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Editorial

Usefulness of Phytochemicals as Anticancer Drugs

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Cancer is a state of uncontrolled proliferation and dedifferentiation of cells in any tissues or organs of the body. The incidence of cancer is rising alarmingly and is one of the leading causes of morbidity and mortality globally. Normal cell division is precisely a planned biological process controlled by regulatory genes and specific metabolic pathways. Exposure of normally functioning cells to carcinogens leads to mutations in the genes causing loss of control of cell division and transform into cancerous. Over a period of time, these cancer cells acquire more mutations; invade to adjoining tissues, escape the process of apoptosis and the cells become eternal. Breakaway parts of the cancer tissues / cells travel through the lymphatic and blood vessels and get deposited in other tissues / organs leading to metastasis, the spread of cancer.

The treatment of cancer includes surgical removal of the affected tissue/s, radiotherapy and chemotherapy. The chemical substances which are cytotoxic or cytostatic are widely in use as chemotherapeutic anticancer substances/drugs in conjunction with other treatment modalities. These drugs generally act through processes like enzyme inhibition, Chemical modification proteins and acting as antimetabolites. All these processes are ultimately aimed at curbing cell growth and uncontrolled division of cancer cells. Anticancer drugs are expected to target the rapidly dividing cancer cells. However, they would also affect the rapidly dividing cells of bone marrow, gastrointestinal epithelium and hair follicle causing undesirable and dreadful side effects of which immunosuppression is one of the major concerns. Further, cancer cells can undergo extensive mutations leading to resistance to the chemotherapeutic agents. Thus, there are limitations to the chemotherapeutic approach for the treatment of cancer. Therefore, chemotherapy with undesirable side effects should be repressed with innovative approaches in drug design and development. Cancer is caused by disorganized functioning of the genes and therefore; the fight against cancer should focus at normalizing the cancer cells.

Plants synthesize distinct chemical substances for protection from insect attack, defense against the disease causing microorganisms and also to make themselves unpalatable as fodder for the herbivores. These substances generally referred to as phytochemicals are secondary metabolites with complex chemical structure and properties. Plants and their formulations are in use since ancient time as medicines. Many alkaloids, flavonoids, tannins, glycosides, resins and oils are of with pharmacological actions. Some of them have been identified with DNA repair, anti-mutagenic, antitumor, anti-angiogenesis as well as immune system boosting capabilities. Certain chemically well characterized compounds with abilities to suppress various cancer types include gossypol, taxol, curcumol, lycobetaine, vincristine, glycyrrhizin, gingerol and indirubin.

Development of anticancer drug involves *in vitro* demonstration of cytotoxicity on cancer cells, *in vivo* corroboration, and clinical trial evaluation. Assessment of cytotoxicity toward cancer cell lines is an established approach for the discovery of anticancer agents. Cell viability assessment of cancer cells is an easy screening method through which chemical compounds can be tested in a short period of time. Several phytochemicals have been discovered from plants and dietary supplements through these processes. Crude phytochemical extracts also been shown to suppress the viability of cancer cells.

Phytochemicals exhibit anticancer effect through diverse mechanisms. Several *in vitro* studies have demonstrated the selective ability to kill the rapidly dividing cell, target abnormally expressed molecules, mitigate oxidative stress, regulate growth factors, inhibit angiogenesis in cancer tissues and induce apoptosis. Methoxy licoflavanone, a flavonoid, has been shown to exert anticancer effect through induction of apoptosis to control cancer growth. There are phytochemicals which have been demonstrated to possess regulatory effect on aggressive cancer cells by repairing damaged DNA, inhibition of mutagenesis,

blocking cancer promoting enzymes and other biomolecules.

Molecular targets and mechanisms of action of anticancer phytochemicals have been studied extensively. However, the exact mechanism by which phytochemicals exert anticancer functions is still a topic of active contemporary research. These molecules perform diverse and complex actions on nuclear and cytosolic factors of a cancer cell. They can either directly absorb the reactive oxygen species (ROS) or promote activities of antioxidant enzymes (e.g., superoxide dismutase, glutathione oxidase and catalase) in the cancer cell.

Phytochemicals can suppress malignant transformation of genetically and phenotypically altered cells exhibiting risk of malignant progression than normal cells. On the other hand, it can halt the metabolic conversion of a molecule into a carcinogen. In addition, they can regulate cellular signaling events involved in growth, invasion and metastasis of cancer cell. Ellagic acid of pomegranate induces apoptosis in prostate and breast cancer cells, as well as inhibits metastasis processes of various types of cancer. The activity of ornithine decarboxylase, the enzyme which signals the cell to proliferate faster and bypass apoptosis can be suppressed by Epigallocatechin gallate (EGCG).

Curcumin, a polyphenol extracted from Curcuma longa promotes the expressions of p21, p16, p53, , extracellular signal regulated kinase , c-JunN-terminal kinase, ElK-1, Bcl-2 and caspases and down regulate the levels of B cell lymphoma 2, early growth response protein 1, mechanistic target of rapamycin, p65, B cell lymphoma extra-large protein, protein kinase B, epidermal growth factor receptor, NF-κB, cell division cycle protein 2, retinoblastoma protein, cellular myelocytomatosis oncogenes and cyclin D1 proteins slowing down the growth of human glioblastoma cells .

DNA methylation, histone modifications and miRNA expressions are some of important epigenetic events in carcinogenesis. Inhibition the activities and reduction of expression of DNA methyl transferases, histone deacylases and histone methyl transferases are some of mechanisms through which phytochemicals exert suppression of cancer initiation and progression. Cancer cells are heterogeneous from the point of view of their tumorigenic potential. A subset of tumor cells namely cancer stem cells have high potency for initiating tumorigenesis.

Cancer stem cells are expected to proliferate with unlimited potential and can cause post treatment tumor regrowth. Considering these potentials of the cancer stem cells, these cells are of significance for development of new therapeutic approaches. Number of phytochemicals have been evaluated and reported to interfere in signaling pathways for preservation of the potency of cancer stem cells. Cyclopamine, a phytochemical from corn lily, target hedgehog signaling and EGCG inhibit Wnt/β-catenin signaling affecting the renewal and invasive abilities of some cancer stem cells.

Bioactive phytochemicals are potential sources for the development of drugs. Several plants and their constitutive phytochemicals have been screened for this purpose and some have reached to the clinical trial stage. The foregoing descriptions on the phytochemicals indisputably provide scope of furthering studies on anticancer potentials of these molecules. The rationale of screening for phytochemicals as drugs capable of suppressing growth is explicable from their spectrum of action as well as specificity. Phytochemicals as substances capable of specifically targeting cancer cells for destruction and can be strategically superior to conventional chemotherapeutic drugs. The spectrum of actions of phytochemicals as anticancer agents are heterogeneous and combination of these molecules might exert better efficacy. Furthermore, there could be a possibility that by the use of these natural biomolecules the deleterious effects on normal cells could be minimized. Therapeutic intervention based upon the combination of anticancer molecules from plants may therefore provide potent and effective therapeutic results.

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