NUTRACEUTICALS AND THEIR APPLICATIONS: AN OVERVIEW

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Summary

The present review highlights the significance and therapeutic applications of nutraceuticals in various diseases. The nutraceuticals can also be used as functional foods offering potential to be utilized without any side effects as majority of them are derived from natural resources. These functional foods may open new avenues in the field of health care in treatment of chronic ailments thereby improving the quality of life.

Key words: functional food, PUFA, Omega-3-fatty acid, vitamins

Introduction

The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" in 1989 by Stephen DeFelice, MD, founder and chairman of the Foundation for Innovation in Medicine (FIM), Cranford, NJ. According to DeFelice, nutraceutical can be defined as, "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease"[1]. However, the term nutraceutical as commonly used in marketing has no regulatory definition [2]. In the marketplace, however, there is some confusion as to the difference among various categories of healthful foods as well as the increasingly fine-line difference between dietary supplements and foods. The following definitions should help clarify the issues.

Dietary supplements are defined as any product (other than tobacco) that is intended to supplement the diet and contains one or more of the following: a vitamin, mineral, herb or other botanical; an amino acid or metabolite; an extract; or any combination of the previously mentioned items. According to U.S. Food and Drug Administration (FDA) regulations, a dietary supplement may be marketed in food form if it is not "represented" as a conventional food and is clearly labeled as a dietary supplement. Specific health or structure/function claims are allowed on dietary supplements provided the FDA deems adequate scientific substantiation exists for the claim.

Fortified foods are enriched with vitamins and minerals, usually at a range up to 100 percent of the Dietary Reference Intake (DRI, formally called the Recommended Daily Allowance or RDA) for that nutrient. Often, these foods are mandated by law to be fortified to a level that replaces nutrients lost during processing, as in adding B vitamins to many baked goods. Breakfast cereals are a food category that has been fortified since the1940s.

Functional foods, according to their generally accepted definition, are "any food or food ingredient that may provide a health benefit beyond the traditional nutrients it contains." . This is a tricky definition because the term "traditional nutrients" refers *only* to vitamins and minerals. The reason is that these are considered essential to the diet and/or correct a classical nutrient deficiency disease; for instance, vitamin C corrects scurvy. Hence, the vitamin D content in sardines, which alleviates rickets, is not an example of a functional food, while soy, which contains soy protein associated with a reduction in cardiovascular disease, is one because soy protein is not considered to be essential. Other functional foods include red grapes and cranberry juice (for the oligomeric proanthocyanidins, OPCs) and oat bran (for the fiber content), all with health benefits attributed to "non-nutrient" compounds as classified by standard agreement of the term. So-called "super-fortified" foods--those fortified with more than 100 percent of the DRI and/or foods that have added botanicals or other supplements--also fall into the category of functional foods. Two examples of the latter are orange juice with echinacea (*Echinacea angustifolia* or *E. purpurea*) and salad dressing with omega-3 polyunsaturated fatty acids (PUFAs). Functional foods may carry health or structure/function claims provided adequate scientific evidence supports the claim.

Medical foods refer to a food formulated to be consumed or administered internally while under the supervision of a physician. The food product is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements are established by medical evaluation. Medical foods may be used to treat diabetes, obesity or heart disease, for example, and may carry specific claims, but in a strict sense are sold through physicians and not through conventional retail outlets [3].

Nutraceuticals may range from isolated nutrients, dietary supplements and diets to genetically engineered ‘‘designer’’ foods, herbal products and processed products such as cereals, soups and beverages. Selected nutritive nutraceuticals are listed in Table 1. Doubtlessly, many of these substances possess important physiological functions and valuable biological activities. Nevertheless, some consideration of certain major and actual nutraceuticals is pertinent.

An actual class of nutraceuticals is represented by the polyunsaturated fatty acids (PUFAs) especially by those of the n-3 and n-6 fatty acid (FA) families. Current interest is devoted to the so-called fish-oils containing a high share of n-3 FA [eicosapentaenoic (EPA) and docosahexaenoic acids (DHA)]. It is claimed that these particular FA exert a protective effect on the development of cardiovascular and inflammatory diseases and the beneficial effects of fish oil supplementation in many other chronic diseases have been advocated. Many recent observations suggest a potential role for fish oils in the treatment of atopic dermatitis and psoriasis. Dietary n-3 FA treatment offers exciting novel possibilities in malignant diseases. There are also indications that premature infants have limited dietary support of the n-3 FA required for the normal composition of brain and retinal lipids [4].

Table 1 List of Nutritive Nutraceuticals

Dietary fiber
Polyunsaturated fatty acids (PUFA, fish oil)
Proteins, peptides, amino aids, keto acids
Minerals
Antioxidative vitamins
Other antioxidants (glutathione, selen, etc.)

Cancer

Treatment of cancer cachexia with fish oils might be a highly interesting future application. Fish oils probably inhibit end-organ effects of tumor-derived lipolytic and proteolytic factors, thereby influencing the activity of a number of receptors and enzymes which have a fundamental role in cellular signaling. Other possible mechanisms include interaction with peroxisome proliferators activated receptor-a (PPARa) which is a gene transcription factor that induces the breakdown of leukotrienes and thus has a role in limiting the duration and extent of inflammation [4]. Glutamine is the most prevalent free amino acid in the human body. Glutamine not only acts as a precursor for protein synthesis, but is also an important intermediate in large number of metabolic pathways. With the recognition that catabolic states are associated with intracellular glutamine depletion, various approaches to maximize glutamine nutrition were introduced. Since native glutamine is poorly soluble in water its administration is not practicable in routine clinical setting. Synthetic stable and highly soluble dipeptides show great potential as a way of providing glutamine which otherwise is difficult to deliver. Indeed, glutamine dipeptides are true nutraceuticals [5, 6]. Future implications of glutamine (dipeptide) therapy are full of promise. A consistent observation is that glutamine-enriched parenteral feeding attenuates the expansion of extracellular and total body water. This interesting finding suggests that provision of glutamine (dipeptides) may influence stress-induced accumulation of extracellular fluid by affecting membrane function and thereby changing the cellular hydration state indeed, an encouraging future therapy in situations with extracellular [7].

During hyperinsulinemic euglycemia, increased glutamine availability blunted insulin action on glucose production and enhanced insulin-mediated glucose utilization [8]. Thus, glutamine (dipeptide) appears to possess a future potential to be of benefit as a nutrient adjuvant during clinical situations associated with insulin resistance, such as diabetes mellitus, sepsis, trauma and others. A further fascinating approach proposes glutamine (dipeptides) as a suitable cardioprotective and rescue agent. The mechanism through which glutamine exerts its beneficial effects may involve maintenance of myocardial glutamate and thus glutathione as well as myocardial high energy phosphates and prevention of myocardial lactate accumulation [9].

Osteoarthritis

Recently Baker and colleagues investigated the relationship of vitamin C intake (evaluated using a food frequency questionnaire) and knee pain over a 30-month period among 324 participants (mostly men) in a longitudinal study of knee osteoarthritis[10]. Pain score was computed as an average of pain scores reported at all visits in their cross-sectional analysis. They found that individuals with low intakes of vitamin C (200 mg for men, 150 mg for women) have significantly more knee pain after adjusting for age, body mass index and energy intake. For example, among smokers in the lowest tertile for vitamin C intake, pain scores were 2.8 times greater than that in all other men. Benefit from vitamin E therapy has been suggested by several small studies of human osteoarthritis, [11,12,13,14] of which the most rigorous was a company-sponsored 6-week double-blind placebo-controlled trial of 400 mg a-tocophorol (vitamin E) in 56 OA patients in Germany [15]. Vitamin-E-treated patients experienced greater improvement in every efficacy measure, including pain at rest (69% better in vitamin E versus 34% better in placebo, P!0.05), pain on movement (62% better on vitamin E versus 27% on placebo, P!0.01) and use of analgesics (52% less on vitamin E; 24% less on placebo,P!0.01). The rapid response in symptoms observed in this study precludes a structural effect in this disorder, and suggests that the beneficial effect might result from some metabolic action such as inhibition of arachidonic acid metabolism.

More recently, many researches have focused on marine algae and their constituents as nutraceuticals and functional foods for their potential health promotion mostly attributed to their u3 fatty acids, antioxidants, and other bioactives. These and other bioactive substances present in products are found effective in reducing the risk of various diet and age related chronic diseases such as cardiovascular disease (CVD) and cancers [16].

While marine algae are primarily used for production of single-cell oil rich in DHA, and other u3 PUFA [17], the left over material after processing contains a variety of antioxidative substances that can potentially be utilized as a source of natural antioxidants. A number of studies evaluating the antioxidant activity of marine algae have revealed high antioxidant efficacy of their extracts which is equal to or better than that of commercial antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and a-tocopherol, and have suggested the use of algal antioxidants in food formulations [18,19].

Green tea has always been considered by the Chinese and Japanese peoples as a potent medicine for the maintenance of health, endowed with the power to prolong life [20]. Recently, Yean Lee and colleagues [21] looked at the effects of the main active green tea constituent, epigallocatechin-3- gallate (EGCG) on chronic lymphocytic leukemia B cells isolated from leukaemic patients. These cells are characterized by their resistance to apoptosis because they secrete and bind vascular endothelial growth factor (VEGF), a potent angiogenic cytokine that also acts as a crucial survival factor for tumour cells. The researchers showed that addition of EGCG to these cells markedly decreased VEGF receptor phosphorylation, leading to the disruption of the VEGF-dependent autocrine pathway that protects the cells from apoptosis and cell death. These results support our observations [22] on the potent inhibition of the activity of VEGF-receptor tyrosine kinase by components of green tea, and provide strong evidence that this inhibitory effect may have profound repercussions on tumours that depend on this cytokine for progression. Of considerable importance is the low concentration of EGCG required to trigger the observed biological effects, because VEGF-receptor activity can be inhibited and apoptosis of leukemia B cells can be induced2 with concentrations of EGCG in the plasma after moderate drinking of green tea (2–4 cups a day) [23].

Obesity

Obesity has become a global epidemic, and the efforts to curb the rise in prevalence of overweight and obesity have so far not been very successful. The "energy gap" is the daily surplus in energy balance that can explain the average weight gain at a population level, and it has been estimated to be 50 100 kcal. As many dietary factors or substances exert effects on the three components of energy balance, one way to affect the energy gap is to use the inherited properties of these substances. Because the positive energy balance is created by an excessive energy intake (i.e. obese individuals have a higher energy intake than normal weight individuals) many efforts have been exerted to reduce energy intake by reduced portion sizes, reduced energy density foods etc. Recently, more physiological approaches are trying to reduce spontaneous energy intake by enhancement of satiety through naturally occurring nutrients and bioactive food substances working on e.g. gastric emptying, and hormones as ghrelin, CCK, GLP-1, PYY etc. Clearly, a high intake of dairy protein is reducing spontaneous food intake, and may be one important mechanism to link low-fat dairy and meat products with better weight control. In the large randomized DIOGENES dietary intervention study at 8 different European centres, both a higher protein content and lower glycemic index improved retention and weight loss maintenance. Now, research are investigating more specific proteins, peptides and amino acids to obtain a better physiological mechanism of action, and to enable the use of this way to promote satiety without increasing total protein intake. Dietary calcium reduces fat absorption, and a sufficient intake may also prevent excessive hunger during weight loss diets. Caffeine, chili, mustard, catechins have beneficial effects on energy balance, although the quantitative importance of this may be modest. In conclusion, manipulation of diet composition with an aim to prevent weight gain and weight re-gain is a promising avenue of research [24].
A disturbance in the gastrointestinalmicroflora or the host response to this flora has been demonstrated to play a critical role in the pathogenesis of inflammatory bowel disease (IBD). This information has led to attempts to modify the bacterial flora with probiotics, as reviewed in detail elsewhere [25, 26].

Ulcerative colitis

The largest study in the treatment of active ulcerative colitis (UC) enrolled 116 patients who were randomized to E. coli Nissle 1917 or standard-care mesalamine therapy [27]. There was no difference in clinical outcomes between groups, so the authors concluded equivalence between therapies. Although this trial was not powered to detect equivalence, a later study of 327 patients with inactive UC assessed E. coli Nissle 1917 against mesalamine and established statistical equivalence [28]. This was the best of all evidence to support the use of probiotics for UC therapy; unfortunately, however, another study assessing maintenance of remission in 120 patients with E. coli Nissle 1917 failed to show any difference from placebo [29]. In a smaller study, patients with UC received BIFICO capsules (Enterococci, Bifidobacteria, Lactobacilli) to maintain remission induced by sulfasalazine . Patients receiving BIFICO demonstrated lower levels of pro inflammatory cytokines and NF-kB, and increased levels of interleukin-10, compared with patients receiving placebo, and relapse in the BIFICOtreated group was significantly less (20%) compared with placebo (93%) at one year [20]. Another small double blinded randomized controlled trial used a symbiotic consisting of a prebiotic (Synergy) and a probiotic (Bifidobacterium longum) to treat patients with active UC.

After one month of treatment, patients receiving symbiotic treatment demonstrated improvement in all clinical parameters [30]. Uncontrolled pilot studies using VSL3 to treat patients with mild to moderate UC suggested that this mixture of probiotic bacteria was effective in inducing remission [31]. Promising preliminary findings have also been reported with the use of Bifidobacteria-fermented milk [32] and S. boulardii [33] treatment. Randomized placebo-controlled trials using VSL3 to treat UC are currently ongoing to confirm the efficacy of this product. A novel protocol for probiotic administration, fecal flora donation from healthy adults, has had promising preliminary results in UC [34]. Interestingly, at 1–13 years post-human fecal infusion, all patients were free of endoscopic and histologic evidence of UC [35].

Pouchitis

Probiotics have been dramatically effective in the management of ileal inflammation following colectomy and ileal pouch formation (pouchitis). Randomized controlled trials have unequivocally shown the preparation VSL3 to be effective in maintenance of antibiotic-induced remission of pouchitis, and in post-surgical prevention of pouchitis [36, 37, 38, 39]. Trials using a fermented milk product Culture containing Lactobacilli and Bifidobacteria have also shown some benefit [40]. However, the use of Lactobacillus GG for treatment of acute active pouchitis did not demonstrate efficacy [41].

Crohn's disease

Limited randomized controlled trials have examined the use of probiotics in the management of Crohn's disease; unfortunately, no strong evidence exists for the adoption of their use. These studies have used a single strain, L. rhamnosus GG, and have failed to demonstrate a clinical effect in the treatment of active disease or maintenance of drug-induced [42] or postoperative remission [43]. Likewise, a trial of E. coli Nissle 1917 did not demonstrate efficacy as maintenance therapy [44]. These trials are small, however, and only used a single strain of bacteria; thus, it remains possible that future larger trials with different multistrain probiotic compounds will have more positive findings.

Alternative treatments for Inflammatory Bowel Disease

Nutraceutical compounds such as turmeric (C. longa), lyprinol (lipid extract of New Zealand green-lipped mussel), polyherbal formulations (Aegle marmeloes, Coriandrum sativum, Cyperus rotundus, Vetiveria zinzanioids) and rutin (3-0-rhamnosyl-glucosyl-quercetin) have all demonstrated varying degrees of anti-inflammatory actions in experimental animal models [45, 46, 47, 48]. Whether these types of compounds will find a place in the treatment of human IBD remains to be shown. Omega-3 fatty acids Omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid and docosahexaenoic acid, are found in high levels in fish oils, and have been shown to attenuate inflammation in animal models [49, 50]. A good review on the use of omega-3 fatty acids in the treatment of IBD has been published [51]. Early studies showed promise for the use of fish oil to reduce the rate of relapse in patients with Crohn's disease [52]. Problems with the use of corn or olive oil as placebo in these earlier studies might have confounded the results, however, as these oils are a source of omega-6 fatty acids, which have demonstrated proinflammatory activity [53].

More recent studies in patients with UC and Crohn's disease have demonstrated no clinical benefit from omega-3 fatty acid supplementation [54, 55]. A randomized, double-blind, placebo-controlled trial published recently examined the efficacy of an oral supplement enriched with fish oil, fructooligosaccharides, gum Arabic, vitamin E, vitamin C and selenium on disease activity and drug usage in patients with UC [56]. In this trial, patients receiving the oral supplement decreased their usage of corticosteroids, suggesting that this type of multi-compound supplementation might have a role as adjunctive, rather than primary, therapy. A recent study has identified an endogenous lipid mediator, Resolvin E1, which is generated from eicosapentaenoic acid in vivo and demonstrates potent anti-inflammatory activity, suggesting a mechanism by which omega-3 fatty acids can modulate inflammatory pathways [57].

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