Nutraceuticals, Functional Foods and Dietary Supplements in Health and Disease

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ABSTRACT

Nutraceuticals, functional food ingredients and dietary supplements are important for health promotion and disease risk reduction. Although a myriad of bioactives are known to render the expected beneficial effects, the mechanisms involved are varied and may work individually or collectively in providing the effects. For example, phenolic compounds are known to act as antioxidants or by mechanisms that are independent of their antioxidant activity. In addition, conjugation of bioactives with other active or inactive components may affect the activity of the resultant products. Therefore, conjugation of phytosterols with docosahexaenoic acid (DHA) was found to lower cholesterol in a mouse model and esters of epigallocatechin gallate with docosahexaenoic acid were able to arrest colon cancer in mice. Processing of bioactives may also alter their bioactives and could therefore influence their efficacy in *in-vitro* and possibly *in vivo* models. In addition, processing by-products from plant sources are particularly rich in a number of bioactives at much higher concentration than those present in the main products and these can be used as value-added ingredients for application in food or as supplements for alleviating certain health problems. Examples will be provided to illustrate the concepts and approaches used and expected benefits.

Key words: nutraceuticals, functional foods, dietary supplements, phenolic compounds and their modification, omega-3 polyunsaturated fatty acids, phytosterols, green tea epigallocatechins gallate, plant by-product, health effects

INTRODUCTION

Functional foods are defined as products that resemble traditional foods but possess demonstrated physiological benefits. However, nutraceuticals are commodities derived from foods, but are used in the medicinal form of pills, capsules or liquids and again render demonstrated physiological benefits. In Canada, the latter group has now been integrated under a new category as natural health products that promote health. This category includes both nutraceuticals and herbal as well as other natural products. In some countries, however, functional foods and nutraceuticals are used interchangeably. Regardless, the main focus of such products is to improve health and reduce disease risk through prevention. The main difference of this category with pharmaceuticals is that they are multi-targeted mixtures and present at low concentration while pharmaceuticals are uni-targeted pure compounds with high dose use.

There are many functional foods and nutraceuticals that are becoming increasingly available in the marketplace, but there is a challenge for the functional food producers because such products should address the issue of sensory acceptability which is not necessary for the nutraceutical or pharmaceutical products. The commodities that have so far reached the market are mainly those belonging to the antioxidants and also omega-3 oils, as well as probiotics, among others. The antioxidant category is primarily composed of phenolic/polyphenolic compounds, but carotenoids as well as phytates, certain vitamins, uric acid and minerals are also included. In addition, phytosterols or plant sterols have found their way to the market, first in Finland over a decade ago and now in many other countries. In more recent work, conjugation of different groups of bioactives or their physical mixtures have been studied in order to examine their additive or possible synergistic as well as unusual effects. The following sections of this overview provide examples to demonstrate the benefits of nutraceuticals and functional foods in health promotion and in reducing the risk of chronic diseases.

PHENOLICS AND POLYPHENOLICS AS ANTIOXIDANTS

Plant foods serve as a rich source of phenolic and polyphenolic compounds. The concentration of phenolics and polyphenolics is mainly in the skin and seeds of fruits, but leaves often provide a richer source of phenolics. An example for this is blueberry leaves that are excellent sources of antioxidants (1). The leaves were more recently found to suppress the expression of

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hepatitis C virus RNA[2]. In cereals and legumes, the bran portion is also dominant in phenolics as compared to the endosperm[3]. The antioxidant potential of cereals follows a similar trend as is exemplified in pearled barley. Although the term antioxidant is frequently used by the public to describe the health benefits of phenolic and polyphenolic compounds, the mechanism(s) by which these effects are rendered is (are) not limited to their antioxidant potential which may be described as their efficacy in scavenging free radicals, chelating pro-oxidant metal ions or acting as reducing agents. Table 1 summarizes the different mechanisms by which phenolic and polyphenolic antioxidants confer their benefits, once consumed. It should also be noted that certain flavonoids may exert their beneficial effects *via* a pro-oxidant effect[4]. In addition, advanced glycation endpoints (AGEs) responsible for diabetes, cataract, neuropathy and alike are among the other mechanisms by which phenolics/polyphenolics are known to promote health[5]. The phenolics occurring in foods may occur in the free, soluble esters and glycosides or insoluble-bound forms.[6] In carrying out extraction operations, the latter group may not be easily procured, if proper procedures to release them are not followed. This may then lead to the underestimation of the reported results. Thus release of the insoluble-bound phenolics is essential. The correspondence of total phenolics with antioxidant potential as well as the contribution of insoluble-based phenolics to the total phenolics in several cases has been summarized in Table 2. These bound phenolics are released during colonic fermentation and hence are of paramount importance in reducing the risk of colon cancer.

Table 1. Mechanisms of action of phenolic and polyphenolic compounds

- Direct Removal of ROS/RNS or potentiation of cellular antioxidant capacity
- Affecting cell differentiation
- Increasing the activity of carcinogen detoxifying enzymes
- Blocking the formation of *N*-nitrosamines
- Altering the estrogen metabolism and/or colonic milieu
- Increasing apoptosis of cancerous cell and/or decreasing cell proliferation
- Affecting DNA methylation and/or maintaining DNA repair
- Preserving the integrity of intracellular matrices
- Other mechanisms

OMEGA-3 OILS AND THEIR HEALTH BENEFITS

Edible marine algae, sometimes referred to as seaweeds, are of interest as good sources of nutrients including protein, long-chain polyunsaturated fatty acids (PUFA), dietary fibres, vitamins and minerals. More recently, many researchers have focused on marine algae and their constituents as nutraceuticals and functional foods for their potential health-promotion mostly attributed to their ω3 fatty acids, antioxidants, and other bioactives. Although the majority of marine algae have low lipid contents, ranging from 0.3% in *U. lactuca* to 7.2% in *Caulerpa lentillifera*[7], algal lipids are rich in PUFA such as C20 : 5ω3 (eicosapentaenoic acid, EPA) and C22 : 6ω3 (docosahexaenoic acid, DHA). The proportions of EPA and DHA in oils from *Skeletonema costatum* and *Crypthecodinium cohnii* were 41 and 37%, respectively[8].

While marine algae are primarily used for production of single-cell oil rich in DHA, and other ω3 PUFA [9, 10], the leftover material after processing contains a variety of antioxidative substances that can potentially be utilized as a source of natural antioxidants.

The omega-3 oils, although originating from phytoplanktons or algae, are transferred to marine fish and mammals through the food web. Lipids from the body of fatty fish such as mackerel and herring, the liver of white lean fish such as cod and halibut, and the blubber of marine mammals such as seals and whales are rich in long-chain ω3 fatty acids. The ω3 PUFA include the essential fatty acid α-linolenic acid (C18 : 3 ω3, ALA) and its long-chain metabolites through elongation and desaturation, EPA, DPA (docosapentaenoic acid, C22 : 5 ω3) and DHA. ALA is abundant in certain plant sources such as flaxseed and to a lesser extent perilla, soybean and canola as well as walnuts[11]. EPA and DHA are mainly derived from marine fish, shellfish and algae, while DPA is present in significant amounts only in oils from marine mammals such as seal blubber oil. The distribution pat-

Table 2. Total phenolic content of selected cereals or their fractions and corresponding antioxidant activity

Material	Total Phenolics	Antioxidant Activity	
Wheat (Soft, bran)	66.91	55.80	
Wheat (Soft, flour)	24.11	27.10	
Barley (outermost layer)	6.26	59.70	
Barley (Innermost layer)	0.51	0.45	
Millet (Kodo, whole grain-soluble)	32.40	95.70	(41.68)
Millet (Kodo, dehulled grain- soluble)	6.86	41.00	
Millet (Kodo, whole grain-bound)	81.60	79.30	(86.1)

Total phenolics are recorded as mg ferulic acid equivalents/g crude extract for wheat and barley and as μmol ferulic acid equivalents/g defatted meal for millet. Antioxidant Activity is measured as μmol Trolox eg/g defatted for wheat and barley in TEAC assay and for millet in ORAC assay. Data are from Liyana-Pathirana and Shahidi[3] and Madhujith *et al*., 2006[35] and Chandrasekara and Shahidi[6], or 2011[34](TEAC value, in parenthesis).

tern of fatty acids in triacylglycerols (TAG) differs in fish and marine mammal oils, which greatly influence the metabolism, deposition and potential health benefits[12]. Long-chain ω3 PUFA are mainly located in the sn-2 position of TAG in fish oils, whereas in marine mammal lipids they are predominantly in the sn-1 and sn-3 positions. More recently, ω3 oils from by-products of fishery and fish processing industries have attracted special attention. By-products from fish processing including heads, frames, skin and viscera contain considerable amounts of ω3 PUFA-rich oil and utilization of marine by-products as good sources of ω3 oil is of great interest[13,14].

The omega-3 oils with their important role in health promotion and prevention/treatment of a number of chronic diseases may be included in foods such as bakery products, pastas, dairy products, spreads and juices, and may also be used as dietary supplements in liquid or capsule forms[11]. In the area of food application of ω3 oils or even as supplement, microencapsulation techniques have been used to protect the oils from oxidation and off-flavour development. The microcapsules produced by a coacervation method are released in the gastrointestinal tract after consumption, hence no adverse effect is noted in the products in terms of flavour perception[15].

The use of omega-3 oils/long-chain ω3 PUFA constitutes one of the most promising developments in human nutrition and disease risk reduction in the past three decades. Long-chain ω3 PUFA are of great interest because of their effectiveness in prevention and treatment of coronary heart disease[16], hypertension[17], diabetes[18], arthritis and other inflammations[19], autoimmune disorders[20] mental health and neural function as in depression and schizophrenia[11] and cancers[21,22] and are essential for maintenance and development of normal growth, especially for the brain and retina[23]. There has been growing evidence showing that regular consumption of fish oils containing ω3 PUFA can lower the rate of incidence and death from cardiovascular disease including ischemic heart disease, nonischemic myocardial heart disease, and hypertension[11]. While the exact biochemical mechanism for cardioprotective effect of ω3 fatty acids is unknown, hypotheses state that this may be attributed collectively to their antiarrhythmic, antiatherogenic and antithrombotic activities. Long-chain PUFA can lower serum triacylglyerols[24], increase membrane fluidity and reduce thrombosis by conversion to eicosanoids[25]. They provide specific physiological functions against thrombosis, cholesterol build-up and allergies[26].

Recently, omega-3 concentrates with a total EPA plus DHA content of 85% as ethyl esters have been used as prescription drugs for reducing blood pressure and triacylglycerols. Products have been sold under the brand name Amacor or Loveza and generic brands are expected to enter the market in 2012. In addition, Eli Lilly markets EPA capsules for treatment of Schizophrenia. This shows that omega-3 oils, not only are used as nutraceuticals and functional food ingredients, they may also be taken as pharmaceuticals.

Table 3. Examples of different forms of omega-3 fatty acid/oil products

Triacylglycerol (TAG) or TAG concentrate
Ethyl ester (EE) or EE concentrate of eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA)
Phospholipid
Calcium and magnesium salts
Chromium (III) – DHA complex
Phytosterol-DHA ester
Epigallocatechin gallate (EGCG) – DHA ester

BIOACTIVE CONJUGATES

In efforts to examine the additive, synergistic or unusual effects of conjugates of different bioactives, Kralovec *et al.*[27] prepared chromium (III) complex of DHA in order to take advantage of its constituent components. Later, we prepared, for the first time, conjugates of major green tea polyphenol or phytosterols with a number of fatty acids, particularly long-chain omega-3 fatty acids (Table 3).

Polyphenols in green tea, known as catechins, account for 30% of the dry weight of tea leaves with epigallocatechin gallate (EGCG) being the most abundant (59% of total polyphenols). EGCG has a multitude of bioactivities and is highly hydrophilic with poor solubility in lipophylic media, hence its absorption *in-vivo* is some-what hindered. Acylation of EGCG with selected fatty acids[28] was found to improve its lipophibicity, thus leading to its potential expanded application in more diverse systems such as fats and oils, lipid-based foods and cosmetics as well as biological systems, including better cellular absorption and bioefficacy under physiological conditions. Moreover, additional perspectives exists using health beneficial omega-3 (PUFA). The esters of EGCG with omega-3 PUFA, especially DHA significantly improved the antioxidant and anti-inflammatory activities of EGCG. Moreover, the EGCG-DHA esters totally arrested colon tumourigensis in mice[29] and exhibited anti-HCV (hepatitis C virus) activity which was 1700-folds greater than that of embelin as a positive control[30]. These findings strongly suggest that modified EGCG products are of great potential as novel ingredients for food and cosmetics and as nutraceutical/pharmaceutical applications. These findings have now been protected through a patent[31].

The esters of phytosterols with omega-3 fatty acids as well as a number of phenolic acids have also been prepared. While most of the research and commercial interest has so far been on phytosterol esters with vegetable oils, this research has successfully used enzymatic or chemoenzymatic preparation of novel phytosterol esters with DHA and other long-chain omega-3 fatty acids as well as for the synthesis of phytosteryl caffeates, ferulates, sinapates and vannilate. We have also found that phytosteryl oleates to have cholesterol lowering effects that exceed those with DHA.

The antioxidant potential of phytosteryl phenolates in a number of *in-vitro* systems have been shown to be system-dependent and being influenced by a number of mechanisms involved in rendering their effects. Phytosteryl phenolates, especially phytosteryl caffeates, ferulates and sinapates, provide an excellent opportunity for their future use as food antioxidants[32]. The cholesterol and triacylglycerol lowering effects of phytosteryl oleates and docosahexeanates is also of much interest as the components of latter products may render combined effects of their constituent moieties. In an apo-E deficient mice, the cholesterol lowering effects of products and in nearly removing atherosclerotic lesion has already been demonstrated[33].

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