

# Nutraceuticals and Nutraceutical Supplementation Criteria in Cancer: A Literature Survey

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**Abstract:** Nutraceuticals are natural and bioactive products with food value to keep energy balance in the body and promise substantial therapeutic value in several diseases. Major nutraceuticals are now part of nutrition supplements at nonprescription counters and their self-prescription is increased at large scale. The current literature suggests the nutraceutical use in most of cancer prevention and management. The biochemical mechanism of nutraceuticals is poorly reported and most of the literature indicates the success of nutraceuticals in experimental animals. Broadly nutraceuticals are antioxidants, omega-3 fatty acids, vitamins, minerals and dietary fibers. Most of the nutraceuticals are derived from plants and animal origin and act as biochemical metabolites either by direct intermediary metabolism or regulating immunity.

**Key Words:** Cancer, immunity, nutraceuticals, metabolites, diet, cancer prevention, nutraceutical supplementation.

## INTRODUCTION

Nutraceutical was first defined in 1989 by Stephen De Felico “as foods, food ingredients or dietary supplements that demonstrate specific health or medical benefits including the prevention and treatment of disease beyond basic nutritional functions”. Later nutraceuticals emerged as potential cancer preventive natural sources from food [1].

### Time Series of Nutraceuticals in Cancer Management

The concept of nutraceuticals was initially considered as natural foods to provide energy as recommended daily requirement in the body for health till year 1990. Later the importance of nutraceuticals was realized as beneficial in different nutritional disorders with growing use of the nutraceuticals as self prescription in cardiovascular, cancer, developmental conditions in the last decade. In new era of 21<sup>st</sup> century showed enormous growing awareness of nutraceuticals as potent therapeutic supplements with accepted concept of nutraceutical medicine as new branch of ‘complementary and alternative medicine’ (CAM). In last nine years, national and federal bodies accepted nutraceuticals as possible nutraceutical therapy in main stream of medical education and health. The healthcare industry demonstrated the shift of growing population from medical treatment of cancer towards non-prescription nutraceuticals as self-medication in cancer management and prevention. The growing awareness of nutraceutical benefits and shift of

healthcare economics in favor of nutraceuticals brought nutraceutical medicine in spotlight of government health policy on systematic use of nutraceuticals in prevention and control of various chronic diseases. In last six years, National Cancer Institute (NCI) and other global efforts have documented fact sheets and several health documents on nutraceuticals in cancer management as shown in Fig. (1). The major efforts were devoted in investigation of inhibitory effect of active nutraceutical component(s) on cell proliferation, cancer oncogenesis to result the reduced metastasis, delayed apoptosis, reduced necrosis and rate of malignancy growth in initial stages. In last two years the use of nutraceuticals in prevention and disease control has been extended further as protective nutrition supplementation policy of center of disease control (CDC) under its independent supervision. However, mechanisms still remain unproven and unvalidated but practice of nutraceuticals as food supplements in cancer prevention is acceptable.

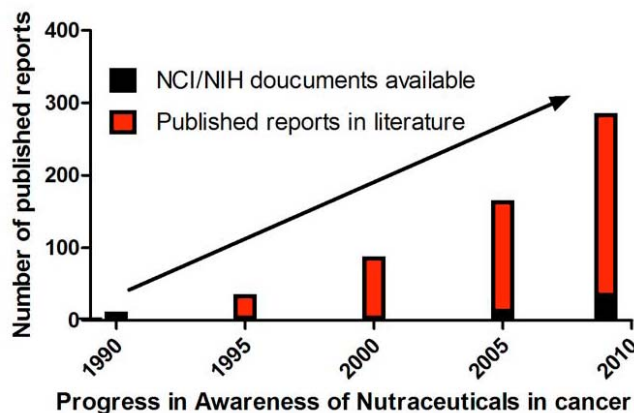
### WHAT ARE NUTRACEUTICALS?

Nutraceuticals are natural bioactive chemical compounds. Nutraceuticals have value in health promoting, disease preventing or semi-medicinal properties. Nutraceuticals are found as natural products from (a) the food industry, (b) the herbal and dietary supplement, (c) pharmaceutical industry, and (d) the newly emerged bioengineered microorganisms, agroproducts or active biomolecules. It may range from isolated nutrients, herbal products, dietary supplements and diets to genetically engineered “custom” foods and processed products such as cereals, soups and beverages [2]. Chemically the nutraceuticals may be classified as isoprenoid derivatives (terpenoids, carotenoids, saponins, tocotrienols, tocopherols, terpenes), phenolic compounds (couramines, tannins, lignins, anthocyanins, isoflavones, flavonones, flavanoids), carbohydrate derivatives (ascorbic acid, oligosaccharides, non-starch polysaccharides), fatty acid and structural lipids (n-3 PUFA, CLA, MUFA, sphingolipids, lecithins), amino acid derivatives (amino

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acids, allyl-S compounds, capsaicnoids, isothiocyanates, indols, folate, choline), microbes (probiotics, prebiotics) and minerals (Ca, Zn, Cu, K, Se) [3].



**Fig. (1).** The figure represents the time line of nutraceuticals in cancer prevention and growing awareness as documented in literature available in last 15 years.

Broadly the nutraceuticals were reported as active natural compounds as compiled in Table 1. Recently, Tripathi *et al.* 2005 reported the chemotherapeutic value to nutraceuticals in cancer. Majority of cancer prevention evidence comes from animals studies on phytochemicals, fat, flavones, phytoestrogens, isoflavonones, genestein, curcumin, capsaicin, epigallocatechin-3-gallate, gingerol, lycopene, antioxidants, vitamins, minerals [3, 4]. Self-described testimonies of nutraceutical medicine and its success accrued over years in favor of liquorice(for peptic ulcer), isoflavones (for cholecarotenoids, saponins, tocotriesterol lowering, osteoporosis), phosphatidylcholine(for hepatitis), ginger(for emetic disorder, dizziness, carminative), kambocha tea (for arthritis), glucosamine(for chondroitin), vitamins C, D, E, minerals Zn, Se, Cu(for lycopene, lutein(for antipain), leupeptin, urokinase inhibitor (for prostate cancer), fenugreek osteoarthritis), lycopene, glucans(for cardiovascular disease), green tea(for cancer), carotenoids, Trigonella foenum-graceum (as anti-diabetic, anti-cancer), noni Morinda citrifolia (for relief blood pressure, muscle pain), Thymus vulgaris, rhus coriaria (for antibacterial activity), sorrel (for immune system), Geranium sanguineum (as antiviral) over years [3, 5]. Lycopene, silbinin, shark cartilage, vitamin D (to decrease osteoporosis and bone pain), green tea, Selenium and vitamin E, Grape seed extract, modified citrus, pectin, Soy, PC-SPES are cited as prostate cancer protective food supplements [5].

### Dilemma of Nutraceuticals

Nutraceuticals may act as essential nutrient, as drug like, as regulatory biochemical metabolite and as phytohormone in the body. Recently, some prominent evidences are reported in favor of cancer inhibitory metabolic activity of nutraceuticals in the human body:

1. Nutraceuticals may act as essential amino acid drug like essential nutrients. For example, tryptophan is needed for protein synthesis at low dose in humans. At high dose, it increases brain 5-hydroxytryptamine levels and thus acts as a drug to treat the insomnia [6].

2. The nutraceutical preparations containing phytoosterols are effective in lowering LDL cholesterol and osteoporosis.
3. Bovine milk fat globule acts as anticancer, anticholesterolemic, coronary heart disease [7].
4. The phytonutrients prevent cell proliferation and play significant role in the prevention of chronic degenerative diseases. Notable examples are ginseng, spirulina, ginkgo biloba, amino acids, glucosamine, chondroitin and Aegle marmelos. Herbal and medicinal plants have shown significant inhibition of cell proliferation [8]. Phytoestrogens play role in reducing necrosis.
5. Vitamin C, vitamin E,  $\beta$ -Carotene, lycopene (carotenoids), lipoic Acid, glutathione(thiols) play role in cancer prevention and inhibition of necrosis; Co-Enzyme Q-10, super oxide dismutase (enzyme), selenium, copper, manganese, zinc (minerals) act as anticancer nutraceuticals in cancer management by delayed apoptosis observed in isolated cancer cells [9].
6. Oligosaccharides were tested in animals. Fructo-oligosaccharides, Inulins, Lactitol, Lactulose, Galacto-oligosaccharides, Soybean oligosaccharides, Lactosucrose, Isomalto-oligosaccharides, Gluco-oligosaccharides, Xylo-oligosaccharides showed reducing cancer cell divisions [10].
7. Polyunsaturated fatty acids (PUFA) such as safflower oil, corn oil, soybean oil, mustard oil, evening primrose oil, flax oil, hemp seeds, borage seeds showed protective effects in heart disease and stroke, rheumatoid arthritis, inflammatory arthritis, inflammatory bowel disease, asthma, cancer, chronic lung failure, kidney transplant, and bone formation [11].
8. Dietary fibers such as oats, dried beans, legumes, chicory as water soluble fibers, apple, orange, apricot, plum, pine apple contain 18-30% fiber contents. The vegetable sources such as cabbage, carrot, lettuce, onion, tomato containing 9 to 12 % fiber contents showed antioxidant and cell proliferation inhibitory properties [12].
9. Wild foods are other major source of nutraceuticals and phytoestrogens. Most of the wild plants, wild mushrooms, wild fungi, wild vegetables, wild nuts, wild fruits and wild flowers as whole are considered as potential natural therapy alternatives [8, 13].
10. Soy isoflavones, genistein, curcumin, capsaicin, epigallocatechin-3-gallate (EGCG), gingerol, lycopene have emerged as established cancer protective nutraceuticals [14].

### ANIMAL STUDIES

A large volume of literature is available on nutraceutical inhibitory effect on cancer cell growth based on observations of cultured cancer cell proliferation, enhanced apoptosis, antioxidant action etc. Still attempts are in the direction of morphological, cytomorphic, histopathology evidences of nutraceutical induced tumor shrinkage, arrested cell growth, delayed premalignancy, delayed oncogenesis, cell DNA cycle inhibition by using 3D localized molecular imaging techniques. Previous studies on micro-MRI and

**Table 1. The Examples of Nutraceuticals are Shown with Their Benefits in Different Cancers and Mechanism of Chemoprotective Action in the Body. The Structure of Active Nutraceuticals are Shown with Mechanism and Their Structure with Formula in Chemical Nomenclature**

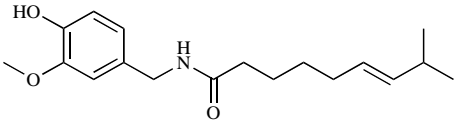
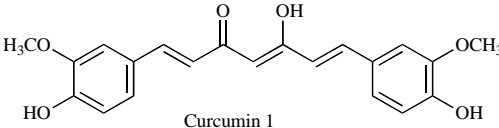
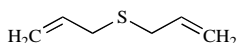
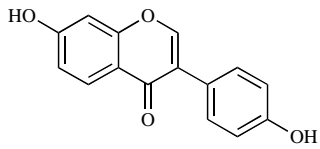
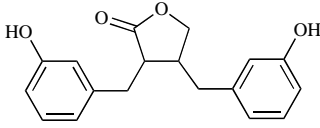
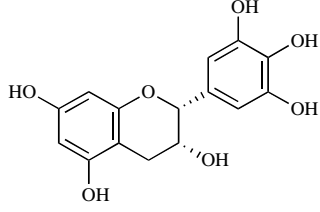
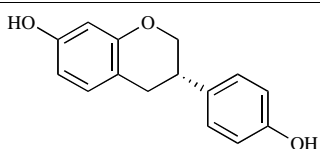
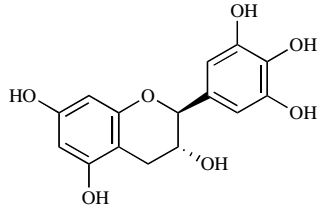
Nutraceuticals	Cancer	Mechanism	Structure
Ajoene (garlic)	PtK2	antineoplasia cytotoxicity	Trithiadodeca-1, 6, 11-triene-9-oxide
Antioxidants	B, Br, P, C, O, G	free radical scavenger	HO <sup>•</sup>
Citrus	G	delayed apoptosis	limonoids
CLA	Br	?	conjugated linoleic acid
Capsaicin	P, Br	VR1receptor/ion channel	
Carnosol	C	O <sup>•</sup> H scanenger	diterpenes
Curcumin	C, P	NKX 3.1gene, cytokines	 Curcumin 1
Dallyl sulphide (garlic)	B, C, P	Cyt Oxidase, LDH, Glu reductase	
Daidzein	C, I	antioxidation upregulation	
Enterolactone	G, I, P	antioxidative	
Epigallocatechin-3-gallate	C, L	DNA metTrans, LDH inhibitor	
Ellagic acid	C, Br, P	antioxidant protection	3, 4, 5-hydroxybenzoic acid
Equol	C, P	??	
Fenugreek	Br, C, G, I, CO, P, PN	cytokines, redox reactions	??
Gingerol	Br, C, G, I, CO, P	VR1 receptor, caspase	methoxy phenyl decanone
Green tea	Br, C, P, CO	reduced MMP 2, 9; cell proliferation	

Table 1. Contd....

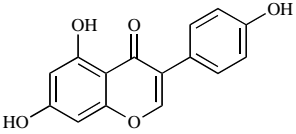
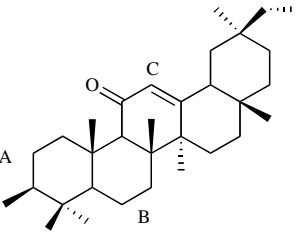
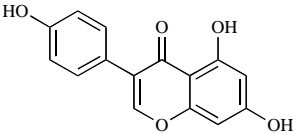
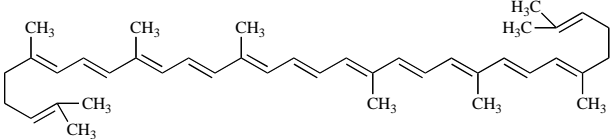
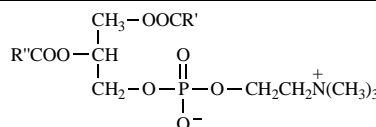
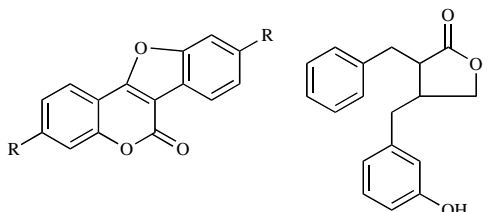
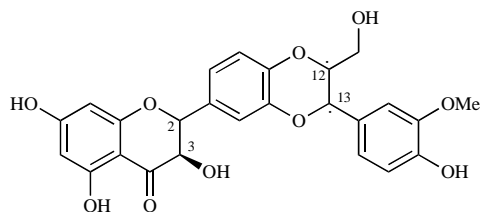
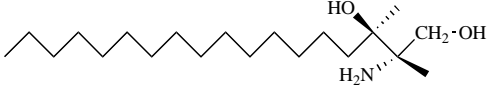
Nutraceuticals	Cancer	Mechanism	Structure
Genestein	Br, P	antiestrogenic, antiangiogenic, DNA endonuclease, caspase	
Grape seed extract	G, L, PN, CO, P	cytotoxicity, antioxidant	proanthocyanins
Glycyrrhizin	G, I, CO	peroximase proliferation	
Isoflavones	Br, P, PN	HMG CoA-LDH inhibitor, caspase	
Kambocha tea	Br, C, G, I, CO	free radical scavenger	??
Lactobacillus acidophilus	G, I, CO	α, β dehydroxylase	membrane phospholipids
Liquorice	G	estrogen receptor agonism	methyl Glabridins
Limonene	Br, CO	farnesyltransferase inhibitor	1 met-4-propenyl-cyclohexene
Lutein	B, S, P	antioxidant	xiazanthin
Lycopene	Br, P, G, I, CO	antioxidant, superoxide scavenger	
Meditarranian diet	G, I, CO, P	antioxidant	hemocyanins, low fat ??
Pectin	G, P	lennin, fibronectin conjugation	galectins 2, 3 in apoptosis
Phosphatidylcholine	G, CO, I	choline transport, phosphorylation	
Phytoesterogen (soy)	Br, C, G, I, CO, P	antioxidant (lunasin, coumestan lignan)	
Silbinin	L, CO	apoptosis, reduced cell growth	
Selenium and vitamin E	Br, C, CO, G, I, P, PN	cdk2, PKC, G1/S DNA breaks	selenoproteins, S-Se-S, S-Se

Table 1. Contd....

Nutraceuticals	Cancer	Mechanism	Structure
Sphingolipid	Br, P, G, I	cell cycle arrest, apoptosis, senescence and differentiation	
Soy, PC-SPES	Br, C, CO, G, I, P, PN, O	G <sub>2</sub> M cell cycle kinase, cytokines	chalcones
αTocopherol	Br, P, CO	antioxidant, antiproliferation	α tocopherol
		cyclooxygenase inhibition, apoptosis	γ tocopherol
Vitamins and minerals:	all cancers	oxidative phosphorylation	active vitamin forms
A		proton pumps	retinal
B		phosphorylation, redox reactions	pyrophosphates
D		1, 25 dihydroxycholecalciferol	calciferol
Folic acid		5-methyltetrahydrofolate	folate bound form
Calcium		calmodulin, Ca <sup>++</sup> channels	hydroxyapatite
Copper		catalase inhibitor, angiogenesis	ceruloplasmin
Potassium		Na/K channels	K+ or bound protein
Zinc		Zn-endopeptidases(MMP) inhibition	cofactor in enzymes

A: Arthritis cancer; B:Bone cancer; Br:Breast cancer; C:Common malignant cancers; CO: Colon cancer; H:Liver cancer; G: Gastric cancer; I:Intestinal cancer;L: Leukemia; P:Prostate cancer; PN: Pancreatic cancer; O:Ovarian cancer(source: Mazzio E Souleman K. US Patent 20070248693 <http://www.freepatentsonline.com/y2007/0248693.html>).

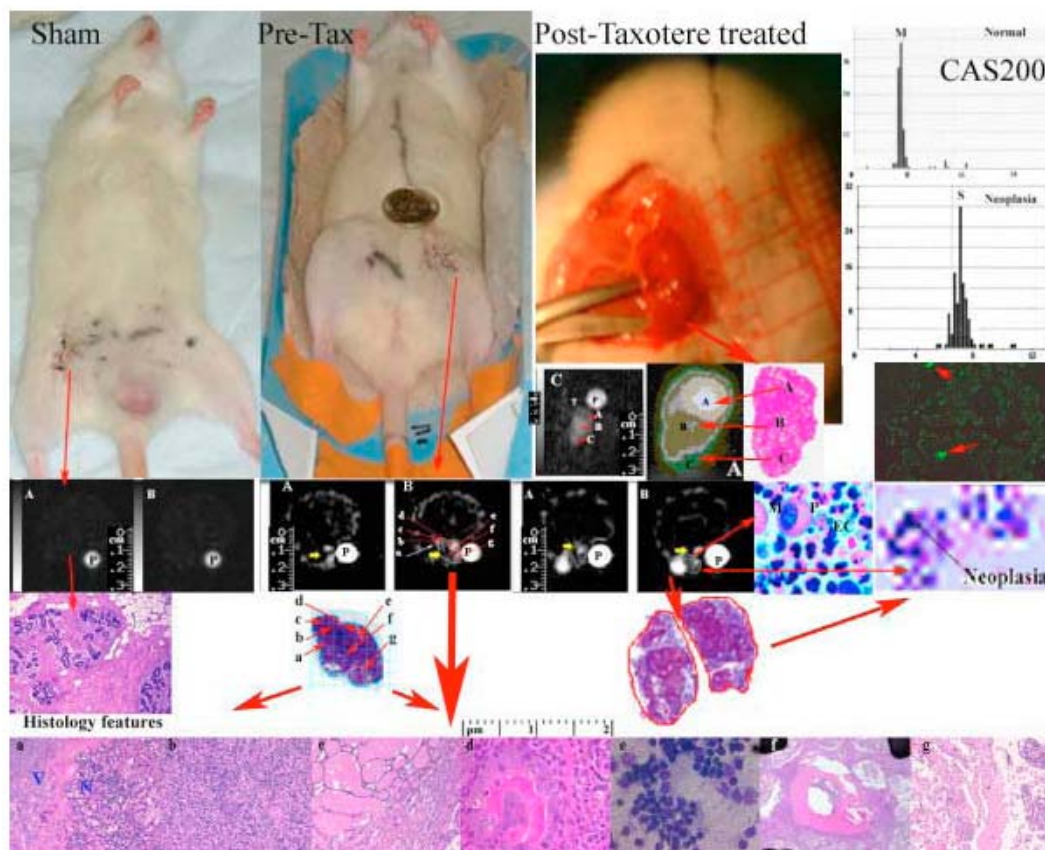
immunostaining suggested the reduced apoptosis in experimental rat MCF-7 explanted breast and mice PC-3 explanted prostate animal tumors. The increased sodium and enhanced apoptosis of tumor cells showed the tumor shrinkage after anticancer intervention to animals after 24 hours as shown in Fig. (2) [15]. Major evidence was the slowed down apoptosis rate (less nuclear beads), reduced proliferation, less cyst size, less necrosis, single strand DNA breaks and poor carcinoma and neoplasia growth in treated groups [16]. The mechanism of these nutraceuticals still not established and it remains to investigate more scientifically diet controlled experimental methods. Moreover the beneficial effects of nutraceuticals in experimental animals were reviewed and two third literature reports on nutraceuticals are documented on experimental animal cancer studies as either reviews or animal bench experiments on cancer prevention. The clinical evidence of nutraceutical cancer prevention success is still based on biochemical mechanisms of nutrients in diets reported over several decades. Some mechanisms of nutraceutical action are reported as immune modulatory, induced apoptosis, removal of free radicals, inhibited cell proliferation, inhibited necrosis. New ayurved (Indian traditional medicine) concepts are also emerging as powerful nutraceuticals in cancer prevention. The growing literature on mechanism of nutraceutical action in the cancer is supporting the extended benefits of nutraceuticals but it further needs more investigations as described in following separate section of new literature evidences.

### BIOCHEMICAL BASIS OF NUTRACEUTICALS IN CANCER PREVENTION

Natural vegetables, herbs, plants, wild foods are complex in structural composition. The biochemical basis of individual source of these foods is not explored due to their

complex nature. Some of the evidences are in favor of the active food principles as nutraceuticals to show anticancer or preventive cancer supplements. Some of nutraceuticals are in the phase of clinical trial or already available as food supplement. Complementary and Alternative Medicine is emerging in prevention of chronic premalignancies as safe practice because of the high risk of mortality and long-term morbidity associated with surgical procedures of cancer management and high side effects of chemotherapy. Herbal medicines have shown reduced cell proliferation in cultured cells. The vitamins, minerals, dietary fat play a role in relation to cancer prevention and control. The mechanisms of nutraceutical action can be discussed broadly in following categories based on active metabolites present in nutraceuticals.

1. The glutathione is the liver's most abundant protective constituent of antioxidant glutathione reductase enzyme. Glutathione functions as a substrate for the two key detoxification processes in the liver: 1. transforming toxins into water soluble forms, 2. neutralizing and "conjugating" with toxins for elimination through the gut or the kidneys. If either of these processes is impaired for any reason, toxins will accumulate in the body and lead to disease. The best nutrition with liver cancer focuses on improving the body's glutathione reserves [4].
2. Some nutraceuticals rich in opiads are tumor inhibiting and these nutraceuticals showed the activity to get rid of toxins such as heavy metals, chemicals, digestive by products, etc. Tobacco plants may also help person to fight against lymphoma [17].
3. The Soy isoflavone Haelan951 (genistein and genistin) was reported to have some role as a chemopreventive agent against cancer in humans [18]. Beta-glycoside



**Fig. (2).** The sham control, pre-treatment and Taxotere post-treated animals (top panels on left) show tumors as SQ sodium (A) and IR sodium (B) images at 0 hr pre-Taxotere and 24 hours post-Taxotere treatment (panels A and B on second row). On third row on left, control tumor histology shows normal vesicles. Pre- and post treated excised tumor histology by trichrome staining is shown with delineated area. On fourth row on left, the excised tumor histology features in high power fields are shown with arrows (active viable cells (a), proliferation (b), necrosis (c), apoptosis (d), mitosis (e), fibrous cyst (f), and infiltrating ductile carcinonoma (g) in different x- and y- coordinate locations after coregistration with IR sodium images. On right, panels on top show a IR sodium MR image before (C) and after non-parametric segmentation by Optimas 6.5 to highlight the different signal intensities that appeared hyperintense, isointense, and gray-green colored on segmented image and histology features showed them as apoptosis (A), necrosis (B) and neoplasia (C). On right, second row shows corresponding S DNA histograms of neoplasia features by CAS 200 (panels on top), apoptosis staining (panel with green stain). On right, third row shows a post-Taxotere treated tumor histology by pentachrome stain to highlight mitotic figures (M) with active PMN cells (P) and high EC volume (EC) and corresponding digitized map of DNA cycle, with neoplasia shown as arrow. Reproduced from reference [15].

conjugate, genistin is abundant in fermented soybeans, soybean products such as soymilk and tofu. The beta-glycosyl bond of genistin is cleaved to produce genistein by microbes during fermentation to yield miso and natto. Soy sauce has high isoflavone but low miso and natto contents. How much soy isoflavones needed? 1.5-4.1 mg/person miso isoflavone and 6.3-8.3 mg/person natto respectively [18, 19].

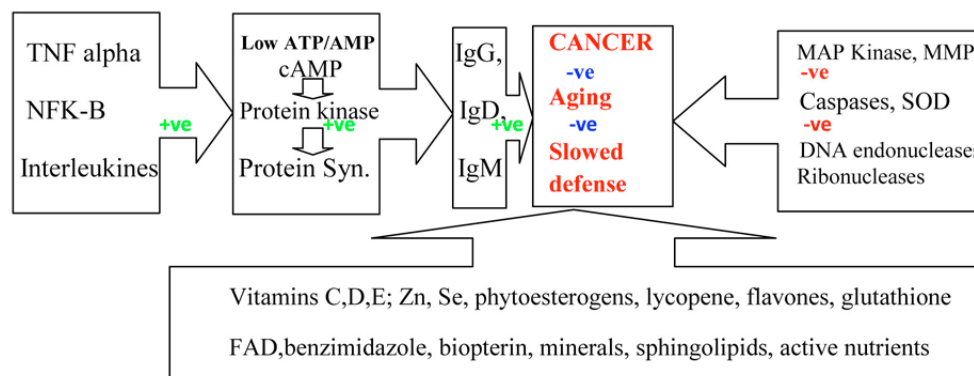
- Green tea has always been considered by the Chinese and Japanese peoples as a potent medicine for the maintenance of health, endowed with the power to prolong life [19]. Recently, Yean Lee *et al.* looked at the effects of the main active green tea constituent, epigallocatechin-3-gallate (EGCG) on chronic lymphocytic leukaemia B cells isolated from leukaemic patients. These cells were characterised by their resistance to apoptosis because they secrete and bind vascular endothelial growth factor [14, 20].
- Some herbal plants act as medicine. The herbal extracts are known to reduce the cell proliferation.

### APOPTOSIS AND IMMUNOLOGICAL LOSS AS BASIS OF CANCER AND ROLE OF NUTRACEUTICALS

Cell mediate immunity is active and strong in youth and deteriorates with age. The major cytokines including inetrleukines, TNF alpha and NFKappaB loose their synergy response and affect cell mediated immunity to synthesize enough IgG, IgM, IgD antibody molecules. Humoral immunity also gets affected by less helper and suppressor lymphocytes. The possible metabolic points likely changed by nutraceuticals in apoptosis cascade and immunity loss are shown in Fig. (3).

### ALTERNATIVE APPROACHES OF NUTRACEUTICALS IN CANCER

Children below 18 years probably do not need nutraceuticals. Adults over 20-40 years need nutraceuticals and monitoring cancer. Persons over sixty years in age, need cancer watch and nutraceuticals as mendatory daily dietary supplements in practice. These senior persons may show the following major symptoms as causes of cancer development [21].



**Fig. (3).** The figure represents the model sketch of cascade of steps to show delayed and slowed down apoptosis and immunity recovery by nutraceuticals based on literature data. Note the possible points where nutraceuticals may likely regulate or control for further metabolism in cell and tissues. +ve sign represents stimulated and –ve sign represents inhibited action of nutraceuticals based on reported literature. (source: <http://www.freepatentsonline.com/y2007/0248693.html>).

- Abrupt and sudden weight loss, infection, overgrowth of localized tumor
- Poor cytokines, inflammatory proteins gradually lead to apoptosis, loss of immunity
- Arteries and veins (and other tissues) become less elastic, as evidenced by our skin. Blood pressure may rise, as arteries lose their elasticity. (The amino acid taurine, found in fish, softens arteries and veins, as well as other connective tissue).
- Inflammation and cholesterol-filled growths (plaques) in our blood vessels reduce their rates of flow. The loss of elasticity causes the heart to pump with less power and force.
- Joints become inflamed, as the immune system ages and disease condition attacks the collagen of the joints.
- Insulin levels begin to rise as old cells become less responsive to insulin, and the pancreas increases its output to compensate. This eventually leads to Type II diabetes and pancreatic cancer in which old cells no longer respond to insulin and end up with heavy cardiovascular damage and cancer.
- Kidneys lose reserve capacity, gradually fail to do normal function and develop renal cancer.
- Reduced cell mediated immunity and humoral immunity leads to immune deficiency and cancer.

#### **PRESENT STATE OF ART ON NUTRACEUTICAL MEDICINE IN CANCER PREVENTION**

The UNISCI article, "Diet Called Most Important Breast Cancer Risk Factor", discusses the relationship between breast cancer and vitamin D, and between breast cancer and animal- versus plant-derived foods [22]. Bottom line: diet and environment exposure are two major risks. Major question is if nutraceuticals can reduce the chance of getting cancer through dietary modifications? Answer is not clear. The statement of National Cancer Institute's recommendations is "to eat at least 5 servings of brightly colored fruits and vegetables a day, to restrict ingestion of animal products (excluding farm-bred fish) while upping vegetable sources of protein (e. g., beans), to consume cooked tomato sauces, and

to insure that we get, perhaps, 200 mcg. a day of selenium. (found in Walmart's OneSource multivitamin capsule)"[23]. FDA requires appropriate scientific evidence regarding safety of nutraceutical use as daily prescription. However, new recommendations suggested that daily diet must contain 6.25 grams of soy protein per serving, micro-compound allicin (a small component of garlic) ad libitum amount, ecosapentanoic acid/docosaheaxanoic acid as polyunsaturated fatty acids (PUFAs) from fish or fish oils. The complementary medicine and alternative medicine approach is emerging as regulated tool to prescribe the norms of nutraceuticals as daily supplements in cancer and other diseases [24]. Fish and fish oils are compiled in Table 2.

#### **Insurance and Prescription**

National and federal agencies such as NCI and FDA need evidences and established data in large trials to approve nutraceuticals in clinical practice. In lack of such evidences and database, still nutraceutical practice remains at the door steps as nonprescription self-prescription available on counter. As a result, insurance companies still shy to accept nutraceuticals as prescription.

#### **Criteria of Suggested Practice of Nutraceuticals in Cancer Prevention**

The use of complementary and alternative medicine (CAM) is increasing rapidly in developed countries [24].

Functional Foods & Nutraceuticals in Cancer Prevention were highlighted as tomato, dietary fibers, soy, phytoestrogens, herbs, cruciferous vegetables [25].

NTP-2000 and NIH-07 diets were reported rich in nutraceuticals to meet recommended daily allowances. NTP-2000 diet has lower protein, higher fiber, and higher fat than the NIH-07 diet. Both diets were suggested as preventive in cancer. Main causative factors of cancer were free radicals, vitamin C, D, E deficiency, Se deficiency, loss of cellular immunity in daily diet [26].

Recently, National Cancer Institute put forth the efforts on alternative ways of cancer prevention as public awareness to main focus on life style, prevention and control care measures, eating habits, hazardous contaminants with several successful attempts of antioxidants, garlic, vitamins [27].

**Table 2. The Table Represents the FDA Approved Major Nutraceuticals with Recommended Quantity and Sources of Nutraceuticals on Shelf in Super Markets**

Nutraceuticals	Quantity Needed	Common American Sources
Vitamin D	400 IU a day(2000 IU)	Walmart's "OneSource" multivitamins
Multivitamin-minerals	As 1 pill daily	Centrum Silver A-Z with minerals
Natural Vitamin E (4 tocopherols + 4 tocotrienols)	Two 400 IU capsules a week (800 mg)	GNC natural Vitamin E
Selenium	200 mcgs. a day	Walmart's "OneSource" multivitamins
Coffee	Ad libitum	home made, Food emporium
Aspirin or ibuprofen*	Baby aspirin a day	nonprescription counter
Chocolate (best if fat-free)	?, 3 servings	home made, Food emporium
Green tea	?, 3 servings	home made, Food emporium
Black tea	?, 1 serving	home made, Food emporium
Lycopene	Cooked tomato sauces	Domino's Pizza
Fish (tuna, salmon, mackerel)** or EHA+DHA	Two servings a week	Fresh phytosterols at Publix
Soy "meat", cheese, milk	Ad libitum	Publix, at the edge of the produce section. mozzarella, sausage, burgers
Broccoli, cabbage, cauliflower	Sulphydrals ad libitum	Piccadilly's tastes pretty good.
Blueberries	A few tablespoons a day	Publix' frozen foods (N. side, S. aisle)
Strawberries	4 or 5 large a day	Publix' frozen foods (N. side, S. aisle)
Orange	One a day	Publix, all supermarkets
Old-fashioned oatmeal	One ounce?	Publix, all supermarkets
Legumes (beans)	Two servings a week	Publix, all supermarkets
Low-fat blueberry yogurt	2 or 3 times a week	Publix, all supermarkets
Yellow vegetables	Ad libitum	Publix(Piccadilly's tastes pretty good).
Purple grape juice, or red wine	A glass a day	Publix, for Welsh's grape juice
Turmeric roots	Two capsules daily	GNC natural body products
Herbs	Two pills daily	St John Warts natural source
Garlic, Soy products	Ad libitum	Walmart's "OneSource" ampoules

\*aspirin and ibuprofen primarily act as anti inflammation. (Other agents such as fish also have anti-inflammatory properties.); \*\*Tuna and mackerel contain mercury, dioxin, and PCB's. The salmon fish is safe. Winn Dixie farm-raised salmon. canned salmon provides omega-3 fatty acids and , taurine which are vital to the nervous and cardiovascular systems (modified from the Source [27-30]).

## NEW LITERATURE BASED EVIDENCES OF NUTRACEUTICALS IN CANCER: YEARS 2002-2008

In recent years during 2002-2008, the major focus was on more evidence based wider use of multivitamin-multimineral combined with isolated bioactive components from plants and functional foods in various cancer types. In last 4 years maximum efforts were devoted on reviews and compilation of evidenced experimental results on nutraceuticals in reducing cancer progress and identification of associations of active food components in diet with reduced cell proliferation, necrosis and apoptosis. However, NCI views that sequential events during the nutraceutical treated cell growth or arrest cancer are controversial [31]. The literature during years 2003-2008 suggested major information for following: 1. direct link of vitamins, minerals in cancer prevention; 2. new bioactive food components with new mechanism of arresting cell growth; 3. more controlled trials and regulated studies

under federal support; 4. new awareness of unpopular foods in cancer prevention; 5. new federal and statutory guidelines on nutraceutical recommended allowances and marketing.

The following information is grouped based on literature on nutraceuticals and nutraceuticals in cancer management with major focus on controlled randomized trials in experimental cancers and clinical cancer subjects. The description is divided into three sections.

### Nutraceuticals in Cancer Prevention During Years 2002-2008

The major nutraceuticals were reviewed and reported as vitamins and minerals, phytochemicals. The vitamins A, B<sub>6</sub>, B<sub>12</sub>, D, E, folate have been reported as anti cancer, immunoprotective and reducing cancer risk in population at risk of cancer and individuals who used self-medication [32-40]. These reports provided the information of growing self-



prescription style among population without any harmful effect and growing confidence of cancer bearing and avoiding chemotherapy. These nutraceutical supplements were reported in controlled epidemiological surveys to reduce morbidity and cancer incidence in clinical studies [41-47]. New information was investigated on successful nutraceutical supplements in present day life style, affluence and daily nutraceutical rich diet with reduced cancer prevalence in these studies. Major minerals as magnesium [48], zinc, micronutrients [49-52], selenium [53-57], calcium and were scientifically explored for their efficacy and safety in cancer prevention. Other new concepts emerged on the role of dietary vitamins as antioxidants in primary and secondary cancers in meta-analysis, randomized trials and epidemiological evidences with established metabolic and biochemical mechanism of these nutraceuticals [58-66]. The fatty acids [67, 68], polyphenols and phytochemicals emerged recently as promising chemopreventive agents to reduce cell proliferation and necrosis, enhanced apoptosis, reduced free radicals [69-75]. Soy phytoestrogens and isoflavones emerged as single potent chemopreventive agents to reduce the cancer risk [76-78]. Around the globe federal and government efforts have accumulated on consensus for statutory policy to use nutraceuticals on their daily requirements, supplementation, combinations and dosage to prevent or manage the cancer [79-83]. Randomized and double blind control trials indicated the increased importance of vitamins, herbs and fresh vegetables as likely protective supplements [84-90], tomato (lycopene) in prostate cancer prevention [91-93], nutritional intervention in different cancers of different body organs in the body [94-100]. New concept of Mediterranean diet was introduced to reduce the risk of cancer along with cardioprotection [101-104]. However, these reports are not conclusive and remain to establish the effectiveness of nutraceuticals if nutraceuticals effect on cancer cell senescence, oncogenesis, transformation, cell-cell contact inhibition, DNA fragmentation, ploidy and anisonucleosis without showing any adverse effect on normal cells.

For interested readers, a tentative sketch is outlined to understand the possible biochemical mechanistic and regulatory pathways and the role of nutraceuticals in cancer cell metabolism shown in Fig. (4).

### **I. Mechanism of Cancer Prevention by Nutraceuticals**

Several approaches have been reported to investigate the role of nutraceuticals on reduced cell damage in the normal cells of the body and possibility of delayed apoptosis, DNA interaction, reduced necrosis, cell proliferation, signaling and maintaining metabolic integrity in the cancer tissue as cancer prevention mechanisms [105-108]. The biomarker of cancer such as metalloproteinases [109], vitamin D hydroxylase [110], interleukins [111], omega-3 fatty acids [112], induced neutropenia [113], DNA adducts [114], DNA methylases [115], polymorphism [116], superoxide dismutase [117] have been discovered as potent indicators of nutraceutical chemopreventive mechanism. Still the action of phytochemicals and role of bacteria is not understood [118, 119]. Recently mechanisms of nutraceuticals were reviewed thoroughly [120]. Sharma *et al.* 2008 established the mecha-

nism of intracellular sodium as major player in breast and prostate tumors to induce delayed apoptosis [121]. The MRI and PET techniques evidenced the coexisting mechanism of reduced glycolysis and intracellular sodium release in tumors as chemoprotective assay [121].

### **II. Cancers in the Human Body and Nutraceutical Protection**

The awareness of cancer prevention by nutraceuticals began in late of the last decade. Still federal agencies restricted the regulatory policies of nutraceutical use in cancer prevention. Complementary and alternative medicine began a new era of harmless non-prescribed drugs with rampant success of self-prescription and on-counter sale of nutraceuticals. In last five years evidenced wider acceptance of nutraceuticals by both public and federal agencies. The major health hazards were identified as breast, prostate, colorectal, ovarian, pancreatic, and skin cancers.

The breast cancer was identified as single major health hazard three decades ago and still it remains a major risk among women. Different nutraceuticals have been reported in reducing breast cancer risk at both self-medication at homes and health centers. The major impact of experimental animal studies was distinct observations of reduced cancer cell growth by nutraceutical intervention and it supported the role of nutraceuticals in cancer prevention and treatment. The major examples of breast cancer preventive nutraceuticals are soy genestein [122-124], isoflavones, multivitamins as scavengers of free radicals, antioxidant, mitochondrial oxidative phosphorylation [125-132].

The prostate cancer was still recognized as single major health hazard among males and remains as main focus of nutraceutical intervention to reduce cancer risk by randomized control clinical trials. The major examples of cancer protective nutraceuticals are multivitamin antioxidants [133, 134], soy isoflavones [135, 136], soy-tomato combo products [137-139]. Majority of experimental animal cancer studies supported the reduced prostate cancer by nutraceutical supplementation. Still it remains to establish the value of nutraceuticals in clinical prescription at health centers. In this direction, lot of academic and global federal efforts are going on to establish the long term benefits of nutraceuticals in prostate cancer risk [140-145]. The increased awareness and self-prescription of nutraceuticals among public for prostate cancer benefits is present major concern of health authorities [146-153].

Lung cancer and esophageal cancer remained as ignored health hazards perhaps due to other responsible environmental factors as main causative determinants of respiratory diseases with possible cancer risks. Recently few reports suggested the possible increased nutraceutical benefits of vitamins A and E in protection against lung cancer [154-157].

Colon and colorectal cancers have been identified as health hazards of modernization in food processing, artificial foods and affluent eating life style in metro cities and fast pace society [158]. The increased incidence of colon, colorectal cancers have shown the processed food diet as

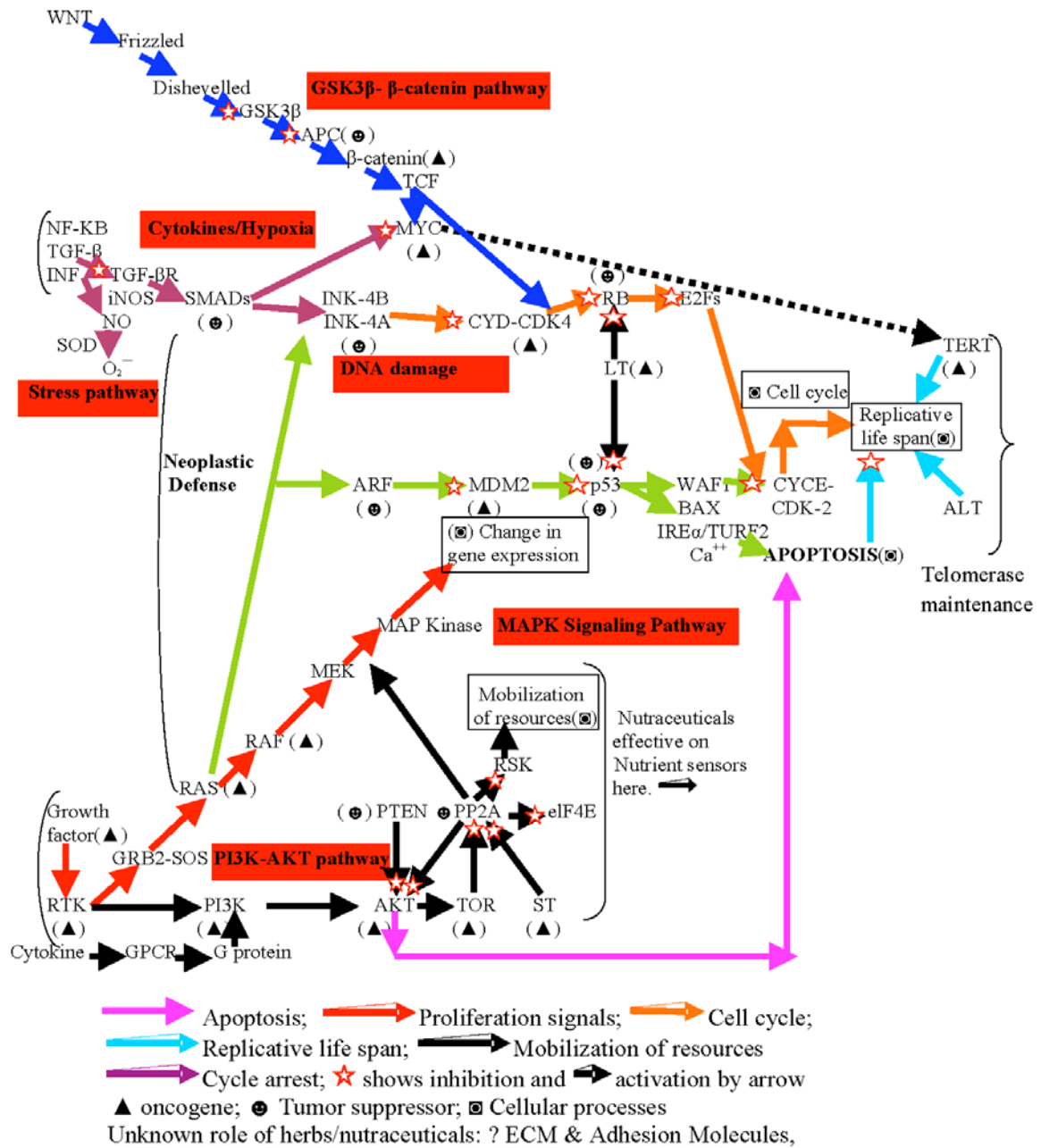


Fig. (4). An eye-view of nutraceutical action based on experiments in literature.

main source of cancer. The colorectal and colon cancer is widely reported as reduced by use of nutraceuticals such as folate [159-163], calcium [164-167], tomato-soy diet [168, 169], fiber [168-171] and vitamins [172].

However, there are hypes and controversies in risk assessment of nutraceutical in esophageal and gastrointestinal cancer management [173]. The several reports highlighted the trade-off between increased neoplasia in gastric cancer and the limits of nutraceuticals to reduce cancer growth [173, 174]. Still efforts are in the direction of antioxidant nutraceuticals to prevent or arrest the gastric cancer growth [175].

The ovarian and endometrial cancers are at increase among privileged woman population and increased awareness of vitamins and minerals have shown a new hope to

reduce the risk of cancer. Vitamin A, D, antioxidants, calcium, folate nutraceuticals still remain a choice as cancer preventive supplements [176-178].

Still efforts are in progress to observe more and more growing use of nutraceuticals in less known cancers. Recently less reported and newly investigated cancer protection by nutraceuticals were evidenced for lymphoma [179], skin cancer [180], pancreatic cancer [181-183]. Recently vitamins and minerals were validated in chemoprevention trial of different cancers [184]. In other recent reports the investigators showed a positive response of different nutraceutical supplements and foods in cancer prevention of different organs in the body as shown in Table 3 with nutraceuticals and references.

**Table 3. The Table Represents the Documented or Approved use of Nutraceuticals in Prevention or Management of Cancer in Different Organs**

Cancer	Nutraceuticals	References
Bone cancer	soy isoflavones	[5]
Breast cancer	lycopene, phytoestrogen	[122-132]
Common cancer	cruciferous vegetables	[25, 184]
Colon cancer	nuts, fibers	[158-172]
Gastric cancer	herbs	[173-175]
Intestinal cancer	sphingolipids	[64, 65, 176]
Liver cancer	silbinin, citrus flavonoids	[25]
Lung cancer	vitamins A and E	[154-157]
Ovary cancer	Vitamin A, D, antioxidants	[176-178]
Pancreatic cancer	Vitamins and isoflavones	[182-184]
Prostate cancer	lycopene, phytoestrogen	[133-153]

### Challenges, Hypes, Hopes and Futuristic Role of Nutraceuticals

Most of the success of nutraceuticals is based on self-prescription and own individual experiences. Still it is far to realize the miraculous benefits of nutraceuticals unless controlled clinical trials support the evidences and facts of nutraceutical preventive therapeutic efficacy. Major challenge is early detection of premalignancy and timely effective oncological treatment. In spite of all tools available, cancer is major health hazard. The major available data on nutraceuticals in cancer comes from epidemiological health and population statistics. The reduced cancer incidence due to nutraceuticals seems a hype but greater hopes are anticipated with advancements in food science. However, still cancer remains a major threat because of high mortality compounded with incomplete success of chemotherapy, oncotherapy and surgery intervention. In future, bioengineered nutraceuticals will play significant role in cancer prevention as alternative oncotherapeutics.

### CONCLUSION

Nutraceuticals still are growing in number and investigations suggest high hopes of nutraceuticals in cancer prevention. The role of governments and globalization will certainly support the health risks and clinical trials on nutraceuticals. The nutraceuticals are becoming popular as they are harmless and natural food constituents. The nutraceuticals are still food supplements and last 5 years demonstrated enormous change in the perception of nutraceuticals as cancer preventive and therapeutic supplements in cancers of different organs.

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