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**Adding Quality Adjusted Life-Years (QALY's) by
nutraceutical food supplementation**

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Abstract

Starting from the 4th decade of life mechanisms of “wear and tear” slowly but steadily degrade cells and systems of the human body. Inflammaging is the continuous low-grade process of inflammation causing oxidative overload, epigenetic and metabolic alterations. These induce age-related diseases that threaten general health and well-being. Aside from early diagnosis and treatment of these diseases and so-called healthy lifestyle, judicious nutraceutical supplementation is of pivotal importance for adding quality adjusted life years.

In the present paper the author describes the rationale for such nutraceutical based on extensive literature review, as well as personal pragmatic and controlled clinical trials.

Introduction

New books are still appearing full of advise to “life young” if you wish to live long.

In fact, the biggest mistake one can make when getting older is to think one is (still) young. In fact, the preparation for a healthy "old age" already begins in the fourth decade of life.

Those who want to live long must, above all, take care not to die early. Evidently, this is a truism. It implies to do the necessary examinations in order to detect any diseases or functional disorders at an early stage, and to have these treated in due time. In addition, adjusting the way of life to prevent age-related diseases, and correcting the mechanisms that cause aging, will increase the probability of a long and healthy life expectancy.

In the present paper the author will focus on the importance of judiciously composed nutraceutical food supplementation for the prevention and correction of “wear and tear” due to so-called inflammaging [1]. In addition, attention will be given to the use of complementary natural substances and plant extracts for preventing or treating the metabolic syndrome or diabetes, or cardiovascular, or neurodegenerative diseases.

Methylation, oxidative stress and inflammation

During ageing a progressive increase of DNA methylation occurs resulting in epigenetic alterations. Depending on which genes are affected this may induce either enhanced expression or inhibition of the respective genes. For instance, hypermethylation by over 15% of second CpG dinucleotide of the human telomerase reverse transcriptase (hTERT) promotor region, that regulates telomere length, is associated with an increased risk of hepatocellular carcinoma, and with paediatric brain cancer [2]. An association between epigenetic changes and cardiovascular disease has been suggested as well [3].

In a controlled trial, the nutraceutical QALY® (formulation in annex) was given to women before conception by in vitro fertilisation (IVF) and was shown to decrease hypermethylation of the hTERT promoter region provoked by ovarian hyperstimulation (fig 1) [4].

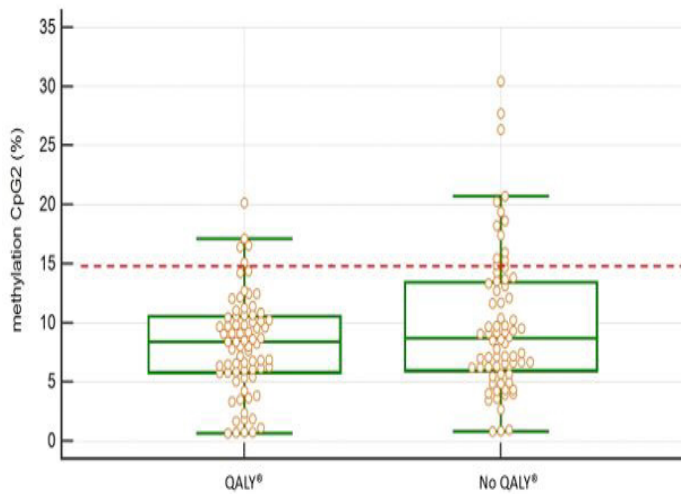


Figure 1: Box and whisker plot showing the percentage of methylation of the second dinucleotide (CpG2) of the hTERT promoter region in follicular cells of women having been treated by ovarian hyperstimulation for In Vitro Fertilization (IVF). The horizontal broken line corresponds with the percentage above which the risk of cancer development in the offspring is increased. The group “QALY®” had taken the food supplement during the process of ovarian stimulation, the group “No QALY®” had taken vitamin B9 (folic acid) only (with permission from [4]).

There are good reasons to accept that altered DNA methylation is associated with aging [5] and can be counteracted.

Another aspect of the administration of the nutraceutical concerns combating “inflammaging” [1]. Long-lasting low-grade inflammation not only results from altered lymphocyte activity, but also from the continuous production of oxygen radicals by cellular metabolism. Oxidative stress induces inflammation, which together with DNA methylation, causes age-related tissue damage and malfunction.

Oxygen radicals convert guanosine into 8-hydroxy-2-deoxyguanosin (8OH-2-dG) that is a DNA mutation [6] associated with carcinogenesis [7]. The concentration of oxidized DNA can dramatically be reduced by antioxidant intake, such as the combination of Astaxanthin and ubiquinol Q10.

In addition, reactive oxygen radicals change the composition of the fatty acids of the cell membrane, in particular that of the long-chain poly-unsaturated eicosapentaenoid and docosahexaenoid acids. The fluidity

of the cell membrane diminishes and the three-dimensional structure of the inlaying receptors is disrupted. This leads to e.g. insulin resistance, or osteoporosis by poor efficiency of circulating estrogens because of altered estrogen receptor sensitivity. Changes of the cell membrane phospholipid composition are also related to aging and senescence [8]. The antioxidants in the nutraceutical QALY® prevent oxidative damage to the fatty acid composition of the cell membrane maintaining its fluidity and optimal functionality.

During their entire life, even starting before birth, modern humans are exposed to man-made persistent chemicals in the environment. These are mostly fat-soluble and increasing amounts accumulate in fat cells and tissues. Aside from direct cellular toxicity reducing cell division and renewal, these chemicals exert hormone disrupting effects [9] and may impair the immune system. Selenium is an essential constituent of the enzyme glutathione peroxidase that can bind toxic chemicals and make them water-soluble so that they can be eliminated via urine. In this way the immune system is safeguarded and can effectively exert its protective function.

It can be concluded that combining various antioxidants, such as the non-toxic carotenoid Astaxanthin and the oxido-reductase Ubiquinol Q10, with the anti-inflammatory extract of Mediterranean pine bark and Selenomethionine synergistically inhibit several mechanisms involved with aging [10,11].

Metabolic syndrome and diabetes

The initial problem in patients with the metabolic syndrome, or prediabetes and type2 diabetes is insulin resistance. Commonly this results from abdominal fat accumulation and hormone imbalance, but oxidative damage affecting the membranous insulin receptor play an important role as well. Typically the blood analyzed 3 to 4 hours after food intake will reveal an elevated concentration of the C-peptide, being a more specific marker than the insulin concentration [12].

In general the concentration of the glycated-hemoglobin A1c is in the so-called grey zone between 5.7 and 6.3 %, whereas glycaemia may still be normal. The prolonged oral glucose challenge test reveals an elevated glycemia after 2 or 3 hours, and other metabolic markers may be abnormal, such as the uric acid concentration. Commonly biological and ultrasound markers of non-alcoholic fatty liver disease (NAFLD) are present. As soon as the fasting glycaemia is elevated and/or glucose is present in the urine, and/or de glycated hemoglobin exceeds 6.3% the diagnosis of diabetes is accepted. In these cases the insulin concentration may drop because of exhaustion of the pancreatic beta cells.

Insulin is a typical growth hormone and its elevated

concentration enhances the risk of cancer [13]. Also glycated hemoglobin can be metabolized to advanced glycation end products (AGE's) that accelerate aging and importantly contribute to vascular damage. In fact, the progressive increase of HgbA1c was found to be the most prominent biological marker associated with aging, even more so than telomere length (fig2).

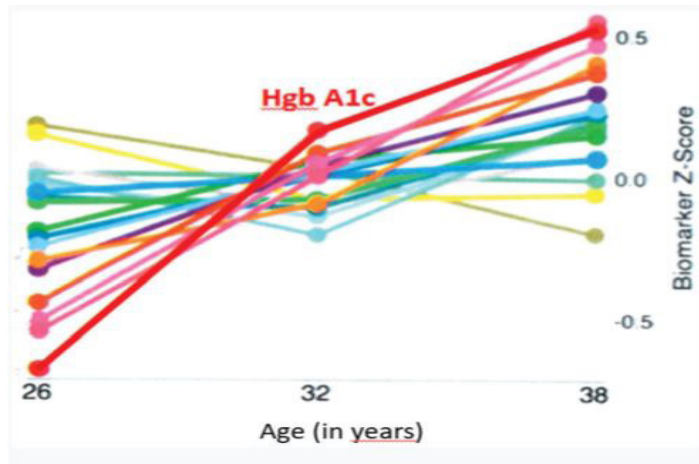


Figure 2: A number of biological markers, including parameters of lung function, telomere length, blood lipid concentrations and biometric variables have been assessed in a large cohort of healthy young persons at the ages of 26, 32 and 38 years (on the horizontal axis). The graph shows the changes of these variables expressed as Z-score (on the vertical axis). The increase of the concentration of HgbA1c is the most prominent biomarker associated with ageing (with permission, [14]).

In addition to the anti-oxidant and anti-inflammatory ingredients of the composed nutraceutical, the extract of bitter melon (*Momordica charantia*) should be given to patients with the metabolic syndrome [15]. This extract acts through the same 5'-AMP-activated protein kinase pathway as the allopathic Metformin, but it is non-toxic and it does not persist as environmental pollutant with xeno-estrogenic effect in surface waters. Moreover, Metformin intake did not reduce mortality rates, nor cardio-vascular disease, nor cancer [16], while increasing the risk of lactic acidosis [17] and renal damage. *Momordica* extract reverses insulin resistance and lowers the concentration of glycated hemoglobin A1C. Its therapeutic effect can be enhanced by combining it with alpha-lipoic acid, that has significant anti-oxidant effects and reinforces the activation of 5'-AMP-activated protein kinase (AMPK)[18]. Alpha lipoic acid also inhibits Nuclear Factor kappa B, that activates the production of inflammatory cytokines.

The combined intake of the nutraceutical with *Momordica* extract and alpha lipid acid was indeed found to halt the evolution of the metabolic syndrome to pre-

diabetes and, ultimately, diabetes. Its therapeutic effect persists during many years of intake, with stabilization, or even reversal, of clinical complications such as NAFLD and neurological impairment [19].

Cardio- and cerebrovascular disease

Aside from the well-know recommendations regarding healthy life style, Mediterranean diet, and regular physical exercise, there are several important contributors to the development of vascular disease, both cardio-vascular and cerebrovascular. Hypertension, hyperlipaemia, elevated homocysteine and insulin resistance are probably the most important factors that can be influenced by nutraceuticals.

The role of insulin resistance and metabolic syndrome in vascular disease should not be underestimated. Recently the triglyceride-glucose index was advocated to be a useful marker of insulin resistance being associated with increased risk of cardio-vascular disease [20]. As mentioned above, the measurement of the concentration of C-peptide in blood taken 4 hours postprandial is also highly informative, completed by the HgbA1c concentration. Treatment with the combination of extract of *Momordica charantia* and alpha lipoic acid should attenuate the development of vascular damage [21].

The cholesterol-saga has changed the entire concept of cardio-vascular prevention with the creation of a multibillion business of cholesterol-lowering drugs and consumer products. However, the number needed to treat (NNT) with statins in order to prevent one incident in primary prevention is very high [22], which makes the cost/benefit ratio excessive [23]. Furthermore statins cause insulin resistance, and the long-term intake is associated with important risk of diabetes progression [24]. Since the number needed to harm (NNH) is at least 4 times lower than the number needed to treat (NNT) statins should not be recommended for healthy ageing.

The alternative is to take the "natural" product, namely fermented red rice (*Monascus purpureus*), that contains Monacoline K which inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) [25]. The latter is an essential enzyme for the biosynthesis of cholesterol, but also of the oxidoreductase coenzyme Ubiquinol Q10. In addition, fermented red rice contains phytosterols and fibres that synergistically enhance the cholesterol lowering effect of Monacoline K and its derivatives. Always the fermented red rice should be completed by adding Q10.

Treatment with fermented red rice not only reduces the total and the low-density-lipoprotein (LDL)-cholesterol, it also increases the concentration of the high-density-lipoprotein cholesterol. By doing so the "atherogenic ratio", which is total cholesterol divided by HDL cholesterol,

decreases [26].

In order to elicit inflammation, LDL-cholesterol must be oxidized in the vascular wall and be phagocytized into the “foam cells” as oxidized LDL-cholesterol. The formation and accumulation of foam cells in the subendothelial space of an artery is the initial step for the development of atherosclerosis. Therefore, the oxidation process is of pivotal importance. Among persons predisposed to atherosclerosis the time needed for the LDL-cholesterol to be oxidized can be doubled by treating them with antioxidants [27]. Antioxidant treatment should, therefore, substantially reduce risk of atherosclerosis and cardiovascular mortality, as has been proven in a controlled prospective cohort trial [28]. In addition, inflammation, assessed by high sensitive CRP concentration in blood, was found to be a better predictor of future cardiovascular events than LDL-cholesterol among patients treated with statins [29]. The extract of Mediterranean pine bark is a rich source of flavonoids which display both anti-oxidant and anti-inflammatory activity by which it has potential cardiovascular benefit [30].

Another important factor predisposing to vascular disease is an elevated concentration of homocysteine in blood [31]. All too often hyper-homocysteinemia is overlooked, though treatment is easily feasible. Indeed, supplementary oral administration of the Vitamins B9 and B12 does rapidly and permanently lower the homocysteine concentration, and reduces the risk of atherosclerosis [32]. In the meantime this supplementation prevents cerebral shrinkage that predisposes to dementia [33].

Cognitive impairment and neurodegenerative diseases

According to recent statistics, dementia and other neurodegenerative diseases have become the most common causes of death. The prevalence of both vascular dementia and Alzheimer’s disease has increased, as is the case for Parkinson’s disease and other neurodegenerative illnesses. The common denominators in these diseases are inflammation [34], impaired cellular metabolism and oxidative damage related to poor cerebrovascular blood supply as well as deficient general health. Aside from the influence of environmental toxins (e.g. pesticides, [35]) and type of medication for treating hypertension [36], there is ample evidence that nutritional factors play a pivotal role [37], among which deficient dietary intake of flavonoids [38], vitamins B and essential amino-acids [39].

Whereas old and new medications that have been developed and even approved for the treatment of e.g. Alzheimer’s disease miss their primary end point [40], nutraceutical supplementation with Vitamins B9 and B12,

but also vitamin D are recommended [41], in particular for older persons residing in a care institution, and patients using medications such as metformin that reduces Vit B 12 absorption [42].

Flavonoids are present in sufficient amounts in so-called healthy diet that is rich in fruits and vegetables. Supplementary administration of flavonoid can compensate for nutritional deficiencies, as seen in ultra-processed food and unbalanced diets consumed by a large proportion of the population. The extract of the Mediterranean pine bark (*Pinus pinaster*) is an excellent source of procyanidins [43], but flavonoids can also be given as e.g. resveratrol from grapes, or curcumin extracts, or blueberries. Several studies have evidenced the high efficiency of flavonoid supplementation on the prevention of dementia [44].

Pine bark extract exerts strong anti-inflammatory action, whereas supplements or plant extracts that improve cellular metabolism and reduce insulin resistance or decrease homocysteine are indicated. Cerebrovascular health is maintained by measures preventing atherosclerosis, and oxidative damage is prevented by anti-oxidants such as Astaxanthin in the biomass of *Haematococcus pluvialis*, or Ubiquinol Q10.

The extract of *Hericium erinaceus* can regenerate and sustain neuronal function, and maintains or sometimes improves cognitive alertness and memory [45]. This extract can prevent and possibly treat neurodegenerative diseases such as Alzheimer’s disease and fronto-temporal dementia [46].

Discussion

Ageing is a privilege as long as the quality of life is good, diseases can be avoided, and physical and mental health are satisfactory. Early diagnosis and hormone replacement therapy [47] and some medicines have tremendous potential in promoting longevity, but the quality of life can be sustained and improved by the timely administration of nutraceuticals that interfere with the mechanisms of aging and “wear and tear”. The judicious combination of selected plant extracts, minerals, vitamins and amino acids constitutes a synergistic mixture that can do just that.

Based on extensive literature study, controlled and pragmatic trials, and many years of clinical experience the author has developed a concept of complementary medicine that may help to attain the result to which everybody aspires. The aging process becomes prominent already during the 4th decade of life. Systematic medical check-ups for common diseases are indicated [48], with particular attention to diseases that have occurred among relatives. Evidently, a healthy life style should be pursued. Regrettably, modern society burdens humanity with

numerous harmful influences and a life style that are not beneficial to physical and mental health. These accelerate the development of common so-called age-related diseases and infirmities. Judicious nutraceutical supplementation may help to overcome these hurdles, while being free of adverse affects. In the end, the benefit/risk ratio should be favorable.

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The first author declares no conflict of interest. He has created the formulation of QALY® and owns the Belgian patent thereof.

Annex: Formulation of the Nutraceutical QALY® (Jonapharma Ltd, Elversele, Belgium)

Astaxanthin, biomass of *Haematococcus -pluvialis*: 2 mg

Oxido-reductase Ubiquinol Q10: 25 mg

Pine bark extract, *Pinus maritima*: 21 mg

Extract of roseroot, *Rhodiola rosea*: 175 mg

Vitamin B9, folic acid: 0.2 mg

Vitamin B12, methylcobalamine: 1.25 µg

Selenomethionine: 14 mg

Zinc bisglycinate: 3 mg Zn

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