Phytochemicals Targeting the ROS Metabolism Could be an Alternate of Gemcitabine Against Pancreatic Cancer

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Pancreatic cancer is a malignant neoplasm originating from transformed cells present in tissues forming the pancreas. It is a fatal disease around the world like in the USA, it is the fourth most common cause of death¹. With the passage of time, the survival rate of patients is going down despite the advancement of the technology like radiotherapy, surgery and chemotherapy. Its overall survival rate reduced from 5 to 3 years, while the median survival rate for the patients with Pancreatic cancer is about 6 months². It has been observed that the only way for the long term survival of patients is Surgical abscission, but lack of early diagnosis and destructive nature of this cancer limits its surgical operation for only 10% of patients. Therefore, chemotherapeutic chemotherapy has been employed as an alternative method to treat such type of patients³.

These days Gemcitabine (Gem) is one of the commonly used chemotherapeutic drug, for the treatment of pancreatic cancer. This drug is most effective but overall survival rate is considerably low. Despite its efficacy, this drug is highly toxic to tumor cells as well as normal cells. Now, there is a need of exploring new mechanisms by using effective anticancer compounds with no or less toxic effects on normal cells. Recent research indicated that Phyto-chemicals targeting ROS metabolism have ability to kill the cancer cells by elevating the level of ROS above a toxic threshold. The toxic threshold can be easily achieved in cancer cells compared to normal cells because cancer cells contain higher level of endogenous ROS than normal cells⁴. Isoalantolactone is a sesquiterpene lactone compound having formula $C_{15}H_{20}O_2$. It was recognized as a potent inhibitor of pancreatic carcinoma cells. It is a plant derived compound used in the traditional medicines for the management of inflammatory diseases, headache and infections⁵. Previous clinical trials indicated that sesquiterpene lactones has been used for breast, kidney, prostate, colorectal, acute myeloid leukemia and non small lung cancer treatments⁶. PANC-1 (Human pancreatic carcinoma, epithelial-like cell line) cells are used as an in vitro model of non-endocrine pancreatic cancer for tumorigenicity studies. NAC (N-Acetyl Cysteine) is a specific ROS inhibitor restored cell

viability and completely blocked isoalantolactone mediated apoptosis in PANC-1 cells⁷.

A research has been carried out by the Khan⁷ to examine the anti-pancreatic cancer potential of isoalantolactone as well as its toxicity to normal cells (*in vitro*) and hepatotoxicity and nephrotoxicity (*in vivo*). MTT assay and flow cytometry has been used to examine the antiproliferative, apoptotic and ROS generating ability of isoalantolactone. They resulted that isoalantolactone inhibited growth of PANC-1 cells and induced apoptosis and ROS generation in a dose dependent manner. Pre-treatment with NAC restored cell viability and blocked the apoptotic effect of isoalantolactone completely. This research provides evidence for the first time that isoalantolactone induces ROS-dependent apoptosis in PANC-1 cells. Pal⁸ informed that the extract of *Inula recemosa* contains alantolactone and isoalantolactone induces apoptosis and amplified ROS generation in HL-60 cells. Lopez-Lazaro⁹ indicated that Phyto-chemicals targeting ROS metabolism can selectively kill the cancer cells by raising the level of ROS above a toxic threshold. The above mentioned investigations supports the conclusion that isoalantolactone may act as a promising chemotherapeutic drug for the treatment of pancreatic carcinoma. Advance research work is needed to validate the *in vivo* contribution of isoalantolactone to tumor therapy.

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