Nutraceuticals and Functional Foods in Health Promotion and Disease Prevention

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Abstract
The effect of dietary factors on health status has been recognized since antiquity. Although some of the dietary phytochemicals and bioactives have traditionally been considered as “antinutrients”, their beneficial effects in human health promotion and disease prevention has recently been acknowledged. While nutraceuticals, sometimes referred to as natural health products, are often used in medicinal forms as tablets, capsules or liquid, functional foods are those that resemble the traditional food, as such, but confer benefits beyond their nutritional role. Among diseases of concern, cancer and coronary heart disease (CHD) are high on the list. In this respect, phenolics of plant origin, as an example, have been found to act as free radical scavengers, inhibitors of cholesterol oxidation and DNA breakage, among others, thus serving as potential cancer preventing agents. The type of phenolics involved depends on the species as well as other variables. On the other hand, marine foods have often been considered as “heart food” because of the role of their omega-3 fatty acid constituents in lowering of triacylglycerol and cholesterol levels and hence the incidence of CHD. This overview provides a detailed account of food phenolics and marine oils in human health and disease prevention.

INTRODUCTION
Epidemiological evidence has pointed to the benefits of increased consumption of fruits and vegetables as well as marine foods in human health promotion and disease prevention (Block et al., 1992; Shahidi and Ho, 2000). While plant foods contain a variety of bioactives that exert their health benefits through synergistic action of the many classes of compounds involved, marine lipids are known to influence health through their omega-3 fatty acid constituents. While initial research had concentrated on examining the benefits of plant-based foods through research into their vitamin C, vitamin E and carotenoid components, more recent work has confirmed that correlations of benefits with individual compounds, such as β-carotene, may contradict their perceived effects if used in the pure form. Hence β-carotene, when used as such, was found to increase the incidence of cancer in smokers (Omenn et al., 1996). Thus, the effects are found to be related to the co-operative and synergistic action of the cocktail or soup of bioactives presents in source materials. These findings have created the foundation for exploration and development of functional foods and nutraceuticals.

The terms nutraceuticals and functional foods have been used to describe extracts and whole foods that have the characteristics of providing protective, preventive and possibly curative effects in the pathogens of cancer and other chronic disease progression. While nutraceuticals refer to components/extracts of food and non-food commodities taken in the medicinal form of tablet, capsule, powder, liquid and potion, functional foods resemble the traditional foods in their look, but both nutraceuticals and functional food groups provide benefits beyond what is rendered by their nutrient components.

There are many different classes of bioactives present in foods, herbal and medicinal plants, depending on the species under consideration. Phenolic and polyphenolic group of compounds constitute an important class with biological activity
(Table 1). While these components exert their effects through an array of possible mechanisms, the antioxidative role (Halliwell, 1996) of such compounds may be exerted by scavenging and neutralizing of free radicals (Wettasinghe and Shahidi, 1999a, b) or chelating prooxidant metal ions (Wettasinghe and Shahidi, 2002).

In case of marine oils, their omega-3 components are known to exert influence on health as well as through their influence on eicosanoids metabolism. Hence, epidemiological studies have indicated that highly unsaturated fatty acids (HUFA) in marine oils lower the level of triacylglycerols and possibly cholesterol, enhance immune-response and help relieve problems associated with rheumatoid arthritis and diabetes, among others. In fact docosahexaenoic acid (22:6n-3, DHA) constitutes a major fatty acid of the gray matter of the brain and the retina of the eye (Shahidi and Finley, 2001). The organs most influenced by the omega-3 fatty acids are those with electrical activity and in addition to the brain and eye, heart is another major organ affected. However, highly unsaturated fatty acids involved are prone to oxidation and require stabilization in order to protect consumers from deleterious affects of oxidation products.

This overview provides an account of the phenolics of nutraceutical, functional foods and medicinal plants as well as the role of phenolics in stabilization of marine oils. The biosynthesis of phenolics and their function in plant resources is also provided.

**BIOSYNTHESIS, CLASSIFICATION AND NOMENCLATURE OF PHENOLICS**

Phenolics and polyphenolics in nutraceuticals, functional foods and herbal products when consumed are known to play an important role in the human body. They constitute, perhaps, the largest group of secondary metabolites originating from phenylalanine, and to a lesser extent, in some plants, from tyrosine (Shahidi and Naczk, 2004). The conversion proceeds via the action of phenylalanine ammonia lyase (PAL) or tyrosine ammonia lyase (TAL) to afford trans-cinnamic acid or p-coumaric acid, respectively. These and related carboxylic acids are known as phenylpropanoids and constitute a C₆-C₃ moiety. The related phenylpropanoids are produced via successive hydroxylation and methylation to other C₆-C₃ compounds and these may in turn be reduced to alcohols, which serve as precursors in lignin synthesis, or may lose a C₂ moiety to afford benzoic acid derivatives; it is also possible that acids involved lose a CO₂ molecule to produce simple phenols. Fig. 1 illustrates a variety of C₆-C₃, C₆-C₁ and C₆ compounds produced in plants (Shahidi, 2000a, b).

The C₆-C₃ compounds, as their CoA adduct, may react with 4 molecules of malonyl CoA to afford stilbenes or chalcones via the action of stilbene synthase or chalcone synthase, respectively. The chalcones involved may subsequently cyclize to produce a wide range of C₆-C₃-C₆ compounds, collectively known as flavonoids. The individual classes of compounds involved include flavones, flavonols, flavonones, flavononols, flavan-3-ols, anthocyanidins, catechins and isoflavones, among others. Fig. 2 illustrates the variety of flavonoids present in nutraceutical, functional foods and medicinal products.

In addition to the above classes of compounds, lignans could be produced by the addition of two molecules of C₆-C₃ while coumarins, cutins and suberins may result from combination and/or transformation of C₆-C₃ compounds. Meanwhile, condensation of gallic acid with sugars leads to the production of hydrolyzable tannins and that of flavan-3-ols with one another affords condensed tannins (Fig. 3).

**ISOLATION, CHARACTERIZATION AND ANTIOXIDANT POTENCY OF PHENOLICS AND POLYPHENOLICS**

Phenolic compounds in different source materials may be extracted into a suitable solvent following removal of their lipid constituents. Solvents often used for this purpose include acetone, ethanol, methanol and water, depending on the nature of phenolics involved and the type of source material under investigation. Therefore, catechins are extracted from green tea into water, while oilseeds, herbales and medicinal plants may be extracted using organic solvents usually containing 5-20% water. Following extraction,
dechlorophyllization of the sample might be necessary in order to prevent the action of chlorophylls as photosensitizers (Wanasundara and Shahidi, 1998). The crude extracts so obtained may be evaluated for their content of phenolics and antioxidant activity and may then be fractionated using appropriate chromatographic procedures. Sephadex LH-20 column chromatography has most often been employed. Fractions are isolated based on their UV absorption intensity at 280 nm and after color development at 490 and 725 nm for sugars and phenolics, respectively. Finally, individual components may be isolated from each fraction using thin layer chromatography (TLC), analytical or preparative HPLC, and possibly gas chromatography-mass spectrometry following derivitization and subjected to spectroscopic analyses to elucidate their chemical structures. Direct use of HPLC-MS might also be considered.

In conjunction with structure elucidation, it is possible to determine the antioxidant capacity of the material under investigation (Shahidi, 1997). The source material, as such or after defatting, may be added to a homogenate of meat, fish, brain, liver or heart tissue to determine its efficacy in prevention of oxidation. In this, the 2-thiobarbituric acid (TBA) test or determination of a dominant aldehyde in the sample, hexanal for model systems rich in omega-6 fatty acids such as linoleic or arachidonic acid and propanal for systems rich in omega-3 fatty acids such as linolenic, eicosapentaenoic (EPA) or docosahexaenoic acid (DHA) might be pursued. For extracts and fractions thereof, similar determinations as well as other auxiliary tests may be carried out. The commonly used procedures may examine a primary product of oxidation, such as conjugated dienes or hydroperoxides, or could use TBA and p-anisidine value, or testing in a β-carotene-linoleate model system as well as oxygen radical absorbance capacity (ORAC), Trolox equivalent antioxidant capacity (TEAC) and other relevant tests such as α,α-diphenyl-β-picrylhydrazyl (DPPH), superoxide, hydroxyl radical and hydrogen peroxide scavenging activities.

As an example, we determined the chemical structures of active components of defatted seeds of borage (Borago officinalis L.) and evening primrose (Oenothera biennis), as given in Fig. 4 (Wettasinghe et al., 2001, 2002). In evening primrose defatted seeds, we were also able to tentatively identify oenothein B (Fig. 5), a known anticarcinogen, which is a high-molecular-weight compound. For many of the medicinal plants, phenolics involved are also varied in their chemical structures. The antioxidant efficacy of extracts prepared arises from the combination of phenolics, which are often present with their precursors and reaction products. Hence, the importance of synergistic actions should be carefully considered.

PHENOLIC CONSTITUENTS AND SYSTEM-DEPENDENCY OF THEIR ANTIOXIDANT ACTIVITY

Phenolic constituents from foods and nutraceuticals may be separated into their lipophilic and hydrophilic fractions by partition into butanol and water. Thus 30% of the crude extract of evening primrose was made up of phenolic compounds. Of this, 39% were lipophilic and 61% hydrophilic. The importance of the presence of both lipophilic and hydrophilic constituents is felt when such extracts are added to whole foods, bulk oils and emulsion systems.

In emulsion systems, the so-called “Polar Paradox Theory” states that compounds with lipophilic character are more effective in protecting oil-in-water emulsions than bulk oils. This is due to the fact that such constituents protect the oil droplets at their interface with water where they are present in a relatively high concentration, hence neutralizing the effect of oxidants. Meanwhile, hydrophilic compounds/extracts will dissolve in the entire aqueous phase, hence are present in low concentrations with little effect. In the bulk oil, however, lipophilic compounds are dissolved and are present in low concentrations while hydrophilic compounds mainly reside in the interface with air at a high concentration, hence protecting the oil from oxidation more effectively than their lipophilic counterparts (Khan and Shahidi, 2002). Thus, compositional characteristics of crude extracts will dictate their efficacy in different systems.
EFFECT OF PROCESSING ON PHENOLICS

Phenolics in foods and nutraceuticals are present in the free, esterified, glycosylated and insoluble-bound forms (Naczk and Shahidi, 1989). Upon processing, hydrolysis, deglycosylation and/or solubilization of phenolics in forms other than in the free form may take place. In addition, washing, heating and other processing steps may lead to the removal, degradation and loss of phenolics from source materials. Thus, it is important to consider processing effects on phenolics when discussing health benefits of such foods and nutraceuticals.

Isoflavones are present at 3-5 mg/g in crude soybean flour. During production of protein concentrates and protein isolates, a portion of isoflavones is removed due to different unit operations involved. Thus, acid-washed concentrates contain 2-3 mg/g of isoflavones while 0.2-0.3 mg/g isoflavones are present in alcohol-washed products. Meanwhile, solubilized and precipitated proteins in the isolates contain 1-2 mg/g isoflavones. In the production of tofu and other soybean-based products up to 80% of isoflavones may be removed as a result of repeated washing operations.

Catechins extracted from green tea contain chlorophylls. Application of the crude extract to an animal model system reflected their antioxidant potency in protecting the product against oxidation. However, in bulk oil model systems, the extracts were pro-oxidative and promoted oxidation. Removal of chlorophylls, using column chromatography, resulted in a dechlorophyllized extract, which performed as an effective antioxidant. When used together with marine oils, dechlorophyllized extracts, exerted a good antioxidant activity, thus the products may render beneficial health effects in terms of prevention of both cancer and cardiovascular diseases (Wanasundara and Shahidi, 1998).

Processing of vegetable and specialty oils is generally carried out to produce a product that is light in color, odorless and presumably superior quality characteristics. However, during refining, bleaching and deodorization 30-95% of the endogenous carotenoids, phospholipids, sterols, tocopherols and tocotrienols may be removed. Hence, the final product is generally less stable than the unprocessed oil and hence requires appropriate packaging, perhaps along with addition of exogenous antioxidants (Shahidi and Shukla, 1996). The deodorizer distillate (DOD) fraction so produced may be further processed in order to produce lecithin, tocols, etc. for use as nutraceutical products (Kanazawa et al., 2002; Shahidi, 2002). However, it is also possible, following refining, bleaching and deodorization, to return tocopherols, sterols and other DOD constituents to the oil in order to produce an appropriately enriched oil with improved stability.

PHENOLICS IN SPICES AND HERBAL PRODUCTS

Although spices and herbs are not placed in the food pyramid, they have long been used in foods in order to improve or modify their flavor and taste. Their types and proportions used in different foods are dictated by local and ethnic backgrounds. However, in addition to their varying flavor effects, spices render protection to foods against deteriorative processes due to oxidative and microbial effects (Madsen and Bertelsen, 1995; Risch and Ho, 1996). Phenolics in spices have been recognized as primary active ingredients responsible for their beneficial effects in food protection as well as potential health benefits and hence a fitting place for spices in the food pyramid has been suggested (Palaniswamy, 2003). Rosemary, sage and turmeric are among widely used spices with known phenolic constituents. The chemical nature of the phenolics involved is diverse; for example, rosemary phenolics include carnosol, epirosmanol, rosmol, isorosmanol, carnosic acid, rosmanol, epirosmanol, carnosic acid, rosmariquinone, rosmarinic acid and rosmaridiphenol, among others. The antioxidative components of sage are similar to those of rosemary as both of these belong to the Labiate family. Extracts of rosemary and sage devoid of any flavor are now commercially available and these may be used at 200-1000 mg/kg level in different products. These oleoresins have GRAS (generally recognized as safe) status and may be used in a variety of functional foods and lipid-containing products. Curcumins in turmeric are also known to possess excellent anticarcinogenic
effects, but turmeric is used mainly, as such in different foods as a colorant.

In addition, certain plant materials are used as components of binder mixes in processed meats or as breading and batter components. Thus, deheated mustard flour, with excellent antioxidant capacity, may be used at a 2% level in processed meats (Saleemi et al., 1993). The phenolics of interest in mustard flour include phenolic acids and phenylpropanoids.

In medicinal plants and herbal products including echinacea, ginseng, ginkgo, St. John’s wort, valerian, kava kava, saw palmeto, black cohosh, devil’s claw, goldenseal, hawthorn, ginger, licorice and milk thistle, active components are often phenolic in nature or include phenolic compounds (Blumenthal, 2000; Lawson and Bauer, 1998). Detailed discussion of the chemical nature of phenolics involved is provided elsewhere (Shahidi and Naczk, 2004).

OTHER BENEFITS OF PHENOLICS IN FOODS AND NUTRACEUTICALS

Phenolics in foods are known to have a myriad of effects, which positively influence health status of consumers. Nuts are often used as a source of condensed energy and healthy foods. Recently, we studied the beneficial health effects of extracts of almond seed and its components on scavenging of free radicals (Siriwardhana and Shahidi, 2002) as well as inhibition of copper-induced LDL cholesterol oxidation. The inhibition of formation of hydroperoxides, as reflected in conjugated dienes is shown in Table 2 (Siriwardhana and Shahidi, unpublished data). Results indicate that at 100 mg/kg, 90.1-99.6% of oxidation of LDL cholesterol was inhibited by both edible and non-edible components of the seed. Similarly, retention of supercoiled DNA is peroxyl radical induced strand scission by extracts of almond extracts was 94.9-99.5%. Thus, phenolics of almond (not reported here), mainly phenolic acids, phenylpropanoids and flavonoids, may have health benefits and prevent cardiovascular and certain types of cancer.

MARINE OILS AND THEIR PROTECTION AGAINST OXIDATION

The consumption of sea foods and marine oils has been on the rise because of perceived health benefits related to their omega-3 fatty acid components (Simopoulos, 1981; Shahidi, 2000c). Marine oils are derived from algal sources, body of fatty fish, liver of white lean fish and blubber or subcutaneous fat of marine mammals. These oils contain different levels of long-chain polyunsaturated fatty acids (LC PUFA) belonging to the omega-3 family (Dyerberg et al., 1975; Bang et al., 1976). Although these fatty acids may be produced from their precursor alpha-linolenic acid, the rate of conversion is between 3% and 5% in healthy individuals. In certain disease conditions, this conversion rate is much lower, hence LC PUFA such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are conditionally essential. The omega-3 fatty acids are effective in reducing high blood pressure, body triacylglycerols and cholesterol, abnormal blood clotting, arthritias and fat deposition. They are also known to ameliorate arthritis and improve diabetic conditions. DHA is a major component of the gray matter of the brain and the retina of the eye. Human milk also contains a reasonable level of DHA, hence infants fed with mother’s milk exhibit a higher IQ and intelligence level than their counterparts fed on formulas devoid of DHA (Shahidi and Finley, 2001).

Despite their multifunctional role in health promotion and disease prevention in the body, LC PUFA are highly prone to oxidation when stored. Upon consumption, LC PUFA are known to increase the body’s burden on natural antioxidants such as α-tocopherol. Therefore, it is important to stabilize marine and algal oils during storage prior to consumption. Addition of crude green tea extract with known anticarcinogenic activity would help protect the LC PUFA, hence allowing realization of full advantage from their cardiovascular benefits (Alasalvar et al., 2002). However, crude extracts were found to enhance oxidation of both menhaden and seal blubber oils (Table 3). A close scrutiny of the results indicated that chlorophylls in the extracts may have acted as photosensitizers. Thus, dechlorophyllization, using column chromatography with TYOPEARL, resulted in the recovery of dechlorophyllized mixed catechins which were
nearly as effective as tert-butylhydroquinone (TBHQ). Meanwhile, of the individual catechins, (-)-epicatechin gallate was more active than TBHQ (results not shown). It is also important that consumption of marine oils be accompanied by intake of an adequate amount of vitamin E. However, suppliers of marine oils generally employ mixed tocopherols for stabilization of the oils and these are usually at a sufficient level to address the increased demand on vitamin E (Shahidi and Kim, 2002).

CONCLUSIONS

Nutraceuticals and functional foods provide means to address the increasing burden on the health care system by promoting health through prevention rather than treatment. Products of concern often contain phenolics and such components render their effects in many ways, amongst which neutralization of reactive oxygen, nitrogen and chlorine species is a main mechanistic approach. Other mechanisms such as chelation of pro-oxidative transition metals may also be involved. Thus, phenolics may be employed for stabilization of LC PUFA, among others. Furthermore, adequate intake of LC PUFA as such or through consumption of marine oils is recommended in order to avoid cardiovascular disease.

Literature Cited


Saleemi, Z.O., Wanasundara, P.K.J.P.D. and Shahidi, F. 1993. Effect of low pungency ground mustard seed on oxidative stability, cooking yield and color characteristics of


### Table 1. Distribution of phytochemicals in different plant foods.

<table>
<thead>
<tr>
<th>Plant Food</th>
<th>Sulfides</th>
<th>Phytates</th>
<th>Phenolic acids</th>
<th>Flavonoids</th>
<th>Coumarins</th>
<th>Lignans</th>
<th>Carotenoids</th>
<th>Indols</th>
<th>Isothiocyanates</th>
<th>Terpenes</th>
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</thead>
<tbody>
<tr>
<td>Garlic</td>
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<tr>
<td>Green tea</td>
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<tr>
<td>Soybean</td>
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<td>-</td>
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<tr>
<td>Cereals</td>
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<td>●</td>
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<td>-</td>
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<td>●</td>
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<tr>
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<tr>
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</table>

### Table 2. Percent inhibition of LDL oxidation and retention of supercoiled DNA by Almond Extracts.

<table>
<thead>
<tr>
<th>Extract</th>
<th>Inhibition of LDL oxidation</th>
<th>Inhibition of DNA Scission</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>10 mg/kg</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>Whole seed</td>
<td>53.9</td>
<td>93.5</td>
</tr>
<tr>
<td>Brown skin</td>
<td>71.9</td>
<td>99.6</td>
</tr>
<tr>
<td>Greenshell cover</td>
<td>36.2</td>
<td>90.1</td>
</tr>
<tr>
<td>Reference (Quercetin)</td>
<td>28.6</td>
<td>83.7</td>
</tr>
</tbody>
</table>

### Table 3. Percent change in particular (PV, meq/kg) of menhaden and seal oils upon addition of green tea extracts.

<table>
<thead>
<tr>
<th>Oil</th>
<th>500 mg/kg</th>
<th>1000 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>As such</td>
<td>Dechlorophyllized</td>
</tr>
<tr>
<td>Manhaden</td>
<td>+32</td>
<td>-39.2</td>
</tr>
<tr>
<td>Seal</td>
<td>+18</td>
<td>-40.8</td>
</tr>
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</table>
Fig. 1. Production of phenolic acids, phenols and phenylpropanoids from phenyl-alanine and tyrosine upon the action of phenylalanine ammonia lyase (PAL), tyrosine ammonia lyase (TAL) and other enzymes.
Fig. 2. Production of flavonoids from phenylalanine via cyclization of chalcones.
Fig. 3. Chemical structures of condensed and hydrolyzable tannins.
Fig. 4. Chemical structures of low-molecular-weight phenolics of borage and evening primrose defatted meals.

Fig. 5. Chemical structure of oenothein B found in evening primrose.