Therapeutic Implications of Phytochemicals in ROS-Induced Cancer

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Abstract

Reactive oxygen species (ROS) stimulate carcinogenesis by prompting genetic transformations, triggering oncogenes, hovering oxidative stress, and stimulating cell propagation. Cancer cells exhibit redox disproportion due to augmented ROS

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S. Chakraborti (ed.), *Handbook of Oxidative Stress in Cancer: Therapeutic Aspects*,
https://doi.org/10.1007/978-981-16-5422-0_14

level as compared to regular healthy cells. Such exceptional variations in cancer cells may, therefore, be subjugated for targeted rehabilitation. Since the last three decades, phytochemicals have fascinated to be considered as probable cancer treatments due to their capability to conserve cellular redox balance with inconsequential toxicity. Numerous phytochemicals have been documented as bio-active ingredients in different plants to defeat advancement and expansion of tumors and cancer. They employ extensive and multifaceted engagements on nuclear and cytosolic features in cancer cell and selectively destroy rapidly multiplying cells. Antioxidants target unusually articulated molecular dynamics, maintain equilibrium in oxidative stress, restrain cell progression aspects, prevent angiogenesis in cancer muscle, and promote apoptosis. They have the ability to captivate ROS or stimulate antioxidant enzymes like superoxide dismutase, glutathione, and catalase. Polyphenols particularly flavonoids and their derivatives, glucosinolates, thiocyanates, phytoesterogens, carotenoids, have antioxidant properties, detoxifying ROS, induce apoptosis, and act as anticancer. The exact molecular mechanism of phenolic phytochemicals to accomplish anticancer roles is of prominent significance. Present evaluation focuses on various phytochemicals as a source of natural antioxidants and their role in cancer chemoprevention.

Keywords

Phytochemicals · Nutraceutical · Antioxidants · Cancer · Reactive oxygen species (ROS) · Oxidative stress

Introduction

The catastrophe of predictable chemotherapy to reduce impermanence rates for common epithelial menaces like carcinoma of lung, colon, breast, prostate, and pancreas designates a serious effort for unconventional tactics to regulate malignancy. The alternative chemo-preventive approach is based on antioxidant phytochemicals with the target of striking or withdrawing the progression of multi-phase carcinogenesis. The carcinogenic progression might be motivated by mutation(s), and subsequently followed by modifications in phenotypic, genetic, and epigenetic measures. Disparity of such regulatory pathways based on pharmacology by application of drugs, antioxidant phytochemicals, micronutrients, and non-nutrients effectively to block mutation channel that causes DNA damage can play effective role in combating cancer (Takuji et al. 2012).

Epidemiological studies advocated a strong evidence among dietary habits, and food consumption and cancer incidences in human. These risk factors have been marked more complex as compared to smoking, pollution, and professional threats associated with death attributed by cancer. A number of antioxidant natural ingredients present in foods offer promising chemo-preventive prospective. Phytochemicals existing in fruits, vegetables, and several plant parts have attracted distinct consideration because of their prospective to inhibit tumor development and effective role in chemo-preventive approaches. They have either defensive or protective,

provide protection against diseases and such constituents may be nutrients isolated from foods, plant sources, and/or genetically modified foods, fruits, and vegetable juices (Peng et al. 2011).

Antioxidant phytochemicals are broadly described as polyphenols, phytoestrogens, carotenoids, and glucosinolates have amazing health benefits and might offer therapeutic fitness welfares by preventing or treating diseases and functional ailments. The phytochemicals carotenoids decrease the risk and reappearance of prostate and breast cancer. The consumption of soybean isoflavones reduces the risk of lung, prostate, colon, and breast cancers, particularly in females after menopause. Isothiocyanates, the other group of phytochemicals similarly diminish the menace of prostate, stomach, colorectal, and breast cancer (Ruiz and Hernández 2016).

Most of the commonly used as food components from cereals, legumes, fruits, vegetables and their juices comprise such antioxidant phytochemicals which are of significant importance. These active ingredients have substantial beneficial prospective in curing numerous disorders either alone or synergistically in combination. They perform encouraging pharmacological effects on health as antioxidants, anti-bacterial, anti-fungal, anti-inflammatory, chemo-preventive by inhibiting DNA damage, immuno-modulator, induce apoptosis, reduce cancer, and protect from UVB-induced carcinogenesis. Cancer chemoprevention involves different biologicals agents to inhibit or reverse tumor growth. It has been observed that these mediators may control cell proliferation, regulate cell cycle, and contribute in various signalling paths interrupted by tumor origination, production, and transmission (Howes and Simmonds 2014). Data from various studies support that bio-active phytochemicals hold chemo-preventive assets, supported by *in vitro* studies on animal models. They might adjust cell proliferation, apoptosis in transformed cells, enhance immunity, and alert malignant cells to cytotoxic mediators (Kotecha et al. 2016).

Reactive Oxygen Species in Cancer

The raised and unbalanced amounts ROS have been virtually found in most of cancers, which enhances the stimulation of tumor expansion and advancement. However, tumor cells also express increased levels of antioxidants to detoxify ROS, and maintain delicate intracellular balance of ROS. Further, the speed of free radical generated, location of its generation, and density are imperative for normal cellular functions in cancer. A unique helpful approach will be optimum amendment to control intracellular ROS effectively, maintaining the balance of oxidation and induced apoptotic signals. Further, alternative beneficial antioxidant phytochemicals may have the potential to prevent development of tumor at early stage, by neutralizing ROS and maintaining oxidative balance. Nevertheless, the effective target cancer cells responsible for ROS-signal sensing trails that regulated diverse stress-controlled cellular purposes must be recognized. The ROS formation in tumor cells, their reclamation, special effects on cellular materials, and major signalling cascades they utilize, and their modulation in therapeutics can play a key role to control cancer (Liou and Storz 2010).

Carcinogenesis and Phytochemicals

Carcinogenesis process involves several stages categorized as progression of divergent biochemical changes of cell constituents that disturb program and initiate transformation of cell to undertake uninhibited cell partition. At every such disturbance, cells suffer variations basically exemplified as tumor instigation, elevation, and advancement (Tokarz and Blasiak 2014). This introduction of tumor is a swift and irrevocable development that surprises by means of acquaintance to a cancer-causing agent, shadowed by dispersal and transference to muscles instigating mutagenic changes in cellular DNA. These introduced changes commence accumulation of auxiliary irrevocable heritable variations that continue through every fresh cycle of cell propagation. Such tumor advancement is comparatively extensive, where active proliferation of cell division and transition continue. Supplementary confirmations have emphasized the life-threatening character of tumor at microlevel on existence and transmutation in pre-neoplastic cancer cells (Quail and Joyce 2013).

Natural phytochemicals have been found to have a wide range of beneficial influence in the inhibition of cancer-causing agents to reach under attack sites and maintenance of oxidative balance by detoxification of ROS. Some of them also improve necessary resistant by improving immunity and increasing eradication of transmuted cancer cells. In conclusion, phytochemicals perform numerous effects on inherent DNA renovation process and might also act to stimulate tumor inhibition and regulation of cell propagation (Royston and Tollefsbol 2015).

Chemoprevention: Types and Approaches

A number of tactics have been adopted for cancer chemoprevention with prime objective to avoid the expansion of disease in common inhabitants or in specific zones with the prevalence of high risk. Such type of preventive approach generally focusses on mediations of smoking people associated with lung cancer, breast and colorectal cancer.

Second ancillary approach is to focus on those persons identified with any kind of tumor or pre-malicious primary stage that may advance toward aggressive malignancy. This approach is followed with the objective to control expansion and regression of malignant cancer.

Further, third line of attack is aimed directly to inhibit the reappearance and advancement of the ancillary new tumors in those persons who have settled cancer.

Dietary Phytochemicals: Role in Cancer Chemoprevention

Phytochemicals include polyphenols, alkaloids, and carotenoids (Howes and Simmonds 2014) and plants generate them for self-protection against external and environmental threats, like ultraviolet rays and ROS. The incorporation of such types of active ingredients in regular diet possibly may offer comparable security as afforded by

them to plant. *Several in vitro* and *in vivo* investigations have confirmed additional supplementary benefits of phytochemicals, further than antioxidant which can also impact the propagation, development, and metastasis in tumor cells (Vauzour et al. 2010). The amount of phytochemicals ingested through food is in straight relation to the nature of dietary ingredients, therefore identification and inclusion of such components in foods that comprise high quantities of anticipated phytochemicals should be the center for important desired approach to prevent cancer. In the fruits, vegetables, cereals legumes, and several other plant foods they are responsible for specific characteristics in the form of color, taste, and flavor. Moreover, they also offer protection to host plant in contrast to various infections of bacteria, viruses, parasites, biotic and abiotic stresses. The list of some cancer chemo-preventive phytochemicals is mentioned in Table 1.

Phytochemicals: Polyphenols

The major sources of polyphenols are fruits, berries, vegetables, beans, juices, and brews, they normally offer protection in contrast to ultraviolet energy and hostility of

Table 1 List of some cancer chemo-preventive phytochemicals

Phytochemicals	Plant source	Role in cancer chemoprevention
Omega, α-linolenic acid (ALA)	Flax seeds, fish oil	Cancer chemo-preventive, reduce risk of CHD
Allicin	Onion, garlic, mustard	Anticancer, anti-inflammatory
Apigenin	Apple, artichoke, basil, celery, cherry, grapes, nuts, parsley	Chemo-preventive, antioxidant, anti-inflammatory, induce apoptosis
Carotenoids	Green leafy vegetables, colored fruits, and vegetables, pumpkin	Anti-carcinogenic, protection against UV light, stimulate repair enzymes
Curcuminoids	Turmeric	Cancer preventive, anti-inflammatory, antioxidant
Polyphenolic acids	Fruits, grapes, pomegranates, berries, tea, mango	Antioxidant, anti-inflammatory, and anticancer
Genistein	Alpha-Alfa sprouts, red clover, chickpeas, peanuts	Antioxidant, anticancer agent
Flavonoids	Fruits, cereals, legumes, plum	Anticancer, protect against UV light, stimulate DNA repair enzymes
Lycopene	Tomato and fruits	Reduce risk of cancer
Resveratrol	Blueberry, red grapes, and red wine	Antioxidant, prevents cancer
Silymarin	Milk thistle	UVB-induced carcinogenesis
Glucosinolates	Cruciferous vegetables, broccoli, cabbage, and cauliflower	Protect DNA damage, reduce risk of ROS and cancer
Ursolic acid	Rosemary and some fruits	Antitumor
Withaferin, Withanolides	*Withania somnifera*	Anticancer, immunomodulator

pathogens. The epidemiological data and experimental revealed the converse relationship among risk of ROS linked progressive diseases and dietary habits with high intake of antioxidant polyphenols. There are substantial indications that food with high antioxidants is related with lesser prevalence of deteriorating diseases. The dietary polyphenols from legumes, corn, nuts, beans, pulses, fruits, vegetables and fruit juices, tea, coffee, and wine offer several times higher protection than that of vitamin C, E, and carotenoids (Prakash and Kumar 2011).

Polyphenols are strong antioxidant and may be in the form of compressed proanthocyanidins, galloyl form besides hexahydroxydiphenoyl and their derivatives as esters or tannins. Earlier they have been traditionally deliberated under anti-nutritional factors, since some of them have antagonistic effects by inhibiting digestive enzymes activities, preventing availability of amino acid, and minerals for uptake besides and few other toxic properties. The greatest significant dietary polyphenols are phenolic acids, tannins, and flavonoids, they defend plants commencing oxidative stress associated damage and act as antioxidant protectants with beneficial role in reducing the risk of cancer (Andjelkovic et al. 2006).

The tea polyphenols comprise flavonols, flavanols, flavones, and phenolic acids as main components, dietary fibers and hemicellulose are associated with ferulic acid in cell wall by ester bonds. Some commonly used fruits and outer layers of seeds are rich in polyphenolic acids in the form of hydrolysable tannins and are commonly esterified with glucose. Citrus fruits are most important sources of flavanones like hesperidin which is found in large quantity in orange juice (Prakash and Kumar 2011).

Quercetin in glycosylated form as rutin is found predominantly in onions, fruits, and vegetables are also its rich source. Anthocyanins are mainly responsible for pigments of fruits, berries, vegetables, and color of flowers. Soybean is prime source of isoflavonoids, genistein, and daidzein and has received significant importance due to their role in inhibition of osteoporosis and cancer. The high consumption of soy rich traditional diets has been observed associated with rare incidences of prostate, breast, and uterus cancer. Silibinin, from *Silybum marianum* the main constituent of its flavonoids combinations had shown optimistic evidences to induce apoptosis, reduce and inhibit cell propagation and tumor angiogenesis in cancer models (Singh et al. 2008a, 2008b).

Flavonoids

These are subclass of natural polyphenols comprising the flavones, flavonols, flavanones, and dihydroflavonols. Flavonols are most abundant group of flavonoids present in foods, and quercetin and kaempferol are important compounds of this cluster. Berries and onions are prominent homes of flavonols, while citrus fruits, tomatoes are prominent source of flavanones. Some other important sources of flavanones (naringenin, hesperetin) are grapes, citrus, oranges, and lemons. Further, another antioxidant polyphenol stilbene affords beneficial effects and resveratrol (3, 4', 5-trihydroxystilbene) mainly found in grapes and red wine exhibited anti-carcinogenic, anti-inflammatory

activities. They are signalling molecule within the cells to control the communication of genetic factor and protein sequences (Pandey and Rizvi 2009).

Further, flavonoids act against ROS, inflammation, tumors and offer health benefits, in addition they are also direct chemical protectants, provide modulatory effects on a number of enzymes. They have bio-active properties like free radical scavenging, inhibition of ROS and oxidative enzymes. They provide anti-proliferative effects in cancers, and inflammatory diseases by scavenging free radicals that signifies health supporting purposes of flavonoids. The major sources of flavonoids are fruits, vegetables, tea, onions, apples, and berries. They have a contrary association among flavonoid intake and reduced risk of coronary heart disease. The ability of flavonoids to act as antioxidants is governed by their molecular structure and position of hydroxyl groups is very important for free radical hunting capacity and health benefits. Quercetin, luteolin, apigenin, myricetin, and kaempferol are dietary flavonoids, and they offer anti-inflammatory, free radical scavenging, and anti-mutagenic properties (Kumar and Andy 2012).

Apigenin

It is a flavone existing in abundance in fruits, vegetables, onions, oranges, tea, wheat sprouts, and several other natural plant sources (Table 2). Apigenin (4′, 5, 7,-tri-hydroxy-flavone) has been found as outstanding anti-inflammatory, antioxidant and has been gradually documented as a cancer chemo-preventive due to presence of anti-mutagenic properties. It has also been revealed to inhibit induced mutagenesis, promote metal chelation, scavenge free radicals, and motivate detoxification of enzymes in cell culture tumor models. In experiments of carcinogenic abuse, it has afforded a protective effect in skin and colon cancer models. It is a strong inhibitor of decarboxylase enzyme that caters with main role in tumor promotion and found to increase the intracellular application of glutathione, with enhancement of protection against ROS. It also reduced UV-induced cancer, tumors, telomerase, fatty acid synthase, and aryl hydrocarbon receptor activity which are relevant to control cancer expansion and advancement. The probable health welfares of apigenin are due to its strong antioxidant and anti-inflammatory activities and growing evidences from

Table 2 Important natural plant sources of Apigenin

Achillea millefolium Yarrow (Aerial parts)	*Gingko biloba* Biloba (leaf)
Apium graveolens Celery (Aerial parts)	*Glycyrrhiza glabra* Liquorice (root)
Artemisia dracunculus Tarragon (Aerial parts)	*Linum usitatissimum* Flax (Aerial parts)
Camellia sinensis Tea (leaves)	*Marrubium vulgare* Horehound (plant)
Chamaemelum nobile Perennial chamomile (Aerial parts)	*Matricaria recutita* Annual chamomile (Aerial parts)
Coriandrum sativum Cilantro (fruits)	*Mentha spicata* Spearmint (leaf)
Digitalis purpurea Purple foxglove (flower)	*Ocimum basilicum* Basil (Aerial parts)
Echinacea spp Coneflower (leaf)	*Origanum vulgare* Oregano (Aerial parts)

experimental studies suggest that higher intake of flavonoids may reduce the risk of several chronic diseases as well as cancer (Patel et al. 2007).

Isoflavonoids

They are produced exclusively by the plants of Fabaceae (Leguminosae) family and their leading food sources are legumes, pulses, beans, soybean, and their products. Soybean is the main dietary source of isoflavones, including genistein and daidzein. These isoflavones have been of significant importance due to their estrogen receptor binding class of compounds, a representative activity of several closely related phytochemicals labelled as phytoestrogens. They prevent the progression of furthermost hormone-reliant and self-regulating cancer cells with significant role in preventing and treating osteoporosis and cancer (Ko et al. 2010). Analysis of epidemiological and scientific data provides sufficient evidences that consumption of soybean and its products potentially decreases the risk of prostate and breast cancer.

The isoflavones due to their antioxidant and anti-proliferative activities also offer supplementary protection against many customary chronic diseases. Cellular damage due to ROS and oxidative stress is a foremost contributing factor of several diseases due to peroxidation and DNA damage leading to mutations isoflavones which have shown protection against such incidences and associated disorders (Messina et al. 2004).

Anthocyanidins

The flavonoids of this group like aglycones of anthocyanins are water soluble and provide color to fruits, vegetable, and flowers. The plants with various colors offer protection in different plant parts, anthocyanins, pigments—apocarotenoids, carotenoids, betalains, condensed tannins, and quinones in conjugation contribute to different colors. They have potential antioxidant activity and expected to offer anti-mutagenic effect through detoxification of ROS and protection of DNA damage caused by free radicals (Prakash et al. 2011). They typically provide color depending on their chemical nature, concentration, pH, interactions with other pigments, and that result in pink, purple, blue, orange, brown, and even black colors (Hatier and Gould 2007).

Phytoestrogens

The prime dietary sources of phytoestrogens are legumes, berries, red wine, flaxseed, asparagus, whole grains, soybean, and soy product. They include non-steroidal phytochemicals with close resemblance in configuration and utility to gonadal estrogen hormone and have potential for use as substitute in hormone replacement therapy (HRT) with favorable impact on cardiovascular and menopausal symptoms. They have prospective for use as substitutes of synthetic selective estrogen receptor modulators (SERMs), used in HRT. They are polyphenolic nature with antioxidant activity,

power of detoxification enzymes, interfere with peroxidation of lipids and lipoprotein and anti-carcinogenic. They have essential structural features very close to with estrogen, with the presence of hydroxyl groups that may be positioned in a stereochemical alignment similar to estrogen. Populations which consume high quantities of isoflavones have less frequencies of osteoporosis and menopause associated complications, and lesser frequency of breast and uterine cancer (Sakamoto et al. 2010).

Resveratrol

Resveratrol (RES, 3,5,4′-trihydroxy-*trans*-stilbene) a natural polyphenol found in various nutritional ingredients like grapes, wine, nuts, and berries. RES consists of two phenolic bracelets, *para* hydroxyl, and second with an *ortho* double hydroxyl groups while two benzene rings are connected by double bond to provide *cis* and *trans* isomers. The *trans* isomer of RES is found in abundance and also offers biological activities. Various studies have reported that RES provides chemo-protective effects, cardio-protective and antioxidant activities (Cai et al. 2018). RES has also been described as phytochemicals that are capable to offer protection and reduce associated disorders prompted by chemotherapeutic drugs. Resveratrol demonstrated protective effect against cardiac, hepatic, gastric, UVR induced skin cancer, and synergistically enhanced efficacy in chemotherapy of cancer (Xiao et al. 2019).

RES controls numerous paths elaborated in cell cycle, apoptosis, inflammation, chemo-protective and potent anticancer. The combination therapy using more than two drugs repeatedly synergistically enhanced superior therapeutic results. RES has been found accomplished facilitating therapy to combat cancer. The synergistic consequences of RES-intervened chemotherapy have also been recognized with intrusive effect in cancer origination (Elshaer et al. 2018).

Curcumin

It is a yellow color diferuloylmethane phenolic compound found in the rhizome of *Curcuma longa* Linn (turmeric). The therapeutic efficacy against number of diseases like diabetes, gastrointestinal ulcers, arthritis, nephrology, hepatic and cardiovascular disorders has been reported. The advantageous activities of it are considered to be associated with its antioxidant and anti-inflammatory activities (Hosseini and Ghorbani 2015). It has also been found as anticancer due to manifold engagements on mutagens, control on cell cycle, and induction of apoptosis, and metastasis at various stages of cancer. It was observed effective to improve bladder, stomach, and uterine cancers. The antitumor action of curcumin is intermediated by its antiproliferative consequence on multiple cancers, inhibitory accomplishment on transcript features and downstream gene merchandises, detoxification of ROS and induction of apoptosis. It has also been promoted that ER trauma and autophagy may also play important role in the induction of apoptosis, induced by curcumin and its derivatives in ovarian tumor cell line (Vallianou et al. 2015).

Terpenoids

The terpenes are a largest class of phytonutrients present in green foods, grains, higher plants, microbes or marine organisms. They are resultant of a collective biosynthetic lane constructed on mevalonate as basis, terpenes or isoprenoids. Their importance in plants is to fix carbon by photosynthetic process by using pigments and sun light. Animals utilize them in hormonal and growth regulatory functions (vitamin A) and also provide a protection from diseases, associated with prolonged oxidative damage, ROS, and deregulation. Several biological activities have been reported from terpenes like anti-inflammatory, anti-cytotoxic, anti-tumor, anticancer, and immunomodulatory. They have distinctive antioxidant function during their interface through free radicals and ROS. They remove free radicals by separating themselves through fatty membranes by taking advantage of their long side chain of carbon. The antioxidants tocotrienols and tocopherols have been reported effective as apoptotic inducers in breast cancer cells. The actions of terpenes reduction of cancer risk may be explained by the impact of dietary fruits, vegetables (Bohlmann and Keeling 2008; Prakash and Kumar 2011).

Carotenoids

They are responsible for various pigments ranging from yellow, orange, and red, in fruits, vegetables, birds, and also in egg yolks. Carotenoids comprised of molecules, carotenes and xanthophylls are two major group of carotenoids and hold a poly-isoprenoid arrangement, with long conjugated chain of double bonds as collective chemical structures. They are tissue specific with biological activity like beta-carotene has vitamin A activity. In epidemiological studies a positive link has been found among higher dietary intake and plasma concentrations of carotenoids with lower risk of diseases. The β-carotene, lycopene, and lutein have shown reduced risk of certain selected type of cancers. The xanthophyll, zeaxanthin, cryptoxanthin, and astaxanthin have antioxidant property and offer tissue specific protection from ROS mediating their effects via cell growth regulation, modulating gene expression, immune response and as modulators of metabolic enzymes (Elliott 2005; Stahl 2005).

Lycopene

It is a natural strong antioxidant carotenoid found in carrot, tomatoes, watermelon, papaya, guava fruits and their products. It has shown possible promise to reduce the risks of tumors, prostate and breast cancer. The possible approach of action as anticancer is due to its anti-proliferative activity, reduction of ROS, and immune boosting achievement. It was found to reduce of prostate cancer in advanced stage and reduction in the risk of breast cancer (Eliassen et al. 2012).

A number of epidemiologic readings supported that intake of lycopene and tomato products contribute to decrease oxidative DNA damage, increase apoptosis

of prostate cancer epithelial cells, and decrease the risk. It was found more bioavailable in processed tomato foodstuffs as compared to raw tomatoes as food processing might have increase the bio-activity (Soares et al. 2019).

Limonoids

These are water soluble terpenes from citrus fruit with wide range of substantial bio-activity found as glucosides and water insoluble aglycones. It was reported that five limonoids, aglycones (obacunone, nomilin, limonin, isoobacunoic acid, ichangin) prompted production significant amounts of glutathione-S-transferase (GST) a most important detoxifying enzyme that catalyzes conjugation of glutathione with several possible carcinogens. Another revision on limonin and nomilin in mice showed reduced incidence of tumors by more than 50%. D-Limonene was also fount to inhibit pancreatic carcinogenesis in experimental models and offer protection against cancer (Stahl 2005).

Glucosinolates

They are mainly found in cruciferous vegetables, and have been reported to activate liver reclamation enzymes. They are pungent with bitter flavor and provide protection against carcinogenesis, mutagenesis, and toxicity of ROS. The crucifer sprouts may offer protection by reducing the risk of cancer more efficiently than the same quantity of vegetables of similar diversity. Food processing, chewing, and digestion, release glucosinolates from brassica vegetables and they are converted by them into biologically active form like indoles, nitriles, thiocyanates, and isothiocyanates (Hayes et al. 2008). These products have been studied for their anticancer properties and found that consumption of cruciferous vegetables is associated with a reduced risk of cancers comprising lung, stomach, colon, and rectum. The glucosinolates have been described to inhibit the formation of endo or exogenous carcinogens and preventing instigation of carcinogenic process. The appliance behind defending properties involves the inflection of carcinogen digestion by initiation of cleansing enzymes and reticence of carcinogen-stimulating enzymes, and protecting DNA from ROS and mutagenic activity. A reducing effect on tumor formation has been shown in by brassica vegetables with positive health benefits. They offer preventive consequences on breast cancer may be due to regulation of cell cycle progression, and induced apoptosis (Vig et al. 2009; Traka and Mithen 2009).

α-Linolenic Acid (ALA)

ALA an essential omega-3 fatty acid found in seeds, nuts, and vegetable oils has shown towards to down-regulate cell propagation of breast, prostate, and bladder cancer. The eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have the

ability to prevent development of breast tumor by altering fatty acid alignment in cell membrane, overpowering associated biosynthesis and manipulating signalling transcriptional process to inhibit cell propagation and prompt apoptosis. It has been found that omega-3 fatty acids can prevent and obstruct the growth of cancers, signifying its importance in cancer functioning. Interestingly, it was found to change the size of colony significantly in cancer cell lines as compared to control (Chamberland and Moon 2015). A fatty acid mixture with high level of CLN on cancer cell lines showed dose-dependent growth-inhibitory effects and induction of apoptosis. The anti-carcinogenic effects of CLN and conjugated linoleic acid (CLA) exhibited strong tumor-growth inhibition and induction of apoptosis in cancer cell lines (Yasui et al. 2009).

Allicin

Allium ingestion offers protection to decrease the menace of cancer, particularly in gastrointestinal tract and preventive effects might be due to sulfur-comprising combinations of such products that decrease carcinogens, and balance redox process through scavenging ROS. Such components provide protection from carcinogenesis by altering biological processes and dropping cancer risk.

Some meta-analysis studies showed that consumption of high amounts of total *Allium* vegetables reduced risk of gastric cancer when comparing the highest and lowest consumption groups for total *Allium* vegetable intake with high heterogeneity of garlic serving per day. It was resolved that owing to dependable indication, dose-response correlation, and reasonable contrivances, a cancer defensive association among *Allium* and vegetables may be apparent (World Cancer Research Fund 2007). Allyl sulfur derivatives from Allium species were also found promising to block DNA alkylation, and offer protection at initial stage of carcinogenesis induced by nitrosamine (Nicastro et al. 2015).

Silymarin

A complex of natural flavonoids found in fruits and seeds of milk thistle (*Silybum marianum L.*) comprises silibinin, isosilybin-b, silydianin, and silychristin. In functional foods it has been used for the protection of liver and to treat chronic epilepsy. It has been found to alter expression of proteins related to cell cycle directives and apoptosis and showed anti-inflammatory, antioxidant, anti-metastasis, and anticancer properties against breast, lung, and prostate (Fig. 1). Further, silymarin has shown promising potential to control development of cancer through its progression inhibitory action and stimulation of apoptosis. Experiments have shown that silibinin improves efficacy of cisplatin and doxorubicin contrary to ovarian and breast cancer and has also showed direct anticancer effects against prostate and breast tumor cells (Kim et al. 2019).

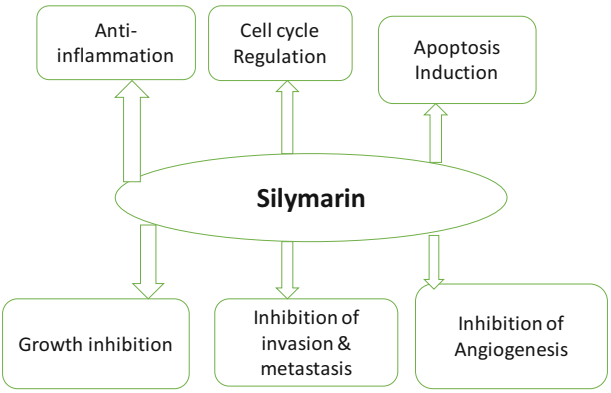

Fig. 1 Possible anticancer mechanism for silymarin (Ramasamy and Agarwal 2008)

Phytochemicals play important role as hepatoprotective, antioxidants, anti-inflammatory, chemo-preventive, induce apoptosis, protect from UVB-induced carcinogenesis, and as preventive agent against ROS and associated disorders like cancer (Prakash and Gupta 2009).

Evidence from several studies demonstrated that dietary phytoestrogens can produce estrogenic effects in the postmenopausal women, and may offer protection against osteoporosis and associated disorders (Fig. 1). Isoflavonoids or soy products and flaxseed have promising potential to lower cholesterols and raise HDL cholesterol to reduce risk of CVDs and they contribute to the lower incidence of CVDs in Asia and vegetarians and may act as cardio-protective (Al-Azzawi and Wahab 2010).

Sulforaphane (SFN)

Sulforaphane is an isothiocyanate (ITC) derived from cruciferous vegetables and shown numerous benefits against pancreatic, prostate, breast, lung, cervical, and colorectal cancers. Their mode of action involves detoxification carcinogens and antioxidants, blockage of metabolic enzymes, inhibit cell cycle arrest, and induction of apoptosis. Their most prominent feature is to potentiate synergistically the activity of several anticancer agents including paclitaxel, docetaxel, and gemcitabine (Kamal et al. 2020).

SFN has been found potential to treat breast cancer by regulating cell survival, inhibiting their proliferation and induces apoptosis also in several other variety of cancers (Xia et al. 2019). The anticancer effects of SFN are mainly associated with mitochondria-related pathways, oxidative stress of ROS, inhibition of DNA damage induced by chemical carcinogens (Bernkopf et al. 2018).

SFN prevents cell explosion, induces apoptosis, breaks cell cycle and has antioxidant activities that play a key role to balance reactive oxygen species (ROS), oxidative stress, anti-inflammatory of significant importance to combat cancer and associated disorders (Kan et al. 2018).

Conclusions

The phytonutrients/phytochemicals present in food, diet, and medicinal plants play a key role in the efficacy and to treat different ailments since long back and are of prime importance for the inhibition and management of chronic degenerative diseases. The resurgence of interest in such phytochemicals for their beneficial roles has eventually lead an urgent need of compilation of their safety, efficacy, structure–function relationships, and molecular mechanism of action. The food ingredients are important in determining the role of phytochemicals in functional foods, health benefits, consumer assertiveness, reasonable benefit for manufacturers producing functional foods and identification of research priorities required to produce such foods with anticipated well-being properties. The future of such dietary supplements holds exciting promise for food industry and to generate super foods to persuade potential investors for monetary rewards also to gratify consumers.

References

Al-Azzawi F, Wahab M (2010) Effectiveness of phytoestrogens in climacteric medicine. Ann N Y Acad Sci 1205:262–267

Andjelkovic M, Camp JV, Meulenaer BD, Depaemelaere G, Socaciu C, Verloo M, Verhe R (2006) Iron-chelation properties of phenolic acids bearing catechol and galloyl groups. Food Chem 98:23–31

Bernkopf DB, Daum G, Brückner M, Behrens J (2018) Sulforaphane inhibits growth and blocks Wnt/β-catenin signalling of colorectal cancer cells. Oncotarget 9(74):33982–33994

Bohlmann J, Keeling CI (2008) Terpenoid biomaterials. Plant J 54:656–669

Cai J, Liu W, Lu F, Kong W, Zhou X, Miao P et al (2018) Resveratrol attenuates neurological deficit and neuro-inflammation following intracerebral haemorrhage. Exp Ther Med 15:4131–4138

Chamberland JP, Moon HS (2015) Down-regulation of malignant potential by alpha linolenic acid in human and mouse colon cancer cells. Familial Cancer 14(1):25–30

Eliassen AH, Hendrickson SJ, Brinton LA, Buring JE, Campos H et al (2012) Circulating carotenoids and risk of breast cancer: pooled analysis of eight prospective studies. J Natl Cancer Inst 104:1905–1916

Elliott R (2005) Mechanisms of genomic and non-genomic actions of carotenoids. Biochem Biophys Acta 1740:147–154

Elshaer M, Chen Y, Wang XJ, Tang X (2018) Resveratrol: an overview of its anti-cancer mechanisms. Life Sci 207:340–349

Hatier J-H, Gould KS (2007) Black coloration in leaves of *Ophiopogon planiscapus* "Nigrescens". Leaf optics, chromaticity, and internal light gradients. Funct Plant Biol 34:130–138

Hayes JD, Kelleher MO, Eggleston IM (2008) The cancer chemo-preventive actions of phytochemicals derived from glucosinolates. Eur J Nutr 47:73–88

Hosseini A, Ghorbani A (2015) Cancer therapy with phytochemicals: evidence from clinical studies. Avicenna J Phytomed 5(2):84–97

Howes MJ, Simmonds MS (2014) The role of phytochemicals as micronutrients in health and disease. Curr Opin Clin Nutr Metab Care 17:558–566

Kamal MM, Akter S, Lin C et al (2020) Sulforaphane as an anticancer molecule: mechanisms of action, synergistic effects, enhancement of drug safety, and delivery systems. Arch Pharm Res 43:371–384

Kan SF, Wang J, Sun GX (2018) Sulforaphane regulates apoptosis- and proliferation-related signalling pathways and synergizes with cisplatin to suppress human ovarian cancer. Int J Mol Med 42(5):2447–2458

Kim S, Choo G, Yoo E, Woo J, Han S, Lee J, Jung J (2019) Silymarin induces inhibition of growth and apoptosis through modulation of the MAPK signalling pathway in AGS human gastric cancer cells. Oncol Rep 42:1904–1914

Ko KP, Park SK, Park B (2010) Isoflavones from phytoestrogens and gastric cancer risk: a nested case-control study within the Korean multicenter cancer cohort. Cancer Epidemiol Biomark Prev 19:1292–1300

Kotecha R, Takami A, Espinoza JL (2016) Dietary phytochemicals and cancer chemoprevention: a review of the clinical evidence. Oncotarget 7(32):52517–52529

Kumar S, Andy A (2012) Health promoting bioactive chemicals from *Brassica*. Int Food Res J 19:141–152

Liou G-Y, Storz P (2010) Reactive oxygen species in cancer. Free Radic Res 44(5):1–31

Messina M, Erdman J Jr, Setchell KDR (2004) Introduction to and perspectives from the Fifth International Symposium on the role of soy in preventing and treating chronic disease. J Nutr 134:1205S–1206S

Nicastro HL, Ross SA, Milner JA (2015) Garlic and onions: their cancer prevention properties. Cancer Prev Res (Phila) 8(3):181–189

Pandey KB, Rizvi SI (2009) Current understanding of dietary polyphenols and their role in health and disease. Curr Nutr Food Sci 5:249–263

Patel D, Shukla S, Gupta S (2007) Apigenin and cancer chemoprevention: progress, potential and promise (review). Int J Oncol 30:233–245

Peng J, Yuan J-P, Wu C-F, Wang J-H (2011) Fucoxanthin, a marine carotenoid present in brown seaweeds and diatoms: metabolism and bioactivities relevant to human health. Mar Drugs 9:1806–1828

Prakash D, Gupta KR (2009) The antioxidant phytochemicals of nutraceutical importance. The Open Nutraceuticals J 2:20–35

Prakash D, Kumar N (2011) Cost effective natural antioxidants. In: Watson RR, Gerald JK, Preedy VR (eds) Nutrients, dietary supplements and nutriceuticals. Humana Press, Springer, pp 163–188

Prakash D, Upadhyay G, Pushpangadan P, Gupta C (2011) Antioxidant and free radical scavenging activities of some fruits. J Complementary Integr Med 8:1–19

Quail DF, Joyce JA (2013) Micro-environmental regulation of tumour progression and metastasis. Nat Med 19:142337

Ramasamy K, Agarwal R (2008) Multi-targeted therapy of cancer by silymarin. Cancer Lett 269(2):352–362

Royston KJ, Tollefsbol TO (2015) The epigenetic impact of cruciferous vegetables on cancer prevention. Curr Pharmacol Rep 1:46–51

Ruiz RB, Hernández PS (2016) Cancer chemoprevention by dietary phytochemicals: epidemiological evidence. Maturitas 94:13–19

Sakamoto T, Horiguchi H, Oguma E (2010) Effects of diverse dietary phytoestrogens on cell growth, cell cycle and apoptosis in oestrogen-receptor-positive breast cancer cells. J Nutr Biochem 21:856–864

Singh RP, Raina K, Sharma G, Agarwal R (2008a) Silibinin inhibits established prostate tumour growth, progression, invasion, and metastasis and suppresses tumour angiogenesis and epithelial-mesenchymal transition in transgenic adenocarcinoma of the mouse prostate model mice. Clin Cancer Res 14:7773–7780

Singh RP, Tyagi A, Sharma G, Mohan S, Agarwal R (2008b) Oral silibinin inhibits in vivo human bladder tumour xenograft growth involving down regulation of survivin. Clin Cancer Res 14:300–308

Soares NCP, Elias MB, Machado CL, Trindade BB, Borojevic R, Teodoro AJ (2019) Comparative analysis of lycopene content from different tomato-based food products on the cellular activity of prostate cancer cell lines. Foods 8(201):1–14

Stahl W (2005) Bioactivity and protective effects of natural carotenoids. Biochim Biophys Acta 1740:101–107

Takuji T, Masahito S, Hisataka M (2012) Cancer chemoprevention by carotenoids. Molecules 17:3202–3242

Tokarz P, Blasiak J (2014) Role of mitochondria in carcinogenesis. Acta Biochim Pol 61:671–678

Traka M, Mithen R (2009) Glucosinolates, isothiocyanates and human health. Phytochem Rev 8:269–282

Vallianou NG, Evangelopoulos A, Schizas N, Kazazis C (2015) Potential anticancer properties and mechanisms of action of curcumin. Anticancer Res 35:645–652

Vauzour D, Rodriguez-Mateos A, Corona G, Oruna-Concha MJ, P.E.S. (2010) Jeremy Polyphenols and human health: prevention of disease and mechanisms of action. Nutrients 2:1106–1131

Vig AP, Rampal G, Singh TS, Arora S (2009) Bioprotective effects of glucosinolates: a review. LWT Food Sci Technol 42:1561–1572

World Cancer Research Fund/American Institute for Cancer Research (2007) Food, nutrition, physical activity, and the prevention of cancer: a global perspective. AICR, Washington DC

Xia Y, Kang TW, Jung YD, Zhang C, Lian S (2019) Sulforaphane inhibits non-muscle invasive bladder cancer cells proliferation through suppression of HIF-1α-mediated glycolysis in hypoxia. J Agric Food Chem 67(28):7844–7854

Xiao Q, Zhu W, Feng W, Lee SS, Leung AW, Shen J, Gao L, Xu C (2019) A review of resveratrol as a potent chemoprotective and synergistic agent in cancer chemotherapy. Front Pharmacol 9:1534

Yasui Y, Kim M, Oyama T, Tanaka T (2009) Colorectal carcinogenesis and suppression of tumour development by inhibition of enzymes and molecular targets. Curr Enzym Inhib 5:1–26