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PLANT POLYPHENOLS: AN EMPHASIS ON MECHANISTIC APPROACHES IN MITIGATION AND TREATMENT OF CANCER

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ABSTRACT

Cancer is the second largest cause of death in worldwide and its incidence continues to increase. Approximately 12 million people get newly diagnosed of cancer every year, and will increase to around 25 million in year 2030. There are several treatment modalities available to cure different types of cancers which include surgery, radiation therapy, chemotherapy, biological therapy and hormone therapy. Amongst them chemotherapy involving the use of cytostatic or cytotoxic agents remains the mainstay of treatment. However, the major obstacle that limits the effective use of chemotherapy is toxic effects induced by the chemotherapeutic agents. Natural products have been used worldwide as traditional medicines for thousands of years to treat various forms of diseases including cancer. Polyphenolic agents are plant metabolites widely spread throughout the plant kingdom. Phenolic acids have shown the potential as effective agents for cancer prevention and treatment through several mechanisms. This article is a compilation of information available on several databases such as PubMed, Directory of Open Access Journals (DOAJ), Elsevier-Sciencedirect, Google Scholar, Springerlink, Taylor & Francis etc. regarding the role of polyphenols in the mitigation and treatment of cancer through several mechanistic pathways as well their protective effect against the cancer chemotherapy induced toxicities.

Keywords: Cancer; Chemopreventive; Chemoprotective; Chemotherapy; Polyphenols

INTRODUCTION:

Cancer subsists as a legion of diseases portrayed by the unrestrained growth and spread of abnormal cells. It is a second most fatal disease worldwide, chiefly influencing the developing or emergent countries. Cancer is an extensive term

referred to a cohort of diseases with capability to produce unrestrained cell growth which cannot be controlled by regulators of kinetics of normal cells **[1]**.

Several conventional types of modalities are available for the management of cancer. Surgical therapies, radiotherapy, surgical knives and chemotherapeutic agents are most widely used treatment approaches. Other modern approaches such as modalities affecting angiogenesis, immunotherapy based on dendritic cell, stem cell therapy and hormone-based therapy are also available **[2]**. Among all treatment strategies, chemotherapy is considered as the mainstay of cancer treatment. Chemotherapeutic agents are the toxic chemical compounds which affect rapidly growing cells **[3]**.

Apart from the tumor/cancer cells, the chemotherapeutic agents also target the fast replicating normal cells, such as cells of gastrointestinal tract, bone marrow cells, hair follicles etc. which result into various dose dependant adverse effects such as nausea, vomiting, fatigue, weakness hair loss etc. **[4]**. Prolonged and vigorous treatment with chemotherapeutic agents leads to multiple vital organ toxicities which become dose limiting toxicities. As a result of this, there is a delay in the next cycle of chemotherapy in turn delay in the recovery of the cancer patient. Hence there is an increased duration and cost of chemotherapy and reduction in efficacy of drug combinations due to dose limiting properties of toxicities. Immunity of the patients is also lowered which can lead to complex infections and consequently fatal conditions yet earlier than death produced due to cancer. None of the agents presently under progress fulfills these requirements completely **[5]**. The chief mechanisms of adverse effects produced by chemotherapeutic agents tend to be oxidative stress and immunosupression. Toxicities related with conventional modalities of cancer therapy emphasize the applicability of newer methods for cancer therapy **[6]**. Hence there is a continuing need for a therapy which is both effective as well as having high specificity for the cancer biology and is effectively targeted to tumor tissue.

Plants have been utilized as medications to cure various types of ailments and with satisfactory outcomes since primordial era. Plant polyphenols compounds are distributed all over plant kingdom embodying about 10,000 varieties of phenolic structures. These compounds are majorly investigated and proved worldwide through several preclinical studies for their valuable effects in various aspects of human well-being **[7-9]**. Several nuts, fruits and vegetables fulfilling significant

components of human food comprise of several phenolic agents which characterize varied chemical entities and have been documented for inhibition of chemical carcinogenesis as well as mutagenesis in preclinical studies and are said to be useful in combating with the oxidative stress and boosting the individual's immune system **[7, 8]**.

PLANT PHENOLICS AND CANCER:

Phenolics execute their anticancer effects through multi-faceted mechanisms such as cell signalling cascades, transcription factors, kinases and regulation of interaction between growth factor and receptor determining the gene expressions in cell cycle arrest, apoptosis and cell survival. Stress-activated AP-1 and NF-kB signal cascades are the major targets in anticancer activity. They are also helpful in boosting body's immune system to identify and demolish cancer cells with inhibition of the development of angiogenesis essential for growth of tumour. Phenolics cause reduction in metastasis by reducing invasiveness and adhesiveness of cancer cells **[10-12]**.

Amplification of the efficiency of radiotherapeutic and chemotherapeutic regimens and the inhibition of resistance towards these agents is an additional important outcome of plant phenolic acids that guarantee advanced research in this field. Plant phenolics have been documented to possess both therapeutic and preventative potential in fighting cancer and thus further guarantee exhaustive research **[13-15]**.

Plant phenolic compounds have been proved to play an important role in restraining all the three important stages of cancer development and metastasis which include the hyperproliferative, inflammatory and transformative processes concerned with initiation and angiogenesis processes essential for tumour development as well as the vascular adhesive characteristics required for tumour dispersion or metastasis **[16-18]**. In light of the affirmative epidemiological support to the fact of phytochemical consumption cambating cancer, several research activities have recognized various mechanisms of cell signaling. This supports the hypothesis and exhibits that several phytochemicals can modify specific cell receptors and their signal transduction mechanisms to inhibit the process of carcinogenesis in both *in vivo* and *in vitro* in animals **[19-22] (Figure 1)**.

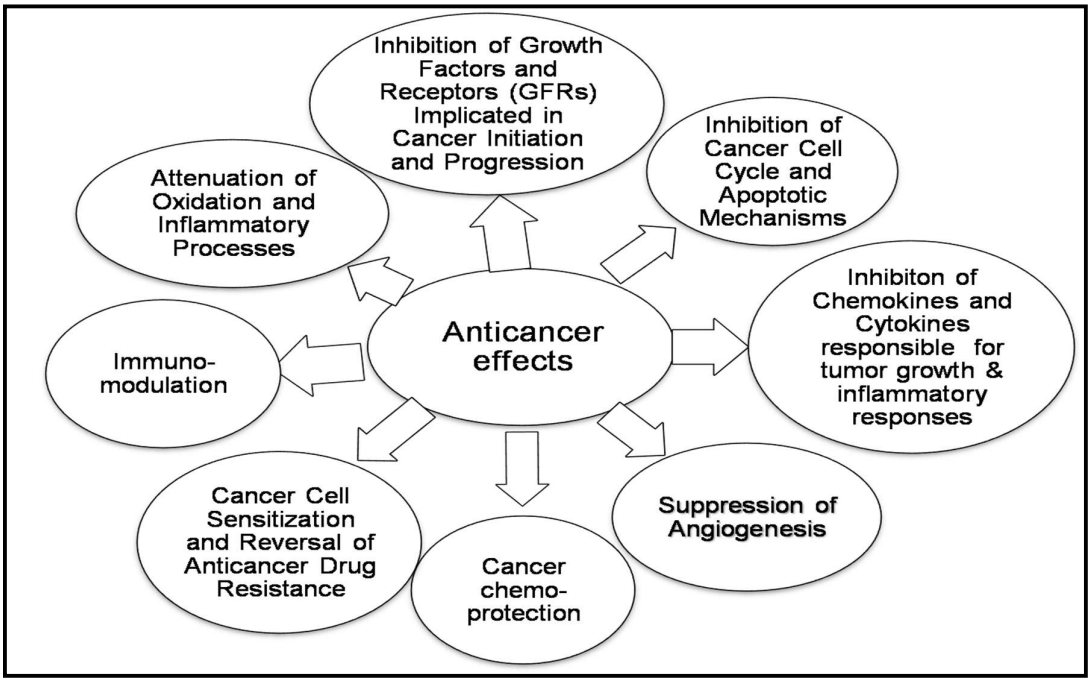

Figure 1: Mechanism of chemoprevention by plant phenolics

MECHANISMS OF POLYPHENOLS INVOLVED IN MITIGATION AND TREATMENT OF CANCER

Effects of phenolic acids on growth factors and receptors (GFRs)

Growth factors are the proteins involved in attachment to particular receptors on cell membranes to obtain a signaling cascade involved in commencement of cell proliferation or cell differentiation needed for tissue repair and growth. Unusual growth expression factor result in a signaling cascade causing uncontrolled cell differentiation and proliferation, inhibition of apoptosis signals eventually resulting into carcinogenesis, progression of tumour and metastasis **[13, 15, 17, 18, 22]**. The key growth factors concerned with carcinogenesis include plate-derived growth factor (PDGF), interleukin1,-2,-6,-8 (IL-1,-2,-6,-8), epidermal growth factor (EGF), transforming growth factors α and β (TGFs-α and -β), fibroblast growth factors (FGFs), inflammation-related cytokines, insulin-like growth factor (IGF), interferon-γ (IFN-γ), factor-α (TNF-α), tumour necrosis colony stimulating factors (CSFs) and erythropoietin (EPO) **[17, 18, 22]**. Several plant phenolics including catechins genistein, curcumin and resveratrol are effective suppressors of a numerous pathways involved in signaling and growth factor binding concerned in cancer **[23, 24]**. Plant phenolics are considered as potential antioxidants and their chief advantageous effects on health such as anti-cancer and anti-atherogenic effects are ascribed to their capability to

inhibit the inflammatory and oxidative signal cascades through transcription factors such as AP-1 and NF-kB and consequent modification of down-stream gene expression **[25, 26]**.

Effect of phenolics on inflammatory processes and oxidation

Inflammatory and oxidative stresses are renowned for being strongly involved in the commencement and progression of carcinogenesis process. Formation of excessive reactive oxygen species (ROS) in cells result into protein damage. RNA and DNA oxidise the polyunsaturated fatty acids of plasma membrane, thereby enhancing the harmful mutations in genome **[13, 17]**. ROS are considered as chief activators of AP-1 and NF-kB transcription factor pathway **[18, 22, 27]**. Several phenolics are powerful antioxidants, having capability of scavenging toxic reactive species like singlet oxygen hydroxy radicals, peroxynitrite nitric oxide and superoxide anions **[28]**. Variety of phenolics are also capable of attenuating generation of ROS through suppression of transcription factors (redox-sensitive) such as NF-kB and AP-1 involved in the execution of the ROS-induced cascade of inflammatory enzymes. Cyclooxygenase-II, xanthine oxidase and lipoxygenase were found to be reduced by various phenolics such as silymarin, resveratrol and curcumin **[29, 25, 30, 31]**. Polyphenols can also enhance the detoxifying enzymes like glutathione-S-transferase (GST) and quinone reductase (QR) capable of protecting cells from endogenous or exogenous intermediary carcinogenic factors **[32, 33]**.

Actions of phenolics on apoptosis and cell cycle

Enhanced expression of growth enhancing mechanisms like cyclin-dependent kinases (CDKs) and cyclin D1 as well as disturbance in normal cell cycle mechanisms and the chief proceedings of carcinogenesis. Phenolics like resveratrol have been documented to suppress various cells at different cell cycle stages (G1, G2, S and S/G2) in several *in vivo* and *in vitro* investigations **[34, 35]**. Epigallocatechin gallate (ECGC) has been reported to execute its anticancer actions directly by suppressing CDKs or by induction of p27 and p21 gene expression indirectly and supressing Rb and phosphorylation of cyclin d1. Resveratrol has also recently been found to block HL-60 cells in phase of S/G2 transition, increasing number of cells in G1/S phase and by inducing apoptotic reactions, probably due to reduced expression of an important anti-apoptotic oncogene i.e. Bcl2 **[35]**.

Actions of phenolics on cytokines and chemokines

Chemokines are the chemotactic cytokines involved in targeting leucocytes, enhancement of inflammatory reactions and regulation of tumour development. They execute their actions on leukocytes by attaching to specific receptors of chemokines such as CXCL8/ IL-8 which activate endothelial chemotactic reactions, angiogenesis and proliferation *in vivo* and have been found in large amounts in various tumours **[36]**. Phenolics such as resveratrol, curcumin, green tea polyphenols, quercetin, theaflavin, black tea, capsaicin and soya genistein have been proved to inhibit cytokine and chemokine expression **[37-40]**.

Phenolic inhibition of angiogenesis

Angiogenesis is considered to be essential for supplying nutrients and oxygen to the tumours assuring their growth and development, their invasiveness and metastasis. Inhibition of angiogenesis leads to the starvation of the tumour preventing metastasis which provides a crucial basis for anticancer research **[36]**. Phenolics have also been documented to inhibit the functioning adhesion molecules of blood vessels reducing the process of metastasis **[41]**.

Chemopreventive action for phenolics

Methylation of DNA is monitored by the demethylating reactions and the actions of DNA-methyltransferases (DNMTs). Hypermethylation of specific genes lead to their silencing at transcriptional state. The methylation process is reversible and hence genes may be re-stimulated by withdrawal of methyl groups **[17, 18, 22]**. Several genes have been found to be hypermethylated and hence in inactivated state or hypomethylated and thereby activated state in cancer cells **[42]**. These comprise of genes responsible for regulation of cell cycle (Rb, p16, p151, p21waf1/cip1), redox enzymes (MnSOD, GPx1 & 4,), genes responsible with DNA repair (MGMT, BRCA1 & 2), drug resistance tumour/apoptosis inhibition (p53), angiogenesis, metastasis and detoxification. All these enzymes are prone to silencing and hypermethylation. Several phenolics such as polyphenols of green tea (catechin, EGCG, epicatechin) and flavonoids (fisetin, myricetin, quercetin) have been documented to re-stimulate the silenced genes in tumor cells by blocking DNMT activity and reverting hypermethylation of their processor DNA in a concentration and time manner.[43,44] Phenolics are also capable to reverting hypomethylation is seen in various cancers, apparently silencing expression of pro-carcinogenic gene **[44]**.

Inhibition of drug resistance and sensitization of cancer cells and by phenolics

Most of the anticancer agents and radiotherapy employed in the treatment of cancer cause the activation of NF-kB survival pathway resulting in to the resistance towards treatment. Co-administration of plant phenolics E.g. curcumin lead to upregulation of proapoptotic pathways (p21, waf1/cip1, p53) simultaneously with downregulation of the mechanisms of cell survival (AKT, PI3K, AP-1, NF-kB) and altering the survival ratio i.e. Bcl-2:Bax to proapoptotic mechanism **[22]**. Resveratrol was documented to increase chemosensitisation by reducing another gene survivin for cell survival **[45, 46]**. EGCG derived from green tea tends to inhibit breast cancer cell growth in human by inhibiting survivin expression which is an inhibitor of apoptotic proteins (IAP) majorly found in cancer cells **[47]**. The destruction of tumor cells by the immune mechanism of host has been considered as the most appropriate anti-cancer strategy as the immune system possesses the potential to completely destroy cancerous cells causing minimum injury to normal cells due to its specialized recognition mechanisms. The activation of immune cell responses targeting the cancer cells can prove to preventive and effective treatment strategy **[48-50]**. Thus, the drug or nutrients regimen that increase anti-tumour effector cell actions have been considered as most appropriate means of cancer treatement. Simplest standpoint of increased immunity towards tumor cells is direct increase in specific activities of cell, specifically those involved in killing tumour cells. The T-cells are chief targets for most of the immunotherapeutic approaches and increase in T-cell activities could increase the anti-cancer immunity. The $CD8^+$ cytotoxic T-cells cause direct killing of particular target cells and the rapid proliferation and extension of the population of T-cell is one of the first responses of T-cell **[51,52]**. Resveratrol at low concentrations has been reported to enhance the concanavalin-induced cell growth with nil action on IL-2 induced cell growth. This difference showed that resveratrol doesn't increase the abnormal growth response; but it increases the upregulation mechanisms signalling for abnormal cell growth, most probably increasing the activation of IL-2 through T-cell receptor which is the most important growth factor of T-cells. Resveratrol did not increase the destructive capacity of T-cells against target cells of lymphoma. The study indicated that the high concentrations of resveratrol can inhibit the actions, showing a biphasic response towards resveratrol suggestive of the applicability of this phenolic compound in clinical studies **[53, 54]**.

CHEMOPROTECTIVE ACTIVITY OF POLYPHENOLS:

Anticancer drugs act either by killing the cancer cells or by modifying their growth. However, major drawback involves limited selectivity and specificity of most of drugs rendering them as most toxic drugs therapy. The most common of toxicities are blood disorders due to myelosuppression, vital organ toxicities, nausea and vomiting, diarrhoea, alopecia (hair loss), mucositis, and cachexia (severe weight loss). These side effects may lead to delay in the next cycle of chemotherapy which in turn delay in the recovery of the cancer patient and subsequently increases the duration and cost of chemotherapy. Being dose limiting, these side effects may affect the efficacy of the chemotherapeutic drug combinations as well. Plant polyphenols have exhibited their potential in improving immune system of cancer patients and ameliorating chemotherapy induced toxicities through several mechanisms without having any negative impact on efficacy of chemotherapeutic agents when used as adjuvants with the major conventional anticancer agents.

Chemoprotective activity of polyphenols against cancer chemotherapeutic agents induced toxicities

a) Protective efficacy of caffeic acid against capecitabine induced renal and hepatic toxicities

In this study, the protective efficacy of caffeic acid was investigated against capecitabine induced liver and kidney toxicities stress and oxidative. Caffeic acid caused significant amelioration of alterations in hepatic and renal biomarkers indicating tissue damage. The protective activity of caffeic acid was ascribed to its capability to improve the antioxidant defense machinery and decrease lipid peroxidation **[55]**.

b) Protective actions of gallic and tannic acids against cisplatin induced nephrotoxicity

In this investigation the protective effect of gallic aid and tannic acid was evaluated against nephrotoxicity induced by cisplatin in rats. The rats were given orally for 7 days with gallic acid and tannic acid at the doses of 20 and 40 mg/kg body weight and exposed to cisplatin (CP) at a single dose of 7.5 mg/kg given intraperitoneally. Cisplatin produced a significant elevation in some of renal biomarkers such as uric acid, creatinine and urea levels, with a significant elevation in malondialdehyde (MDA) content and reduction in reduced glutathione (GSH), catalase, glutathione peroxidase (GPx), superoxide dismutase (SOD) and glutathione S transferase (GST)

in kidney tissue in comparison with control group. Pretreatment with gallic acid and tannic acid ameliorated all the biochemical alterations with improvement in histological renal damage. These results indicated the nephroprotective activities of both gallic and tannic acids against cisplatin induced nephrotoxicity **[56]**.

c) Immunomodulatory activity of gallic acid against cisplatin and cyclophosphamide induced immunosuppression

In this investigation, immunomodulatory action of gallic acid was studied against immunosuppression induced by cisplatin and cyclophosphamide in swiss albino mice using haematological parameters and haemagglutination antibody titre response. Increase in of antibody titre values and improvement in haematological alterations indicated the immunomodulatory action of gallic acid on cisplatin and cyclophosphamide induced myelosuppression. Results indicated the usefulness of gallic acid as an adjuvant drug which can be used with immunosuppressive drugs to overcome their toxicities on immune system **[57]**.

h) ***Protection of 2-pyrocatechuic acid against carboplatin and 5-fluorouracil induced toxicities***

2-pyrocatechuic acid showed protective effect against carboplatin induced hematological toxicities and 5-fluorouracil induced cardiotoxicity and nephrotoxicity 10, 30 and 100 mg/kg by ameliorating heamtological parameters, hepatic biomarkers and histopathology and renal biomarkers and histopathology respectively **[58-60]**.

d) Chemoprotective potential of zingerone in cyclophosphamide induced hepatotoxicity

Zingerone, a polyphenolic alkanone was evaluated for its chemoprotective activity against cyclophosphamide-induced hepatotoxicity. CP significantly increased the level of hepatic biomarkers such as aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase drastically caused alteration in lipid profile and deficiency in antioxidant defense mechanism by decreasing the levels of antioxidant enzymes i.e. glutathione, catalase, glutathione peroxidase and glutathione-S-transferase. Also a subsequent elevation in lipid peroxidation, nitrite production and marked damage to DNA was observed. The normalisation of hepatic biomarkers, lipid profile, antioxidant status and improvement in DNA damage by pre- and co-treatment with zingerone clearly indicate the ameliorative potential of zingerone against CP-induced organ toxicity and oxidative stress. The protective potential of zingerone

was ascribed to its strong antioxidant activity **[61]**.

e) Effect of p-coumaric acid on oxidative stress induced by doxorubicin in rat hearts

In this study, the capability of p-coumaric (PC) acid to protect the cardiac tissue against oxidative stress induced doxorubicin (DOX) was evaluated. DOX caused increase in the levels of various serum cardiac biomarkers such as creatine phosphokinase (CPK) and lactic dehydrogenase (LDH) in rats which were significantly reduced by administration of PC. PC pretreatment also ameliorated the levels of catalase (CAT), superoxide dismutase (SOD) and glutathione (GSH) in cardiac tissues in comparison with DOX control rats. MDA levels in the cardiac tissues were found to be significantly reduced after pretreatment with PC as compared to DOX contol rats. The results indicated that PC causes antioxidant action against DOX induced oxidative stress and hence can be used as adjuvant therapy in treatment of cancer **[62]**.

f) Protection of kolaviron against renal and hepatic oxidative damage induced by cisplatin

The action of kolaviron on altered biochemical parameters induced by cisplatin alterations in rats was studied. cisplatin at a dose of 10 mg/kg i.p. caused a significant elevation in serum levels of blood urea nitrogen, alanine aminotransferase, creatinine alkaline phosphatase and aspartate aminotransferase exhibiting of hepatic and renal damage. It also caused increase in the interleukin-6, tumor necrosis factor-alpha and reactive species of thiobarbituric acid levels with significant reduction in levels of the superoxide dismutase (SOD) and catalase (CAT) in kidney as well as liver. These alterations were significantly reversed by kolaviron administration at a dose of 100 and 200 mg/kg orally for 6 days prior and 3 days with cisplatin. The results revealed that kolaviron can be pharmacologically exploited for its adjuvant use in cancer therapy **[63]**.

*g) **Protection of gentisic acid against carboplatin and 5-fluorouracil induced toxicities***

Gentisic acid at the doses 10, 30 and 100 mg/kg showed protective effect against carboplatin induced hematological toxicities and 5-fluorouracil induced hepatotoxicity in wistar rats by ameliorating heamtological parameters and hepatic biomarkers and histopathology respectively **[64, 65]**.

CONCLUSION

It can be concluded that plant polyphenols have shown the potential as effective agents for cancer mitigation through several mechanisms in several preclinical and

clinical studies. They have also exhibited their chemoprotective ability against cancer chemotherapy induced toxicities in various studies. In future they can be used not only as potent anticancer agents but also as adjuvants with chemotherapeutic agents to prevent their toxicities.

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