

NUTRACEUTICALS AND CANCER MANAGEMENT

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1. ABSTRACT

The use of complementary and alternative medicine (CAM) is increasing rapidly in developed countries, which is already in use as traditional medicines in various Asian countries. The Indian system of medicine, named as Ayurveda has an edge in this field. Many plant products are in use as herbal medicine, as food supplement or as spices, in every day cooking. Some of them have been well studied in various experimental models of cancer, both *in vivo* and *in vitro* models. They have shown significant inhibition of cell proliferation. Some of them are in the phase of clinical trial or already available as food supplement. Cancer patients are specially exploring the use of CAM, because of the high risk of mortality and long-term morbidity associated with surgical procedures of cancer management and high side effects of chemotherapy. This paper reviews different class of phytomedicines, used in Indian system of medicine, and also in Europe, which have shown positive results in preventing cancer progression. It also covers the role of vitamins, minerals,

dietary fat in relation to cancer control. The mechanisms of action of these phytomolecules have also been discussed.

2. INTRODUCTION

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. It has been suggested by several studies that frequent consumption of vegetables and fruits decreases the risk of colon cancer, the third most common cancer in both men and women (1). Diet, high intake of grains, legumes, fruits, vegetables and other edibles rich in phytoestrogens (2), high-fiber (3), low-fat diet (4) have their own importance in preventing colon cancers and others like breast (5), prostate (6), and lung cancer (7), which are more prevalent in the developed countries.(8) Dietary components may prevent cancer from reaching its invasive and metastasis stages or they may

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reduce the risk of secondary complications or modify the behavior of established cancer.(9,10) According to a recent report, functional foods represent an exploding market, an estimated value of \$29 billion a year, in the United States alone. The food industry is pouring millions of dollars into this transformation, and if the health claims on these products, prove to be true and the food is tasty, they may succeed. It is expected that over the next few years "there will be a glut of foods, designed to optimize health, and that supermarkets of the future will have entire sections set aside for the prevention of chronic illnesses.

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. This seems to be one of the main reasons, why these herbal food supplements are not in use as it should be, by the suffering humanity. Therefore, keeping in view the pressing demand of alternative medicine, especially for the chronic disorders, World Health Organization (WHO) and National Institute of Health (NIH), USA have taken it as a mission to validate the claims of these medicinal plants and to develop them as a safe, scientifically proven food supplement. This review focuses some of the past researches, establishing the role of medicinal plant products in cancer management. This will help the readers to plan the future experiments in this field. (11)

3. ETIOLOGY OF CANCER

Carcinogenesis results from the accumulation of multiple sequential mutations and alterations in nuclear and cytoplasm molecules, culminating to invasive neoplasms (12). These events can be divided into three phases: initiation, promotion, and progression. Initiation is a rapid process, involving carcinogen binding to the target and DNA damage (13). In the promotion phase, which is generally reversible, tumor promoters, acting as mitogens, induce clones of initiated cells to expand. Promotion is a consequence of the functional loss of regulatory proteins and cellular check points, important for proliferation and apoptosis. Progression defines the stage in which phenotypically and genotypically altered cells develop irreversible macroscopic changes. Both promotion and progression phases are of long duration, probably of many years. This model allows a convenient classification of chemo-preventive agents to the groups that can block initiation or suppress promotion and progression (14).

4. NUTRACEUTICALS AND CANCER

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, where as semi-purified plant product, not taken as regular food, is named as functional food (16). 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 (17). Functionally they may be classified as dietary fiber, antioxidants, detoxifying agents, immunity-potentiating agents and neuropharmacological agents, with variety of chemicals with differing potency.

Some of the well studied phytochemicals in relation to tumor prevention includes curcumin (turmeric) (18), capsaicin (green chilies) (19), epigallocatechin gallate (green tea) (20), gingerol (ginger) (21), genistein (soya beans) (22), resveratrol (grapes) (23), caffeic acid phenyl ester (propolis from honey bee) (24), sulforaphane (25) (cruciferous vegetables) (26), silibinin (27), St. John's wort (28), indole-3-carbinol (cabbage) (29), tangeretin (citrus species) (30), apigenin (tea, cabbage, garlic) (31), allicin (garlic) (32), lycopene (tomatoes) (33), emodin (aloes) (34), diallyl sulfide (garlic) (35), quercetin (rhododendron cinnabarium) (36), anethole (fennel, camphor) (37), β -carotene (38).

5. PHYTOCHEMICALS WITH ANTI CANCER PROPERTIES

Nutritional modulation may be beneficial in the treatment of cancer patients (39). 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 (40). In addition, certain supplemental micronutrients, nutraceuticals and functional foods may have potential to reduce the risk of developing cancer, or retarding the rate of growth and metastases of established malignant disease. It may also be helpful in reducing toxicity, associated with chemotherapy and radiation therapy, and may lead to better life conditions by reducing cancer cachexia (41). They may inhibit cell proliferation and induce apoptosis in the cancer cells.

The phytochemicals have shown different mechanism of actions at different cellular levels. Most of them have emerged as a versatile source of antioxidants and there by 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.

6. POSSIBLE MECHANISMS OF ACTION OF NUTRACEUTICALS AS CHEMO-PREVENTIVE AGENT

Chemoprevention can be defined as the use of natural or synthetic chemicals to reverse, suppress, or to prevent the process of carcinogenesis. Solid cancer 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.

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Ultimately, such agents prevent the growth and survival of cells already committed for malignancy.

Bioactive substances in a dietary compound, even in very low concentrations, may have a far greater impact than previously appreciated on the regulation of gene expression. Continuing research on the effects of nutraceuticals on gene expression should provide insight into the mechanisms of prevention of diseases such as obesity, diabetes, atherosclerosis, hypertension and cancer by dietary manipulations. A few current studies on the action of selected nutraceuticals on the activity of transcription factors such as activator protein (AP-1), including nuclear factor κ B (NF κ B), sterol response element binding proteins (SREBPs), peroxisome proliferator-activated receptor- γ (PPAR γ), modulation of the expression of antioxidant genes like Bcl-2 as final targets in the signal transduction cascade and gene regulation, have paved a path to further investigate these molecules in a great detail, using various genetic diseased animal models. (42)

7. CANCER CACHEXIA AND FOOD SUPPLEMENT

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 (43). They usually show cancer 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. Although foods with relatively low carbohydrates, moderate high-quality protein, fiber, and fat rich in omega-3 fatty acid series is considered to be beneficial for such patients. However, certain medicinal plants, especially acting on the liver and gastrointestinal system, may prove to be better food supplement in improving the quality of life. Nutritional intervention can be a powerful tool for controlling malignant disease and for reducing toxicity associated with chemotherapy and radiation therapy. (44, 45)

8. FAT AND CANCER

Low fat and high fiber diets can further enhance the efficacy of standard cancer therapeutic agents; (46) the proposed mechanisms for these effects include the production of increased levels of butyric acid (47) and binding of potential mutagens in the gastrointestinal tract by high fiber and reduced levels of growth promoting agents such as prostaglandins, certain fatty acids and estrogen by low fat. Functional foods relatively low in soluble carbohydrate; moderate amounts of protein that includes sources of arginine, and moderate amounts of fat supplemented with omega-3 long-chain polyunsaturated fatty acids have been shown to be beneficial. Other nutraceuticals of interest in patients with cancer include antioxidant vitamins, trace minerals, glutamine, protease inhibitors, garlic and tea polyphenols.

Increased dietary and serum levels of omega-3 fatty acids are associated with a number of health benefits, including improved disease-free interval, survival time, and quality of life (48). It has been further suggested by several animal studies that consumption of omega-3 fatty acids can slow the growth of cancer xenografts and metastatic cancer (49, 50). It may reduce the side effects of ongoing chemotherapy and increase its efficacy along with enhanced longevity of cancer patients (51). The mechanism behind its action appears to be through suppressing the expression of cyclooxygenase-2 in tumors, thus decreasing proliferation of cancer cells and reducing angiogenesis in the tumor. It also suppresses the expression of AP-1 and ras oncogenes, implicated in tumor promotion; induces the differentiation of cancer cells; inhibits the activation of NF- κ B activation and expression of Bcl-2, resulting to enhanced apoptosis of cancer cells. It also reduces the cancer-induced cachexia.

9. NUTRACEUTICALS AND IMMUNE MODULATION

Nutraceuticals can significantly raise natural killers cell (NK cell) function and tumor necrosis factor (TNF α) in patients with late stage cancer (52). An aggressive combination of immuno-active nutraceuticals has been suggested to be effective in significant improvement in NK cell function, other immune parameters and hemoglobin in patients with late stage cancers. (53)

10. MEDICINAL PLANTS IN APOPTOSIS

Programmed cell death (apoptosis), has generated considerable interest in recent years. It is a highly conserved mechanism of self-defense. Both extra-cellular signals and intracellular events have been associated to this event. Enhancement of apoptosis may reduce the cancer growth as this process is down regulated in cancer tissues (54). Recently, a variety of plant extracts have been investigated for their ability to influence the apoptotic process such as *Rubia cordifolia* (55), *Semicarpus anacardium* (56), isolated compounds like bryonolic acid (from *Trichosanthes kirilowii* var. *Japonica*, crocin (from saffron) and allicin (from *Allium sativum*) (57). Several mechanisms have been identified to underlie the modulation of programmed cell death by plants including endonuclease activation, induction of p53, activation of caspase 3 protease via a Bcl-2-insensitive pathway, activation of free-radical formation and accumulation of sphinganine (58).

11. SOME SPECIFIC EXAMPLES

The palm fruit (*Elaeis guineensis*) yields palm oil, a palmitic-oleic rich semi solid fat and the fat-soluble minor components, vitamin E (tocopherols, tocotrienols), carotenoids and phytosterols. A recent innovation has led to the recovery and concentration of water-soluble antioxidants from palm oil milling waste and characterized by its high content of phenolic acids and flavonoids. Palm vitamin E (30% tocopherols, 70% tocotrienols) has been

suggested to have significant antioxidant, cholesterol lowering, anti-cancer and anti- atherosclerosis effects. These are attributed largely to its tocotrienol content. It has shown significant protection against skin, breast and other cancers (59, 60).

Sugar beet roots, cucumber fruits, New Zealand spinach leaves, and turmeric rhizomes, have been shown to decrease the skin tumor incidence, its multiplicity and later onset of skin tumors, induced by DMBA and croton oil. Among them turmeric was found to be most potent, as evidenced by 87.2% decrease in skin tumors.(61)

12. FLAVONES

Flavonoids are well-known phytochemicals that are produced by various plants in high quantity. They have been of interest owing to their observed biological effects *in vitro* such as free-radical scavenging, modulation of enzymatic activity, and inhibition of cellular proliferation, as well as their potential utility as antibiotic, anti-allergic, anti-diarrhea, anti-ulcer, and anti-inflammatory agents. The chemopreventive activity of flavonoids is dependent on their structural features. A study has indicated that the number, position and substitution of hydroxyl groups of the A and B rings of flavonoid, and unsaturation of the C2-C3 bond are important factors, affecting the action of these flavones as assessed in terms of FPTase inhibition activity in a cell line. Franke *et al.* (6) examined several flavones, flavonols, flavanones, catechins, and isoflavones and found that the flavonones hesperetin, hesperedin and the catechins exhibited the highest levels of inhibition of transformation.

It affects the mRNA levels of genes, important in cell cycle control and apoptosis. Flavonoids have also been investigated with respect to their interaction with enzymes associated with DNA topology. Some of the flavones act through topoisomerase II activity modulation. DNA topoisomerase II is an enzyme that catalyzes the double-strand breakage and rejoining of DNA; it is pivotal for several cell functions (4). Several flavonoids, including genistein, can inhibit DNA topoisomerase II activity by stabilizing the cleavage complex, thereby facilitating apoptosis (62, 63). In addition, the core structure of the flavones, 2-phenyl-4H-1-benzopyran-4-one, affects proliferation, differentiation, and apoptosis in a human colon cancer cell line (64, 65).

The natural product quercetin, a flavonoid, found in many fruits and vegetables, have shown antitumor, anti-inflammatory, antiallergic, and antiviral activities (66). Quercetin at concentrations of 25 and 50 μ M, significantly inhibited the growth of PC-3 and DU-145 prostate cancer cell line, whereas it did not affect colony formation by the poorly aggressive LNCaP prostate cancer cell line or the normal fibroblast cell line BG-9. Using the gene array methodology, it was found that quercetin significantly inhibited the expression of specific oncogenes and genes, controlling G(1), S, G(2), and M phases of the cell cycle. Moreover, it has been shown to reciprocally up-regulate the expression of several tumor suppressor genes (67).

13. PHYTOESTROGENS

Phytoestrogen are a special group of flavones, because of their specific binding to the estrogen receptors, and include certain isoflavonoids, flavonoids, stilbenes, and lignans. They act as alternative sources of estrogenic compounds [68] and do not possess the untoward effects of estrogen. It has therapeutic potential for the management of chronic diseases related to postmenopausal stage. [69]. Consumption of phytoestrogens in the human diet has been associated with a number of beneficial effects, particularly relating to chronic diseases like cardiovascular disease, osteoporosis, hormone-dependent cancers, including cancer of the breast, endometrium, prostate, colon, rectum, stomach and lung, (70,71). Some of the active phytoestrogens, which have also shown anti tumor activity in different studies includes puerarin from Kudzu vine (*Pueraria lobata*) (72), formononetin from clovers, fenugreek and Black cohosh (*Actaea racemosa* syn. *Cimicifuga racemosa*), (73, 74), glabridin and glabrene from the root of licorice (*Glychiriza echinata*) (75).

14. ISOFLAVONES OF SOY PROTEIN

Soy protein is mainly composed of genistein and daidzein, however, a metabolic derivative of daidzein is equol, which is a potent antioxidant, formed in the intestinal tract in only a subset of the population (76, 77). Further a significant correlation has been found between an isoflavone-rich soy-based diet, urinary isoflavone levels, and reduced incidence of breast cancer or mortality from prostate cancer in humans.

Soya has been shown to increase the length of the menstrual cycle and/or to delay menstruation in premenopausal women. It reduces the levels of luteinising hormone (LH), follicle stimulating hormone (FSH) and progesterone at various stages of the cycle. The protective effects of phytoestrogens include increased latency, reduced incidence and multiplicity of tumors, and more rapid maturation of undifferentiated end buds to differentiated lobules (78). These effects, which appear to be estrogen receptor (ER) mediated, are associated with increased epidermal growth factor receptor (EGFR) and progesterone receptor (PR) expression in the pre-pubertal rat mammary gland. In studies, where rats have been fed with standardized soy extract instead of pure isoflavone, it took longer time to develop chemically induced mammary adenocarcinomas, than in control animals. However, in the end of the study, no difference in tumor multiplicity or incidence was observed between treatment and control group.

15. GENISTIEN

Genistein (5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one) is an isoflavone derived from soya beans and is believed to be a contributor to the cancer preventive activity of soya. It is unique among a number of flavonoid and isoflavonoid compounds tested in having both strong estrogen agonist activity and strong growth inhibitory activity against breast cancer cells. Thus,

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genistein may induce early mammary gland differentiation resulting in a less active EGF signaling pathway in adulthood that, in turn, suppresses development of mammary gland cancer (79). In contrast, equol has strong estrogen agonist activity but little growth inhibitory activity. Genistein is more effective in inhibiting growth of non-neoplastic human mammary cell lines than it is in inhibiting growth of mammary cancer cells. This supports the notion that early exposure to genistein may be important for breast cancer chemoprevention.

Further inverse relationship has been observed between high phytoestrogen intake and incidence of mortality due to prostate cancer. By the administration of genistein there has been decrease in androgen-related prostate-specific antigen and prostate cancer cell growth *in vitro* and *in vivo* conditions (80). Genistein has been found to inhibit the H₂O₂ and TNF α induced activation of NF κ B in prostate cancer cell lines (PC3) by reducing the phosphorylation of I κ B followed by the nuclear translocation of NF κ B (81). Genistein inhibited the PMA-induced AP1 activity (82), expression of c-FOS in A-431 cells (83).

Daidzein only exhibits weak inhibitory effects on growth of benign and malignant human prostate epithelial cells, but its metabolite equol had potent inhibitory effects at micromolar concentrations (84). Thus, conversion of daidzein to equol may be an important factor in dietary prevention of prostate cancer. In addition genistein and daidzein independently modify cytokine production. The interleukin-6 synthesis by these two cell lines was also inhibited in the range of approximately 20% compared with the control group. They also reduced the ovarian cancer cell proliferation via estrogen receptor-dependent pathway (85).

In addition to effects on breast and prostate cancers, genistein and related isoflavones also inhibit cell growth and development of chemically induced cancer in stomach, bladder, lung, and blood. Inhibition of the growth of human stomach cancer cell lines *in vitro* by genistein and biochanin A involves stimulation of a signal transduction pathway leading to apoptosis (86). Genistein strongly inhibits growth of leukemia cells when targeted to them by linkage to a monoclonal antibody, and a prenyl isoflavone derivative (ipriflavone) was developed as an oral treatment for acute leukemias (87). The prenyl group might help target the isoflavone to hydrophobic sites of action. At low concentrations, genistein induces the phase II detoxifying enzyme quinone reductase in colonic cells; biochanin A and coumestrol also have this ability but daidzein and formononetin are inactive. Induction of a carcinogen detoxifying system could provide a partial explanation for anticancer effects of phytoestrogens (88).

In addition to the above mentioned phytochemicals, there are several other plant products, which have been suggested to have promising effect in regulating the proliferation of the transformed cells. They include *Rubia cordifolia*, which is rich in anthraquinones and has been shown to inhibit the c fos expression and proliferation of A 431 cells (55). Similarly, *Semecarpus anacardium*, rich in polyphenolics, has been shown the

arrest of cell cycle of DU 145 cells at the stage of cytokinesis (Cell division/Mitosis phase) (56).

Similarly isolated compounds like curcumin (turmeric), capsaicin (green chilies), epigallocatechin gallate (green tea), gingerol (ginger), genistein (soya beans), resveratrol (grapes), caffeic acid phenyl ester (CAPE) (propolis from honey bee), sulphoraphane (cruciferous vegetables), silymarin (St. John's wort), indole-3-carbinol (cabbage), tangeretin (citrus species), apigenin (tea, cabbage, garlic), allicin (garlic), diallyl sulfide (garlic), lycopene (tomatoes), emodin (aloes), quercetin (rhododendron cinnabarium), anethole (fennel, camphor), β -carotene, bryonolic acid (from *Trichosanthes kirilowii* var. *Japonica*, crocin (from saffron) and allicin (from *Allium sativum*), glucosinolates, indoles (e.g. indole-3-carbinol) and phytoalexins in cruciferous vegetables (89), flavonoids (other than isoflavones) in fruit, vegetables and beverages like tea and wine (90) have also been shown to inhibit the proliferation of tumor cells by using different signaling pathways (91).

Sulphorphanes consists of two phytochemicals: 1-isothiocyanol-(4R)- (methylsulfinyl) butane, which is found in cruciferous vegetables like broccoli and known to suppress the activation of NF κ B and regulates the activation of MAPKs and NRF by reacting with KEAP1 (92). The second compound is 6-methyl sulphinylhexyl isothiocyanate (6-HITC), which is found in *Wasabia japonica* and is known to induce GST, which is an antioxidant and also inhibit nuclear translocation of Nrf2 (93). Further, CAPE is an acid phenyl ethyl ester obtained from honeybee hives and it is known to stimulate the Nrf2-KEAP1 complex and increases activity and expression of HO-1 and also known to decrease the tumorigenesis. Silymarin is a mixture of flavano lignans from *Silybum marianum* and is known to suppress the activation of NF κ B. Indole-3-carbinol, found in cabbage (*Brassica* species) and Tangeretin (5,6,7,8,4' pentamethoxyflavone) in citrus species, were found to alter the patterns of β -catenin mutation by chemically induced rat colon tumors. It inhibits adhesion, migration and invasion of cultured human breast carcinoma cells and up regulates E-cadherin and β -catenin.

Apigenin (4',5,7-trihydroxy flavone) is found in chamomile tea, cabbage, garlic (*Alium sativa*), French peas and guava is known to inhibit MAPK activity. It stimulates the p53- p21/waf response pathway. It also inhibits I κ B kinase activity and thereby inhibits the transcriptional activation of COX-2 and inducible nitric oxide synthetase (iNOS) (94). Allicin [S-(2-propenyl) 2-propene-1-sulfinothioate] found in Garlic is known to induce the formation of apoptotic bodies, nuclear condensation and a typical DNA ladder in cancer cells. It also induces the activation of Caspase-3, 8 and 9 and cleavage of poly (ADPribose) polymerase. Diallyl sulfide found in Garlic is known to affect the mRNA of N-acetyltransferase (NAT) expressed in human colon cancer cell lines. Emodin (1,3,8-trihydroxy-6-methyl-9,10-anthracenedione) found in *Aloe barbadensis* decreases the activation of NF κ B (95).

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Similarly, fresh corn products contain a mitogenic compound with estrogenic activity. The compound stimulates proliferation of ER-positive and ER-negative breast cancer cells, but does not compete for binding to ER (98). Safflower (*Carthamus tinctorius* L.) seeds have long been clinically used in Korea to promote bone formation and to prevent osteoporosis. It has also shown antiproliferative property in a preliminary study. Sorghum is another rich source of various phytochemicals including tannins, phenolic acids, anthocyanins, phytosterols and policosanols (99).

Besides, there are several other compounds with estrogenic activity, although not common dietary components, are consumed by humans as herbal remedies. They include isoflavonoids and chalcone (isoliquiritigenin) from licorice root, phenylbutanone glucoside lindleyin from Rhubarb, which binds to estrogen receptor and may be responsible for the biological effects. Ginseng contains several bioactive triterpenoid compounds, among which the glycoside ginsenoside stimulates proliferation of human breast cancer cell lines in an ER-dependent manner, and can activate ER element reporter gene constructs in transfected HeLa cells. However, corresponding aglycone exhibited no significant activity (96). Extracts from *Polygonum*, *Cassia*, *Aloe*, and *Rheum* species enhance cell proliferation in estrogen-sensitive human breast cancer cell lines, and this is due to the activity of anthraquinones. Emodin and 2,6-dihydroxyanthraquinone were among the most potent, and also inhibited 17 β -estradiol binding to human ER (97).

16. CURCUMIN

Curcumin is known to induce apoptosis in malignant cell lines by suppressing a number of key elements in cellular signaling pathways pertinent to growth, differentiation and malignant formation. It is one of the extensively investigated phytochemical, with regard to chemopreventive potential. It inhibits the TNF- α induced COX-2 transcription and NF κ B activation by inhibiting the I κ B degradation, through down regulation of NF κ B inducing kinase (NIK) and I κ B kinase. Curcumin inhibited the catalytic activity of ERK 1/2 in different cell systems (100). Alternatively curcumin acts through another transcription factor NRF2, which normally exists in an inactive state as a consequence of binding to KEAP1 protein (101). Curcumin is unstable at neutral and basic pH and more than 90% of curcumin decomposes rapidly in buffer systems at this pH. It gets degraded to ferulic acid ([4-hydroxy-3-methoxy cinnamic acid]) and feruloyl methane (4-hydroxy-3-methoxycinnamoyl methane).

17. CAPSAICIN

Capsaicin is a pungent ingredient present in hot red chili peppers (Capsicum genus : Solanaceae family). It protects against the free radical induced pulmonary damage by its pretreatment. It also possesses antiplatelet and anti-inflammatory activity, which is associated with its interference with phospholipase A2 (102). It induces the growth inhibition and apoptosis in the transformed cells of

human origin, including ovarian carcinoma, mammary adenocarcinoma and promyelocytic leukemia (HL-60) cells in culture by the inhibition of plasma membrane NADH oxidase activity (103). The apoptosis induced by capsaicin has been regulated by Bcl-2 and the protein phosphatase calcineurin (104).

18. EPIGALLOCATECHIN-3-GALLATE (EGCG)

EGCG ((-)-Epigallocatechin-3-gallate) is an antioxidant and chemopreventive polyphenol, isolated from green tea, which is associated with reduced frequencies of several types of malignant tumors. EGCG has also been reported to attenuate the nitric oxide production through the suppression of inducible nitric oxide synthase (iNOS) expression (105).

19. GINGEROL

Gingerol, 1-[4'-hydroxy-3'-methoxyphenyl]-5-hydroxy-3-decanone, isolated from Ginger (*Zingiber officinale* Family: Rosaceae) one of the most frequently consumed dietary condiments throughout the world. Besides its extensive use as a spice, this rhizome has also been used in traditional oriental herbal medicine for the management of various symptoms like common cold, digestive disorders, rheumatism, neuralgia, colic and motion-sickness. It has also been associated with anti-inflammatory, analgesic, antipyretic, antihepatotoxic and cardiogenic effects. Gingerol has been found to possess substantial antioxidant activity as determined by inhibition of phospholipid peroxidation induced by the FeCl₃ – ascorbate system (Aeschbach *et al* 1994). Gingerol also exerts an inhibitory effect on xanthine oxidase, responsible for the generation of superoxide anion (106, 107).

20. LYCOPENE

Lycopene found in Tomatoes (*Lycopersicon esculentum*), decreases the NF κ B activation, inhibits proliferation by reducing the insulin like growth factor -I (IGF-I) receptor signaling and cell cycle progression and reduces the binding capacity of AP-1 transcriptional complex. It also acts as an antioxidant. (108)

21. ANTIOXIDANTS AND CANCER

Antioxidants are suggested to enhance the body's defenses against harmful reactive oxygen species, generated endogenously or exogenously. Polyphenols from plants compose the majority of this class. Recently, it has been shown that bioavailability of these molecules are very low, therefore it becomes logical to use them in different combinations of various medicinal plants. This finding also supports the concept behind the use of polyherbal formulations in traditional systems of medicine in various countries such as ayurveda in India. The potential role of antioxidant vitamins (ascorbic acid, beta-carotene, alpha-tocopherol), minerals (selenium) and non-vitamin natural antioxidants (e.g. glutathione) in the prevention of cancer diseases has already been reviewed extensively in the past. Free radical production is a chain reaction and has 3 steps

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namely initiation, propagation and termination. These antioxidants have also been classified, based on their site of action. However, these FR, once produced, damage the macromolecules by attacking at the double bonds. Oxygen radicals, especially the hydroxyl radical (.OH) modify nitrogen bases, split DNA, stimulate oncogene activators and probably in many other ways participate in carcinogenesis. Number of experimental and epidemiological studies has suggested a correlation between increased cancer risk and low antioxidant status in laboratory animals and in humans. Significant protective effects of ascorbic acid, beta-carotene, alpha-tocopherol and selenium against the incidence of gastrointestinal and lung cancer has also been shown in several studies. (109)

22. 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. Its action may be through the modulation of immune function or through antioxidant properties or by direct effect such as inhibition of N-nitrosamine formation or cell-to-cell interactions and modulation of the enzyme activity. It may be important for the patients undergoing chemotherapy and radiotherapy because in that stage, requirement for antioxidant compounds increases. Thus, supplementation with micronutrients as adjuvant in cancer patients may prove to be helpful (110).

Antioxidant, vitamin and minerals are always protective to the cancer as they protect the DNA damage from the free radical attack and Cancer is a disease of the genome. Several epidemiological studies have suggested the role of diets rich in fruits and vegetables in cancer protection. Individual antioxidants such as vitamin A (retinoids), vitamin E (primarily alpha-tocopheryl succinate), vitamin C (primarily sodium ascorbate) and carotenoids (primarily polar carotenoids) induce cell differentiation and growth inhibition to various degrees in rodent and human cancer cells by complex mechanisms. The suggested mechanisms for these effects include the inhibition of protein kinase C activity, prostaglandin E1-stimulated adenylate cyclase activity, expression of c-myc, H-ras, and a transcription factor (E2F), and induction of transforming growth factor-beta and p21 genes. Besides, these vitamins may enhance the anti tumor effects of x-irradiation, chemotherapeutic agents and hyperthermia thereby acting as biological response modifiers. They also reduce the toxicity of several standard tumor therapeutic agents in normal cells. Selenium has been associated with several positive benefits related to chronic diseases, ageing and cancer. Similarly, bee honey and Nigella grains have shown significant protection against oxidative stress and carcinogenesis (80%) induced by methylnitrosourea (MNU) in rats.

23 .CONCLUSION

The incidence of cancer is continually rising. Concomitantly phytomedicines are growing increasingly

important since they are used more readily. Numerous papers have been published on pharmacological activities and the clinical assessment of some of them in relation to cancer control. Although some studies have confirmed the positive response but their mechanisms of action are still not clear. Many of them have same mechanism and can be grouped together, based on that pathway. To understand the potential of these Asian traditional medicine- remedies, as a source of health care, their safety, efficacy and quality need to be assessed. There is an urgent need to investigate some of the potential medicinal plants on better experimental models and also clinically to bring them to masses.

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