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Conceptual Editorial

Anticancer properties of horticultural based food

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Now-a-days, cancer is considered as one of the leading causes of mortality and morbidity, and has become the most serious life-threatening disease, affecting people of all ages worldwide. It is the second most common cause of death after cardiovascular diseases in developed countries. As per the study of Indian Council of Medical Research (ICMR), the incidence of cancer is likely to go up from 9.8 lakh cases in 2010 to 11 lakh in 2020. While some cancers can be cured if detected early, treatment of others remain a great challenge. In accordance with the recent report from the World Health Organization (WHO), the average number of new diagnosed cases of cancer in the World overcomes 14 million per year and, among these, more than 60% result in death (8.8 million in 2015). The term "cancer" can be described as a set of complex processes involving impaired cells death, unlimited cell proliferation and temporal–spatial changes in cell physiology that often leads to malignant tumor formation resulting in invasion of distant tissues to form metastasis. Multistage carcinogenesis (namely initiation, promotion and progression) is a widely accepted hypothesis in the development of cancers, resulting from extensive DNA damage. DNA damage as a term encapsulates both frank single and double-stranded DNA breaks, as well as stable modifications to nitrogen bases in DNA or its sugar-phosphate backbone, caused by external (e.g., IR) or internal sources (e.g., reactive oxygen species (ROS) generated during oxidative metabolism), which impact the cell by disrupting gene function and/or impairing transcription, DNA replication and cell proliferation. The oxidative hypothesis of carcinogenesis claims that many carcinogens can generate free radicals that damage cells, setting these cells to malignant changes. DNA contains reactive groups in its bases that are highly susceptible to free radical attack and oxidative DNA damage can lead to deleterious mutations. Most oxidative lesions are efficiently repaired by specific DNA glycosylases, but unrepaired lesions accumulate with age. When the cells divide, the lesions become fixated and mutations and cancer may result. Cancer cells are characterized by mutations and genetic instabilities which consequently lead to impaired regulation of cell cycle, uncontrolled proliferation and overcoming of apoptosis and similar checkpoint mechanisms. Anticancer treatments usually use compounds that target fast-dividing cells. This approach, regrettably, has a negative side effect because normal, fast-dividing cells such as hair follicles and epithelial cells in the digestive system are also affected. Furthermore, one of the aggravating circumstances is that many cancer cells gradually develop resistance to conventional forms of therapy.

Fruits and vegetables (F & V) provide a diversified low caloric, and protective, micro-nutrient rich diet. Low F & V intake is considered as the sixth main risk factor for mortality in the world. Overall it is estimated that low F & V intake is attributable to approximately 2.7 million (4.9%) annual deaths, and causes about 31% of ischaemic heart diseases (IHD), 11% of stroke and 19% of gastro-intestinal cancers and still significantly associated (protective) with lung/pharyngeal/laryngeal/oral cancer, type-2 diabetes mellitus, bone-health,

vision/cataract and micronutrient deficiency state. A commonly accepted estimate among experts is that at least one third of cancer cases are related with diet. Based on the evidence from the accumulated studies indicates that there is a low risk of cancers in people with a high intake of fruits and vegetables. The potential number of cancer cases that might be prevented if half the U.S. population increased its fruit and vegetable consumption by one serving each per day. The cancer risks were estimated using U.S. Environmental Protection Agency (EPA) methods, cancer potency estimates from rodent bioassays, and pesticide residue sampling data from the U.S. Department of Agriculture (USDA). The resulting estimates are that approximately 20,000 cancer cases per year could be prevented by increasing fruit and vegetable consumption. Total vegetable intake is inversely related to breast cancer risk. Reduced risk is also related to high intake of allium vegetables and fresh legumes. High intake of citrus fruits and Rosaceae fruits are inversely associated with breast cancer risk. The high intake of total vegetables, certain fruits, milk, and eggs may reduce the risk of breast cancer, whereas high consumption of animal-source foods may increase the risk. Approximately 200 studies that examined the relationship between fruit and vegetable intake and cancers of the lung, colon, breast, cervix, esophagus, oral cavity, stomach, bladder, pancreas, and ovary are reviewed. A statistically significant protective effect of fruit and vegetable consumption was found in 128 of 156 dietary studies in which results were expressed in terms of relative risk. For most cancer sites, persons with low fruit and vegetable intake (at least the lower one-fourth of the population) experience about twice the risk of cancer compared with those with high intake, even after control for potentially confounding factors. It would appear that major public health benefits could be achieved by substantially increasing consumption of these foods.

Chemoprevention through diet modification, i.e., increased consumption of plant-based food, has emerged as a most promising and potentially cost-effective approach to reduce the risk of cancer. Research Fund (WCRF) report (Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective, World Cancer Research Fund/American Institute for Cancer Research, Washington DC, 1997) estimated that adequate consumption of fruit and vegetables could reduce by 23% the incidence of all cancer types, classifying as "convincing" the level of available scientific evidence. In this regard, natural compounds from plants are proving to be suitable candidates for such a therapy. Interfering with the process of carcinogenesis through diet or by the added digestion of natural compounds has been termed as "chemoprevention". An increasing importance is being given today to alternative medicine and dietary approach in prevention and treatment of cancer.

There are many categories of plant bioactive compounds, such as alkaloids, glycosides, polyphenols, tannins, gums, resins and oils, and many of these phytochemicals have been shown to possess low intrinsic toxicity and exert prominent effects on cancerous *versus* normal cells. An encouraging fact is that, in the last few decades, nearly 70% of all anticancer drugs are originated from natural sources or are derivatives of natural products. Phytochemicals can be defined as substances found in edible fruits and vegetables that may be ingested daily by humans (in gram quantities), and that exhibit a potential for modulating human metabolism in a manner favourable for the prevention of cancer and other degenerative diseases. Any reduction in the risk of disease that is associated with a high antioxidant nutrient intake may result from consuming a mix of foods rich in antioxidants rather than consuming antioxidants as single nutrients. The important group of phytochemicals include carotenoids (α-Carotene, β-Carotene, β-Cryptoxanthin, Lutein, Zeaxanthin, Astaxanthin and Lycopene) and phenolics. ROS scavenging capacity of phenolic acids (Hydroxybenzoic acid -Gallic, Protocatechuic, Vannilic and Syringic; Hydroxycinnamic acid-p-Coumaric, Caffeic, Ferulic and Sinapic), Flavonoids (Flavonols-Rutin, Quercetin, kaempferol, Myricetin, Galangin, Isorhamnetin and Fisetin; Flavones-Apigenin, Chrysin, Luteolin, Orientin, Baicalein and Acacetin; Flavanols (Catechins)- Catechin, Epicatechin, Epigallocatechin,

Epicatechingallate and Epigallocatechingallate, Proanthocynidins and Thearubigins;Flavanones-Eriodictyol, Hesperetin, Butin, Poncirin, Sakuranin and Naringenin; Anthocynidins-Cynidin, Capensinidin, Pelargonidin, Rosinidin, hirsutidin, Delphinidin, Peonidin and Malvidin; Isoflavonoids- Genestein, Daidzein, Glycitein, Biochanin A, barbigerone and Formononetin) has made them an inseparable part of anticancer diet for human.

Flavonoids are naturally occurring polyphenols that are ubiquitous in plant-based foods such as fruits, vegetables and teas as well as in most medicinal plants. Over 10,000 flavonoids have been characterized over the last few decades. Flavonoids comprise of several sub-classes including flavonols, flavan-3-ols, anthocyanins, flavanones, flavones, isoflavones and proanthocyanidins. Flavonoids have been shown to be able to act as antioxidants by scavenging free radicals, an activity related to their phenol rings containing hydroxyl groups. Flavonoids have the ability to act as reducing agents, making them capable of donating hydrogens to free radicals and causing their removal. Flavonoids can also act as singlet oxygen quenchers and as chelators of transition metals such as copper and iron, which are known pro-oxidants in foods. Certain flavonoids have anticarcinogenic activity due to their ability to induce the hepatic enzymes affecting the metabolism of carcinogens (e.g. benzo[a]pyrene), and their effect on the metabolic activation of benzo [a] pyrene. Citrus fruits are particularly high in a class of phytochemicals known as the limonoids (limonin and nomilin). It has been determined by animal studies that citrus limonoids and derivatives have certain biological activities that may be used as chemopreventive agents for cancer. Apart from the anticancer activity, flavonoid-mediated health benefits include antioxidant activity through the removal of free radicals, which are capable of damaging lipids, proteins and DNA, antiinflammatory, neuroprotective and antiproliferative activity, as well as an ability to modulate signalling pathways involved in central cell processes. Apigenin (amost abundant flavonoid) is found in significant quantities in a variety of vegetables and fruits such as parsley, celery, chamomile, oranges, thyme, onions, honey and spices, as well as beverages derived from plants; tea, beer and wine. It is a secondary plant metabolite, usually found in nature in glycosylated form, more soluble than its pure form which is unstable and quite insoluble in water and organic solvents. The actions of apigenin in inhibiting the cell cycle, diminishing oxidative stress, improving the efficacy of detoxification enzymes, inducing apoptosis, and stimulating the immune system are also known. The beneficial effects of apigenin have been established well on a variety of cancers (head and neck, breast, prostrate, colorectal, pancreatic, skin, liver and cervical and ovary).

Glutathione S-transferase (GST) is a major detoxifying enzyme system that catalyses the conjugation of glutathione with electrophiles that induce activated carcinogens. The glutathione conjugates are usually less reactive and more water soluble, and hence, facilitate excretion. Many chemicals that are GST enhancers have been found to inhibit chemically induced carcinogenesis. The phytochemical classes (flavonoids, glucarates, carotenoids, coumarins, mono-terpenes, tri-terpenes and phenolic acids) found in citrus have already been identified by the United States National Cancer Institute as warranting further research with regard to protection against cancer and cardiovascular disease. Limonin and nomilin follow the same trend as their ability to induce GST activity. Nomilin, being a much better inducer of GST, was more active as an inhibitor of carcinogenesis than the less effective limonin. The primary problem is that limonin is intensely bitter. A second problem is that this citrus chemical is only soluble in organic solvents. A third problem is that the concentration of limonin and nomilin in citrus juices is fairly low and, therefore, the overall consumption of these two specific limonoids is not high. Moreover, many other structure-related limonoids such as ichigan, isoobacunoic, obacunone, and others, act as good GST inducers.

Tumour promoters, such as epidermal growth factor (EGF), 12-O-tetradecanoylphorbol-13-acetate (TPA), and tumour necrosis factor-alpha, can induce neoplastic cell transformation by regulating MAPKs, PI3K/Akt

signalling, AP-1, and NFjB. Cyanidin, an anthocyanidin found in fruits and vegetables, has been reported to possess anti-cancer effects. It has been found that cyanidin, but not cyanidin-3-glucoside, inhibits the EGF-induced Akt/p70S6K phosphorylation. Moreover, cyanidin directly suppressed the activity of PI3K by binding to PI3K directly in an ATP-competitive manner, which indicates that PI3K is one of the molecular targets of cyanidin.

The protective effects of β-carotene, at least from food, although not necessarily as an isolated molecule, are thought to occur through one or more of several modes. These modes include singlet oxygen quenching (photo protection), antioxidant protection and enhancement of the immune response. Singlet oxygen is a highly reactive form of oxygen that participates in reactions that can alter or destroy important cellular components such as membranes, enzymes and nucleic acids (e.g. DNA). β-Carotene may function as a redox reagent, an immunological regulator or by increasing cell-to-cell communications.

Carotenoids have been shown to enhance both specific and non-specific immune functions in addition to enhancing tumour immunity. It has been postulated that carotenoids may enhance activity by (i) quenching excessive reactive species formed by various immunoactive cells, (ii) quenching immunosuppressive peroxides and maintaining membrane fluidity, (iii) helping to maintain membrane receptors essential for immune functions, and (iv) acting in the release of immunomodulatory lipid molecules such as prostaglandins and leukotrienes.

Vitamin C may protect against cancer through several mechanisms, in addition to inhibiting DNA oxidation. One potential mechanism is chemoprotection against mutagenic compounds such as nitrosamines, which can be formed by reaction of nitrite or nitrate (common in food and cigarette smoke) with amines and amides. Vitamin C prevents the reaction of nitrites with amines and amides that form potent carcinogenic nitrosamines within the digestive tract, and prevents oxidation of specific chemicals to their active carcinogenic forms.

Dietary fibre is commonly defined as 'plant polysaccharides and lignin, which are resistant to hydrolysis by the digestive enzymes of man'. They are generally classified into two groups: soluble and insoluble dietary fibres. Soluble fibres are highly fermentable and are associated with carbohydrate and lipid metabolism, while insoluble fibres contribute to faecal bulk and reduce transit time. The mechanisms by which fibre can influence colon cancer include physical dilution of colon content, absorption of bile acids and carcinogens, decreased transit time, altered bile acid metabolism and the effects of fermentation, namely, the production of short-chain fatty acids, lowering of pH and stimulation of bacterial growth.

The possible anticarcinogenic mechanism mediated by substances supplied by Horticultural based diet includes antioxidant effects, effects on cell differentiation, increased activity of carcinogens detoxifying enzymes, blocked formation of nitrosamines, altered estrogen metabolism and altered colonic milieu (including bacterial flora, bile acid, composition, pH, fecal bulk), preserved integrity of intracellular matrixes, effect of DNA methylation, maintenance of normal DNA repair, increased apoptosis of cancer cells and decreased cellproliferation.