

Role of Nutraceuticals in Cancer Therapy

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Abstract

Nutraceuticals are natural bioactive products with food value and promising therapeutic properties in several diseases. Current cancer treatments, such as chemotherapy, radiotherapy and surgery, induce unintended side effects compromising also health and well-being of patients. Emerging studies suggest that some plant-based agents may impact cellular and molecular processes underlying tumor progression. However, some of these molecules might also play an antagonistic activity against classic therapeutic agents. The aim of this article is to review the current knowledge underpinning the use of nutraceuticals in cancer prevention and therapy.

Keywords: nutraceuticals, prevention, cancer, phytochemicals, epigallocatechin-3-gallate, resveratrol, quercetin

1. Introduction

A large number of studies have demonstrated that dietary habit is one of the most important determinants of chronic diseases such as cardiovascular disease, diabetes, gallstones, neurodegenerative diseases, cataract and several types of cancer (Smith-Warner et al., 2000). Such an association between dietary habit and disease shows that food has a direct impact on health. Cancer is a growing health problem around the world particularly with the steady rise in life expectancy, increasing urbanization and the subsequent changes in environmental conditions and lifestyle (Andersen, Holst, & Vogel, 2013). The transformation of a normal cell into a cancerous phenotype requires stages of initiation, progression, and promotion by altering specific genes. Although predisposition of cancer cannot be signaled out by a single factor, a panel of factors places some people at a higher risk. Most of the high-risk cases may have a genetic background, but dietary choices could dictate the outcome of health (Pericleous, Mandair, & Caplin, 2013). The predominant forms of cancer, as determined by population and epidemiological studies, are those of the lung and bronchus, breast, colorectal and prostate (Jemal et al., 2011). These cancers are prevalent in the western parts of the world, while their incidence is much lower in Asian countries. A well-balanced diet that includes more of vegetables and fruits with less fat/meat intake is a staple of many Asian countries (Fernandes, 1989). So, many hypotheses highlight that diet and environment greatly influence cellular function and health (Bazzan, Newberg, Cho, & Monti, 2013). In addition to the nutrients, human diets of plant origin contain hundreds of compounds which may not be considered as nutrient. However, they play an important role in the maintenance of health. Traditional systems of medicine in different countries are practicing these herbs for health management since centuries, but in most of the cases, claims are not scientifically validated.

2. Nutraceuticals

Phytochemicals are plant-based chemicals that mediate their positive health benefits directly, by affecting specific molecular targets or indirectly as stabilized conjugates affecting metabolic pathways (Priyadarsini & Nagini, 2012). Plants acquired a wide-range of phytochemicals through evolution to protect themselves from highly reactive oxygen species and for their own defense mechanism. In the past few years, the demand for food products containing bioactive compounds as well as non-food products (i.e. dietetics and pharmaceuticals) has increased.

These kind of products which have incorporated phytochemical enriched extracts to exploit beneficial physiological effects cannot be classified as “food”. So, a new term was coined between nutrients and pharmaceuticals called Nutraceuticals. Dr. Stephen DeFelice first coins the term nutraceuticals in 1989 and he defined nutraceuticals as “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” (Kalra, 2003).

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. For example, in early 19th century several food industries began to add iodine in the salt to prevent goiter. This represents the attempts towards creating functional components.

Later the importance of nutraceuticals was realized as beneficial in different nutritional disorders with growing use of the nutraceuticals as self-prescription. In new era of 21st 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).

About 2000 years ago, Hippocrates, the well-recognized father of medicine, suggested “Let food be thy medicine and medicine be thy food” emphasizing the relationships between nutrition and human health and in particular between appropriate foods for health and their therapeutic benefits.

The plant products have been defined as food, food supplement, functional food and nutraceuticals, depending upon its isolation step.

Pure extracted phytomolecule is named as nutraceuticals, whereas semi-purified plant product, not taken as regular food, is named as functional food (Roudebush, Davenport, & Novotny, 2004). Food supplements are those products which can be taken regularly as food to maintain the general health.

Plant foods contain a variety of components including micronutrients, polyunsaturated fatty acids, and secondary metabolites such as glucosinolates, flavonoids, polyphenols, phytoestrogens, phytosterols, lignans, terpenes, phytates etc (Orzechowski, Ostaszewski, Jank, & Berwid, 2002).

3. The Use of Nutraceuticals in the Cancer Patient

It has also been estimated that one-third of all cancers deaths are preventable by life-style changes including appropriate nutrition (Danaei, Vander Hoorn, Lopez, Murray, & Ezzati, 2005).

Although promising results obtained *in vitro* with several cell systems, no mechanism-based preclinical studies have been performed to date. This lack of preclinical data led to the failure of the first large-scale clinical studies of phytochemicals performed in the 1990s.

Botanicals have a long history of use in the treatment of cancer. Many cancer chemotherapeutics drugs are derived from plants including the alkaloids of the Vinca species (vincristine and vinblastine) and the Pacific yew *Taxus brevifolia* (Taxol).

Ancient cultures throughout the world used a plethora of techniques to treat and prevent disease, and to maintain health. One subset of these techniques is plant extracts. It is often found that the same or similar plants are used in a number of cultures for the same symptoms or diseases, signifying that are probably medicinally quite effective for those types of ailments.

Despite medical advances, cancer remains a worldwide health problem and a number of plant extracts are used for treating and preventing cancer.

Nutritional modulation may be beneficial in the treatment of cancer patients (Weisburger, 1999).

There is evidence that foods, relatively low in simple carbohydrates with moderate amounts of high-quality protein, fiber, and fat (especially fats of the omega-3 fatty acid series) are beneficial for cancer patients (Tuomisto et al., 2004).

In addition, nutraceuticals may also be helpful in reducing toxicity, associated with chemotherapy and radiation therapy, and may lead to better life conditions by reducing cancer cachexia (Grimble, 2003).

The phytochemicals have shown different mechanism of actions at different cellular levels. Most of them have emerged as a versatile source of antioxidants affecting the signaling pathway related to redox mediated transcription factors. Besides, they directly modulate the endocrine system, immunological cascade and enzymes related to inflammation. Some of them have shown direct effect on DNA repair and cleavage process.

4. Molecular Targets of Nutraceuticals in Cancer Care

Initial *in vitro* studies found that phytochemicals may help the tumorigenic actions of carcinogens, blocking their mutagenic activity and suppressing cell proliferation (Surh, 2003).

Chemoprevention can be defined as the use of natural or synthetic chemicals to reverse, suppress, or to prevent the process of carcinogenesis. Solid cancers in early stage, are generally detected as intraepithelial neoplasia or carcinoma *in situ*, which correspond to the promotion and progression stages. Therefore “anti-promotion” and “anti-progression” agents may be of particular clinical interest.

Dietary bioactive substances, even in very low concentrations, may have a great impact on the regulation of gene expression. Continuing research on the effects of nutraceuticals on gene expression should provide a better knowledge of prevention’s mechanisms of diseases, such as obesity, diabetes, atherosclerosis, hypertension and cancer, by dietary manipulations.

In addition, it was found that phytochemicals protect against lipid peroxidation and modulate innate and inflammatory responses (Issa, Volate, & Wargovich, 2006).

These effects of plant extracts in combination with their lack of toxicity make them potentially efficient agents in the fight against cancer.

However, each compound’s mechanism of action and its effectiveness in a specific type of cancer must be studied in order to apply the correct compound to the appropriate clinical situation.

The term “nutritional genomics” was coined to describe the research at the interface of plant biochemistry, genomics and human nutrition (DellaPenna, 1999).

A few studies on the action of selected nutraceuticals on the activity have paved a path to further investigate these molecules in a great detail, using various genetic diseased animal models (Orzechowski et al., 2002).

Besides the active role of nutraceuticals and functional foods in the control of cancer progress, there is also a great need to develop the food supplements as the add-on therapy to provide better quality of life for a cancer patient (Ogilvie, 1998).

In fact, some cancer patients show cachexia, which may be defined as significant alterations in their carbohydrate, protein and fat metabolism, resulting to bad quality of life, reduce response to therapy, and shorten survival span. Nutritional modulation may be beneficial in the treatment of cancer patients to reverse these metabolic alterations. Nutritional intervention can be a powerful tool for controlling malignant disease and for reducing toxicity associated with chemotherapy and radiation therapy (McCullough & Giovannucci, 2004).

Moreover, nutraceuticals can significantly raise natural killers cells (NK cells) function and tumor necrosis factor (TNF α) in patients with late stage cancer (See, Mason, & Roshan, 2002).

5. Main Phytochemicals Studied for Cancer Care

Dietary phytochemicals can be classified depending on their chemical structures, botanical origin, biological properties, biosynthesis, etc.

5.1 Polyphenols

Polyphenols are plant secondary metabolites that contain one or more hydroxyl group attached to a benzene ring in their structure. More than 8000 different polyphenols found in food (mainly, wine, tea, coffee, cocoa, vegetables and cereals) are present in the human diet (Lecour & Lamont, 2011).

They may be classified into different groups according to their number of phenol rings and the structure that links these rings. In this context, the groups of phenolic acids, flavonoid, stilbenes and curcuminoids are the most important for their capacity for blocking initiation of carcinogenic process and to suppress cancer progression.

5.1.1 Epigallocatechin-3-gallate

EGCG (epigallocatechin-3-gallate) is the major catechin found in green tea (*Camellia sinensis*). The frequent consumption of green tea in Asian countries has been related to several health benefits and it is recognized as the most effective cancer-preventive beverage.

The antitumor properties of EGCG has been recognized on multiple cancer cell lines, including less common tumors such as anaplastic thyroid carcinoma (De Amicis et al., 2013) and malignant mesothelioma (Ranzato et al., 2012).

Most studies determining the anticancer drug properties of EGCG are preclinical; so, for better understanding of specific effects, clinical trials should be carefully designed to evaluate EGCG effectiveness.

The clinical applications of green tea have the limitation of low bioavailability and conversion into inactive methylated metabolites. Moreover, the biotransformation of the green tea polyphenols is different in human from rat and mouse, which may explain the inter-species difference in anti-carcinogenic properties (Clifford, van der Hooft, & Crozier, 2013).

Furthermore, the genetic polymorphisms in gene responsible for the biotransformation of EGCG, such as catechol-O-methyltransferase (COMT), need to be considered when designing green tea efficacy studies (Moyers & Kumar, 2004).

However, the wide range of antitumor effects exerted by EGCG suggests that this compound is a potential tool for cancer prevention and therapy, both alone and in combination with antitumor drugs or other phytochemicals.

5.1.2 Resveratrol

Resveratrol is the most important stilbene related to cancer. It possesses a natural anti-proliferative activity due to its role as a phytoalexin (plant antibiotic). It is believed to have also multiple bioactivities including anti-cancer, anti-carcinogenesis and anti-inflammatory effects (Singh, George, & Ahmad, 2013).

The mechanisms by which resveratrol might produce these effects are not completely understood, but the main molecular mechanism seems to be the activation of sirtuin proteins (Nakata, Takahashi, & Inoue, 2012).

There is considerable interest in developing resveratrol for cancer prevention and treatment. The plasma pharmacokinetics of resveratrol in humans are now reasonably well defined, and studies have shown that repeated daily doses are safe and well tolerated (Gescher, Steward, & Brown, 2013).

However, pharmacokinetics studies of resveratrol have shown a poor bioavailability (only 1%) due to extensive glucuronidation and sulfation as well as metabolism by gut bacterial enzymes (Scott, Steward, Gescher, & Brown, 2012).

5.1.3 Quercetin

Quercetin, a representative member of the flavonoid class, is a plant-derived compound obtained from various fruits and vegetables that can reach levels in the human diet as high as 16-25 mg/day (Hertog, Feskens, Hollman, Katan, & Kromhout, 1993).

The effects of quercetin are considered to be related to the induction of cell apoptosis through multiple mechanisms. *In vivo* studies of the anticancer effects of quercetin have demonstrated that oral administration can prevent induced carcinogenesis, particularly in the colon and furthermore, quercetin can inhibit melanoma growth, invasion, and metastatic potential (Zhang, Chen, Ouyang, Cheng, & Liu, 2012).

Similar to resveratrol, the low bioavailability is the main problem for quercetin (Dajas, 2012).

6. Vitamins and Minerals in Cancer Management

The role of vitamins A, C, E and trace elements like selenium has been suggested to prevent cancer in several independent studies. Supplementation with micronutrients as adjuvant in cancer patients may prove to be helpful (Misotti & Gnagnarella, 2013).

Ascorbate (vitamin C) is an essential nutrient in the human diet, but is also widely used as a medicinal product, and has long been held as a remedy for various diseases (Levine, Rumsey, Daruwala, Park, & Wang, 1999).

Studies focusing on the mechanism of ascorbate toxicity reported the induction of apoptosis through cell cycle arrest, activation of the apoptosis factors and interference with iron uptake in cells. However, ascorbate is known to act as an electron donor in redox reactions, and a body of evidence supports the idea that oxidative stress plays a major role in the mechanism of ascorbate toxicity in tumor cells (Ranzato, Biffo, & Burlando, 2011).

Other studies *in vitro* and *in vivo* are evaluating the real potentialities of ascorbate, combining it also with chemotherapeutic drugs (Martinotti, Ranzato, & Burlando, 2011; Volta et al., 2013).

7. Combined Therapy: A New Promise?

Although chemotherapy has advanced into the era of targeted drugs, the antitumor efficacies of current therapies are limited, most likely because of the high degree of cancer clonal heterogeneity, intra-tumor genetic heterogeneity and cell signal complexity (Komarova & Boland, 2013).

Clinical data have generally shown that some cancer are particularly chemoresistant, and in agreement with this kind of evidence, best results in the medical treatment of the disease have been obtained with combinations of different compounds.

However, the combination treatment is associated with certain degree of dose-related toxicity. Therefore, the

development of personalized mechanism-based and targeted therapeutic strategies to improve therapeutic efficacy and minimal side effects is considered very important for the successful treatment of cancers.

To achieve high efficacy and low toxicity in cancer therapy, selecting therapeutical agents is a critical step in designing strategy. In recent years, some dietary agents, recognized as anti-cancer agents, acquired more importance in combined therapy.

These agents can exert their anti-cancer activities through regulation of different cell signaling pathways. Importantly, these nutraceuticals are non-toxic and therefore conventional cancer therapies combined with these nutraceuticals may exert enhanced anti-cancer activity through synergistic action (Sarkar & Li, 2006).

Thus, the combination treatment may also decrease the systemic toxicity caused by chemotherapeutics or radiotherapy because lower dosed of chemotherapeutics agents could be used when combined with nutraceuticals whereby toxicity could be minimized.

By considering that at concentrations that are toxic for mesothelioma cells (Ranzato et al., 2011) ascorbate is well tolerated by the human body, Martinotti and coworkers attempted at finding partner compounds which could act synergistically with ascorbate against mesothelioma cell growth. They therefore tested common chemotherapeutic drugs used in mesothelioma therapy, such as cisplatin, etoposide, gemcitabine, imatinib, paclitaxel, and raltitrexed, and other compounds not yet used in clinical settings, but that are considered promising antitumor agents.

Isobologram analyses, based on *in vitro* cytotoxicity tests, have shown synergistic interactions of ascorbate with EGCG and gemcitabine, a classic chemotherapeutic drug (Martinotti et al., 2011).

These authors demonstrated also a new possible therapy for mesothelioma, based on a novel, synergistic combination of active nutrients/drug (so called AND therapy), based on EGCG, ascorbate and gemcitabine, all used at pharmacological doses (Volta et al., 2013).

This AND mixture, i.e. a combination of ascorbate, EGCG and gemcitabine, induces cell cycle deregulation and apoptosis in mesothelioma cells. Most importantly, the mechanism is synergistic, and involves an impairment of free cytosolic Ca^{2+} , the up-regulation of DAPK2, the repression of NF- κ B, and a block of cell cycle that prevents cells from entering into the G2/M phase (Martinotti, Ranzato, Parodi, Vitale, & Burlando, 2013). These data are in line with previous findings, and suggest that the mixture could be profitably used as a clinical treatment for malignant mesothelioma, possibly yielding higher response rates in patients without scaling up drug dosages.

8. Present Limitations of Nutraceuticals in Cancer

That certain herbal supplements have the potential to interfere with drug therapy is well known. For example, anti-coagulant properties have been documented for ingestion of garlic supplements and warfarin interactions have been shown for ginger and ginkgo (Posadzki, Watson, & Ernst, 2013).

Probably the most well-documented drug-herb interaction is the potential for St. John's Wort (*Hypericum perforatum*) to induce cytochrome P4503A4, a major cytochrome involved in the metabolic activation of certain cancer drugs.

Antagonism of selective estrogen receptor modifiers such as tamoxifen has been demonstrated for the isoflavones characteristic of soy.

Anthranoid-containing plants (including senna (*Cassia senna*) and cascara (*Rhamnus purshiana*) and soluble fibers (including guar gum and psyllium) can decrease the absorption of drugs (Fugh-Berman, 2000).

Recent studies have also demonstrated that some anti-oxidants obtained from plant extracts may increase the resistance to chemotherapy if used in patients with advanced stages of cancer (Zhang, 2010).

9. Future Directions

Nature is a promising source of active principles against cancer cells. Phytochemicals exert a range of fascinating and important biological effects on human cells.

Application of phytochemicals in cancer care has boosted the nutraceuticals industries to produce large number of phytochemicals containing nutraceuticals with various composition and health claim.

The challenge now is to develop dietary supplements that can help prevent or delay the onset of nutrition-related diseases in a specific population groups. This will be possible with a better understanding of the molecular basis for the ways in which these components affect human health.

In this context, the following areas of research are gaining special attention:

- application of -omics technologies to gain better understanding of the role of phytochemicals in biological processes;
- analysis of the role of dietary compounds on epigenetics and on human health;
- assessment of biomarker to monitor the effects of dietary components on diseases.

10. Conclusions

The incidence of cancer is continually rising. Concomitantly phytochemicals are growing increasingly important since they are used more readily. Although some studies have confirmed the positive response but their mechanisms of action are still not clear.

Nutraceuticals provide a promising source of compounds with chemopreventive effects because they are inexpensive and most of them have no evidence of toxicity.

More studies are required to find the most important targets for phytochemicals in order to perform tailored clinical studies to give rise to consistent results for the management of cancer prevention and treatment.

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