



Benefit of Nutraceuticals in Cancer Therapy

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ABSTRACT

In older days human being think cancer is no answer, means not treatable. In current scenario observed that 30–40% of the cancer can be avoided by only changing the life style and way of taking diet. Cancer is a public health concern, and a major source of global morbidity and mortality. The conventional cancer therapies such as systemic therapy, surgery and radio-therapy have brought concomitant adverse effects such as multidrug resistance, cytotoxicity to adjacent normal cells and high financial burden in accessing them. When a diet is compiled according to the guidelines here it is likely that there would be at least a 60–70 percent decrease in breast, colorectal, and prostate cancers, and even a 40–50 percent decrease in lung cancer, along with similar reductions in cancers at other sites. Such diet would be conducive to preventing cancer and would favour recovery from cancer as well.

Keywords: nutraceuticals, cancer, polyphenols, flavonoids, dietary fibers.

INTRODUCTION

Cancer is a disease that is identified by its characteristic unrestricted cell growth and propagation. It is a situation where cells are no longer regulated by the body's normal growth control mechanisms and so have gained the ability to divide and proliferate indefinitely, resisting aging and normal programmed cell death. It is a product of multi-step process requiring the addition of many genetic and epigenetic changes over time.[1-2] The World Health Organization predicts that by 2050 there will be around 27 million cases with an annual mortality rate of 17.5 million individuals.[3] Nutraceuticals is defined as "Any substance that may be measured a food or part of a food and provides medical or health benefits including the prevention and treatment of disease". [4] The attempts towards creating the functional components. Nutraceuticals are the new generation of food which has the edge between drug and food. About 2000 years ago, the well-recognized father of medicine Hippocrates (460-377 BC) underlined "Let food be thy medicine and medicine be the food. Functional foods have one or more compounds with biochemical and physiological functions helpful to human health.[5] Nutraceuticals can be categorized in several ways. So based on food sources, mechanism of action and chemical nature, they can be classified as follows:[6]

- Dietary Fibre
- Probiotics & Prebiotics
- Polyunsaturated fatty acids
- Antioxidant vitamins
- Polyphenols
- Spices



Fig 1. Classification of nutraceuticals

Nutraceutical role in cancer

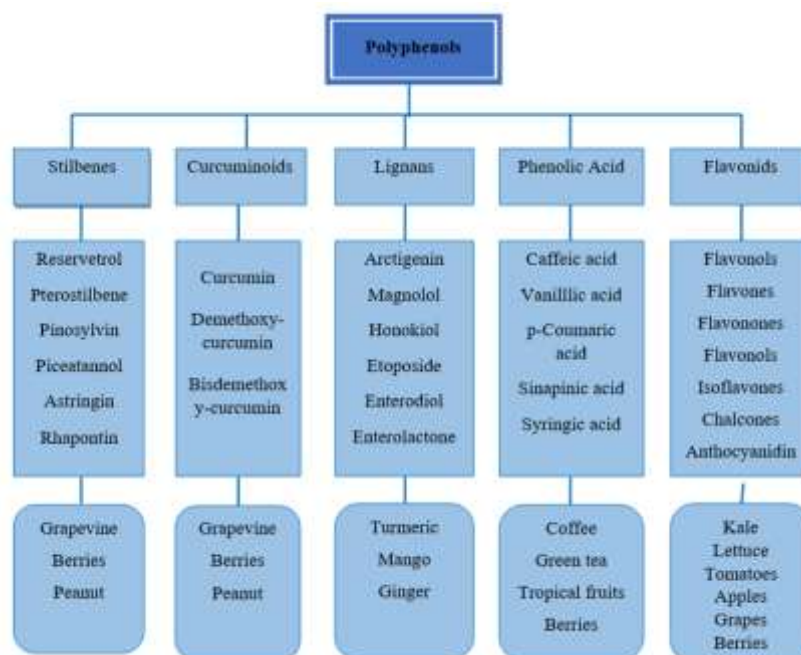
Nutraceutical oncology is the application of nutraceuticals and functional foods in cancer prevention, treatment and management. In recent times, researches have shown that about 64% to 81% of human cancer patients take various nutraceuticals supplements such as vitamins and minerals, or herbal supplements, even with about 68% of their physicians unconscious of their supplement use. [7-9] Foods low in simple carbohydrates with logical amounts of high-quality protein, fiber, and fat (especially fats of the omega-3 fatty acid series) are beneficial for cancer patients. Also, certain supplemental micronutrients, nutraceuticals and functional foods have potential to reduce the risk of developing cancer. They are also important in reducing toxicity connected with chemotherapy and radiation therapy, and may lead to better life conditions by reducing cancer cachexia.[10]

Nutraceuticals use in the cancer treatment

It has also been estimated that one-third of all cancers deaths are preventable by life-style changes including suitable nutrition.[11] 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 lead 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 soothing 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, indicating 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.[12] 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.[13] 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.[14]

Polyphenols

Polyphenols are plant secondary metabolites that include 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. [15]. They are naturally occurring compounds found largely in fruits, vegetables, cereals and beverages. Fruits like grapes, apple, pear, cherries and berries have up to 200–300mg polyphenols per 100 grams fresh weight. A glass of red wine or a cup of tea or coffee contains about 100mg polyphenols. Polyphenolic compounds have the ability to influence and alter a wide range of biological mechanisms and events implicated in the development of cancer. Additionally, they can serve as pharmacological enhancers that enhance immune response operation and buffer living tissue from oxidative stress induced damages.[16] Despite widespread evidence linking the polyphenols to the cancer management, only a small number of the preventive consequences of specific chemicals have been solidly established in clinical trials as a result of variations in dosage and other extraneous variable. [17-18]. Cereals, dry legumes and chocolate also contribute to polyphenolic intake.[19] New chemo protective medicines that are safer than current treatment shaves in research centralized on naturally occurring plant compounds. As a result, this class of compounds has been investigated for their potential to inhibit the development and growth of tumours, migration, inflammatory processes, and cell death. [20]



These substances as possible anticancer drugs will be facilitated by the fact that polyphenols can be isolated utilizing inexpensive, environmentally friendly methods, including ultrasound-assisted extraction, and that upon sterilization, polyphenols retain the preponderance of their characteristics. Among diverse plants species, over 8000 polyphenolic metabolites have been discovered. Studies evaluating the potential health advantages of polyphenols, such as prevention of oxidative stress cardiovascular problems, hypoglycaemia, bronchitis, neurological condition, and even ageing.[21]

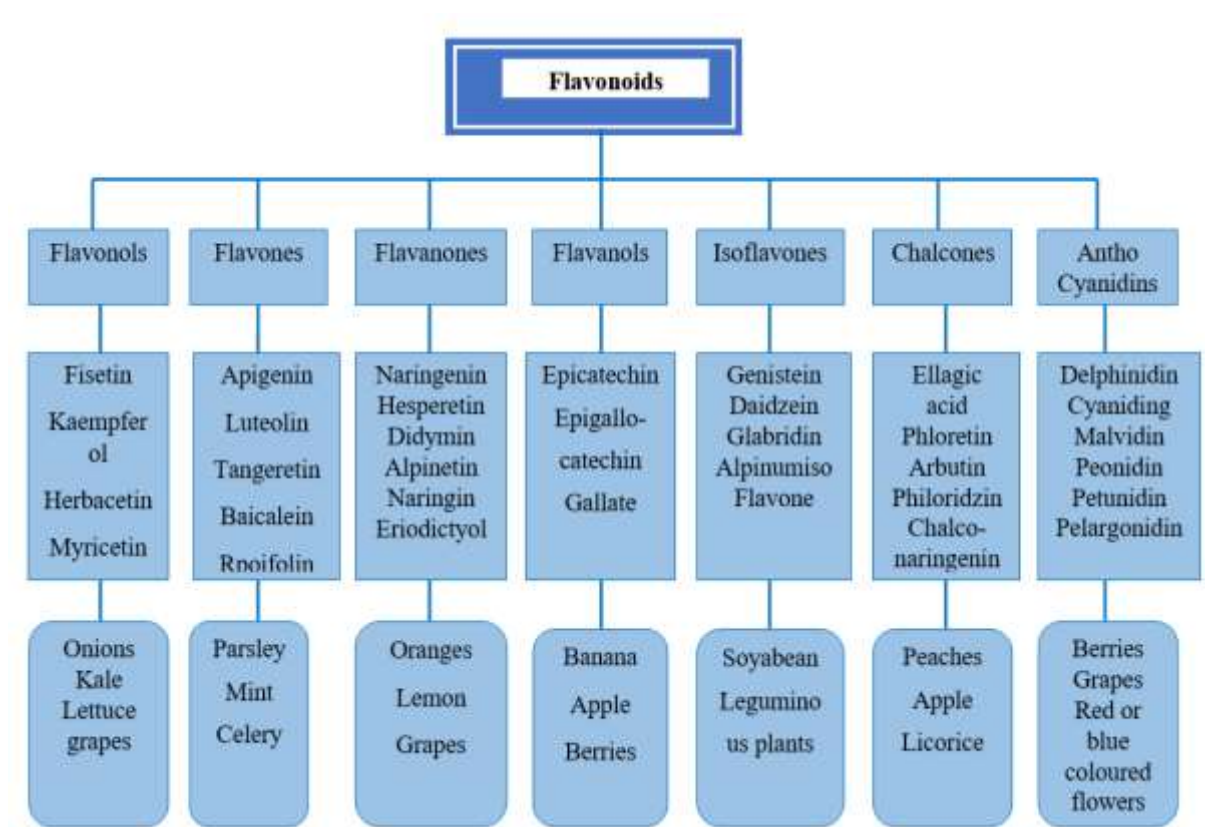
1. Stilbenes: Stilbenes, also known as stilbenoids, are hydroxylated metabolites of stilbene that are synthesized in a diverse range of plants, including cannabis, berries, vines, and nuts. Additionally, trees produce stilbenes as other by products, which antioxidant properties [22-23] Resveratrol is the most well-known member of the stilbene family and provides a number of medical advantages and there have been several investigations on them. [24] According to research, resveratrol inhibits the growth of a wide variety of human malignancies in vitro, including those of the mammary, epidermis, ovarian, gastrointestinal, prostate, colorectal, hepatic, pancreatic, cervical, laryngeal, nasopharyngeal, lymphoid, and myeloid cancers.[25]

2. Curcuminoids: Curcumin is well-known for its anti-inflammatory and antioxidant qualities. Curcumin's ability to reduce tumorigenesis and angiogenesis and decrease cellular proliferation has been established in different cancer models.[26] Curcumin derivatives are helpful in the treatment of colon cancer cells. Curcumin can inhibit cancer proliferation and invasion in besides controlling tumorigenesis, angiogenesis, and triggering cell death.[27] Numerous research centralized on pulmonary carcinoma, indicate that curcumin affects signal transduction restriction and State network activation. Because of its associations with arachidonate pathway in addition to its in vivo anti-angiogenic capabilities, curcumin may exert anti-tumour effects.[28] Curcumin has proven benefits against a number of malignancies, particularly colon, pancreas, ovarian, prostate, pulmonary, myeloma, and squamous cell carcinoma. [29-30]

3. Lignans: Lignans are diphenolic chemicals that can be detected in very modest levels plants, such as cabbage, legumes, beans, wheat, seeds (sesame, pumpkin, flax) and various berries. Lignans, is well recognized for its strong antioxidant capabilities. Owing to their potential to duplicate the actions of human hormones, lignans could be employed as anticancer medications. [31] According to several research, arctigenin prevents the proliferation of immune cells. The caspase-3 protein, which is essential for the destruction of cancerous cells, is activated more actively in response to the presence of arctigenin. [32] Together with magnolol and obovatol as analgesics, honokiol has been prescribed in conventional treatments to address depression and anxiety issues. Multiple studies have discovered that honokiol has the capacity to destroy tumour cells in different types of cancer. [33]

4. Phenolic acids: The two types of phenolic acids are either benzoic acid derivatives or cinnamic acid derivatives. P-coumaric acid is the phenolic acid that has so far demonstrated therapeutic benefits that make it a viable option in the therapeutic strategies for the administration of cancer. A multitude of fruits and vegetables contain the natural component p-coumaric acid, which is formed from cinnamic acid and has been shown to have anticancer and antioxidant effects.[34] Many plants contain significant quantities of vanillic acid, which has been utilized in traditional medicine for a number of ailments. The plant metabolites, vanillic acid, has been investigated for the treatment of colon cancer by operating on a different cellular process.[35] Vanillic acid has demonstrated to exert anti-proliferate and anti-angiogenic effects on the cancerous cells. Ferulic acid has demonstrated antineoplastic effect in a variety of malignancies, including colon and lung cancer as well as tumours of the nervous system. [36] Ferulic acid may trigger cell death in LNCaP cells while it may induce cell cycle interruption in PC-3 cells. Its optimization approaches in preventing tumour metastasis are yet uncertain. The plant metabolite ferulic acid is reduced to create poly ferulic acid, which functions as a drug delivery carrier and has anticancer activities. [37]

5. Flavonoids: It comprises the most studied group of polyphenols. More than 4,000 varieties of flavonoids have been identified, many of which are liable for the attractive colours of the flowers, fruits and leaves. They are divided into six subclasses: Flavonols, flavones, flavanones, flavanols, anthocyanidines and isoflavones. Quercetin, myricetins, catechins etc., are some most common flavonoids.[38] Flavonoids possess a wide range of chemotherapeutic actions, including modulating the activity of enzymes that search reactive oxygen species, participating in cycle arrest, inducing cell death and autophagy, and reducing the multiplication and pervasiveness of cancerous cells. Flavonoids operate as antioxidants under normal circumstances and are strong pro-oxidants in the cancerous cells, stimulating the cell apoptosis and by the decreased expression of pro-inflammatory signaling pathways. [39] Flavonoids have a wide range of antitumor actions, including modulating the functions of reactive oxygen species scavenging enzymes, participating in cycle arrest, inducing autophagy, and inhibiting the multiplication and intrusiveness drug delivery systems that contain kaempferol. Kaempferol therapy had a substantial anti-proliferative impact on the stomach cancer cells MKN28 and SGC7901 despite appearing to have any negative effects on healthy intestinal epithelial cells. [40]



Flavanols : Flavanols, which are primarily create in foods like apples, grapes, cereals, oats, peaches, oranges, berries, red onion oranges, cruciferous vegetables, egg, plants berries,cabbage, peppers, potatoes, spinach, aloe vera, thyme, soyabean. [41] Additionally noted is a decrease in the docetaxel sensitivity of cancerous cells when quercetin is added to docetaxel chemotherapy for prostate cancer. As a consequence of intensifying cancer cell apoptosis and decreasing tumour development, cancer therapy becomes more effective. In another study, kaempferol therapy had a large anti-proliferative impact on the stomach cancer cells MKN28 and SGC7901 despite appearing to have any negative effects on healthy intestinal epithelial cells.

Flavones: Herbs, red or purple plants, and vegetables primarily contain flavones. Flavones often function in plants as defence mechanisms against disease caused on by infections. The most famous example is luteolin, which has been employed as a yellow pigment since olden days. Wool has also been dyed with apigenin. [42] Wogonin is also well-known for being one of the key components in Japanese herbal medicines. Their effective antibacterial, antioxidant, antimicrobial, antitumor, and anticancer properties, this family of flavonoids has attracted medical attention. According to research, apigenin (30–60mg/kg/week) can stop the progression of stomach cancer and the gastritis caused by *Helicobacter pylori*. It is believed that luteolin could play a significant role in the treatment of cancer because of its positive impacts on the human body, including its antioxidant properties and anti-inflammatory properties, capacity to neutralize free radicals, promotion of glucose metabolism, and ability to change the immune response. This flavoneis typically used with other cancer medications to support the anticancer properties of luteolin.[43] By enhancing the activity of the caspase-3and Baxproteins,the administration of luteolin along with oxalipatin, a traditional anticancer medication was advantageous in preventing the growth of cancer cells, and inhibited the multiplication of gastric cancer cells in vitro.

Flavanones: Flavone is the source of the colourless ketones known as flavanones. Because of their antioxidant capacity, radical scavenging ability, cardioprotective, anti-inflammatory, antimicrobial, and anticarcinogenic activities, flavanones have been more significant in medicine during the recent decades. Most frequently, hesperetin and naringenin are tested as likely anti-cancer medications.The anticancer effects of hesperetin on particular malignancies have been extensively studied and published in a number of journals.It prevents the uptake of glucose by different cancer cell lines, lowers NF- κ B activity, which slows the growth of tumours, and improves lethality by causing the production of intracellular ROS. Interestingly, experiments evaluating the anticancer benefits of naringenin and hesperetin administration were conducted in vitro and in vivo for human pancreatic cancer. naringenin and hesperetin together could be employed as aviable non-toxic cancer therapeutic approach to halt the growth of pancreatic cancer. [44]

Flavanols: Flavanols include catechin and its derivatives. Flavanols are abundant in tea and chocolate.These substances offer protection from perilous intruders like micro-organisms, fungus, bugs, and herbivorous animals. The advantages of flavanols for human well-being have so been extensively researched. Discovering a correlation between drinking green tea and an increased risk of developing malignancy has been the subject of extensive research. An apparent illustration is the study's confirmation that drinking up to seven cups of green tea (catechin) per day some what lowers the risk of developing prostate cancer.[45] Even though epigallocatechin gallate is a flavanol that is frequently present in nature, its usefulness in cancer therapy is restricted by issues with poor stability, poor absorption, and liver toxicity.

Isoflavones: In terms of potential therapeutic uses, genistein and daidzein are the subgroup's most extensively researched substances. But other isoflavones, such as glabridin and alpinum isoflavone, have sparked interest as promising cancer treatments for numerous tumours. Genistein has been shown to play a role in the controlling of several genes linked to the development of cancer through a number of mechanisms. Additionally, other research has looked into how genistein interacts with other anticancer medications. Cisplatin and genistein combinations at various doses as a potential anticancer therapy for cervical cancer cells have been proven effective from previous investigations. In breast cancer cell lines, daidzein decreased the expression of multidrug resistance-associated protein.[46]

The greatest dose of daidzein was necessary in this instance to see a sizable reduction in tumour size. The authors also noted that the combination therapy including daidzein and consistent exercise stimulates apoptosis in breast cancer cells.

Chalcones: Chalcones can be found in a wide range of vegetables and fruits including apples, cherries, shallots, onions, and green beans, as well as in some culinary herbs like liquorice. Ellagic acid, which has been researched as a potential anticancer agent, is the chalcone that has received the greatest interest in the field of medicine. Through the comparison of many possibilities, the advantages of using ellagic acid to cure tumors have been researched for decades. Few researchers have attempted to encapsulate ellagic acid in order to boost its poor permeability as well to improve its regulated distribution. [47] Two distinct biopolymers were used to nano encapsulate ellagic acid, which were subsequently evaluated against MCF-7 breast cancer cells. In comparison to non-encapsulated ellagic acid, the cytotoxicity of encapsulated was enhanced by the controlled release of ellagic acid. Additionally, it slowed the growth of malignant cells. [48]

Anthocyanidins: Plants contain water-soluble compounds called anthocyanidins. The hues of the fruits, blossoms, and foliage are due to them. Anthocyanins are present in berries and other fruits that are consumed by people. Owing to their physicochemical characteristics, these kinds of phytochemicals are also widely employed in the pharmaceutical industries to lower the risk of developing different ailments like over weight, enhance cognition and age-related impairments, or strengthen the immune system. [49] Anthocyanidins from the plant *Cyanomorium coccineum* have demonstrated anticancer properties, and studies on various leukaemia cell lines have shown that they have an inhibitory effect on cell proliferation. Numerous studies have shown delphinidin to have antitumor properties. Delphinidin boosted the activation of Caspase-3, Caspase-7, and Caspase-8, effectively promoting the death of cancer cells, according to studies that examined the effectiveness of the compound against prostate cancer. [50]

Antioxidants & vitamins

The role of antioxidant vitamins such as ascorbic acid, lycopene, beta-carotene, alpha tocopherol, retinoids and non-vitamin natural antioxidants (e.g. glutathione) in the prevention of cancer diseases had already been reported. Free radical production is a chain reaction and has 3 steps namely initiation, propagation and termination. These free radicals once produced, damage macromolecules by attacking at the double bonds. Antioxidant supplementation has however been seen to counteract other cancer therapy such as chemotherapy and radiotherapy. This is because these therapies cause cancer cell death. [51] Moss in the year 2007, investigated articles and reviews to find out the use of a-tocopherol for the amelioration of radiation-induced mucositis; pentoxifylline and vitamin E to correct the adverse effects of radiotherapy; melatonin alongside radiotherapy in the treatment of brain cancer; retinol palmitate as a treatment for radiation-induced proctopathy; a combination of antioxidants (and other naturopathic treatments) and the use of synthetic antioxidants like amifostine and dexrazoxane, as radioprotectants. With few exceptions, most of the studies draw positive conclusions about the interaction of antioxidants and radiotherapy. [52] Currently, evidence is growing that antioxidants may provide some benefit when combined with certain types of chemotherapy. Because of the potential for positive benefits, a randomized controlled trial evaluating the safety and efficacy of adding antioxidants to chemotherapy in newly diagnosed ovarian cancer is underway at the University of Kansas Medical Center. [53]

Spices

It across the globe, over 80 spices are grown and out of them near 50 spices are cultivated in India. As the Scientific studies have shown the antioxidant, anti-inflammatory and immune modulatory effects of these spices, which are utilized in prevention and treatment of several cancers, including lung, liver, breast, stomach, colorectum, cervix, and prostate cancers. Their main mechanisms of action include inducing apoptosis, inhibiting proliferation and migration and invasion of tumors, and sensitizing tumors to radiotherapy and chemotherapy. [54] Spices are the rich reservoir of many therapeutically active compounds viz. alkaloids, phenolic compounds, flavonoids, quinines, amino acids, polypeptides, terpenoids, vitamins etc. Approximately 180 chemical compounds from spices have been authenticated to be used against different degenerative diseases. Out of them, numerous bioactive are also being ferulic as the evidenced for cancer risk management. Cinnamaldehyde, allyl isothiocyanate, gingerol, tumerone, shagol, sulfur-containing compounds, zingiberene, anethole, estragole, acid, caryophyllene, alliin, 1,8-cineole, thymoquinone, eugenyl acetate, eugenol, limonene, sabinencamphene, rutin, curcuminoids, curcumin, myrceneajoene, linalool, cuminaldehyde, phenethyl isothiocyanate, myristicin, capsaicin, methiin, trigonelline, citral, safrole, quercetin, rosmarinic acid, allicin, and many other compounds derived from spices play a pivotal role in cancer prevention.[55]

Probiotics and Prebiotics

Probiotics are also defined as beneficial bacteria or other microorganisms that are added in foods, which add to the friendly microbial flora in the intestinal tract. Examples of common strains include Lactobacillus and Bifidobacterium families of bacteria. Some are naturally found in fermented foods like sauerkraut and yogurt; while some are added as nutraceutical ingredients in some foods usually displayed on the food's label. [56] Prebiotics are non-digestible foods in human digestive system (onions, garlic, bananas, Jerusalem artichoke, chicory root, beans, skin of apples, or other fiber) that have the capability to stimulate the favourable growth and activities of indigenous probiotic bacteria. [57,58] Examples of prebiotics are the inulin-type fructans,

which include native inulin, enzymatically hydrolyzed inulin or oligofructose, and synthetic fructooligosaccharides. Probiotics in Cancer Therapy In recent years, there has been growing interest in the possible application of probiotics as a part of combination therapy with conventional treatment of cancer. An early but controlled and comparative study on 223 patients carried out in 1993 showed that combination therapy including radiation and treatment with heat-killed *L. casei* strains (LC9018) and improved the induction of immune response mechanisms against cancer cells thereby enhancing tumor regression in patients with carcinoma of the uterine cervix. [59] Research on azoxymethane-induced CRC mice model treated by the probiotic mix composed of seven different strains of lactobacilli, bifidobacteria, and streptococcus demonstrated suppression of colon carcinogenesis due to modulation of mucosal CD4+ T polarization and changes in the gene expression. Furthermore, latest experiment investigating the effects of *B. infantis* administration in CRC rat model demonstrated a considerable attenuation of chemotherapy-induced intestinal mucositis correlated with decreased level on proinflammatory cytokines (IL-6, IL-1 β , TNF- α) and increased CD4+ CD25+ Foxp3+ T regulatory cell response [60]. The most recent experiments on mice have illustrated the key role of gut microbiota (*Bacteroides* and *Bifidobacterium*) in anti-PD-L1 (Programmed death-ligand 1) and anti-CTLA-4 (cytotoxic T-lymphocyte-associated protein-4) therapies [61]. Immunomodulatory effect was exhibited in intensified activation of dendritic cells and also promotion of antitumor T cell response.

Dietary fibers

Dietary fibers are endogenous components of plant materials in the diet, which are resistant to digestion by enzymes produced by humans. Fibers can be broadly classified into soluble and insoluble fibers. Soluble fiber can be mainly derived from oat bran and fruit pectin. Wheat, rye, rice and most other grains are main sources of insoluble fibers. Legumes, beans, peas, certain fruits and vegetables are excellent sources of both soluble and insoluble fibers. [62] High fiber foods may help reduce your overall calorie intake and help you maintain a healthy weight, which is vital to reducing cancer risk," says Erma Levy, research dietitian in Behavioral Science at MD Anderson Cancer Center.

Dietary fibre role of reduce colorectal cancer

1. It binds carcinogens to the stool and expels them from the body.
2. Good bacteria in the colon convert fibre into short-chain fatty acids. Short-chain fatty acids reduce the ability of cells in the intestine to become cancerous.
3. By helping us to feel fuller for longer, fibre plays a key role in maintaining a healthy weight.
4. Reducing absorption of carbohydrates into the blood reduces insulin resistance, therefore reducing risk of diabetes and some cancers. [63]

Vitamins and minerals

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. [64] Ascorbate (vitamic 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 .Other studies in vitro and in vivo are evaluating the real potentialities of ascorbate, combining it also with chemotherapeutic drugs .[65]

Nutraceuticals as chemo preventive agents [67]

- [Tomato \(Lycopene and \$\beta\$ -Carotene\)](#)
- [Essential Oils from Aromatic Plants](#)
- [Bee Propolis \(Caffeic Acid Phenethyl Ester\)](#)
- [Brown Algae \(Fucoxanthin\)](#)
- [Curcuma](#)
- [Fruits and Vegetables](#)
- [Garlic: Allyl Sulfur Compounds](#)
- [Ginger \(Gingerols and 6-Shogaol\)](#)
- [Saffron \(Crocins\)](#)
- [Olive Leaf \(Oleuropein\)](#)
- [Honey](#)

- [Soybeans and Phytoestrogen Rich Foods \(Genistein, Daidzein\) Tea \(Catechins Including \(-\)-Epigallocatechin-3-gallate\)](#)
- [Vitamins \(C, D and E\)](#)
- [Minerals \(Namely Selenium\)](#)

BENEFIT OF NUTRACEUTICAL IN CANCER THERAPY

Substances used as chemotherapy are majorly alkylating agents (e.g., cyclophosphamide, temozolomide, cisplatin, oxaliplatin), anti-metabolites (e.g., methotrexate, cytarabine, fluorouracil, capecitabine), anti-tumor antibiotics (e.g., doxorubicin, epirubicin, bleomycin), topoisomerase inhibitors (e.g. etoposide, irinotecan) and microtubule stabilizers (e.g. paclitaxel, docetaxel). That leading to some dangerous ailments such as cardiovascular diseases which are the most common causes of death to cancer survivors.[68] Also, cancer radiotherapy is limited by the maximum tolerated dose of radiation to adjacent normal tissues. Thus, effective radiotherapy is considered in terms of how to maximize cancer cell killing capacity within the capacity of acceptable dose that adjacent healthy tissues can tolerate from radiation injury. [69] Nutraceuticals have also been found to be dosage friendly as there are no cases of dose toxicity to the body. They are generally safer than chemotherapeutic drugs and radiotherapy. They are also cost effective relative to conventional methods.[70]

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. [71] 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 and soluble fibers (including guar gum and psyllium) can decrease the absorption of drugs. 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. [72]

CONCLUSION

In nutraceuticals, cancer a promising field of study, which requires more clinical researches to push it into the future. It is the future of cancer prevention, treatment and management. Scientists should seriously to work out the modalities for a standardized nutraceutical oncology. 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.

REFERENCES

1. Bommer U, P. k. (2014). cancer council australia oncology education committee. cancer biology. *sabesan s, olver I, eds*.
2. Mitra S, D. R. (2018). natural products for the management and prevention of breast cancer. *Evidence based complementry and alternative medicine*, 1-23.
3. Sharma A, K. M. (2018). polyphenols in food :cancer prevention and apoptosis induction. *Curr Med Chem* 25:, 4740-4750.
4. Andlauer W, F. P. (2002). a piece of history, present status and outlook . *food Res int*, 171-176. Block KI, G. C. (2015). 276-304.
5. Ferrari Ck .Functional food, h. a. (2004). towards biochemical mechanisms of health aging. *Biogerontology* , 275-89.
6. Chadha R, B. y. (2015). Cocrystallization in Nutraceuticals.In Glebovsky v,ed. *Recrystallization in Materials processing*.
7. OB., N. (2017B). Nutraceuticals: Chemoradiation Sensitizers and Adverse Effect Resolver. *Herbal Medicine* . ; 3: 2.
8. t, S. K. Nutraceuticals: A Role in the Management of the Cancer Patient? *Veterinary Meeting and Expo 2012 Proceeding*. 2012)
9. Wargovich MJ, M. J. (2010; 29:). . Nutraceutical use in late-stage cancer. *Cancer Metastasis Rev.* . 503–510.
10. tripathi , y. (2005). nutraceuticals and cancer management,. *frontiers in bio science*, 1607-1618.
11. Danaei, G. V. (2005). Causes of cancer in the world comparative risk assessment of nine behavioural and environmental risk factors. 1784-1793.
12. Weisburger, J. H. (1999). Antimutagens, anticarcinogens, and effective worldwide cancer prevention. 85-93.
13. Tuomisto, J. T. (2004). Risk-benefit analysis of eating farmed salmon. *Science* 305,. 476-477;.
14. Grimble, R. F. (2003). Nutritional therapy for cancer cachexia. *Gut*, . 1391-1392. .

15. ranzato, e. (2014). role of nutraceuticals in cancer therapy . *food research*, 3_18.
16. Cullen JM, B. M. (2016);. An overview of molecular cancer pathogenesis, prognosis, and diagnosis. In: Tumors in domestic animals. . . *Hoboken, NJ: John Wiley and Sons*, , 1-26.
17. Chen X, Z. H. (2021). D. Cell death in pancreatic cancer: From pathogenesis to therapy. . *Nat Rev Gastroenterol Hepatol*. , :804-23.
18. Marmouzi I, E. S. (2018). he pharmacology of avenanthramides: Polyphenols. In: Polyphenols: Prevention and treatment of human disease. . *Academic Press*. , ;3-13.
19. kb pandey, r. s. (2009). plant polyphenols as dietary antioxidants in human health and disease. *oxidative medicine and cellular longevity*, 270-278.
20. Mukherjee AK, B. S. (2001;8). Advances in cancer therapy with plant based natural products. *Curr Med Chem*. , 1467-86.
21. Mao X, G. C. (2017). Oxidative stress-induced diseases and tea polyphenols. *Oncotarget*. 81649-61.
22. Sirerol JA, R. M. (2016). . Role of natural stilbenes in the prevention of cancer. . *Oxid Med Cell Longev*
23. Faustino C, F. A. (2018;24). Cytotoxic stilbenes and derivatives as promising antimetabolic leads for cancer therapy. . *Curr Pharm Des*, 4270-311. .
24. Ko JH, S. G. (2017;18). The role of resveratrol in cancer therapy. *Int J Mol Sci*, 12.
25. Jiang Z, C. K. (2017). . Resveratrol and cancer treatment:Updates. . *Ann N Y Acad Sci*.; :59-69.
26. Zhang Y, K. A. (2019). The progresses in curcuminoids-based metal complexes: Especially in cancer therapy. *Future Med Chem*. , :1035-56.
27. Chen D, D. F. (2016;22). Dimethoxy curcumin induces apoptosis by suppressing survivin and inhibits invasion by enhancing E-cadherin in colon cancer cells.: *Med Sci Monit*. , 3215-22.
28. Yang CL, L. Y. (. 2012;). Curcumin blocks small cell lung cancer cells migration, invasion, angiogenesis, cell cycle and neoplasia through Janus kinase-STATE signalling pathway. . *PLOS ONE*, 37960.
29. Zoi V, G. V. (2021;). The role of curcumin in cancer treatment. *Biomedicines*.). 9.
30. Teiten MH, D. M. (2014;19). Hybrid curcumin compounds: A new strategy for cancer treatment. *Molecules*. 20839-46.
31. H, A. (2007;). Lignans and human health. *Crit Rev Clin Lab Sci*. :483-525.
32. Wang Y, W. X. (2010). Nanoparticle delivery strategies to target doxorubicin to tumor cells and reduce side effects. *Ther Deliv*., 273-87.
33. Ong CP, L. W. (2019). A review of its anticancer potential and mechanisms. *Cancers*. 48.
34. Pei K, O. J. (2016). p-Coumaric acid and its conjugates: Dietary sources, pharmacokinetic properties and biological activities.. *J Sci Food Agric*, 2952-62.
35. Ho K, Y. L. (.2009). Apoptosis and cell cycle arrest of human colorectal cancer cell line HT-29 induced by vanillin. *Cancer Epidemiol*. 155-60.
36. Damasceno SS, D. B.-F. (2017). J. Chemical properties of caffeic and ferulic acids in biological system: implications in cancer therapy. . *A review. Curr Pharm Des*., 3015-23.
37. Bondi ML, M. G. (2009). Acid-Loaded Lipid Nanostructures as Drug Delivery Systems for Alzheimers Disease:Preparation, Characterization and Cytotoxicity Studies. . *Curr Nanosci*., 26-32.
38. kb pandey, r. s. (2009). plant polyphenols as dietary antioxidants in human health and disease. *oxidative medicine and cellular longevity*, 270-278.
39. L., L. M. (2002;). Cancer preventive effects of flavonoids-a review. *Biomed Pharmacother*. 296-301. .
40. Song H, B. J. (2015). Kaempferol inhibits gastric cancer tumor growth: An in vitro and in vivo study.. . *Oncol Rep*, :868-74.
41. Tian S, S. Y. (2019). Functional properties of polyphenols in grains and effects of physicochemical processing on polyphenols. . *J Food Qua*, 1-8.
42. Singh M, K. M. (2014). An important scaffold for medicinal chemistry . *Eur J Med Chem*., 206-39.
43. Chowdhury AR, S. S. (2002;). an emerging anti-cancer flavonoid, poisons eukaryotic DNA topoisomerase I. *Biochem J*. , 653-61.
44. Lee J, K. D. (2019;). Combined administration of naringenin and hesperetin with odown regulation of FAK and p38 signaling pathway.
45. Yang CS, W. H. (2016). Cancer preventive activities of tea catechins. *Molecules*. 1679.
46. Rigalli JP, T. G. (2016). The phytoestrogen genistein enhances multidrug resistance in breast cancer cell lines by translational regulation of ABC transporters. *Cancer Lett*. translational regulation of ABC transporters. *Cancer Lett*. 165-72.
47. Ríos JL, G. R. (2018;). A pharmacological update of ellagic acid . *Planta Med*, 2018;.

48. Jaman MS, S. M. (2018). Ellagic acid, sulforaphane, and ursolic acid in the prevention and therapy of breast cancer: Current evidence and future perspectives. *Breast Cancer*. . 517-28.
49. Mottaghipisheh J, D. A. (2022;). The promising therapeutic and preventive properties of anthocyanidins/anthocyanins on prostate cancer. *Cells*. . 1070.
50. Ko H, J. M. (2015). prostate cancer cells to TR Delphinidin sensitize AIL-induced apoptosis, by inducing DR5 and causing caspase-mediated HDAC3 cleavage. *Oncotarget* t. 9970-84.
- 51 . tripathi , y. (2005). nutraceuticals and cancer management,. *frontiers in bio science*, 1607-1618.
52. Moss, R. 2. (n.d.). Do antioxidants interfere with radiation therapy for cancer? *Int Can. Ther.*, . 281- 292.
53. Drisko, J. C. (n.d.). The use of antioxidant therapies during chemotherapy. 334-339.
54. nwanobi, o. (2017). nutraceuticals. *herbal medicine*, 2.
55. M.H, M. (2019). Spices; a mechanistic anticancer treatise j. nu.tech.trition food reasearch.
56. SA., E. S. (2012). Functional Foods and Nutraceuticals -modern approach to food science. *world applied sciences*, 691- 708.
57. Ramaa CS, S. A. (2006; 7). *Current Pharmaceutical Biotechnology.*, 15-23.
58. RK., S. (2018). Need of Nutraceuticals/Functional Food Products for Health Benefits to Worldwide People. *Journal of Biotechnology and Biomedical Science*. ; , 1-13.
59. Okawa T, N. H. (n.d.). EEfect of LC9018 combined with radiation therapy on carcinoma of the uterine cervix.A phase III, multicenter, randomized, controlled study. *Cancer* . 1949-1954.
60. Mi H, D. Y. (2017). *Biochem* 42;:, 2330–2341.
61. Vétizou M, P. J. (2015). Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota *Science* . 1079–1084.
62. Ramaa CS, S. A. (2006; 7). *Current Pharmaceutical Biotechnology.*, 15-23.
63. <https://www.cancersa.org.au>. (n.d.). /prevention/lifestyle-factors/diet/how-dietary-fibre-cuts-your-cancer-risk] .
64. Misotti, A. M. (2013). .Vitamin supplement consumption and breast cancer risk:. *a review. Ecancermedalscience*, 365.
65. Martinotti, S. R. (2014). Combination of ascorbate/epigallocatechin-3-gallate/gemcitabine synergistically induces cell cycle deregulation and apoptosis in mesothelioma cells. . *Toxicol Appl Pharmacol* , 35-41.
66. Misotti, A. M. (2013). .Vitamin supplement consumption and breast cancer risk:. *a review. Ecancermedalscience*, 365.
67. Seid Mahdi Jafari, S. M. (n.d.). *Nutraceuticals and Cancer Signaling*. Publish your researchOpen access publishing.
68. Palumbo MO, K. P. (2013;). Systemic cancer therapy: achievements and challenges that lie ahead. .. *Frontiers in Pharmacology*, 4: 57.
69. Chen H, K. M. (2017; 8:). Improving radiotherapy in cancer treatment: Promises and challenges. *Oncotarget*. 62742–62758.
70. Block KI, G. C. (2015). 276-304.
71. Posadzki, P. W. (2013). Herb-drug interactions: an overview of systematic reviews. *Br J Clin Pharmacol*. 603-618.
72. Zhang, D. D. (2010). The Nrf2-Keap1-ARE signaling pathway: The regulation and dual function of Nrf2 in cancer. , 1. *Antioxid Redox Signal.*, 623-1626.