

New Concepts in Nutraceuticals as Alternative for Pharmaceuticals

Hamid Nasri, Azar Baradaran¹, Hedayatollah Shirzad², Mahmoud Rafeian-Kopaei²

Department of Nephrology, Division of Nephropathology, Isfahan University of Medical Sciences, Isfahan, Iran, ¹Department of Pathology, Isfahan University of Medical Sciences, Isfahan, Iran, ²Medical Plants Research Center, Shahrekord University of Medical Sciences, Shahrekord, Iran

Correspondence to:

Prof. Mahmoud Rafeian-Kopaei,
Medical Plants Research Center,
Shahrekord University of Medical
Sciences, Sharekord, Iran.
E-mail: rafeian@yahoo.com

Date of Submission: May 30, 2014

Date of Acceptance: Nov 06, 2014

How to cite this article: Nasri H, Baradaran A, Shirzad H, Rafeian-Kopaei M. New Concepts in Nutraceuticals as Alternative for Pharmaceuticals. *Int J Prev Med* 2014;5:1487-99.

ABSTRACT

Nutraceuticals are products, which other than nutrition are also used as medicine. A nutraceutical product may be defined as a substance, which has physiological benefit or provides protection against chronic disease. Nutraceuticals may be used to improve health, delay the aging process, prevent chronic diseases, increase life expectancy, or support the structure or function of the body. Nowadays, nutraceuticals have received considerable interest due to potential nutritional, safety and therapeutic effects. Recent studies have shown promising results for these compounds in various complications. In the present review much effort has been devoted to present new concepts about nutraceuticals based on their diseases modifying indications. Emphasis has been made to present herbal nutraceuticals effective on hard curative disorders related to oxidative stress including allergy, alzheimer, cardiovascular, cancer, diabetes, eye, immune, inflammatory and Parkinson's diseases as well as obesity. The recently published papers about different aspects of nutraceuticals as alternative for pharmaceuticals were searched using scientific sites such as Medline, PubMed, and Google Scholar. The used terms included nutraceutical and allergy, alzheimer, cardiovascular, cancer, diabetes, eye, immune, inflammatory or Parkinson.

Keywords: Antioxidants, disease modifiers, herbal nutraceuticals, nutraceutical products, nutraceuticals, oxidative stress

INTRODUCTION

Nutraceutic is a term derived from "nutrition" and "pharmaceutics." The term is applied to products that are isolated from herbal products, dietary supplements (nutrients), specific diets, and processed foods such as cereals, soups, and beverages that other than nutrition are also used as medicine.^[1]

In the US, the term "nutraceutical" products are regulated as drugs, food ingredients and dietary supplements. The term is not defined the same in different countries, but is usually defined as a product isolated from foods that is generally sold in medicinal forms not usually associated with food. A nutraceutical product may be defined as a substance, which has physiological benefit or provides protection against chronic diseases.^[1] Nutraceuticals

may be used to improve health, delay the aging process, prevent chronic diseases, increase life expectancy, or support the structure or function of the body.^[2]

Nutraceuticals, in contrast to pharmaceuticals, are substances, which usually have not patent protection. Both pharmaceutical and nutraceutical compounds might be used to cure or prevent diseases, but only pharmaceutical compounds have governmental sanction.^[3]

A dietary supplement is considered as a product that bears or contains one or more of the following dietary ingredients: A mineral, a vitamin, an amino acid, a medical herb or other botanical, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients. Nutraceuticals are of these nutritional supplements which are used for health purposes other than nutrition.^[4]

Some popular nutraceuticals include ginseng, *Echinacea*, green tea, glucosamine, omega-3, lutein, folic acid, and cod liver oil. Majority of the nutraceuticals possess multiple therapeutic properties.

Nowadays, nutraceuticals have received considerable interest due to potential nutritional, safety and therapeutic effects. A market research recently proposed that the worldwide nutraceuticals market is expanding and would reach US \$250 billion by 2018.^[5]

Recent studies have shown promising results for these compounds in various pathological complications such as diabetes,^[6,7] atherosclerosis,^[8,9] cardiovascular diseases (CVDs),^[10,11] cancer,^[12,13] and neurological^[14,15] disorders. These conditions involve many changes, including alterations redox state.^[16,17] Most of nutraceuticals have antioxidant activity with the ability to counteract this situation.^[18,19] Hence, they are considered as healthy sources of health promotion, especially for prevention of life threatening diseases such as diabetes,^[20,21] infection,^[22,23] renal,^[24,25] and gastrointestinal^[26,27] disorders.

In the present review much effort has been devoted to present new concepts about nutraceuticals based on their diseases modifying indications. Emphasis has been made to present herbal nutraceuticals effective on hard curative disorders related to oxidative stress, including allergy, alzheimer, cardiovascular,

cancer, diabetes, eye, immune, inflammatory and Parkinson's diseases, as well as obesity.

METHODS

The recently published papers about different aspects of nutraceuticals as alternative for pharmaceuticals were searched using scientific sites such as Medline, PubMed and Google Scholar. The used terms included nutraceutical and allergy, alzheimer, cardiovascular, cancer, diabetes, eye, immune, inflammatory or Parkinson.

Allergy and nutraceuticals

Allergy is a hypersensitivity disorder of the immune system. An allergic reaction usually occurs when a person's immune system reacts to normally harmless substances. Allergic reactions are distinctive because of excessive activation of certain white blood cells called mast cells and basophils by a type of antibody called immunoglobulin E. This reaction results in an inflammatory response which can range from uncomfortable to dangerous.^[28]

Quercetin protects low-density lipoprotein (LDL-C) from becoming damaged, especially to blood vessels. LDL-C is an underlying cause of heart disease and quercetin acts as an antioxidant and scavenges free radicals. Diabetic patients are at higher risk of blood vessel damage from oxidative stress. Therefore, quercetin is beneficial in these patients, too.^[29]

Alzheimer's disease and nutraceuticals

Alzheimer's disease (AD) is the most common form of dementia. There is no cure for the disease and eventually leads to death. Most often, AD is diagnosed in people over 65 years of age,^[30] although the less-prevalent early-onset Alzheimer's can occur much earlier. There were 26.6 million sufferers worldwide in 2006 and is predicted to affect 1 in 85 people globally by 2050.^[31]

Women are more affected in comparison to men, at a ratio of almost 2:1. Several lines of evidence suggest that oxidative stress might be related to a number of neurodegenerative disorders including AD. Nutraceutical antioxidants such as curcumin, lutein, lycopene, turmerin and β -carotene may exert positive effects on specific diseases by combating oxidative stress. The growing trends in nutraceutical usage are due to the belief that these compounds are able to postpone the development of

dementias such as AD.^[30] There are several recently published papers showing the positive effects of different nutraceutical plants such as *Zizyphus jujube*, *Lavandula officinalis* on AD, learning or memory.^[32-34]

Cardiovascular diseases and nutraceuticals

Worldwide, the prevalence of CVD and the researches in this area is increasing.^[35-39] CVD is a term which is used for disorders of the heart and blood vessels and includes coronary heart disease (heart attack), peripheral vascular diseases, cerebrovascular disease (stroke), hypertension, heart failure, and so on. It is believed that low intake of vegetables and fruits is associated with a high mortality in CVD.^[40] Majority of the CVD are preventable. Many studies have reported a protective role for a diet rich in vegetables and fruits against CVD.^[41-43]

Nutraceuticals in the form of vitamins, minerals, antioxidants, dietary fibers and omega-3 polyunsaturated fatty acids (*n*-3 PUFAs) together with physical exercise are recommended for prevention and treatment of CVD. The molecules such as polyphenols alter cellular metabolism and signaling, which is believed to reduce arterial disease.^[44,45]

Flavonoids are widely distributed in vegetables, onion, endives, cruciferous, grapefruits, apples, cherries, pomegranate, berries, black grapes, and red wine, and are available as flavones, flavanones and flavonols,^[46-48] playing a major role in prevention and curing the CVD. Flavonoids block the angiotensin-converting enzyme, block the cyclooxygenase enzymes that break down prostaglandins, and prevent platelet aggregation. They also protect the vascular system that carries oxygen and nutrients to cells.^[49,50] Anthocyanins, tannins (proanthocyanidins), tetrahydro- β -carboline, stilbenes, dietary indoleamines, serotonin and melatonin, in plant foods are hypothesized to impose health benefits.^[51] Orange juice containing pulp is rich in flavonoids. Hesperidin is a flavanone glycoside which is classified as a citrus bioflavonoid. 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. Hesperidin is used for the treatment of venous insufficiency and hemorrhoids.^[52]

Flavonoid intake was significantly inversely associated with mortality from coronary heart

disease and the incidence of myocardial infarction. Flavonoids in regularly consumed foods may reduce the risk of death from coronary heart disease, especially in elderly people.^[53]

The rhizome of *zingiber officinalis* is a common condiment for various foods and beverages. It has a long history of medicinal use and has a positive effect on CVD. Ginger has potent antioxidant and antiinflammatory activities and recently it has been recommended for various diseases including hypertension and palpitation.^[54] This plant has a good protective effect on toxicity of synthetic drugs, too.^[55,56]

Phytosterols compete with dietary cholesterol by blocking the uptake as well as facilitating its excretion from the body. Hence, they have the potential to reduce the morbidity and mortality of CVD. Phytosterols occur in most plant species and although green and yellow vegetables contain significant amounts of sterols, their seeds concentrate them.^[57,58]

Buckwheat seeds possess phytosterols, flavonoids, flavones, proteins and thiamin-binding proteins, etc., Buckwheat proteins lower blood cholesterol and hypertension.^[59] Dietary fibers have also cholesterol-lowering property with beneficial effects in prevention and alleviation of CVD and diabetes.^[60-63]

Fatty acids of the omega-3 series (*n*-3 fatty acids) present in fish are dietary components affecting plasma lipids and the CVD, like arrhythmias. Octacosanol, present in whole grains, fruits and leaves of many plants, has lipid lowering property, with no side-effects.^[64,65]

Cancer and nutraceuticals

Cancer has emerged as a major public health problem in developing countries. According to the World Cancer Report the cancer rates are increasing and it would be 15 million new cases in the year 2020 that is, a rise in 50%. A healthy lifestyle and diet can help in prevention of cancer.^[39] Carotenoids are a group of phytochemicals responsible for different colors of the foods. They have antioxidant activities and effective on cancer prevention. Recent interest in carotenoids has focused on the role of lycopene in human health, especially in cancer disease.^[66]

Plants rich in daidzein, biochanin, isoflavones and genistein, also inhibit prostate cancer cell growth.^[29] Because of the unsaturated nature of lycopene it is

considered to be a potent antioxidant and a singlet oxygen quencher. Lycopene concentrates in the prostate, testes, skin and adrenal where it protects against cancer.^[66,67] The linkage between carotenoids and prevention of cancer and CAD, heightened the importance of vegetable and fruits in human diet.

Lycopene contained vegetables and fruits exert cancer-protective effect via a decrease in oxidative stress and damage to DNA.^[67] Lycopene is one of the major carotenoids and is found exclusively in tomatoes, guava, pink grapefruit, water melon and papaya.^[68]

β -carotene has antioxidant activity and prevents cancer and other diseases. Among the carotenes, β -carotene has the most antioxidant activity. Alpha-carotene possesses 50–54% of the antioxidant activity of β -carotene, whereas epsilon carotene has 42–50% of the antioxidant activity.^[68]

Chronic inflammation is associated with a high cancer risk. Chronic inflammation is also associated with immune-suppression, which is a risk factor for cancer. Ginseng is an example of an antiinflammatory molecule that targets many of the key players in the inflammation-to-cancer sequence.^[69]

Nowadays, phytochemicals with cancer-preventive properties have been on high attention.^[70] Chemopreventive components in fruits and vegetables, among other beneficial health effect, have potential anticarcinogenic and antimutagenic activities. A broad range of phyto-pharmaceuticals with a claimed hormonal activity, called “phyto-estrogens,” is recommended for prevention of prostate and breast cancers.^[71]

Citrus fruit flavonoids are able 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, curcumin from curry and soya isoflavones possess cancer chemopreventive properties.^[72] Soybean seems to offer protection against breast, uterine, lung, colorectal, and prostate cancers. β -carotene found in yellow, orange, and green leafy vegetables and fruits such as tomatoes, lettuce, oranges, sweet potatoes, broccoli, cantaloupe, carrots, spinach, and winter squash has anticancer activity.^[72]

Saponins are reported to possess antimutagenic and antitumor activities and might 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 soapberry, soapwort and soapbark. They are also present in tomatoes, potatoes, alfalfa, spinach, and clover. Commercial saponins are extracted mainly from *Yucca schidigera* and *Quillaja saponaria*.^[73]

Tannins also scavenge harmful free radicals and detoxify carcinogens. Tannins present in grapes, lentils, tea, blackberries, blueberries and cranberries is a proven anticarcinogen is used in alternative medicine and to prevent cancer. Ellagic acid, present in walnuts, pecans, strawberries, cranberries, pomegranates and red raspberry seeds, is an anticancer agent.^[73]

Pectin is a soluble fiber found in apples has been shown to prevent prostate cancer metastasis by inhibiting the cancer cells from adhering to other cells in the body. Several studies have shown that pectin decreases serum cholesterol levels. Naturally occurring phenolic acid derivatives are reported to possess potential anticancer properties. Phenolic compounds such as curcumin, gallic acids, ferulic and caffeic acid are reported to possess anticancer activity.^[74]

Glucosinolates and their hydrolysis products, including indoles and isothiocyanates, and high intake of cruciferous vegetables has been associated with lower risk of colorectal and lung cancer. Bio-transformation products of glucosinolates include dithiol thiones, isothiocyanates, and sulforaphane. They block the enzymes that promote tumor growth, particularly in liver, colon, lung, breast, stomach and esophagus.^[75]

The sulfur compounds, in garlic have been found to boost the immune system and reduce atherogenesis and platelet stickiness and cancer. Sulforaphane rich in broccoli is a potent phase 2 enzyme inducer. It produces D-glucarolactone, 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.^[76]

Curcumin is a polyphenol derived from the plant *Curcuma longa*, commonly called turmeric. Curcumin has been reported to possess antioxidative, anticarcinogenic, and antiinflammatory properties.^[77-80]

Consumption of fruits and vegetables having cysteine, glutathione, selenium, Vitamin E,

Vitamin C, lycopene, and various phytochemicals elevates the levels of antioxidative capacity.^[79-82] However, more investigations are needed to determine their beneficial effects in cancer prevention or treatment.^[83]

Large scale clinical trials suggest that some agents such as green tea, Vitamins D and E, selenium, lycopene, soy, antiinflammatory and inhibitors of 5 α -reductase are effective in preventing prostate cancer. Cancer was not prevented by β -carotene, N-acetylcysteine, α -tocopherol, retinol, retinyl palmitate, or isotretinoin in smokers.^[83] Ongoing trials may help define new avenues for chemoprevention.

Several studies have shown the values of alternative and complementary medicine as adjuvant to chemotherapy or radiotherapy. Complimentary therapy may be reliable and useful supportive measure for prostate cancer patients.^[83] Majority of the studies have shown a preventive role for nutraceuticals in cancer, however more elaborate studies are needed.

Diabetes and nutraceuticals

The most common form of diabetes is type 2 diabetes with 95% prevalence and is associated with obesity. Although various drugs for prevention and treatment of diabetes have been introduced, however, globally the total number of people with diabetes with various causes is increasing.^[84-86] Diabetes, not only imposes considerable economic burdens on individual patients and their families but also places substantial economic burdens on society.^[87]

In recent years a wide range of herbal dietary supplements and herbal medicines have scientifically proven to benefit type 2 diabetes mellitus in preclinical studies,^[88,89] however, few have been proven to do so in properly designed randomized clinical trials.^[90]

Isoflavones, are phytoestrogens which have structural/functional similarities to human estrogen. Soy isoflavones have been studied most and their consumption have been associated with lower incidence and mortality rate of type II diabetes, heart disease, osteoporosis and certain cancers.^[78]

Omega-3 fatty acids have been suggested to reduce glucose tolerance in patients predisposed to diabetes. For the synthesis of a 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.^[91]

Lipoic acid is an antioxidant which is used for the treatment of diabetic neuropathy and seems to be effective as a long-term dietary supplement for protection of diabetics from complications.^[92] 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.^[93] A lot of plants extracts such as Toucium polium, cinnamon and bitter melon have been shown to prevent or treat diabetes.^[94-96]

Eye disorders and nutraceuticals

Healthy lifestyle with a diet containing foods rich in antioxidants, such as $n-3$ fatty acids, lutein and zeaxanthin appears beneficial for age-related macular degeneration (AMD). High content of polyphenolic flavonoids in nutraceuticals have been shown to possess antioxidant activity. Herbs or herbal extracts, such as green tea, *Allium* spp., Vitamins C and E, polyphenols, carotenoids (mainly lycopene and β -carotene), and coenzyme Q10 possess antioxidant properties and effective in AMD.^[83]

Astaxanthin is an important naturally occurring carotenoid in the marine world such as sea bream, salmon, trout, and shrimps. It possesses a number of essential biological functions such as protecting against oxidation process, protecting against ultra violet light effects, immune response and pigmentation, in aquatic animals. It is also a very potent antioxidant. Astaxanthin offers powerful protection for the eyes and prevents macular degeneration. Astaxanthin protects heart from oxidative damage, protects the nervous system from degenerative diseases like AD and boosts immune system function.^[31]

Lutein is a carotenoid which is found in many vegetables and fruits including sweet potatoes, carrots, squash, tomatoes, mangoes, corn, and leafy greens such as kale and collards. Lutein and Zeaxanthin are used for the treatment of visual disorders. Food sources of zeaxanthin, include egg yolks, corn, green vegetables and fruits, such as brussel sprouts, cabbage, kale, broccoli, green beans, green peas, lettuce, kiwi, collard greens, spinach, and honeydew lutein and zeaxanthin also occur in plants in the form of mono- and diesters of fatty acids. A new source of these carotenoids is marigold flower (*Tagetes erecta*) that contains approximately

86% by weight of the carotenoids zeaxanthin and lutein.^[31]

Immune system and nutraceuticals

A wide variety of nutraceuticals have been shown to impose crucial roles in immune status and susceptibility to some diseases conditions. Nutraceuticals that belong to the category of immune boosters are useful to improve immune function. They include extracts from the coneflowers, or herbs of the genus *Echinacea*, such as *Echinacea angustifolia*, *Echinacea pillida*, *Echinacea purpurea*. The coneflowers in particular are a popular herbal remedy used in the central United States, an area to which they are indigenous. *Astragalus mongolicus*, *Astragalus membranaceus*, and other herbs of the *Astragalus* genus are also effective immune boosters. *Astragalus* stimulates development and transformation of stem cells in the marrow and lymph tissue to active immune cells. Phytoestrogens mostly are recommended for prevention of various diseases related to hormonal imbalance. There is a special interest in soy isoflavones as potential superior alternatives to the synthetic selective estrogen receptor modulators, which are currently applied in hormone replacement therapy. Garlic and morphine also are good example of the nutraceuticals, which respectively stimulate and suppress immune system.^[71,97]

The effect of herbal medicines and bacteria on the immune system and intestinal epithelial cell function has led to new credence for the use of nutraceuticals and probiotics in clinical settings. Probiotics are effective in conditions such as infectious diarrhea in children and recurrent *Clostridium difficile* induced infections.^[97]

Supplementation with probiotics (live viable microbial organisms) may provide maturational signals for the lymphoid tissue and improve the balance of pro and antiinflammatory cytokines. Probiotics manipulate the intestinal microflora to maintain a normal balance between pathogenic and nonpathogenic bacteria. Usage of these agents in the treatment of specific diseases has evolved into the ability to very high index of safety, reduction of antibiotic use and the public's positive perception about "alternative" or "natural" therapies. Most probiotic preparations are comprised of one or more lactic acid bacteria. Within this group, strains

of *Lactobacillus*, *Bifidobacterium* sp. and occasionally *Streptococcus* are most commonly used.^[98]

Inflammation and nutraceuticals

Inflammation is characterized by swelling, pain, redness and heat, and is the response of body tissues to irritation or injury. Nutraceuticals that their influence on osteoarthritis has been tested are ginger, soybean, unsaponifiable, glucosamine, chondroitin, S-adenosylmethionine. Although they are safe and well tolerated, however, the results are hampered by heterogeneity of the studies and inconsistent results. Vitamins C and D are micronutrients for which evidence of benefit exists. Cat's claw is a potent antiinflammatory agent. Scientists have attributed the efficacy of cat's claw to compounds called oxindole alkaloids; however, water-soluble cat's claw extracts that do not contain significant amounts of alkaloids do not possess strong antioxidant and antiinflammatory effects.^[99]

Resveratrol that is present in the fruits of *Vaccinium myrtillus*, *Vaccinium angustifolium*, *Vaccinium ashei*, and *Vaccinium corymbosum* shows the strongest sirtuin-like deacetylase action of any known phytochemical. Sirtuins are chemicals that inhibit cyclooxygenase-1 enzyme and can extend the lifespan of yeast and fruit flies. They possess antiinflammatory and antifungal activities.^[100]

The omega-3 and omega-6 series have a significant role on diseases by generating potent modulatory molecules for inflammatory responses, including prostaglandins, leukotrienes, and interleukins. Gamma linolenic acid (GLA) is produced in the body from linoleic acid, an essential fatty acid of omega-6 series. GLA is a nutraceutical used for treating problems with inflammation and autoimmune diseases. Preformed GLA is present in trace amounts in nuts, green leafy vegetables, vegetable oils, such as seed oil, borage oil, *Oenothera biennis* oil, blackcurrant and hemp seed oil. GLA is metabolized to dihomogamma linolenic acid which undergoes oxidative metabolism by lipoxygenase and cyclooxygenase enzymes to produce antiinflammatory eicosanoids.^[101]

Herbal nutraceuticals with antiinflammatory activity are also available. Gentianine, present in Gentian root, is an effective antiinflammatory agent. Bromelain, a proteolytic enzyme found in extracts of stinging nettle, turmeric, pineapple,

teas and extracts of turmeric or curcumin has antiinflammatory activity.^[102]

Osteoarthritis is a debilitating joint disorder which affects the number of population. In 2004, the costs associated with all forms of arthritis were approximately 86 billion dollars. Joint discomfort from any joint disorders may reduce physical activity in subjects, resulting in energy imbalance and weight gain. Increased weight can exacerbate existing problems, through additional stress on joints.^[101]

Glucosamine and chondroitin sulfate are widely used to alleviate symptoms of osteoarthritis. These nutraceuticals seem to regulate gene expression and synthesis of NO and PGE₂, providing a plausible explanation for their antiinflammatory activities.^[46]

Obesity and nutraceuticals

Obesity is, nowadays, a global public health problem with about 315 million people involved. Obesity is a risk factor for many disorders such as hypertension, congestive heart failure, angina pectoris, hyperlipidemia, respiratory disorders, osteoarthritis, cancer, renal vein thrombosis and reduced fertility.^[103]

One of the primary causes of obesity is the increased availability of high-fat, energy-dense foods. 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 such as capsaicin conjugated linoleic acid, *Momordica charantia* and *Psyllium* fiber possess potential antiobese properties.^[104]

Although excessive consumption of energy-rich foods such as snacks, processed foods and drinks causes weight gain, however, caloric restriction and increased physical activity has been shown to be only moderately successful in managing obesity. Therefore, researchers and obese individuals are seeking the help of nutraceuticals and pharmaceuticals to prevent or treat obesity. An effective nutraceutical that can increase energy expenditure and/or decrease caloric intake is desirable for body weight reduction. Herbal stimulants, such as caffeine, ephedrine, chitosan, ma huang-guarana, and green tea

are effective in facilitating body weight loss.^[105] However, their use is controversial due to their ability to cause side-effects. Green tea extract and 5-hydroxytryptophan may promote weight loss, while the former increases the energy expenditure, the latter decreases appetite.^[105,106]

Parkinson's disease and nutraceuticals

Parkinson's disease is a degenerative disorder of the central nervous system, which its motor symptoms result from the destruction of dopamine-generating cells in the substantia nigra, with unknown causes. The most obvious symptoms are movement-related including rigidity, slowness of movement, shaking and difficulty with walking and gait. The symptoms in advanced stages of the disease include thinking and behavioral problems. Depression is the most common psychiatric symptom and symptoms include sensory, emotional and sleep problems. Parkinson's disease is more common in older people, with most cases occurring after the age of 50.^[107]

Although at present there are not sufficient scientific data to recommend nutritional supplements for Parkinson's disease, some of these supplements have shown some promising results in preliminary studies. Vitamin E, glutathione, and creatine seem to be protective against Parkinson's disease.^[108]

Miscellaneous complications and nutraceuticals

Angiogenesis is an enzymatic 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. Antiangiogenic compounds may prevent diseases involving degenerative process such as multiple sclerosis, arthritis, osteoporosis, diabetes, cancer, AD and Parkinson's diseases. Some bioactive compounds such as curcumin, flavins, isoflavones and catechins, resveratrol, proanthocyanidins, flavonoids, Saponins, terpenes, Chitin, chitosan, Vitamins B₃ and D₃, Fatty acids, peptides and amino acids are potentially effective angiogenic compounds.^[109]

Moringa oleifera Lam has an impressive range of medicinal uses and is a good source various amino acids and phenolics, protein, vitamins, β -sitosterol,

caffeoylquinic acid, kaempferol and β -carotene with high nutritional and therapeutic values. Various parts of this plant like leaves, seed, bark, fruit, roots, flowers and immature pods act as cardiac and circulatory stimulants, possess antitumor, antipyretic, antiepileptic, antiinflammatory, diuretic, antihypertensive, antidiabetic, cholesterol lowering, antiulcer, antispasmodic, antioxidant, hepatoprotective, antibacterial, and antifungal activities.^[110]

Toxicity potential of nutraceuticals

A large number of people believe that nutraceuticals, especially medicinal plants, are important remedies to address health issues with no side-effects. This belief has been raised from the fact that they have been used for a long period without serious toxicities. Although this is true for a wide variety of nutraceuticals and they generally have less side effects in comparison to pharmaceuticals, but conventional medicine is considered that if a drug is to be effective, inevitably, it will have toxic or side-effects.^[111] The medical establishment considers herbal medicines as drugs, and as such, they must have side effects. Therefore, they need to be prepared with correct ingredients and use with caution, too.^[112]

People consume thousands of species of plants and other nutraceuticals to meet their basic nutritional needs, but only a limited number of them have received significant safety studies. Many remain poorly understood and largely undeveloped, and their wild relatives are threatened with extinction and in need of conservation attention. Stewardship of these valuable plant resources will require rigorous science combined with an approach that respects and values traditional knowledge systems.^[112]

Antitoxicity of nutraceuticals

Most of the synthetic drugs possess toxicity properties, and nutraceutical compounds, particularly herbal nutraceuticals have been investigated for their potential in combating the toxic effects of toxins and other medications.^[113,114]

Although the toxicology of drugs is complex, there is great evidence for involvement of oxidative stress in the toxicity of a wide variety of drugs.^[115,116] Most of plants possess antioxidant activity and other than various specific ways to

combat toxins and synthetic drugs, they generally may reduce their toxicity by reduction of oxidative stress.^[117-119] Kidney and liver are two organs which more than others are involved in toxic effects of other drugs as well as toxins.^[120,121] In this regard there are a wide variety of studies investigating the protective activities of nutraceuticals, especially medicinal plants against toxins and other drugs and promising results have been achieved.^[122-124]

DISCUSSION

Nowadays, nutraceuticals have received high interests due to their potential nutritional and safety profile, other than therapeutic capability. Pharmaceutical and nutritional companies are aware of the changing trends which are due to the advantages of these compounds. Most of the nutraceuticals possess multiple therapeutic benefits.^[1] The present study devoted towards a better understanding of the nutraceuticals based on their pharmaceutical and therapeutic indications.

It should be noted that there might be a lot of confusion related to the terminology of nutraceuticals such as phytochemicals, pharmafoods, medical foods, functional foods, dietary supplements, designer foods, etc., There is thin dividing line in their interchangeable usage by different people on different occasions. Pharmaceuticals are mostly considered as medications which are used mainly to treat diseases, however nutraceuticals are the substances which are mostly considered to prevent diseases.^[2] This distinction between pharmaceuticals and nutraceuticals is very erroneous and superficial. Pharmaceuticals and nutraceuticals both can cure and prevent disease(s) however, only pharmaceuticals have governmental sanction.^[1] Pharmaceuticals are compounds which usually possess patent protection due to expensive testing. However, nutraceuticals do not need these testing documents.^[4]

Medical foods or medicinal foods are a specific category of therapeutic agents that are considered for the nutritional management of a specific disease. For example, medicinal foods are designed to manage inflammatory conditions, cancer, hyperhomocysteinemia, pancreatic exocrine insufficiency and other diseases.^[125,126] They also play a substantial protection against numerous age-related or chronic diseases. Herbal medicines

that are used as a nutrient are considered in this category.^[5,40]

Nutraceuticals found in many fruits and vegetables are responsible for health benefits. Due to these health benefits of nutraceuticals, they might regularly be taken to cure or reduce the risk factors such as high cholesterol, high blood pressure and diabetes.^[127,128] Some of the most popular nutraceutical products marketed today are botanicals such as ginseng, ginkgo biloba, St. John's wort and *Echinacea*.^[3]

The list of nutraceuticals being studied is changing continually and reflects ongoing market developments, research, and consumer interest. With rapidly increasing interest in the nutraceutical consumption, substantial researches are absolutely necessary to warrant the nutraceuticals usage safe and effective.

The mechanistic actions of nutraceuticals are not fully clear. However, they might be involved a wide variety of biological processes, including activation of signal transduction pathways, antioxidant defenses, gene expression, cell proliferation, differentiation and preservation of mitochondrial integrity.^[2]

CONCLUSIONS

Nutraceuticals might be defined as substances that have physiological benefits or provide protection against chronic diseases. Nutraceuticals may be used to improve health, delay the aging process, prevent chronic diseases, increase life expectancy, or support the structure or function of the body. Nowadays, nutraceuticals have received considerable interest due to potential nutritional, safety and therapeutic effects. Recent studies have shown promising results for these compounds in various complications. In the present review much effort has been devoted to provide their diseases modifying indications related to oxidative stress including allergy, Alzheimer, cardiovascular, cancer, diabetes, eye, immune, inflammatory and Parkinson's diseases as well as obesity.

REFERENCES

1. Kalra EK. Nutraceutical – Definition and introduction. *AAPS Pharm Sci* 2003;5:E25.
2. Zhao J. Nutraceuticals, Nutritional Therapy, Phytonutrients, and Phytotherapy for Improvement of Human Health: A Perspective on Plant Biotechnology Application, Bentham Science Publishers; 2007. Available from: <http://www.benthamscience.com/biot/samples/biot1-1/Zhao.pdf>. [Last accessed on 2012 Mar 24].
3. Chauhan B, Kumar G, Kalam N, Ansari SH. Current concepts and prospects of herbal nutraceutical: A review. *J Adv Pharm Technol Res* 2013;4:4-8.
4. Zeisel SH. Regulation of “nutraceuticals”. *Science* 1999;285:1853-5.
5. Hardy G. Nutraceuticals and functional foods: Introduction and meaning. *Nutrition* 2000;16:688-9.
6. Baradaran A, Madihi Y, Merrikhi A, Rafeian-Kopaei M, Nasri H. Serum lipoprotein (a) in diabetic patients with various renal function not yet on dialysis. *Pak J Med Sci* 2013;29 Suppl: 354-7.
7. Nasri H. Impact of diabetes mellitus on parathyroid hormone in hemodialysis patients. *J Parathyr Dis* 2013;1:9-11.
8. Madihi Y, Merrikhi A, Baradaran A, Rafeian-kopaei M, Shahinfard N, Ansari R, *et al.* Impact of sumac on postprandial high-fat oxidative stress. *Pak J Med Sci* 2013;29:340-5.
9. Setorki M, Rafeian-Kopaei M, Merrikhi A, Heidarian E, Shahinfard N, Ansari R, *et al.* Suppressive impact of *anethum graveolens* consumption on biochemical risk factors of atherosclerosis in hypercholesterolemic rabbits. *Int J Prev Med* 2013;4:889-95.
10. Khosravi-Boroujeni H, Mohammadifard N, Sarrafzadegan N, Sajjadi F, Maghroun M, Khosravi A, *et al.* Potato consumption and cardiovascular disease risk factors among Iranian population. *Int J Food Sci Nutr* 2012;63:913-20.
11. Khosravi-Boroujeni H, Sarrafzadegan N, Mohammadifard N, Sajjadi F, Maghroun M, Asgari S, *et al.* White rice consumption and CVD risk factors among Iranian population. *J Health Popul Nutr* 2013;31:252-61.
12. Shirzad H, Burton RC, Smart YC, Rafeian-kopaei M, Shirzad M. Natural cytotoxicity of NC-2+cells against the growth and metastasis of WEHI-164 fibrosarcoma. *Scand J Immunol* 2011;73:85-90.
13. Shirzad M, Kordyazdi R, Shahinfard N, Nikokar M. Does Royal Jelly affect tumor cells? *J HerbMed Pharmacol* 2013;2:45-8. Rafeian-Kopaei M, Baradaran A. Plants antioxidants: From laboratory to clinic. *J Nephrothol* 2013;2:152-3.
14. Akhlaghi M, Shabaniyan G, Rafeian-Kopaei M, Parvin N, Saadat M, Akhlaghi M. Citrus aurantium blossom and preoperative anxiety. *Rev Bras Anesthesiol* 2011;61:702-12.
15. Roohafza H, Sarrafzadegan N, Sadeghi M, Rafeian-Kopaei M, Sajjadi F, Khosravi-Boroujeni H.

- The association between stress levels and food consumption among Iranian population. *Arch Iran Med* 2013;16:145-8.
16. Baradaran A, Nasri H, Nematbakhsh M, Rafieian-Kopaei M. Antioxidant activity and preventive effect of aqueous leaf extract of *Aloe Vera* on gentamicin-induced nephrotoxicity in male Wistar rats. *Clin Ter* 2014;165:7-11.
 17. Nasri H, Tavakoli M, Ahmadi A, Baradaran A, Nematbakhsh M, Rafieian-Kopaei M. Ameliorative effect of melatonin against contrast media induced renal tubular cell injury. *Pak J Med Sci* 2014;30:261-5.
 18. Parsaei P, Karimi M, Asadi SY, Rafieian-Kopaei M. Bioactive components and preventive effect of green tea (*Camellia sinensis*) extract on post-laparotomy intra-abdominal adhesion in rats. *Int J Surg* 2013;11:811-5.
 19. Kafash-Farkhad N, Asadi-Samani M, Rafieian-Kopaei M. A review on phytochemistry and pharmacological effects of *Prangos ferulacea* (L.) Lindl. *Life Sci J* 2013;10:360-7.
 20. Mirhoseini M, Baradaran A, Rafieian-Kopaei M. Medicinal plants, diabetes mellitus and urgent needs. *J HerbMed Pharmacol* 2013;2:53-4.
 21. Akbari F, Ansari-Samani R, Karimi A, Mortazaei S, Shahinfard N, Rafieian-Kopaei M. Effect of turnip on glucose and lipid profiles of alloxan-induced diabetic rats. *Iran J Endocrinol Metab* 2013;14:1-7.
 22. Bahmani M, Vakili-Saatloo N, Maghsoudi R, Momtaz H, Saki K, Kazemi-Ghoshchi B, *et al.* A comparative study on the effect of ethanol extract of wild *Scrophularia deserti* and streptomycin on *Brucella melitensis*. *J HerbMed Pharmacol* 2013;2:17-20.
 23. Karimi A, Moradi MT, Saeedi M, Asgari S, Rafieian-Kopaei M. Antiviral activity of *Quercus persica* L.: High efficacy and low toxicity. *Adv Biomed Res* 2013;2:36.
 24. Rafieian-Kopaei M. Metformin and renal injury protection. *J Renal Inj Prev* 2013;2:91-2.
 25. Rafieian-Kopaei M, Baradaran A, Merrikhi A, Nematbakhsh M, Madihi Y, Nasri H. Efficacy of co-administration of garlic extract and metformin for prevention of gentamicin-renal toxicity in wistar rats: A Biochemical Study. *Int J Prev Med* 2013;4:258-64.
 26. Kiani MA, Khodadad A, Mohammadi S, Ghayour Mobarhan M, Saeidi M, Jafari SA, *et al.* Effect of peppermint on pediatrics' pain under endoscopic examination of the large bowel. *J HerbMed Pharmacol* 2013;2:41-4.
 27. Hosseini-asl K, Rafieian-kopaei M. Can patients with active duodenal ulcer fast Ramadan? *Am J Gastroenterol* 2002;97:2471-2.
 28. Grammatikos AP. The genetic and environmental basis of atopic diseases. *Ann Med* 2008;40:482-95.
 29. Kruger CL, Murphy M, DeFreitas Z, Pfannkuch F, Heimbach J. An innovative approach to the determination of safety for a dietary ingredient derived from a new source: Case study using a crystalline lutein product. *Food Chem Toxicol* 2002;40:1535-49.
 30. Glenville M. Nutritional supplements in pregnancy: Commercial push or evidence based? *Curr Opin Obstet Gynecol* 2006;18:642-7.
 31. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimers Dement* 2007;3:186-91.
 32. Rabiei Z, Rafieian-Kopaei M, Heidarian E, Saghaei E, Mokhtari S. Effects of *Zizyphus jujube* extract on memory and learning impairment induced by bilateral electric lesions of the nucleus basalis of Meynert in rat. *Neurochem Res* 2014;39:353-60.
 33. Rabiei Z, Rafieian-kopaei M, Heidarian E, Saghaei E, Mokhtari S. Effects of *Zizyphus jujube* extract on memory and learning impairment induced by bilateral electric lesions of the nucleus basalis of meynert in rat. *Neurochem Res* 2014;39:353-60.
 34. Rabiei Z, Rafieian-Kopaei M, Mokhtari S, Alibabaei Z, Shahrani M. The effect of pretreatment with different doses of *Lavandula officinalis* ethanolic extract on memory, learning and nociception. *Biomed Aging Pathol* 2013.
 35. Ghorbani A, Rafieian-Kopaei M, Nasri H. Lipoprotein (a): More than a bystander in the etiology of hypertension? A study on essential hypertensive patients not yet on treatment. *J Nephropathol* 2013;2:67-70.
 36. Behradmanesh S, Nasri P. Serum cholesterol and LDL-C in association with level of diastolic blood pressure in type 2 diabetic patients. *J Renal Inj Prev* 2012;1:23-6.
 37. Nasri H. Comment on: Serum cholesterol and LDL-C in association with level of diastolic blood pressure in type 2 diabetic patients. *J Renal Inj Prev* 2012;1:13-4.
 38. Asgary S, Keshvari M, Sahebkar A, Hashemi M, Rafieian-Kopaei M. Clinical investigation of the acute effects of pomegranate juice on blood pressure and endothelial function in hypertensive individuals. *ARYA Atheroscler* 2013;9:326-31.
 39. Nasri H, Sahinfard N, Rafieian M, Rafieian S, Shirzad M, Rafieian-kopaei M. Effects of *Allium sativum* on liver enzymes and atherosclerotic risk factors. *J HerbMed Pharmacol* 2013;2:23-8.
 40. Rafieian-Kopaei M. Medicinal plants and the human needs. *J HerbMed Pharmacol* 2012;1:1-2.
 41. Hu FB, Willett WC. Optimal diets for prevention of

- coronary heart disease. *JAMA* 2002;288:2569-78.
42. Behradmanesh S, Nasri H. Association of serum calcium with level of blood pressure in type 2 diabetic patients. *J Nephropathol* 2013;2:254-7.
 43. Hajivandi A, Amiri M. World kidney day 2014: Kidney disease and elderly. *J Parathyroid Dis* 2014;2:3-4.
 44. Shahbazian H. World diabetes day; 2013. *J Renal Inj Prev* 2013;2:123-4.
 45. Asgary S, Sahebkar A, Afshani M, Keshvari M, Haghjooyjavanmard SH, Rafieian-Kopaei M. Clinical evaluation of blood pressure lowering, endothelial function improving, hypolipidemic and anti-inflammatory effects of pomegranate juice in hypertensive subjects. *Phytother Res* 2013.
 46. Gharipour M, Ramezani MA, Sadeghi M, Khosravi A, Masjedi M, Khosravi-Boroujeni H, *et al.* Sex based levels of C-reactive protein and white blood cell count in subjects with metabolic syndrome: Isfahan Healthy Heart Program. *J Res Med Sci* 2013;18:467-72.
 47. Khosravi-Boroujeni H, Mohammadifard N, Sarrafzadegan N, Sajjadi F, Maghroun M, Khosravi A, *et al.* Potato consumption and cardiovascular disease risk factors among Iranian population. *Int J Food Sci Nutr* 2012;63:913-20.
 48. Khosravi-Boroujeni H, Sarrafzadegan N, Mohammadifard N, Sajjadi F, Maghroun M, Asgari S, *et al.* White rice consumption and CVD risk factors among Iranian population. *J Health Popul Nutr* 2013;31:252-61.
 49. Nasri H, Motamedi P, Dehghani N, Nasri P, Taheri Z, Kinani F, *et al.* Vitamin D and immune system. *J Renal Endocrinol* 2014;1:5-7.
 50. Asgary S, Kelishadi R, Rafieian-Kopaei M, Najafi S, Najafi M, Sahebkar A. Investigation of the lipid-modifying and antiinflammatory effects of *Cornus mas* L. supplementation on dyslipidemic children and adolescents. *Pediatr Cardiol* 2013;34:1729-35.
 51. Iriti M, Faoro F. Grape phytochemicals: A bouquet of old and new nutraceuticals for human health. *Med Hypotheses* 2006;67:833-8.
 52. Garg A, Garg S, Zaneveld LJ, Singla AK. Chemistry and pharmacology of the Citrus bioflavonoid hesperidin. *Phytother Res* 2001;15:655-69.
 53. Rafieian-Kopaei M, Baradaran A, Rafieian M. Plants antioxidants: From laboratory to clinic. *J Nephropathol* 2013;2:152-3.
 54. Ghayur MN, Gilani AH, Afridi MB, Houghton PJ. Cardiovascular effects of ginger aqueous extract and its phenolic constituents are mediated through multiple pathways. *Vascul Pharmacol* 2005;43:234-41.
 55. Bahmani M, Vakili-Saatloo N, Gholami-Ahangaran M, Karamati SA, Khalil-Banihabib E, Hajigholizadeh GH, *et al.* A comparison study on the anti-leech effects of onion (*Allium cepa* L) and ginger (*Zingiber officinale*) with levamisole and triclabendazole. *J HerbMed Pharmacol* 2013;2:1-3.
 56. Nasri H, Nematbakhsh M, Ghobadi SH, Ansari R, Shahinfard N, Rafieian-kopaei M. Preventive and curative effects of ginger extract against histopathologic changes of gentamicin-Induced tubular toxicity in rats. *Int J Prev Med* 2013;4:316-21.
 57. Gita C. Functional food attributes of n-3 polyunsaturated and conjugated linoleic acid enriched chicken eggs. *Curr Top Nutraceutical Res* 2004;2:113-21.
 58. Khosravi-Boroujeni H, Mohammadifard N, Sarrafzadegan N, Sajjadi F, Maghroun M, Khosravi A, *et al.* Potato consumption and cardiovascular disease risk factors among Iranian population. *Int J Food Sci Nutr* 2012;63:913-20.
 59. Li SQ, Zhang QH. Advances in the development of functional foods from buckwheat. *Crit Rev Food Sci Nutr* 2001;41:451-64.
 60. Hamid AA, Luan YS. Functional properties of dietary fiber prepared from defatted rice bran. *Food Chem* 2000;68:15-9.
 61. Rahimi Z, Mansouri Zaveleh O, Rahimi Z, Abbasi A. AT2R -1332 G: A polymorphism and diabetic nephropathy in type 2 diabetes mellitus patients. *J Renal Inj Prev* 2013;2:97-101.
 62. Nasri H. Adiponectin and kidney. *J Renal Endocrinol* 2014;1:2-3.
 63. Nasri H. On the occasion of the world diabetes day 2013; diabetes education and prevention; a nephrology point of view. *J Renal Inj Prev* 2013;2:31-2.
 64. Sidhu KS. Health benefits and potential risks related to consumption of fish or fish oil. *Regul Toxicol Pharmacol* 2003;38:336-44.
 65. Heidarian E, Rafieian-Kopaei M, Ashrafi K. The Effect of hydroalcoholic extract of *Allium latifolium* on the liver phosphatidate phosphatase and serum lipid profile in hyperlipidemic rats. *J Babol Univ Med Sci* 2013;15:37-46.
 66. Willis MS, Wians FH. The role of nutrition in preventing prostate cancer: A review of the proposed mechanism of action of various dietary substances. *Clin Chim Acta* 2003;330:57-83.
 67. Shirzad H, Kiani M, Shirzad M. Impacts of tomato extract on the mice fibrosarcoma cells. *J HerbMed Pharmacol* 2013;2:13-6.
 68. Stahl W, Sies H. Bioactivity and protective effects of natural carotenoids. *Biochim Biophys Acta* 2005;1740:101-7.
 69. Shirzad H, Tajji F, Rafieian-Kopaei M. Correlation between antioxidant activity of garlic extracts and

- WEHI-164 fibrosarcoma tumor growth in BALB/c mice. *J Med Food* 2011;14:969-74.
70. Shirzad H, Shahrani M, Rafieian-Kopaei M. Comparison of morphine and tramadol effects on phagocytic activity of mice peritoneal phagocytes *in vivo*. *Int Immunopharmacol* 2009;9:968-70.
 71. Limer JL, Speirs V. Phyto-oestrogens and breast cancer chemoprevention. *Breast Cancer Res* 2004;6:119-27.
 72. Thomasset SC, Berry DP, Garcea G, Marczylo T, Steward WP, Gescher AJ. Dietary polyphenolic phytochemicals – Promising cancer chemopreventive agents in humans? A review of their clinical properties. *Int J Cancer* 2007;120:451-8.
 73. Li H, Wang Z, Liu Y. Review in the studies on tannins activity of cancer prevention and anticancer. *Zhong Yao Cai* 2003;26:444-8.
 74. Nasri H, Sahinfard N, Rafieian M, Rafieian S, Shirzad M, Rafieian-kopaei M. Turmeric: A spice with multifunctional medicinal properties. *J HerbMed Pharmacol* 2014;3:5-8.
 75. Higdon JV, Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: Epidemiologic evidence and mechanistic basis. *Pharmacol Res* 2007;55:224-36.
 76. Tamadon MR, Baradaran A, Rafieian-Kopaei M. Antioxidant and kidney protection; differential impacts of single and whole natural antioxidants. *J Renal Inj Prev* 2014;3:41-2.
 51. Asadi-Samani M, Bahmani M, Rafieian-Kopaei M. The chemical composition, botanical characteristic and biological activities of *Borago officinalis*: A review. *Asian Pac J Trop Med* 2014;7:22-8.
 77. Ardalan MR, Rafieian-Kopaei M. Antioxidant supplementation in hypertension. *J Renal Inj Prev* 2014;3:39-40.
 78. Tavafi M. Diabetic nephropathy and antioxidants. *J Nephrothol* 2013;2:20-7.
 79. Baradaran A. Lipoprotein (a), type 2 diabetes and nephropathy; the mystery continues. *J Nephrothol* 2012;1:126-9.
 80. Rahimi-Madiseh M, Heidarian E, Rafieian-kopaei M. Biochemical components of *Berberis lycium* fruit and its effects on lipid profile in diabetic rats. *J HerbMed Pharmacol* 2014;3:15-9.
 81. Rafieian-Kopaei M, Nasri H. Ginger and diabetic nephropathy. *J Renal Inj Prev* 2013;2:9-10.
 82. Behradmanesh S, Derees F, Rafieian-Kopaei M. Effect of *Salvia officinalis* on diabetic patients. *J Renal Inj Prev* 2013;2:51-4.
 83. Brouns F. Soya isoflavones: A new and promising ingredient for the health foods sector. *Food Res Int* 2002;35:187-93.
 53. Ardalan MR, Rafieian-Kopaei M. Antioxidant supplementation in hypertension. *J Renal Inj Prev* 2014;3:39-40.
 84. Bahmani M, Zargaran A, Rafieian-Kopaei M, Saki M. Ethnobotanical study of medicinal plants used in the management of diabetes mellitus in the Urmia, Northwest Iran. *Asian Pac J Trop Med* 2014;7:348-54.
 85. Roshan B, Stanton RC. A story of microalbuminuria and diabetic nephropathy. *J Nephrothol* 2013;2:234-40.
 86. Tavafi M. Diabetic nephropathy and antioxidants. *J Nephrothol* 2013;2:20-7.
 87. Baradaran A. Lipoprotein (a), type 2 diabetes and nephropathy; the mystery continues. *J Nephrothol* 2012;1:126-9.
 88. Rahimi-Madiseh M, Heidarian E, Rafieian-kopaei M. Biochemical components of *Berberis lycium* fruit and its effects on lipid profile in diabetic rats. *J HerbMed Pharmacol* 2014;3:15-9.
 89. Rafieian-Kopaei M, Nasri H. Ginger and diabetic nephropathy. *J Renal Inj Prev* 2013;2:9-10.
 90. Tolouian R, T Hernandez G. Prediction of diabetic nephropathy: The need for a sweet biomarker. *J Nephrothol* 2013;2:4-5.
 91. Sirtori CR, Galli C. N-3 fatty acids and diabetes. *Biomed Pharmacother* 2002;56:397-406.
 92. Coleman MD, Eason RC, Bailey CJ. The therapeutic use of lipoic acid in diabetes: A current perspective. *Environ Toxicol Pharmacol* 2001;10:167-72.
 93. Singh B. Psyllium as therapeutic and drug delivery agent. *Int J Pharm* 2007;334:1-14.
 94. Momeni A. Serum uric acid and diabetic nephropathy. *J Renal Inj Prev* 2012;1:37-8.
 95. Nasri H, Rafieian-Kopaei M. Herbal medicine and diabetic kidney disease. *J Nephropharmacol* 2013;2:1-2.
 96. Kazemi S, Asgary S, Moshtaghian J, Rafieian M, Adelnia A, Shamsi F. Liver-protective effects of hydroalcoholic extract of *Allium hirtifolium* boiss. In rats with alloxan-induced diabetes mellitus. *ARYA Atheroscler* 2010;6:11-5.
 97. Gupta P, Andrew H, Kirschner BS, Guandalini S. Is lactobacillus GG helpful in children with Crohn's disease? Results of a preliminary, open-label study. *J Pediatr Gastroenterol Nutr* 2000;31:453-7.
 98. Fuller R. Probiotics in human medicine. *Gut* 1991;32:439-42.
 99. Rafieian-Kopaei M. Identification of medicinal plants affecting on headaches and migraines in Lorestan Province, West of Iran. *Asian Pac J Trop Med* 2014;7: 376-9.
 100. Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, *et al.* Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. *Science* 1997;275:218-20.

101. Rouhi-Broujeni A, Heidarian E, Darvishzadeh-Borojeni P, Rafeian-Kopaei M, Gharipour M. Lipid lowering activity of moringa pergerina seeds in rat: A comparison between the extract and atorvastatin. *Res J Biol Sci* 2013;8:150-4.
102. Nasri H, Ardalan MR, Rafeian-Kopaei R. On the occasion of world hypertension day 2014. *J Parathy Dis* 2014;2:19-20.
103. Caterson ID, Gill TP. Obesity: Epidemiology and possible prevention. *Best Pract Res Clin Endocrinol Metab* 2002;16:595-610.
104. Rubin SA, Levin ER. Clinical review 53: The endocrinology of vasoactive peptides: Synthesis to function. *J Clin Endocrinol Metab* 1994;78:6-10.
105. Boozer CN, Nasser JA, Heymsfield SB, Wang V, Chen G, Solomon JL. An herbal supplement containing Ma Huang-Guarana for weight loss: A randomized, double-blind trial. *Int J Obes Relat Metab Disord* 2001;25:316-24.
106. Rafeian-Kopaei M, Sewell RD. Newer antidepressants: Analgesia and relative monoamine reuptake inhibitory potency. *J Pharm Pharmacol* 1994;46 Suppl 2:1088.
107. Losso JN. Targeting excessive angiogenesis with functional foods and nutraceuticals. *Trends Food Sci Technol* 2003;14:455-68.
108. Anwar F, Latif S, Ashraf M, Gilani AH. Moringa oleifera: A food plant with multiple medicinal uses. *Phytother Res* 2007;21:17-25.
109. Baradaran A, Madihi Y, Merrikhi A, Rafeian-Kopaei M, Nematbakhsh M, Asgari A, *et al.* Nephrotoxicity of hydroalcoholic extract of *Teucrium polium* in Wistar rats. *Pak J Med Sci* 2013;29:329-33.
110. Ateyyat MA, Al-Mazra'awi M, Abu-Rjai T, Shatnawi MA. Aqueous extracts of some medicinal plants are as toxic as Imidacloprid to the sweet potato whitefly, *Bemisia tabaci*. *J Insect Sci* 2009;9:15.
111. Baradaran A. Beyond mineral metabolism, the bright immunomodulatory effect of vitamin D in renal disease. *J Nephroarmacol* 2012;1:17-8.
112. Nasri H, Behradmanesh S, Ahmadi A, Rafeian-Kopaei M. Impact of oral vitamin D (cholecalciferol) replacement therapy on blood pressure in type 2 diabetes patients; a randomized, double-blind, placebo controlled clinical trial. *J Nephropathol* 2014;3:29-33.
113. Nasri H, Shirzad H. Toxicity and safety of medicinal plants. *J HerbMed Pharmacol* 2013;2:21-2.
114. Heidarian E, Rafeian-Kopaei M. Protective effect of artichoke (*Cynara scolymus*) leaf extract against lead toxicity in rat. *Pharm Biol* 2013;51:1104-9.
115. Nasri H, Ahmadi A, Baradaran A, Nasri P, Hajian S, Pour-Arian A, *et al.* A biochemical study on ameliorative effect of green tea (*Camellia sinensis*) extract against contrast media induced acute kidney injury. *J Renal Inj Prev* 2014;3:47-9.
116. Moussavi MR. Osteoporosis in chronic kidney disease; a mini-review on current knowledge. *J Parathy Dis* 2013;1:5-8.
117. Rafeian-Kopaei M, Baradaran A, Rafeian M. Oxidative stress and the paradoxical effects of antioxidants. *J Res Med Sci* 2013;18:629.
118. Nasri H, Rafeian-Kopaei M. Oxidative stress and aging prevention. *Int J Prev Med* 2013;4:1101-2.
119. Rafeian-Kopaei M, Baradaran A, Rafeian M. Plants antioxidants: From laboratory to clinic. *J Nephropathol* 2013;2:152-3.
120. Heidarian E, Rafeian-Kopaei M. Effect of silymarin on liver phosphatidate phosphohydrolase in hyperlipidemic rats. *Biosci Res* 2012;9:59-67.
121. Hajivandi A, Amiri M. World Kidney Day 2014: Kidney disease and elderly. *J Parathy Dis* 2014;2:3-4.
122. Nasri H, Rafeian-Kopaei M. Protective effects of herbal antioxidants on diabetic kidney disease. *J Res Med Sci* 2014;19:82-3.
123. Nasri H, Rafeian-Kopaei M. Tubular kidney protection by antioxidants. *Iran J Public Health* 2013;42:1194-6.
124. Rafeian-Kopaei M, Beyki A, Nasri H. Antioxidant therapy in hemodialysis patients. *J Isfahan Med Sch* 2013;31:1-4.
125. Shirzad H, Burton RC, Smart YC, Rafeian-kopaei M, Shirzad M. Natural cytotoxicity of NC-2+cells against the growth and metastasis of WEHI-164 fibrosarcoma. *Scand J Immunol* 2011;73:85-90.
126. Azadmehr A, Hajiaghaee R, Afshari A, Amirghofran Z, Rafeian-Kopaei M, Darani YH, Shirzad H. Evaluation of *in vivo* immune response activity and *in vitro* anti-cancer effect by *Scrophularia megalantha*. *J Med Plants Res* 2011;5:2365-8.
127. Gharipour M, Ramezani MA, Sadeghi M, Khosravi A, Masjedi M, Khosravi-Boroujeni H, *et al.* Sex based levels of C-reactive protein and white blood cell count in subjects with metabolic syndrome: Isfahan Healthy Heart Program. *J Res Med Sci* 2013;18:467-72.
128. Khosravi-Boroujeni H, Mohammadifard N, Sarrafzadegan N, Sajjadi F, Maghroun M, Khosravi A, *et al.* Potato consumption and cardiovascular disease risk factors among Iranian population. *Int J Food Sci Nutr* 2012;63:913-20.

Source of Support: Nil, **Conflict of Interest:** None declared.