ABSTRACT

Chemotherapy plays an important role in the treatment of cancer. Among the variety of chemotherapy drugs, cisplatin was the first class of platinum containing anticancer drugs widely used across the globe for the treatment of various types of solid tumors. The effectiveness of cisplatin treatment is often limited by tumor drug resistance and dose limiting side effects. Thus, the use of natural agents in combination with chemotherapeutic drugs is a promising strategy for enhancing the therapeutic outcome. Due to the anticarcinogenic properties and their low toxicity, multiple phytochemicals may serve as chemosensitizers for enhancing the therapeutic effect of classical chemotherapeutics.

Research studies have offered rich information about chemosensitization and chemoprotection by plant polyphenols. Ferulic acid (FA) is a dietary polyphenol widely available in wide variety of plant sources. Besides its various beneficial biological activities like anticarcinogenic, radiosensitizing and radioprotective activity, it possesses both antioxidant and prooxidant properties which is considered to be the base for solving the problem of the present research.

The aim of the present study was to study the chemosensitizing and chemoprotective effects of FA in cisplatin chemotherapy using in vitro and in vivo cancer models.

The hypothesis of the present study was planned to be worked out in 5 phases: Phase I: Chemosensitizing effects of FA in cervical cancer cell lines in vitro (HeLa and SiHa); Phase II: Chemosensitizing effects of FA in Dalton’s
lymphoma (DLA) cell lines \textit{in vitro}; Phase III: Protective effects of FA on normal human lymphocytes \textit{in vitro}; Phase IV: Therapeutic enhancement of cisplatin by FA on DLA induced solid tumor studies in mice (\textit{in vivo}) and Phase V: Chemoprotective effects of FA during cisplatin therapy in DLA induced ascites tumor model in mice (\textit{in vivo}).

The results of the Phase I study showed that FA chemosensitized HeLa and SiHa cells to cisplatin therapy by increasing cytotoxicity, decreasing the optimum dosage level of cisplatin, increasing ROS levels and lipid peroxidation (TBARS, CD and LOOH), decreasing antioxidant (SOD, CAT, GPx and GSH) levels, increasing mitochondrial membrane depolarization, decreasing clonogenic cell survival, increasing apoptotic morphological changes, and enhancing nuclear condensation and DNA damage. It is also found that chemosensitization of FA was effected through signaling pathways of apoptosis by upregulating the expression of apoptotic proteins like caspase 3, 8, 9 and p53 and downregulating the antiapoptotic protein Bcl-2. All the results of phase I study differ significantly (p<0.05) in FA (pretreated) and cisplatin treated cancer cells when compared to cisplatin alone treated cells.

In the phase II study on DLA cell lines, FA significantly (p<0.05) augmented the cytotoxic effects of cisplatin, increased lipid peroxidation and decreased antioxidant levels in DLA cells primed with FA prior to cisplatin treatment, when compared to cancer cells treated with cisplatin alone.
The protective effect of FA on normal cells was studied in phase III studies. It was found that FA did not show any cytotoxic action on normal human lymphocytes when administered alone. Moreover, on treatment along with the cytotoxic agent cisplatin, FA significantly (p<0.05) increased the viability of cisplatin treated cells when compared to cisplatin alone treated normal cells.

FA was found to enhance the antitumor activity of cisplatin in phase IV studies. The size and volume of solid tumor were significantly decreased in FA and cisplatin treated tumor induced mice when compared to cisplatin alone treated solid tumor mice. The results of phase IV studies showed that FA potentiated the therapeutic effects of cisplatin in chemotherapy.

In phase V studies, DLA induced mice treated with FA and cisplatin exhibited significant (p<0.05) alterations in the hematological parameters (RBC, total WBC, WBC differential counts, Hb, PCV and platelets). The cell viability and antioxidant (SOD, CAT, GPx and GSH) levels were significantly (p<0.05) increased and lipid peroxidation indices were significantly (p<0.05) decreased. It was also found that FA significantly (p<0.05) increased the survival of cisplatin treated mice on comparison with cisplatin alone treated mice. FA reduced the toxic effects of cisplatin rendered to organs such as liver and kidney by altering the histological architecture to that of normal. Therefore, the chemoprotective effects of FA were confirmed from results of the phase V studies.

On the whole, from the results of all the phases (phase I-V) of the present study, it is clear that the dietary polyphenol FA chemosensitized the cancer cells
HeLa, SiHa and Dalton’s lymphoma, protected normal human lymphocytes from chemotherapy and showed chemoprotective effects on animal models during cisplatin chemotherapy.