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NEUTRACEUTICALS AS ADJUNCT TREATMENT DURING CHEMO- OR RADIO-THERAPY FOR CANCER: A REVIEW

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ABSTRACT: Today, Proliferation is being observed in neutraceutical industry due to health seeking consumer trend. Neutraceutical has evolved from health promoting to disease preventing supplements. Various herbs and their phytochemicals discussed in the present review can prove potent neutraceuticals as they are pharmacologically safe and provide advantages in terms of suppressing tumor progression, increasing the sensitivity of chemo- and radio-therapeutics, and alleviate the side effects of chemo- and radio-therapy. The review has been devoted towards better understanding of potential of these neutraceuticals as combinational therapy in cancer treatments.

INTRODUCTION: During the last decade an enormous growing awareness of nutraceuticals, as potent therapeutic supplements, is observed with accepted concept of nutraceutical medicine as new branch of 'complementary and alternative medicine (CAM). "Nutraceutical" term was coined by Dr Stephen DeFelice (Chairman of the Foundation for Innovation in Medicine) through combination of "Nutrition" and "Pharmaceutical" in 1989¹. "Let food be thy medicine and medicine be thy food" as said by Hippocrates provide basic idea for the dynamic relationships between nutrient (or any substance in the diet that brings about a physiological effect) and health. Nowadays, claims about the ability of foods, including herbs and spices, to lower disease risk or to enhance the quality of life continue to held interest on our lives².

Neutraceutical has evolved from health promoting to disease preventing supplements. Recently, attention has been on nutraceuticals in the form of phytochemicals that possess cancer preventive properties.

Cancer has evolved globally as a deadly disease. The WHO has given an estimation of 21.4 million new cases of cancer by 2030 and of 13.2 million cancer deaths that will occur annually around the world³. Chemotherapy and radiotherapy are major conventional cancer therapy but have serious side effects and complications (e.g. fatigue, pain, diarrhea, nausea, vomiting, and hair loss). Also, some cancers are relatively chemo- or radio-resistant and highly refractory to cytotoxic chemotherapy or radiotherapy due to which systemic cytotoxic chemotherapy and radiotherapy are not much effective at improving patient survival^{4,5}.

In this scenario, combination therapies pave an effective way to treat cancer. Many phytochemicals derived from herbs are reported to have potential anticarcinogenic and antimutagenic activities,

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among other beneficial health effect. Also, many plants are reported to reduce side effects of chemotherapy and radiotherapy. This review provides a discussion of these herbs and their compounds to be used as nutraceuticals. These nutraceuticals should be useful in combination with chemo- or radio-therapy for cancer to reduce their side effects and to enhance the effectiveness of the treatment.

Neutraceuticals emerged as promisingly effective adjunct therapy in cancer patients during chemo- or radio-therapy: Curcumin (Di-feruloyl-methane) from Turmeric (*Curcuma longa*) has emerged as powerful cancer protective nutraceutical. Pre-clinical cancer research using curcumin has shown that it inhibits carcinogenesis in various types of cancers such as colorectal, pancreatic, gastric, prostate, and hepatic cancer. Also, suppress cancer at every step, i.e. proliferation, angiogenesis, and metastasis⁶.

Curcumin is effective in combination with radiation even in radiotherapy-resistant prostate cancer⁷. Furthermore, it enhances the activity of other anticancer agents in the treatment of chemo-resistant and multidrug-resistant (MDR) cancer⁸. Other nutraceuticals that can prove very effective in combination with chemo- and radiotherapy are Gingerols from ginger (*Zingiber officinale*) and Ginsenosides from Ginseng (*Panax ginseng*). Various cancers including that of the ovary, cervix, colon, rectum, liver, urinary bladder, oral cavity, neuroblastoma and leukaemia are reportedly inhibited by Gingerols via inducing apoptosis. It is reported to be effective even in chemotherapy resistant ovarian cancer^{9, 10}.

Ginger possesses antioxidant, antimutagenic and anti-inflammatory properties and reduces side effects of chemotherapy & radiotherapy, too¹¹. On the other hand, Ginseng is used as potent chemopreventive agent and effectively regress stomach, liver, pancreas, and colon cancer by inhibiting the inflammation-to-cancer sequence and also¹².

Its anti-oxidation and immune modulation properties provide promising radio-protector activity¹³. Ginsenoside Rf is reported to reduce doses of morphine in terminally ill cancer patients and polysaccharides of Ginseng reduce side effects

of chemotherapy & radiotherapy. In addition, 50% lower risk of cancer recurrence is recorded in patients taking ginseng in an epidemiological study^{14,15}. These facts indicate the role of ginseng and ginger as powerful nutraceuticals for treatment of cancer as combination treatment with chemo and radiotherapy.

Many other Nutraceuticals which are currently elucidated for their chemopreventive properties include green tea polyphenols (e.g., EGCG), soya derived genistein, red grape skin derived resveratrol, silymarin, caffeic acid phenethyl ester, oleandrin, ursolic acid, flavopiridol, emodin, black pepper containing piperidine, and betel leaf derived betulinic acid. These phytochemicals reportedly sensitize tumor cells to chemotherapeutic agents and radiation therapy by inhibiting pathways responsible for treatment resistance¹⁶.

Many commonly known herbs are recognized to reduce side effects of chemotherapy & radiotherapy: *Aloe vera* and *Aegle marmelos* possesses significant antioxidant activity and reduces side effects of chemotherapy & radiotherapy^{17, 18}. Aloe-emodin isolated from *Aloe vera* induces apoptosis in various sarcomas & inhibits spread of stomach cancer¹⁹. Alexin B is another compound from *Aloe vera* which is reported to be very effective against leukaemia¹¹.

Smoked marijuana (*Cannabis Sativa*) is reported to treat the nausea caused by cancer chemotherapy and so aid the cancer treatment process²⁰. Amooranin, a triterpene acid isolated from *Amoora rohituka*, is found to be very effective in both chemotherapy-sensitive and chemotherapy-resistant cancers²¹.

Azadirachta indica and *Andrographis paniculata* are very well known for their medicinal value. Both these plants inhibit the side effects of chemotherapy & radiotherapy. Andrographolide, active diterpene component of *Andrographis paniculata*, is strongly active against cancers of breast, ovary, stomach, colon, prostate, kidney, nasopharynx malignant melanoma and leukemia²². Whereas Nimbolide, a natural triterpenoid of *Azadirachta indica* leaves and flowers, is found to restrain growth & spread of various cancers including colon cancer, malignant lymphoma, malignant melanoma and leukaemia by inducing

apoptosis. Ethanolic extract of *Azadirachta indica*, regress prostate cancer by showing antiandrogenic effect and apoptosis²³.

Ocimum sanctum is too a known herb which have strong antioxidant and radioprotective properties. *Ocimum sanctum* also protects against various cancers, particularly the breast cancer, and reduces side effects of chemotherapy & radiotherapy²⁴.

All the above stated herbs can be used in food formulations so as to provide nutraceuticals for adjuvant treatment during chemo- or radio-therapy for cancer.

Phytochemicals, from commonly known medicinal plants, which are potent nutraceuticals that can be used in cancer treatments: *Withania somnifera* is again an effective medicinal herb. It possesses Withanolides with antiproliferative and antiangiogenic properties efficient against various cancers like that of breast, lung, colon and central nervous system. Withaferin A is effective even in androgen-refractory prostate cancers, where as the metastatic colony formation of malignant melanoma is reportedly regressed by Withanolide D. This herb reduces side effects of radiotherapy & chemotherapy as well²⁵.

Other herbs which can be stated along with include *Emblica officinalis* and *Ginkgo biloba*, valued for reducing side effects of radiotherapy & chemotherapy. Ellagic acid isolated from *Emblica officinalis* is a powerful antioxidant and can inhibit mutations in genes²⁶. Ginkgetin and Ginkgolides (A & B), of *Ginkgo biloba* prevent multiplication of various aggressive cancers such as invasive oestrogen-receptor negative breast cancer, glioblastoma multiforme, hepatocellular carcinoma and cancers of ovary, colon, prostate and liver by inducing apoptosis²⁷.

Gossypol isolated from *Gossypium hirsutum*, is too very effective phytochemical against chemotherapy & radiotherapy-resistant cancers of prostate, breast, ovary, lung, pancreas, head & neck and brain. It shows effective telomerase activity in cancerous cells²⁸. Thymoquinone and dithymoquinone are phytochemicals of *Nigella sativa* have strong anticancer activity against various cancers and

plant reduces side effects of chemotherapy & radiotherapy²⁹.

Another herb which aid chemotherapy in cancer patients is *Berberis vulgaris*. Berberine, is active compound of this herb which possesses strong anticancer activity against prostate cancer, liver cancer and leukaemia. It not only makes some chemotherapy drugs to penetrate easily through the critical blood-brain barrier but also interferes with P-glycoprotein in chemotherapy-resistant cancers³⁰. All the above stated phytochemicals of herbs should be researched for their use as nutraceuticals adjunct therapy during cancer treatment.

Phytochemicals from other anticancer herbs which will help to alleviate the symptoms if you already suffer from cancer treatments: Alfalfa, very well known for its high nutrition value, is reported to counteract the effects of chemotherapy. It increases the production of white blood cells and replaces those lost during treatments. Anticancer herbs include the garden variety rosemary that helps to prevent carcinogenic chemicals from attaching themselves to cells and causing the mutations that lead to cancer. Colchicine from Autumn Crocus is known as anticancerous since it interrupts the division of cancerous cells¹¹.

Betulinic Acid is another potent anticancerous compound from *Betula Alba* (Birch) especially effective in the treatment of prostate cancer patients. *Camptotheca Acuminata* (Xi Shu, Happy Tree) contains antineoplastic, used to prevent the mutation of cells into cancerous cells with the possibility of preventing or reducing the disease into one that is benign.

Lapacho Tree (*Tabebuia Impetiginosa*) possess Beta-lapachone which is being researched for its anti-cancer properties on pancreatic cancer. May apple (*Podophyllum Peltatum*) has Etoposide compound which is useful in anticancer drugs which kill the cancerous cells through the process of enzyme-mediated DNA scission. Vinblastine, being an anti-cancer drug extracted from the periwinkle slows down microtubule formation in cancer cells¹¹.

All the herbs are discussed with anti cancerous properties of their phytochemicals which can serve as nutraceuticals in cancer treatment.

Spices as nutraceuticals with anticancerous activity: As already discussed, turmeric and ginger prove to have very effective anticancerous property. Another potent nutraceutical among spices is Garlic (*Allium sativum*) which is well known for medicinal value for thousands of years. Currently, much of the preclinical studies has reported that garlic have an anticancer effect on various tumors and especially on colon tumors by controlling DNA repair, inhibiting cell proliferation and angiogenesis, inducing differentiation and apoptosis, inhibiting metabolism, and scavenging carcinogen-induced free radicals^{31,32}.

The sulphhydryl compounds (e.g. allicin and alliin) are active compounds in garlic that have the ability to block the formation of cancer - causing substances. Even a decreased risk of stomach, esophageal, and colorectal cancer with increased consumption of garlic is shown by many epidemiological studies³¹. A study has found that garlic intake of 10 g per day could reduce the risk of prostate cancer by 50 percent³³.

Other spices with reported anticancer activity include cardamom, cinnamon, clove and cumin. Cardamom has also been demonstrated to decrease colon carcinogenesis through its anti-inflammatory, antiproliferative, proapoptotic activities, enhanced detoxifying enzyme (GST activity) and by decreasing lipid peroxidation³⁴. Whereas, cinnamon extracts is known to suppress the in vitro growth of *H. pylori*, a recognized risk factor for gastric cancer, gastric mucosa-associated lymphoid tissue lymphoma, and possibly pancreatic cancer^{35,36}.

Also, it is very much effective against angiogenesis because it directly inhibits VEGF-induced EC proliferation, migration and tube formation as well as mitogen-activated protein kinase- and Stat3-mediated signaling pathway in endothelial cells³⁷. Clove extracts, too, is reported to have potent anticancer activity that might interfere with β -catenin activity in colon cancer³⁸. Thymoquinone (TQ), the most abundant component of black cumin

seed oil, has been reported to exhibit antioxidant, antimicrobial, anti-inflammatory, and chemo preventive properties^{39,40}.

Commonly used antioxidant herbs which are potent nutraceuticals include oregano, thyme, cilantro (coriander) and basil. Basil is reported to have chemo- protective potential for colon cancer as well. Maitake mushroom extract is known to limit or even reverse tumor growth. Also, it enhances the benefits of chemotherapy and lessens the side effects of anti-cancer drugs. It can be taken as nutraceuticals by patients undergoing cancer treatment^{2,11}.

All these reports have stirred considerable interest in the potential use of these spices as nutraceuticals to suppress human cancers.

CONCLUSION: The potent nutraceuticals discussed in the review should be researched further for their potential use as they are pharmacologically safe and provide advantages in terms of suppressing tumor progression, increasing the sensitivity of chemo- and radio- therapeutics, improving an organism's immune system function, and lessening the damage caused by chemo- and radio-therapeutics. The review should provide the knowledge of potent nutraceuticals from herbal medicines that are capable of enhancing the efficacy of and diminishing the side effects and complications caused by chemo- and radio- therapy when used as adjunct therapy in cancer treatment.

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