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Topic: Natural Products and Hepatocellular Carcinoma

Curcumin: an adjuvant therapeutic remedy for liver cancer

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ABSTRACT

The molecular signalling pathways for hepatocellular carcinoma and hepatoblastoma have been extensively studied. The treatment of these highly vascular tumors mainly revolves around chemotherapy and surgery. Yet there is a high associated morbidity and mortality due to advanced stages, adverse effects owing to chemotherapy and recurrence. The role of Curcumin as an adjuvant remedy is explored in this article. Curcumin stimulates apoptosis of cancer cells, acts as anti-proliferative agent, has anti-angiogenic action, prevents tumor invasiveness and metastasis and prevents recurrence. It also has been proven to decrease the adverse effects of chemotherapeutic agents and has a synergistic anticancer action. It acts at the molecular level and affects the various metabolic pathways involved in tumorigenesis. It also promotes healing and has anti-inflammatory, anti-oxidant and anti-infective action. This natural phytocompounds has immense anti-cancer potential and holds future promise as an adjuvant remedy to treat liver cancer.

Key words: Curcumin; hepatoblastoma; hepatocellular carcinoma; diferuloylmethane

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INTRODUCTION

Primary liver cancer characterised by active neovascularization is among the most common lethal cancers worldwide and can occur at any age. Hepatocellular carcinoma (HCC) occurs in older children and adults and has a high prevalence in developing Asian and African countries. In children under five years of age, hepatoblastoma (HB) accounts for more than 90% of primary hepatic malignant tumors and HCC for 12.5%.[1]

With recent advances in diagnostic technology, the incidence of HCC and HB has been increasing in the past decades, especially in Europe and North America.[2] Risk

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factors for HCC include cirrhosis, hepatocarcinogenic like aflatoxins and nitrosamines, dietary and environmental carcinogens by generation of reactive oxygen species (ROS) and infections like hepatitis B and C viruses.[2]

The current management of liver tumors is not satisfactory. Chemotherapy, surgery, and radiofrequency ablation are all directed at reducing the tumor bulk. However, in the majority of cases, tumor recurrence and relapse occurs on completion of therapy. Also, liver cancer is diagnosed at an advanced stage quite frequently; hence the available chemotherapy regimens fail to offer a complete cure. Even if chemotherapy has been instituted timely, the available chemotherapeutic agents are reported to show severe adverse effects. Angiogenesis plays a significant role in human HCC tumor progression and recent studies are focussing on anti-angiogenic agents targeting specific tumor vasculature.[3]

In this regard, discovery of natural phytocompounds having anti-tumor and anti-angiogenic activities could have greater clinical significance as they do not affect physiology and survival of normal cells. Many phytochemicals have proven anti-tumor action including catechins, quercetin in apples and onions, resveratorl in grapes, red wine, peanuts, and ellagic acid in pomegranates.[4-7] This review describes firstly the molecular pathology of liver cancers and then summaries the evidence based literature that describes the various proven mechanism demonstrating the anti-tumor potential of curcumin in turmeric (*Curcuma longa*) and thus exploring its role as an adjuvant therapeutic remedy for liver cancer.

CURCUMIN

Curcumin is the active phytoconstituent of turmeric. It has been widely used as a therapeutic medicine in Indian traditional medicine. Of late, scientists all over the world have recognized its therapeutic potential as an anti-inflammatory, anti-oxidant and anti-cancer agent.[8-11] Curcumin inhibits lipid peroxidation and maintains the normal concentration of intracellular antioxidant enzymes like catalase, glutathione peroxidase and superoxide dismutase and scavenges reactive oxygen species effectively.[12,13]

TUMORIGENESIS AND MOLECULAR BIOLOGY OF LIVER CANCER

Tumorigenesis of liver cancer is a complex process. The recognition of tumor stem cells and their molecular signaling has opened new pathways for therapeutic strategies. The liver has great potential to regenerate after the loss of hepatic tissue which depends on proliferation of existing mature hepatocytes.

Growth factors like hepatocyte growth factor, epidermal growth factor and transforming growth factor (TGF)-alpha control normal hepatic regeneration via DNA synthesis stimulation. TGF-β and activin serve as negative feedback mechanisms and regulate the end point of the hepatocyte proliferation. This termination is regulated by the ratio of liver to body mass thus providing a check on the extent of liver regeneration.[14]

Liver stem cells are proposed to be from dual origins, intrahepatic with short-term proliferative capacity present within the canals of Herring and interlobular bile ducts and extrahepatic derived from bone marrow and peripheral blood cells with long-term proliferation capacity.[15]

MOLECULAR SIGNALING PATHWAYS IN LIVER CANCER

Liver cancer stem cells have many signals to maintain self-renewal and pluripotency including EpCAM, Wnt/β-catenin pathway, Sonic Hedgehog pathway, and Notch pathway, which play a decisive role in the regulation and maintenance of stemness and in tumor formation. Tumorigenesis results from uncontrolled activation of these pathways. Wnt pathway proteins regulate the cellular fate and self-renewal of stem cells.[16] The Notch pathway is involved in cellular differentiation, fate of the cell, cellular proliferation, apoptosis, and cell adhesion. Notch signaling in the liver is involved in cholangiocyte differentiation.[17]

HEPATOCELLULAR CARCINOMA

EpCAM signaling pathway

EpCAM consists of a large extracellular, a single transmembrane and a short intracellular domain. There is a cross-talk between EpCAM signaling and the Wnt pathway.[18,19]

Wnt/β-catenin signaling pathway

The Wnt/β-catenin pathway is essential for development, growth, survival, regeneration, and self-renewal.[20] Disruption of Wnt/β-catenin signaling by mutational and non-mutational events is associated with many cancers, including HCC. Disrupted Wnt/β-catenin signaling pathway has been reported in around one third of all HCCs.[21] However, the point at which cross-talk occurs in the signaling cascades of Wnt/Frizzled and EpCAM remains unknown.

SALL4 signaling pathway

As an oncofetal gene, SALL4 is expressed at high levels in fetal-liver progenitor cells but not in adult hepatocytes, and it has an important role in hepatic cell lineage commitment.[22,23]

TGF-β family

The TGF-β family controls cellular differentiation and proliferation in both cancer stem cells and cancer cells. Impaired TGF-β signaling through the activation of

interleukin-6 in hepatic stem/progenitor cells can cause HCC.[24] TGF-β inhibits cell proliferation and promotes tumor cell invasion. Many studies have reported a reduction of TGF-β receptors in up to 70% of HCCs that also correlated with metastasis within the liver. On the other hand, high TGF-β levels have been correlated with advanced clinical stages of HCC. This twofold role of TGF-β signaling in HCC is explained by the tumor microenvironment and selective loss of TGF-β-induced antiproliferative pathway. Tumor cells that have selectively lost their growth-inhibitory response to TGF-β, but retain a functional TGF-β signaling pathway may exhibit increased migration and invasive behaviour on TGF-β stimulation. Cells with dysfunctional TGF-β signaling have been reported to be cancer progenitor cells giving rise to HCC.[25]

The Notch signaling pathway

This plays an important role in stem cell self-renewal and differentiation. Notch signaling is important in liver embryogenesis, bile duct formation; angiogenesis and endothelial sprouting. However, other signaling pathways have a control on whether Notch functions as a tumor suppressor or oncogene.[26] The increased expression of genes involved in this pathway has been shown in CD133-positive liver cancer cells *vs.* CD133-negative cells. The activated intracellular form of Notch-3, and the Notch ligand Jagged, is highly expressed in HCC. Activation of Notch-1 signaling increases the death receptor 5 (DR5) expression with augmentation of tumor necrosis factor (TNF)-related apoptosis-inducing ligand induced apoptosis *in vitro* and *in vivo*.[27]

Sonic Hedgehog pathway

Activation of Hedgehog signalling is related to liver cancer.[28] Up to 60% of human HCCs express Sonic Hedgehog. After specific blockade of the sonic Hedgehog pathway, concomitant down regulation of Gli-related target genes is observed. Furthermore, tumorigenic activation of SMO can mediate over expression of c-*myc*, a gene having an important pathogenic role in liver carcinogenesis.

miRNAs

miRNAs directly interact with specific messenger RNAs (mRNAs) through base pairing and inhibiting the expression of target genes. MiRNAs can undergo anomalous regulation during carcinogenesis, and can act as oncogenes or tumor suppressor genes. MiR-181 also regulates the Wnt/β-catenin signaling pathway with a positive feedback loop within stem cells. This is used by cancer cells to self-propagate continuously, metastasize and develop drug resistance.

HEPATOBLASTOMA

The best characterized pathways in pathogenesis of HB

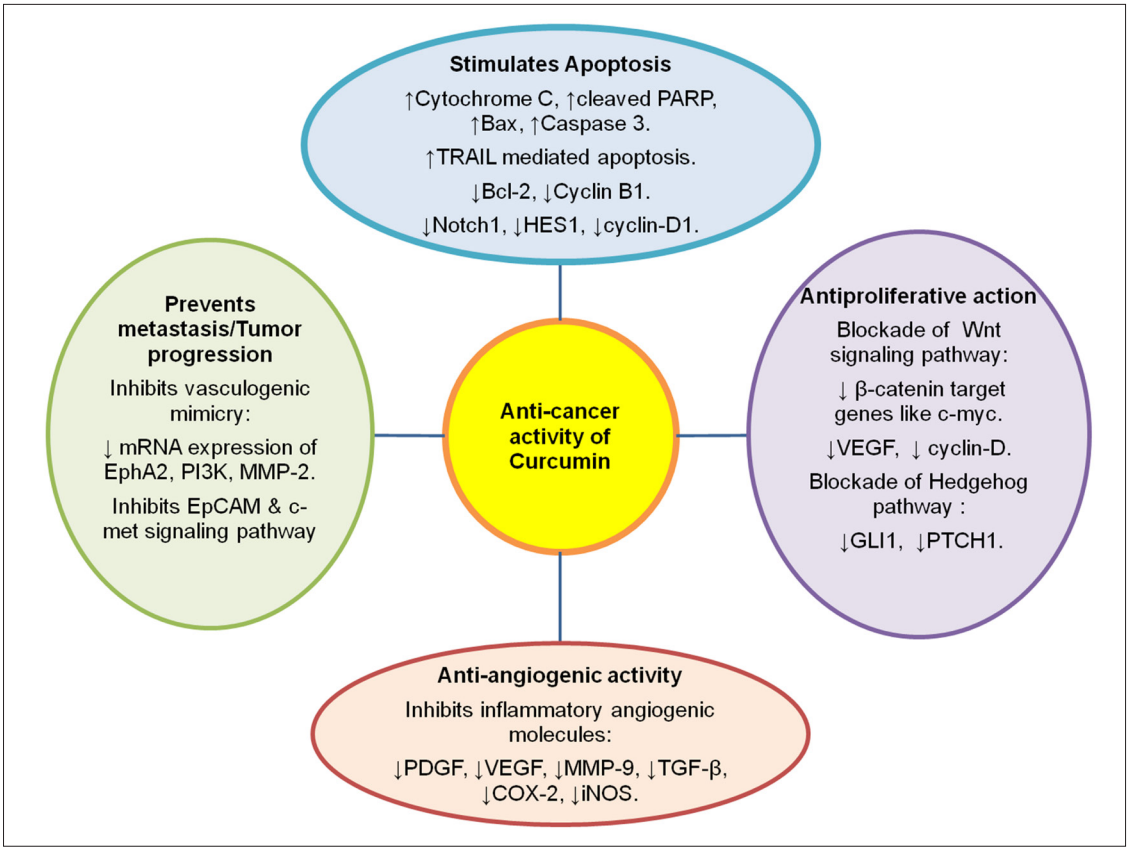

Figure 1: Flow chart depicting the various anti-cancer properties of curcumin. VEGF: vascular endothelial growth factor; MMP: matrix metalloproteinase; PDGF: platelet derived growth factor; TGF: transforming growth factor; COX: cyclooxygenase; iNOS: inducible nitric oxide synthase; EpCAM: epithelial cell adhesion molecule

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