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Curcumin: An overview

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Abstract
Medicinal plants play key role in the treatment of carious health issues. Developing countries like India rely on medicinal plants for the for their healthcare needs. *Curcuma longa*, famous for its variety of the rapeutic uses since ancient history till today. A phytopolyphenol pigment of the plant *Curcuma longa* with a variety of pharmacologic properties. Curcumin is the active ingredient in the herbal remedy and dietary spice turmeric having wide range of therapeutic properties that covers anti-inflammatory, anticancer, antioxidant and antimicrobial. As an effective therapeutic agent & a spice and food coloring compound that has shown increasing potential as an immune-health agent also useful in variety of conditions, including multiple myeloma, cancers of various categories.

Keywords: *Curcuma longa*, curcumin, cancer, inflammation, antioxidant

Introduction
Medicinal plants nowadays playing its role taking care of many health issues. The practice of traditional medicine is widespread in China, India, Japan, Pakistan, Sri Lanka and Thailand. In China about 40% of the total medicinal consumption is attributed to traditional tribal medicines. In Japan, herbal medicinal preparations are more in demand than mainstream pharmaceutical products. Medicinal plants, because of its high values and least side effects, used around the globe seems to be useful and found quite encouraging as it revert back to the olden history where herbs and its usage found interesting episodes. The cost and availability of herbals & its utilization resources transferred from one generation and other keeps the information alive and useful to all. Medical care becoming costly and much painful and the affordability will be question for the poor. So there is a great demand with the usage of medicinal plants with its health coverage and minimum ill effects [1, 2].

Curcumin, derived from the plant *Curcuma longa*, is a gold-colored spice commonly used in the Indian subcontinent, is a traditional Indian curry spice contains Curcumin 0.3-5.4%, volatile oil 4-14%, sugars, resins, protein, vitamins and minerals. It has been shown to exhibit antioxidant, anti-inflammatory, antiviral, antibacterial, antifungal, and anticancer activities and thus has a potential against various malignant diseases, diabetes, allergies, arthritis, Alzheimer's disease, and other chronic illnesses. (6, 24 & 27) It is also used as a yellow food coloring and has been used in traditional medicine in India and Ancient Egypt. Curcumin, which gives the yellow color to turmeric, was first isolated almost two centuries ago, and its structure as diferuloylmethane was determined in 1910.

Since the time of Ayurveda (1900 BC) numerous therapeutic activities have been assigned to turmeric for a wide variety of diseases and conditions, including those of the skin, pulmonary, and gastrointestinal systems, aches, pain, wounds, sprains, and liver disorders. These effects of curcumin mediated through the regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinases and other enzymes. It disrupts cell signal transduction by various mechanisms including inhibition of protein kinase C. It showed the inhibition of tumor cell proliferation and suppression of chemically induced carcinogenesis and tumor growth in animal models [1] Curcumin has antioxidant, anti-inflammatory, antiviral actions. It inhibits the growth of H*elicobacter pylori*, which causes gastric ulcers and has been linked with gastric cancers. It is used many foods as coloring, including mustard, margarine, processed cheese, cakes, curry powder, soft drinks and sweets [2]. Considering the recent scientific bandwagon that multitargeted therapy is better than monotargeted therapy for most diseases, curcumin can be considered an ideal "spice for life '[9].

Curcuma longa

Curcumin (diferuloyl methane) is a polyphenol derived from the plant *Curcuma longa*, commonly called turmeric. Extensive research over the last 50 years has indicated this polyphenol can both prevent and treat cancer. The anticancer potential of curcumin stems from its ability to suppress proliferation of a wide variety of tumor cells, down-regulate transcription factors NF-kappa B, AP-1 and Egr-1; down-regulate the expression of COX2, LOX, NOS, MMP-9, uPA, TNF, chemokines, cell surface adhesion molecules and cyclin D1; down-regulate growth factor receptors (such as EGFR and HER2); and inhibit the activity of c-Jun N-terminal kinase, protein tyrosine kinases and protein serine/threonine kinases [15].

Curcumin and Cancer

Cancer is a multifunctional disease recognized as a major worldwide health problem, affecting men and women in economically developed countries as well as in developing regions Unfortunately, cancer remains an unsolved health issue despite the significant advances in our understanding of various aspects of its initiation, progression, metastasis and interactions with the immune system and other normal cells in the tumor microenvironment. Worldwide, an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and almost 10.0 million cancer deaths (9.9 million excluding nonmelanoma skin cancer) occurred in 2020. Female breast cancer has surpassed lung cancer as the most commonly diagnosed cancer, with an estimated 2.3 million new cases (11.7%), followed by lung (11.4%), colorectal (10.0%), prostate (7.3%), and stomach (5.6%) cancers. Lung cancer remained the leading cause of cancer death, with an estimated 1.8 million deaths (18%), followed by colorectal (9.4%), liver (8.3%), stomach (7.7%), and female breast (6.9%) cancers [9, 10].

A major challenge in cancer chemotherapy has been developing safe and clinically efficacious chemotherapeutic agents. With its low toxicity profile, curcumin (diferuloylmethane), a naturally occurring flavonoid derived from the rhizome of *Curcuma longa*, has great promise. *In vitro* and *in vivo* preclinical studies have shown its inhibitory anticancer, antioxidant, anti-inflammatory, antiproliferative and proapoptotic activities [16] The multiple mechanisms of the antitumor effect of curcumin putatively include down-regulating the expression of gene products such as nuclear factor-kappa B, growth suppression, inducing apoptosis, and modulating various signal transduction pathways and the expression of many oncogenes. The mechanisms underlying the antitumor activity of curcumin have not, been completely delineated. [3] Curcumin (diferuloyl methane), the major yellow pigment from the rhizomes of turmeric (*Curcuma longa* Linn), has anticancer properties. Infection with high-risk human papillomaviruses (HPV) leads to development of cervical carcinoma, predominantly through the action of viral oncoproteins E6 and E7.The present study aims at analyzing the antitumor and antiviral properties of curcumin, on HPV associated cervical cancer cells. [11] Cancer chemoprevention involves the use of either natural or synthetic chemicals to prevent the initiation, promotion, or progression of cancer. The plant-derived compound curcumin has shown promising abilities as a cancer chemoprevention and chemotherapy agent *in vitro* and *in vivo* but exhibits poor bioavailability. Both curcumin & dimethoxy curcumin compounds were rapidly degraded *in vivo* but dimethoxy curcumin was more stable. Compared with curcumin, dimethoxy curcumin is more stable in cultured cells, more potent in the ability to kill cancer cells by apoptosis, less extensively metabolized in microsomal systems, and more stable *in vivo*. It is likely that the differential extent of apoptosis induced by curcumin and dimethoxy curcumin *in vitro* is associated with the metabolite profiling and/or the extent of stability. [7] Much of its beneficial effect is found to be due to its inhibition of the transcription factor nuclear factor kappa B (NF-kappa B) and subsequent inhibition of proinflammatory pathways [11, 22].

Curcumin exerts its anticancer activity through promoting reactive oxygen species (ROS) generation [21] A concentration-dependent regulation of Curcumin on cell proliferation, viability and ROS generation, and effect of water-soluble antioxidants ascorbic acid (ASA), N-acetyl-cysteine (NAC) and reduced glutathione (GSH) on the antioxidant and anticancer activity of Cur were investigated in human myeloid leukemia cells (HL-60 cells). Although Cur concentration- and time-dependently decreased the proliferation and viability of cells, its effect on ROS generation (as indicated by the level of malondialdehyde, MDA) varied with its concentrations. I.e., low concentrations of Curcumin diminished the ROS generation, while high Curcumin promoted it. Studies showed that all water-soluble antioxidants ASA, NAC and GSH significantly enhanced both the antioxidant and the anticancer activity of low Curcumin. Considering that the extra accumulation of ROS is harmful to normal cells [16].

Curcumin exhibits anticancer activity *in vivo* and triggers tumor cell apoptosis *in vivo* and *in vitro*. Several *in vitro* studies suggest that curcumin-induced apoptosis is associated with reactive oxygen species (ROS) production and/or oxidative stress in transformed cells. It promoted a dose-and time-dependent G2/M cell cycle arrest and/or apoptosis in COLO 16 cells. Apoptosis induction in COLO 16 cells was associated with DNA fragmentation, cell shrinkage, the externalization of cell membrane phosphatidylserine, and mitochondrial disruption, which were preceded by an increase in intracellular ROS production. Pharmacologically lowering the mitochondrial bioenergetic capacity, as well as the constitutive ROS levels, in COLO 16 cells suppressed the cytotoxic effects of curcumin [5].

It represents a near-perfect starting point for drug discovery. Consequently, a number of research groups have taken the natural product as a starting point to prepare and biologically evaluate a wide variety of curcumin analogues. One widely used structural modification truncates the central conjugated beta-dike tone in curcumin to the monocarbonyl dienone. Both simple curcumin analogues and the protein conjugate evidence antiangiogenic activity in cell culture. The implication is that the fVIIa-TF targeting process, like the dienone drugs, permits a double-pronged attack with the

potential to destroy a tumor directly by apoptosis. [4].

In *Journal of Cellular Biochemistry*, abnormal human skin cells were, likewise, exposed to curcumin and shown to be a potent inhibitor of abnormal cell growth. In another recent study out of Rutgers University, several nutrients were studied including green tea, components of red wine, and curcumin regarding abnormal cells [7]. All of these nutrients appeared to inhibit abnormal cellular growth, but by different mechanisms. In the June edition of the journal *The Prostate*, researchers from New York studied the effects of curcumin on abnormal prostate cells [5]. It was found that curcumin inhibited abnormal cellular growth by interfering with the growth factor receptor pathways and other mechanisms. Curcumin may inhibit growth factor collaboration between abnormal prostate cells and osteoblast/stromal cells. Osteoblast cells are bone-forming cells, while stromal cells are composed of connective tissue.

Curcumin to be cytotoxic to cervical cancer cells in a concentration-dependent and time-dependent manner. The cytotoxic activity was selectively more in HPV16 and HPV18 infected cells compared to non-HPV infected cells. Balance between tumor cell proliferation and spontaneous cell death via apoptosis had an important role in regulation of tumor cell growth. Curcumin-induced apoptosis in cervical cancer cells. Curcumin also down regulated the expression of COX-2, a gene regulated by NFkappa B. Binding of AP-1, an indispensable component for efficient epithelial tissue-specific gene expression of HPV was also selectively down regulated by curcumin. These results provide attractive data for the possible use of curcumin in the management of HPV associated tumors. The anticancer effect of curcumin on human B cell non-Hodgkin's lymphoma and compare its effects on human B cell non-Hodgkin's lymphoma cells and normal peripheral blood mononuclear cells (NPBMNCs).

Exposure of human hepatoma cells to Curcumin led to a significant decrease of histone acetylation. Histone acetyltransferase (HAT) and histone deacetylase (HDAC) are the enzymes controlling the state of histone acetylation *in vivo*. Curcumin treatment resulted in a comparable inhibition of histone acetylation in the absence or presence of trichostatin A (the specific HDAC inhibitor), and showed no effect on the in *vitro* activity of HDAC. Curcumin induces histone hypoacetylation *in vivo*, where the ROS generation plays an important role. Considering the critical roles of histone acetylation in eukaryotic gene transcription and the involvement of histone hypoacetylation in the loss of cell viability caused by high concentrations of Curcumin, these results open a new door for us to further understand the molecular mechanism involved in the *in vivo* function of curcumin. [15] Curcumin, its efficacy appears to be related to induction of glutathione S-transferase enzymes, inhibition of prostaglandin E (2) (PGE (2)) production, or suppression of oxidative DNA adduct (M (1) G) formation. A dose-escalation study to explore the pharmacology of curcumin in humans. Levels of curcumin and its metabolites in plasma, urine, and feces were analyzed by high-pressure liquid chromatography and mass spectrometry. Three biomarkers of the potential activity of curcumin were translated from preclinical models and measured in patient blood leukocytes: glutathione S-transferase activity, levels of M (1) G, and PGE [2] production induced ex*vivo*. Dose-limiting toxicity was not observed. Levels of curcumin and its metabolites in the urine can be used to assess general compliance. [12] Curcumin presents strong antioxidant and anticancer properties. The effect of curcumin was compared in two different leukemia cell lines: K562 and Jurkat. Cell death was induced in both cell lines, and apoptosis pathways were investigated by Western blot analysis. Decreases in pro-caspase 8 and 9 levels were observed. BH [3] interacting domain death agonist (Bid) was also cleaved. Jurkat cells appeared to be more sensitive to curcumin, and apoptosis takes place earlier. [13] Western blot and flow cytometry were used to examine the abundance of signal protein molecules expressed in tumor cells. Curcumin inhibited the proliferation of K562 cells and the inhibitory effect was correlated with down-regulation of the abundance of p210bcr/ abl, which may ultimately lead to retard the Ras signal transduction pathway [14] Curcumin might be worthy of being evaluated as a potential chemotherapeutic agent to CML Curcumin in turmeric has been widely used for centuries in the Asian countries without any toxic effects. Epidemiological data also suggest that curcumin may be responsible for the lower rate of colorectal cancer in these countries. It is a naturally occurring powerful anti-inflammatory medicine. It inhibits lipooxygenase activity and is a specific inhibitor of cyclooxygenase-2 expression. It inhibits the initiation of carcinogenesis by inhibiting the cytochrome P-450 enzyme activity and increasing the levels of glutathione-S-transferase. Curcumin inhibits the promotion/progression stages of carcinogenesis. The anti-tumor effect of curcumin has been attributed in part to the arrest of cancer cells in S, G2/M cell cycle phase and induction of apoptosis. Curcumin inhibits the growth of DNA mismatch repair defective colon cancer cells. Curcumin may have value as a safe chemotherapeutic agent for the treatment of tumors exhibiting DNA mismatch repair deficient and microsatellite instable phenotype. Curcumin should be considered as a safe, non-toxic and easy to use chemotherapeutic agent for colorectal cancers arise in the setting of chromosomal instability as well as microsatellite instability. [17] Studies revealed the potential effect of curcumin against tumour cells. Curcumin inhibited the growth and promoted cell death in three different melanoma cell lines. It appears to work by suppressing the production of the proteins in the cancer cells that normally protect the cells from cell death. Topical application of curcumin also inhibited the growth of the cancer cells Curcumin was applied as a noninvasive topical paste to the tumors and inhibition of tumor growth was observed. Curcumin can stop the spread of multiple myeloma, a cance. rof the bone marrow. Curcumin stopped the activation of processes known to lead to the spread of myeloma cells and triggered apoptosis. Apoptosis is a process where cancer cells program themselves to die. It can stop the growth of human pancreatic cancer cells, according to a study in the journal Cancer. Curcumin inhibited the production of interlukin-8, a protein produced by white blood cells that contributes to tumor growth. [23] Several plant-derived polyphenolic compounds are considered to possess anticancer and apoptosis-inducing properties in cancer cells. Such compounds are recognized as naturally occurring antioxidants but also exhibit prooxidant properties under appropriate conditions. Evidence in the literature suggests that the antioxidant properties of polyphenolics such as gallotannins, curcumin, and resveratrol may not fully account for their chemo preventive effects. [19, 29]. The active constituent curcumin in turmeric showed cytotoxicity to lymphocytes and Dalton's lymphoma cells indicated that turmeric extract and curcumin reduced the development of animal tumors.

Curcumin and Inflammation

Inflammation results from a complex series of actions and/or reactions triggered by the body's immunological response to tissue damage. The processes of healing and infection fighting produce a moderate level of inflammation. Chronic inflammation leads to degenerative conditions like arthritis, arteriosclerosis, etc. Several clinical studies have compared the effects of curcumin at dosages of 400 mg. per day to 1200 mg. per day to the drug phenylbutazone [26] Curcumin was as effective as phenylbutazone in treating post-operative and arthritis. Curcumin, the active ingredient from the spice turmeric is a potent antioxidant and anti-inflammatory agent. [18, 25] Curcumin prevents the synthesis of several inflammatory prostaglandins and leukotrienes. Curcumin has a similar action to aspirin except that curcumin does not cause vascular thrombosis the way aspirin does. Curcumin's anti-inflammatory properties may be attributed to its ability to inhibit pro-inflammatory arachidonic acid, as well as neutrophil function during inflammatory states.

Curcumin inhibits enzymes which participate in the synthesis of inflammatory substances in the body. The natural anti-inflammatory activity of curcumin is comparable in strength to steroidal drugs, and some nonsteroidal drugs, and does not have the same have dangerous side effects. It has been recently demonstrated to possess discrete Chemopreventive activities. However, the molecular mechanisms underlying such anticancer properties of curcumin still remain unrealized, although it has been postulated that induction of apoptosis in cancer cells might be a probable explanation. Curcumin was found to decrease the Ehrlich's ascites carcinoma (EAC) cell number by the induction of apoptosis in the tumor cells as evident from flow-cytometric analysis of cell cycle phase distribution of nuclear DNA and oligonucleosomal fragmentation. Probing further into the molecular signals leading to apoptosis of EAC cells, we observed that curcumin is causing tumor cell death by the up-regulation of the proto-oncoprotein Bax, release of cytochrome c from the mitochondria, and activation of caspase-3. The status of Bcl-2 remains unchanged in EAC, which would signify that curcumin is bypassing the Bcl-2 checkpoint and overriding its protective effect on apoptosis. [23] Because curcumin, a compound with anti-inflammatory and anticancer activity, inhibits induction of nitric oxide synthase in activated macrophages and has been shown to be a potent scavenger of free radicals whether it can scavenge nitric oxide directly.[20] Curcumin reduced the amount of nitrite formed by the reaction between oxygen and nitric oxide generated from sodium nitroprusside. Other related compounds, e.g. demethoxycurcumin, bisdemethoxycurcumin and diacetylcurcumin were as active as curcumin, indicating that the methoxy and the phenolic groups are not essential for the scavenging activity. Curcumin to be a scavenger of nitric oxide. Because this compound is implicated in inflammation and cancer, the therapeutic properties of curcumin against these conditions might be at least partly explained by its free-radical scavenging properties, including those toward nitric oxide [25].

It was found that mice pretreated with curcumin experienced a clear reduction in intestinal inflammation when exposed to an irritant as compared to controls. There was a reduction in DNA binding and inhibition of NF-kappa B activation. [26] Curcumin may correct a cellular malformation that causes cystic fibrosis. In experiments with mice, curcumin corrected the cystic fibrosis defect and significantly increased the survival of the mice [27].

Discussion and conclusion

In recent years, there has been a gradual revival of interest in the use of medicinal plants in developing countries because herbal medicines have been reported safe and thousands of rural communities and families still rely on folklore medicine to cure diseases in developing countries. The vitamins and nutrients rich medicinal plants effectively used for health issues invariably because of such benefits. Medicinal plants have been source of wide variety of biologically active compounds for many centuries and used extensively as crude material or as pure compounds for treating various disease conditions [24].

Free-radicals can originate from environmental chemicals, tissue injury, infections, and auto-immune processes. Antioxidants protect the body from damage from free-radicals. Extracts of turmeric and its curcumin component exhibit strong antioxidant activity, comparable to vitamins C & E. Several studies have demonstrated curcumin's ability to reduce oxidative stress. It appears that curcumin's role as an antioxidant may be due in part to its ability to down regulate nitric oxide formation. Nitric oxide is a key element in inflammation and may contribute to carcinogenesis. It has been proved already that Curcumin down-regulates NF-kappaB in human Multiple Myeloma cells, leading to the suppression of proliferation and induction of apoptosis, thus providing the molecular basis for the treatment of MM with this pharmacologically safe agent. Pharmacological studies have demonstrated that curcumin from *Curcuma longa* is an antimutagen as well as an antipromotor for cancer.

Daidzein and acetyl boswellic acid have been shown to be effective inducers of cell differentiation in HL-60 cells. Guided by the chemotaxonomic principle of plants, harringtonine and homoharringtonine isolated from Cephalotaxus hainanesis have exhibited significant antileukemia activity and are widely used in clinics in China. There is little convincing epidemiological evidence that intakes of polyphenols are inversely related to the incidence of cancer whereas a number of studies suggest that high intake of flavanoids may be protective against cancer. In contract numerous cell cultures and animal models indicate potent anticancerogenic activity by certain polyphenol mediated through a range of mechanisms including antioxidant activity, enzyme modulation, gene expression, apoptosis, up regulation of gap junction communication and P- glycoprotein activation [28].

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