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## A REVIEW ON CURRENT ASPECTS OF NUTRACEUTICALS AND DIETARY SUPPLEMENTS

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### ABSTRACT:

Using food products to promote health and cure disease is renowned. Currently, most of the drug molecules available in the formulations were anciently used in their crude form. Dr Stephen De Felice first coins the term Nutraceuticals in 1989 to provide medical or health benefits including the prevention and treatment of diseases. Although the term "nutraceutical" is now recognized internationally as a linguistic combination of "nutrient" and "pharmaceutical", and is accepted as "Any substance that may be considered a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease." The greatest challenge will remain in the public policy and regulatory arenas, which will encourage research and development of products providing health benefits and permit truthful, nonmisleading communications of these products while protecting public health and maintaining public confidence. Nutraceuticals have received considerable interest because of their presumed safety and potential nutritional and therapeutic effects". Pharmaceutical and nutritional companies are aware of the monetary success taking advantage of the more health-seeking consumers and the changing trends resulting in a proliferation of these value-added products aimed at heart health to cancer. Some popular nutraceuticals include glucosamine, ginseng, echinacea, folic acid, cod liver oil, omega-3 eggs, calcium-enriched orange juice, green tea etc. Majority of the nutraceuticals are claimed to possess multiple therapeutic benefits though substantial evidence is lacking for the benefits as well as unwanted effects. The present review has been devoted towards better understanding of the nutraceuticals based on their disease specific indications.

### Introduction:

The fact that food and optimal health are closely correlated is not a novel concept. About 2500 years ago, Hippocrates (460–377 BC), the renowned father

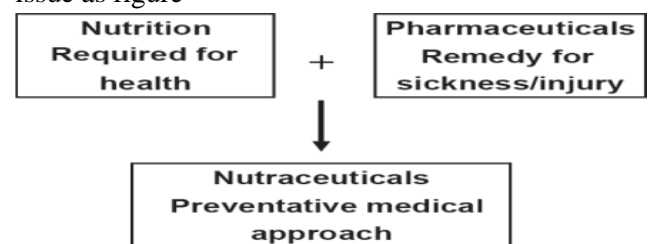
of modern medicine, conceptualized the relationship between the use of appropriate health foods and their therapeutic benefits and quoted, "Let food be thy medicine, and medicine be thy food"<sup>1</sup>. Consumers are

deeply concerned about how their health care is managed, administered and priced. They are frustrated with the expensive, high-tech, disease-treatment approach predominant in modern medicine; the consumer is seeking complementary or alternative beneficial products and the red tape of managed care makes nutraceuticals particularly appealing<sup>2</sup>. The terminologies like “nutraceuticals”, “functional foods”, “dietary supplements” “designer foods”, “medical foods”, “pharmafoods”, “phytochemicals” etc create a lot of confusion. There seems to be thin dividing line in their interchangeable usage by different people on different occasions. “Pharmaceuticals” may be considered as drugs used mainly to treat diseases, while “nutraceuticals” are those that are intended to prevent diseases. The above distinction between pharmaceuticals and nutraceuticals is cute, but superficial and erroneous. Pharmaceuticals are substances which have (or have had) patent protection as a result of expensive testing to conform to the specifications of respective Governments. However, many nutrients may never receive government approval since no one could justify the expense of testing requirements for substances that cannot be protected by patent laws. Both pharmaceuticals and nutrients can cure and prevent disease(s) but only pharmaceuticals have governmental sanction. Many pharmaceuticals have their origin in plants and animals and are no less "natural" than nutrients. Classic example of nutrients is synthetic vitamins. Nutraceuticals sometimes referred as “functional foods”, have caused heated debate because they blur the traditional dividing line between food, and medicine. When food is being cooked or prepared using "scientific intelligence" with or without the knowledge of how or why it is being used, then the food is called as "functional food." Thus, functional food provides the body with the required amount of vitamins, fats, proteins, carbohydrates necessary for healthy survival. When functional food aids in the prevention and/or treatment of disease(s)/disorder(s) other than deficiency conditions like anemia it is called a “nutraceutical”<sup>3</sup>. Thus, a functional food for one consumer can act as a nutraceutical for another. Examples of nutraceuticals include fortified dairy products (milk as such is a nutrient and its product casein is a pharmaceutical) and citrus fruits (orange juice is nutrient and its constituent ascorbic acid is a pharmaceutical). A dietary

supplement is a product that is intended to supplement the diet that bears or contains one or more ingredients like, vitamin, mineral, a herb, an amino acid or a concentrate, metabolite, constituent, extract, or combinations of these. “Medical foods” are a specific category of therapeutic agents that are intended for the nutritional management of a specific disease. An example of medical foods is formulations intended to manage patients with inborn errors in amino acid metabolism. Newer medical foods are designed to manage hyperhomocysteinemia, pancreatic exocrine insufficiency, inflammatory conditions, cancer cachexia, and other diseases. The use of nutraceuticals, as an attempt to accomplish desirable therapeutic outcomes with reduced side effects, as compared with other therapeutic agents has met with great monetary success<sup>4,5</sup>. The preference for the discovery and production of nutraceuticals over pharmaceuticals is well appreciated by the pharmaceutical and biotechnology companies<sup>6</sup>.

### CONCEPTS OF NUTRACEUTICALS

In the pharmaceutical development process, it is a requirement to have clinical test results from animal tests and studies, for verification of the effects. On the other hand, in the case of nutrition, there was no verification method for foods in preventing diseases in the past<sup>7</sup>. In recent years however, as food composition has been scientifically proven to cause lifestyle-related diseases, and has become a social issue as figure



### REGULATORY ASPECTS OF NUTRACEUTICALS

The regulatory framework of nutraceuticals in India needs attention from the relevant authorities. Globally, the regulatory authorities are aware of changing needs of consumers and proactively protect consumers by amending existing laws to accommodate changes but in India old laws such as Prevention of Food adulteration Act, 1954, which regulates packaged foods, still exist for manufacturers. In addition, they

need to abide by many other cumbersome laws such as<sup>7</sup>:

- Standards of Weights and Measures Act, 1976, and the Standards of Weights and Measures
- (Packaged Commodities) Rules, 1977 (SWMA)
- Infant Milk Substitutes, Feeding bottles and infant foods (regulation of production, Supply and Distribution) Act, 1992 with Rules, 1993 (IMS)
- Edible Oils Packaging (Regulations) Order, 1998
- Fruit Products Order 1955 (FPO)
- Meat product Order 1973
- Milk and Milk Products Order 1992
- Vegetable Oils Products (Regulation) Order 1998 (VOP)
- Atomic Energy Act, 1962 and Atomic Energy (Control or irradiation of Food) Rules 1996
- Consumer Protection Act 1986 and the Consumer Protection (Amendment) Act, 2002 and Rules 1987
- Environment Protection Act, 1986 and Rules 1986
- Agricultural Produce (Grading and Marking) Act, 1937 (as amended up to 1986) and 49
- General Grading and Marking Rules 1986 and 1988 (AG Mark)
- Bureau of Indian Standards (BIS) Act 1986

Further, there is lack of clarity in classifying functional foods and Nutraceuticals. This causes confusion amongst the regulators. At times, the drug regulators are tempted to classify these products as drugs. This has resulted in trouble for genuine manufacturers. The revolutionary step to introduce Food Safety and Standards Act will replace the old PFA. The new act will take India on the path of new regulatory framework to make it capable of global competition<sup>8</sup>. On the other hand in United States the Watershed legislation was passed in 1994 to regulate the manufacture and marketing of nutraceuticals. This law, known as the Dietary Supplement Health and Education Act (DSHEA), reversed 45 years of increasing FDA regulation of health-related products<sup>9</sup>. The passage of the Food and Drug Administration Modernization Act of 1997 (FDAMA) made additional options available to the manufacturers of nutraceuticals. This legislation was the result of a reform effort that spanned nearly two decades. It brings about a balance in FDA regulations between approving therapeutic products so that they can benefit patients and protecting public health by assuring that those products are safe and effective<sup>10</sup>. In 1993, the Ministry of Health and Welfare in Japan established a

policy of “Foods for Specified Health Uses” (FOSHU) by which health claims of some selected functional foods are legally permitted. In 2001, a new regulatory system, foods with health claims (FHC) with a ‘foods with nutrient function claims’ (FNFC) system and newly established FOSHU was introduced<sup>7</sup>. In addition, the Govt. changed the existing FOSHU, FNFC and other systems in 2005. Such changes include the new Subsystems of FOSHU such as

- Standardized FOSHU
- Qualified FOSHU
- Disease risk reduction claims for FOSHU<sup>11</sup>

### Categories of nutraceuticals

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 categories<sup>12</sup>:

1. Substances with established nutritional functions, such as vitamins, minerals, amino acids and fatty acids - Nutrients
2. Herbs or botanical products as concentrates and extracts - Herbals
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.

#### (a) 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. Antioxidants, in general, may be useful in the prevention of cancer and cerebrovascular disease<sup>13</sup>. High dietary intake of vitamin E may prevent Parkinson’s disease<sup>14</sup>. Agus et al., determined that the oxidized form of vitamin C, dehydroascorbic acid, readily crosses the blood brain barrier<sup>15</sup>. These findings have implications for increasing the uptake of antioxidants in the central nervous system; thus, some feel that this has the potential for improving the treatment of Alzheimer’s disease. Jialal and Fuller found that the combination of vitamin E, C and beta carotene has been useful in reducing low density lipoprotein oxidation and subsequent atherosclerosis<sup>16</sup>. Vitamin supplement is associated with increased antibody titre response to both hepatitis B and tetanus vaccines as a result of macrophage and

T cell stimulation<sup>17</sup>. 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<sup>18,19</sup>. Those suffering from asthma and skin cancer have also been evaluated with selenium for its potential use, although results have been inconclusive<sup>20</sup>. Zinc is an essential component of more than hundred enzymes involving digestion, metabolism and wound healing. L-arginine is a semi-essential amino acid that is a substrate for nitric oxide production. Ceremuzynski et al., demonstrated that supplementation of L-arginine improved exercise capacity in patients, who had angina<sup>21</sup>. A list of common nutrients with their health benefits is given in Table

Nutrients	Health benefits
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### Fat Soluble Vitamins

- Vitamin A: Antioxidant, essential, for growth and development, maintains healthy vision, skin and mucous membranes, may aid in the prevention and treatment of certain cancers and in the treatment of certain skin disorders.
- Vitamin D: Essential for formation of bones and teeth, helps the body absorb and use calcium
- Vitamin E: Antioxidant, helps form blood cells, muscles, lung and nerve tissue, boosts the immune system
- Vitamin K: Essential for blood clotting

### Water Soluble Vitamins

- Vitamin C: Antioxidant, necessary for healthy bones, gums, teeth and skin, helps in wound healing, may prevent common cold and attenuate its symptoms
- Vitamin B1: Helps to convert food in to energy, essential in neurologic functions
- Vitamin B2 : Helps in energy production and other chemical processes in the body, helps maintain healthy eyes, skin and nerve function
- Vitamin B3: Helps to convert food in to energy and maintain proper brain function
- Vitamin B6: Helps to produce essential proteins and convert protein in to energy
- Vitamin B12: Helps to produce the genetic material of cells, helps with formation of red blood cells, maintenance of central nervous system and synthesizes amino acids and is

involved in metabolism of fats, protein and carbohydrates

- Folic acid : Necessary to produce the genetic materials of cells, essential in first three months of pregnancy for preventing birth defects, helps in red blood cell formation, protects against heart disease
- Pantothenic acid: Aids in synthesis of cholesterol, steroids and fatty acids, crucial for intraneuronal synthesis of acetylcholine

### Minerals

- Calcium: Essential for building bones and teeth and maintaining bone strength, important in nerve, muscle and glandular functions
- Iron: Helps in energy production, helps to carry and transfer oxygen to tissues
- Magnesium: Essential for healthy nerve and muscle function and bone formation, may help prevent premenstrual syndrome (PMS)
- Phosphorous: Essential for building strong bones and teeth, helps in formation of genetic material, energy production and storage

### Trace elements

- Chromium: With insulin helps to convert carbohydrates and fats into energy
- Cobalt: Essential component of vitamin B12, but ingested cobalt is metabolized in vivo to form the B12 coenzymes
- Copper: Essential for hemoglobin and collagen production, healthy functioning of the heart, energy production, absorption of iron from digestive tract
- Iodine: Essential for proper functioning of the thyroid Selenium Antioxidant, essential for healthy functioning of the heart muscle
- Zinc: Essential for cell reproduction, normal growth and development in children, wound healing, production of sperm and testosterone

### Vitamin like compounds

- Biotin: Required for various metabolic functions
- L-Carnitine: Oxidation of fatty acids, promotion of certain organic acid excretion and enhancement of the rate of oxidative phosphorylation

- Choline: Lipotropic agent used to treat fatty liver and disturbed fat metabolism

Vitamin F: Involved in proper development of various membranes and synthesis of prostaglandins, leukotrienes and various hydroxy fatty acids

- Inositol: Lipotropic agent necessary for amino acid transport and movement of potassium and sodium
- Taurine Aids: in retinal photoreceptor activity, bile acid conjugation, white blood cell antioxidant activity, CNS neuromodulation, platelet aggregation, cardiac contractility, sperm motility, growth and insulin activity.

**(b) Herbs** <sup>7,23</sup>

Herbs or botanical products as concentrates and extracts. Common herbs and their therapeutic relevance are shown in Table

Herbals (Botanical source)	Therapeutic activity
Aloe vera gel(Aloe vera L.N.L. Burm.)	Dilates capillaries, anti-inflammatory, emollient, wound healing properties.
Chamomile (Matricaria recutita L.)	Anti-inflammatory, spasmolytic, antimicrobial, wound Healing.
Echinacea (Echinacea purpurea L.)	Immunostimulant, treatment of cold and flu symptoms
Ephedra (Ephedra sinica Stapf.)	Bronchodilator, vasoconstrictor, reduces bronchial Edema
Evening primrose oil (Oenothera biennis L.)	Dietary supplement of linoleic acid, treatment of atopic eczema
Feverfew (Tanacetum parthenium L.)	Treatment of headache, fever and menstrual problem, severity and duration of migraine headaches
Garlic (Allium sativum L.)	Antibacterial, antifungal, antithrombotic, hypotensive anti-inflammatory
Ginger (Zingiber officinale Rosc.)	Carminative, antiemetic, cholagogue, positive inotropic
Ginseng (Panax ginseng)	Adaptogen
Ginkgo (Ginkgo biloba L.)	Vasodilation, increased peripheral blood flow, Treatment of post thrombotic syndrome
Goldenseal (Hydrastis canadensis L.)	Antimicrobial, astringent, antihemorrhagic, treatment of mucosal inflammation, dyspepsia, gastritis
Horehound (Marrubium vulgare L.)	Expectorant, antitussive, choleric

Licorice (Glycyrrhiza glabra L.)	Expectorant, secretolytic, treatment of peptic ulcer
Melissa (Melissa officinalis L.)	Topical antibacterial and antiviral
Plantago seed (Plantago arenaria Waldst)	Cathartic
St. John's wort (Hypericum perforatum L.)	Anxiolytic, anti-inflammatory, antidepressant, monoamine oxidase inhibitor.
Valerian (Valeriana officinalis L.)	Spasmolytic, mild sedative, sleep aid
Willow bark (Salix alba L.)	Anti-inflammatory, analgesic, antipyretic, astringent, treatment of rheumatic and arthritic.

**(a) Dietary Supplement**

Dietary supplements are products administered through mouth that contain a dietary ingredient intended to add something to the foods you eat. Examples of dietary supplements are black cohosh for menopausal symptoms, ginkgo biloba for memory loss, and glucosamine/chondroitin for arthritis. They also serves specific functions such as sports nutrition, weight-loss supplements and meal replacements. Supplement ingredients may contain vitamins, minerals, herbs or other botanicals, amino acids, enzymes, organ tissues, gland extracts, or other dietary substances. They are available in different dosage forms, including tablets, capsules, liquids, powders, extracts, and concentrates<sup>7,23</sup>. They could be categorized as shown in Table

Dietary supplements	Significance
Ketogenic diets	Comprised of foods with high fat and low protein and carbohydrate content, have been reported to improve seizure control. However, these diets are widely acknowledged to be unpalatable <sup>7</sup> .
Minimally refined grains	Cereals and grains fortified with calcium may reduce the incidence of diabetes and prevents gastrointestinal cancers <sup>7</sup> .
Phytoestrogens	Found in soya flour and linseeds and have been documented to enhance oestrogens levels when hormonal levels are low. This action may prevent against both hot flushes and breast cancer <sup>7</sup> .

Several species of edible mushrooms	Tonnage, Lentinus, Pleurotus, Auricularia, Flammulina, Tremella, Hericium and Grifola have varying degrees of immunomodulatory, lipid lowering and antitumor without any significant toxicity.
Glucosamine sulfate and chondroitin sulfate	They are effective and safer to alleviate symptoms of osteoarthritis <sup>7</sup> .
Peptides/Hydrolysates	Found in casein and whey protein and have A.C.E. inhibitor activity. Buckwheat proteins used as flour reduces cholesterol, hypertension; improve constipation and obesity by acting similar to dietary fibers and interrupting the in-vivo metabolism <sup>7</sup> .
Dairy foods	Containing friendly or probiotic bacteria claimed to promote gut health. Bio yoghurts containing Lactobacillus acidophilus and Bifidobacteria lead the sector <sup>7</sup> .

## NUTRACEUTICALS AND DISEASES

### Cardiovascular diseases

Worldwide, the burdens of chronic diseases like cardiovascular diseases, cancers, diabetes and obesity is rapidly increasing. In 2001, chronic diseases contributed approximately 59% of the 56.5 million total reported deaths in the world and 46% of the global burden of disease. Cardiovascular diseases (CVD) is the name for the group of disorders of the heart and blood vessels and include hypertension (high blood pressure), coronary heart disease (heart attack), cerebrovascular disease (stroke), heart failure, peripheral vascular disease, etc. Majority of the CVD are preventable and controllable. It was reported that low intake of fruits and vegetables is associated with a high mortality in cardiovascular disease<sup>8,9</sup>. Optimal nutrition, nutraceuticals, vitamins, antioxidants, minerals, weight reduction, exercise, cessation of smoking, restriction of alcohol and caffeine plus other lifestyle modifications can prevent, delay the onset, reduce the severity, treat, and control hypertension. Nutrients and nutraceuticals with calcium channel blocking activity (thus antihypertensive activity) include  $\alpha$ -Lipoic acid, magnesium, Vitamin B6 (pyridoxine), Vitamin C, N-acetylcysteine, Hawthorne, Celery,  $\omega$ -3 fatty acids etc. Flavonoids are widely distributed in onion, endives, cruciferous vegetables, black grapes, red wine, grapefruits, apples, cherries and berries<sup>23</sup>. Flavonoids block the angiotensin-converting enzyme (ACE) that raises blood pressure; by blocking the "suicide" enzyme cyclooxygenase that breaks down prostaglandins, they prevent platelet stickiness and hence platelet aggregation. Flavonoids

also protect the vascular system and strengthen the tiny capillaries that carry oxygen and essential nutrients to all cells. Hesperidin is a flavanone glycoside which is classified as a citrus bioflavonoid. Sweet oranges (*Citrus sinensis*) and tangelos are the richest dietary sources of hesperidin. The peel and membranous parts of lemons and oranges have the highest hesperidin concentrations. Therefore, orange juice containing pulp is richer in the flavonoid than that without pulp. The anticancer properties of ginger are attributed to the presence of certain pungent vullinoids, viz. [6]-gingerol and [6]-paradol<sup>20</sup>. Cholesterol has long been implicated as a significant risk factor in cardiovascular disease. Sterols occur in most plant species and are called as phytosterols. Although green and yellow vegetables contain significant amounts, their seeds concentrate the sterols. Phytosterols compete with dietary cholesterol by blocking the uptake as well as facilitating its excretion from the body<sup>23</sup>. *Fagopyrum esculentum* Dietary fiber preparation from defatted rice bran has laxative and cholesterol-lowering ability with attendant benefits towards prevention or alleviation of cardiovascular disease, diabetes, diverticulosis and colon cancer. It has been suggested that rice bran is a good fiber source (27%) that can be added to various food products<sup>25</sup>. Milk and eggs are the important animal sources of nutraceuticals like proteins and polyunsaturated fats or essential fatty acids (EFAs). EFAs are required for production and rebuilding of cells, to reduce blood pressure, lower cholesterol and triglycerides, reduce the risk of blood clots, help prevent many diseases including arthritis, arrhythmias, and other cardiovascular diseases<sup>26</sup>. Fatty acids of the omega-3 series (n-3 fatty acids) present in fish are well established dietary components affecting plasma lipids and the major cardiovascular disorders, such as arrhythmias<sup>27,28</sup>.

### Current status of nutraceuticals in CVD

Because of the extremely long history of CVD, the causal relationship of nutrition/physical exercise on major CVD events is still difficult to assess prospectively<sup>29</sup>. The relationship between calcium and risk of hypertension is inconsistent and inconclusive, and the relationship between calcium and risk of pregnancy-induced hypertension and preeclampsia is highly unlikely<sup>30</sup>. Treatment with beta carotene, vitamin A, and vitamin E may increase mortality. The potential roles of vitamin C and selenium on mortality need further study<sup>31</sup>. There are possibilities to develop nutraceuticals to prevent and manage thrombosis risk in women with thrombophilic gene mutations<sup>32</sup>.

### Obesity

Obesity, defined as an unhealthy amount of body fat, is a well established risk factor for many disorders like

angina pectoris, congestive heart failure, hypertension, hyperlipidemia, respiratory disorders, renal vein thrombosis, osteoarthritis, cancer, reduced fertility etc. Obesity is now a global public health problem, with about 5 million people are estimated to fall into the WHO-defined obesity categories. One of the primary causes this rapid rise in obesity rates is the increased availability of high-fat, energy-dense foods<sup>23</sup>. Excessive consumption of energy-rich foods (snacks, processed foods and drinks) can encourage weight gain, which calls for a limit in the consumption of saturated and trans fats apart from sugars and salt in the diet. Caloric restriction and increased physical activity has been shown to be only moderately successful in managing obesity. Thus many health care practitioners and obese individuals are seeking the help of pharmaceuticals and nutraceuticals to treat obesity. A tolerable and effective nutraceutical that can increase energy expenditure and/or decrease caloric intake is desirable for body weight reduction. Herbal stimulants, such as ephedrine, caffeine, ma huang-guarana, chitosan and green tea have proved effective in facilitating body weight loss. However, their use is controversial due to their ability to cause undesired effects. Buckwheat seed proteins have beneficial role in obesity and constipation acting similar to natural fibers present in food. 5-hydroxytryptophan and green tea extract may promote weight loss, while the former decreases appetite, the later increases the energy expenditure<sup>23</sup>.

#### **Current status of nutraceuticals in obesity**

A blend of glucomannan, chitosan, fenugreek, G. sylvestre, and vitamin C in the dietary supplement significantly reduced body weight and promoted fat loss in obese individuals. Further studies are needed to establish a long term efficacy and adverse effect potential<sup>33</sup>. There is a very high prevalence of obesity globally and hence nutrition and exercise play a key role in its prevention and treatment. Nutraceutical interventions are currently being investigated on a large-scale basis as potential treatments for obesity and weight management. Nutraceuticals like conjugated linoleic acid (CLA), capsaicin, Momordica Charantia (MC) and Psyllium fiber possess potential antiobese properties<sup>34</sup>.

#### **Diabetes**

Diabetes mellitus is characterized by abnormally high levels of blood glucose, either due to insufficient insulin production, or due to its ineffectiveness. The most common forms of diabetes are type 1 diabetes (5%), an autoimmune disorder, and type 2 diabetes (95%), which is associated with obesity. Gestational diabetes occurs in pregnancy<sup>45</sup>. Globally the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2034<sup>46</sup>.

Diabetes, like most chronic health conditions, not only places substantial economic burdens on society as a whole but also imposes considerable economic burdens on individual patients and their families. In US alone an estimated the expenditures for health care for people with diabetes totaled \$85.7 (11.9% of total health care expenditures) in 1992<sup>47</sup>. Diet therapy is the cornerstone for the management of gestational diabetes mellitus. Although there is widespread use of herbal dietary supplements that are believed to benefit type 2 diabetes mellitus, few have been proven to do so in properly designed randomized trials. Isoflavones are phytoestrogens; they have a structural/functional similarity to human estrogen and have been consumed by humans world-wide. Of all phytoestrogens, soy isoflavones have been studied most. A high isoflavone intake (20–100 mg/day) is associated with lower incidence and mortality rate of type II diabetes, heart disease, osteoporosis and certain cancers. Omega-3 fatty acids have been suggested to reduce glucose tolerance in patients predisposed to diabetes. For the synthesis of the long chain n-3 fatty acids, insulin is required; the heart may thus be particularly susceptible to their depletion in diabetes. Ethyl esters of n-3 fatty acids may be potential beneficial in diabetic patients. Docosahexaenoic acid modulates insulin resistance and is also vital for neurovisual development. This is especially important in women with gestational diabetes mellitus which foster the recommendation for essential fatty acids during pregnancy. Lipoic acid is a universal antioxidant, now used in Germany for the treatment of diabetic neuropathy. It is possible that lipoic acid may be more effective as a long-term dietary supplement aimed at the prophylactic protection of diabetics from complications. Dietary fibers from psyllium have been used extensively both as pharmacological supplements, food ingredients, in processed food to aid weight reduction, for glucose control in diabetic patients and to reduce lipid levels in hyperlipidemia. Good magnesium status reduces diabetes risk and improves insulin sensitivity; chromium picolinate, calcium and vitamin D appear to promote insulin sensitivity and improve glycemic control in some diabetics; extracts of bitter melon and of cinnamon have the potential to treat and possibly prevent diabetes. However it has been suggested that nutraceuticals with meaningful doses of combinations may substantially prevent and presumably could be marketed legally<sup>23</sup>.

#### **Cancer**

In the year 2000, malignant tumors were responsible for 12 per cent of the nearly 56 million deaths worldwide from all causes. According to the World Cancer Report the cancer rates there would be 15 million new cases in the year 2020 i.e. a rise in 50%.

Cancer has emerged as a major public health problem in developing countries, matching the industrialized nations. A healthy lifestyle and diet can help in preventing cancer<sup>54,55</sup>. People who consume large amount of lutein-rich foods such as chicken eggs, spinach, tomatoes, oranges and leafy greens experienced the lowest incidence of colon cancer. Chronic inflammation is associated with a high cancer risk. At the molecular level, free radicals and aldehydes, produced during chronic inflammation, can induce deleterious gene mutation and posttranslational modifications of key cancer-related proteins. Chronic inflammation is also associated with immune suppression, which is a risk factor for cancer. Ginseng as an example of an antiinflammatory molecule that targets many of the key players in the inflammation-to-cancer sequence. Recently, attention has been on phytochemicals that possess cancer-preventive properties. Besides chemopreventive components in vegetables and fruits, some phytochemicals derived from herbs and spices also have potential anticarcinogenic and antimutagenic activities, among other beneficial health effect. A broad range of phyto-pharmaceuticals with a claimed hormonal activity, called "phyto estrogens", is recommended for prevention of prostate/breast cancer<sup>58</sup>. Flavonoids found in citrus fruit appear to protect against cancer by acting as antioxidants. Soyfoods are a unique dietary source of isoflavones, the polyphenolic phytochemicals exemplified by epigallocatechin gallate from tea<sup>60</sup>, curcumin from curry and soya isoflavones possess cancer chemopreventive properties. The main soybean isoflavones, genistein, daidzein, biochanin inhibits prostate cancer cell growth. Carotenoids are a group of phytochemicals that are responsible for different colors of the foods. Recent interest in carotenoids has focused on the role of lycopene in human health. Because of the unsaturated nature of lycopene it is considered to be a potent antioxidant and a singlet oxygen quencher. Lycopene prevents cancer, cardiovascular disease, and gastrointestinal tract. It concentrates in the skin, testes, adrenal and prostate where it protects against cancer. The linkage between carotenoids and retinoids and the prevention of cancer coronary artery diseases, and advanced age-related macular degeneration heightened the importance of value-added fruits in human diet. Recently, it was reported that lycopene containing fruits and vegetables exert cancer-protective effect via a decrease in oxidative and other damage to DNA in humans. Lycopene is one of the major carotenoids in western diets and is found almost exclusively in tomatoes, water melon, guava, pink grapefruit and papaya. Beta-carotene, the important precursor of vitamin A has anti-oxidant properties and help in preventing cancer and other diseases. Among

the carotenes, beta carotene is the most active as antioxidants. Alpha carotene possesses 50 % to 54 % of the antioxidant activity of beta carotene, whereas epsilon carotene has 42 % to 50 % of the antioxidant activity. Alpha and beta carotenes, along with gamma carotene and the carotenes lycopene and lutein<sup>68</sup> which do not convert to vitamin A, seem to offer protection against lung, colorectal, breast, uterine and prostate cancers.  $\beta$ -Carotene is the more common form and can be found in yellow, orange, and green leafy fruits and vegetables. These can be carrots, spinach, lettuce, tomatoes, sweet potatoes, broccoli, cantaloupe, oranges, and winter squash. Saponins are reported to possess antitumor and antimutagenic activities and can lower the risk of human cancers, by preventing cancer cells from growing. Saponins are phytochemicals which can be found in peas, soybeans, and some herbs with names indicating foaming properties such as soapwort, soapbark and soapberry. They are also present in spinach, tomatoes, potatoes, alfalfa and clover. Commercial saponins are extracted mainly from *Yucca schidigera* and *Quillaja saponaria*. The non-sugar part of saponins has also a direct antioxidant activity, which may result in other benefits such as reduced risk of cancer and heart diseases. Tannins also called proanthocyanidins, detoxify carcinogens and scavenge harmful free radicals. Tannins in cranberries also protect against urinary tract infections. It is present in blackberries, blueberries, cranberries, grapes, lentils, tea and wine. Ellagic acid is a proven anti-carcinogen is used in alternative medicine and to prevent cancer. It is present in strawberries, cranberries, walnuts, pecans, pomegranates and the best source, red raspberry seeds. Pectin is a soluble fiber found in apples. A new form of citrus pectin called modified citrus pectin (MCP) has been shown to prevent prostate cancer metastasis by inhibiting the cancer cells from adhering to other cells in the body. Several studies have also shown pectin to have positive influences in decreasing serum cholesterol levels, without effecting serum triglyceride levels. Pectin also has the ability to reduce the rise of blood sugar when combined with meal. Naturally occurring phenolic acid derivatives are reported to possess potential anticancer properties<sup>35,36</sup>. Phenolics such as ferulic, caffeic, gallic acids and curcumin are reported to possess anticancer activity<sup>37</sup>. Glucosinolates are found in cruciferous vegetables including the Brassica crops—Brussels sprouts, broccoli, cauliflower, cabbage, watercress, oilseed rape, and mustard and are powerful activators of liver detoxification enzymes<sup>38</sup>. Glucosinolates and their hydrolysis products, including indoles and isothiocyanates, and high intake of cruciferous vegetables has been associated with lower risk of lung and colorectal cancer They also regulate white blood



cells and cytokines. White blood cells are the scavengers of the immune system and cytokines act as "messengers," coordinating the activities of all immune cells. Bio-transformation products of glucosinolates include isothiocyanates, dithiolthiones and sulforaphane. They block the enzymes that promote tumor growth, particularly in the breast, liver, colon, lung, stomach and esophagus<sup>39</sup>. The sulfur compounds, in garlic were found to kill bacteria and parasites, boost the immune system and reduce atherogenesis and platelet stickiness. All members of the cruciferous family” broccoli, cauliflower, cabbage, bok choy, Brussels sprouts, collards, cress, kale, kohlrabi, mustard” contains a group of closely related sulfur compounds known as glucosinolates. Sulforaphane rich in broccoli is a potent phase 2 enzyme inducer. It produces Dglucarolactone, a significant inhibitor of breast cancer. Sulforaphane is an antioxidant and stimulator of natural detoxifying enzymes. Sulforaphane has been reported to reduce the risk of breast cancer and prostate cancer. Thiosulfonates an organosulfur phytochemical is present in garlic and onions (*Allium cepa*). Onions are rich in two chemical groups that have perceived benefits to human health, which include anticarcinogenic properties, antiplatelet activity, antithrombotic activity, antiasthmatic and antibiotic effects<sup>40</sup>. Curcumin (diferuloylmethane) is a polyphenol derived from the plant *Curcuma longa*, commonly called turmeric. Curcumin, an active yellow pigment of turmeric reported to possess anticarcinogenic, antioxidative and anti-inflammatory properties. The anticancer potential of curcumin stems from its ability to suppress proliferation of a wide variety of tumor cells. Top of Form Beet roots, cucumber fruits, spinach leaves, and turmeric rhizomes, were reported to possess anti tumor activity. Non-prescription antioxidants and other nutrients (patients using beta-carotene; vitamins A, C, and E; selenium; cysteine; B vitamins; vitamin D3; vitamin K3; and glutathione as single agents or in combination.) do not interfere with therapeutic modalities for cancer<sup>23</sup>.

#### **Current status of nutraceuticals in cancer**

Approximately 20-30% of Americans consume multivitamin supplements daily, indicating high public interest in the prevention of cancer and other chronic diseases through a nutrition-based approach. Because epidemiologic studies generally evaluate foods rather than specific bioactive food components, a systematic approach to determining how combinations of vitamins and minerals may interact to ameliorate cancer risk is necessary to further our understanding of the potential benefits and risks of supplement use. Increasing consumption of vegetables and fruits elevates the levels of antioxidative

components, for example, selenium, vitamin E, vitamin C, lycopene, cysteine-glutathione and various phytochemicals. These detrimental processes of heme catalysis of oxidative damage hypothesized here are not well recognized. More investigative studies in this field to be done Large scale clinical trials suggest that some agents such as selenium, lycopene, soy, green tea, vitamins D and E, anti-inflammatory and inhibitors of 5 $\alpha$ -reductase are effective in preventing prostate cancer. In order to demonstrate clinical benefit with the minimum adverse effects. Appropriate selection of agent(s), trial design and end points is critical in selecting the most promising regimens to accomplish these goals<sup>23</sup>. Cancer was not prevented by beta-carotene, alphatocopherol, retinol, retinyl palmitate, N-acetylcysteine, or isotretinoin in smokers. Ongoing trials may help define new avenues for chemoprevention. The concept of chemoprevention in lung cancer is still in its infancy, but in the future it may have a significant impact on the incidence and mortality of lung cancer. Several studies have demonstrated the improvement in quality of life and the value of complimentary medicine as an adjuvant to chemotherapy or radiotherapy. Complimentary therapy might serve as a valuable and useful supportive measure for prostate cancer patients. Majority of the studies indicate a preventive role of nutraceuticals in cancer, however more elaborate randomized double blind studies are needed<sup>23,41</sup>.

#### **Immune boosters and anti-inflammatory agents**

**Immune boosters**  
Various nutrients in the diet play a crucial role in maintaining an “optimal” immune response, on the organism’s immune status and susceptibility to a variety of disease conditions. a broad range of phytopharmaceuticals with a claimed hormonal activity, called “phyto-estrogens”, is recommended for prevention of various diseases related to a disturbed hormonal balance. In this respect, there is a renewed interest in soy isoflavones (genistein, daidzein, biochanin) as potential superior alternatives to the synthetic selective estrogen receptor modulators (SERMs), which are currently applied in hormone replacement therapy. Phytochemicals integrate hormonal ligand activities and interfere with signaling cascades; their therapeutic use may not be restricted to hormonal ailments only, but may have applications in cancer chemoprevention and/or certain inflammatory disorders as well. Nutraceuticals that belong to the category of immune boosters and/or anti-viral agents are useful to improve immune function and accelerate wound-healing. They include extracts from the coneflowers, or herbs of the genus *Echinacea*, such as *Echinacea purpurea*, *Echinacea angustifolia*, *Echinacea pillida*, and mixtures thereof; extracts from herbs of the genus *Sambuca*, such as elderberries; and

Goldenseal extracts. The coneflowers in particular are a popular herbal remedy used in the central United States, an area to which they are indigenous. The extract derived from the roots contains varying amounts of unsaturated alkyl ketones or isobutylamides. Goldenseal is an immune booster with antibiotic activity, and includes compounds like berberine and hydrastine, which stimulate bile secretion and constrict peripheral blood vessels respectively. Astragalus membranaceus, Astragalus mongolicus, and other herbs of the genus Astragalus are also effective immune boosters in either their natural or processed forms. Astragalus stimulates development and transformation of stem cells in the marrow and lymph tissue to active immune cells. The effect of plant and bacteria on systemic immune and intestinal epithelial cell function has led to new credence for the use of probiotics and nutraceuticals in the clinical setting. The probiotics have been found to be effective in conditions like infectious diarrhea in children and recurrent *Clostridium difficile* induced infections. Evidence is being acquired for the use of probiotics in other gastrointestinal infections, irritable bowel syndrome and inflammatory bowel disease<sup>23,41</sup>. The dietary approach to allergy has evolved to include active stimulation of the immature immune system in order to support the establishment of tolerance. Supplementation with probiotics may provide maturational signals for the lymphoid tissue and improve the balance of pro- and anti-inflammatory cytokines. Enteral polymeric feeding is effective in Crohn's disease. Most probiotic preparations are comprised of one or more lactic acid bacteria (LAB). Within this group, strains of *Lactobacillus*, *Bifidobacterium* sp. And occasionally *Streptococcus* are most commonly used. A supplementary use of oral digestive enzymes and probiotics is also an anticancer dietary measure towards decreasing the incidence of breast, colon-rectal, prostate and bronchogenic cancer<sup>23</sup>.

### **Inflammatory disorders**

Inflammation is the response of body tissues to injury or irritation, characterized by pain and swelling and redness and heat. Arthritis is a general term that describes inflammation in joints. Some types of arthritis associated with inflammation include: rheumatoid arthritis shoulder tendinitis or bursitis gouty arthritis and polymyalgia rheumatica. Micronutrients for which preliminary evidence of benefit exists include vitamin C and vitamin D. In addition, numerous nutraceuticals that may influence osteoarthritis pathophysiology, including glucosamine, chondroitin, Sadenosylmethionine, ginger and avocado/soybean unsaponifiables, have been tested in clinical trials. These products are safe and well tolerated, but interpretation of the collective

results is hampered by heterogeneity of the studies and inconsistent results. Scientists previously attributed the efficacy of cat's claw to compounds called oxindole alkaloids; more recently, however, water-soluble cat's claw extracts that do not contain significant amounts of alkaloids were found to possess strong antioxidant and anti-inflammatory effects are independent of their alkaloid content. Resveratrol is present in the fruits of bilberry (*Vaccinium myrtillus*), the lowbush "wild" blueberry (*Vaccinium angustifolium*), the rabbiteye blueberry (*Vaccinium ashei* Reade), and the highbush blueberry (*Vaccinium corymbosum*). Although blueberries and bilberries were found to contain resveratrol, the level of this chemoprotective compound in these fruits was <10% that reported for grapes. Resveratrol shows the strongest sirtuin-like deacetylase action of any known phytochemical. Sirtuins have been shown to extend the lifespan of yeast and fruit flies. It acts as an anti-inflammatory agent, antifungal and inhibits cyclooxygenase-1 enzyme. Other beneficial health effects include anti-cancer, antiviral, neuroprotective, anti-aging and life-prolonging effects. The omega-3 and omega-6 series play a significant role in health and disease by generating potent modulatory molecules for inflammatory responses, including eicosanoids (prostaglandins, and leukotrienes), and cytokines (interleukins) and affecting the gene expression of various bioactive molecules. Gamma linolenic acid (GLA, all cis 6, 9, 12-Octadecatrienoic acid, C18:3, n-6), is produced in the body from linoleic acid (all cis 6,9-octadecadienoic acid), an essential fatty acid of omega-6 series by the enzyme delta-6- desaturase. Preformed GLA is present in trace amounts in green leafy vegetables, nuts, vegetable oils, such as evening primrose (*Oenothera biennis*) oil, blackcurrant seed oil, borage oil and hemp seed oil, and from spirulina, cyanobacteria. It is a nutraceutical used for treating problems with inflammation and auto-immune diseases. Anti-inflammatory herbal nutraceuticals and anti-inflammatory nutraceutical compounds derived from plants or herbs may also be used as anti-inflammatory agents. These include bromelain, a proteolytic enzyme found in pineapple; teas and extracts of stinging nettle; turmeric, extracts of turmeric, or curcumin, a yellow pigment isolated from turmeric<sup>23</sup>.

### **Osteoarthritis**

Osteoarthritis (OA), a debilitating joint disorder, is the most common form of arthritis in the United States, where it affects an estimated 21 million people. In 2004, the direct and indirect health care costs associated with all forms of arthritis were approximately 86 billiondollars. Joint discomfort from OA and other joint disorders may reduce physical activity in individuals experiencing this

condition, resulting in energy imbalance and weight gain. Increased weight can exacerbate existing problems, through additional stress on joints<sup>42</sup>. Glucosamine (GLN) and chondroitin sulfate (CS) are widely used to alleviate symptoms of OA. These nutraceuticals have both nutrient and pharmaceutical properties and seem to regulate gene expression and synthesis of NO and PGE2, providing a plausible explanation for their anti-inflammatory activities<sup>43</sup>.

### **Allergy**

Allergy is a condition in which the body has an exaggerated response to either a drug or food. Quercetin (QR) belongs to a group of polyphenolic substances known as flavonoids. QR is a member of the class of flavonoids called flavonols. It is widely distributed in the plant kingdom in rinds and barks. Especially rich sources of QR include onions, red wine and green tea. QR is a natural antihistamine and opposes the actions of the histamine in the body. Histamines are responsible for allergic and inflammatory reactions. It can help reduce the inflammation that results from hay fever, bursitis, gout, arthritis, and asthma<sup>44</sup>. QR inhibits some inflammatory enzymes, such as lipid peroxidases, and decreases leukotriene formation. QR has anti-inflammatory, antiviral, immunomodulatory, anticancer and gastroprotective activities. QR blocks an enzyme that leads to accumulation of sorbitol, which has been linked to nerve, eye, and kidney damage in those with diabetes. QR also possesses potent antioxidant properties. It protects LDL cholesterol from becoming damaged. QR prevents damage to blood vessels by certain forms of cholesterol and other chemicals produced by the body. LDL cholesterol is an underlying cause of heart disease. QR also works as an antioxidant by scavenging damaging particles in the body known as free radicals. People with diabetes are at higher risk of blood vessel damage from free radicals<sup>45</sup>.

### **Vision improving agents**

Lutein is one of the carotenoids, found in many fruits and vegetables including mangoes, corn, sweetpotatoes, carrots, squash, tomatoes and dark, leafy greens such as kale, collards and bok choy. Lutein dipalmitate is found in the plant *Helenium autumnale*. Lutein also known as helenien is used for the treatment of visual disorders. Zeaxanthin is used in traditional Chinese medicine mainly for the treatment of visual disorders. Food sources of zeaxanthin, include corn, egg yolks and green vegetables and fruits, such as broccoli, green beans, green peas, brussel sprouts, cabbage, kale, collard greens, spinach, lettuce, kiwi and honeydew. Lutein and zeaxanthin are also found in nettles, algae and the petals of many yellow flowers. In green vegetables, fruits and egg

yolk, lutein and zeaxanthin exist in non-esterified forms. They also occur in plants in the form of mono- or diesters of fatty acids. A new source of these carotenoids, a crystalline lutein product, is an extract from the marigold flower (*Tagetes erecta*) that contains approximately 86% by weight of the carotenoids lutein and zeaxanthin<sup>23</sup>.

### **Alzheimer's disease**

Alzheimer's disease (AD) is characterized by progressive dementia with memory loss as the major clinical manifestation. In 1996, approximately 4 million people in the United States were clinically diagnosed with AD; which is expected to triple in the next 50 years. Women are more affected than men at a ratio of almost 2:1 due in part to the larger population of women who are over 70. Several lines of evidence strongly suggest that oxidative stress is etiologically related to a number of neurodegenerative disorders including Alzheimer's disease. Nutraceutical antioxidants like  $\beta$ -Carotene, curcumin, lutein, lycopene, turmerin etc may exert positive effects on specific diseases by neutralizing the negative effects oxidative stress, mitochondrial dysfunction, and various forms of neural degeneration. A great deal of research has pointed to deleterious roles of metal ions in the development of Alzheimer's disease, by the augmentation of oxidative stress by metal ion. The growing trend in nutraceutical intake is in part a result of the belief that they postpone the development of dementias such as Alzheimer's disease. However, pathogenic events centered on metal ions are expected to be aggravated by frequent nutraceutical intake<sup>23</sup>.

### **Parkinson's disease**

Parkinson's disease is a brain disorder that results from nerve damage in certain regions of the brain causing muscle rigidity, shaking, and difficult walking, usually occurring in mid to late adult life. Canadian researchers indicated that vitamin E in food may be protective against Parkinson's disease. Creatine appeared to modify Parkinson's disease features as measured by a decline in the clinical signs. Researchers have also studied glutathione to determine its effect on nerve and its power as an antioxidant. The appropriate long-term dosing, side-effects and the most effective method of administration are not yet clear. Nutritional supplements have shown some promising results in preliminary studies, it is important to remember that there is not sufficient scientific data to recommend them for Parkinson's disease at present. The patients should be cautioned that over-the-counter medications do have sideeffects and interactions with other drugs and are also expensive<sup>23</sup>.

### **Miscellaneous**

In our modern society women can be over-fed, but undernourished which can lead to nutrient deficiencies

with adverse impact on the pregnancy outcome. Good quality nutritional supplements (combinations rather than isolated single nutrients) can play a valuable role in the health of the pregnant mother and the baby though emphasis must always be on eating a good diet. There is also insufficient evidence to identify adverse effects and to say that excess multiple-micronutrient supplementation during pregnancy is harmful to the mother or the fetus. Angiogenesis is an enzymatic process involved in almost all classes of enzymes. It is a process that is generally down regulated in healthy individuals. Antiangiogenic compounds are selective against newly formed blood vessels while sparing existing ones may not lead to side effects even after prolonged exposure. Available indirect evidences suggest that antiangiogenic compounds may prevent diseases involving degenerative process like, arthritis, multiple sclerosis, Alzheimer's, Parkinson's, osteoporosis, diabetes and cancer. Many inhibitors of angiogenesis are being isolated from functional foods. Naturally occurring bioactive compounds are speculated to be potentially effective and safe anti-angiogenic compounds. Such compounds include catechins, flavins, Curcumin, Isoflavones, Resveratrol, proanthocyanidins, flavonoids, Saponins, terpenes, Chitin, chitosan, Vitamins B3, Vitamin D3, Fatty acids, peptides and amino acids (alpha 2-macroglobulin, arginine, phenylalanine etc. Psyllium, a dietary fiber is valuable in the management of irritable bowel syndrome, inflammatory bowel disease-ulcerative colitis, colon cancer, constipation. *Moringa oleifera* Lam (Moringaceae) has an impressive range of medicinal uses with high nutritional value. Different parts of this plant contain a profile of important minerals, and are a good source of protein, vitamins, beta-carotene, amino acids and various phenolics. It provides a rich and rare, combination of zeatin, QR, beta-sitosterol, caffeoylquinic acid and kaempferol. With water purifying powers and high nutritional value. Various parts of this plant such as the leaves, roots, seed, bark, fruit, flowers and immature pods act as cardiac and circulatory stimulants, possess antitumor, antipyretic, antiepileptic, antiinflammatory, antiulcer, antispasmodic, diuretic, antihypertensive, cholesterol lowering, antioxidant, antidiabetic, hepatoprotective, antibacterial and antifungal activities, and are being employed for the treatment of different ailments in the indigenous system of medicine, particularly in Asia<sup>23</sup>.

## CONCLUSION

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