WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Nutraceutical Used in Cancer Therapy

Mr. Adarsh Yadav, Mr. Nitesh Kumar Prajapati (Assistant professor), Mr. Abhishek Dubey, Miss Riya Yadav

S. N. College of Pharmacy, Jaunpur

ABSTRACT.

Nutraceuticals are naturally bioactive compounds that possess nutritional benefit with and potential therapeutic effects against various diseases. Existing cancer therapies, including chemotherapy, radiation therapy, and surgical procedures, often cause adverse effects that negatively impact patients' health and quality of life. Recent research indicates that certain plant-derived compounds may influence the cellular and molecular mechanisms involved in cancer development. However, certain of these compounds may also exhibit opposing effects against conventional treatment agents. This article aims to examine the existing understanding supporting the application of nutraceuticals in cancer prevention and treatment.

1.Introduction

A substantial body of research has shown that dietary patterns are among the most significant factors influencing the development of chronic illnesses such as cardiovascular conditions, diabetes, gallstones, neurodegenerative disorders, cataracts, and various types of cancer. This connection between eating habits and disease indicates that nutrition has a direct effect on overall health. Cancer is becoming an increasingly serious global health concern, especially due to the continuous increase in life expectancy, growing urbanization, and the resulting shifts in environmental factors and lifestyle.

The transformation of a healthy cell into a malignant one involves multiple stages—including initiation, promotion, and progression—through the modification of specific genes. While no single cause can be pinpointed for cancer susceptibility, a combination of various elements places certain individuals at greater risk. In many high-risk scenarios, genetic predisposition plays a role; however, dietary habits can significantly influence health outcomes.

According to population-based and epidemiological research, the most common types of cancer include those affecting the lungs and bronchial tubes, breasts, colon and rectum, and prostate gland. These cancers are more prevalent in Western countries, whereas their occurrence is notably lower in Asian regions. A balanced diet—typically rich in fruits and vegetables and lower in fats and meats—is characteristic of many Asian diets.

As a result, numerous theories suggest that diet and environmental factors strongly affect cellular functions and overall well-being. Beyond essential nutrients, plant-based diets also contain a wide range of bioactive compounds that are not classified as nutrients but play crucial roles in maintaining health. Traditional medicinal systems across various cultures have used these plant-derived substances for centuries in promoting health, although many

2.Nutraceuticals

Phytochemicals are naturally occurring compounds found in plants that promote health either directly by interacting with specific molecular targets or indirectly by forming stable complexes that influence metabolic processes. Through evolution, plants have developed a diverse array of phytochemicals to defend themselves against reactive oxygen species and other environmental stressors. In recent years, there has been a growing interest in both food items enriched with bioactive substances and non-food applications such as nutritional supplements and pharmaceutical products. Products that contain phytochemical-rich extracts designed to harness positive physiological effects cannot be strictly categorized as “food.” As a result, a new term was introduced to bridge the gap between nutrition and pharmaceuticals.

Nutraceuticals. The term "nutraceuticals" was first introduced by Dr. Stephen DeFelice in 1989, who defined them as “foods, food components, or dietary supplements that provide specific health or therapeutic benefits, including the prevention and management of diseases, beyond their basic nutritional value”. The idea of nutraceuticals was originally viewed as natural foods intended to supply energy according to the body’s recommended daily needs for maintaining health until the 1990s. For instance, in the early 19th century, various food manufacturers started fortifying salt with iodine to prevent goiter. This exemplifies early efforts to develop functional food components.

Subsequently, the significance of nutraceuticals was recognized for their advantages in managing various nutritional disorders, accompanied by an increasing trend of self-prescription. In the 21st century, there has been a remarkable rise in awareness of nutraceuticals as powerful therapeutic agents, with the emerging acceptance of nutraceutical medicine as a new discipline within "complementary and alternative medicine" (CAM).

Approximately 2000 years ago, Hippocrates, widely regarded as the father of medicine, famously stated, "Let food be thy medicine and medicine be thy food," highlighting the connection between nutrition and human health, particularly the role of suitable foods in promoting wellness and providing therapeutic effects. Plant-based products have been categorized as food, dietary supplements, functional foods, or nutraceuticals, depending on the level of extraction or processing involved. Pure isolated plant-derived compounds are referred to as nutraceuticals, whereas partially purified plant products that are not consumed as regular food are classified as functional foods. Dietary supplements are products intended for regular consumption to support overall health. Plant-based foods contain a wide range of constituents including micronutrients, polyunsaturated fatty acids, and secondary metabolites such as glucosinolates, flavonoids, polyphenols, phytoestrogens, phytosterols, lignans, terpenes, and phytates, among others.

3.The Use of Nutraceuticals in the Cancer Patient

It is estimated that approximately one-third of all cancer-related deaths can be avoided through lifestyle modifications, including proper nutrition. Although encouraging outcomes have been observed in vitro using various cell models, no mechanism-driven preclinical investigations have been conducted so far. This absence of preclinical evidence contributed to the unsuccessful results of the initial large-scale clinical trials involving phytochemicals carried out in the 1990s.

Botanical remedies have a long-standing history in cancer treatment. Numerous anticancer drugs are derived from plants, including alkaloids from the Vinca genus (vincristine and vinblastine) and the Pacific yew tree, ***Taxus brevifolia*** (Taxol).

Ancient civilizations worldwide employed a wide variety of methods to treat and prevent illnesses and to promote health. Among these approaches, plant extracts played a significant role. It is frequently observed that the same or similar plants are used across different cultures to address identical symptoms or diseases, suggesting their likely medicinal effectiveness for those conditions

Despite advancements in medicine, cancer continues to be a global health challenge, and various plant extracts are utilized for both the treatment and prevention of cancer. Nutritional intervention may offer benefits in the management of cancer patients.

Research indicates that diets low in simple sugars but containing moderate levels of high-quality protein, fiber, and fats—particularly omega-3 fatty acids—are advantageous for individuals with cancer.

Moreover, nutraceuticals may aid in mitigating the side effects associated with chemotherapy and radiation therapy, potentially improving quality of life by alleviating cancer-related wasting syndrome, known as cachexia.

Phytochemicals exhibit various mechanisms of action at multiple cellular levels. Many of these compounds have proven to be a diverse source of antioxidants that influence signaling pathways associated with redox-regulated transcription factors. Additionally, they directly regulate the endocrine system, immune responses, and enzymes involved in inflammation. Some phytochemicals have also demonstrated direct effects on DNA repair and cleavage processes.

4.Molecular Targets of Nutraceuticals in Cancer Care

Initial in vitro studies indicated that phytochemicals may inhibit the tumor-promoting effects of carcinogens by blocking their mutagenic potential and reducing cell proliferation.

Chemoprevention is defined as the use of natural or synthetic substances to reverse, inhibit, or prevent the development of cancer. Early-stage solid tumors are typically identified as intraepithelial neoplasia or carcinoma in situ, corresponding to the promotion and progression phases of carcinogenesis. Therefore, agents with "anti-promotion" and "anti-progression" properties could hold significant clinical value.

Dietary bioactive compounds, even at very low concentrations, can significantly influence the regulation of gene expression. Ongoing research into the impact of nutraceuticals on gene expression is expected to enhance our understanding of disease prevention mechanisms—such as those for obesity, diabetes, atherosclerosis, hypertension, and cancer—through dietary interventions.

Furthermore, phytochemicals have been shown to protect against lipid peroxidation and to regulate innate immunity and inflammatory processes. These effects of plant extracts, combined with their low toxicity, make them promising candidates as effective agents in cancer prevention and treatment. However, the specific mechanism of action of each compound and its efficacy against particular cancer types must be thoroughly investigated to ensure the correct application in clinical settings. The term "nutritional genomics" was introduced to describe research at the intersection of plant biochemistry, genomics, and human nutrition.

Several studies investigating the effects of selected nutraceuticals on biological activity have paved the way for more detailed exploration of these compounds using various genetic disease animal models. In addition to the active role of nutraceuticals and functional foods in managing cancer progression, there is a significant need to develop dietary supplements as complementary therapies to improve the quality of life for cancer patients.

Indeed, some cancer patients experience cachexia, which is characterized by substantial disruptions in carbohydrate, protein, and fat metabolism, leading to poor quality of life, decreased treatment responsiveness, and reduced survival time. Nutritional modulation may be beneficial in treating cancer patients by reversing these metabolic disturbances. Nutritional strategies can serve as effective tools for managing malignancies and minimizing the adverse effects associated with chemotherapy and radiation treatments.

Furthermore, nutraceuticals have been shown to significantly enhance the activity of natural killer (NK) cells and increase tumor necrosis factor (TNFα) levels in patients with advanced-stage cancer**.**

5.Main Phytochemicals Studied for Cancer Care

Dietary phytochemicals can be categorized based on their chemical composition, botanical source, biological activities, biosynthetic pathways, and other criteria.

Polyphenols

Polyphenols are plant secondary metabolites characterized by one or more hydroxyl groups attached to a benzene ring in their molecular structure. Over 8,000 distinct polyphenols, commonly found in foods such as wine, tea, coffee, cocoa, vegetables, and cereals, are part of the human diet.

They can be divided into various classes depending on the number of phenolic rings and the types of linkages between these rings. In this regard, phenolic acids, flavonoids, stilbenes, and curcuminoids are particularly significant due to their ability to inhibit the initiation of carcinogenesis and to hinder cancer progression.

EGCG (epigallocatechin-3-gallate) is the primary catechin present in green tea (*Camellia sinensis*). Regular consumption of green tea in Asian countries has been associated with various health benefits and is considered one of the most potent cancer-preventive beverages.

The anticancer properties of EGCG have been demonstrated across multiple cancer cell lines, including rarer tumors such as anaplastic thyroid carcinoma and malignant mesothelioma.Most research assessing the anticancer potential of EGCG has been conducted in preclinical settings; therefore, well-designed clinical trials are necessary to thoroughly evaluate the specific effects and efficacy of EGCG in humans.

The clinical use of green tea is limited by its low bioavailability and its conversion into inactive methylated metabolites. Additionally, the metabolism of green tea polyphenols differs between humans and rodents, which may account for species-specific variations in their anticancer effects.

Moreover, genetic variations in enzymes responsible for the metabolism of EGCG, such as catechol-O-methyltransferase (COMT), must be taken into account when designing studies to assess the effectiveness of green tea. Nevertheless, the broad spectrum of antitumor activities exhibited by EGCG indicates that this compound holds promise as a potential agent for cancer prevention and treatment, both as a standalone therapy and in combination with anticancer drugs or other phytochemicals.

Resveratrol

Resveratrol is the most significant stilbene associated with cancer. It exhibits natural anti-proliferative properties due to its function as a phytoalexin (a plant-derived antibiotic). It is also believed to possess multiple bioactivities, including anticancer, anticarcinogenic, and anti-inflammatory effects.

The exact mechanisms through which resveratrol exerts these effects are not fully elucidated, but the primary molecular pathway appears to involve the activation of sirtuin protein.

There is substantial interest in advancing resveratrol for cancer prevention and therapy. The plasma pharmacokinetics of resveratrol in humans are now fairly well characterized, with studies indicating that repeated daily administration is safe and well tolerated.

Quercetin

Quercetin, a prominent member of the flavonoid family, is a plant-derived compound found in various fruits and vegetables, with dietary intake levels reaching as high as 16–25 mg per day.

The biological effects of quercetin are thought to be linked to the induction of apoptosis through multiple pathways. In vivo studies investigating the anticancer properties of quercetin have shown that oral administration can prevent chemically induced carcinogenesis, particularly in the colon. Additionally, quercetin has been found to suppress melanoma growth, invasion, and metastatic capabilities.

Similar to resveratrol, poor bioavailability remains a major limitation for quercetin.

6. Vitamins and Minerals in Cancer Management

The roles of vitamins A, C, E, and trace elements such as selenium have been proposed to contribute to cancer prevention in several independent studies. Supplementation with micronutrients as an adjunct therapy in cancer patients may prove beneficial.

Ascorbate (vitamin C) is an essential nutrient in the human diet, but it is also widely used as a therapeutic agent and has long been regarded as a treatment for various illnesses.

Research focusing on the mechanisms of ascorbate's cytotoxicity has revealed its ability to induce apoptosis through cell cycle arrest, activation of apoptotic factors, and disruption of iron uptake in cells. Additionally, ascorbate functions as an electron donor in redox reactions, and accumulating evidence supports the notion that oxidative stress plays a central role in ascorbate-induced toxicity in tumor cells**.**

Further in vitro and in vivo studies are investigating the true potential of ascorbate, including its use in combination with chemotherapeutic agents.

Combined Therapy:A New Promise? Although chemotherapy has evolved into the era of precision drugs, the anticancer effectiveness of current regimens remains constrained, probably due to extensive tumor clonal diversity, genetic heterogeneity within tumors, and the intricacy of cellular signaling networks.

Clinical findings have generally demonstrated that some cancers are notably resistant to chemotherapy, and in line with this evidence, the best therapeutic outcomes have been achieved through the administration of combined drug regimens.

Nevertheless, combination therapies are linked to a certain extent of dose-dependent adverse effects. Consequently, the advancement of personalized, mechanism-oriented, and targeted treatment strategies to enhance therapeutic success and reduce side effects is deemed essential for effective cancer management. To attain high effectiveness and reduced toxicity in cancer treatment, choosing therapeutic agents is a vital step in formulating a strategy. Recently, certain dietary compounds, recognized for their anticancer properties, have gained greater prominence in combination therapies.

These substances can exert their anticancer effects by modulating different cellular signaling cascades. Importantly, these nutraceuticals are non-toxic, so conventional cancer treatments combined with these nutraceuticals may demonstrate enhanced anticancer efficacy through synergistic interactions.

Thus, combination therapies may also lessen systemic toxicity caused by chemotherapy or radiation therapy because lower doses of chemotherapeutic agents can be used in conjunction with nutraceuticals, thereby reducing adverse side effects.

Given that ascorbate is well tolerated by the human body even at concentrations toxic to mesothelioma cells, Martinotti and collaborators sought partner compounds that could act synergistically with ascorbate against mesothelioma cell proliferation. They evaluated commonly used chemotherapeutic drugs in mesothelioma treatment, including cisplatin, etoposide, gemcitabine, imatinib, paclitaxel, and raltitrexed, as well as other promising antitumor agents not yet introduced in clinical practice.

Isobologram analyses, based on in vitro cytotoxicity assays, revealed synergistic interactions between ascorbate, EGCG, and gemcitabine, a classical chemotherapeutic drug.

These researchers also proposed a novel therapeutic regimen for mesothelioma, termed active nutrients/drug (AND) therapy, involving a synergistic combination of EGCG, ascorbate, and gemcitabine, all applied at pharmacological doses .

This AND formulation—comprising ascorbate, EGCG, and gemcitabine—induces disruption of the cell cycle and programmed cell death in mesothelioma cells. Crucially, the mechanism is synergistic and involves disturbance of free cytosolic Ca^{2+}, increased expression of DAPK2, inhibition of NF-κB, and cell cycle arrest that prevents progression into the G2/M phase.

These results corroborate previous findings and suggest that this combination could be effectively employed as a clinical intervention for malignant mesothelioma, potentially yielding higher patient response rates without escalating drug dosages.

7. Present Limitations of Nutraceuticals in Cancer

Nature is a promising source of active principles against It is widely recognized that various herbal remedies can interfere with pharmaceutical treatments. For example, garlic has been shown to exhibit blood-thinning effects, and adverse interactions with warfarin have been observed for both ginger and ginkgo. One of the most extensively studied herb-drug interactions involves St. John's Wort (*Hypericum perforatum*), which has been found to stimulate cytochrome P450 3A4—an essential enzyme involved in the metabolism of certain anticancer medications. Additionally, the isoflavones present in soy products have been shown to counteract the effects of selective estrogen receptor modulators (SERMs), such as tamoxifen.

Moreover, botanical products containing anthraquinones—such as senna (*Cassia senna*) and cascara (*Rhamnus purshiana*)—as well as dietary fibers like guar gum and psyllium, may hinder the absorption of specific medications. Furthermore, recent research indicates that some antioxidants derived from botanical extracts might contribute to increased chemotherapy resistance in patients with late-stage cancer.

8. Future Directions

Cancer cells can be influenced by a variety of biologically active plant-derived compounds known as phytochemicals, which exhibit a wide range of intriguing and significant effects on human cellular functions. The incorporation of phytochemicals into cancer management has significantly driven the growth of the nutraceutical industry, leading to the development of numerous products containing these bioactive compounds, each with distinct formulations and health benefit claims.

The current challenge lies in formulating dietary supplements that can aid in the prevention or delay of nutrition-related illnesses within specific demographic groups. Achieving this goal requires a deeper understanding of the molecular mechanisms through which these substances influence human physiology.

In this regard, the following research areas are receiving increasing attention:

- utilization of *omics* technologies to enhance comprehension of the involvement of phytochemicals in biological pathways;
- investigation of how dietary elements impact epigenetic mechanisms and overall human health;
- evaluation of biomarkers to track the influence of nutritional components on disease progression and prevention.

9. Conclusions.

Cancer rates are continuously increasing worldwide. At the same time, the importance of plant-based medicines is also on the rise, as they are being adopted more frequently in health practices. Although several investigations have shown favorable outcomes, the exact biological pathways through which these natural agents operate are still not fully understood.

- Functional foods and nutraceuticals offer a valuable source of compounds with cancer-preventive potential, as they are cost-effective and generally lack harmful side effects.
- Nonetheless, additional research is essential to determine the most relevant biological targets of these phytoconstituents. This will allow the development of customized clinical trials, aimed at producing reliable and reproducible results for the prevention and treatment of cancer.

References

Andersen, V., Holst, R., & Vogel, U. (2013). Systematic review: diet-gene interactions and the risk of colorectal cancer. *AlimentPharmacolTher*,*37*, 383-391. http://dx.doi.org/10.1111/apt.12180

Bazzan, A. J., Newberg, A. B., Cho, W. C., & Monti, D. A. (2013). Diet and Nutrition in Cancer Survivorship and Palliative Care. *EvidBasedComplementAlternatMed*,*2013*, 917647. http://dx.doi.org/10.1155/2013/917647

Clifford, M. N., van der Hooft, J. J., & Crozier, A. (2013). Human studies on the absorption, distribution, metabolism, and excretion of tea polyphenols. *AmJClinNutr*,*98*, 1619S-1630S. http://dx.doi.org/10.3945/ajcn.113.058958

Dajas, F. (2012). Life or death: neuroprotective and anticancer effects of quercetin. *JEthnopharmacol*,*143*,383-396. http://dx.doi.org/10.1016/j.jep.2012.07.005

Danaei, G., Vander Hoorn, S., Lopez, A. D., Murray, C. J., & Ezzati, M. (2005). Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. *Lancet*,*366*, 1784-1793. http://dx.doi.org/10.1016/S0140-6736(05)67725-2

DeAmicis,F.,Perri,A.,Vizza,D.,Russo,A.,Panno,M.L.,Bonofiglio,D.,…Ando,S.(2013).Epigallocatechin gallate inhibits growth and epithelial-to-mesenchymal transition in human thyroid carcinoma cell lines. *JCellPhysiol*,*228*, 2054-2062. http://dx.doi.org/10.1002/jcp.24372

DellaPenna,D.(1999).Nutritionalgenomics:manipulatingplantmicronutrientstoimprovehumanhealth.

Science,*285*,375-379.http://dx.doi.org/10.1126/science.285.5426.375

Fernandes, G. (1989). The influence of diet and environment. *CurrOpinImmunol*,*2*, 275-281. http://dx.doi.org/10.1016/0952-7915(89)90200-8

Fugh-Berman,A.(2000).Herb-druginteractions.*Lancet*,*355*,134-138.

http://dx.doi.org/10.1016/S0140-6736(99)06457-0

Gescher, A., Steward, W. P., & Brown, K. (2013). Resveratrol in the management of human cancer: how strong is the clinical evidence? *AnnNYAcadSci*,*1290*, 12-20. http://dx.doi.org/10.1111/nyas.12205

Grimble, R. F. (2003). Nutritionaltherapy for cancer cachexia. *Gut*, *52*, 1391-1392.

http://dx.doi.org/10.1136/gut.52.10.1391

Hertog, M. G., Feskens, E. J., Hollman, P. C., Katan, M. B., & Kromhout, D. (1993). Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. *Lancet*,*342*, 1007-1011. http://dx.doi.org/10.1016/0140-6736(93)92876-U

Issa, A. Y., Volate, S. R., & Wargovich, M. J. (2006). The role of phytochemicals in inhibition of cancer and inflammation:Newdirectionsandperspectives.*JFoodComposAnal*,*19*,405-419.

http://dx.doi.org/10.1016/j.jfca.2006.02.009

Jemal,A.,Bray,F.,Center,M.M.,Ferlay,J.,Ward,E.,&Forman,D.(2011).Globalcancerstatistics.*CACancerJClin*,*61*, 69-90.

http://dx.doi.org/10.3322/caac.20107

Kalra, E. K. (2003). Nutraceutical- Definition and introduction. *Aaps Pharmsci*, http://dx.doi.org/10.1208/ps050325

Komarova, N. L., & Boland, C. R. (2013). Cancer: calculated treatment. *Nature,499*, 291-292. http://dx.doi.org/10.1038/499291a

Lecour,S.,&Lamont,K.T.(2011).Naturalpolyphenolsandcardioprotection.*MiniRevMedChem,11*, 1191-1199. http://dx.doi.org/10.2174/138955711804586766

Levine, M., Rumsey, S. C., Daruwala, R., Park, J. B., & Wang, Y. (1999). Criteria and recommendations for vitamin C intake. *JAMA,281*, 1415-1423. http://dx.doi.org/10.1001/jama.281.15.1415

Martinotti, S.,Ranzato, E.,& Burlando, B.(2011). In vitro screening of synergistic ascorbate-drug combinations for the treatment of malignant mesothelioma. *ToxicolInVitro,25*, 1568-1574. http://dx.doi.org/10.1016/j.tiv.2011.05.023

Martinotti, S., Ranzato, E., Parodi, M., Vitale, M., & Burlando, B. (2014). Combination of ascorbate/epigallocatechin-3-gallate/gemcitabine synergistically induces cell cycle deregulation and apoptosisinmesotheliomacells.*ToxicolApplPharmacol,274*,35-41.

http://dx.doi.org/10.1016/j.taap.2013.10.025

McCullough,M.L.,&Giovannucci,E.L.(2004).Dietandcancerprevention.*Oncogene,23*,6349-6364. http://dx.doi.org/10.1038/sj.onc.1207716

Misotti,A.M.,&Gnagnarella,P.(2013).Vitaminsupplementconsumptionandbreastcancerrisk:areview.

Ecancermedicalscience,7,365.

Moyers,S.B.,&Kumar,N.B.(2004).Greenteapolyphenolsandcancerchemoprevention:multiple mechanisms and endpoints forphase II trials. *Nutr Rev*, *62*, 204-211.

http://dx.doi.org/10.1111/j.1753-4887.2004.tb00041.x

Nakata, R., Takahashi, S., &Inoue, H. (2012). Recent advances in the study on resveratrol. *BiolPharmBull,35*, 273-279. http://dx.doi.org/10.1248/bpb.35.273

Ogilvie, G. K. (1998). Interventional nutrition for the cancer patient. *ClinTechSmallAnimPract,13*, 224-231. http://dx.doi.org/10.1016/S1096-2867(98)80007-8

Orzechowski,A.,Ostaszewski,P.,Jank,M.,&Berwid,S.J.(2002).Bioactivesubstancesofplantoriginin food--impact on genomics. *ReprodNutrDev,42*, 461-477. http://dx.doi.org/10.1051/rnd:2002037

Pericleous, M.,Mandair, D., & Caplin,M.E.(2013). Dietandsupplements andtheir impact on colorectalcancer.

JGastrointestOncol,4,409-423.

Posadzki, P., Watson, L., & Ernst, E. (2013). Herb-drug interactions: an overview of systematic reviews. *BrJClinPharmacol,75*, 603-618.

Priyadarsini, R. V., & Nagini, S. (2012). Cancer chemoprevention by dietary phytochemicals: promises and pitfalls. *CurrPharmBiotechnol,13*, 125-136. http://dx.doi.org/10.2174/138920112798868610

Ranzato, E., Biffo, S., & Burlando, B. (2011). Selective ascorbate toxicity in malignant mesothelioma: a redox Trojan mechanism. *AmJRespirCellMolBiol,44*, 108-117. http://dx.doi.org/10.1165/rcmb.2009-0340OC

Ranzato, E., Martinotti, S., Magnelli, V., Murer, B., Biffo, S., Mutti, L., & Burlando, B. (2012). Epigallocatechin-3-gallate induces mesothelioma cell death via H_2O_2 -dependent T-type Ca^{2+} channel opening. *JCellMolMed,16*, 2667-2678. http://dx.doi.org/10.1111/j.1582-4934.2012.01584.x

Roudebush,P.,Davenport,D.J.,&Novotny,B.J.(2004).Theuseofnutraceuticalsincancertherapy.*VetClinNAm-Small,34*(1), 249-269. http://dx.doi.org/10.1016/j.cvsm.2003.09.001

Sarkar, F. H., & Li, Y. (2006). Using chemopreventive agents to enhance the efficacy of cancer therapy. *CancerRes,66*, 3347-3350. http://dx.doi.org/10.1158/0008-5472.CAN-05-4526

Scott,E.,Steward,W.P.,Gescher,A.J.,&Brown,K.(2012).Resveratrolinhumancancerchemoprevention- choosingthe' right'dose. *MolNutrFood Res*, *56*,7-13.http://dx.doi.org/10.1002/mnfr.201100400

See, D., Mason, S., & Roshan, R. (2002). Increased tumor necrosis factor alpha (TNF-alpha) and natural killer cell (NK) function using an integrative approach in late stage cancers. *ImmunolInvest,31*, 137-153. http://dx.doi.org/10.1081/IMM-120004804

Singh, C. K., George, J., & Ahmad, N. (2013). Resveratrol-based combinatorial strategies for cancer management. *AnnNYAcadSci,1290*, 113-121. http://dx.doi.org/10.1111/nyas.12160

Smith-Warner, S. A., Elmer, P. J., Tharp, T. M., Fosdick, L., Randall, B., Gross, M., … Potter, J. D. (2000). Increasing vegetable and fruit intake: randomized intervention and monitoring in an at-risk population. *CancerEpidemiolBiomarkersPrev,9*, 307-317.

Surh, Y. J. (2003). Cancer chemoprevention with dietary phytochemicals. *NatRevCancer,3*, 768-780. http://dx.doi.org/10.1038/nrc1189

Tuomisto, J. T., Tuomisto, J., Tainio, M., Niittynen, M., Verkasalo, P., Vartiainen, T., … Pekkanen, J. (2004). Risk-benefit analysis of eating farmed salmon. *Science305*, 476-477; author reply 476-477. http://dx.doi.org/10.1126/science.305.5683.476

Volta, V., Ranzato, E., Martinotti, S., Gallo, S., Russo, M. V., Mutti, L., … Burlando, B. (2013). Preclinical demonstration of synergistic Active Nutrients/Drug (AND) combination as a potential treatment for malignant pleural mesothelioma. *PLoSOne,8*, e58051. http://dx.doi.org/10.1371/journal.pone.0058051

Weisburger, J. H. (1999). Antimutagens, anticarcinogens, and effective worldwide cancer prevention. *JEnvironPatholToxicolOncol,18*, 85-93.

Zhang, D. D. (2010). The Nrf2-Keap1-ARE signaling pathway: The regulation and dual function of Nrf2 in cancer. *AntioxidRedoxSignal,13*, 1623-1626. http://dx.doi.org/10.1089/ars.2010.3301

Zhang, X., Chen, L. X., Ouyang, L., Cheng, Y., & Liu, B. (2012). Plant natural compounds: targeting pathways ofautophagyasanti-cancertherapeuticagents.*CellProlif,45*,466-476. http://dx.doi.org/10.1111/j.1365-2184.2012.00833.x