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Review article

# Biological activities of curcuminoids, other biomolecules from turmeric and their derivatives – A review

Augustine Amalraj [a], Anitha Pius [b], Sreerag Gopi [b], Sreeraj Gopi [a, *]

[a] R&D Centre, Aurea Biolabs Pvt Ltd, Kolenchery, Cochin, India
[b] Department of Chemistry, The Gandhigram Rural Institute – Deemed University, Gandhigram, Dindigul, 624 302, Tamil Nadu, India

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ABSTRACT

In recent years, several drugs have been developed deriving from traditional products and current drug research is actively investigating the possible therapeutic roles of many Ayruvedic and Traditional Indian medicinal therapies. Among those being investigated is Turmeric. Its most important active ingredient is curcuminoids. Curcuminoids are phenolic compounds commonly used as a spice, pigment and additive also utilized as a therapeutic agent used in several foods. Comprehensive research over the last century has revealed several important functions of curcuminoids. Various preclinical cell culture and animals studies suggest that curcuminoids have extensive biological activity as an antioxidant, neuroprotective, antitumor, anti-inflammatory, anti-acidogenic, radioprotective and arthritis. Different clinical trials also suggest a potential therapeutic role for curcuminoids in numerous chronic diseases such as colon cancer, lung cancer, breast cancer, inflammatory bowel diseases. The aim of this review is to summarize the chemistry, analog, metal complex, formulations of curcuminoids and their biological activities.
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## 1. Introduction

Natural products have been used in traditional medicines for thousands of years, and have shown promise as a source of components for the development of new drugs.[1,2] Turmeric (*Curcuma longa Linn*) is a member of the *Zingiberaceae* family and is cultivated in tropical and subtropical regions around the world and it is originates from India, Southeast Asia and Indonesia.[3] Turmeric powder is used extensively as a coloring and flavoring agent in curries and mustards. Turmeric has been used in India to maintain oral hygiene.[4] It has traditionally been used for medical purposes for many centuries in countries such as India and China for treatment of jaundice and other liver ailments.[5,6] Turmeric is one of the most popular medicinal herbs, with a wide range of pharmacological activities such as antioxidant,[7] anti-protozoal,[8] anti-venom activities,[9] anti-microbial,[10] anti-malarial,[11] anti-inflammatory,[12] anti-proliferative,[13] anti-angiogenic,[14] anti-tumor[15] and anti-aging[16] properties. It has also been used to treat ulcers, parasitic infections, various skin diseases, anti-immune diseases and curing the symptoms of colds and flus.[17] The pharmacological activity of turmeric has been attributed mainly to curcuminoids consists of curcumin (CUR) and two related compounds demethoxy curcumin (DMC) and bisdemethoxycurcumin (BDMC).[3] CUR itself appears as a crystalline compound with a bright orange-yellow color. Curcuminoids are commonly used as coloring agent as well as food additives. World Health Organization (WHO) stated the acceptable daily intake of curcuminoids as a food additive in the range of 0–3 mg/kg. Curcuminoids and turmeric products have been characterized as safe by the Food and Drug Administration (FDA) in USA. The average intake of turmeric in the Indian diet is approximately 2–2.5 g for a 60 kg individual which corresponds to a daily intake of approximately 60–100 mg of CUR.[18] Curcuminoids have achieved the potential therapeutic interest to cure immune related, metabolic diseases and cancer due to a vast number of biological targets and virtually no side effects.[17,18]

## 2. Methodology

Systemic literature searches were carried out using following databases; Pubmed, Scifinder, Scopus, ScienceDirect, Medline, Embase, Google Scholar and Web of Science using the key words,

* Corresponding author.
*E-mail address:* sreeraj.gopi@plantlipids.com (S. Gopi).
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turmeric, *C. longa*, curcuminoids, curcumin, bioavailability, bioenhancer, pharmacokinetic, phytosome, liposome, analogs, metal complexes and nanoparticles (NPs) and a library search for articles published in peer-reviewed journals and also locally available books.

## 3. Discovery of curcumin

Curcumin is the active ingredient of the dietary spice turmeric and is extracted from the rhizomes of *C. longa*, a plant in the *Zingiberaceae* family. It was first discovered about two centuries ago when Vogel and Pelletier reported the isolation of a "yellow coloring matter" from rhizomes of *C. longa* and named it curcumin.[19] It is characterized by Milobedeska et al[20] and first synthesized by Lampe et al.[21]

## 4. Isolation of curcumin

Curcumin is insoluble in water; an organic solvent has been used for its isolation. Anderson et al[22] developed a technique for isolating CUR from ground turmeric. They magnetically stirred the ground turmeric in dichloromethane and heated at reflux for 1 h. The mixture was suction-filtered, and the filtrate was concentrated in a hot-water bath maintaining at 50 °C. The reddish-yellow oil residue was triturated with hexane and the resulting solid was collected by suction filtration. Further TLC analysis (3% methanol and 97% dichloromethane) showed the presence of all three components.[22] Bagchi[23] explained extraction of CUR from turmeric powder with the use of a solvent consisting of a mixture of ethanol and acetone. Chemical analyses have shown that turmeric contains carbohydrates (69.4%), moisture (13.1%), protein (6.3%), fat (5.1%) and minerals (3.5%). The essential oil (5.8%) obtained by steam distillation of the rhizomes contains α-phellandrene (1%), sabinene (0.6%), cineol (1%), borneol (0.5%), zingiberene (25%) and sesquiterpines (53%), curcumin (3–6%) is responsible for the yellow color.

## 5. Physical, chemical and molecular properties of curcuminoids

Two active components of turmeric are the volatile oil and curcuminoids and both are present in oleoresin extracted from the turmeric root. The essential oils are composed mainly of sesquiterpenes, many of which are specific for the Curcuma genus. The aroma of this spice is principally derived from α- and β-turmerones and aromatic turmerone (Ar-turmerone).[24] The chemical structures of curcuminoids make them much less soluble in water at acidic and neutral pH, but soluble in methanol, ethanol, dimethyl sulfoxide and acetone. The curcuminoids give a yellow-orange coloration to turmeric powder due to the wide electronic delocalization inside the molecules that exhibit strong absorption between 420 to 430 nm in an organic solvent. The curcuminoids are a mixture of curcumin, chemically a diferuloylmethane [1,7-bis(4-hydroxy-3-methoxy-phenyl)-hepta-1,6-diene-3,5-dione] mixed with its two derivatives, demethoxy curcumin [4-hydroxycinnamoyl-(4-hydroxy-3-methoxycinnamoyl) methane] and bis-demethoxy curcumin [bis-(4-hydroxy cinnamoyl) methane], defining the chemical formulae as $C_{21}H_{20}O_6$, $C_{20}H_{18}O_5$ and $C_{19}H_{16}O_4$ respectively.[17] The chemical structures of important constituents present in turmeric are given in Fig. 1. They share the same structure with two benzenemethoxy rings, joined by an unsaturated chain. It has three important functions: an aromatic methoxy phenolic group; α,β-unsaturated β-diketo linker and keto-enol tautomerism. All these compounds exist in the trans-trans keto-enol form. The aromatic groups provide hydrophobicity and the linker give flexibility. The tautomeric structures also influence the hydrophobicity and polarity. The hydrophobicity of curcuminoids makes them poorly soluble in water. Three acidity constants (pKa) were measured for curcuminoids as follows, pKa1 = 8.38 ± 0.04, pKa2 = 9.88 ± 0.02 and pKa3 = 10.51 ± 0.01.[25] Typical curcuminoids composition of popular Indian varieties was found to be in the range of CUR 52–63%, DMC 19–27% and BDMC 18–28%.[17]

The aim of this review was to overview the biological activities of curcuminoids and other biomolecules from turmeric and also discussed the effects and applications of curcuminoids and its different types of derivatives.

## 6. Biological activities of curcuminoids

Curcuminoids from turmeric and their derivatives have been shown to possess a wide range of biological activities including antioxidant, anti-inflammatory, anticancer, antimicrobial, neuroprotective, cardioprotective and radioprotective effects etc., and are illustrated in Fig. 2. The potential of curcuminoids in various biological activities involving multiple mechanisms is given in Table 1 and Fig. 3.

### *6.1. Neuroprotective effects and medicinal use in Alzheimer's disease (AD)*

The pathogenesis of neurodegenerative diseases such as Alzheimer or Parkinson is multi-factorial with a complex combination of genetic components and environmental factors. Toxic reactions, including inflammation, glutamatergic toxicity, dysfunction of mitochondrial activity and ubiquitin/proteasome system, the activation of apoptosis pathways, the elevation of iron and nitric oxide and the alteration of the homeostasis of antioxidants/oxidation are involved in the pathogenesis of neurodegenerative diseases.[26] Dohare et al[27] explained the mechanisms of the neuroprotection against experimental cerebral ischemia by curcuma oil isolated from the rhizomes of *C. longa*. Curcuma oil suppressed the rise in the intracellular concentration of $Ca^{2+}$-a common component in the signaling pathways. The high levels of NO generated by NOS isoforms that are partially responsible for exacerbating the neuronal damage were reduced by curcuma oil. Curcuma oil prevented post-ischemic brain neutrophil infiltration and NO metabolites and reduced the production of ROS. Curcuma oil suppressed the elevated protein level of Bax, and the mitochondrial translocation and activation of Bcl-2 that is triggered by altering mitochondrial membrane potential. Curcuma oil exerted its major action in the penumbral region of the infarct that is protected by modulation of apoptosis. The neuroprotective effect was due to the reduction of NO-induced formation of peroxynitrite and apoptosis in the transient MCAo model in rat. Dohare et al[28] also studied on CUR administrated at various dose levels after 4 h of clot implant in the rat embolic stroke model. The rats were scored at 24 h after surgery for neurological dysfunction, locomotor activity and motor coordination test, infarct volume, edema volume, brain tissue nitrate/nitrite, myeloperoxidase, GSH and GSH-Px activity. The flow cytometric estimation in neuronal rich cell population the level of ROS, NO and peroxynitrite generation were studied at 24 h, which contributed to serve neuronal cytotoxicity were selectively inhibited by CUR treatment. Ischemia induced increase in brain infarct volume and edema volume were significantly attenuated by CUR treatment. The neurobehavioral assessment, locomotor activity and motor coordination further strengthen the above biochemical data there by indicating neuroprotective effect of CUR administrated at 4 h after ischemia in rat focal embolic stroke model. Sahoo et al[29] investigated the effect of CUR on oxidative stress parameters such as antioxidant defense enzymes and oxidized (GSSG) and reduced glutathione (GSH) levels in testis of L-thyroxine (T4)-induced

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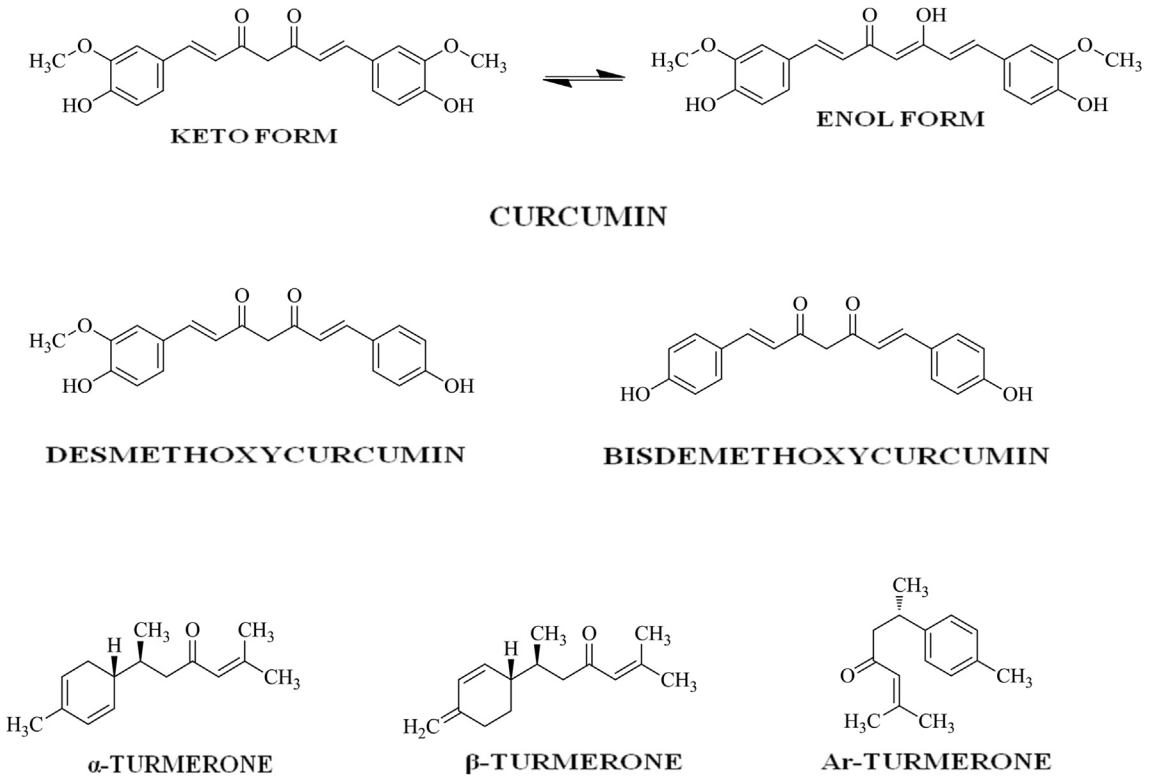


**Fig. 1.** Chemical structures of important constituents present in turmeric.

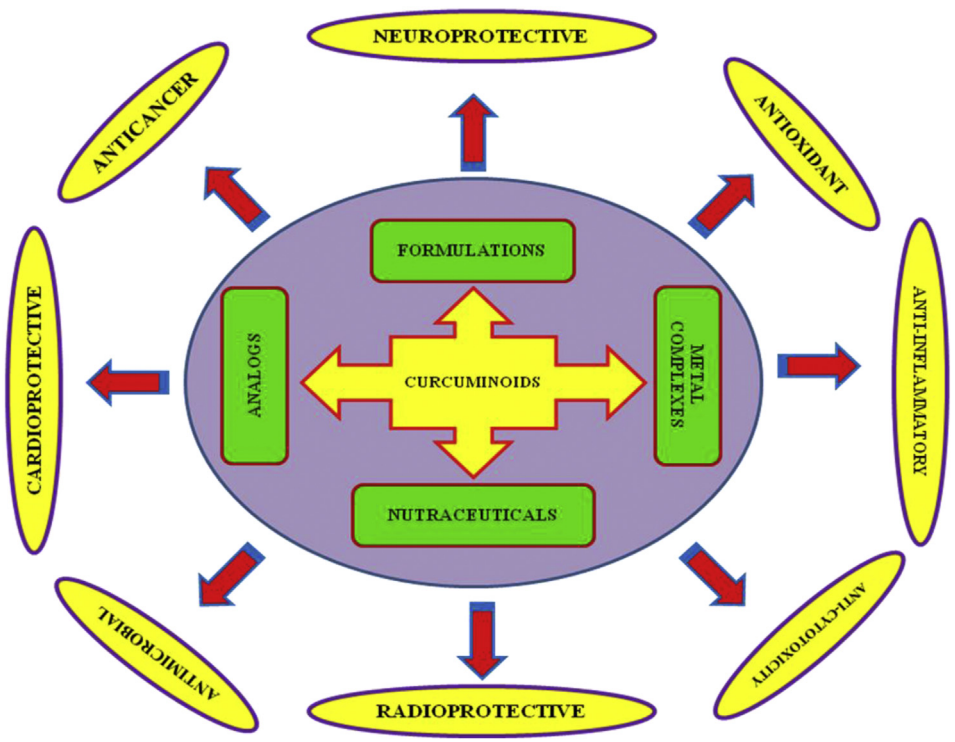


**Fig. 2.** Schematic representation of multiple biological activities of curcuminoids and their derivatives.

hyperthyroid rats. CUR was efficient in protecting testis from oxidative stress generated by T4 mainly by restoring antioxidant enzymes to the level of euthyroid animals up to some extent. Three curcuminoid constituents such as CUR, DMC and BDMC are significantly suppress nitric oxide production by LPS-activated microglia and the relative potency was DMC > BDMC > CUR and also verified by RTPCR analysis of iNOS mRNA. These curcuminoid constituents are attenuated the expression of mRNA and proteins of

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**Table 1**
The potential of curcuminoids in various biological activities involving multiple mechanisms.

| Disease/Activity | Model used and study design | Dose/frequency | Effect of curcuminoids treatment | References |
|---|---|---|---|---|
| Neuroprotective activity | Sprague–Dawley male rats | Curcuma oil – 250 mg/kg | Curcuma oil suppressed the rise in the intracellular concentration of $Ca^{2+}$-a common component in the signaling pathways.<br>Curcuma oil prevented post-ischemic brain neutrophil infiltration and NO metabolites and reduced the production of ROS.<br>Neuroprotective effect was due to the reduction of NO-induced formation of peroxynitrite and apoptosis in the transient MCAo model in rat. | Dohare et al[27] |
| Neuroprotective activity | Sprague–Dawley male rats | CUR – (300 mg/kg) | Neuronal cytotoxicity was selectively inhibited by CUR treatment.<br>Ischemia induced increase in brain infract volume and edema volume were significantly attenuated by CUR treatment. | Dohare et al[28] |
| Oxidative stress | Wistar male rats | L-thyroxine (0.0012%) + 200 mg vitamin E + 30 mg curcumin | CUR was efficient in protecting testis from oxidative stress generated by T4 mainly by restoring antioxidant enzymes | Sahoo et al[29] |
| Neuroprotective activity | New born Sprague–Dawley rats | Curcuminoids (1–10 μM) | CUR, DMC and BDMC are significantly suppressed nitric oxide production by LPS-activated microglia and the relative potency was DMC > BDMC > CUR | Zhang et al[30] |
| Neuroprotective activity | Sprague–Dawley rats of both sexes | CUR (50–200 mg/kg) | The administration of CUR significantly ameliorated HIV-1gp120 V3 loop peptide-induced neuronal damage and dysfunctions, and upregulated the expression of the BDNF.<br>CUR supplementation can be an effective therapy to counteract the deleterious effects of gp120 on HIV-1-associated dementia. | Tang et al[31] |
| Oxidative stress | Wistar male rats | CUR (5 and 50 mg/kg) | CUR can be an effective prophylactic agent in the prevention of oxidative stress by Hcy | Ataie et al[26] |
| Oxidative stress | Swiss albino inbred mice | CUR (50, 100 and 200 mg/kg) | CUR administration significantly reduced the progression of kindling and attenuated the oxidative stress in mice.<br>Control both development of seizure and oxidative stress during epilepsy. | Agarwal et al[32] |
| Memory acquisition ability | KM mice | CUR (50 and 150 mg/kg) | The therapeutic potential CUR found as a novel memory-improving drug through its manipulation of the nNOS/NP signal pathway and a preventive agent upon the deterioration of cognitive faculties. | Yu et al[33] |
| Mitochondrial dysfunction in the brain | Male mice-SAMP8 and SAMR1 | CUR (500 mg/kg) | Significant decreases were observed in mitochondrial function and energy production in brain cells from SAMP8 | Eckert et al[34] |
| Neuroprotective activity | Streptozotocin induced Wistar male rats | CUR (60 mg/kg) | Supplementation of CUR to STZ-induced diabetic rats has beneficial effects in reducing the alterations in glutamergic receptors, oxidative stress and imbalanced glutamate metabolism. | Jayanarayanan et al[35] |
| Neuroprotective and antioxidant activity | Ketamine-induced model of mania in female adult Wistar rats | CUR (20 and 50 mg/kg) | Pretreatment of rats with CUR prevented behavioral and pro-oxidant effects induced by ketamine. | Gazal et al[36] |
| Neuroprotective activity | Sprague-Dawley (Preganant for 14.5 days) | CUR (500 nmol/L) | CUR exhibited a neuroprotective effect through wnt3a and β-catenin expression was significantly increased in the group receiving 500 nmol/L CUR. | Chen et al[37] |
| Depressive disorder | Human study aged 18 to 65 met the DSM-IV criteria for major depressive disorder | CUR (500 mg twice a day) | CUR was significantly more effective than placebo in improving several mood-related symptoms. | Lopresti et al[38] |
| Neuroprotective activity | Wistar male rats | CUR (25 and 50 mg/kg) | CUR treatments increased neuronal viability and attenuated the immunoreactivity for COX-2 and TNF-α in the hippocampus. | de Alcantara et al[39] |
| Premenstrual syndrome (PM) | 70 women with PM | CUR (100 mg/kg) | CUR reduced severity of PMS symptoms can be through increasing serum BDNF levels. | Fanaei et al[40] |

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**Table 1** (*continued*)

| Disease/Activity | Model used and study design | Dose/frequency | Effect of curcuminoids treatment | References |
|---|---|---|---|---|
| Oxidative stress and inflammation | Males and females who were not originally receiving lipid-lowering therapy | CUR (500 mg twice a day) | Curcuminoid therapy in changing circulating concentration of the protein. Short-term supplementation with curcuminoid-piperine combination significantly improves oxidative and inflammatory status in patients with MetS. | Panahi et al[41] |
| Neuroprotective activity | SH-SY5Y cells | 0.1% of 10 mM CUR solution | Inhibition of 6-OHDA induced neurotoxicity in SH-SY5Y cells. | Jaisin et al[42] |
| Transthyretin amyloidose | Transgenic mice | CUR (2% w/w) | CUR reduced TTR load, lowered cytotoxicity associated with TTR aggregation by decreasing activation of death receptor Fas/CD95, endoplasmic reticulum (ER) chaperone BiP and 3-nitrotyrosine in tissues. | Ferreira et al[43] |
| Oxidative stress | Wistar male rats | CUR (300 mg/kg) | Dose dependent anti-seizure effect. Significantly increased the latency to myoclonic jerks, clonic seizures and generalized tonic-clonic seizures. | Mehla et al[44] |
| Alzheimer's disease | Sprague–Dawley male rats | Curcuminoids and its individual components (CUR, DMC and BDMC) – (3–10 mg/kg) | Curcuminoids and its individual components were showed dose dependent inhibition in frontal cortex and hippocampus with *ex vivo* AChE assay. Effective in memory enhancing effect. | Ahmed et al[45] |
| Alzheimer's disease | Amyloid-β-peptide-infused Sprague-Dawley male rats | Curcuminoids and its individual components (CUR, DMC and BDMC) – (3–10 mg/kg) | Curcuminoids increased synaptophysin expression. | Ahmed et al[46] |
| Alzheimer's disease | Aβ+ibotenic acid-infused Sprague –Dawley male rats | Curcuminoids and its individual components (CUR, DMC and BDMC) – (3–10 mg/kg) | DMC effectively decreased GFAP levels in the hippocampus. DMC showed as maximal rescuing effect. | Ahmed et al[47] |
| Alzheimer's disease | Murine neuroblastoma (N2A) cell model | CUR and DMC (1–40 μM) | CUR was more active than DMC in inhibiting the APP and Tau IRES activity | Villaflores et al[48] |
| Antitumor activity | MCF-7 human breast tumor cells | Curcuminoids and cyclocurcumin (1–20 μM) | DCM is a better inhibitor than CUR and BDMC due to the presence of both phenolic hydroxyl groups, methoxyl groups and the diketone moiety. | Simon et al[49] |
| Antitumor activity | Human leukemic cell lines K562 | CUR (1–15 μM) | CUR affected the WT1 binding of protein-promoter. It attenuated WT1 auto-regulatory function through inhibition of PKCa signaling in K562 cells. | Semsri et al[50] |
| Antitumor activity | He La cells | Curcuminoids (1 mg/mL) | Loading plot and variable importance in projection in orthogonal partial least squares were confirmed correlation with antitumor activity | Jiang et al[51] |
| Antitumor activity | Mouse 3T3-L1 fibroblast cells | CUR (1.25–20 μM) | Decreased plasma free fatty acid levels. Improved insulin sensitivity. | Xie et al.[52] |
| Antitumor activity | Human carbonyl reductase 1 | CUR (0.50–50 μM) | Increases the efficacy of daunorubicin in cancer tissue decreases cardiotoxicity | Hintzpeter et al[53] |
| Antitumor activity | Mouse hepatoma H22 tumor model | *Rhizoma Paridis* saponins combined with turmeric | Significantly inhibited tumor growth rate through suppressing levels of amino acids, lipid compounds and carbohydrates in the tumor tissues. | Man et al[54] |
| Antioxidant activity | Phosphomolybdenum and linoeic acid peroxidation method | Curcuminoids (50–100 mg/L) | Good antioxidant capacity | Jayaprakasha et al[55] |
| Antioxidant activity | DPPH method | CUR (0.05 mM) | The reaction between CUR and DPPH in fact takes place only by the SPLET mechanism. The antioxidant activity of CUR has due to the presence of phenolic groups. | Galano et al[56] |
| Antioxidant activity | Twenty one β-thalassemia/Hb E patients | CUR (250 mg twice a day) | Levels of MDA, SOD, GSH-Px in RBC, serum NTBI were higher. Levels of RBC GSH were lower. | Kalpravidh et al[7] |
| Antioxidant activity | Wistar strain rats | CUR (200 mg/kg) | Anti-inflammatory, hepatoprotective and cardioprotective effects of CUR correlated with its antioxidant activity | Naik et al[57] |
| Antioxidant activity | Sprague–Dawley rats: 6 males and 6 females | Curcuminoids (150 mg/kg) | Significant reduction in the amount of urinary biomarkers of oxidative stress such as allantoin, m-tyrosine, 8-hydroxy-2'-deoxyguanosine and 3-nitrotyrosine. | Dall'Acqua et al[58] |

(*continued on next page*)

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**Table 1** (*continued*)

| Disease/Activity | Model used and study design | Dose/frequency | Effect of curcuminoids treatment | References |
|---|---|---|---|---|
| Anticancer activity | HT1080 human fibrosacroma and NIH3T3 fibroblasts cells | CUR, DMC and BDMC – (0–10 μM) | CUR, DMC and BDMC significantly decreased urokinase plasminogen activator.<br>Three forms of curcuminoids significantly inhibited collagenase, MMPs. | Yodkeeree et al[59] |
| Anticancer activity | HCT116 human colon cancer cells | diAcetylCurcumin, CUR, BDMC | The combination of natural burneol and DCUR induced G2/M phase arrest in HepG2 | Basile et al[60] |
| Anticancer activity | MDA-MB-231 human breast cancer cells and NIH3T3 fibroblasts | DMC (1–15 μM) | Treatment of DMC inhibited the DNA binding activity of nuclear factor-kappa B | Yodkeeree et al[61] |
| Anticancer activity | 58 breast cancer patients | CUR (20 μM) | Maspin upregulation as one of the mechanisms involved in CUR mediated apoptosis. | Prasad et al[62] |
| Anticancer activity | MDA-MB-453, MDAMB- 468 and MCF7 cells | Rosemary/carnosic acid synergize with CUR (0.2–4 μg/mL) | Combination of carnosic acid and CUR can be effective to prevent and treat triple negative breast cancer | Einbond et al[63] |
| Anticancer activity | MDA-MB-231 cells | CUR, DMC, and BDMC (20 μM) | Curcuminoids-PDT significantly inhibited cell viability in breast cancer cell lines.<br>DMC-PDT has the highest anti-proliferative effect. | Lin et al[64] |
| Anticancer activity | Human lung adenocarcinoma A549 cells and the cis-platin resistant A549/DDP cells | CUR (5–20 μM) | Combined CUR and DDP treatment inhibited A549/DDP cells proliferation, reversed DDP resistance and triggered apoptotic death. | Ye et al[65] |
| Anticancer activity | NSCLC A549 cell line | BDMC (1–80 μM) | BDMC significantly decreased smoothened and the transcription factor glioma-associated oncogene 1 expression.<br>BDMC inhibited the viability of NSCLC cells. | Hong et al[66] |
| Cardioprotective activity | Male Sprague–Dawley rats | CUR (75 mg/kg) | Some amelioration in cardiac function, infarct sixe and serum biochemical markers were noted. | Hong et al[67] |
| Radioprotecive effect | Female Sprague Dawley rats | CUR (50 mg/kg) | Less cell necrosis.<br>Lycopene and CUR reduced the structural damage to the salivary glands. | Lopex-Jornet et al[69] |
| Radioprotecive effect | Peripheral blood from healthy individuals | CUR (1.4–140 μM) | Radiosensitization is related to the G2-checkpoint abrogation.<br>Significant increase was observed in the yield of radiation-induced chromatid breaks. | Sebastia et al[70] |
| Sexually transmitted infections | Human semen | 0.7 mg CUR/2 ml *In Situ* gel | Box-Behnken Design has maximum residence time, good efficacy in terms of contraception and highest user compliance. | Patel et al[71] |
| Sexually transmitted infections | Adult female Wistar Albino rats | CUR (100 mg/kg and 200 mg/kg) | Restored the hormone and lipid profile, antioxidant and glycemic status. | Reddy et al[72] |
| Sexually transmitted infections | Adult male Wistar rats | Turmeric (4% w/w) | Improvement of antioxidant status in the epididymides and testes of L-NAME-induced hypertensive rats.<br>Restoration of systolic blood pressure, sperm motility, testosterone level. | Akinyemi et al[73] |
| Anti-esophageal adenocarcinoma activity | OE33 and Flo-1 cell lines | CUR (6.25–50 μM) | CUR alone inhibited NF-kB activity and induced apoptosis in both Flo-1 and OE33 EAC cell lines | Hartojo et al[74] |
| Anti-nephrotoxicity | Male Wistar-Albino rats | CUR (200 mg/kg) | Significant decrease in inflammation and apoptosis during histopahtological examination | Hismiogullari et al[75] |
| Antiviral activity | Madin-Darby canine kidney (MDCK) cells | CUR (30 μM) | CUR interrupts virus-cell attachment, which leaded to inhibition of influenza virus propagation. | Chen et al[76] |
| Antifungal activity | Pathogens of *Candida albicans* | CUR and DMC (20–200 μg/mL) | The antifungal effect of CUR was stronger than that of DMC due the existence of methoxy group | Zhang et al[77] |
| Anti-angiogenic effects | Human microvascular endothelial cells, zebrafish and Matrigel plugs mouse | Ar-turmerone (14.4–231.1 μM) | Significantly inhibited the proliferation, tube formation and motility of HMEC-1 cells at non-cytotoxic concentrations.<br>Significantly inhibited the blood vessel growth, confirmed by the *in vivo* studies using Matrigel plugs mouse model. | Yue et al[78] |

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**Table 1** (*continued*)

| Disease/Activity | Model used and study design | Dose/frequency | Effect of curcuminoids treatment | References |
|---|---|---|---|---|
| Anti-angiogenic and anti-proliferative activities | Human colon cancer cells and endothelial cells | CUR and Ar-turmerone (0.4–7.0 μg/mL) | Turmeric extract provided better antiangiogenic and antiproliferative activities than the CUR alone did. | Yue et al[79] |
| Anti-immunomodulatory activity | Human peripheral blood mononuclear cells | Polar fractions of *Curcuma longa* | Stimulatory effects on PBMC proliferation by (methyl-3H)-thymidine incorporation assay. | Yue et al[13] |
| Anti-proliferative activity | HMEC-1 cells | Curcuminoids and α-turmerone | Curcuminoids and α-turmerone significantly inhibited proliferation of cancer cells.<br>Two turmerones are showed stimulatory effects on PBMC proliferation and cytokine production. | Yue et al[80] |
| Anti-inflammatory | RAW264.7- A mouse macrophage cell line | BDMC (10 μM) | Inhibition of calmodulin dependent protein kinase II or extracellular signal regulated kinase 1/2 lead to reduction in inhibition by BDMC of LPS induced inducible nitric oxide synthase expression and nitric oxide production. | Kim et al[81] |
| Anti-inflammatory | Male Mdr1a$^{-/-}$ and male FVB/NTac mice | CUR (0.2 % w/w) | Action of CUR against inflammation has proved via multiple molecular pathways including reduced immune response, increased xenobiotic metabolism, resolution of inflammation through decreased neutrophil migration and increased barrier remodeling | Cooney et al[82] |
| Anti-acidogenic activity | *Streptococcus mutans* | Turmeric extracts (100 μL) | Separated fraction from turmeric and curcuminoids had inhibitory effects on the sucrose-dependant adherence of *S. mutans* to saliva-coated hydroxyapatite discs. | Pandit et al[2] |
| Anti-arthritic activity | Female albino Wistar rats | CUR (30 mg/kg) | Reducing arthritis.<br>Significantly alleviating hepatocellular injury caused by methogtrexate. | Banji et al[83] |
| Anti-arthritic activity | Male Sprague–Dawley rats | CUR (30 μg/kg) | CUR exhibited superior anti-arthritic effect through augmenting SOM secretion from the endocrine cells in small intestines | Yang et al[84] |
| Anti-Acanthamoebic activity | *Acanthamoeba castellanii* | Resveratrol and curcuminoids (10–100 μg) | Pre-exposure of organisms prevented amoeba binding by 57% and 73% respectively.<br>Cytotoxicity of host cells was inhibited by 86%. | Aqeel et al[85] |
| Mutagenicity | *Salmonella typhimurium* auxotroph mutant strains TA97 | CUR (10–50 % w/w) | A significant induction in the frequency of bacterial his$^{+}$ revertant colonies by paclitaxel at different concentrations was observed.<br>A significant reduction in platelet activation by on PLGA films containing 30% and 50% by weight curcumin. | Vieira et al[86] |
| Hepatoprotective activity | Adult Swiss albino mice | CUR (5 μM) | The release of lactate dehydrgenase was significantly reduced along with lipid peroxidation | Naik et al[87] |
| Arsenic toxicity | Adult male albino Wistar rats | THC (80 mg/kg) | A significant protective effect on mitochondria, which is a crucial element involved in both triggering and mediating the hepatoprotective response in hepatic cells. | Muthumani et al[88] |
| Chromium toxicity | Male Wistar rats | CUR (100–400 mg/kg) | CUR treatment attenuated $K_2Cr_2O_7$-induced renal dysfunction, histological damage, oxidant stress, and the decrease in antioxidant enzyme activity both in kidney tissue and in mitochondria. | Molina-Jijon et al[89] |

TNF-α in a concentration-dependent manner and the relative potency was also DMC > BDMC > CUR. Curcuminoids can be used as potential therapeutic implications for various neurodegenerative diseases.[30]

Tang et al[31] demonstrated that intracerebroventricular (ICV) administration of [Human immunodeficiency virus-1 (HIV-1)] HIV-1 gp120V3 loop peptide caused spatial learning and memory dysfunction, diminished LTP and produced significant oxidative brain damage. The administration of CUR significantly ameliorated HIV-1gp120 V3 loop peptide-induced neuronal damage and dysfunctions, and upregulated the expression of the BDNF. CUR supplementation can be an effective therapy to counteract the deleterious effects of gp120 on HIV-1-associated dementia. Antioxidant property of CUR can be responsible for protection against

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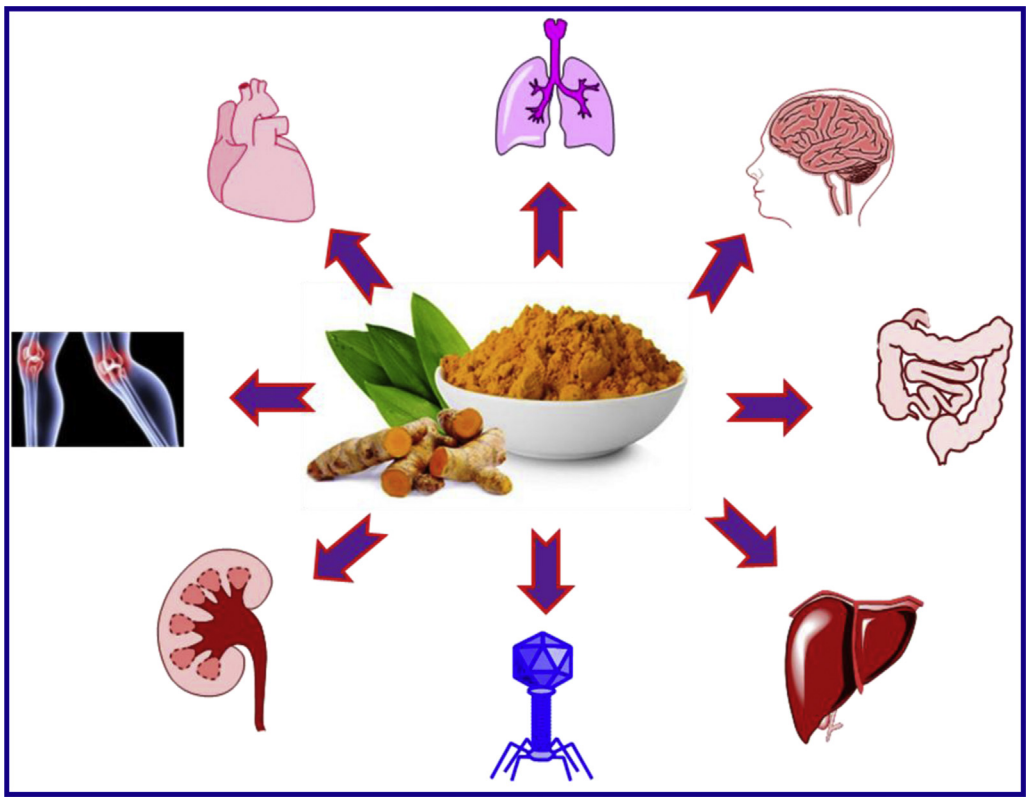

**Fig. 3.** Various biological activities with different mechanism of curcuminoids and their derivatives.

homocystein (Hcy) oxidative stress, possibly by increasing the endogenous defenses against oxidative stress. CUR can scavenge super oxide anion (SOA) from hippocampus tissue. Protective effects of CUR against lipid peroxidation have decreased malondialdehyde (MDA) and SOA formation. CUR could prevent neurotoxicity of Hcy in the rat hippocampus. Hyperhomocysteinemia may be one of the pathological reasons for neurodegenerative disorders such as sporadic AD or Parkinson's disease, CUR can be an effective prophylactic agent in the prevention of oxidative stress by Hcy. The mechanism of CUR for protecting the hippocampus against the toxicity of Hcy might be to inhibit the generation of ROS in brain of rats.[26] Epilepsy is a chronic neurological disorder. Agarwal et al[32] studied the effect of acute administration of CUR at various doses orally pentylenetetrazole induced kindling in mice. Two oxidative stress markers such as malondialdehyde (MDA) and glutathione were estimated in brain tissues of rodents. CUR dose dependently suppressed the progression of kindling in mice. The increased levels of MDA and glutathione were also reduced by CUR in kindled animals. CUR could be a promising candidate to control both developments of seizure and oxidative stress during epilepsy.

Yu et al[33] investigated the effects of CUR on memory decline of aged mice with a focus upon the possible contribution of the neuronal nitric oxide synthase (nNOS)/nitric oxide (NO) pathway in the memory amelioration effect of CUR. Chronic administration of CUR significantly ameliorated the memory acquisition ability of aged male mice in the novel object recognition and passive avoidance tasks. Immunoblotting revealed that chronic treatment of curcumin increased nNOS expression in the prefrontal cortex, amygdale and hippocampus, as well as the enhancement of nNOS activity and NO concentration. The therapeutic potential CUR found as a novel memory-improving drug through its manipulation of the nNOS/NP signal pathway and a preventive agent upon the deterioration of cognitive faculties. Eckert et al[34] investigated the suitability of the fast-aging senescence-accelerated mouse-prone 8 (SAMP8) strain and its normally aging control senescence-accelerated mouse-resistant 1 (SAMR1) as a model for the age-dependent changes in mitochondrial function in the brain. Significant decreases were observed in mitochondrial function and energy production in brain cells from SAMP8 as compared to SAMR1 mice, which appeared to be driven by a reduced expression of complex V of the mitochondrial respiratory chain and was accompanied by enhanced mitochondrial fission. CUR-treatment of SAMP8 mice restored mitochondrial function to an extent comparable to that in SAMR1 control animals, perhaps by induction of the nuclear receptor PGC1a, and may thus be a promising dietary agent that may slow down brain aging and prevent mitochondrial dysfunction. Jayanarayanan et al[35] investigated the neuroprotective effect of CUR in glutamate mediated excitotoxicity in cerebral cortex of streptozotocin induced diabetic rats. They reported that the supplementation of CUR to STZ-induced diabetic rats has beneficial effects in reducing the alterations in glutamergic receptors, oxidative stress and imbalanced glutamate metabolism. A novel therapeutic role of CUR was confirmed by reducing the glutamate mediated excitotoxicity in cerebral cortex of diabetes through modulating the altered neurochemical parameters.

Effective treatments for preventing mood episodes in patients with bipolar disorder (BD) are urgently needed, because BE is perhaps the psychiatric disorder with the highest mortality rate. Gazal et al[36] investigated the protective effects of CUR, in a model of mania induced by ketamine administration in rats. Ketamine treatment induced hyperlocomotion in the open-field test and oxidative damage in prefrontal cortex (PFC) and hippocampus (HP) evaluated by increased lipid peroxidation and decreased total thiol content. Ketamine treatment reduced the activity of the antioxidant enzymes superoxide dismutase and catalase in the HP. Pretreatment of rats with CUR prevented behavioral and pro-oxidant

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effects induced by ketamine. CUR might be a good agent for preventing intervention, reducing the episode relapse and the oxidative stress associated with the manic phase of BD. Chen et al[37] demonstrated the relationship between the neuroprotective effects of CUR and the classical wnt signaling pathway using Sprague-Dawley rats. Neural stem cells from the anterior two-third of the fetal rat brain were passage three times using the half media replacement method and identified using cellular immunofluorescence. Western-blotting method indicated Wnt3a and β-catenin expression was significantly increased in the group receiving 500 nmol/L CUR. Cells in the IWR1-treated group showed decreased wnt3a and β-catenin expression wnt3a and β-catenin was also decreased in the IER1 with 500 nmol/L CUR group. CUR can activate the wnt signaling pathway, which provides evidence that CUR exhibited a neuroprotective effect through the classical wnt signaling pathway. Lopresti et al[38] investigated the antidepressant effects of CUR supplementation in people with major depressive disorder by a randomized, soluble-blind, placebo-controlled study. Fifty six individuals with major depressive disorder were treated with CUR (500 mg twice a day) or placebo for 8 weeks. CUR was significantly more effective than placebo in improving several mood-related symptoms. These findings have provided a partial support for the antidepressant effects of CUR in people with major depressive disorder.

de Alcantara et al[39] studied the neuroprotective action of CUR in a model of global ischemia. CUR treatments increased neuronal viability and attenuated the immunoreactivity for COX-2 and TNF-α in the hippocampus. The CUR reversed most of the neurochemical and immunohistochemical alterations of the ischemic group. The involvement of inflammation in brain ischemic episode and the anti-inflammatory property of CUR, as well as its antioxidant activity observed even at lower doses and it emphasized the potential benefit of CUR in the prevention or treatment of stroke. Premenstrual syndrome (PMS) is a variety of physical, mental and behavioral symptoms that start during the late luteal phase of the menstrual cycle and the symptoms disappear after the onset of menses. Serum brain-derived neurotrophic factor (BDNF) levels during the luteal phase in women associated with PMS have more alterations than women not suffering from PMS. Fanaei et al[40] evaluated the effect of CUR on serum BDNF level and PMS symptoms severity in women with PMS by randomized, double-blinded, placebo-controlled clinical trial. CUR reduced severity of PMS symptoms can be through increasing serum BDNF levels. CUR can be considered as an effective therapeutic option for PMS. Panahi et al[41] reported the effectiveness of supplementation with a bioavailable curcumionoid preparation on measures of oxidative stress and inflammation in patients with metabolic syndrome (MetS). The importance of C-reactive protein (CRP) as a risk marker and risk factor for cardiovascular disease, a meta analysis of randomized controlled trials was performed to estimate the effect size of curcuminoid therapy in changing circulating concentration of the protein. Short-term supplementation with a curcuminoid-piperine combination significantly improves oxidative and inflammatory status in patients with MetS. Curcuminoids could be an effective CRP-lowering agent. Oxidative stress (OS) plays a pivotal role in the pathogenesis of Parkinson's disease (PD). Jaisin et al[42] provided insight into the neuroprotective mechanism of diferuloylmethane has antioxidant properties that explain its inhibition of 6-hydroxydopamine (6-OHDA) induced neurotoxicity in SH-SY5Y cells. CUR has antioxidant properties that explain its inhibition of 6-OHDA induced increases in the Bax/Bcl-2 ratio, p53 phosphorylation and dopaminergic cell death. The results have shown the use of CUR as a potential treatment of oxidative stress related neurodegenerative diseases. The transthyretin amyloidoses (ATTR) are devastating diseases characterized by progressive neuropathy and/or cardiomyopathy for which novel therapeutic strategies are needed. Ferreira et al[43] examined the effect of CUR on transthyretin (TTR) amyloidogenesis *in vivo*, using a well characterized mouse model for familial amyloidotic polyneuropathy (FAP). CUR bound selectively to the TTR thyroxine-binding sites of the tetramer over all the other plasma proteins. CUR was found to significantly increase TTR tetramer resistance to dissociation. Immunohistochemistry (IHC) analysis of mice tissues demonstrated that CUR reduced TTR load in as much as 70% and lowered cytotoxicity associated with TTR aggregation by decreasing the activation of death receptor Fas/CD95, endoplasmic reticulum (ER) chaperone BiP and 3-nitrotyrosine in tissues. CUR can be used for the prevention and treatment of TTR amyloidosis. Mehla et al[44] examined the effect of CUR against seizures, cognitive impairment and oxidative stress in pentylenetetrazole-induced kindling in rats. CUR showed dose dependent anti-seizure effect and significantly increased the latency to myoclonic jerks, clonic seizures and generalized tonic-clonic seizures, improved the seizure score and decreased the number of myoclonic jerks. Pentylenetetrazole (PTZ) kindling induced a significant oxidative stress and cognitive impairment which was reversed by pretreatment with CUR in a dose-dependent manner. The potential of CUR was as an adjuvant to AEDs in epileptic patients with the dual advantages of better seizure control as well as less cognitive impairment.

Ahmed et al[45] evaluated the acetylcholinesterase (AChE) inhibitory and memory enhancing activities of curcuminoids by *in vitro* and *ex vivo* models of AchE inhibitory activity with Morris water maze test on memory in rats. Curcuminoids inhibited AChE activity in the *in vitro* assay with IC 50 value of 67.69 for CUR, 16.84 for DMC and 19.67 μM for BDMC. Curcuminoids and its individual components were showed dose dependent inhibition in frontal cortex and hippocampus with *ex vivo* AChE assay and their effect on memory at a fixed dose showed a significant and comparable effect in scopolamine-induced amnesia moreover effective in memory enhancing effect. Curcuminoids mixture could be used for AD. Ahmed et al[46] investigated the effect of curcuminoid mixture and individual constituents on special learning and memory in an amyloid-beta peptide-infused rat model of AD and on the expression of PSD-95, synaptophysin and camkIV. Curcuminoids possessed memory enhancing effect in the AD model, where the parent curcuminoid mixture was found less effective, but the CUR was more effective and this was supported by the expression level of genes. The effects of curcuminoids on synaptophysin in the hippocampus after the long duration treatment, their mixture and three major constituents increased synaptophysin expression. DMC was the most effective compared to the neurotoxin group. The compounds of curcuminoids salvaged PSD-95, synaptophysin and camkIV expression levels in the hippocampus in the rat AD model, which suggested multiple target sites with the potential of curcuminoids in spatial memory enhancing and disease modifying in AD. Ahmed et al[47] reported the effect of a curcuminoid mixture and its individual components on inflammatory and apoptotic genes expression in AD using an Aβ+ibotenic acid-infused rat model. The curcuminoid mixture and DMC effectively decreased GFAP levels in the hippocampus. The effect of curcuminoid mixture and BDMC on apoptotic genes expression decreased caspase-3 levels in the hippocampus, where BDMC showed as a maximal rescuing effect. Villaflores et al[48] investigated the effects of CUR and DMC on the internal ribosome entry site of the amyloid-β precursor protein (APP) and tau protein through a bi-cistronic reporter assay for screening of anti-AD agents. IRES element (APP and Tau) was flanked by gene sequences from β-galactosidase and secreted alkaline phosphatase (SEAP). The expression of the β-galactosidase protein was controlled by the cytomegalovirus promoter, which corresponded to the cap-dependent translation. CUR was more

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active than DMC in inhibiting the APP and Tau IRES activity because DMC failed to inhibit APP-IRES but was able to reduce Tau activity only at the highest concentration. CUR was able to attenuate the expression of APP, C-terminal protein, tau pS262 and tau pS396 while DMC failed to inhibit APP and C-terminal protein. The bicistronic vector reporter assay provided a novel, simple and effective platform in screening and establishing the mechanistic action of potential compounds for the treatment and management of AD.

### 6.2. Antitumor-activity

Curcuminoids are the main component of turmeric and have a range of pharmacological activities. The effect of curcuminoids and cyclocurcumin examined on the proliferation MCF-7 human breast tumor cells. DMC is a better inhibitor than CUR and BDMC due to the presence of both phenolic hydroxyl groups, methoxyl groups and the diketone moiety. Cyclocurcumin had no effect on MCF-7 cell proliferation suggested that the diketone system of curcuminoids appears to be the part of the molecule involved in the antiproliferative effect of curcuminoids.[49] Semsri et al[50] investigated the effect of pure CUR on Wilm's tumor 1 (WT1) gene expression in leukemic K562 cells line was mediated through PKCa signaling upstream of WT1 transcription factor auto-regularly function. Pure CUR affected the WT1 binding of protein-promoter, WT1-mRNA decrease and levels of protein in K562 cells contributed to the pure CUR anti-proliferative effect. It can be attenuated WT1 autoregulatory function through inhibition of PKCa signaling in K562 cells, it can also be useful in the upcoming development of therapeutic approaches for leukemic patients. Jiang et al[51] have identified the antitumor constituents in curcuminoids from *C. longa* on He La cells were measured using an MTT (3−4,5-dimethyl thiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay based on the composition and activity relationship. Curcuminoids were significantly correlated with antitumor activity via loading plot and variable importance in projection in orthogonal partial least squares and a correlation coefficient in canonical correlation analysis. The role of CUR in inhibiting lipolytic action was examined upon various stimulations in 3T3-L1 adipocytes. Treatment with CUR attenuated TNF-α-mediated lipolysis by suppressing phosphorylation of extracellular signal related kinase 1/2(ERK1/2) and reversing the downregulation of perilipin protein in TNF-α-stimulated adipocytes. The antilipolytic effect could be a cellular basis for CUR decreasing plasma free fatty acid levels and improving insulin sensitivity.[52]

CUR is a potent tight binding inhibitor of human carbonyl reductase 1 (CBR1) through occupied binding sites of CBR1 as a cofactor that decreases daunorubicinol formation. CUR can give up the potential to enhance the therapeutic effectiveness of daunorubicin by preventing heart tissue damage through the inhibition of CBR1 mediated reduction of daunorubicin to daunorubicinol. The inhibition of CBR1 can increase the efficacy of daunorubicin in cancer tissue and simultaneously decrease its cardiotoxicity.[53] Metabolic profile of Rhizoma paridis saponins combined with the turmeric intervention in H22 hepatocarcinoma mice tumor growth was validated by histopathological examination. It mediated by tumor environment and significantly inhibited tumor growth rate through suppressing levels of amino acids, lipid compounds and carbohydrates in the tumor tissues. Rhizoma paridis saponins combined with turmeric could be a good anticancer agent that targets on cancer metabolisms by starving tumors, reducing feasibility of cancer cells.[54]

### 6.3. Antioxidant activity

Curcuminoids possess powerful antioxidant activity as demonstrated in many chemicals *in vitro* tests and in several *in vivo* trails. The antioxidant activities and capacities of curcuminoids have been studied by Jayaprakasha et al[55] with *in vitro* model system such as phosphomolybdenum and linoeic acid peroxidation method. These compounds could be used in food systems to enhance the shelf life due to their good antioxidant capacity. The antioxidant mechanism of CUR was explained by using density functional theory with five different mechanisms are considered such as single electron transfer (SET), radical adduct formation (RAF), H atom transfer from neutral curcumin (HAT), H atom transfer from deprotonated curcumin (HAT-D) and sequential proton loss electron transfer (SPLET). The reaction between curcumin and DPPH in fact takes place only by the SPLET mechanism, whereas the reaction with $-OCH_3$ and other alkoxyl radicals are governed by the HAT mechanism. The contribution of the HAT mechanism to the overall reaction with curcumin and $-OCH_3$ were found to be higher than 95%, regardless of the solvent polarity and of the reacting curcumin isomer. The antioxidant activity of curcumin has been confirmed by experimentally mainly due to the presence of phenolic groups in CUR.[56]

Kalpravidh et al[7] evaluated hematological profile, oxidative stress and antioxidant parameters in twenty one β-thalassemia/Hb E patients treated with curcuminoids (2 capsules of 250 mg) for 12 months. Higher levels of malonyldialdehye, superoxide dismutase, glutathione peroxidase in red blood cell, serum non-transferrin bound iron (NTBI) and lower level of glutathione in red blood cell showed the increased oxidative stress in β-thalassemia/Hb E patients. All parameters returned close to baseline levels after 3 months treatment. Curcuminoids can be used to ameliorate oxidative damage in patients with β-thalassemia/Hb E disease. Naik et al[57] investigated the protective effects of CUR on experimentally induced inflammation, hepatotoxicity and cardiotoxicity using different animal models with biochemical parameters such as serum marker enzymes and antioxidants in target tissues. CUR treatment inhibited carageenin and albumin induced edema, cotton pellet granuloma formation. The increased relative weigh to the liver and heart in $CCl_4$ induced liver injury and isoproterenol induced cardiac necrosis were reduced by CUR treatment. CUR also inhibited iron catalyzed lipid peroxidation in liver homogenates, scavenged nitric oxide spontaneously generated from nitroprusside and inhibited heat induced hemolysis of rat erythrocytes. Anti-inflammatory, hepatoprotective and cardioprotective effects of CUR can be correlated with its antioxidant activity by both the *in vitro* and *in vivo* results. Curcumin can be a useful adjuvant in drug therapy along with standard drugs in oxidative stress induced diseases.

Metabolomics can be used as an attractive approach for completely elucidate and studies on the *in vivo* antioxidant effects or oral administration of a *C. longa* extract. The experiment was carried out by 12 healthy rats with particular attention to urinary markers of oxidative stress over a 33 days period and changes in the 24 h urine samples metabolom were evaluated by $^1$H NMR and HPLC-MS. The evaluation of the effects of the Curcuma extract on urinary composition in healthy rats by a metabolomic approach led to evidence for an *in vivo* antioxidant effect caused by a significant reduction in the amount of urinary biomarkers of oxidative stress, such as allantoin, m-tyrosine, 8-hydroxy-2′-deoxyguanosine and 3-nitrotyrosine. Metabolomics based study strongly supported an *in vivo* antioxidant effect of the oral administration of *C. longa* extract to healthy rats.[58]

### 6.4. Anticancer activity

Yodkeeree et al[59] examined the comparison of the influence of CUR, DMC and BDMC on the expressions of urokinase plasminogen activator, metalloproteinases (MMPs), membrane type 1 (MT1-MMP), tissue inhibitor of MMPs and *in vitro* invasiveness of

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human fibrosarcoma cells. The differential potency for inhibition of cancer cell invasion was BDMC > DMC > CUR. Zymography analysis exhibited that CUR, DMC and BDMC significantly decreased urokinase plasminogen activator, active MMPs from the cells in a dose dependent manner, in which BDMC and DMC showed higher potency than CUR. Three forms of curcuminoids significantly inhibited collagenase, MMPs. DMC and BDMC showed higher antimetastasis potency than CUR by the differentially down-regulation of ECM degradation enzymes. Basile et al[60] synthesized more stable form of CUR which is BDMC and diacetylcurcumin than CUR to enhance the activity in the physiological medium and improved nuclear cellular uptake. The mechanism of their chemotherapeutic effect was studied by the role in proliferation in the HCT116 human colon cancer cells. Both compounds damaged correct spindles formation and induced a p53 and $p21^{CIP1/WAF1}$-independent mitotic arrest, which is more stable and long lasting for BDMC. The anticancer effect of natural borneol with DMC has investigated with HepG2 cell line by MTT assay, flow cytometry and western blotting assay. Natural burneol-DMC showed in a significant decrease in cell viability due to pretreatment of natural burneol enhanced the cellular uptake of DMC. Natural burneol-DMC induced HepG2 cells growth was inhibited by induction of G2/M arrest due to by accumulation of the G2/M cell population. The combination of natural burneol and DMC induced G2/M phase arrest in HepG2 through ROS overproduction and it can be the potential for the development of chemosensitizer in the treatment of human cancer.

DMC inhibited adhesion, migration and invasion of MDA-MB-231 human breast cancer cells. MDA-MB-231 cells treated with DMC had decreased levels of ECM degradation-associated proteins, including matrix metalloproteinase-9 (MMP-9), membrane type-1 matrix metalloproteinase (MT1-MMP), urokinase plasminogen activator and urokinase plasminogen receptor even at the level of urokinase plasminogen inhibitor was upregulated. DMC also reduced the expression of intercellular adhesion molecule-1 and chemokine receptor 4. Treatment of DMC inhibited the DNA binding activity of nuclear factor-kappa B, which mediates the expression of MMPs, urokinase plasminogen, intercellular adhesion molecule-1 and chemokine receptor 4. The mechanism of DMC mediated anti-invasive activity strongly suggested that the involvement of modulation of the expression of invasion-associated proteins, possibly by targeting nuclear factor-kappa B in MDA-MB-231 cells (Yodkeeree et al, 2010).[61] Maspin, a serine protease inhibitor can suppress tumor growth and metastasis *in vivo* and tumor cell motility and invasion *in vitro* in breast cancer. Prasad et al[62] determined the clinical significance of maspin expression in invasive ductal carcinomas (IDCs) of breast in North Indian population and modulation of its expression by CUR. CUR modulated maspin expression in breast cancer cells by altering the expression of Bcl-2 and p53 proteins, liked to programmed cell death pathways, pointing maspin upregulation as one of the mechanisms involved in CUR mediated apoptosis. Einbond et al[63] examined the ability of rosemary/carnosic acid to inhibit the growth of human breast cancer cells and to synergize with CUR. Human breast cancer cells treated with rosemary/carnosic acid and assessed effects on cell proliferation, cell cycle distribution, gene expression patterns, activity of the purified Na/K ATPase and combinations with CUR. Rosemary/carnosic acid potently inhibits proliferation of ER-negative human breast cancer cells and induces G1 cell cycle arrest. Carnosic acid is selective for Her2 over expressing cells and can thus have the ability to inhibit the growth of cancer stem cells. The combination of carnosic acid and CUR can be effective to prevent and treat triple negative breast cancer. Photodynamic therapy (PDT) has been developed as a therapeutic modality, which could induce cell death via the formation of ROS under illumination. Curcuminoids-PDT significantly inhibited cell viability in breast cancer cell lines, in particular DMC-PDT has the highest anti-proliferative effect. DMC could be considered as a new photsensitizer in PDT for cancer treatment, it is confirmed with resulted in the reversion of cell viability, a reduced LC3 conversion and PARP cleavage by pre-treatment with a singlet oxygen scavenger or JNK inhibitor in the DMC-PDT. DMC-PDT has been more effective than DMC alone in inhibiting cell viability in breast cancer cell lines and can be a potential photosensitize in cancer therapy.[64]

The effects of curcumin on HIF-1α in cisplatin (DDP) sensitive and A549 and resistant A549/DDP cell lines were examined by RT-PCR and Western blot on the basis of CUR as a chemosensitizer in lung cancer. Combined CUR and DDP treatment clearly inhibited A549/DDP cells proliferation, reversed DDP resistance and triggered apoptotic death by promoting HIF-1α degradation and activating caspase-3 respectively. CUR offered an impetus to anticancer strategies through reducing HIF-1α dependent P-gp that might be a potent way for the overcoming MDR and expanding life time and quality in lung cancer patients. CUR with other chemotherapeutic agents can be used as a promising favorable strategy for lung cancer treatment.[65] CCK-8 assay method for cytotoxicity, flow cytometry for evaluation of apoptosis, western blot analysis, electron microscopy and quantification of GFP-LC3 punctuates for autophagy and apoptosis of lung cancer cell were used to investigate the effects of BDMC on non-small cell lung cancer (NSCLC) cell line, A549 and the highly metastatic lung cancer 95D cells. BDMC treatment significantly decreased smoothened and the transcription factor glioma-associated oncogene 1 expression and also inhibited the viability of NSCLC cells. BDMC induced the apoptotic cell death with the induction of autophagy in NSCLC cells. Blockage of autophagy by the autophagy inhibitor 3-methyladeine repressed the growth inhibitory effects and induction of apoptosis by BDMC. BDMC induced autophagy played a pro-death role in NSCLC by inhibiting Hedgehog signaling.[66]

### 6.5. Cardioprotective effects

CUR has extensive cardioprotective effects against diabetic cardiovascular complications, cardiac hypertrophy and myocardial infarction. Hong et al[67] assessed and explored the molecular mechanism of the cardioprotective effects of CUR by a rat model of coronary artery ligation. The genechip results suggested that gene expression in the border zone of infracted left ventricle of rats is a dimensional process after myocardial infarction. After treatment with CUR some amelioration in cardiac function, infarct sixe and serum biochemical markers were noted. Cardioprotective effects CUR are associated with cytokine-cytokine receptor interaction, ECM-receptor interaction, focal adhesions and colorectal cancer. The idiopathic pulmonary arterial hypertension is a complex disease that mainly affects pulmonary arterial circulation. This undergoes a remodeling with subsequent reduction of flow in the small pulmonary arteries. Because of this damage an increased vascular resistance gradually develops and over time it carries out in hears failure. CUR has been considered a potent anti-inflammatory agent useful for inflammatory diseases. Long investigations of anti-inflammatory effects of CUR showed a role for inactivation of NF-jB mediated inflammation.[68]

### 6.6. Radioprotective or radiosensitizing effect

Curcuminoids are well antioxidant polyphenols with radiomodulatory properties, radioprotecting non-cancerous cells while radiosensitizing tumor cells. Lopez-Jornet et al[69] investigated the possible protective effects of lycopene and CUR on the parotid glands of 40 female Sprague Dawley rats during irradiation of

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radiotherapy. Morphological and histopathological analyses showed less cell necrosis in the group treated with CUR than other groups. Lycopene and CUR given 24 h before irradiation reduced the structural damage to the salivary glands. Sebastia et al[70] reported the dual action viz radioprotecive and radiosensitive of polyphenols presence in CUR. They proposed for the observed radiosensitization is related to the G2-checkpoint abrogation by compromising its effectiveness to arrest the damaged cells in the G2-phase, resulting in a significant increase in the yield of radiation-induced chromatid breaks. These polyphenols exert simultaneously a dual mode of action but the overall radioprotective or radiosensitizing net effect would depend on the cell-cycle status of the cells at the time of irradiation.

### 6.7. Sexually transmitted infections

Sexually transmitted infections and unplanned pregnancies present a great risk to the reproductive health of women. Female controlled vaginal products directed toward disease prevention and contraception is needed urgently. Patel et al[71] developed poloxamer based thermo sensitive contraceptive vaginal *in situ* hydrogel of CUR, a plant derived CUR compound. Biodegradable hydrogels impregnated with Poloxamers and HPMC K4M could lead to the development of a non-hormonal, women friendly, long acting and biocompatible intravaginal contraceptive dosage form. The dosage form was optimized using a three-factor, three-level Box-Behnken Design (BBD). From BBD, it is concluded that batch containing 19.96% Poloxamer 407, 3.83% Poloxamer 188, 0.91% HPMC K4M was optimized, which could have maximum residence time, good efficacy in terms of contraception and highest user compliance. The dosage form could be used additionally as a spermicide inside a condom. CUR showed many beneficial effects similar to Clomiphene citrate in treating polycystic ovary syndrome (PCOS) condition and inducing ovulation. CUR restored the hormone and lipid profile, antioxidant and glycemic status as well as ovarian morphology in Letrozole induced PCOS animals due to its multiple pharmacological activities which could be useful in managing PCOS condition and prevent ovarian cell dysfunction, ovulation and thereby improving fertility. CUR can be a promising drug for treating clinical and pathological abnormalities in PCOS condition.[72] Akinyemi et al[73] investigated the preventive effects of turmeric rhizomes on some biomarkers of male reproductive function in L-NAME-induced hypertensive rats. Dietary supplementation with turmeric rhizome was associated with restoration of systolic blood pressure, sperm motility, testosterone level and an improvement of antioxidant status in the epididymides and testes of L-NAME-induced hypertensive rats. Turmeric rhizomes could be harnessed as functional foods to prevent hypertension-mediated male reproductive dysfunction.

### 6.8. Anti-esophageal adenocarcinoma activity and anti-nephrotoxicity

Hartojo et al[74] investigated the effects of CUR on NF-kB activity, cell viability and as a chemosensitizing agent with 5-Fluorouracil (5-FU) or cisplatin (CDDP) in esophageal adenocarcinoma (EAC). CUR alone inhibited NF-kB activity and induced apoptosis in both Flo-1 and OE33 EAC cell lines as determined by Western blot analysis, NF-kB reporter assays and Caspase-Glo 3/7 assays. NF-kB inhibiting activity of CUR was shown to increase apoptosis and enhance both 5-FU and CDDP-mediated chemosensitivity suggested that it may have potential application in the therapy of patients with EAC. Hismiogullari et al[75] studied the protective effect of CUR on carbon tetrachloride ($CCl_4$)-induced nephrotoxicity to evaluate the detailed mechanisms by which CUR exerts its protective action with thirty male Wistar-Albino rats. Administration of $CCl_4$ significantly increased the levels of renal function test such as creatinine and blood urea nitrogen. Treatment of $CCl_4$ significantly elevated the oxidant status of renal tissues while decreasing its anti-oxidant status. CUR displayed a renal protective effect as evidenced by a significant decrease in inflammation and apoptosis during histopahtological examination. The administration of $CCl_4$ resulted in an increase in malondialdehyde (MDA) production due to an increase in membrane lipid peroxidation. CUR can have an important role to play in protecting the kidney from oxidative abuse.

### 6.9. Antiviral and antifungal activity

The anti-influenza activity of CUR was evaluated by Chen et al.[76] They reported that the treatment with 30 μM CUR reduced the yield of virus by over 90% in cell culture. Plaque reduction test and HI test clearly showed that CUR interrupts virus-cell attachment, which leaded to inhibition of influenza virus propagation. Time of drug addition experiments demonstrated CUR had a direct effect on viral particle infectivity that was reflected by the inhibition of hemagglutination; this effect was observed in H1N1 as well as in H6N1 subtype. CUR can be a promising potential for using as an anti-influenza drug. Zhang et al[77] investigated and compared the action of curcuminoids on the causal pathogens of *Candida albicans* growth by microcalorimetry. The antifungal effect of CUR was stronger than that of DMC. It was confirmed by the structural activity relationship that the existence of the methoxy group might enhance lipophilicity of the mother nucleus, which made it easier for the molecular to enter into the cell membrane of fungi to inhibit its growth.

### 6.10. Anti-angiogenic and anti-proliferative activities

The anti-angiogenic effects of Ar-turmerone were evaluated in human microvascular endothelial cells, zebrafish and Matrigel plugs mouse models. Ar-turmerone significantly inhibited the proliferation, tube formation and motility of HMEC-1 cells at non-cytotoxic concentrations. It exerted anti-angiogenic activity by down-regulation of Angiopoietin-2 and Tie-2 expression in zebrafish. It significantly inhibited the blood vessel growth, confirmed by the *in vivo* studies using Matrigel plugs mouse model. Ar-turmerone can be used as a potential anti-angiogenic agent.[78] Yue et al[79] also demonstrated the enhancement of anti-proliferative and anti-angiogenic activities of CUR in the presence of turmerones in human colon cancer cells and endothelial cells respectively. The superior anti-tumor effects of turmeric extract, which contains CUR, turmerones and other constituents were verified in tumor bearing mice, indicating the potential use of turmeric for colorectal cancer adjuvant therapy.

### 6.11. Anti-immunomodulatory activity

The immunomodulatory activities of the polar fraction of *C. longa* hot water extracts were investigated using human peripheral blood mononuclear cells (PBMC). The high polarity fraction of the hot water extract was exhibited stimulatory effects on PBMC proliferation by (methyl-3H)-thymidine incorporation assay. The immunostimulatory effects of *C. longa* polysaccharides on PBMC revealed the potential use of curcuminoids and polysaccharides as an adjuvant supplement for cancer patients whose immune activities were suppressed during chemotherapies.[13] The anti-proliferative activities of the curcuminoids and two turmerones (α-turmerone and Ar-turmerone) compounds were isolated from the rhizome of *C. longa* using human cancer cell lines HepG2, MCF-7

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and MDA-MB-231. Curcuminoids and α-turmerone significantly inhibited proliferation of cancer cells in a dose dependent manner. Two turmerones are shown stimulatory effects on PBMC proliferation and cytokine production. The anti-proliferative effect of curcuminoids, α-turmerone and immunomodulatory activities of Arturmerone revealed the potential use of curcuminoids and turmerones as a chemopreventive agent.[80]

### 6.12. Anti-inflammatory

Kim et al[81] explained an anti-inflammatory BDMC signaling pathway leading to heme oxygenase-1 expression was mediated via rapid elevation of intracellular $[Ca^{2+}]_i$, that subsequently led to downstream activation of calmodulin/calmodulin dependent protein kinase II, extracellular signal regulated kinase 1/2 and NF-E2-related factor-2. The biological relevance of the signaling pathway to the anti-inflammatory capacity of BDMC was demonstrated by *in vitro* inflammation model by blocking the $Ca^{2+}$ release from IP3 channels or inhibition of calmodulin dependent protein kinase II or extracellular signal regulated kinase 1/2 lead to reduction in inhibition by BDMC of LPS induced inducible nitric oxide synthase expression and nitric oxide production. $Ca^{2+}$/calmodulin-dependent protein kinase II-extracellular signal regulated kinase ½-NF-E2- related factor-2 cascade as a novel anti-inflammatory pathway mediating BDMC signaling to heme oxygenase-1 expression in macrophages. Cooney et al[82] reported reducing capacity CUR against colon inflammation in the Mdr1a$^{-/-}$ mouse model of human inflammatory bowel disease using a combined transcriptomics and proteomics approach. Colon mRNA transcript levels were assessed using microarrays and colon protein expression was measured using 2D gel electrophoresis and LCMS protein identification and the colonic histological injury score was also determined. The action of CUR against inflammation has proved via multiple molecular pathways, including reduced immune response, increased xenobiotic metabolism, resolution of inflammation through decreased neutrophil migration and increased barrier remodeling.

### 6.13. Anti-acidogenic and anti-arthritic activity

Curcuminoids and other main components of turmeric had inhibitory effects on the virulence properties of streptococcus mutans biofilms such as bacterial adherence, acidogenicity and aciduricity without killing target bacterium. These compounds can be utilized for controlling dental biofilms and subsequent dental caries formation.[2] The effect of curcumin in combination with a subtherapeutic dose of methotrexate was investigated to salvage hepatotoxicity, oxidative stress and producing synergistic anti-arthritic action with methotrexate by Wistar albino rats were induced with arthiritis through subplantar injection of Freund's Complete Adjuvant and pronounced arthritis after 9 days of injection. The concomitant use of CUR with methotrexate was capable of exerting a beneficial therapeutic effect by reducing arthritis and also significantly alleviating hepatocellular injury caused by methogtrexate. The main advantages of the usage of the combination was a reduction in dose of methotrexate by half, synergistic anti-arthritic action at both dose levels of CUR, reduction in hepatocellular injury and a prominent antioxidant action.[83] Yang et al[84] reported the hypothesis that gut hormones serve as an intermediary agent for the anti-arthritic action of CUR. The protein and mRNA levels of gut hormones in CUR-treated rats were analyzed by ELISA and RT-PCR. Somatostatin (SOM) depletory and receptor antagonist were used to verify the key role of SOM in CUR-mediated anti-arthritic effect. Oral administration of CUR exhibited superior anti-arthritic effect through augmenting SOM secretion from the endocrine cells in the small intestines via cAMP/PKA and $Ca^{2+}$/calmodulin-dependent kinase II signaling pathways.

### 6.14. Anti-acanthamoebic activity

Acanthamoeba is an opportunist protest pathogen and infect the cornea to produce eye keratitis and the central nervous system to produce fatal granulomatous encephalitis. The anti-acanthamoebic potential of resveratrol and curcuminoids were investigated by Aqeel et al[85] with adhesion and cytotoxicity assays were performed using primary human brain microvascular endothelial cells, which contribute the blood-brain barrier. Pre-exposure of organisms to 100 μg resveratrol and DMC prevented amoeba binding by 57% and 73% respectively, while cytotoxicity of host cells was inhibited by 86%. From the results, resveratrol and DMC exhibited strong anti-acanthamoebic effects.

### 6.15. Mutagenicity and hepatoprotective activity

Vieira et al[86] studied and compared the mutagenicity and blood compatibility of curcumin using drug eluting stent components such as paclitaxel and sirolimus by Ames test for assessing mutagenicity and measuring platelet activation and fibrinogen adsorption on poly (DL-lactide-co-glycolide, PLGA) film to evaluate blood compatibility. A significant induction in the frequency of bacterial his$^{+}$ revertant colonies by paclitaxel at different concentrations was observed and also a significant reduction in platelet activation by on PLGA films containing 30% and 50% by weight CUR. Intrinsic hydrophobic properties of CUR could favor fibrinogen adsorption on PLGA films.

Naik et al[87] have used the liver slice culture model to demonstrate hepatoprotective activity of CUR *in vitro*; ethanol used as a hepatotoxin and the cytotoxicity of ethanol is estimated by quantitating the release of lactate dehydrgenase. The release of lactate dehydrgenase was significantly reduced along with lipid peroxidation and the activity of antioxidant enzymes was kept low indicated that CUR by its antioxidant activity of antioxidant enzymes was kept low indicated that CUR by its antioxidant activity reduced the oxidative stress induced by ethanol and protected the liver cells *in vitro*.

### 6.16. Arsenic and chromium toxicity

Arsenic is a human carcinogen and a potent hepatotoxin. Environmental exposure to arsenic imposes a serious health hazard to human and other animals worldwide. Muthumani et al[88] reported tetrahydrocurcumin (THC) pretreatment markedly ameliorated the arsenic-induced dyslipidemia, mitochondrial toxicity and ultrastructural alterations in rat liver. It is confirmed by the hepatic-mitoprotective nature of THC. The possible mechanism was suggested that the THC could be due to quenching of free radicals by THC, lowering of lipid peroxidases, lipids and improving the antioxidant-enzyme activities and $Ca^{2+}$, thereby improving the hepatic mitochondrial function in arsenic intoxicated rats. THC exhibited a significant protective effects on mitochondria, which is a crucial element involved in both triggering and mediating the hepatoprotective response in hepatic cells. THC can be an effective antioxidant phytochemical entity against arsenic-induced mitochondrial damage and oxidative stress.

Molina-Jijon et al[89] reported the role of mitochondria in the protective effects of CUR, direct and indirect antioxidant, against the renal oxidant damage induced by the hexavalent chromium [Cr (VI)] compound potassium dichromate ($K_2Cr_2O_7$) in rats. CUR treatment attenuated $K_2Cr_2O_7$-induced renal dysfunction, histological damage, oxidant stress, and the decrease in antioxidant

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enzyme activity both in kidney tissue and in mitochondria. The prevention of mitochondrial function played a key role in the protective effects of CUR pretreatment against $K_2Cr_2O_7$-induced renal oxidant damage.

## 7. Metal complexes of curcuminoids and their biological activities

Metal complexes of curcuminoids and their derivatives exhibited favorable biological activity compared to the parent ligands (Table 2). Metal ions can be complexed with the β-diketo moiety of curcuminoids. The formed metal complexes often possess a high stability and activity.

### 7.1. Anti-cytotoxicity

A class of ferrocenyl oxovanadium (IV) complexes of curcuminoids viz. [VO(Fc-tpy)(CUR)]($ClO_4$) (1), [VO(Fc-tpy)(BDHC)]($ClO_4$) (2), [VO(Fctpy)(BDMC)]($ClO_4$) (3) and [VO(Ph-tpy)(CUR)]($ClO_4$) (4), of 40-ferrocenyl-2,20:60,200-terpyridine(Fc-tpy) and 40-phenyl-2,20:60,200-terpyridiine (Ph-tpy) and monoanionic curcumin (CUR), bisdehydrocycurcumin (bDHC) and bis-demethoxy curcumin (BDMC) were designed, prepared and characterized and their photo-induced DNA cleavage activity and phototoxicity studied by visible light. The complexes showed remarkable PDT activity in HeLa cells compared to the normal 3T3 cells. The presence of both methoxy and hydroxyl groups are essential in the curcuminoid moiety to achieve the desired cytotoxic effect which is confirmed by the MTT assay. ICP-MS and fluorescence microscopic studies exhibited significant cellular uptake of the complexes within 4 h of treatment with complexes. These complexes can be very important to develop the medicinal chemistry of bioorganometallic complexes as metal based photocytotoxic agents.[90] Two ruthenium-arene complexes containing curcuminoid ligands (η6-p-cymene) Ru(CUR)Cl-CUR -thiophene aromatic curcuminoids have been synthesized by Lei et al.[91] The complexes were evaluated for their *in vitro* antiproliferative activities against Hela human cervical epithelioid cancer, as well as BEL-7404 and SMMC-7721 human liver cancer cell lines. These complexes showed moderately active cytotoxicity against three carcinoma cell lines and displayed lower $IC_{50}$ values than 1. Agarose gel electrophoresis results indicated that the DNA binding activity by pBR322 plasmid DNA of the two complexes correlated quite with their cytotoxicity.[91] Copper (II) complexes [Cu(Fc-aa)(CUR)] (1–3) of CUR and N-ferroceynlmethyl-L-amino acids (Fc-aa), viz ferrocenylmethyl-L-tyrosine (Fc-TyrH), ferrocenylmethyl-L-tryptophan (Fc-TrpH) and ferrocenylmethyl-L-methionine (Fc-MetH) were prepared to investigate the DNA photocleavage activity, photocytotoxicity and cellular localization in HeLa ad MCF-7 cancer cells. Acetylacetonate (acac) complexes [Cu(Fc-aa)(acac)] (4–6) were prepared and used as controls. The

**Table 2**
Various curcuminoids based metal complexes and their potential application in different biological applications.

| Disease/Activity | Metal complexes | Model used and study design | Effect of curcuminoids treatment | References |
|---|---|---|---|---|
| Anti-cytotoxicity | Ferrocenyl oxovanadium (IV) complexes of curcuminoids | HeLa and Hep G2 cells and in normal fibroblast cells (3T3) | Significant cellular uptake of the complexes within 4 h of treatment. The complexes showed remarkable PDT activity in HeLa cells compared to the normal 3T3 cells. | Balaji et al[90] |
| Anti-cytotoxicity | Ruthenium-arene complexes containing curcuminoid ligands | Cervical (HeLa) and liver cancers (BEL-7404 and SMMC-7721) cells | These complexes showed moderately active cytotoxicity against three carcinoma cell lines and displayed lower IC50 values than 1. | Lei et al[91] |
| Anti-cytotoxicity | CUR -copper (II) complexes | HeLa and MCF-7 cells | Showed remarkable *in vitro* photocytotoxic activity on cancer cells in visible light. Great potential for releasing their clinical applications in PDT. | Goswami et al[92] |
| Neuroprotective activity | Manganese complexes of CUR | Male ICR mice and NG108-15 cells | Better neuroprotective effects in both 2VO-water maze task and cell culture models. | Vajragupta et al[93] |
| Neuroprotective activity | Gallium (III) and copper (II)-CUR complexes | xanthine/xanthine oxidase assay | Charge delocalization of metal complexes play an important role in determining the scavenging ability. | Ferrari et al[94] |
| Anti-oxidant activity | Copper (II) complexes of CUR | xanthine/xanthine oxidase assay and DPPH assay | Cu (II)-CUR complex having distortion from square planar geometry is exhibited a better superoxide dismutase activity and good free radical scavenger. | Barik et al[95] |
| Anti-oxidant activity | Curcuminoids complexes with Ga (III), In (III) and $[VO]^{2+}$ | Diabetic treated male Wistar rats | Acetylation of CUR and BDC significantly decreased the antioxidant potential of compounds containing these ligands. | Mohammadi et al[96] |
| Anticancer | Mixed-ligand oxo-bridged iron(III) complexes with CUR | HeLa and MCF-7 cancer cells | One of the complexes had a strong absorption band in the visible region and showed promising photocytotoxicity in HeLa and MCF-7 cancer cells in visible light. | Sarkar et al[97] |
| Anti-rheumatoid arthritis | Vanadyl curcumin complex | HIG82 synoviocytes and A7r5 smooth muscle cells | Vanadyl curcumin was more effective in inhibition of smooth muscle cell growth, synoviocyte proliferation and mouse lymphoma cell growth than CUR alone. | Thompson et al[98] |
| Antimicrobial activity | CUR based metallointercalators with amino acid | pBR322 circular plasmid DNA | Complexes are exhibited better activity against bacteria and fungi. | Chandrasekar et al[99] |

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design of the complexes is based on to stabilize the hydrolytically unstable CUR, which possesses rich photochemistry, on binding to a Cu (II) center, which in turn is bound to the ferrocene-appended amino acids for better redox activity and lipophilicity. The Cu (II) complexes 1–3 showed visible light-induced plasmid DNA cleavage activity and they are nontoxic in dark to the cancer cells showed a significant photoenhanced cytotoxicity with visible light. The photodynamic therapy (PDT) effect was compared well with reported for the FDA approved porphyrin drug Photofrin®. Design and incorporation of biocompatible CUR and ferrocene-appended reduced Schiff bases of amino acids to a Cu (II) center have resulted in a new class of compounds have shown remarkable *in vitro* photocytotoxic activity on cancer cells in visible light, thus presenting a great potential for releasing their clinical applications in PDT.[92]

### 7.2. Neuroprotective activity

Three manganese complexes of CUR and related compounds, diacetylcurcumin (AcylCUR) and ethylenediamine derivatives (CURED) were synthesized and evaluated by *in vitro* for anti-lipid peroxidatioin and superoxide dismutase activity. The complexes potentiated neuroprotective effects against learning and memory impairment in transient cerebral ischemic mice and on $H_2O_2$-induced cell damage in NG108-15 cells. The prepared manganese complexes of CURCURx and AcylCURCURx showed better neuroprotective effects in both 2VO-water maze task and cell culture models. The protective effect of Acyl-CURCURx was clearly demonstrated by MPTP-induced dopaminergic neurotoxicity in mice and also suggested a role for super oxide dismutase mimics in the protection of neutrodegeneration mediated by chemicals and drugs. AcylCURCURx and CURCURx can be the most promising neuroprotective agent for vascular dementia.[93] Ferrari et al[94] investigated the metal complexing ability of substituted curcuminoids of new chelating molecules using gallium (III) and copper (II), with biological properties comparable with curcumin with improved stability as new potential Alzheimer's disease therapeutic agents. The K2T derivatives originate from the insertion of a $-CH_2COOC(CH_3)_3$ group on the central atom of the diketonic moiety of curcumin. In aqueous solution the prevalent form is the diketo one, but the addition of metal ion ($Ga^{3+}$ and $Cu^{2+}$) causes the dissociation of the enolic proton creating chelate complexes and shifting the tautomeric equilibrium towards the keto-enol form. The bond dissociation energy (BDE) values of the ligands suggested that charge delocalization plays an important role in determining the scavenging ability. Ga (III) can be very promising as superoxide-scavengers to use in super oxide dismutase mimics.

### 7.3. Antioxidant activity

Two stoichiometrically different copper (II) complexes of curcumin (1:1 and 1:2 for copper:curcumin) were investigated for their superoxide dismutase activity, free radical scavenging ability and antioxidant potential. Depending upon the structure, these two complexes possess different superoxide dismutase activities, free radical scavenging abilities and antioxidant potentials. EPR spectra of the complexes showed that the 1:2 Cu (II)-CUR complex is square planar and the 1:1 Cu (II)-CUR complex is distorted orthorhombic. The 1:1 complex would be able to undergo and sustain the distortion from square planar geometry to the distorted tetrahedral one during its reaction with superoxide radical. This allows for the compound to remain intact and undergo many redox cycles and can be act as efficient antioxidant. On the other hand the 1:2 complex is planar but rigid and cannot undergo the distortion and therefore is a less powerful antioxidant. Thus the 1:1 Cu (II)-CUR complex having distortion from square planar geometry is exhibited a better superoxide dismutase activity and also a good free radical scavenger.[95] CUR complexes with Ga (III), In (III) and $[VO]^{2+}$ have been synthesized by Mohammadi et al.[96] A ligand bis [4-acetyl-3-hydroxyphenyl]-1,6-heptadiene-3,5-dione (DABC) also prepared and characterized. Acetylation of CUR and BDC significantly decreased the antioxidant potential of compounds containing these ligands, but did not affect cytotoxicity in mouse lymphoma cells. The DABC displayed moderate cytotoxicity and readily formed a vanadyl bisligand complex, which also showed modest anticancer potential.

### 7.4. Anticancer activity

Photoactive metal complexes have emerged as potential candidates in the photodynamic therapy (PDT) of cancer. Sarkar et al[97] reported the synthesis, characterization and visible light-triggered anticancer activity of two novel mixed-ligand oxo-bridged iron (III) complexes, viz., $[\{Fe(L)(acac)\}_2(\mu\text{-}O)](ClO_4)_2$ (1) and $[\{Fe(L)(CUR)\}_2(\mu\text{-}O)](ClO_4)_2$ (2), where L is bis-(2-pyridylmethyl)-bezylamine. The control complex 1 is inactive both in the light and dark. Complex 2 had a strong absorption band in the visible region and showed promising photocytotoxicity in HeLa and MCF-7 cancer cells in visible light. It also accumulated in the cytoplasm and induced apoptosis, which was triggered by the photoinduced formation of ROS.

### 7.5. Anti-rheumatoid arthritis

A vanadyl curcumin complex was prepared by Thompson et al[98] for anti-rheumatoid arthritis. Vanadyl curcumin was more effective in inhibition of smooth muscle cell growth, synoviocyte proliferation and mouse lymphoma cell growth than CUR alone. It was an efficient inhibitor of synoviocyte proliferation and suggested striking potential as a particular non-toxic treatment for rheumatoid arthritis. The vanadyl curcumin complex was ineffective as an insulin mimetic agent proved by an acute and chronic screening test moreover, it also proved to be exceptionally non-toxic, with no evidence of negative symptomatology during a month-long treatment period.

### 7.6. Antimicrobial activity

Curcumin based metallointercalators with amino acid such as cysteine has been synthesized by Chandrasekar et al.[99] The ligand is coordinated via ketimine, carbonyl and enolic oxygen of CUR analog and the complexes have the composition of metal-ligand type. The prepared complexes are strong intercalators and the potential nucleases as compared to CUR based free ligand and the complexes are also exhibited better activity against bacteria and fungi than the ligand.

## 8. Biological activities of various curcuminoid formulations

Curcuminoids and their analogs are often a source of biological activities such as drugs or drug templates with limited toxicity and high activity (Table 3).

### 8.1. Drug delivery systems

Polymeric-CUR implants were developed to overcome the poor biopharmaceutical quality. These implants are a viable alternative of delivery of CUR to circumvent its bioavailability problem with the traditional oral route and to harness its complete therapeutic potential. These implements were found to provide higher CUR

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**Table 3**
Various curcuminoids based formulations and their prospective application in different biological applications.

| Disease/Activity | Formulations | Model used and study design | Effect of curcuminoids treatment | References |
|---|---|---|---|---|
| Anti-cytotoxicity | CUR conjugated AuNPs | HeLa cells, glyoma cells and Caco2 | HA-CUR@AuNPs exhibited more cytotoxicity comparing to free CUR with enhanced targeting and improved efficacy | Manju and Sreenivasan[103] |
| Anti-cytotoxicity | Starch based microspheres with CUR | Caco-2 and HCT-116 tumor cell lines | CUR-microspheres showed a very promising devise for the controlled release of CUR for the treatment of colon cancer.<br>CUR-loaded microspheres presented much higher activity against Caco-2 and HCT-116 tumor cell lines than free CUR. | Pereira et al[104] |
| Anti-cytotoxicity | Liposome encapsulation of CUR | MCF7 cancer cells | Liposomal encapsulation of CUR can enhance cellular effect of the drug. | Hasan et al[105] |
| Anti-cytotoxicity | CUR-PENPs based on HA/CS | C6 glioma cells | CUR-PENPs showed stronger dose dependent cytotoxicity against C6 glioma cells and higher performance in uptake efficiency in C6 cells. | Yang et al[106] |
| Anticancer | Tf-CUR-SLNPs | MCF-7 breast cancer cells | The cytotoxicity, anticancer activity ROS and cell uptake was found to be increased considerably with Tf-CUR-SLNPs compared to CUR, CUR-SSS and CUR loaded SLNPs. | Mulik et al[107] |
| Anticancer | CUR- PTX administrated in oil-in-water nanoemulsion | SKOV3 turmor-bearing nu/nu female mice | These nanoemulsion formulations can serve as an effective delivery carrier for oral administration of anticancer agents. | Ganta et al[108] |
| Anticancer | Carboxymethylcellulose-THC conjugates | Human colon adenocarcinoma cell lines (HT-29) | High selective cytotoxicity against HT-29.<br>Sustained release in the colon to be an effective treatment for colonic cancer. | Plyduang et al[109] |
| Anticancer | BDMC analog loaded chitosan-starch nanocomposite | MCF-7 breast cancer cell lines and VERO cell lines | BDMCA-CS showed good drug entrapment efficiency and percentage drug content.<br>*In vitro* drug release profile showed a very slow, sustained diffusion controlled release and polymeric erosion of the drug. | Subramanian et al[110] |
| Anti-cancer anti-aging and anti cytotoxic effect | "Cureit"- a novel bio available CUR formulation | Hyaluronidase inhibition assay human vascular endothelial cells | Inhibit elestases activity at higher concentration.<br>Highest inhibition of 42% to hyaluronidase | Gopi et al[111–113] |
| Anti-cancer and anti cytotoxic effect | CUR loaded mixed micelles of Pluronic F-127 and Gelucire® 44/14 | Human lung cancer cell line A549 | CUR-MM showed significant improvement in cytotoxic activity as 3 folds and oral bioavailability as around 55 folds of CUR as compared to CUR alone. | Patil et al[114] |
| Antioxidant activity | Encapsulated CUR into NPs consisting of ethyl cellulose and/or methyl cellulose | DPPH assay method | Nanoencapsulation protected CUR from photodegradation and can retained its antioxidant capacity. | Suwannateep et al[115] |
| Antioxidant activity | Ethanol and glycerol catalyzed CUR encapsulated nanoemulsions | DPPH assay method | The CUR encased bionanoemulsions showed a radical scavenging activity of more than 90% as compared with pure CUR. | Malik et al[116] |
| Antibacterial and antioxidant activity | Tetra hydrocurcuminoids incorporated chitosan | Disk-diffusion method and DPPH assay method | THC-chitosan have retained their bioactivity against *Listeria innocua*.<br>High free radical scavenging activity against DPPH | Portes et al[117] |
| Antibacterial activity | Asymmetric and glycosylated curcuminoids | *Enterococcus faecalis* and *Escerichia coli* | Glycosylation of the aromatic substituents of CUR lead to an extensive reduction of phototoxicity towards the model bacteria. | Tovsen et al[118] |
| Neuroprotective effect | CUR-SLNPs | Male Lacca mice | Histopathology of brain sections of CUR-SLNPs treated groups indicated significant improvements. | Kakkar and Kaur[119] |

**Table 3** (*continued*)

| Disease/Activity | Formulations | Model used and study design | Effect of curcuminoids treatment | References |
|---|---|---|---|---|
| Neuroprotective effect | CUR-SLNPs | Male Wistar rats | An improvement of 90% in cognition and 52% inhibition of acetylcholinesterase versus cerebral ischemic group were observed after administration of CUR-SLNPs. Levels of superoxide dismutase, catalase, glutathione and mitochondrial complex enzyme activities were significantly increased. | Kakkar et al[120] |
| Neuroprotective effect | CUR loaded nanostructured lipid carriers | Male CD1 mice | CUR can able to decrease histone acetylation in the CNS when induced in NLCs. Western blot analysis showed NLC-CUR in mice induces a marked hypoacetylation of histone 4 (H4) at lysine 12 (K12) in the spinal cord compared with control group. | Puglia et al[121] |
| Neuroprotective effect | Pyrazole and isoxazole derivatives of CUR | Insect cell culture medium (IPL-41) | Pyrazole CUR offered neuroprotective action in the excitotoxic cascade by inhibiting CaMKII activity. | Mayadevi et al[122] |
| Neuroprotective effect | CUR derivatives | Murine GLUTag L cell line | CUR significantly stimulated GLP-1 secretion in GLUTag cells and significant increase involved the $Ca^{2+}$-CaMKII pathway. | Takikawa et al[123] |
| Neuroprotective effect | Recemic tetrahydrocurcumin, tetrahydrodemethoxycurcumin and tetrahydrobis demethoxycurcumin dihydropyrimidinone analogs | AChE inhibitor | The evaluation of acetylcholinesterase inhibitors for Alzheimer's disease of these analogs showed that they exhibited higher inhibitory activity than the CUR. | Arunkhamkaew et al[124] |
| Neuroprotective effect | CUR based diarylheptanoid analogs | Human U87 MG GBM and neuroblastoma (NB) SK-N-SH and SK-N-FI cells. | Analogs proved efficacious against neuroblastoma (SK-N-SH and SK-N-FI) and glioblastoma multiforme (U87MG) cell lines. | Campos et al[125] |
| Neuroprotective effect | CUR micelles | NMRI mice, PC12 cells and mouse brain mitochondria | CUR micelles improved bioavailability of native CUR around 10–40 fold in plasma and brain of mice. CUR micelles proved to be more efficient in preventing mitochondrial swelling in isolated mouse brain mitochondria and protecting PC12 cells form nitrosative stress than native CUR. | Hagl et al[126] |
| Anti-diabetic activity | CUR, curcumin C3 complex® and tetra hydrocurcuminoids | Hep3B human hepatoma cells and H4IIE rat hepatoma cells | Curcuminoids effectively suppressed dexamethasone-induced PEPCK and G6Pase in H4IIE rat hepatoma and Hep3B human hepatoma cells. | Kim et al[127] |
| Anti-malarial activity | Curcuminoids-loaded lipid NPs | Malaria induced Albino mice | *In vivo* pharmacodynamic activity revealed two fold increases in antimalarial activity of curcuminoids entrapped in lipid NPs. | Nayak et al[128] |
| Anti-malarial activity | Curcuminoid loaded liposome | *Plasmodium berghei* infected Albino mice | It showed improvement of antimalarial activity in combination with standard antimalarial drug artemisinin and also prevent recrudescence. | Aditya et al[11] (2012) |
| Antifungal and antibacterial activity | Curcuminoids with polyethylene glycol | Agar well-diffusion method and disk diffusion method | All extracts exhibited a 100% inhibitory effect on the growth of tested fungi and showed low antibacterial activity. | Perko et al[6] |
| Anti-cytotoxicity | Aromatic ring glycosylation of CUR | cDDP-sensitive human ovarian carcinoma cell line | Compounds displayed a good selectivity and much less toxic against non-tumorigenic Vero cells. | Ferrari et al[129] |

(*continued on next page*)

**Table 3** (*continued*)

| Disease/Activity | Formulations | Model used and study design | Effect of curcuminoids treatment | References |
|---|---|---|---|---|
| Anti-cytotoxicity | Different substituents at the 4-position of the phenyl group in CUR | Human epidermoid carcinoma cell line A-431 and human glioblastoma cell line U-251 | CUR-analogs exhibited selective and potent cytotoxic activity against human epidermoid carcinoma cell line A-431 and human glioblastoma cell line U-251 indicated their specific potential in the chemoprevention and chemotherapy of skin cancer and glioma. | Zhang et al[130] |
| Anti-cytotoxicity | Fifteen CUR analogs | Human prostate cancer cell lines, androgen-dependent LNCaP and androgen-independent PC3 | Cell morphology study revealed that the cytotoxicity of CUR analogs or CUR-anti-androgen conjugates detected from both prostate cancer cell lines might be due to the suppression of pseudopodia formation. | Shi et al[131] |
| Anti-cytotoxicity | Triazole-curcuminoids | SY-SY5Y and HeLa cells | Inhibit NF-kB without showing cytotoxicity. | Caprioglio et al[132] |
| Anti-inflammation | Seven N-unsubstituted curcuminoid pyrazoles | Caco-2 cells, human epithelial intestinal cells | Significantly down-regulated MMP-9 activity on inflammation-induced intestinal epithelial cells. | Claramunt et al[133] |
| Anti-inflammation | Curcuminoid analogs | U937 and RAW 264.7 cell culture | Significant dose-response inhibitory action upon the synthesis of NO due to suppression of both iNOS gene and enzyme expression without any effects upon scavenging of nitrite. | Tham et al[134] |
| Anti-inflammation | Aromatic and heterocyclic aromatic curcuminoids | Female Wistar rats | Prepared curcuminoids had potent activity in the antiarthritic assay with little gastric or systemic toxicity compared with the vehicle-treated controls. | Khan et al[12] |
| Anti-inflammation | 3(5)-trifluoromethyl-5(3)-substituted-styryl-1H-pyrazoles derived from curcuminoids | NOS inhibitory activity | Inhibition percentages of the iNOS isoform higher than 50%. | Nieto et al[135] |
| Anti-inflammation | CUR bisacetamides | Bovine serum albumin assay and A549 cancer cell line | All the compounds exhibited potent to good anti-inflammatory, antioxidant and significant cytotoxic activities. | Sribalan et al[136] |
| Anti-inflammation | Dimethylamino curcuminoids | Bovine serum albumin assay | Dimethylamino curcuminoid derivatives have shown potent anti-inflammatory properties than parent CUR. | Banuppriya et al[137] |
| Antimicrobial activity | Chemically modified natural curcuminoids | Protozoa of the *Trypanosoma* and *Leishmania* species. | 1,7-bis(4-hydroxy-3-methoxyphenyl) hept-4-en-3-one was the most active compound and more active than the standard veterinary drug diminazene aceturate. | Changtam et al[8] |
| Antimicrobial activity | Structurally modified 55 CUR, DMC and BDMC analogs | *Mycobacterium tuberculosis* | The presence of a suitable para-alkoxyl group on the aromatic ring which is attached in close proximity to the nitrogen function of the isoxazole ring and a free para-hydroxyl group on another aromatic ring enhances the biological activity. | Changtam et al[138] |
| Antibacterial activity, antifungal activity and cytotoxicity | Curcumin derivatives with sulfonamides | *Bacteria: S.aureus, B.cereus, S. typhi, P.aeruginosa* and *E. coli*<br>*Fungai: A. niger, A. flavus, T. viride* and *C. lunata*<br>Human cell lines HeLa, Hep G-2, QG-56 and HCT-116. | One sulfonamide molecule attached on carbonyl group of CUR showed the most potent biological activity against tested bacteria and fungi and also displayed higher cytotoxicity than CUR | Lal et al[139] |
| Antimicrobial activity | C5-curcumin-2-hexadecynoic acid | Methicillin-resistant *S. aureus* strains | The conjugate was active against eight MRSA strains at MICs due to the presence of 2-hexadecynoic acid (2-HAD) and also increased 4−8 fold its antibacterial activity. | Sanabria-Rios et al[140] |
| Anticancer activity | 12 symmetrical curcuminoids | Fos-Jun-DNA complex formation | The products are nearly 90 times more effective than CUR. | Hahm et al[141] |

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**Table 3** (*continued*)

| Disease/Activity | Formulations | Model used and study design | Effect of curcuminoids treatment | References |
|---|---|---|---|---|
| Anti-cancer and anti-angiogenesis activity | Symmetrical α,β-unsaturated and saturated ketones curcuminoids | Human tumor cell lines | The analogs were more efficacious than CUR and the commonly used chemotherapeutic drug, cisplatin against a variety of tumor cell lines. More effective in the anti-angiogenesis assays run at Emory and as potent as the anti-angiogenic drug TNP-470. | Adams et al[142] |
| Anticancer activity | Cyclic analogs of CUR with aromatic aldehydes | Murine and human cancer cell lines | Significant anticancer activity against representative murine and human cancer cell lines during *in vitro* bioassays. | Youssef et al[143] |
| Anticancer activity | Sixty one CUR-related compounds | Prostate cancer PC-3 cells, pancreas cancer Panc-1 cells and colon cancer HT-29 cells by MTT assay | Studied CUR-compounds were 34 −117 fold more active than CUR for inhibiting the growth of cultured human prostate, pancreas ad colon cancer cells. | Wei et al[144] |
| Anticancer activity | C5-CUR-FA containing decanoic acid or palmitic acid moieties | Colorectal adenocarcinoma cell | Inhibition of both NFkB and DNA topoisomerase I by C5-CUR-FA conjugates is associated with their anticancer activity. | Sanabria-Rios et al[145] |
| Anticancer activity | CUR analogs such as ethyl CUR and 3,5-bis (substituted cinnamylidene)-N-alkyl-4-peperidone. | DMH-induced colon cancer in albino rats | 3,5-bis (substituted cinnamylidene)-N-alkyl-4-peperidone is the most active against the administration of the prophylactic treatment for the induction of cancer by 1,2-dimethylhydrazine. | Youssef et al[146] |
| Anticancer activity | Five series consisting of 43 CUR analogs | β-catenin protein and low β-catenin/Tcf transcriptional activity, HEK293T cells | These analogs were more potent than parent CUR as effective Wnt inhibitors and anti-invasive agents in human osteosarcoma. | Leow et al[147] |
| Antioxidant activity | CUR analogs − condensation of protected hydroxyl benzaldehyes with acetylacetone followed by deprotection | Superoxide free radical nitroblue tetrazolium and DPPH free radical scavenging methods | These analogs showed cytotoxicity to lymphocytes and promising tumor-reducing activity on Dalton's lymphoma ascites tumor cells. | Venkateswarlu et al[148] |
| Antioxidant activity | Three different lipids lipo − CUR formulation | Phosphate buffered saline, human blood, plasma and culture medium RPMI-1640 + 10% FBS | Liposomal CUR had higher stability than free CUR.<br>Liposomal CUR had stronger inhibitory effects on concanavalin A stimulated human lymphocyte, splenocyte and lymphoblastoid cell line proliferation. | Chen et al[149] |
| Antioxidant activity | t-Boc-protected amino acids with CUR. | DPPH method, β-carotene bleaching method and Ames test | These amino acid derivatives showed high antioxidant and antimutagenic activities than CUR due derivatization at the phenolic position of CUR. | Parvathy et al[150] |
| Antioxidant activity | Ferrocenyl-substituted CUR derivatives | DPPH, $ABTS^{+}$ and galvinoxyl radical. | Derivatives exhibited antioxidant effect and protective effects on $Cu^{2+}$/GSH-induced oxidation of DNA. | Li et al[151] |
| Antioxidant and anticytotoxicity activity | 4H-pyrimido [2,1-b] benzothiazole, pyrazole and benzylidene derivatives of CUR | DPPH, superoxide and nitric oxide radical scavenging activity evaluation methods<br>Hep-G2, HCT-116 and QG-56 cell lines by MTT assay method | Derivatives of CUR exhibited better antioxidant activity than CUR due to involvement of electron in free radical capturing ability of molecules by phenolic hydroxyl group. | Sahu et al[153] |
| Anti-tumor activity | CUR analogs | DTNB assay | Analogs inhibited TrxR even in the low micromolar rang.<br>Analogs with furan moiety have excellent inhibitory effect on TrxR. | Qiu et al[154] |
| Anti-tumor activity | Aldehyde-free 2-hydroxycinnamldehe (HCA) CUR analog | SW620 colon tumor cells | 2-hydroxycurcuminoids have strong generator of ROS and strongly inhibited the growth of SW 620 colon tumor cells due to the presence of β-diketone moiety of curcuminoids. | Han et al[155] |
| Anti-tumor activity | (Mariva®) - a patented formulation | Randomized double blind placebo-controlled trial, eighty subjects | The prepared curcuminoids suppressed systematic oxidative stress in patients and antioxidant effects have shown significant improvement of health related quality of life. | Panahi et al[15] |

(*continued on next page*)

**Table 3** (*continued*)

| Disease/Activity | Formulations | Model used and study design | Effect of curcuminoids treatment | References |
|---|---|---|---|---|
| Anti-diabetic activity | Mono-carbonyl analogs of CUR | Human 11β-HSD1 and adult rat testicular 11β-HSD1 | These analogs were highly selective and favoring 11β-HSD1 and showed anti-diabetic effects without any associated toxicity. | Yuan et al[156] |
| Cardiovascular activity | CUR mimics with diverse alkylsulfonyl and substituted benzenesulfonyl modifications | Endothelin-1 (ET-1) induced rabbit basilar artery | Synthetic CUR mimics can act as dual antagonist scaffold of L-type $Ca^{2+}$ channel and endothelin A/B2 receptor in vascular smooth muscle cells | Park et al[157] |
| Radioprotective effect | CUR analog (bis-1,7-(2-hydrocyphenyl)-hepta-1,6-diene-3,5-dione) | γ-radiation induced male Sprague-Dawley rats, | CUR-analog showed a significant decrease in the levels of thiobarbituric acid reactive substances and DNA damage. CUR analogs protected the hepatocytes against γ-radiation-induced damage by inhibition of peroxidation of membrane lipids and free radicals-induced DNA stand break formation | Srinivasan et al[158] |
| Anti-tuberculosis activity | Monocarbonyl analogs of CUR | *Mycobacterium tuberculosis* (Mtb) and *Mycobacterium marinum* (Mm) | The analogs were proved their inhibition efficiency of *in vitro* growth of Mm and Mtb by disk diffusion and liquid culture assays. | Baldwin et al[159] |
| Anticarcinogenic activity | Bisdemethoxycurcumin analog (BDMC-A) | DMH induced male Wistar rats | BDMC-A influenced on histological changes, cholesterol, bile acids and phospholipid metabolism in DMH-treated rats through its chemopreventive effect. | Devasena et al[160] |

concentrations in plasma, brain and to some extent in liver over a period of 3 months as compared to dietary administration. CUR delivered directly into the systemic circulation was found to be more efficacious in inducing the expression of CYP1A1 and the activity of CYP3A4 enzymes required for its chemopreventive activity against various environmental carcinogens. The presence of significantly higher concentrations of CUR in tissues such as brain showed the potential of this system for patients suffering with Alzheimer's disease and brain gliomas, where CUR has shown significant potential in various *in situ* and cell culture studies.[100] β-lactoglobulin and nanoemulsion were used as carriers to deliver CUR. The digestion and permeability of curcumin of β-lactoglobulin and the nanoemulsion were studied using *in vitro* gastrointestinal model and Caco-2 cell monolayer model respectively. The water solubility and the pH stability of CUR significantly were increased by binding with β-lactoglobulin. The β-lactoglobulin complex and nanoemulsion were resistant to pepsin but sensitive to trypsin. This property is beneficial for CUR for being delivered into the intestinal tract without its release in the stomach. The permeation rate of β-lactoglobulin-CUR complex was higher than that of digested β-lactoglobulin-CUR complex, both the digestion-absorption and direct diffusion route may exist at the same time in the intestinal tract because the β-lactoglobulin was very sensitive to trypsin.[101] Chopra et al[102] have synthesized biodegradable and non-toxic polymer such as poly (lacticco-glycolic) acid (PLGA) encapsulated formulation of CUR (PLGA-CUR-NPs) with photosafe nature. The cell cycle analysis, CPDs formation, ethidium bromide/acridine orange ratio analysis and comet assay are confirmed a significant DNA damage in the cells due to free CUR but not in PLGA-CUR-NPs. The low level sustained release of CUR from PLGA-CUR-NPs could be a promising way to protect the adverse biological interactions of photodegradation products of CUR upon the exposure of UVA and UVB. The applicability of PLGA-CUR-NPs could be suggested as a prolonged radical scavenging ingredient in CUR containing products and could be used as a career of choice to transport the CUR to disease target sites.

### 8.2. Anti-cytotoxicity

Manju and Sreenivasan[103] demonstrated the fabrication of water soluble CUR conjugated gold NPs to target various cancer cell lines. CUR conjugated to hyaluronic acid (HA) to get a water soluble conjugate (HA-CUR) Gold nanoparticles (AuNPs) were prepared by reducing chloroauric acid using HA-CUR, which played the dual role of a reducing and stabilizing agent and subsequently anchored folate conjugated PEG. Their interaction with cancer cell lines, such as HeLa cells, glyoma cells and Caco2 was followed by flow cytometry and confocal microscopy and the results showed significant cellular uptake and internalization of the particles by cells. HA-CUR@AuNPs exhibited more cytotoxicity comparing to free CUR with enhanced targeting and improved efficacy. Starch based microspheres modified by grafting vinyl groups from glycidyl methacrylate (GMA) were prepared by emulsion method to be applied as a device for controlled release of CUR. The microspheres showed to be a very promising devise for the controlled release of CUR, especially for the treatment of colon cancer, which in general decreases the pH of the colon. At simulated gastric fluid the fraction released of CUR was 100% and in a controlled manner, due to the sustained diffusion of CUR to the media and also due to the degradation of the polymer matrix. The CUR-loaded microspheres presented much higher activity against Caco-2 and HCT-116 tumor cell lines than free CUR.[104] Hasan et al[105] reported an approach of encapsulation a CUR by nanoliposome to achieve an improved bioavailability of a poorly absorbed hydrophobic compound and also demonstrated that liposomal preparations to deliver CUR increase its bioavailability. Liposomes composed of salmon's lecithin improved curcumin bioavailability compared to the same type of fatty acids in different proportions of rapeseed and soya lecithins. A real-time label-free cell analysis system based on real-time cell impedance monitoring was used to investigate the *in vitro* cytotoxicity of liposomal preparations. Liposomal encapsulation of CUR can enhance cellular effect of the drug. Polyelectrolyte complex nanoparticles (PENPs) based on hyaluronic acid/chitosan (HA/CS) as carrier were successfully

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prepared for water-insoluble curcuminoids and explored *in vitro* performance against brain glioma cells. Encapsulation of CUR into the PENPs was achieved with high encapsulation efficiency and drug loading capacity. CUR-PENPs showed stronger dose dependent cytotoxicity against C6 glioma cells and higher performance in uptake efficiency in C6 cells. Cellular uptake of CUR-PENPs was found to be governed by multi-mechanism in C6 cells, involving active endocytosis, macropinocytosis, clathrin, caveolae and CD44-mediated endocytosis. CUR-PENPs could be a promising carrier for therapy of brain gliomas.[106]

### 8.3. Anticancer activity

Transferrin-mediated curcumin solid lipid nanoparticles (Tf-CUR-SLNPs) were formulated by the homogenization method to increase photostability and to enhance their anticancer activity against MCF-7 breast cancer cells. The cytotoxicity, ROS and cell uptake was found to be increased considerably with Tf-CUR-SLNPs compared to CUR solubilized surfactant solution (CUR-SSS) and CUR loaded SLNPs suggested the targeting effect. The anticancer activity of CUR is enhanced with Tf-CUR-SLNPs compared to CUR-SSS and CUR loaded SLNPs. The increased efficacy of CUR against MCF-7 breast cancer cells using targeting effect of Tf-Cur-SLNPs confirmed the potential of proposed drug delivery in the treatment of breast cancer.[107] Paclitaxel (PTX) and many other hydrophobic anticancer drugs are not amenable for oral administration due to solubility limitations, P-glycoprotein mediated efflux and metabolism in the gastrointestinal tract. Ganta et al[108] investigated the effect of CUR in oral bioavailability and therapeutic efficacy of PTX administrated in oil-in-water nanoemulsion to SKOV3 tumor-bearing nu/nu mice. CUR pretreatment increased PTX oral bioavailability as well as tumor accumulation. Increased tumor concentrations of PTX, especially in nanoemulsions, correlated with the enhanced therapeutic response. These nanoemulsion formulations can serve as an effective delivery carrier for oral administration of anticancer agents with poor aqueous solubility. Pretreatment with CUR was especially beneficial for enhancing oral bioavailability and antitumor therapeutic efficacy and could potentially have significant impact on the clinical management of cancer.

Plyduang et al[109] reported a novel synthesis of water soluble polymeric macromolecules prodrugs; THC an active metabolite of CUR was conjugated with a hydrophilic polymer, carboxymethylcellulose (CMC) with the high degree of substitution can specifically deliver the drug to the colon. The polymer conjugates showed chemical stability at various pH values along the gastrointestinal tract with increased water solubility. 4-amino-THC showed a higher selective cytotoxicity against HT-29 than normal colon cells nearly 4 fold. The use of THC-CMC conjugates can be a promising colon-specific drug delivery system with its sustained release in the colon to be an effective treatment for colonic cancer. BDM analog loaded chitosan-starch (BDMCA-CS) nanocomposite particles were developed using different ratios of chitosan and starch by ionic gelation method. The formulation BDMCA-CS 3:1 showed good drug entrapment efficiency and percentage drug content, followed by BDMCA-CS 1:3. *In vitro* drug release profile of the BDMCA-CS nanocomposite particles showed a very slow, sustained diffusion controlled release and polymeric erosion of the drug. The cancer cells targeting ability of the BDMCA-CS nanocomposite particles were confirmed by performing MTT assay on MCF-7 breast cancer cell lines and VERO cell lines. The CS nanocomposite of ratio 3:1 can be a better delivery tool for BDMCA to treat breast cancer.[110]

"Cureit®" – a novel bioavailable CUR formulation was synthesized by our research group and checked for its potential to inhibit hyaluronidase. It has shown a higher inhibition of 42%. The cytotoxic effect of Cureit was also established by a spectrophotometrical study using MTT on the effects of Cureit on cell proliferation. "Cureit" could be a useful for anti-aging and anti-cancer medication. Elastases inhibiting activity of Cureit in human cell lines were described through spectrophotometrical study and it inferred that "Cureit" can inhibit elestases activity at higher concentration.[111–113]

CUR loaded mixed micelles (CUR-MM) of Pluronic F-127 (PF127) and Gelucire®44/14 (GL44) were prepared by a solvent evaporation method to enhance its oral bioavailability and cytotoxicity in human lung cancer cell line A549. Controlled release of CUR from CUR-MM was revealed by the *in vitro* dissolution profile. CUR-MM showed significant improvement in cytotoxic activity as 3 folds and oral bioavailability as around 55 folds of CUR as compared to CUR alone. Significant improvement in cytotoxic activity and oral bioavailability of CUR when formulated into mixed micelles could be attributed to solubilization of hydrophobic CUR into the micelle core along with P-gp inhibition effect of both, PF127 and GL44. The formulation of mixed micelles of PF127 and GL44 which can act as promising carrier systems for hydrophobic drugs like CUR with significant improvement in their oral bioavailability.[114]

### 8.4. Antioxidant and antibacterial activity

CUR was encapsulated into NPs consisting of ethyl cellulose (EC) and/or methyl cellulose (MC) to overcome instability in exposed to light or heat or loses activity during storage, especially in the application on the skin within a cosmetic or pharmaceutical formulations. The sun exposure test was confirmed that CUR was protected by the nanoparticles, whereas non-encapsulated CUR completely degraded. Both CUR-EC and CUR-ECMC nanospheres showed similar radical protection factor values as free CUR in lotion, but application on pig ear skin revealed a better radical scavenging activity by CUR encapsulated in the nanospheres than by CUR in lotion. Nanoencapsulation protected CUR from photodegradation and can retain its antioxidant capacity.[115] Ethanol and glycerol catalyzed CUR encapsulated nanoemulsions using cottonseed oil with mild cationic, anionic and nonionic surfactant have been prepared to augment the antioxidant ability of CUR. The CUR encased bionanoemulsions showed a radical scavenging activity of more than 90% as compared with pure CUR with free radical 2,2-diphenyl-1-picrylhydrazyl (DPPH).[116]

Two tetra hydrocurcuminoids, THC1 (5-hydroxy-1,7- bis(4-hydroxy-3-methoxypenyl)hept-4-en-3-one) and THC2 (5-hydroxy-1,7-bis(4-hydroxy-3,5-dimethoxyphenyl) hept-4-en-3-one) were incorporated into a chitosan film to demonstrate both antibacterial and antioxidative properties. The resulting THC-chitosan films exhibited a high free radical scavenging activity against DPPH in methanol, which was due to a progressive release of the THCs into the solvent. THC-chitosan have retained their bioactivity against *Listeria innocua*, THCs alone were not bioactive enough against listerial strains. The association of natural antioxidants and bioactive biopolymers can be particularly useful to develop high-performance food packaging.[117] Tovsen et al[118] evaluated the *in vitro* phototoxic potential of synthetic asymmetric and glycosylated curcuminoids on planktonic model bacteria, such as *Enterococcus faecalis* and *Escerichia coli* in the presence or absence of pharmaceutical excipients (Pluronic ic® F127, PEG 400 and HPγCD) by counting the colony forming units. Glycosylation of the aromatic substituents of CUR and thereby removal of the para-OH groups, lead to an extensive reduction of phototoxicity towards the model bacteria.

### 8.5. Neuroprotective effect

Kakkar and Kaur[119] prepared solid lipid NPs of CUR (CUR-SLNPs) with enhanced bioavailability and investigated its therapeutic role

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in alleviating behavioral, biological and histochemical changes upon oral administration of $AlCl_3$ in male Lacca mice. Adverse effects of $AlCl_3$ were completely reversed by oral administration of CUR-SLNPs. Histopathology of the brain sections of CUR-SLNPs treated groups indicated significant improvements and also highlighted the potential of the use of CUR-SLNPs for treatment of AD. Kakkar et al[120] also investigated CUR-SLNPs in the experimental paradigm of cerebral ischemia by bilateral common carotid artery occlusion (BCCAO) model in rats. An improvement of 90% in cognition and 52% inhibition of acetylcholinesterase versus cerebral ischemic group were observed after administration of CUR-SLNPs. Levels of superoxide dismutase, catalase, glutathione and mitochondrial complex enzyme activities were significantly increased, but lipid peroxidation, nitrite and acetylcholinesterase levels decreased after CUR-SLNPs administration. Gamma-scintigraphic study showed 16.4 and 30 times improvement in brain bioavailability upon oral and i.v administration of CUR-SLNPs versus solubilized CUR. CUR-SLNPs with their improved bioavailability have been an effective armament against cerebral ischemic insult and could be an attribute to enhanced antioxidant potential and resultant superoxide anion production achieved by packaging CUR into a suitable carrier system for improved brain delivery. Puglia et al[121] formulated CUR loaded nanostructured lipid carriers (NLC-CUR) in order to improve the bioavailability and stability of CUR after systemic administration with increased effects in the central nervous system (CNS). NLC-CUR were systematically injected and the effects in the CNS were compared with CUR control formulation containing DMSO-CUR. CUR can able to decrease histone acetylation in the CNS when induced in NLCs. Western blot analysis showed that intraperitoneal injection of NLC-CUR in mice induces a marked hypoacetylation of histone 4 (H4) at lysine 12 (K12) in the spinal cord compared with the control group. This approach can ameliorate the pharmacokinetics of CUR that allowed a better permeation in the CNS.

Mayadevi et al[122] reported curcumin and its analogs such as two pyrazole derivatives and an isoxazole derivative showed inhibition of the $Ca^{2+}$-dependent and $Ca^{2+}$-independent activities of calcium/calmodulin dependent protein kinase II (CaMKII) *in vitro*. Pyrazole derivative, (3,5-bis[β-(4-hydroxy-3-methoxyphenyl) ethenyl] pyrazole was more effective as an inhibitor of CaMKII and was more effective on $Ca^{2+}$ independent in the case of purified CaMKII and also in PSD and cytosolic CaMKII fractions. The pyrazole CUR offered neuroprotective action in the excitotoxic cascade by inhibiting CaMKII activity. Glucagon-like peptide-1 (GLP-1) is a hormone secreted from enteroendocrine L-cells. Enhancing the GLP-1 action is an important target for prevention and treatment of type 2 diabetes. Takikawa et al[123] reported CUR significantly stimulated GLP-1 secretion in GLUTag cells and significant increase involved the $Ca^{2+}$-CaMKII pathway and was independent of the cAMP/PKA, PKC and MEK-ERK pathways.

Recemic tetrahydrocurcumin (THC), tetrahydrodemethoxycurcumin (THDC) and tetrahydro bisdemethoxycurcumin (THBDC) dihydropyrimidinone (DHPM) analogs were synthesized by utilizing the multi-component Biginelli reaction in the presence of copper sulfate as catalyst. The evaluation of acetylcholinesterase inhibitors for Alzheimer's disease of these analogs showed that they exhibited higher inhibitory activity than the CUR. THBDC-DHPM demonstrated the most potent inhibitory activity with excellent $IC_{50}$ value, which is slightly more potent than that of galanthamine.[124] A series of CUR based diarylheptanoid analogs were synthesized using multiple carbon-carbon bond formation on the multifaceted catalytic properties of titanocene complexes and evaluated their anti-glioblastoma and anti-neuroblastoma properties. These analogs proved efficacious against neuroblastoma (SK-N-SH and SK-N-FI) and glioblastoma multiforme (U87MG) cell lines.[125]

Hagl et al[126] prepared new CUR micelles and investigated the bioavailability *in vivo* in NMRI mice and the effects of native CUR and a newly developed CUR micelles formulation on mitochondrial function *in vitro* in PC12 cells and *ex vivo* in isolated mouse brain mitochondria. CUR micelles improved bioavailability of native CUR around 10–40 fold in plasma and brain of mice. CUR micelles proved to be more efficient in preventing mitochondrial swelling in isolated mouse brain mitochondria and protecting PC12 cells from nitrosative stress than native CUR. CUR micelles might be a suitable substance for the prevention of mitochondrial dysfunction and neurodegeneration, which both may promote age-associated disorders like AD.

### 8.6. Anti-diabetic activity

Kim et al[127] investigated the potential anti-diabetic mechanisms of CUR, curcumin C3 complex® and tetra hydrocurcuminoids (THC). They also demonstrated that curcuminoids effectively suppressed dexamethasone-induced phosphoenol pyruvate carboxy kinase (PEPCK) and glucose6-phosphatase (G6Pase) in H4IIE rat hepatoma and Hep3B human hepatoma cells. In addition curcuminoids increased the phosphorylation of AMP-activated protein kinase (AMPK) and its downstream target acetyl-CoA carboxylase (ACC) in H4IIE and Hep3B cells with 400 times with CUR to 1,00,000 times with THC the potency of metformin. AMPK mediated suppression of hepatic gluconeogenesis can be a potential mechanism mediating glucose-lowering effects of curcuminoids and can offer a complementary approach in the management of diabetes.

### 8.7. Anti-malarial activity

Curcuminoids-loaded lipid nanoparticles for parenteral administration were successful prepared using trimyristin, tristerin and glyceryl monostearate as a solid lipid and medium chain triglyceride (MCT) as liquid lipid by a nanoemulsion technique employing high-speed homogenizer and ultrasonic probe. The *in vivo* pharmacodynamic activity revealed two fold increases in anti-malarial activity of curcuminoids entrapped in lipid nanoparticles when compared to free curcuminoids at the tested dosage level. Lipid nanoparticles may increase drug concentrations in the site of action and can help to treat cerebral malaria.[128] Aditya et al[11] explored the potential of liposomes for the intravenous delivery of curcuminoids, with malaria affected mouse as a model. Curcuminoid loaded liposome formulations were prepared by the thin film hydration from phosphatidycholine. The anti-malarial activity of curcuminoids loaded liposomes was evaluated in *Plasmodium berghei* infected mice. It showed promise and improved anti-malarial activity in combination with standard anti-malarial drug artemisinin and also prevent recrudescence.

### 8.8. Antifungal activity

Isolation of curcuminoids were performed using various extraction methods and different solvents, all obtained extracts showed strong antifungal activities against all tested fungal strains, whereas antibacterial activities of the extracts were only mild. Highest yields of extractions and highest purities of extracts with high antioxidant activities were obtained with extraction methods applying ethanol as solvent. The dark colored curcuminoids extract obtained using ethanol as a solvent was mixed with polyethylene glycol (PEG) and formulated into a powder using PGGS™ method. All extracts exhibited a 100% inhibitory effect on the growth of tested fungi and showed low antibacterial activity. The formulation was conducted by a dissolution study with simulated gastric fluid for applied as a food supplement with biological activity. The

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release in the intestinal tract showed a desirable dissolution of the active compounds, which indicated that the micronized curcuminoids extract/PEG is a suitable formulation for curcuminoids delivery in the human gastrointestinal tract.[6]

### 8.9. Anti-cytotoxicity

New CUR derivatives were synthesized through the aromatic ring glycosylation of CUR in order to improve fundamental features of drug bioavailability via water solubility with a greater kinetic ability. The binding of glucose to CUR reduced the cytotoxicity of the derivatives towards cisplatin (cDDP)-sensitivity and resistant human ovarian carcinoma cell lines, the compounds also displayed a good selectivity since they are much less toxic against non-tumorigenic Vero cells.[129]

A series of CUR analogs were synthesized with different substituents at the 4-position of the phenyl group for *in vitro* cytotoxicity against a panel of human cancer cell lines. Several CUR-analogs exhibited selective and potent cytotoxic activity against human epidermoid carcinoma cell line A-431 and human glioblastoma cell line U-251 indicated their specific potential in the chemoprevention and chemotherapy of skin cancer and glioma.[130] Fifteen new CUR analogs were designed, synthesized and evaluated for cytotoxicity against two human prostate cancer cell lines, androgen-dependent LNCaP and androgen-independent PC3. Twelve analogs are conjugated of CUR and methyl curcumin with a flutamide or bicalutamide like moiety. Two compounds are C4-mono- and difluoro-substituted analogs of dimethyl curcumin. A cell morphology study revealed that the cytotoxicity of CUR analogs or CUR-anti-androgen conjugates detected from both prostate cancer cell lines might be due to the suppression of pseudopodia formation.[131] Caprioglio et al[132] (2016) were delivered a new class of triazole-curcuminoids by replacing the 1,3-dicarbonyl moiety with a 1,2,3-triazone ring as a possible strategy to generate new compounds with different potency and selectivity compared to CUR and obtained a proof-of-principle library of 28 compounds tested for their cytotoxicity such as SY-SY5Y and HeLa cells and for their ability to inhibit NF-kB. They found that some compounds were able to inhibit NF-kB without showing cytotoxicity, while others activated NF-kB signaling.

### 8.10. Anti-inflammatory activity

Seven N-unsubstituted curcuminoid pyrazoles have been synthesized from the corresponding β-dikeones and evaluated the possibility of curcuminoid pyrazoles regulating the activity of matrix metalloproteinases (MMPs) by human intestinal epithelial cells *in vitro*. Zymographic analysis revealed that three compounds significantly down-regulated MMP-9 activity on inflammation-induced intestinal epithelial cells, making them or original candidates for the treatment of inflammatory bowel diseases.[133] Tham et al[134] synthesized a series of CUR analogs and describe the effects of 2,6-bis-4-(hydroxyl-3-methoxybezylidiine)-cyclohexanone (BHMC) upon nitric oxide and cytokine synthesis in cellular models of inflammation. BHMC showed a significant dose-response inhibitory action upon the synthesis of NO due to suppression of both iNOS gene and enzyme expression without any effects upon scavenging of nitrite. BHMC has a very minimal effect upon iNOS activity with no effect at all upon the secretion of PGE2 but has a strong inhibitory effect upon MCP-1 and IL-10 secretion and gene expression. BHMC should be considered a promising drug lead for preclinical and further pharmacological studies. A variety of novel aromatic and heterocyclic aromatic curcuminoids were synthesized, characterized by Khan et al[12] and determined their anti-inflammatory activities by oral administration of female Wistar rats. Among these, four novel curcuminoids notified as RK-97, RK-103, RK-104 and RK-106 in which the bis-methoxy-phenyl group of CUR was replaced with bis-dimethoxybutenolidyl, ascorbate, bis-naphthyl and bis-furanyl derivatives respectively had potent activity in the antiarthritic assay with little gastric or systemic toxicity compared with the vehicle-treated controls. Of the curcuminoids the furan RK-106 was the only compound to inhibit production of TNFa and IL-1b in a monocytic cell-line THP-1 *in vitro*. The inactivity of RK-106 on the production of PGE2 may be related to its absence of gastrotoxicity. This RK-106 may warrant the development of new low gastrotoxic anti-inflammatory agents with selective inhibitory activity of cytokine inflammatory mediators.

Six new 3(5)-trifluoromethyl-5(3)-substituted-styryl-1H-pyrazoles have been synthesized and their tautomerism studied in both solution and solid state. Five out of the six compounds presented inhibition percentages of the iNOS isoform higher than 50%; only two of the studied compounds showed an inhibition of about 50% with regards to the NOS inhibitory activity.[135] A series of novel CUR bisacetamides have been synthesized for enriching their biological activities such as *in vitro* antioxidant, anti-inflammatory and cytotoxic activities. All the compounds exhibited potent to good anti-inflammatory, antioxidant and significant cytotoxic activities.[136] Three series of dimethylamino curcuminoids viz. 4-phenylaminomethyl curcumin, arylidene curcumin and pyrazole curcumin derivatives have been synthesized and studied for their *in vitro* anti-inflammatory, antioxidant and antibacterial activities. Dimethylamino curcuminoid derivatives have shown potent anti-inflammatory properties than parent CUR. Molecular docking interactions proved the dimethylamino curcuminoids derivatives have very good cyclooxygenase inhibition.[137]

### 8.11. Antimicrobial activity

The natural curcuminoids have been modified and gave 46 analogs and 8 pairs of 1:1 mixture of curcuminoid analogs and these parent curcuminoids and their analogs were assessed against protozoa of the *Trypanosoma* and *Leishmania* species. Among modified curcuminoid analogs tested, 8 pure analogs and 5 isomeric mixtures of analogs exhibited high antitrypanosomal activity in submicromolar order of magnitude. Among these highly active analogs, 1,7-bis(4-hydroxy-3-methoxyphenyl) hept-4-en-3-one was the most active compound and more active than the standard veterinary drug diminazene aceturate. Curcuminoids carrying a conjugated enone motif were significantly more active against *Trypanosoma brucei brucei B48*. This enone motif was found to contribute to particularly high trypanocidal activity against all *Trypanosoma* species and strains tested. All curcuminoids exhibited lower toxicity to HEK cells than to *T. brucei brucei* blood stream forms.[8] The curcuminoid constituents such as CUR, DMC and BDMC have been structurally modified to 55 analogs and antimycobaterial activity against *Mycobacterium tuberculosis* has been evaluated by Changtam et al.[138] Among them the highly active curcuminoids, the isoxazole analogs are the most active group, with mono-O-methylcurcumin isoxazole being the most active compound; it was 1131-fold more active than CUR and was 18 and 2-fold more active than the standard drugs kanamycin and isoniazid respectively. This compound exhibited high activity against the multidrug resistant *M. tuberculosis* clinical isolates. The structural requirements for a curcuminoid analog to exhibit antimycobacterial activity are the presence of an isoxazole ring and two unsaturated bonds on the heptyl chain. The presence of a suitable para-alkoxyl group on the aromatic ring which is attached in close proximity to the nitrogen function of the isoxazole ring and a free para-hydroxyl group on another aromatic ring enhances the bioavailability activity.

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Five series of CUR derivatives with sulfonamides have been synthesized and evaluated for *in vitro* antibacterial activity, antifungal activity and cytotoxicity. Among these compounds, the bioassay showed containing one sulfonamide molecule attached to the carbonyl group of CUR showed the most potent biological activity against tested bacteria and fungi and also displayed higher cytotoxicity than CUR. When two sulfonamide molecules are attached to both carbonyl groups their activity decreased slightly. Diazotized CUR with sulfonamide is more active than their pyrazoles and oxazoles.[139] Sanabria-Rios et al[140] were successfully performed the synthesis of C5-curcumin-2-hexadecynoic acid (C5-CUR-2-HAD) conjugate in three synthetic steps and in an overall yield of 13%, and tested for antibacterial activity against methicillin-resistant *Staphylococcus aureus* (MRSA) strains. The conjugate was active against eight MRSA strains at MICs due to the presence of 2-hexadecynoic acid (2-HAD) and also increased 4–8 fold its antibacterial activity.

### 8.12. Anticancer activity

Hahm et al (2002)[141] synthesized 12 symmetrical curcuminoids, with slight modified version of Pabon's method for an inhibitor more potent than CUR. Among these, three products are exhibited a remarkably high inhibitory activity against Fos-Jun-DNA complex formation. The product BJC005 is nearly 90 times more effective than CUR. A series of novel CUR analogs were synthesized by Adams et al (2004)[142] for anticancer and anti-angiogenesis activities. These analogs are symmetrical α,β-unsaturated and saturated ketones. The analogs were more efficacious than CUR and the commonly used chemotherapeutic drug, cisplatin against a variety of tumor cell lines and also these compounds can be exerted impressive blockade of endothelial cell proliferation. Several compounds were more effective in the anti-angiogenesis assays run at Emory and as potent as the anti-angiogenic drug TNP-470. Some of the analogs effectively reduced the size of human breast tumors grown in female athymic nude mice and showed little toxicity. These analogs can potentially be an effective chemotherapeutic agent. A series of 15 novel cyclic analogs of CUR were synthesized by condensation of 2-acetylcycloalkanones with a variety of aromatic aldehydes resulted in the formation of 2-arylidene-6-(3-arylacryoyl)-cycloalkanone derivatives under microwave conditions and analyzed for *in vitro* cytostactic activity. These analogs showed significant anticancer activity against representative murine and human cancer cell lines during *in vitro* bioassays.[143]

Sixty one CUR-related compounds were synthesized by Wei et al[144] and evaluated for their anticancer activity towards cultured prostate cancer PC-3 cells, pancreas cancer Panc-1 cells and colon cancer HT-29 cells by MTT assay. Structure activity relationship has shown the response of potent anticancer activity viz tetrahydropyran-4-one or tetrahydrothiopyran-4-one as a core structure, methoxy groups in the aromatic ring and nitrogen heterocycles in the distal rings as the promising lead structures. Some of the studied CUR-compounds were 34–117 fold more active than CUR for inhibiting the growth of cultured human prostate, pancreas ad colon cancer cells. The studied active compounds were potent stimulators of apoptosis and can be useful for anticancer activity. Sanabria-Rios et al[145] have synthesized C5-curcumin-fatty acid conjugates (C5-CUR-FA) containing decanoic acid or palmitic acid moieties through a two-step synthetic route, 10 analogs in order to determine survey activity relationship (SAR) study using the colorectal adenocarcinoma cell (CCL-229). Decanoic acid moiety at the meta position in C5-CUR-FA conjugates is important for their anticancer activity effect. C5-CUR-FA conjugates can affect the replication process of cancer cells, inhibited the relaxing activity of the human DAA topoisomerase I at minimum inhibitory concentrations. The hypothesis of the results are also strongly supported that the inhibition of both NFkB and DNA topoisomerase I by C5-CUR-FA conjugates are associated with their anticancer activity.

Chemopreventive effects in 1,2-dimethylhydrazine-induced colon cancer in the albino rats model was performed by CUR and CUR analogs such as ethyl curcumin and 3,5-bis (substituted cinnamylidene)-N-alkyl-4-peperidone. Chemopreventive treatment with various forms of CUR extracts caused a reduction in the number of tumor cells ever after 4 weeks. Among these compounds 3,5-bis (substituted cinnamylidene)-N-alkyl-4-peperidone is the most active against the administration of the prophylactic treatment for four weeks before the induction of cancer by 1,2-dimethylhydrazine.[146] Leow et al[147] synthesized a total of five series consisting of 43 CUR analogs and screened in HEK293T cells for inhibition of β-catenin transcriptional activity. These analogs were more potent than parent CUR as effective wnt inhibitors and anti-invasive agents in human osteosarcoma. SAR studies revealed that the wnt inhibitory effects could be markedly enhanced by introducing conformational restriction in the central linker and appropriate ring substituents such as a strong electron donating group at the 40 ring position. Synthesized analogs especially dibenzylideneecyclohexanones and dibenzylideneecyclopentanones templates can be a promising scaffolds for development as chemotherapeutic agents for the treatment and prevention of osteosarcoma.

### 8.13. Antioxidant activity

A series of CUR analogs was synthesized through the condensation of appropriately protected hydroxybenzaldehyes with acetylacetone followed by deprotection. The antioxidant activity of these analogs was determined by superoxide free radical nitroblue tetrazolium and DPPH free radical scavenging methods. These analogs showed cytotoxicity to lymphocytes and promising tumor-reducing activity on Dalton's lymphoma ascites tumor cells.[148] Chen et al[149] have prepared different liposome formulations [three different lipids (Lipo- CUR; high-lipo- CUR and high lipo high CUR) and CUR] and the stability was verified by *in vitro* study with phosphate buffered saline, human blood, plasma and culture medium RPMI-1640 + 10% FBS, it is confirmed that liposomal CUR had higher stability than free CUR. Liposomal CUR had stronger inhibitory effects on concanavalin A stimulated human lymphocyte, splenocyte and lymphoblastoid cell line proliferation. Liposomal CUR can be useful for intravenous administration to enhance the bioavailability and efficacy. CUR-amino acid conjugates synthesized by the reaction of t-Boc-protected amino acids with CUR. These amino acid derivatives showed high antioxidant and antimutagenic activities than CUR because of derivatization at the phenolic position of CUR. Conjugates of CUR with alkyl-substituted amino acids and the CUR-cysteine conjugate have shown much superior antioxidant activity than CUR, but all the conjugates displayed very high antimutagenic activities.[150]

Ferrocenyl-substituted CUR derivatives such as 1,7-bis(p-hydroxy-m-methoxyphenyl)-4-ferrocenylidene-hepta-1,6-diene (FCU), 1-(p-hydroxy-m-methoxyphenyl)-3-hydroxy-7-ferrocenyl-hepta-1,4,6-trien-5-one (FFT) and 1-(p-hydroxy-m-methoxyphenyl)-5-ferrocenyl-penta-1,4-diene-3-one (FDZ) were synthesized and evaluated their antioxidant activities in 2,20-azohis (2-amidinopropane hydrochloride) (AAPH), $Cu^{2+}$/glutathione (GSH) and hydroxyl radical (OH) induced oxidation of DNA and in trapping 2,20-diphenyl-1-picrylhydrazyl (DPPH), 2, 20 azinobis(3-ethylbenzothiazoline-6-sulfonate) cationic radical ($ABTS^{+}$), and galvinoxyl radicals. FCU, FFT and FDZ exhibited protective effects on $Cu^{2+}$/GSH-induced oxidation of DNA. The introduction of the

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ferrocenyl group into CUR enhanced the antioxidant ability of the FCU, FFT and FDZ.[151] Therapeutically potential of a mucoadhesive formulation containing curcuminoids from *C. longa* exerted protective action against duodenal mucosa damage caused by 5-Fluorouracil in mice and also stimulated cell proliferation, reduced weight loss, myeloperoxidase levels and malondialdehyde formation.[152]

A series of CUR derivatives were designed and synthesized viz. 4H-pyrimido [2,1-b] benzothiazole, pyrazole and benzylidene derivatives for their cytotoxicity and antioxidant activity. SAR study results showed that derivatives of CUR exhibited better antioxidant activity than CUR due to involvement of electron in the free radical capturing ability of molecules by the phenolic hydroxyl group. These CUR derivatives can be used as promising antioxidant and anti-cancer drug candidates.[153]

### 8.14. Antitumor activity

A series of CUR derivatives were synthesized and evaluated the inhibitory activities on thioredoxin reductase (TrxR) of all analogs by *in vitro* DTNB assay. Most of the analogs inhibited TrxR even in the low micromolar range. Structure-activity relationship analysis revealed that the analogs with furan moiety have an excellent inhibitory effect on TrxR in an irreversible manner, indicated that the furan moiety can serve as a possible pharmacophore during the interaction of CUR analogs with TrxR.[154] Aldehyde-free 2-hydroxycinnamldehye (HCA) analog were synthesized based on the CUR, which is called as 2-hydroxycurcuminoids for the effect of antitumor activity against various human tumor cells *in vitro* and *in vivo*. 2-hydroxycurcuminoids have a strong generator of ROS and strongly inhibited the growth of SW 620 colon tumor cells due to the presence of β-diketone moiety of curcuminoids. These analogs can be used as chemotherapeutic agent against human tumors.[155]

A study was investigated the impact of a bioavailability enhanced preparation of curcuminoids (Mariva®) – a patented formulation of curcuminoids with soy phosphatidylcholine in a 1:2 weight ratio) on the biomarkers of systemic oxidative stress in patients with solid tumors receiving standard chemotherapy regiments. The prepared curcuminoids suppressed systematic oxidative stress in patients and antioxidant effects have shown significant improvement of health related quality of life.[15]

### 8.15. Anti-diabetic activity

A series of mono-carbonyl analogs of CUR were designed and synthesized by removing the reactive β-diketone moiety, which is responsible for the pharmacokinetic limitation of CUR. CUR analogs significantly inhibited and rat 11β-hydroxysteroid dehydrogenase type 1 activities (11β-HSD1). The level of these inhibitors was 4–20 times more than that of CUR and these analogs were highly selective and favoring 11β-HSD1. These analogs showed anti-diabetic effects without any associated toxicity and can potentially used novel therapeutic agents targeting 11β-HSD1 for the treatment of diabetes.[156]

### 8.16. Cardiovascular activity

Park et al[157] synthesized a library of CUR mimics with diverse alkylsulfonyl and substituted benzenesulfonyl modifications through a simple addition reaction of important intermediate, 1-(3-Amino-phenyl)-3-(4-hydroxy-3-methoxy-phenyl)-propenone, with various sulfonyl chloride reactants and then tested their vasodilatation effect on depolarization (50 mM $K^+$) and endothelin-1 (ET-1) induced basilar artery contraction. Among the tested compounds, six CUR-mimcs in a depolarization-induced vasoconstriction and seven compounds in an ET-1 induced vasoconstriction showed strong vasodilation effect. Based on their biological properties, synthetic CUR mimics can act as a dual antagonist scaffold of L-type $Ca^{2+}$ channel and endothelin A/B2 receptor in vascular smooth muscle cells. The synthesized compounds can be used as promising novel drug candidates to treat hypertension related to the over expression of L-type $Ca^{2+}$ channels and endothelin peptides/receptors - mediated cardiovascular diseases.

### 8.17. Radioprotective effect

Srinivasan et al[158] evaluated the radioprotective effect of CUR analog (bis-1,7-(2-hydrocyphenyl)-hepta-1,6-diene-3,5-dione) on γ-radiation induced toxicity in primary cultures of isolated rat hepatocytes. Pretreatment with different concentrations of CUR-analog showed a significant decrease in the levels of thiobarbituric acid reactive substances and DNA damage and protected the hepatocytes against γ-radiation-induced damage by inhibition of peroxidation of membrane lipids and free radicals-induced DNA stand break formation. CUR-analog administration prior to radiation therapy can be useful for cancer patients to prevent normal cell damage.

### 8.18. Anti-tuberculosis activity

Baldwin et al[159] synthesized a series of monocarbonyl analogs of CUR and evaluated for their capacity to inhibit growth of the pathogenic mycobacteria such as *M. tuberculosis* (Mtb) and *Mycobacterium marinum* (Mm). Several analogs were proved their inhibition efficiency of *in vitro* growth of Mm and Mtb by disk diffusion and liquid culture assays. Structural activity analysis of the analogs indicated that Michael acceptor properties are critical for inhibitory activity.

### 8.19. Anticarcinogenic activity

Devasena et al[160] studied the effect of bis-1,7-(2-hydroxyphenyl)-hepta-1,6-diene-3,5-dione, a bisdemethoxycurcumin analog (BDMC-A) on 1,2-dimethylhydrazine (DMH) induced colon carcinogenesis in male Wistar rats and effects were compared with CUR as a reference drug. The results suggested that BDMC-A can be influenced on histological changes, cholesterol, bile acids and phospholipid metabolism in DMH-treated rats through its chemopreventive effect. The terminal phenolic groups and the conjugated bonds in the central seven carbon chain may be responsible for the anticarcinogenic action of the BDMC-A.

## 9. Nutraceutical applications of curcuminoids

Food plant extracts, with medicinal values and lesser side effects are a source of chemically diverse compounds. Curcuminoids, present in *C. longa*, an established food and medicinal plant, are known for their hypoglycemic property. CUR was found to be a very effective in antagonizing the S9-mediated mutagenicity of several food-derived heterocyclic amines. The structural activity relationship between CUR and its naturally occurring derivatives DMC, BDMC and other structural related natural and synthetic analogs of CUR, namely tetrahydrocurcumin, dibenzoylmethane, dibenzoylpropane, vanillin, ferulic acid, isoferulic acid and caffeic acid by Ames Salmonella/reversion assay against different classes of cooked food mutagens. A methoxy group on the benzene ring, unsaturation in the side chain and a central β-diketone moiety in the CUR molecule is the important structural requirements responsible for the high antimutagenic potential of CUR against

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cooked food heterocyclic amines.[161] CUR-encapsulated oil-in-water microemulsion was prepared by Lin et al[162] using food-acceptable components such as lecigthin and Tween 80 as the surfactants and ethyl oleate as the oil phase. These formulations were not only preventing the degradation process of CUR but also increasing the concentration of CUR in aqueous solution. Dose-response and time-dependent studies are showing that the encapsulated CUR formula was the suitable formulation with reduced particle diameter and maximum permeation capability. These formulations can be suitable for delivery in nutraceuticals and functional food filed. Turmeric powder blended wheat bread was developed by Lim et al[9] and analyzed for different physical characteristics, bioactive components and antioxidant activities as affected by different substitution levels of turmeric powder in bread. The incorporation of turmeric powder significantly increased the CUR, total phenolic contents and antioxidant activities of bread. A 4% substitution of wheat flour with turmeric powder showed acceptable sensory scores which were comparable to wheat bread. Turmeric powder containing breads can be developed as a health promoting functional foods.

BDMC from *C. longa* acted as an inhibitor to inactivate human pancreatic α-amylase (HPA) which determines the mechanistic action of BDMC, which uncompetitively inhibited HPA with a 1:1 stoichiometry, a therapeutic target for oral hypoglycemic agents in type-2 diabetes. BDMC could be developed as a leading anti-diabetic compound for future developments of functional foods and newer inhibitors for controlling starch digestion and post-prandial hyperglycemia.[163] Microparticles of curcuminoids from *C. longa* extract were successfully prepared by the spray drying technique using polyvinylpyrrolidone as a carrier. The solubility of the curcuminoids and CUR of the prepared microparticles remarkably improved 100 folds, it also confirms the potential of the ternary solid dispersion to improve the dyeing and nutraceutical properties of these compounds.[164]

Highly soluble, stable and orally uptake CUR was developed by Bergonzi et al[165] with an oil/water microemulsion using food grade components. Three microemulstions were developed by non-ionic surfactants with containing a variety of oils such as olive oil, wheat germ oil, vitamin E. The optimal formulation consisted of 3.3 g/100 g of vitamin E, 53.8 g/100 g of Tween 20, 6.6 g/100 g of ethanol and water (36.3/100 g), with a maximum solubility of CUR up to 14.57 mg/ml and a percentage of permeation through the artificial membrane of about 70%. The developed formulation can meet the ADI of this molecule fixed by EFSA in 0–3 mg/kg/day due its very high solubility of CUR.[165] *In vitro* gastrointestinal digestion models were used to investigate *in vitro* bioaccessibility of curcuminoids delivered with buttermilk. The bioaccessibility of curcuminoids was influenced by the presence of the buttermilk and ethanol as a carrier, and increased significantly with increasing amount of bile extract. The solublization of curcuminoids in ethanol before adding into buttermilk had greater *in vitro* bioaccessibility than the direct addition of curcuminoids to buttermilk without ethanol. Curcuminoids did not significantly influence the digestibility of protein or lipids. Buttermilk could be used as a carrier for curcuminoids particularly delivered with food for enhanced bioaccessibility.[166]

Laokuldilok et al[167] reported the odor masking property, encapsulation efficiency and physicochemical properties of turmeric extract prepared by a binary blend of wall materials such as brown rice flour (BRF) and β-cyclodextrin (β-CD). Odor-masking potential of the binary blend wall materials, BRF was provided benefits beyond basic nutrition to human health moreover the addition of β-CD showed more effectiveness on masking properties and efficiency of curcuminoids encapsulation. A novel encapsulation of blending of BRF and β-CD as a carrier agent with the appropriate amount of turmeric powder exhibited a high ability for odor masking and high retention of bioactive compounds. CUR-loaded nanoemulsions were produced by the emulsification inversion point method to increase its use as natural additives within the food industry. The most stable formulations were composed of 20% soybean oil, 10% Tween 80 and 20% glycerol and were produced with an anchor blade impeller, this combination of parameters resulted in 0.07% encapsulation of the CUR. After 60 days, 70% of the initial CUR remained in the nanoemulsion systems. The emulsification inversion point method can be extremely promising for the applications in food formulations due to their extended capacity to preserve the CUR.[168]

## 10. Conclusions

Curcuminoids are the promising natural compound with a large variety of therapeutic properties, particularly biological targets and interactions, linked to numerous diseases. Unfortunately the clinical applications of curcuminoids are restricted by their poor solubility, low absorption and bioavailability, high metabolism rate. To overcome these limitations, curcuminoids and their derivatives have been modified and attached with lipids, micelles, nanoparticles, liposome and metal complexes. In this review, the following properties of curcuminoids alone and in association with other modified form have been shown to have effective on neuroprotective, antitumor, antioxidant, anticancer, anti-inflammatory, anti-acidogenic, radioprotective, sexually transmitted infections, anti-esophageal, anti-nephrotoxicity, antimicrobial, antiviral, anti-angiogeneic, anti-proliferative, anti-immunomodulatory, hepatoprotectivity, antimalarial, anti-cytotoxicity and anti-diabetic properties. Overall, it is clear from the studies described that curcuminoids are highly promiscuous and can be used as a novel drug in future.

## Conflict of interest

None declared.

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