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Vishwal Kale
Department of Pharmaceutical Chemistry, Dattakala Collage of Pharmacy, Swami, Chincholi, Maharashtra, India

Pankaj Patil
Department of Pharmaceutical Chemistry, Dattakala Collage of Pharmacy, Swami, Chincholi, Maharashtra, India

Pratiksha Pandere
Department of Pharmaceutical Chemistry, Dattakala Collage of Pharmacy, Swami, Chincholi, Maharashtra, India

Dr. Sudarshan Nagaraled
Department of Pharmaceutical Chemistry, Dattakala Collage of Pharmacy, Swami, Chincholi, Maharashtra, India

Amit Pondkule
Department of Pharmaceutics, Dattakala Collage of Pharmacy, Swami-Chincholi, Maharashtra, India

Corresponding Author:
Vishwal Kale
Department of Pharmaceutical Chemistry, Dattakala Collage of Pharmacy, Swami, Chincholi, Maharashtra, India

Emerging role of curcumin N enhancing cancer therapy

Vishwal Kale, Pankaj Patil, Pratiksha Pandere, Dr. Sudarshan Nagarale and Amit Pondkule

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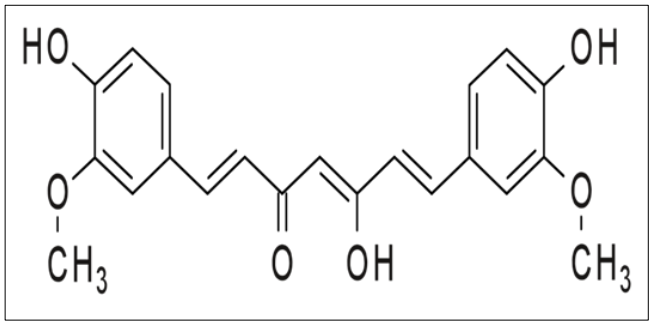
Abstract
One of the greatest public health issues is cancer, which is the second major cause of death for mortality in the globe. The rate of prevalence and fatality of cancer continue to be high despite significant advancements in cancer therapy. Therefore, the hunt for more effective and benign cancer treatment methods is at the forefront of scientific inquiry. The primary component of the *Curcuma longa* plant, curcumin, has drawn a lot of interest as an antioxidant, anti-inflammatory, and anticancer agent over the past 20 years. Based on literature data from experimental and clinical evaluations of curcumin in cancer cell lines based on animal models, and human subjects, in regards to their anticancer activities, primary modes of action, and cellular targets, this review article examines the medicinal chemistry and medicinal chemistry of curcumin and its derivatives. The discipline of pharmacology was described. In addition, current developments in curcumin delivery systems for cancer cells were emphasized.

Keywords: Curcumin, *Curcuma longa* plant, cancer therapy, antioxidant, anti-inflammatory

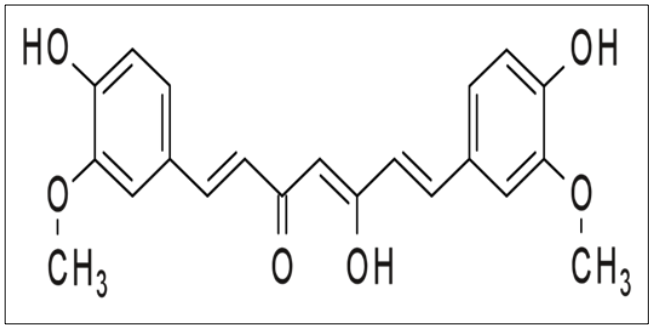
Introduction
Cancer is one of the most prevalent illnesses in the world. Tens of millions of people obtain a cancer diagnosis each year in the entire world and more than half of those people go on to develop the disease. In many countries, cancer ranks the second most common cause of death following cardiovascular diseases. With significant improvement in treatment and prevention of cardiovascular diseases, cancer has or will soon become the number one killer in many parts of the world. As elderly people are most susceptible to cancer and population aging continues in many countries, cancer will remain a major health problem around the globe [1]. There are several general strategies to target specific cancer cells to inhibit tumor development, progression and metastasis without causing severe side effects [2]. In addition to anticancer agents that have been chemically synthesised, a multitude of anticancer compounds with various mechanisms of action have been isolated from plant sources, including B. Taxus brevifolia, Catharanthus roseus, Betula alba, Cephalotaxus species, Erythroxylum previllei, *Curcuma longa*, etc [3]. Among them, curcumin is the most important component of the turmeric (*Curcuma longa*) rhizome and was first extracted in pure crystalline form from the turmeric plant in 1870. The bio functional properties of curcumin and its derivatives, such as their anti-tumor, antioxidant, and anti-inflammatory properties, have garnered a great deal of attention in the last 20 years [4]. These properties are attributed to key elements of curcumin structure. Therefore, many scientific papers have shed light on the structure-activity relationship (SAR) of curcumin to improve its physicochemical and biological properties. Due to the importance of cancer as a leading cause of death and the continued search for more potent and less toxic anticancer agents, this review focuses primarily on cur cumin's anticancer activity, is beyond the scope of this review and has been reviewed elsewhere [5]. The major a mechanism of action by which curcumin exerts its unique anticancer activity include the induction of apoptosis and inhibition of tumor growth and invasion by suppressing various cell signaling pathways [6]. Several studies have reported anti-tumor activity of curcumin in breast cancer, lung cancer, head and neck squamous cell carcinoma, prostate cancer, and brain tumors, demonstrating its ability to target multiple cancer cell lines. Another strategy is to improve the physiochemical characteristics and anticancer effects of curcumin by using various delivery mechanisms.

The anticancer properties of curcumin and its analogues in various cancer cell lines, animal models, human clinical trials, and the numerous curcumin delivery systems that have been employed in cancer therapy are all included in this review. It focuses on recent literature. The plant *Curcuma longa*, also known as turmeric, yields the polyphenol known as curcumin (diferuloylmethane). Due to its nontoxicity and numerous beneficial therapeutic qualities, such as its anti-oxidant, analgesic, anti-inflammatory, and antibacterial activity, curcumin has been widely employed in Ayurvedic medicine for centuries. More recently, curcumin has been discovered to have anti-cancer properties through its impact on numerous biological pathways that are involved in carcinogenesis, metastasis, tumorigenesis, oncogene expression, cell cycle control, and apoptosis. Curcumin has demonstrated anti-proliferative effects in a variety of malignancies and is an inhibitor of the transcription factor NF-B and downstream gene products (including c-myc, Bcl-2, COX-2, NOS, Cyclin D1, TNF-, interleukins, and MMP-9). Additionally, curcumin influences numerous cell adhesion molecules and growth factor receptors that are implicated in metastasis, tumour angiogenesis and tumour growth [7].

Structrure of Curcumin



Enol form



Keto form

Curcumin contains a seven carbon linker as well as two aromatic O-methoxyphenolic groups and one,-unsaturated -diketone moiety. Two,-unsaturated carbonyl groups link the phenolic aromatic ring systems together. It is a diketone tautomer that exists in water as a keto form and in enolic form in organic solvents. The diketones easily deprotonate to create enolates and form stable enols. The,-unsaturated carbonyl group functions as a potent Michael acceptor and is added nucleophilically. Curcumin is not very soluble in water due to its hydrophobic nature. But it dissolves readily in organic liquids. Recent research from multiple different independent groups has shown that several curcumin analogues lacking the b-diketone spacer and having a 5-carbon enone spacer either retained or improved growth-suppressive effects against a variety of cancer cells. Nevertheless, only the b-diketo form has been examined in a number of recent research that entail calculations of energy-minimized structures and subsequent docking experiments, despite the fact that curcumin mostly occurs in the enol form. In addition to curcumin glucuronide and curcumin sulphate, dihydrocurcumin (DHC), hexahydrocurcumin (HHC), octahydrocurcumin (OHC), and tetrahydrocurcumin (THC) have also been identified as curcumin metabolites [8].

Natural Analouges

Any lead compound's structural changes are essential for changing its physiological activity, especially those that have an impact on the interactions with receptors. The pharmacokinetics of a substance is also affected by structural changes, which change how it is absorbed, distributed, metabolised, and excreted. Along with its synthesised analogues, a molecule's naturally occurring analogues must undergo a thorough analysis in order to create a pharmacological profile. Numerous structure-activity relationship (SAR) studies have been carried out on the curcumin molecule and its synthetic analogues. Since the curcumin molecule has more molecular targets than any other chemical thus far known, it is unique in its physiological effects. Some of these are capsaicin, ferulic acid, cinnamic acid, caffeic acid, chlorogenic acid, gingerol, paradol zingerone, eugenol, dibenzoylmethane, dehydrozingerone, cassumuins A and B, and yakuchinone [9].

Relative Potency of Curcummin and its Natural analogue

Cur cumin's natural analogues, such as caffeic acid and ferulic acid, are more effective at inhibiting lipid peroxidation than curcumin itself. These acids, as well as the chlorogenic acid, are less effective than curcumin at preventing inflammation and skin tumour growth caused by 12-O-tetradecanoylphorbol-13-acetate. Additionally, it was discovered that capsaicin was more effective than curcumin at reducing acidic glycoprotein and inflammation in rats with arthritis. According to studies, capsaicin and curcumin are 1,000 times more potent than eugenol at preventing the production of superoxide radicals. Additionally, curcumin and capsaicin both have a strong inhibitory effect on the metabolism of arachidonic acid. When it comes to preventing the synthesis of conjugated dienes and spontaneous lipid peroxidation, dehydrozingerone is less effective than Curcumin [10]. It was discovered that dehydrozingerone had similar anti-Epstein-Barr virus antigen early antigen activation activity to curcumin, but was less effective than Iso eugenol. Inducing phase II enzymes, blocking 7, 12-dimethylbenz[a]anthracene-induced breast cancers in mice, and inhibiting 12-Otetradecanoylphorbol-13-acetate-induced skin inflammation and tumour promotion, dibenzoylmethane was another substance that was 10-fold more powerful than curcumin. A natural substance from the same family called 6-gingerol was found to be a mutagen more than a hundred times greater than curcumin while being less effective at stopping inflammation, epidermal ornithine decarboxylase activity, and the promotion of skin tumours in mice. Yakuchinone A and B were equally effective as curcumin at

preventing the generation of nitric oxide, superoxide, and lipid peroxidation when they were used to counteract the effects of lipopolysaccharide. Curcumin is less effective than cassumunins A and B at protecting thymocytes from the toxicity caused by H_2O_2 [11].

SAR of Curcumin

Two o-methoxy phenol units, two enone moieties, and a 1, 3-diketone$1, 3-keto-enol system make comprises curcumin's distinctive structural elements. All of these molecular architectural locations have seen attempts to change their structure. Curcumin derivatives, curcumin analogues, and metal complexes of curcumin can all be categorised as modifications of the fundamental curcumin structure used in chemical synthesis to access related molecules. Curcumin derivatives are substances that have the same fundamental structural components as curcumin, including the two dimethoxy-substituted benzene rings, the -C[C-CO-CH2-CO-C] C-linker, and the oxy substituents on the benzene rings. The second category, known as curcumin analogues, includes all additional substances thought to or asserted to have structural similarities to curcumin. The class of curcumin derivatives is now outnumbered by curcumin analogues. The third group consists of curcumin and its analogues in the form of metal complexes. In order to develop analogues, a variety of molecular alterations have been made to curcumin's basic site. The functional groups in curcumin are often derivatized to create the curcumin derivatives. The phenolic hydroxy group, for instance, could be glycosylated, alkylated, or amino acylated. [12] Demethylation of the methoxy groups might result in hydroxy groups. It is possible to introduce substituents on the C7 chain by acylating, alkylating, or substituting an arylidene group (Ar-CH]) for the reactive methylene group of the linker. The structural similarities between curcumin's analogues and other compounds range greatly, from (ferrocenyl-CH CH-CO) 2 CH2 to methyl ferulate. The carbonyl groups and double bonds in the C7 linker are hydrogenated to create its most basic analogues, such as DHC, THC, HHC, and OHC. Curcumin is reduced to produce these compounds. Curcumin-derived analogues can also be made by taking advantage of the core b-diketone unit's reactivity with hydrazine, its substituted derivatives, and hydroxylamine. [13] Due to such heterocyclizations, the core 1, 3-diketone$1, 3-keto-enol system is obscured and rigidized in bis (styryl) parasols and isoxazoles. More recently, curcumin ethylene diamine adducts, bisthiosemicarbazone, and monosemicarbazone have all been reported in the literature. There is a substantial correlation between curcumin structure and activity as determined by 3D-QSAR and molecular docking. The results of the study demonstrated that for improved activity in this class of chemical, negatively charged substituents, H-bond acceptors at the R1, R2, R3, and R4 locations, and the substitution at the C-4 position of the linker are essential. Phenyl rings at the two sides of the molecule are required for the cytotoxicity of curcumin derivatives to be comparable to that of bicalutamide, a well-known and clinically used antiandrogenic (AR) antagonist. Here, the hydrophobicity of the benzene ring is crucial to the antiandrogenic effects. The two phenyl rings in curcumin are substituted with methoxy and hydroxyl groups at positions 3 and 4, respectively [14]. It has been observed to go through significant phase I and II metabolism *in vitro* and *in vivo* through oxidation, reduction, glucuronidation, and sulfation. Both of curcumin's phenyl rings' 4-OH groups undergo glucuronidation and sulfation as well. Its stability is enhanced by the 4-OH groups' protection. The linker, the aromatic rings, and steric hindrances are all essential for its activity, according to earlier studies on the association between the structures of curcumin-related compounds and their capacity to suppress the proliferation of cultured cancer cells. By using benzyl piperidone as a linker, the compounds that are linked to curcumin have a greater capacity for cytotoxicity. According to SAR research for aromatic rings, reactive groups like methoxy can boost activity [15].

Curcumin's anti-cancer properties in several cancer types

The uncontrolled growth and death of cells is one of the primary causes of cancer. Different forms of cancer are caused by uncontrolled cell proliferation, which occurs when cells avoid death because apoptotic signals are absent [16]. The intrinsic pathway and the extrinsic pathway are the two main pathways that produce apoptotic signals. The intrinsic route suppresses the expression of the antiapoptotic proteins Bcl-2 and Bcl-Xl by activating the mitochondrial membrane [17]. The Bcl-xL protein is more effectively suppressed when curcumin is present because it throws off the equilibrium in the mitochondrial membrane potential. Apoptosis associated to tumour necrosis factor (TNF) is triggered by the extrinsic apoptotic pathway by activating the death receptors (DRs) on cells. The death receptors DR 4 and DR 5 are expressed more frequently when curcumin is present. Through the inhibition or down regulation of intracellular transcription factors, *in vitro* studies demonstrated curcumin's and its derivatives' extraordinary capacity to cause apoptosis in many cell lines. These factors consist of the following: NF-B, activator protein 1 (AP-1), cyclooxygenase II (COX-2), nitric oxide synthase, matrix metalloproteinase-9 (MMP-9), and STAT3. Through interactions with various molecular targets, curcumin and its derivatives has been the subject of numerous researches looking into its capacity to reduce a variety of malignant carcinomas (Figure 1).

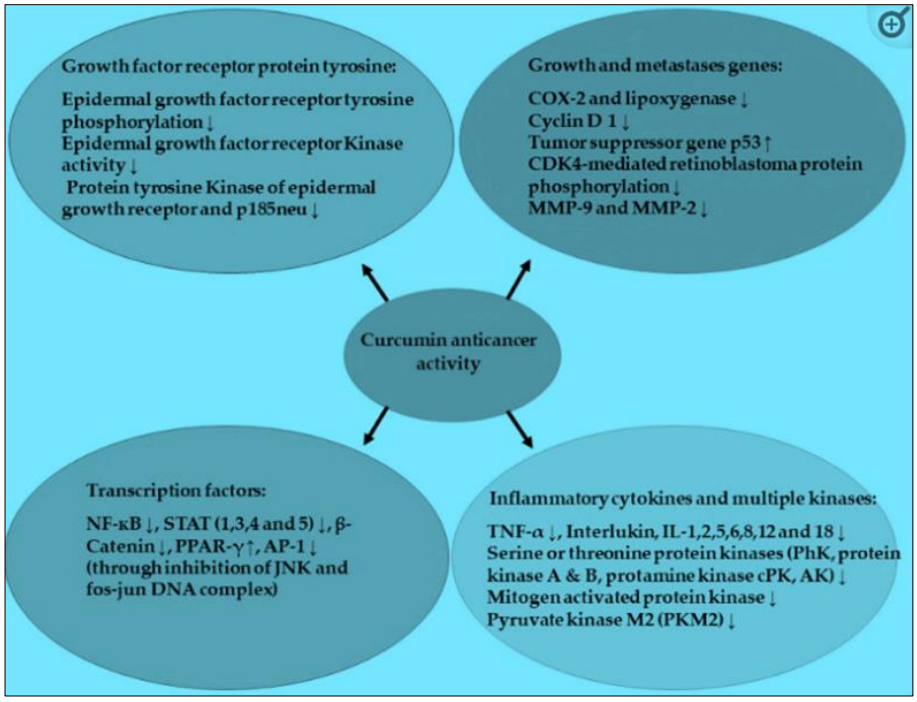


Fig 1: The main molecular targets of curcumin in cancer cells. ↑: Increase; ↓: Decrease; MMP: Matrix metalloproteinase; AP-1: Activation protein-1.

With regard to reducing the growth and proliferation of cancer cells in a variety of malignancies, including prostate, colorectal, breast, pancreatic, brain, head, and neck cancers, curcumin has demonstrated highly encouraging results.

Prostate Cancer

According to a recent estimate by the American Cancer Society, 2.9 million men in the country have been diagnosed with prostate cancer (PCa), making it the second highest cause of cancer-related death in males. By interfering with a number of cellular pathways, such as mitogen-activated protein kinase (MAPK), epidermal growth factor receptor (EGFR), and nuclear factor (NF-B), curcumin has proved a potent ability to inhibit proliferation and induce apoptosis in prostate cancer both *in vitro* and *in vivo*. According to a recent study, curcumin has the capacity to activate protein kinase D1 (PKD1), which inhibits prostate cancer by weakening the oncogenic signalling of -catenin and MAPK. As a result, it has been proposed as a potential therapeutic target for cancer generally and prostate cancer specifically [18].

Colorectal Cancer

The most prevalent types of malignant cancer are lung cancer, prostate cancer, and colorectal cancer, respectively. More than half of colon cancer patients experience relapses even if they get chemotherapy and surgical excision of the tumour tissue. When curcumin was used to treat HCT 116 colorectal cancer cells, miR-21 gene regulation caused a cell cycle halt in the G2/M phase and reduced the growth of the tumour tissue. However, due to curcumin's capacity to target nuclear factor (NF-B), an *in vivo* research in mice with colorectal cancer showed a better response to radiation therapy when paired with curcumin. By combining curcumin with ERRP, a pan-erb B inhibitor, another study was able to increase the inhibitory action of curcumin against colon cancer cells [19].

Cancer of the head and neck squamous cells

With more than 30,000 cases reported each year, head and neck squamous cell carcinoma (HNSCC) is the sixth most frequent malignancy in the world. Typically, larynx, pharynx, paranasal cavities, and the oral cavity develop HNSCC. Curcumin has been shown in *in vitro* studies using different head and neck cancer cell lines to be able to inhibit cell growth due to its effects on a number of cellular pathways involved in cell proliferation, most notably NF-B and STAT3, which are found to be overexpressed in a number of head and neck carcinomas. As a result of curcumin's ability to reduce NF-B activity and prevent interleukin-6 (IL-6) from causing STAT3 to phosphorylate, cancer cells are unable to proliferate [20].

Breast Cancer

According to a meta-analysis of 21 retrospective studies, breast cancer recurrence is still found to be a significant problem despite lumpectomy, radiation therapy, chemotherapy, and endocrine therapy. In the breast cancer cell lines MDA-MB-231 and BT-483, the impact of curcumin on NF-B, matrix metalloproteinases (MMPs), and cell-cycle regulatory proteins was assessed. Curcumin also resulted in the upregulation of the p53 gene and a decrease in the levels of the antigen ki-67, which in turn prevented breast tumour growth. Curcumin also inhibits the inflammatory cytokine CXCL1/2, according to a different study conducted on MDA-MB-231 cells. It has also been noted that dimethyl curcumin (ASC-J9), which blocks a variety of steroid receptors, is beneficial against estrogen-dependent breast cancer [21].

Brain Cancer and Glioblastoma

In the UK, it is expected that between 2014 and 2035, the incidence rate of central nervous system (CNS) cancers, including brain tumours, will rise by 6%. In humans, glioblastoma (GBM), the most prevalent malignant brain cancer, makes up 15% of all CNS malignancies. Apoptosis,

autophagy, angiogenesis, invasion, and metastasis are only a few of the cellular pathways that can be used to treat brain cancers because curcumin has several molecular targets. Curcumin was able to pass the blood-brain barrier (BBB) in high amounts, despite the fact that it is often thought of as the rate-limiting step for many anticancer drugs. Curcumin was also able to induce G2/M cell cycle arrest in U-251 malignant glioma cells by upregulating protein kinase 1 (DAPK1). This finding implies that curcumin decreases DAPK1 and not only causes cell arrest but also inhibits STAT3 and NF-B and activates caspase-3 [22].

Table 1: Overview of Clinical Study

Type of Cancer	Type of Study	No of Patients	Dose of Curcumin	Endpoints	Results
Breast	Phase I clinical trial	14	0.5-8 g/day for 7 days plus docetaxel	VEGF-b levels, toxicity, safety, efficacy, maximum tolerated dose of curcumin, and tumour markers	No cancer growth, partial responses in some individuals, little undesirable side effects, and lowered VEGF levels.
Colorectal	Pilot study	26	2.35 g/day for 14 days	Safety, tolerance, levels of curcumin in colonic mucosa	Safe and well tolerated, Prolonged biologically active levels of curcumin achieved in colon tissue
Intestinal Adenoma	Randomized controlled trial	44	1.5 g BID for 12 months	total number of polyps, average size of polyps, and side effects	No discernible clinical response and few negative consequences
Pancreatic	Phase I/II clinical trial	21	8 g/day for 14 days plus gemcitabine	patient compliance, toxicity, efficacy	Safe and well-tolerated, with a 161-day median overall survival time
	Phase I clinical trial	16	200–400 mg/day for 9 months	Safety, pharmacokinetics, NF-κB ^{m} activity, cytokine levels, efficacy and quality of life	Improved quality of life, good bioavailability, no substantial changes in NF-B activity or cytokine levels.
Prostate	Randomized controlled trial	85	100 mg plus 40 mg soy isoflavones for 6 months	Serum PSA ^{n} levels	PSA levels that were lower in participants with baseline values under 10 g/mL
	Randomized controlled trial	40	3 g/day for 3 months as a supplement to radiotherapy	Clinical progression-free survivals, modifications in antioxidant enzyme activity, and biochemical modifications	Significant antioxidant impact, reduced PSA levels
Solid tumors	Randomized controlled trial	80	180 mg/day for 8 weeks	alterations in quality of life and inflammatory mediator levels in the serum	Improved quality of life, reduced levels of inflammatory mediators

Conclusion

Several clinical studies on human subjects have been conducted to assess the effectiveness and safety of treatment with curcumin in various cancer types, either solely or in conjunction with supplementary chemotherapy drugs. These studies have been conducted in addition to those conducted in human cell cultures or animal models. In Table 1, an overview of a portion of these clinical researches is presented.

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