Natural Products and Their Benefits in Cancer Prevention

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1 Introduction

The search for new sources of natural antioxidants from plant material may have beneficial therapeutic potential for those diseases associated with oxidative stress, including cancer. Natural products are rich in flavonoids, phenolic, alkaloids carotenoids, and organosulfur compounds, these bioactive components are known to combat oxidative stress-mediated diseases pathogenesis, including cancer. A novel approach for preventing cancer is chemoprevention using natural products for suppression, prevention, or reversion premalignancy before the induction of aggressive cancer. Natural products are fruits, vegetables, grains, spices, nuts, herbs, and medicinal plants. During the last few decades, it was found that cancer risk is decreased by having a diet rich in fruits, vegetables, green tea, and legumes and has led research to discover many plant constituents specially phytochemicals that might help in the protection against oxidative stress and blocking specific carcinogenic pathways.

Oxidative stress has been reported to be a major risk factor for cancer, and antioxidants have proved to possess cytotoxic potential effect in various cancer models, in vitro and in vivo. Although there are hundreds of synthetic chemicals that are currently used as a cancer chemotherapeutic agents, yet they have side effects to the normal cells. Therefore, it is essential to search for natural products that have antioxidants and anticancer properties. Natural plants contain phytochemicals that effectively inhibit cancer proliferation by scavenging free radicals, inhibit oxidative stress and thereby extending protective effects against cancer.

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In recent years the complementary and alternative medicine have gained greater emphasis; there are at least 1000 indigenous plants that possess medicinal properties for treating chronic human diseases, including cancer. These plants have the ability to prevent the risk of developing various forms of cancer and cancer treatment by modifying tumor behavior. Medicinal plants are important elements of indigenous medical system that have persisted in developing countries. Many of the botanical chemopreventions are currently used as potent anticancer agents; this chapter aims to present the antioxidant properties and chemopreventive effect of a wide variety of natural plants. The chapter summarizes the anticancer effects of phytochemicals as it exhibits in vitro and in vivo anti-proliferation, anti-metastasis, antiangiogenesis, anti-multidrug resistance, and autophagy regulation actions.

2 Antioxidant Properties of Natural Plants

Human used a wide variety of plants as treatment approximately 60,000 years ago [1]. Several scientific evidence have proven that oxidative stress induces the formation of lipid peroxides and other reactive oxygen species that play an important role in cancer pathogenesis [2]. Products of lipid peroxides result in the formation of highly reactive products such as malondialdehyde, which can bind to cellular proteins leading to pleiotropic effects and mutagenicity [3]. Several clinical studies suggested that various natural products are rich in phytochemicals and protect against oxidative stress insults and carcinogenesis [4, 5]. Phytochemicals are bioactive compounds present in plants where they are produced as secondary metabolites to protect themselves from several pathogenic agents. Most bioactive phytochemicals belong to one of five groups: polyphenols, carotenoids, alkaloids, nitrogen-containing compounds, and organosulfur compounds [6].

Oxidative stress insults increased oxidation of thiol (sulfhydryl) groups of different proteins, and subsequent proteins modification and inhibition of cellular antioxidant enzymes [7]. Serum thiol groups, including glutathione, are often diminished in subjects with different types of cancers [8, 9]. A large number of experimental and epidemiological studies have indicated that the reactive oxygen species contribute to organ injury in many systems [10]. As a consequence, different types of molecules, such as proteins, lipids, and nucleic acids, can be damaged, resulting in severe metabolic dysfunction, including lipid peroxidation, protein oxidation, membrane disruption, and DNA damage [11].

Plant products like vegetables, fruits, flowers, and grains are potential source of natural antioxidants and other phytochemicals [12]. The majority of antioxidants are phenolic compounds [13]. These antioxidants differ in structure like the number of phenolic hydroxyl groups and their location, causing difference in their antioxidative ability [14]. Antioxidants are capable to scavenge the free radicals causing reduction in oxidative stress caused by photons and oxygen [15]. Accordingly, they are responsible for the potent of antioxidant action of plants which are essential for optimal well-being [16].

Antioxidants act as the first line of defense against oxidative stress by inhibiting the formation of reactive nitrogen and oxygen species and prevent damage to biologically essential molecules like protein, DNA, and lipid [17]. Phytonutrients such as phenolic acids and flavonoids consider antioxidant and anti-inflammatory properties which can decrease the inflammatory process associated with chronic conditions like cancer [18]. Phenolic compounds are responsible for significant mechanisms of actions including scavenging of free radicals, blocking reactive oxygen species production, detoxifying enzymes, impacting cell cycle, suppression of tumors, apoptosis, modulation of signal transduction and metabolism [19]. There is strong scientific evidence for the protective effect of dietary intake of natural products and medicinal plants against human chronic diseases, including cancer [20]. Natural plants are rich in bioactive ingredients and are considered as the most widespread form of medication for a multitude of health problems in populations throughout the world [21]. These protective effects with potential health benefits are mainly due to the presence of phytochemicals [22]. Molecular mechanism-based cancer chemoprevention by phytochemicals seems to be vital in delaying or preventing the incidence of cancer [23].

3 Anticancer Properties of Selected Natural Products

Acridocarpus orientalis plant showed potential antioxidant activities [24]. Numerous studies have shown that *Allium cepa* or onion has sulfur-containing amino acid, S-methyl cysteine sulphoxide, which is shown to prompt powerful antioxidant activity. Studies indicated that this plant is rich in a constituent called diallyl trisulfide that inhibits growth of cultured human prostate cancer cells in association with apoptosis induction [25]. In cultured human prostate cancer cells, diallyl trisulfide treatment has been shown to cause cell cycle arrest, apoptosis induction, and transcriptional repression of androgen receptor. Furthermore, diallyl trisulfide treatment inhibited angiogenesis in human umbilical vein endothelial cells. Studies have provided novel insights into the molecular circuitry of apoptotic cell death resulting from diallyl trisulfide exposure in human prostate cancer cells [26–28].

Caralluma tuberculata possesses moderate cytotoxic activity on breast cancer and other cancer cells in vitro, which may indicate a source of activity in vivo of interest to future drug design [29]. *Caralluma* species are natural sources of a wide variety of pregnane glycosides, which induce caspase-dependent apoptosis in cancer cells [30, 31].

Carica papaya L. is a potent antioxidant and has an in vitro and in vivo protective effect against oxidizing agent in cancer experimental models [26, 27, 32]. Papaya peel extract is rich in phenolic contents that combat oxidative stress by increasing antioxidant enzymatic activities that are impaired during cancer pathogenesis [33, 34].

Curcuma longa plant has been commonly perceived in decreasing lipid peroxides and free radicals attack in cancer models [35]. In human cancer cell lines,

curcumin has been shown to decrease ornithine decarboxylase activity, a rate-limiting enzyme in polyamine biosynthesis that is frequently upregulated in cancer and other rapidly proliferating tissues. Numerous studies have demonstrated that pretreatment with curcumin can abrogate carcinogen-induced tumorigenesis in different models and organs [36]. The cell proliferation assay indicated that extracts from the *Curcuma longa* exerted anti-proliferative activity in cancer cells, the molecular mechanisms underlying this protective effect is that certain pro-apoptotic molecules, including caspase-3, checkpoint kinase 2, and tumor protein 53, exhibited increased activity in cancer cells, but when treated with the *Curcuma longa* extract, the cells exhibited an opposite effect [26, 27].

Dodonaea viscosa shows high free radical scavenging activity [37]. They are rich in naturally derived triterpenoid saponins (ginsenosides and saikosaponins) and steroid saponins (dioscin, polyphyllin, and timosaponin) that demonstrate various pharmacological effects against mammalian diseases [38].

Haplophyllum tuberculatum contains phenolic compounds as main phytochemicals which exhibit antioxidant potential properties [39]. In cancer cell line, CCRF-CEM, it has cytotoxic effects in a mechanisms involved cell cycle distribution, apoptosis, caspases activities and mitochondrial function [40].

Momordica charantia is rich in polyphenols and carotenoids and exhibits a wide range of biological effects, including anti-inflammatory, antiaging, anti-atherosclerosis, and anticancer [38]. It showed powerful DPPH radical scavenging activity comparing to vitamin E; it also exhibited enhanced iron chelating activity than vitamin E, but they were weaker than vitamin E in free radical scavenging, xanthine oxidase inhibitory, and anti-lipid peroxidation activities [41]. Some studies have reported that oral administration of the *Momordica charantia* juice or seed powder showed a significant reduction in oxidative stress [42].

Moringa oleifera trees grow well in Jamaica and their parts are popularly used locally for various purposes and ailments. Antioxidant activities in *Moringa oleifera* samples from different parts of the world have different ranges [43]. Extracts from the *Moringa oleifera* leaves, root core, and outer parts have protective activity against hepatocarcinoma and breast and colorectal cancer cell lines, as all extracts kill the different cancer cells with different ratios, suggesting its therapeutic use as a natural source of anticancer compounds [44, 45].

Moringa peregrine reduced radicals significantly and showed strong antioxidant activity; it is a tropical tree growing in southeast of Iran. All parts of this plant have nutritional uses and pharmacological activities [46]**.** All Moringa leaf and seed extracts showed pronounced antioxidant activities in a dose-dependent manner and the effects depend strongly on the solvent used for extraction. Extracts of both leaves and seeds of Moringa exhibit antioxidant potential by combating superoxide anion radicals suggesting that *M. peregrina* is a promising plant with antioxiant therapeutic effect [47, 48].

Oxalis corniculata is an important herbaceous and subtropical plant from the genus *Oxalis*, and has a therapeutic effect and medicinal uses like treatment for cancer [49]; this is based on the antioxidant properties of active compounds such as vitamin C, isoorientin, isovitexin, and swertisin [50]. Phytochemical studies of

Oxalis corniculata have shown the presence of a combination of oleic, linoleic, linolenic, stearic acids, palmitic acid, and tannins [51].

Phyllanthus emblica L. exhibited inhibitory activities against melanogenesis in a mechanism involving selective cytotoxicity to cancer cells with no or low toxicity to the normal wild-type cells [52]. Every part of this plant possesses high medicinal value, where the polyphenols found in *E. officinalis*, especially tannins and flavonoids, are key responsible elements for major bioactivities and pharmacological activities through various mode of actions including antioxidant, anticancer, and cytoprotective properties [53, 54].

Portulaca oleracea provides the basis for the therapeutic importance of studied plants as inhibitors of oxidative stress and antitumor cell proliferation based on its high content of bioactive compounds such as cinnamic acids, caffeic acid, alkaloids, cardiac glycosides, coumarins, flavonoids, glycosides, alanine, saponins, anthraquinone, catechol, and tannins [55, 56]. *P. oleracea* extract inhibits the growth of colon cancer stem cells and it may elicit its effects through regulatory and target genes that mediate the tumor formation in colon cancer stem cells [57].

Prosopis cineraria extract produced an increase in nonenzymatic antioxidants and enzymatic antioxidants [58]. This plant has potency to scavenge the cellular free radicals, mainly hydrogen peroxide, and the results showed that this plant extract had the maximum efficacy to inhibit lipid peroxidation and DNA damage and was found to be potent and possessed significant cytotoxicity towards Ehrlich ascites carcinoma tumor model [59].

Punica granatum peel extract protects against cancer diseases by combating reactive oxygen species generation in experimental cancer model [60]. Pomegranate (*Punica granatum*) is rich in polyphenols, particularly anthocyanins and tannins which have antagonistic interactions against cancer and used in dietary-based cancer chemoprevention and treatment.

Rubus occidentalis has a wide variety of polyphenolics, ellagic acid, sanguiin H-6, and flavonol derivatives with different phytonutrient profiles [61]. Numerous in vitro studies have confirmed the activity of this fruit extract against certain types of human cancers [62]. Bioactive compounds of berry have significant anticancer effects through various complementary mechanisms of action including the induction of metabolizing enzymes, modulation of gene expression, and their effects on cell proliferation, apoptosis, and subcellular signaling pathway [63]. In vitro evidence from different cancer models suggested that berry polyphenols may modulate cellular processes essential for cancer cell survival, such as proliferation and apoptosis [64].

Teucrium stocksianum is a natural herbicide with a strong antioxidant activity and high total phenolic content, and cytotoxicity and phytotoxicity assays indicated that it is rich in saponins, n-hexane, and chloroform fractions that might play a vital role in the treatment of neoplasia [65]. The plant extract also displayed marked phytochemical and antioxidant activity and produce substantial number of antioxidant potential properties [66]. Phytochemical composition of this plant are flavonoids, tannins, saponins, anthraquinone, steroid, phlobatannin, terpenoid, glycoside,

and reducing sugars which collectively have free radical scavenging properties against oxidative stress-mediated carcinogenesis [67].

Vaccinium myrtillus exhibited significant antioxidant capacity and is commonly used as an ingredient for the design of new food products or food supplements; it is rich in phenolic compounds such as anthocyanins from blueberry [68]. Several research studies indicate that this fruit is rich in bioactive compounds, including flavonoids, anthocyanin, β-carotenoids, vitamins, and phenolic acids, which protect DNA, and thus it has a therapeutic effectiveness during chemotherapy [69–71].

Zingiber officinale extract administration in animal cancer experimental studies had significantly reduced oxidative stress-induced cancer models [72]. The anticancer properties were ascribed to the free radical scavenging activity of *Z. officinale* and thereby combating oxidative stress-mediated carcinogenesis [73]. In silico investigation demonstrated that the synergetic effects of β-phellandrene with other compounds in *Z. officinale* might be responsible for its anticancerous activity [73].

Zizyphus spina-christi is a rich source of bioactive compounds with medicinal properties in chemoprevention of cancer by ameliorating the intracellular glutathione depletion as well as abrogating pro-apoptotic events associated with cancer [74]. The anticancer effect of *Ziziphus spina-christi* on breast cancer cells was investigated, and providing a scientific basis for its utility in traditional medicine [75]. The cytotoxic activity of *Z. spina-christi* extracts against the early stage of carcinogenesis in tumor cell lines is by preventing oxidative stress, and it can be concluded that *Z. spina-christi* is a good candidate for new cytotoxic chemopreventive agents [76].

4 Conclusion

Phytochemicals containing foods cause a decline in the risk of different types of cancers, and gained considerable recognition as a functional food in the modern era. Experimental studies and human clinical trials illustrated that natural products are rich in polyphenols isoflavones, flavanoid, catechins, carotenoids, and many other constituents that help in protecting against the deleterious impact of reactive oxygen species and its associated carcinogenesis. High intake of natural products counteract the oxidative stress-mediated carcinogenesis, and hence represent a therapeutic effectiveness during chemotherapy of cancer patients as supported by results of case-control studies. Natural products supplements in the diet represent a section of whole health program, along with an increased intake of vegetables and hence to help in the primary prevention of cancer initiation.

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