

**Effect of Curcumin on Anticancer activity: A Review**

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**Abstract**

Turmeric (*Curcuma longa*) is extensively used trendy Indian medicinal plant which belongs to the family of Zingiberaceae. Curcumin, an significant constituent of turmeric, is known for a variety of biological activities, primarily due to its antioxidant mechanism. Epidemiological annotations are suggestive that turmeric consumption may reduce the risk of some form of cancers and render other protective biological effects in humans like antidiabetic, anti-inflammatory, anti-angiogenic, anti-oxidant, wound healing and anti-cancer effects. This review summarizes the most appealing biological effects of curcumin. Curcumin is a tautomeric compound accessible in enolic form in organic solvents and as a keto form in water. This review article summarizes a different role and activity of Curcumin. The purpose of this review is to give a epigrammatic overview of the plethora of research concerning the health benefits of curcumin.

**Keywords:** Curcumin, Anticancer, Breast Cancer, Gastric Cancer, Lung Cancer, Hematological Cancer, Colorectal Cancer, Pancreatic Cancer.

**Introduction**

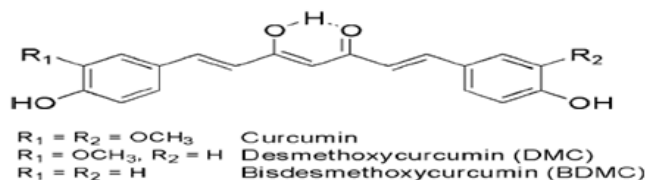
Turmeric is an Indian rhizomatous herbal plant (*Curcuma longa*) of the ginger family (Zingiberaceae) of famous medical benefits [1, 2]. Fig. 1 shows *Curcuma longa*. The medicinal benefits of turmeric could be credited to the occurrence of vigorous morality called curcumin oids. One of the most appealing components of curcumin oid is curcumin, which is a small molecular weight polyphenolic compound and lipophilic in character, hence insoluble in water and also in ether but soluble in ethanol, dimethylsulfoxide, and other organic solvents [3]. Curcumin is stable at the acidic pH of the stomach [4]. The other constituents present are volatile oils including tumerone, atlantone and zingiberone and sugars, proteins and resins [2]. The vigorous constituent of turmeric- curcumin is isolated from *curcuma longa* and it provides colour to turmeric.

Such bioactive constituent has been scrupulously investigated [5]. Curcumin (1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione) is moreover called diferuloylmethane [6]. It is a

tautomeric composite obtainable in enolic form in organic solvents and as a keto form in water Fig. 2.



Fig. 1: curcuma longa



#### Chemical Structures of Curcuminoids

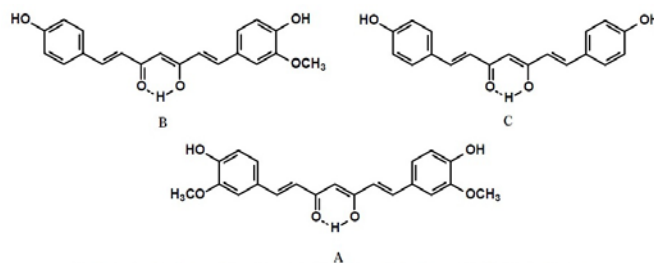
#### Chemical Properties of Curcumin

Curcumin [1, 7-bis (hydroxyl-3-methoxyphenyl)-1,6-heptadiene-3, 5-dione] (C<sub>21</sub>H<sub>20</sub>O<sub>6</sub>), is the most significant vigorous constituent liable for the biological movement of turmeric (Figure 3). It was initially isolated from the drug in 1815, but its arrangement was not elucidated awaiting 1913. Curcumin is insoluble in water, but soluble in ethanol and acetone. The naturally going on ratio of curcuminoids in curcumin are about 5% bisdemethoxy curcumin, 15% demethoxy curcumin, and 80% curcumin [7].

Curcumin is quite unstable in phosphate buffer at pH 7.4, and the stability is strongly improved by either lowering the pH, or by adding glutathione, Nacetyl cysteine, ascorbic acid or rat liver microsomes [8].

Chemical synthesis of curcumin analogues has resulted in compounds with stronger anti-oxidant and cancer chemo protective activities [9].

As a dictatorial precondition for the registration of curcumin as a prospective therapeutic agent in human medicine, a consistent process for measuring its concentration in plasma and/or urine is required. Several methods for measuring curcumin in biological fluids have been published, but more recently HPLC and isocratic liquid chromatographic (ILC) methods were developed [10, 11]. These methods were claimed by the authors to be reproducible, accurate, sensitive and specific. The assays only required minimum amounts of fluid (about 0.2 mL) and were proficient to detect concentrations of curcumin down to 2.5 ng/mL. However, this is higher than that expected to be present in body fluids of humans either consuming or being treated with the substance. Heath et al [12] have also published an HPLC method for the quantitation of tetrahydrocurcumin in plasma and urine.



Chemical structures of (A) curcumin, (B) demethoxycurcumin and (C) bisdemethoxycurcumin

#### Pharmacological Activity with Mode of Action or Biological Activities

**Anti-Viral Activity:** It has been demonstrated that curcumin as a plant derivative has a wide range of antiviral activity against different viruses: papillomavirus virus (HPV), influenza virus, Hepatitis B virus (HBV), Hepatitis C virus (HCV), adenovirus, coxsackie virus, Human norovirus (HuNoV),

Respiratory syncytial virus (RSV) and Herpes simplex 1 (HSV-1). [13,14,15,16,17] Curcumin functionalized graphene oxide shown synergistic antiviral effect against respiratory syncytial virus infection. Respiratory syncytial virus (RSV), which is measured as the most important viral pathogen of the lower respiratory tract of infants, has been implicated in severe lung disease.

Developing a  $\beta$ -cyclodextrin (CD) functionalized graphene oxide (GO) compound, which displayed tremendous antiviral activity and curcumin loading efficiently, showed that the compound could prevent RSV from infecting the host cells by unswervingly inactivating virus and inhibiting the viral affection, which obsessed the prophylactic and therapeutic effects towards virus. The antiviral produce of curcumin was a dose-dependent manner. [18] Curcumin inhibit activity of inosine-mono phosphate dehydrogenase (IMPDH) enzyme in either noncompetitive or competitive manner. By self-consciousness of IMPDH this lad to reduce the level of intracellular guanine nucleotides which required for adequate RNA and DNA synthesis. Curcumin mechanism occupy in viral entry or other life cycle stages rather than the reproduction of viral RNA. Therefore, by inhibition of IMPDH Curcumin have potential anti-proliferative, antiviral and antiparasitic effects. [19]

#### **Anti-Inflammatory Activity**

Curcumin possesses major anti-inflammatory activity in keen as well as in chronic models of inflammation. It is as potent as phenylbutazone in the carrageen an oedema test but only half as strong in chronic tests. Curcumin has been verified to be safe in six human trials and has verified anti-inflammatory activity. It may apply its anti inflammatory activity by inhibition of a number of different molecules that play a role in

inflammation. [20,21] Curcumin has been shown to control numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status and enzymes that have been allied to inflammation. [22] Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) is a major mediator of inflammation in most diseases, and this effect is regulated by the activation of a transcription factor, nuclear factor(NF)- $\kappa$ B. Whereas TNF- $\alpha$  is said to be the most potent NF- $\kappa$ B activator, the expression of TNF- $\alpha$  is also regulated by NF- $\kappa$ B. In addition to TNF- $\alpha$ , NF- $\kappa$ B is also activated by most inflammatory cytokines; gram-negative bacteria; various disease-causing viruses; environmental pollutants; chemical, physical, mechanical, and psychological stress; high glucose; fatty acids; ultraviolet radiation; cigarette smoke; and other disease-causing factors. Therefore, agents that down regulate NF- $\kappa$ B and NF- $\kappa$ B-synchronized gene products have potential effectiveness against several of these diseases. Curcumin has been shown to block NF- $\kappa$ B activation improved by several different inflammatory stimuli. Curcumin has also been shown to suppress inflammation through many different mechanisms beyond the scope of this review, thereby supporting its mechanism of action as a potential anti-inflammatory agent. [23]

#### **Anti-Oxidant**

Curcumin has been shown to improve systemic markers of oxidative stress it can modulate the activity of GSH, catalase, and SOD enzymes active in the neutralization of freeradicals. [24, 25, 26] There is evidence that it can increase serum activities of antioxidants such as superoxide dismutase (SOD) A recent systematic review and meta-analysis of randomized control data associated to the effectiveness of supplementation with purified curcuminoids on oxidative anxiety parameters—indicated a important consequence of

curcuminoids supplementation on all investigated parameters of oxidative anxiety as well as plasma activities of SOD and catalase, as well as serum concentrations of glutathione peroxidase (GSH) and lipid peroxides. It is noteworthy to point out that all of the studies included in the meta-analysis utilized some sort of formulation to overcome bioavailability challenges, and four out of the six used piperine. Curcumin's effect on free radicals is passed out by several different mechanisms. It can scavenge different forms of free radicals, such as reactive oxygen and nitrogen species (ROS and RNS, respectively) also, it can inhibit ROS-generating enzymes such as lipoxygenase/cyclooxygenase and xanthine hydrogenase/oxidase. In addition, curcumin is a lipophilic compound, which makes it competent searcher of peroxy radicals, therefore, like vitamin E, curcumin is also considered as a chain-breaking antioxidant.

#### **Anti-Bacterial**

The antibacterial study of curcumin shows the ability to inhibit growth of a variety of periodontopathic bacteria and Porphyromonas gingivitis Arg- and Lys-specific proteinase (RGP and KGP, respectively) activities. In addition, curcumin suppressed P. gingivitis homotypic and Streptococcus gordonii biofilm formations in a dose-dependent manner. Bacterial growth was concealed just about completely at very low concentrations of curcumin. A concentration of 20 µg/mL of curcumin inhibited these P. gingivitis biofilm formations by more than 80%. On the other hand, 100 µg/mL of curcumin did not restrain the growth of Aggregatibacter actinomycetemcomitans. Furthermore, at relatively high concentrations, curcumin targets bacterial membranes (Escherichia coli). [32,33]

#### **Anti-Arthritis**

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is characterized by hyperplasia of the synovial fibroblasts. Curcumin is known to possess potent anti-inflammatory and anti-arthritic properties. Curcumin treatment was carried out on patients with active rheumatoid arthritis and compared with diclofenac sodium reference group. Fascinatingly, the curcumin group showed the maximum percentage of perfection in overall rheumatoid arthritis scores and these scores were extensively better than the patients in the diclofenac sodium group. More prominently, curcumin group was initiated to be safe and did not relate with any adverse events compared to diclofenac sodium group. It is believed that curcumin antioxidant, antiproliferative, anti-inflammatory and immune suppressive activities shared in the improvement of symptoms to patients suffering from rheumatoid arthritis. [34]

#### **Anti-Cancer**

One-fifth of the deaths worldwide annually are caused by various types of cancers. Cancer is a result of successive genetic and epigenetic alterations resulting in apoptosis, uncontrolled cell proliferation, metastasis, and angiogenesis. [27, 28] Anti-cancer activity of curcumin has been extensively investigated recently, and significant improvements in gastrointestinal, melanoma, genito-urinary, breast, and lung cancers have been seen [29,30] Many studies pointed out anticancer activities of curcumin alone or in combination with conventional chemotherapy drugs in treatment of cancer and its cancer-related complications.

In-vitro and in-vivo studies have specified that curcumin avoids carcinogenesis by involving two primary processes: Angiogenesis and tumor growth. Curcumin analogs

S1- S3 containing sulfone strongly inhibited the growth of human prostate, colon, lung and pancreatic cancer cells. Scientific studies of plants used in various types of ethnic medicine have led to the discovery of many valuable drugs, including taxol, camptothecin, vincristine and Vinblastine. [31]

### **Breast Cancer**

Nowadays, breast cancer is the most widespread malignant tumor among the female adult population. It is the leading cause of death due to the presence of cancer in women around the world [35]. Although the best approach to enhancing breast cancer outcomes and survival remains early detection, the use of different drugs is still an effective treatment for breast cancer. Because more than 70% of breast cancer cases are estrogen receptor (ER) positive type, antiestrogens are often used as the main treatment. However, growing evidence has shown that the combination of different drugs represents the best strategy in breast cancer management.

In the proliferation of breast cancer cells, NF- $\kappa$ B—the pro inflammatory transcription factor plays a key role. It regulates more than 500 different genes and governs the expression of proteins involved in cellular signaling pathways, resulting in the development of cancers and inflammation. Compounds able to interact with NF- $\kappa$ B, by its inhibition, may be used in cancer therapy. Curcumin displayed the ability to affect the breast cancer cell proliferation and invasion by downregulating the NF- $\kappa$ B inducing genes [36].

Another target that acts on the proliferation of breast cancer cells is the human epidermal growth factor receptor 2 (HER2), a tyrosine kinase (TK) receptor belonging to EGFR family. The HER2 is considered as a drug target for cancer therapy since its overexpression is involved in the development of many types of cancer.

Curcumin, alone or in combination with its analogues, may inhibit breast cancer cell lines though inhibiting of HER2-TK [37]. Its suppressing action towards HER2 was improved in selectivity by immune-liposome encapsulation.

### **Lung Cancer**

Lung cancer is a widespread tumoral disease and it is the major cause of cancer-related mortality in men worldwide. Depending on the stage and the tumor's aggressiveness, the five-year survival rate in populations with lung cancer varies from 4–17% [38]. Recently, much progress has been made in regards to improving early diagnosis, lung cancer screening, and innovative therapies.

Curcumin exhibited its therapeutic efficiency in lung cancer treatment by means of the downregulation of NF- $\kappa$ B in human lung cancer cell lines A549 and also by acting on the JAK2/STAT3 signaling pathway, inhibiting JAK2 activity. Further more, curcumin self-conscious cell proliferation and induced apoptosis of human non-small cell lung cancer cells via the upregulation of microRNA-192-5p and restraint of the PI3K/Akt signaling pathway [39].

### **Hematological Cancers**

Hematological tumors include different group of cancers that affect the blood, bone marrow, and lymphatic systems. The most widespread categories are lymphoma, leukemia, and multiple myeloma [40].

Leukemia is a cancer concerning the blood or bone marrow characterized by an anomalous proliferation of blood cells. Curcumin has been found to suppress TNF- $\alpha$ -induced nuclear trans location and DNA binding of NF- $\kappa$ B through suppression of I $\kappa$ B $\alpha$  phosphorylation and degradation in the human myeloid ML-1a cells. Moreover, curcumin exhibited apoptosis in B-cell chronic lymphocytic leukemia (CLL-B) via



downregulation of STAT3, AKT, NF- $\kappa$ B, and X-linked inhibitor of apoptosis protein (XIAP). It also upregulated the pro apoptotic protein BIM [41].

### **Gastric Cancer**

Gastric cancer is one of the prominent causes of mortality worldwide in men and women. It is often diagnosed in the final stages because of the absence of symptoms in early stages of development [42].

Many studies reported the pharmacological efficiency of curcumin in the treatment of gastric cancer.

Curcumin exerted its antitumor action by means of inhibition of anti apoptotic proteins of the Bcl-2 family and elevated the expression of p53, Bax, procaspases 3, 8, and 9.

Curcumin caused dissipation of mitochondrial membrane potential (MMP) and the release of cytochrome c into the cytosol of SGC-7901 cells eliciting apoptosis. Moreover, the downregulation of Bcl-2 and upregulation of Bax that provoked the cleavage of caspase-3 and increased cleaved PARP was also reported [43].

The strong antioxidant activity exhibited by curcumin by inhibition of ROS also contributed to cancer chemoprevention.

### **Colorectal Cancer**

Colorectal cancer is one of the most widespread cancers, affecting men and women equally. Because of its malignant features, patients rarely heal, and recurrence is common. In colorectal cancer, curcumin exhibited its therapeutic action by affecting several cell signaling pathways.

Curcumin inhibited DMH (1,2-Dimethylhydrazine)-induced rat colorectal carcinogenesis and the growth of the in vitro cultured HT 29 cell line by suppressing the PPAR $\gamma$  signal transduction pathway [76]. In addition, curcumin also suppressed the expression of

cyclooxygenase-2 (COX 2), p53, and pre-mRNA processing factor 4B (Prp4B) [44].

The AMP-activated protein kinase (AMPK) pathway has gained more interest as an important pathway involved in cancer control. Curcumin has been reported as an inhibitor of colorectal cancer invasion by means of AMPK-induced inhibition of NF- $\kappa$ B, uro kinase-type plasminogen activator (uPA) activator, and matrix metalloproteinase-9 (MMP9) [45]

### **Pancreatic and Hepatic Cancers**

Pancreatic cancer is a very fatal type of cancer with a one-year survival rate of only 10–28% and a five-year survival rate of around 7% [46]. Mutations in oncogenes and tumor suppressor genes as well as alterations of different signaling pathways are involved in the initiation, promotion, and progression of pancreatic cancer.

Curcumin has been shown to have an effect on pancreatic cancer cells' vitality, in vitro and in vivo, by means of inhibition of NF- $\kappa$ B, COX-2, CD-31, VEGF, and IL-8. In addition, curcumin treatment also inhibited STAT3 activation in patients with pancreatic cancer [47].

In pancreatic cancer cells, curcumin has been reported to induce FoxO1 expression in pancreatic cancer cells by acting on PI3K/Akt signaling, which caused cell cycle arrest and apoptosis induction. Moreover, curcumin induced apoptosis by inhibition of PI3K/Akt signaling and upregulation of PTEN [48]

### **Other Cancers**

The second most common type of cancer diagnosed in men is prostate cancer. In prostate cancer, curcumin exhibited its therapeutic effects by modulating multiple cell signaling pathways. In human androgen-independent (DU145) and androgen-dependent (LNCaP) prostate cancer cell lines, curcumin decreased

the expression of antiapoptotic genes Bcl2 and Bcl-xL, and induced procaspase-3 and procaspase-8 leading to apoptosis. Treatment of cells with curcumin inhibited both constitutive (DU145) and inducible (LNCaP) NF- $\kappa$ B activation, and potentiated TNF-induced apoptosis [49].

Curcumin has been reported to abolish CAF (cancer-associated fibroblast)-induced invasion and EMT (epithelial–mesenchymal transition), and inhibited ROS production and CXCR4 and IL-6receptor expression through inhibiting MAOA/ mTOR/ HIF-1 $\alpha$  (monoamine oxidase A/mammalian target of rapamycin/hypoxia-inducible factor-1 $\alpha$ ) signaling, thereby supporting the therapeutic effect of curcumin in prostate cancer [50].

### Conclusion

Curcumin has show worldwide used for its complete benefits for health, which appear to act primarily through its anti-oxidant and anti-inflammatory mechanisms. These benefits are best achieved when curcumin is combined with agents such as, carbohydrates, piperine, which increases its bioavailability significantly. Research suggests that curcumin can help in the management of oxidative and inflammatory conditions, metabolic syndrome, anti inflammatory, anxiety, and antidiabetic hyperlipidemia. It may also help in the management of multification used of Pharmacological activity in health and also improve the health for body benefits for human health, thus enhancing recovery and subsequent performance in active people. In additional, a relatively sufficient dose can provide health benefits for people that do not have diagnosed health conditions.

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