

## **Turmeric (*Curcuma longa*): from a variety of traditional medicinal applications to its novel roles as active antioxidant, anti-inflammatory, anti-cancer, and anti-diabetes.**

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**ABSTRACT.** *Curcumin longa*, which is commonly known as Turmeric, is an herbaceous perennial plant from the *Curcuma* genus that prospers in mainly Eastern Asia. Through a series of forms including powder and extract, the plant has been traditionally used to assist in inflammation and wound healing. Turmeric has been shown to alleviate the pain of inflammation in diseases such as rheumatoid arthritis and psoriasis, overall promoting the immune system response of acute inflammation for its therapeutic abilities and alleviating chronic inflammation. Not only has it been shown to assist in inflammation, but Turmeric has been shown to assist in preventing and battling cancer through its cytotoxic activities while boosting apoptosis to control the growth and distribution of cells. Along with these abilities, this plant assists with the pain and inflammation involved with diabetes. Turmeric is able to do this because of it being largely composed of a substance called Curcumin, a mixture of Turmeric oil and resin.

### **1. INTRODUCTION**

Turmeric (*Curcumin longa*) belongs to the genus *Curcuma*, a member of ginger family, Zingiberaceae [1, 2]. Turmeric, a rhizomatous herbaceous perennial plant with oblong, pointed leaves and funnel-shaped yellow flowers, grows up to 1m high with a short stem and is mainly distributed in China, India and Asia [2]. The rhizomes are boiled, dried, and then ground to prepare distinctive bright yellow spice powder that is widely used as a natural food product in curry powder and food-coloring agent in Asian cuisine [2, 3]. Turmeric rhizome powder, as natural food preservative, preserves the freshness of the food through its antioxidant mechanism and add unique flavor and fragrance to the food [4, 5, 6, 7]. A mixture of turmeric powder and lime has been used as a household remedy to treat inflammation and assist in wound healing [8]. *Curcumin longa* also is an effective home remedy for diarrhea, sore throat, cough, and the common cold, when taken orally with tea or hot milk.

Commercially available natural Turmeric contains three curcuminoids: curcumin (75%), demethoxycurcumin (15%), bisdemethoxycurcumin and also volatile oil (10%).[9] Curcumin (diferuloylmethane), the main biological active polyphenol component of Turmeric, is believed to have numerous putative health benefits in almost all disorders of the body.[10] The word curcumin stems from the Persian word “kurkum”[*curcuma*], which means saffron, making up 2% to 5% of the spice [8, 11].

Curcumin [1,7-bis(4-hydroxy-3methoxypheny)-1,6-heptadiene-3,5-dione] is a mixture of resin and Turmeric oil and also a hydrophobic molecule that passes easily through the plasma membrane into the cytosol of the human cells.[12] It is a lipophilic molecule that is stable in the acidic environment of the stomach.[9] Curcumin works by modulating multiple molecular targets while using cell signaling proteins, cell cycle protein, cytokines and chemokines, enzyme, receptors and cell surface adhesion molecules.[9] Numerous lines of evidence revealed that curcumin, the key active constituent of *C.longa* extract, contains hepatoprotective, renoprotective, antiproliferative, and anti-tumor agent properties.[13] The combination of Curcumin ingestion with aerobic exercise training has been shown to increase vasodilation, which also decreases blood pressure.[7]

## 2. COMPOSITION

Turmeric is a rich source of various volatile oils, including turmerone, atlantone, zingiberone, and other constituents such as sugars, proteins, resins, lignin, salts, resins. The root contains 10% resin which is a glucoside.[14] It is a very rich source of many essential vitamin such as vitamins A, E and C. It is evident that the essential oil that contains extracts of Turmeric and its curcumin component exhibit strong antioxidant activity due to vitamins C and E and has a beneficial effect on gastrointestinal tract and liver ailments due to the p-tolyl methyl carbinol.[6] Recent studies reveal that this volatile oil in turmeric assists in the treatment of inflammation in the digestive system and hepatitis.[6] Turmeric powder has been traditionally used in Indian cooking as a rich source of fat, magnesium, and silicon and is high in iron, manganese, niacin, potassium, selenium, and sodium.[6] Phytochemical studies of turmeric have shown the presence of curcumin, demethoxycurcumin, bisdemethoxycurcumin, zingiberene, curcumenol, curcumol, eugenol, tetrahydrocurcumin, triethylcurcumin, turmerin, turmerones, and turmeronols.[15] Turmeric is made up three curcuminoids: 75% diferuloylmethane (also called curcumin), 16% demethoxycurcumin, and 8% bisdemethoxycurcumin. The present data revealed that most of the therapeutic effects of Turmeric are due to presence of curcumin. [15] Curcumin is also the component that gives turmeric its yellow colour.[14, 15]

Curcumin, a polyphenol compound with a molecular formula  $C_{21}H_{20}O_6$ , can exist in two tautomeric forms: a keto form (an aldehyde) and a stable enol form (an alcohol).[15] Curcumin is an oil-soluble pigment, hydrophobic in nature at an acidic and neutral pH, and soluble in alkali, acetone, methanol and ethanol.[5] Curcumin is stable at high temperatures but unstable in the presence of light, and precautions should be taken to avoid exposure.[14] When curcumin comes in contact with any acidic conditions, its color turns from yellow to deep red.[5]

## 3. BIOAVAILABILITY

Although curcumin has many health benefits, it has been shown to have extremely low-serum levels, limited tissue distribution and half-life after oral administration. This appears to be due to poor absorption, high rate of metabolism in the liver and intestinal wall, inactivity of metabolic products and/or rapid elimination and clearance from the body. These are the effects of reduced bioavailability of curcumin. Therefore, poor bioavailability of curcumin limits its therapeutic efficacy.[14]

By giving attention to the most effective roles of this plant against numerous human disorders, an intense search has been commenced for curcumin without these problems. The use of adjuvants such as piperine that can block the metabolic pathway of curcumin is the most common way to increase its bioavailability.[16]

Piperine is an inhibitor of hepatic and intestinal glucuronidation of curcumin.[17] The pilot studies summarized that piperine enhances the serum level and the extent of absorption and bioavailability of curcumin in both rats and humans with no adverse effects. Concomitant administration of curcumin raised the bioavailability rate up to 2000% in the patients.[17]

The curcumin phytosome preparation, which is the complexation of curcumin with phospholipids, show significantly higher serum concentration compared with curcumin extract due to their enhanced capacity to cross the lipid bio-membranes and to reach the systemic circulation.[14]

The phytosomized extract enhances oral bioavailability and its tissue distribution of curcumin in the spleen, heart, liver, kidney, lung and brain.[18] Other approaches have been undertaken to improve the bioavailability of curcumin, such as the use of nanoparticles, liposomes, micelles, and structural analogues.[19]

#### 4. CLINICAL EFFICACY AND MECHANISM OF ACTION

##### 4.1. Anti-cancer Effects

Cancer is characterized by an abnormal increase in cell proliferation and in some cases spreads to other parts of the body.[16] Curcumin is known for its cytotoxic activities against cancer cells of the blood, skin, oral cavity, lung, pancreas, and intestinal tract and represses angiogenesis and metastasis in animal models. The study shows that there is a significant inhibitory effect on the proliferation, transformation, and metastasis of tumors with the use of curcumin in a patient with the cancer.[20]

The major mechanisms by which curcumin induces cytotoxicity in tumor cells are regulation of various transcription factors, growth factors, inflammatory cytokines, protein kinase, and other enzymes. Curcumin also down regulates expression of genes promoting cell proliferation, angiogenesis, and resistance to chemotherapy.[20]

The anti-proliferation effect of curcumin is mediated by arresting the tumor cells in the cell cycle's regulatory proteins. However, the effect depends on the concentration of curcumin, duration of treatment and the cell type. Cyclin D1 is an important protein that regulates cell cycle progression through the G1 phase of the cell cycle and can function as a transcriptional co-regulator. The overexpression of cyclin D1 has been linked to the development and progression of the breast, esophagus, head and neck, and prostate cancers.[20]

Apoptosis is the death of a cell that occurs as a normal and controlled part of an organism's growth. It is now clear that some oncogenic mutation disrupts apoptosis, leading to tumor initiation, progression and metastasis. A cancer study shows that curcumin is a cytotoxic anticancer agent and induces apoptosis by activating CHOP/GADD135, an activator of apoptosis.[20]

Curcumin has been shown to have cytotoxic and DNA damaging activity in human hepatoma HepG2 cell *in vitro* condition. *Curcumin longa* demonstrated a strong cytotoxic activity on the human colon carcinoma by inducing G2/M phase cell cycle arrest in tumor cell.[20] Most primary solid tumors are dependent on angiogenesis for survival, growth, invasion and metastasis. In a study, it was found that curcumin shows an inhibitory response on the proliferation of human vascular endothelial cells *in vitro* and suppresses the FGF-2-induced angiogenic response *in vivo* which could be a starting point for the development of a new anti-angiogenic drug.[20]

Chemotherapeutic drugs such as doxorubicin, tamoxifen, cisplatin and camptothecin have a cytotoxic effect on cells. Curcumin showed important anti-cytotoxic effects against chemotherapeutic drugs. The radio protection and radio sensitization effects of curcumin play an important role in the management of the cancers. The radiation and curcumin at 2 and 4-M concentration synergistically demonstrate significant enhancement in the treatment of tumors that recur and become radio resistant.[20]

Curcumin is the primary curcuminoid being studied in vast areas of chemopreventive and chemotherapy activities against many tumor cell lines. Several studies have been performed on the use of curcumin in the inhibition of proliferation of a variety of cancer cell lines including brain, cervical, prostate, breast, gastric, hepatic, leukemia, oral epithelial, ovarian, pancreatic, bladder, and colon tumor cell.[21, 22] curcumin also leads to apoptosis in DU145 prostate carcinoma, A549 lung carcinoma, and HT29 colon carcinoma with an IC<sub>50</sub> (50% inhibitory concentration) of about 10-75  $\mu$ M.[23]

Curcumin has the ability to inhibit proteins that enhance cell proliferation (cyclin D1) and angiogenesis (VEGF). In one study, the inhibitory effect of Curcumin on the proliferation,

migration, and other function of the cancerous B16F10 cell demonstrates its potential use as an anti-carcinogenic and anti-metastatic in the brain. The use of solubilized curcumin by intracranial injection as an anticancer agent could eliminate the adverse side effects of chemotherapy and radiation therapy.[21]

Curcumin shows synergistic and potentiating effect with anticancer drug such as 5-fluorouracil (5-fu), all-trans retinoic acid, cisplatin, celecoxib, and doxorubicin.[22] Curcumin has the ability to eliminate superoxide anions, hydroxyl radicals, peroxides, and nitrite radicals that are carcinogenic reactive oxygen species.[22]

To overcome its poor bioavailability, curcumin has been polymerized by a condensation reaction to produce a polymer that has backbone-typed, curcumin-derived high polymers. These curcumin-containing polymers are water-soluble curcumin and have more cytotoxic activity toward OVCAR-3 (ovarian adenocarcinoma), MCF-7 breast cancer cell lines than curcumin.[23]

It is now well established that curcumin has the ability to induce apoptosis in cancer cell line while not affecting the normal function of the host cells.[24] Curcumin, a well-described phytochemical, has been shown to be an efficacious treatment for cancer because it has shown free radical scavenging activities.[25] Curcuminoids present in Turmeric also affects multiple processes and signaling pathways that initiate and proceed to various cancer cell lines.[16]

Esophageal cancer is cancer that occurs in esophagus- a tube that runs from the throat to the stomach- and usually begins in the tissue lining the inside of the esophagus. Curcumin was found a good candidate for preventing and treating esophageal cancer, thereby suggesting its potential for the inhibition of inflammatory markers such as NF-kB and increasing the incident of apoptosis.[16]

The mechanism of action of curcumin in treatment of gastric cancer has been shown by decreasing the expression level of human epidermal growth factor receptor 2 and the activity of p21- activated kinase1. Curcumin also causes growth inhibition in human gastric cancer cell lines by the induction of G1-phase to S phase arrest through the downregulation of cyclin D1.[16]

According to several studies, Curcumin can be a good source for being used for treating hepatocellular carcinoma (HCC) or liver cancer. The studies show that there is a significant inhibitory effect on MMP-9 secretion in HCC cells with the use of curcumin. In the study, curcumin found in Turmeric effectively suppressed the expression of Chk1 protein, arrested the cell cycle at the G2/m phase and caused apoptosis in hepatoma cell lines.[16]

#### **4.2. Anti-oxidant Effects**

Antioxidants play a very important role in protecting the body against the oxidative stress and free radical damage which often are the cause of various diseases.[26] It has been suggested that antioxidant activity of curcumin is an important property of Turmeric plant used in treatment of chronic diseases, DNA damage, mutagenesis, carcinogenesis and inhibition of pathogenic bacterial growth.[26]

The antioxidant properties of curcumin have been studied extensively, and are found to be related to the hydroxyl group or the methylene group of the  $\alpha$ -diketone (heptadiene-dione) moiety.[26] Curcumin, water, and fat soluble of turmeric have shown to have an antioxidant effect comparable to vitamin C and much more than that of the radical-scavenging activity of vitamin E.[6, 14] Tetrahydrocurcumin, a major metabolite of curcumin, is an antioxidant substance which has protective effect on oxidative stress in the body. The bioavailability of curcumin is due to the presence of tetrahydrocurcumin antioxidant action.[13]

The phenolic groups are an important component of curcumin and induce hydrogen bond acceptor activities.[13] Curcumin has shown to be a very significant scavenger of free radicals including hydroxyl radicals and nitrogen dioxide radicals. In addition, curcumin exhibits a potent lipid-soluble antioxidant and also inhibits lipid peroxidation in animal models.[26] Curcuminoids are natural phenols that exist in enolic and  $\beta$ -diketone forms. Curcumin possess both phenolic groups and  $\beta$ -diketonics (two types of natural antioxidant) in the same molecule.[14] The protective effect of

curcuminoids in turmeric on human keratinocyte from hypoxanthine/xanthine oxidase injury have been proven.[25]

The essential trace elements of turmeric plant such as Fe, Cu, Zn, Mn, Ca, Mg and Se are known to possess strong antioxidant effects. These metals are involved in constituents of superoxide dismutase, oxide reductase, glutathione and metallothionein which could increase the production of metal-dependent enzyme, thereby the accumulation of pathological concentration of oxygen radicals would be decrease.[13]

In chronic liver disorders (alcoholic and nonalcoholic fatty liver diseases and drug-induced liver injury caused by the imbalanced defense mechanism of antioxidants and overproduction or incorporation of free radicals), biological molecules and key cellular component in the liver are damaged by ROS production. The antioxidant medicines may have beneficial effect, but for the long-term use, they are associated with serious complication.[27]

In the study done on 18 healthy men for 75 days, it was found that the hydroalcoholic extract of *curcumin longa* are mainly responsible for decreasing in concentration of serum lipid peroxide.[25] Studies revealed that fermented *Curcuma longa* L. (FC) has the hepatoprotective effect. FC improves the impaired antioxidant status in the rat liver, as indicated by decreasing oxidative stress via preventing lipid preoxidation and improving hepatic antioxidant status.[27]

If the liver is damaged, the liver enzymes ALT and AST will increase in the blood, signaling liver disease. Thus, the reduction of ALT and AST levels cause improvement in hepatic function.[28] Beneficial effects of curcumin on hepatic function is related to its pleiotropic anti-oxidant activity. It prevents formation and scavenges reactive oxygen species and reactive nitrogen species.[28]

#### 4.3. Anti-diabetes Effects

More than two hundred million people around the world are affected by Diabetes mellitus (DM). These numbers are expected to double in fifteen years. The most important medical concern following DM would be its effect on the organs of the body. Hyperglycemia (high level of sugar in the blood) can cause many complications in diabetic people.[29]

The effect of curcumin on a variety of diseases has been widely studied during past decades.[29] A study shows that curcumin can have possible hypoglycemic effects through some functions, including the increase of blood insulin levels by stimulating the function of surviving pancreatic beta cells, decreasing the amount of beta 2-adrenoceptors, and upregulating the activity of the insulin receptor gene in the skeletal muscle of STZ-induced type1 diabetic rats.[29]

The data shows that curcumin can be effective in improving the pathological changes related to chronic diabetic conditions by suppressing the inflammation, oxidative stress, hyperglycemia and hyperlipidemia. However, the effectiveness of curcumin is limited because of its poor bioavailability. Recently, some improved formulations of curcumin have been designed to increase its physicochemical and pharmacokinetic properties.[29]

In patients suffering from diabetic nephropathy, which is the most serious complication of diabetic mellitus, the intake of curcumin supplementation at the dose of 66.3 mg per day for eight weeks was effective in reducing proteinuria (abnormal amount of protein in the urine), hematuria (blood in the urine), and systolic blood pressure in patients with uncontrollable lupus nephritis.[29]

Diabetes mellitus type1 is an autoimmune condition in which the body attacking its own pancreas with antibodies, finally causes insulin deficiency.[30] A study has shown that oral administration of water soluble curcumin derivative (NCD) for forty days decreased the blood glucose level and increased plasma insulin and C-peptide in diabetic rats. Furthermore, the level of lipid peroxides in the pancreas and liver will decrease through the improvement of a lipid profile and oxidative status following the use of water soluble curcumin derivative, which directly improved the diabetic condition.[30]

One of the pathogenic causes of both types of diabetes mellitus is oxidative stress which led to Pancreatic  $\beta$ -cell apoptosis, resulting in the reduction of insulin secretion. Curcumin longa has shown to protect Pancreatic  $\beta$ -cell from apoptotic and oxidative damage and increases the antioxidant status of pancreatic  $\beta$ -cells. The explanation might be due to the presence of curcumin in *Curcumin longa* which has antioxidant and anti-apoptotic properties.[31] It must be kept in mind that further investigation on the preparation and standardization of the dose and pharmacological and toxicological evaluation of the active principle of *Curcumin longa* will help this plant to be employed in new antidiabetic drugs.[31]

Inflammation has been shown to precede the onset of type 2 (non-insulin-dependent) diabetes. Inflammatory cytokines, transcription factors such as NF-kB and tumor necrosis factors- $\alpha$  have been linked with insulin resistance and the development of type 2 diabetes. Curcumin increases the activation of PPAR- $\gamma$ , which regulates fatty acid storage and glucose metabolism.[17] The use of curcumin in the management of type 2 diabetes is due to its antioxidant nature, free radical scavenging properties and hypocholesterolemic effect.[17]

Another complication of diabetes mellitus is hyperlipidemia, an abnormally high concentration of fats or lipids in the blood. Curcumin has been shown to reduce serum and liver cholesterol, triglycerides, free fatty acids, phospholipids, and LDL cholesterol levels. Another finding also indicated that curcumin normalizes serum high-density lipoprotein (HDL) cholesterol in diabetic rats after treatment.[17] Curcumin was found to inhibit diabetic retinopathy suggesting its potential in suppressing oxidative stress, inflammation and an increase in -OHdG and nitrotyrosine.[17]

Numerous lines of evidence suggest that diabetes is a risk factor for neuropsychiatric deficits including stroke, cerebrovascular diseases, diabetic encephalopathy, depression, and anxiety.[17] Diabetic encephalopathy is a serious complication of both type 1 and types 2 diabetes, which involves direct neuronal damage caused by intracellular glucose. Regular anti-hyperglycemic regimens with the use of curcumin could be used for the treatment of diabetic encephalopathy.

Curcumin significantly decreased cognitive deficiency, cholinergic dysfunction, and serum levels of tumor necrosis factor (TNF) and also prevent brain lipid peroxidation in diabetic rats.[17]

This result shows that curcumin, with its lipid lowering and antioxidant properties, could be used as a supplement in diabetic patients with hyperglycemia and hyperlipidemia.[17]

#### 4.4. Anti-inflammatory Effects

Inflammation is the initial response to irritation, injuries, and infection triggered by the immune system. Acute inflammation has a therapeutic potential for wound healing and fighting infection, but chronic inflammation can trigger the immune system for long periods and may result in chronic illnesses including pulmonary, cardiovascular, metabolic, and neurologic diseases, obesity, type II diabetes, arthritis, pancreatitis, and cancer.[9]

Turmeric has been used in Indian folk medicine for reducing pain, swelling, wound healing and inflammation. The effectiveness of turmeric oil in reducing pain and inflammation is comparable to chemical drugs, such as phenylbutazone. The phenolics compound derived from a rhizome of *C. longa* such as curcumin has demonstrated anti-inflammatory activity *in vivo* and *in vitro*.[25]

Cyclooxygenase (COX-2) lipoxygenase (LOX) are two enzymes that involve in inflammation by transforming arachidonic acid in prostaglandins which mediate inflammation and pain.[14] Curcumin as a nontoxic natural compound shows to be effective in modulating the inflammatory response by down regulating COX-2, lipoxygenase, and inducible oxide synthase (iNOS) enzymes. It is also found that curcumin inhibits the inflammatory cytokines, tumor necrosis factor-alpha (TNF- $\alpha$ ), protein kinases, adhesion molecules, redox status and enzymes that have been linked to inflammation.[14, 17] Curcumin also demonstrated to be efficacious in reducing spermatic cord edema, spermatic cord tenderness, pain at the operative site, and tenderness at operative site.[32]

The hydroxyphenyl unit is assumed to be the pharmacologically active principles of curcumin which is responsible for the anti-inflammatory actions.[19]

Therapeutic implication of curcumin in the prevention of arachidonic acid metabolism and inflammation in mouse skin epidermis is via down regulation of the cyclooxygenase and lipoxygenase pathway.[14]

Rheumatoid arthritis (RA) is a chronic inflammatory disease. Common symptoms of arthritis include tenderness or pain at the joint, reduced motion, stiffness, swelling and difficulty walking. Non-surgical treatments include anti-inflammatory and pain medications such as acetaminophen and opioid, NSAIDs (non-steroid anti-inflammatory drug), and intra articular glucocorticoids injections in joint diseases. Since all of these agents have side effects, safe alternative sources have to be explored. Curcumin has been proven to be effective in the treatment of arthritis, and based on data obtained from the experiment done on arthritic rats, oral administration of curcumin has shown to decrease the glycoprotein levels and molecular weight, thereby lowering paw inflammation in arthritic rats.[17] The experimental evidence suggests that curcumin synergistically augments the growth-inhibitory and pro-apoptotic effects of celecoxib in osteoarthritis disorder. The effect was mediated through inhibition of COX-2 activity. This result warrants a novel combination treatment in OA (osteoarthritis) and other rheumatologic disorder.[17]

Curcumin also has shown to be effective in the treatment of psoriasis, which is a pro-inflammatory skin disease. Pharmacological activities of curcumin for the treatment of psoriasis are based on its anti-proliferative, anti-inflammatory, differentiation-modifying, or some combination of these actions. Curcumin was found to suppress psoriasis by inhibiting the keratinocyte proliferation.[17]

## 5. CONCLUSION

Through the reports of studies mentioned that reached their conclusions using *Curcumin longa* plant, the extracts used from the above mentioned plant have been scientifically validated to be used for the alleviation of pain and in assistance to relieving chronic inflammation. The powders and extracts used from this plant contain antioxidant, anti-inflammatory, anti-cancer, and anti-diabetes agents that allow it to be incredibly useful in its traditional medicinal applications. Along with these agents, the bioavailability of Turmeric has been increased through the combination of Turmeric and Piperine, enhancing its absorption and therapeutic efficacy, making the plants extracts more useful. As well as the increased bioavailability, increased evaluation of Turmeric in the future will allow to be used in more antidiabetic drugs, increasing its pain alleviating properties.

## Conflict of Interest

Authors declare no conflict of interest.

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