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Curcumin -Role in Cancer

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Abstract
Cancer is a hyper proliferative disorder which mainly arises from mutation of somatic cells. Cancer cells have the capacity to proliferate, transform and invade somatic cells. Recent studies have proved, this deadly disorder "Cancer" can now be inhibited by a liposoluble polyphenolic pigment "Curcumin" which is derived from *Curcuma longa* plant, commonly known has turmeric. The yellow colour of turmeric contains three curcumin namely diferuloylmethane, desmethoxycurcumin and bisdesmethoxycurcumin. Mainly diferuloylmethane helps in treatment of cancer. The main inhibitory effect of curcumin on tumor cells is by initiating benzo[a]pyrene and DMBA. The anticancer property of curcumin has an effect on many cell-signalling pathway involved in mutagenesis, oncogenes, cell cycle regulation, apoptosis, tumorigenesis. Curcumin is chemopreventive for various cancer. Curcumin inhibits proliferation of tumor cells but not normal cells. Curcumin processes anticancer properties in variety of cancers such as head and neck squamous cell carcinoma, pancreatic carcinoma, colon cancer, breast adenocarcinoma, ovarian carcinoma, lung cancer cells etc.

Keywords – curcumin, somatic cells, turmeric, benzo[a]pyrene, chemopreventive.

INTRODUCTION

Day by day advancement of cancer biology has a great deal but still the rate of death of cancer hasn't changed for past 50 years. There is decrease in availability of drugs for the treatment of cancer due to the presence of high toxin present in the drugs.[1] Cancer is caused by the dysregulation of multiple cell signaling pathways.[2] Cancer has more than 500 different types of dysregulated genes . The dysregulated gene may occur over duration of 20-30 years before the cancer begins to show its signs and symptoms. Thus cell signaling pathway is unable to prevent cancer. [3] Studies have found that cancer results from interaction of environmental exposures and genetic susceptibility. [4] Curcumin (diferuloymethane) is one of the component of turmeric which is a rhizome of the plant *Curcuma longa*. *Curcuma longa* is an east Indian plant which is a member of the Zingiberacae (ginger)family and it's a perennial plant in Southeast Asia.[5] It is commonly used in the preparation of curries.[6] Curcumin act as a flavouring and colouring agent in food.[7] It is also consumed as dietary supplements for decades and it is considered pharmacologically safe.[8] It acquires several active components, which all contribute to its chemopreventive and anti-inflammatory power.[9-11] It targets causative factors which are involved in cancer development and if any interruption of one of the causative factors helps in preventing cancer thus providing even greater protection and prevention of DNA damage.[12] Curcumin either arises from the CH2 group or OH group of the β- di ketone and the phenolic OH group plays an important role in biological activity of curcumin .[13] Curcumin induce cell death in malignant cancer cell lines including K562 , MCF-7 and HeLa cells.[14-16]

ANTICARCINOGENIC ACTIVITY OF CURCUMIN

The process by which normal cells develop into a malignant tumour is called Carcinogenesis. Traditional it has been divided into 3 stages 1. Initiation- normal cells become transformed 2.Promotion- transformed cells become preneoplastic 3.Progression -finally preneoplastic cells become neoplastic [17]. Apoptosis is called spontaneous cell death. It is the innate way of destroying abnormal cancerous cells. Curcumin works at the cellular level, thus apoptosis encourages cancerous cells to self-destruct so they may not able to grow and multiply. Due to the property of abnormal chemistry of cancer cells curcumin is able to identify this feature and initiate the process of apoptosis thus this results in helping the immune system. Curcumin was considered to counteract the altered functionality of proliferative and apoptotic pathways in order to exert its anticancer activity. Many evidences suggests that curcumin shows anticancer effects at lower doses at much faster rate compared to other anticancer drugs. The regulation of numerous biochemical cascades, including various transcription factors, growth factors, inflammatory cytokines, protein kinases, and other enzymes are mediated by the effects of anticancer property of curcumin [18**].** The anticancerous property of curcumin have been reported in many preclinical models including breast, colon, gastric, head and neck, hepatic, ovarian, pancreatic and prostate cancer, leukemia and multiple myeloma, and there are several review articles described based on this. [19] This polyphenol that is curcumin modulates various targets which is either through direct interaction nor modulation of gene expression and also including inflammatory biomarkers, growth factors and their cell signalling pathways, protein kinases and protein phosphatases, tumour suppressor genes, transcription factors, proapoptotic pathways, and oncoproteins [20]. Curcumin acts as an inhibitory agent of tumour formation and promotion. Thus tumours are mainly destroyed by inducement of benz (a) pyren, 7, 12-dimethylbenz (a) anthracen or phorbol esters [21]. In rats the formation of colon adenocarcinoma is blocked by a bisdemethoxycurcumin analog (BDMC-A) [22]. Curcumin with the help of down regulation of the survival genes, early growth response-1 (*egr-1*), *c-myc*, *bcl-2, Bcl-xL* etc. and up regulation of apoptotic genes, *p53, bax, Bcl-xs* etc. can alter the expression of genes involved in tumour growth and apoptosis [23]. The *p53 which is a* tumour suppressor gene *is now named "guardian of genome"* and is situated at the crossroads of a network of signaling pathways and these are required for cell growth regulation and apoptosis [24]. A variety of tumour cell lines including

those derived from breast carcinoma, basal cell carcinoma, prostate carcinoma, colon carcinoma, hepatocellular carcinoma, leukemia, lymphoma, melanoma, kidney cancer and rhabdomyosarcoma can obtain apoptosis by inducement p53-dependent and -independent which is present in curcumin [25-26]. Curcumin has the ability to bind directly with DNA and RNA. Through this direct binding its β-diketone moiety is facilitated and interaction with other macromolecules is mediated through the α, β-unsaturated β-diketone moiety, carbonyl and enolic groups of the β-diketone moiety, methoxy and phenolic hydroxyl groups, and phenyl rings [20]. With the help of these macromolecular interactions, curcumin is able to inhibit tumour proliferation, growth, metastasis, invasion, and angiogenesis. Curcumin mainly bring about cell death by the process of apoptosis, but there are some body cells that are resistant to apoptosis, these cells are shown to induce mitotic catastrophe [27] and autophagy [28]. Oncoproteins is considered as one of the most important contributors to tumorigenesis. Curcumin is also been able to targets most of the important oncoproteins, such as Mdm2, c-Myc, N-myc, c-Met, Ras, and Fos, that are linked to major cancer types [29].

IN VITRO

Studies of *In vitro* have proved that curcumin has the ability to inhibits lipo-oxygenase and cyclo-oxygenase activities in phorbol 12-myristate 13-acetate (PMA) - which is the main cause for inducement of inflammation of fibroblast cells [30].Curcumin has also inhibited the Fanconi anaemia (FA)/BRCA pathway which is a DNA-damage response pathway required for repairmen of cisplatin cross-links, as well as in ovarian tumour lines and MCF7 breast tumour cell lines. This response sensitized the cell lines to cisplatin by inducing apoptotic cell death [31]. In other studies of In vitro, the presence of curcumin also enhances the cytotoxic effects of chemotherapeutic drugs including doxorubicin [32], tamoxifen [33], cisplatin and camptothecin, daunorubicin, vincristine (VCR) and melphalan [34]. Curcumin has come to inhibiting the activity of xanthine oxidase (XO) in vitro in PMA treated NIH3T3 cells. The major cause of PMA-mediated tumour promotion is due to the induction of XO since curcumin has marked ability to inhibit PMA-induced increases the activity appears to lie in its direct inactivation of the XO protein [35, 36].

IN VIVO:

The main aspect of using this method, was first obtained to protect against colon tumours in cases of chemical carcinogenesis at high concentrations (37-41). Recently found chemo sensitization of curcumin has also been further demonstrated in vivo. [42]

INVADING CANCER CELLS

Normal tissue are invaded by cancerous cells with the aid of enzymes called matrix metalloproteinases. In cell culture studies, curcumin has also been found to inhibit the several activity of matrix metalloproteinases [43-47]. In order to increase the rate of growth of tumour cells, these cells must develop new type of blood vessels by a process known as angiogenesis. In recent studies has found in in cultured vascular endothelial cells [48, 49] and in an animal model [50] curcumin is able to inhibit angiogenesis.

COLON CANCER

Colon cancer which is one of the few important cancers of the gastrointestinal tract has become a major cause of cancer-related deaths in the developed nations such as the United States [51]. In colon cancer, use of curcumin or along with the combination of chemotherapeutic drugs may be able to help to overcome some of the resistance as well as improves the efficacy of chemotherapeutic drugs [52]. The development of chemically-induced cancer in animals containing colon cancer can now be inhibited by the accumulation of oral curcumin [53—55]. Bisdehydroxycurcumin which is a growth inhibitory action of curcumin is used in treating colon cancer. [56, 57]. Curcumin when combined with other polyphenols like resveratrol has the property to suppresses colon cancer [58]. Curcumin reduces levels of secondary bile acids which is more favourable to optimal colon health thus they help in creating a gastrointestinal micro environment . These are nothing but a natural secretions that contribute to cancer risk in our day to day life [59]. In order to look for additive or synergistic activity in cell kill several studies have proven that curcumin in combination with cytotoxic agents is used to treat cancer. In studies related to human colon cancer cell lines is given that in order to demonstrate synergistic inhibitory effects on the growth of the cancer cells *in vitro,* curcumin was combined with 5-fluouracil (5-FU) and it was also associated with reduced expression of Cox-2 protein [60].

PROSTATE CANCER

In androgen-independent prostate cancer cell lines (PC-3 and DU-145) curcumin has a cytotoxic effects of chemotherapeutic agents (5-FU, doxorubicin, and paclitaxel) and in the combination treatment group a significant degree of G1-cell cycle arrest was observed [61]. Curcumin; dimethoxycurcmin which is a growth inhibitory activity of curcumin helps in inhibiting prostate cancer.[62-64] Curcumin contributes itself in the action of inhibition of proliferating cells and also in induction of apoptosis through several different molecular targets within the PI3K/PKB signalling pathway. For example in apoptosis prostate cancer cells, basal activity of Akt/PKB being induced is inhibited [65]. Curcumin has been reported to enhance TNF-□-induced apoptosis in prostate cancer cells [66]. In fact, curcumin induces apoptosis in both androgen-dependent and androgen independent prostate cancer cells [67].

BREAST CANCER

Aggarwal and his colleagues considered that curcumin have a potential effects on chemotherapy in advanced breast cancer and in inhibition of lung metastasis. Since the potent of NF-*κ*B suppressor is Curcumin, while NF-*κ*B is activated by the most conventional chemotherapeutic agents .Curcumin has an action in inhibiting paclitaxel-

induced NF-κB activation by using paclitaxel (Taxol)-resistant breast cancer cells including human breast cancer xenograft, and it is noted that these effects were observed through inhibition of IκBα kinase activation and IκBα phosphorylation and degradation. In addition to this action, curcumin also plays a role in suppression of several chemical expression such as the paclitaxel-induced expression of several antiapoptotic (XIAP, IAP-1, IAP-2, Bcl-2, and Bcl-xl), proliferative (Cox-2, c-myc, and cyclin D1), and metastatic (VEGF, MMP-9, and ICAM-1) proteins [68]. Curcumin; curcumin +fluorouracil; curcumin + tamowifen; curcumin + vinblastin; RL66; RL71 which are the inhibitory activities of curcumin, helps in inhibiting breast cancer. [69-74]

ANTI-INFLAMMATORY ACIVITY OF CIRCUMIN

In vivo studies have demonstrated that curcumin also has anti-inflammatory effect For example, Inflammation induced by carrageenan was inhibited by curcumin [75, 76] and acute lung injury induced by Cyclophosphamide [77]. Two enzymes involved in inflammation cyclooxygenase 2 (COX-2) and lipoxygenase (LOX) is proven to be inhibited by curcumin [78]. In addition curcumin also inhibits the production of pro-inflammatory monocyte/macrophage-derived cytokines [interleukin-8 (IL-8), monocyte inflammatory protein-1(MIP-1), monocyte chemotactic protein-1 (MCP-1), interleukin-1b (IL-1b), and tumour necrosis factor-a (TNF- a)] in PMA- or LPS-stimulated peripheral blood monocytes and alveolar macrophages [79]. It is found that curcumin also inhibits PLA2, COX-2, and 5-LOX activities in cultured cells [80]. Keratinocytes and Fibroblasts is protected against H2O2-induced damages with the help of curcumin and it also allows reduction of oxidative and inflammatory stress in Alzheimer patients [81 -82].

ANTIOXIDANT ACTIVITES OF CURCUMIN

The property of antioxidant activity of the curcuminoids comes by virtue of their chemical structure. There are two methoxylated phenols connected by two a, B unsaturated carbonyl groups present in curcuminoids that exist in a stable form [83] One of the effective scavenger of reactive oxygen species is curcumin and it is also a reactive nitrogen species in the test tube (*in vitro*) [84,85]. Some studies has suggested that curcumin can inhibit oxidative DNA damage because curcumin taken in a form of Oral administration in a dose of 3.6 g/day for 7 days had resulted in decrease of oxidative DNA adducts in colorectal cancer tissues. [86].The inhibition of lipid peroxidation using linoleate, a polyunsaturated fatty acid that is able to be oxidized and form a fatty acid radicalis has shown to be done by curcumin. Curcumin acts as a chain-breaking antioxidant at the 3' position, resulting in an intramolecular Diels-Alder reaction and neutralization of the lipid radicals [87]

CONCLUSION:

After extensive research over the past few decades for the treatment of cancer, now scientist have found the magnificent plant "CURCUMIN". This single plant have the ability to several types of cancer, in addition it also has other antibiotic properties. There is a fast growing research going on curcumin which is required to explore more of its antibiotic properties.

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