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REVIEWS: CURRENT TOPICS

Proceedings from the "Third International Conference on Mechanism of Action of Nutraceuticals"☆

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Abstract

The "Third International Conference on Mechanisms of Action of Nutraceuticals" (ICMAN 3) was held to bring investigators from around the world together to find answers and share experience relevant to the role of nutraceuticals in health and disease. Dietary supplements are currently receiving recognition as being beneficial in coronary heart disease, cancer, osteoporosis and other chronic and degenerative diseases such as diabetes, Parkinson's and Alzheimer's diseases. This gave impetus to investigate the mechanisms of action of nutraceuticals and related bioactive compounds in disease pathologies. Many lines of evidence indicate that the mechanistic actions of natural compounds involve a wide array of biological processes, including activation of antioxidant defenses, signal transduction pathways, cell survival-associated gene expression, cell proliferation and differentiation and preservation of mitochondrial integrity. Furthermore, many of these compounds exert anti-inflammatory actions through inhibition of oxidative stress-induced transcription factors (e.g., NF-κB, AP-1), cytotoxic cytokines and cyclooxygenase-2. It appears that these properties play a crucial role in the protection against the pathologies of numerous age-related or chronic diseases. This review summarizes the latest research finding in functional foods and micronutrients in the promotion of health and reduction of risk for major chronic diseases as presented in this symposium.

Keywords: ICMAN; Nutraceuticals; Diabetes; Neurodegenerative diseases; Cancer; Cardiovascular

1. Introduction

1.1. Nutraceuticals: scientific evidence for their biological function

Nutritional supplements and functional foods are currently receiving international recognition as having potentially beneficial effects on health when consumed as part of a varied diet on a regular basis and at effective levels. Both the scientific community and the food industry are motivated to extend quality of life, and in particular, to treat chronic aging diseases [1]. Mounting evidence from epidemiological studies, animal research, clinical trials and research in nutritional biochemistry suggests that some dietary supplements may be beneficial in coronary heart disease [2], cancer [3], osteoporosis [4] and other chronic and degenerative diseases such as diabetes [5], Parkinson's and Alzheimer's diseases [6]. Scientists have sought to identify the exact components in these diets that confer the protection against these maladies. For example, people who ate the greatest amount of lutein-rich foods as chicken eggs, spinach, tomatoes, oranges and leafy greens experienced the lowest incidence of colon cancer [7]. Flavonoids found in citrus fruit appear to protect against cancer by acting as antioxidants [8]. Additionally, omega-3 fatty acids, primarily found in fish oil, may play a role in protection from cancer and heart disease [9]. Further research will uncover which individuals in the population are most likely to benefit from a functional food and a better understanding of how known functional components in foods could expand the role of diet in disease prevention and treatment.

☆ November 12–14, 2004 at the Maggie Valley Resort, in Haywood County, Western NC, USA.

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The beneficial effects of nutraceuticals and functional foods had been ascribed to their high content of polyphenolic flavonoids. These compounds have been shown to possess antioxidant/radical scavenging activity and increase the capacity of endogenous antioxidant defenses, thus, modulating the cellular redox state [10]. Numerous studies in the past 10 years have shown that beyond their well-established antioxidant actions, flavonoids appear to regulate various signaling pathways involved in cellular survival, growth, and differentiation. For example, they have been shown to modulate protein kinase activities, such as mitogen-activated protein kinase (MAPK) [11] and protein kinase C (PKC) [12], modulate the activity of the signal transducers and activator of transcription 1 (STAT-1) factor, functioning as modulator of cytokine signaling and sensors responding to cellular stress [13], serve as ligands for transcription factors and alter protease activities [14]. Thus, diets rich in antioxidants appear to be a promising approach to help strengthen the physiological antioxidant defense system and improve chronic diseases [15].

A note of caution, however, should be provided that although many supplements are clearly beneficial, maximum efficacy and prevention of adverse reactions or toxicity can only be achieved by using special prudence that must be implemented when taking supplements.

This review gives an overview of the presentations at the Third International Conference on Mechanisms of Action of Nutraceuticals (ICMAN 3) held on November 12–14, 2004, at the Maggie Valley Resort, Haywood County, Western NC, USA. The timing of this report could not be better, in view of the new American "Dietary Guidelines for Americans 2005," a federal government's science-based advice to promote health and reduce risk of chronic diseases through nutrition and physical activity.

2. Nutraceuticals in obesity and diabetes

Diabetes mellitus is a chronic disease that requires long-term medical attention both to limit the development of its devastating complications and to manage them when they do occur. The two basic types of diabetes mellitus are referred to as types 1 and 2. Type 1 diabetes generally occurs in young, lean patients and is characterized by the marked inability of the pancreas to secrete insulin because of autoimmune destruction of the beta cells, a process that involves oxidative stress. Type 2 diabetes typically occurs in individuals older than 40 years who have a family history of diabetes, and is characterized by a peripheral insulin resistance with an insulin-secretory defect that varies in severity. Chronic elevation of blood glucose is the fundamental cause of diabetic complications, affecting multiple organs in both type 1 and 2 diabetes. "It seems that the more we come to understand the two major types of diabetes, the more we appreciate the underlying similarities between them. Modulation of the intra-islet inflammatory mediators in type 1 and type 2 diabetes appears as a promising new therapeutic approach," said Dr. Nurit Kaiser (Hadassah-Hebrew University Medical Center, Jerusalem, Israel). Yet, type 1 diabetes is recognized as a condition of absolute insulin deficiency, whereas type 2 diabetes is characterized by relative insulin deficiency resulting from a combination of beta cell failure and varying degrees of insulin resistance [16]. Type 2 diabetes risks are associated with low birth weight and rapid weight gain during childhood. Dr. Nick Hales (Department of Clinical Biochemistry, University of Cambridge, England) reported that studies of rat (and more recently mouse) models in which fetal and/or postnatal growth restriction is produced by feeding rat dams just under half the normal amount of protein. This research has revealed that age-dependent loss of glucose tolerance culminating in frank clinical symptoms of diabetes is observed in the offspring of such dams [17]. For this reason, diabetes treatment focusing on managing glucose and insulin levels should also include nutritional intervention in childhood.

Recently, clinical studies were conducted to assess the growth, diabetes control, dietary intake and compliance with a gluten-free diet in children with insulin-dependent diabetes mellitus and coeliac disease. Introduction of a gluten-free diet may be associated with excess weight gain [18]. Dr. Jill Norris (University of Colorado Health Sciences Center, Denver, CO, USA) reported on clinical observation revealing association of both early (<3 months) and late (≥ 7 months) introduction of any type of cereal into the infant diet with increased risk of diabetic autoimmunity [19].

Dr. Elliot Berry (Hebrew University-Hadassah Medical School, Jerusalem, Israel) pointed to obesity as the underlying cause for the insulin resistance syndrome and its complications (diabetes, hypertension and dyslipidemia). Diabetes occurs more frequently in people who consume high-fat-containing food, especially saturated fatty acids. Restricting the consumption of saturated and trans-fats may restore blood lipid levels, improve some diabetic parameters and slow the progression of diabetes. The recommended treatment may involve behavioral modification and provide motivation for a radical change in lifestyle including exercise and modified nutrition, such as that encountered in the Mediterranean diet. Lifestyle intervention means regular exercise, weight loss and healthful eating habits [20].

Dr. Goede Schueler (DSM Nutritional Products, Basel, Switzerland) introduced virtual screening (VS) as an effective tool to select the best set of natural compounds for this indication. R-lipoic acid (R-LA), a natural coenzyme and antioxidant, decreases the levels of serum lactate and pyruvate in diabetic patients, increases glucose uptake by activating insulin-signaling pathways, and has been successfully used for the treatment of diabetic neuropathy. Dr. Mulchand Patel (State University of New York at Buffalo, Buffalo, NY, USA) discussed the likely ability of R-LA to increase glucose metabolism by

increasing glucose uptake and activation of pyruvate dehydrogenase complex, which plays a key role in oxidation of glucose-derived pyruvate [21].

Maghrani et al. [22] described beneficial effects of natural compounds extracted from plants. Aqueous extract of *Triticum repens* (a plant belonging to the Gramin family) significantly decreased the blood glucose levels in streptozotocin-diabetic rats being normalized after 2 weeks of daily oral administration. Similarly, the hypoglycemic activity of other plant extracts such as *Crassula argentea* (Akiko Kojima-Yuasa et al., Osaka City University, Osaka, Japan) and Fraxinus excelsior (M. Maghrani, UFR PNPE, BP 21, Errachidia, Morocco) has been evaluated and confirmed in different animal models.

3. Nutraceuticals for cardiovascular diseases

Growing interest has centered on the role of flavonoids (phenolic phytochemicals) from fruit, vegetables and grains, in regards to their anticancer and anti-inflammatory action, as well as to the beneficial effects on cardiovascular and neurodegenerative diseases (for extensive reviews, see Refs. [6,10,23,24]). The emphasis has been placed on their high antioxidant ability, which can protect cells against the adverse effects of reactive oxygen species (ROS). Lester Packer (Department of Molecular Pharmacology and Toxicology, School of Pharmacy, Health Sciences Campus, University of Southern California, Los Angeles, CA) highlighted the crucial role antioxidants play in preventing oxidative stress and maintaining the physiological redox status of cellular constituents. "Antioxidants may quench free radicals, change their redox state, be targeted for destruction, regulate oxidative processes involved in signal transduction, affect gene expression and pathways of cell proliferation, differentiation and death." This is being achieved at various subcellular and molecular levels including antioxidants that interact with the redox antioxidant network such as ascorbic acid (vitamin C) and α-tocopherol (vitamin E), thiols (glutathione, thioredoxin, lipoic acid), bioflavonoids, carotenoids and induction of phase 2 enzymes and immune cell stimulation [25,26]. Dr. Packer discussed the conditions under which redox-active substances could exert antioxidant as well as prooxidant action in different organ systems and in various cell types. Consistent with this, Werner Siems et al. (Loges-School for Physical Medicine and Rehabilitation Bad Harzburg) reported that β-carotene might have harmful effects mediated by its cleavage products, which can have a high reactivity toward biomolecules. β-Carotene cleavage product formation and impairment of mitochondrial respiration by these substances was significantly reduced in the presence of the antioxidants vitamin E, vitamin C, urate, various SH donors, SOD and catalase, and the protective effects were concentration dependent [27]. α-Tocopherol in combination with ascorbic acid was most effective.

Pomegranate juice (POM) is one of the richest sources of polyphenolic dietary antioxidants found that has multiple beneficial effects in the body, in paricular, in the heart. Dr. Michael Aviram et al. (Lipid Research Laboratory, Rambam Medical Center and Technion Faculty of Medicine, Haifa, Israel), working with flavonoids from POM (tannins, anthocyanins) and red wine (quercetin), reported a significant inhibition of copper ion-induced low-density lipoprotein (LDL) oxidation and preservation of paraoxonase 1 (PON1) activity in vitro. PON1 is an enzyme associated with serum high-density lipoprotein (HDL). Dietary supplementation of these antioxidants to the atherosclerotic E^0 mice (apolipoprotein E-deficient mice) reduced serum oxidative stress and increased serum PON1 activity [28]. Most importantly, the atherosclerotic lesion size was significantly reduced in these mice. In healthy subjects, consumption of POM for 2 weeks resulted in a significant 20% increase in serum PON1 activity and their LDL and HDL were more resistant to copper ion-induced oxidation [29]. Pomegranate juice consumption for 1 year by atherosclerotic carotid artery stenosis (CAS) patients resulted in a significant reduction, by up to 30%, in their common carotid intima-media thickness. These results were accompanied by an increase in the patients' serum PON1 activity by 83%, and by 60−90% decrease in the patient's serum LDL basal oxidative state and LDL susceptibility to copper ion-induced oxidation [29]. Thus, dietary intervention with appropriate nutraceuticals may be of significant relevance in cardiovascular disease development and progression. Dr. Risa Schulman (POMWonderful, California) provided an excellent overview of the properties of POM, preclinical safety studies and clinical research.

A significant body of evidence indicates that the intake of dietary long-chain polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (synonymously called omega-3 fatty acids) have profound heart health benefits. Omega-3s are found mainly in fat-rich fish including salmon, rainbow trout, mackerel and sardine. They were found to be particularly beneficial for overweight individuals with hypertension who are on weight loss diets by lowering triglycerides, reducing abnormal heart rhythms, reducing blood pressure and improving blood-clotting regulation. Studies on cardiac arrhythmias [30] do not give any clear evidence on the efficacy of n-3 fatty acids in human. However, a trend toward reduction in ventricular extrasystoles in patients with ventricular tachyarrhythmias has been observed after supplementation with omega-3 fatty acids [31]. In animal models, however, omega-3 fatty acids prevent fatal ischemia-induced cardiac arrhythmias. In light of these controversial results, Dr. Herbert Woolf (BASF) emphasized in his presentation the recommendation of the Office of Dietary Supplements of the National Institutes of Health concerning the need of additional research to address questions about the effect of omega-3 fatty acid on cardiovascular disorders. These studies should encompass specific subpopulations, including people at high risk of

sudden cardiac arrest death or with diabetes, congestive heart failure or other chronic diseases.

4. Nutraceuticals and cancer

Numerous epidemiological studies have shown a strong correlation between frequent consumption of fresh fruits and vegetables and a decreased cancer risk (for review, see Refs. [24,32,33]). This is believed to rely, to a great extent, on their high content of antioxidant flavonoids acting as effective scavengers of ROS, inducers of phase II detoxifying enzymes and activating transcription factors and endogenous antioxidant enzyme such as glutathione peroxidase and catalase [34]. Many of these dietary compounds appear to act on multiple target signaling pathways. These include the activator protein-1 (AP-1) and/or nuclear factor kappa B (NF-κB) known to be extremely important in tumor promoter-induced cell transformation and tumor promotion, and both are influenced differentially by the MAPK pathways [35].

Several preclinical animal studies have been conducted that demonstrate the remarkable chemopreventive activity of flavonoids such as green tea catechins, curcumin, anthocyanins, quercetin or silibinin. Gary Stoner et al. (Department of Internal Medicine, Division of Hematology and Oncology, Ohio State University College of Medicine and Public Health, Columbus, OH) showed that freeze-dried black raspberry, strawberry and blackberry powders at concentrations of 5% and 10% fed to Fischer-344 rats before, during and after treatment with the esophageal carcinogen, *N*-nitrosomethylbenzylamine (NMBA), inhibit the number of esophageal tumors by 40–60% relative to NMBA controls [36]. This inhibition correlated with a reduction in DNA damage. Chemoprevention by berries was also reported in oral cavity cancers. Oral cavity cancers represent 2.5% of the cancer incidences in the United States and are ranked sixth worldwide, said Dr. Christopher Weghorst (Division of Environmental Health Science, School of Public Health, The Ohio State University). An extract of lyophilized black raspberries dramatically inhibits the in vitro proliferation of cells derived from a human oral squamous cell carcinoma (SCC-83), in a dose dependent manner and to a maximum of 40%, suggesting that the chemoprevention of human oral cancer by raspberry extract components is possible [37]. Mechanistic studies indicate that berries inhibit the growth of premalignant esophageal cells, in part, through down-regulation of cyclooxygenase-2 (COX-2) and down-regulation of the transcription activators, AP-1 and NF-κB in JB-6 mouse epidermal cells [38]. Also, the green tea polyphenol epigallocatechin-3-gallate (EGCG) and the soy isoflavone genistein inhibit activation of NF-κB and AP-1 thereby suppressing the COX-2 induction in mouse skin in vivo and/or cultured human mammary epithelial (MCF10A) cells [39]. In this context, Young-Joon Surh (College of Pharmacy, Seoul National University, Seoul, South Korea) found that curcumin, a yellow coloring agent contained in turmeric (*Curcuma longa* L., Zingiberaceae) inhibits expression of COX-2 in mouse skin treated with the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate (TPA) through inactivation of the eukaryotic transcription factor NF-κB [40]. Curcumin has been shown to suppress carcinogenesis in other organs such as the oral cavity, skin, liver, lung, colon, stomach and breast to lower blood cholesterol, to promote wound healing, to prevent skin wrinkling, to inhibit inflammation, to suppress rheumatoid arthritis and to inhibit HIV replication, reported Dr. Shishir Shishodia (Cytokine Research Section, Department of Bioimmunotherapy, The University of Texas M. D. Anderson Cancer Center). Curcumin mediates this wide variety of therapeutic effects through the regulation of the transcription factors NF-κB and signal transducer and activator of transcription 3 (STAT-3), and suppression of IκB kinase [41]. Dr. Shishir Shishoida also reported that combination of two subeffective low concentrations of celecobix and curcumin, such that each per se does not have biological effect, resulted in blockade of NF-κB activation.

Rajesh Agarwal et al. (University of Colorado Health Sciences Center, Department of Pharmaceutical Sciences), presented their findings on silibinin, the major active compound of silymarin. Silibinin is a nontoxic flavonoid compound that is responsible for the antihepatotoxic efficacy of the commonly consumed dietary supplement milk-thistle extract. A series of studies in the last 10 years has demonstrated the cancer preventive and anticancer activity of silymarin and silibinin against skin cancer in mouse models. The authors choose to concentrate on silibinin effects on prostate cancer (PCA), which constitutes a second leading cause of cancer deaths in males in the western population. Silibinin induced CDKIs Kip1/p27 and Cip1/p21 in human PCA LNCaP and DU145 cells [42], and this induction resulted in complete decrease in the kinase activity of CDKs and cyclins, culminating in G1 arrest and cell growth inhibition. Based on recent preclinical PCA prevention studies, this group is currently embarking in a phase I/II dose-escalation clinical trial with silibinin.

5. Nutraceuticals in brain development and age-associated neurodegeneration

Aging is characterized by decrements in tissue function and accumulation of mitochondrial DNA mutations, particularly in tissues like the brain that contain postmitotic cells. Many lines of evidence suggest that oxidative stress resulting in ROS generation and inflammation play a pivotal role in the age-associated cognitive decline and neuronal loss in neurodegenerative disease including Alzheimer's, Parkinson's and Huntington's diseases [43,44]. Damage to proteins caused by oxidative stress is considered to be one of the major contributors to the aging process and to age-associated diseases. A cardinal feature of the chemical pathology found in neurodegenerative diseases is the

accumulation of iron at sites where the neurons die. The buildup of an iron gradient in conjunction with ROS (superoxide, hydroxyl radical and nitric oxide) at the site of neurodegeneration is thought to constitute a major trigger in neuron toxicity and demise, common to all theses diseases. Dr. Jackob Moskovitz (Department of Pharmacology and Toxicology, Pharmacy School, University of Kansas, Lawrence, KS) said that sulfoxide oxidation of certain methionine residues may lead to the development and progression of neurodegenerative diseases. Free and protein-bound methionine sulfoxide (MetO) can be reversed to methionine by a family of enzymes denoted as methionine sulfoxide reductases [45]. Therefore, malfunction of methionine sulfoxide reductases may lead to enhanced cellular toxicity, by oxidation and accumulation of several proteins or peptides such as amyloid-beta peptides, α-synuclein and cytochrome *c*.

Future treatment of neurodegenerative diseases and aging depends on availability of effective brain permeable iron-chelating and radical scavenger neuroprotective drugs that would prevent the progression of the neuronal loss. However, the iron chelators or radical scavengers available either do not cross the blood–brain barrier or have a very short half-life in vivo. Dr. Moussa Youdim (Eve Topf and NPF Centers of Excellence, Technion-Faculty of Medicine, Haifa), developed a series of brain-permeable iron chelators that overcome these constrains. "Our objective with these drugs is to 'iron-out iron' from the brain," said Youdim. VK28 is a morphilino iron chelator equipotent to that of the prototype iron chelator desferrioxiamine in iron chelation potency but in contrast to desferrioxiamine; VK28 crosses the blood brain barrier. When injected systemically or given orally, it prevents nigrostriatal dopamine (DA) neurodegeneration in the 6-hydroxydopamine and MPTP models of Parkinson's disease and the kainate model of temporal lobe epilepsy. This prototype iron chelator has been further developed into several multifunctional compounds including HLA-20 and M30, which possess the propargylamine moiety of the successful neuroprotective-neurorescue, monoamine oxidase inhibitor anti-Parkinson drug, rasagiline [46,47]. "We consider the multifunctional drugs HLA-20 and M30 to have a superior neuroprotective activity as compared to the parent compounds rasagiline or VK-28," summarized Youdim. Indeed, M30 has been shown not only to have neuroprotective activity in neuronal cell culture and in vivo, but also to possess neurorescue activity in neuroblastoma SHSY-5Y cells. The latter property has been attributed to its ability to down-regulate Bad and Bax and to induce GAP43 and neurite formation.

Increasing number of in vivo and in vitro studies have shown that dietary antioxidant flavonoids, a family of polyphenols found in fruits and vegetables, as well as in plant beverages such as tea, pomegranate juice, raspberry, blueberries and red wine, exert a protective role in neurodegeneration, most probably due to their well-established potent radical scavenging, transition metal chelating and anti-inflammatory activities [48–50]. Dr. Silvia Mandel (Eve Topf and US National Parkinson's Foundation Centers of Excellence for Neurodegenerative diseases and Departments of Pharmacology, Technion, Haifa) presented most recent findings concerning the neuroprotective and neurorescue properties of the major catechin component of green tea extract (EGCG). In her experimental paradigms, EGCG was able not only to prevent but also to rescue the neurons even when administered up to 3 days after serum support deprivation [51]. The relative long-term serum starvation period imposed on the cells before supplementation with EGCG may be reminiscent of the slowly progressive neurodegeneration of the DA-containing neurons in PD and aging, thus representing a better model for drug therapeutics studies. The neurorescue action of EGCG together with its recently reported neurite outgrowth property could be of major benefit, especially in neurodegenerative diseases and in the aging brain where a prominent mass of synapse connections and consequent brain function have been disrupted [6].

Recent evidence indicates that besides their well-established antioxidant and iron chelating properties, polyphenol catechins have a profound effect on cell survival/death genes and signal transduction pathways [11,52]. Dr. Orly Weinreb from the same institute compared the gene expression profile of EGCG to three other neuroprotective drugs, DA, R-apomorphine (R-APO) and the pineal indoleamine hormone melatonin, at both low and high concentrations. In low concentrations, EGCG (1 μM), DA (10 μM) and R-APO (1 μM) behaved as potent neuroprotective agents, decreasing the expression of the proapoptotic genes bax, bad, gadd45 and fas ligand. However, in contrast to the other antioxidants, EGCG did not affect the expression of the antiapoptotic bcl-w, bcl-2 and bcl-xL [53]. These results revealed a significant functional homology between these drugs in activating genes coding for signal transducers, transcriptional repressors, and growth factors, which may account for their similar mechanisms of action.

Another group of flavonoids are those found in the extract of *Ginkgo biloba* leaves called EGb 761. Previous clinical trials with AD patients have reported potential benefits in cognitive function and memory impairment from treatment with the antioxidant extract of *G. biloba* [54]. Dr. Yuan Luo (Department of Biological Sciences, The University of Southern Mississippi, Hattiesburg, MS), has previously demonstrated that the *G. biloba* extract extends the life span of *C. elegans*. In this report, she described studies that employed the *C. elegans* model to determine biochemical processes that regulate the onset of muscle degeneration due to aging. Ultrastructure changes observed under electron microscopy show that the age-dependent muscle degeneration was delayed by EGb 761 treatment.

Age-related macular degeneration (AMD) is a slowly progressive neurodegenerative disease of the macular region of the retina resulting in impairment of principal

retinal functions due to exposure to light and accumulation of ROS. It is the most common cause of severe vision loss among aged people in the industrialized countries. Recent studies on AMD showed mutation of mtDNA in both photoreceptors and retinal pigment epithelium (RPE), suggesting that mitochondrial dysfunctions may also play a role in the development of this disease. Dr. Janos Feher (Ophthalmic Neuroscience Program, Department of Ophthalmology, University of Rome "La Sapienza," Rome) postulated that early intervention with cellular lipid metabolism, a metabolic rather than an antioxidant approach, may be a more specific way for attenuating retinal aging and for treating early AMD. This formed the basis for a recent 12-month clinical study to test this hypothesis [55] with a composition of acetyl-L-carnitine (ALC, a fatty acid carrier through the mitochondrial inner membrane), n-3 fatty acids (n-3 FA, structural components of all cell membranes, involved in the regulation of neuronal development) and coenzyme Q10 (CoQ10; an integral part of the mitochondrial electron transport chain and plasma membrane redox system). A significant improvement was observed in the treated group by the end of the study period. This suggests that an appropriate combination of compounds that affect mitochondrial lipid metabolism may improve visual functions and retinal alterations in early AMD and that mitochondria may be a new target for treating AMD similarly to other age-related neurodegenerative diseases.

Choline and folic acid are dietary components essential for normal function of all cells. Both are widely available as nutritional supplements. Choline, or its metabolites, assures the structural integrity and signaling functions of cell membranes; it is the major source of methyl groups in the diet (one of choline's metabolites, betaine, participates in the methylation of homocysteine to form methionine), and it directly affects nerve signaling, cell signaling and lipid transport/metabolism. The availability of both nutrients for normal development of brain is critical. Dr. Steven H. Zeisel (Department of Nutrition, School of Public Health and School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill NC) found that choline deficiency in the pregnant rodent decreased, and choline supplementation increased the rate of cell division in the stems cells forming fetal hippocampus and septum. Folic acid deficiency in the pregnant dam also can slow stem cell division in the septum of the fetus and that the migration of cells from the hippocampal neuroepithelium to the dentate gyros was perturbed in choline-deficient fetuses. Choline deficiency was associated with poor memory performance in offspring. The investigators concluded that both nutrients must be present at a specific time in brain development [56]. If folic acid is unavailable or deficient in the first few weeks of pregnancy, the brain does not form normally. Thus, pregnancy is a period when special attention must be given to dietary intake of both choline and folic acid.

6. Conclusions

There is no doubt that many nutraceuticals, functional foods and naturally occurring polyphenols that have been investigated and reported on in this symposium have other physiological and pharmacological activities in addition to their well-characterized antioxidant actions. Increasingly, prominent researchers and the scientific community are reporting that these substances and products are extremely active, have profound effect on cell metabolism and often demonstrate few adverse effects. In many cases, it can be argued that nutraceuticals offer an advantage over the synthetic drugs under development by the pharmaceutical industry.

Indeed, it is the novel pharmacological activities that are arousing interest in their possible clinical use for prevention and therapeutics in several diseases. Unfortunately, there are far too few controlled studies with most of these micronutrients, and considerable skepticism about their efficacy exists, largely because their molecular mechanisms responsible for beneficial health effects remain unknown. This can only be resolved if critical well-controlled studies are performed to establish their usefulness for human health. Pharmaceutical companies often lack motivation to pursue these studies because of difficulty in obtaining intellectual property rights through patents. It is hoped that grant-awarding agencies, both the government, such as the office of dietary supplements at NIH, or the private sector, will give serious consideration to this issue and support such studies.

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