REVIEW ARTICLE

A REVIEW IN CURCUMINOIDS: CHEMISTRY, ANTICANCER ACTIVITY AND FUTURE PROSPECTS

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(Received 09 May 2023) (Accepted 04 April 2024)

ABSTRACT

Curcumin is a biologically active phytochemical which manifests therapeutic activities in numerous health conditions, including cancer. Several curcuminoids obtained naturally and synthesized artificially also showcase anti-cancer and anti-tumorigenic effects. However, its water insolubility poses difficulties in its application to biological systems, lowering its availability in living tissues, which can be overcome by using various micro-encapsulation and nano-formulations of curcumin. When used in combination with other chemotherapeutic drugs, curcumin enhances the anti-carcinogen potential and reduces the side effects induced via chemotherapy. Structural modelling of basic pharmacophores of curcumin can enhance its biological and pharmacokinetic properties, as revealed by structure-activity relationship studies of curcumin. Various clinical trials of curcumin have proven its worth as an anti-neoplastic agent in humans, with minimal side effects. Its mechanism of action involves blockage of cell-signalling pathways and cellular enzymes, promotion of immunomodulatory effects and induction of programmed cell death in cancerous cells. Curcumin is an interesting molecule with diverse effects on various diseases, but its absolute potential has yet to be reached. Hence, more in-depth studies and clinical trials are needed. This review outlines curcumin's chemical properties and summarizes its anti-cancer and pharmacokinetic potential.

Keywords: Cancer, natural products, curcumin, anticancer, SAR, clinical trials

INTRODUCTION

Spices impart colour, aroma and taste to food and have been used as condiments worldwide for ages. Due to the presence of several bioactive compounds such as antioxidants, some spices are also used as medicine and have various health benefits. For example, curcumin in turmeric, eugenol in cloves and capsaicin in red pepper are known to control cellular oxidation. These prevent the production of oxygen-free radicals and also interfere with the signal transduction pathways[1,2]. Compounds such as curcumin and thymoquinone regulate various inflammatory processes. Some spices belonging to the genus *Cinnamomum* possess antimicrobial properties[3,4]. Certain compounds in spices, such as thymoquinone, exhibit regulatory effects on the immune system[5,6]. In short, spices elicit antioxidant[7-12], immunomodulatory and anti-inflammatory[13-15] effects. Since growth and metastasis of cancer are linked with inflammatory reactions[13-14] immune responses and oxidative stress, spices can be used as an alternative to treat and prevent cancer[16-19].

The majority of deaths across the globe are caused due to cancer. As per the data of 2020, out of the 19 million new cases of cancer reported, there were about 9.9 million deaths across the globe. This number will increase by about 70% in the next 20 years. The most extensive

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https://doi.org/10.53879/id.61.05.14041

approaches for cancer treatment are radiotherapy, surgery and chemotherapy. Radiation and surgery are plausible only if a tumour is small and localized. Chemotherapy is practical only for small-sized tumours[20,21]. Moreover, these treatments may produce certain side effects. Hence, it is necessary to have new anti-cancer drugs which can minimize the side effects. Spices are such alternatives which can reduce indigestion, nausea and vomiting induced by chemotherapy[22,23]. This review outlines curcumin's chemical properties and summarizes its anti-cancer and pharmacokinetic potential. SAR and the mechanism of action of curcumin have also been discussed.

TURMERIC AND CURCUMIN

Occurrence of curcumin

Turmeric (vernacular name: Haldi) is a flavouring substance that imparts yellow colour to Asian food. It has been used as a medicine in the Indian Ayurveda for millennia. Curcumin (1), the main pigment of turmeric, is a yellow-coloured polyphenolic compound[24-26].

Extracted from the underground rhizome of *Curcuma longa*, curcumin, a secondary metabolite, possesses anti-tumorigenic, anti-cancer, antioxidant, anti-microbial, anti-alzheimer and anti-arthritic characteristics. The radical trapping ability of curcumin makes it useful as an anti-oxidant[24-38]. Curcumin has also been reported in the rhizomes of various Zingiberaceae plants, such as *C. zedoaria*[39]. Curcumin, along with some curcumin-related diarylhepatnoids, were found in *C. xanthoriza*[40]. Using high-performance liquid chromatography, a large amount of curcumin was detected in the rhizomes of *Zingiber cassumunar*[41]. In *C. zerumbet*, curcumin, diterpenes, and flavonoids were identified in the rhizomes[42]. Presence of curcumin in *C. aromatic*[43], *C. hyneana*[44], *C. chuanyujin*[45], *C. phaeocaulis*[46], *C. areruginosa*[44], *C.amada*[47], *C. wenyujin*[48], *C.soloensis*[44], *C.oligantha*[49] and *C. mannga*[44], has been ascertained using modern analytical methods, namely, nuclear magnetic resonance spectroscopy, high-performance thin-layer chromatography, photodiode array detection-high performance liquid chromatography, liquid chromatography-mass spectroscopy. Rhizomes of *Curcuma* spp. also contain curcuminoids, phenolic compounds structurally related to curcumin. Demethoxycurcumin (2) and bis-demethoxycurcumin (3), are the chief curcuminoids present in curcumin-containing rhizomes (Fig. 1). Attempts have been made to isolate and estimate these compounds to study their physical chemical and biological characteristics. These curcuminoids were isolated successfully for the first time by implementing reversed-phase HPLC and TLC[50]. Other more accurate and rapid techniques like UPLC (Ultra Performance Liquid Chromatography) and LC-MS/MS have also been employed for the isolation and quantitative analysis of curcuminoids[51,52]. The occurrence of curcuminoids in nature is quite rampant (Table I)—Uehara *et al*. isolated hydrated curcumin derivative (4) in the rhizomes of *C. xanthorrhiza*[53]. Similar hydrated curcuminoids were also identified in the rhizomes of *C. longa*[54]. Another curcumin analogue, 5'-methoxycurcumin (5), a potent antioxidant, was isolated by Masuda *et al.* from the rhizomes of *C. xanthorrhiza*[55]. Three curcumin analogues, cassumunins A, B and C (6-8), exhibiting antioxidant and anti-inflammatory effects, were found in *Z. cassumunar*[56]. A 5'-substitued derivative, bisabocurcumin (9), was obtained from *C. longa*[57]. *Alpinia blepharocalyx*, a Zingiberaceae family plant, produces seeds that embody diarylheptanoids and a dihydro-analogue of bis-demethoxycurcumin[58]. Two derivatives of curcumin (10, 11), belonging to diarylheptanoid family have been obtained from the rhizomes of *C. domestica* [59]. Further, the rhizomes of *Z. cassumunar* constituted three

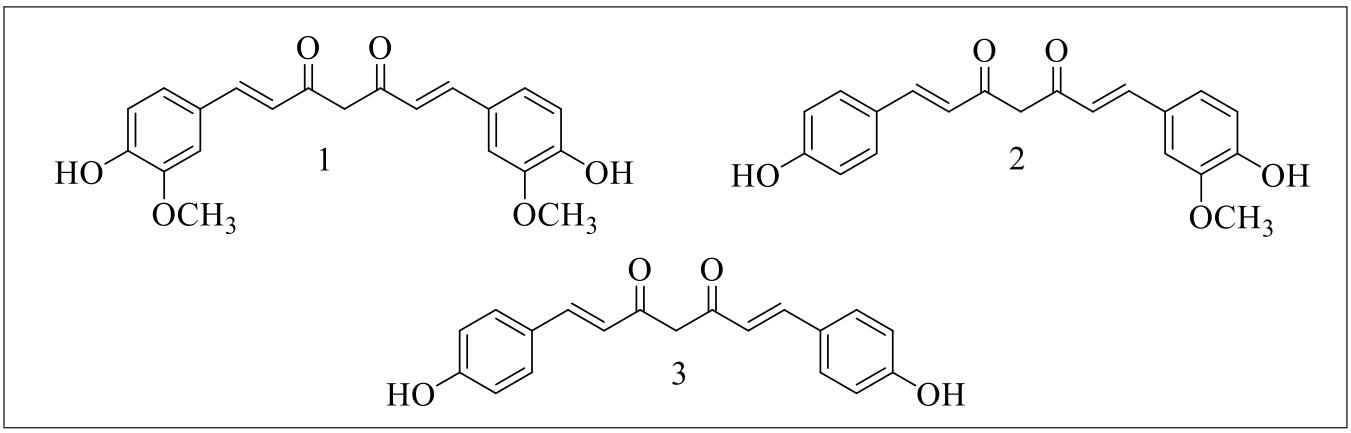
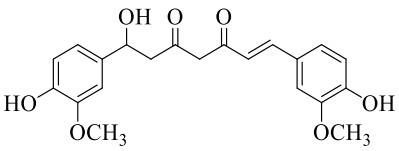
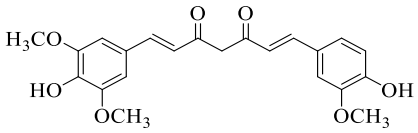
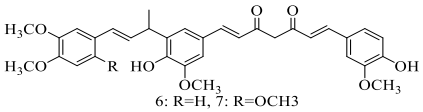
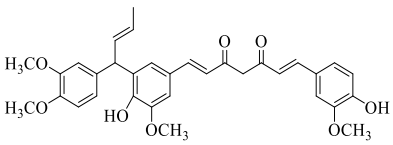
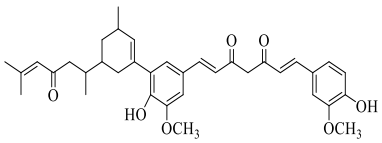
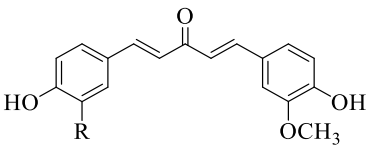
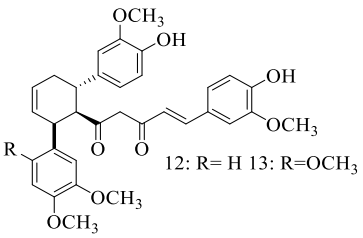
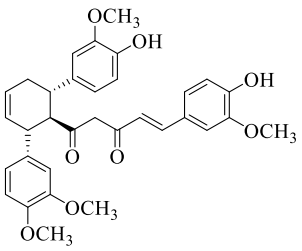
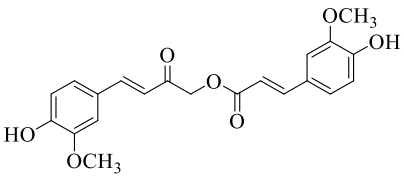


Fig. 1: Structure of (1) Curcumin, (2) Demethoxycurcumin, (3) Bis-demthoxycurcumin[1-2]

Table I: Some natural curcuminoids[53-57, 59-61]

Structure No.	Structure of curcumin compound	Name of plant	References
4		*C. xanthorrhiza*	53, 54
5		*C. xanthorrhiza*	55
6, 7	 6: R=H, 7: R=OCH3	*Z. cassumunar*	56
8		*Z. cassumunar*	56
9		*C. longa*	57
10, 11	 10: R= H, 11: R= OCH_3	*C. domestica*	59
12, 13	 12: R= H 13: R=OCH_3	*Z. cassumunar*	60
14		*Z. cassumunar*	60
15		*C. longa*	61

curcuminoids with a modified alkyl region, known as cassumunarins A-C (12-14). These possess anti-inflammatory and antioxidant properties[60]. Another curcuminoid, calebin A (15), isolated from *C. longa,* has methoxy groups too and is found to be beneficial in treatment of Alzheimer's disease[61].

CHEMISTRY OF CURCUMIN

Curcumin (diferuloylmethane) is a phytochemical, having the IUPAC name (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (Fig. 2).

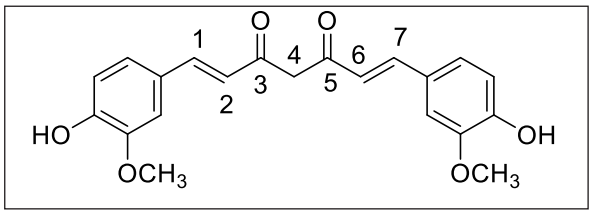


Fig. 2: (1*E*, 6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione[24]

Curcumin, having molecular weight of 368.38 g mol^{-1}, is a lipophilic compound with poor solubility in aqueous medium but fairly soluble in ethanol, DMSO (dimethylsulfoxide) and other organic solvents. Its melting point is 183 °C. It has an intense yellow colour in acidic and neutral solutions, which changes to deep red in an alkaline medium. Curcumin has two phenolic moieties and an enolizable β-diketone moiety. Due to conjugated phenolic, olefinic and diketone units, curcumin possesses distinct chemical properties.

EFFECT OF pH

Curcumin exists in keto-enol tautomeric forms. In acidic and neutral solutions keto form is more stabilized[62]. At pH 3 to 7, curcumin is a potent donor of H-atom. Beyond pH 8, curcumin exists in an enolate form and acts primarily as an electron donor. This contributes to its radical scavenging ability[63].

The keto tautomer (Fig. 3) can exist in cis and trans forms. pH, temperature, and solvent polarity remarkably affect the keto-enol equilibrium[64]. The pharmacological activities of curcumin are greatly affected by the keto-enol ratio[65]. Tautomers of curcumin separated via liquid chromatography/mass spectroscopy revealed that in water/ acetonitrile solution, curcumin existed in the enol form[66]. However, in non-polar solvents like CCl_4 and solid state, the keto form is predominant.

DEGRADATION PRODUCTS OF CURCUMINOIDS

In the presence of sunlight, curcuminoids undergo photo-oxidation, which result in their oxidative cleavage yielding p-hydroxybenzaldehyde, p-hydroxybenzoic acid, ferulic aldehyde, ferulic acid, vanillin and vanillic acid as the degradation products[67]. On photo-oxidation, a cyclic derivative of curcumin is obtained[68] (Fig. 4). The resistance to photo-oxidation by curcuminoids has also

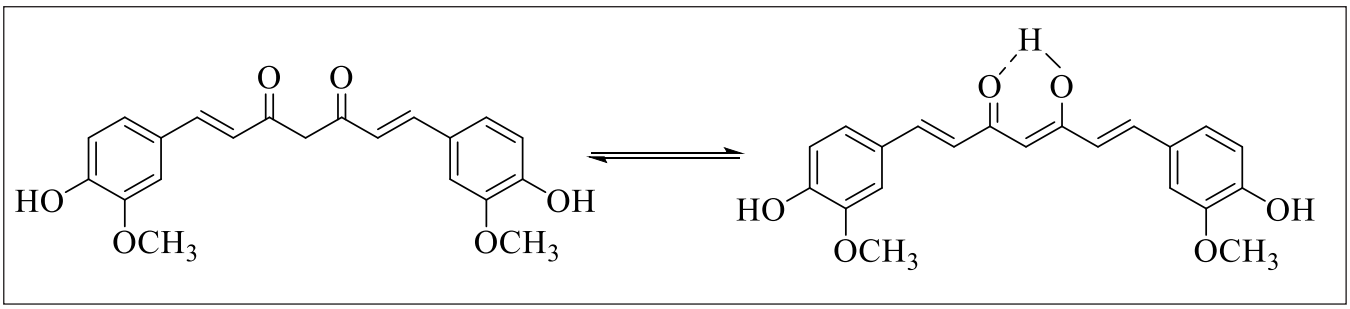


Fig. 3: Tautomerism of curcumin[62, 63]

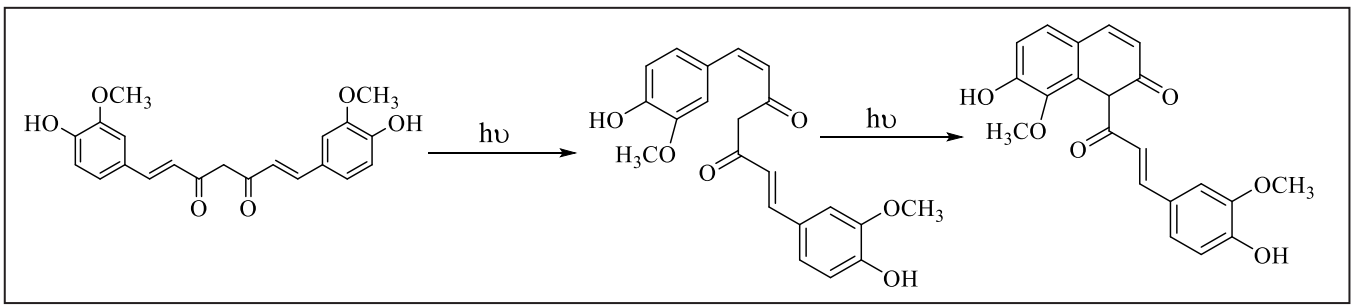


Fig. 4: Photo-oxidation of curcumin[69]

been analyzed. Price and Buescher studied the effects of oxygen and solvent systems on the photo-oxidation of curcuminoids. Curcumin was the most stable curcuminoid in methanol sparged with air, while demethoxycurcumin had the greatest stability in methanol sparged with nitrogen against light-induced oxidation[69]. On exposure to ozone, the brilliant yellow hue of curcumin faded due to its decomposition to vanillin and vanillic acid via the electrophilic addition of ozone to the olefinic bonds of curcumin[70].

The lipoxygenase-catalyzed oxidation of curcumin yielded an interesting rearranged product, as reported by Schneider and coworkers[71,72] (Fig. 5).

On biomimetic oxidation with hydrogen peroxide catalyzed by [TAPFe (III) Cl], curcumin afforded a C-C coupled dimer[73] (Fig. 6).

The poor solubility of curcumin in water limits its application in biological systems. Although curcumin dissolves in an alkaline medium, its stability is highly reduced in such conditions. In addition, various degradation products are formed. A study delineated ferulic acid and feruloyl methane formation by the alkaline degradation of curcumin via retro-Claisen condensation[74]. Another study on the kinetics of curcumin degradation revealed that the decomposition was pH-dependent and faster in alkaline medium, where nearly 90% of curcumin decomposed within 30 minutes.

The initial product obtained on alkaline degradation of curcumin was trans-6-(4'-hydroxy-3'-methoxy-phenyl)-2,4-dioxo-5-hexanal, the chief product, while ferulic acid, feruloyl methane and vanillin were obtained as minor products[62] (Fig. 7). Alkaline degradation of curcumin obeyed pseudo-first-order kinetics and the rates were maximum at pH 10.2[75].

STRUCTURE ACTIVITY RELATIONSHIP

Remodelling the chemical structure of a drug not only influences its receptor binding and pharmacological activity but also affects its physiochemical properties and pharmacokinetics[76]. An in-depth analysis of a drug molecule's natural and synthetic analogues is necessary to determine the key pharmacophore present in its structure[77]. Curcumin contains two hydroxy and methoxy-substituted phenyl rings, connected via a keto-enol linker of 7-C atoms. Although it is derived naturally, its chemical

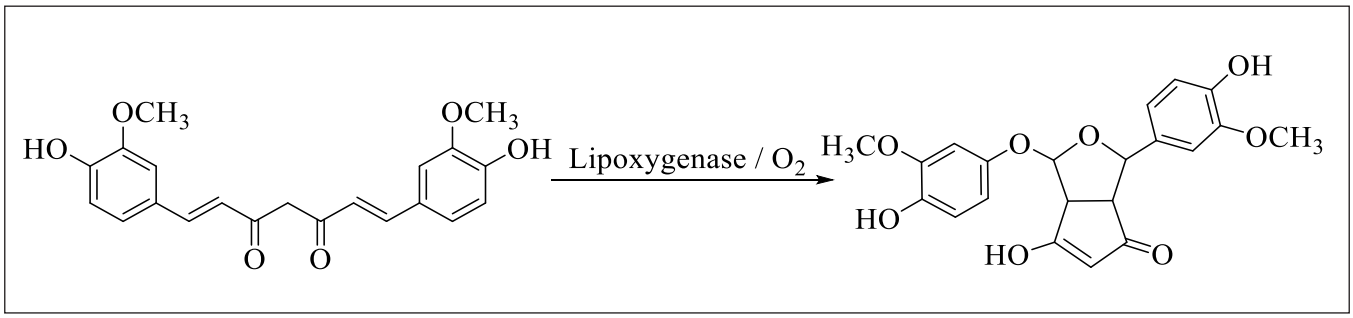


Fig. 5: Product obtained from oxidation of curcumin by lipoxygenase[71,72]

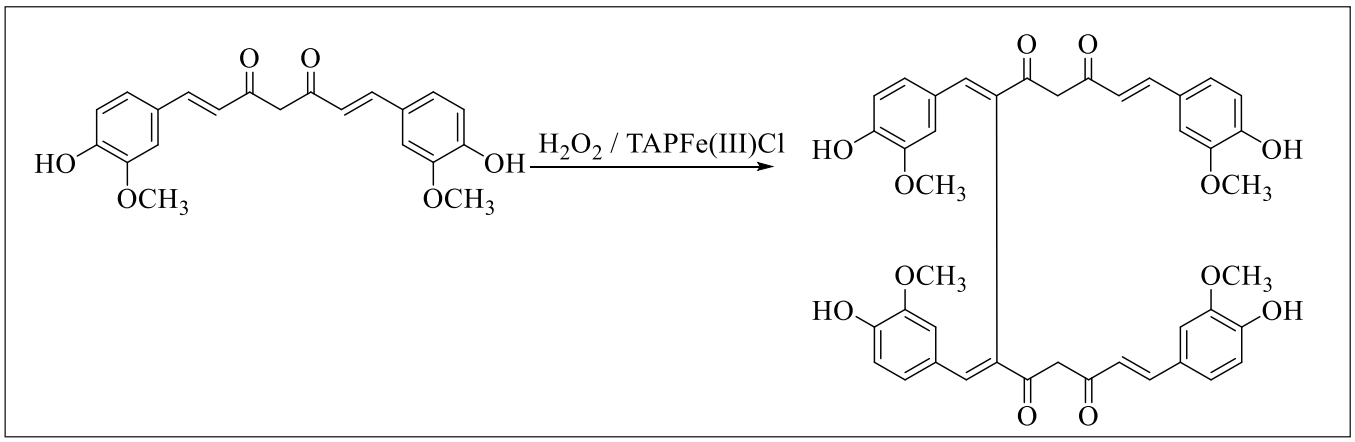


Fig. 6: Dimer of curcumin formed by H_2O_2 catalyzed oxidation of curcumin[73]

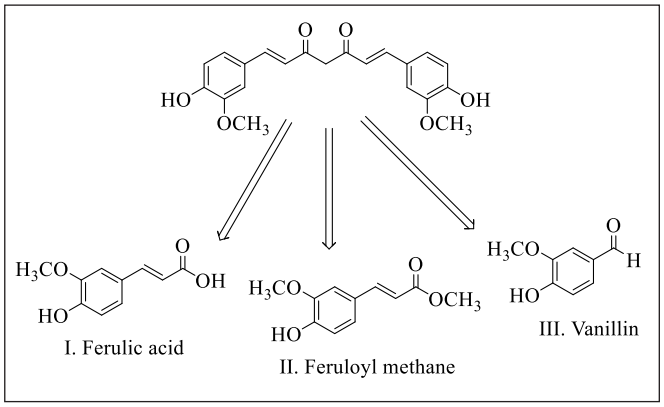


Fig. 7: Products of alkaline hydrolysis of curcumin[70]

analogues can be prepared by the reaction of aromatic aldehydes and acetylacetone; multiple analogues have been synthesized using this assembly method for instance, compounds having alkyl substituents at 4th carbon of the C7 linker. Synthesis of such modified derivatives leads to the production of potent anti-cancer drugs that inhibit cell growth in various stages of cancer[78,79]. SAR studies shown that coplanarity of β-diketone moiety and the H-atom donating group in curcumin analogues were essential for antiandrogenic activity.

Further, its antiandrogenic activity was enhanced significantly on shortening of diketone linker moiety from seven (C7) to five carbon atoms (C5)[80]. The introduction of the -CH_3 at both second and six positions of carbon resulted in a new curcumin derivative. Due to the steric hindrance offered by methyl groups on the double bonds, this derivative gained resistance against reduction by metabolizing enzymes[81]. In addition, it caused a more pronounced inhibition of proliferation of endothelial cells than curcumin both *in vitro* and *in vivo*[81]. Dimethylcurcumin or 1,7-bis-(3,4-dimethoxyphenyl)-5-hydroxyhepta-1,4,6-trien-3-one (ASC-J9), a newly developed analogue of curcumin, enhanced the disintegration of androgen receptor (AR) and efficiently arrested the proliferation and invasion of castration-resistant prostate cancer (CRPC) cells[82-84]. It was also found effective for restricting the expansion of estrogen-dependent MCF-7 breast cancer cells[85]. Even though the activity and target ability of the molecule was enhanced by methylation, its hydrophobic character also increased several fold compared to curcumin, which fettered its administrable dosage in cancer treatment[86].

Moreover, new curcumin analogues synthesized by glycosylation of aromatic ring (pharmacophore) improved aqueous solubility and kinetic stability of the molecule. This, caused the betterment of therapeutic activity of the molecule[87]. Curcumin undergoes metabolism via oxidation, reduction and conjugation (glucuronidation and sulfation). Conjugation occurs at the 4'OH groups on both the curcumin phenyl rings. This masking of the 4'OH groups enhances the stability of the molecule.

Additionally, it was found that the absence of methoxy groups in curcumin analogues reduced its therapeutic effect[88]. Furthermore, the addition of hydrophobic substituent to the C-4 position of the linker improved the antiandrogenic activities[89]. Negatively charged substituent or hydrogen bond acceptors at R_1, R_2, R_3, and R_4 positions (Fig. 8) also enhanced the biological activity of the molecule[90].

Another study pointed out that the methoxy group on the phenyl ring played a crucial role in inhibiting TNF-induced NF-κB activation. Thus, the relative potencies of curcumin analogues follow the order: curcumin > demethoxycurcumin > bis-demethoxycurcumin[91]. Tetrahydrocurcumin (THC) was inactive due to the absence of conjugated double bonds in the linker[91]. Certain derivatives of curcumin, such as THC, possessing a saturated diketone moiety, high level of hydrogenation and lower levels of methoxylation, exhibited enhanced anti-cancer and anti-inflammatory activities compared to curcumin[92]. A comparative study on curcumin and its modified analogues indicated that o-methoxy substituted phenolic units of curcumin displayed higher antioxidant activity. Also the hydrogenation of conjugated double bonds of the C7 linker in curcumin to THC significantly amplified antioxidant activity[93]. For instance, the antioxidant activity of THC was remarkably higher than dihydro curcumin (DHC) and unmodified curcumin[94,95]. Curcumin, possessing an α,β-unsaturated ketone unit, inhibited the activation of STAT3 and induced apoptosis. However, THC, devoid of such an electrophilic moiety, could not restrain the STAT3 signalling pathway. Hence, curcumin's electrophilic character is crucial for STAT3 inhibition during cancer treatment[96]. Construction of Cu^{2+}/ Ni^{2+}/ Zn^{2+}-curcumin-conjugated DNA complexes increased curcumin's solubility and emphasized its DNA-binding ability. Such complexes exhibited stronger antibacterial activity and enhanced cytotoxicity against several prostate cancer cell lines[97]. Besides anticancer and anti-inflammatory action, curcuminoids also manifest neuroprotective effects against lead-induced neurotoxicity. This is done primarily by chelate formation by the diketone moiety[98]. The conjugated diketone moiety of curcumin is the key pharmacophore which causes the suppression of NF-κB transcription factor. However, no specific connection was found between the inhibitory activity of curcumin and its

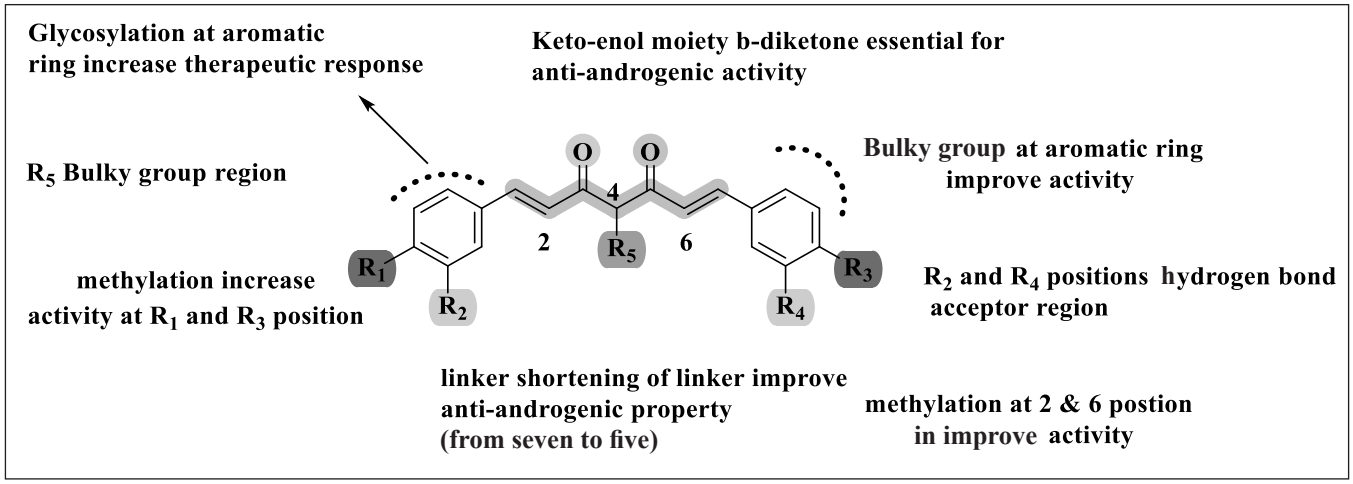


Fig. 8: SAR of curcumin for antiandrogenic activity[76-91]

analogues against NF-κB with the antioxidant activity[99]. The pH responsive property of curcumin was utilized in synthesizing curcumin-based nano-assemblies, which augmented the anti-cancer potential of curcumin via disruption of endosomes[100].

EFFECT OF CURCUMIN ON CANCER

Despite noteworthy advances in medicine, cancer is still regarded as the most invasive and fatal disease. The naturally occurring polyphenol curcumin exhibits anti-cancer properties and is capable of preventing, delaying, and reversing the carcinogenesis process. It induces apoptosis in a variety of tumour cells, modulates signal transduction pathways, alters gene expressions and inhibits tumour growth. The mechanism of its cancer-preventive action in various types of cancers has been reviewed below.

Nasopharyngeal cancer

In human nasopharyngeal carcinoma (NPC-TW 076) cells, curcumin impelled G2/M phase arrest and programmed cell death, the regulation of which was found to be correlated with apoptosis-inducing factor, caspase-3-dependent pathways and depolarization of mitochondria[101]. In a similar study, the proliferation of CNE-2z human NPC cell lines was substantially inhibited by curcumin and apoptosis was prompted by activating caspase-3, which was related to the negative-regulation of Bcl-2, NF-κB and positive-regulation of Bax[102]. Moreover, the radio sensitivity of NPC, which is correlated with lnc RNAs (long non-coding RNAs) profiles, was also influenced by curcumin. Curcumin remarkably altered the expression of lncRNAs and mRNAs. lncRNAs have an important role in IR-induced radio-resistance. Curcumin caused reversal of IR-induced differentially expressed lncRNAs in nasopharyngeal cancer cells and hence, enhanced their radio sensitivity[103]. Another study revealed that curcumin obstructed microRNA-125a-5p expression, and subsequently, TP53(tumour protein 53) gene expression was amplified, thus, inhibiting NPC activity[104]. In an *in vitro* study conducted on mouse xenografts, the uncontrolled NPC growth was hampered by curcumin. In the ERK-1/2 signalling pathway, protein expression was also altered by curcumin[105].

Lung cancer

In small-cell lung carcinoma, curcumin treatment enhanced Bax expression, while Bcl-xL and Bcl-2 expressions were suppressed, leading to apoptosis. This was caused by an increase in intracellular ROS (reactive oxygen species) levels. Curcumin also caused an abrupt decrement in the mitochondrial membrane potential and the released cytochrome-c into the cytosol; caspase-3 and caspase-9 were also activated later[106]. Furthermore, curcumin treatment attenuated the enzymatic activity of EGFR[107]. In another study, the EGR-1(early growth responses) modulated the crosstalk between Wnt signalling pathways and adherens junctions, proving that EGR-1 controlled the proliferation and invasion of cells. It was validated that a reduction in EGR-1 was caused by curcumin treatment. Anti-proliferation and anti-migration activities were also exhibited by curcumin in NSCLC[108]. According to a study, in SCC (squamous cell lung carcinoma) tumours, the therapeutic target was the STAT3. The PIAS3 was responsible for the inhibition of STAT3 endogenously, but its expression in SCC tumour cell lines was inhibited. Curcumin treatment enhanced the endogenous expression of PIAS3 and consequently, the proliferation and cell activity were reduced in Calu-1 cells[109]. Another study proved that curcumin-induced

apoptosis was dependent on microRNA-192-5p/215 induction, and the transcriptional target of miR-192-5p/215 was XIAP (X-linked inhibitor of apoptosis), which confirmed that miR-192-5p/215-XIAP pathway was a crucial target in non-small cell lung cancer[110]. A study underlined that curcumin treatment stimulated DNA impairment in human lung cancer cells. Curcumin also restrained the expression of DNA-repair proteins such as MDC1 (mediator of damage checkpoint 1), 14-3-3 protein σ, BRCA1 (breast cancer susceptibility gene 1) and MGMT (O6-methylguanine-DNA methyltransferase)[111]. Some studies on animals evaluated the anti-cancer properties of curcumin on lung cancer cells. In orthotopic human NSCLC xenografts, tumour growth was notably brought down by curcumin, and the life expectancy of treated athymic mice was significantly increased[112,113]. Moreover, curcumin exerted inhibitory effects on JAK2 activity and reduced tumour spheres of H460 cells by disrupting the JAK2/STAT3 signalling pathway. Tumor growth was greatly suppressed by curcumin in a lung cancer xenograft mouse model[114].

Hepatobiliary cancer

In hypoxia tumors, the transcription factor HIF (Hypoxia-inducible factor)-1 is essential for angiogenesis and cell survival. Curcumin lowered the levels of HIF-1α and HIF-2α proteins in hypoxia, while in normoxia, the transcriptional activity of HIF and the ARNT (aryl hydrocarbon receptor nuclear translocator) protein levels were reduced due to curcumin. Additionally, curcumin also adversely affected the survival of Hep3B hepatoma cells[115]. Curcumin protected and reversed diethylnitrosamine (DENA)-induced hepatocarcinogenesis and damages caused by it in rats[116]. Curcumin significantly lowered the gene expression of IL-2 (interleukin-2) and IL-6 (interleukine-6), levels of IL-2, IL-6, α fetoprotein (AFP), malondialdehyde (MDA) and alanine aminotransferase (ALT) in serum; while the gene expression and activities of glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase were greatly enhanced by curcumin. The expression of caspase-3 was enhanced, while there was a reduction in the high expression of angiogenic and anti-apoptotic transforming growth factor-β. Curcumin also regularized lipid peroxides and liver marker enzymes (AST and ALT)[117]. Furthermore, the growth of liver cancer in nude mice was effectively delayed by curcumin, in a dose-dependent manner[118].

A study conducted on cholangiocarcinoma cells revealed that apoptosis and antiproliferation in CCA cells were induced by curcumin. The formation of superoxide anion and reduction in the redox potential of the cell-induced apoptosis. The up-regulation of the Bax protein and TP53 gene was related to apoptosis and oxidative stress[119]. The feasibility of cholangiocarcinoma cells was reduced in comparison to the control. Also, the caspase activity and cleaved poly (ADP) ribose polymerase expression was reinforced, indicating that curcumin-induced apoptosis in CCA cells[120].

Breast cancer

Curcumin lowered the levels of HIF-1α and HIF-2α proteins in normoxia, while HIF transcriptional activity and ARNT protein levels in MCF-7 breast carcinoma cells were lowered in both normoxia and hypoxia[115]. Moreover, curcumin treatment suppressed the mitogen-activated protein kinase, PKC-α(protein kinase C-α) and nuclear factor-κB pathway, leading to reduction of (TPA)-induced-(MMP)-9 expression and cell invasion[121]. Additionally, the migration of breast carcinoma stem cells was aggravated because of the destruction of E-cadherin. Curcumin impeded β-catenin nuclear translocation. Thus restoring E-cadherin expression and obstructing the migration of breast cancer stem cells[122].

An aggressive breast cancer phenotype, unresectable triple-negative breast carcinoma is caused due to the absence of the progesterone receptor, estrogen receptor and EGFR2. Curcumin inhibited the aggressive cell division of triple-negative breast cancer by the down-regulation of EGFR signalling pathway[123,124]. Besides, using curcumin as an adjuvant during 5-fluorouracil treatment augmented the therapeutic efficiency of 5-fluorouracil by maintaining the viability of normal cells. Thus allowing higher dosage and prolonged treatment with 5-fluorouracil[125]. Additionally curcumin therapy sensitized retinoic acid-resistant triple negative breast carcinoma cell to retinoic acid mediated growth reduction[126]. Investigators have looked into the antitumorigenic potential of curcumin in breast cancer using a number of animal models. One such study corroborated that curcumin inhibited angiogenesis and tumour growth in mice breast cancer models, which was associated with the down-regulation of PECAM-1, p65 and cyclin D1 expressions[127]. Further, it was demonstrated that curcumin exhibited immunomodulatory effects on metastatic breast cancer by altering M1/M2 macrophage balance in tumors[128]. Similarly, curcumin treatment caused a notable decrease in cell proliferation and tumour volume in breast cancer xenografts[129].

Gastric cancer

Treatment of curcumin in gastric cancer cells induced loss in membrane potential of mitochondria and elevated the apoptosis rate, which was associated with enervated

ATP-sensitive potassium channel (KATP) opening[130]. Additionally, KLF4 (Krüppel-like factor 4) was a potent therapeutic target in human gastric carcinoma cells, and curcumin can act as a promising therapeutic strategy in gastric cancer. KLF4 overexpression in combination with curcumin prompted apoptosis and hampered the proliferation and invasion of gastric cancer cells[131]. Furthermore, curcumin reduced the density of lymphatic vessels in an *in vivo* gastric cancer model. Detection of downregulation of Prospero homeobox 1, LYVE-1(lymphatic vessel endothelial receptor), VEGFR-3 mRNA expression and podoplanin underlined that curcumin inhibited lymph node metastasis in gastric cancer[132]. Another study shed light on the lowering of expression of glycolytic enzymes and induction of G2/M phase cell cycle arrest by curcumin, hence restricting the growth of cancerous cells[133]. It was revealed in an *in vivo* study that a blend of 5-fluorouracil/oxaliplatin and curcumin showed effective reduction of BGC-823 tumour expansion in xenografts[134].

Colorectal cancer

Curcumin averted adenomas and aberrant crypt foci (ACF) colorectal cancer model in mice. The synthesis of 5-HETE (5- hydroxyeicosatetraenoic acid) and PGE2 (pro-carcinogenic eicosanoids prostaglandin E2) was inhibited by curcumin, thus attenuating carcinogenesis in colon cancer cells[135]. Besides, curcumin checked the development of human colon cancer cell lines and induced apoptosis via DNA fragmentation, with nuclear condensation[136]. In addition, curcumin subdued the activity and expression of hexokinase-II and caused the dissociation of hexokinase-II, leading to mitochondrial-mediated apoptosis[137]. Furthermore, curcumin involved epigenetic DLEC1 to exert an inhibitory effect on anchorage-independent growth of human colon cancer cells[138]. Moreover, 5-fluorouracil treatment was found ineffective for colorectal cancer, but the blend of curcumin and 5-fluorouracil reduced the chemoresistance of carcinoma due to suppressed proliferation in 5-fluorouracil resistant cells and enhanced cellular apoptosis. The EMT-suppressive microRNAs in cells resistant to 5-fluorouracil were upregulated by curcumin[139].

Prostate cancer

In prostate cancer, the invigorated activity of androgen receptors (AR) and amplification of co-activator protein p300 and cAMP response element-binding protein (CREB) result in hostile phenotypes and failure of hormone therapy. Curcumin reduced the acetylation of histone and altered the chromatin landscape, consequently suppressing the CBP and p300 habitation at sites of AR activity, thereby declining tumor enlargement and delaying the emergence of castrate-resistant disease[140]. Moreover, curcumin treatment curbed the inhibitor of DNA binding one by small interfering RNA, inhibiting prostate cancer cell proliferation (PC-3) and growth of xenografted tumours in mouse model[141]. Similarly, the development of PC-3 tumour in SCID (severe combined immune deficiency) mice with PC-3 xenograft was inhibited by the combination of curcumin and α-tomatine[142]. A recent study demonstrated the synergistic effect of curcumin with metformin on LNCaP prostate cancer cell lines. This combination induced apoptosis, Bax expression and cytotoxicity within 48 h and could be considered as a potent anti-cancer agent[143].

Uterine cancer

Treatment with curcumin-based cream resulted in the selective elimination of HPV+ cervical cancer cells and the repression of EGFR expressions and antigen E6 transformation, which simultaneously induced p53. The study revealed that the intravaginal application of curcumin-based vaginal cream in mice eradicated HPV+ cancer cells without harming the non-cancerous cells[144]. In addition, curcumin arrested the proliferation and apoptosis of inhuman endometrial carcinoma cells by depressing their AR expressions through the Wnt signal pathway[145]. Another study revealed that the expression of argyrophilic nucleolar organization region protein (AgNOR) was much higher in malignant cells than in normal cells. By hypermethylation of global DNA in HeLa cells, a decrease in AgNOR protein pools was induced by curcumin. Thus, curcumin might be effective against HeLa cells at low micromolar concentrations[146]. In addition, curcumin hindered angiogenesis and tumour growth in cervical cancer xenografted mice by repressing COX-2 (cyclooxygenase-2), EGFR and VEGF (vascular endothelial growth factor)[147].

Hematopoietic cancer

Curcumin, alone or incorporated with other drugs, induced apoptosis in hematopoietic cancer. For instance, the overexpression of the WT1 (Wilms' tumour) gene in patients who have acute myeloid leukaemia was strongly repressed via protein kinase C inhibitor, indicating that curcumin attenuated external WT1 (+/+) expression during post-translational process[148,149]. The exogenous WT1 (+/+) half-life was also reduced[148]. Another similar study demonstrated that curcumin inhibited clonogenicity and cell proliferation in a dose-dependent way and also arrested the cell cycle at G2/M phase. WT1 levels were also lowered by curcumin[149]. In addition, a study unveiled that the treatment of curcumin in the presence of Cu^{2+} in CCRF-

CEM human T-cell leukaemia cells damaged the DNA plasmids almost completely. Results were not the same on treatment with curcumin or Cu^{2+} alone[150]. In leukemic cells derived from acute promyelocytic leukaemia (APL), curcumin treatment hindered cell growth and promoted cellular apoptosis. Curcumin-induced apoptosis was stimulated by an augmentation in endoplasmic reticulum (ER) stress, which resulted in misfolded N-CoR protein accumulation in ER[151]. Further, in Burkitt's lymphoma cell lines, pretreatment of curcumin caused sensitization of lymphoma cells to IR-induced apoptosis, and G2/M phase arrest was increased[152]. Moreover, curcumin-induced rapid generation of ROS incited apoptosis in HuT-78 cells by regulating different cell death and cell survival pathways[153].

Other cancers

Curcumin also exhibits anti-cancer properties in various other types of cancers. For example, curcumin is a potent alternative for the treatment of glioblastomas. Curcumin reduced NF-κB pathways and the activation of phosphatidylinositol 3-kinase (PI3K)/PKA, followed by the down-regulation of Bcl-xl NF-κB-regulated protein and impelled mitochondrial dysfunction[154]. Furthermore, curcumin restricts cellular growth, migration and invasion in pancreatic cancer. Curcumin also prompted cellular apoptosis, related with enhanced expression of miR-7 and reduced expression of SET-8, a target of miR-7[155]. In another study, in a dose-dependent fashion, curcumin repressed the cell incursion, activity, and migration abilities of K1 thyroid cancer cells. The expression and activity of MMP-9 were also suppressed by curcumin. Besides, curcumin caused the inhibition of hypoxia-induced ROS regulation and reduced mRNA expression levels of HIF-1α in K1 cells[156,157]. Additionally, in head and neck squamous cell carcinoma (HNSCC) cell lines, the pro-apoptotic Bik was elevated by curcumin, while survival signalling by NF-κB and Akt was down-regulated[158]. Several cancers, such as oral squamous cell carcinoma[159] and peripheral nerve sheath tumors[160], can also be effectively treated with curcumin.

CLINICAL STUDIES

Several clinical studies validate curcumin's effectiveness, safety and tolerability against cancer[161]. Oral administration of curcumin at 6 g day^{-1} for 4-7 weeks produced no toxicity in patients[162]. Even at high doses of 12 g day^{-1}, curcumin was found safe but had poor bioavailability[163,164]. In the phase I, dose escalation clinical study of liposomal curcumin (Lipocurc™), the maximum safe dosage for anti-cancer treatments in patients with metastatic or locally advanced cancer was marked down to 300 (mg m^{-2}) (NCT02138955)[165]. In patients with advanced breast cancer with metastasis, the intravenous treatment of curcumin combined with paclitaxel demonstrated that it did not cause any major health concerns (NCT03072992). It was, however, helpful in reducing fatigue[166]. In random, double-blind, placebo-controlled clinical trial, severity of dermatitis caused by radiation in breast carcinoma patients was reduced by orally administering curcumin (6 g daily) during radiotherapy[167]. In another study, the maximum recommended dose of curcumin in metastatic breast cancer was 6000 mg day^{-1}, weekly for 21 days, in combination with the standard dose of docetaxel[168]. A clinical study (phase II) on the anti-tumorigenic effects of curcumin on colorectal cancer revealed that administration of curcumin at 2 g and 4g in patients caused the prevention of colorectal neoplasia and decreased ACF levels 150. Further, the general health of patients with colorectal cancer was boosted by curcumin administration through enhanced expression of p53 molecule in tumour cells and consequent increase in cellular apoptosis[169].

In phase I and II clinical trials of curcumin, the tolerable and safe dose of curcumin in combination with gemcitabine was estimated to be eight g day^{-1} [170,171] in patients with advanced stages of pancreatic cancer. Low doses of lapidated curcumin at 80 mg day^{-1} in middle-aged people (40-60 years old) promoted improvement of health[172]. A combination of curcumin and quercetin at doses of 480 mg and 20 mg, respectively, has shown a reduction in polyp numeral and mass of intestinal adenomas in patients with adenomatous polyposis by oral administration for six months. Treatment with curcumin (480 mg) combined with quercetin (20 mg) orally three times a day for six months resulted in a reduction in polyp numeral and mass of ileorectal adenomas in patients with familial adenomatous polyposis (FAP)[173]. Treatment with curcumin and piperine negated lipid peroxidation and further enhanced the GSH levels of 20 tropical pancreatitis patients[174]. The treatment of curcumin combined with isoflavones in a clinical trial indicated that they synergistically affect the production of PSA in prostate cells and exhibit anti-androgenic effects[175]. In ulcerative colitis, administration of curcumin (3g day^{-1}) in mesalamine-treated patients caused subsidence in patients with mild-moderate disease (NCT01320436)[176].

FUTURE PROSPECTS

Curcumin is a pleiotropic molecule. Due to its unique chemical structure, it has diverse therapeutic and biological effects on cancer. It also showcases antioxidant, anti-arthritic, anti-microbial and anti-angiogenic properties. Clinical studies reveal that it is safe for humans, causing no significant side effects. However, its lipophilic character

and below-par solvability in aqueous medium curtails its applicability in biological systems. Other reasons for its low bioavailability are its rapid metabolism, poor absorption and quick systemic elimination from the body. To overcome these shortcomings, numerous nano-formulations of curcumin, such as nanoparticles, cyclodextrins, micelles, and liposomes, have been developed, which have proven to be quite promising and can increase their efficacy and bioavailability.

Further, these act as nano-delivery vehicles and enhance the ease of administration of curcumin and reduce any toxicity caused. However, these formulations of curcumin are non-target-specific. Hence, reforms in target-specific delivery need to be contemplated. Many clinical trials have been conducted, but there is still scope for future large-scale trials to explore the potentiality of curcumin as an anti-neoplastic drug, as an adjuvant therapy in cancer and in the treatment of several other diseases. High doses of curcumin have been administered in most clinical trials, which seems rather impractical. Curcumin exhibits synergistic effects with various anti-cancer drugs such as cisplatin, avastin, paclitaxel, docetaxel, etc. and enhances their therapeutic action. More such combinations need to be discovered, which can reduce the side-effects of traditional therapies and facilitate better recovery of patients. Hence, more thorough studies on curcumin-based combination therapy are required.

CONCLUSION

Cancer is a notorious disease, posing a huge threat to humankind. Chemotherapy is a treatment modality in cancer that produces serious side effects and toxicity in patients. Hence, scientists are in search of novel drugs that are not only efficient but also non-toxic. Phytochemicals such as curcumin and its natural and synthetic analogues have shown cancer-preventing and eradicating effects in humans, with little or no considerable side effects. With a few modulations in the basic pharmacophore structure of curcumin, its therapeutic action may increase manifold.

Moreover, nano-encapsulation of curcumin enhances its effectiveness and bioavailability, irrespective of its water insolubility. It is effective against various cancers when used alone or in combination with other drugs. Its therapeutic potential and bio-activity necessitate a more detailed inspection of the mechanism of its action. Further, advancement in target specificity, mode of administration and wide clinical trials are recommended to validate it as a drug safe for human use.

ACKNOWLEDGEMENT

The study was financially supported from CSJM University Kanpur under CV Raman Minor Research Project (CSJMU/R&D/CVR/21/2023).

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