Role of Dietary Antioxidants in Chemoprevention of Nitrosamines-Induced Carcinogenesis

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Abstract

Cancer is a persistent public health challenge globally, and it is now one of the leading causes of mortality even in developed countries. Carcinogenesis is a complex multistep process of apparent molecular changes that eventually reprogram and transform normal cells into abnormal ones of uncontrolled cellular growth and division. Cancer-causing agents or carcinogens are those substances capable of initiating or promoting the process of carcinogenesis, essentially by alteration of the DNA – the key cellular genetic material. While carcinogens have varying mechanisms of action, a significant number of them exert their carcinogenicity through production of free radicals. High concentration of free radical in the body results in oxidative stress that leads to changes in the structure of DNA molecules, resulting in the mutation of protein/lipid structures, making of

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pro-inflammatory and anti-inflammatory cytokines, and excitation of stress-induced transcription factors, which concertedly play important roles in carcinogenesis. Many of the known chemical carcinogens fall among fairly well-defined chemical groups, like polycyclic aromatic hydrocarbons (PAHs), aromatic amines, and nitrosamides and nitrosamines. Nitrosamines are conspicuously excellent; several hundred have been tested, and most are potent experimental carcinogens, so their carcinogenicity has been widely studied. They exhibit their toxicity essentially by oxidative stress mechanism through generation of reactive oxygen species (ROS) methyl radicals, which methylate the nucleobases in nucleic acids leading to adenine thymine-guanine cytosine (AT-GC) transition mutations, resulting in tumors at both local and distant sites. Several studies have established that antioxidants have the ability to neutralize this effect and hence can prevent or attenuate the carcinogenic potentials of these amines. Interestingly, numerous diets are abundantly rich in these chemopreventive antioxidants, including lycopene (in tomatoes, watermelon, paw-paw, and grape seeds); flavonoids (in spinach and other green leafy vegetables); carotenoids (in carrots, mango, and other colorful fruits); phytoestrogens, mainly isoflavones like genistein and daidzein (in soya beans, fava beans, and peanut); isothiocyanates (in cruciferous vegetables such as cabbage, cauliflower, spring greens, and watercress); curcumin (in turmeric); selenium (in edible fish, lean meats and poultry, shellfish, eggs, beans); and vitamin E (in sunflower seed oil, almonds, and wheat germ oil). These phytonutrients, antioxidant vitamins and minerals, can potentiate antioxidant, anti-inflammatory, and immunological responses, including induction of apoptosis through increased expression and modulation of proapoptotic genes and inhibition of cell cycle progression. The established effects of this dietary antioxidant on nitrosamines imply, by extension, similar chemopreventive benefits against other carcinogens with oxidative stress as their underlying mechanism. Hence, the need for more advocacies on the use of medicinal natural substances from food plants as preventive and chemotherapeutic antioxidants for diseases such as cancer prevention and management can never be overemphasized.

Keywords

Dietary antioxidant · Nitrosamines · Carcinogenesis · Chemoprevention

Introduction

Inside our bodies on daily bases, lots of cell destruction and repair happen. The system makes a new cell to replace the destroyed ones each time. During this complex process of cell replacement, many mistakes occur. Most of these errors are amended by some other systems in the body or cause the death of the newly produced cell, while the normal one is produced. Sometimes, however, these errors are not corrected. This may have little or no effect on health if it does not affect

important genes, but issues arise when the error affects genes that regulate cell growth, which permits the newly produced cell to replicate independent of the checks and balances that regulate normal cell growth. This leads to uncontrollable cell multiplication and proliferation, which can result to mass of abnormal cell (tumor), either benign or malignant (cancerous). Carcinogenesis is a multiple-step process, which is known for progression of definite molecular differentiation that ultimately transforms and reprograms a cell to undergo uncontrolled cellular division and growth (Ritesh et al. 2016). Research over time has disclosed lots of crucial molecular players and aimed pathways for this disruption. It has shown the essential principles associated with inactivation of tumor suppressor genes and aberrant activation of proto-oncogenes. At every disruption, cells go through changes basically represented by tumor stage differentiations (initiation, promotion, and progression), which ultimately result in cancer.

Cancer, the second prominent cause of mortality in most wealthy countries, is considered to be preventable. The process of oxidation, which is a ubiquitous cellular process contributing to the production of ROS, can initiate oxidative radicals. Hence, low ROS level performs like mitogens, which promote cell rapid growth and survival, while ROS at moderate level leads to a short-time or everlasting cell cycle arrest and cell initiation, promotion, and progression. Also, high concentration of ROS causes oxidative damage, mostly in the DNA, leading to mutations which finally result to cancer (Kumari et al. 2018). Hence, oncogenic transformations are observed in cancer cells at persistent high levels of ROS, as well as alteration in metabolic, genetic, and tumor microenvironments. A number of carcinogens owe their activity to the activation and promotion of free radicals in the body. High concentration of free radicals in the body can alter DNA structure, resulting in the activation of several stress-induced transcription factors like pro-inflammatory protein nuclear factor-$_{\kappa}$B (NF-kB), alteration of lipids and proteins, and production of pro-inflammatory and anti-inflammatory cytokines, which play crucial roles in carcinogenesis. Research has shown that excessive oxidative stress to cells result to lots of pathological state. It has been reported that antioxidant plays important mitigating and specific roles (Tomusiak-Plebanek et al. 2018). Therefore, agent that boosts antioxidant enzyme activities as they target the inactivation of ROS potentially prevents initiation and progression of cancer.

Despite different types of chemotherapeutic treatment used in the management of cancer, which are expensive and often traumatic, significant suppression of tumors is still rarely achieved, and great numbers of deaths still occur each year due to the adverse effects associated with anticancer drugs over prolonged treatment periods and high relapse rate. Fluoropyrimidine 5-fluorouracil (5-FU), for instance, is an anticancer drug used specifically for colorectal cancer (CRC) treatment. 5-FU is purely an S-phase active chemotherapeutic agent, which inhibits thymidylate synthase (TS) and incorporates its metabolites into RNA and DNA. The conversion of 5-FU to 5-fluoro-2′deoxy-5′ monophosphate, leading to the prevention of TS and DNA production which is the mechanism of action of 5-FU, has been established to cause DNA damage (double- and single-strand breaks) (Mehmet and Idil 2015). It was predicted that 13.3 million recent cancer cases were to amount US$ 290 billion

in 2010, which was expected to increase up to US$ 458 billion by 2030 based on the 2011 World Economic Forum (Aghajanpour et al. 2017). Many of these cancers and deaths are preventable basically via natural products (nutrition and foods) as numerous studies have reported relation between functional foods and cancer reduction.

There are a vast number of plant species on Earth that have been identified to contain chemical compounds that originally act as defense agents against predator like cardiac glycosides, protective agents such as flavonoids, attractive agents like aromatic smell, and nutritive agents that serve nutritional purposes. Some of these chemical compounds also have therapeutic values that range from nutrient to medicine. Most of them serve as antioxidant, and dietary antioxidants are known to proffer chemopreventive and ameliorative effects to radical damage on DNA and other tissues/organs of the body, which are the root cause of almost all cancers. These measures prevent or delay the onset of cancer formation.

Causes of Chemical Carcinogenesis

Several external and internal factors have been reported to act as carcinogens. Population variation in most cancer rate of occurrence implies that environmental factors, such as dietary trends, may play a remarkable role in the cause of disease (Otemuyiwa and Adewusi 2012). Through epidemiological studies, "Western-style food" that consists of low fiber, high fat, and low vitamin D/calcium has been identified as one of the major dietary factors that facilitate the development of various forms of cancer. A report involving a "Western-style food"-fed mice showed that oxidative stress was activated in the colon of the mice, which further promoted severe inflammation in the colon mucosa. Diets high in animal fat and protein have also been suggested to increase an individual's risk for developing colon cancer, as cooking of red meat has shown to produce heterocyclic aromatic amines (HAAs), dietary chemicals found to be carcinogenic in animal studies (Irabor 2014).

A number of chemicals are involved in carcinogenesis and are accordingly referred to as chemical carcinogens. That is, it is an agent capable of inducing cancer in animals or humans. Hundreds of it have been recognized as such due to rat or mice experiments. A limited number of them are occupational carcinogens, due to the fact that they cause cancer to the persons exposed to them in the workplace. Human cancer has also been found to be caused by some drugs. Lists of human carcinogens, which differ based on the strength of accepted evidence, have been published (Ostry et al. 2017).

Carcinogenesis, mostly initiated from chemical carcinogens, is a prolonged process with lots of stages, not well understood, and varieties of other factor are known that initiate or inhibit cancer development. It takes commonly about 20 or more years for occupational cancer to become apparent from first exposure, and difficulties in linking cause and effect are partly due to this time lag. Nevertheless, some former occupational cancers have been virtually eliminated through identification of carcinogenic factors, as well as changes in industrial practices and various legislative measures. Examples are bladder cancer in rubber workers and cancer of

the scrotum in chimney sweeps, cotton spinners, and tar workers (Armstrong and Doll 1975).

Cancers that arose from occupational hazards have been easier to identify when there is great increase in the risk of workers developing a particular type of cancer or a very uncommon form of cancer in the entire population. For instance, working conditions in the chemical industry using certain aromatic amines led to a 30-fold increase in the risk of bladder cancer among workers. Also, some rare forms of cancer, such as peritoneum and hemangiosarcoma of the liver and mesothelioma of the pleura, have arisen in workers that are exposed to vinyl chloride and asbestos dust, respectively. However, limitations of epidemiology are such that it is hard to identify a cause of cancer where such cancer is already common in the general population (e.g., colon cancer), as well as where there is less proportional increase in risk.

Many known chemical carcinogens are found among some fairly well-defined chemical classes, like aromatic amines and nitro compounds, polycyclic aromatic hydrocarbons (PAHs), N-nitrosamines/N-nitrosamides, and alkylating agents. The accepted occupational carcinogens are not included as part of N-nitroso compounds but are outstanding in most of the tested potent experimental carcinogens. Inorganically, occupational exposure to largely uncertain compounds of nickel, arsenic, and chromium has been discovered to cause cancers in humans.

Carcinogenicity of N-nitroso Compounds

The interaction between nitrogen-containing organic compound, like amide, amine, urethane, guanidine, cyanamide, or urea, and nitrosating agent, like nitrogen oxide, forms nitroso compounds. They are classified into two categories: nitrosamides and nitrosamines. These two differ in the mechanism of their mutagenicity/carcinogenicity and chemical stability. Nitrosamines require chemical modification in an enzyme-catalyzed reaction before they exhibit carcinogenic and mutagenic activity, which can be local at site of application or diffused to other body parts. They also tend to be very stable once they are formed. By contrast, the nitrosamides can be hydrolyzed, mostly in an alkaline and neutral solution (Morton and Laffoon 2008).

Reactions of nitrites, nitrates, and other proteins produce nitrosamines. Whenever amines, amides, or ureas come into contact with nitrites in the stomach or mouth, nitroso compounds may be formed. They are highly reactive alkylating chemical agents that introduce alkyl radicals into active molecules of biological system and thereby alter their normal functioning. Generally, good correlation exists between alkylating agent cancer inductions and alkylation reaction types with nucleic acids (Faustino-Rocha et al. 2015). Reactions, predominantly by an SN_1-type mechanism (Fig. 1), such as dimethylnitrosamine (DMN), N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), and N-methyl N-nitrosourea (MNU), are potent carcinogens, while reactions by an SN_2-type mechanism, such as methyl methanesulfonate and dimethyl sulfate, are mostly less active carcinogens. They occur in foods and N-nitrosodimethylamine (NDMA), which is among the most occurring nitrosamine in diets.

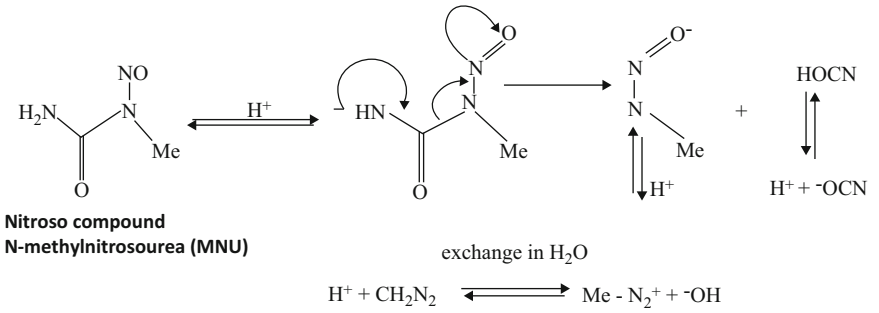

Fig. 1 Mechanism of action of MNU

Nitrosamines are potent carcinogen that can induce malignant tumors in different tissues of various species of animal. High intake of nitrites and NDMA has been reported to have resulted in an increased cancer risk. Most of these nitroso compounds do not require metabolic activation by cytochrome P^{450}. They exhibit their toxicity by transferring their methyl group to the nucleic acid's nucleobases, and this can lead to adenine/thymine-guanine/cytosine (AT-GC) transition mutations (Lawley and Shah 1972). Evidence has shown that DNA of the liver is methylated after injection of MNU into rats or mice.

Dietary Cancer Prevention

Dietary cancer prevention geared toward identification of initial stages of cellular transformation and agents that can specifically impact on them. Phytochemicals that occur naturally have been observed to show wide range of cellular effects. For example, there are phytochemicals that can prevent carcinogens from getting to the targeted sites and also support detoxification of ROS molecules, while some may enhance innate immune surveillance and improve the elimination of transformed cells. Others may have impacts on intrinsic DNA repair mechanisms and or may influence tumor suppressor genes, inhibiting cellular proliferation pathways. Most of these phytochemicals in food serve as chemopreventive agents to different forms of cancers at different cancer stages.

Chemoprevention

This is an administration of certain agents or substances to prevent initiation and block or delay the onset or cancer progression. Traditionally, food-derived chemoprotective agent's beneficial effects had been assessed either individually or as a few putative active constituents and often at pharmacological doses. Carcinogenesis being a process over time, which involves cellular growth and division, makes the concept of chemoprevention very important. Chemopreventive agents

inhibit or slow this process of carcinogenesis, and this can prevent cancers potentially from becoming significant clinically. Agents of cancer chemoprevention include anti-promotion and anti-progression, which prevents the survival and growth of cells already committed to become malignant (Kumar et al. 2016). Therefore, successful agents must have low toxicity for them to maintain their purpose of keeping something from occurring.

Dietary Intervention

This is a type of whole-food-based approach for treatment and prevention of cancer, which also involves changes in food consumption designs necessary to reduce cancer development. It has been established that many diets are abundantly rich in these chemopreventive agents like micronutrients, fiber, and phytochemicals, including lycopene (in tomatoes, watermelon, paw-paw, and grape seeds); phytoestrogens, mainly isoflavones like genistein and daidzein (in soya beans, broad bean, fava beans, peanut); isothiocyanates (in cruciferous vegetables such as cabbage, cauliflower, spring greens, watercress); curcumin (in turmeric); selenium (in seafood, poultry and lean meats, beans and peas, soy products, eggs); vitamin E (in wheat germ oil, almonds, sunflower seeds); etc. These phytonutrients, antioxidant vitamins and minerals, can potentiate anti-inflammatory, anti-oxidant, and immunological responses, including the induction of apoptosis through increased expression of proapoptotic genes, NF-κB inhibition of cell cycle progression, and modulation of expression of androgen-responsive genes. These elements are excellent materials for sources of chemopreventive drugs, if identified. Higher vegetable intake, fruits, and legumes are related with minimal cancer risk in all ethnic groups. Population studies have also shown that diets rich in fiber and presumably lower in fat are related with lower cancer incidences (Slattery et al. 2000).

Lycopene

Major sources of lycopene in the diet are from tomatoes (other sources include guava, grapefruit, and watermelon). They gave tomatoes their color, and they are also one of the most common carotenoids consumed in the Western diet (Mandair et al. 2014). They have multiple conjugated double bonds, a potent antioxidant, and a free radical quencher. It's widely but uniformly distributed in human tissues. It may reduce DNA damage and improve oxidative stress defense. Genetic mutations can occur due to oxidation, which can eventually lead to malignancy. Antioxidants like lycopene are potential preventive agents of cancers.

Epidemiologic studies also suggest that lycopene, a vitamin A analog, is related with a reduced risk of prostate cancer and other forms of cancer. Lycopenes are powerful antioxidants with potentials of DNA repair, which adds to their role as chemopreventive agents. Mandair et al. (Mandair et al. 2014) showed pathways where lycopene acts anti-carcinogenic role in a phase I and phase II in vitro studies. Another study of lycopene 4 mg twice daily for 1 year, conducted by Mohanty et al. (Mohanty et al. 2005) in 40 patients with evidence of high-grade prostatic

intraepithelial neoplasia (HGPIN) in transurethral resection of the prostate, revealed 66% reduction of prostate cancer after treatment for 1 year. As such, lycopene was considered as an effective chemopreventive agent in the treatment of HGPIN, with good tolerability and no toxicity. It was stated that the biological prostate cancer protective mechanisms appear to be related either to the anti-inflammatory and antioxidative or apoptosis-inducing properties, such as the ability to induce G0/G1 cycle arrest, and delayed in vivo growth of different cancer cells (Ivanov et al. 2007). Lycopene, also found in some other African food such as paw-paw (papaya), disrupts cancer cell cycle, induces mass deaths of cancer cells, and promotes anti-inflammatory activity, which works to suppress formation and progression of cancer. Inflammation as an important factor of cancer formation, the pro-inflammatory cytokine interleukin-8 formation, has been documented by Yang et al. (Yang et al. 2012) to be prevented by lycopene.

Vitamins

Vitamins are necessary for maintenance of healthy living. They are diverse organic substances provided in minimal quantities in our diets and are found in different chemical forms and structures. Vitamins have very important biochemical functions in contributing toward maintenance of health and have special therapeutic roles in the treatment of related disorders. Originally, most vitamins were used for the prevention of deficiency syndromes related with low intake of nutrients. Antioxidant vitamins are however one of the chemopreventive agents that have shown high level of promise in human cancer chemoprevention. Antioxidant vitamins, such as vitamins E, C, as well as D, are thought to prevent cancer by scavenging and rendering free radicals ineffective, terminating chain reactions, and confining damage to few areas of the membrane as a result of their ability to transfer phenolic hydrogen to a peroxyl free radical of a peroxidized polyunsaturated fatty acid. This results to minimal oxidative damage, as well as stimulation of the immune system to inhibit tumorigenesis (Hawk et al. 2004).

Vitamin E is found in spinach, tomatoes, peanuts, wheat germ oil, soybean oil, sunflower seed and oil, broccoli, mango, and other foods. It is a widespread term used to describe a group of naturally occurring compounds called tocopherols and tocotrienols, as well as vitamin E derivatives like succinate, nicotinate, and acetate (Mandair et al. 2014). Tocopherols are fat-soluble compounds. Among the tocopherols, α-tocopherol is biologically the most active and concentrated highly in the hydrophobic inside part of the cell membrane. It is the principal defense against oxidant-induced injury in the membrane and protects against lipid peroxidation. It is a potent antioxidant, inhibitory agent and has been implied as a potential preventive agent of numerous cancers. It triggers cancer cell apoptosis and inhibits the formation of free radical.

Several authors have reported that low consumption of foods rich in antioxidants, such as vitamins C and E, is one of the environmental factors that may play a role in the etiology of Parkinson's disease, because they are oxidation-reduction coenzymes that can play the role of antioxidants and protect cells against injuries of oxygen free radical. Also, many clinical trials have proven the effectiveness of vitamins C, E, etc.

in the treatment of hepatocellular carcinoma patients (Iliemene and Atawodi 2019). An in vitro study reported encouraging results of a 40% decrease in the number of cancer cells in 72 h of vitamin E succinate treatment. Significant reduction in the incidence of prostate cancer was recorded in the animal model of prostate cancer work, which uses transgenic mice administered with vitamin E supplementation (Venkateswaran et al. 2004). An additional study by the same group of researchers discovered that mice given vitamin E, selenium, and lycopene supplementation at an early stage had only a 10% prostate cancer incidence compared to the control group with 75%.

Vitamin D and vitamin D analogs have been referred to as potential cancer preventive agents. This is because it has been reported that the potent metabolite of vitamin D, 1,25-dihydroxyvitamin D3 (calcitriol), prevents the growth of both cancer cell lines and primary cultures of human prostate cancer cells (Brawley 2002). Studies show that calcitriol alters cell cycle progression through the binding of the bioactive form to the vitamin D receptor, as such, regulating differentiation, proliferation, and apoptosis, though hypercalcemia (a vitamin D side effect) has been associated with high dose of vitamin D above physiologic levels. As such, calcitriol (vitamin D analog), which has more potent or comparable anti-proliferative effects but is less likely to produce hypercalcemia, has been developed. Marshall et al. (Marshall et al. 2012) conducted a research where men placed on active surveillance diagnosed with low-grade prostate cancer were supplemented with vitamin D at a daily dose of 4000 IU for 1 year. It was reported that 55% of them showed a reduced number of positive cores or decrease in Gleason score. The study concluded that those with minimal risk of PCa under active surveillance may benefit from vitamin D supplementation. It has been established that above 200 genes have been controlled by calcitriol. They include genes responsible for the regulation of cellular proliferation, apoptosis, differentiation, and angiogenesis.

Carotenoids

Quite a number of carotenoids are known to possess antioxidant activity. Epidemiological studies as described by Saini et al. (Saini et al. 2020) showed that the consumption of carotenoid's rich diet is associated with a minimal cancer incidence. There are handful of African diets with vitamin A from plants such as spinach, carrots, pumpkin, peppers, mangos, cowpeas, apricots, broccoli, tomatoes, and many others.

β-carotene (vitamin A), a powerful anticancer nutrient, also known as anti-xerophthalmic vitamin or retinal, is equally a fat-soluble vitamin. It plays a function of trapping peroxy free radical in tissues at low-oxygen partial pressures but may have pro-oxidant effects at higher oxygen concentration. It prevents the oxidant-induced nuclear factor-kB (NF-kB) activation, interleukin (IL)-6, and tumor necrosis factor-α production and also affects apoptosis of cells (Niizuma et al. 2006). Induction of apoptosis by retinoid has been demonstrated in various cancer cells in vitro and in vivo. The competence of β-carotene to work as an antioxidant is a result of the stabilization of organic peroxide free radicals located at its conjugated alkyl structure (Robert et al. 1996). Since β-carotene is effective at low

concentrations of oxygen, it complements the vitamin E antioxidant properties, which is effective at higher concentrations of oxygen. The antioxidant properties of β-carotene and vitamin E may well account for their anticancer activity. In vitro oxidative damage was demonstrated to be quenched with β-carotene in combination with lutein. Combination of β-carotene, selenium, and vitamin E has been reported to reduce stomach cancer by 21% (Ziegler et al. 1996).

Vitamin A, as well as retinoids, is also a modulator of epithelial cell proliferation and differentiation. They are able to invert cancerous progression in the airway by complex mechanisms. These mechanisms necessarily rely on the retinoid's capacity to control gene expression through nuclear transduction signal modulation mediated by nuclear retinoid receptors. The receptors function as a ligand-activated transcription factors. It has been shown that expression of retinoic acid receptor (RAR-β), one of these receptors, is blocked in the initial stages of head and neck carcinogenesis (premalignant lesions of the oral cavity and tumors adjacent to dysplastic tissues), as well as in lung carcinogenesis (Xu et al. 1994).

Cabbage contains appreciable amount of β-carotene, and eating cabbage has been associated as a dependable way of obtaining cancer-fighting β-carotene. Cabbage equally contains indole-3-carbinol (I3C), which has been confirmed by studies to have the ability of disrupting cancer cell cycle. Sarkar and Li (Sarkar and Li 2004) stated that I3C induces mass deaths of prostate cancer cells and suppresses growth of colon and cervical cancer cell. Hormone-sensitive cancers like prostate tend to thrive where there is hormonal imbalance. I3C is known to be helpful for keeping hormones in a balance state. Cabbage is able to fight off different forms of cancer equally by keeping hormones in a balanced state. Beta carotene and I3C act as potent antioxidants in addition to their anticancer role.

Uncontrolled systemic inflammation is an underlying pro-cancer activity. There are some other types of carotenoid with anticancer activities such as canthaxanthin commonly found in edible mushroom. It is an ROS quencher that prevents proliferation in colon cancer. Flucoxanthin is another type of carotenoid that prevents cancer cell line development, as well as inhibitory effect of apoptosis induction (Aghajanpour et al. 2017). Several studies have linked foods rich in beta carotene and other antioxidants to a significant reduction in cancer incidence.

Isothiocyanates

These are sulfur-containing compounds mainly found in cruciferous vegetables like cabbage, broccoli, sprouts, cauliflower, wasabi, and Brussels sprout. They are largely responsible for the typical flavor of those vegetables. They are versatile cancer-preventive compounds at all major stages of tumor growth. Epidemiological studies have demonstrated that intake of isothiocyanate dietarily is related with reduced risk of certain form of human cancers.

They have shown induction of cell cycle arrest, angiogenesis and inhibition of anti-inflammatory activity, tumor invasion, and inhibition of extracellular signal-regulated kinases in in vivo and in vitro studies. Bosetti et al. (Bosetti et al. 2012) found from seven cohorts and six population-based case-control studies that a significant decrease in prostate cancer risk was demonstrated overall in the group

administered with cruciferous vegetables. In a recent study, it was established that consumption of cruciferous vegetables reduced PhIP adduction to DNA in response to a cooked meat meal (Stewart and Amanda 2018). Isothiocyanates and their metabolites have been demonstrated by several studies to have assisted in lowering the risk of different types of cancer development by modulation in cytoprotective biotransformation enzymes. It equally possesses anti-inflammatory activity via prevention of nuclear factor kappa-B, cell cycle arrest, and apoptosis induction (Aghajanpour et al. 2017).

Numerous mechanisms have been proposed for isothiocyanate chemopreventive activity. It induces apoptosis and cell growth inhibition by covalently bonding/modification of certain nucleophile-containing proteins. They inhibit cytochrome P^{450} to activate carcinogens and induce phase II enzymes to detoxify carcinogens as well. Chemopreventive activities of isothiocyanates equally arise by direct and indirect interaction with cell component at cellular and molecular levels.

Polyphenols

Polyphenols (polyhydroxyphenols) are a group of mainly natural but also synthetic or semisynthetic phytochemical compounds found in plant-based foods, like fruits, vegetables, whole grains, cereal, etc. They are characterized by the presence of multiple phenol units as building blocks per molecule. They are the most abundant antioxidant in our diet. About 8000 polyphenolic compounds have been identified in whole plant foods. They include flavonoids, phenolic acids, lignans, stilbenes, and polymeric lignans and are generally divided into hydrolyzable tannins (gallic acid esters of glucose and other sugars) and phenylpropanoids, such as lignins, flavonoids, and condensed tannins (Claudine et al. 2004). The division of polyphenols into tannins, lignins, and flavonoids is derived from the diverse arrangements of simple phenolic units arising from synthesis during secondary plant metabolism of the shikimate pathway as well as classical divisions based upon the relative significance of each base component to different fields of study. For example, tannin chemistry originated due to the importance of tannic acid to the tanning industry, lignins due to the chemistry of soil and plant structure, and flavonoids due to the chemistry of plant secondary metabolites for plant defense mechanism.

Recently, polyphenols are accorded increasing attention by food manufacturers as well as consumers, and this is essentially a result of their antioxidant properties' recognition coupled to their availability and abundance in various diet as well as their probable role in the prevention of various diseases associated with oxidative stress (Claudine et al. 2004). Epidemiological studies have suggested links between the consumption of polyphenol-rich foods or beverages and the prevention of some diseases. A glass of red wine or cup of tea or coffee, a bar of chocolates, or a serving of dry legumes contains reasonable quantities of polyphenols enough to contribute to our polyphenolic intake (Tanu and Sunil 2015). Some animal and clinical studies suggest that biochemical properties of polyphenols play an important role in the enhancement of healthy living.

An in vivo study showed that the seed of *Dioclea reflexa*, which is rich in polyphenol and flavonoids, statistically boasted antioxidant enzymes and reduced

colon carcinogenesis in animal model (Iliemene and Atawodi 2019). In this study, it has been demonstrated that polyphenols contribute positively to human health in the fight against cancer because of their antioxidant, anti-inflammatory, and other biological effects (Iliemene and Atawodi 2019; Tanu and Sunil 2015). It was established that bioactive compounds, 2-(4-ethylphenyl)-5-hydroxy-3-methyl-6,7-dihydrofurochromen-4-one and a tolylethylidenebenzofurone, identified as 4-hydroxy-2-(1-p-tolylethylidene)-5,6-dihydrofuro-3-one, which were isolated from the seeds of *Dioclea reflexa*, possess potent antioxidant and anti-inflammatory activities which could be exploited for treatment of diseases like cancer that are facilitated through free radical mechanisms (Igwe and Okwu 2013). Overall, it has been demonstrated (Fig. 2) that the process of carcinogenesis can be attenuated by

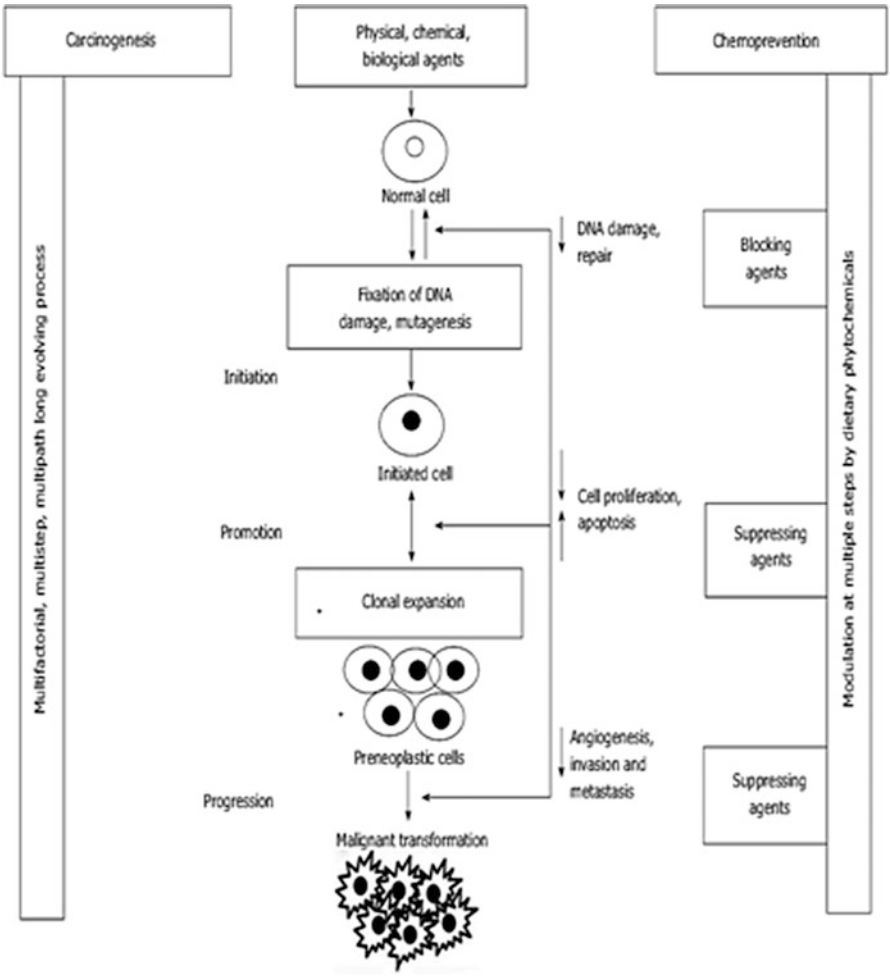

Fig. 2 Modulation of carcinogenesis with dietary phytochemicals

polyphenols through numerous mechanisms, including promotion of tumor cell death via apoptosis, as well as radical scavenging of singlet oxygen and free radicals that are responsible for DNA damage, tumor proliferation, and progression (Alam et al. 2018).

Reports from studies have shown that dietary polyphenols modulate some cell signaling pathways that include nuclear factor kappa-B (NF-kB), extracellular signal-regulated protein kinase (ERK), activator protein-1 DNA binding (AP-1), nuclear factor erythroid 2-related factor 2 (Nrf2), mitogen-activated protein kinases (MAPK), and phosphoinositide 3 (PI3)-kinase/protein kinase B (Mellor et al. 2012). They can influence peripheral glucose uptake in insulin-sensitive and non-insulin-sensitive tissues, muscle cells, and adipocytes. Clinical trials in human showed that consumption of dark chocolates containing high amounts of polyphenols was accompanied with improvement of endothelial function in individuals with stage 1 hypertension and attenuates acute transient hyperglycemia-induced endothelial dysfunction and oxidative stress in type 2 diabetes mellitus (Mellor et al. 2012).

The structure of polyphenols affects their physical, chemical, and biological properties (metabolic, toxic, therapeutic, etc.), bioavailability, antioxidant activity (Table 1), specific interactions with cell receptors and enzymes, and other properties (Atawodi 2010). To comprehend their human health impact and benefits, it is important to understand the physicochemical nature of the main polyphenols ingested, their major dietary origin (Table 2), the quantities available and consumed in different diets (Table 3), their bioavailability and the factors controlling their bioavailability. Generally, polyphenols are known to accumulate in the target tissue to induce their biological activities, and their metabolites are mainly excreted via bile and urine.

Table 1 Antioxidant chemopreventive agents and their effect on cancer

Preventive agent	Effect on cancer
Vitamin E	Antioxidant and inhibitory effect
Isoflavones	Inhibitory effects, decrease proliferation, and increase apoptosis
Lycopene	Antioxidant and DNA repair ability
Vitamin A	Antioxidant effect
Isothiocyanates	Induce cell cycle arrest and angiogenesis and inhibit tumor invasion, anti-inflammatory activity
Vitamin D	Inhibits growth of primary cultures of human PCa cell and cancer cell lines
Lutein	Efficient in cell cycle progression and inhibits growth of a number of cancer cell types
β-Cryptoxanthin	Anti-inflammatory effects; inhibits risks of some cancer
Astaxanthin	Modification of gap junction communications
Canthaxanthin	Free radical scavengers and potent quenchers of reactive oxygen species
Fucoxanthin	Anti-cancer and anti-inflammatory
α- and β-Carotene	In moderate dose, increase enhance gap junctional intercellular communication

Table 2 Some cancer preventive compounds in African foods

Plant sources	Major family of chemopreventive phytochemical	Specific cancer active phytochemicals
Tomato (*Lycopersicon esculentum* Mill)	Carotenoids	Lycopene
Chili pepper (*Capsicum annuum*)	Vanilloids	Capsaicin
Green tea (*Camellia sinensis*)	Polyphenols (Catechins)	(−) epigallocatechin gallate (EGCG), (−) epicatechin, (−) epicatechin-3-gallate and (−) epigallocatechin-3-gallate
Soya beans (*glycine max*)	Polyphenols (isoflavones)	Genistein
Moringa (*Moringa oleifera*)	Polyphenols	Ellagic acid, gallate, methyl gallate, catechol, kaempferol, and quercetin
Turmeric (*Curcuma longa* Linn)	Polyphenols	Curcumin
Grape	Phytoalexins	Resveratrol

Flavonoids

The most studied and possibly the largest group of polyphenols are the flavonoids, which include several thousand compounds, such as flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids. Flavonoids, low molecular weight polyphenols of plant origin, are a group of naturally occurring and structurally similar compounds containing two spatially separate aromatic rings that are found in red wine, green tea, chocolate, and other plant-derived foods (Vinita et al. 2013). Flavonoids have been hypothesized as important contributors to the free radical scavenging and defense system in a number of ways. For example, functional hydroxyl groups in flavonoids facilitate their antioxidant roles by scavenging free radicals and/or by chelating metal ions, which could be crucial in the prevention of radical generation (Kumar et al. 2013), and subsequent damage of biomolecules. Some flavonoids can inhibit enzymes responsible for the production of superoxide anion, like xanthine oxidase. Others could chelate metal ions like Fe and Cu, thus restraining these metals from participation in the Fenton reaction.

Flavonoids may also act as free radical scavengers by donating electrons to superoxide or lipid peroxy radicals or stabilize free radicals by complexing with them. It is difficult to estimate the quantity and extent of dietary flavonoid contribution to our free radical defense system since many have a high pro-oxidant activity and poor absorbance. They are widely distributed in a variety of fruits and vegetables across human food supply chain and are considered to have potential anti-carcinogenic, anti-leukemic, anti-inflammatory, anti-allergic, and antiviral effects (Jain et al. 2013). Generally, we consume relatively large quantities of flavonoids (approximately 800 mg/day), and there is evidence that in addition to their

Table 3 Phytonutrient content of fruits and vegetables, servings, serving sizes, and daily dose

Phytonutrient	Food/food product	Phytonutrient/food source (mg/100 g)	Phytonutrient/serving (mg)	Serving size	Daily dose
Lycopene	Tomato juice	9.0	22.0	1 cup (243 g)	5.7–10.5 mg/day
	Tomato soup (condensed)	10.9	13.7	1 cup (245 g)	
	Watermelon	4.5	13.0	1 wedge (1/16) of melon	
	Tomato paste	28.8	9.2	2 table spoons (32 g)	
	Guava	5.2	8.6	1 cup (165 g)	
	Canned tomatoes	2.7	6.5	1 cup (249 g)	
	Tomato powder	46.3	4.6	10 g	
	Raw tomatoes (red)	2.6	3.2	1 medium (123 g)	
	Tomato ketchup	16.7	2.5	1 table spoon (15 g)	
	Pink grape fruit	1.4	1.7	½ fruit (123 g)	
B-carotene (μg/100 g)	Papaya	185	125 g/bowl	1½ bowls	200 μg/day
	Mango	2450	130 g/bowl		
Selenium	Rice, brown, long grain, cooked		19 mcg	1 cup (250 g) (www.cookitsimply.com)	50–70 μg/day
	Baked beans, canned, plain, or vegetarian	3 μg/100 g (Mark et al., 2013)	13 mcg	1 cup	
	Spinach, frozen, boiled		11 mcg	1 cup	
	Green peas, frozen, boiled	<0.5 μg/100 g (Mark et al., 2013)	2 mcg	1 cup	

(continued)

Table 3 (continued)

Phytonutrient	Food/food product	Phytonutrient/food source (mg/100 g)	Phytonutrient/serving (mg)	Serving size	Daily dose
Calcium	Yogurt, soy	121 mg/100 g USDA, 2018	206 mg	175 g (¾ cup)	1000–1200 mg/day
	Ricotta cheese	206 mg/100 g USDA, 2018	269–356 mg	125 mL (½ cup)	
	Beverages (cashew, almond, coconut)	45, 70, 14 mg/100 g respectively (USDA, 2018)	223–331, 319, 312, 177–223 mg, respectively	250 mL (1 cup)	
	Broccoli, raw		21 mg	½ cup	
	Kale, fresh, cooked	150 mg/100 g (USDA, 2018)	94 mg	1 cup	
	Kale, raw, chopped	254 mg/100 g (USDA, 2018)	24 mg	1 cup	
Vitamin E	Spinach (boiled)	4 mg/100 g (from calculation that 1cup = 30 g)	0.6 mg	½ cup	4–15 mg/day
	Tomatoes	1.42 mg/100 g (www.traditionaloven.com)	0.7 mg	1 medium	
	Peanuts, dry roasted	4.93 mg USDA, 2018	2.2 mg	1 ounce (28.35 g) USDA, 2018	
	Corn oil	14.3 mg/100 g (https://oilhealthbenefits.com/corn-oil/)	1.9 mg	1 tablespoon	
	Wheat germ oil	240–420 mg/100 g (Sizova, 2016)	20.3 mg	1 tablespoon	
	Almonds, dry roasted	23.9 mg (USDA, 2018)	6.8 mg	1 ounce (28.35 g) USDA, 2018	
	Soybean oil	8.18 mg of α-tocopherol and 64.26 mg of γ-tocopherol/100 g	1.1 mg	1 tablespoon (13.6 g) USDA, 2018	
	Sunflower seeds, dry roasted	26.10 mg/100 g	7.4 mg	1 ounce (128 g) USDA, 2018	

	Sunflower oil	41.08 mg/100 g (USDA, 2018)	5.6 mg	1 tablespoon	
	Broccoli, chopped, boiled		1.2 mg	½ cup	
	Mango, sliced	0.90 mg/100 g (USDA, 2018)	0.7	½ cup	
Vitamin A	Spinach, frozen, boiled	603 μg/100 g RAE (USDA, 2018)	573 mcg RAE	½ cup	400–900 mcg RAE
	Carrots, raw	835 μg/100 g RAE (USDA, 2018)	459 mcg RAE	½ cup	
	Pumpkin pie	448 μg/100 g RAE (USDA, 2018)	488 mcg RAE	1 piece	
	Peppers, sweet, red, raw	157 μg/100 g RAE (USDA, 2018)	117 mcg RAE	½ cup	
	Mangos, raw	54 μg/100 g RAE (USDA, 2018)	112 mcg RAE	1 whole	
	Cowpeas, boiled		66 mcg RAE	1 cup	
	Apricots, dried	180 μg/100 g RAE (USDA, 2018)	63 mcg RAE	10 halves	
	Broccoli, boiled		60 mcg RAE	½ cup	
	Tomato juice, canned	23 μg/100 g RAE (USDA, 2018)	42 mcg RAE	¾ cup	
Genistein	Soya bean	21.4–78.3 mg/100 g Mujić et al., 2011	24½ cup (BCERC, 2007)	½ cup (100 g) (www.cookitsimply.com)	50–100 mg/day

antioxidant activity, they can contribute to the maintenance of vitamin E as an antioxidant, thereby reducing the risk of many diseases including cancer.

Flavonoids are also known for their ability to influence the quality and stability of foods by acting as flavorants, colorants, and antioxidants. Although flavonoids are known to possess varying biological activities, their best known and widely studied property is their capacity to act as antioxidants. The antioxidant property of flavonoids is a universal function that all groups of flavonoids were identified to possess and is mostly dependent upon the arrangement of functional groups around the nuclear structure. Specifically, the hydroxyl group's total number configuration and substitution substantially impact the varying antioxidant mechanisms and activities, such as radical scavenging and chelation of metal ion ability (Pandey et al. 2012).

Lots of flavonoids are known for different biochemical functions. For example, diosmin found in *Scrophularia nodosa* L. and citrus fruits is known for its ability to improve activities of lipid-metabolizing enzymes, decrease lipid peroxidation, and enhance antioxidant status (Srinivasan and Pari 2012). Fisetin found in strawberries, onion, and persimmon is known for reducing cataract formation. Morin found in *Prunus dulcis*, *Chlorophora tinctoria*, *Psidium guajava*, fruits, and wine, hesperidin found in orange, and apigenin found in orange, tea, onions, and wheat sprout are known for inhibition of ROS generation, apoptotic protein translocation, antioxidant gene upregulation, and Bcl-2 gene expression (Ramachandran and Baojun 2015). Naringenin found in grape fruits, orange, and tomato is known for increasing antioxidant enzyme (SOD) and decreasing inflammatory cytokines and oxidative stress (Bhattacharya et al. 2014).

Isoflavones are subclass of the flavonoids commonly found in plants, such as soybeans, other legumes, and nuts. Genistein, glycetein, and daidzein are the main soy-derived isoflavones. They are classified as phytoestrogens because they have weak estrogenic activity. Messina et al. *(*Messina et al. 2006*)* revealed in an in vitro study the inhibitory effects of these isoflavones on signaling pathways, oncogene expression, and steroid metabolism. This was also supported by an in vivo work according to Bemis et al. *(*Bemis et al. 2004*)*, where a genistein-containing preparation reduces tumor growth of androgen-sensitive prostatic cancer cells by decreasing proliferation and increasing apoptosis. Swami et al. *(*Swami et al. 2005*)* also reported from an in vitro study that genistein and daidzein inhibit the growth of PCa cells. Genistein is regarded as a potent inhibitor of angiogenesis, metastasis, and protein-tyrosine kinase and lessen the level of oxidative DNA damage, thereby decreasing the growth of cancer cells. It can inhibit cell invasion by inhibiting transforming growth factor-β-mediated phosphorylation of the p38 mitogen-activated protein kinase 2 and the 27 kDa heat shock protein (Xu and Bergan 2006). Genistein was also reported to enhance the ability of endoglin, a component of the transforming growth factor beta receptor complex, thereby aiding the suppression of mortality of PCa cell. Daidzein on the other hand acts as a radiosensitizer against cancer cells and as an inhibitor of cell growth. It inhibits by synergizing with radiation, affecting APE1/Ref-1, NF-kappa-B, and HIF-1alpha (Singh-Gupta et al. 2010). Combination of daidzein and genistein has been demonstrated to induce cell apoptosis in benign prostate hyperplasia cells at concentration of 25 μM.

Combination of various active soy-derived compounds has been demonstrated to be more effective and possibly safer chemopreventive agents than the individual compound (Hsu et al. 2010).

Calcium

Calcium is a dietary mineral commonly found in some food which includes soy milk, beverages (cashew, almond, and coconut), broccoli, kale, yogurt, cheese, and other dark-colored vegetables. It can also be found in certain grains and legumes such as peas, beans, lentils, and peanuts. Calcium forms the constituent of bones and teeth and is also needed for blood clotting and normal functioning of the nerves, heart, and muscles. Daily required dose intake of calcium varies according to age (Table 3) and is higher in children and teenagers between the ages of 9 and 18. Calcium can be absorbed into the cell through the spaces between cells passively by diffusion or actively through the intestinal cells by binding to calbindin, a transport protein. Higher dietary calcium intake has been reported to be inversely associated with cancer proliferation (Williams et al. 2012). However, the underlying mechanistic pathways, which can explain observed effects of calcium on cancer, are yet to be clearly elucidated but may not be unrelated to the cellular calcium-dependent channel function.

A nutritional cohort study that analyzed the diet, medical history, and lifestyle of more than 120,000 men and women reported a 31% reduced colon cancer risk in those who took 500 mg of calcium supplements per day or more (McCullough et al. 2003). The exact mechanism of colon cancer risk reduction is still unclear, but it has been reported that at biochemical level, calcium binds to fatty acids and bile acids to form insoluble calcium soap complexes in the gastrointestinal tract. These acids stimulate proliferation when they cause damage to cells, but the calcium soap complexes reduce the ability of the acids or their metabolites to cause injury to cells in the lining of the colon. A proliferating cell in the lining of the colon can also be directly reduced in the presence of calcium, thereby causing the cells to undergo differentiation which in turn leads to reduction in cellular proliferation. Calcium may equally enhance cell signaling, which could lead to cancer cell differentiation and/or death. Study by Changwoo et al. (Changwoo et al. 2015) also stated that the colorectal cancer risk was significantly reduced in both men and women with highest intake of calcium compared with those on the lowest calcium intake.

In the colon epithelial cells, intracellular calcium reduces cancer by promoting inflammatory responses. When calcium ionizes, it inhibits the irritating and potentially toxic effects of free fatty and bile acid in the colonic wall. Colon cancer risk management with calcium may differ based on the cancer location due to various differences between colorectal subsites. The walls of the rectum are thicker than that of the colon. Rectum has high proportion of endocrine cells, while colons possess high proportion of goblet cells. Though few human studies that examined the association between cancer risk and calcium by colorectal subsites are with conflicting results, some revealed a significant decrease in colon cancer risk in the group with highest calcium intake both in the rectum and distal colon when compared with proximal colon (Changwoo et al. 2015).

Astaxanthin

This is a phytonutrient that serves as a functional food commonly found in green algae, salmon, and trout. They act as antioxidants that are highly potent in cancer chemoprevention. They have free radical scavenging ability, potent quenchers of ROS, and chain-breaking antioxidants. It has been reported that astaxanthin has the ability to traverse the blood-brain barrier and scavenge free radicals in the brain, as such proffer neuroprotection to the brain. Several authors have reported the anti-inflammatory activity of astaxanthin by means of limiting activity of nitric oxide synthase as well as synthesis of prostaglandin E2 and tumor necrosis factor-alpha (TNF-α). Some studies reported that anticancer activity of astaxanthin is based on its modification of gap junction communications that are essential to homeostasis, growth regulation, and cellular developments. In cancer cells, the gap junctional intercellular communications are faulted, but astaxanthin changes the phosphorylation pattern of gap junction protein connexin, as well as influences the channel functions (Aghajanpour et al. 2017). Other researchers reported the inhibitory role of astaxanthin in nitrosamine-induced carcinogenesis in rat model by suppression of cell proliferation. This happens as a result of its ability to modulate the expression of several inflammatory cytokines, which are linked to inflammation-associated carcinogenesis (Aghajanpour et al. 2017). Another study demonstrated astaxanthin inhibition of preneoplastic liver cell lesion development, which was induced by AFB1 in rats through the deviation of AFB1 metabolism to detoxification pathways. Prevention of transplanted Meth-A tumor cell growth has been reported of astaxanthin in dietary supplementation.

Conclusion

Chemical carcinogens like nitrosamines were implicated in etiology of various deadly diseases (including cancer) with oxidative stress as part or whole of the underlying mechanism. The established effects of dietary antioxidant on nitrosamines and by extension other oxidizing carcinogens are a promising component of dietary cancer prevention approach. Recently, there is a general advocacy promoting the use of natural constituents from food and medicinal plants as beneficial antioxidants for cancer disease prevention and management. Although majority of studies have principally focused on the conceivable benefits of the individual phytochemical supplements and their preventive roles in carcinogenesis, classical clinical outcomes have established greater cumulative synergistic effects of various antioxidant as well as non-antioxidant phytochemicals; hence, consumption of whole food material with chemopreventive potential is more preferred than the consumption of a single phytochemical supplement.

Future Direction

The future direction of this chapter will gear toward identifying checkpoints in oxidative stress pathways, which will aid in the identification of possible druggable

sites for future cancer drugs. Also, in-depth understanding of oxidative stress mechanism and effect on cancer will lead to better preventive and management schemes, accompanied with identifying more antioxidants from our diets and their ameliorative/preventive effects on oxidative stress.

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