# Cancer chemoprevention: alternative strategies

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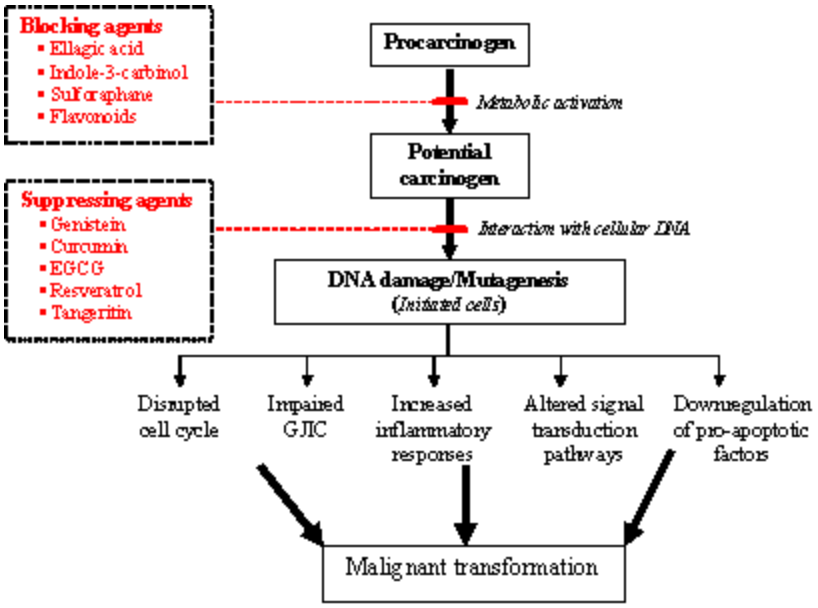
As it stands today, cancer is the second leading death cause in the world. In 2005, out of 58 million deaths worldwide 7.6 million people died of cancer. Based on projections, cancer deaths will continue to rise with an estimated 9 million people dying from cancer in 2015, and 11.4 million dying in 2030. Statistical data show that men are largely plagued by lung, colon, rectum and prostate cancer whilst women increasingly suffer from breast, colon, rectum and stomach cancer. More than 70% of all cancer deaths occur in low and middle-income countries, where resources available for prevention, diagnosis and treatment of cancer are limited or nonexistent. Whilst current clinical therapies including radiation, chemotherapy, immunosuppression and surgery are limited (and also costly) as indicated by the high morbidity and mortality rate from cancer, there is an imperative need for new treatment modalities. There has been in the past decades several independent concepts related to the carcinogenic process indicating that new intervention strategies can be developed that could diminish cancer incidence.

Chemoprevention is a novel approach emphasizing on the prevention or delay of carcinogenesis by means of pharmacologic, biologic, and nutritional intervention. This includes the interference of new drugs with specific cell cycle elements, oncogene products, growth factors, hormone receptors and telomerase activity. Chemoprevention by targeting key components of the apoptosis regulatory pathways which include the anti-apoptotic Bcl-2 family of proteins, IAPs in particular XIAP, cIAP1, cIAP2, survivin, NF-κB, caspases, tyrosine kinases and key signaling routes (the PI-3K/PKB pathway, the Stat3/5 pathway and the MAPK pathway) seems to be a rational approach in reducing the incidence of cancer. Targeting of the tumour microenvironment, more particularly inflammatory mediators and reactive oxygen/nitrogen species, upregulation of gap junctional intercellular communication (GJIC), regulation of upstream kinases of intracellular signalling cascades, downstream transcription factors, modulation by pharmacological or nutritional means the levels of biotransformation enzymes that promote the elimination of endogenous and environmental carcinogens and reduction of angiogenesis are some proposed chemopreventive strategies. In this particular context, nutrition, particularly the use of diets containing antioxidants, has been suggested for cancer prevention. Epidemiological and experimental studies highlight the protective roles of a range of dietary phytochemicals more particularly phenolics for the control and containment of carcinogenesis. Polyphenols encompass a wide range of biological, pharmacological and medicinal properties. They comprise the simple phenols, phenolic acids phenylpropanoids, quinones, flavonoids, tannins and the less common stilbenes and lignans. Flavonoid is a broad class of polyphenols with more than 6000 structures. These compounds have been characterized into major groups consisting of flavones, isoflavones, flavanones, flavanonols, flavonols, flavanols, flavan-3,4-diols and anthocyanidins. They have been reported for their multiple biological activities including antioxidant, antibacterial, antiviral, anticarcinogenic, anti-inflammatory, anti-thrombotic anti-allergic, immune stimulating, estrogenic and vasodilatory actions amongst others. Several of these pharmacological effects are related to their interaction with several enzymes including protein kinases, cycloxygenase, lipoxygenase and xanthine oxidase and to their free radical scavenging and metal chelating properties. These pleiotropic properties have made phenolic compounds suitable for cancer chemoprevention that entails the use of naturally occurring phytochemicals to prevent the onset and/or the progress of carcinogenesis. Flavonoids have been shown to be potent biomodulators at the cellular, subcellular and molecular levels and they can act as mediators of cell differentiation, apoptosis, protein/enzyme. (-)-Epigallocatechin-3-gallate, the major catechin found in tea inhibits cervical cancer cell growth in vitro through the regulation of gene expression, cell cycle progression and

apoptosis. Several anthocyanins and phenolic acids protect against DNA mutation by scavenging free radicals and also by protecting DNA nucleophilic sites. In addition to their free radical scavenging properties, some phenolic antioxidants such as genistein act through enhancing the activity of a number of antioxidant enzymes, including catalase, glutathione peroxidase, glutathione reductase, and superoxide dismutase therefore maintaining the genome integrity. The implication of inflammatory processes and oxidative stress on carcinogenesis indicate the therapeutic benefit of natural anti-inflammatory agents that exert their activity mostly through the antioxidative property. Phenolics including (+) epigallocatechin gallate, capsaicin, curcumin, caffeic acid phenyl ester (CAPE) and resveratrol have been reported to down-regulate proinflammatory mediators e.g TNF-α, IL-8. Moreover the ability of phenolic components to downregulate the proinflammatory enzymes COX and iNOS enhanced their prophylactic potentials in cancer. Several compounds for example resveratrol, gingerol, CAPE, curcumin, EGCG, capsaicin have been reported to mediate their anti-carcinogenic via COX and iNOS inhibition.




Antiangiogenic and apoptosis inducing effect of the polyphenols makes them suitable chemopreventive In addition antioxidative effect of phytochemicals has recently been linked to antiangiogenesis since reduction of oxidative stress by polyphenols leads to an altered cellular redox state, resulting in a reduced activation of transcription factors such as AP-1, p53 and NF-κB, which regulate the expression levels of the key angiogenic factors VEGF. The ability of phenolic compounds to target protein kinases and transcription factors also enhances their chemopreventive potential. Several phenols including curcumin, flavonoids, genistein, resveratrol, catechins, have been identified to target enzymes of the signal transduction pathways including mitogen activated protein kinases (MAPKs), protein kinase C, phosphatidylinositol-3-kinase (PI3K), protein kinase B/Akt, glycogen synthase kinase (GSK). This can prevent the aberrant activation of the cellular signaling network, hence reducing neoplastic transformation. In addition MAP kinase cascades transmit and amplify signals involved in apoptosis and flavonoids have received considerable attention as signaling molecules. The intricate link between MAPK activation and inhibition of GJIC has been widely discussed thus MAPK inhibitors are prospective therapeutic compounds against carcinogenesis. Several phenolic constituents including CAPE, resveratrol, epicatechin, apigenin, tangeretin have been described to restore GJIC. The procyanidin B5-3'-gallate has been shown to have cancer chemopreventive and/or anticarcinogenic effects in mouse skin two-stage carcinogenesis model. Oligonol, a catechin rich product derived from the

oligomerization of polyphenols induced apoptosis in MCF-7 and MDA-MB 231 human breast cancer cell lines by modulating pro-apoptotic Bcl-2 family proteins and ERK/MAPK signaling pathway.

From the above examples and the high number of ongoing and completed studies in this research area, it is clear that plant derived antioxidants can meaningfully contribute towards the management of the biochemical and physiological features of cancer and oxidative stress related disorders. However bioavailability concerns arises and this can be resolved by future clinical trials that in addition will advance our understanding of the efficacy and safety of many chemopreventive extracts with therapeutic potential. There now exist clear trends to show that the mainstream pharmaceutical research is moving away from single molecule or single target approach to combinations and multiple target approaches. Plant extracts that contain several pluripharmacological compounds have been reported to act on multiple molecular and cellular targets and such approach is gaining support to fight cancer. It is noteworthy that in spite of growing evidence in support of the potential prophylactic use of food plant derivatives and extracts there is still a tendency for a number of scientists, as rightly pointed out by Professor Hamblin (Leukemia Research 30 (2006) 649–650) to "back away from the word "natural" for fear of being contaminated by the beards and sandals brigade flogging organic produce, acupuncture meridians, radio-ionic diagnosis and snake oils of various flavors". For sure, there is a mindset to change!

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