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Review on Various Biological Activities of Curcumin

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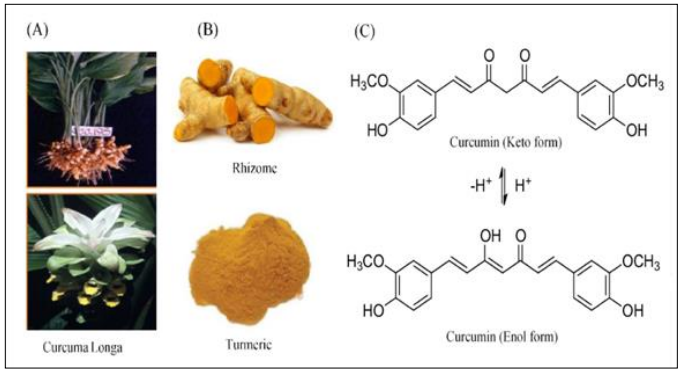
Abstract
Curcumin, a yellow substance belonging to the polyphenols super family, is the active component of turmeric, a common Indian spice, which is derived from the dried rhizome of the Curcuma longa plant. Numerous studies have demonstrated that curcumin possesses anti-oxidant, anti-inflammatory and anticancerous properties. The purpose of this review is to focus on the anti-tumor effects of curcumin. Curcumin inhibits the STAT3 and NF-κB signaling pathways, which play key-roles in cancer development and progression. Also, inhibition of Sp-1 and its housekeeping gene expressions may serve as an important hypothesis to prevent cancer formation, migration, and invasion. Recent data have suggested that curcumin may act by suppressing the Sp-1 activation and its downstream genes, includingADEM10, calmodulin, EPHB2, HDAC4, and SEPP1 in a concentration- dependent manner in colorectal cancer cell lines; these results are consistent with other studies, which have reported that curcumin could suppress the Sp. Clinical trials of curcumin have been completed or are ongoing for various types of cancer. This review presents the molecular mechanisms of curcumin indifferent types of cancer and the evidence from the most recent clinical trials.
Keywords: Curcumin, Cancer, Cell signaling pathways

Introduction

Curcuma longa, commonly known as turmeric, is a herbaceous plant belonging to the ginger family.[1] The plant produces a variety of secondary metabolites including flavonoids, alkaloids, tannins and phenolic acids [2], among which the active hydrophobic polyphenol diferuloy methane, named curcumin, is of special notice[3].Curcumin is used in the treatment of various health conditions, including inflammatory disorders, liver disease, metabolic syndrome, neurodegenerative diseases and, most importantly, in several types of cancer. The chemical structure of curcumin, as well as the most important curcuminoids, namely demethoxy curcumin and bis-demethoxy curcumin, is presented in Figures, Given below



Cancer is among the primary causes of death worldwide and, despite the high-level of global awareness and the development of multitargeted therapeutic options, death rates from cancer are still significantly high[2]. Cancer cells are characterized by disruption of several signaling pathways including those responsible for angiogenesis, proliferation, metabolism, migration,

Immune modulation and survival[3]. Curcumin has been found to affect cancer cells in a variety of ways leading to the prevention of cancer formation. Its most prominent effects on cancer are summarized in Figure 2.

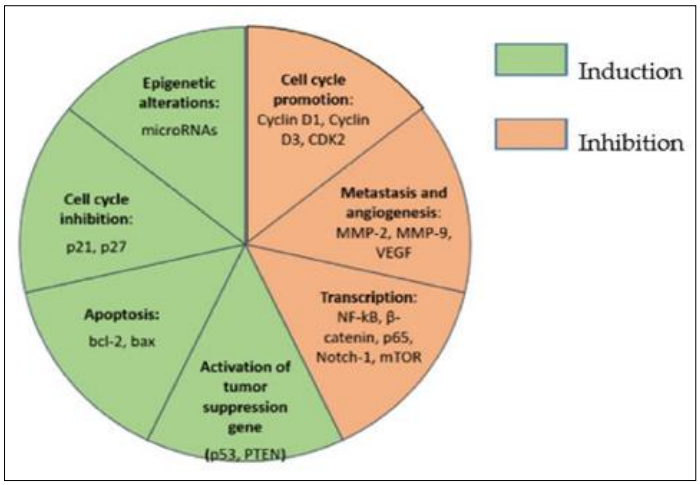


Figure No. 2 : Summarized effects of curcumin on cancer cells

Key: CDK2, cyclin-dependent kinase 2; MMP-2, matrix metallopeptidase 2 MMP-9, matrix metallopeptidase 9; VEGF, vascular endothelial growth factor; NF-kb, nuclear factor kappa-light-chain-enhancer of activated B cells, mTOR, mechanistic target of rapamycin; PTEN, phosphatase and tensin homolog; bcl-2, B-cell lymphoma-2; bax, Bcl-2-associated X protein.

Curcumin has shown promising results in the treatment of several types of cancer both alone and in combination with other antineoplastic agents. It affects several signaling pathways and can thus effectively modify both the development and the growth of various tumors.[4] This review summarizes the immunomodulatory effects of curcumin and the most recent evidence on the effectiveness of the growth of tumors[5] Curcumin acts on the regulation of different immune modulators, resulting in some of its anticancer properties.ROS are molecules derived from oxygen with the ability to act as secondary messengers in several cellular signaling pathways. They participate in inflammation and in curcumin in the treatment of different types of cancer in vitro both alone and in combination with other chemotherapeutic agents.[6]

2. Immunomodulatory Effects of Curcumin[7]

Chronic inflammation disorders and infectious diseases are responsible for the development of several types of cancer, contributing to genomic instability, which is considered a hallmark of cancer. The inflammatory process results in the production of several pro-inflammatory molecules, including reactive oxygen species (ROS),nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb), cytokines, AKT, the transcription factor activator protein-1 (AP-1), and cyclooxygenase-2 (COX-2), which are involved in both the initiation and cell survival, differentiation and proliferation, resulting in the progress of different types of cancer [11]. Curcumin binds directly to ROS scavengers and may thus suppress the growth and metastasis of some types of cancer[12].

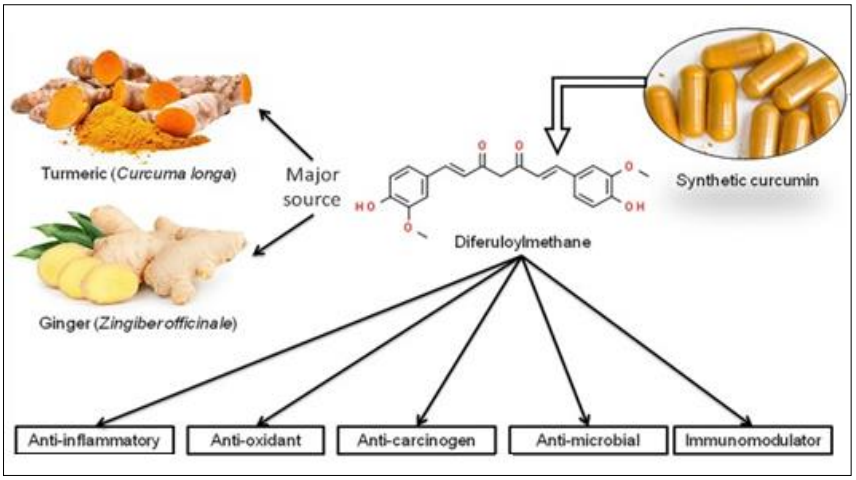


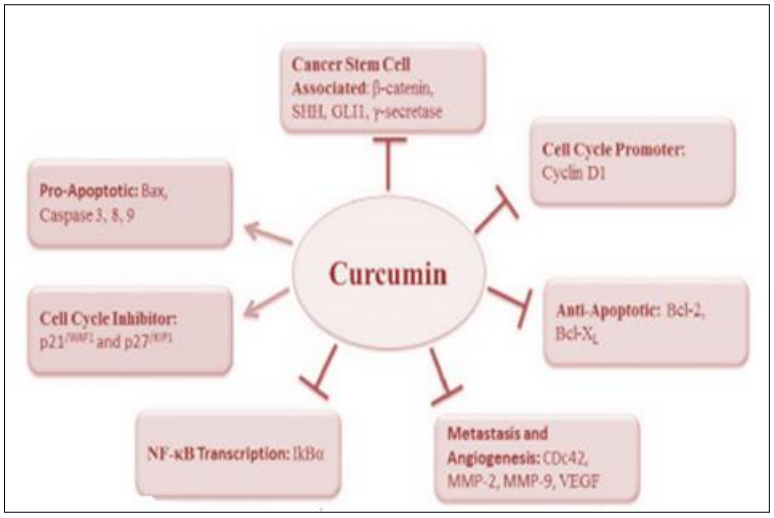
Figure No. 3 :-Immunomodulatory Effects of Curcumin[13]

Anticancer properties of curcumin

Curcumin has long been used as a dietary ingredient with known health benefits. Extensive research over the last decade has shown that curcumin possesses anticancer activities and could be used as a preventive or treatment agent against cancers, either as a single or combination therapy with chemotherapeutic agents. [14]Curcumin exhibits biological activities in various stages of carcinogenesis including inhibition of oncogenic activation, prevention of cancer-related inflammation, inhibition of cancer cell proliferation, induction of apoptosis and anionic, prevention of metastasis and sensitization of cancer cells to chemotherapy.[15]

Cancer Prevention

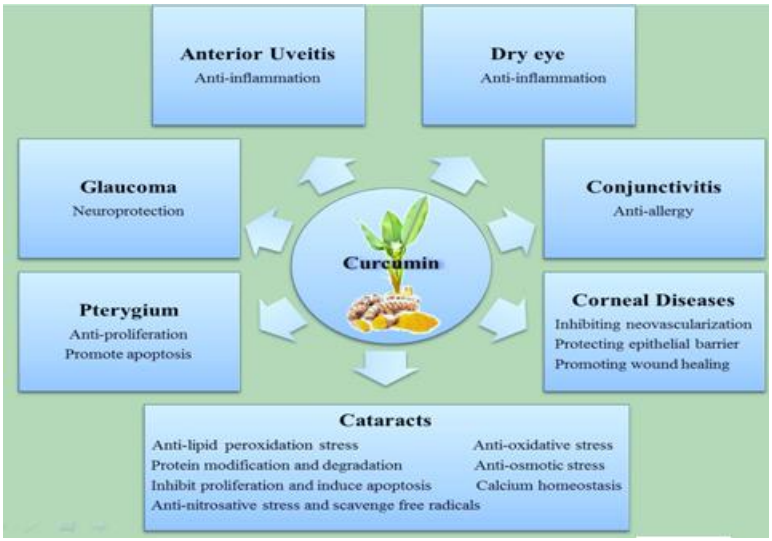
Cancer is multistep process driven by genetic instability. Continuous exposure to environment and endogenous genotoxic agents can cause substantial DNA damage. The damage molecule can be transmitted during cell division producing mutated clones that can give rise to the expansion of premalignant cell population possessing uncontrolled proliferative and invasive properties. Curcumin has been established as a chemo preventive agent that has the ability to suppress or retard the carcinogenic process induced by various chemical carcinogens [16].In animal models of gastric and colon cancer curcumin inhibits the development of cancerous and precancerous lesions induced by N-methyl-N'-nitro-N-nitrosoguanosine (MNNG), a known mutagenic agent causing DNA methylation. In the study, MNNG was given in drinking water at the concentration of 100 ppm for 8 weeks, and then 0.2% or 0.5% of curcumin was fed to the rats for 55 weeks. The results showed that the number of atypical hyperplasia in curcumin-treated rats was significantly less than that in the control group. Similarly, the curcumin analog bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione was shown to inhibit the tumorigenic effect of 1,2-dimethylhydrazine in rats (Devasena et al., 2003). Furthermore, natural and synthetic curcuminoids exhibit an inhibitory effect on mutagenesis induced by 2-acetamidofluorene (2-AAF) (Anto et al., 1996).[17] In the study, up to 87% of 2-AAF-induced papilloma was inhibited by bis-(p-hydroxy cinnamoyl)methane (curcuminoid III), while 70% and 68% of the papilloma were inhibited by feruloyl-phydroxy cinnamoyl methane (curcuminiod II) and diferuloylmethane (curcuminoid I), respectively. The most potent curcuminoid was salicyl curcuminoid which completely inhibited the papilloma formation.[18]



Anti-inflammatory activity

Epidemiological studies have supported the concept that cancers frequently originate at the site of chronic inflammation. This event has increasingly been accepted as the seventh hallmark of cancer. Inflammation is a vital physiological process in response to injury, which leads to the mediation of inflammatory cells in the presence of enzymes and cytokines for repairing tissue damage. [19] The linkage between cancer and inflammation is generally characterized as being intrinsic or extrinsic. The extrinsic pathway is induced by inflammation that facilitates cancer development, while the intrinsic pathway is driven by genetic instability causing inflammatory environment-related cancer.[20] Both processes mediate the transcription factors involved in cell proliferative function and persistent activation of this event can lead to cancer A considerable number of reports have described the linkage between cancer preventive properties and anti-inflammatory action of curcumin. Mechanistically curcumin inhibits the induction of nitric oxide synthase (NOS) by activated macrophages. [21]

Anti-Cancer Activity: Suppression of Carcinogenesis



Curcumin has been studied in multiple human carcinomas including melanoma, head and neck, breast, colon, pancreatic, prostate and ovarian cancers [22,23]. Epidemiological studies attribute the low incidence of colon cancer in India to the chemo preventive and antioxidant properties of diets rich in curcumin[24].The mechanisms by which curcumin exerts its anti-cancer effects are comprehensive and diverse, targeting many levels of regulation in the processes of cellular growth and apoptosis. Besides the vertical effects of curcumin on various transcription factors, oncogenic and signaling proteins, it also acts at various temporal stages of carcinogenesis from the initial insults leading to DNA mutations through the process of tumor genesis, growth and metastasis (Figure 2).Because of the far-reaching effects and multiple targets of curcumin on the cell growth regulatory processes, it holds much promise as a potential chemotherapeutic agent for many human cancers. Curcumin's potent anti-oxidant and free-radical quenching properties play an important role in the inhibitory effects of the compound on the initial stages of carcinogenesis. It has been shown that curcumin has the ability to suppress UV irradiation-induced DNA mutagenesis and induction of cellular SOS functions[25].Inaddition to the inhibitory effects on the production of nitric oxide and the ability to scavenge DNA damaging superoxide radicals, curcumin also affects both the Phase I and Phase II enzymes of the hepatic Cytochrome p450 enzyme system involved in the oxidation and detoxification of toxic substances. Curcumin has been shown to inhibit the Phase I enzymes (including Cytochrome p450 isoforms and p450 reductase)which are induced in response to toxin exposure and create a host of carcinogenic metabolites that contribute to DNA adduct formation during the oxidation of such substances [26]

Health Benefits of Curcumin[30]

Figure No. 6: Health Benefits of Curcumin[31]

A model illustrating the multiple molecular targets of curcumin in various cancers

Anticancer Effects of Curcumin

Curcumin was used as a remedy in ancient Chinese and traditional Indian medicine for the treatment of various ailments. The medicinal application of curcumin has been in use since the Unani and the Vedic ages. Curcumin disrupts the signaling pathways and molecular targets involved in the initiation and progression of various cancers (Fig. 6). The following are the different forms of cancer for which curcumin has been shown to be an efficacious treatment. These results fuel the momentum of its clinical use in cancer management.

Digestive System Cancers

1) Esophageal Cancer

Esophageal cancer arises in the tissues lining the esophagus ,the muscular tube through which food passes from the throat to the stomach. In the United States, there will be an estimated17,460 (13,950 men and 3,510 women) new cases resulting in15,070 (12,040 men and 3,030 women) deaths from esophageal cancer in 2012[32]. Curcumin is considered a potential candidate for the treatment and prevention of esophageal cancer due to its inhibition of inflammatory markers such as NFjB. Curcumin not only inhibits NF-jB but also increases the occurrence of apoptosis and the accumulation of drugs in the esophageal adeno carcinoma cells [33]. Additionally, treatment with curcumin reversed the bile acid induction of COX-2 and suppression of gene expression associated with sodium dismuatase-1 in the esophageal HET-1A epithelial cell lines[34].Curcumin modulates a variety of molecular targets and induces apoptosis-independent death by mechanisms such as autophagy in esophageal cancer cells[35].Recently, it has been reported that curcumin modulated Notch-1 signaling an inhibited NF-jB and its downstream targets including Bcl2,cyclin D1, VEGF and MMP-9 in oral squalors cell carcinomas[36]. Furthermore, curcumin abrogated the bile-induced NFjB activity and DNA damage, and promoted apoptosis, in vivo, as a result suggesting its chemo preventive use in the rat esophagus[37]. It has been shown that curcumin fed to rats during the cancer initiation and post initiation stages repressed the occurrence of esophageal carcinogenesis by 27 and 33%, cancer initiation and post initiation stages repressed the occurrence of esophageal carcinogenesis by 27 and 33% respectively[38].

2) Gastric Cancer[39]

Gastric cancer refers to a cancer that arises from any part of the stomach. According to the American Cancer Society survey, there will be an estimated 21,320 (13,020 men and 8,300 women) new cases and 10,540 (6,190 men and 4,350 women) deaths resulting from gastric cancer in the United States in2012

3) Intestinal Cancer

Intestinal cancer arises in the small intestine, the organ which transports food from the stomach to the colon during the digestion process.[39]

4) Hepatic Cancer:-

Hepatic cancer is also called hepato cellular carcinoma (HCC) or liver cancer, as the liver is the location where this cancer originates. In 2012, in the United States, a total of 28,720 (21,370 men and 7,350 women) new cases of hepatic cancer will have been diagnosed and 20,550 (13,980 men and 6,570 women) patients will die from this type of cancer.[40]

5) Pancreatic Cancer

Pancreatic cancer is a major cause of cancer related mortalities accounting for 6% of all cancer-related deaths in men and women. It is estimated that a total of 43,920 (22,090 men and 21,830 women) new cases and 37,390 (18,850 men and 18,540 women) deaths related to pancreatic cancer will occur in the United States in 2012 [41]

Effect on Cell Cycle Regulation and Apoptosis

Cellular growth and proliferation is a highly regulated event in normal cells, and derangements of the cell cycle can lead to uncontrolled proliferation and contribute to the malignant phenotype of tumor cells. The mammalian cell cycle consists of four main stages: G1,S, G2 and M, with G1 and G2 being referred to as “gap” phases between the events of DNA synthesis and mitosis, respectively . In addition, there is a fifth phase, referred to as G0 which represents a state of quiescence outside the cell cycle in which cells are not actively dividing or preparing to divide. Control of the cell cycle is accomplished via the coordinated interaction of cyclins with their respective cyclin-dependant kinases (CDKs) to form active complexes and drive cells into the next phase

at the appropriate time.[41] Inactivation of Rb and p53 proteins occurs by phosphorylation for the progression of the cell cycle from the G1 to the S phase. Kinase function of CDK4 is activated by cyclin D1 and inactivated by p16 proteins.

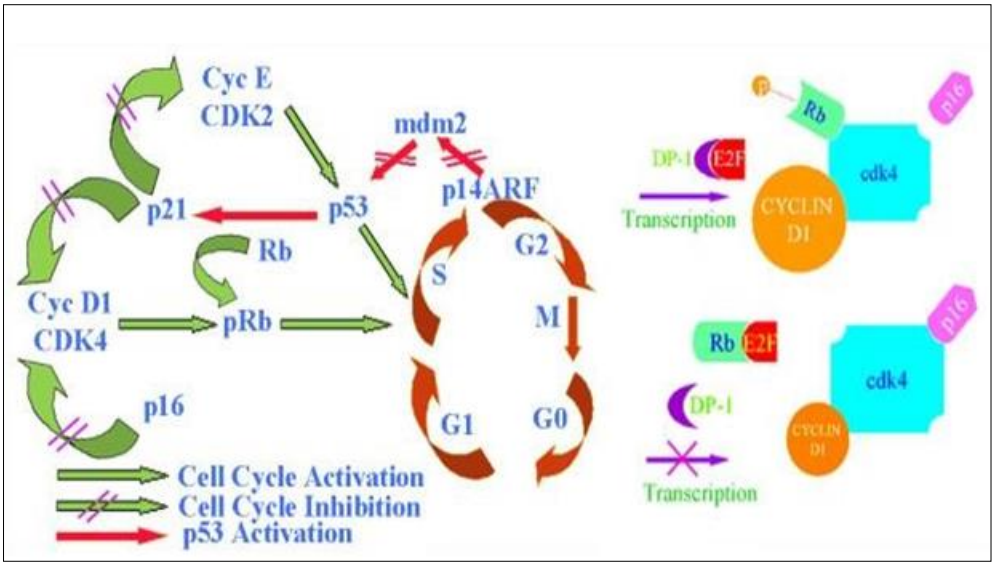


Figure No.7: Cell cycle regulation by Rb and p53 tumor suppressor proteins.

Conclusion

Cancer is not one disease but a combination of many; to effectively halt tumor progression, a drug that can target multiple dysregulated proteins would be ideal. Targeted therapies have their limitations, the most prominent being that cancer cells develop resistance to them. In some patients whose cancer develops resistance to imatinib, for example, a mutation in the BCR-ABL gene has changed the protein so, that it no longer can bind to this drug. In most such cases, another targeted therapy that could overcome this resistance is not available. Combinations of targeted therapies with either other targeted therapies or more traditional therapies may be the solution to this problem. Curcumin and its analogues have been demonstrated to possess various anticancer properties in a series of cancer cell lines, such as pancreatic, lung, ovarian, oral, colorectal, breast carcinoma and even in melanoma cells. In the future, further research will ascertain or not the potential of curcumin analogues as effective chemotherapy agents.

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