

Naturally occurring products in cancer therapy

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ABSTRACT

Natural products have been used for the treatment of various diseases and are becoming an important research area for drug discovery. These products, especially phytochemicals have been extensively studied and have exhibited anti-carcinogenic activities by interfering with the initiation, development and progression of cancer through the modulation of various mechanisms including cellular proliferation, differentiation, apoptosis, angiogenesis, and metastasis. This concept is gaining attention because it is a cost-effective alternative to cancer treatment. In this article, we have discussed some of the naturally occurring products used in cancer treatment.

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Oral cancer is defined as the cancer of mouth and pharynx including cancer of lips, tongue, floor of the mouth, palate, gingiva, alveolar mucosa, buccal mucosa, oropharynx, tonsils, uvula and salivary glands. Cancer is the biggest cause of mortality worldwide, responsible for 8.2 million death/year and rising according to the global scientific report released on the February 5, 2014.^[1] Factors such as obesity, poor diet, tobacco, radiation, environmental pollutants, lack of physical activity and age increases cancer risk. These factors may cause cancer by damaging genes directly and/or indirectly in combination with existing genetic mutation within cells.^[2]

Epidemiology

Epidemiological studies have shown that diet containing fruits and vegetables reduce the risk of several types of cancer.^[3] Intake of fruits and vegetables has been successfully used in the

prevention of chronic disease associated with oxidative stress condition including cancer.^[4,5] WHO projects 10,000,000 cases of cancer per year worldwide and 6,000,000 deaths from cancer per year worldwide. And it also projected 15 million cases/year in 2020. It is been estimated that 80% of the world population relies on plant-based medicine for primary health care and 75% of all pharmaceuticals were discovered by examining the use of plants in traditional medicine.

Carcinogenesis

The transformation of normal cell to cancer cell occurs through three distinct phases, initiation, promotion, and progression. Initiation of cancer occurs in the normal cells due to exposure of carcinogenic and mutagenic agents. The initiated cells are irreversibly altered and are at greater risk of neoplastic transformation. However, initiation alone is not sufficient for tumor formation.^[6] In promotion phase, tumor promoters convert the initiated cells into neoplastic cells.^[7,8] Progression involves a stepwise evolution of neoplastic cells into higher degree of malignancy.

Chemopreventive Agents in Oral Carcinogenesis

Various phytochemicals obtained from vegetables, fruits, spices, teas, herbs, and medicinal plants, such as flavonoids

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carotenoids, phenolic compounds and terpenoids, have been extensively investigated for their anti-cancer activities due to their safety, low toxicity and general availability.^[9] In this article we discuss (a) use of phytochemicals, including curcumin, resveratrol, apigenin, quercetin, genistein, lycopene, isothiocyanates (b) their mechanism of action, such as anti-oxidant properties, inhibition of cell cycle, induction of apoptosis, regulation of angiogenesis.

Curcumin

Curcumin (diferuloylmethane), a yellow pigment belongs to the class of polyphenols present in the rhizomes of turmeric is used in cooking in India. It is also used as a cosmetic and in some medical preparations. Multiple therapeutic activities of curcumin have also been considered to be associated with its anti-oxidant and anti-inflammatory properties. The anti-inflammatory effect of curcumin is most likely mediated through its ability to inhibit cyclooxygenase-2, lipoxygenase (LOX), and inducible nitric oxide synthase.^[10] Curcumin has the capability to inhibit carcinogen bioactivation via suppression of specific cytochrome P450 isozymes, as well as to induce the activity or expression of phase II carcinogen detoxifying enzymes.^[11] Combination of phenethylisothiocyanate and curcumin caused suppression of epidermal growth factor (EGF) receptor phosphorylation and inhibition of EGF-induced phosphorylation and induction of phosphatidylinositol 3-kinase in prostate cancer-3 cells.^[12] It regulates tumor cell growth through multiple cell signaling pathways, including cell proliferation pathway, cell survival pathway, caspase activation pathway, tumor suppressor pathway, death receptor pathway, mitochondrial pathways and protein kinase pathway.

Resveratrol

Resveratrol (trans-3, 5, 4-trihydroxystilbene) a naturally occurring phytoalexin, is found at a high concentration in the skin of red grapes and red wine. Resveratrol is known to have anti-oxidant, anti-inflammatory and antiproliferative effects on a variety of cancer cells *in vitro* and in various animal models.^[13] Resveratrol has been identified as an effective candidate for cancer prevention based on inhibitory effects on cellular events associated with cancer initiation, promotion, and progression.^[14] It has been shown to inhibit tumor necrosis factor- α -mediated matrix metalloproteinase-9 expression in HepG2 cells by down regulation of the nuclear factor-kB signaling pathway.^[15] Various studies revealed multiple intracellular targets of resveratrol, which affect cell growth, inflammation, apoptosis, angiogenesis, and invasion and metastasis.^[16]

Apigenin

Apigenin, a naturally occurring plant flavone, abundantly present in common fruits and vegetables possesses anti-oxidant, anti-mutagenic, anti-carcinogenic, anti-inflammatory, anti-growth, and anti-progression properties.^[17] Apigenin is effective in carcinogenesis, topical application of apigenin inhibited dimethyl benzanthracene-induced skin tumors,^[18]

and also diminished ultraviolet-induced cancer incidence and increased tumor free survival experiment.^[19]

Earlier studies demonstrated that the apigenin promotes metal chelation, scavenges free radicals and stimulates phase II detoxification enzymes in cell culture and *in vivo* tumor models.^[20]

Quercetin

Quercetin is a dietary flavonoid abundant in variety of foods including apples, berries, brassica vegetables, grapes, onions, shallots, tea, and tomatoes as well as many seeds, nuts, barks and leaves.^[21] It usually occurs as o-glycosides with D-glucose as glycosides have been identified.^[22] Among polyphenols, quercetin is one of the most potent anti-oxidants, as demonstrated in different studies.^[23,24] It has been shown to inhibit oxidative species generating enzymes such as xanthine oxidase, LOX, and nicotinamide adenine dinucleotide phosphate oxidase.^[25] It is a potent anti-cancer agent, exhibiting different activities such as cell cycle regulation, interaction with type II estrogen binding sites and tyrosine kinase inhibition.^[26]

Isothiocyanates

Isothiocyanates (ITCs) are electrophilic compounds that play a major role in potential chemopreventive effects associated with high intake of cruciferous vegetables such as watercress, brussels sprouts, broccoli, cabbage, horseradish, radish, and turnip.^[27] Cruciferous vegetables have been widely accepted as potential diet components that may decrease the risk of cancer.^[28] Epidemiological studies show that the dietary intake of ITCs is associated with reduced risk of certain human cancers.^[29] ITCs display anti-carcinogenic activity by reducing the activation of carcinogens and increase their detoxification.

Genistein and ursolic acid

Genistein is an isoflavone compound found in soybean and related products such as tofu, soy milk and soy sauce.^[30] And is a promising cancer chemotherapeutic agent.^[31] It inhibits the growth of cancer by increasing apoptosis, including cell cycle delays and modulating intercellular signaling pathways.^[32]

Ursolic acid is a **pentacyclic** triterpene compound widely found in food, medicinal herbs, apple peel and is able to exhibit a wide range of pharmacological functions, including anti-oxidant, anti-tumor, anti-inflammatory activities.^[33]

Conclusion

Natural products play a major role in chemotherapy drugs, and primarily target proliferating tumor cells. Chemoprevention by phytochemicals is of great interest and is considered to be an inexpensive, readily applicable, acceptable, and accessible approach to cancer control and management. Several phytochemicals are in preclinical or clinical trials for cancer chemoprevention. Epidemiological studies have shown that

high dietary consumption of vegetables and fruits reduced the risk of cancer. Severe toxicity is a major drawback in conventional radiotherapy and chemotherapy.

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