Review Article

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Potential of Dietary Polyphenols in Prevention and Treatment of Cancer

Renu Dayal*, K.P. Mishra**

Author Affiliation: *Institute of life Science, Lucknow. **Ex Bhabha Atomic Research Center, Mumbai & Professor Emeritus, BM International Research Center, Jain Vishva Bharati Institute (JVBI), Rajasthan, India.

Abstract

Polyphenols and flavonoids from natural products possess antioxidant properties which are known to prevent as well as treat cancer. Natural compounds from plant kingdom are non-toxic in a wide range of concentrations and are safe for long term usage. Many studies have demonstrated anticancer properties of many polyphenols and other antioxidants involving cell cycle modulation, transcription factor NF-κB and protein kinases. Research results from our laboratory have shown enhanced cytotoxic activity of a number of polyphenols, such as triphala, ellagic acid, curcumin, biochanin A and others in tumor cells in combination with radiation whereas normal cells were protected against the damage. The present paper gives a brief review of differential action of polyphenols in tumor and normal cells and outlines the mechanism of action through induction of apoptosis in oxidatively stressed cells. It is suggested that antioxidants drive cells to survival or death depending upon the level of homeostasis. Results point to clinical evaluation of some of these polyphenols for practical applications in cancer radiotherapy.

Keywords: Polyphenols; Cancer; Antioxidants; Oxidative Stress; Chemoprevention.

Introduction

There is increasing evidence to suggest that sedentary life styles, food habits, environmental changes produce adverse effects on human health [1-5]. Among them, stress related diseases like diabetes, coronary heart diseases and cancer pose major health issues to people around the world. It is reported that changing lifestyle in developing countries have worsened the situation of cancer prevalence [6]. Furthermore, recent reports suggest that obesity causes major risk factor for various types of cancer including oesophagus (adenocarcinoma), colo-rectum, breast (postmenopausal), endometrium and kidney [6-8].

Reprint Request: K.P. Mishra, 504, Neelyog Residency CHS Ltd, K-1, Pant Nagar, Ghatkopar(East), Mumbai–400075, Maharastra, India.
E-mail: mishra_kaushala@rediffmail.com

Research findings are in agreement that food habits and diet patterns are directly associated with cancer induction and progression. Pertinent to it, bioactive compounds from herbs and spices were investigated for disease prevention and management in wide range of concentrations which may exceed those commonly used in food preparations [9-15]. Reports have appeared suggesting that regular intakes of fruit, vegetables and whole grains are associated with reduced risk of chronic diseases including cancer [10,15,16]. Moreover, epidemiological studies suggest that high dietary intake of fruits, vegetables and whole grains are strongly associated with reduced risk of chronic diseases including cancer. WHO report of 2003 suggested convincing linkage between diet related factors and cancer prevalence. It has been found that fruits and vegetables showed preventive effect against cancers of oral cavity, esophagus, stomach and colorectum, while preserved and red

meat, salt-preserved foods and high salt intake, very hot drinks and foods probably increase the risk of colorectal, stomach, oral cavity, pharynx and oesophagus cancer respectively [17-18].The case control study conducted by Salem et al. (2011) suggests that total fat content increases risk of prostate cancer which was attenuated by the consumption of food rich in tomato and garlic content [19].

The therapeutic value of medicinal plant / herb lies in their bioactive compounds which possess specific physiological action in the human body. It is well established that herbs serve an important role in maintaining redox homeostasis that determines the fate of diseased cell. Furthermore, dietary antioxidants such as polyphenols, flavonoids, tannins derived from herbs and spices are known to prevent stress related adverse health consequences [13,20,21]. Polyphenols are secondary metabolites of plants, primarily occurring in conjugated forms with one or more hydroxyl (-OH) groups attached to benzene ring. Epidemiological studies on polyphenol consumption and human cancer risk suggest the protective effects of certain food items and polyphenols [13,22,23]. Polyphenols and other bioactive compounds are reported to exert their effects by scavenging oxygen free radicals and inhibiting the lipid peroxidation and protecting cellular macromolecules such as DNA from oxidative damage [11,12,14,24-26]. Commonly, polyphenols are recognized as naturally occurring antioxidants but they may act as pro-oxidants catalyzing DNA degradation in the presence of transition metal ions such as, iron and copper [27-29]. Antioxidants derived from herbs have potential to inhibit and / or influence pathways which regulate cell division, cell cycle proliferation, apoptosis and detoxification [11,15,21,30,31]. It has been reported that herbals like Triphala exhibit differential toxicity to normal and tumor cells [11,12]. The molecular mechanism is reported to involve differences in their ability to induce apoptosis in normal and tumor cells with and without irradiation. It is known that a number of antioxidants are safe across broad range of intakes; doses beyond tolerable limits of cellular environment serve as pro-oxidants to them. Culinary herbs and spices generally serve as antioxidants (AOs) but may serve as pro-oxidants at higher concentrations. It is important to be noted that herbs and spices are generally recognized as safe at their minimum effective concentration normally available in foods and herbal preparations.

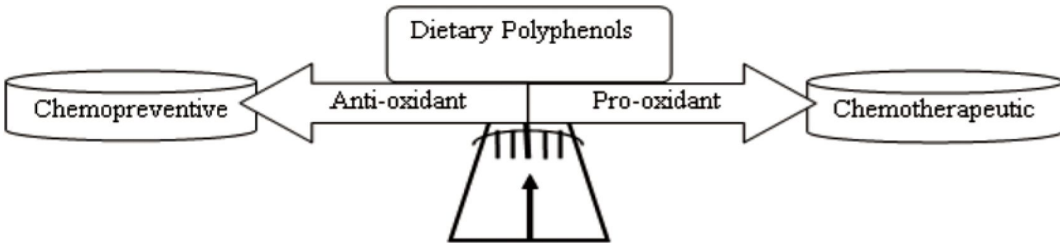

Fig. 1: Cartoon image depicting the delicate balance between anti-oxidant and pro-oxidant behavior of dietary polyphenols

Research findings especially reports from our group have demonstrated differential roles of many herbal antioxidants and their formulations in cellular studies [11,12,25,32-35]. The same drug that was involved in sensitization of tumor cells was found to be protective or inactive towards healthy cells together with radiation. It is to be noted that herbals possess pluripotent activity, display synergistic mode of action, produce selective effect on the target and also have low toxicity and are cost effective. Our publications have shown that many bioactive compounds of natural origin rich in polyphenols, flavonoids, and alkaloids possess radiosensitizing and radioprotective properties [11,12,33,34,36-41].

This review is aimed to summarize the chemo-preventive properties of some readily available dietary polyphenols such as gallic acid, curcumin, betulinic acid against cancer as observed in cell culture models. The major focus of the present review is to present the molecular mechanisms of chemo-preventive and therapeutic activities of dietary polyphenols with particular emphasis on their ability to control intracellular signaling cascade considered as relevant targets in a cancer preventive approach.

Experimental Studies and Proposed Mode of Action

Cancer cells are consequence of shutting down of built-in apoptosis and therefore, it is more relevant to search for compounds involved in regaining apoptosis mechanisms for bringing back normal cellular status. Results have shown that bioactive compounds and their derivatives present in different diets were involved in protection of normal cells as

antioxidant against oxidative damage. On the other hand, the same compound behaved as pro-oxidant inducing oxidative damage, membrane alterations, cell cycle arrest leading to apoptosis in transformed / cancer cells. Their molecular mechanism of action is reported to involve differences in their ability to induce apoptosis in normal and tumor cells with or without irradiation. AOs have ability to recognize the cytosolic redox status of cells which is known to be different in normal and tumor cells. As discussed earlier, antioxidants are found to upregulate endogenous defense machinery in normal cells and underlying mechanisms of action include cell cycle arrest, alterations in survival signaling, apoptosis and regulation of detoxifying enzymes.

In what follows we provide results of our studies on some polyphenols on normal and tumor cells in combination with gamma radiation. Also, references are cited from other studies where required. Results have allowed to conclude that differential action of polyphenol compounds on normal and tumor cells consist in the cytosolic redox status of respective cells. Involvement of signaling mechanisms is noticed in the manifestation of toxic cellular responses to drug or combinations of drug and radiation.

Triphala Enhances Tumor Radiotoxicity

Triphala (TPL) is an Ayurvedic herbal formulation consisting of equal proportions of three myrobalans, namely, Amalaki (*Emblica officinalis*), Bibhitaki (*Terminalia bellirica*), and Haritaki (*Terminalia chebula*). Results from our studies have demonstrated differential toxicities to normal and tumor cells. It was found that triphala along with gamma irradiation produced radio-sensitization to breast cancer cell lines *in vitro* [11,12]. It was further found that normal mouse hepatocytes and spleen cells were unaffected at concentrations of triphala that were toxic to the breast cancer cell line, MCF 7 . It was concluded that TPL enhanced radiotoxicity of cancer cell lines but spared normal cells primarily due to differences in the induced reactive oxygen species (ROS). More recently, Sharma et al. (2011) reported that TPL up-regulated glutathione in normal cells leading to prevention of stress mediated peroxidative damage in endoplasm [26]. Also, gallic acid (GA; 3,4,5-trihydroxybenzoic acid), an important stress buster antioxidant and anticancer agent is reported present in Triphala. In another study conducted by Russel and coworkers (2011), it was found that combined treatment of GA with flutamide induced greater toxicity to prostate cancer cells than either of the compounds alone with concomitant low toxicity to normal cells [32]. Lu et al.(2012) have reported that chebulinic (CI) present in TPL can significantly and specifically inhibit vascular endothelial growth factor-A (VEGF) induced angiogenesis by suppressing VEGF receptor-2 (VEGFR-2) phosphorylation [43].

Ellagic Acid Sensitizes Tumor Cells to Radiation

Natural antioxidant, Ellagic Acid (EA) is abundant in berry and nut fruits like strawberries, raspberries, wolfberries, grapes ,walnuts, pomegranate [44], oak-aged red wine, peach and other plant foods.

Extensive studies were carried out in our laboratory on the combined effects of radiation and ellagic acid (EA) both *in vitro* and *in vivo* on normal and tumor cells. Interestingly, human cervical cell line have shown increased ROS generation as a function of radiation dose [37]. Ellagic acid mediated increased cytotoxicity of tumor cells was found associated with the increased intracellular ROS level. In contrast, EA protected significantly the normal splenic lymphocytes against radiation- induced oxidative stress. *In vitro* and *in vivo* studies have further demonstrated anti-cancer activity on many cancer cells such as cervical, oesophagus, breast, colon, prostate and pancreas [45-53]. It was suggested that EA arrested cell-cycle in S phase, stimulated apoptosis via FAS-independent and caspase 8-independent pathway in human colon cancer cell line and protected DNA damage in normal colon cells line [45]; induce G0 / G1 arrest, promoted ROS and Ca^{2+} production [51]. It possess the ability to reduce endogenous oxidative DNA damage by DNA excision repair protein (ERCC5) and DNA ligase III (DNL3) [46]. In recent studies, EA mediated apoptosis via mitochondrial pathway in human neuroblastoma cell line was suggested to be dose and time-dependent [52]. Vanella et al. (2013) showed antiproliferative and pro-differentiation properties of EA inducing DNA damage in cancer cells [49,50]. EA is reported to stimulate apoptosis and decrease proliferation in human pancreatic adenocarcinoma cells through DNA fragmentation, mitochondrial depolarization, release of cytochrome, and the downstream caspase activation in pancreatic cancer cells. Furthermore, it is reported to block the NF-κB binding activity in dose-dependent manner [47]. Malik and coworkers (2011) reported dose-dependent inhibition of cell growth and apoptosis in human prostate cancer cells. Underlying mechanism involved cleavage of poly (ADP-ribose) polymerase (PARP), decreased levels of anti-apoptotic protein Bcl-2 and up-regulated pro apoptotic protein Bax [48]. Recent investigation from our research group showed that EA together with

gamma radiation induced apoptosis via upregulation of ROS, calcium levels and caspase-3 activity resulting in decreased mitochondiral potential [53].

Eugenol Acts as Prooxidant as Well as Antioxidant

Eugenol (4-Allyl-2-methoxyphenol) is an active component of Indian medicinal plants, clove (*Syzygium aromaticum*) , tulsi (*Oscimum sanctum*) and other aromatic plants like cinnamon, bay leaves. It has been demonstrated that modulation of phytochemical properties of model as well as cellular membranes by inclusion of antioxidants like eugenol caused inhibition of membrane oxidative damage. Results from our studies demonstrated significant enhanced bilayer rigidity in irradiated phoshpholipids liposomal as model membrane due to free radical mediated reaction of lipoxy radicals [36,38].

It was found that eugenol displays both prooxidant and antioxidant activities at different doses. It enhanced H_2O_2 induced cytotoxicity resulting in damage to cell membrane and DNA in resistant cancer cell line [35]. The anti-cancer and chemopreventive mechanisms of eugenol involved decreased glutathione level and increased lipid peroxidation in breast cancer cells accompanied with cell shrinkage, membrane blebbing , intracellular non protein thiol depletion and induces apoptosis via DNA fragmentation [54,55]. Arif et al.(2011) demonstrated strong synergistic interaction between eugenol- gemcitabine, which may enhance the therapeutic index of prevention and / or treatment of cervical cancer [21]. Their results suggest that eugenol exerts its anticancer activities *via* induction of apoptosis and anti-inflammatory properties with significant downregulation of Bcl-2, COX-2, and IL-1β on treatment with eugenol [21].

Curcumin Acts as Tumor Radiosensitizer

Turmeric (*Curcuma longa*) is one of the most popular dietary ingredient of Indians. Curcumin (1,7-bis (4-hydroxy 3-methoxy phenyl)-1,6-heptadiene- 3,5-dione) is one of three curcuminoids of turmeric, a highly promising natural antioxidant with multiple mechanisms to prevent cancer [56]. Curcumin modulates multiple molecular pathways involved in the complex carcinogenesis process to exert its chemopreventive effects through several mechanisms: promoting apoptosis, inhibiting survival signals, scavenging reactive oxidative species (ROS), and reducing the inflammatory cancer microenvironment [56-58]. This polyphenol acts as a radiosensitizer – in prostate cancer by down regulation of pro-survival factors. Studies in our laboratory showed that exposure of phenolic compound curcumin prior to irradiation decreased breast cancer cell (MCF-7) survival to 38% as compared to 52% by radiation alone. Interestingly, treatment of MCF-7 cells with curcumin caused significant enhancement of gamma radiation-induced cell death, potentially mediated via ROS independent pathway [39]. Studies have proven that various bioactive components of turmeric sensitize tumor cells towards radiation exposure by upregulating apoptotic gene with simultaneous downregualtion of survival factors like NF-kB, Cox-2, Akt, STAT3, anti-apoptotic and multidrug resistant proteins [25,59-64].

Nigella Sativa (Ns) *Protects Cells Against Oxidative Damage*

Common Asian spice *Nigella sativa* (Black Cumin) also known as black seed, kalonji appears to be effective at doses used to season food products. The results from our laboratory showed that the macerated extract of NS seeds protected the liver, spleen, brain and intestines both in normal as well as tumor bearing mice [33-34]. This study concludes that macerated extract of NS seeds has protective effects against radiation-induced damage and biochemical alterations which could be attributed to the ability to scavenge free radicals and its antioxidant properties. The results obtained from the different experimental systems suggest the radioprotective ability of ethanol extract NS involving prevention of radiation-induced oxidative damage [20]. Furthermore, significant free radical scavenging and protection against DNA damage in cell free systems was found. Parallel investigations by other researchers demonstrated significant anti-cancer activities against a number of cancer cells such as breast cancer, hepatic, cervical squamous carcinoma cells, hence support our findings [65-69]. Alenzi et al. (2010) demonstrated up-regulation of antioxidant, indicated a potential clinical application to minimize the toxic effects of treatment with anticancer drugs [65]. Majdalawieh and co-workers demonstrated modulating effect of NS seeds in splenocyte proliferation, Th1 / Th2 cytokine profile, macrophage function and NK anti-tumor activity [66]. Ng et al. (2011) showed that thymoquinone from *N. sativa* efficiently eliminated SiHa cells via apoptosis with down-regulation of Bcl-2 protein [67].

Cytoprotection and Cytotoxic Activity of Helicteres Isora (HI)

H. isora is a tropical south-east Asian shrub available throughout India. The twisted shape of the

fruit resembles that of a deer's horn. Significant presence of polyphenols in fruits of HI [70], though hardly been investigated for chemotherapeutic property prompted us to investigate anticancer activity of fruits (results under communication). Aqueous and alcoholic extracts from fruits and bark of HI are reported to display antioxidant activity such as free radical scavenging [70-73]. Pradhan et al.(2008) demonstrated cytoprotective role of methanolic extract of fruits of HI alongwith antitumor activity [72]. Raman et al. (2012) reported anticancer activity and presence of antioxidants in acetone extract of fruits of HI [73].

Tumor Radiosensitization by Biochanin A

Biochanin A (BCA; 5,7-Dihydroxy-4'-methoxyis oflavone) is a major dietary isoflavone of soy cabbage, alfalfa and red clover, that possess chemopreventive properties. One of our new study describes positive radiosensitizing effect of flavonoid, BCA, on the growth of radioresistant human colon cancer HT29 cells *in vitro*. We found that combined treatment yielded an additive increase of caspase-3 in these radioresistant colon cells. Treatment combined with irradiation caused significant decrease of cell proliferation along with substantial increase of ROS, lipid peroxidation and mitochondrial membrane potential. Furthermore, it was also found that combined treatment yielded an additive increase of caspase-3 in these radioresistant colon cells [41]. Recent investigations by many other researchers have shown positive results of BCA against drug resistant factors of prostate , pancreatic, breast cancer cells. BCA overcame Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-resistance by engaging both intrinsic and extrinsic apoptotic pathways and by regulating the NF-êB activity [74]. Sehdev et al.(2010) found that BCA can selectively target cancer cells and inhibit multiple signaling pathways in HER-2-positive breast cancer cells [75]. Kole at al.(2011) have shown that anti-proliferative and anti-inflammatory activities of BCA was mediated by the inhibition of iNOS expression, p38-MAPK and ATF-2 phosphorylation and blocking NF-kB nuclear translocation [76].

Moreover, BCA is found effective in reducing pancreatic cancer cell survival by inhibiting their proliferation and inducing apoptosis by reducing their colony formation ability via dose-dependent apoptosis and inhibiting activation of Akt and MAPK [77].

Anti Cancer Effects of Betulinic Acid

Betulinic acid (BA; 3β, hydroxy-lup-20(29)-en-28-oic acid), a natural triterpene abundant in the outer bark of white birch trees, *Betula alba* L and other tree species . There are many evidences that indicate BA as a potent antioxidant source possessing anti-cancer activity . According to Simone Fulda, mitochondrion-targeted agents such as betulinic acid hold great promise as a novel therapeutic strategy in the treatment of human cancers [78]. Betulinic acid is reported to inhibit colon cancer cell and tumor growth and induces proteasome-dependent and-independent down regulation of specificity proteins (Sp) transcription factors[79]. In one of their recent investigations Mertens-Talcott and co-workers reported that BA decreases ER-negative breast cancer cell growth *in vitro* and *in vivo*. This anticancer effect of BA was at least in part based on interactions with the microRNA-27a-ZBTB10-Sp-axis causing increased cell death [80]. In one of our recent investigations positive cytotoxic effect of BA on breast cancer cell lines was observed [42]. Our results have shown that anti-tumor activity of BA is not restricted to melanoma and neuroectodermal tumors but it also causes cytotoxicity in breast cancer cells. Treatment MCF-7 and T47D cell lines with BA resulted in a dose dependent inhibition of cell proliferation and induction of p53 independent apoptosis. Furthermore, the induction of apoptosis also showed an alteration in membrane permeability, encompassing the role of membrane damage in BA induced apoptosis [42]. In another report by Yi et al. (2014) hepatoprotective role of BA was demonstrated with improved tissue redox system and decreased lipid peroxidation [81].

Perspectives on Polyphenols with Relevance to Cancer Therapy

Development of diet-derived constituents is one of the major goal in prevention of stress related diseases such as for cancer chemoprevention, cardiovascular disease, diabetes. Various studies have suggested that dietary polyphenols are more than just antioxidants. They have multiple biological functions including anticancer effects. A popular belief is that dietary polyphenols possess anticancer property since they are antioxidants that are free radical scavengers and regulate redox balance essential to maintain appropriate balance between cell proliferation and death. They are recognized as naturally occurring antioxidants but may act as pro-oxidants catalyzing DNA degradation in the presence of transition metal ions such as copper [27-29]. The ability to generate ROS or binding and cleavage of DNA by dietary polyphenols in presence of transition metal ions are similar to many conventional anticancer drugs [21,82,83]. A well

recognized anticancer activity of dietary polyphenols is DNA fragmentation mediated apoptosis. It is assumed involve mobilization of intra- and extra-cellular copper [30]. A report from Khan et al.(2012) suggested DNA cleavage by resveratrol and Cu^{2+}, where it was found that resveratrol forms a complex with Cu^{2+} reducing it to Cu^{1+} with formation of another oxidized species of resveratrol [30].

Polyphenols inhibit cell growth, by inducing cell cycle arrest and / or apoptosis; inhibit proliferation, differentiation, inflammation, angiogenesis, and / or metastasis; and exhibit anti-inflammatory and / or antioxidant effects [14,31,56,84]. Moreover, as chemopreventive agents, polyphenols have been reported to hinder with cancer initiation, promotion and progression [14,15, 56]. Henceforth, the probable mode of cytoprotection and mechanisms associated with their biological effects includes (i) antioxidant and free radical scavenging activity (ii) trapping of activated metabolites of carcinogens (iii) prevention of mutagenicity and genotoxicity (iv) Inhibition of biochemical markers of tumor initiation and promotion (v) Differential role of detoxification enzymes. Our previous research findings are accordance with the proposed hypothesis. Increasing body of scientific evidence developed over the years has demonstrated the potential role of antioxidants in both prevention of healthy cells and killing of diseased cells.

Taken together, it can be said that, dietary polyphenols as antioxidants usually functions in protective mode. Plant polyphenols are important components of human diet and as antioxidants a number of them are considered to possess therapeutic property against many types of cancer. In recent years, a large number of studies have attributed a protective effect to natural food, herbs and spices containing these compounds against cancer and other stress related diseases [13]. Epidemiological studies concerning polyphenol consumption and human cancer risk suggest the protective effects of certain food items and polyphenols [13,22,23]. The pro-oxidant activity in curative mode activity is most prominent under *in vitro* conditions such as at a high pH in the presence of high concentrations of transition metal ions and oxygen molecules. They possess pro-oxidant activities both *in vitro* and *in vivo*, that may contribute to some of their biological properties such as antioxidant, pro-oxidant and anticancer effects [13,22,84]. Reports have shown that the phenol ring (ring B- in particular) of polyphenols causes free radical generation, oxidation of endogenous enzymes such as glutathione [21,24,85]. For instance, dietary polyphenol quercetin contains a catechol B ring that is oxidized by peroxidases to quinone with subsequent reaction with glutathione forming quercetin glutathionyl byproducts [24,85].

Conclusion

We have shown that several herbal compounds in combination with ionizing radiation enhance tumor cell killing and act as radiosensitizers while leave normal cells unaffected or even cause protection to them. It is suggestive that the differential behavior of the studied bioactive compounds is due to multiple mode of actions at different cellular targets under different cyotosolic status. It has been found that cytotoxic action was induced by upregulating reactive oxygen species thus disturbing the antioxidant status of cancer cells. The data provided herein provides a good scientific rationale for undertaking clinical trials of above mentioned herbal drugs. Reasonable amount of these plants and their byproducts are safe across a broad range of dose limits and can be consumed as dietary supplements.

Conflict of Interest

Declared None

References

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