

Review Article

Nutraceuticals - Global status and applications: a Review

Sapkale Anita P*, Thorat Mangesh S., Vir Prasad R and Singh Meera C.

Smt Kashibai Navale College of Pharmacy, Kondhwa (BK), Pune, Maharashtra, India.

ABSTRACT

In recent years there is a growing interest in nutraceuticals which provide health benefits and are alternative to modern medicine. Nutraceutical-rich vegetables and fruits are an important component of a healthy diet. It has been shown that people consuming healthy diets, living active lifestyles, not smoking and not indulging in excessive alcohol consumption tend to have a reduced risk of CVD. There has been an explosion of consumer interest in the health enhancing role of physiologically-active specific nutraceuticals. Such products include food supplements, dietary supplements, value-added processed foods as well as non-food supplements such as tablets, soft gels, capsules etc. The explosive growth, research developments, lack of standards, marketing zeal, quality assurance and regulation will play a vital role in its success or failure.

Keywords: Macronutrients, micronutrients, Nutraceutical, Prebiotics, Probiotics.

1. INTRODUCTION

About 2000 years ago, Hippocrates correctly emphasized "Let food be your medicine and medicine be your food".

The term "Nutraceutical" was first coined by Dr. Stephen L. DeFelice as "a product isolated or purified from foods and sold in medicinal forms. They have physiological benefit" Nutraceutical is a combination of two words¹.

1. Nutrition and
2. Pharmaceutical.

Nutraceuticals are food product that provides health as well as medical benefits; including the prevention and treatment of disease. Phytochemicals and antioxidants are two specific types of nutraceuticals. Research has proved that foods with phytochemicals may help to provide protection from diseases such as cancer, diabetes, heart disease, and hypertension, e.g. carotenoids found in carrots. With the passage of the Dietary Supplement Health and Education Act of 1994, the definition of nutraceuticals has been expanded to include vitamins, minerals, herbs and other botanicals, amino acids and any dietary substance for use by humans to supplement the diet by increasing total dietary intake and subsequently increased the use of nutraceuticals dramatically. In recent years there is a growing interest in nutraceuticals which provide health

benefits and are alternative to modern medicine. Nutrients, herbals and dietary supplements are major constituents of nutraceuticals which make them instrumental in maintaining health, act against various disease conditions and thus promote the quality of life.

2. DEFINITION

Several terms need to be defined in order to gain an understanding of nutraceuticals.

Nutrient: As defined by AAFCO (1996), "a feed constituent in a form and at a level that will help support the life of an animal." The chief classes of feed nutrients are proteins, fats, carbohydrates, minerals and vitamins.

Feed: As defined by AAFCO (1996), "edible materials which are consumed by animals and contribute energy and/or nutrients to the animal's diet."

Food: As defined by the Food, Drug and Cosmetic Act (1968), "an article that provides taste, aroma or nutritive value. Food and Drug Administration (FDA) considers food as 'generally recognized as safe' (GRAS)."

Drug: As defined by AAFCO (1996), "a substance intended for use in the diagnosis, cure, mitigation, treatment or

prevention of disease in man or other animals. A substance other than food intended to affect the structure or any function of the body of man or other animals.”

Dietary Supplement: As defined by the Dietary Supplement Health and Education Act (DSHEA, 1994), “a product that contains one or more of the dietary ingredients such as vitamin, mineral, herb, or other botanical, and amino acid (protein) also includes any possible component of the diet as well as concentrates, constituents, extracts or metabolites of these compounds.”

Nutraceutical: As commonly defined by the dietary supplement industry, “any nontoxic food component that has scientifically proven health benefits, including disease treatment and prevention.”

Veterinary Nutraceutical: As defined by the newly created North American Veterinarian Nutraceutical Council, Inc. (NAVNC), “a substance which produced in a purified or extracted form and administered orally to patients to provide agents required for normal body structure and function and administered with the intent of improving the health and well-being of animals.”

3. CLASSIFICATION OF NUTRACEUTICALS

Numerous nutraceuticals currently are available in the market. The following chart represents a sample Nutraceuticals are non-specific biological therapies used to promote wellness, prevent malignant processes and control symptoms. These can be grouped into the following three broad categories⁸.

3.1. Substances with established nutritional functions, such as vitamins, minerals, amino acids and fatty acids - *Nutrients*

3.2. Herbs or botanical products as concentrates and extracts - *Herbals*

3.3. Reagents derived from other sources (e.g. pyruvate, chondroitin sulphate, steroid hormone precursors) serving

specific functions, such as sports nutrition, weight-loss supplements and meal replacements – *Dietary supplements*.

3.1. Nutrients

The most commonly known nutrients are antioxidant, water and fat-soluble vitamins. Many potential benefits have been attributed to antioxidant use in the form of dietary intake or supplementation^{9,13}. Antioxidants, in general, may be useful in the prevention of cancer and cerebrovascular disease. High dietary intake of vitamin E may prevent Parkinson's disease¹⁰. Agus *et al.*, determined that the oxidized form of vitamin C, dehydro ascorbic acid, readily crosses the blood brain barrier¹¹. Vitamin supplement is associated with increased antibody titre response to both hepatitis B and tetanus vaccines as a result of macrophage and T cell stimulation¹³. Those genetically predisposed to pancreatic cancer have low serum levels of selenium; thus, it is assumed that supplementation with selenium may help to prevent this condition^{14,15}. Zinc is an essential component of more than hundred enzymes involving digestion, metabolism and wound healing.

3.2. Herbals

Herbals are as old as human civilization and they have provided a complete storehouse of remedies to cure acute and chronic diseases. The knowledge of herbals has accumulated over thousands of years so that today we possess many effective means of ensuring health care³.

3.3. Dietary supplements

Dietary supplements have also been developed to manage a variety of diseases. For instance, pre packaged, nutritionally balanced meals that meet the recommendations of national health organizations influenced multiple risk factors for patients with cardiovascular disease and increased patient compliance with dietary restrictions¹⁸. Ketogenic diets, comprised of foods high in fat and low in protein and carbohydrate content, have been reported to improve seizure control. However, these diets are widely

acknowledged to be unpalatable, making sustained compliance with dietary restrictions difficult¹⁹. Phytoestrogens have been documented to enhance oestrogen levels when hormonal levels are low or to weaken the effects of oestrogen when levels are high. This action may prevent against both hot flushes and breast cancer. Other common foods that may have potential therapeutic value include edible mushrooms. Zbar and NiteBite are two products in the form of bars that contain sucrose, protein and uncooked starch in order to provide continuous glucose release to diabetics during the night. Immune milk products are promising examples of health promoting nutraceuticals. Numerous casein and whey protein derived angiotensin-I-converting enzyme inhibitory peptides/hydrolysates have been identified. These peptides/hydrolysates may be classified as nutraceuticals due to their ability to provide health benefits⁴⁹. Buckwheat has been used and will be better used as an important raw material for functional food production.

4. Macronutrients and micronutrients

4.1. Vitamins

There is much information about the essential roles of various vitamins in maintaining normal metabolism and health status. Deficiency of any kind of vitamins can cause distinguishable clinical symptoms. Scientific knowledge about vitamin metabolism and functions are well accumulated. Therefore, most nutraceutical or nutritional therapy products contain some vitamins, such as common vitamins like vitamin A, vitamin Bs, vitamin C, vitamin D, and vitamin E. A large portion of vitamin sources for human beings is from plant foods, plant biotechnology thus has been used for improvement of contents of vitamins in crops. An excellent example is "Golden Rice", a transgenic rice with a high level of the pro-vitamin A carotenoid in its grains. Currently, absorption studies with Golden rice are being carried out with humans, to test the efficiency of absorption and conversion of beta-carotene into vitamin A. The dairy starter bacterium

Lactococcus lactis has the potential to synthesize both folate (vitamin B11) and riboflavin (vitamin B2). Vitamin C is essential to prevent disease associated with connective tissue and to improve cardiovascular and immune cell functions, and it is also used to regenerate vitamin E. Vitamin E has been touted as a panacea for age-related diseases, including cardiovascular disease and Alzheimer's disease and, thus, the demand for this nutraceutical has increased dramatically in recent years. These vitamin-overproducing crops, such as soybean and barley, not only increase nutritional value of foods, but also can make such foods as good medicines served for vitamin-deficient people.

4.2. Minerals

Ca, I, Zn, Fe, Mn, Mg, and other mineral elements are essential components for human health. Deficiency of any one of these minerals may cause serious health problems. Dietary Ca, Zn, Fe, and other minerals are taken from both meats and plant foods. Due to various reasons, mineral deficiencies, mainly Ca, Zn, and Fe deficiencies, are the major health problems in developing countries, particularly for infants and children. Zn or Fe deficiency causes poor growth, impaired immune function, and delayed mental development. Although numerous mineral supplements or mineral-containing nutraceuticals are available on the market, poor absorption of Ca, Zn, and Fe by the humans significantly limits effectiveness of these supplements. Many reasons, such as dietary habits, lipids and vitamin cofactors, or mineral-mineral interactions during absorption, as well as health status of individual, can influence their absorption. Nevertheless, increasing dietary Ca, Fe, and Zn in plant foods is an important strategy to enhance mineral nutrition⁴.

4.3. Flavonoids

As multiple benefits of eating flavonoid-rich plant foods for human health are well documented, increasing particular bioactive flavonoid species in plant foods has become of great interest. Genetically

modified tomatoes contain high levels of flavonols such as quercetin, kaempferol, and glycosides and flavones such as luteolin, lycopene and luteolin-7-glucoside in their peel tissue, resveratrol level in *Brassica napus* seed has also dramatically increased. Most flavonoids from flavonoid-rich foods are extensively metabolized by human body, which can affect their antioxidant capacity. Flavonoids are absorbed from the gastrointestinal tracts of humans and animals and excreted either unchanged or as flavonoid metabolites in the urine and feces. In addition to flavonoids, fruits and vegetables contain many macro- and micronutrients that may directly or indirectly affect their absorption, activity, and metabolism. Absorption and metabolism of most plant secondary metabolites can occur either inside the gut (such as by microorganisms) or inside liver cells by P450 enzymes.

4.4. Terpenoids

Terpenoids are the most diverse and largest class of plant natural products with wide industrial application, as provitamin A, vitamin E, flavors, pharmaceuticals, perfumes, insecticides, and anti-microbial agents. Other valuable terpenoid compounds that have been modified include the introduction of β -carotene to tomato fruits and rice and zeaxanthin to potato tubers. Tomato is a major food crop and the principal source of the carotenoid lycopene. Epidemiological studies have clearly shown the great benefits of consumption of tomato to human health due to tomato carotenoids, mainly lycopene, β -carotene, and lutein¹⁴.

5. Nutraceuticals differ from Functional food

Nutraceuticals slightly differ from functional foods. When food is being cooked or prepared using "scientific intelligence" with or without knowledge of how or why it is being used, the food is called Functional food. Thus, functional food provides the body with the required amount of vitamins, fats, proteins, carbohydrates, etc. needed for its healthy survival.

When functional food aids in the prevention and/or treatment of disease(s) and/or disorder(s) other than anemia, it is called a Nutraceutical. (Since most of the functional foods act in some way or the other as antianemic, the exception to anemia is considered so as to have a clear distinction between the two terms, functional food and nutraceutical.) Examples of nutraceuticals include fortified dairy products (e.g. milk) and citrus fruits (e.g. orange juice).

6. Traditional versus Non traditional foods

Nutraceuticals on the market today consist of both traditional foods and nontraditional foods.

Traditional nutraceuticals are simply natural, whole foods with new information about their potential health qualities. There has been no change to the actual foods, other than the way the consumer perceives them. Example includes lycopene in tomatoes, omega-3 fatty acids in salmon. Nontraditional nutraceuticals, are foods resulting from agricultural breeding or added nutrients and/or ingredients, to boost their nutritional values. Examples include β -carotene-enriched rice, and soybeans, orange juice fortified with calcium, cereals with added vitamins or minerals¹².

7. Food or Drug

Using the above definitions, it is still difficult to determine what is and what isn't a nutraceutical. Are nutraceuticals considered food or feeds? According to definition, a feed is an edible substance that contributes energy or nutrients to an animal's diet. Feeds can make claims only about the nutrients they contain and the scientific functions of those nutrients. Nutraceuticals either include the word "food" or state they are "required for normal body structure and function." A potential difference between a feed and a nutraceutical is that a nutraceutical is unlikely to have an established nutritive value (Boothe, 1997). Feeds are required to have nutritive value and are accountable, via labeling, for these values.

Another difference between a feed (food) and a nutraceutical is that feed is generally recognized as safe (GRAS).

8. Food and Health

Food habits develop in early infancy. In fact, it is known that initial phases of life (intra-uterine period and the first year of life) are sensitive to nutritional factors¹⁶. Exclusive breastfeeding up to six months, with breastfeeding lasting up to two years or longer in combination with the introduction of balanced complementary feeding (CF), are emphasized by the World Health Organization (WHO) as important measures of public health, with effective impact on the reduction in the risk of developing chronic diseases. It is now known that children after the age of two years should be fed a nutritionally balanced diet similar to that of adults, particularly a diet low in sugar, salt and fat, and rich in complex carbohydrates, fruits and vegetables. The generation of scientific research linking foods of plant origin and health worldwide has resulted in acknowledgement that plant bioactive compounds have anti-oxidant and other healthy properties^{17, 18}. This suggests that dietary behavioral changes, such as increasing consumption of fruits, vegetables, and whole grains, and related changes in lifestyle, are practical strategies for significant reduction of the incidence of diseases²⁰.

8.1. Cardiovascular diseases (CVD, including heart disease and stroke), represent the primary cause of death, with high negative impact on both human health and community social costs in Western countries. Cardiovascular diseases and tumors, together, contribute to more than 60 % of deaths in economically-developed countries²². In economically-developed countries, CVDs acquire a character of epidemic proportions, and surpass infectious diseases in mortality. Recent studies implicate reactive oxygen species (ROS) in the pathogenesis of both acute and chronic heart diseases as a result of cumulative oxidative stress²³. Important risk factors for CVD include obesity, high

blood cholesterol level, high blood pressure and type 2 diabetes. The risk of CVD is increased not only by the consumption of poor diets, but also by lifestyle habits such as smoking and alcohol intake²⁴. It is also known that diets leading to elevated serum total cholesterol, LDL-cholesterol, and triacylglycerol concentrations, while leading to reduced HDL cholesterol concentrations, lead to reduced risk of coronary artery disease. As a result, treatment of hypercholesterolemia has focused on increasing fecal excretion of cholesterol and bile acids, and reducing hepatic cholesterol synthesis through diet modification among the few optional strategies available^{25,26}. Consequently, a general nutritional plan to minimize hypertension risk includes attaining and maintaining a healthy body weight; consuming a diet rich in calcium, phosphorus, and magnesium; and consuming alcoholic beverages and sodium in moderation.

8.2. Obesity is a medical condition characterized by accumulation of excess body fat. As a condition, obesity is associated with reduced life expectancy and/or increased health problems²². Obesity is therefore not just a cosmetic problem²³. Numerous studies indicate that higher levels of body fat are associated with an increased risk of many adverse health conditions. Weight loss is increasingly recognized as bringing major health benefits to overweight people and is linked with increases in life expectancy of people having obesity-related complications. Overweight and obesity have increased over the past 20 years in many regions of the world, particularly the prevalence of obesity in childhood. Obesity is not only restricted to the developed world; it is also becoming a growing burden for the developing countries¹³. Data from the International Obesity Task Force (IOTF) indicate that, worldwide, over 20 million children under the age of six are obese or overweight. Obesity is a multi factorial problem and its development is due to multiple interactions between genes and environment.

8.3. Cancer development, a dynamic and long-term process, involves many complex factors with stepwise progression, ultimately leading to an uncontrolled spreading and growth of cancerous cells throughout the body, called metastasis. Epidemiological studies have provided convincing evidence that dietary factors can modify carcinogenesis. Laboratory research has further demonstrated that a number of bioactive dietary components or natural products have the ability to prevent cancer^{17,18}. In addition, many food constituents with yet undefined nutritional benefits have been found to possess anti-mutagenic and anti-carcinogenic properties. Such promising research provides a strong support for the acceptance in the future of bioactive components of food as chemo preventative agents

8. 4. Joint diseases affect people of all ages mainly the elderly. Main joint diseases are:

Osteoarthritis- Degenerative damage and loss of the articular cartilage of the joint due to loss of protein substance between the bones of joints.

Rheumatoid Arthritis- Rheumatoid arthritis (RA) is a chronic, inflammatory disorder that may affect many an organs and tissues but principally affect joints. In this condition inflammatory synovitis produced that causes distruction of articular cartilage.

9. Nutraceutical use in some diseases

9.1. Glucosamine and Chondroitin

Glucosamine is a precursor to a molecule called a glycosaminoglycan-this molecule is used in the formation and repair of cartilage.

- Source-bovine or calf cartilage
- Glucosamine sulphate in several European countries used as first line of treatment for arthritis. There side effects and contraindications are less but diabetics need to be careful as glucosamine might have an effect on insulin resistance. Glucosamine sulphate stimulates the production of hyaluronic acid in joint fluid. Hyaluronic acid relieves pain and improves mobility by repairing

damaged cartilage. In vitro experiment of Glucosamine has shown a dose dependent increase in proteoglycan after administering it. It is marketed usually as hydrochloride or sulfate salt. Both compounds have anti inflammatory effects. Combination of Glucosamine and Chondroitin are available.

Chondroitin is the most abundant glycosaminoglycan in cartilage and is responsible for the resiliency of cartilage.

9.2. Methylsulfonyl Methane

Methylsulfonyl Methane (MSM) is sold as nutritional and dietary supplement often used in combination with glucosamine and Chondroitin for helping to treat or prevent. MSM is the oxidized form of dimethyl sulfoxied; a natural organic form of sulfur. Both this compound used for pain and inflammation. MSM has advantage over DSMO as it is odourless and doses not cause skin irritation. MSM provide source of sulphur for the formation of the cartilage matrix or the antioxidant system¹⁵.

10. Probiotics, Prebiotics and Synbiotics

The human gut is populated by a wide array of bacterial species, the latter bearing important

metabolic and immune functions, all leading to marked effects on the nutritional and health status of the host. Probiotics, according to a consensus definition, are 'living micro-organisms, which upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition'^{26,27}, alternatively probiotics are loosely known as live microorganisms belonging to natural biota with low or no pathogenicity, but with functions of importance to the health and well being of the host^{28,29}. Numerous probiotic microorganisms (e.g., *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri*, bifidobacteria and certain strains of *Lactobacillus casei*, the *Lactobacillus acidophilus*-group, *Escherichia coli* strain Nissle 1917, certain enterococci, especially *Enterococcus faecium* SF68, and the probiotic yeast *Saccharomyces boulardii*) are used in probiotic food,

particularly fermented milk products, or have been investigated with regard to their medicinal use. New genera and strains of probiotics are emerging; some with high health benefits as in *Lactobacillus plantarum* isolates (PCS20, PCS22, PCS25 and PCS26) from Slovenian cheese with high antimicrobial and immunomodulatory capabilities. An international expert group of the International Life Sciences Institute (ILSI) has evaluated the categorized and published evidence of functionality of different probiotics in four areas of (human) application, namely, (i) metabolism, (ii) chronic intestinal inflammatory and functional disorders, (iii) infections, and (iv) allergy²⁹. The effects of probiotics on human health are positive and well defined in diarrhoea treatment, however there are no clinical results regarding the dose of probiotics or duration of such treatments²⁷. Probiotics have been shown to have applications in alleviating symptoms of allergies, cancer, AIDS, respiratory and urinary tract infections²⁷, symptoms associated with aging, fatigue, autism, and in reducing the risks of osteoporosis, obesity and possibly type 2 diabetes. The concentration of probiotics needed to obtain a clinical effect is often quoted as $\geq 10^6$ colony forming units (cfu) per milliliter in the small bowel and $\geq 10^8$ cfu/g in the colon. The dose for treatment of an acute illness by a particular probiotic agent may be lower or higher, in the order of 10-fold or 100-fold or more in terms of cfu. In acute infectious diarrhoea, it seems that higher doses of probiotics given for short courses are more effective than lower doses. In chronic or immunological diseases (allergic, inflammatory and/or immune diseases), the effects of probiotics depend also on the interactions between the respective microorganisms and gut immune system, and duration of treatment. To evaluate the efficacy of probiotics it may be essential to identify specific target groups of individuals with more specific higher susceptibilities to the potential effects of probiotics.

A **prebiotic** is "a selectively fermented ingredient, or a fiber that allows specific

changes, both in the composition and/or activity of the gastrointestinal microflora, resultantly conferring benefits on the well being and health of host ". Other, more specific effects of prebiotics on health are indirect, namely prevention of diarrhoea or obstipation, modulation of the metabolism of the intestinal flora, cancer prevention, effects on lipid metabolism, stimulation of mineral adsorption and immunomodulatory properties. Today, only bifidogenic, nondigestible oligosaccharides (particularly inulin, its hydrolysis product oligofructose, and (trans) galactooligosaccharides), fulfill all the criteria for prebiotic classification³⁰.

Probiotics and prebiotics share unique roles in human nutrition, largely centered on manipulation of populations or activities of the microbiota that colonize the human GI tract²⁸. Regular consumption of probiotics or prebiotics has health implications that include enhanced immune function, improved colonic integrity, decreased incidence and duration of intestinal infections, down-regulated allergic response, and improved digestion and elimination. It is noteworthy that human subjects and their enteric microbiota have evolved together to reach a state of mutual tolerance. There is mounting evidence from both animal models and human studies to suggest that inflammatory bowel disease (IBD) is a result of a malfunction of this mutual relationship.

11. Proximate analysis for nutritional contents

The recommended methods of the Association of Official Analytical chemists (AOAC, 1999) were used for the determination of moisture, ash, crude lipid, crude fibre and nitrogen content.

11.1. Estimation of energy value

The sample calorific value was estimated (in Kcal) by multiplying the percentage crude protein, crude lipid and carbohydrate by the recommended factor (2.44, 8.37 and 3.57 respectively) used in vegetable analysis.

11.2. Mineral analysis

The mineral elements comprising sodium, calcium, potassium, magnesium, iron, zinc and phosphorus were determined according to the method of Shahidi et al. (1999) and Nahapetian and Bassiri (1975) with some modifications. 2.0 g of each of the processed samples was weighed and subjected to dry ashing in a well-cleaned porcelain crucible at 550°C in a muffle furnace. The resultant ash was dissolved in 5.0 ml of HNO₃/HCL/H₂O (1:2:3) and heated gently on a hot plate until brown fumes disappeared. To the remaining material in each crucible, 5.0 ml of de-ionized water was added and heated until a colourless solution was obtained. The mineral solution in each crucible was transferred into a 100.0 ml volumetric flask by filtration through Whatman No.42 filter paper and the volume was made to the mark with de-ionized water. This solution was used for elemental analysis by atomic absorption spectrophotometer. A 10 cm long cell was used and concentration of each element in the sample was calculated on percentage (%) of dry matter i.e. mg/100 g sample. Phosphorus content of the digest was determined colorimetrically according to the method described by Nahapetian and Bassiri (1975)²³.

11.3. Vitamins analysis

Determination of vitamin A was by the method of Davies (1976).

Determination of vitamin A was by the method of Davies (1976). Determination of thiamine (B1) Riboflavin (B2), Niacin (B3), vitamin E was by spectrophotometric method while pyridoxine Vitamin B6 was by titremetry. These methods are as described by AOAC (1999). Ascorbic acid (vitamin C) was determined titremetrically by the method of Barakat et al. (1973).

Preparation of fat free sample

2.0 g of each of the processed sample was defatted with 100 ml of diethyl ether using a Soxhlet apparatus for 2 h.

11.4. Other analysis

Amino acid determination was carried out using ion-exchange chromatography with

Technicon Sequential Multisample Amino Acid Analyzer, TSM (Technicon Instruments Corporation, Dublin, Ireland), as outlined in Adeyeye and Afolabi (2004). Determination of Alkaloid, Saponin, Phenols were according to the methods of Harborne, 1973 as described by Obadoni and Ochuko (2001). Tannin was determined by the method of Van-Burden and Robinson (1981), Hydrocyanic acid according to Bradbury et al. (1991), while Phytic acid was estimated by the method of Wheeler and Ferrel (1971).

12. Increasing Prospects for the Functional Food Industry

Production of functional foods is being recognized as the number one global food industry as changing trends in population demography, consumer affluence, increased education, life expectancy and improved healthcare give rise to a rapidly emerging diet and health conscious consumer clientele (Belem, 1999, Childs 1999; Dillard & German, 2000; Drouin & Gosselin 2002). Increasing health consciousness has been one of the most important stimulating factors for rapid global growth of the nutraceutical and functional food industry (Hasler, 2000). In a survey of public opinion conducted in 1998 by the International Food Information Council (IFIC), about 95% of the participants expressed a view that some foods are capable of reducing health risks and that consumption of these foods can result in an improved quality of life. In another survey the American Dietetic Association / ADA (2000) reported that 85% of participants believe that nutrients and diet are important to them. Moreover, personal use of Alternative Medicines (AM) in the United States of America (USA) doubled (to 40%) during a period of seven years from 1990 - 1997.

Nutraceuticals and functional foods have been reported to have significant biological actions and their use across the globe continues to increase due to historical and more recent reports of clinical success through use of these products. Primary factors associated with increased popularity of nutraceuticals and functional foods that have generated

interest within the public have been reported by a number of different scientific groups as well as government agencies (Belem, 1999; Breithaupt, 2004; Childs, 1999; De Felice, 1995; DellaPenna, 1999; Drouin & Gosselin, 2002; Elliott & Ong, 2002; Govt of Canada, 2003; Hardy, Hardy & Ball, 2003; Hasler, 2000; LFRA, 2001; McNamara, 1997; Peterson & Dwyer, 1998).

Some of the most important are:

12.1. An Increase in Public Health Consciousness

Increased access to information through education and an enquiring media has resulted in a rapidly emerging self-care movement among consumers. As well, our understanding of the mode of action, health promoting effects and value added properties of food and non-food products is increasing rapidly. When coupled with increased economic prosperity, health awareness is driving more consumers to take a more protective role in managing their health; people are less willing to simply wait and implement health care advice provided by a medical community in response to health problems²².

12.2. An Aging Population

Increase in age of the baby-boomer birth cohort and recognition of their limited mortality is precipitating need for a more responsive, if not sympathetic health care system that promises to help them manage the vast array of age-related maladies that this group now is facing.

12.3. Escalating Health Care Costs

Exponential increase in expenditures within the health care system and concern for maintenance and sustainability of the system is forcing many consumers to seek out more cost-effective alternatives to those being provided by traditional forms of high cost professional and structured medicine.

12.4. Recent Advances in Research and Technology

Advances in the areas of food technology, food biochemistry and the nutritional

sciences (including nutritional genomics) are providing consumers with access to fresh and often supplemented produce with recognizable health benefits that previously were not available. New methods being used by the functional food industry to isolate, characterize, extract and purify nutraceuticals from bacterial, plant and animal sources are resulting in decreased costs to the industry as well as providing new options for use of functional food products²¹.

12.5. Changes in Government Regulations and Accountability

Changes in policies and laws governing distribution and marketing of food are recognizing the current shift in attitude towards consumer awareness and accountability of government to the people it represents. Increased Recognition of Functional Food Benefits: increased numbers of reports now recognize health and clinical benefits associated with access to high quality and nutritional foods.

12.6. Expansion of the Global Marketplace

Better communications and transport for marketable goods is resulting in a more accessible global market place and an increase in international business opportunities. This, coupled with increased recognition for proprietary patented products is resulting in a more business-friendly environment for expansion of industry.

12.7. A Sympathetic Media

A supportive and promotional environment is being generated by the media in response to significant advances being made in research and development of food, its processing, packaging and transportation. Together these changes are resulting in sweeping global acceptance and demand for functional foods and nutraceutical derivatives²⁸.

12.8. Science-based Evidence Is Contributing to the Popularity of Functional Foods

There is increasing recognition of the need for scientific evidence to support nutritional and medicinal claims being made within the functional food and nutraceutical industry. In 1997 Clydesdale called for development of an international dialogue on the types of validation required to recognize health claims being made for functional foods and food components. According to Dillard & German (2000) the health promoting effects of phytochemicals and nutraceuticals and/or functional foods likely are due to a complex mix of biochemical and cellular interactions which together promote overall health of the individual. Major chemical groups now recognized as having potential health promoting effects, at least under some circumstances are the phenolics, flavonoids, alkaloids, carotenoids, pre- and pro-biotics, phytosterols, tannins, fatty acids, terpenoids, saponins, and soluble and insoluble dietary fibres.

13. Current status of nutraceuticals in

13.1. Food with function claims

In 1984, the Education Ministry (currently Ministry of Education, Culture, Sports, Science and Technology) launched the project "Systematic Analysis of Food Functions" as a special project by a Research Grant Study Group. This project is the world's first proposal of the effects of food on human bodies as a "Function", especially through the research on prevention of life-style related diseases. With advancement of "functional food" research, "Functional Foods (Tokutei Hoken-yo Shokuhin; "TOKUHO" in short Japanese" or Food for Specified Health Uses; FOSHU" was put into effect in 1991. In 1993, when Shiseido marketed rice with less allergens, as the first product of TOKUHO, "Nature", world famous English academic journal, introduced in the article "Physiologically functional food" as a brand-new food concept from Japan.[15] It had a big impact and "Functional Food" was acknowledged internationally as a

future food category for human health. In 2002, "standardized Food with Nutrient Function Claims; FNFC" was set up in addition to the existing FOSHU (TOKUHO) foods. The conditions for permission are the confirmed effectiveness and safety through tests of the human body and quantitative data of the functional ingredient. Furthermore, TOKUHO was followed by "Standardized FOSHU", "Disease Risk Reduction FOSHU" and "Limited Conditional FOSHU" at the time of revision in February, 2005. The concept of "Disease Risk Reduction FOSHU" is to specifically designate the foods which are medically and nutritionally proven to reduce the risk of diseases. This is one of the measures for stepping forward with disease prevention, however, there are only two kinds of elements designated in this category at the moment; calcium and folic acid. "Standardized FOSHU" is the food on which has received permission, after evaluating whether the ingredients comply with the standards set by the authority. This shows that TOKUHO has been penetrating the Japanese market. Meanwhile, "FNFC" lists only five kinds of minerals and 12 kinds of nutrients.

13.2. A Global Picture of the Nutraceutical Industry

The functional food and nutraceutical industry represents in excess of a \$75.5 billion US industry with prospects of growing to \$167 billion by 2010. Operationally, the industry relies upon a network of supportive stakeholders (Fig. 1) with a vested interest, in one form or another in providing consumers with alternative health products with potential to prevent diseases resulting from nutrient deficiencies or with products that have beneficial physiologic effects beyond those simply attributed to their nutrient content. Support from groups within the network is essential to development and maintenance of a strong popularized consumer base within the industry and is one of the key factors behind establishment, ongoing operation, expansion and commercialization of the

global functional food and nutraceutical industry. Although popularity of products marketed as functional foods and nutraceuticals is highly variable.

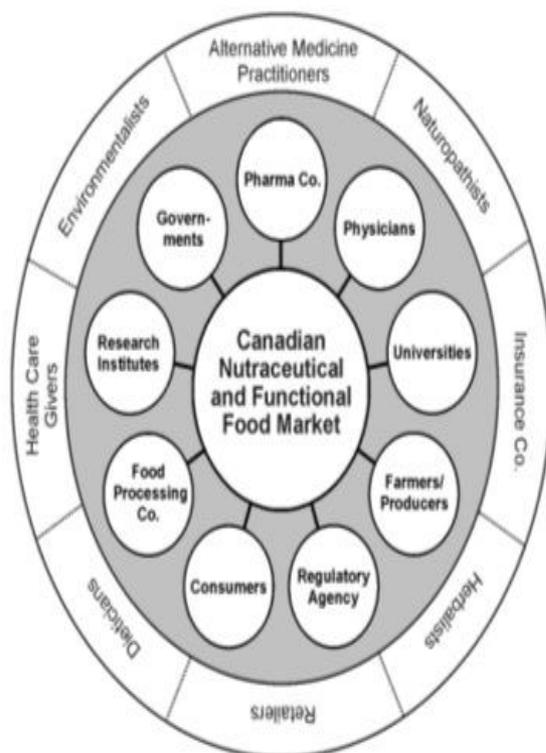


Fig. 1: Principal stake-holders in the emerging global nutraceutical and functional food industry

The United States of America (USA) currently possesses the largest and most rapidly expanding functional food and nutraceutical market in the world. In 2006 value of the industry was \$21.3 billion. Its strong domestic market supports major imports from Japan, North and South Korea, China, India, Brazil, the European Union (EU), Australia, New Zealand and other parts of the world. For the USA it has been suggested that about 50% of its multi-billion dollar food market can be related to use of nutraceuticals and functional food products. By comparison the Canadian nutraceutical and functional food market is relatively young and is growing. Nutraceutical and functional food markets in the EU have grown over the past eight years, from about \$1.8 billion out of a \$5.7 billion global market in 1999 to \$8 billion out of a global market of \$75.5

billion in 2006. While growth in this market has been significant, it appears to be trailing in growth seen in other parts of the world; *i.e.*, world market share in 1999 was about 30% but, in 2006 only represented about 10% of total estimated world expenditures.

Major trading partners with the EU are the USA, Japan, south, south-east, far east and middle east Asia and Pacific regions. Eastern cultures have a long history of use of traditional medicines associated with health foods in forms of recognized nutritional foods, food supplements, medicinal herbs, and crude powdered drugs derived from plant, animal and marine sources. India and China are the two most important countries known for their production of traditional functional food products and nutraceuticals. Both of these countries have large populations, in particular in rural, remote and inaccessible areas which are totally dependent upon herbal remedies and other naturally available bioresources which they use to treat common ailments, and as general preventive and protective medications. In India the most common forms of functional foods and nutraceuticals are available as traditional Indian Ayurvedic Medicines (IAM); these are marketed under different brand names. India is the home of a large number of medicinal herbs, spices and tree species that have a substantially large domestic market with no major foreign competition at present. India has a large share of the international functional food and nutraceutical market, and exports products to the far east, south-east, west and middle east Asia as well as to parts of north Africa and the EU. However, India's major export destination is the USA and Japan. Estimated value of the industry is \$10 billion per annum with exports of \$1.1 billion per annum making a significant contribution to the export market. There is a steady demand for functional foods and nutraceuticals in the country and a friendly business environment. However, because of less stringent regulations, cheap labour, lower production costs and the enormous market involved, China has the potential to emerge as a leader in the international market. Japan, Hong Kong, Korea and

Singapore are major importers of TCMs and represent 66% of Chinese plant drug exports. The annual Chinese herbal drug production is estimated at \$48 billion, with estimated exports of \$3.6 billion. Japan is the second largest market in the world for nutraceutical products after the United States. Its nutraceutical market has exhibited a steady average growth rate of 9.6% per annum for the past decade, and in 2006 its functional food industry was estimated to have a value of \$27.1 billion. Two types of functional foods have been approved by the Japanese government; *i.e.*, those with approved health claims or FOSHU (Foods for Specified Health Use) and foods that may provide health benefits (without any health claims). Other large, emerging international markets in south and south-east Asia are seen in Taiwan, Sri Lanka, Thailand, the Philippines, Vietnam, Lagos, Kampuchea, Indonesia, Malaysia, North and South Korea. In addition Australia and New Zealand are emerging quickly as international competitors. Investment in research and development of high quality functional food and nutraceutical products along with promotional support from both the industry and government has helped in rapid establishment of the industry in these two countries and in their catching a share of the expanding global market.

13.3. Other consideration Labeling and Health Claims

Health claims on nutraceuticals serve to alert consumers to a food's health potential by stating that certain foods or food substances, as part of an overall healthy diet, may reduce the risk of certain diseases. Examples include folic acid in breakfast cereals, fiber in fruits and vegetables, calcium in dairy products and calcium or folic acid in some dietary supplements. Food and food substances can qualify for health claims only if they meet FDA requirements. The FDA initially authorized seven health claims in 1993 as part of the 1990 Nutrition Labeling and Education Act (NLEA). Since 1993, the FDA has authorized six more claims. Under the NLEA, companies petition the FDA to consider new health claims

through rule-making. However, this process may require more than a year to complete because of the necessary scientific review and the need to issue a proposed rule to allow for public comment. In an effort to accelerate this information to consumers, the Food and Drug Administration Modernization Act of 1997 included a provision intended to expedite the process that establishes the scientific basis for health claims. Although food manufacturers may use health claims to market their products, the intended purpose of health claims is to benefit consumers by providing information on healthful eating patterns that may help reduce the risk of heart disease, cancer, osteoporosis, high blood pressure, dental cavities or certain birth defects.

Health claims are among the various types of claims allowed in food labeling. They show a relationship between a nutrient (or other substances in a food) and a disease or health-related condition. They differ from the more common claims that highlight a food's nutritional content, such as "low fat," "high fiber" and "low calorie." Health claims also are different from structure/function claims, which also may appear on conventional food or dietary supplement labels. Manufacturers may make statements about a food substance's effect on the structure or function of the body for example, "calcium builds strong bones." Unlike health claims, structure/function claims do not deal with disease-risk reduction. Also, the FDA does not pre approve or authorize structure/function claims. Rather, when the manufacturer uses a structure/function claim, the company is responsible for making sure the claim is truthful and not misleading.

Nutrient-content claims indicate the presence of a specific nutrient at a certain level.

Structure and function claims describe the effect of dietary components on the normal structure or function of the body. Dietary-guidance claims describe the health benefits of broad categories of foods. Qualified health claims convey a developing relationship between components in the diet and risk of

disease, as approved by the FDA and supported by the weight of credible scientific evidence available. Nutraceuticals have no official meaning and do not constitute a distinct category of foods. Most often, they are simply natural, whole foods consumers have been eating for thousands of years. As a result, the FDA regulates them in the same way they regulate all foods: The safety of ingredients must be assured in advance, and all claims must be substantiated, truthful and non misleading²⁷.

13.4. Safety and Efficacy

Nutraceuticals hold great potential, as evidenced by products such as Benecol, an alternative to margarine that contains plant stanol esters, which have been shown to reduce cholesterol. Yet, they also may hold the potential for harm, as was the case with ephedrine, a widely used botanical ingredient in weight-loss products. The substance was banned by the FDA after it was linked to significant adverse health effects, including heart attack and stroke. Consumers desire the increased health control these products offer and the promised health benefits. The danger is that many of these products do not provide consumers with solid information about their safety and effectiveness, possible side effects, interactions with prescription medicines or the impact they may have on existing medical conditions. Clinical research on specific nutraceutical products sold would help substantiate the potential medical or health values of these products. As a result, patients and health care professionals would know the facts about the benefit and the safety of the products being taken²⁶.

14. Biotechnology on plant nutrition for human health

Biotechnology is the technique utilizing various living organisms to produce desired products or to carry out tasks for purposes of human being. The oldest biotechnology may be fermentation of microorganisms to make breads and soups. The new technology can use genetically modified organisms, such as

transgenic plants or engineered bacteria, to benefit human beings. Now, scientists are using genetic or metabolic engineering to increase crop yields and certain nutrients (like vitamins, minerals, and essential amino acids or fatty acids) and medicinal compounds, or even produce vaccines, antibodies, or medicines that are traditionally generated by animals or human body. Many current biotechnologies applied in agriculture, food science, and medicine, are focused on human health. After decades of development, biotechnology has created a number of results such as various new cultivars either by traditional crossing or transgenic breeding. Super-rice that exhibits high yields has been invented by Chinese scientists, Golden Rice with high levels of the pro-vitamin A carotenoid, beta-carotene, was invented by Swiss and German scientists, and many other crops have been invented with improved agricultural traits such as drought-, salt-, insect-, or disease resistance, that have also significantly improved yields of many crops. Dietary nutrient deficiencies e.g. lack of vitamin A, I, Fe or Zn, are a major source of morbidity (increased susceptibility to disease) and mortality worldwide. These deficiencies especially affect children by impairing their immune systems and normal development and causing disease and ultimately death²⁹. The best way to avoid micronutrient deficiencies is dietary supplements or diets rich in vegetables, fruits and animal products. Another approach is eating more nutrient enhanced staple foods, such as sweet potatoes or Golden Rice, which are rich sources of pro-vitamin A.

CONCLUSION

Currently, due to the lack of enough knowledge about usage, outcome, and safety of many nutraceuticals, phytonutrients as well as their corresponding therapies, many efforts have been put on these studied. However, from many aspects of nutritional value including quality and quantity, our food pantries is very limited in supplying adequate nutrients for human being, as indicated by an investigation³⁰. Therefore,

how to produce the nutritional products in plant foods is becoming a major issue. Increasing contents and qualities of many desired nutrients in plant foods is a huge metabolic engineering project. Manipulation of biosynthetic or metabolic pathways and overproduction of nutrients such as vitamins, minerals, long-chain

polyunsaturated fatty acids, and other phytonutrients including flavonoid, terpenoid, and alkaloid in crops or medicinal plants have made a number of successes. These engineered crops have been one of the most expected breakthroughs in plant biotechnology.

Nutraceuticals product list

Momordica charantia	Bitter Gourd	Bitters 10%, Charantin 0.4%
Mucuna pruriens	Cow Itch Plant	L-DOPA 15 - 60%
Ocimum sanctum	Holy Basil, St. Joseph Wort	Tannins 7%
Phaseolus vulgaris	Kidney Bean	Activity 8000 units
Phyllanthus niruri	-	Bitters 1.5%
Piper longum	Indian Long Pepper	Piperine 5%
Piper nigrum	Black Pepper	Piperine 4%
Pterocarpus marsupium	Indian Kino Tree	Pterostillbene 4%, Flavones 5%
Punica granatum	Pomegranate	Ellagic acid 8%
Salacia reticulata	Kotalahimbatu	Saponins 15%, Flavones 5%
Sapindus trifoliatus	Soapnut-tree	Saponins 20%
Terminalia arjuna	Arjuna	Tannins 25%, Arjunic acid 1%
Terminalia bellerica	Belleric myroblan	Tannins 10%
Terminalia chebula	Chebulic myroblan	Tannins 20%
<u>Tinospora cordifolia</u>	Tinospora Gulancha	Bitters 1.5%
Tribulus terrestris	Small Caltrops	Saponins 20% - 60%
Valeriana wallichii	Valerian rhizome	Valeric acid 0.8%

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