Curcumin and its Anti-Cancer Properties: Kitchen to the Laboratory

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Abstract

Curcumin is a naturally derived hydrophobic polyphenolic compound extracted from the rhizome (turmeric) of the herb Curcuma longa. It has been used as a common Indian spice in the form of turmeric since time immemorial. Curcumin is an active ingredient of turmeric and has been found to have many health benefits.

Our main aim is to highlight curcumin's biological activity and anti-cancer properties.

Curcumin is a bright yellow-colored substance; curcumin plays a vital role in anti-cancer therapy by suppressing cell proliferation and metastasis. Curcumin has regulatory effects on secondary signaling molecules and the further downstream process leading to regulation of transcription factors like nuclear factor-kappa light chain enhancer of activated B cell or NF-kB. Cancer cells have enhanced telomerase activity; therefore, their DNA never shortens due to the loss of telomeres. Curcumin initiates p53 protein-dependent and protein-independent G2/M phase cell cycle arrest. Curcumin has plenty of targets like growth factor receptors (Epidermal Growth Factor Receptor or EGFR), enzymes, and cytokines. Curcumin has poor bioavailability due to its low solubility in water (0.0004mg/mL at normal pH 7) and hence produces poor effects when administered orally. Curcumin also produces toxicity in patients when consumed in high concentrations.

The 21st century is the age of technology. We see that nanotechnology has enabled us to design curcumin-encapsulated, which reduces its bulk size and brings it within 100 nm. Particles like liposomes (phospholipid vesicles), polymer micelles, SLNs, and microspheres are some drug target delivery systems that can solve problems of transporting curcumin. Nanocurcumins can also be extracted from pure curcumin without any carriers. It is under clinical trial where curcumin has been used as an adjuvant with other chemical agents to control the spread of cancer.

Keywords: Adjuvant, Anti-cancer, Curcumin, Health benefits, Polyphenol.

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Introduction

Turmeric (*Curcuma longa* L.) is a member of the *Zingiberaceae* family cultivated in the tropical and subtropical regions of the world. An age-old spice originating from the Indian subcontinent and has been an indispensable element of the daily diet of a common Indian since ancient times. Besides being used as a spice, it also finds use as a coloring agent, flavoring agent, and natural preservative to improve its freshness and nutritive value, palatability, aesthetic appeal and to prolong the shelf-life of perishable food items.[1] As a powder form, it is called turmeric and has been used as a spice in vegetarian and non-vegetarian food preparations; it also has digestive properties.[2] Turmeric plant used as a medicinal plant since ancient times in India.

Turmeric is one of the most famous traditional medicinal herbs with a wide range of pharmacological properties. In several medical conditions, turmeric has an anti-inflammatory response, aids in digestion, and strengthens immunity. Turmeric is also found to maintain sound oral health[3] ; hence, it can be considered a superfood. Curcumin was extracted as a pure crystal from the turmeric plant for the first time in 1870.[4] Curcumin is obtained from the rhizomes of the root of a plant belonging to the ginger family.[5] Curcumin has tremendous potential for treating human diseases like treatment as jaundice and other liver ailments[6,7], anti-oxidant,[8] anti-protozoal,[9] anti-venom activities,[10] anti-microbial,[11] anti-malarial, [12]anti-inflammatory,[13] anti-proliferative,[14] anti-angiogenic,[15] anti-tumor[16] and anti-aging [17]properties.

Recent research studies have discovered the new anti-carcinogenic activities of turmeric. The chief compound that displays the anti-carcinogenic effect is curcumin (a polyphenol compound), the most active of all the components of turmeric. Cancer is a disorder that can start at a miniature level, *i.e.*, at the level of nucleotides but can undergo significant amplification to have a deleterious effect on the whole organism. Curcumin and its analogs show anti-cancer activity in different cancer cell lines.

This review aims to focus on the anti-cancer activity of curcumin by highlighting the multi-dimensional pathways. It can act to overcome drug resistance in cancer cells. The

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purpose of this review is to focus on the anti-carcinogenic effects of curcumin found in turmeric.

Morphological Characteristic

Curcuma longa is a beneficial plant belonging to the Zingiberaceae family. It is a perennial, herbaceous plant that belongs to the tuberous rhizomes or underground stem, which are the source of bright yellow spice and dye. Usually, this herbaceous plant measures up to 1.2-1.5m in height with a short stem and grows in favorable environmental conditions. It is an erect plant with an underground stem (rhizome) from where four or five leaves with long sticks are formed, alternate disposition, lancet in form, flat and dark green on the upper surface, pale green beneath. Generally, each leafy shoot bears 8-12 leaves, and the colors of the flowers are yellow-white. Usually flowers do not produce any viable seeds.

Chemical Composition

Only about 20 species of the genus Curcuma *L.* have been studied phytochemically.[18] It has a bright yellow color (Figure 1), as it is a natural phenol of the diarylheptanoid structure belonging to the group of curcuminoids. Many researchers have isolated more than 230 compounds from turmeric. Normally these compounds belong to the phenolic compounds and terpenoids. Some compounds are such as diarylheptanoids, diarylheptanoids, monoterpenes, sesquiterpenes, diterpenes, triterpenoids, alkaloids, sterols, etc.[19] Chemical analysis shows that curcumin contains the following components (Table 1).[20,21]

The curcuminoids are a mixture of curcumin, chemically a diferuloylmethane [1,7-bis(4-hydroxy-3-methoxy-phenyl)-hepta-1,6-diene-3,5-dione] mixed with its two derivatives, dimethoxy curcumin [4-hydroxycinnamoyl-(4-hydroxy-3-methoxycinnamoyl) methane] or (DMC) and bis-demethoxy curcumin [bis-(4-hydroxy cinnamoyl) methane] or (BDMC) and shows the chemical formulae as $C_{21}H_{20}O_6$, $C_{20}H_{18}O_5$, and $C_{19}H_{16}O_4$ respectively.[22] Among these three curcuminoids, curcumin is the most abundant. Generally, it is composed of two phenyl rings substituted with hydroxyl and methoxyl groups and is connected by a seven-carbon keto-enol linker (C7) (Figure 2). Curcumin is poorly soluble in water, although it is soluble in organic solvents, like ethyl alcohol, methyl alcohol, or acetone. Its melting point is about 183°C.

The biosynthetic mechanism involves two cinnamic acid units coupled together by malonyl-CoA. Cinnamic acid, which is derived from the amino acid phenylalanine (Phy), acts as the chief precursor for curcumin synthesis[23] (Figure. 3).

Biological Activities of Curcuminoids

Curcuminoids from turmeric and their derivatives have been reported to possess a great variety of biological activities (Figure 4).

Anti-inflammatory Activity

Studies conducted show that curcumin can block the activation of certain factors that trigger the inflammatory process in the body. The release of prostaglandins is thought to be associated with inflammation. Curcumin is found to inhibit arachidonic acid-derived prostaglandin-endoperoxide synthase or Cyclooxygenase-2 (COX-2) and Lipooxygenase (LOX).[24] Profound inhibitory activity of curcumin was observed when the inactivation of nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) occurred.[25]

The essential oils extracted from the rhizome help in preventing inflammation of joints. Hence curcumin is

Figure 1: Rhizome root of the Curcumin plant.

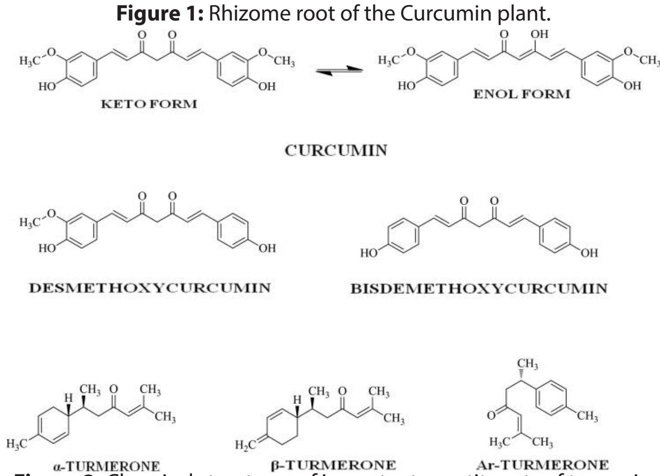

Figure 2: Chemical structures of important constituents of turmeric.

Table 1: Chemical composition of turmeric [20,21]

Constituents	*Composition (w/w)*
Carbohydrate	(60-70)% ≅ 69.4%
Protein	(6-8) ≅ 6.3%
Fat	(5-10)% ≅ 5.1%
Minerals	(3-7)% ≅ 3.5%
Essential oils	(3-7)% ≅ 5.8%
Fiber	(2-7)%
Moisture	13.1%
α-phellandrene	1%
Sabinene	0.6%
Cineol	1%
Borneol	0.5%
Zingiberene	25%
Sesquiterpines	53%
Curcumin	(3-6) %

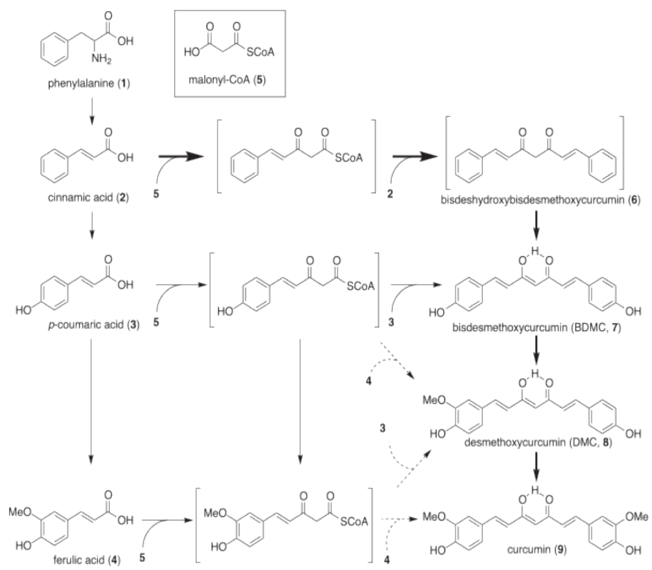

Figure 3: Biosynthesis of curcumin.

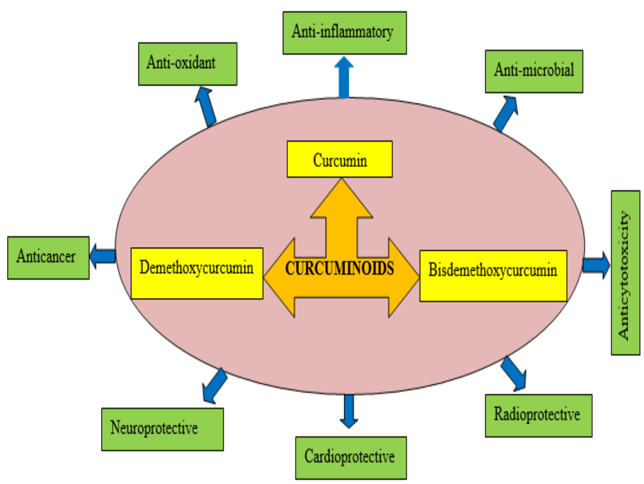

Figure 4: Schematic representation of multiple biological activities of curcuminoids and their derivatives.

also used in arthritis. Curcumin is found to exert its anti-inflammatory effect on patients with gastritis and peptic ulcers by reducing chronic pain and burning sensation.

Anti-oxidant Activity

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) and its derivatives are widely used as an anti-oxidant and a free radical scavenging dietary supplement. Thus, they can play protective functions like scavenging hazardous oxidants directly and chelating with a metal ion to block radical chain reactions. Curcumin, an extremely potent lipid-soluble anti-oxidant, plays an important role in neutralizing reactive oxygen species (ROS) and protecting the cells from oxidative damage. The free radical scavenging activity of curcumin may be due to the

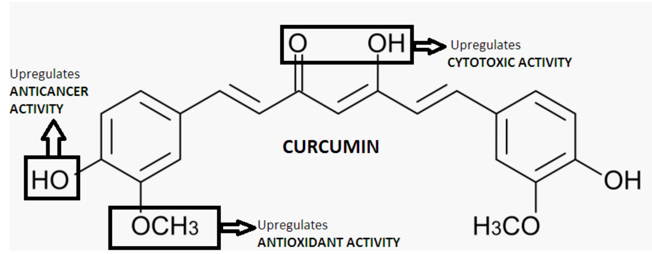

Figure 5: Active functional groups in the polyphenolic structure

presence of either phenolic -OH group or the -CH_2 group of the β-diketone moiety.

Curcumin can also act as a promoter by increasing the expression of the enzyme heme-oxygenase-1 (HO-1), which catalyzes the degradative action on heme. Degradation of heme component produces components like biliverdin, iron, and carbon monoxide (CO) and exhibits cellular protective activity against oxidative stress and production of free radicals.

Curcuminoids and their analogs play a significant role in reducing hemolysis and lipid peroxidation of red blood cells. Curcumin has also shown potential for treating Alzheimer's disease (a condition exhibiting degeneration of neurons) by reducing their oxidative damage.[26]

Anti-microbial Activity

Essential oils extracted from *Curcuma longa* exhibit essential antibacterial and antifungal properties. Curcuma oil was tested against Gram-positive and Gram-negative bacteria cultures of *Staphylococcus albus*, *S. aureus*, and *Bacillus typhosus*. It shows inhibiting the growth of gram-positive bacteria such as *S. albus* and *S. aureus* in concentrations up to 1 to 5,000 µg.[27] Its protective capacity was also observed against some protozoa like *Plasmodium falciparum* and *Leishmania major*.[28]

Role of Curcumin on Hepatic and Oral Health

Curcumin has a hepatoprotective effect against liver damage caused due to compounds toxic to health which includes carbon tetrachloride (CCl_4), acetaminophen (paracetamol) and fungal toxin (*Aspergillus aflatoxin*).[29] Curcumin also protects the liver cells from galactosamine by inhibiting TNF-α mediated necrosis. Due to its anti-oxidant properties, turmeric inhibits the production of pro-inflammatory cytokines, which has an additional protective effect on the liver.[30] A salt derived from sodium curcumin is found to exhibit increased secretion of bile from the liver, subsequently an increase in excretion of pigments like biliverdin, bilirubin, and bile salts, as well as increasing bile solubility. Due to the increase release of bile salts, it prevents gall stone formation. Raw turmeric powder, when messaged with hand, tends to heal dental problems by reducing swelling of gums and toothache.

Role of Curcumin on Cardiovascular Diseases

Curcumin has been found to have a significant role in the prevention of atherosclerosis owing to its capability to prevent the growth of a thrombus in the blood vessels. Additionally, it also plays a role in the inhibition of platelet aggregation. The fall in serum cholesterol levels has been attributed to the administration of curcumin, as it helps to decrease lipid uptake by the walls of intestines and subsequent conversion by bile into free fatty acids. Curcumin has been found to maintain calcium levels to prevent arrhythmias and heart failures.

Anti-Cancer Activities Of Curcumin

Cancer is one of the leading causes of death worldwide. Researchers are being conducted continuously to develop viable and efficient anti-cancer agents. The available chemotherapeutic agents used commonly to treat cancer tend to have a profound effect on the patient. Some patients often succumb to the side effects caused by the chemotherapy rather than cancer itself. Curcumin, since being a plant derivative, is a potential non-toxic compound that can stop certain cancers (Figure 5).

The production of certain transcription factors in the cancer cells enables them to skip the programmed cell death machinery or apoptosis. Curcumin and its analogs induce apoptosis by inhibiting intracellular transcription factors such as STAT1 and NF-kB.[31] Several studies have suggested that curcumin has the potential to target cancer stem cells (CSCs) through the regulation of CSC self-renewal pathways, including the Wnt/β-catenin pathway.[32]

Curcumin up-regulates the p53 tumor suppressor gene functions, which are also known as the 'Guardian of the genome'. It produces some downstream transcriptional factors like p21, APO1, which play a role in cell cycle arrest and inducing pro-apoptotic proteins like the PUMA and NOXA. Curcumin up-regulates CASPASE family proteins which start the CASPASE cascade leading to cell death. It also down-regulates anti-apoptotic genes like [Bcl-2 and Bcl-X (L)].[33]

Curcumin has also been shown to inhibit several types of the cytokines like IL-1, 2, and 5, which produce inflammation, and it also down-regulates TNF-α. Cancer cells tend to have a strong property of undergoing respiration through glycolysis even if oxygen is present in an adequate amount (aerobic glycolysis) (Figure 6). This is called the Warburg effect.

It is also observed that the anti-cancer mechanism for curcumin occurs through decreasing glucose uptake and lactate production. Since chemotherapy remains the core treatment for cancer, drug-resistant tumors have evolved over time, showing resistance against chemotherapeutic agents. Therefore, new drugs have to act such that they can convert drug resistance to drug susceptibility. The above points highlight the fact that the potential of curcumin to act as an anti-carcinogenic agent increases because its mechanism of action includes multiple pathways or one drug for multiple targets that are not limited to single intracellular signaling, which is of significant importance in an increase of cancer survivability.[34]

Curcumin is hydrophobic, so it easily passes through the plasma membrane. After entering into the plasma membrane, it binds to the fatty acyl chains of membrane lipids through hydrophobic interactions and causes low availability of curcumin inside the cytoplasm.[35] Curcumin is found to be poorly soluble in water, reducing its bioavailability, but with the advent of nanoparticles, a novel therapeutic agent called nano-curcumin, unlike the former, was found to be freely dispersible in water in the absence of any surfactants.[36]

Curcumin and its analogs have been demonstrated in several cancer cell lines, such as pancreatic, lung, ovarian, oral, colorectal, breast carcinoma, and even melanoma cells.[37]

Conclusion

The present review highlights the multi-dimensional approach in cancer therapy, overcoming the drug resistance induced by traditional chemotherapeutic agents, which make cancer cell lines resistant to drugs. This study shows that curcumin can exert a positive effect on different kinds of cancers. Therefore, further *in vivo* studies will help clarify

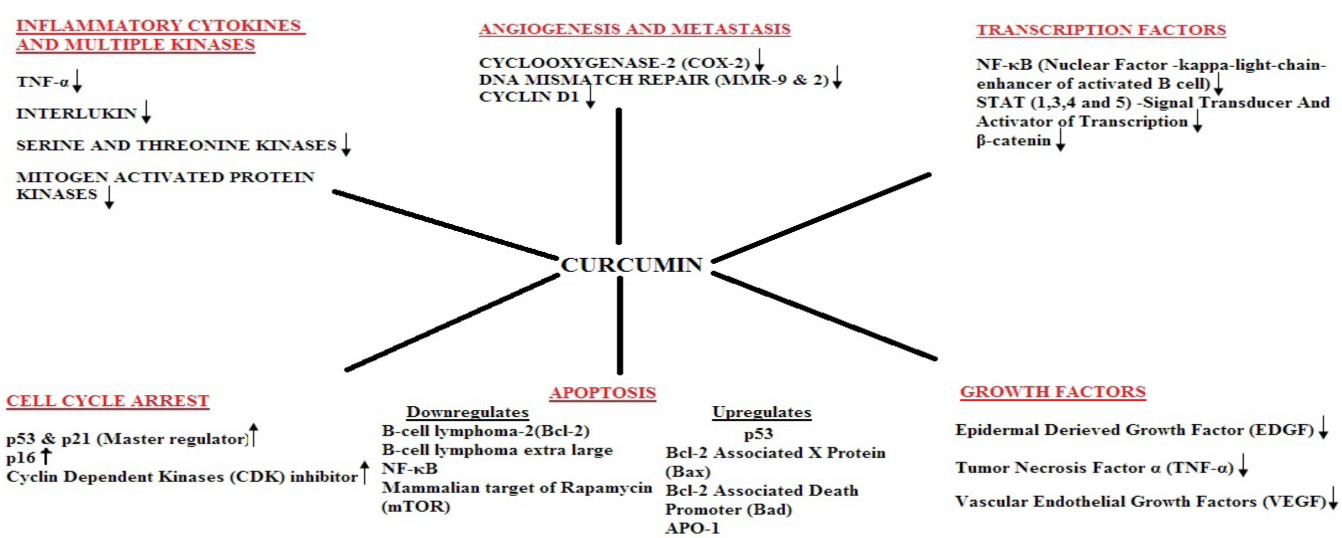

Figure 6: Anti-cancer mechanism of curcumin.

the anti-cancer activities and their underlying mechanisms more accurately.

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