

**THE ROLE OF BIOPHENOLS /FLAVONOIDES/ IN
THE CHEMOPREVENTION OF OXIDATIVE STRESS DISEASES**

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Integrated therapy is becoming more and more highlighted in countries with developed health care. Integrated therapy is the combination of traditional therapy and the so-called substitution therapy based on health-conscious diet and lifestyle, and its aim is healing, lowering the risks of disorders, preserving the health status by prevention, and all together: improving quality of life. "The life we receive is not short but we make it so..." /Seneca/

We take the substances necessary for the function of our cells and organs by eating – except for the oxygen, which is the basis of aerobic life. Oxygen gets to our bloodstream by breathing and transported to our cells and tissues attached to hemoglobin molecules. Our diet – and our lifestyle, of course – play an important role in preserving our health and life quality and also facilitate various healing processes. In integrated therapy the doctor's most important tasks – in the interest of healthy people – are: improving health consciousness, by promoting and establishing dietary and lifestyle chemoprevention. Health-conscious dietary habits and lifestyle can be affected by various factors like: diseases, age, financial factors, life cycle effects, psychological factors /qualification, education, socialization/, religion, politics, media, marketing, etc.

The new results of phyto science – which is a new, complex, multidisciplinary science (medical sciences + physiology + biochemistry + chemistry + microbiology + dietary-, agricultural-, and food sciences) – and dietary genomics confirm and support the necessity of integrated therapy. This is particularly true from the aspect of oxidative stress and the diseases associated to it.

Oxygen – being the basis of aerobic life – is a dangerous friend. Under controlled conditions, oxygen has a vital role in energy production and oxidative metabolic processes in the mitochondrion, in the cytosol, in the endoplasmic reticulum, and in the peroxisome. In certain electron transport processes of the mitochondrion and in various enzymatic /XO, NADPH/ reactions negatively charged free radicals, Reactive Oxygen Species /ROS/, are created from the oxygen molecules by electron uptake.

From this nitrogen monoxide ($\text{NO}\bullet$) reaction, reactive peroxynitrite (Reactive Nitrogen Species /RNS/) is formed. From the $\text{O}_2\bullet^-$ superoxide anion (produced by superoxide dismutase /SOD/) and in the peroxisomes (produced by oxidases) hydrogen peroxide (H_2O_2) is formed. From the hydrogen peroxide - during the Fenton-reaction with the help of Fe^{2+} and Cu^+ metallic ions - an extremely reactive free radical, hydroxyl radical can be formed. As a consequence of the abovementioned process, $\text{RO}\bullet$ and $\text{ROO}\bullet$ free radicals can be formed from the lipids. UV radiation or radioactive substances may also lead to the formation of $\text{O}_2\bullet^-$, $\text{OH}\bullet$, $\text{NO}\bullet$ free radicals in our body. ROSs, H_2O_2 , $\text{OH}\bullet$, and $\text{NO}\bullet$ are essential for the proper hormonal function of our body but only under controlled conditions and in a limited amount. Controlling, localizing and repairing the damages caused by oxidative and/or nitrosative stress is the task of our immune system. If our antioxidant defense system, made of macromolecules [endogenous, 1st line, preventive antioxidant enzymes: catalase (CAT),

superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione transferase (GTx), glutathione reductase (GRx), thioredoxin reductase (TRx); endogenous, 3rd line, repair antioxidant enzymes: lipase, protease, transferase, DNA repair enzymes] and micromolecules and elements [exogenous, 2nd line dietary antioxidants: Vitamin C and E, albumin, carotenoids, biophenols, melatonin, glutathion /GSH/, Zn, Se, etc.] functions adequately – which includes proper consumption and utilization of all these substances–, then the level of the reactive forms is kept low, the oxidative damage repair mechanisms work well, and the redox balance (the balance of oxidants and antioxidants) of our body is finally achieved. If this balance isn't achieved and the oxidative processes become dominant, the so-called oxidative stress develops. When the reactive ROS and RNS forms get in interaction with cellular or organic biomolecules – meaning the antioxidant protective/repair system does not work properly – they can cause constructional changes, and can interrupt or modify certain cell signal transduction pathways. These changes can become the starters or indicators of the so called oxidative stress diseases like aging, cardiovascular diseases, Type 2 diabetes, age-related eye diseases /cataract, macular degeneration/, neurodegenerative diseases (Alzheimer's and Parkinson's disease), and various cancer types. The aim of the antioxidant prevention and protection is to inhibit and positively influence the development of oxidative stress, to prevent and slow down age-related pathological oxidative processes, to decrease and improve oxidative effects, to neutralize toxic oxidative products and to facilitate their excretion.

The effect of nutritional phytochemical materials is defined by two main factors: bioaccessibility (the material which is potentially at the place of intestinal absorption) and bioavailability (the material which has been absorbed, got into the circulation, and can be used by the body). Of course, these things depend on various factors like rate of digestion, metabolism, transport, interactions, inter- and intracellular concentrations and the general condition of the individual. That is the reason why antioxidant effects of a complex vegetable product or ingredient should not be assigned to only one component! Chemopreventive phytochemical materials act as complements; they express their effects in a synergetic manner with synergetic mechanisms. Isolated components can lose their positive physiological effects, can even become toxic and have an adverse effect on another mechanism when not in their natural complex nutritional environment. For instance, the lycopene content of tomato is important in the prevention of prostate cancer, but lycopene has its full potential only in conjunction with other phytochemicals, which means that the chemopreventive effects of isolated lycopene are smaller than of the whole tomato extracts. One should never forget that the interpretation of 'in vitro' antioxidant data to 'in vivo' results requires great caution, or sometimes it is not possible at all. Bioactivity is not equal to positive health protective effect!

The largest group of nutritional, plant-based exogenous antioxidants is the so called secondary plant metabolites, polyphenols or biophenols and the in particular, the

flavonoides. Biophenols are polyphenols with typical, dosage dependent physiological effects. Their main types are: phenolic benzoic acids, phenolic cinnamic acids, hydrolysable (ellagitannins) and non-hydrolysable /condensed/ (proanthocyanidins) tannins, stilbenes /e.g. resveratrol/, lignans és flavonoides. Flavonoides are plant-based poly- or biophenols, which contain – mainly in annular structures – the typical 1:3-diphenylpropan frame. Isoflavonoids are annular compounds with a 1:2-diphenylpropan skeleton. Main basic types: chalcones, flavans, flavanones, flavones, anthocyanidins. In plants, they occur in the forms of their glycosides /anthocyanines are the 3-O-glycosides of anthocyanidines/.

Szent-Györgyi Albert was the pioneer researcher of the physiological effects of flavonoides. He considered flavonoides as vitamins /the name 'P-vitamin' comes from him, and also the saying "Flavonoides are life's grey eminences." which still holds true/, but today we know that flavonoides are not vitamins, although some of the flavonoid effects are vitamin-like. Biophenols/flavonoides can decrease the risk of chronic diseases and can affect their courses, so biophenols/flavonoides are essential for healthy aging, reaching the genetically determined lifetime, and improving our quality of life. Biophenols/flavonoides are biological response-modifiers, lifetime-essential compounds.

The effects of flavonoides are of different mechanisms. It is wrong to claim that flavonoides are only free radical scavengers, neutralizers. Among their primary mechanisms there are general, not specific ones, which are in connection only with the phenol OH presence, but there are more specific ones, which are attached to the presence of proper structural elements and units. Their main physiological effects are: free radical scavenging and neutralizing; metal chelate formation; specific interactions with molecular targets: e.g. the modulation of cellular signal transduction processes; the inhibition of inflammation and cellular proliferation, the inhibition of lipid peroxidase (LOX) and cyclooxygenase (COX) enzymes, so the decrease of producing inflammation mediators (leukotrienes, prostaglandins); interactions with CYP450 Phase I and II metabolizing enzymes, etc. When judging the physiological effects of flavonoides, we should take into account that the blood and tissue level of flavonoides is very low (a few mM-s). They are hard to absorb, they act only together with their metabolites. Their effects are dose- and nutrition dependent; in large doses they can be toxic. They dominantly synergetic, thus they only show significant pharmacological activities only in complex compounds. They are nutritional components, and indispensable in maintaining the normal cellular function and the redox balance.

The scientific monographs and publications in the attached reference list are here to support the health protective and chemopreventive effects of biophenols/flavonoides. The results so far published can be connected to various therapeutic indications. Of course, there are certain flavonoid-type drugs, e.g. Rutascorbin (rutoside), Venoruton (monoxerutin), etc. At the field of oncology – mainly from the experimental data from different cell lines – it is commonly known that biophenols/flavonoides have various inhibitory effects /e.g.

antioxidant effects, protein kinase C modulation, blocking of cell cycle, stunning of matrix-metalloproteinases (MMP-2,9), etc./. Extensive evidence supports the theory that combined consumption of antioxidants is the most optimal way of the chemoprevention of different tumors (e.g. colorectal, breast, liver and prostate cancer). Nutrigenomics-based, personal and health-conscious phytochemical cancer prevention combined with screening is the future. On the basis of our current knowledge, the main goals of cancer prevention are the following: early and regular screening; to decrease oxidative stress; to enhance the antioxidant system's protective activity; to increase the cellular detoxification capacity – especially regarding carcinogenic compounds –; to suppress the abnormally activated and pro-inflammation signaling pathways, to positively influence the production and activity of redox-regulated transcription factors (e.g. NF- κ B, AP-1); to regulate and decrease the production of the proteins included in cell proliferation; to induce pre-malignant and malignant cells' apoptosis and to inhibit neovascularisation. Of course, we need to be careful since even today there are still many unexplained questions left open. E.g., when should surgery performed to be efficient? According to the data available so far, antioxidants are most efficient in the phase of "initialization" by the inhibition of DNA damages, so daily health-conscious nutritional chemoprevention seems to be the most efficient against tumor initialization. Decisive factors are the bioaccessability, bioavailability, complex composition, and safety of tumor preventive nutritional phytochemicals. Phytochemical antioxidants have an important role in integrated therapy, in a form, time, and under circumstances determined by prevention. According to science's current – frequently controversial – statements and results, we can use antioxidants before or after chemo- or radiotherapy, but we should not use them during chemo- or radiotherapy without consulting a physician.

By the data available so far, it can be claimed that flavonoides help in absorbing calcium, so the consumption of flavonoides is advantageous in the prevention of osteoporosis. The biophenols' effects are also positive in the prevention and slowing down of age-related eye diseases /glaucoma, cataract, macular degeneration/ and in the prevention of diabetic retinopathy. For instance, it is commonly known for awhile that the antocianin content of colored berry fruits facilitates nighttime vision. Metabolic syndromes, cardiovascular diseases, hypertension, and type 2 diabetes are all in connection with oxidative stress, so for the prevention of these states and for state-impacting, the consumption of phytochemical antioxidants is recommended. Biophenols are advantageous in aspect of the inhibition of heart-attack and stroke, and they enhance the regeneration after the mentioned states. Antioxidants, plant fibers, and magnesium have important roles in the prevention of type 2 diabetes. In the case of gout, the serum's uric acid level is high because of the strong xanthine oxidase (XO) activity, which level can be lowered by certain biophenols /catechins (green tea), proanthocyanidins (grapes, apple)/. Biophenols have a confirmed positive effect on the prevention and improvement of brain aging, neurodegenerative mutations since these states are mostly the results of age related, and oxidative stress originated processes. These effects are confirmed with a lot of data in case of Alzheimer's and Parkinson's

diseases, in particular. Men's sterility is often in connection with oxidative stress. Oxidative stress and the inflammatory process induced by it are often presented in case of liver diseases /e.g. cirrhosis, hepatocellular carcinoma, non-alcoholic steatohepatitis (fatty liver)/.

Alcohol is oxidant, it increases the production of OH, decreases the activity of antioxidant enzymes and the vitamin E level of the plasma. Complex nutritional antioxidant intake decreases oxidative stress caused by alcohol.

The simplest and safest way of chemoprevention of oxidative stress diseases is nutritional antioxidant intake and health-conscious lifestyle. The number of medicines used in antioxidant therapy is very low. Some of these medicines /e.g. Edaravon (Radicut), Ebselen/ are used in the inhibition of brain stroke. Canolol is plant-originated, styrene-typed, ROS scavenger with strong anti-inflammatory effects.

Standard, fruit- and vegetable-based nutrition is good, but it only provides a relatively limited range of nutritional antioxidants /e.g. biophenols (flavonoides)/, in a low, poorly utilized concentration.

Because of this, properly utilizable dietary supplements enriched in phytochemicals of good quality (antioxidants) are having a greater and greater role. Dietary supplements are in between the categories: 'food' and 'medicine'. According to the latest provisions of the European Union, dietary supplements are not medicines; they cannot be assigned with healing effects. In relation to dietary supplements we can make nutritional and health statements. Health statements can be functional statements based on the commonly accepted facts of science and the latest scientific results, or statements lowering the risks of diseases and children's development problems. A good dietary supplement does not contain any toxic materials either from natural materials, or from manufacturing or storing technologies, so a good dietary supplement is safe. Its ingredients are well-utilized and synergistically enhance each other's effects and the quantity of active substances is lower than the medicine dosage, so they cannot cause overdose.

The dietary supplements of the Flavon-Family – Flavon Max, Flavon Max Plus+, Flavon Kids, Flavon Green, Flavon Active and Flavon Protect – comply with all the above mentioned criteria. The members of Flavon-Family are scientifically confirmed /see attached scientific publications/, health-conscious chemopreventive dietary supplements rich in antioxidants and in accordance with legal regulations, which can – mainly due to their jam consistency – facilitate transport of the following compound groups to the body:

biophenols (flavonoids), vitamins, carotenoids, polysaccharides, nitrogen compounds (melatonin, betalains), organosulphur compounds (glutathione, glucosinolates), terpenes, elements/trace elements, prebiotics (insuline, pectines).

The members of Flavon-Family are not medicines, their positive physiological effects on the body cannot be identified as medical effects, and their main task is nutritional chemoprevention and improvement of life quality. The members of Flavon-Family are confirmed and successful dietary supplements which are amongst the best in the world of similar products. This is proved by many prestigious national (2009: Hungarian Agricultural Quality Award; 2011: Hungarian Quality Product Award) and international (2012: Monde Selection Grand Gold Quality Award) awards and recognitions.

The Flavon-Family is in accordance with the commonly accepted and scientifically confirmed statement according to which the consumption of high amount of fruit and vegetable synbiotics has chemopreventive, health protective, and quality of life improving effects.

The Flavon-Family helps us to achieve the most important human goal, the realization of healthy aging.

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