Review

Ellagic Acid: A potent Radio-sensitizer in Cancer Radiotherapy

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Abstract:
The cytotoxic effect of radiotherapy of cancer is limited due to commonly observed radio-resistance in the clinic. It is, therefore, necessary to develop new strategies to enhance the radiosensitivity of tumor cells by combining therapeutic drugs with optimized radiation doses to improve the treatment outcome. Over the years, research has gained momentum in studying various herbal drugs that have the potential to sensitize tumor cells to ionizing radiation. Herbal drugs possess the property of non-toxic doses to higher concentrations and thereby minimize the undesirable side effects. Our lab recently reported the combined effects of radiation and ellagic acid (EA) in generation of increasing ROS as a function of radiation dose in HeLa thereby exhibiting the radiosensitizing effect. This article reviews the mechanism of action of EA involving ROS, cell cycle arrest, apoptosis and activation of signaling molecular cascade as observed in radiosensitization of some tumor cell lines. These studies suggest its potential usefulness in clinics for improving cancer radiotherapy which works by the mechanism of increasing the oxidative stress through generation of ROS in cancer cells.
Keywords: Radiosensitiser, Cancer, Radiation therapy, Ellagic Acid

Introduction

Cancer therapy still depends on ionizing radiation as one of its most effective tools. Ionizing radiation works by inducing damage not only at the molecular, cellular, tissues and organ system but also at the whole body system either directly or indirectly. A basic phenomenon of reactive oxygen species and reactive nitrogen species formation takes place when a biological system is exposed to radiation. These reactive species formed have a potential to damage DNA, proteins, lipids; including the plasma membrane (1). Lately, clinicians have commonly observed occurrence of tumors either being poorly responsive or even non-responsive to therapeutic drugs and radiotherapy thereby limiting cancer treatment. Thus it becomes a prime responsibility of researchers to embark on active research in providing multimodality treatment involving radiotherapy and systemic drugs Novel systemic

treatment choices also include immunotherapy, and are no strict chemotherapeutic agents. Hence logical strategy would be to augment the tumor cell cytotoxicity but concurrently protecting normal cells from the adverse effects. This has led to remarkable awareness among researcher in identifying herbal compounds which would induce apoptosis in tumor cells but exhibit a protective effect on normal cells when used in combination with radiotherapy. The success of this strategy would pave way for improvement of cancer radiotherapy. Certain naturally occurring compounds which are a part of the human diet and are devoid of toxicity within certain doses are of major interest to be considered as a choice for radiation therapy (2). This article aims to summarize natural products as potential radiosensitizer with an emphasis to EA.

1. Radiomodulators: Herbals

Polyphenols in fruits and vegetables exhibit cytotoxic effects in various pathological conditions including cancer. Since these polyphenolic compounds show diverse properties like anti-proliferative, pro-oxidative, anti-oxidative, immune simulative, antimicrobial, anti-inflammatory, etc. they are receiving more attention as radioprotectors and radiosensitizer than those currently available drugs (3). These natural compounds have a long history of safety in terms of traditional usage in humans for several years, their holistic mode of action and countering of the toxic effects of certain constituents, synergism and novel source of new drugs etc. have been considered worthy as radiomodulators.

Radiosensitiser are compounds that when combined with radiation would achieve greater tumor inactivation than would have been expected from the additive effect of each modality (4). They are also defined as agents that do not exhibit a significant therapeutic effect of their own, but act to enhance the therapeutic effect of radiation (5).They are believed to work at different levels of cellular phases and one of the suggested mechanisms of treating cells with the particular radiosensitizer before irradiation probably consists in synchronizing them in sensitive cell cycle phase. Studies have shown presence of compound during irradiation amplifies the effects by multi-factorial mechanisms including toxic reactions of free radicals (6-11). Natural products used as radiosensitizer when included after radiation show their effect by inhibiting repair of the radiation-induced lethal and sub-lethal damage apart from down-regulation of numerous pro-survival factors (2).

1.1 Herbals and apoptosis

Compounds to be considered as potential adjuvants in radiotherapy should indicate a strong mechanistic rationale for a differential response between tumor and normal tissues. Lethal properties of ionizing radiation can be enhanced by the use of radiation sensitizers when administered in conjugation with radiation therapy. They upsurge radiosensitivity without being inherently toxic and give rise to substantial increase in the radiation sensitivity of neoplasm over normal tissues. Much of the laboratory work which has been carried out in vitro has shown that many herbal compounds act as radiosensitizer (7-10). Their practical approach depends on the exploitation of the difference between the tumor cells and normal cells. Hypoxic cells have been seen in many tumor cells which are resistance to lethal effects of ionizing radiation and so they prove to be a potential barrier for the success of radiotherapy. Hypoxia selective radiosensitizer can be exploited in radiotherapy as they have the potential to augment sterilization in solid tumors that have acquired resistance due to hypoxia and have expanded their vascular resource. If toxicities are not additive, combinations of radiosensitizers and radioprotectors might prove more effective than either individual approach. It is the need of time to find out newer, better and

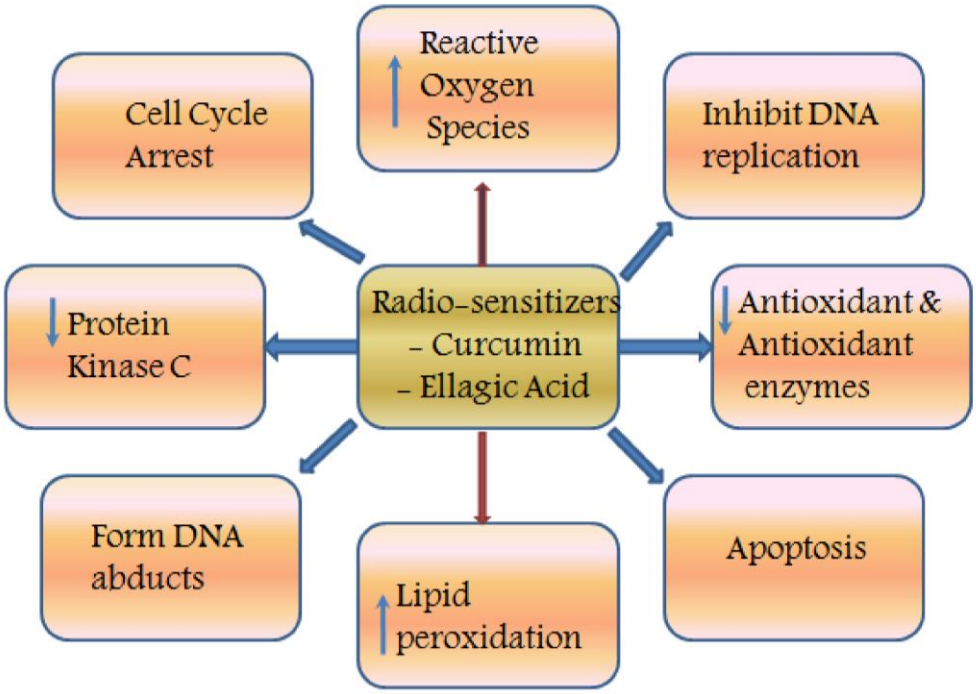

Figure 1: A summary of various mechanisms to boost radiosensitization in cancer cells using herbal radiosensitizer.

When given in combinations with radiation natural compounds like curcumin, ellagic acid etc. demonstrate cytotoxic effect in a variety of cancers by increasing ROS, lipid peroxidation , arresting the cells in a particular phase of the cell cycle, inhibiting DNA replication and repair, decreasing the antioxidant enzymes etc. eventually leading to apoptosis.

efficient compounds in a large amount as good scientific data on clinical trials have accumulated during the past few years. This would definitely lead in the deeper understanding and role of radiosensitizer along with its benefits in clinical radiotherapy. The need today is to unravel the specific mechanism of action of the various bioactive compounds and understand how they act in combination with radiation.

1.2 Rationale of herbal radiosensitizer

Radiosensitizing in vitro and invivo by plant polyphenols has been recently documented for their effects on tumors (12-16). Some of the natural products that can be used as radiosensitizer are resveratrol from *Vitis vinefera*, withafirein A from *Withaferin somnifera*, taxol from *Taxus bataccca*, ginestein from soybean etc. Some whole extracts of plants like *Azardiracta indica, Tinospora cordifolia* etc. have also shown the radiosensitizing effects. These compounds when combined with radiation treatment show an additive effect in tumor cell killing and/ or inactivation thereby were augmenting the therapeutic effect of radiation treatment (4, 5). Figure 1 elucidates mechanisms that enhance the cancer cell radiosensitivity when herbal compounds are used as radiosensitizers in cancer radiotherapy. A flavone, Flavopiridol exhibits radiosensitizing effect on malignant glioma cells (17). Gossypol from gossipium species results in regression of human prostate cancer (18). Kasten

Table1: List of herbal radiosensitizer and their mechanism of action on various cancers

Herbal compound	Mechanism of Action	Cancer Category	Cell line	Reference
Curcumin	• Inhibits growth • Downregulates prosurvival factors	Prostate cancer	LNCaP	(20)
EA	• Enhances radiation mediated oxidative stress • Decreases antioxidant enzymes	Cervical Cancer	HeLa	(6)
Caffeic acid	• Depletes Glutathione • Inhibits NF-kB activity	Colorectal adenocarcinoma	CT26	(7)
Sesamol	• Decreases GSH, SOD, GPx • Increases lipid hydroperoxides	Cervical Cancer	HeLa	(57)
Diospyrin	• Regulates genes of cell cycle & apoptosis • Downregulates p53, p21	Breast cancer	MCF-7	(8)
Triphala	• Increases tumor cell killing	Breast cancer	MCF-7; T47D	(9)
Tocopherol Succinate	• Decreases cell viability • Increases ROS generation • Changes in plasma membrane fluidity	Breast cancer	MCF-7	(10)
Betulinic Acid	• Increases cell cytotoxicity of radio resistant cells	Head and neck cancer	SCC9 ; SCC25	(55)
	• Induces radiosensitivity in glioma cells under hypoxia	Malignant glioma	251MG ; U343MG	(56)

pisula showed that radiosensitization of tumor cells is due to compromised double strand break repair and not due to enhanced apoptosis (19). Curcumin renders radiosensitizing effect by inhibiting the growth of PC-3 (human prostate cancer cell line) cells lines and down-regulating the pro-survival factors which are induced by radiation(20). EA on a similar lines has shown to enhance the radiation mediated oxidative stress and the consequent cytotoxicity in tumor cells by decreasing the antioxidant enzymes like SOD, glutathione peroxidase and catalase (6). Table 1 lists few herbal radiosensitizers with their mechanism of action.

2. Ellagic acid (EA)

EA (Figure2) is a plant-derived polyphenol, possessing antioxidant, antiproliferative, and

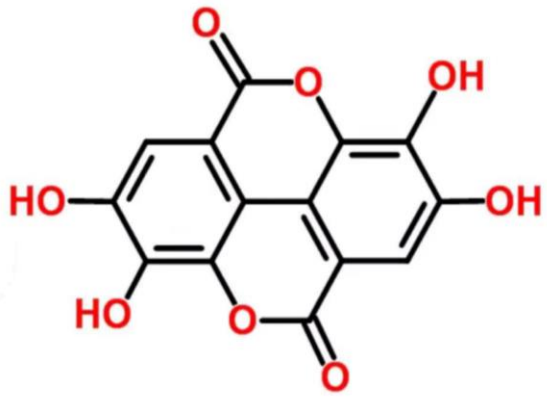

Figure 2: Structure of Ellagic Acid
Ellagic acid is a natural antioxidant found in strawberries, raspberries, blackberries, and walnuts etc. is known to exert strong anti- cancer, anti-proliferative and antioxidant activities.

antiatherogenic activities. Plants produce EA to protect themselves from microbiological infection and pests. EA has also been said to reduce heart disease, birth defects, liver problems, and to promote wound healing. In plants, ellagic acid is present in the form of ellagitannin, which is EA bound to a glucose molecule. It is usually present in the form of hydrolysable tannins called ellagitanins- esters of glucose with hexahydroxydiphenic acid-that when hydrolyzed yield EA (21, 22). It is found in raspberries, strawberries, cranberries, walnuts, pecans, pomegranates, and other plant foods. When raspberries, strawberries, and pomegranates are freeze-dried they yield the highest levels of EA. Extracts from red raspberry leaves or seeds, pomegranates, or other sources are said to contain high levels of EA and are available as dietary supplements in capsule, powder, or liquid form.

EA seems to possess some anti-cancer properties which have been seen in a variety of cells and tissues like breast, liver, lung, colon etc. (23). EA activates various signaling pathways, including apoptosis, protection from oxidative DNA damage, or LDL-oxidation and alteration of growth factor expression, as well as through the expression of p53, NF-kB, and PPAR family responsive genes (12). It can act as an anti-oxidant, and has been found to cause cell death in cancer cells invitro. In other laboratory studies, EA seems to reduce the effect of estrogen in promoting the growth of breast cancer cells in tissue cultures. There are also reports that it may help the liver to break down or remove some cancer-causing substances from the blood.

EA from red raspberries causes growth cycle arrest of cancer cells, thus inhibiting cell division (mitosis) and cellular proliferation. It also prevents the destruction of HPV oncogenes (genes responsible for cancer induction) in cervical cells. These genes are regarded as the safeguard of normal cellular division, and which when inactivated results in abnormal cell division/proliferation. In vitro and invivo research has shown that EA may slow the growth of some tumors caused by certain carcinogens. It prevents the binding of carcinogens to DNA and strengthens connective tissue, which may keep cancer cells from spreading. It has the ability to inhibit mutations within a cell's DNA. Furthermore, it is considered to be a cancer inhibitor which has the ability to cause apoptosis in cancer cells.

Dr. Nixon (47) examined the ability of EA to prevent colon and cervical cancers from developing. His research and findings indicate that EA can effect in different ways as mentioned below.

a) Cancer causing mutagens in serum can be detoxified when EA activates the detoxifying enzymes present in the liver.
b) Binding the carcinogens to DNA/abduct formation can be prevented by EA.
c) Highly destructive oxygen free radicals can be scavenged and cleared by antioxidant property of EA.
d) EA stimulates the immune system to destroy cancer cells.
e) EA induces apoptosis in cancer cells

2.1 EA induced apoptotic radiosensitivity

Our group investigated the potential of EA as a radiosensitizer in HeLa cells. A significant increase of 2.5 fold in ROS was observed when HeLa cells were treated with increasing concentration of EA with different doses of γ- radiation (1-6 Gy). An additive effect was observed in the generation of ROS. Percentage cell viability significantly decreased by 46% in 24 hrs in vivo. The antioxidant enzyme system was also drastically affected i.e. SOD levels decreased by 62%, catalase by 52% and GSH-Px by 52% in tumors aspirated from mice subjected to the combined treatment of radiation and EA. Also, the GR levels decreased by 26%.The mitochondrial potential also reduced by 37% in the mice treated with radiation and EA in vivo. Therefore, EA can be said to be a pro oxidant invitro at concentrations at 100µmol/l in HeLa cells and generation of ROS increases with increasing concentration of EA. It can be concluded that EA enhances radiation-induced oxidative stress and cytotoxicity *in vitro* in HeLa cells and *in vivo* in Ehrlich Ascites Carcinoma transplanted Swiss mice (6).

In HeLa cells, the magnitude of superoxide's generation was found substantially higher than in cells either treated with radiation or EA alone. As compared to control the SOD levels decreased by 30% and GPx decreased by 47%. The p53 protein which is a pro- apoptotic protein was seen to be unregulated in HeLa cells treated with both EA and radiation compared to cells treated with either EA or radiation. HeLa cells also showed elevated Caspase-3 activity after 24 h when treated with EA and radiation (13). Based on the above finding a model of effect of EA and/ or radiation is shown (Figure3).

2.2 EA and cancer cells

In MOLT-4, a human leukemic cell line, EA synergistically with Quercitin enhanced apoptosis (14, 24). Lansky EP et al demonstrated that EA acts against human PC-3 prostate cancer cells exhibiting anti- tumor activities (15). Also, at Louisiana State University Researchers showed that EA exhibited selective toxicity and apoptosis induction in cell lines like in MCF-7, Hs 578T, Caco-2, DU 145 and human prostate cancer cells. The mode of action of EA was found to be linked with decreased ATP production that is vital for the survival of cancer cell. Mutation defensive properties in rat esophagus against the mutagenicity of the nitrosamine N-nitrosomethylbenzylamine (NMBA) were observed by de Boer JG et.al. at University of Victoria, Canada(25). EA induced cell cycle arrest at the G1 phase in 48 h and subsequently lead to apoptosis in 72 h in T24 human bladder cancer cells in vitro (26, 27).

2.3 EA as radiosensitizer

One of the commonly reported mechanisms of radiosensitization is that of enhanced generation of ROS and RNS. The final cellular response is affected by the transient surge of radiation-induced ROS/RNS. The incidence of this is strongly attributed to the interaction of radiation with water molecules in the biological system to produce a variety of ROS and RNS. It has been estimated that about 70% of cell injury is caused by hydroxyl radicals who further leads to activation of pro-inflammatory factors both *in vitro* and *in vivo,* lipid peroxidation, DNA and protein oxidation etc. (28-33). ROS generators like diospyrin and plumbagin and β-lapachone (34-36), are pro- oxidants and therefore, can induce the apoptotic pathways in tumor cells by damaging their DNA, depolarization of the mitochondria etc. Maytansinol and vinca alkaloids augment radiation effect by interfering with the microtubules and thereby inhibiting tumor proliferation (37). Similarly flavonoids like that of EA and silibinin are known to exhibit the pro-oxidant activity and act as an inducer of intracellular oxidative stress in tumor cells which also induces the formation of reactive oxygen species of about 2.5 and 2 fold in vitro and invivo respectively. Cell viability was significantly greater

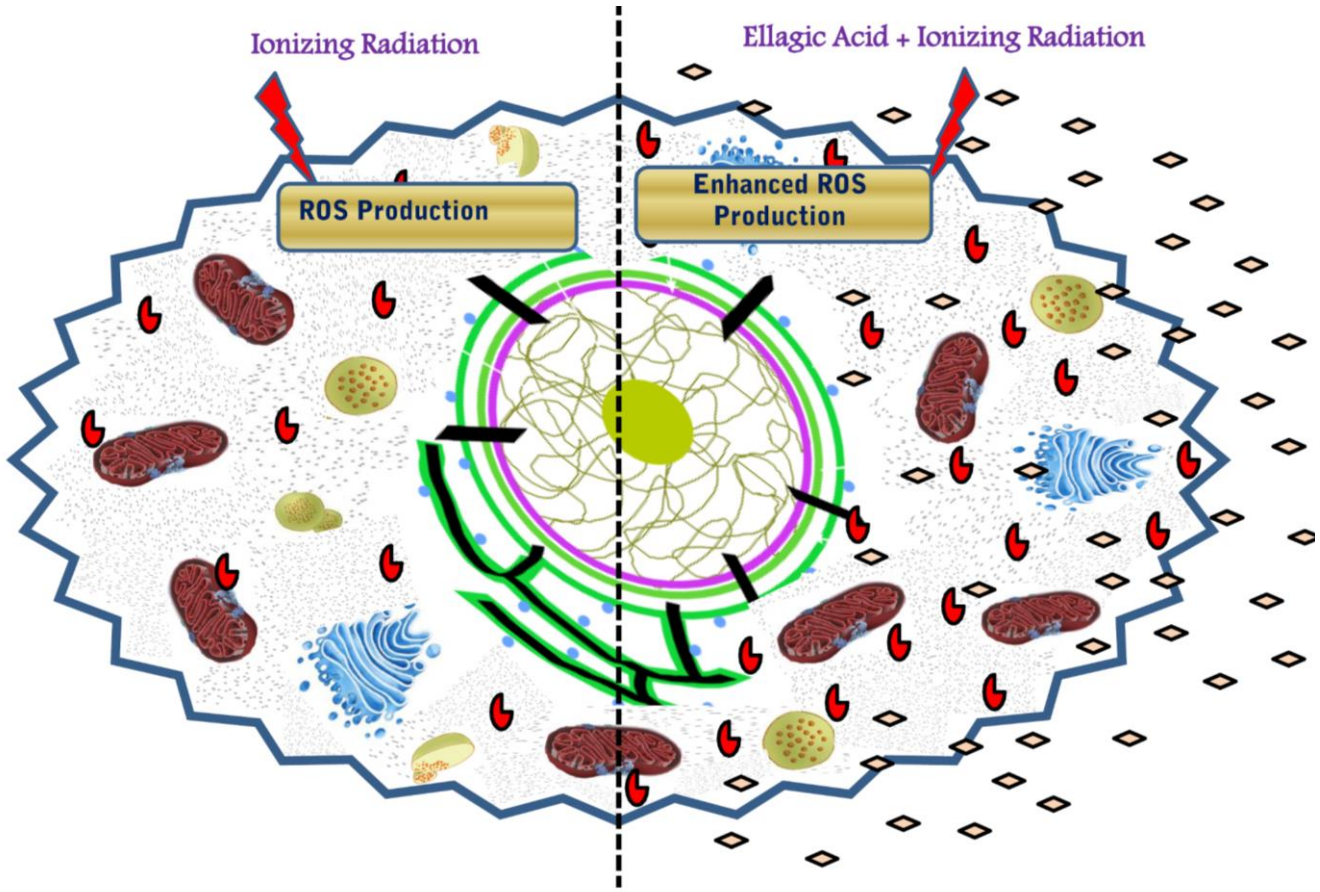

Figure 3: Model showing effect of ionizing radiation alone and in combination with EA on cancer cell.
When the cells are treated with radiation alone there is an increase in the levels of ROS. Combinatorial treatment of chemotherapeutic dietary compound like EA (orange) and radiation leads to enhanced increase in levels of ROS, drops the mitochondrial potential by release of cytochrome C from the mitochondria (light blue) and increases caspase-3 (red) expressions pushing the cells apoptosis.

in cells treated with EA prior to radiation. Tumor transplanted mice exhibited about 45% increases in splenic lymphocytes and oxidative stress persisted up to 24h.There was a decrease observed in the antioxidant enzymes like superoxide dismutase, catalase, and glutathione reductase in tumor cells in vivo. The transmembrane mitochondrial potential drop exhibited by EA signifies the contribution of mitochondrial permeability alterations in ROS in cells subjected to the combinatorial treatment of radiation and EA (6).

In a study of yeast rad52 mutants, which lack recombinational DNA repair pathway, it was found that protection was solely brought about by reducing DNA damage rather than by interfering with DNA repair when EA was used in various concentrations of 100, 200 and 500mM suggesting the radioprotective effect of EA (16).

In a recent study in which swiss albino mice were exposed to 6 Gy of Electron Beam Radiation and then EA for 15 consecutive days revealed advancement in the levels of antioxidants and antioxidative enzymes compared to irradiated group. There was a substantial reduction in the

Table 2: Mode of Action followed for EA-induced apoptosis in various cancer cell lines.

Cancer category	Cell line	Action Mechanism	Reference
Breast cancer	MCF-7	Cycle arrest in the G0/G1 phase, γ-H2AX foci formation, drop in mitochondrial membrane potential, changes in nuclear morphology, decrease in Bcl-2, increase in Bax, PARP.	(58, unpublished data)
Cervical cancer	HeLa	Augmented oxidative stress, decrease in antioxidants enzymes like SOD, catalase, GPx; drop in MMP, increase in p53 and PARP, cell cycle arrest at G1 phase, γ-H2AX foci formation.	(6)
Prostate cancer	LnCap	Down regulation of CYP2J2, CYP4F2 and CYPA22 mRNAs, Decreased levels of VEGF, FGF, G-CSF, HGF and IL-15	(59)
Bladder cancer	T24	Induced G0/G1-phase arrest of the cell cycle and apoptosis, increased p53 and p21, decreased CDK2, promoted caspase-3 activity	(26)
Pancreatic adenocarcinoma	MIA, PaCa-2, and PANC-1	Decreased NF-κB activity, loss in mitochondrial membrane potential (Δψm), cytochrome C release and caspase-3 activation	(60)
Colon adenocarcinoma	Caco-2	Down-regulation bcl-XL, release of cytochrome *c, caspase9 and 3 activated,* cell-cycle arrest in S phase ,down-regulation of cyclins A and B1, upregulation of cyclin E, induction of apoptosis by FAS-independent, caspase 8-independent pathways,	(61)
Ovarian carcinoma	ES-2 and PA-1	Elevates p53 and Cip1/p21, decrease in cyclin D1 and E levels, induced caspase-3-mediated apoptosis by increasing the Bax/Bcl-2 ratio, arrest in G1 phase, accumulation of p53 and Cip1/p21 and reduction of cyclins D1 and E.	(62) .
Melanoma	1205Lu, WM852c and A375	G1 cell cycle arrest, increased levels of apoptosis, decreased synthesis of IL-1β and IL-8, decreased NF-κβ activity,	(63)
Nasopharyngeal carcinoma	NPC-BM1	Bcl-2 down-regulation, DNA fragmentation, increased caspase-3 activity decreasing telomerase activity	(64)
Osteogenic sarcoma	HOS	Increase in chromosomal DNA degradation and hypodiploid DNA content ,significant time-dependent nuclear fragmentation, upregulation of Bax and activation ofcaspase-3, Induction of apoptosis	(65)

levels of membrane lipid peroxidation in the treated groups compared to irradiated control. The findings suggest the protective potential of EA on radiation-induced biochemical changes in mice may be due to its free radical scavenging and increased antioxidant levels (38).

Oral administration of natural antioxidants, EA (200 micro moles), curcumin (400 micro moles), and bixin (200 micro moles) per kilogram body weight lead to the induction of micronuclei and chromosomal aberrations produced due to whole irradiation (1.5-3.0 Gy) in mice was found to be significantly inhibited. The inhibition of micronucleated polychromatic and normochromatic erythrocytes, led by these antioxidants was comparable to that of α-tocopherol (200 micro moles) administration. EA and curcumin were as effective as α-tocopherol in reducing the number of bone marrow cells with chromosomal aberrations and chromosomal fragments. Additionally, these antioxidants showed potential in inhibiting the DNA strand breaks produced that were formed in rat lymphocytes after irradiation. The study suggested that EA, curcumin and bixin showed protection towards radiation induced chromosomal damage (39). Since EA enhanced radiation-induced oxidative stress and subsequent cytotoxicity in tumor cells in vitro and in vivo, it holds a good promise in clinics as a radiosensitizer.

2.4 EA and DNA damage

Results have indicated that EA provides protection against chromosome damage produced by radiation in normal cells. EA significantly inhibits chromosomal aberrations and micronuclei induction produced by whole body irradiation (1.5-3.0 Gy) in mice when orally administered (200 micro moles) per kilogram body weight. It induced inhibition of micronucleated polychromatic and non-mochromatic erythrocytes. EA worked as effectively as α-tocopherol in significantly reducing the number of bone marrow cells with chromosomal aberrations and chromosomal fragments. DNA unwinding studies in rat lymphocytes showed that antioxidants inhibited the DNA strand breaks produced upon radiation (39).

A dose dependent study of modulation effect of EA reveals that at 10μM EA reduces the unknown adducts whereas 100μM was required to reduce the 8-oxodG (40).It has been known that hydroxyl radical causes damages to the DNA whereas singlet oxygen plays a vital role in the generation of 8-oxo-dG (41, 42). At lower concentrations EA proves to be more effectual on hydroxyl radicals causing DNA damage. EA shows elevated likeliness to bind the poly dA-dT than poly dG-dC (43, 44).This explains the discrepancy of lower dose effects. Besides, EA not only prevents the formation of DNA-carcinogen adducts by similar mechanisms (45) but also modifies the metabolism of carcinogens (46, 47).

EA alters the gene expression of the LNCaP human prostate cancer cell lines which are known to be androgen sensitive. In 48 h, more than two-fold difference was noted in the expression of 593 genes from untreated cells. Most interesting was the expression of alteration in p53 responsive genes and in p300, Apaf-1, NFkBp50 and PPAR families of genes involved in signaling pathways leading to growth inhibition (22).

2.5 EA inhibits HPV oncogene expression

Being known for its anti-cancer activity in vitro and in vivo; EA inhibits protein kinase CK2, and block signaling cancer related pathways that might induce tumors. Also, it is known to restart the latent cellular defense mechanism which has been identified as a promoter of tumorogenesis. In HPV 18 positive HeLa cells EA induced cell cycle arrest, a dose-dependent and caspase dependent cell death. EA potentially inhibited the E6 and E7 viral oncogenes and the phosphorylation of CK2. p53 expression was augmented whereas a decrease in cyclin A was observed. Cytochrome C

release in the cytosol and activation of Caspase-3 was also seen. Hence these results suggest the anti- tumor properties can prevent the HPV-induced cervical cancer (48).

2.6 EA associated signaling pathways

At 10^{-5} M, EA induces G1 arrest within 48 h and inhibits overall cell growth and induced apoptosis in CaSki cells after 72 h of treatment. Activation of p21, the cdk inhibitory protein by EA suggests its role in cell cycle regulation of cancer cells (49). EA is one of the most interesting substances with pro-apoptotic and antioxidant action that determines apoptosis, down regulation of IGF-II, activates p21 (waf1/Cip1) a cyclin-dependent kinase inhibitor able to arrest the cell cycle at the G1, and prevents the destruction of p-53 gene by cancer cells. A multistep process inducing programmed death in cancer cells has been observed and this process inhibits the mitotic phase and blocks the cells in G1/S transition phase, prevents p53 destruction by cancer cells, determines IGF-II down-regulation, activates gene p21 (wafl/Cip1) and enhances NK-cell mediated antitumor immune response (25-27, 50).

EA exhibits antiangiogenic properties by specifically inhibiting VEGFR-2 and PDGFR activities and the phosphorylation of their substrates, leading to an inhibition of VEGF-induced endothelial cells migration and PDGF-induced smooth muscle cell migration, as well as to an inhibition of the morphogenic differentiation of endothelial cells into capillary-like structures (51).

At concentrations 10 to 50 mmol/L, EA stimulates apoptosis in human pancreatic adenocarcinoma cells. It decreases proliferation by up to 20-fold at 50 mmol/L. EA does not directly affect mitochondria but stimulates the mitochondrial pathway of apoptosis by causing mitochondrial depolarization, cytochrome C release, and the downstream caspase activation. NF-κB binding activity was observed to decrease dependening on the dose. Furthermore, inhibition of NF-κB activity using IkB wild-type plasmid prevented the effect of EA on apoptosis (52).

EA was found to be pro-oxidant in vitro at the concentration of 100 micro mol/l in HeLa cell and the generation of ROS increases with the increased concentration of EA. Tumor cells showed response to the treatment of either radiation or EA, which is implicated in its potential of increasing intracellular ROS generation, but more pronounced response was seen in cancer cells treated with the combination of radiation and EA in vitro as well as in vivo. The enhancement of radiation-induced oxidative stress by EA persisted up to 24 h (13).*Terminalia chebula* a plant containing EA as a major constituent was shown to induce apoptosis in human osteosarcoma (HOS-10), breast (MCF-7) and prostate cancer cell line (50). Apoptosis with down-regulation of insulin like growth factor (IGF-II) and activation of p21 was seen in colon cancer cells treated with EA (51). Table 2 gives an idea of various signaling mechanisms that EA induces in different kind of tumors.

3. Conclusion and Perspectives

In view of the fact that radiotherapy fails in the later stages of cancer due to the radio-resistant tumor cells, it is most important in radiobiology to increase the oxidative damage of the tumor cells by using a tumor-selective cytotoxic agent. Many studies have recently shown that EA exhibits the anti-proliferative and antioxidant properties *in vitro* as well as *in vivo* models. This has stimulated primary research into the potential health benefits of its consumption (52). EA has a chemoprotective as well as radio-protective effect in cellular models by reducing oxidative stress in normal cells (53, 54).This oxidative stress is observed due to oxygen and several other free radical species that are associated with the induction of DNA single- and double-strand breaks. Naturally occurring antioxidants are being

extensively analyzed for their ability to protect DNA against such injury in normal cells but simultaneously damage the DNA of tumor cells via ROS generation. The ameliorative effect of EA against the radiation induced biochemical alterations is attributed to its free radical scavenging properties and their ability to induce antioxidant enzymes. All these studies prove EA as an effective inducer of apoptosis and hence a potential therapeutic in the treatment of cancer cells.

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Abbrevations

ROS	reactive oxygen species
RNS	reactive nitrogen species
EA	Ellagic Acid
NF-kB	nuclear Factor kappa B
PPAR	peroxisome proliferator-activated receptors
HPV	human papilloma virus
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
PDGF	platlet derived growth factor
PDGFR	platlet derived growth factor receptor
SOD	superoxide dismutase
GSH-Px	glutathione peroxidase
GR	glutathione reductase

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