A perspective on the chemical structures and molecular mechanisms of curcumin and its derivatives and analogs in cancer treatment (Review)

LUJIE ZHU[1,2], YANGHAN WANG[2] and QILIN WANG[1,3]

[1]Shandong Key Laboratory of Applied Technology for Protein and Peptide Drugs, School of Pharmaceutical Sciences and Food Engineering, Liaocheng University, Liaocheng, Shandong 252059, P.R. China; [2]Department of Biological Science, College of Agriculture and Biology, Liaocheng University, Liaocheng, Shandong 252059, P.R. China; [3]State Key Laboratory of Macromolecular Drugs and Large-scale Preparation, School of Pharmaceutical Sciences and Food Engineering, Liaocheng University, Liaocheng, Shandong 252059, P.R. China

Received December 25, 2024; Accepted June 10, 2025

DOI: 10.3892/ijo.2025.5782

Abstract. Curcumin is a polyphenolic nutraceutical compound, which has a variety of pharmacological properties that may prevent or treat cancer, chronic inflammation, depression, anxiety and nerve damage. However, due to the poor solubility of curcumin in water and instability, it has limited applications. Therefore, a series of curcumin derivatives or analogs have been designed and synthesized to optimize the physicochemical and therapeutic properties and pharmacokinetic features of curcumin. Curcumin derivatives or analogs have been shown to possess beneficial biochemical effects, thus have been considered as potential medications. The present review summarized the structural characteristics and classification of available curcumin derivatives or analogs, and described the molecular mechanisms of curcumin and its derivatives as potential pharmaceutical drugs in various types of cancer, such as lung, prostate, breast and colorectal cancer. The present review also discussed the adverse effects and limitations of curcumin and its derivatives/analogs in preclinical and clinical trials. Analysis of the existing studies on curcumin may potentially contribute to the design and synthesis of innovative curcumin derivatives or analogs as drugs and tools in therapeutic, preventative and diagnostic medical applications in associated diseases.

Correspondence to: Professor Qilin Wang, Shandong Key Laboratory of Applied Technology for Protein and Peptide Drugs, School of Pharmaceutical Sciences and Food Engineering, Liaocheng University, 1 Hunan Road, Dongchangfu, Liaocheng, Shandong 252059, P.R. China
E-mail: wql@lcu.edu.cn

Key words: curcumin, derivatives, analogs, molecular mechanism, antitumor activity, cancer treatment

Contents

1. Introduction

Curcumin is a natural β-diketone polyphenolic compound extracted from the rhizome of *Curcuma longa* and other plants, such as *Curcuma zedoaria* and *Curcuma aromatica* Salisb. (1,2). Previous research has demonstrated that curcumin presents a variety of biological properties, such as anti-inflammatory (3,4) and antitumor effects (5,6), neuroprotection during surgery (7), depression and anxiety relief (8,9) and antiviral and antibacterial effects (10,11). Cancer, chronic inflammation, depression, anxiety and nerve damage are complex diseases that afflict patients and present challenges for medical workers; therefore, researchers aim to identify effective compounds in the treatment and relief of these diseases. Curcumin is considered one such potential compound; however, a limitation is that curcumin is poorly soluble in water, unstable and has a low bioavailability (12-16). Therefore, to improve the pharmacological properties of curcumin, scientists have aimed to design and synthesize new molecular structures of curcumin (9,17-19). Consequently, the molecular structures of curcumin have been optimized through structural modification or hybridization, which has resulted in different curcumin derivatives or analogs that have

beneficial modified physicochemical properties and improved pharmacological activities compared to that of curcumin.

By optimizing the dosage form of curcumin and generating emulsions, liposomes and polymer micelles, the solubility of curcumin derivatives has been improved. Furthermore, in order to improve the bioavailability of curcumin, curcumin and its derivatives have been encapsulated and delivered in an indirect manner based on nanoparticles and microemulsions (5,15). Curcumin analogs also have the capacity to chelate metal ions and may act as metal-chelating agent for pharmaceutical applications (20). The present review mainly summarizes the chemical structures and modification of curcumin and its derivatives/analogs, as well as their molecular mechanisms in cancer treatment.

2. Chemical structures and physicochemical properties of curcumin

Curcumin is extracted from the rhizome of *Curcuma longa*, *Curcuma aromatica* and *Acorus* of the Araceae family (1,2), and is a natural polyphenolic compound containing two β-keto groups. Curcumin is a yellow crystal with a melting point of 183˚C and its molecular formula is $C_{21}H_{20}O_6$. The primary structure of curcumin is a 1,7-diarylheptane skeleton, containing two β-keto moieties and two O-methylated phenols (21,22). The presence of two phenolic hydroxyl groups at the ends of the molecular structure makes it prone to conjugation under alkaline conditions, resulting in keto-enol tautomerism (23) (Fig. 1).

In an alkaline environment, curcumin primarily exists stably in its enol form and is reddish brown in color. In acidic and neutral environments, the structure of curcumin changes to the ketone form, which appears luminous yellow (23). These features make curcumin a chemical acid-base indicator. Natural curcumin, due to its long unsaturated aliphatic chain and benzene ring structure, is insoluble in water at room temperature, but is soluble in alcohol, acetone and other organic or alkaline solvents. In an acidic environment, natural curcumin is stable (24). The characteristic yellow color of turmeric is due to the presence of curcuminoids; of the components in curcuminoids, besides curcumin, there are demethoxycurcumin, bisdemethoxycurcumin and cyclocurcumin (Fig. 2A-C). Curcumin is the main bioactive ingredient of turmeric, containing 3-5% of the total composition (25).

In total, two natural curcumin derivatives, demethylcurcumin and bisdemethylcurcumin, exist in nature, which are also the two main forms of curcumin metabolized in the body (26). Demethylcurcumin is a diketone compound containing three phenolic hydroxyl groups, based on the structure of curcumin, where the methyl group bonded to hydroxyl oxygen at one end of the aryl ring is replaced by hydrogen (Fig. 3A). Bisdemethylcurcumin is also a diketone compound containing four phenolic hydroxyl groups on the basis of the structure of curcumin, where both methyl groups on the hydroxyl oxygens on the two aryl rings are replaced by hydrogens (Fig. 3B).

The physiological function of curcumin predominantly depends on the structure of phenolic hydroxyl groups and diketo moieties. Phenolic hydroxyl groups are prone to chemical reactions with active oxygen and free radicals, and are oxidized into keto groups. Furthermore, curcumin can scavenge reactive oxygen species (ROS) generated either in the mitochondria, by substance metabolism or in response to environmental factors, and exhibits antioxidant and anti-inflammatory activities (3,4). Curcumin also reacts easily with strong electron-absorbing groups and produces ROS, which exerts a toxic effect on tumor cells. It has been shown that the substituent groups on the 4' carbon atom of the acyl ring of curcumin are the key to its pharmacological activity (27). If large groups that cannot form hydrogen bonds are introduced to the 4' carbon atom of the acyl ring, the pharmacological activity of curcumin is decreased. However, the introduction of small groups, such as hydroxyl (-OH), which can form hydrogen bonds to the 4' carbon atom of the acyl ring, can increase the biological activity of the compound, but at the same time it may reduce selectivity (16,27). Therefore, in order to obtain derivatives with optimal biological activity and selectivity, it is necessary to select groups with appropriate volume and hydrogen bond-forming ability.

Curcumin and curcuminoids have been commonly researched due to their promising functional groups, such as scaffolds of α,β-unsaturated β-diketone, α,β-unsaturated ketone and β'-hydroxyl-α,β-unsaturated ketone connected with acyl rings on both sides. At present, the primary methods of structural modification of curcumin and curcuminoids include: To increase or decrease benzene substituents, change the length of fatty acid chains, change the structure of diketones, substitute acyl rings with heterocyclic rings or reduce unsaturated bonds or to hybridize with other effective pharmaceutical structures.

3. Structural modification of curcumin and its derivatives/analogs

Hydrogenated curcumin derivatives. Curcumin is metabolized rapidly and extensively in both animals and humans. When administered orally, curcumin is successively transformed to several reduced forms, including tetrahydrocurcumin (THC), hexahydrocurcumin (HHC) and octahydrocurcumin (OHC), in the liver as well as in the intestinal mucosa, by phase I metabolism (Fig. 4). HHC is a major metabolite of curcumin, with lower levels of octa-, tetra- and dihydro products being produced from curcumin metabolism (27-29).

THC and OHC are common hydrogenation products of curcumin. THC is formed by hydrogenation of double bonds on aliphatic chains in the structure of curcumin. OHC is a product of further hydrogenation of carbonyl oxygen to hydroxyl on THC. Compared with curcumin, THC is more water soluble and more easily absorbed by organisms, with advantages of increased water solubility and chemical stability (30,31).

Due to the presence of a number of hydroxyl substituents on these curcuminoids, the solubility and bio-absorbability of the aforementioned compounds, such as THC, HHC and OHC, are greater when compared with those of curcumin. Furthermore, the change of a diketo structure to hydroxyl groups reduces its cytotoxicity and enables the phenolic hydroxyl groups to exert anti-inflammatory and antioxidant effects (32,33).

HHC has the same phenolic groups as the enol form of curcumin; therefore, it presents with a number of the same biological and pharmacological activities as curcumin.

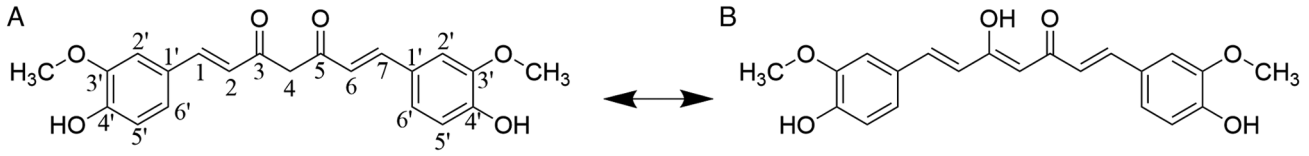

Figure 1. Molecular structures of ketone and enol structures of curcumin. (A) Ketone and (B) enol. Under alkaline conditions, the presence of two phenolic hydroxyl groups at the ends of the molecular structure makes it prone to conjugation, resulting in keto-enol tautomerism.

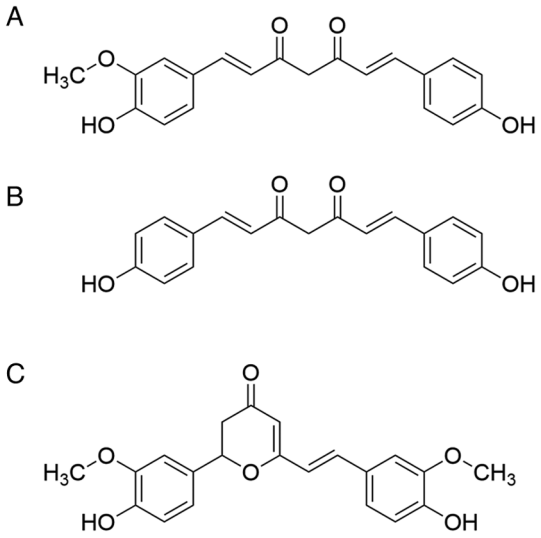

Figure 2. Molecular structures of curcuminoids. (A) Demethoxycurcumin, (B) bisdemethoxycurcumin and (C) cyclocurcumin.

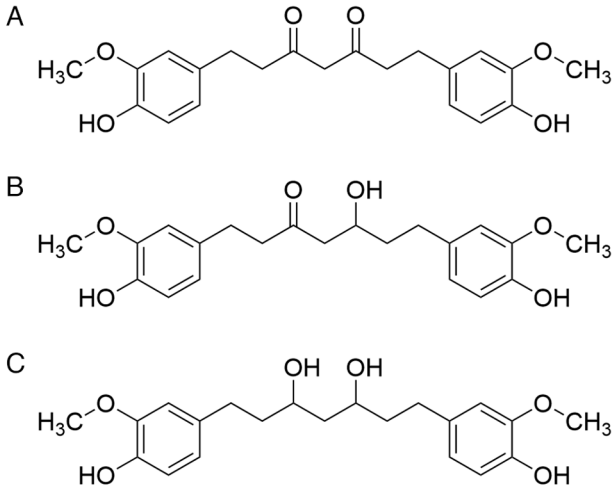

Figure 4. Hydrogenated curcumin derivatives. (A) Tetrahydrocurcumin, (B) hexahydrocurcumin and (C) octahydrocurcumin. These three hydrogenated curcumins are the metabolites of curcumin in the liver as well as in the intestinal mucosa by phase I metabolism.

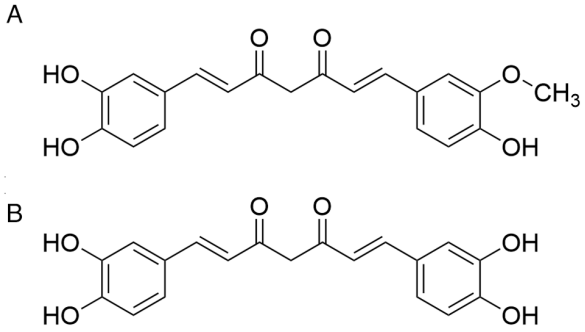

Figure 3. Molecular structures of demethylcurcumin and bisdemethylcurcumin. (A) Demethylcurcumin and (B) bisdemethylcurcumin are the two main forms of curcumin metabolized in the body. In contrast to curcumin, demethylcurcumin and bisdemethylcurcumin are formed due to one or two methyl groups on the hydroxyl oxygens on the aryl rings being replaced by hydrogen, respectively.

However, since HHC has no olefinic double bonds, it is more stable than curcumin at pH 7.4. Notably, HHC exhibits an increased chemical stability and bioavailability compared with that of parent curcumin in the treatment of Caco-2 human epithelial colorectal adenocarcinoma cells (34,35). With enhanced pharmacological activities, the use of hydrogenated curcumin derivatives may be more promising as therapeutic drugs than that of curcumin.

The metabolites of curcumin have gained increasing attention (30-33), the reason for which is that some metabolites of curcumin, such as HHC and THC, have similar and potentially improved bioactivities compared with that of curcumin. The bioactive degradative products contribute to the pharmacological effects of curcumin, which may suggest why natural curcumin with poor oral bioavailability demonstrates efficacy in *in vivo* studies (32-36).

Aryl-modified curcumin derivatives. Acyl ring-modified substituents are a type of curcumin derivative that were previously developed, and are characterized by the original substituents on the acyl ring of curcumin being either replaced with new substituents or with new substituents added while keeping the original substituents unchanged on the acyl ring. In a previous study, the phenolic hydroxyl groups were replaced with halogens (Fig. 5), and it was found that its photodynamic force (photodynamic inactivation, PDI) was raised with the increase in halogen atomic number ($_{9}$F, $_{17}$Cl and $_{35}$Br) (37). Curcumin produces cytotoxic ROS through electron transfer and energy transfer stimulated with blue light, which is known as the PDI. ROS can lead to different degrees of damage to cell membrane structures, DNA, RNA and proteins; therefore, halogenated curcuminoids have been testified to have improved anticancer activity in 518A2 melanoma cells (37).

In other studies, the phenolic hydroxyl groups in the aryl ring are protected by using reversible groups, so that phenolic hydroxyl groups are not easily oxidized in the external environment, and their stability, biological activity and selectivity as drugs can be increased to a certain extent (38,39). For example, Fang *et al* (38) replaced the methoxy group with dimethylaminomethyl in order to introduce basic groups

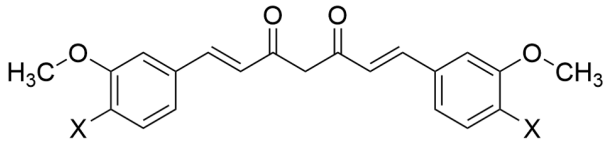

Figure 5. Halogenated curcumin derivative. Phenolic hydroxyl groups on curcumin are replaced by halogens, where X represents F, Cl or Br.

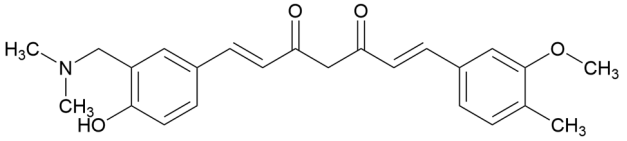

Figure 6. Dimethylaminomethyl curcumin derivative. The methoxy group on one acyl ring is replaced by dimethylaminomethyl, which increases the water solubility of the curcumin derivative and the steric hindrance of the molecule to protect the active phenolic hydroxyl group.

(Fig. 6). The introduction of basic groups has been shown to make the curcumin derivative more easily soluble in water and increase the steric hindrance of the molecule to protect the active phenolic hydroxyl group. The substitution of phenolic hydroxyl groups with different physiological activities can improve the potential of penetrating the blood-brain barrier and selectivity against certain types of cancer cells, such as in liver cancer HepG2 cells, gastric cancer SGC-7901 cells, lung cancer A549 cells and colorectal cancer HCT-116 cell lines (38,40).

Numerous studies on curcumin derivatives have focused on the modification of phenolic hydroxyl groups (38,39); other studies have also utilized the chemical properties of the phenolic hydroxyl group to make curcumin ether or ester (16,41). The resulting derivatives of curcumin, AB1 and AB2, are more stable than curcumin and exhibit enhanced solubility in water (16,41). Recently, using novel galactosylated chitosan (GC)-modified nanoparticles (GC@NPs), based on poly(ethylene glycol) methyl ether-block-poly(lactide-co-glyc olide), for drug loading of curcumin has been shown to lead to superior inhibition of tumor growth compared with that of free curcumin in hepatocellular carcinoma. This finding demonstrates that GC@NPs may be a promising curcumin nanocarrier for tumor therapy with a good biosafety profile and high therapeutic efficacy (42).

Monocarbonyl-modified analogs. The diketo moiety of curcumin is prone to enol tautomerism and unstable in terms of its chemical properties. In order to overcome these defects, researchers have developed a variety of monocarbonyl analogs of curcumin (MACs) (16), namely mono-ketone curcumin (Fig. 7), which has a shorter aliphatic chain connection compared with that of natural curcumin, has increased water solubility and is more stable; it has been experimentally demonstrated that shorter fat chains are associated with increased water solubility and stability (43). Monocarbonyl-modified compounds are mainly a combination of hydrogenated curcumin derivatives or analogs, acyl ring substituent and diketone-modified derivatives aforementioned, some of which exhibit certain anticancer, such as in colon cancer, and antibacterial activities (44,45). MACs have been shown to exhibit increased anticancer properties compared with that of curcumin. In recent years, numerous studies have emphasized the pharmaceutical significance of MACs as effective anticancer agents in hepatocellular carcinoma and colorectal cancer (46-48).

Bis-imino and bis-amino curcumin derivatives. A novel set of curcumin analogs has been synthesized from a bis-aldehyde derivative of hydroxybenzylidene cyclohexanone and various alicyclic and aromatic amines, which include bis-amino and

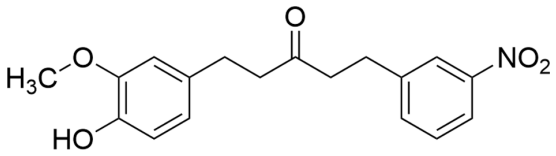

Figure 7. Monocarbonyl-modified compound. This monocarbonyl curcumin analog has only one keto group in the aliphatic chain, which makes its water solubility higher and more stable.

bis-imino curcumin derivatives (Fig. 8A and B). A characteristic of bis-amino and bis-imino curcumin derivatives is that they have a Schiff base moiety (49). Bis-imino and bis-amino curcuminoids have been tested for anticancer activity against MCF7 human breast carcinoma cells, and some of them, such as 3k, 3b and 3l, have been shown to exert more potent anticancer activity in MCF-7 cells compared with that of curcumin, as determined by MTT assay (49). The IC_{50} values of these three compounds (3k, 3b and 3l) were <10 μg/ml, while methotrexate and curcumin have IC_{50} values in the range of 100-300 μg/ml.

Aliphatic chain-modified substituents. The phenolic hydroxyl group in the acyl ring of curcumin is an important pharmacophore, which can improve the water solubility of curcumin derivatives, and the antioxidant activity can be effectively increased when multiple phenolic hydroxyl groups are present in the molecule (50). The carbon-4 atom between β-diketone of curcumin can be linked to various groups, such as 4-phenylaminomethyl curcumin, arylidene curcumin and pyrazole curcumin, to form curcumin analogs (Fig. 9). As for these designed analogs, the addition of more phenolic hydroxyl groups have been shown to possess increased beneficial physicochemical and biological activities, such as anti-inflammatory, antioxidant and antibacterial activities via inhibition of cyclooxygenase *in vitro* (50), which may be applied in cancer treatment.

Diketone-modified derivatives. The molecular modification of diketone-modified derivatives predominantly changes the carbon-oxygen double bond (carbonyl group) of curcumin into a carbon-nitrogen double bond. Due to the properties of three lone pairs of electrons in the nitrogen atom, these derivatives can be coupled with active molecules to form curcumin-active molecule conjugates (Fig. 10). In addition, diketone-modified conjugates may be further combined with aliphatic chain C4-modified derivatives to form more complex structures (16). Diketone-modified derivative modification is a relatively novel research direction, which not only improves the physicochemical properties of curcumin, but also displays

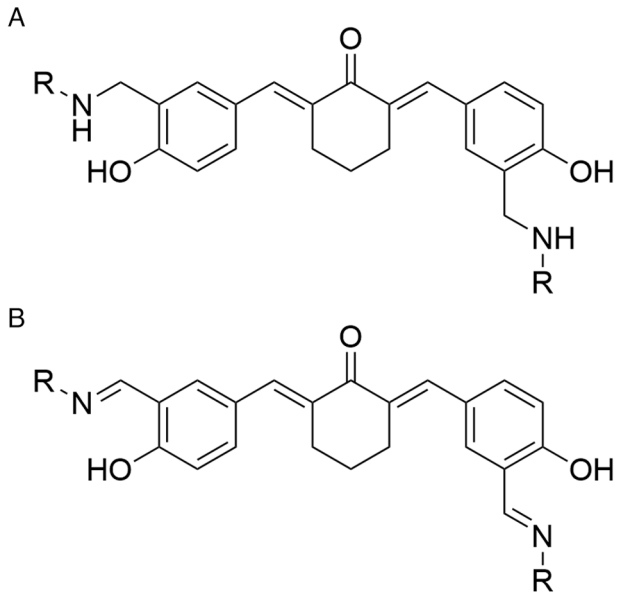

Figure 8. Bis-imino and bis-amino curcumin derivatives. (A) Bis-amino curcumin and (B) Bis-imino curcumin.

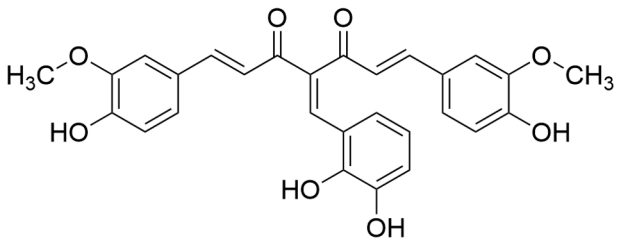

Figure 9. Aliphatic chain-modified substituent. The carbon 4 atom between the β-diketones of curcumin is linked to aromatic aldehydes with two phenolic hydroxyl groups.

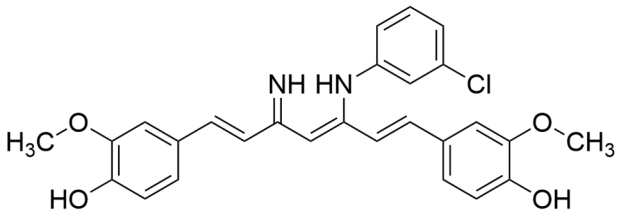

Figure 10. Modified diketone derivative. In the structure, the carbon-oxygen double bonds (carbonyl group) of curcumin in the long unsaturated aliphatic chain are replaced with carbon- nitrogen bonds.

certain physiological activities, such as reducing β-amyloid secretion in human neuroblastoma SH-SY5Y cells and in CHO cells, and inhibiting iNOS expression and NO production induced by lipopolysaccharide in brain microglia (16,51).

Curcumin-piperlongumine (CP) hybrid. The instability of the chemical structure of curcumin and the toxic side effects of piperlongumine both limit their potential applications. Piperlongumine is an alkaloid extract from *Piper longum* L., which has been proven to exert anti-inflammatory and antitumor activities with relatively high toxicity (52). To overcome these disadvantages, a novel CP hybrid molecule was designed and synthesized using a molecular hybridization strategy (Fig. 11). Compared with its parent compounds, CP displays enhanced structural stability and safety, which effectively inhibits cell proliferation, and induces apoptosis mediated by cell cycle arrest and through the regulation of JNK signaling in lung cancer cells (52).

Metal-chelating curcumin derivatives. In addition to the aforementioned curcumin derivatives and hybrids, by pairing or chelating with metal atoms or metal ions, curcumin may be modified into different derivatives. As such, two zinc (Zn)-containing complexes have been designed and synthesized where curcumin and bipyridine were used as ligands chelated with metal Zn. Curcumin or analogs have also been coordinated with other metals, such as copper, palladium and aluminum (Fig. 12) (53-56). Curcumin may also be modified with a moiety containing a metal atom to form Zn(II)-curcumin-based coordination complexes, thus the physicochemical properties and functional activities of curcumin can be improved (57). These types of metal-chelating curcumin derivatives have been investigated in *in vitro* studies, such as in the human neuroblastoma cell line SH-SY5Y (57).

In conclusion, in order to overcome the limitations of curcumin, including poor water solubility, unstable chemical properties, low bioavailability, fast metabolic rate and photodegradability, numerous measures have been adopted to modify curcumin, such as using distearoyl phosphatidylethanolamine-polyethylene glycol and GC@NPs as carriers (42). Curcumin micelle formation, liposome encapsulation, β-cyclodextrin curcumin and food gel delivery systems have also been constructed to address the aforementioned limitations (58-61).

4. Molecular mechanism of curcumin and its derivatives/analogs as antitumor medications

The antitumor activity of curcumin has been widely researched regarding the pharmacological functions of curcumin. At present, studies have reported that antitumor activities of curcumin and its derivatives/analogs have been exerted in numerous cancer cell lines, including head and neck squamous cell carcinoma, lung, breast, prostate, colon and brain cancer (Table I) (34,35,37,38,40,42,44,49,52,55).

The molecular mechanisms underlying the antitumor activities of curcumin and its derivatives/analogs include induction of apoptosis and autophagy, inhibition of cell and invasion and improving the sensitivity of cancer cells to anticancer drugs through a variety of signaling pathways. These mechanisms are involved in inducing or inhibiting the expression of various types of enzymes, transcription factors, cytokines or growth factors, such as MAPK (62-64), cyclooxygenase (COX)-2 (65), NF-κB (65,66), Wnt/β-catenin (67), STAT (63,68-73), TNF-α (74) and epidermal growth factor (EGF) (75). The present review focused on lung, prostate, breast and colorectal cancer (CRC) to illustrate the antitumor molecular mechanism of curcumin and its derivatives/analogs.

Lung cancer. Lung cancer is the leading cause of cancer-related mortality and has a high incidence rate. The latest cancer

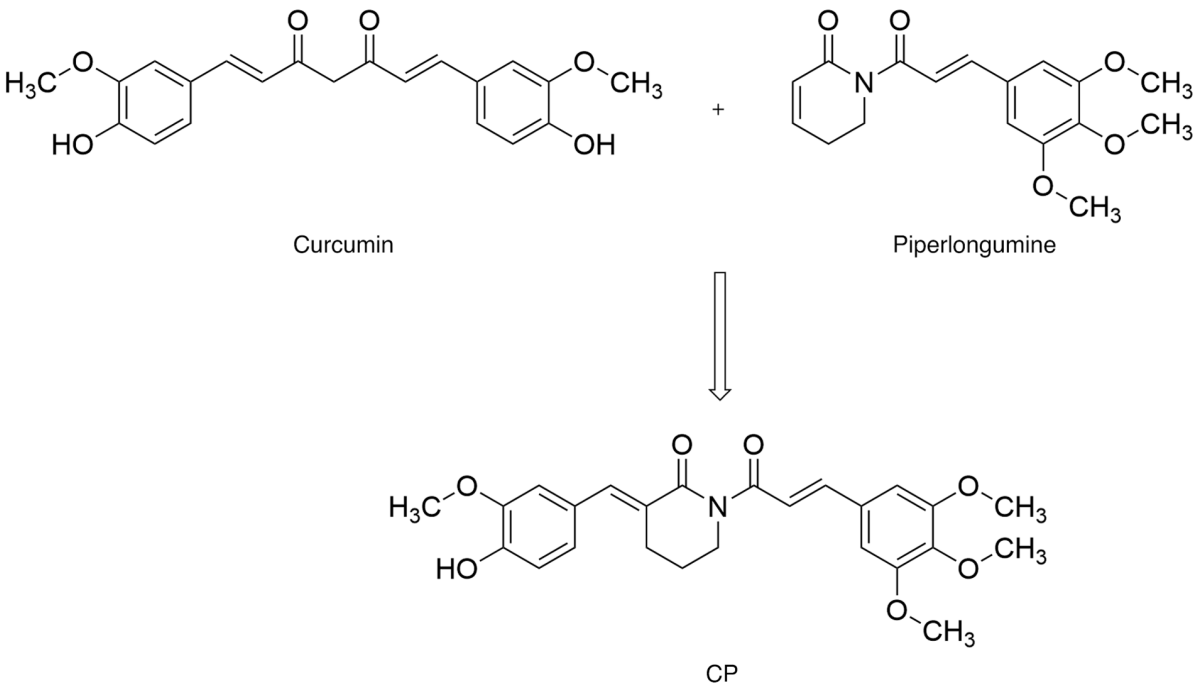

Figure 11. Curcumin-piperlongumine hybrid molecule. The curcumin-piperlongumine hybrid molecule is synthesized using a molecular hybridization strategy based on the structure of curcumin and piperlongumine, which reduces the instability of the chemical structure of curcumin and the toxic side effects of piperlongumine.

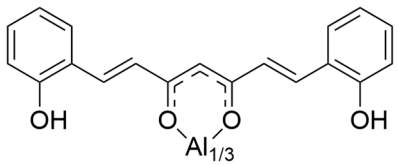

Figure 12. Curcumin metal-chelating derivative. Curcumin is coordinated with the metal aluminum to form a metal-chelating derivative.

report from the International Agency for Research on Cancer, a subsidiary of the World Health Organization, revealed that in 2022, there were 2.481 million new cases of lung cancer worldwide, accounting for 12.4% of all new cancer cases globally; therefore, lung cancer is considered the leading cancer worldwide. In addition, lung cancer is also the leading cause of cancer-associated mortality; in 2022, lung cancer caused 1.817 million deaths, accounting for 18.7% of all cancer deaths (76). Curcumin is a key polyphenolic nutraceutical compound that is often utilized in Chinese herbs for the treatment of lung cancer (77). Numerous studies have reported that curcumin and its derivatives can induce apoptosis in lung cancer by affecting various molecular pathways, such as NF-κB (63,78,79), PI3K/Akt/mTOR (80-82), vascular endothelial growth factor, microRNAs (miRNAs/miRs) and long non-coding RNAs (83-85). Curcumin can also induce autophagy and cell cycle arrest to attenuate the viability and proliferation of lung cancer cells (86). In addition, it has been found that curcumin can increase the efficacy of radiotherapy and chemotherapy, and enhance chemotherapy-or radiotherapy-mediated apoptosis by targeting signaling pathways, such as the EGF receptor (EGFR) and NF-κB cascades (85). In tumor cells, curcumin can induce the expression of TNF and other related factors, thereby inhibiting the activation of NF-κB and preventing the NF-κB dimer from entering the nucleus to promote apoptosis (66).

It has been shown that curcumin may exert epigenetic regulatory effects on miRNAs (83-85,87). In A427 and A549 lung cancer cells, curcumin administration has been shown to inhibit cell proliferation, migration, invasion and viability. Furthermore, curcumin could simultaneously increase the expression levels of miR-192-5p, and reduce β-catenin, cyclin D1 and c-Myc expression levels. By contrast, genetic knockdown of miR-192-5p prevents the inhibitory effects of curcumin on the progression of A427 and A549 cells. A dual-luciferase reporter gene assay demonstrated that miR-192-5p binds to c-Myc. These results indicated that upregulation of miR-192-5p, potentially by targeting c-Myc, may enhance the inhibitory effects of curcumin on non-small cell lung cancer cells via the Wnt/β-catenin signaling pathway (87).

Prostate cancer. Prostate cancer is one of the most common and prevalent types of cancer in men worldwide (76). Previous studies have demonstrated that curcumin has the ability to inhibit proliferation and induce apoptosis in prostate cancer cells by interfering with signaling pathways, such as NF-κB, MAPK and EGFR (88-90). JARID1D, as a histone H3 lysine 4 demethylase, exhibits low expression level in advanced prostate cancer, which is involved in rapid invasion and metastasis in patients with prostate cancer. Curcumin could increase the expression levels and demethylation activity of JARID1D, and further affect the androgen receptor and epithelial-mesenchymal transition (EMT) signaling cascade to inhibit prostate cancer metastasis (91).

In humans, the ubiquitin-conjugating enzyme E2 C (UBE2C) is upregulated in prostate cancer compared with

Table I. Applications of curcumin derivatives/analogs in cancer cells.

Type of cucumin derivative/analog	Cancer type (cell line)	(Refs.)
Hydrogenated curcumin derivatives	Colorectal adenocarcinoma (Caco-2/human)	(34,35)
Halogenated curcumin derivative	Melanoma (518A2/human)	(37)
Aryl-modified curcumin derivatives	Hepatocellular carcinoma (HepG2/human), gastric adenocarcinoma (SGC-7901/human), lung adenocarcinoma (A549/human), colon cancer (HCT116/human)	(38,40)
Monocarbonyl-modified analogs	Colon cancer (CT26/mouse)	(44,45)
Bis-imino and bis-amino curcumin derivatives	Breast carcinoma (MCF7/human)	(49)
Diketone-modified derivatives	Pheochromocytoma (PC12/mouse)	(51)
Curcumin-piperlongumine hybrid	Lung cancer (H466/human, H129/human)	(52)
Metal-chelating curcumin derivatives	Human prostate and colon cancer cells	(55)

benign prostatic hyperplasia. Administration of curcumin in *in vitro* prostate cancer (PCa) cell models decreased the expression levels of UBE2C and simultaneously increased miR-483-3p expression levels; notably, a dual-luciferase reporter gene assay was used to demonstrate the binding of miR-483-3p to UBE2C. Furthermore, when UBE2C was knocked down by small interfering RNA (siRNA), PCa cell proliferation, migration and invasion were inhibited, thus suggesting that curcumin exerts its antitumor activity via modulation of the UBE2C/miR-483-3p axis, through reducing UBE2C and increasing miR-483-3p in PCa (92).

The PI3K/Akt/mTOR signaling pathway promotes apoptosis and inhibits proliferation, and serves a key role in cell cycle regulation (93). Curcumin was shown to activate the PI3K/Akt/mTOR signaling pathway in tumor cells, thereby downregulating the expression of PI3K, Akt and mTOR, and promoting apoptosis of different types of tumor cells, such as ovarian carcinoma cells and colon cancer cells (94-96). In addition to curcumin, certain derivatives have also shown anticancer activity against prostate cancer. The novel curcumin analogue NL13 targeting Polo-like kinase 4 (PLK4) presents effective antitumor properties by disrupting the PLK4-Akt-CCNB1/CDK1 pathway and induces apoptosis in prostate cancer (97).

Recently, through in-depth network pharmacology and molecular docking studies, it has been identified that SRC, PIK3R1, STAT3, AKT1, HSP90AA1, ESR1, EGFR, HSP90AB1, MAPK8 and MAPK1 are the core targets of curcumin. Molecular docking experiments have shown that the binding energy of curcumin to these core targets is <-1.85 kJ mol^{-1}, which indicates that curcumin can spontaneously bind to these core targets. Consequently, curcumin interferes with the cyclic process of prostate cancer cells, thereby inhibiting their proliferation. These results have been verified at multiple levels, such as mRNA expression, protein expression and immune infiltration (98). This finding may provide more potential targets for curcumin and its derivatives in cancer treatment.

Breast cancer. Breast cancer is a leading cause of mortality in women worldwide, which has attracted extensive research attention due to its high drug resistance and malignancy (76,99). As a natural medicine, curcumin has been investigated in combination with various antitumor drugs in breast cancer cells. When combined with thymoquinone or doxorubicin, curcumin can induce the apoptosis of MCF-7 and MDA-MB-231 breast cancer cells through downregulating PI3K and Akt protein levels (100,101). It has been shown that upregulation of COX-2 is involved in carcinogenesis, invasiveness and malignant tumor metastasis. Notably, curcumin combined with celecoxib has been reported to exert a synergistic growth inhibitory effect through downregulation of COX-2 pathways in MDA-MB-231 cells (102). When combined with luteolin, curcumin synergistically inhibits triple-negative breast cancer by suppressing cell proliferation, colony formation and transformation via regulation of the IFN and TGF-β signaling pathways (103).

Due to drug resistance in breast cancer, curcumin has recently been combined with linc-RoR siRNA. Linc-RoR is a long intergenic noncoding RNA that modulates stem cell differentiation, and promotes metastasis and invasion in breast cancer. Using polyamidoamine dendrimers, synergistic anticancer effects of co-delivery of linc-RoR siRNA and curcumin have been shown against MCF-7 breast cancer cells (104).

In MCF-7 cells, curcumin alone has been shown to decrease cell proliferation via the downregulation of proliferating cell nuclear antigen, estrogen receptor α, β-catenin, vimentin and E-cadherin, which are associated with epithelial-mesenchymal transition (105). Meanwhile the antitumor activities of various curcumin analogs or derivatives, such as NC2603, N17, pentagamavunone-1 and dimethyl curcumin (ASC-J9), have been investigated to induce cell death in breast cancer cells (106-111).

CRC. CRC ranks third behind lung cancer and prostate cancer as the most common types of malignant cancer (76,86). Chronic gut inflammation is a risk factor for colorectal carcinogenesis. Although patients with CRC often receive chemotherapy or have their tumors removed during treatment, due to liver metastases, ~50% of patients suffer from relapses (112,113).

miR-34a is a p53-inducible miRNA with tumor-suppressive capacities. In a large proportion of CRC cases, miR-34a and miR-34b/c genes are downregulated, not only commonly during intestinal carcinogenesis, but also causally in CRC formation. As a natural phytopolyphenol compound, curcumin

has been shown to induce miR-34a and miR-34b/c expression in a ROS/Nrf2-dependent and p53-independent manner to suppress CRC metastasis (114).

miR-21 gene expression levels are upregulated in CRC cells (115). After curcumin treatment in HCT116 CRC cells, the cell cycle has been shown to be arrested in the G_2/M phase, which may result in tumor growth inhibition. In addition, administration of curcumin could downregulate miR-21 by inhibiting activator protein binding to the miR-21 promoter (116). In another study, difluorinated curcumin, a novel curcumin analog, has been indicated to inhibit the proliferation of colon cancer cells, by downregulating miR-21 in HCT116 and HT-29 chemoresistant colorectal cancer cells, and also in SW620 metastatic colon cancer cells by affecting the miR-21-PTEN-Akt pathway (117).

In CRC cells lines tested (HCT116, SW480, LoVo and HT29), curcumin treatment has been reported to significantly induce cell apoptosis by arresting cells in the sub-G_1 phase, and the components of the NOD-like receptor protein 3 (NLRP3) inflammasome have been revealed to be elevated in SW480 and HCT116 cell lines (118). Curcumin and crocin treatment could cooperatively reduce cell viability and induce apoptosis in SW-480 cells by modulating the expression of Bax, Bcl-2, caspase-3, caspase-8, and caspase-9, Janus kinase 2 (JAK2), STAT3 and Akt1 genes. Furthermore, co-administration of curcumin and crocin had synergistic effects to increase cell cycle arrest at sub-G_1 phase and to induce autophagy in SW-480 cells (119).

An *in vivo* study of a CRC mouse model, curcumin was found to improve response to radiation therapy due to its ability to target NF-κB (120). In combination with EGFR-related protein, a pan-erb B inhibitor, curcumin showed enhanced inhibitory activity against colon cancer cells (121). The Notch1 pathway is involved in cell differentiation, proliferation, apoptosis and adhesion, and the anti-apoptotic protein Bcl-2 suppresses the activities of Notch1 and caspase-3. Curcumin has an inhibitory effect on Bcl-2, which could restore the activity of the Notch1 pathway and caspase-3 and lead to the apoptosis of tumor cells (122,123).

Other studies have also shown that curcumin can inhibit the metastasis and invasion of tumor cells, the formation of new blood vessels and can reduce the supply of nutrients to tumor cells (124,125). Curcumin and its derivatives/analogs, alone or combination with other antitumor drugs, may exert antitumor effects through multiple molecular mechanisms in different types of cancer cells. The mechanisms and applications of curcumin and its derivatives/analogs in other types of cancer are summarized in Table II (114,126-139).

5. Limitations and side effects of curcumin and its derivatives/analogs in preclinical and clinical studies

Curcumin, as a natural polyphenolic compound, has shown potential in the fields of anti-inflammatory, antioxidant and antitumor activities, and displays various advantages, such as alleviating chemotherapy side effects, preventing second primary tumors, improving quality of life for patients with cancer and as synergistic chemotherapy (140-148) (Table III). However, the unsafety and side effects of curcumin have attracted much attention in preclinical and clinical studies (144,149-154). It has been demonstrated that curcumin and its derivatives present translational potential in several pharmaceutical fields; however, the existing limitations (Table III) need to be overcome through technological innovation and further clinical trials. Future research should focus on optimizing delivery systems, scaling up clinical trials and exploring combination treatment strategies.

Lower bioavailability and stability. Due to its poor water solubility, rapid metabolism (half-life, ~1 h) and lower bioavailability (<1%), curcumin requires a high dose to reach an effective blood concentration, which also increases the risk of side effects (155). To improve the bioavailability of curcumin, polymer micelles and liposomes or lipid carriers are often used (7,15), but these preparations may introduce new irritant or allergy risks. In addition, due to the unstable structure of β-diketone, natural curcumin is inclined to degrade rapidly in the body, requiring a high dose or frequent use, resulting in cumulative toxicity risk (156). Therefore, optimization of synthetic derivatives/analogs of curcumin to enhance solubility or bioavailability is necessary. For example, by removing the β-diketone structure of curcumin, MACs have shown improved chemical stability and antitumor activity (44,45). Preclinical studies have also testified that the hepatotoxicity of these derivatives is markedly lower compared with that of natural curcumin, and the anti-inflammatory effect is improved. Chelating curcumin with metal ions can enhance antioxidant activity and reduce direct irritation to the gastrointestinal tract (53-56). Therefore, optimization of synthetic derivatives/analogs of curcumin or coordinating them with metals, such as zinc, copper, palladium and aluminum, is ongoing (53-56). Nanoparticle or liposome encapsulation have been explored to reduce gastrointestinal irritation by improving solubility and targeting, reducing the effective dose (113-115).

Research limitations. Curcumin derivatives/analogs have the potential to reduce kidney damage and neuropathy caused by chemotherapy drugs, but further clinical data are needed to validate this, and the safety of their long-term metabolites is of concern. The sample size in trials so far has been relatively small; for example, only 37 cases were assessed in a previous radiation dermatitis test of nanocurcumin. Results have also shown high heterogeneity (I^2=95.7% in a meta-analysis of radiation dermatitis) and lack long-term follow-up data, such as in precancerous lesion studies (150,144) (Table III). In addition, a large proportion of studies are small-scale randomized controlled trials or animal experiments (150,144). Regarding the therapeutic effectiveness of curcumin derivatives/analogs in patients with cancer, the optimal dosages for different conditions necessitate further investigation in a larger scale to provide a specific clinical recommendations. While structural optimization and formulation improvements can notably reduce side effects, their long-term safety needs to be further validated.

Dose standardization issues. Inconsistencies in the use of curcumin and its derivatives/analogs have been found in clinical trials for cancer treatment, mainly due to their pharmacokinetic characteristics, bioavailability and individual differences(149,157). Curcumin has a very low oral

Table II. Summary of curcumin or curcumin derivatives/analogs in cancer treatment.

Agent	Type of cancer	Mechanism	Significance	Clinical application	(Refs.)
Curcumin	Colorectal cancer	Regulates regulatory T cells/T helper 17 cells immune balance. Inhibits inflammatory pathways, such as NLRP3. Induces G_0/G_1 phase arrest. Up-regulation of proapoptotic protein Bax.	Synergistically inhibits HCT-116 cell proliferation by combination with 5-FU. Reduces the need for chemotherapy dose.	Prevention of inflammation-related cancer. Reduction of drug resistance with adjuvant chemotherapy.	(126,127)
	Multiple types of cancer	Regulates ROS levels and inflammatory microenvironment. Inhibits tumor growth by multiple signaling pathways, such as the Wnt/β-catenin and Janus kinase pathways.	Broad-spectrum antitumor activity *in vitro*. Enhances the efficacy by combination with paclitaxel and other drugs.	Multi-target therapeutic potential. Optimization of bioavailability to improve efficacy.	(114,128-129)
Curcumin/curcumin derivatives/analog	Oral cancer	Activating the caspase pathway. Inhibit EGFR/MAPK signaling pathway. Decrease the expression of MMP-2/9. Inhibit epithelial-mesenchymal transition.	Inhibits SCC-25 cell proliferation. Reduces tumor volume and increase apoptosis rate in preclinical models.	Reduces complications of chemoradiotherapy. Potential adjunctive therapeutic drugs.	(130-132)
	Hepatocellular carcinoma	Inhibits NF-κB, PI3K/Akt and MAPK signaling pathway. Induces cell apoptosis. Inhibits tumor angiogenesis.	Significantly inhibits the proliferation of hepatocellular carcinoma cells *in vitro*. Prolong survival by combination with sorafenib.	Potential combination therapy strategies. Improves chemotherapy sensitivity and reduce side effects.	(133-136)
Nanocurcumin	Multiple myeloma	Improves the water solubility and target therapy by nanoparticles. Enhances drug enrichment in tumor tissue.	Nano-delivery system significantly improves the blood concentration and stability of curcumin.	Improves the feasibility of clinical. transformation	(137-139)

Table III. Advantages and disadvantages of curcumin and its derivatives/analogs in cancer treatment.

A, Advantages

Advantage	Characteristics	Intervention	(Refs.)
Alleviating chemotherapy side effects	Reduces kidney damage caused by cisplatin.	Dose, 80 mg nanocurcumin twice daily for 5 days.	(140)
	Relieve mouth sores and pain caused by radiation therapy with the topical use of curcumin mouthwash or nanocurcumin capsules.	For oral mucositis, 0.1% curcumin mouthwash or 40 mg nanomicelles (1 min thrice daily for 3 weeks).	(141)
	Reduces neuropathy induced by vincristine.	For peripheral neuropathy induced by vincristine, 3 mg/kg oral curcumin capsules twice daily for 3 months.	(142)
Prevention of second primary tumors	Reduces the head and neck cancer by combination with metformin.	Curcumin (600 mg tablets) or metformin (500 mg tablets) twice daily for 36 months.	(143)
Improvement of the life quality	Reduces nausea, decrease appetite, fatigue and other symptoms during radiotherapy or chemotherapy.	Dose, 500 mg oral curcumin gel 3 times daily for 7 weeks.	(144)
	Improves radiation dermatitis (reduced severity score).	Curcumin administered orally, 800 mg twice daily for 8 weeks.	(145)
Synergistic chemotherapy	Shows synergistic antitumor effects in colon cancer models combined with paclitaxel, capecitabine and other chemotherapy drugs.	Co-delivery system with different curcumin and other chemotherapy drugs.	(146-148)

B, Disadvantages

Advantage	Characteristics	Intervention	(Refs.)
Low bioavailability	Oral absorption rates are low (<1%) and rely on nanomaterials or prodrug technologies (such as TBP1901) improved targeting.	Dose range, 80-12,000 mg/day, but the efficacy is limited.	(149)
Research limitations	Small sample sizes. For example, there were only 35-40 cases in the radiation dermatitis test of nanocurcumin.	Four 500 mg curcumin capsules, 3 times a day, for 3 weeks, Curcumin (n=20), Placebo (n=20); 2 g curcumin orally three times per day, for 7 weeks, Curcumin (n=18), Placebo (n=17).	(150,144)
	High heterogeneity (I^2=95.7% in meta-analysis of radiation dermatitis).		
	Lack of long-term follow-up data, such as precancerous lesion studies.		
Dose standardization	Doses vary widely from study to study; unclear optimal thera peutic window.	Dose range, 120-1500 mg/day.	(151)
Potential side effects	Gastrointestinal discomfort: diarrhea and nausea (~5%).	Upper limit of safe dose is typically ≤8 g/day.	(152-154)
	Drug interactions: may enhance the effect of anticoagulant or hypoglycemic drugs.		
	Risk of hepatotoxicity: case reports of high doses.		

bioavailability (<1%), mainly due to its poor water solubility and rapid intestinal metabolism. Although plasma concentrations of curcumin can be increased by modification through liposomes, nanocarriers or prodrugs, such as TBP1901, difficulties to maintain effective therapeutic concentrations in clinical trials are present (149). For example, in a previous study, the plasma concentration of liposome curcumin at the maximum tolerated dose in patients was demonstrated to be 3.9 μM, which is notably lower than the effective concentration *in vitro*, which is typically 10-50 μM (157). This mismatch between dose and efficacy results in limited clinical effectiveness.

The metabolic pathway of curcumin and its derivatives is complex; the half-life is short (1-2 h) and the pharmacokinetics of different dosage forms are significantly different. For example, the prodrug TBP1901 is 50-fold more efficient in bone marrow than in blood, but the mechanism of its transformation in the human body, which is dependent on β-glucuronidase (GUSB), is not yet fully understood (149). The results lack a reliable pharmacokinetic model support for dose design, which makes it difficult to predict the effective dose range. *In vitro* studies have shown that the inhibitory effect of curcumin derivatives is dose-dependent, but increased doses can trigger toxic reactions, such as the induction of oxidative stress or inhibition of key enzyme activities, leading to safety concerns. Clinical trials often fail to determine the optimal therapeutic window due to the difficulty of dose increasing (151-154).

The metabolism and efficacy of curcumin are also influenced by the patient genotype, intestinal flora and tumor microenvironment. For example, the expression of GUSB in different tumor tissues is different, which results in poor prodrug conversion efficiency (149). Both curcumin β-D-glucuronide and its active metabolite, aglycone curcumin, were previously detected in the blood after TBP1901 injection in GUSB-proficient mice, whereas only curcumin β-D-glucuronide was detected in GUSB-impaired mice. These results suggest that GUSB may serve a pivotal role in the conversion of TBP1901 into aglycone curcumin *in vivo*. It has been verified that TBP1901 itself has minimal antitumor effects *in vitro*, whereas it demonstrates notable antitumor effects *in vivo*. In addition, inadequate stratification of patient populations in clinical trials, such as different cancer types or molecular typing, leads to difficulty in harmonizing dose standards, for example the wide dose range (120 mg-1,500 mg/day) that has been suggested has led to conflicting results in a number of studies (151-154).

A large proportion of existing clinical studies have focused on short-term efficacy and the evaluation of long-term safety is insufficient (150,144). For example, curcumin has been shown to present a risk of hepatotoxicity in animal models, but the long-term dose threshold in humans has not been defined (151). In addition, curcumin may alter the metabolism of other drugs through drug interactions during combination chemotherapy (158), which means that curcumin-drug interactions should be considered when curcumin or curcumin analogs are administered in clinical or preclinical trials. Therefore, dose adjustment is required, but relevant studies are limited.

Gastrointestinal discomfort and liver toxicity. The most common side effects of curcumin are gastrointestinal reactions, including nausea, diarrhea, a burning feeling in the stomach and bloating (Table III). The irritation may result from direct stimulation of the gastrointestinal mucosa, especially at high doses (>8 g/day) or on an empty stomach. Clinical trials have shown that ~5% of the subjects report mild gastrointestinal discomfort, but symptoms usually resolve after tapering or stopping the drug.

Animal studies in preclinical trials have shown that long-term high-dose intake of curcumin (400 mg/kg/day) may lead to elevated liver enzymes (ALT and AST) and liver histopathological changes (152-154,159), possibly related to the accumulation of metabolites of curcumin in the liver. Previous clinical studies have not observed significant liver toxicity, but case reports suggest that excessive doses (>12 g/day) or prolonged use may cause liver dysfunction, especially in patients with underlying liver disease. For example, one study has reported a case of autoimmune hepatitis induced by curcumin supplements (152,154,160). Although up to now, there are few reports on liver toxicity caused by curcumin or curcumin analogs, the existing reports imply the potential importance of curcumin as drug supplementation triggering liver injury.

In addition, patients with liver and gallbladder diseases, bleeding disorders and those taking anticoagulant or hypoglycemic drugs should be cautious of using curcumin as treatment (154). Curcumin inhibits platelet aggregation and may increase the risk of bleeding (161). In addition, curcumin can enhance the hypoglycemic effect, leading to a risk of hypoglycemia. Anticoagulants (such as warfarin) and hypoglycemic drugs should therefore not be taken with curcumin supplements (162,163).

In summary, the safety of curcumin is closely related to its chemical structure, dose and individual differences. The development of derivatives has improved its choice clinical application, but it is still necessary to weigh the efficacy and potential risks.

6. Other biological effects of curcumin or its derivatives/analogs

Antioxidant effects. A number of diseases are closely related to increased levels of ROS in the body, thus removing excess ROS is an important method for disease prevention and pain relief. Curcumin or its derivatives, as a class of polyphenols, are able to adsorb free radicals, thus exerting antioxidant effects in the body (164). Numerous studies have also shown that the phenolic hydroxyl group, β-diketo moieties and carbon-carbon double bond of curcumin are preferred structures for removing ROS. The antioxidant activity of curcumin is similar to that of vitamin C and E, which may regulate the physiological activity of some antioxidant enzymes, such as glutathione (GSH) peroxidase, catalase and superoxide dismutase. Curcumin may also increase the content of GSH in cells to clear ROS, which protects lipids or hemoglobin from oxidation (164-166).

Anti-inflammatory effects. The resistance of curcumin to inflammation is mainly mediated by the inflammatory pathways of NF-κB (167), JAK/STAT, PI3K/Akt (168), MAPK, Nrf2/antioxidant chemical response elements and the NLRP3

inflammasome (169,170). In addition, curcumin can reduce the expression of the inflammatory factors IL-1β, IL-6, TNF-α, prostaglandin E2 and COX-2 by inhibiting the degradation of IκBα and the phosphorylation of NF-κB subunits p65 and p50 (167), thus possessing anti-inflammatory effects.

In the JAK/STAT pathway, curcumin can significantly reduce the levels of JAK/STAT conjugate, the expression levels of inflammatory factors and can alleviate the inflammatory response (168). Similarly, curcumin can directly reduce the levels of inflammatory factors during the inflammatory process or reduce the levels of inflammatory factor precursors and pro-inflammatory factors to achieve anti-inflammatory effects (171-173). In summary, curcumin can exert anti-inflammatory action through multiple signaling pathways at cellular level.

Antibacterial effects. Since the 1960s, methicillin-resistant *Staphylococcus aureus* (MRSA) has disseminated globally and has become a leading cause of bacterial infections in both healthcare and community settings. Experimental results have shown that curcumin has notable inhibitory effects on *S. aureus, Escherichia coli, Bacillus subtilis* and *Clostridium aerogenes* (174-176). For MRSA, curcumin has shown a significant inhibitory effect at a concentration of 125-500 μg/ml and acts synergistically with oxacillin. Curcumin is therefore a potential candidate for the development of drug formulations to treat MRSA infections (177,178).

The antibacterial effects of curcumin are reflected in two aspects: i) The chemical structure of curcumin itself serves an antibacterial role; and ii) curcumin is a natural photosensitizer, which can enhance antibacterial activity and produce cytotoxic ROS under the irradiation of blue light. ROS can facilitate oxidative stress reaction in bacterial infections and lead to bacterial adhesion, cell disruption and DNA damage. Therefore, curcumin alone or in combination with other antibacterial drugs may be widely utilized in the pharmaceutical field (179).

Antiviral effects. The antiviral capability of curcumin or its derivatives is demonstrated in two aspects: i) Curcumin and its derivatives directly act on viruses; and ii) curcumin and its derivatives indirectly resist viruses by regulating the relevant host proteins.

Direct antiviral effect. *In vitro* studies have shown that curcumin can directly interfere with the adsorption of the viral envelope to host cells without degrading viral nucleic acid or destroying viral particles. The molecular mechanism is that the structure of unsaturated diketone moieties of curcumin can influence the fluidity of the viral envelope, leading to the conformation alteration of glycoproteins and reduce the adsorption of host cell membranes (180-182).

In addition to weakening the adsorption of viruses on host cells, curcumin can target some virus-related enzymes or proteins and interfere with viral replication. For example, curcumin has shown good inhibitory effect against hepatitis C and B viruses (182,183). Curcumin can suppress the function of viral integrase by binding to acidic amino acid residues in the catalytic core region. At the same time, curcumin can induce the degradation of key proteins, such as the transactivator Tat, and inhibit the proliferation of HIV (184,185).

Indirect antiviral effect. By regulating various host-related signal pathways, curcumin may induce antiviral effects. For example, curcumin can activate the Nrf2/HO-1 signaling pathway of host cells, stimulate the production of a variety of antioxidant enzymes and simultaneously inhibit multiple inflammatory pathways stimulated by viruses and release IFN to achieve antiviral effects (184,186,187).

Neuroprotective effect. Alzheimer's disease (AD) is a progressive, complex neurodegenerative disorder that poses an increasing threat to healthcare systems around the world due to the rapid increase in the aging population. This aging disorder is associated with amyloid-β peptide aggregation, tau hyperphosphorylation, neuroinflammation and oxidative stress. Thus far, therapeutic strategies designed to treat AD neurodegeneration have proven unsuccessful, the reason for this may be that single-target drugs are unable to limit the progressive deterioration of brain functions (188-191). Therefore, the therapeutic strategies used to treat AD have switched from over-emphasizing a single deleterious process to considering AD neurodegeneration as the result of different pathogenic mechanisms and their interplay. Phytochemical compounds are emerging as a natural source and as multi-target agents in traditional pharmacological medicine. Curcumin has been considered such a natural multi-target agent (188).

Previous studies have shown that curcumin can improve the memory ability and development of the hippocampal nerve in AD model rats (189-191). Curcumin has the capability to prevent cerebral stroke edema, and to reduce cerebral ischemia-reperfusion injury, cerebral ischemia injury and spinal cord injury (192-194). In addition, curcumin may serve a role in the cerebral cortex, inhibit the activation of hippocampal microglia and the release of inflammatory factors and exert anti-depressive effects (195). Curcumin, a natural product, has the ability to induce hHO-1 and phase II enzyme expression in astrocytes and cultured hippocampal neurons, potentially via activation of the transcription factor Nrf2, which exerts a significant cytoprotective effect on cultured neurons exposed to oxidative stress (196,197). These results indicate that curcumin may have the therapeutic capacity to restore cellular homeostasis and rebalance redox equilibrium (196), thus counteracting neurodegenerative inflammation in AD and multiple sclerosis, producing positive cognitive and behavioral outcomes (194,198). The development of novel delivery systems and formulations may enhance the therapeutic potential of curcumin in the treatment of neurodegenerative diseases.

7. Conclusions

Curcumin, a polyphenolic natural constituent derived from *Curcuma longa* and other plants, has been shown to exert potential antitumor activities in various types of cancer, and may present antioxidant, anti-inflammatory, anti-depressive and neuroprotective biological roles. The molecular mechanisms of its antitumor activities involve a variety of enzymes, transcription factors, cytokines and growth factors, such as MAPK, COX-2, PI3K/Akt, NF-κB, Wnt/β-catenin, STAT, TNF-α and EGF. Therefore, curcumin gained increasing attention from researchers and may be considered a promising novel compound with low toxicity to a variety of biological targets.

Since ancient times, curcumin, with turmeric as the main carrier, has been used in traditional Chinese herbs, and has been recorded in the 'Compendium of Materia Medica', 'Shennong Materia Medica', 'Qianjin Fang' and 'Tang Materia Medica'. Turmeric has been a staple in traditional dishes and medicines since ancient times, especially in Southeast Asia, India and China.

The unique molecular structure of curcumin has endowed it with potential and value in food and pharmaceutical research, especially in cancer treatment. Despite this, challenges remain regarding its limited bioavailability and the scarcity of comprehensive human clinical trials. In order to overcome the limitations of curcumin, curcumin derivatives or analogs have been developed and applications in clinical research and medical drugs investigated. At present, the key concept regarding the design and synthesis of curcumin derivatives is that some structural fragments of curcumin can be modified to retain or moderately enhance the basic biological activities of curcumin, which may thus improve the stability, solubility and bioavailability of curcumin and reducing toxicity. In addition to modifications of the curcumin molecule, suitable drug carrier materials have been developed for its delivery. With the ongoing development of research, additional pharmacological functions of curcumin may be identified, including the promotion of wound healing, the reduction of blood glucose levels and potential applications in the treatment of diabetes and AIDS, which reflect the potential of curcumin in the field of novel therapeutic strategies or as a treatment adjunct, and further underscore the potential of traditional medicine in the modern medical system.

Acknowledgements

No applicable.

Funding

This work was supported by grants from the Natural Science Foundation of Shandong Province (grant no. ZR2020MC066).

Availability of data and materials

Not applicable.

Authors' contributions

ZL performed data collection and manuscript drafting. WY performed data collection and plotting. WQ wrote and revised the manuscript. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Cheregi MC, Tirsoaga A, Ion C, Iorgulescu EE, David IG and Noor H: Curcumin electroanalysis at a disposable graphite electrode. Biosensors (Basel) 15: 137, 2025.
2. Monton C, Chuanchom P, Popanit P, Settharaksa S and Pathompak P: Simplex lattice design for optimization of the mass ratio of Curcuma longa L., Curcuma zedoaria (Christm.) Roscoe and Curcuma aromatica Salisb. to maximize curcuminoids content and antioxidant activity. Acta Pharm 71: 445-457, 2020.
3. Abdul-Rahman T, Awuah WA, Mikhailova T, Kalmanovich J, Mehta A, Ng JC, Coghlan MA, Zivcevska M, Tedeschi AJ, de Oliveira EC, *et al*: Antioxidant, anti-inflammatory and epigenetic potential of curcumin in Alzheimer's disease. Biofactors 50: 693-708, 2024.
4. Gao F, Liang W, Chen Q, Chen B, Liu Y, Liu Z, Xu X, Zhu R and Cheng L: A curcumin-decorated nanozyme with ros scavenging and anti-inflammatory properties for neuroprotection. Nanomaterials (Basel) 14: 389, 2024.
5. Miyazaki K, Xu C, Shimada M and Goel A: Curcumin and andrographis exhibit anti-tumor effects in colorectal cancer via activation of ferroptosis and dual suppression of glutathione peroxidase-4 and ferroptosis suppressor protein-1. Pharmaceuticals (Basel) 16: 383, 2023.
6. Li M, Guo T, Lin J, Huang X, Ke Q, Wu Y, Fang C and Hu C: Curcumin inhibits the invasion and metastasis of triple negative breast cancer via Hedgehog/Gli1 signaling pathway. J Ethnopharmacol 283: 114689, 2022.
7. Zhang Y, Yang J, Gong Y, He S, Wen P, Jiang Y, He J, Zhu B and Li L: In vitro and in vivo supplementation with curcumin promotes hippocampal neuronal synapses development in rats by inhibiting GSK-3β and activating β-catenin. Mol Neurobiol 61: 2390-2410, 2024.
8. Aktaş A, Yiğit F, Delibaş B, Kaplan AA, Hamour HM, Marangoz AH, Kaya A, Altun G and Kaplan S: The effects of Garcinia kola and curcumin on the dorsal root ganglion of the diabetic rat after peripheral nerve transection injury. J Chem Neuroanat 136: 102395, 2024.
9. Chen L, Hua B, He Q, Han Z, Wang Y, Chen Y, Ni H, Zhu Z, Xu L, Yao M and Ni C: Curcumin analogue NL04 inhibits spinal cord central sensitization in rats with bone cancer pain by inhibiting NLRP3 inflammasome activation and reducing IL-1β production. Eur J Pharmacol 970: 176480, 2024.
10. Fan X, Huang J, Zhang W, Su Z, Li J, Wu Z and Zhang P: A multifunctional, tough, stretchable, and transparent curcumin hydrogel with potent antimicrobial, antioxidative, anti-inflammatory, and angiogenesis capabilities for diabetic wound healing. ACS Appl Mater Interfaces 16: 9749-9767, 2024.
11. Li S, Wei N, Wei J, Fang C, Feng T, Liu F, Liu X and Wu B: Curcumin and silver nanoparticles loaded antibacterial multifunctional pectin/gelatin films for food packaging applications. Int J Biol Macromol 266(Pt 1): 131248, 2024.
12. Xu XY, Meng X, Li S, Gan RY, Li Y and Li HB: Bioactivity, health benefits, and related molecular mechanisms of curcumin: Current progress, challenges, and perspectives. Nutrients 10: 1553, 2018.
13. Tsuda T: Curcumin as a functional food-derived factor: Degradation products, metabolites, bioactivity, and future perspectives. Food Funct 9: 705-714, 2018.
14. Heger M, van Golen RF, Broekgaarden M and Michel MC: The molecular basis for the pharmacokinetics and pharmacodynamics of curcumin and its metabolites in relation to cancer. Pharmacol Rev 66: 222-307, 2013.
15. Zhang Q, Zhong Y, Yan LN, Sun X, Gong T and Zhang ZR: Synthesis and preliminary evaluation of curcumin analogues as cytotoxic agents. Bioorg Med Chem Lett 21: 1010-1014, 2011.
16. Chainoglou E and Hadjipavlou-Litina D: Curcumin in health and diseases: Alzheimer's disease and curcumin analogues, derivatives, and hybrids. Int J Mol Sci 21: 1975, 2020.
17. Moreno-Q G, Herrera-R A, Yepes AF, Naranjo TW and Cardona-G W: Proapoptotic effect and molecular docking analysis of curcumin-resveratrol hybrids in colorectal cancer chemoprevention. Molecules 27: 3486, 2022.
18. Moreno-Quintero G, Betancur-Zapata E, Herrera-Ramírez A and Cardona-Galeano W: New hybrid scaffolds based on 5-FU/Curcumin: Synthesis, cytotoxic, antiproliferative and pro-apoptotic effect. Pharmaceutics 15: 1221, 2023.
19. Wang JQ, Wang X, Wang Y, Tang WJ, Shi JB and Liu XH: Novel curcumin analogue hybrids: Synthesis and anticancer activity. Eur J Med Chem 156: 493-509, 2018.

20. Al-Thubaiti EH: Antibacterial and antioxidant activities of curcumin/Zn metal complex with its chemical characterization and spectroscopic studies. Heliyon 9: e17468, 2023.
21. Sethiya A, Agarwal DK and Agarwal S: Current trends in drug delivery system of curcumin and its therapeutic applications. Mini Rev Med Chem 20: 1190-1232, 2020.
22. Jagannathan R, Abraham PM and Poddar P: Temperature-dependent spectroscopic evidences of curcumin in aqueous medium: A mechanistic study of its solubility and stability. J Phys Chem B 116: 14533-14540, 2012.
23. Leung MHM, Addicoat MA, Lincoln SF, Metha GF and Kee TW: Time-resolved keto-enol tautomerization of the medicinal pigment curcumin. Phys Chem Chem Phys 26: 14970-14979, 2024.
24. Kharat M, Du Z, Zhang G and McClements DJ: Physical and chemical stability of curcumin in aqueous solutions and emulsions: Impact of pH, temperature, and molecular environment. J Agric Food Chem 65: 1525-1532, 2017.
25. Lestari ML and Indrayanto G: Curcumin. Profiles Drug Subst Excip Relat Methodol 39: 113-204, 2014.
26. Burapan S, Kim M and Han J: Curcuminoid demethylation as an alternative metabolism by human intestinal microbiota. J Agric Food Chem 65: 3305-3310, 2017.
27. Somparn P, Phisalaphong C, Nakornchai S, Unchern S and Morales NP: Comparative antioxidant activities of curcumin and its demethoxy and hydrogenated derivatives. Biol Pharm Bull 30: 74-78, 2007.
28. Jude S, Amalraj A, Kunnumakkara AB, Divya C, Löffler BM and Gopi S: Development of validated methods and quantification of curcuminoids and curcumin metabolites and their pharmacokinetic study of oral administration of complete natural turmeric formulation (Cureit™) in human plasma via UPLC/ESI-Q-TOF-MS spectrometry. Molecules 23: 2415, 2018.
29. Morales NP, Sirijaroonwong S, Yamanont P and Phisalaphong C: Electron paramagnetic resonance study of the free radical scavenging capacity of curcumin and its demethoxy and hydrogenated derivatives. Biol Pharm Bull 38: 1478-1483, 2015.
30. Girst G, Ötvös SB, Fülöp F, Balogh GT and Hunyadi A: Pharmacokinetics-driven evaluation of the antioxidant activity of curcuminoids and their major reduced metabolites-A medicinal chemistry approach. Molecules 26: 3542, 2021.
31. Zhang ZB, Luo DD, Xie JH, Xian YF, Lai ZQ, Liu YH, Liu WH, Chen JN, Lai XP, Lin ZX and Su ZR: Curcumin's metabolites, tetrahydrocurcumin and octahydrocurcumin, possess superior anti-inflammatory effects in vivo through suppression of TAK1-NF-κB pathway. Front Pharmacol 9: 1181, 2018.
32. Almalki Z, Algregri M, Alhosin M, Alkhaled M, Damiati S and Zamzami MA: In vitro cytotoxicity of curcuminoids against head and neck cancer HNO97 cell line. Braz J Biol 83: e248708, 2021.
33. Chen CY, Lien JC, Chen CY, Hung CC and Lin HC: Design, synthesis and evaluation of novel derivatives of curcuminoids with cytotoxicity. Int J Mol Sci 22: 12171, 2021.
34. Pratti VL, Thomas M, Bhoite R and Satyavrat V: Investigating bioavailability of curcumin and piperine combination in comparison to turmeric rhizomes: An in vitro study. J Exp Pharmacol 16: 37-47, 2024.
35. Iglesias DE, Cremonini E, Oteiza PI and Fraga CG: Curcumin mitigates TNFα-induced Caco-2 cell monolayer permeabilization through modulation of NF-κB, ERK1/2, and JNK pathways. Mol Nutr Food Res 66: e2101033, 2022.
36. Huang Y, Cao S, Zhang Q, Zhang H, Fan Y, Qiu F and Kang N: Biological and pharmacological effects of hexahydrocurcumin, a metabolite of curcumin. Arch Biochem Biophys 646: 31-37, 2018.
37. Schmitt F, Subramaniam D, Anant S, Padhye S, Begemann G, Schobert R and Biersack B: Halogenated Bis(methoxybenzylidene)-4-piperidone curcuminoids with improved anticancer activity. ChemMedChem 13: 1115-1123, 2018.
38. Fang L, Gou S, Liu X, Cao F and Cheng L: Design, synthesis and anti-Alzheimer properties of dimethylaminomethyl-substituted curcumin derivatives. Bioorg Med Chem Lett 24: 40-43, 2014.
39. Feng JY and Liu ZQ: Phenolic and enolic hydroxyl groups in curcumin: Which plays the major role in scavenging radicals? J Agric Food Chem 57: 11041-11046, 2009.
40. Fang X, Fang L, Gou S and Cheng L: Design and synthesis of dimethylaminomethyl-substituted curcumin derivatives/analogues: Potent antitumor and antioxidant activity, improved stability and aqueous solubility compared with curcumin. Bioorg Med Chem Lett 23: 1297-1301, 2013.
41. Cui L, Wang S, Zhang J, Wang M, Gao Y, Bai L, Zhang H, Ma G and Ba X: Effect of curcumin derivatives on hen egg white lysozyme amyloid fibrillation and their interaction study by spectroscopic methods. Spectrochim Acta A Mol Biomol Spectrosc 223: 117365, 2019.
42. Huang M, Liu J, Fan Y, Sun J, Cheng JX, Zhang XF, Zhai BT and Guo DY: Development of curcumin-loaded galactosylated chitosan-coated nanoparticles for targeted delivery of hepatocellular carcinoma. Int J Biol Macromol 253(Pt 6): 127219, 2023.
43. Liang G, Shao L, Wang Y, Zhao C, Chu Y, Xiao J, Zhao Y, Li X and Yang S: Exploration and synthesis of curcumin analogues with improved structural stability both in vitro and in vivo as cytotoxic agents. Bioorg Med Chem 17: 2623-2631, 2009.
44. Zhang J, Feng Z, Wang C, Zhou H, Liu W, Kanchana K, Dai X, Zou P, Gu J, Cai L and Liang G: Curcumin derivative WZ35 efficiently suppresses colon cancer progression through inducing ROS production and ER stress-dependent apoptosis. Am J Cancer Res 7: 275-288, 2017.
45. Subhedar DD, Shaikh MH, Nawale L, Sarkar D, Khedkar VM and Shingate BB: Quinolidene based monocarbonyl curcumin analogues as promising antimycobacterial agents: Synthesis and molecular docking study. Bioorg Med Chem Lett 27: 922-928, 2017.
46. Cao W, Yu P, Cao Y, Feng S and Yin N: Synthesis and antitumor evaluation of amino acid conjugates of monocarbonyl curcumin in hepatocellular carcinoma cell. Sci Rep 15: 8181, 2025.
47. Wen J, Zhao L, Li Z, Pi C, Feng X, Shi P, Yang H, Chen L, Wang X, Liu F, *et al*: Preparation and anti-colon cancer effect of a novel curcumin analogue (CA8): In vivo and in vitro evaluation. Front Pharmacol 15: 1464626, 2024.
48. Clariano M, Marques V, Vaz J, Awam S, Afonso MB, Perry MJ and Rodrigues CMP: Monocarbonyl analogs of curcumin with potential to treat colorectal cancer. Chem Biodivers 20: e202300222, 2023.
49. Mathur P, Mori M, Vyas H, Mor K, Jagtap J, Vadher S, Vyas K, Devkar R and Desai A: Synthesis of novel Bis-imino and Bis-amino curcuminoids for evaluation of their anticancer and antibacterial activity. ACS Omega 7: 45545-45555, 2022.
50. Banuppriya G, Sribalan R, Padmini V and Shanmugaiah V: Biological evaluation and molecular docking studies of new curcuminoid derivatives: Synthesis and characterization. Bioorg Med Chem Lett 26: 1655-1659, 2016.
51. Kotani R, Urano Y, Sugimoto and Noguchi N: Decrease of amyloid-β levels by curcumin derivative via modulation of amyloid-β protein precursor trafficking. J Alzheimers Dis 56: 529-542, 2017.
52. Zhang Q, Hui M, Chen G, Huang H, Wang S, Ye Y, Wang Y, Wang M, Zhang S, Huang L, *et al*: Curcumin-Piperlongumine hybrid molecule increases cell cycle arrest and apoptosis in lung cancer through JNK/c-Jun signaling pathway. J Agric Food Chem 72: 7244-7255, 2024.
53. Corrêa RLGQ, de Moraes MMF, de Oliveira KT, Aoto YA, Coutinho-Neto MD and Homem-de-Mello P: Diving into the optoelectronic properties of Cu(II) and Zn(II) curcumin complexes: A DFT and wavefunction benchmark. J Mol Model 29: 166, 2023.
54. Sareen R, Jain N and Dhar KL: Curcumin-Zn(II) complex for enhanced solubility and stability: An approach for improved delivery and pharmacodynamic effects. Pharm Dev Technol 21: 630-635, 2016.
55. Valentini A, Conforti F, Crispini A, De Martino A, Condello R, Stellitano C, Rotilio G, Ghedini M, Federici G, Bernardini S and Pucci D: Synthesis, oxidant properties, and antitumoral effects of a heteroleptic palladium(II) complex of curcumin on human prostate cancer cells. J Med Chem 52: 484-491, 2009.
56. John VD, Ummathur MB and Krishnankutty K: Synthesis, characterization, and antitumour studies of some curcuminoid analogues and their aluminum complexes. J Coord Chem 66: 1508-1518, 2013.
57. Pucci D, Crispini A, Mendiguchía BS, Pirillo S, Ghedini M, Morelli S and De Bartolo L: Improving the bioactivity of Zn(II)-curcumin based complexes. Dalton Trans 42: 9679-9687, 2013.
58. Liu X, Wu Z, Guo C, Guo H, Su Y, Chen Q, Sun C, Liu Q, Chen D and Mu H: Hypoxia responsive nano-drug delivery system based on angelica polysaccharide for liver cancer therapy. Drug Deliv 29: 138-148, 2022.
59. De Leo V, Milano F, Mancini E, Comparelli R, Giotta L, Nacci A, Longobardi F, Garbetta A, Agostiano A and Catucci L: Encapsulation of curcumin-loaded liposomes for colonic drug delivery in a pH-responsive polymer cluster using a pH-driven and organic solvent-free process. Molecules 23: 739, 2018.

60. Nikolić L, Urošević M, Nikolić V, Gajić I, Dinić A, Miljković V, Rakić S, Đokić S, Kesić J, Ilić-Stojanović S and Nikolić G: The formulation of curcumin: 2-hydroxypropyl-β-cyclodextrin complex with smart hydrogel for prolonged release of curcumin. Pharmaceutics 15: 382, 2023.
61. Tan KX, Ng LE and Loo SCJ: Formulation development of a food-graded curcumin-loaded medium chain triglycerides-encapsulated kappa carrageenan (CUR-MCT-KC) gel bead based oral delivery formulation. Materials (Basel) 14: 2783, 2021.
62. Wu MF, Huang YH, Chiu LY, Cherng SH, Sheu GT and Yang TY: Curcumin induces apoptosis of chemoresistant lung cancer cells via ROS-regulated p38 MAPK phosphorylation. Int J Mol Sci 23: 8248, 2022.
63. Zhi TX, Liu KQ, Cai KY, Zhao YC, Li ZW, Wang X, He XH and Sun XY: Anti-Lung cancer activities of 1,2,3-triazole curcumin derivatives via regulation of the MAPK/NF-κB/STAT3 signaling pathways. ChemMedChem 17: e202100676, 2022.
64. Tung CL, Jian YJ, Chen JC, Wang TJ, Chen WC, Zheng HY, Chang PY, Liao KS and Lin YW: Curcumin downregulates p38 MAPK-dependent X-ray repair cross-complement group 1 (XRCC1) expression to enhance cisplatin-induced cytotoxicity in human lung cancer cells. Naunyn Schmiedebergs Arch Pharmacol 389: 657-666, 2016.
65. Lee J, Im YH, Jung HH, Kim JH, Park JO, Kim K, Kim WS, Ahn JS, Jung CW, Park YS, *et al*: Curcumin inhibits interferon-alpha induced NF-kappaB and COX-2 in human A549 non-small cell lung cancer cells. Biochem Biophys Res Commun 334: 313-318, 2005.
66. Kashyap VK, Nagesh PKB, Singh AK, Massey A, Darkwah GP, George A, Khan S, Hafeez BB, Zafar N, Kumar S, *et al*: Curcumin attenuates smoking and drinking activated NF-κB/IL-6 inflammatory signaling axis in cervical cancer. Cancer Cell Int 24: 343, 2024.
67. Wang JY, Wang X, Wang XJ, Zheng BZ, Wang Y, Wang X and Liang B: Curcumin inhibits the growth via Wnt/β-catenin pathway in non-small-cell lung cancer cells. Eur Rev Med Pharmacol Sci 22: 7492-7499, 2018.
68. Petiti J, Rosso V, Lo Iacono M, Panuzzo C, Calabrese C, Signorino E, Pironi L, Cartellà A, Bracco E, Pergolizzi B, *et al*: Curcumin induces apoptosis in JAK2-mutated cells by the inhibition of JAK2/STAT and mTORC1 pathways. J Cell Mol Med 23: 4349-4357, 2019.
69. Feng C, Xia Y, Zou P, Shen M, Hu J, Ying S, Pan J, Liu Z, Dai X, Zhuge W, *et al*: Curcumin analog L48H37 induces apoptosis through ROS-mediated endoplasmic reticulum stress and STAT3 pathways in human lung cancer cells. Mol Carcinog 56: 1765-1777, 2017.
70. Alexandrow MG, Song LJ, Altiok S, Gray J, Haura EB and Kumar NB: Curcumin: A novel Stat3 pathway inhibitor for chemoprevention of lung cancer. Eur J Cancer Prev 21: 407-412, 2012.
71. Wu L, Guo L, Liang Y, Liu X, Jiang L and Wang L: Curcumin suppresses stem-like traits of lung cancer cells via inhibiting the JAK2/STAT3 signaling pathway. Oncol Rep 34: 3311-3317, 2015.
72. Yang CL, Liu YY, Ma YG, Xue YX, Liu DG, Ren Y, Liu XB, Li Y and Li Z: Curcumin blocks small cell lung cancer cells migration, invasion, angiogenesis, cell cycle and neoplasia through Janus kinase-STAT3 signalling pathway. PLoS One 7: e37960, 2012.
73. Xu X and Zhu Y: Curcumin inhibits human non-small cell lung cancer xenografts by targeting STAT3 pathway. Am J Transl Res 9: 3633-3641, 2017.
74. Shi HS, Gao X, Li D, Zhang QW, Wang YS, Zheng Y, Cai LL, Zhong RM, Rui A, Li ZY, *et al*: A systemic administration of liposomal curcumin inhibits radiation pneumonitis and sensitizes lung carcinoma to radiation. Int J Nanomedicine 7: 2601-2611, 2012.
75. Zhang L, Tao X, Fu Q, Ge C, Li R, Li Z, Zhu Y, Tian H, Li Q, Liu M, *et al*: Curcumin inhibits cell proliferation and migration in NSCLC through a synergistic effect on the TLR4/MyD88 and EGFR pathways. Oncol Rep 42: 1843-1855, 2019.
76. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
77. Cho HK, Park CG and Lim HB: Construction of a synergy combination model for turmeric (*Curcuma longa* L.) and Black Pepper (*Piper nigrum* L.) extracts: Enhanced anticancer activity against A549 and NCI-H292 human lung cancer cells. Curr Issues Mol Biol 46: 5551-5560, 2024.
78. Tsai JR, Liu PL, Chen YH, Chou SH, Cheng YJ, Hwang JJ and Chong IW: Curcumin inhibits non-small cell lung cancer cells metastasis through the Adiponectin/NF-κb/MMPs signaling pathway. PLoS One 10: e0144462, 2015.
79. Pi C, Zhao W, Zeng M, Yuan J, Shen H, Li K, Su Z, Liu Z, Wen J, Song X, *et al*: Anti-lung cancer effect of paclitaxel solid lipid nanoparticles delivery system with curcumin as co-loading partner in vitro and in vivo. Drug Deliv 29: 1878-1891, 2022.
80. Liu F, Gao S, Yang Y, Zhao X, Fan Y, Ma W, Yang D, Yang A and Yu Y: Antitumor activity of curcumin by modulation of apoptosis and autophagy in human lung cancer A549 cells through inhibiting PI3K/Akt/mTOR pathway. Oncol Rep 39: 1523-1531, 2018.
81. Wang N, Feng T, Liu X and Liu Q: Curcumin inhibits migration and invasion of non-small cell lung cancer cells through up-regulation of miR-206 and suppression of PI3K/AKT/mTOR signaling pathway. Acta Pharm 70: 399-409, 2020.
82. Jiao D, Wang J, Lu W, Tang X, Chen J, Mou H and Chen QY: Curcumin inhibited HGF-induced EMT and angiogenesis through regulating c-Met dependent PI3K/Akt/mTOR signaling pathways in lung cancer. Mol Ther Oncolytics 3: 16018, 2016.
83. Lin SS, Lai KC, Hsu SC, Yang JS, Kuo CL, Lin JP, Ma YS, Wu CC and Chung JG: Curcumin inhibits the migration and invasion of human A549 lung cancer cells through the inhibition of matrix metalloproteinase-2 and -9 and Vascular endothelial growth factor (VEGF). Cancer Lett 285: 127-133, 2009.
84. Li X, Ma S, Yang P, Sun B, Zhang Y, Sun Y, Hao M, Mou R and Jia Y: Anticancer effects of curcumin on nude mice bearing lung cancer A549 cell subsets SP and NSP cells. Oncol Lett 16: 6756-6762, 2018.
85. Ashrafizadeh M, Najafi M, Makvandi P, Zarrabi A, Farkhondeh T and Samarghandian S: Versatile role of curcumin and its derivatives in lung cancer therapy. J Cell Physiol 235: 9241-9268, 2020.
86. Weng W and Goel A: Curcumin and colorectal cancer: An update and current perspective on this natural medicine. Semin Cancer Biol 80: 73-86, 2022.
87. Pan Y, Sun Y, Liu Z and Zhang C: miR1925p upregulation mediates the suppression of curcumin in human NSCLC cell proliferation, migration and invasion by targeting cMyc and inactivating the Wnt/βcatenin signaling pathway. Mol Med Rep 22: 1594-1604, 2020.
88. Cheng MA, Chou FJ, Wang K, Yang R, Ding J, Zhang Q, Li G, Yeh S, Xu D and Chang C: Androgen receptor (AR) degradation enhancer ASC-J9® in an FDA-approved formulated solution suppresses castration resistant prostate cancer cell growth. Cancer Lett 417: 182-191, 2018.
89. Dorai T, Cao YC, Dorai B, Buttyan R and Katz AE: Therapeutic potential of curcumin in human prostate cancer. III. Curcumin inhibits proliferation, induces apoptosis, and inhibits angiogenesis of LNCaP prostate cancer cells in vivo. Prostate 47: 293-303, 2001.
90. Mukhopadhyay A, Bueso-Ramos C, Chatterjee D, Pantazis P and Aggarwal BB: Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines. Oncogene 20: 7597-7609, 2001.
91. Xie Q, Hu Y, Zhang C, Zhang C, Qin J, Zhao Y, An Q, Zheng J and Shi C: Curcumin blunts epithelial-mesenchymal transition to alleviate invasion and metastasis of prostate cancer through the JARID1D demethylation. Cancer Cell Int 24: 303, 2024.
92. Li W, Wang F, Wang X, Xu W, Liu F, Hu R and Li S: Curcumin inhibits prostate cancer by upregulating miR-483-3p and inhibiting UBE2C. J Biochem Mol Toxicol 38: e23645, 2024.
93. Chen Z, Ni R, Hu Y, Yang Y and Tian Y: Arnicolide D inhibits proliferation and induces apoptosis of osteosarcoma cells through PI3K/Akt/mTOR pathway. Anticancer Agents Med Chem 24: 1288-1294, 2024.
94. Huang SL, Chang TC and Sun NK: Curcumin reduces paclitaxel resistance in ovarian carcinoma cells by upregulating SNIP1 and inhibiting NFκB activity. Biochem Pharmacol 212: 115581, 2023.
95. Ismail NI, Othman I, Abas F, Lajis NH and Naidu R: The curcumin analogue, MS13(1,5-Bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadiene-3-one), inhibits cell proliferation and induces apoptosis in primary and metastatic human colon cancer cells. Molecules 25: 3798, 2020.
96. Ahmad I, Hoque M, Alam SSM, Zughaibi TA and Tabrez S: Curcumin and plumbagin synergistically target the PI3K/Akt/mTOR pathway: A prospective role in cancer treatment. Int J Mol Sci 24: 6651, 2023.
97. Qiao X, Zheng K, Ye L, Yang J, Cui R, Shan Y, Li X, Li H, Zhu Q, Zhao Z, *et al*: NL13, a novel curcumin analogue and polo like kinase 4 inhibitor, induces cell cycle arrest and apoptosis in prostate cancer models. Br J Pharmacol 181: 4658-4676, 2024.

98. Li J, Wang X, Xue L and He Q: Exploring the therapeutic mechanism of curcumin in prostate cancer using network pharmacology and molecular docking. Heliyon 10: e33103, 2024.
99. Zhu J, Li Q, Wu Z, Xu Y and Jiang R: Curcumin for treating breast cancer: A review of molecular mechanisms, combinations with anticancer drugs, and nanosystems. Pharmaceutics 16: 79, 2024.
100. El-Far AH, Saddiq AA, Mohamed SA, Almaghrabi OA and Mousa SA: Curcumin and thymoquinone combination attenuates breast cancer cell lines' progression. Integr Cancer Ther 21: 15347354221099537, 2022.
101. Sarkar E, Kotiya A, Khan A, Bhuyan R, Raza ST, Misra A and Mahdi AA: The combination of curcumin and doxorubicin on targeting PI3K/AKT/mTOR signaling pathway: An in vitro and molecular docking study for inhibiting the survival of MDA-MB-231. In Silico Pharmacol 12: 58, 2024.
102. Alqahtani AM, Chidambaram K, Pino-Figueroa A, Chandrasekaran B, Dhanaraj P and Venkatesan K: Curcumin-Celecoxib: A synergistic and rationale combination chemotherapy for breast cancer. Eur Rev Med Pharmacol Sci 25: 1916-1927, 2021.
103. Wang X, Zhang L and Si H: Combining luteolin and curcumin synergistically suppresses triple-negative breast cancer by regulating IFN and TGF-β signaling pathways. Biomed Pharmacother 178: 117221, 2024.
104. Vahedi F, Javan B, Sharbatkhari M, Soltani A, Shafiee M, Memarian A and Erfani-Moghadam V: Synergistic anticancer effects of co-delivery of linc-RoR siRNA and curcumin using polyamidoamine dendrimers against breast cancer. Biochem Biophys Res Commun 705: 149729, 2024.
105. Palacios-Navarro L, Crispin LA, Muñoz JP and Calaf GM: Effects of curcumin and estrogen receptor alpha in luminal breast cancer cells. Diagnostics (Basel) 14: 1785, 2024.
106. Nishimura FG, Sampaio BB, do Couto GO, da Silva AD, da Silva WJ, Peronni KC, Evangelista AF, Hossain M, Dimmock JR, Bandy B, *et al*: The transcriptome of BT-20 Breast cancer cells exposed to curcumin analog NC2603 reveals a relationship between EGR3 gene modulation and cell migration inhibition. Molecules 29: 1366, 2024.
107. Huai Z, Li Z, Xue W, Li S, Huang Y, Cao X, Wei Q and Wang Y: Novel curcumin derivatives N17 exert anti-cancer effects through the CSNK1G3/AKT axis in triple-negative breast cancer. Biochem Pharmacol 229: 116472, 2024.
108. Novitasari D, Nakamae I, Jenie RI, Yoneda-Kato N, Kato JY and Meiyanto E: Pentagamavunone-1 inhibits aggressive breast cancer cell proliferation through mitotic catastrophe and ROS-mediated activities: In vitro and in vivo studies. Saudi Pharm J 32: 101892, 2024.
109. Nishimura FG, Sampaio BB, Komoto TT, da Silva WJ, da Costa MMG, Haddad GI, Peronni KC, Evangelista AF, Hossain M, Dimmock JR, *et al*: Exploring CDKN1A upregulation mechanisms: Insights into cell cycle arrest induced by NC2603 curcumin analog in MCF-7 breast cancer cells. Int J Mol Sci 25: 4989, 2024.
110. Verderio P, Pandolfi L, Mazzucchelli S, Marinozzi MR, Vanna R, Gramatica F, Corsi F, Colombo M, Morasso C and Prosperi D: Antiproliferative effect of ASC-J9 delivered by PLGA nanoparticles against estrogen-dependent breast cancer cells. Mol Pharm 11: 2864-2875, 2014.
111. Zhang B, Deng Y, Xu D and Zhao X: Dimethylcurcumin and copper sulfate-loaded silk nanoparticles for synergistic therapy against breast cancer. ACS Biomater Sci Eng 11: 1539-1548, 2025.
112. Nautiyal J, Banerjee S, Kanwar SS, Yu Y, Patel BB, Sarkar FH and Majumdar AP: Curcumin enhances dasatinib-induced inhibition of growth and transformation of colon cancer cells. Int J Cancer 128: 951-961, 2011.
113. Villegas C, Perez R, Sterner O, González-Chavarría I and Paz C: Curcuma as an adjuvant in colorectal cancer treatment. Life Sci 286: 120043, 2021.
114. Liu C, Rokavec M, Huang Z and Hermeking H: Curcumin activates a ROS/KEAP1/NRF2/miR-34a/b/c cascade to suppress colorectal cancer metastasis. Cell Death Differ 30: 1771-1785, 2023.
115. Sazanov AA, Kiselyova EV, Zakharenko AA, Romanov MN and Zaraysky MI: Plasma and saliva miR-21 expression in colorectal cancer patients. J Appl Genet 58: 231-237, 2017.
116. Mudduluru G, George-William JN, Muppala S, Asangani IA, Kumarswamy R, Nelson LD and Allgayer H: Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. Biosci Rep 31: 185-197, 2011.
117. Roy S, Yu Y, Padhye SB, Sarkar FH and Majumdar AP: Difluorinated-curcumin (CDF) restores PTEN expression in colon cancer cells by down-regulating miR-21. PLoS One 8: e68543, 2013.
118. Dal Z and Aru B: The role of curcumin on apoptosis and NLRP3 inflammasome-dependent pyroptosis on colorectal cancer in vitro. Turk J Med Sci 53: 883-893, 2023.
119. Hosseini SS, Reihani RZ, Doustvandi MA, Amini M, Zargari F, Baradaran B, Yari A, Hashemi M, Tohidast M and Mokhtarzadeh A: Synergistic anticancer effects of curcumin and crocin on human colorectal cancer cells. Mol Biol Rep 49: 8741-8752, 2022.
120. Kunnumakkara AB, Diagaradjane P, Guha S, Deorukhkar A, Shentu S, Aggarwal BB and Krishnan S: Curcumin sensitizes human colorectal cancer xenografts in nude mice to gamma-radiation by targeting nuclear factor-kappaB-regulated gene products. Clin Cancer Res 14: 2128-2136, 2008.
121. Reddy S, Rishi AK, Xu H, Levi E, Sarkar FH and Majumdar AP: Mechanisms of curcumin- and EGF-receptor related protein (ERRP)-dependent growth inhibition of colon cancer cells. Nutr Cancer 55: 185-194, 2006.
122. Sun H, Liao F, Tian Y, Lei Y, Fu Y and Wang J: Molecular-Scale investigations reveal the effect of natural polyphenols on BAX/Bcl-2 interactions. Int J Mol Sci 25: 2474, 2024.
123. Sha J, Li J, Wang W, Pan L, Cheng J, Li L, Zhao H and Lin W: Curcumin induces G0/G1 arrest and apoptosis in hormone independent prostate cancer DU-145 cells by down regulating notch signaling. Biomed Pharmacother 84: 177-184, 2016.
124. Liao H, Wang Z, Deng Z, Ren H and Li X: Curcumin inhibits lung cancer invasion and metastasis by attenuating GLUT1/MT1-MMP/MMP2 pathway. Int J Clin Exp Med 8: 8948-8957, 2015.
125. Mohankumar K, Francis AP, Pajaniradje S and Rajagopalan R: Synthetic curcumin analog: Inhibiting the invasion, angiogenesis, and metastasis in human laryngeal carcinoma cells via NF-kB pathway. Mol Biol Rep 48: 6065-6074, 2021.
126. Fernandez-Muñoz KV, Sánchez-Barrera CÁ, Meraz-Ríos M, Reyes JL, Pérez-Yépez EA, Ortiz-Melo MT, Terrazas LI and Mendoza-Rodriguez MG: Natural alternatives in the treatment of colorectal cancer: A mechanisms perspective. Biomolecules 15: 326, 2025.
127. Shadnoush M, Momenan M, Seidel V, Tierling S, Fatemi N, Nazemalhosseini-Mojarad E, Norooz MT and Cheraghpour M: A comprehensive update on the potential of curcumin to enhance chemosensitivity in colorectal cancer. Pharmacol Rep 77: 103-123, 2025.
128. Imtiaz I, Schloss J and Bugarcic A: Interplay between traditional and scientific knowledge: Phytoconstituents and their roles in lung and colorectal cancer signaling pathways. Biomolecules 15: 380, 2025.
129. Guo Y, Su J, Jiang S, Xu Y, Dou B, Li T, Zhu J and He K: Transcriptomics and metabonomics study on the effect of exercise combined with curcumin supplementation on breast cancer in mice. Heliyon 10: e28807, 2024.
130. Sowa-Kasprzak K, Józkowiak M, Olender D, Pawełczyk A, Piotrowska-Kempisty H and Zaprutko L: Curcumin-Triterpene type hybrid as effective sonosensitizers for sonodynamic therapy in oral squamous cell carcinoma. Pharmaceutics 15: 2008, 2023.
131. Semlali A, Beji S, Ajala I, Al-Zharani M and Rouabhia M: Synergistic effects of new curcumin analog (PAC) and cisplatin on oral cancer therapy. Curr Issues Mol Biol 45: 5018-5035, 2023.
132. Lee AY, Fan CC, Chen YA, Cheng CW, Sung YJ, Hsu CP and Kao TY: Curcumin inhibits invasiveness and epithelial-mesenchymal transition in oral squamous cell carcinoma through reducing matrix metalloproteinase 2, 9 and modulating p53-E-cadherin pathway. Integr Cancer Ther 14: 484-490, 2015.
133. Li Y, Deng X, Tan X, Li Q, Yu Z, Wu W, Ma X, Zeng J and Wang X: Protective role of curcumin in disease progression from non-alcoholic fatty liver disease to hepatocellular carcinoma: a meta-analysis. Front Pharmacol 15: 1343193, 2024.
134. Man S, Yao J, Lv P, Liu Y, Yang L and Ma L: Curcumin-enhanced antitumor effects of sorafenib via regulating the metabolism and tumor microenvironment. Food Funct 11: 6422-6432, 2020.
135. Huang T, Chen H, Pan H, Wu T, Ren X, Qin L, Yuan K and He F: Comprehensive analysis of bioinformatics and system biology reveals the association between Girdin and hepatocellular carcinoma. PLoS One 19: e0315534, 2024.

136. Han H, Alsayed AMM, Wang Y, Yan Q, Shen A, Zhang J, Ye Y, Liu Z, Wang K and Zheng X: Discovery of β-cyclocitral-derived mono-carbonyl curcumin analogs as anti-hepatocellular carcinoma agents via suppression of MAPK signaling pathway. Bioorg Chem 132: 106358, 2023.
137. Mukherjee D, Dash P, Ramadass B and Mangaraj M: Nanocurcumin in oral squamous cancer cells and its efficacy as a chemo-adjuvant. Cureus 14: e24678, 2022.
138. Lakshmanan A, Akasov RA, Sholina NV, Demina PA, Generalova AN, Gangadharan A, Sardar DK, Lankamsetty KB, Khochenkov DA, Khaydukov EV, *et al*: Nanocurcumin-loaded UCNPs for cancer theranostics: Physicochemical properties, in vitro toxicity, and in vivo imaging studies. Nanomaterials (Basel) 11: 2234, 2021.
139. Louisa M, Wanafri E, Arozal W, Sandhiutami NMD and Basalamah AM: Nanocurcumin preserves kidney function and haematology parameters in DMBA-induced ovarian cancer treated with cisplatin via its antioxidative and anti-inflammatory effect in rats. Pharm Biol 61: 298-305, 2023.
140. Mehrab H, Sharifi M, Akhavan A, Aarabi MH, Mansourian M, Mosavi E and Moghaddas A: Curcumin supplementation prevents cisplatin-induced nephrotoxicity: A randomized, double-blinded, and placebo-controlled trial. Res Pharm Sci 18: 648-662, 2023.
141. Ramezani V, Ghadirian S, Shabani M, Boroumand MA, Daneshvar R and Saghafi F: Efficacy of curcumin for amelioration of radiotherapy-induced oral mucositis: A preliminary randomized controlled clinical trial. BMC Cancer 23: 354, 2023.
142. Eghbali A, Adibifar M, Ghasemi A, Afzal RR, Moradi K, Eghbali A, Faress F and Ghaffari K: The effect of oral curcumin on vincristine-induced neuropathy in pediatric acute lymphoblastic leukemia: A double-blind randomized controlled clinical trial. BMC Cancer 25: 344, 2025.
143. Kekatpure V, Subramaniam N, Sunny S, Nambiar S, Sarah T, Vasudevan V, Rao A, Murali A, Kolur T, Krishnamurthy A, *et al*: Two by two factorial design using metformin and curcumin for second primary head and neck cancer prevention trial. Asian Pac J Cancer Prev 25: 1935-1943, 2024.
144. Dahka SM, Afsharfar M, Tajaddod S, Sohouli MH, Shekari S, Nafouti FB, Alizadeh A, Kachaei HS, Abbasi K, Mohseni GK, *et al*: Impact of curcumin supplementation on radiation dermatitis severity: A systematic review and meta-analysis of randomized controlled trials. Asian Pac J Cancer Prev 24: 783-789, 2023.
145. Chaiworramukkul A, Seetalarom K, Saichamchan S and Prasongsook N: A Double-Blind, placebo-controlled randomized phase IIa study: Evaluating the effect of curcumin for treatment of cancer anorexia-cachexia syndrome in solid cancer patients. Asian Pac J Cancer Prev 23: 2333-2340, 2022.
146. Panahi Y, Saberi-Karimian M, Valizadeh O, Behnam B, Saadat A, Jamialahmadi T, Majeed M and Sahebkar A: Effects of curcuminoids on systemic inflammation and quality of life in patients with colorectal cancer undergoing chemotherapy: A randomized controlled trial. Adv Exp Med Biol 1328: 1-9, 2021.
147. Wei Y, Wei Y, Sheng L, Ma J, Su Z, Wen J, Li L, Jia Q, Liu H, Si H, *et al*: Construction of curcumin and paclitaxel co-loaded lipid nano platform and evaluation of its anti-hepatoma activity in vitro and pharmacokinetics in vivo. Int J Nanomedicine 18: 2087-2107, 2023.
148. Guo F, Jiao Y, Ding W, Du Y, Luo S, Wang M, Wang Y, Wu F, Wang L and Yang G: Synergistic effects of multidrug/material combination deliver system for anti-mutidrug-resistant tumor. Int J Pharm 649: 123669, 2024.
149. Abe T, Horisawa Y, Kikuchi O, Ozawa-Umeta H, Kishimoto A, Katsuura Y, Imaizumi A, Hashimoto T, Shirakawa K, Takaori-Kondo A, *et al*: Pharmacologic characterization of TBP1901, a prodrug form of aglycone curcumin, and CRISPR-Cas9 screen for therapeutic targets of aglycone curcumin. Eur J Pharmacol 935: 175321, 2022.
150. Gutsche LC, Dörfler J and Hübner J: Curcumin as a complementary treatment in oncological therapy: A systematic review. Eur J Clin Pharmacol 81: 1-33, 2025.
151. Zeng L, Yang T, Yang K, Yu G, Li J, Xiang W and Chen H: Efficacy and safety of curcumin and *Curcuma longa* extract in the treatment of arthritis: A systematic review and meta-analysis of randomized controlled trial. Front Immunol 13: 891822, 2022.
152. Liu S, Liu J, He L, Liu L, Cheng B, Zhou F, Cao D and He Y: A comprehensive review on the benefits and problems of curcumin with respect to human health. Molecules 27: 4400, 2022.
153. Huang M, Zhai BT, Fan Y, Sun J, Shi YJ, Zhang XF, Zou JB, Wang JW and Guo DY: Targeted drug delivery systems for curcumin in breast cancer therapy. Int J Nanomedicine 18: 4275-4311, 2023.
154. Alam MS, Anwar MJ, Maity MK, Azam F, Jaremko M and Emwas AH: the dynamic role of curcumin in mitigating human illnesses: Recent advances in therapeutic applications. Pharmaceuticals (Basel) 17: 1674, 2024.
155. Anand P, Kunnumakkara AB, Newman RA and Aggarwal BB: Bioavailability of curcumin: Problems and promises. Mol Pharm 4: 807-818, 2007.
156. Gupta SC, Patchva S and Aggarwal BB: Therapeutic roles of curcumin: Lessons learned from clinical trials. AAPS J 15: 195-218, 2013.
157. Kanai M, Imaizumi A, Otsuka Y, Sasaki H, Hashiguchi M, Tsujiko K, Matsumoto S, Ishiguro H and Chiba T: Dose-escalation and pharmacokinetic study of nanoparticle curcumin, a potential anticancer agent with improved bioavailability, in healthy human volunteers. Cancer Chemother Pharmacol 69: 65-70, 2012.
158. Mashayekhi-Sardoo H, Mashayekhi-Sardoo A, Roufogalis BD, Jamialahmadi T and Sahebkar A: Impact of curcumin on microsomal enzyme activities: Drug interaction and chemopreventive studies. Curr Med Chem 28: 7122-7140, 2021.
159. Imam Z, Khasawneh M, Jomaa D, Iftikhar H and Sayedahmad Z: Drug induced liver injury attributed to a curcumin supplement. Case Rep Gastrointest Med 2019: 6029403, 2019.
160. Lukefahr AL, McEvoy S, Alfafara C and Funk JL: Drug-induced autoimmune hepatitis associated with turmeric dietary supplement use. BMJ Case Rep 2018: bcr2018224611, 2018.
161. Bhat PA, Chat OA and Dar AA: Exploiting co-solubilization of warfarin, curcumin, and rhodamine B for modulation of energy transfer: A micelle FRET On/Off switch. Chemphyschem 17: 2360-2372, 2016.
162. Servida S, Piontini A, Gori F, Tomaino L, Moroncini G, De Gennaro Colonna V, La Vecchia C and Vigna L: Curcumin and gut microbiota: A narrative overview with focus on glycemic control. Int J Mol Sci 25: 7710, 2024.
163. Jabczyk M, Nowak J, Hudzik B and Zubelewicz-Szkodzińska B: Curcumin in metabolic health and disease. Nutrients 13: 4440, 2021.
164. Lin X, Bai D, Wei Z, Zhang Y, Huang Y, Deng H and Huang X: Curcumin attenuates oxidative stress in RAW264.7 cells by increasing the activity of antioxidant enzymes and activating the Nrf2-Keap1 pathway. PLoS One 14: e0216711, 2019.
165. Zhou Y, Jia Z, Wang J, Huang S, Yang S, Xiao S, Xia D and Zhou Y: Curcumin reverses erastin-induced chondrocyte ferroptosis by upregulating Nrf2. Heliyon 9: e20163, 2023.
166. Zhang J, Sun X, Chai X, Jiao Y, Sun J, Wang S, Yu H and Feng X: Curcumin mitigates oxidative damage in broiler liver and ileum caused by aflatoxin B1-contaminated feed through Nrf2 signaling pathway. Animals (Basel) 14: 409, 2024.
167. Chen B, Li H, Ou G, Ren L, Yang X and Zeng M: Curcumin attenuates MSU crystal-induced inflammation by inhibiting the degradation of IκBα and blocking mitochondrial damage. Arthritis Res Ther 21: 193, 2019.
168. Kooshki L, Zarneshan SN, Fakhri S, Moradi SZ and Echeverria J: The pivotal role of JAK/STAT and IRS/PI3K signaling pathways in neurodegenerative diseases: Mechanistic approaches to polyphenols and alkaloids. Phytomedicine 112: 154686, 2023.
169. Grilc NK, Sova M and Kristl J: Drug delivery strategies for curcumin and other natural Nrf2 modulators of oxidative stress-related diseases. Pharmaceutics 13: 2137, 2021.
170. Ruan H, Zeng X and Shen S: Mechanism of curcumin inhibiting NLRP3 inflammatory body and improving atherosclerotic endothelial cell injury. Discov Med 36: 121-128, 2024.
171. Peng Y, Ao M, Dong B, Jiang Y, Yu L, Chen Z, Hu C and Xu R: Anti-Inflammatory effects of curcumin in the inflammatory diseases: Status, limitations and countermeasures. Drug Des Devel Ther 15: 4503-4525, 2021.
172. Chen G, Liu S, Pan R, Li G, Tang H, Jiang M, Xing Y, Jin F, Lin L and Dong J: Curcumin attenuates gp120-Induced microglial inflammation by inhibiting autophagy via the PI3K pathway. Cell Mol Neurobiol 38: 1465-1477, 2018.
173. Chowdhury I, Banerjee S, Driss A, Xu W, Mehrabi S, Nezhat C, Sidell N, Taylor RN and Thompson WE: Curcumin attenuates proangiogenic and proinflammatory factors in human eutopic endometrial stromal cells through the NF-κB signaling pathway. J Cell Physiol 234: 6298-6312, 2019.

174. Li Y, Tan L, Liu F, Li M, Zeng S, Gui Y, Zhao Y and Wang JJ: Effects of soluble Antarctic krill protein-curcumin complex combined with photodynamic inactivation on the storage quality of shrimp. Food Chem 403: 134388, 2023.
175. Wang JJ, He T, Chen L, Xu G, Dong S, Zhao Y, Zheng H, Liu Y and Zeng Q: Antibacterial efficiency of the curcumin-mediated photodynamic inactivation coupled with L-arginine against Vibrio parahaemolyticus and its application on shrimp. Int J Food Microbiol 411: 110539, 2024.
176. Bhavya ML and Hebbar HU: Efficacy of blue LED in microbial inactivation: Effect of photosensitization and process parameters. Int J Food Microbiol 290: 296-304, 2019.
177. de Andrade Neto JB, de Farias Cabral VP, Nogueira LF, da Silva CR, do Amaral Valente Sá LG, da Silva AR, da Silva WM, Silva J, Marinho ES, Cavalcanti BC, *et al*: Anti-MRSA activity of curcumin in planktonic cells and biofilms and determination of possible action mechanisms. Microb Pathog 155: 104892, 2021.
178. El-Mahdy AM, Alqahtani M, Almukainzi M, Alghoribi MF and Abdel-Rhman SH: Effect of resveratrol and curcumin on gene expression of methicillin-resistant staphylococcus aureus (MRSA) toxins. J Microbiol Biotechnol 34: 141-148, 2024.
179. Zheng D, Huang C, Huang H, Zhao Y, Khan MRU, Zhao H and Huang L: Antibacterial mechanism of curcumin: A review. Chem Biodivers 17: e2000171, 2020.
180. Mounce BC, Cesaro T, Carrau L, Vallet T and Vignuzzi M: Curcumin inhibits Zika and chikungunya virus infection by inhibiting cell binding. Antiviral Res 142: 148-157, 2017.
181. Li Y, Wang J, Liu Y, Luo X, Lei W and Xie L: Antiviral and virucidal effects of curcumin on transmissible gastroenteritis virus in vitro. J Gen Virol 101: 1079-1084, 2020.
182. Anggakusuma, Colpitts CC, Schang LM, Rachmawati H, Frentzen A, Pfaender S, Behrendt P, Brown RJ, Bankwitz D, Steinmann J, *et al*: Turmeric curcumin inhibits entry of all hepatitis C virus genotypes into human liver cells. Gut 63: 1137-1149, 2014.
183. Thongsri P, Pewkliang Y, Borwornpinyo S, Wongkajornsilp A, Hongeng S and Sa-Ngiamsuntorn K: Curcumin inhibited hepatitis B viral entry through NTCP binding. Sci Rep 11: 19125, 2021.
184. Prasad S and Tyagi AK: Curcumin and its analogues: A potential natural compound against HIV infection and AIDS. Food Funct 6: 3412-3419, 2015.
185. Zhang HS, Ruan Z and Sang WW: HDAC1/NFκB pathway is involved in curcumin inhibiting of Tat-mediated long terminal repeat transactivation. J Cell Physiol 226: 3385-3391, 2011.
186. Dai J, Gu L, Su Y, Wang Q, Zhao Y, Chen X, Deng H, Li W, Wang G and Li K: Inhibition of curcumin on influenza A virus infection and influenzal pneumonia via oxidative stress, TLR2/4, p38/JNK MAPK and NF-κB pathways. Int Immunopharmacol 54: 177-187, 2018.
187. Hesari A, Ghasemi F, Salarinia R, Biglari H, Hassan AT, Abdoli V and Mirzaei H: Effects of curcumin on NF-κB, AP-1, and Wnt/β-catenin signaling pathway in hepatitis B virus infection. J Cell Biochem 119: 7898-7904, 2018.
188. Piccialli I, Tedeschi V, Caputo L, D'Errico S, Ciccone R, De Feo V, Secondo A and Pannaccione A: Exploring the therapeutic potential of phytochemicals in Alzheimer's disease: focus on polyphenols and monoterpenes. Front Pharmacol 13: 876614, 2022.
189. Alamro AA, Alsulami EA, Almutlaq M, Alghamedi A, Alokail M and Haq SH: Therapeutic potential of vitamin D and curcumin in an *in vitro* model of Alzheimer disease. J Cent Nerv Syst Dis 12: 1179573520924311, 2020.
190. Yuan J, Botchway BOA, Zhang Y, Tan X, Wang X and Liu X: Curcumin can improve spinal cord injury by inhibiting TGF-β-SOX9 signaling pathway. Cell Mol Neurobiol 39: 569-575, 2019.
191. Panzarini E, Mariano S, Tacconi S, Carata E, Tata AM and Dini L: Novel therapeutic delivery of nanocurcumin in central nervous system related disorders. Nanomaterials (Basel) 11: 2, 2020.
192. Lee Y, Park HR, Lee JY, Kim J, Yang S, Lee C, Kim K, Kim HS, Chang SC and Lee J: Low-dose curcumin enhances hippocampal neurogenesis and memory retention in young mice. Arch Pharm Res 46: 423-437, 2023.
193. Yavari N, Sharifi ZN, Rekabdar Y and Movassaghi S: Protective effect of curcumin on CA1 region of hippocampus in rat model of ischemia/ reperfusion injury: Galen Med J 11: e1062, 2022.
194. Zhang L, Ma Z, Wu Z, Jin M, An L and Xue F: curcumin improves chronic pain induced depression through regulating serum metabolomics in a rat model of trigeminal neuralgia. J Pain Res 13: 3479-3492, 2020.
195. Zhang L, Han Y, Wu X, Chen B, Liu S, Huang J, Kong L, Wang G and Ye Z: Research progress on the mechanism of curcumin in cerebral ischemia/reperfusion injury: A narrative review. Apoptosis 28: 1285-1303, 2023.
196. Racchi M, Uberti D, Govoni S, Memo M, Lanni C, Vasto S, Candore G, Caruso C, Romeo L and Scapagnini G: Alzheimer's disease: New diagnostic and therapeutic tools. Immun Ageing 5: 7, 2008 .
197. Scapagnini G, Colombrita C, Amadio M, D'Agata V, Arcelli E, Sapienza M, Quattrone A and Calabrese V: Curcumin activates defensive genes and protects neurons against oxidative stress. Antioxid Redox Signal 8: 395-403, 2006.
198. Sadek MA, Rabie MA, El Sayed NS, Sayed HM and Kandil EA: Neuroprotective effect of curcumin against experimental autoimmune encephalomyelitis-induced cognitive and physical impairments in mice: An insight into the role of the AMPK/SIRT1 pathway. Inflammopharmacology 32: 1499-1518, 2024.