

Review Article**Cancer chemoprevention through functional food of plant origin****Nayanathara Thathsarani, Gayathree Nayanajeehwi, Uthpala Jayawardena, Nayanakanthi Nilakarawasam, Chanika D. Jayasinghe***Department of Zoology, Faculty of Natural Sciences, The Open University of Sri Lanka, Nawala, Nugegoda, Sri Lanka*

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Abstract

“Eat to beat the odds”, a hot topic of researchers and among the people attributing towards the name of functional food. Functional foods represent one of the most intensively investigated areas in food and nutrition sciences today for their disease preventive activity and health promotion in addition to their nutritional value. They are not extra ordinary food but those among the fruits, vegetables, nuts, oils, herbal beverages and some products of animals or microorganisms that we consume day today lives. Recent experimental evidences suggest functional food play a major role in cancer prevention. An adequate consumption of functional food is known to delay the onset and progression of cancer and convinces as a promising new approach to reduce incidences and mortality associated with common cancers such as colorectal, breast, lung, liver, pancreatic and blood. The bioactive compounds in functional food, either individually or synergistically, are known to disrupt many molecular and cellular pathways leading to carcinogenesis. Further, cancer chemoprevention using functional food is a more feasible approach due to its cost effectiveness and low toxicity in chronic administration. The present review briefs the chemopreventive potential of functional foods; the common fruits and vegetables that are frequently consumed. This review attempts to highlight the bioactive components or phytochemicals responsible for cancer chemopreventive activity. Further, this review discusses the underlying molecular or cellular mechanisms of cancer chemopreventive activity of the functional foods listed herein and emphasizes their application as chemopreventive functional food.

Keywords: Functional food, fruits, vegetables, cancer, chemoprevention, phytochemicals

Introduction

Cancer is a global scourge and one of the leading causes of morbidity and mortality. Despite the advances in diagnostic and therapeutic interventions, the incidences of cancer are increasing at an exponential rate and represents the leading cause of deaths worldwide resulting 9.6 million deaths in 2018 (WHO, 2018). Cancer is a hysterical growth of cells which can invade and spread to different distant locations of the body (Reuter et al., 2010). It develops gradually through a series of multistage process during which cells undergo profound metabolic and behavioural changes, leading them to proliferate excessively, to escape surveillance by the immune system, and ultimately to invade distant tissues to form metastases

(Fridlender et al., 2015). Its functional perspective is divided into three phases, initiation, promotion and progression (Reuter et al., 2010).

Cancer management strategies range from conventional approaches such as surgeries with adjuvant radiation or chemotherapy to novel endocrine or immune therapy (WHO, 2018). However, clinical applications of these modalities are constrained by undesirable side effects and may dramatically reduce the quality of life of patients (Fridlender et al., 2015). Hence, it is a pertinent requirement to explore safe alternative pathways to control cancer.

During the past two decades, cancer therapeutics has undergone a paradigm shift towards prevention rather than treating the end stage disease (Sporn and Suh, 2002). Such a complementary scenario will thrive in safeguarding the wellbeing of both high-risk individuals and general population. A multidisciplinary approach including changes in life style, diet, nutrition, physical activities is suggested as an effective mean of reducing the incidences of cancer

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(Landis-Piwowar and Iyer, 2014). In addition, there is a re-orientation of cancer therapeutic, targeting disruption or delay of the molecular pathways that lead to carcinogenesis, termed as chemoprevention (Landis-Piwowar and Iyer, 2014).

Cancer chemoprevention encompasses the chronic administration of a synthetic, natural or biological agent to reduce or delay the occurrence of malignancy (Sporn and Suh, 2002). Recently, several synthetic drugs; tamoxifen and raloxifene were approved as effective chemotherapeutic agents against breast cancer, finasteride for colon cancer by the Food and Drug Administration (FDA) (Landis-Piwowar and Iyer, 2014). In addition, substantial evidences accumulated from epidemiological studies suggest a putative role of functional food in cancer prevention (Ferraz da Costa et al., 2017).

Chemoprevention strategies mainly inhibit the development of invasive cancer either by hindering the DNA damage that initiates carcinogenesis or by reversing the premalignant cell progression (Hong and Sporn, 1997). At molecular level, cancer chemoprevention aims at disruption of signaling pathways of main stages of carcinogenesis: initiation, promotion, and progression (De Flora and Ferguson, 2005). Cancer chemoprevention strategies are categorized into primary, secondary and tertiary chemoprevention (Steward and Brown, 2013). Primary chemoprevention is to prevent the development of the disease in high risk population. Secondary chemoprevention aims to prevent the progression of precursor lesions to malignancy. This is applicable to patients who are diagnosed for a cancer. Tertiary chemoprevention is directed at prevention relapses or second cancers in individuals with prior cancers. Among the chemopreventive compounds, phytochemicals can potentially act on various metabolic and different signaling pathways that control cell growth, proliferation, differentiation, survival and cell death (Surh, 2003) also the studies have been conducted for decades have already revealed the chemopreventive properties of animal and microorganism derivatives as well.

Recently, functional food has gained considerable attention due to their nutritional benefits and the ability to reduce the risk of certain diseases by consuming them. Functional foods are not extra ordinary food but those among the food we are consuming day today lives. These foods are rich in chemical constituents that can inhibit or delay the process of carcinogenesis (Landis-Piwowar and Iyer, 2014). These functional foods include dietary phytoconstituents (mainly fruits and vegetables), zoo chemicals and compounds from microorganisms (Kwak et al., 2014). Absence of apparent toxic effects has allowed daily consumption of functional food without close medical supervision (Shklar and Schwartz, 1993). Further, constituents in functional food singly or synergistically modulate multiple

pathways of carcinogenesis (Shklar and Schwartz, 1993). At cellular levels the constituents of functional food regulate signal transduction pathways such as Nuclear factor-E2 related factor 2 (Nrf2), kappa-light-chain-enhancer of activated B cells (NF- κ B), mammalian target of rapamycin (mTOR), signal transducer and activator of transcription 3 (STAT3), (Landis-Piwowar and Iyer, 2014), epigenetic modifications such as DNA methylation, acetylation (Jayasinghe et al., 2015) and angiogenesis. Hence, convinces daily consumption of functional food as a promising new approach to prevent and delay the process of carcinogenesis (Go et al., 2001).

In this perspective, the present review aimed to summarize the scientific evidences on cancer chemopreventive activity of commonly used functional food. In the first part of this review, the term functional food is broadly explained. Then this review will discuss the cancer chemopreventive activity of functional food of plant origin. The molecular and cellular mechanisms underlying the cancer chemoprevention activity of functional food will be discussed broadly in this review. Further, it highlights avenues of future research of developing chemo-preventive agent from functional food and the regulations in commercialization as a nutraceutical.

Functional food

The principle of "Let food be thy medicine and medicine be thy food," espoused by Hippocrates (Lucock, 2004) nearly 2,500 years ago, is receiving renewed interest with the emergence of the concept of functional food. Functional food are implicated in prevention of many chronic diseases related to lifestyle such as diabetes, arteriosclerosis, allergies, and cancers and even many infectious diseases (Aghajanzpour et al., 2017).

A proper definition for functional food has not formulated. According to the definition of The European commission's concerted Action on functional food science in Europe, coordinated by International Life Science institute of Europe has described functional food as if it is satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either on improved state of health and well-being and/or reduction of risk of diseases (Lang, 2007). Functional food as nutraceuticals were first developed and regulated in Japan in the 1980s then has spread to North Europe and North America (Lang, 2007). People transform towards nutraceuticals because they have understood the quality attributes such as healthful properties and nutritional value of the product, attributes of taste, health and safety, practical packaging, freshness,

purity and naturalness. In terms of health advancements, people have distinguished the prevention of health problems, and improvement of the body functions to strengthen the body (Kraus, 2015).

These functional food of plant origin are categorized including dietary phytochemicals of fruits and vegetable origin (Lee et al., 2012). Phytochemicals can function as chemopreventive agents against certain stages of the cancer mechanism (Spagnuolo et al., 2015). Not only phytochemicals but also the zoo chemicals and functions of microorganisms too have been modulated the mechanisms of cancer (Kwak et al., 2014).

Cancer chemoprevention through functional food

Consumption of functional food has been effectively generated health benefits rather than continuing the chemotherapy with synthetic therapeutic drugs. The evidences from epidemiological, *in vivo*, *in vitro* and clinical trial data indicate that a plant-based diet can reduce the risk of chronic diseases, particularly cancer. There are components in a plant based diet other than traditional nutrients that can reduce the cancer risk (Rafter, 2007). Functional food is directed towards chemoprevention of cancer in which occurrence of this disease is prevented by administration of one or several chemical compounds (Wattenberg, 1985).

The new pathways oriented with dietary functional food cancer chemoprevention includes, nutrition modulation of DNA damage and repair mechanisms, DNA methylation pathways (Jayasinghe et al., 2015) influencing gene expression and cellular phenotypes, antioxidant rearranging and oxidative stress modulation, target receptors and signaling pathways including cell cycle control and anti-angiogenic properties (Landis-Piwowar and Iyer, 2014). These biological mechanisms must be optimized by functional food to achieve cancer chemoprevention (Surh, 2003).

Cancer chemopreventive properties of common fruits

Available scientific evidences support that frequent consumption of fruits result in increased level of plasma ascorbic acid, alpha-tocopherol, beta-carotene, vitamin A, and may reduce the risk of cancer progression (Huang et al., 1994). Phytochemicals present in fruit exert strong antioxidant and antiproliferative activities and mostly the synergistic activity contributes to the prevention or delaying of cancers (Liu, 2004). This section will explore the cancer chemopreventive activity of some of the common fruits we consume in our day to day life.

Apple

Apple (*Malus domestica*) is one of the most popular fruit crop around the world. Apple is consumed as fresh fruit or juice obtained by crushing the apple. It is rich in polyphenols (Alonso-Salces et al., 2001) such as hydroxycinnamic acids, catechins,

epicatechins, flavan-3-ols/procyanidins, flavonols, dihydrochalcones, and anthocyanins (Jaganathan et al., 2014). The experiments conducted around the world have highlighted a cancer chemopreventive activity of apple with possible molecular interpretations.

It was proven that the apple peel extract significantly and dose dependently reduced the proliferation of HT29 cells (human colon cancer cell line), but not MCF-7 cells (breast cancer cell line). The inhibitory effects attributed to the synergistic effects are mostly from vitamin C and anthocyanidin present in apple (Olsson et al., 2004). A parallel study has revealed apple polyphenol fractions rich in procyanidins inhibited human metastatic colon carcinoma (SW620 cells). Further it was observed an inhibition in protein kinase C activity and a significant increase in extracellular signal-regulated kinases 1 and 2 and c-jun N-terminal kinases expression (Gossé et al., 2005). Apart from that, flavonoid-enriched apple fraction AF4 of Northern Spy apples has induced cell cycle arrest, DNA topoisomerase II inhibition, and apoptosis in human liver cancer HepG2 cells (Sudan and Rupasinghe, 2014).

Berries

The chemical compounds in berries possessed properties of chemoprevention as well as protection against a variety of chronic diseases (Kristo et al., 2016). There are several varieties of berries. Those includes blackberry, black raspberry, blueberry, cranberry, red raspberry and strawberry (Seeram, 2008). The anticancer potential of berries has been attributed to polyphenols (flavonoids, proanthocyanidins, ellagitannins, gallotannins, phenolic acids), stilbenoids, lignans, and triterpenoids (Seeram, 2008). Berry phytochemicals revert the damage resulting from oxidative stress and inflammation exerts preventive activity against cancers (Seeram, 2008). Antiproliferation and anti-tumor effect of blueberry and black raspbeberry upon August Copenhagen Irish (ACI) female rat model has revealed its ubiquitous effect upon breast cancer in reducing tissue proliferation, tumor burden and down regulating CYP1A1 (gene encodes a member of the cytochrome P450 superfamily of enzymes) expression while black raspberry delay tumor latency (Ravoori et al., 2012). Similarly, animals received 5% blue berry reduced the tumor volume and multiplicity of mammary tumor. The effect was due to down regulation of the CYP1A1 and ER- α gene expression (Jeyabalan et al., 2014). The berries would also be effective upon esophageal cancers because the polyphenols have been able to reduce NMBA (N-nitroso methyl benzyl amine) induced tumors in rat esophagus *in vivo* animal model (Stoner et al., 2007).

Pomegranate

Pomegranate (*Punica granatum* L.) is a popular fruit around the world and has been used for the prevention and treatment of a multitude of diseases (Sharma et al., 2017). It has been investigated that the phytochemicals in pomegranate fruit can alter multiple signaling pathways involved in inflammation, cellular transformation, hyperproliferation, angiogenesis, tumorigenesis and metastasis (Khan et al., 2008). Pomegranate fruit is rich with anthocyanidins (delphinidin, cyaniding and pelargonidin) anthocyanins, ellagitannins, and hydrolysable tannins (Sharma et al., 2017). Flavonoid rich pomegranate extracts have shown acute antioxidant effect. Anthocyanidin has well functioned to inhibit hydrogen peroxide induced lipid peroxidation in the rat brain homogenate and the extract had exhibited scavenging activity against free radical hydroxyl and radical oxygen (Noda, 2002). Pomegranate is also rich with luteolin, ellagic acid and punicic acid. The experiment has been done to reveal inhibition of the progression to a metastatic stage (Wang et al., 2012). It was tested upon cell cultures of DU145 and PO3 hormone independent prostate cancer epithelial cell lines and Lnc α P androgen responsive prostate cancer cell lines. It has inhibited the growth of hormone dependent and hormone refractory prostate cancer cells and inhibited their migration and their chemotaxis towards stromal cell derived factor 1 α (SDF 1 α), a chemokine that is important in prostate cancer metastasis (Wang et al., 2012). Another experiment has provided an evidence for remarkable tumor growth inhibitory effects of oral consumption of pomegranate fruit extract (PFE) using TRAMP (Transgenic Adenocarcinoma Mouse Prostate model) upon prostate carcinogenesis. The results have proved the PFE supplementation resulted in parallel and more significant inhibition of IGF/I/Akt/mTOR (The mammalian target of rapamycin (mTOR), pathways in the prostate tissues and tumors. The extract has possessed antiproliferative and pro apoptotic properties against human prostate cells (Adhami et al., 2011).

Citrus fruits

Citrus fruits are the ones that contain high concentration of citric acid (8% by weight) and the best examples are the sweet orange (*Citrus sinensis*), tangerine (*Citrus reticulata*), grapefruit (*Citrus vitis*), lime (*Citrus aurantifolia*) and lemon (*Citrus limonum*) (Okwi and Emenike, 2006). Citrus fruits contain phytochemicals such as low molecular phenolic (hydroxy benzoic and hydroxycinnamic acids, acetophenones, terpenoids, flavonoids, stilbenes and condensed tannins (Okwi and Emenike, 2006). Most importantly there are about 40 limonoids in citrus fruits and among them limonin and nomilin have been identified as the major ones and are abundant in grapefruit (*Citrus vitis*) and orange juice (*Citrus sinensis*) (Okwu, 2008). These Limonoids inhibit tumor formation by stimulating the enzyme glutathione S-transferase (GST) (Craig, 2002). Citrus

fruits are also rich in various types of flavonoids such as quercetin, myricitin, rutin, tangeritin, naringin and hesperidin (Okwu, 2008). These flavonoids are water-soluble antioxidants and prevent the oxidative cell damage and have strong anti-cancer activity and inhibit all stages of carcinogenesis (Okwu, 2008). Naringenin (NGN) also possesses anti-tumor activity and has been experimentally tested *in vivo* rat models. Naringenin could decrease the number of metastatic tumor cells in the lung (Quin L et al., 2011). Naringenin has been able to downregulate EMT (Epithelial to mesenchyme transition) marker expression at both mRNA and protein levels by inhibiting TGF- β /SMAD 3 (transforming growth factor beta signal-B1) pathway in the pancreatic cells, respectively (Arumugum et al., 2009). The antitumor effect of NGN has been succeeded in both lung and pancreatic cancers. HT-29 colon cancer cells when exposed to NGN concentrations have showed significant inhibition in cell proliferation in carcinogen injected rat model (Vanamala, 2006). Naringenin could act over liver cancers (Subramanian, 2013). The anti-carcinogenic effect of NGN has been successfully experimented via *in vivo* rat model and has been suggested that NGN effectively suppress N-nitrosodethylamine initiated hepatocarcinogenesis. Appearance of preneoplastic lesions has been suppressed by modulating xenobiotic metabolizing enzymes (XME) decreasing liver marker enzymes.

Avocado

Avocado (*Persea americana* Mill.) is a widely consumed fruit containing many cancer preventing nutrients, vitamins and phytochemicals (Ding et al., 2007). Avocado fruit is rich in phenolics, flavonoids, carotenoids, ascorbic acid and vitamin E and exhibit strong antioxidant activity (Vinha et al., 2013). It was evident that avocado extract can arrest cell cycle, inhibit cell growth, and induce apoptosis in precancerous and cancer cell lines. It was evident that a chloroform extract of avocado fruits target multiple signaling pathways and increase intracellular reactive oxygen species leading to apoptosis (Ding et al., 2007). Further, avocado fruits extracted into 50% methanol have induced the proliferation of human lymphocyte cells and decrease chromosomal aberrations induced by cyclophosphamide (Paul et al., 2011). Another study demonstrated, that avocado extracts have potent inhibitory effect on the proliferation and selective killing of human oral transformed/premalignant and malignant cells TE1177 (primary human oral epithelial cells) were transformed with retrovirus containing HVP16/E6 or HVP16/E7 via reactive oxygen species (ROS) induced apoptosis (Ding et al., 2007). Avocado fruit contain high amount of lutein,

carotenoids (zeaxanthin, α -carotene, and β -carotene) and vitamin E (Lu et al., 2015). An acetone extract of avocado has inhibited the growth of both androgen-dependent (LNCaP) and androgen-independent (PC-3) prostate cancer cell lines *in vitro*. It was also revealed that incubation of PC-3 cells with acetone extract of avocado has resulted cell cycle arrest at the G₂/M by an increase in p27 protein expression (Lu et al., 2015).

Mango

Mangifera indica L. is a world-wide popular fruit due to its unique taste and nutritional value (Ribeiro and Schieber 2010). This fruit crop is mainly distributed in tropical and subtropical areas. Mango has great antioxidant and anti-proliferative properties, attributed to its phenolic content. Mango is rich in polyphenols (Noratto et al., 2010) that possesses anticancer activities. The potential cancer chemoprevention of the secondary metabolites (phenolic extracts obtained from mango samples) was evaluated using the induction of quinone reductase activity, concluding that fruit polyphenols have the potential for cancer chemoprevention (Oliveira et al., 2016).

Several mango varieties (Francis, Kent, Ataulfo, Tommy Atkins, and Haden) were tested for the anticancer activities using several cell lines including Molt-4 leukemia, A-549 lung, MDA-MB-231 breast, LNCaP prostate, and SW-480 colon cancer cells and the non-cancer colon cell line CCD-18Co (Noratto et al., 2010). This study revealed Ataulfo mango variety selectively inhibited the growth of colon SW-480 cancer cells by approximately 72%, while the growth of non-cancer colonic myofibroblast CCD-18Co cells were not inhibited (Noratto et al., 2010).

However, another study conducted with flesh and peel extracts of three different types of cultivars Irwin (IW), Nam Doc Mai (NDM), and Kensington Pride (KP), revealed the Mango flesh extracts from all three cultivars did not inhibit cell growth, but the peel extracts only NDM reduced MCF-7 cell proliferation. Further, both peel and flesh extracts did not significantly change ERK (Extracellular Receptor Kinase) phosphorylation compared to controls; however, some reduced relative maximal peak after adenosine triphosphate stimulation, with NDM peel extract having the greatest effect among the treatments. It was also evident that the mango inter-fruit and intra-fruit (peel and flesh) extract possessed varied antiproliferative effects and signalling in MCF-7 breast cancer cells and highlighted the peel and the flesh and cultivar differences are important factors to consider when assessing potential chemopreventive bioactive compounds in plants extracts (Taing et al., 2015).

Grapes

It is a wide held belief that the regular consumption of grapes (*Vitis vinifera*) or its product reduces the incidences of cancer. Grapes are rich in Anthocyanins, flavonols and resveratrol and these phytochemicals are responsible for many biological

activities, such as antioxidant, cardioprotective, anticancer, anti-inflammation, antiaging and antimicrobial properties (Xia et al., 2010). Among the phytochemicals, Resveratrol has been identified as a strong cancer chemopreventive agent due to bioactivities such as an antioxidant and antimutagen and anti-inflammatory activities. Further, it can induce phase II drug-metabolizing enzymes and inhibit cyclooxygenase and hydroperoxidase functions (Jang et al., 1997). Particularly trans-resveratrol (trans-3,4',5-trihydroxystilbene), has recently being identified as potential chemopreventive agent against skin cancers (Aziz et al., 2015). The cancer chemopreventive activity of trans-resveratrol was tested on SKH-1 hairless mouse model (Aziz et al., 2015).

Further, resveratrol has induced apoptotic cell death in HL60 human leukemia cell line. Resveratrol treatment has enhanced CD95L expression on HL60 and T47D breast carcinoma cells. It has indicated that the resveratrol-mediated cell death is specifically CD95-signaling dependent (Clément et al., 1998).

Two other phytochemicals present in grapes; trans-astringin and trans-piceatannol has also been identified as potential cancer-chemopreventive agents by a mechanism which shows an inhibition of cyclooxygenases and preneoplastic lesion formation in carcinogen-treated mouse mammary glands in organ culture (Waffo-Tégou et al., 2001).

Banana

Banana (*Musa sapientum*) is one of the famous fruits for its delicious taste and nutritional value. Banana fruit has commonly been used as source of energy and nutritious and the diseases preventive activity is less investigated. A study has investigated the cytotoxicity activity of banana pulp and peel against the colon cancer cell line HCT-116 has revealed the hexane extract of banana peel had the highest cytotoxic activity (Dahham et al., 2015).

Papaya

Papaya (*Carica papaya*) is the most widely consumed fruit around the world (Ikram et al., 2015). This fruit is especially rich in carotenoids, such as lycopene, β -cryptoxanthine and β -carotene which accounts for the bioactive properties of papaya fruit (Ikram et al., 2015). The cancer chemopreventive properties of papaya fruit at different ripening stages (RS1, RS2, RS3, RS4) has been investigated using MCF-7 (estrogen receptor positive), MDA-MB-231 (estrogen receptor negative) and MCF-12F (in non-tumoral mammary epithelial cells) (Sancho et al., 2014). The lipophilic extracts of papaya fruit at RS4 ripening stages exhibited significant inhibition of MCF-7 cell proliferation at 72 hours indicating that papaya fruit can act as a cancer

chemopreventive agent (Sancho et al., 2014). Addition to papaya fruit, papaya leaf is also a popular food in some countries and consumed as cooked, boiled or fresh as a salad (Ikram et al., 2015). Different extracts of papaya leaves possess significant *in vitro* anticancer activity against types of cancers including human oral squamous cancer cell line (SCC25) (Nguyen et al., 2013), solid cancer cell lines derived from cervical carcinoma (Hela), breast adenocarcinoma (MCF-7), hepatocellular carcinoma (HepG2), lung adenocarcinoma (PC14), pancreatic epithelioid carcinoma (Panc-1), and mesothelioma (H2452), haematopoietic cell lines, including T cell lymphoma (Jurkat), plasma cell leukemia (ARH77), Burkitt's lymphoma (Raji), anaplastic large cell lymphoma (Karpas-299) (Otsuki et al., 2010), MDA-MB-231 (non-hormone dependent breast cancer) (Maisarah et al., 2014) and Hep 2 (human laryngeal carcinoma) (Jayasinghe and Udugama, 2016). The immunomodulatory properties of papaya leaf may also contribute to the cancer chemopreventive activity (Jayasinghe et al., 2017).

Water melon

Watermelon (*Citrullus lanatus*) is a popular fruit around the world and consumption has been associated with chemoprotection of cancer (Choudhary et al., 2015). Watermelon is rich in *cis*-isomeric lycopene which gives the distinctive aroma of watermelon is imparted by medium- and short-chain fatty acids along with geraniol, β -ionone. Lycopene is a vibrant tetrapenic carotenoid with powerful antioxidant potential (Naz et al., 2014). Lycopene affects different types of cancer (breast, prostate and lung) development and exerts a direct impact on gene and inhibits mutation (Nahum et al., 2001). It was revealed it can inhibit human breast and endometrial cancer cell growth by interfering with the G₁ phase of cell cycle. It was explained that the reduction of the cyclin D level and retention of p27 in cyclin E-CDK2, has led to the inhibition of G₁ CDK activities (Nahum et al., 2001). Moreover, watermelon contains β -carotene, vitamins (B, C and E), minerals (K, Mg, Ca and Fe), amino acid (citrulline) and phenolics which reduce the DNA mutation and tumor metastasis (Naz et al., 2014). The antioxidant property of lycopene activates the transcription system within the body to inhibit carcinogenesis and mutagenesis (Linnewiel et al., 2009).

Cancer chemo preventive potential of common vegetables

Cruciferous vegetables

Cruciferous vegetables belong to Brassica genus of plants eg: broccoli, Brussels sprouts, cabbages, water cress, radishes, turnips, bok choy and cauliflower. Epidemiological studies have conferred that the intake of cruciferous vegetable reduces the incidence of lung, pancreas, bladder, prostate, thyroid, skin, stomach and colon cancer (Keck and Finley, 2004). Sulforaphane (SFN), found in cruciferous vegetables, has been shown to have chemopreventive activity *in vitro* and *in vivo*. Sulforaphane protects cells from

environmental carcinogens and also induces growth arrest and/or apoptosis in various cancer cells (Chuang et al., 2007). Further, the high concentration of Glucosinolates (GLs) and their hydrolysis products (GLsHP) occurring in crucifers also confers the chemopreventive activity (Bansal et al., 2012).

Broccoli is a cruciferous vegetable. It consists of glucoraphanin and sulforaphane. The anti-inflammatory, apoptosis inducing properties, induction of cell cycle arrest have been tested over animal and cell models to assess cancer chemopreventive properties (Krish et al., 2007; Olsen and Halkier, 2010).

Ethyl acetate extracts of some cruciferous vegetable extracts prepared from freeze-dried cabbage and acidified Brussels sprouts have demonstrated bifunctional activity on estrogen-dependent human breast cancer (MCF-7). It has been found that low concentrations of these extracts behave as an antiestrogen while high concentration behaves as estrogen agonist (Ju et al., 2000).

Water cress (*Nasturtium officinalis*) is another common cruciferous vegetable. Experimental evidences suggest that the juice of water cress has significantly increased the activities of ethoxyresorufin-O-deethylase at high doses only and NAD(P)H-quinone reductase in a dose-dependent manner in HepG2 (human-derived hepatoma cell line) and thus, exerts a cancer chemopreventive potential (Lhoste et al., 2004).

Beetroot

Beta vulgaris (beet) commonly named as beetroot has shown promising cancer chemopreventive activity. Experiments conducted using mice skin and lung bioassays also revealed a significant tumor inhibitory effect (Kapadia et al., 1996). It has further validated the FDA approved red food color E162, suppressing the development of multi-organ tumors in experimental animals. Also *Beta vulgaris* inhibited the growth rate of the PC-3 cells. This study has also investigated the effect of doxorubicin at the same concentration level has completely inhibited the growth of the PC-3 cells in three days. Similarly, comparative studies in the normal human skin FC and liver HC cell lines showed that the beetroot extract had significantly lower cytotoxic effect than doxorubicin. The results suggest that betanin, the major betacyanin constituent, may play an important role in the cytotoxicity exhibited by the red beetroot extract. Further studies are needed to evaluate the chemopreventive potentials of the beetroot extract when used alone or in combination with doxorubicin to mitigate the toxic side-effects of the latter. Suggest that beetroot ingestion can be one of the useful means to prevent cancer (Kapadia et al., 1996).

Pumpkin

Pumpkin (*Cucurbita moschata*) is an edible plant that has been frequently used as functional food. Pumpkins contain unsaturated fatty acids, phytoestrogens, alkaloids, flavonoids (apigenin, luteolin, quercetin, and kaempferol), and vitamins E which accounts for various medical properties such anti-diabetic, antioxidant, anti-carcinogenic, anti-inflammatory (Yadav et al., 2010). Recently pumpkin seeds have also gained considerable attention as a nutraceutical due to health promoting activities (Lestari and Meiyanto, 2018). Pumpkin seeds include important phytoestrogen compounds, *i.e.*, secoisolariciresinol and lariciresinol that have estrogenic-like effect and believe to reduce hormone-dependent tumors (Lestari and Meiyanto, 2018).

A white polysaccharide purified (PW) from pumpkin with an average molecular weight of 34 kDa have exhibited a potential cancer chemopreventive and therapeutic activity against hepatocellular carcinoma (HCC) HepG2 cells. This polysaccharide has induced apoptosis which involved a caspase-3-mediated mitochondrial pathway. Further, the cleavage of poly (ADP-ribose) polymerase (PARP) was observed in PPW-treated HepG2 cells, which altogether account for apoptotic cell death.

Supplementation of cucurbitacin B has reduced pancreatic cancer cell lines. Cucurbitacin B exhibited a dose- and time-dependent G₂-M-phase arrest and apoptosis of pancreatic cancer cells. This was associated with inhibition of activated JAK2, STAT3, and STAT5, increased level of p21^{WAF1} even in cells with nonfunctional p53, and decrease of expression of cyclin A, cyclin B1, and Bcl-XL with subsequent activation of the caspase cascade (Thoennissen et al., 2009).

Carrot

Carrot (*Daucus carota* L.) is an important root vegetable that possess many health benefits (Arscott and Tanumihardjo, 2010). A correlation between routine consumption of carrot and prevention of gastric cancer has been validated in epidemiological studies (Sharma et al., 2012). Carrot is rich in phytochemicals such as carotenoids (alpha, beta), vitamins (thiamine, riboflavin, niacin), and phenolic compounds. Available scientific evidences reiterated the antioxidant, antimutagenic, and antitumor activities of carrot (Sharma et al., 2012).

Several studies have indicated that consumption of carrot reduces the gastric cancers (Fallahzadeh et al., 2015). Carrots provide high source beta carotenoids and known to lower incidence of epithelial cancers, particularly lung cancer (Krinsky, 1990). In animals, carotenoids possess antioxidant activity by acting as effective chain-breaking antioxidants and singlet oxygen quenchers, and some also serve as precursors for retinoids (vitamin A). Animals are unable to synthesize carotenoids. They must obtain them from dietary sources (Krinsky, 1990). A study which has conducted to investigate the

anticancer activity of three major carotenoids (beta-carotene, astaxanthin and canthaxanthin) has revealed the mammary tumor growth in BALB/c mice was inhibited by the all three types of carotenoids while astaxanthin exhibited the highest activity (Omenn et al., 1996).

Beans

Navy beans are a good source of proteins and fibers. Other than that it contains B vitamins and minerals (Iron, calcium, copper, zinc, phosphorous, potassium and magnesium) (Bobe et al., 2008). The study has determined the feasibility of navy bean powder to be included in meals for increased total fiber intake and for consuming the amount that is associated with colorectal cancer chemoprevention. This expected desire was experimentally conducted through a clinical trial. This has confirmed the feasibility of intake of navy bean powder (NBP) without any gastro intestinal discomfort. Decreased total caloric intake and increased fiber intake in NBP treated group compared to control group provide the expected rationale for evaluating these effects in a long term cohort investigation of cooked NBP intake for primary and secondary colorectal cancer prevention (Borresen et al., 2014). Dry beans and zolfino beans are also consists of substantial amounts of flavonoids. The experiments have already established their antiradical activities, anti-oxidant and anti-inflammatory effects. Zolfino appears the most effective in inhibiting AR activity (Aldose reductase) beneficially impact deleterious metabolic activities (Balestri et al., 2016).

Safety considerations of functional food

The common fruits and vegetables listed herein have been consumed by humans over centuries and therefore possess time-proven safety. However, the safety considerations should be paramount as there could be intrinsic (drug interaction) and/or extrinsic (contamination and adulteration) toxic effects (de Mel et al., 2017). Hence, toxicological evaluation is imperative to reduce the risk associated with frequent and long-term consumption of these functional foods. The novel human-based toxicological models such as cell-based cytotoxicity assays, organ cultures and bioengineered organs on chips, molecular biological models would provide more reliable information about the toxic effect of functional food.

Conclusion

The present review focuses the cancer chemopreventive activity of functional food categorized into fruits and vegetables that we commonly consume at regular basis. Functional food act as effective cancer preventive agents due to their synergistic actions. Their applications over blocking and suppressing carcinogenesis have made the tremendous

popularity and usage of functional food. Chemotherapy has been replaced by chemoprevention because the synthetic therapeutic drugs cause irreversible side effects and alternatively down regulate the metabolic functions of the body. Non toxicity, cost effectiveness, naturalness, and protective mechanisms of functional food have taken a novel approach in cancer realm. The application of the therapeutic potential of functional food is at a peak in both clinical studies and experimental fields. The anti-tumor, anti-proliferative, anti-carcinogenic, anti angiogenic, anti-inflammatory and apoptosis induction capabilities of the bioactive compounds are successfully striking among the people specially for their prevention and protective behaviors. More precise clinical trials and experiments at molecular levels are in need to understand the anti-cancer property of the functional food. The toxicity of the bioactive compounds when orally administered must be thoroughly examined before they are introduced and to be tested in clinical trials for the desired expectations. Collectively, there will be a great promise in the cancer chemoprevention using functional food consumed as daily diet as a safe route of drug administration.

Conflicts of Interest

There are no conflicts of interest

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