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Ellagic acid as a potential anti-cancer drug

Abstract

Existing cancer treatments regimes comprise using synthetic agents that damage DNA not only to kill cancer cells but also the normal cells. But due to the competency of DNA repair mechanisms in the cells, both healthy and cancer cells get protected against the effects of these treatments and develop drug resistance in due course of time. It is therefore essential to include a modality that would inflict the DNA damage and benefit from inhibition of DNA damage repair. Combinatorial studies of radiation with herbal compounds, in laboratories have exhibited synergistic effects. Such compounds include ellagic acid (EA). It not only exhibits a radiosensitization effect on tumor cells but also a radioprotective effect on normal cells. Because EA exhibits chemotherapeutic radiosensitizing, radioprotecting and anti-carcinogenic activities, it hold a great potential in clinics.

Keywords: ellagic acid, bioavalability, flavonoids, antioxidant, radiosensitization

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Abbreviations: EA, ellagic acid; SOD, superoxide dismutase; GPx, glutathione peroxidase; DNA, deoxyribonucleic acid

Introduction

Cancer development and progression occurs when the cells suffers when the molecular network linking proliferation and tumor suppression gets disengaged. But this link plays a vital role in cell regulation and homeostasis. Defects in apoptosis play important roles in tumor pathogenesis, allowing neoplastic, as well as genetically unstable cells, to survive. Moreover, deregulation of apoptosis affects chemo- and radio resistance, increasing the threshold for cell death and facilitating metastasis.[1]

Although, radiotherapy is the one of the most common used treatment regime for cancers, it is also known for the hazardous effects it causes to normal tissues. Radiation not only damages the DNA but also plasma membrane including other cellular organelles. There is an increased production of ROS which leads to a series of biochemical reactions and signaling that culminate into apoptotic death. In the mitochondrial pathway of apoptosis, cytochrome C, caspases 3 and 9 are involved.[2–4] Clinicians not only face a challenging task of maximizing radiation induced tumor cell killing but simultaneously minimizing the normal tissue toxicity. To overcome this challenge, clinicians can now use herbal polyphenolic compounds like curcumin, triphala, ellagic acid etc. that exhibits cytotoxic effects on tumor cells by pushing them to undergo apoptosis within 48h.[2,5–7] Importantly, these herbal compounds show no or very negligible toxicity to normal cells.

Effect of radiation on normal cells in presence of EA

EA is a flavonoid found in raspberries, pomegranates etc. It inhibits lipid peroxidation induced by radiation damage in rat liver microsomes in a dose and concentration dependent manner.[8] Oral administration of EA significantly inhibited the induction of micronuclei aberrations produced by whole body exposure of gamma radiation (1.5-3Gy). EA, effectively reduced the cells of bone marrow with chromosomal aberrations and fragmentation. It inhibited the formation of micro-nucleated mono-and polychromatic erythrocytes. DNA strand breaks produced during irradiation of rat lymphocyte were also inhibited by EA. At 200uM/kg b.w. significantly reduced the lung collagen hydroxyproline in rats that received whole body irradiation and produced lung fibrosis within 2 months. Also, the serum and lipid peroxidations were found to be significantly dropped which were high after radiation. When NIH3T3 cells were treated with radiation, the damage was quiet profound. But when these cells were treated with EA prior to radiation, 50% less damage was observed. The cell growth increased and the cell morphology looked healthy. Antioxidant like EA not only protects normal healthy cells from radiation induced damage but also aids in repairing the damage and a healthy survival.[5] Figure 1 shows some of the mechanism of radioprotection.

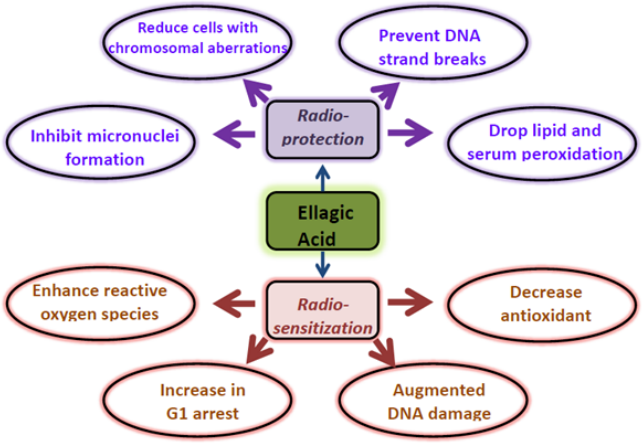

Figure 1 Some of the mechanisms by which EA exhibits radio-protective effect on normal cells and radio-sensitizing effect on tumor cells.

Effect of radiation on tumor cells in presence of EA

EA was found to significantly increase the radiation induced apoptosis in irradiated cells. The cells treated with EA or radiation showed significantly increased reactive oxygen species (ROS) generation and decrease in antioxidant enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GPx) indicating induction of increased oxidative stress by EA or irradiation.[9–11]

Experiments conducted with combined treatment of cells with EA and γ radiation showed substantial increase in ROS and up-regulation of p53 protein. On the other hand, pre-incubation of cells with ascorbic acid, an antioxidant practically abolished the combined effects of EA and radiation on p53 up-regulation and induction of apoptosis. It was further found that EA and radiation treated cells showed up-regulation of Bak protein and increased capase-3 activity after 5h and 24h respectively. But, cells pretreated with ascorbic acid, U-73122, an inhibitor of phospholipase C, EGTA, a chelator for calcium, and cyclosporine, an inhibitor of membrane potential of mitochondria showed practically no up-regulation in Bak protein expression and caspase-3 activity after treatment of HeLa cells with EA and radiation suggesting the involvement of ROS, phospholipase C, intracellular calcium and mitochondrial membrane potential in EA and radiation-induced Bak up-regulation and apoptosis. These results indicate triggering of the redox mediated apoptotic inducing cascade signals resulting in folds increase in apoptotic death in cervix cancer cells treated with EA and γ radiation.[2,12,13]

EA seem to exhibit cytotoxicity even at a concentration of 10μM. At such low concentration also EA has been able to radiosensitize breast and cervical cancer cells making them vulnerable to radiation insult. The DNA damaged could not be repaired even after 24h as was seen in ΄Y-H2AX foci. This not only lead to an increase in PARP for repairing DNA damage but also arrested the cells in the G1 phase of the cell cycle. The cells also lost their reproductive capability and therefore had to undergo cell death. These cells followed the intrinsic pathway of apoptosis where Bcl2 was down-regulated, Bad was up regulated and caspase cleaved PARP. A similar kind of effect was seen in breast cancer too. Figure 1 shows some of the mechanism of radiosensitization (unpublished).

Bioavalability enhancement of EA

Rapid elimination of EA from the body after administration is a major limitation factor. But understanding its nutritional and therapeutic benefits researchers have been investigating strategies for enhanced EA bioavability. A complex of EA formulated with phospholipids seem to be maintained at effectively higher concentartions (Cmax=0.54ug/ml) in serum for a longer period than pure EA (Cmax=0.21ug/ml). In a study, where EA was administered by subcutaneous silastic implants there was a progressive increase of 53+15, 130+30 and 185+72 for 8,16 and 28 weeks whereas in treatment without the silastic implants the plateauing of EA at 8 weeks was observed. This aided in achieving a 7-fold higher plasma EA levels. The oral bioavalability increased to 5% from 0.2% whwn directed by continuous systemic transfer. Animals who received EA through a polycaprolactone implants showed >150 fold higher plasma EA (589+78ng/ml) resulting in a higher bioavalability.[14]

Conclusion

Although a lot of studies have been carried out in various laboratories pertaining to the use of herbal compounds with radiation, not many reach the clinics. But studies like these should be encourages clinically as well taking into consideration the patients healthy life after the harsh treatment regime. EA, is one such compound which has been tested as a chemotherapeutic, radiasensitizer, antioxidant etc. EA studies have been performed on various tumor types in laboratories exhibit a significant anti-carcinogenic activity. In some studies evaluation is also performed in mice models. EA and ionizing radiation may prove to be an effective anticancer drug in clinics for treatment of cancer.

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Conflict of interest

Author declares that there is no conflict of interest.

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