

ROLE OF NUTRACEUTICALS IN CANCER

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ABSTRACT

Plant produces a non-nutrient chemical substance called phytochemicals which is evolved in plants to protect themselves against highly reactive oxygen species and for their own defence mechanism. When the human ingests these plant foods composed of phytochemicals associated with antioxidant properties (capacity to scavenge free radicals) human developed the chemical defence mechanisms accounting for the availability of the required species in the diet. In today's developing world virtually many humans knowingly or unknowingly exposed to environmental carcinogenesis or dietary carcinogenesis which leads to metabolic activation of normal cells which cause chronic illnesses. So a demand for pharmaceuticals consist of natural bioactive principles has been increased because of side effects associated with synthetic drugs. These extracted pharmaceuticals products have nutrient properties helps to get defined health goal and these pharmaceuticals not only help to treat chronic disease and also to prevent other diseases. These kinds of products cannot be classified as 'food', so a new term was designated between nutrients and pharmaceuticals called Nutraceuticals. This paper reviews different classes of phytochemicals and its mechanism of prevention and treatment to cancer.

Keywords: Phytochemicals, Reactive oxygen species, Cancer, Nutraceuticals.

INTRODUCTION

A large number of epidemiological studies have consistently shown that dietary habit is one of the most important determinants of chronic diseases such as cardiovascular disease, type-II diabetes, gallstone, neurodegenerative diseases (e.g. Parkinson disease), cataract and several types of cancer (e.g. gastrointestinal cancer). Such an association between dietary habit and disease shows that food has a direct impact on health. It is generally accepted that abundant consumption of food from plant origin reduces the risk of chronic illnesses and helps to get defined health goal. While comparing naturally occurring drugs and synthetic drugs, naturally occurring drugs seem to be safe and effective, although synthetic drugs have onset of action, they have more side effects. By this, the above facts have encouraged several medical organizations and health care organizations around the world to recommend intake of increased amount of plant derived food, in order to get good health status and to postpone the development of diseases.

It is well known that foods are the sole source of nutrients used to meet our nutritional need apart from essential nutrients (proteins, carbohydrates, fats, minerals, and vitamins) in plant foods. Plants also produce non-nutrient chemical substances which have health related effects called Phytochemicals.

Plants acquired a wide-range of phytochemicals through evolution to protect themselves against highly reactive oxygen species and for their own defence mechanism. When the human ingests these plant foods composed of phytochemicals associated with antioxidant properties (capacity to scavenge free radicals) human developed the chemical defence mechanism accounting for the availability of the required species in their diet.

In the past few years demand for food products containing bioactive compounds as well as non-food products (i.e. dietetics and pharmaceuticals) has increased. Therefore, pharmaceutical industries commercialized their pharmaceuticals products containing bioactive compounds in the form of capsules, pills, gels, liquors, solutions, etc. These products which have incorporated phytochemical enriched extracts or food extracts have beneficial physiological effects on human health. These kinds of substances cannot be classified as "Food", so a new term was designated /coined between nutrients and pharmaceuticals called Nutraceuticals.

Nutraceuticals and Functional Foods

Nutraceuticals is defined as "Any substance that may be considered a food or part of a food and provides medical or health benefits including the prevention and treatment of disease"¹. The concept of nutraceuticals is not entirely new to humans and it has considerably evolved over the years. For example; in early 19th century several food industries began to add iodine in the salt to prevent goiter (an enlargement of thyroid gland due to iodine deficiency). This represents the attempts towards creating the functional components. Nutraceuticals are the new generation of food which has the interface between drug and food. About 2000 years ago, the well recognized father of medicine Hippocrates (460-377 BC) highlighted "*Let food be thy medicine and medicine be thy food*" emphasize the relationship between nutrition and human health, and conceptualized the relationship between the use of appropriate foods for health and their therapeutic benefits.

Functional foods are foods that have one or more compounds with biochemical and physiological functions beneficial to human health². When consumed regularly they provide specific health-beneficial effects (i.e. healthier status or lowering the risk of diseases-beyond their nutritional properties). The definition for nutraceuticals and functional foods is not yet clear. For example, 250mg of phytochemical extract formulated in the form of capsule is called Nutraceuticals. At the same time 250mg of phytochemical extract formulated in the form of food formulation (i.e. 250mg of extract dissolved in 1L of juice) would be a new functional food. However, nutraceuticals and functional foods constitute a great promise to improve health and prevent aging-related chronic diseases.

Phytochemicals

The word "*phyto*" is the Greek word which means plant therefore phytochemicals means plant chemicals. Phytochemicals are the bioactive non - nutrient plant compounds in fruits, vegetables, grains, and other plant foods that have health related effects. It is estimated that more than 5000 phytochemicals have been identified, but still a large number of phytochemical profiles are needed to fully understand the health benefits of phytochemicals³.

Classification of Phytochemicals

Phytochemicals can be classified as carotenoids, phenolics, alkaloids, nitrogen-containing compounds and organosulphur compounds.

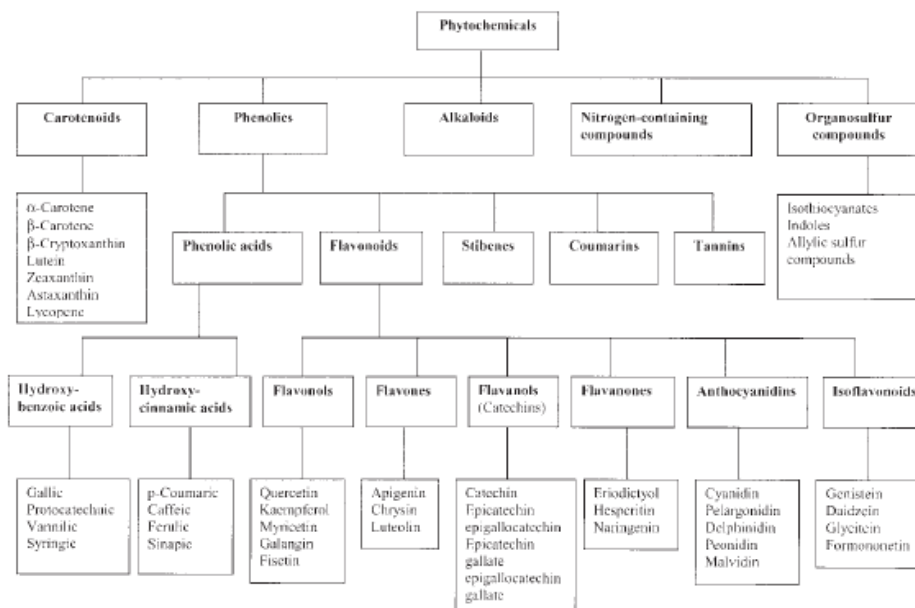


Fig. 1: Classification of dietary Phytochemicals (Source: 3)

Functionally these phytochemicals may also be classified as antioxidants, anticarcinogenic, antimutagenic, anti-oestrogenic, anti-inflammatory, immunopotentiating, cardio-protective and neuropharmacological agents, and also as a source of dietary fiber (non-starch polysaccharides). Phytochemicals are a wide variety of chemicals differing in their potential functions.

Reactive Oxygen Species and Risk of Diseases

Reactive Oxygen Species (ROS)

Paradoxically, Oxygen in the atmosphere is one of the important determinant of aerobic life in the earth because it gives energy in the form of ATP (1mol of O₂ can generate 3 mol. of adenosine tri phosphate) for the living things and is also a lethal toxin. The cost of fuel - efficient aerobic catabolism is oxidative damage to cellular components. Oxygen is a bi-radical element which means it searches electrons to compensate for the two unpaired electrons. This condition leads to essence of "Oxidation" as a result, H₂O (low toxic value) will be the final product of oxidation which can be achieved

through different steps by generating intermediates in each step that are more oxidative than O₂ and are called ROS. Like ROS, there are several other Reactive species (a group substance which have the capacity to oxidize the biological substrates) such as Reactive Nitrogen Species, Reactive Chlorine Species and many other represented as carbon, lipidic, and generic radical depend on the nature of compound. However ROS is considered to be the most important Reactive Species (RS), because the entire body of RS in the cells tends to be transformed into ROS by subsequent reaction.

Oxidative Stress

Oxidative stress is a condition generated by a body in the presence/production of a large amount of RS and/or lack of antioxidant defence, potentially oxidative stress can damage the cellular components of body leading to many common diseases. But diabetes, cancer, cardiovascular, and neurodegenerative diseases are the most common chronic diseases implicated by oxidative stress. So it is necessary to maintain appropriate equilibrium between oxidation and antioxidants for well being life⁴.

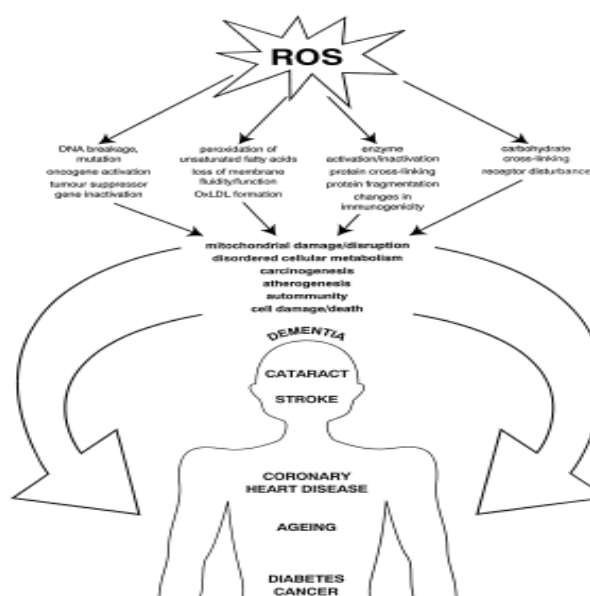


Fig. 2: Reactive oxygen species and risk of diseases (Source: 5)

Dietary Antioxidants

In humans, a sophisticated and co-operative array of antioxidants defend mechanism have evolved against toxic oxygen intermediates through nutrition and it is an accepted concept that the increased intake of antioxidants through nutrition may lower the risk of such diseases supported by biochemical and epidemiological evidence⁵.

“A dietary antioxidant is a substances in food that significantly decreases the adverse effects of reactive oxygen species (ROS), reactive nitrogen species, or both on normal physiological function in human” by Dietary Antioxidants and Related Compounds of Food panel in Food and Nutrition Board⁴.

CHEMOPREVENTIVE PHYTOCHEMICALS IN CANCER

Biology of Cancer

Carcinogenesis is a multistep process in which normal cells accumulate several mutations in the genes involved in growth control, induction of angiogenesis and resistance to apoptosis in order to grow and invade the host tissues and there are more than 100 different types of cancer and sub types of tumors can be found in specific organ. Hanahan and Weinberg have suggested that the alterations in cell physiology lead to the formation of malignant tumor⁶. These include

1. Self-efficiency in growth signals, which means tumor cells can be constitutively active without the need for exogenous signals.
2. Insensitivity to growth-inhibitory (antigrowth – inhibit cell proliferation) signals.
3. Evasion of apoptosis process (programmed cell death).
4. Undefined replicating potential
5. Angiogenesis has to be initiated to ensure the sufficient oxygen and nutrient supply for sustained tumor growth.
6. Tissues undergo invasion and metastasis.

These six capabilities are common to all types of human tumors. The process of cancer development might takes place over several years (even decades), offering a large therapeutic option for preventing the development of cancer. Small tumors that formed over a life-time always remain in microscopic and in harmless state. More strikingly 98% of humans had latent tumors in the thyroid and these are rarely observed in clinic. In the absence of an appropriate blood supply and low genetic diversity of precancerous cells are more vulnerable to anticancer molecules. Clinically observed cancer shows that precancerous cells have overwhelmed the anticancer defence and acquired the capability to grow and invade the host tissues. Our natural defence mechanism helps to control the growth of small tumors that formed spontaneously over a life-time⁷.

Nutritional modulation such as nutraceuticals, functional foods, supplemental micronutrients have the potential to reduce the growth rate of cancer cells. In addition, it reduces the toxicity associated with chemotherapy and radiation therapy and they inhibit cell proliferation and induce apoptosis in cancer cells⁸.

“Chemoprevention is the utilization of non-toxic chemical substances to interfere with neoplastic development”. Chemopreventive phytochemicals are predominantly present in plant derived foods which are the potential modifiers of undesired signal transduction pathways that lead to cancer mediated by nuclear factor-kappa B (NF-kB)⁹. Chemopreventive phytochemicals that are known to suppress carcinogenesis by blocking NF-kB activation process are curcumin (turmeric), catechins (tea), silymarin (artichoke), caffeic acid, phenethyl ester (honey- bee propolis), sanguinarine, anethole (fennel, anise, coriander), emodin (aloe), capsaicin (red chilli), resveratrol (red grapes, peanuts and berries), ursolic acid (basil and rosemary), betulinic acid (fravopiridal, oleandrin (oleander) ellagic acid (pomegranate), lycopene (tomato), ajoene, allicin, diallyl sulfide (garlic), Beta-carotenes (carrots), eugenol and isoleugol (cloves), 6-gingerol (ginger).

Researchers identified that NF-kB is a transcription factor involved in the development of cancer by altering the genes of cell survival, cell adhesion, inflammation, differentiation and growth. In normal cells, Inhibitory IκB protein inhibits the nuclear localization sequences of NF-kB, retaining it to the cytoplasm. In the developmental process of cancer NF-kB is activated by a large number of stimuli such as environmental carcinogenesis (cigarette smoke, industrial emissions, gasoline vapors etc), tumor promoters (okadaic acid, phorbol esters), and inflammatory agents. Ultimately through phosphorylation and ubiquitination these stimuli promote the disassociation of IκB alpha which facilitate the entry of NF-kB into the nucleus for binding to the kB regulatory elements and activate the transcription of target genes. Activated target genes establish the early and late stages cancer such as expression of cyclin D₁, apoptosis suppressor proteins (Bcl-2 and Bcl-X_L- are the genes which involved in the expression of protein that blocks apoptotic pathway) and matrix metallo proteases, vascular endothelial growth factor (VEGF) required for metastasis and angiogenesis¹⁰. Although the NF-kB activation leads to cancer, maintaining the appropriate level of NF-kB activity is crucial for normal cellular proliferation¹¹.

Patients undergoing chemotherapy and radiotherapy treatment require more antioxidants. Thus individual antioxidants vitamin A (retinoids), vitamin E (primarily alpha-tocopheryl succinate), vitamin C (primarily sodium ascorbate) and carotenoids (primarily polar carotenoids) as supplementation to cancer patients proved to be helpful. Its potential action may be through inhibition of protein kinase C activity, expression of C-myc, H-ras, a transcription factor (E2F) and induction of transforming growth factor -beta and p21 genes. Apart from these actions vitamins may also act as biological response modifiers by enhancing the anti tumor effects of x-irradiation, chemotherapeutic agents and hyperthermia⁸. A concentration of plasma selenium level is strictly associated with the risk of prostate cancer. High level of selenium plays a potential role in anticancer activity by inducing apoptosis, inhibiting cellular proliferation and protects the cells from peroxide damage (key component of glutathione peroxidase)¹². Combination of antioxidant vitamin and minerals may have the potential to protect the DNA damage that cause chronic diseases.

Apoptosis (programmed cell death) is an interesting cellular process in the self-defence. To reduce the risk of cancer growth enhancing the apoptosis is an essential factor. Combination of selenium and vitamin E may activate multiple molecular targets for apoptosis induction¹³. Phytochemicals potentially downregulates the antiapoptotic molecules such as Bcl-2 or Bcl-X_L and upregulates proapoptotic molecules such as Bax or Bak through mitochondria-mediated pathway¹⁴. Phytochemicals also helps to activate proapoptotic c-jun n-terminal kinase (induce positive regulators of cell cycle regulation) and inhibit antiapoptotic NF-kB signaling pathways. Consuming cruciferous vegetables such as broccoli, brussels sprouts, cabbage, and cauliflower may lower the risk of prostate cancer in humans. During metabolism glucosinolates in cruciferous vegetables give rise to several breakdown products, mainly indole-3-carbinol (I3C). Indole derivatives have potential inhibitory effects on proliferation and exert their effects in induction of an apoptotic cell response. In acidic pH I3C is converted into polymeric products among which 3,3'-diindolylmethane (DIM). I3C and DIM have potential inhibitory effects on prostate cancer cells through induction of apoptosis in PC3 cells through mitochondrial pathway, which involves in the translocation of cytochrome c from the mitochondria to the cytosol and the activation of initiator caspase-9, and effector caspases-3 and -6 leading to poly ADP-ribose cleavage and induction of apoptosis¹⁵. I3C also prevent hormone-related cancer such as breast and prostate by inducing tumor necrosis factor related apoptosis-inducing ligand (TRAIL) mediated apoptosis. It has been reported that TRAIL can induce apoptotic cell death in a variety of tumor cell types¹⁶.

Curcumin is a yellow color flavoring agent in foods belongs to curcuma species that can enhance TRAIL -induced apoptosis in various cancer cell lines. TRAIL can also known as APO2L, is a member of TNF family. TRAIL induce apoptosis to various tumor cells, but it does not cause any toxicity to normal cells because

TRAIL needs four membrane-bound death receptors (DR4, DR5, DcR1, and DcR2) in this DR4 and DR5 are reserved cytoplasmic region called 'death domains' which is required for TRAIL-induced apoptosis. DcR1 and DcR2 protect normal cells by acting as decoy receptors. Curcumin treatment results in the upregulation of DR5 and makes the cancer cells to become more sensitive to cytotoxic activities of TRAIL¹⁷. Curcumin can effectively down-regulates the transcription factors such as NF-kappa B, angiopoietin-1, inducible nitric oxide and blocks the activity of Jun N-terminal kinase. On the other hand curcumin also able to prevent the induction of VEGF synthesis and also affect other growth factors involved in angiogenesis¹⁸. Cruciferous vegetable also helps to prevent the DNA damage from reactive oxygen species and electrophiles by being an antioxidant and inactivate the metabolic activation of cytochrome P450 which initiate carcinogenesis¹⁹. The ability of these molecules and others like genus *Allium*²⁰ can potentially reduce the risk of carcinogenesis²¹.

Inflammation is responsible in development of several cancers like breast cancer, colorectal, lung cancer²². Improper up- regulation of cyclooxygenase (COX-2) and nitric oxide synthase (enzymes which mediate inflammatory response) involved in certain types of cancers. Dietary phytochemicals present in edible and medicinal plant have anti-inflammatory and anti-oxidative properties which potentially contribute in chemopreventive activities. For example curcumin, epigallocatechin -3- gallate (EGCG) and resveratrol from grapes have been shown to inhibit the expression COX-2 and nitric oxide synthase by blocking NF-kB activation²³.

Normally, late stage cancer patients are associated with an impaired immune-physiological condition like decreased activity of natural killer (NK) cells and cytokine production. Therefore, increasing the production of cytokines and NK activity would be beneficiary to late stage cancer patients. In this respect nutraceuticals can significantly induce the production of cytokines such as tumour necrosis factor, interleukins, interferons and potentially activate macrophages, T lymphocytes, natural killer cells in patients with late stage cancer²⁴.

Interleukin-6 (IL-6) is a cytokine which plays a crucial role in immune physiology. Excessive production of IL-6 promotes carcinogenesis such as breast, lung, colon, prostate, ovarian cancers. Normally excessive production of IL-6 is controlled by hormonal feedback mechanism using sex steroids (estrogen, testosterone). After menopause loss of sex steroids results in increased production of IL-6. A large number of therapeutic approaches aimed to modulate IL-6 gene expression to prevent cancer progression by recommending phyto-estrogens and soy isoflavones (genistein, daidzein, biochanin)²⁵.

Angiogenesis is a crucial process in the development of cancer which is stimulated by formation of new blood vessels from endothelial cells with sustained oxygen and nutrient supply. During angiogenesis endothelial cells are stimulated by various growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet derived growth factor (PDGF), hepatocyte growth factor (HGF), angiopoietins and receptors belonging to the family epithelial growth factors²⁶. VEGF and FGF are considered to be the important factors in angiogenesis^{27,28}. Angioprevention is a novel concept that analyzes the mechanisms on how and why chemopreventive agents could exert their antiangiogenic effects aimed at controlling tumor growth as hypothesis including both natural and synthetic chemopreventive agents. Ultimately, naturally derived chemopreventive agents provided an encouraging result in inhibiting the angiogenesis²⁹.

Polyphenols possess strong antiangiogenic activities that can potentially inhibit angiogenesis which are epigallocatechin-3-gallate (EGCG), resveratrol, curcumin, genistein that can potentially inhibit angiogenesis³⁰. Polyphenols from red wine and green tea can strongly inhibit the formation of new blood vessels and it also shows the antioxidant properties that directly scavenge reactive oxygen species³¹. Polyphenols in green tea is commonly known as catechins. The major catechins in green tea are EC, ECG, EGC, EGCG. In this EGCG is an abundant catechins in green tea, it can potentially inhibit the VEGF- a key receptor in tumor angiogenesis²⁷. Low dosage delivery (concentrations achievable through diet) of EGCG is

effective in inhibiting VEGF-mediated signaling in *in-vitro* condition, suggesting that this antiangiogenic effect is relevant *in vivo*³². Accordingly for conclusive evidence, the chemopreventive agents efficacy against prostate cancer (CaP) in animal models that closely emulates human diseases were found. The autochthonous transgenic adenocarcinoma of the mouse prostate (TRAMP) model has spontaneously develops metastatic CaP by oral infusion of a natural polyphenol fraction isolated from green tea at a human achievable dose (approximately 6 cups of green tea per day) strongly inhibits development of prostate cancer and increases the survival of transgenic mice that spontaneously develop this cancer³³.

Interestingly, consumption of green tea is also associated with beneficiary effects to some patients with chronic lymphocytic leukemia³⁴. In a similar way, anthocyanidin³⁵ and ellagic acid a natural polyphenol found in several fruits and nuts known to inhibit VEGF and PDGF receptors that play a complementary role in angiogenesis³⁶. This combined inhibition of VEGF and PDGF leads to inhibition of angiogenesis process in both *in vitro* and *in vivo* assays^{35,36}. This growing evidence suggests that antiangiogenic property of phytochemicals plays a crucial role in their chemopreventive activity by preventing the formation of new blood vessel that is necessary for cancer development.

CONCLUSION

Nature is a promising source of active principles against cancer cells. Antioxidant phytochemicals do exert a range of fascinating and potentially important biological effects on human cells. In most cases the development of cancer is associated with generation of ROS. Chemopreventive phytochemicals with antioxidant properties could minimize the disease associated with the generation of ROS and also chemopreventive phytochemicals has the ability to inhibit the carcinogenesis process by targeting macromolecules expressed on cancer cells. These chemopreventive agents can be used in combination with chemotherapeutic agents to enhance the effect at lower doses and thus minimize chemotherapy induced toxicity. Phytochemicals can be used not only to treat cancer but also to prevent it because of their pharmacological safety¹⁰.

Application of these chemopreventive phytochemicals in chemoprevention has boosted the nutraceuticals industries to produce large number of phytochemicals containing nutraceuticals with various composition and health claims. One of the obvious weaknesses of phytochemicals research is that much of the research is conducted *in vitro*³⁷. To analyze the antioxidant capacity of phytochemicals *in vitro* assays like oxygen radical absorption capacity assay, Trolox equivalent antioxidant capacity assay, Ferric reducing/antioxidant power assay, ABTS, lipid peroxidation etc. have been extensively used to define and claim the 'goodness' of nutraceuticals products. Clinical trials that evaluate the actual physiological effects in humans are scarce and results are controversial. Using animal models to investigate the biological activities of the phytochemical is not clear because of the physiological differences between animals and human in metabolizing the active compounds and the bioavailability of the compound. These differences also occur between different animal models (i.e. between mice and rat) which may give contradicting experimental results.

Ingesting high doses of phytochemical extracts may not be effective or safe or may have toxic effects. It is necessary to differentiate the physiologic (nutritional) dose from the pharmacological dose. Clinically, pharmacological dose needs doctor's prescription to treat specific disease; physiologic dose are use to improve or maintain optimal health. In the case of antioxidant micronutrients the physiological dose is not equal to pharmacological dose the excessive intake of antioxidant micronutrients can be toxic. The proper physiological dose should follow the recommended Dietary Allowance³⁸. In biological systems toxins may become micronutrients and nutrients may be toxic in certain situation⁵.

Another important aspect that remains to be elucidated is the controversial issue related to cancer patients. Since cancer induces desperate conditions and emotional situations, patients tend to try alternate complementary therapies involving nutraceuticals.

However, these may have adverse side effects in progress and skew the results of trials³⁹. For example, Tamoxifen is a chemotherapeutic drug used to treat cancer. Several breast cancer patients discontinued chemotherapy because it was 'poisonous' so many patients are attracted towards natural products because it is natural and less toxic. Heterogeneity of information about natural products like immune-boosters and high dosages can cure diseases increases the likelihood for misuse. So the physicians should enquire carefully about the use of natural products by patients⁴⁰. The public should avoid following the advice of doubtfully qualified physicians in recommending the natural products. Nutraceuticals are destined to play an important role in future therapeutic developments and their success will be governed by control of purity, safety and efficacy without inhibiting innovation⁴¹.

Nutraceutical industry is a dynamic and evolving industry that offers exciting opportunities to merge scientific discovery with growing consumer interest in health-enhancing foods and it will continue to have great appeal because they are more convenient for today's life style⁴². Although, Nutraceuticals field offers a good opportunity for phytochemicals research but still, several hurdles have to be crossed in research for beneficiary effects in human health. There is an urgent need to set up an *in vivo* system to test the biological potency of a given diet with a specific biological property (antioxidant property and inhibition of carcinogenesis) and the gap between the scientific community with updated knowledge on nutraceuticals and health care professional has to be filled. Anyhow, future research in the science of nutrition may be directed towards evaluating the potency of phytochemicals in foods.

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