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REVIEW ARTICLE

A Review on the Role of Nutraceuticals as Simple as Se^{2+} to Complex Organic Molecules Such as Glycyrrhizin That Prevent as Well as Cure Diseases

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Abstract Nutraceuticals are nutritional medicines which are present in edible food items. Most of them are anti-oxidants with various other biological properties viz, anti inflammatory, anti atherogenic, anticancer, anti viral, anti aging properties etc. They are as simple as minerals like Se^{2+} to complex organic molecules such as glycyrrhizin (Ca^{2+}, K^{+} salts of glycyrrhizic acid). They can prevent as well as cure various diseases. Most of the medical people are not aware of the importance of the nutraceuticals as such matters are not part of their text books. Many still think that vitamins are the major nutritional medicines. Actually other dietary principles like terpenes, carotenes, phytosterols, polyphenols, flavanoids, di and poly sulphides, their sulfoxides and their precursor amino acids are necessary to scavenge free radicals in the body which are reactive oxygen species to protect and maintain the vitamin levels in the body. They down regulate the activities of those enzymes which are increased in diseases and they increase those that remove oxidants and detoxify carcinogens. They are immune boosters too. Recently glucosinolates, non toxic alkaloids, certain proteins and even fiber are included in the list of nutraceuticals.

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Introduction

Dr. Stephen De Felice first coined the term nutraceutical in 1989 while he was presenting a paper in a conference, and he defined the nutraceuticals as "food or parts of food that provide medical or health benefit including the prevention and treatment of diseases" [1]. The term functional food is also used to refer nutraceuticals/nutritional medicines. In the states of Canada and Great Britain, a functional food, but a nutraceutical is in an isolated form or concentrated form. The part of the word "ceutical" is used because they are medicines as well as nutritional factors [2]. In our opinion the term nutraceutical should be essentially used to represent chemically identified compound with medicinal effects and also naturally present in our diet that could be isolated anytime. When one or more nutraceuticals are present in a diet or items such as edible fiber (e.g., rice bran) is present in the same or it can be added to it that can be simply termed as a functional food. The true nutraceuticals are mentioned in Table 1 along with newly added items such as vitamins, minerals and fibre. One can agree to the inclusion of items such as vitamins in the class of nutraceuticals even though they have properties far above and different from true nutraceuticals, e.g., vitamin A becomes the part of rhodopsin in retina, other fat soluble vitamins D, E and K have different roles from nutraceuticals but all of them prevent or cure diseases. Thiamine becomes the part of thiamine pyrophosphate (TPP) that is the coenzyme for pyruvate decarboxylase. Likewise all B vitamins function as parts of different co-enzymes. However all of them prevent or cure diseases. Traditionally

each vitamin has got its own identity, status and nutritional importance along with carbohydrates, proteins and minerals. If the vitamins are strictly included in the class of nutraceuticals many doctors shall continue to speak and write on vitamins as the major members of the nutraceuticals as at present what they are doing. This will enable them to ignore a dozen of other nutritional medicines which are true nutraceuticals as given in Table 1. The senior author came across many articles written by doctors who think vitamins are the major nutraceuticals and one need not worry about a group of nutritional medicines present in various food items along with vitamins. But this will sideline the role of true nutraceuticals about which the biochemists aim to advocate and propagate in future for the health and welfare of humans along with all other five nutritional items mentioned above. Actually the true nutraceuticals are as essential as the vitamins to prevent or cure many diseases e.g., cancer of all types, cardiovascular diseases, hepato toxicity, arthritis, radiation damages, hyper cholesterolemia, oxidative damages to various tissues, cataract, allergies, inflammation, hypertension, oestrogen over production, platelet aggregation, bacterial and viral related infections, vitamin A and E destruction in blood, destruction of antioxidant enzymes such as catalase, SOD, glutathione peroxidase, glutathione reductase etc. and for detoxification of heavy metals. One can see the differences in the roles of vitamins and true nutraceuticals which were highlighted by Marcia Zimmerman in her paper [3]. Therefore the readers may not ignore the use of food items containing true nutraceuticals with or without vitamins.

In the new table minerals are also included in the list of nutraceuticals. They function as co-factors for various enzyme actions, e.g., salivary amylase requires chloride ions, glutathione peroxidase requires Se^{2+}, catalase requires iron and arginase requires manganese. More over iron deficiency leads to anemia, copper deficiency leads to Wilson's disease and iodine deficiency leads to goiter. Thus they also prevent or cure many diseases. Therefore in the larger sense fiber and minerals are justifiably included in the Table 1, but if we want to include vitamins in the same table a foot note should be added that they alone will not carry out all the functions attributed to nutraceuticals on the contrary vitamins may be destroyed in the body by oxidants in the absence of antioxidant nutraceuticals. We have to keep in our mind that nutraceuticals are those nutritional medicines not ever thought of by the doctors or biochemists in the teaching field for a long time because so far no mention is made about them in their text books and each one preaches and writes in his/her own way. Therefore we have to reckon with the importance of this article. Only a few research workers do investigation on them and propagate their use. Therefore we are writing a review mainly on this part of research on the role of chemically identified nutraceuticals apart from all other functional foods.

Many of these new products which find their origin in plant kingdom are being promoted to treat various disease states. This is an obvious choice, as many plants produce secondary metabolites such as alkaloids, tannins (condensed polyphenols) etc. to protect themselves from oxidants and bacterial/viral infections. These constituents may be useful in the treatment of human infections that lead to body ailments affecting heart, lungs, liver, alimentary tracts, eyes and bones. Besides the above action, nutraceuticals act as agents with various properties as mentioned below.

Antioxidant Activity

Nutraceuticals have been reported to possess potent anti oxidant activity. The chemo protective action of epigallocatechin, epigallocatechin gallate (EGCG), epicatechin gallate (ECG) etc. (see Table 2) are due to their inhibiting action on enzymes such as lipoxygenase and cyclooxygenase [4]. EGCG, ECG inducing ARE-mediated gene expression through the activation of MAPK proteins [5], (ERK, JNK and p38). Another polyphenol Curcumin of turmeric inhibits mitochondrial proton F0F1-ATPase/ATP synthase [6], increasing the expression of GSTP1 by activating ARE and Nrf2, increasing CAT, SOD activity and heat shock proteins 70 expression, decreasing the activity of iNOS, decreasing malondialdehyde (MDA), NO(2)(−) + NO(3)(−) and myeloperoxidase (MPO) level and serum transaminase concentration explain the mode of action of polyphenols [7].

The following findings also explains the mode of action of various polyphenols. Ellagic acid, Gallic acid and Corilagin inhibits tyrosinase, xanthine oxidase and the formation of superoxide radical [8]. Caffeic acid (+)-catechin inhibits peroxynitrite-mediated oxidation of dopamine [9]. Quercetin prevents lactate dehydrogenase (LDH) leakage and increase the antioxidant enzymes such as SOD, CAT, GPx, and GR activity along with GSH content in tissues [10]. Quercetin also decrease MDA and lipoperoxidation, increasing Cu/Zn SOD and GPx mRNA [11]. Further it also increase the expression and activity of NADPH: quinone oxidoreductase-1 (NQO1) [12] and enhance γ-glutamylcysteine synthetase (γ-GCS) [13]. Resveratrol inhibits O-acetyltransferase and sulfotransferase activities preventing the oxidative DNA damage [14]. Such action of resveratrol inhibit the production of H2O2 and MPO activity, increase GSH levels and SOD activities as well as decreasing the levels of MPO and oxidized GR [15]. (−)-Epicatechin procyanidin EGCG, ECG etc. inhibit recombinant human platelet 12-lipoxygenase and 15-lipoxygenase [16].

Table 1 Classification of nutraceuticals, sources and potential benefits

Class	Source	Potential benefits
1. Carotenoids		
Beta-carotene	Carrots, various fruits	Neutralizes free radicals, which may damage cells; bolsters cellular antioxidant defenses
Lycopene	Tomatoes and processed tomato products	May contribute to maintenance of prostate health
2. Dietary fiber		
Insoluble fiber	Wheat bran	May contribute to maintenance of a healthy digestive tract, hypocholesterolemic
Soluble fiber	Pectins of fruits e.g. apple	May contribute to maintenance of a healthy digestive tract, hypocholesterolemic
3. Fatty acids		
Monosaturated fatty acids	Tree nuts	May reduce risk of coronary heart disease
4. Flavonoids		
Flavonols	Onions, apples, tea, broccoli	Neutralize free radicals, which may damage cells; bolster cellular antioxidant defenses
5. Isothiocyanates		
Sulforaphane	Cauliflower, broccoli, cabbage, kale, horseradish	May enhance detoxification of undesirable compounds and bolster cellular antioxidant defenses
6. Phenols		
Caffeic acid, ferulic acid their derivatives and related compounds	Apples, pears, citrus fruits, some vegetables, turmeric, Grapes, tea, gooseberries	May booster cellular antioxidant defenses; may contribute to maintenance of vision and heart health
7. Plant stanols/sterols		
Stanol/sterol esters	Fortified table spreads, stanol ester dietary supplements	May reduce risk of coronary heart disease
8. Polyols		
Sugar alcohols (xylitol, sorbitol, mannitol, lactitol)	Some chewing gums and other food applications	May reduce risk of dental caries (cavities)
9. Prebiotics/probiotics		
Lactobacilli, bifidobacteria	Yogurt, other dairy and nondairy applications	May improve gastrointestinal health and systematic immunity
10. Phytoestrogens		
Isoflavones (daidzein, genistein)	Soybeans and soy-based foods	May contribute to maintenance of bone health, healthy brain and immune functions; for women, maintenance of menopausal health
11. Soy protein		
Soy protein	Soybeans and soy-based foods	May reduce risk of coronary heart disease
12. Sulfides/thiols		
a. Dithiolthiones		
b. Allyl sulphoxy aminoacids	Cruciferous vegetables	May contribute to maintenance of healthy immune function
	Allium vegetables	
c. Allicin, Ajoen	Do (crushed forms)	Do
13. Tocotrienol (isoprenoids)	Grains, palm oil	Anticancer (breast cancer), promotes cardiovascular health
14. Saponins	Soyabeans	Lowers cholesterol level, anticancer activity (colon)
15. Glucosinolates	Cruciferous vegetables	Anticancer (bladder cancer)
16. Alkaloids		
Quinine	Cinchona	Antimalarial
Tropane alkaloids	Solanaceous members: deadly night shade datura	In treatment of heart ailments
Morphine	Opium poppy	Anti depressent, pain killer
Ergot alkaloids	Fungus: *Claviceps purpurea*	Abortifacient
Vincristine	periwinkle	Antineoplastic

Table 1 continued

Class	Source	Potential benefits
Vinblastine	Periwinkle	Antineoplastic
Coumarin	Fenugreek	Hypoglycemic
Scopoletin	Fenugreek	Hypoglycemic
Fenugreekine	Fenugreek	Hypoglycemic
Trigonelliine	Fenugreek	Hypoglycemic
17. Non carotenoid terpenoids		
Perillyl alcohol	Cherries and mints	Anticancer
Saponins	Legumes (chicks, peas, fenugreek)	Reduces cholesterol levels
Terpenol	Carrots	Anticancer
Terpene limonoids	Peels and membrane of citrus fruit	Anticarcinogenic
18. Anthraquinones		
Senna	Legumes and pulses	Purgative
Barbaloin	Aloe	Laxative, helmintic
19. Terpenes		
Menthol	Plants of mint family	Topical pain reliever and antipyretic
Borneol	Pine oil	Disinfectant
Santonin	Worm wood	Photosensitizer
Gossypol	Cotton	Contraceptive

Anti Inflammatory Effects

Inflammation is the response of body tissues to injury or irritation, characterized by pain and swelling and redness and heat. Oxidative stress induced inflammation is mediated by the activation of NF-κB and AP-1. It affects a wide variety of cellular signaling processes leading to generation of inflammatory mediators and chromatin remodeling [17]. The latter allows expression of pro-inflammatory genes such as interleukin-1beta (IL-1β), IL-8, tumor necrotic factor alpha (TNF-a), and inducible nitric oxide synthase (iNOS) [18]. The undesired effects of oxidative stress have been found to be controlled by the antioxidant and/or anti-inflammatory effects of nutraceuticals. Catechins can inhibit the release of some allergic reactions factors such as leucotrienes/prostaglandins by modifying activities of multiple enzymes taking part in inflammatory states of the human body [19]. Procyanidins inhibit transcription and secretion of IL-1β in peripheral blood mononuclear cells [20]. EGCG, ECG downregulate CD11b expression, attenuating adhesion and migration of peripheral blood CD8+ T cells in peripheral blood CD8+ T cells [21]. Resveratrol inhibits stimulation of caspase-3 and cleavage of PARP induced by IL-1β in human articular chondrocytes and suppressess the expression of iNOS mRNA and protein by inhibiting the activation of NF-κB and inhibits NO generation [22]. The flavanoids apigenin, luteolin and quercetin block the expression of intercellular adhesion molecule-1 (ICAM-1), VCAM-1, and E-selectin inhibits prostaglandin synthesis and IL-6, 8 productions in human endothelial cells [23].

The above nutraceuticals also inhibits NO production and iNOS protein expression [24]. Curcumin decreases MPO activity and TNF-α on chronic colitis reducing nitrites levels and the activation of p38 MAPK downregulating COX-2 and iNOS expression [17], Upregulating MAP kinase phosphatase-5 [25]. It also suppresses the induction of COX-2 and Inos inhibiting the expression of ICAM-1 and MCP-1, Suppressing the Janus kinase (JAK)-STAT via activation of Src homology 2 domain-containing protein tyrosine phosphatases (SHP-2) [26].

Anti Diabetic Activity

Flavonoids, especially quercetin, has been reported to possess antidiabetic activity. Quercetin stimulates insulin release and enhances Ca^{2+} uptake from isolated islets cell which suggest a role for flavonoids in noninsulin-dependent diabetes [27]. Curcumin inhibits diabetes-induced elevation in the levels of IL-1β, VEGF, and NF-κB, decreasing oxidatively modified DNA and nitrotyrosine [28]. EGCG, ECG, (−)-Epigallochatechin inhibit sodium dependent glucose transporter and sodium-free glucose transporter [29]. Quercetin reduces blood glucose levels inhibiting sodium-dependent vitamin C transporter 1 (SVCT1) and GLUT2 [30]. Mangiferin inhibits sucrase, isomaltase, and aldose reductase [31].

Table 2 Structure, action and sources of nutraceuticals

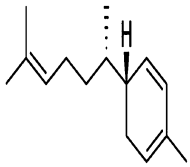
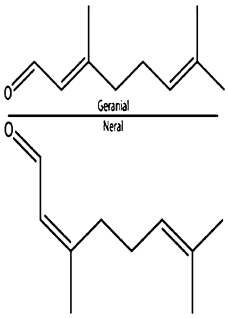
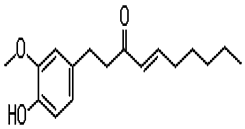
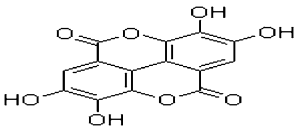
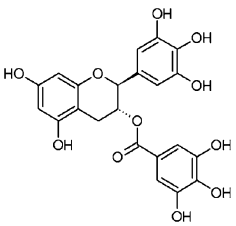
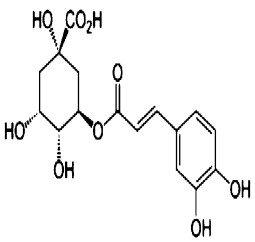
Name and structure	Neutraceutical action	Sources	References
1. Zingiberene 	Heart diseases, clotting defects, anti platelet aggregation	Ginger	[64]
2. Citral 	Cancers, induction of apoptosis	Lemon grass	[65]
3. 6-Shogaol 	CHD, cancers, anti platelet aggregations and apoptosis	Ginger	[66]
4. Ellagic acid 	Block pro carcinogens, reduce esophageal, and colon cancers and induction of apoptosis	Strawberries, raspberries, pomegranate	[67]
5. Ellagi tannins condensed polyphenols	Anti carcinogenic, induction of apoptosis	Strawberries, raspberries, pomegranate	[67]
6. Catechin, gallocatechin Caffeic acid, anthocyanins Gallocatechin gallate 	CHD and cancer induction of apoptosis	Strawberries, raspberries, pomegranate	[18]
7. Chlorogenic acid 	Anticarcinogenic induction of apoptosis	Blueberries, tomatoes, coffee, tender garlic leaves	[68]

Table 2 continued

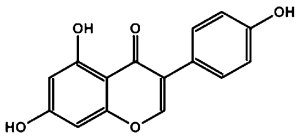
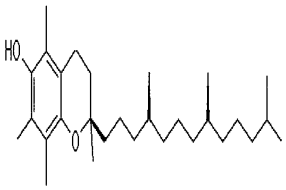
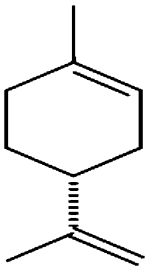
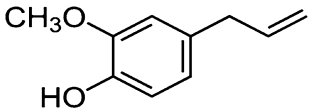
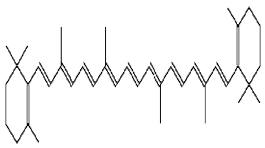
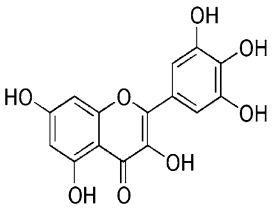
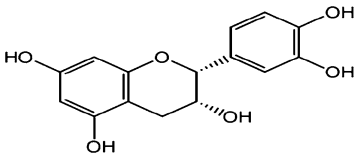
Name and structure	Neutraceutical action	Sources	References
8. Genistein 	Prevent breast and prostate cancer induction of apoptosis	Soyabean	[69]
9. Vitamin E 	Prevent conversion of nitrates and nitrites to nitrosamines (carcinogens)	Germinated seeds, fish oils	[70]
10. Limonene 	CHD, cancer induction of apoptosis	Black pepper, carda	[71]
11. Eugenol 	CHD, cancer induction of apoptosis, anti microbial	Clove, all spice, ginger	[72]
12. β-Carotens 	CHD, cancer, induction of apoptosis	Carrots, tomatoes, apricot, sweet potatoes, yellow fruit, pumpkins	[73]
13. Myricetin 	Hepato protective, anti viral	Nutmeg, black pepper, carrots, parsley	[74]
14. Epi catechin 	CHD, cancer, induction of apoptosis	Tea, beans	[48]
15. Epigallocatechin (a tannin polyphenol with 5 hydroxyl group)	Cancer and CHD, induction of apoptosis	Red wine, apple, cherry	[75]

Table 2 continued

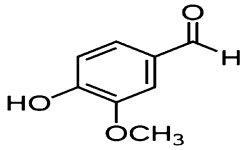
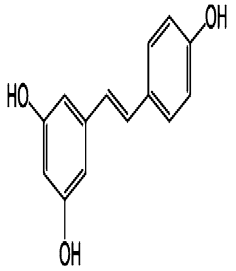
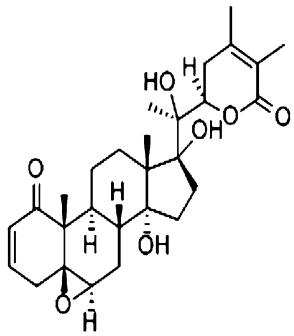
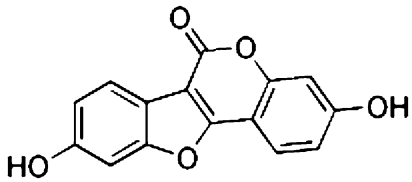
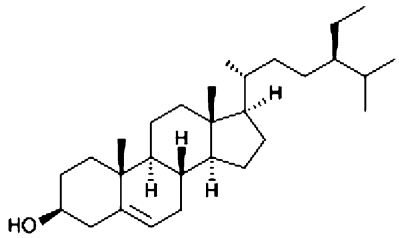
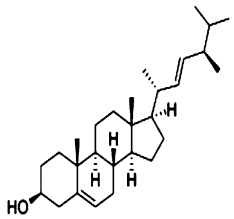
Name and structure	Neutraceutical action	Sources	References
16. Vanillin 	Induction of apoptosis	Vanilla	[76]
17. Resveratrol 	CHD	Red wine	[77]
18. WithaperuvinE 	Anti lipid peroxidation activity	Roots of *physalis peruvianna* L.	[78]
19. Coumestrol 	Prevents breast and prostate cancer by preventing estradiol to its receptors	Legumes, soya beans, spinach	[79]
20. Beta-sistosterol 	Reduces blood cholesterol level, plays some role in the possible effect of herbal therapy in benign prostatic hypertrophy	Rice bran, wheat germ, corn oil, pumpkins and soyabean	[80]
21. Brassicasterol 	Hypocholesterolemic	Algae, oil seed rape	[81]

Table 2 continued

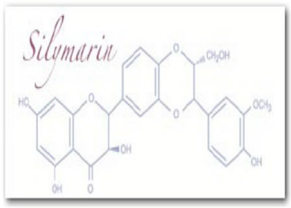
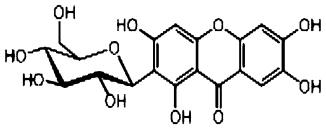
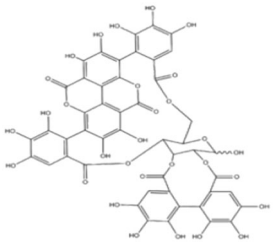
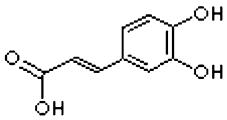
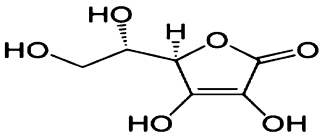
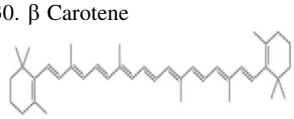
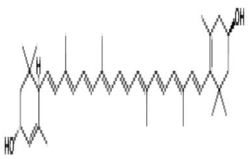
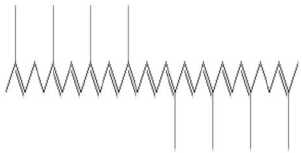
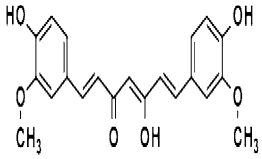
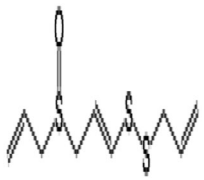
Name and structure	Neutraceutical action	Sources	References
22. Silymarin 	Protective against skin cancer	Artichokes and milk thistle	[82]
23. Mangiferin 	Protects DNA from radiation	Mango	[31]
24. Glycyrrhizic acid	Protects DNA from radiation	*Glycyrrhiza glabra*	[83]
25. Punicalogin 	Protects DNA from radiation	Pomegranate	[84]
26. Caffeicacid, anthocyanins 	CHD	Coffee seeds	[85]
27. Ellagic acid and Phyllemblic acid (polyphenols)	B(ap)induced cancers, lung and stomach cancer	Amla (gooseberry)	[37]
28. Vitamin C 	CHD, cataract, cold cit	Amla, cabbage, cauliflower, broccoli, potatoes, black, pepper, tomatoes	[86]
29. Vitamin E	CHD, prostate cancer, Alzheimer's disease	Eggs, vegetable oils, ground nuts, oats	
30. β Carotene 	CHD, lung cancer	Carrot, tomatoes, sweet potatoes, apricot, papaya	[87]
31. Lutein 	Eye diseases	Dark coloured vegetables, leaves, orange, spinach	[88]

Table 2 continued

Name and structure	Neutraceutical action	Sources	References
32. Lycopene 	Anti tumor, induced apoptosis	Tomatoes	[89]
33. Curcumin 	Antitumor, immuno stimulant, induction of apoptosis	Turmeric	[90]
34. Ajoene 	Antitumor, immuno stimulant, induction of apoptosis, antiplatelet aggregation	Garlic and its oils	[91]
35. Allicin type compounds	Antitumor, Immuno stimulant, Induction of apoptosis, detoxification of heavy metal poisoning e.g., lead, cadmium, arsenic, anti viral action e.g., chikungunya, anti bacterial action e.g., jaundice	Garlic, onion and their oils	[35, 38, 40, 41, 91, 92]

Hepato Protective Activity

Proanthocyanidin increases the expression of Bcl-xL attenuating acetaminophen-induced hepatic DNA damage, apoptotic and necrotic cell death of liver cells [32]. Daidzein ameliorates the D-galactosamine-induced increase in malondialdehyde-protein adducts and cytosolic SOD activities in liver [33]. Genistein reduces experimental liver damage caused by CCl_4 by preventing lipid peroxidation and strengthening antioxidant systems [34]. Similar effects were found by our group using leucopelargonin and garlic oil in CCl_4 treated rats [35].

Immuno Boosters

Nutraceuticals have a protective effect on immune cell functions. They could increase macrophage chemotaxis, phagocytosis, microbicidal activity, and natural killer function, and increase lymphoproliferation. Curcumin could prevent tumor-induced T cell apoptosis by down-regulating Bax level and augmenting Bcl-2 expression and restore cytokine-dependent Jak-3/Stat-5a signaling pathway in T cells of tumor bearer [36]. Caffeic acid, ellagic acid and ferulic acid could inhibit apoptosis through the Bcl-2 independent mechanism in normal human peripheral blood mononuclear cells [37]. Garlic containing food complex also stimulates immune response and prevent viral fevers such as chikungunya [38]. Garlic oil and its sulphides stimulates B-cells, T-cells, Nk cells and macrophages in various system [39, 40].

Effects on Cardio Vascular System

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 [41]. Tea may display a protective role against cardiovascular diseases via a number of different mechanisms, one of which are its antioxidative properties. As a result of LDL cholesterol oxidation, monocytes are recruited to the arterial wall and monocyte-derived macrophages accumulate the excessive amount of oxidised LDL and become lipid laden foam cell [42]. One of the underlying mechanisms by which EGCG affects lipid metabolism is by interfering with the micellar solubilization of cholesterol in the digestive tract, which then in turn decreased cholesterol absorption [43].

Antithrombogenic Effects

Platelet aggregation plays a pivotal role in the physiology of thrombotic diseases. Activated platelets adhering to vascular endothelium generate lipid peroxides and oxygen free radicals which inhibit the endothelial formation of prostacyclin and nitrous oxide. Selected flavonoids such as quercetin, kaempferol and myricetin were shown to be effective inhibitors of platelet aggregation. Flavonols are particularly antithrombotic because they directly scavenge free radicals, thereby maintaining proper concentration of endothelial prostacyclin and nitric oxide [44].

Anti Atherosclerotic Effects

Studies have shown that nutraceuticals exerted anti-atherosclerosis and cardioprotection. Resveratrol suppresses the expression and activity of COX-2 suppressing activation of AP-1 [45]. It also Inhibits the expression and binding activity of the monocyte chemotactic protein-1 (MCP-1) receptor, CCchemokine receptor-2 (CCR2) [46]. Moreover it increases NO and NOS levels increasing intracellular cyclc GMP (cGMP) level and decreasing atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) levels [47]. (−)-Epicatechin inhibits 7β-OH-cholesterol formation in endothelial cells [48]. Proanthocyanidin reduces cardiomyocyte apoptosis by inhibiting ischemia–reperfusion-induced activation of JNK-1 and c-Jun [49] Polyphenolic compounds may reduce the arterial pressure in rats and enhance the vasorelaxant process. The rapid uptake of oxidatively-modified LDL via a scavenger receptor leads to the formation of foam cells. Flavonoids may directly scavenge some radical species by acting as a chain breaking antioxidant [50]. Phyto sterol competes with dietary cholesterol for uptake in the intestines. They have demonstrated the ability to block the uptake of cholesterol and facilitate its excretion from the body. Cholesterol has long been implicated as a significant risk factor in cardiovascular disease.

Anti Microbial Activity

Green tea catechins can act as inhibitors of some enzymes important for microorganisms. Inhibitory effect of green tea catechins on cysteine proteinases (Arg-gingipain and Lysgingipain) in *Porphyromonas gingivalis* was observed by Okamoto et al. [51]. EGCG was effective in inhibiting protein tyrosine phosphatase (PTPase) [52].

Anti Bacterial Activity

Reactive oxygen species (ROS) are generated by catechin for destroying bacteria. EGCG reacted with the dissolved oxygen in aqueous solution, resulting in the generation of hydrogen peroxide [53]. These authors suggested that the recycling redox reactions between Cu(II) and Cu(I), involving catechins and hydrogen peroxide on the cell surface, must be of significance to the mechanism of bacteriocidal action.

Anti Cancer Effects

Programmed cell death has received phenomenal attention in the past few years. Apoptosis was coined to describe programmed cell death, a process involved in cell death involved in cellular development and aging distinct from necrosis. Apoptotic cells die by design whereas necrotic cells die by accidental and lethal injury. Apoptosis involves characteristic changes within the nucleus. Endonucleases are activated and begin to degrade the nuclear DNA in the presence of some nutraceuticals. Ajoen, Allicin, Alliumin, Allixin Organo-sulphur compounds leads to apoptosis through activation of caspases, release of cytochrome C from mitochondria, effect on p53, activation of Bax and down regulation of Bcl-2 [54, 55].

The mechanism of curcumin induced apoptosis has been studied by Deeb et al. [56] in LNCaP prostate cancer cells, where curcumin induces apoptosis by enhancing tumour necrosis factor related apoptosis inducing ligand (TRAIL). Another study by Woo et al. [57] using Caki cells indicates that curcumin induces apoptosis through down regulation of Bcl-xL and IAp, release of cytochrome c and inhibition of AKt, which are markedly blocked by N-acetyl cysteine, indicating the role of ROS in curcumin induced cell death. Curcumin has been shown to inhibit the activation of NF-kB by inhibiting the phosphorylation and degradation of IkBα [58]. Silymarin, Silibinin release of cytochrome C from mitochondria, activation of caspases, increase of p53, mitochondrial membrane potential changes, G1 cell cycle arrest, G2/M arrest [59, 60].

By this mechanism DNA is degraded into fragments, the size of oligonucleosomes and larger fragments. So the search for therapeutic agents targeting cellular apoptotic components is regarded as a promising feature in the therapeutic treatment of a wide variety of diseases. It is now known that mitochondria play a central regulatory role in apoptosis, particularly through cytochrome C pathway. Mitochondria and radical species are intimately involved in the apoptosis. Increased oxidative stress from ROS and RNS changes the cellular redox potentials, depletes glutathione, and decreases reducing equivalents like NADP and NADPH. These intracellular changes are sufficient to induce the formation of mitochondrial permeability transition pores, leading to the subsequent release of cytochrome c and the activation of the caspases cascade [61]. Epicatechins act as anticancerogens due to the activation of the second phase detoxication enzymes which accelerate the removal of activated chemical cancerogenes from cells [62].

Effect on Central Nervous System

Recently, there has been considerable interest in the neuroprotective effects of nutraceuticals. Hydroxytyrosol attenuating Fe^{2+}- and NO-induced cytotoxicity, increasing cellular ATP, reducing lipid peroxidation, hyperpolarizing basal mitochondrial membrane potential. Resveratrol stimulating AMP kinase activity, preventing fibrosis, NF-κB activation and TGF-β increases induced by chronic CCl_4 treatment, activating the phosphorylation of PKC protecting dopaminergic neurons activating sirtuin family of NAD-dependent histone deacetylases secreting transthyretin to prevent Aβ aggregation [63].

Various classifications of nutraceuticals are now adopted depending upon their uses and their sources.

Classification

Since the introduction of nutraceutical is very simple and risk free many of the multinational pharmaceutical firms are switching over to nutraceutical manufacturing. The old proverb; "an apple a day will keep the doctor a day". This was a statement included in an article published in "Role of dietary fibers and nutraceutical in preventing diseases" by Dr. Bhaskaran former principal of Pariyaram Medical College, Kannur. He further stated that consumers are turning increasingly to food supplements to improve the well being when pharmaceuticals failed. A statement from Dr. Bhaskaran presently the HOD Pharmacology at Pariyaram Medical College prompted as to make a review on all available nutraceuticals screened by various workers the world over.

In United States of America, Japan and Europe rely increasingly on nutraceuticals, to improve their health, regulators and lawmakers are reacting to develop appropriate regulations; given that most health claims accompanying these products are supported by little or no research. Nutraceuticals now include a wide variety of products, such as Echinacea, St. John's wort; oil from fish, garlic and flaxseeds, glucosamine and chondroitin, calcium-fortified juices and plant sterols. Iceland's largest diary company recently introduced the world's first milk to lower high blood pressure. In United States alone six out of ten consumers take some type of food supplement and 30–40 % take herbal supplement. Even some physicians are recommending natural products before prescribing pharmaceuticals. The trend also reflects the growth of a new paradigm "selfcare".

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