GENERAL ARTICLE

Natural Chemoprotectants for Mitigating the Side Effects of Cancer Therapy

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Introduction:

Cancer is one of the leading causes of morbidity and mortality globally cancer is responsible for one in eight deaths worldwide which is more than AIDS, tuberculosis, and malaria while it has taken together. Moreover, the number of cancer deaths has been estimated to increase from 7.1 million in 2002 to 11.5 million in 2030 (Prakash *et al.*, 2013). The most common strategies for the treatment of cancer usually include a combination of surgery, radiotherapy, and chemotherapy. Chemotherapeutic drugs usually target the rapidly dividing cells and hence affect the cancer cells that show uncontrolled growth. However, normal cells are also affected due to the cytotoxic effects of chemotherapy. This leads to serious side effects of the chemotherapeutic agents. Chemo-protectants are natural or synthetic chemical compounds that exhibit the ability to ameliorate or inhibit the toxic or adverse effects of chemotherapeutic agents and radiation therapy, without compromising the anticancer activity of the drugs or antitumor prospective of the chemotherapeutic drugs. Ideal chemo-protectants should not interfere with the therapeutic potential of the drugs and must not alter the normal serum enzyme levels or induce toxicity themselves. Recently a few chemical chemo-protectant drugs have been introduced that have been useful in ameliorating the side

Abstract

Globally cancer disease is one of the leading causes of morbidity and mortality. The most common strategies for the treatment of cancer usually include a combination of surgery, radiotherapy, and chemotherapy. Chemotherapeutic drugs usually target the rapidly dividing cells and hence affect the cancer cells that show uncontrolled growth. However, normal cells are also affected due to the cytotoxic effects of chemotherapy. This leads to serious side effects of the chemotherapeutic agents. Chemoprotectants are natural or synthetic chemical compounds that exhibit the ability to ameliorate or inhibit the toxic or adverse effects of chemotherapeutic agents and radiation therapy, without compromising the anticancer activity of the drugs or antitumor prospective of the chemotherapeutic drugs. Ideal chemo-protectants should not interfere with the therapeutic potential of the drugs and must not alter the normal serum enzyme levels or induce toxicity themselves. We focused on some recent chemo-protectants potentially are in use for treatment of cancer patients.

effects of chemotherapy (Table-1)

Table 1: Chemical Chemo-protectants & respective mechanisms

Drug: Mechanism	Chemoprotectant
Cisplatin:	Amifostine (Ethiol) Free radicalscavenger, Prevention of membrane damage, protection of DNA, protection from nephrotoxicity, decrease in neutropenia, reduction of xerostomia resulting from radiotherapy in head and neck cancer
Cisplatin, Doxorubicin:	Aprepitant (Emend) Anti-emetic, an increase in activity of ondansetron. Anti-emetic action eases the strong emetic side effects of chemotherapy
Doxorubicin:	Dexrazoxane Prevention of cardiomyopathy cardiotoxicity in breast cancer
Filgrastim (Neupogen)* & Sargramostim (Leukine)	It can be used to prevent or treat neutropenia resulting from myeloablative chemotherapy
Mesna (sodium-2-mercapto-ethanesulfonate) :	Cyclophosphamide & ifosfamide Binds to acrolein which is a toxic metabolite generated by metabolism of these drugs

Doxorubicin inhibits topoisomerase 2 leading to inhibition of cancer cell proliferation. Cyclophosphamide is

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another chemotherapeutic drug that is known to cause bladder toxicity and cardiotoxicity and suppresses the immune system. Dexrazoxane is used to lower the undesired side effects of Doxorubicin (Pommier *et al.*, 2010). Amifostine is the generic name of drug Ethyol which reduces the side effects of chemotherapy. It can be also used to cure dry mouth problems and neck cancer treatment undergoing patients. Glutathione has been reported as a potential chemo-protectant. Mesna alleviates the toxic effects of ifosfamide and cyclophosphamide which produce acrolein which is toxic to the bladder (Beauchamp *et al.*, 1985). Many natural compounds have been discovered that have chemoprotective potential. These chemo-protectants have different activities including anticancer, antitumor, anti-angiogenic, and antioxidant compounds. Some of the chemo-protectants have been used as adjuvants in cancer chemotherapy (Piccolella & Pacifico, 2015). Many natural products have been the most important and vital source in drug development and discovery from ages. The ancient knowledge of traditional medicines has been proven to behave several health benefits. Some of these natural chemo-protectants have been listed in the table-2.

Table-2: Natural chemo-protectants and their effects

Source	Active compound	Chemo-protective Effect	Reference (Year)
Grapes, berries	Resveratrol	Neuroprotective, cardioprotective & hepatoprotective	Scalbert <i>et al.</i> (2005)
Grapes	Cyanidin	Inhibit cell proliferation	Singh <i>et al.</i> (2016)
Tomato	Lycopene, (red carrots, water-melons, & red papayas)	Chemo-preventive in prostate cancer effects .	Agarwal <i>et al.</i> (2001)
Tea, Broccoli, Grapes	Kaempferol	Antiangiogenic, anti-cancer & radical scavenging effects	Boam (2015) Luo <i>et al.</i> (2009)
Turmeric	Curcumin	Induces apoptosis in tumour cells	Shehzad <i>et al.</i> (2010)
Green peppers	Luteolin	Induces apoptosis & inhibit the cell proliferation, metastasis & angiogenesis in tumour cells	Lin <i>et al.</i> (2008)
Soy beans	Genistein	Increased tumour latency period, suppress tumour growth	Sarkar & Li (2004)
Ashw-gandha	Withaferin	Inhibit cell proliferation umbilical vein endothelial cell (HUVEC)	Palliyaguru <i>et al.</i> (2016) Lee & Choi (2016)
Bitter melon	Momocharin, momordicin	Inhibition of cancer cell & cancer stem cell growth, induction of apoptosis	Dandawate <i>et al.</i> (2016)

Anticancer compound obtained from plants Polyphenols:

Resveratrol: it is present in many foods like peanuts, grapes, and red wines. Green tea has the polyphenolic compound gallatechines. Many studies show that consuming the food which has polyphenols reduces the risk of cancer and act as a natural antioxidant. (Scalbert *et al.*, 2005). Polyphenols have been shown to interfere with proteins of cancer cells and retard their growth. Polyphenols induce acetylation, methylation or phosphorylation in the cancer cell. Many studies reveal that the TNF factor is suppressed by curcumin treatment. Resveratrol degrades the DNA in the presence of cull. (Gonzalez *et al.*, 2011).

Brassinosteroids: these are compounds which occur naturally in plants. They participate in hormone signalling for growth and differentiation of cells root cells and stem cell elongation and other functions such as disease resistance and stress tolerance. Brassinosteroids are known to be capable of growth inhibition in cell lines of T-cell leukaemia, multiple myeloma, cervical carcinoma, lung carcinoma and osteosarcoma. Brassinosteroids have an affinity towards Estrogen receptor (ER) and Epithelial growth factor receptor (EGFR-2) and it has the anticancer activity, due to blocking capacity of these receptors. Brassinosteroids are nontoxic and can be taken orally as part of the patient's dietary intake (Greenwell *et al.*, 2015).

Cyanidin: this pigment can be extracted from red berries such as grapes, blackberry, cranberry etc. Inclusion of these berries in the diet lowers the risk of cancer which has been attributed to antioxidant and radical scavenging properties. They inhibit cancer cell proliferation by inhibiting NOS and COX₂ genes in colon cancer. Moreover, Yarla *et al.*, 2016 reported that cyanidin blocked Fyn kinase signalling. Moreover, ethanol-induced activation of ErbB₂/CSrc/FAK was inhibited by cyaniding-3-glucoside in breast cancer cells. Cyanidin-3-O-rutinoside, cyanidin-3-O-glucoside, and ethanol extract of raspberries selectively inhibited growth and induced apoptosis in tumorigenic rat oesophagus cell line. Prostaglandin E₂ secretion and UVB induced COX₂ expression are blocked by cyanidin in the epidermal skin cell line. It is due to the suppression of NF- κ B and AP-1 that is regulated by MAPK (Zhou *et al.*, 2009).

Lycopene: it is a red colour phytochemical pigment present in red carrots, red papayas, tomatoes and red watermelon. It is concluded that lycopene showing chemopreventive effects and also having the antioxidant property (Konijeti *et al.*, 2010). Lycopene is known to be used in prostate cancer. It activates cancer-preventive enzymes and acts on phase 2 detoxification. It also the cause of inhibition of cancer cell proliferation and suppress the insulin -growth factor. Lycopene has been shown to be effective in cancers like Breast cancer, endometrial cancer, colon cancer, prostate

GENERAL ARTICLE

cancer (Agarwal *et al.*, 2001).

Kaempferol: it is found in various fruits and vegetables like tea broccoli, grape *etc.* kaempferol possesses anti-angiogenic, anticancer, and radical scavenging effects (Tu *et al.*, 2016). Kaempferol shows cytostatic activity in PC₃, HeLa and K₅₆₂ human cancer cell lines. Kaempferol acts as an aryl hydrocarbon receptor (AhR) antagonist resulting in ABCG₂ upregulation (Nagula & Wairkar, 2019). It was reported that it induces apoptosis in ovarian cancer cells by p53 also found that kaempferol induces p53 mediated apoptosis, (Gopalakrishnan *et al.*, 2008).

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