular weight[10].

The only official definition of antioxidants is related to dietary antioxidants[9]. Dietary antioxidants are substances in food, which significantly decrease the adverse effect of reactive oxygen species (ROS), reactive nitrogen species or both on normal physiological function in humans[11].

Figure 1 shows antioxidant hierarchy according to *in vitro* potency. The most active antioxidants are endogenous antioxidant systems, which can be stimulated according to the need. Classic examples of this category are catalases and peroxidases. Antioxidants that can be defined as 'shock absorbers' are next and they are available in blood and tissues, but, unlike enzymatic antioxidants, their production cannot be stimu-

lated after oxidative stress. This class consists of albumin, transferrin and uric acid. The third class consists of essential antioxidants (vitamins and amino acids) and substances that are produced as intermediates for more complex molecules (squalene is produced during the synthesis of cholesterol) or make part of a more complex macromolecule (coenzyme Q10 as part of cytochromes). The fourth and largest class is represented by natural compounds such as carotenoids (about 600) and flavonoids/polyphenols (about 6000)[9].

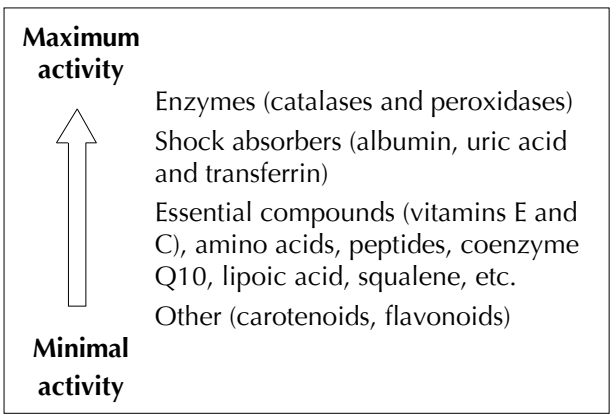

Fig. 1. Antioxidant hierarchy[9].

Antioxidant enzymes like superoxide dismutase, glutathione peroxidase and catalases play an important role in the antioxidant defense. The above stated enzymes utilize disabling of free radicals and are located on subcellular organelle or in cytosol of eukaryotic cells[12]. The function of these enzymes is dependent on sufficient supply of the microelements selenium, copper, zinc, iron, and manganese. Due to decreased supply of microelements, environmental pollution and constant stimulation of the immune system (allergies, infections, chronic diseases, etc.), this system is frequently inadequate to completely perform its function.

Non-enzyme antioxidants are low molecular weight agents. They are found in extra- and intercellular fluids, and most of them are consumed by food. The most significant microelements, antioxidants which have to be taken with food are vitamins A (or provitamin A, beta carotene), C and E, and the minerals selenium, zinc, copper, manganese and iron.

Antioxidants can also be classified into liposoluble (located mainly on membranes, either of cells or of lipoproteins) and hydrosoluble (circulating freely in the blood). The highly liposoluble vitamin E has the affinity for lipoproteins, while highly hydrosoluble vitamin C circulates freely and has minimal connection with proteins[9].

The functional classification divides antioxidants according to their localization into membrane antioxidants (vitamin E, β-carotene, vitamin A), circulating antioxidants (vitamin C, amino acids, polyphenols), cytosol antioxidants (lipoic acid, squalene, coenzyme Q10, which are intermediate products in the synthesis of endogenous molecules or macromolecules, i.e. cytochromes), and system antioxidants (selenium and zinc, amino acid L-cysteine)[9].

The classification of antioxidants according to direct and indirect activity[9]:

- direct activity of an antioxidant: refers to the capacity of a molecule to 'break the chain'
- indirect antioxidant activity: refers to the molecules affecting the processes that stimulate the production of reactive species, e.g., steroids, nonsteroidal anti-inflammatory drugs, statins, and some antihypertensive drugs.

In vitro potency can be determined only for direct antioxidants.

Important Nutrients for Slowing the Ageing Process

The term anti-aging medicine strives to redefine aging as a goal or target for biomedical and scientific intervention, challenging the way aging has been understood up to now. The fact that aging is 'natural' is no longer accepted since there are ways to influence it[13].

Diet plays an important role in the treatment of different diseases and the right choice of nutrients can help in prevention of illness and increase the quality of life. Epidemiological studies suggest strong connection between the intake of specific dietary elements (e.g., antioxidants) and a decrease in the risk of cancer, coronary heart diseases or cataract[10].

According to Sebastian *et al.*, 37% of men and 47% of women use at least one type of dietary supplements, mostly multivitamin and mineral preparations. The intake of food supplements significantly corrects the deficits in folic acid, vitamins E and B12, and iron. Persons who regularly consume dietary supplements have the intake of calcium above the average. Also, a significant correlation is observed in regular intake of food supplements and respecting dietary recommendations[14].

A large group of substances including vitamins, carotenoids, flavonoids, and minerals have *in vitro* or *in vivo* clinically significant antioxidant characteristics.

Carotenoids and flavonoids, along with some vitamins and melatonin, are among those substances worth of considering. All those natural compounds can be found in various foods, vegetables and beverages and can be considered as a significant source of antioxidants. Flavonols, flavones, anthocyanins, catechins, and proanthocyanidins are the most common classes of flavonoids, whereas dietary carotenoids include carotene, cryptoxanthin, lutein, zeaxanthin and lycopene. Carotenoids and flavonoids are secondary metabolites synthesized by plants, mostly after various stresses (mechanical, chemical, UV radiation, environmental, and microbiologic stresses). Reactive oxygen species in plants induce cascade reaction leading to the production of carotenoids and polyphenolic compounds that protect plants from cell injury[10].

Beta-carotene is a plant pigment which the body can turn into vitamin A; it serves as an antioxidant and strengthens the body[15]. Rich sources of beta-carotene are yellow and orange fruits and vegetables and green vegetables with dark green leaves. Vitamin A (retinol) helps in division of cells to divide freely in the process of differentiation. Vitamin A prevents penetration of microorganisms that cause disease, by keeping cell membranes, stimulating immunity, and it is needed for bone, protein and growth hormone formation. Vitamin A is crucial for good vision and potentially important for prevention of eye diseases like glaucoma and cataract, which predominantly occur in older age.

Many experimental researches have studied the etiology of macular degeneration and cataracts in older ages investigating the role of antioxidants originating from food (vitamin C, E and carotenoids). Epidemiological studies have shown that antioxidants influence a delay in first ever eye diseases characteristic of older age. Although it is not possible to conclude that antioxidant nutrients play a significant role in the prevention of macular and cataract degeneration, a summary of epidemiologic evidence shows that it would be prudent to include vitamins C and E, and carotenoids, especially xanthophylls[16]. Food sources of such substances are livers, milk and dairy products, and oil of northern sea fish.

Vitamin C is a hydrosoluble vitamin, which acts as a strong antioxidant. One of its most important functions is protection of low-density lipoprotein (LDL) cholesterol from oxidative damage[17]. Vitamin C is essential for the formation of collagen. The main food sources of vitamin C are broccoli, red paprika, pomegranate, acerola, citrus fruit, strawberry, tomatoes, and green vegetables in general.

Vitamin E is an antioxidant protecting cellular membranes and other liposoluble body parts like LDL cholesterol. The protection of LDL cholesterol from oxidation can decrease the rate of heart disease such as coronary disease.

It is recommended to take a natural form of vitamin E, d-α-tocopherols. Natural vitamin E can be found as d-alfa tocopherols or a combination of Alfa, Beta, Gama, Delta tocopherols, called mixed natural tocopherols. The food sources of vitamin E are wheet seed oil, nuts, beans, herbal oil, egg yolk, and green leafed vegetables.

Ubiquinone or coenzyme Q_{10} is an essential component of chain transferring mitochondrial electrons. It has been demonstrated to inhibit initiation and propagation of lipid peroxidation. The antioxidant formula is ubiquinol ($CoQ_{10}H_2$), which is a product of reduced ubiquinone. Furthermore, besides the antioxidant power it is considered to help in regeneration of other antioxidants soluble in fat, like α-tocopherols[12]. Coenzyme Q10 is a basic bodily coenzyme the synthesis of which decreases with aging. This coenzyme protects from UV radiation damages and when applied locally on the skin and taken orally (dosage 60 mg/day) evidently influences a decrease of wrinkles. Its mechanism on the skin relies on the encouragement of collagen synthesis and elastin, skin restoration and antioxidant action[18].

Selenium is an essential element, a natural antioxidant, which can be found in the body in a small amount. It acts closely with vitamin E in some metabolic processes and induces regular body growth and fertility. It is considered that selenium preserves elasticity of tissue by postponing oxidation of multiple unsaturated fatty acids[19].

Soybean and non-fermented soy products like tofu are a rich and unique source of isoflavones, genistein and daidzein, which are mentioned as phytoestrogens in the literature. Phytoestrogens are herbal compounds

with estrogenic effect in human and animals. These isoflavons inhibit the growth in hormone-dependent and hormone-independent cancer cells in culture. The estrogens can stimulate the growth of glands in experimental animals. Genistein can act as an antagonist of estrogens and reduces the risk of promoting the growth of estrogen sensitive tumors[20].

There are around 40 limonoids with limonin and nomilin as the main representatives. Limonoids inhibit the occurrence of tumors by stimulating the glutathione S-transferase (GST) enzyme.

Lemon and orange oils contain significant amounts of limonene, a terpenoid with anti-cancer activity. Citrus fruit pulp and white coating are rich in glucarates. These substances are investigated because of their potential activities on breast cancer prevention and alleviation of premenstrual symptoms[21].

Short Review of Most Important Studies

Many studies suggest that supplements of vitamin E, vitamin C or both contribute to decrease in the risk of specific chronic diseases such as Alzheimer's disease, senile macular degeneration, some cancer types, cataract and ischemic heart disease[22]. Miller *et al*. in 2005 conducted a meta-analysis on the connection between vitamin E and mortality rate. They compared the results of 19 randomized, placebo-controlled studies with a total of 135,967 subjects. Doses given to subjects varied from 16.5 IU to 2000 IU a day. They concluded that studies with low doses of vitamin E mostly showed a beneficial impact[23]. The immanent conclusion is that the doses of vitamin E should not be higher than 400 IU, and the recommendation on the upper limit of intake, which now amounts to 1000 mg should be reconsidered.

Soon after this meta-analysis was published, the American Journal of Clinical Nutrition has published an article stating that the overviews of numerous clinical studies with high doses of antioxidants (vitamins E and C) do not show any adverse effects in regard to the upper limits determined. The Food and Nutrition Board established the upper intake limits of 2000 mg for vitamin C and 1000 mg for vitamin E[22].

It seems that more optimistic results can be expected from studies using lower doses of antioxidants. The best example might be the double-blind, randomized clinical study including 12,735 volunteers monitored since 1994. The subjects took an antioxidant preparation of 120 mg vitamin C, 30 mg vitamin E, 6 mg beta-carotene, 100 mcg selenium, and 20 mg zinc. After eight years, a lower incidence of cardiovascular disease and cancer was observed in men[24].

In 2001, Cornelli *et al*. proved that a combination of low doses of antioxidants (close or less than RDA) taken during one week in a liquid form decreased oxidative stress in healthy volunteers. Higher doses did not demonstrate such effect, while very large doses can have a prooxidative effect[25].

Another study showed that long-term consumption (for 12-36 months) of vitamin C and E, individually or in combination in daily doses of 500 and 182 mg, did not modify antioxidative plasma ability but did increase lipoprotein resistance to oxidation in a group of subjects who took the combination of these two vitamins[26].

Therefore, it is concluded that it is not desirable to use a high dose of just one antioxidant, since it is possible that its prooxidative activity supersedes its antioxidative activity. It is better to use a combination of antioxidants in doses close to RDAs, and if the RDA is not defined, then regular food intake of those antioxidants is recommended. Increased intake of fruits and vegetables rich in antioxidants (extra virgin olive oil, tea, wine, coffee, black chocolate) may follow or substitute supplements[9].

Vascular endothelium is one of the tissues most sensitive to oxidative stress. In order to ensure the most complete antioxidative mix, Cornelli *et al*. in 2001 examined the effect of three antioxidants in a group of volunteers: group 1, vitamin E, vitamin A, beta carotene, selenium, zinc and L-cysteine; group 2, vitamin C, citrus flavonoids, coenzyme Q10 and vitamin B6; and group 3, a combination of the previous two. All compounds were administered in small doses (below RDA for most of the compounds). The results showed that only the combination of all compounds with antioxidant activity was actually efficient in decreasing oxidative stress, especially when consumed in liquid form[25].

The results of two blind, controlled studies, where antioxidant therapy in a liquid form was compared to placebo in two groups of patients with peripheral arterial disease showed that after 4 weeks of treatment, differences in clinical indicators of the disease were

statistically significantly different before and after treatment in the group of patients treated with antioxidants[9].

One clinical study examined the efficiency of two antioxidant preparations (emulsion for local application and preparation for *per os* administration) on skin elasticity in menopausal women. The skin condition was significantly better in women that received the antioxidant combination (locally + *per os*) *vs*. those administered it only *per os*. Both oral and local preparations were efficient, but only the combination of the two improved skin elasticity[9].

Recently, a study was conducted to test the efficacy of oral supplement containing lycopene, soy extract and vitamin C. The aim of the study was to assess whether daily consumption of a particular formulation for 6 months would induce a change in the general state of the skin and, in particular, in its biomechanical properties and quality. Results showed stimulation of cell proliferation and an increase in collagen and hyaluronic acid content as compared to controls[27].

Conclusion

One of the aging theories connects aging with excessive formation of free radicals, and its balance can be re-established by adequate intake of antioxidants. A large group of substances have clinically significant antioxidant characteristics. Diet has an important role in the treatment of many diseases and the right choice of nutrients can help in disease prevention and improve the quality of life. Regular intake of antioxidant rich foods (fruit, vegetables, and whole-wheat grains) has a favorable health impact, which can slow down or delay the aging process of the skin.

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Sažetak

ULOGA NUTRACEUTIKA U ANTI-AGINGU

D. Vranešić-Bender

Široki pojam nutraceutika odnosi se na sve vrste hrane sa zdravstvenim ili medicinskim učinkom. U svijetu funkcionalne hrane i nutraceutika regulativa se razvija usporedno s razvojem novih proizvoda. Ne postoje ujednačeni zakonski propisi pojedinih zemalja o upotrebi gore navedenog nazivlja. Postoji nekoliko teorija kojima se pokušava protumačiti fenomen starenja čovjeka, a najzanimljivija teorija koja se tiče prehrane je teorija slobodnih radikala i potencijalna uloga antioksidansa u procesu starenja. Velika skupina supstanca uključujući vitamine, karotenoide, flavonoide i minerale imaju *in vitro* ili *in vivo* antioksidativne karakteristike koje su klinički značajne. Potražnja za anti-aging supstancama podrijetlom iz hrane i bilja u iznimnom je porastu, a sastojci koji su osobito popularni u ovome segmentu su antioksidansi, poglavito koenzim Q10, fitoestrogeni, probiotici i omega-3 masne kiseline. Sastojci su to koji imaju povoljno djelovanje na probavni i imuni sustav te ometaju upalne i degenerativne procese u organizmu. Izazov u ovome polju u budućnosti leži u kombiniranju strateške upotrebe kozmeceutika i nutraceutika u svrhu intervencije u biološke procese starenja kože i druge degenerativne promjene na koži.

Ključne riječi: *starenje, antioksidansi, dodatci prehrani, nutraceutici*