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REVIEW ARTICLE

The therapeutic potential of curcumin and its related substances in turmeric: From raw material selection to application strategies

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Abstract

Turmeric (*Curcuma longa* L.) is a medicinal plant used extensively in Chinese and Indian traditional medicine as a home remedy for various diseases. It has been used for medical purposes for centuries. Today, turmeric has become one of the most popular medicinal herbs, spices, and functional supplements worldwide. Curcuminoids are linear diarylheptanoids from the rhizomes that include curcumin and two related compounds: demethoxycurcumin and bisdemethoxycurcumin, which are the active components of the *C. longa* plant, play a crucial role in numerous functions. This review summarises the composition of turmeric and the properties of curcumin regarding its antioxidant, anti-inflammatory, anti-diabetic, anti-colorectal cancer, and other physiological activity. In addition, the dilemma of the application of curcumin due to its low water solubility and bioavailability was discussed. Finally, this article provides three novel application strategies based on previous studies: using curcumin analogues and related substances, gut microbiota regulation, and using curcumin-loaded exosome vesicles and turmeric-derived exosome-like vesicles to overcome application limitations.

Keywords: Anti-colorectal cancer, Anti-inflammation, Curcumin, Exosome vesicles, Gut microbiota

1. Introduction

Turmeric (*Curcuma longa* L.) is a medicinal plant that is used extensively in Chinese and Indian traditional medicine as a home remedy for various diseases. It is botanically related to ginger (Zingiberaceae family). It is a perennial plant with a short stem, large leaves, and rhizomes of various shapes that are often branched and have a brownish-yellow peel [1]. Today, turmeric is grown in several parts of the world, including Southeast Asia, China, and South America [2]. It has been used for medical purposes in India and China for many centuries to treat liver ailments [3] and other inflammation-related symptoms [4]. Turmeric has become one of the most popular medicinal herbs, spices, and functional supplements. The popularity of turmeric can be attributed to its pharmacological activity, including it antioxidant [5], antibacterial [6], anti-inflammatory [7], anti-tumour [8], and antiaging properties [9]. These functional activities of turmeric have been attributed to its rich curcuminoid content [1,2]. Curcuminoids (Fig. 1) are linear diarylheptanoids from the rhizomes that include curcumin (CUR) and two related compounds: demethoxycurcumin (DMC) and bisdemethoxycurcumin (BDMC) [2]. Curcumin is a crystalline compound with a bright orange-yellow colour. It is often used as a food colouring and additive [2]. In the current international regulations, curcumin is

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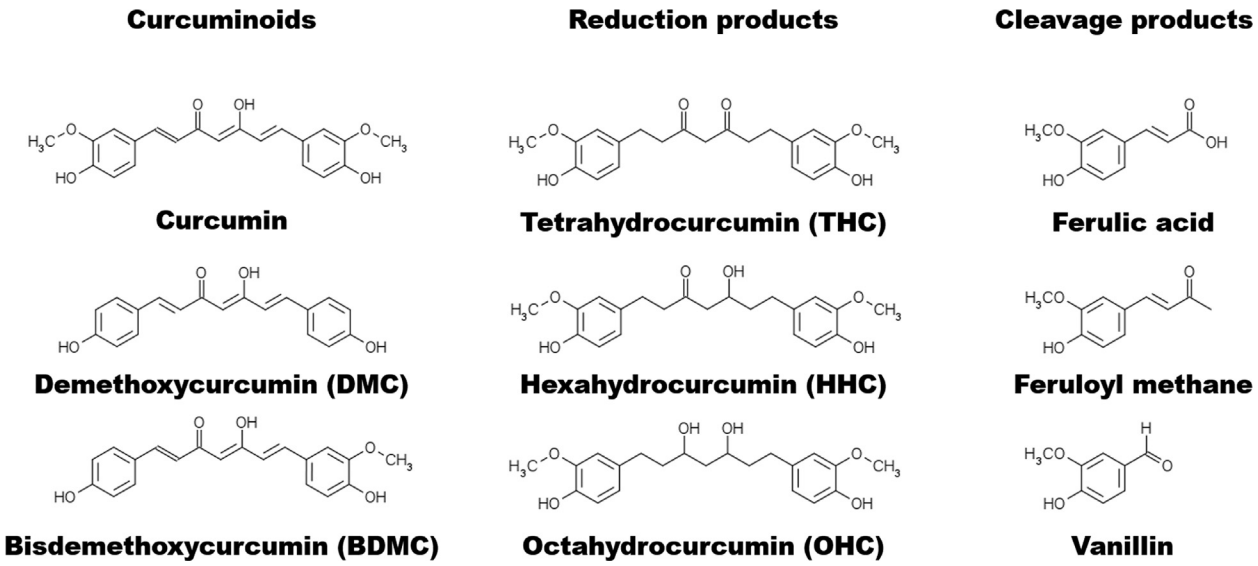

Fig. 1. Curcuminoids found in Curcuma longa, curcumin metabolites (reduction), and its degradation products (cleavage).

considered a safe food additive. The World Health Organization (WHO) evaluated the acceptable daily intake (ADI) of curcumin as a food colouring additive in the range of 0–3 mg/kg [10]. The United States Food and Drug Administration (USFDA) has declared curcumin as 'generally regarded as safe' (GRAS). It is worth noting that most researchers consider curcumin to exhibit a wide variety of pharmacological properties and is relatively safe in animals and humans [11]; however, high doses (>50,000 ppm) ingested in order to overcome the low bioavailability of curcumin have some side effects and safety concerns [12]. Overall, if the bioavailability of curcumin can be effectively improved, it has the potential to improve or even cure diseases [13].

2. Composition of turmeric

Curcumin ($C_{21}H_{20}O_5$) is also known as diferuloylmethane or (1*E*,6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione, DMC ($C_{20}H_{18}O_5$) is also known as (1*E*,6*E*)-1-(4-hydroxy-3-methoxyphenyl)-7-(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione, and BDMC ($C_{19}H_{16}O_4$) is also known as (1*E*,6*E*)-1,7-bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione. These three major curcuminoids are also found in other *Curcuma* species at different concentrations and proportions. Curcuminoids were only detected in a few species, such as *C. longa* and *C. phaeocaulis,* and geographical differences affect its content. In China, *C. longa (Jianghuang)* rhizomes from Pengzhou Sichuan contain the highest amount of curcuminoids (40.36 mg/g), which are almost 20-fold higher than those found in *C. longa (Huangsi Yujin)* collected from the same area [14]. In another study, *C. longa* rhizomes from the Zhengzhou pharmacies market exhibited a higher amount of curcuminoids (172.6 mg/g) [15]. Of note, curcuminoid content is related to geographical location; in Nepal, turmeric that is cultivated in warmer climates (Southern Nepal) has higher curcuminoid content than turmeric samples from cooler climates (Northern Nepal) [16]. In India, samples collected from different geographical regions also have different curcuminoid content; the main reason is the different environmental conditions across the Indian subcontinent. The maximum and minimum amount of curcuminoids were found to be present in samples of turmeric from Erode (South province, 50.27 mg/g) and Surat (West province, 14.08 mg/g) [17]. In Brazil, different samples in the same area contained different amounts of curcuminoids in the rhizome, from 18.2 mg/g to 23.3 mg/g. The curcumin content in the two samples is not much different and is mainly due to the difference in the content of DMC and BDMC [18]. Different *Curcuma* species may have different curcuminoid content, curcuminoids, and xanthorrhizol (XNT) content, which can be used as a specific marker to differentiate *Curcuma xanthorriza* and *C. longa* [19]. The guidelines of the *Taiwan Herbal Pharmacopeia* [20] and *The Pharmacopoeia of the People's Republic of China 2020 Edition* [21], two official compendiums of Chinese drugs, state that medicinal turmeric must contain more than 1% curcumin, and almost all turmeric rhizome samples meet this specification. However, this guideline is limited to

the rhizome of turmeric. The curcumin content of the root is much lower than that of the rhizome [14]; therefore, the plant localisation or extract of medicinal turmeric must be considered for a standardised dose of curcumin [22]. Furthermore, ingested turmeric products may contain metabolites and degradation products of curcumin. Curcumin will easily degrade in neutral to alkaline solutions and is cleaved into ferulic acid, feruloyl methane, and vanillin (Fig. 1) [23]. Tetrahydrocurcumin (THC), hexahydrocurcumin (HHC), and octahydrocurcumin (OHC) (Fig. 1) are hydrogenated derivatives of curcumin [24] that appear as metabolites after curcumin is metabolised by cells or animals. Because of their structure, they are functionally closely related to curcumin [25]. In addition to the extraction and isolation of curcuminoids from turmeric, chemical synthesis is a strategy for obtaining curcuminoids [26,27]. The earliest record of chemical synthesis of curcumin was in 1913 [28]; since then, many studies have explored preparation methods of curcumin by chemical synthesis [26,29,30]. Unlike curcumin extracted from turmeric, which often contains a variety of curcuminoids, chemical synthesis can prepare specific, high-purity curcuminoids by adjusting conditions and precursors. This makes it possible to examine the chemical structure and mechanism of action of curcuminoids more precisely when discussing the function of curcuminoids.

3. Function of curcumin and curcuminoids

3.1. Antioxidant

As cells grow, oxygen consumption leads to the production of reactive oxygen species (ROS) [31]. ROS are forms of activated oxygen that include free radicals, such as superoxide anion radicals ($O_2^{\cdot-}$), hydroxyl radicals ($^{\bullet}OH$), and non-free-radical species, such as H_2O_2 and singlet oxygen ($^1O_2$) [32]. ROS in cells cause the peroxidation of membrane lipids, leading to lipid peroxides. Furthermore, ROS can damage intracellular chemical composition, such as nucleic acids, lipids, proteins, and carbohydrates [25], which affect the inner workings of the cell. Generally speaking, antioxidant systems (e.g., the glutathione cycle and superoxide dismutase) in cells scavenge ROS and free radicals [33]; however, as the oxidative pressure increases, these systems may be overloaded and become ineffective. It has been confirmed that ROS production is directly related to many diseases [34]. Dietary antioxidants can protect the human body from free radicals and the effects of ROS. The curcuminoid structure contains several functional groups, including the β-diketone group, carbon–carbon double bonds, and phenyl rings containing hydroxyl and methoxy substituents [35]. Interestingly, the demethoxy and hydrogenated derivatives of curcumin, such as THC, HHC, and OHC, were remarkably more potent than curcumin in *in vitro* antioxidant assays [24]. Due to the loss of the ortho-methoxyphenolic group, BDMC does not have hydrogen donating activity [36].

3.2. Anti-inflammatory

Inducible nitric oxide synthase (iNOS) is one of the critical enzymes producing nitric oxide (NO) from the amino acid L-arginine, and iNOS-derived NO plays a crucial role in blood pressure regulation, inflammation, infection, and the progression of malignant diseases [37]. In macrophages, iNOS serves as a mediator of non-specific host defence and plays an essential role in clearing bacterial, viral, fungal, and parasitic infections [38]. When macrophages are stimulated, iNOS produces NO, which regulates blood pressure and has antibacterial activity. However, when the iNOS-derived NO is overproduced, it causes excessive expansion of blood vessels and tissue damage [39]. In this case, inducible haem oxygenase 1 (HO-1) plays a regulatory role as a rate-limiting enzyme; it catalyses the metabolism of haem into bilirubin, carbon monoxide (CO), and iron ions to regulate iNOS-mediated production of NO [40,41]. HO-1 and CO suppress the expression of iNOS and NO production in activated macrophages by deactivating nuclear factor-kappa B (NF-κB) [38,40,42]. Surprisingly, curcumin has a similar function; it indirectly inhibits NO production via inhibition of iNOS through suppression of NF-κB [36,43,44]. The NO-scavenging activity of curcumin and its derivatives, curcumin and THC, is potent, and the IC_{50} values are: curcumin ≈ THC > DMC > BDMC ≈ HHC > OHC [36]. Cyclooxygenase (COX) has two isozymes: COX-1 and COX-2. Its function is to catalyse the synthesis of prostaglandin from arachidonic acid. The role of COX-1 is to protect the gastric mucosa and maintain kidney function; the role of COX-2 is to promote prostacyclin (PGI_2) production, which causes inflammation [45]. Curcumin, DMC, and BDMC are reported to inhibit COX-1 and COX-2 (32.0%, 38.5%, and 39.2% COX-1 inhibitory activity at a dose of 125 μg/mL; 89.7%, 82.0%, and 58.9% COX-2 inhibitory activity at a dose of 125 μg/mL, respectively). The COX-1 inhibitory effect of these compounds was slightly below that of the positive controls Aspirin (μg/mL), ibuprofen (2.06 μg/mL),

and naproxen (2.52 μg/mL); however, they exhibited higher COX-II inhibitory activity than positive controls [45]. Furthermore, RAW264.7 macrophages treated with curcumin exhibited increased expression of HO-1 and decreased expression of iNOS protein and decreased iNOS promoter activity, which reduced NO production [38]. Moreover, curcumin can block lipopolysaccharide (LPS)-mediated expression of tumour necrosis factor α (TNF-α), interleukin (IL)-1β, and IL-6. Curcumin may alleviate inflammation through the nuclear factor-E2-related factor 2 (Nrf2)/HO-1 pathway [46]. Furthermore, the anti-inflammatory effect may be associated with activator protein-1 (AP-1) [47]. NF-κB and AP-1 are two transcription factor genes that are crucial to the LPS-induced inflammatory response and are commonly overexpressed in cancer cells [48]. In this situation, by inhibiting NF-κB, curcumin treatment results in the death of malignant cells and inhibits inflammation. Of note, one study suggested that the role of curcumin in the inflammatory system was like a pro-drug that requires oxidative activation to a reactive metabolite to exert anti-inflammatory effects [49]. Stably transfected RAW264.7 cells showed reduced luciferase activity expressed downstream of an NF-κB response element when treated with Curcuminoids and induced with LPS. Furthermore, NF-κB inhibition by curcumin and DMC involves the oxidation of these compounds into reactive electrophiles (Fig. 2) [50]. In contrast, BDMC is less likely to undergo spontaneous oxidative transformation due to the lack of ortho-methoxy groups that can accelerate the oxidation of the phenolic hydroxyl [51]. This also explains why curcumin and DMC have similar inhibitory pathways [36,45], while BDMC is different. In view of the lack of uncertainty of curcumin oxidative *in vivo*, the anti-inflammatory potential of oxidation-independent BDMC may be a new research direction.

3.3. Anti-diabetes

Diabetes is a chronic metabolic disease. According to the guidelines published by the American Diabetes Association in 2021, diabetes is diagnosed under one of the following conditions: glycosylated haemoglobin (HbA1c) ≥6.5%, fasting plasma glucose ≥126 mg/dL, or 2-h plasma glucose ≥200 mg/dL, or random blood glucose ≥200 mg/dL [52]. Diabetes can be categorised into four types: insulin-dependent type 1 diabetes, non-insulin-dependent type 2 diabetes, gestational diabetes, and diabetes caused by other factors. Among these types, type 2 diabetes accounts for most cases of diabetes. In addition, due to the functional loss of blood sugar utilisation, diabetes often causes dyslipidaemia, which promotes mitochondria to produce ROS and causes macrophages to produce pro-inflammatory factors, such as iNOS and ROS, eventually leading to complications, such as heart, kidney, and liver disease [53]. Incretin is a collective term for peptide hormones that act on pancreatic β cells to stimulate insulin secretion [54]. Research has discovered that curcumin can inhibit gluconeogenesis enzymes glucose-6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPUC), and adenosine 5′-monophosphate-activated protein (AMP) kinase activity to suppress liver gluconeogenesis and glycolysis. Moreover, curcumin can increase the effect of insulin in inhibiting glycolysis [55]. In an animal model, treatment with 15 mg/kg and 30 mg/kg curcumin significantly reduced blood sugar, vasoconstrictor pressure, proteinuria, polyuria, serum creatinine, and blood urea nitrogen (BUN) in male diabetic Sprague–Dawley rats; furthermore, it reduced the production of kidney lipid peroxidation products (malondialdehyde) and increased the activity of antioxidant enzymes glutathione, catalase, and superoxide dismutase [56]. Recent research highlighted that curcumin could significantly increase GLP-1 secretion in GLUTag cells [57]. The secretion of GLP-1 requires a β-diketone structure and an aromatic ring with at least one methoxy group; curcumin has a β-diketone structure with two methoxy groups, making it the most potent candidate. In contrast, BDMC, which lacks a methoxy group, and THC, which lacks the β-diketone structure, cannot stimulate GLP-1 secretion [57,58]. In a clinical trial, 240 subjects who met the pre-diabetes criteria were divided into control and placebo groups. After treatment with 1.5 g of curcuminoids daily for 12 months, there was a significant decrease in the subjects' diabetes indicators (glycated haemoglobin, fasting blood glucose, and glucose tolerance), improved pancreatic β-cell function, and increased performance of anti-inflammatory factor adiponectin [59]. Together, these data support the therapeutic potential of curcumin in controlling diabetes.

3.4. Anti-colorectal cancer

One of the basic concepts of cancer is the balance between cell proliferation and cell death [60]. When the apoptotic signals lose their function, cells proliferate out of control, leading to cancer [61]. Apoptotic signals are generated through two main pathways: in the intrinsic pathway, the mitochondrial membrane inhibits the expression of anti-

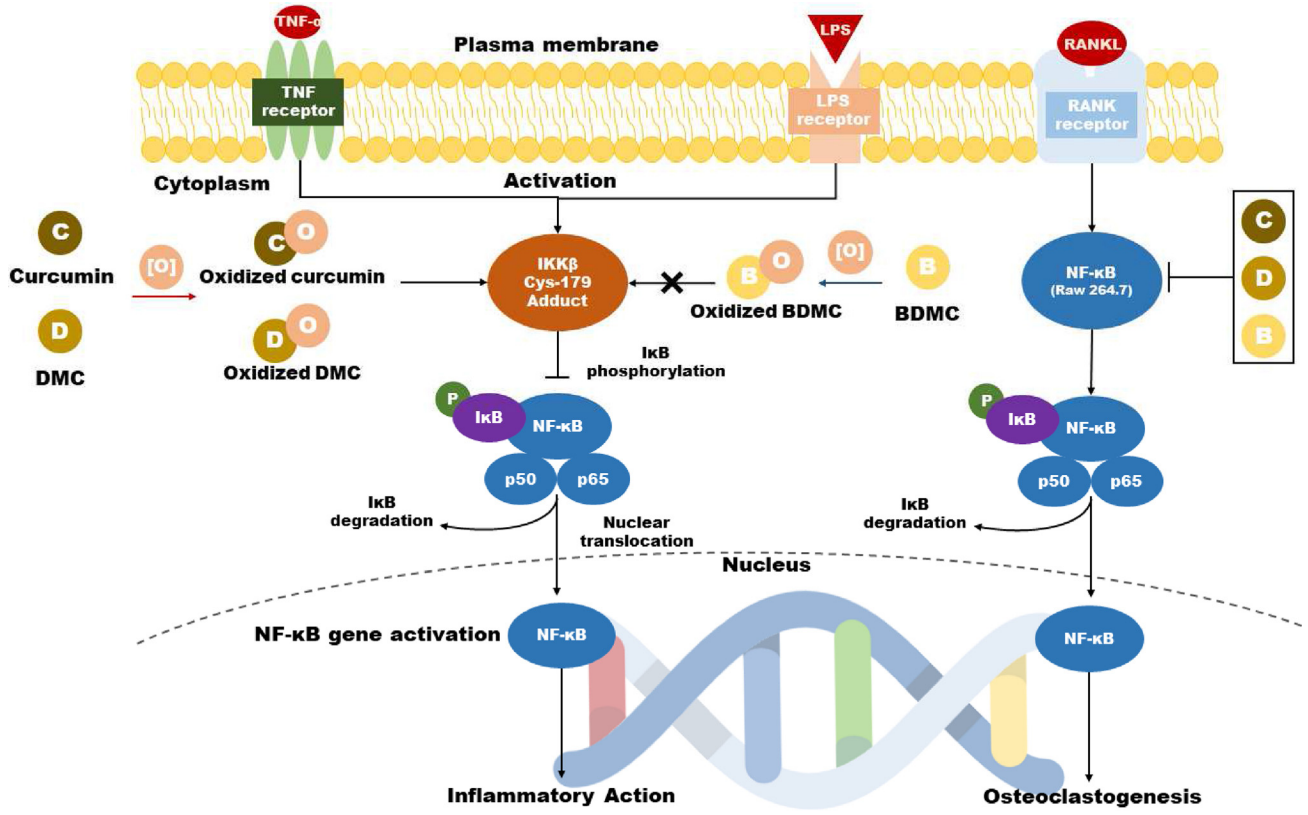

Fig. 2. Mechanistic differences in the inhibition of NF-κB by curcumin, DMC, and BDMC.

apoptotic proteins Bcl-2 and Bcl-xL; in contrast, increasing the death receptors in the extrinsic apoptotic pathway triggers TNF-related apoptosis [62]. A study highlighted that curcumin disturbed the balance of mitochondrial membrane potential and increased the inhibition of Bcl-xL protein [63]. Furthermore, a study has revealed that curcumin significantly increases the expression of death receptor 5 (DR5) on both the mRNA and protein level [64]. Curcumin modulates tumour cell growth by regulating multiple cell signalling pathways. In addition to the cell survival pathway (Bcl-2, Bcl-xL) and death receptor pathway (DR4, DR5), there is the cell proliferation pathway (cyclin D1, c-myc), caspase activation pathway (caspase-8, -3, -9), tumour suppressor pathway (p53, p21), mitochondrial pathways, and protein kinase pathway (JNK, Akt, and AMPK) [65]. In the aforementioned pathways (Fig. 3), curcumin has shown significant anticancer effects *in vitro* and *in vivo* against several types of cancer, including prostate cancer, breast cancer, and colorectal cancer.

Colorectal (colon) cancer is one of the leading tumours globally. It is considered among the third most common cancers worldwide, with an array of high morbidity and mortality, being the fourth highest cause death [66,67]. Unfortunately, although treatment is mainly based on surgical resection, many patients continue to have a high risk of tumour recurrence [68]. COX-2 overexpression is observed in up to 90% of sporadic colon cancers and 40% of colon adenomas [69]. Therefore, specific COX-2 inhibitors have been clinically studied as agents for colon cancer chemoprevention; however, there are still doubts about their safety as they may increase cardiovascular risk [70,71]. Studies have shown that administration of curcumin can reduce the levels of oxidative DNA adduct 3-(2-deoxy-β-di-erythro-pentafuranosyl)-pyr[1,2-α]-purin-10(3*H*) one (M_1G) in malignant colorectal cells without changing the level of COX-2 protein (Table 1.) [72].

Unlike in clinical studies, both M_1G and COX-2 protein are reduced in animal models following treatment with curcumin [73]. This outcome is hypothesised to be due to the ability of curcumin to inhibit COX-2, which is mainly caused by the reduction or conjugation of generated species [74]. In HCT 116 colorectal cancer cells treated with curcumin, the cell cycle was arrested in the G2/M phase via miR-21 gene regulation, which inhibited tumour tissue growth [75]. In another study, curcumin induced senescence and inhibited the growth

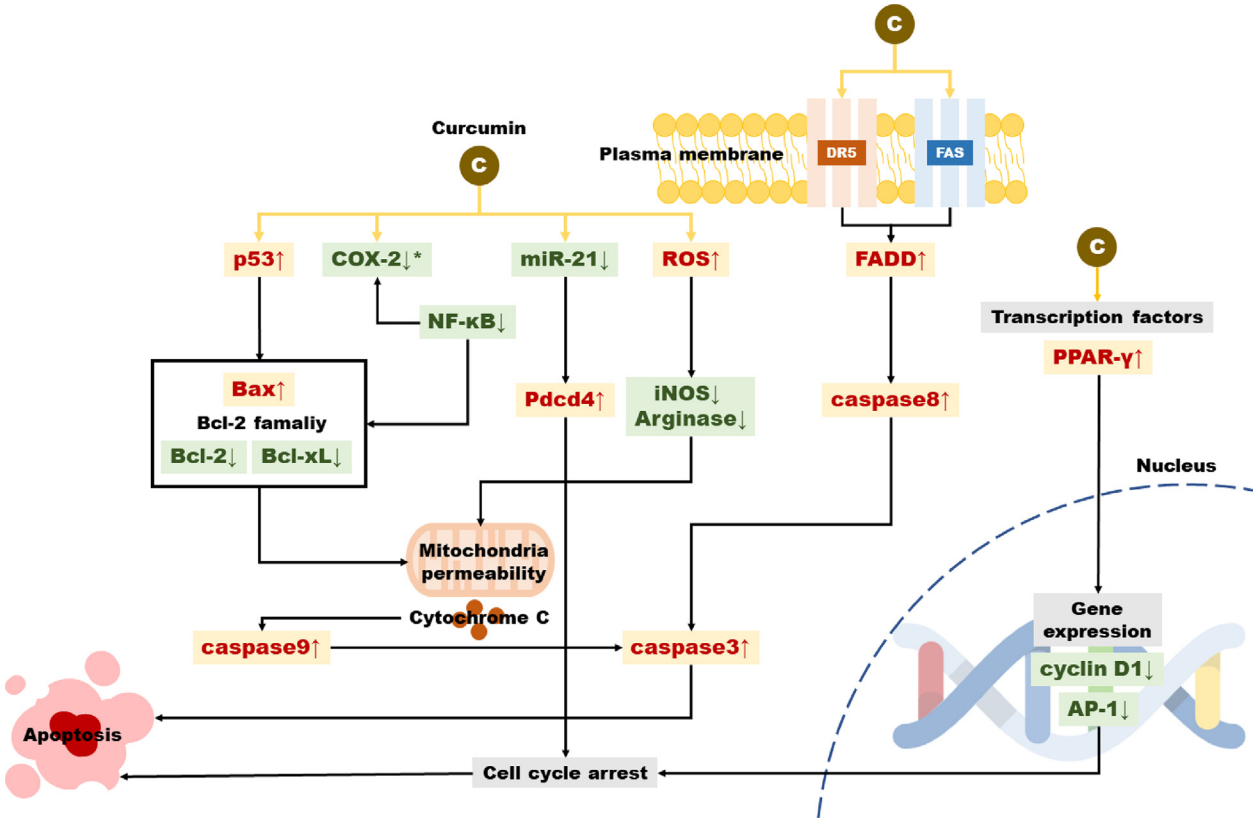

Fig. 3. Mechanism of induction of apoptosis by curcumin in colorectal cancer.

of HCT116 colorectal cancer cells [76]. In an *in vivo* model, curcumin significantly reduced aberrant crypt foci (ACF) and iNOS expression and arginase activity in 1,2-dimethylhydrazine (DMH)-induced ACF mice [77]. Furthermore, a curcumin-supplemented diet increased survival, decreased colon weight/length ratio, and decreased tumour burden in rats with AOM-induced colon cancer [78]. Although curcumin seems effective in preventing or treating colon cancer *in vivo* and *in vitro*, oral administration of curcumin results in its rapid metabolism, and approximately 60–70% of the compound is excreted in the faeces [67]. In clinical trials, quantifiable serum levels are not achieved until high doses are administered [69]. This observation can be attributed to the low bioavailability of curcumin. Because of the limited clinical effects of curcumin alone [79], current studies tends to increase the bioavailability of curcumin or administer it as an adjuvant treatment [80]. In an *in vivo* study in HCT116 xenograft nude mice, curcumin targeted NF-κB and improved the response of radiation therapy to colorectal cancer [81]. Another *in vitro* model study confirmed that curcumin prevented the proliferation and post-irradiation clonogenic survival of multiple colorectal cancer cell lines by suppressing radiation-induced NF-κB activation [82]. In addition to radiation therapy, curcumin combined with chemotherapy has been extensively studied. In a study evaluating a combination treatment regimen of 5-fluorouracil (5-FU) and curcumin in colorectal cancer cells, cell cycle analysis revealed that treatment with curcumin and 5-FU led to accumulation of colorectal cancer cells in the S cell cycle phase and induction of apoptosis [83]. In another study, when compared with treatment with 5-FU alone, pre-treatment with curcumin significantly enhanced the effect of 5-FU on colorectal cancer cells [84].

3.5. Other physiological activities

Curcumin has potential in the treatment of a variety of cancers in addition to colorectal cancer. Prostate cancer is the second most commonly diagnosed cancer in men, and ranks fifth as the leading cause of death globally [85]. The current mainstream treatment methods of localised and androgen-dependent prostate cancer (ADPC) include hormonal treatment, surgery, and radiotherapy. However, these cancerous cells progress to androgen-independent prostate cancer (AIPC) over

Table 1. Effects of curcumin in colon cancer.

Model	Curcumin dose/ concentration	Affected signalling pathways	Mechanism	Reference
Clinical trial	450, 1800, 3600 mg/day	Curcumin reduces the adenoma burden in patients with colorectal cancer.	M_1G ↓ COX-2 -	[72]
In vivo Female F344 rats	2% mixed with daily diet	Curcumin prevents colon cancer in rodent models.	M_1G ↓ COX-2 ↓	[73]
In vitro HCT116	10 μM	Curcumin regulates miR-21, tumour growth, invasion, and metastasis of colorectal cancer.	AP-1 binding ↓ miR-21 ↓ Pdcd4 ↑	[75]
In vitro HCT116	10 μM	Curcumin induces cell cycle arrest and cellular senescence and down-regulates autophagosome formation.	ATG5 protein ↓ Cleavage of PARP ↑ Cell viability ↓ p53 ↑	[76]
In vivo Specific pathogen-free wild-type (WT) 129/SvEv mice Germ-free*Il10*$^{-/-}$mice	0.05% and 1% diets	Curcumin reduced or eliminated colonic tumour burden in AOM-induced colon cancer.	Tumour burden ↓ Colon weight/length ratio ↓ bacterial richness ↑	[78]
In vivo Swiss-Webster male mice	60 mg/kg	Curcumin modulates polyamines synthesis, morphological changes, oxidative stress, and alters homeostasis and tumour development.	Arginase Activity ↓ ACF formation ↓ Nitrotyrosine ↑ formation↓ Apoptosis ↑ HES-1 ↑ TGF-β ↑ Lipid peroxides ↓	[77]
In vivo HCT116 xenograft in nude mice	1 g/kg	Curcumin targets NF-κB to improve the response of radiation therapy.	Tumour regrowth ↓ Ki-67 proliferation index ↓ NF-κB activity ↓	[81]
In vitro HCT116 HT29 SW620	25 μM	Curcumin inhibits the proliferation and post-irradiation clonogenic survival of multiple colorectal cancer cell lines.	NF-kB activity ↓ BCL-xL ↓ BCL-1 ↓ Cyclin D1 ↓ COX-2 ↓	[82]
In vitro HCT116	20 μM	Curcumin enhances anti-proliferation and induces apoptosis in 5-FU treatment.	Caspase-8 ↑ Caspase-9 ↑ Caspase-3 ↑ Bax ↑ PARP ↑ BCL-xL ↓ Cyclin D1 ↓	[83]
In vitro HCT116	20 μM	Curcumin enhances chemosensitivity in 5-FU treatment.	Cell growth ↓ Colonspheres ↓ Apoptosis ↑	[84]

time and are no longer dependent on hormones [86]. Research has shown that curcumin inhibits the proliferation of prostate cancer cells and induces apoptosis [87] by interfering with several cellular pathways, including mitogen-activated protein kinase (MAPK), epidermal growth factor receptor (EGFR), and NF-κB [86,88]. The dilemmas faced in the treatment of breast cancer and prostate cancer are similar. After lumpectomy, radiotherapy, chemotherapy, and endocrine therapy, the recurrence rate of breast cancer remains high [89]. A study evaluated the effects of curcumin on cell cycle regulatory proteins, matrix metalloproteinases (MMPs), and NF-κB in MDA-MB-231 and BT-483 breast cancer cells. The results indicated that curcumin exhibited antiproliferative activity by down-regulating NF-κB [90]. Furthermore, curcumin has *in vivo* and *in vitro* effects in head and neck squamous cell carcinoma [91,92] and ovarian cancer through similar pathways [93,94].

In addition to the aforementioned functionalities, curcumin can reduce mouse oxidized protein,

cytokine IL-1β, astrocyte skeleton protein glial fibrillary acidic protein (GFAP), insoluble and soluble amyloid β-amyloid expression, and inhibit microgliosis to prevent Alzheimer's disease [95]. Furthermore, curcumin has *in vivo* antibacterial activity that can prevent and restore damage to the stomach caused by *Helicobacter pylori* [96]. Recent studies have reported the antiparasitic properties of curcuminoids (DMC and BDMC), which inhibited TGR activity, giving them the ability to fight *Taenia crassiceps* cysticercosis. Moreover, curcuminoids (including curcumin, DMC, and BDMC) can effectively inhibit neuraminidase activity to inhibit influenza viruses H1N1 and H9N2. Of note, several studies have stated that curcumin has the potential to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [97,98]. In addition, studies have mentioned that curcumin can inhibit autoimmune deficiency syndrome (AIDS), Parkinson's disease, allergies, cardiovascular diseases, and other physiological activities [11,99−102].

4. Application dilemma

Although curcumin has been shown to exhibit therapeutic and protective effects in various diseases, studies have shown that oral administration of 8 g/day of curcumin will only results in a plasma concentration of about 2.5 ng/mL [103]. This is due to the low water solubility and bioavailability of curcumin, and it is also degraded by the digestive system or converted into metabolites [104]. In general, higher doses may be more effective, but further consideration should be given to potential side effects.

Turmeric and curcumin have been used for decades as food additives, supplements, and medicines. According to reports by the Joint United Nations and World Health Organization Expert Committee on Food Additives (JECFA) and European Food Safety Authority (EFSA), the ADI of curcumin is 0−3 mg/kg body weight [10,105,106]. A long-term curcumin carcinogenicity study by the National Toxicology Program (NTP) revealed that the incidence of malignant neoplastic lesions (carcinomas) did not reach statistical significance and the observed effects were not dose-dependent, were in agreement with historical control values, and were not consistent across sexes and/or species; these observations eliminated concerns of genotoxicity [107]. Nevertheless, there are still some records of side effects in previous research. For example, diarrhoea, headache, rash, and yellow stool have been reported after oral administration of 500−12000 mg of curcumin; however, the same study stated that a daily intake of up to 12000 mg of curcumin has no harmful effects on individuals [108]. In another study, dose-limiting toxicity was not observed up to 3600 mg of curcumin. Still, patients reported two types of gastrointestinal adverse events, and a rise in serum alkaline phosphatase levels was also observed [109]. These concerns make administering high doses of curcumin less optimal. At present, the most studied strategy is the modification of curcumin and its delivery systems, using nanoparticles [110−112], micellization [113−115], and chemical conjugation [104,116−118]. The application of these technologies can improve the stability, solubility, *in vivo* absorption, biological activity, and safety of curcumin without increasing the dosage. Recent studies have begun to explore more strategies that can help improve the application of curcumin.

5. Novel application strategies

5.1. Curcumin analogues and related substances

The main functionalities of curcumin are derived from three reactive functional groups on the chemical structure, including one diketone moiety and two phenolic groups. These groups determine the biological activity of curcumin, including hydrogen donation reactions, reversible and irreversible nucleophilic addition reactions, hydrolysis, degradation, and enzymatic reactions [27]. Analogues or degradation products that are different from curcumin can also promote or reduce its functionality. Therefore, direct supplementation of curcumin analogues or degradation products may be a potential strategy to improve its effectiveness (Table 2).

5.1.1. Curcumin analogues

DMC and BDMC are the most abundant curcuminoids after curcumin, and research has shown that their functions may be better than curcumin [119]. For example, in the MDA-MB-231 human breast cancer cell line, DMC exhibited anti-invasive activity by modulating the expression of invasion-associated proteins [120]. In human glioma U87 cells, DMC bound more efficiently to the Bcl-2 putative active site and induced Bcl-2-mediated G2/M arrest and apoptosis [121]; similar results were observed in MCF-7 cells [122]. In HER2-overexpressing bladder cancer cells, it significantly suppressed the expression of HER2, preferentially inhibited cell proliferation, and induced apoptosis. In human cervical cancer HeLa cells, it suppressed migration and invasion via inhibition of NF-κB pathways [123].

Table 2. Activities of curcumin analogues, metabolites, and degradation products.

Curcumin analogues/ related substances	Bioactivity	Reference
Demethoxycurcumin (DMC)	• Suppressed migration and invasion in MDA-MB-231 human breast cancer cell line.	[120]
	• Induced Bcl-2-mediated G2/M arrest and apoptosis in human glioma U87 cells.	[121]
	• Exerted a cytostatic effect at G2/M in MCF-7 human breast tumour cells.	[122]
	• Inhibited cell proliferation and induced apoptosis in HER2-overexpressing bladder cancer cells.	[125]
	• Increased the sensitivity of cisplatin-resistant cancer cells.	[124]
	• The inhibition and degradation activity of bacteria.	[126,127]
Bisdemethoxycurcumin (BDMC)	• Cytotoxic against human ovarian cancer OVCAR-3 cells.	[128]
	• Prevented DMH-induced colon carcinogenesis.	[129]
	• Accelerated gastric ulcer healing.	[130]
	• Induced apoptotic cell death in Hep 3B cells.	[131]
	• Inhibited MCF-7 breast cancer cell proliferation.	[132]
	• Inhibited adipogenesis in 3T3-L1 preadipocytes and suppressed obesity.	[133]
	• Used as an antibacterial agent to relieve antibiotic resistance.	[134]
Tetrahydrocurcumin (THC)	• Ameliorated oxidative stress-induced renal injury.	[139]
	• Alleviated the oxidative stress caused by cholesterol intake.	[140]
	• Antioxidant and vascular protective effects in L-NAME-induced hypertension.	[141]
	• Ameliorated insulin resistance in fatty acid-induced hepatic steatosis.	[142]
	• Preventative effects on azoxymethane-induced colon carcinogenesis.	[143]
	• Anti-angiogenic effects on implanted hepatocellular carcinoma.	[144]
Ferulic acid	• Improved cardiovascular and kidney structure and function in hypertensive rats.	[148]
	• Attenuated acute renal injury induced by cisplatin.	[149]
	• Improved cognitive function.	[150–152]
	• Inhibited cell proliferation and invasion in HeLa and CaSki cervical cancer cells.	[153]
Vanillin	• Induced G0/G1 arrest and apoptosis in human HT-29 colon cancer cells.	[156]
	• Induced apoptosis in human hepatic carcinoma HepG2 and neuroblastoma SH-SY5Y cells.	[157]
	• Reduced apoptosis and exerted neuroprotective effects in rats with spinal cord injury.	[158]
	• Promoted early neurofunctional development in neonatal rats.	[159]
Calebin A	• Protected cells from beta-amyloid insult.	[161]
	• Inhibited cell growth and induced apoptosis in drug-resistant human gastric cells.	[162]
	• Regulated survival and inflammatory gene products, leading to inhibition of cell growth and chemosensitisation.	[160]
	• Suppressed NF-κB-mediated proliferation, invasion, and metastasis of human colorectal cancer cells.	[163]

Furthermore, some studies reported that DMC increased the sensitivity of cisplatin-resistant cancer cells, such as A549 human alveolar basal epithelial adenocarcinoma cells [124] and HER2-over-expressing bladder cancer cells [125]. In addition to its antagonistic effects on specific cancer cells, DMC has potential as an antimicrobial against pathogens such as *Candida albicans* ATCC 10231 [126] and methicillin-resist *Staphylococcus aureus* [127].

Compared with DMC, BDMC has two fewer methyl groups, which means it has better water solubility and bioavailability. The structure of BDMC is responsible for its loss of antioxidant activity [36]; however, it has an increased anti-inflammatory effect [50]. However, there appears to be a trend in other specific conditions. In human ovarian cancer OVCAR-3 cells, BDMC exhibited higher cytotoxic activity than curcumin and DMC against ovarian cancer cells [128]. In a DMH-induced carcinogenesis *in vivo* model, intragastric BDMC significantly reduced the number and size of tumours in the colon in addition to hepatic oxidative stress [129]. In a gastric ulcer model, BDMC suppressed iNOS-mediated inflammation and directly accelerated gastric ulcer healing [130]. In human liver cancer Hep3B cells, BDMC decreased cell viability and induced S phase arrest, DNA damage, and cell apoptosis [131]. In human breast cancer MCF-7 cells, BDMC increased the concentration of ROS in the cells, inhibiting cancer cell proliferation [132]. In addition to its anti-cancer effects, BDMC has anti-obesity effects; it inhibited adipogenesis in 3T3-L1 preadipocytes and suppressed obesity in a high-fat-diet-induced *in vivo* model [133]. Finally, BDMC has antimicrobial effects and may be a potential natural antibacterial agent to ameliorate antibiotic resistance [134]. DMC and BDMC are potent and are comparable to curcumin in many studies; however, their properties are more anti-inflammatory than purely anti-oxidative due to chemical structural factors, and both have better water solubility and bioavailability than curcumin [135]. These two compounds can be used as alternative strategies where curcumin fails.

THC is one of the primary metabolites of curcumin; it lacks an α,β-unsaturated carbonyl moiety [136] and has different spectral properties from curcumin, usually producing white crystals at room temperature. Due to its higher bioavailability and different biological activity and molecular mechanisms than curcumin, some studies suggest that it has more potential for development than curcumin [137]. THC is well known for its anti-oxidative activity. During the anti-oxidative process, the β-diketone moiety C–C bond will be cleaved and exhibit anti-oxidative activity [138]. THC can be used against ferric nitrilotriacetate (Fe-NTA)-induced oxidative renal damage in male ddY mice [139], and it can effectively alleviate oxidative stress in cholesterol-fed rabbits [140]. Furthermore, THC has shown antioxidative and vascular protective effects in L-NAME-induced hypertension in rats [141]. In fatty acid-induced hepatic steatosis, THC ameliorated insulin resistance in HepG2 cells [142]. Some studies have shown that THC has partial anticancer effects, such as preventing azoxymethane-induced colon carcinogenesis [143], and anti-angiogenic effects on implanted hepatocellular carcinoma in nude mice [144]. Overall, THC is more effective than curcumin in oxidative stress-related diseases due to its excellent antioxidant effect. Overall, the chemical structure of THC enhances its antioxidant effects; therefore, it can be more effective in oxidative stress-related diseases.

5.1.2. Curcumin related substances

Ferulic acid and vanillin were structurally identified as curcumin-derived radical reaction products [145], and both have higher water solubility as curcumin degradation products [146]. Although studies have highlighted that the two compounds may not be major curcumin degradation products [147], as long-studied and biologically active phenolic compounds, they may still retain some functional properties of turmeric after degradation. Research has confirmed that ferulic acid improves cardiovascular and kidney structure and function in hypertensive rats [148] and has the ability to attenuate acute renal injury induced by cisplatin [149]. Furthermore, studies have shown that ferulic acid improves cognitive function [150–152]. Regarding anti-cancer activity, ferulic acid can significantly inhibit cell proliferation and invasion in HeLa and CaSki, two cervical cancer cells [153]. Ferulic acid may not possess as effective biological activity as curcumin, but its use as an adjunct to curcumin can compensate for its mechanical deficiencies [150].

Although vanillin and ferulic acid have similar structures, vanillin is more remarkable in food applications. Like curcumin, it is a common flavour additive and is probably the most widely used flavouring agent for sweet foods. Furthermore, its antioxidant activity helps stabilise the oxidation and degradation of food components [154]. Vanillin and ferulic acid have similar biological activity, including antioxidant, anti-inflammatory, neuroprotective, and anticancer properties [155]. In human colon cancer HT-29 cells, vanillin arrests the cell cycle in G0/G1 phase and significantly increases apoptosis in the sub-G0 phase [156]; this effect has also been reported in human hepatic carcinoma and neuroblastoma cells [157]. Recent studies have found that, in addition to its neuroprotective effects [158], vanillin promotes early neurological development and improves hypoxic-ischaemic brain damage in neonatal rats [159]. More notably, due to its lack of toxicity in rats [162], vanillin is well-suited for curcumin application strategies.

Calebin A (4-[3-methoxy-4-hydroxyphenyl]-2-oxo-3-enebutanyl-3-[3-methoxy-4- hydroxyphenyl] propenoate) is a compound that had not been isolated or identified in turmeric until recently [160]. It was originally identified to protect cells from beta-amyloid insult [161]. Follow-up studies found that it can inhibit cell growth and induce apoptosis in drug-resistant human gastric carcinoma MDR cell line SGC7901/VINCRISTINE. It resulted in a reduction in S phase and G2/M phase arrest and modulated the activity of MAPK family members [162]. Studies have reported that calebin A inhibits the NF-κB activation pathway via interaction with p65 and enhances multiple cancer cell apoptosis [160]. In addition, one study reported that calebin A had anti-proinflammatory and anti-tumour activity in TNF-β-stimulated colorectal cancer cells [163] and enhanced the effect of the anticancer drug 5-FU [164]. Despite the sparsity of research on calebin A, according to the current literature, it has potential in cancer prevention and treatment.

In conclusion, the strategy of applying curcumin analogues and related substances to replace curcumin is based on its structural activity. Ideally, it increases bioavailability, leaving the active structure unchanged. According to the reported results, curcumin analogues and related substances have many different efficacy aspects and application potential.

5.2. Gut microbiota regulation

The gut microbiota is an entire population of microorganisms located in the gut [165]. It is associated with a variety of human diseases, including intestinal disorders, such as inflammatory bowel disease (IBD) [166] and irritable bowel syndrome (IBS) [167],

and metabolic diseases, such as obesity and diabetes [168–170]. The bioavailability of curcumin is extremely poor; however, studies have pointed out that with administered orally, curcumin has preferential distribution and accumulation in the intestinal tract and can reach the level of biological activity [171]. In the intestinal tract, curcumin has a regulatory impact on the gut microbiota, influencing microbial abundance, variety, and composition [172]. Curcumin significantly increases the proportion of beneficial microbiota relative to pathogenic microbiota by increasing the abundance of *Bifidobacterium, Lactobacillus*, and butyrate-producing bacteria and reducing the abundance of Prevotellaceae, Coriobacteriaceae, enterobacteria, and *Enterococcus*. In addition to its anti-inflammatory and anti-colorectal cancer activity, these changes in the intestinal microbiota can explain the immunomodulatory and anti-hyperlipidaemic effects of curcumin [173]. Furthermore, the reduction of Prevotellaceae, Bacteroidaceae, and Rikenellaceae, which are often linked to the onset of systemic diseases [172], demonstrates the potential of curcumin as a dietary supplement. One study reported that curcumin dramatically shifted the overall structure of a high-fat diet, disrupted gut microbiota towards that of lean rats fed a normal diet, and altered the gut microbial composition [174]. Some studies suggest that this can be attributed to the curcumin promotes a shift from pathogenic to beneficial bacterial strains and further affect intestinal metabolisms, such as fatty acids [175,176] and bile acid [176,177].

In addition to directly regulating the intestinal microbiota, leading to changes in microbial richness, diversity, and composition, curcumin is biotransformed into various metabolites, such as dihydrocurcumin (DHC), THC, and ferulic acid by intestinal microbiota via demethylation, hydroxylation, demethoxylation, and decomposition [175,178]. For example, studies have shown that *Escherichia coli* from the intestinal tract will sequentially convert curcumin into DHC and THC [179]. Take the THC mentioned in Section 5.1.1 as an example, the amount of THC and its conjugates (as sulfates and glucuronides) were higher in the liver and serum after dietary administration of either curcumin or THC compared to the amount of curcumin and its conjugates. Therefore, THC is more readily absorbed from the gastrointestinal tract than curcumin [139]. In addition to this, some studies have reported that many of these metabolites are more biologically active and bioavailable than curcumin [175,180,181]. The above research note that curcumin not only achieves health benefits by regulating gut microbiota, but also by being metabolized by these microorganisms to produce bioavailable metabolites with similar effects to curcumin, thus increasing health benefits [173].

5.3. Exosome vesicles

Previous studies on improving curcumin bioavailability have focused on chemical or microbial modification, binding phospholipids to form complexes, entrapment using liposomes, and nanoparticles as carriers [80,104,119,182–184]. Exosomes are extracellular microvesicles with a particle size between 30 nm and 150 nm that carry a large number of proteins, lipids, RNA, and DNA and can be used as intercellular messaging tools [182]. Because exosomes have the ability to shuttle in and out of cells, the use of exosomes as nano-drug carriers has potential for new therapeutic applications [185]. In addition, many studies have suggested that exosomes as drug carriers have the potential to overcome the technology-related limitations of traditional nanoparticles [186]. For example, exosomes have a longer circulating half-life, are more easily internalised by cells, and can be linked to one or more tumour-recognition ligands to enhance their targeting capabilities, which make exosomes ideal nanoparticle drug delivery vesicles [187]. Many studies have used exosomes to coat curcumin and deliver it to targeted cells via membrane fusion [182,188].

The coating of functional components with exosomes can be divided into two methods: active and passive. The passive method only requires co-culture with functional components and cells or purification of exosomes from the culture medium of the cell culture and mixing them so that functional components can diffuse into exosomes via concentration difference (Fig. 4) [189]. In 2010, a study combined exosomes from mouse lymphoma with curcumin to produce curcumin-coated exosomes [182]. Subsequent studies have confirmed that curcumin treatment of exosomes produced by chronic myelogenous leukaemia (CML) can attenuate their ability to promote angiogenesis and regulate endothelial barrier tissue, thereby affecting tumour progression [190]. Another study used curcumin to intervene in mouse brain endothelial cells (MBECs) to produce curcumin-containing exosomes. It was confirmed that curcumin could ameliorate oxidative stress during endothelial cell damage and regulate tightness. Expression of connexins (ZO-1, claudin-5, and occludin) and adhesion junction protein (VE-cadherin) and increase endothelial cell permeability [191]. In contrast, the active method is more

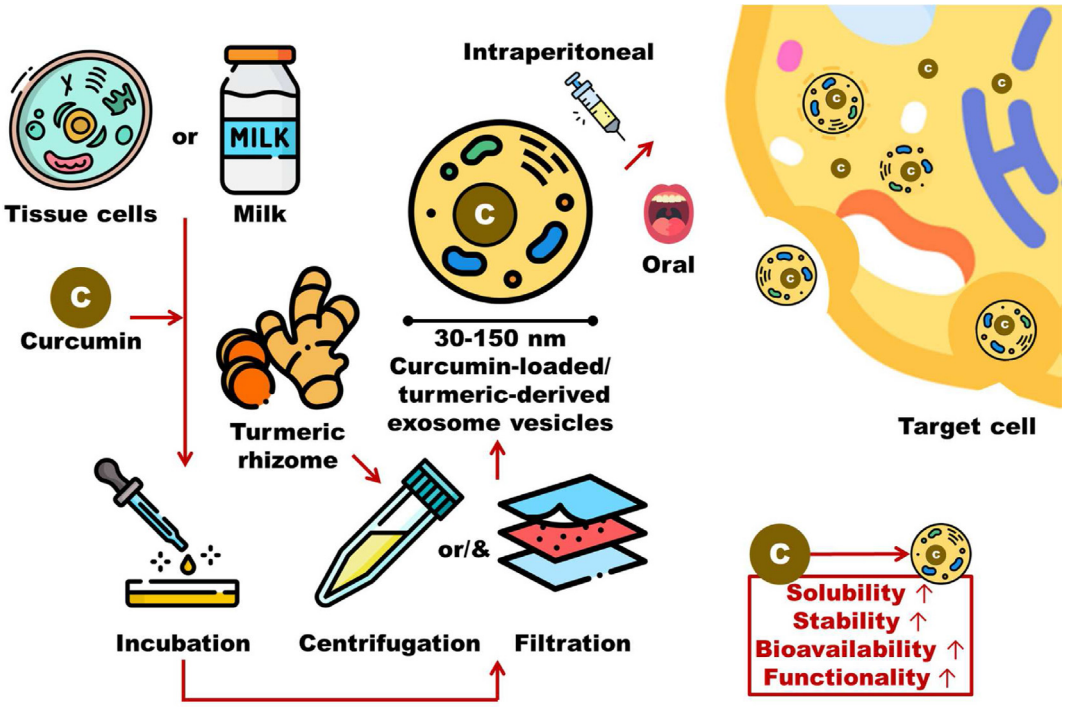

Fig. 4. Curcumin-loaded exosome vesicle preparation and its advantages.

complicated and involves techniques such as ultrasound, extrusion, membrane perforation, or repeated freezing and thawing [192].

Studies have shown that curcumin coating of exosomes effectively increases the concentration of curcumin in the plasma and improve bioavailability. Injection of 100 mg/kg body weight of curcumin in exosomes can reach the highest plasma concentration in 30 min (1250 ng/mL), which is 5–10-fold that of curcumin alone [182]. Other studies have confirmed that exosome coating effectively improves the solubility, stability, and bioavailability of curcumin [183,184]. In recent years, the exosome drug delivery system has been an emerging research field that is a promising and novel concept. Existing literature clarifies that exosome-coated curcumin has anti-inflammatory [182,184], endothelial protective [183,191], neuroprotective [193], and anti-cancer properties [194]. Turmeric-derived exosome-like vesicle-related research has begun to attract attention. Turmeric-derived nanoparticles (TDNPs) or turmeric-derived nanovesicles (TNVs) isolated from turmeric can effectively alleviate colitis. Research indicates that oral administration of TDNPs prevents colitis and promotes wound repair in colitis [195]. Meanwhile, another study reported that oral administration of TNVs restored the damaged gut barrier, modulated gut microbiota, reshaped the macrophage phenotype, then increased its anti-inflammatory effect [196]. Compared with nanoparticle delivery systems, TDNPs and TNVs are natural colon-targeting therapeutics that have the advantages of low toxicity and ease of large-scale production. Although there are very few related studies, this is a topic with great potential for future research based on the current results.

6. Conclusion

Curcumin, the active component of *C. longa* extract, has been extensively studied in recent decades. These studies have confirmed its antioxidant, anti-inflammatory, anti-diabetes, and anti-cancer effects. However, the application of curcumin has been restricted by its low water solubility, which results in low cellular uptake, poor oral bioavailability, and low chemical stability. These factors make its clinical effectiveness and *in vivo* efficacy lower than its *in vitro* activity. Structural modification, synergistic combination therapy, and drug delivery systems are currently the most common solutions that are proven to increase the bioavailability of curcumin and improve its effectiveness. With the development of innovative technologies, there are an increasing number of strategies to solve this problem. For example, after passing through the digestive system and undergoing microbial metabolism, curcumin may be metabolised into a more biologically active form, thereby affecting overall body functions and

organs. Therefore, directly involving these metabolites or degradants may achieve more direct effects. In addition, curcuminoids and curcumin analogues provide similar biological activity but higher bioavailability because of their structural similarity to curcumin. We can also take advantage of the low bioavailability of curcumin and allow it to directly regulate gut microbiota, leading to changes in microbial richness, diversity, and composition. Finally, the application of an exosome vesicle delivery system, greatly improves the bioavailability of curcumin and provides the possibility of targeted therapy. Overall, these successful findings provide valuable information for the future study of curcumin. Furthermore, the potential function and development of curcumin should be established.

Conflict of interest

All authors declare that there are no conflicts of interest.

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References

[1] Chattopadhyay I, Biswas K, Bandyopadhyay U, Banerjee RK. Turmeric and curcumin: biological actions and medicinal applications. Curr Sci 2004:44–53.
[2] Amalraj A, Pius A, Gopi S, Gopi S. Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives–A review. J Tradit Complement Med 2017;7:205–33.
[3] Jayaprakasha GK, Jena BS, Negi PS, Sakariah KK. Evaluation of antioxidant activities and antimutagenicity of turmeric oil: a byproduct from curcumin production. Z Naturforsch C Biosci 2002;57:828–35.
[4] Lantz R, Chen G, Solyom A, Jolad S, Timmermann B. The effect of turmeric extracts on inflammatory mediator production. Phytomedicine 2005;12:445–52.
[5] Tilak JC, Banerjee M, Mohan H, Devasagayam T. Antioxidant availability of turmeric in relation to its medicinal and culinary uses. Phytother Res 2004;18:798–804.
[6] Naz S, Jabeen S, Ilyas S, Manzoor F, Aslam F, Ali A. Antibacterial activity of Curcuma longa varieties against different strains of bacteria. Pakistan J Bot 2010;42:455–62.
[7] Aggarwal BB, Yuan W, Li S, Gupta SC. Curcumin-free turmeric exhibits anti-inflammatory and anticancer activities: identification of novel components of turmeric. Mol Nutr Food Res 2013;57:1529–42.
[8] Li M, Yue GG-L, Tsui SK-W, Fung K-P, Bik-San Lau C. Turmeric extract, with absorbable curcumin, has potent anti-metastatic effect in vitro and in vivo. Phytomedicine 2018;46:131–41.
[9] Lima CF, Pereira-Wilson C, Rattan SI. Curcumin induces heme oxygenase-1 in normal human skin fibroblasts through redox signaling: relevance for anti-aging intervention. Mol Nutr Food Res 2011;55:430–42.
[10] JECFA. Sixty-first report of the Joint FAO/WHO Expert committee on food additives. 2004.
[11] Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol 2009;41:40–59.
[12] López-Lázaro M. Anticancer and carcinogenic properties of curcumin: considerations for its clinical development as a cancer chemopreventive and chemotherapeutic agent. Mol Nutr Food Res 2008;52:S103–27.
[13] Latruffe N. Natural products and inflammation. Multidisciplinary Digital Publishing Institute; 2017.
[14] Li R, Xiang C, Ye M, Li H-F, Zhang X, Guo D-A. Qualitative and quantitative analysis of curcuminoids in herbal medicines derived from Curcuma species. Food Chem 2011;126:1890–5.
[15] Li H-X, Zhang H-L, Zhang N, Wang N, Yang Y, Zhang Z-Z. Isolation of three curcuminoids for stability and simultaneous determination of only using one single standard substance in turmeric colour principles by HPLC with ternary gradient system. LWT–Food Sci Technol 2014;57:446–51.
[16] Poudel A, Pandey J, Lee H-K. Geographical discrimination in curcuminoids content of turmeric assessed by rapid UPLC-DAD validated analytical method. Molecules 2019;24:1805.
[17] Ashraf K, Mujeeb M, Ahmad A, Ahmad N, Amir M. Determination of curcuminoids in curcuma longa linn. By UPLC/Q-TOF–MS: an application in turmeric cultivation. J Chromatogr Sci 2015;53:1346–52.
[18] Osorio-Tobón JF, Carvalho PI, Barbero GF, Nogueira GC, Rostagno MA, de Almeida Meireles MA. Fast analysis of curcuminoids from turmeric (Curcuma longa L.) by high-performance liquid chromatography using a fused-core column. Food Chem 2016;200:167–74.
[19] Erpina E, Rafi M, Darusman LK, Vitasari A, Putra BR, Rohaeti E. Simultaneous quantification of curcuminoids and xanthorrhizol in Curcuma xanthorrhiza by high-performance liquid chromatography. J Liq Chromatogr Relat Technol 2017;40:635–9.
[20] (Taiwan) MoHaW. Taiwan Herbal Pharmacopeia (IV). 2021.
[21] Commission CP. The Pharmacopoeia of the People's Republic of China 2020 edition. 2020.
[22] Jiang T, Ghosh R, Charcosset C. Extraction, purification and applications of curcumin from plant materials-A comprehensive review. Trends Food Sci Technol 2021;112:419–30.
[23] Zhu J, Sanidad KZ, Sukamtoh E, Zhang G. Potential roles of chemical degradation in the biological activities of curcumin. Food Funct 2017;8:907–14.
[24] Somparn P, Phisalaphong C, Nakornchai S, Unchern S, Morales NP. Comparative antioxidant activities of curcumin and its demethoxy and hydrogenated derivatives. Biol Pharm Bull 2007;30:74–8.
[25] Jankun J, Wyganowska-Świątkowska M, Dettlaff K, Jelińska A, Surdacka A, Wątróbska-Świetlikowska D, et al. Determining whether curcumin degradation/condensation is actually bioactivation. Int J Mol Med 2016;37:1151–8.
[26] Pabon H. A synthesis of curcumin and related compounds. Recl Trav Chim Pays-Bas 1964;83:379–86.
[27] Priyadarsini KI. The chemistry of curcumin: from extraction to therapeutic agent. Molecules 2014;19:20091–112.
[28] Lampe V, Milobedzka J. Studien über curcumin. Ber Dtsch Chem Ges 1913;46:2235–40.
[29] Rao EV, Sudheer P. Revisiting curcumin chemistry part I: a new strategy for the synthesis of curcuminoids. Indian J Pharm Sci 2011;73:262–70.
[30] Venkateswarlu S, Ramachandra MS, Subbaraju GV. Synthesis and biological evaluation of polyhydroxycurcuminoids. Bioorg Med Chem 2005;13:6374–80.
[31] Barros L, Ferreira M-J, Queiros B, Ferreira IC, Baptista P. Total phenols, ascorbic acid, β-carotene and lycopene in

Portuguese wild edible mushrooms and their antioxidant activities. Food Chem 2007;103:413–9.
[32] Gülçin İ. Antioxidant and antiradical activities of L-carnitine. Life Sci 2006;78:803–11.
[33] Ak T, Gülçin İ. Antioxidant and radical scavenging properties of curcumin. Chem Biol Interact 2008;174:27–37.
[34] Halliwell B, Gutteridge JM. [1] Role of free radicals and catalytic metal ions in human disease: an overview. Methods Enzymol 1990;186:1–85.
[35] Wright JS. Predicting the antioxidant activity of curcumin and curcuminoids. J Mol Struct THEOCHEM 2002;591: 207–17.
[36] Morales NP, Sirijaroonwong S, Yamanont P, Phisalaphong C. Electron paramagnetic resonance study of the free radical scavenging capacity of curcumin and its demethoxy and hydrogenated derivatives. Biol Pharm Bull 2015;38:1478–83.
[37] Alderton WK, Cooper CE, Knowles RG. Nitric oxide synthases: structure, function and inhibition. Biochem J 2001; 357:593–615.
[38] Kim KM, Pae H-O, Zhung M, Ha H-Y, Ha YA, Chai K-Y, et al. Involvement of anti-inflammatory heme oxygenase-1 in the inhibitory effect of curcumin on the expression of pro-inflammatory inducible nitric oxide synthase in RAW264. 7 macrophages. Biomed Pharmacother 2008;62: 630–6.
[39] Chung H-T, Pae H-O, Choi B-M, Billiar TR, Kim Y-M. Nitric oxide as a bioregulator of apoptosis. Biochem Biophys Res Commun 2001;282:1075–9.
[40] Oh G-S, Pae H-O, Lee B-S, Kim B-N, Kim J-M, Kim H-R, et al. Hydrogen sulfide inhibits nitric oxide production and nuclear factor-κB via heme oxygenase-1 expression in RAW264. 7 macrophages stimulated with lipopolysaccharide. Free Radic Biol Med 2006;41:106–19.
[41] Willoughby D, Moore A, Colville-Nash P, Gilroy D. Resolution of inflammation. Int J Immunopharmacol 2000;22: 1131–5.
[42] Oh G-S, Pae H-O, Choi B-M, Chae S-C, Lee H-S, Ryu D-G, et al. 3-Hydroxyanthranilic acid, one of metabolites of tryptophan via indoleamine 2, 3-dioxygenase pathway, suppresses inducible nitric oxide synthase expression by enhancing heme oxygenase-1 expression. Biochem Biophys Res Commun 2004;320:1156–62.
[43] Manikandan R, Beulaja M, Thiagarajan R, Priyadarsini A, Saravanan R, Arumugam M. Ameliorative effects of curcumin against renal injuries mediated by inducible nitric oxide synthase and nuclear factor kappa B during gentamicin-induced toxicity in Wistar rats. Eur J Pharmacol 2011; 670:578–85.
[44] Jung KK, Lee HS, Cho JY, Shin WC, Rhee MH, Kim TG, et al. Inhibitory effect of curcumin on nitric oxide production from lipopolysaccharide-activated primary microglia. Life Sci 2006;79:2022–31.
[45] Ramsewak R, DeWitt D, Nair M. Cytotoxicity, antioxidant and anti-inflammatory activities of curcumins I–III from Curcuma longa. Phytomedicine 2000;7:303–8.
[46] Liu L, Shang Y, Li M, Han X, Wang J, Wang J. Curcumin ameliorates asthmatic airway inflammation by activating nuclear factor-E2-related factor 2/haem oxygenase (HO)-1 signalling pathway. Clin Exp Pharmacol Physiol 2015;42:520–9.
[47] Divya CS, Pillai MR. Antitumor action of curcumin in human papillomavirus associated cells involves downregulation of viral oncogenes, prevention of NFkB and AP-1 translocation, and modulation of apoptosis. Mol Carcinog 2006;45:320–32.
[48] Perrone D, Ardito F, Giannatempo G, Dioguardi M, Troiano G, Lo Russo L, et al. Biological and therapeutic activities, and anticancer properties of curcumin. Exp Ther Med 2015;10:1615–23.
[49] Edwards RL, Luis PB, Varuzza PV, Joseph AI, Presley SH, Chaturvedi R, et al. The anti-inflammatory activity of curcumin is mediated by its oxidative metabolites. J Biol Chem 2017;292:21243–52.
[50] Edwards RL, Luis PB, Nakashima F, Kunihiro AG, Presley S-H, Funk JL, et al. Mechanistic differences in the inhibition of NF-κB by turmeric and its curcuminoid constituents. J Agric Food Chem 2020;68:6154–60.
[51] Gordon ON, Luis PB, Ashley RE, Osheroff N, Schneider C. Oxidative transformation of demethoxy-and bisdemethoxycurcumin: products, mechanism of formation, and poisoning of human topoisomerase IIα. Chem Res Toxicol 2015;28:989–96.
[52] Association AD. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2021. Diabetes Care 2021;44:S15–33.
[53] Maradana MR, Thomas R, O'Sullivan BJ. Targeted delivery of curcumin for treating type 2 diabetes. Mol Nutr Food Res 2013;57:1550–6.
[54] Lovshin JA, Drucker DJ. Incretin-based therapies for type 2 diabetes mellitus. Nat Rev Endocrinol 2009;5:262–9.
[55] Fujiwara H, Hosokawa M, Zhou X, Fujimoto S, Fukuda K, Toyoda K, et al. Curcumin inhibits glucose production in isolated mice hepatocytes. Diabetes Res Clin Pract 2008;80: 185–91.
[56] Sharma S, Kulkarni SK, Chopra K. Curcumin, the active principle of turmeric (Curcuma longa), ameliorates diabetic nephropathy in rats. Clin Exp Pharmacol Physiol 2006;33: 940–5.
[57] Takikawa M, Kurimoto Y, Tsuda T. Curcumin stimulates glucagon-like peptide-1 secretion in GLUTag cells via Ca2+/calmodulin-dependent kinase II activation. Biochem Biophys Res Commun 2013;435:165–70.
[58] Tsuda T. Curcumin as a functional food-derived factor: degradation products, metabolites, bioactivity, and future perspectives. Food Funct 2018;9:705–14.
[59] Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. Diabetes Care 2012;35:2121–7.
[60] Wong RS. Apoptosis in cancer: from pathogenesis to treatment. J Exp Clin Cancer Res 2011;30:1–14.
[61] Bauer JH, Helfand SL. New tricks of an old molecule: lifespan regulation by p53. Aging Cell 2006;5:437–40.
[62] Tomeh MA, Hadianamrei R, Zhao X. A review of curcumin and its derivatives as anticancer agents. Int J Mol Sci 2019; 20:1033.
[63] Balasubramanian S, Eckert RL. Curcumin suppresses AP1 transcription factor-dependent differentiation and activates apoptosis in human epidermal keratinocytes. J Biol Chem 2007;282:6707–15.
[64] Jung EM, Lim JH, Lee TJ, Park J-W, Choi KS, Kwon TK. Curcumin sensitizes tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through reactive oxygen species-mediated upregulation of death receptor 5 (DR5). Carcinogenesis 2005;26:1905–13.
[65] Ravindran J, Prasad S, Aggarwal BB. Curcumin and cancer cells: how many ways can curry kill tumor cells selectively? AAPS J 2009;11:495–510.
[66] Labianca R, Beretta G, Gatta G, De Braud F, Wils J. Colon cancer. Crit Rev Oncol Hematol 2004;51:145–70.
[67] Selvam C, Prabu SL, Jordan BC, Purushothaman Y, Umamaheswari A, Zare MSH, et al. Molecular mechanisms of curcumin and its analogs in colon cancer prevention and treatment. Life Sci 2019;239:117032.
[68] Carrato A. Adjuvant treatment of colorectal cancer. Gastrointest Cancer Res 2008;2:S42.
[69] Johnson JJ, Mukhtar H. Curcumin for chemoprevention of colon cancer. Cancer Lett 2007;255:170–81.
[70] Bäck M, Yin L, Ingelsson E. Cyclooxygenase-2 inhibitors and cardiovascular risk in a nation-wide cohort study after the withdrawal of rofecoxib. Eur Heart J 2012;33:1928–33.
[71] Lévesque LE, Brophy JM, Zhang B. The risk for myocardial infarction with cyclooxygenase-2 inhibitors: a population study of elderly adults. Ann Intern Med 2005;142:481–9.
[72] Garcea G, Berry DP, Jones DJ, Singh R, Dennison AR, Farmer PB, et al. Consumption of the putative

chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. Cancer Epidemiol Biomark Prev 2005;14:120–5.
[73] Sharma RA, Ireson CR, Verschoyle RD, Hill KA, Williams ML, Leuratti C, et al. Effects of dietary curcumin on glutathione S-transferase and malondialdehyde-DNA adducts in rat liver and colon mucosa: relationship with drug Levels1. Clin Cancer Res 2001;7:1452–8.
[74] Ireson C, Orr S, Jones DJ, Verschoyle R, Lim C-K, Luo J-L, et al. Characterization of metabolites of the chemopreventive agent curcumin in human and rat hepatocytes and in the rat in vivo, and evaluation of their ability to inhibit phorbol ester-induced prostaglandin E2 production. Cancer Res 2001;61:1058–64.
[75] Mudduluru G, George-William JN, Muppala S, Asangani IA, Kumarswamy R, Nelson LD, et al. Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. Biosci Rep 2011;31:185–97.
[76] Mosieniak G, Adamowicz M, Alster O, Jaskowiak H, Szczepankiewicz AA, Wilczynski GM, et al. Curcumin induces permanent growth arrest of human colon cancer cells: link between senescence and autophagy. Mech Ageing Dev 2012;133:444–55.
[77] Bounaama A, Djerdjouri B, Laroche-Clary A, Le Morvan V, Robert J. Short curcumin treatment modulates oxidative stress, arginase activity, aberrant crypt foci, and TGF-β1 and HES-1 transcripts in 1, 2-dimethylhydrazine-colon carcinogenesis in mice. Toxicology 2012;302:308–17.
[78] McFadden R-MT, Larmonier CB, Shehab KW, Midura-Kiela M, Ramalingam R, Harrison CA, et al. The role of curcumin in modulating colonic microbiota during colitis and colon cancer prevention. Inflamm Bowel Dis 2015;21:2483–94.
[79] Cruz-Correa M, Hylind LM, Marrero JH, Zahurak ML, Murray-Stewart T, Casero Jr RA, et al. Efficacy and safety of curcumin in treatment of intestinal adenomas in patients with familial adenomatous polyposis. Gastroenterology 2018;155:668–73.
[80] Carroll RE, Benya RV, Turgeon DK, Vareed S, Neuman M, Rodriguez L, et al. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. Cancer Prev Res 2011;4:354–64.
[81] Kunnumakkara AB, Diagaradjane P, Guha S, Deorukhkar A, Shentu S, Aggarwal BB, et al. Curcumin sensitizes human colorectal cancer xenografts in nude mice to γ-radiation by targeting nuclear factor-κB–regulated gene products. Clin Cancer Res 2008;14:2128–36.
[82] Sandur SK, Deorukhkar A, Pandey MK, Pabón AM, Shentu S, Guha S, et al. Curcumin modulates the radiosensitivity of colorectal cancer cells by suppressing constitutive and inducible NF-κB activity. Int J Radiat Oncol Biol Phys 2009;75:534–42.
[83] Shakibaei M, Mobasheri A, Lueders C, Busch F, Shayan P, Goel A. Curcumin enhances the effect of chemotherapy against colorectal cancer cells by inhibition of NF-κB and Src protein kinase signaling pathways. PLoS One 2013;8:e57218.
[84] Shakibaei M, Buhrmann C, Kraehe P, Shayan P, Lueders C, Goel A. Curcumin chemosensitizes 5-fluorouracil resistant MMR-deficient human colon cancer cells in high density cultures. PLoS One 2014;9:e85397.
[85] Rawla P. Epidemiology of prostate cancer. World J Oncol 2019;10:63.
[86] H Lajis N, Abas F, Othman I, Naidu R. Mechanism of anticancer activity of curcumin on androgen-dependent and androgen-independent prostate cancer. Nutrients 2020;12:679.
[87] Dorai T, Cao YC, Dorai B, Buttyan R, 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 2001;47:293–303.
[88] Mukhopadhyay A, Bueso-Ramos C, Chatterjee D, Pantazis P, Aggarwal BB. Curcumin downregulates cell survival mechanisms in human prostate cancer cell lines. Oncogene 2001;20:7597–609.
[89] Ramachandran C, Fonseca HB, Jhabvala P, Escalon EA, Melnick SJ. Curcumin inhibits telomerase activity through human telomerase reverse transcritpase in MCF-7 breast cancer cell line. Cancer Lett 2002;184:1–6.
[90] Liu Q, Loo WT, Sze S, Tong Y. Curcumin inhibits cell proliferation of MDA-MB-231 and BT-483 breast cancer cells mediated by down-regulation of NFκB, cyclinD and MMP-1 transcription. Phytomedicine 2009;16:916–22.
[91] Wang D, Veena MS, Stevenson K, Tang C, Ho B, Suh JD, et al. Liposome-encapsulated curcumin suppresses growth of head and neck squamous cell carcinoma in vitro and in xenografts through the inhibition of nuclear factor κB by an AKT-independent pathway. Clin Cancer Res 2008;14:6228–36.
[92] Wilken R, Veena MS, Wang MB, Srivatsan ES. Curcumin: a review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Mol Cancer 2011;10:1–19.
[93] Li-duan Z, Qiang-song T, Cui-huan W. Growth inhibition and apoptosis inducing mechanisms of curcumin on human ovarian cancer cell line A2780. Chin J Integr Med 2006;12:126–31.
[94] Yunos NM, Beale P, Yu JQ, Huq F. Synergism from sequenced combinations of curcumin and epigallocatechin-3-gallate with cisplatin in the killing of human ovarian cancer cells. Anticancer Res 2011;31:1131–40.
[95] Lim GP, Chu T, Yang F, Beech W, Frautschy SA, Cole GM. The curry spice curcumin reduces oxidative damage and amyloid pathology in an Alzheimer transgenic mouse. J Neurosci 2001;21:8370–7.
[96] De R, Kundu P, Swarnakar S, Ramamurthy T, Chowdhury A, Nair GB, et al. Antimicrobial activity of curcumin against Helicobacter pylori isolates from India and during infections in mice. Antimicrob Agents Chemother 2009;53:1592–7.
[97] Zahedipour F, Hosseini SA, Sathyapalan T, Majeed M, Jamialahmadi T, Al-Rasadi K, et al. Potential effects of curcumin in the treatment of COVID-19 infection. Phytother Res 2020;34:2911–20.
[98] Rocha FAC, de Assis MR. Curcumin as a potential treatment for COVID-19. Phytother Res 2020;34:2085–7.
[99] Aggarwal BB, Surh Y-J, Shishodia S. The molecular targets and therapeutic uses of curcumin in health and disease. Springer Science & Business Media; 2007.
[100] Kurup VP, Barrios CS. Immunomodulatory effects of curcumin in allergy. Mol Nutr Food Res 2008;52:1031–9.
[101] Gupta SC, Patchva S, Koh W, Aggarwal BB. Discovery of curcumin, a component of golden spice, and its miraculous biological activities. Clin Exp Pharmacol Physiol 2012;39:283–99.
[102] Shehzad A, Khan S, Sup Lee Y. Curcumin molecular targets in obesity and obesity-related cancers. Future Oncol 2012;8:179–90.
[103] Kunati SR, Yang S, William BM, Xu Y. An LC–MS/MS method for simultaneous determination of curcumin, curcumin glucuronide and curcumin sulfate in a phase II clinical trial. J Pharm Biomed Anal 2018;156:189–98.
[104] Xu X-Y, Meng X, Li S, Gan R-Y, Li Y, Li H-B. Bioactivity, health benefits, and related molecular mechanisms of curcumin: current progress, challenges, and perspectives. Nutrients 2018;10:1553.
[105] Kocaadam B, Şanlier N. Curcumin, an active component of turmeric (Curcuma longa), and its effects on health. Crit Rev Food Sci Nutr 2017;57:2889–95.
[106] Additives EPoF, Food NSat. Scientific Opinion on the re-evaluation of curcumin (E 100) as a food additive. EFSA J 2010;8:1679.

[107] Program NT. NTP toxicology and carcinogenesis studies of turmeric oleoresin (CAS No. 8024-37-1)(major component 79%-85% curcumin, CAS No. 458-37-7) in F344/N rats and B6C3F1 mice (feed studies). Natl Toxicol Program Tech Rep Ser 1993;427:1−275.
[108] Lao CD, Ruffin MT, Normolle D, Heath DD, Murray SI, Bailey JM, et al. Dose escalation of a curcuminoid formulation. BMC Complement Altern Med 2006;6:1−4.
[109] Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, et al. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin Cancer Res 2004;10:6847−54.
[110] Adahoun MA, Al-Akhras MH, Jaafar MS, Bououdina M. Enhanced anti-cancer and antimicrobial activities of curcumin nanoparticles. Artif Cells Nanomed Biotechnol 2017; 45:98−107.
[111] Joung HJ, Choi MJ, Kim JT, Park SH, Park HJ, Shin GH. Development of food-grade curcumin nanoemulsion and its potential application to food beverage system: antioxidant property and in vitro digestion. J Food Sci 2016;81: N745−53.
[112] Sari T, Mann B, Kumar R, Singh R, Sharma R, Bhardwaj M, et al. Preparation and characterization of nanoemulsion encapsulating curcumin. Food Hydrocoll 2015;43:540−6.
[113] Thapa RK, Cazzador F, Grønlien KG, Tønnesen HH. Effect of curcumin and cosolvents on the micellization of Pluronic F127 in aqueous solution. Colloids Surf B Biointerfaces 2020; 195:111250.
[114] Bai F, Diao J, Wang Y, Sun S, Zhang H, Liu Y, et al. A new water-soluble nanomicelle formed through self-assembly of pectin−curcumin conjugates: preparation, characterization, and anticancer activity evaluation. J Agric Food Chem 2017; 65:6840−7.
[115] Lübtow MM, Nelke LC, Seifert J, Kühnemundt J, Sahay G, Dandekar G, et al. Drug induced micellization into ultrahigh capacity and stable curcumin nanoformulations: physico-chemical characterization and evaluation in 2D and 3D in vitro models. J Control Release 2019;303:162−80.
[116] Sehgal A, Kumar M, Jain M, Dhawan D. Modulatory effects of curcumin in conjunction with piperine on benzo (a) pyrene-mediated DNA adducts and biotransformation enzymes. Nutr Cancer 2013;65:885−90.
[117] Hussain A, Somyajit K, Banik B, Banerjee S, Nagaraju G, Chakravarty AR. Enhancing the photocytotoxic potential of curcumin on terpyridyl lanthanide (III) complex formation. Dalton Trans 2013;42:182−95.
[118] Valentini A, Conforti F, Crispini A, De Martino A, Condello R, Stellitano C, et al. Synthesis, oxidant properties, and antitumoral effects of a heteroleptic palladium (II) complex of curcumin on human prostate cancer cells. J Med Chem 2009;52:484−91.
[119] Anand P, Thomas SG, Kunnumakkara AB, Sundaram C, Harikumar KB, Sung B, et al. Biological activities of curcumin and its analogues (Congeners) made by man and Mother Nature. Biochem Pharmacol 2008;76:1590−611.
[120] Yodkeeree S, Ampasavate C, Sung B, Aggarwal BB, Limtrakul P. Demethoxycurcumin suppresses migration and invasion of MDA-MB-231 human breast cancer cell line. Eur J Pharmacol 2010;627:8−15.
[121] Luthra PM, Kumar R, Prakash A. Demethoxycurcumin induces Bcl-2 mediated G2/M arrest and apoptosis in human glioma U87 cells. Biochem Biophys Res Commun 2009;384: 420−5.
[122] Simstein R, Burow M, Parker A, Weldon C, Beckman B. Apoptosis, chemoresistance, and breast cancer: insights from the MCF-7 cell model system. Exp Biol Med 2003;228: 995−1003.
[123] Lin C-C, Kuo C-L, Huang Y-P, Chen C-Y, Hsu M-J, Chu YL, et al. Demethoxycurcumin suppresses migration and invasion of human cervical cancer HeLa cells via inhibition of NF-κB pathways. Anticancer Res 2018;38:2761−9.
[124] Chen Y, Hong C, Chen X, Qin Z. Demethoxycurcumin increases the sensitivity of cisplatin-resistant non-small lung cancer cells to cisplatin and induces apoptosis by activating the caspase signaling pathway. Oncol Lett 2020;20:1.
[125] Kao CC, Cheng YC, Yang MH, Cha TL, Sun GH, Ho CT, et al. Demethoxycurcumin induces apoptosis in HER2 overexpressing bladder cancer cells through degradation of HER2 and inhibiting the PI3K/Akt pathway. Environ Toxicol 2021;36:2186−95.
[126] Hamzah H, Hertiani T, Pratiwi SUT, Murti YB, Nuryastuti T. The inhibition and degradation activity of demethoxycurcumin as antibiofilm on C. Albicans ATCC 10231. Res J Pharm Technol 2020;13:377−82.
[127] Li Q-Q, Kang O-H, Kwon D-Y. Study on demethoxycurcumin as a promising approach to reverse methicillin-resistance of Staphylococcus aureus. Int J Mol Sci 2021;22: 3778.
[128] Syu W-J, Shen C-C, Don M-J, Ou J-C, Lee G-H, Sun C-M. Cytotoxicity of curcuminoids and some novel compounds from Curcuma zedoaria. J Nat Prod 1998;61:1531−4.
[129] Devasena T, Rajasekaran K, Menon VP. Bis-1, 7-(2-hydroxyphenyl)-hepta-1, 6-diene-3, 5-dione (a curcumin analog) ameliorates DMH-induced hepatic oxidative stress during colon carcinogenesis. Pharmacol Res 2002;46:39−45.
[130] Mahattanadul S, Nakamura T, Panichayupakaranant P, Phdoongsombut N, Tungsinmunkong K, Bouking P. Comparative antiulcer effect of bisdemethoxycurcumin and curcumin in a gastric ulcer model system. Phytomedicine 2009;16:342−51.
[131] Huang TY, Peng SF, Huang YP, Tsai CH, Tsai FJ, Huang CY, et al. Combinational treatment of all-trans retinoic acid (ATRA) and bisdemethoxycurcumin (BDMC)-induced apoptosis in liver cancer Hep3B cells. J Food Biochem 2020;44:e13122.
[132] Li Y-B, Gao J-L, Zhong Z-F, Hoi P-M, Lee SM-Y, Wang Y-T. Bisdemethoxycurcumin suppresses MCF-7 cells proliferation by inducing ROS accumulation and modulating senescence-related pathways. Pharmacol Rep 2013;65:700−9.
[133] Lai C-S, Chen Y-Y, Lee P-S, Kalyanam N, Ho C-T, Liou W-S, et al. Bisdemethoxycurcumin inhibits adipogenesis in 3T3-L1 preadipocytes and suppresses obesity in high-fat diet-fed C57BL/6 mice. J Agric Food Chem 2016;64:821−30.
[134] Wang S, Kang O-H, Kwon D-Y. Bisdemethoxycurcumin reduces methicillin-resistant Staphylococcus aureus expression of virulence-related exoproteins and inhibits the biofilm formation. Toxins (Basel) 2021;13:804.
[135] Lu PS, Inbaraj BS, Chen BH. Determination of oral bioavailability of curcuminoid dispersions and nanoemulsions prepared from Curcuma longa Linnaeus. J Sci Food Agric 2018;98:51−63.
[136] Aggarwal BB, Deb L, Prasad S. Curcumin differs from tetrahydrocurcumin for molecular targets, signaling pathways and cellular responses. Molecules 2014;20:185−205.
[137] Lai C-S, Ho C-T, Pan M-H. The cancer chemopreventive and therapeutic potential of tetrahydrocurcumin. Biomolecules 2020;10:831.
[138] Sugiyama Y, Kawakishi S, Osawa T. Involvement of the β-diketone moiety in the antioxidative mechanism of tetrahydrocurcumin. Biochem Pharmacol 1996;52:519−25.
[139] Okada K, Wangpoengtrakul C, Tanaka T, Toyokuni S, Uchida K, Osawa T. Curcumin and especially tetrahydrocurcumin ameliorate oxidative stress-induced renal injury in mice. J Nutr 2001;131:2090−5.
[140] Naito M, Wu X, Nomura H, Kodama M, Kato Y, Kato Y, et al. The protective effects of tetrahydrocurcumin on oxidative stress in cholesterol-fed rabbits. J Atheroscler Thromb 2002;9:243−50.
[141] Nakmareong S, Kukongviriyapan U, Pakdeechote P, Donpunha W, Kukongviriyapan V, Kongyingyoes B, et al. Antioxidant and vascular protective effects of curcumin and tetrahydrocurcumin in rats with L-NAME-induced hypertension. Naunyn-Schmiedeberg's Arch Pharmacol 2011;383: 519−29.
[142] Chen J-W, Kong Z-L, Tsai M-L, Lo C-Y, Ho C-T, Lai C-S. Tetrahydrocurcumin ameliorates free fatty acid-induced

hepatic steatosis and improves insulin resistance in HepG2 cells. J Food Drug Anal 2018;26:1075−85.
[143] Lai CS, Wu JC, Yu SF, Badmaev V, Nagabhushanam K, Ho CT, et al. Tetrahydrocurcumin is more effective than curcumin in preventing azoxymethane-induced colon carcinogenesis. Mol Nutr Food Res 2011;55:1819−28.
[144] Yoysungnoen P, Wirachwong P, Changtam C, Suksamrarn A, Patumraj S. Anti-cancer and anti-angiogenic effects of curcumin and tetrahydrocurcumin on implanted hepatocellular carcinoma in nude mice. World J Gastroenterol 2008;14:2003−9.
[145] Masuda T, Hidaka K, Shinohara A, Maekawa T, Takeda Y, Yamaguchi H. Chemical studies on antioxidant mechanism of curcuminoid: analysis of radical reaction products from curcumin. J Agric Food Chem 1999;47:71−7.
[146] Shen L, Ji H-F. The pharmacology of curcumin: is it the degradation products? Trends Mol Med 2012;18:138−44.
[147] Gordon ON, Schneider C. Vanillin and ferulic acid: not the major degradation products of curcumin. Trends Mol Med 2012;18:361−3.
[148] Alam MA, Sernia C, Brown L. Ferulic acid improves cardiovascular and kidney structure and function in hypertensive rats. J Cardiovasc Pharmacol 2013;61:240−9.
[149] Bami E, Ozakpinar OB, Ozdemir-Kumral ZN, Köroglu K, Ercan F, Cirakli Z, et al. Protective effect of ferulic acid on cisplatin induced nephrotoxicity in rats. Environ Toxicol Pharmacol 2017;54:105−11.
[150] Okuda M, Fujita Y, Sugimoto H. The additive effects of low dose intake of ferulic acid, phosphatidylserine and curcumin, not alone, improve cognitive function in APPswe/PS1dE9 transgenic mice. Biol Pharm Bull 2019;42:1694−706.
[151] Salamanova E, Atanasova M, Dimitrov I, Doytchinova I. Effects of curcumin and ferulic acid on the folding of amyloid-β peptide. Molecules 2021;26:2815.
[152] Meng G, Meng X, Ma X, Zhang G, Hu X, Jin A, et al. Application of ferulic acid for Alzheimer's disease: combination of text mining and experimental validation. Front Neuroinform 2018;12:31.
[153] Gao J, Yu H, Guo W, Kong Y, Li Q, Yang S, et al. The anticancer effects of ferulic acid is associated with induction of cell cycle arrest and autophagy in cervical cancer cells. Cancer Cell Int 2018;18:1−9.
[154] Burri J, Graf M, Lambelet P, Löliger J. Vanillin: more than a flavouring agent—a potent antioxidant. J Sci Food Agric 1989;48:49−56.
[155] Arya SS, Rookes JE, Cahill DM, Lenka SK. Vanillin: a review on the therapeutic prospects of a popular flavouring molecule. Adv Trad Med 2021;21:1−17.
[156] Ramadoss DP, Sivalingam N. Vanillin extracted from Proso and Barnyard millets induce apoptotic cell death in HT-29 human colon cancer cell line. Nutr Cancer 2020;72:1422−37.
[157] Naz H, Tarique M, Khan P, Luqman S, Ahamad S, Islam A, et al. Evidence of vanillin binding to CAMKIV explains the anti-cancer mechanism in human hepatic carcinoma and neuroblastoma cells. Mol Cell Biochem 2018;438:35−45.
[158] Chen H, Zheng J, Ma J. Vanillin ameliorates changes in HIF-1 α expression and neuronal apoptosis in a rat model of spinal cord injury. Restor Neurol Neurosci 2019;37:21−9.
[159] Lan X-B, Wang Q, Yang J-M, Ma L, Zhang W-J, Zheng P, et al. Neuroprotective effect of Vanillin on hypoxic-ischemic brain damage in neonatal rats. Biomed Pharmacother 2019;118:109196.
[160] Tyagi AK, Prasad S, Majeed M, Aggarwal BB. Calebin A, a novel component of turmeric, suppresses NF-κB regulated cell survival and inflammatory gene products leading to inhibition of cell growth and chemosensitization. Phytomedicine 2017;34:171−81.
[161] Park S-Y, Kim DS. Discovery of natural products from Curcuma longa that protect cells from beta-amyloid insult: a drug discovery effort against Alzheimer's disease. J Nat Prod 2002;65:1227−31.
[162] Li Y, Li S, Han Y, Liu J, Zhang J, Li F, et al. Calebin-A induces apoptosis and modulates MAPK family activity in drug resistant human gastric cancer cells. Eur J Pharmacol 2008;591:252−8.
[163] Buhrmann C, Popper B, Kunnumakkara AB, Aggarwal BB, Shakibaei M. Evidence that Calebin A, a component of curcuma longa suppresses NF-κB mediated proliferation, invasion and metastasis of human colorectal cancer induced by TNF-β (Lymphotoxin). Nutrients 2019;11:2904.
[164] Buhrmann C, Kunnumakkara AB, Popper B, Majeed M, Aggarwal BB, Shakibaei M. Calebin a potentiates the effect of 5-FU and TNF-β (Lymphotoxin α) against human colorectal cancer cells: potential role of NF-κB. Int J Mol Sci 2020;21:2393.
[165] Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Reddy DN. Role of the normal gut microbiota. World J Gastroenterol 2015;21:8787−803.
[166] Ferreira CM, Vieira AT, Vinolo MAR, Oliveira FA, Curi R, Martins FdS. The central role of the gut microbiota in chronic inflammatory diseases. J Immunol Res 2014;2014.
[167] Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Irritable bowel syndrome: a microbiome-gut-brain axis disorder? World J Gastroenterol 2014;20:14105.
[168] Larsen N, Vogensen FK, Van Den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One 2010;5:e9085.
[169] Everard A, Cani PD. Diabetes, obesity and gut microbiota. Best Pract Res Clin Gastroenterol 2013;27:73−83.
[170] Gurung M, Li Z, You H, Rodrigues R, Jump DB, Morgun A, et al. Role of gut microbiota in type 2 diabetes pathophysiology. EBioMedicine 2020;51:102590.
[171] Pan M-H, Huang T-M, Lin J-K. Biotransformation of curcumin through reduction and glucuronidation in mice. Drug Metab Dispos 1999;27:486−94.
[172] Shen L, Liu L, Ji H-F. Regulative effects of curcumin spice administration on gut microbiota and its pharmacological implications. Food Nutr Res 2017;61:1361780.
[173] Zam W. Gut microbiota as a prospective therapeutic target for curcumin: a review of mutual influence. J Nutr Metab 2018;2018.
[174] Feng W, Wang H, Zhang P, Gao C, Tao J, Ge Z, et al. Modulation of gut microbiota contributes to curcumin-mediated attenuation of hepatic steatosis in rats. Biochim Biophys Acta Gen Subj 2017;1861:1801−12.
[175] An C-Y, Sun Z-Z, Shen L, Ji H-F. Biotransformation of food spice curcumin by gut bacterium Bacillus megaterium DCMB-002 and its pharmacological implications. Food Nutr Res 2017;61:1412814.
[176] Ohno M, Nishida A, Sugitani Y, Nishino K, Inatomi O, Sugimoto M, et al. Nanoparticle curcumin ameliorates experimental colitis via modulation of gut microbiota and induction of regulatory T cells. PLoS One 2017;12:e0185999.
[177] Hong T, Zou J, Jiang X, Yang J, Cao Z, He Y, et al. Curcumin supplementation ameliorates bile cholesterol supersaturation in hamsters by modulating gut microbiota and cholesterol absorption. Nutrients 2022;14:1828.
[178] Lou Y, Zheng J, Hu H, Lee J, Zeng S. Application of ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry to identify curcumin metabolites produced by human intestinal bacteria. J Chromatogr B 2015;985:38−47.
[179] Hassaninasab A, Hashimoto Y, Tomita-Yokotani K, Kobayashi M. Discovery of the curcumin metabolic pathway involving a unique enzyme in an intestinal microorganism. Proc Natl Acad Sci USA 2011;108:6615−20.
[180] Gao Y, Zhuang Z, Gao S, Li X, Zhang Z, Ye Z, et al. Tetrahydrocurcumin reduces oxidative stress-induced apoptosis via the mitochondrial apoptotic pathway by modulating autophagy in rats after traumatic brain injury. Am J Transl Res 2017;9:887.
[181] Zeng Y, Qiu F, Liu Y, Qu G, Yao X. Isolation and identification of phase 1 metabolites of demethoxycurcumin in rats. Drug Metab Dispos 2007;35:1564−73.

[182] Sun D, Zhuang X, Xiang X, Liu Y, Zhang S, Liu C, et al. A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. Mol Ther 2010;18:1606–14.
[183] Kalani A, Kamat PK, Kalani K, Tyagi N. Epigenetic impact of curcumin on stroke prevention. Metab Brain Dis 2015;30: 427–35.
[184] Aqil F, Munagala R, Jeyabalan J, Agrawal AK, Gupta R. Exosomes for the enhanced tissue bioavailability and efficacy of curcumin. AAPS J 2017;19:1691–702.
[185] Whiteside TL. The potential of tumor-derived exosomes for noninvasive cancer monitoring: an update. Expert Rev Mol Diagn 2018;18:1029–40.
[186] Kooijmans SA, Vader P, van Dommelen SM, van Solinge WW, Schiffelers RM. Exosome mimetics: a novel class of drug delivery systems. Int J Nanomedicine 2012;7:1525–41.
[187] Aqil F, Kausar H, Agrawal AK, Jeyabalan J, Kyakulaga A-H, Munagala R, et al. Exosomal formulation enhances therapeutic response of celastrol against lung cancer. Exp Mol Pathol 2016;101:12–21.
[188] Zhuang X, Xiang X, Grizzle W, Sun D, Zhang S, Axtell RC, et al. Treatment of brain inflammatory diseases by delivering exosome encapsulated anti-inflammatory drugs from the nasal region to the brain. Mol Ther 2011;19:1769–79.
[189] Gupta A, Pulliam L. Exosomes as mediators of neuroinflammation. J Neuroinflammation 2014;11:1–10.
[190] Taverna S, Fontana S, Monteleone F, Pucci M, Saieva L, De Caro V, et al. Curcumin modulates chronic myelogenous leukemia exosomes composition and affects angiogenic phenotype via exosomal miR-21. Oncotarget 2016;7:30420.
[191] Kalani A, Kamat P, Chaturvedi P, Tyagi S, Tyagi N. Curcumin-primed exosomes mitigate endothelial cell dysfunction during hyperhomocysteinemia. Life Sci 2014; 107:1–7.
[192] Luan X, Sansanaphongpricha K, Myers I, Chen H, Yuan H, Sun D. Engineering exosomes as refined biological nanoplatforms for drug delivery. Acta Pharmacol Sin 2017;38: 754–63.
[193] Oskouie MN, Aghili Moghaddam NS, Butler AE, Zamani P, Sahebkar A. Therapeutic use of curcumin-encapsulated and curcumin-primed exosomes. J Cell Physiol 2019;234: 8182–91.
[194] Zhang H-G, Kim H, Liu C, Yu S, Wang J, Grizzle WE, et al. Curcumin reverses breast tumor exosomes mediated immune suppression of NK cell tumor cytotoxicity. Biochim Biophys Acta Mol Cell Res 2007;1773:1116–23.
[195] Liu C, Yan X, Zhang Y, Yang M, Ma Y, Zhang Y, et al. Oral administration of turmeric-derived exosome-like nanovesicles with anti-inflammatory and pro-resolving bioactions for murine colitis therapy. J Nanobiotechnol 2022;20: 1–17.
[196] Gao C, Zhou Y, Chen Z, Li H, Xiao Y, Hao W, et al. Turmeric-derived nanovesicles as novel nanobiologics for targeted therapy of ulcerative colitis. Theranostics 2022;12: 5596.