**RESEARCH ARTICLE**

# Natural approach: An alternative to conventional therapy for cancer management

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**ABSTRACT**

Complementary and alternative medicine uses are common amongst cancer patients. Nutraceuticals are amongst the most commonly used group of discourses. These are considered by the general public to be safe, cause less side-effects and less probable to induce addiction. Natural therapies may be most helpful in supporting conventional cancer treatments. Natural therapies may help boost immune function and minimize the severity of side effects caused by surgical procedure, chemotherapy and radiation.

**Keywords:** Cancer, Nutraceuticals

## INTRODUCTION

Cancer is a disease caused by autonomous proliferation of genetically damaged cells. These cells do not respond to normal regulatory mechanisms and as a result, they continue to proliferate, thus robbing nutrients from nearby normal cells and eventually crowding adjacent healthy tissue. Malignant tumors are considered dangerous because they can undergo metastasis. The vast majority of cancerous tumors is carcinomas derived from epithelial tissue, such as skin, various glands, breasts and the lining of most internal organs.

### Origin of cancer

Single damaged cells are capable of causing a tumor, hence a tumor is a clone derived from a cell in which heritable changes have taken place. All types of genetic damages such as point mutations, deletions, inversions and chromosomal rearrangements or losses have been reported. These changes result in the loss of function or altered function of molecules involved in cell growth or proliferation.

### Stages of carcinogenesis

Carcinogenesis is a process of accumulation of diverse progressive mutations and alterations in nuclear and cytoplasmic molecules (Colic, 2002). The events of carcinogenesis are divided into three phases: Initiation, Promotion and Progression. Initiation is a very quick process, involving DNA damage.

The promotion phase is random, in which tumor promoters act as mitogens and induce clones of initiated cells to multiply. Progression is a stage in which phenotypic and genotypic changes occurs in the cell. The initiationphase of carcinogenesis is a permanent change in the genome of the cell that gives it a growth advantage over neighboring cells. Following initiation and promotion, these cells move to progression. During progression, genetically vulnerable precancerous cells, which have already acquired significant growth advantage over normal cells, further receive second round of mutations and acquire invasion and metastatic proficiency.

**Complementary and Alternative Medicine**

Complementary and Alternative Medicine (CAM) approach has gained recognition among cancer patients in the past few years. Complementary medicine is used in addition to standard treatments and alternative medicine is used instead of standard treatments. According to the National Center for Complementary and Alternative Medicine, CAM is classified into five domains: whole medical systems, mind-body medicine, biologically based practices, manipulative and body-based practices, energy medicine (NCCAM, 2011). The biological based practices include a variety of products, such as herbs, vitamins and minerals. These products are usually always sold as dietary supplements. These supplements have indicated that they are helpful.

All the conventional therapies discussed so far are associated with several side effects and at times lead to development of new cancer. Thus new strategies are needed in the treatment of cancer. The recent view is to look for the metabolic, biochemical or other changes that lead to cancer and target specific steps by using phytochemicals and nutrients. This therapy has been called as cellular regulation.

Cellular regulation works at the level of:

**a)** Inhibition of tumor growth
**b)** Inhibition of invasion and metastasis
**c)** Encapsulation of tumors
**d)** Selective elimination of cancer cells or apoptosis
**e)** Inhibition to formation of new blood vessels
**f)** Neutralization of free radicals
**g)** Inhibition of inflammation

Bioactive substances as dietary supplements, even in very low concentrations have shown to have a far greater impact on gene regulation than expected. Findings, related to the effects of nutraceuticals on gene expression provide an insight into prevention and treatment of various diseases. Promising nutraceuticals, effective in cancer therapy include allicin, apigenin, butein, caffeicacid, capsaicin, catechingallate, celastrol, curcumin, epigallocatechin gallate (EGCG), flavopiridol, gambogic acid, genistein, plumbagin, quercetin, resveratrol, sanguinarine, silibinin, sulforaphane, taxol, γ-tocotrienol and zerum bone to name a few (Figure 1). They have been reported to be very effective in the process of tumor genesis, survival, proliferation, invasion, angiogenesis and metastasis. Some of the cancer fighting properties of nutraceuticals is discussed below:

**Regulation of cancer cell proliferation by nutraceuticals**

Proliferation is one of the major characteristics of Tumorigenesis. In normal cells, proliferation is regulated by a delicate balance between growth signals and anti-growth signals. The growth is controlled by cell cycle regulators at G1/S, Sand during the G2/M phases of cell cycle. Currently, a number of inhibitors of cell cycle regulators, including nutraceuticals, are being developed as therapeutic intervention for cancer prevention. Nutraceuticals

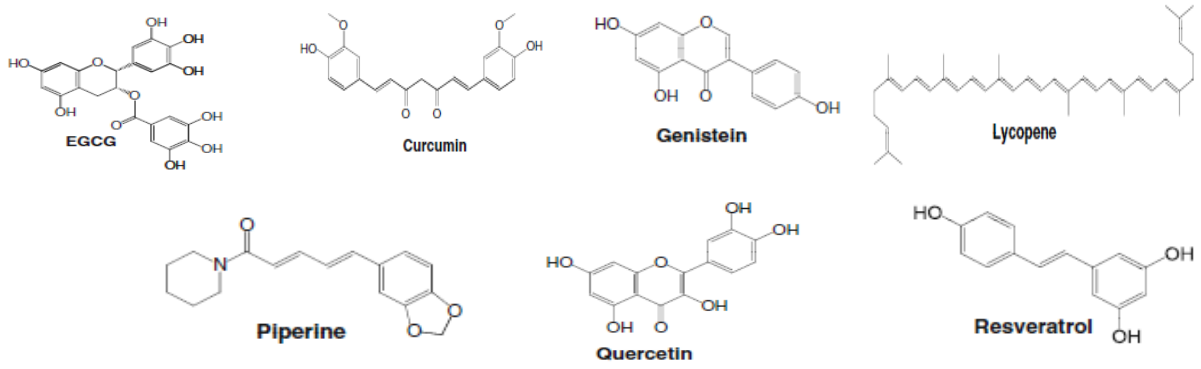


**Figure1:Chemical structure of some nutraceuticals**

have been shown to halt cell cycle progression by targeting one or more steps in the cell cycle. Most nutraceuticals prevent transition of cancer cells from G1-S phase. Some act throughp53 and some through Rb.

EGCG, a tea catechins is reported to induce the expression of Cdk inhibitorp21/WAF1/CIP1and p27/KIP1, decrease the expression of cyclin D1 and inhibited Cdk2 and Cdk4 kinases (Gupta *et al* 2003). Thus, EGCG exerts its growth-inhibitory effects through modulation of the activities of several key G1regulatory proteins such as Cdk2 and Cdk4 or mediating the induction of p21 and p27.Quercetin induced cell cycle arrest *in-vitro*at the G1 phase by elevating p53, p21and p27 in human hepatoma cell line (Hung, 2007). Nutraceuticals also prevent tumor cell proliferation by preventing transitions from the G2 to M phase as shown by numerous studies. Curcumin exhibited antiproliferative activity accompanied with decreased expression of cyclin-D1 and CDK-4 in breast cancer cell lines MDA-MB-231 and BT-483 (Liu *et al*., 2009).

**Regulation of tumor cell survival by nutraceuticals**

Homeostasis refers to removal of unnecessary, damaged, aged or misplaced cells by genetically programmed process known as apoptosis. Cancer cells show loss of this function through mutation in p53 tumor suppressor gene. EGCG was found to inhibit survival of Ewing family tumors (EFT) through inhibition of IGFIR activity, induceapoptosis via up-regulation of Bax and decreased expression of Bcl-2, Bcl-XL and myeloid cell leukemia (Mcl)-1 proteins (Kang *et al*., 2010). EGCG also modulates apoptosis and cancer inhibition by membrane receptor associated signaling pathways (HsuandLiou *et al*., 2011). EGCG also enhanced apoptosis through upregulating expression of the apoptopic caspase-3 protein anddown regulation of gelsolin, a regulator of actin filament assembly and breakdown (Hsu and Liou, 2011).

Some nutraceuticals have the potential to inhibit survival of tumor cells through mediation of signal transducers and activators of transcription protein (STAT)-3. Most nutraceuticals target by inhibiting NF-κB activation, thereby inhibiting NF-κB-regulated antiapoptotic proteins. Garcinol induced apoptosis in human breast cancer cell lines MCF-7and MDA-MB-231 through caspase activation and down-regulation of NF-κB-regulated genes (Ahmad *et al*., 2010). Plumbagin induced apoptosis with concomitant inactivation of Bcl-2and the DNA binding activity of NF-κB in breast cancer cells (Ahmad, 2008).

**Regulation of tumor cell angiogenesis by nutraceuticals**

Angiogenesis is a process in which new blood vessels are formed from pre-existing ones and are classified as either physiological or pathological. The angiogenic cascade during tumor development releases angiogenic factors, which bind to receptors on ECs, leading to EC activation, degradation of basement membrane by proteases, migration and proliferation of ECs. Signaling pathway in tumor angiogenesis is exceedingly complex, involving various angiogenic mediators. The major signaling mediators include VEGF, Platelet Derived Growth Factor (PDGF), fibroblast growth factors (FGFs),epidermal growth factor (EGF), ephrins, angiopoietins, endothelins, integrins, cadherins and notch (Gordon *et al*., 2010). Various nutraceuticals have been shown to negatively regulate tumor cell angiogenesis. EGCG, for example, inhibited ephrin-A1-mediated EC migration as well as tumor angiogenesis through inhibition in ERK-1/ERK-2activation (Tang *et al*., 2007). EGCG also inhibits angiogenesis by enhancing the activity of FOXO transcription factors (Singh *et al*. 2011).

Quercetin inhibited hypoxia-induced VEGF expression in NCI-H157cells, which correlates with suppression in STAT-3 tyrosine phosphorylation, suggesting that inhibition of STAT-3 function may play a role in inhibition of angiogenesis (Anso *et al*., 2010). Resveratrol suppressed the growth of new blood vessels in animals. It directly inhibited capillary endothelial cell growth and blocked both VEGF and FGF receptor-mediated angiogenic responses by inhibition of phosphorylation of MAPK in ECs. Curcumin completely prevented induction of VEGF synthesis in microvascular ECs stimulated with glycation end products by down-regulation of NF-κB and AP-1 activity.

**Regulation of cancer cell invasion by nutraceuticals**

Tumor cell invasion and metastasis are interrelated and involve cell growth, adhesion, migration and proteolytic degradation of tissue barriers such as extracellular matrix and basement membrane. Numerous proteolytic enzymes, including MMPs

(mainly MMP-2and MMP-9) and intercellular adhesion molecule (ICAM; mainly ICAM-1), are reported to participate in degradation of these barriers. Strengthening collagen in the ECM and inhibiting MMPs through micronutrients such as lysine, proline and ascorbic acid and effect of EGCG or green tea extract with micronutrients synergistically enhanced anti-carcinogenic activity in HepG2 cells have been reported (Roomi *et al*., 2012). It has been shown that, EGCG also down regulates the activity of MMP-9 via FAK/ERK/NF-κB and AP-1 in the human breast cancer cell line MDA-MB-231 (Sen *et al*., 2010). Curcumin exerted a dose and time-dependent inhibitory effect on the invasion and migration of mouse rat hybridretina ganglion cell lines (N18) (Lin *et al*. 2010). This inhibited invasion with down-regulation of PKC, FAK, NF-κB, p65, Rho A, MMP-2 and MMP-9. EGCG inhibited fibroblast conditioned medium-induced production of pro and active forms of MMP-2 and MMP-9. Resveratrol reduced the migratory and invasive ability of A549 lung cancer cells and was associated with inhibition of NF-κB activation and expression of MMP-2and MMP-9 (Liu *et al*., 2010).

## CONCLUSION

The incidence of cancer is rising in developing countries.Concomitantly nutraceuticals are growing increasingly important since they are applied more readily.Numerous papers have been published on pharmacological activities and the clinical judgment of some of them in relation to cancer control.There is an urgent need to investigate some of the potential nutraceutical on better experimental models and also clinically to bring them to the masses.

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