MINI-REVIEW

Curcumin: a Polyphenol with Molecular Targets for Cancer Control

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Abstract

Curcumin, is a polyphenol from *Curcuma longa* (turmeric plant), is a polyphenol that belongs to the ginger family which has long been used in Ayurveda medicines to treat various diseases such as asthma, anorexia, coughing, hepatic diseases, diabetes, heart diseases, wound healing and Alzheimer's. Various studies have shown that curcumin has anti-infectious, anti-inflammatory, anti-oxidant, hepatoprotective, thrombosuppressive, cardio protective, anti-arthritic, chemo preventive and anti-carcinogenic activities. It may suppress both initiation and progression stages of cancer. Anticancer activity of curcumin is due to negative regulation of inflammatory cytokines, transcription factors, protein kinases, reactive oxygen species (ROS) and oncogenes. This review focuses on the different targets of curcumin to treat cancer.

Keywords: Curcumin - cancer - molecular targets of curcumin

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Introduction

Curcuma longa rhizome is known as turmeric, which was habitually quoted in traditional Chinese medicine & archaic medicinal transcripts for averting & remedy of human disorders. (Sharma et al., 2006). Dried turmeric powder is also used in sub-continental cooking as a key ingredient in all kinds of curry (Shanmugam et al., 2015). It is also acknowledged as Haridra, Haldi, Zirsood, Halada, Holdi, Manjaland Indian Saffron. Turmeric has been referred -Generally Recognized as Safe (GRAS) status by the USFDA (Azmi et al., 2015).

Yellow pigmented turmeric powder has plentiful curcuminoids that contain curcumin (77%), demethoxycurcumin (17%), and bis-demethoxycurcumin (3%). Curcumin is a polyphenol (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione). Curcuma designates as Ayiurvedic medicine noticeably designates curcumin as a potent active ingredient for countless ailments such as asthma, allergy, bronchial hyperactivity, sinusitis, anorexia, , cough, coryza , and hepatic disease (Shanmugam et al., 2015). Curcumin may help to avoid renal failure in diabetes (Soetikno et al., 2013), heart disease (Li et al., 2012), wound healing, Alzheimer's (Kapakos et al., 2012). There are various studies about its anti-infectious, anti-inflammatory, anti-oxidant, hepatoprotective, thrombosuppressive, cardioprotective, anti-arthritic , chemopreventive, and anti-carcinogenic properties (Chen et al., 2006; Divya and Pillai, 2006). Curcumin has also been shown to regulate multiple cellular molecular targets (Shanmugam et al., 2011).

Cancer is one of the most acute health disease worldwide, affecting peoples from different groups all sexes and ages. In 2005, cancer was the second directing factor of death among people and reported as 13% of the total 58 million deaths globally. Cancer is also a problematic economically with a very high level of expenses connected to it. For example, The National Institute of Health (NIH), USA estimates that $209.9 billion were invested in cancer research worldwide in 2005 (Donipati and Sreeramulu, 2015). Cancer is an increased cell division disease in which a healthy cell loses its cellular homeostasis and starts to constitutively stimulate cell cycle involving genes, survival, metastasis, and angiogenesis. Curcumin interacts with extracellular and intracellular targets, on the basis of different chemical characteristics, that are responsible for cancer initiation and progression, in this manner to inhibit cancer progression (Gupta et al., 2011; Shanmugam et al., 2015). Increasing evidences propose that dysfunction of inflammatory pathways have a main role in cancer occurrence (Sethi et al., 2012). Chronic inflammation causes the augmented production of pro-inflammatory molecules such as cytokines, ROS, over expression of oncogenes, intracellular signaling pathway mediators, cyclooxygenase (COX-2), transcription factors such as nuclear factor κB (NF-κB), protein kinases B (AKT), activator protein 1 (AP1), signal transducer and activator of transcription 3 (STAT3) that results in cancer initiation and proliferation (Lemmon and Schlessinger, 2010; Shanmugam et al., 2015; Siveen et al., 2014). The various molecular targets by curcumin are shortened in Figure 1.

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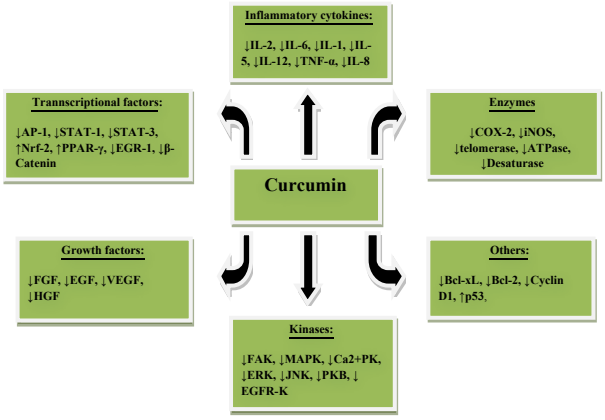

Figure 1. Different Targets for Cancer Management by Curcumin

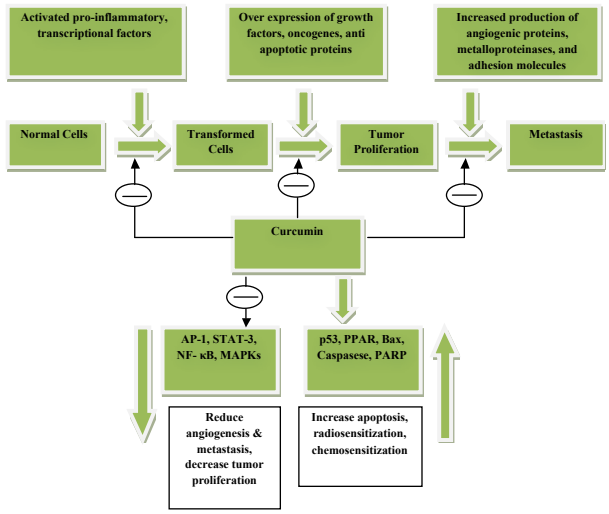

Figure 2. Potential Roles of Curcumin in Cancer

Curcumin's Target Molecules

Transcriptional Factors:

Activator Protein (AP)-1: AP-1 is related to oncogenes that stimulate mitogenic, pro-angiogenic & signals of anti-apoptosis (Lopez-Bergami et al., 2010; Roux and Blenis, 2004). ERK1/2 (MAPK family) phosphorylate and stimulate AP-1 (Kolch and Pitt, 2010) that causes up-regulation of Cyclin D1 encoded gene CCND1. AP-1 is related to cancer development and up regulation of NF-ϰB and AP-1 expression in chemo resistant and radio resistant glioma cells. Cur-cumin sensitizes human and rat glioma cells to radiation and chemical treatments in T98G, U87MG, and T67 cells, and inhibit the expression of AP-1 and NF-ϰB molecules (Shanmugam et al., 2015).

Peroxisome proliferator-associated receptor gamma (PPAR-γ): PPAR- γ related to nuclear receptor family. Activated PPAR-γ is related to cell differentiation and suppression of cancer cell growth (Gee et al., 2014) PPAR-γ was activated by curcumin that inhibit the cell proliferation followed by suppression of EGFR gene and cyclin D1 gene expression. It was reported that curcumin induced apoptosis by activation of PPAR-γ in cholangio carcinoma(Shanmugam et al., 2015).

Nuclear Factor Kappa B (NF-ϰB): NF-ϰB protein contains five different family members including NF-ϰB1, NF-ϰB2, Rel A, Rel B, and c-Rel. All members of the family have common Rel homology domain (RHD: hgv300aa). RHD is responsible for DNA binding and reacttion with inhibitor of NF- ϰB, i.e IϰBs (Low and Tergaonkar, 2013; Sethi and Tergaonkar, 2009). Various agents trigger NF-ϰB such as growth factors, viral & gram-negative bacterial products, oxidative stress inducers, mitogens, pro-inflammatory cytokines, chemotherapeutic agents, and environmental factors (such as UV, hydrogen peroxide, smoke of cigerette), and gamma radiation (Chaturvedi et al., 2011; Li and Sethi, 2010). On the activation by TNF-α and IL-1β, NF-ϰB can be phosphorylated at S19 and S23 serine residues, by both IKKα and β (Cildir et al., 2013; Sethi et al., 2008). The phosphorylated NF-ϰB moves towards nucleus and starts transcription of oncogenes that stop the apoptosis activity and begins the uncontrolled cell division &transformation, metastasis, and angiogenesis. Curcumin can abolish NF-ϰB pathway in various cancers such as breast cancer (Huang et al., 2013; Zong et al., 2012) colorectal cancer, , human bladder cancer , human oral squamous carcinoma, cutaneous T-cell lymphoma, head and neck squamous cell cancer, pancreatic cancer, adenoid cystic carcinoma, human tongue squamous cell cancer, prostate carcinoma, medulloblastoma, human biliary carcinoma, gastric carcinoma, lymphoma, ovarian carcinoma, T-cell and NFAT activation, Myeloid-derived suppressor cells, rhabdomyosarcoma, esophageal adenocarcinoma , human epidermoid carcinoma, esophageal squamous cell carcinoma, , non-Hodgkin's lymphoma , Hodgkin's lymphoma , and thyroid carcinoma (Shanmugam et al., 2015).

Nuclear factor E2-related factor 2 (Nrf2): Nrf2 is main transcription factor for genes encoding phase II anti-oxidant enzymes that is involved in detoxification process. High similarity exists between Nrf2 and ARE (anti-oxidant response element) which are acts like transcription regulators for phase II anti-oxidant enzymes such as GST. GST acts as anti-oxidant and helps in detoxification of various xenobiotic in tumor cells. Curcumin regulates anti-oxidant enzymes, inhibits p53 activation and inflammation due to oxidative stress in liver of mice. Curcumin also modulates inflammatory mediators such as COX2 & iNOS in liver of lymphoma bearing mice (Das and Vinayak, 2015).

Signal Transducer and Activator of Transcription (STAT): The STAT family has seven members: STAT 1 to 6 and STAT 5 has two members including STAT5a and STAT 5b. Their size ranges from 750 to 850 amino acids (Subramaniam et al., 2013). STAT3 protein, out of whole STAT family, is responsible for oncogenic signaling pathways, and controls intra-cellular signal transduction pathways of various pro-inflammatory cytokines and growth factors. STAT3 proteins can be activated through various cytokines (IL-6, EGFR, PDGF, leukemia inhibitory factor (LIF), Oncostatin M, and the ciliary neurotrophic factor (CNTF) family of cytokines), which mediate their signals through the gp130 protein. IL-6 release is essential event for tumor formation as its higher concentrations are associated with hepatocellular

Table 1. Curcumin's Clinical Trials for Different Types of Cancers

Types of Cancer	Dosage	Effect of curcumin	Reference
Colorectal cancer	Ingestion of 2.35 g curcuminoids (capsules) daily for 14 days.	↓cell proliferation, cell division, cell movement, and DNA damage, ↑ apoptosis	(Nunez-Sanchez et al., 2015)
Oral carcinoma	0-100 μM. less cell viability at 100 μM.	Inhibitor of AP-1 and NF-kB, also suppress HPV16/E6 oncogene	(Mishra et al., 2015)
Pancreatic cancer		Inhibit NFκB anti-apoptotic activity & anti-oncogenic activity of STAT-1 and interferon-γ production	(Fiala, 2015)
Skin cancer	1.25–3.12 μM curcumin with blue light at 405 nm combined with 630 /660 nm red light	strong anti-proliferative effect on TNF-α,↑ apoptosis, inhibited NF-κB activity	(Niu et al., 2015)
Breast cancer	300 mg/kg/day of curcumin	reduced he cell viability, ↓expression of VEGFR 2/3, deregulate the expression of cyclin D1, PECAM-1, & p65, which are regulated by NF-κB	(Bimonte et al., 2015; Ferreira et al., 2015a; Ferreira et al., 2015b)
Head and neck cancer	12.5 -25 μM of curcumin	upregulation of pro-apoptotic Bik, down-regulation AKT and NF-κB	(Xi et al., 2015)

carcinoma (HCC). Moreover, activated STAT3 has been involved in multiple cancers such as head and neck cancer, leukemias, lymphomas, and multiple myeloma, making it a potential target for cancer therapy. Under normal physiological conditions, STAT3 prevents apoptosis by up-regulating the expression of anti-apoptotic proteins such as Bcl-2 and Bcl-xL enhancing cell survival and growth. Curcumin inhibit interleukin IL-6 induced STAT3 phosphorylation and consequent STFAT3 nuclear translocation in multiple myeloma (Shanmugam et al., 2015).

Pro-inflammatory cytokines

Tumor necrosis factor alpha (TNF-α) and interleukins: TNF-α is involved in initiation & development of tumor and acts as growth factor for tumor cells. TNF-α actually activates NF-κB that involves into tumor synthesis. About all cells when come to contact with TNF-α, NF-κB activated and triggered the expression of inflammatory genes (5-LOX, COX-2, inflammatory cytokines, molecules that adhere with cells, and inducible nitric oxide synthase (iNOS) (Shanmugam and Sethi, 2013). Curcumin inhibits the expression of TNF-α at transcription level and combination with sulforaphane inhibits iNOS, TNF-α, COX-2 and IL-1. It was reported that in leukemia, curcumin inhibits the level of TNF-α mRNA in K562 cell lines(Shanmugam et al., 2015).

Oncogenic kinases: Protein kinases such as IκB kinases, MAPKs (p38 MAPK, JNK1/2) and ERK1/2 are related to the stimulation of NF-κB and AP-1 that involve in cancer progression. For cancer remedy and prevention, they are targets molecules. In pancreatic and lung adenocarcinoma cells, it has been illustrated that curcumin down-regulates ERK1/2 activity, JNK stimukation, induced by various molecules such as anisomycin, γ-radiation, ionomycin, TNF-α, UV-C etc, suppressed by curcumin (Shanmugam et al., 2015)

Induction of apoptosis occurred through increasing ROS scavenging enzymes and decreasing 4 hydroxynonenal and malon-di-aldehyde. Phosphorylation and activation of MAPK pathway factors c Jun N terminal kinase, p38 and extracellular signal-regulated kinases by curcumin, induces apoptotic activity (Yao et al., 2015).

Other Protein Kinases and Inflammatory Mediators

Cyclin D1: Cyclin D1 belongs to cyclin protein family and it is a sub unit of cdk4 & cdk6. It was studied that cyclin D1 level is very high in many types of cancers including breast, head & neck, lung, liver, colon carcinoma. Cyclin D1 is activated by NF-κB pathways. Curcumin inhibits the cyclin D1 regulation by suppressing the NF-κB pathway. In vivo, study showed that NF-κB regulated gene products like cyclin D1 inhibited by curcumin, consequently , inhibited tumor proliferation and angiogenesis (Bimonte et al., 2015)

p53: p53 is, tumor inhibitor protein, responsible for apoptosis, cell cycle, autophagy, metabolism and reactive oxygen species (Tyagi and Prasad, 2015). Inactivation of p53 and activation of NF- κB are the main cause of cancer. Curcumin induces apoptosis of cancerous cell by stimulation of p53 expression and inactivation of NF-κB. p53 dependent apoptosis prompt by curcumin in basal cell carcinoma. In human melanoma cell, curcumin up-regulates p53. In MCF7 cell lines of breast cancer, curcumin induces apoptosis by increasing level of p53, DNA binding activity and belated increase of effector Bax expression. In colorectal cancer, curcumin also up-regulates the p53 in cancerous cells and triggers apoptotic activity. In nasopharyngeal cancer, curcumin increased the level of FOXO3a and p53 (Wu et al., 2014)

Roles of Reactive Oxidative Stress (ROS)

Reactive oxidative species cause damage mutations in DNA leading to cancer disease and mitochondrial apoptosis. ROS scavenging is necessary to avoid cancer. Curcumin induced glutathione-S-transferase (GST) and quinine reductase, these enzymes neutralize ROS species. Curcumin also induces another ROS scavenging enzyme-hemeoxygenase1 that triggers regulation of nuclear factor 2. Curcumin also used ROS to kill cancer cells ((Park et al., 2013)

In Vivo Studies

Curcumin has been tested on various animal test models of cancer for various organ specific cancers such as breast, head and neck (Gao et al., 2012), oral (Zlotogorski et al., 2013), hepatocellular carcinoma, prostate, pancreatic, colon (Sareen et al., 2013), gastric (Chung et al., 2013), stem cells cancer (Norris et al., 2013) and on multi-drug resistant cancer cells or chemo resistant cells(Park et al., 2013; Shehzad et al., 2013). Figure 2 shows the potential role of curcumin to control cancer.

Clinical Trials with Curcumin

Anti-cancer activity of curcumin has been successfully illustrated by various clinical trials for different kinds of cancer including lung, breast, oral, pancreatic, colorectal, prostate, and head & neck squamous cell carcinoma (Devassy et al., 2015). Safety and efficacy of curcumin are illustrated by 65 clinical trials and 35 ongoing trials. Curcumin has been used in many countries including USA, India, South Africa, Pakistan, Nepal, Japan, China, Korea, Thailand and Turkey as supplement medicine. Limitations of curcumin are low bioavailability, low solubility & poor pharmacokinetics. These issues can be solved by effective delivery system. To increase bioavailability of curcumin, various curcumin formulations have been developed like tablets, powder, liposomal encapsulation, capsules, emulsions and nanoparticles (Naksuriya et al., 2014; Yallapu et al., 2015). Curcumin function has been increased in combination with different compounds like quercetin, docetaxel, gemcitabine, acetylcysteine, mesalamine, pantoprazole, sulfasalazine, prednisone, peperinebioperine, , lactoferrin, and soy isoflavones (Gupta et al., 2013)

Conclusion

Various preclinical and clinical trials demonstrated that curcumin is very effective to treat cancer. Different studies shows that curcumin suppresses various molecules such as AP-1, NF-κB, interleukins (IL-6) & ROS species and down regulate oncogenes, intracellular mediated pathways, STAT3 and protein kinases B so that it inhibits angiogenesis, cell proliferation, metastasis, radio resistant and chemo resistant. Clinical trials of curcumin show the safety, efficacy and non-toxicity, curcumin has approves as safe molecule to treat not only cancer but also other inflammatory diseases. However, curcumin has low bioavailability, low solubility and poor pharmacokinetics. Formulation of curcumin such as nanoparticles, liposomes, encapsulation etc, is the step to increase bioavailability and effectiveness of curcumi and hence to become a potential anti-cancer drug.

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