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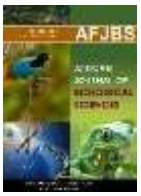

Nanotechnology-enabled Curcumin Formulation in Cancer Therapy with special Emphasis on Nanoemulsion

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ABSTRACT

Background

Curcumin, a polyphenolic compound extracted from turmeric, has emerged as a promising natural anticancer agent due to its potent bioactive properties. However, its clinical application has been overdue by challenges such as limited bioavailability and stability. Nanoemulsion-based delivery systems have emerged as a viable strategy to address the limitations of curcumin. These systems offer enhanced solubility, absorption, and efficacy of curcumin, thereby improving its therapeutic potential in cancer treatment. This review comprehensively examines the use of curcumin nanoemulsions as anticancer agents, focusing on various formulation strategies employed to optimize their physicochemical properties. Additionally, it explores the pharmacokinetic profile of curcumin nanoemulsions and their therapeutic efficacy in different cancer models. Furthermore, the review delves into the underlying mechanisms of action responsible for curcumin's anticancer effects within nanoemulsion formulations. Moreover, it provides a concise overview of patented formulations, ongoing clinical trials, and commercially available products, all serving to substantiate the efficacy and applicability of curcumin in cancer therapy. In conclusion, this review underscores the potential of curcumin nanoemulsions as promising candidates for cancer therapy. Despite current challenges, such as limited clinical translation, the review emphasizes the importance of translational research and personalized medicine approaches in advancing the clinical application of curcumin nanoemulsions. Overall, this comprehensive overview serves as a valuable resource for researchers and clinicians seeking to connect the therapeutic benefits of curcumin nanoemulsions in cancer treatment.

Keywords: Curcumin, cancer, nanoemulsion, drug delivery, structural activity relationship (SAR)

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Background

Cancer remains a significant global health challenge, ranking as a leading cause of morbidity and mortality worldwide [1–4] , In 2020 alone, nearly 10 million deaths were attributed to cancer. The most prevalent types of cancer in terms of new cases recorded in 2020 included breast, lung, colon and rectum, prostate, non-melanoma skin, and stomach cancers. The total estimated cases of all cancer type up to 2022 reached 19,976,499, with a projected increase to 13,114,359 by 2050, marking a substantial rise of 65.6%. Similarly, the estimated deaths from all cancers up to 2022 amounted to 9,743,832, with an anticipated increase to 8,434,223 by 2050, representing an 86.6% rise (WHO). Projections from the International Agency for Research on Cancer (IARC) indicate a further escalation in cancer cases and deaths by 2030, with an estimated 21.4 million new cancer cases and 13.2 million cancer-related deaths. This surge underscores the urgent need for enhanced preventive measures, early detection strategies, and effective treatment interventions to address the growing burden of cancer, particularly among the elderly population, where a 67% increase in cancer incidence is anticipated [5]. The anticipated 67 percent increase in cancer incidence among individuals aged 65 or older underscores a significant demographic shift in cancer prevalence [6]**.** This phenomenon reflects the pressing need for a deeper understanding of the underlying causes of cancer, a question that has captivated researchers for generations [7]. Cancer is a complex class of disorders characterized by the uncontrolled proliferation of abnormal cells, a process that disrupts the delicate balance between cell death and cell proliferation [8,9]. This imbalance is widely recognized as one of the primary contributors to the development and progression of cancer [10]. The dysregulation of cell death pathways, particularly the evasion of apoptosis, is a hallmark feature underlying various cancer types [11]. Two main pathways, intrinsic and extrinsic, are responsible for initiating apoptotic signals. The intrinsic pathway acts by modulating mitochondrial membrane integrity and downregulating anti-apoptotic proteins such as B-cell lymphoma-extra large (Bcl-xL) and B-cell lymphoma 2 (Bcl-2) [12,13]**.** Conversely, the extrinsic pathway is activated by death receptors (DRs) on cell surfaces, initiating the tumor necrosis factor (TNF)-related apoptosis cascade [14]. Notably, a 1950 World Health Organization (WHO) symposium highlighted significant regional disparities in cancer incidence, pointing to environmental exposures as primary contributors to cancer development rather than solely genetic factors [15]. Curcumin (CUR), the principal bioactive constituent derived from the Curcuma longa plant, has attracted considerable scientific

attention due to its wide-ranging therapeutic properties, including antioxidant, inflammatory diseases [16], diabetes [17], lung and chronic kidney diseases [18,19], neurological disorders [20], metabolic disease [21], liver problems [22], cardiovascular disease [23], digestive disorders [24], and anticancer properties [25]. Derived from turmeric rhizomes, this hydrophobic, orange-yellow phytochemical is primarily found in the Indian subcontinent and Southeast Asia [26]. Recognized as a safe polyphenolic compound for human consumption, CUR has garnered significant attention for its potential as an anticancer agent [27]. Its antioxidant properties are attributed to its ability to inhibit reactive oxygen species (ROS) [28,29], enabling it to scavenge these highly reactive molecules. This antioxidative activity extends to normal cells, where CUR demonstrates a Michael addition reaction [30], functioning as a Michael acceptor. This structural attribute enhances CUR's efficacy as an anticarcinogenic agent [22,31] and influences multiple cellular signaling pathways implicated in growth, cytokine regulation, and apoptosis. CUR exerts its anticancer effects by inhibiting the activation of NF-kappa B, a pivotal factor in promoting cancer cell survival. Moreover, it hinders cancer cell proliferation by downregulating cyclin D expression, suppressing p21-activated kinase 1 (PAK1) activity, and arresting cells at the G2/M phase. Additionally, CUR induces apoptosis by activating caspase-3 and impeding the Akt/mTOR/p70S6 pathway. Furthermore, it targets other critical pathways such as NF-κB, STAT3, and COX-2, thereby augmenting its anticancer properties [28,29]. Despite the extensive evidence supporting CUR's potential as an anticancer agent from numerous in vitro, in vivo, and clinical studies, there remains a critical need for further comprehensive research. This includes meticulously designed clinical trials aimed at elucidating its efficacy, safety profile, and optimal therapeutic dosages across different types of malignancies in the human population [12]. However, the clinical application of CUR is hindered by several challenges, including its poor aqueous solubility, chemical instability, limited bioavailability, and rapid metabolic degradation. Addressing these challenges is essential to fully realize the therapeutic potential of curcumin in cancer treatment [32]. The classification of curcumin as a PAINS, or pan-assay interference compound, is a subject of debate. PAINS compounds are characterized by their tendency to display activity across various assays by interfering with assay readouts rather than through specific interactions with compound targets. Curcumin has been observed to exhibit several behaviors typical of PAINS compounds, including covalent labeling of proteins [33–35], metal

chelation, redox reactivity, aggregation, membrane disruption, interference with fluorescence, and structural decomposition [36–40].

The limitations inherent in conventional drug delivery systems, such as tablets, capsules, and emulsions, significantly compromise their therapeutic effectiveness. These systems often result in systemic adverse effects due to unregulated biodistribution and release profiles, leading to inconsistent plasma drug concentrations [41]. dditionally, many formulations exhibit poor bioavailability, necessitating higher doses or frequent administrations, thereby negatively impacting patient adherence and convenience. Furthermore, the absence of targeted drug delivery mechanisms contributes to nonspecific drug distribution, diminishing overall therapeutic efficacy and potentially affecting unintended areas of the bodsy [42]. These challenges underscore the critical need for innovative drug delivery technologies to enhance the overall efficacy, safety, and patient adherence to drug therapies [43]. Nanoemulsion-based delivery systems present numerous advantages over conventional topical dosage forms like ointments and gels. Composed of safe and well-characterized ingredients, nanoemulsions (NEs) are engineered to produce stable emulsions. They enhance the solubility of drugs with poor water solubility by encapsulating them within the core of NE droplets [44]. Addressing drug stability concerns is paramount in product development, and NEs excel in improving the stability of chemically unstable compounds by shielding them from oxidative and photolytic degradation. Moreover, NEs facilitate targeted drug delivery by transporting agents to specific areas. Their unique size range enables droplets to navigate through skin pores and hair follicles, reaching mucosal membranes without disrupting normal tissues. These characteristics position NE-based delivery systems as promising candidates for enhancing drug delivery across various applications [9].

Conventional nanosystems hold particular appeal for drugs classified under the Biopharmaceutics Classification System (BCS) as class IV, such as CUR, which necessitate enhancements in solubility, pharmacokinetics, and permeation [45,46]. Established pharmaceutical formulation techniques have been adapted for the development of CUR-containing formulations (see **fig.1),** including nanoparticle-based delivery systems [47], liposomal delivery systems [48], self-microemulsifying drug delivery systems [49], gastroretentive floating drug delivery systems [50], micelles, and phospholipid complexes [51]. While strides have been made in various approaches, achieving a fundamental and clinically significant enhancement in oral bioavailability continues to be a challenging objective [52]. The

emergence of nanotechnology has transformed drug delivery, presenting avenues to enhance the effectiveness of traditional chemotherapeutic drugs while mitigating multidrug resistance, reducing toxicity, and prolonging product efficacy. Nanoparticles, characterized by their nano-scale dimensions, possess distinctive pharmacokinetic attributes and can be customized to navigate biological barriers, facilitating precise delivery to designated organs, cells, or organelles. In the case of CUR, the dimensions of the nanosystem have been demonstrated to significantly impact its biodistribution [45]. NEs represent a widely employed colloidal delivery system for encapsulating lipophilic bioactive compounds. These systems consist of oil droplets dispersed within an aqueous solution and stabilized by an emulsifier, resulting in particles typically ranging in size from 20 nm to 200 nm [53,54]. Their unique properties make them promising candidates as carriers for hydrophobic compounds such as CUR, as they can significantly enhance its solubility, sometimes by as much as 1400-fold [55]. NEs are favored for enhancing the oral bioavailability of various bioactive compounds due to their exceptional physical stability, excellent dispersibility, straightforward production process, low opacity, and high surface area.

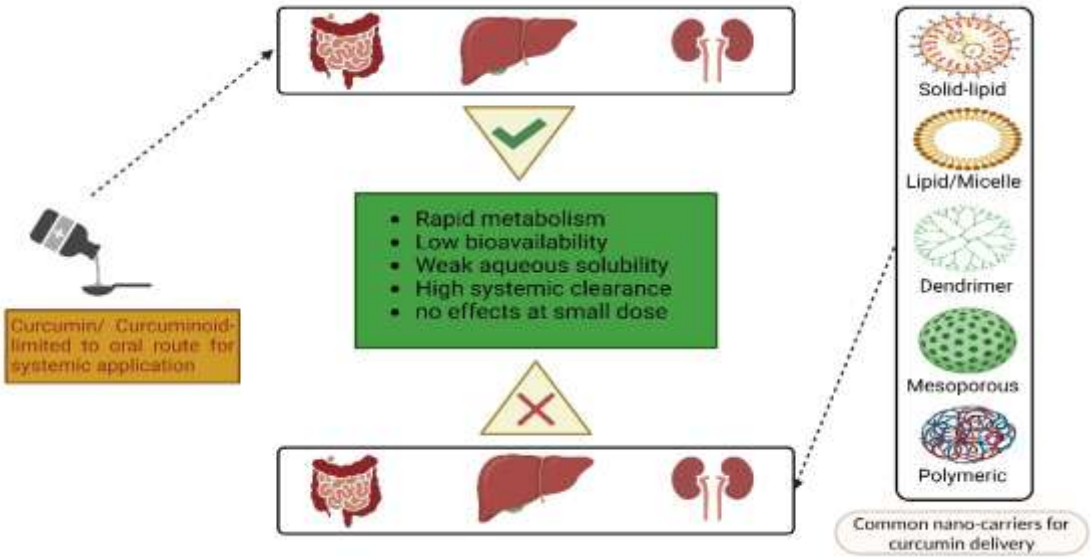

Figure 1. Diagram illustrating the constraints of curcumin bioavailability and advancements in delivery facilitated by nano-carriers (created via Biorender.com)

Main Text

Historical Significance of Curcumin and Its Role in Traditional Medicine

Cancer treatments, including immunotherapy, chemotherapy, radiotherapy, and surgery, while effective, often come with significant side effects [56–58]. As a result, there is growing interest in natural products, such as fruits, vegetables, tea, and spices, for their potential role in cancer prevention and management [59–66]. Among these natural remedies, CUR, a yellow pigment derived from the rhizome of Curcuma longa (Family: Zingiberaceae), stands out as a major component of turmeric. Curcumin has gained widespread recognition for its diverse beneficial activities and is being explored for its potential therapeutic applications in cancer [67]. Turmeric contains a class of compounds known as curcuminoids, consisting of curcumin, demethoxycurcumin, and bisdemethoxycurcumin, with curcumin being the predominant curcuminoid, constituting approximately 2-5% of turmeric. It not only imparts the characteristic yellow color to the spice but also accounts for the majority of its therapeutic effects [68,69]. Recognized as the active ingredient of the Curcuma longa plant [70], CUR has garnered considerable attention for its medicinal properties. With a rich historical and cultural legacy spanning over two millennia in Asian medicinal practices, particularly in Ayurveda in India and traditional Chinese medicine, CUR has been extensively utilized for its therapeutic benefits. In Ayurvedic traditions, it was employed to address various conditions ranging from eye infections to skin ailments. Additionally, the consumption of a turmeric-based drink postpartum has been a longstanding tradition in Indian culture [71]. Its awareness in the Western world grew significantly from Marco Polo's 14th-century observations and Vasco de Gama's explorations, underscoring its global significance in both traditional and modern medicine [72,73]. Curcuma has undergone continuous cross-breeding and selection processes, resulting in the development of numerous known species within the Curcuma genus [41]. Over 100 species have been reported to date, with Curcuma longa (syn. Curcuma domestica), Curcuma aromatica, and Curcuma xanthorrhiza being among the most common [74]. These species are cultivated extensively in tropical and subtropical regions worldwide, particularly in Asian countries such as India, Burma, Bangladesh, China, Indonesia, Japan, Taiwan, Thailand, and Vietnam. Curcumin, a bioactive compound derived from Curcuma [25,75,76]. It has been extensively studied for its potential therapeutic effects on various human carcinomas, including melanoma, head and neck,

breast, colon, pancreatic, prostate, and ovarian cancers [77–82]. Its potent antioxidant properties and ability to scavenge free radicals play a crucial role in inhibiting the initial stages of carcinogenesis. Studies have demonstrated that curcumin can suppress UV irradiation-induced DNA mutagenesis and the induction of cellular SOS functions, highlighting its potential as a preventive and therapeutic agent against cancer development and progression [83]. On the other hand, CUR has been shown to stimulate the expression of Phase II enzymes responsible for the detoxification of harmful metabolites. These enzymes include glutathione S-transferase, glutathione peroxidase, and glutathione reductase. Through this mechanism, CUR exhibits an inhibitory effect on carcinogenesis, as evidenced by studies conducted in numerous animal models representing various tumor types. These models include oral cancer, mammary carcinoma, and intestinal tumors, among others [69,84,85].

Chemistry and Mechanisms of Curcumin as an Anti-Cancer Agent

CUR, with a chemical formula of $C_{21}H_{20}O_6$ and a molecular weight of 368.37 g/mol, exhibits hydrophobic properties and has a melting point of 183°C. Its maximum absorption (λ max) occurs at 430 nm in methanol and at 415–420 nm in acetone [86,87]. Separation of CUR from CUR mixtures, which include demethoxycurcumin and bisdemethoxycurcumin, can be achieved through column chromatography using silica gel and various solvent mixtures such as dichloromethane/acetic acid or methanol/chloroform. This process yields three distinct fractions, with curcumin further purified using eluents like chloroform/dichloromethane and ethanol/methanol mixtures on silica gel [88]. The structural elucidation and synthesis of CUR were conducted by Milobedeska et al. and Lampe et al., respectively [89,90]. The IUPAC name of CUR is (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione. It belongs to the linear diarylheptanoid class of natural products, characterized by two oxy-substituted aryl moieties linked through a 7-carbon chain. As depicted in **fig.2A**, CUR features two hydrophobic phenyl groups connected by a relatively flexible linker. This structural arrangement enables the molecule to adopt various conformations, facilitating optimal interactions with aromatic and hydrophobic amino acid residues of proteins, including p–p and van der Waals interactions [91]. Chemically, CUR is a bis-α, β-unsaturated β-diketone, commonly referred to as diferuloylmethane. It displays keto–enol tautomerism, as illustrated in **fig.2B**, with a predominant keto form observed in acidic and neutral solutions, as well as within the cell

membrane. This preference arises from the heptadienone linkage between two methoxyphenol rings, containing a highly activated carbon atom [86,92] and in alkaline medium, CUR stabilizes in its enol form. Commercial CUR typically comprises approximately 77% diferuloylmethane, 17% demethoxycurcumin, and 6% bisdemethoxycurcumin [93], collectively referred to as curcuminoids.

The central β-diketone functionality of CUR is flanked by sterically demanding unsaturated phenolic groups, forming a wide and flat β-diketone ligand -CHQCH-C6H4(OH)(OMe)-3,4. This structural arrangement gives CUR a shape reminiscent of an eagle, with two large wings attached to the β-diketone unit [94]. CUR possesses two distinct hydroxyl groups: one in the form of a phenolic moiety and the other as an enolic moiety [95]. These phenolic -OH groups serve as additional centers of reactivity, facilitating the interconversion between the keto and enol forms of CUR. The transformation between these forms is highly influenced by the polarity of the surrounding environment, allowing CUR to traverse various barriers encountered during biochemical processes (see **table. 1**). Furthermore, the presence of the phenolic group enhances CUR's antioxidant activity by augmenting its capacity to scavenge radicals [95]. Studies have revealed that the keto form of CUR predominates in acidic environments, while the enol form is favored in alkaline conditions. In a neutral medium, CUR typically exists in its keto form. Furthermore, in non-polar and moderately polar solvents, the enol form tends to be more stabilized compared to the keto form, with a stabilization energy ranging from 5 to 8 kcals/mol, depending on the solvent's characteristics. The computed dipole moment of CUR in its ground state is measured at 10.77 D [88]. Sandur et al. demonstrated that CUR exhibits superior potency in suppressing tumor necrosis factor (TNF)-induced nuclear factor-kappa B (NF-kB) activation compared to its derivatives, desmethoxycurcumin and bisdesmethoxycurcumin. This finding suggests a critical role of the methoxy groups present on the phenyl rings of CUR [96]. Interestingly, the combination of curcuminoids has shown increased nematocidal activity compared to individual compounds, indicating a potential synergistic effect [89].

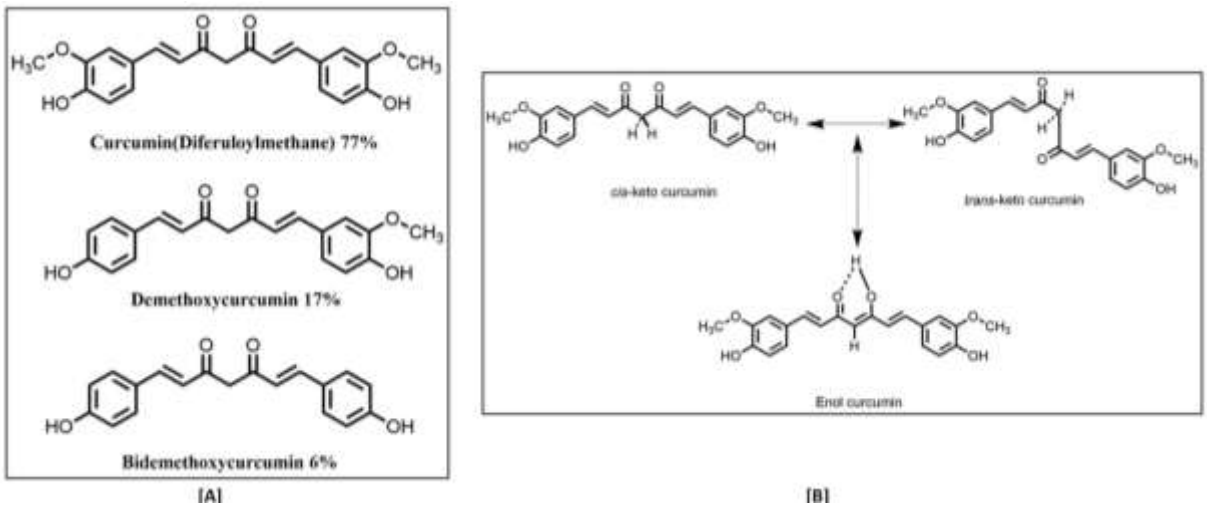

Figure 2. diagram illustrating **[A]** major constituents of curcuma longa with their chemical structure **[B]** various isoforms of CUR

The structure-activity relationship (SAR) of CUR elucidates how its chemical structure correlates with its biological activity, particularly its anticancer properties, and how modifications can enhance its effectiveness as in **fig.3**:

1. The presence of α, β-unsaturated carbonyl groups in the central structure of CUR are crucial for its biological activity.

2. Phenolic groups and the α-diketone motif in CUR's structure are considered essential for its antioxidant potential.

3. The α, β-unsaturated carbonyls in CUR serve as Michael acceptors, facilitating nucleophilic additions under biological conditions, thereby potentially enhancing its bioavailability and activity.

4. Structural modifications, such as substitutions in the side aryl rings (e.g., furan motifs), have been shown to enhance inhibitory effects on enzymes involved in cancer pathways.

5. CUR analogs, including pyrazole and isoxazole derivatives, have demonstrated increased anti-tumor potency against breast cancer cells compared to CUR itself, as evidenced by lower IC50 values, indicating higher efficacy [72,86,94].

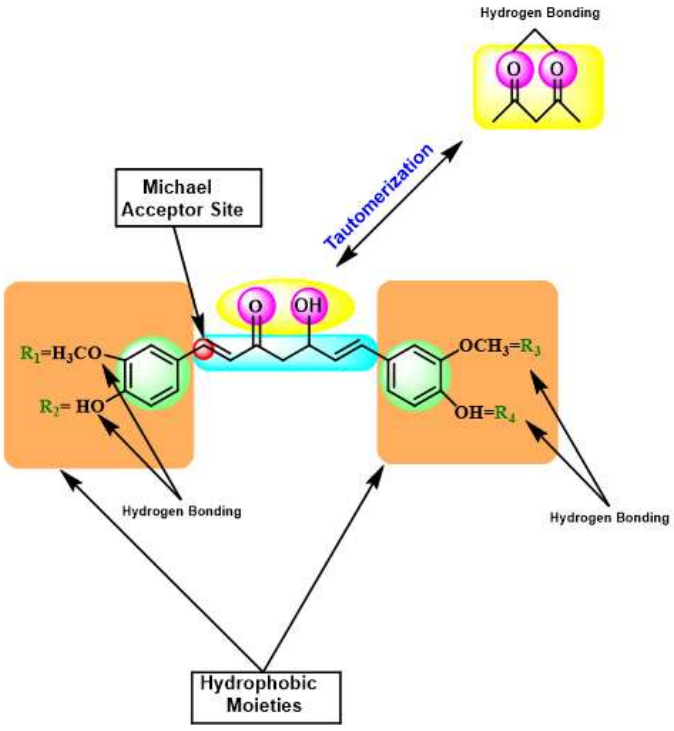

Figure 3. The main pharmacophores and potential substitution positions in CUR structure

Table 1. Table presenting different curcumin derivatives with varied chemical modifications and their corresponding activities.

CUR Derivative	Chemical Modification	Activities	Ref.
Dimethyl curcumin (ASC-J9)	Methyl groups substitution on R2 and R4	Enhanced activity toward prostate and breast cancer	[97–99]
Vanadium, gallium, and indium complexes	Metal complexation by the β-diketones	Enhanced cytotoxic activity	[100]
Tetrahydrocurcumin (THC)	Hydrogenated diketone moiety	Enhanced antioxidant activity but loss of DNA binding and STAT3 [a] inhibition properties	[101,102]
Modified aromatic rings curcumin compounds	Introduction of cyclohexane bridge	Improved mitochondrial membrane permeability during lymphoma therapy	[103]

Metallo-curcumin (Cu2+/Ni2+/Zn2+)	Metal complexation by the β-diketones	Enhanced water-solubility and improved DNA binding	[104]
Glycosylated curcumin derivative	Glycol groups substitution on the aromatic rings	Higher potency, aqueous solubility, and chelating properties	[105]
Cu^{2+} conjugate of synthetic curcumin analogues	Conjugation reaction on the keto-enol moiety	Stronger inhibition of TNF [b]-induced NF-κB [c] activation in leukemic KBM-5 cells	[106]
Cyclic curcumin derivatives	Boron trioxide-mediated aldol condensation	Enhanced cytostatic, antitumor, and antioxidant activity	[107]
Curcumin carbocyclic analogues	Introducing carboxyl group at the diketone moiety	Enhanced antioxidant activity and stronger inhibition of HIV [d] 1 protease	[23]
Hydrazinocurcumin	Replacing the diketone moiety with hydrazine derivative	Higher efficacy in inhibition of colon cancer progression via antagonism of Ca^{2+}/CaM [e] function	[108,109]
Semicarbazone	Introducing $NNHCONH_2$ at the keto-enol moiety	Enhanced antioxidant, antiradical, and antiproliferative activity	[110]

[a] STAT3: signal transducer and activator of transcription 3; [b] TNF: Tumor necrosis factor; [c] NF-κB: nuclear factor κ-light-chain-enhancer of activated B cells; [d] HIV: Human immunodeficiency virus; [e] Ca^{2+}/CaM: calcium/calmodulin

Mechanism of curcumin

CUR demonstrates potent anti-inflammatory properties by effectively inhibiting key inflammatory pathways such as NF-κB and COX-2, which play pivotal roles in the onset and advancement of malignancies [95,111–114]. Its diverse interactions with transcription factors, growth factors, and intracellular biomolecules, including DNA, RNA, and proteins involved in cellular signaling cascades, collectively contribute to suppressing tumor cell proliferation as depicted in **fig.4** [1,72,95,115]. Serving as a robust antioxidant, CUR attenuates oxidative stress by scavenging free radicals, thereby preserving genomic integrity and hindering oncogenic progression. Additionally, CUR directly interacts with proteins such as cyclooxygenase-2 (COX-2), lipoxygenase, GSK3b, and various other regulatory enzymes, while also modulating intracellular redox balance [116–118]. CUR triggers apoptosis in cancer cells through both

intrinsic and extrinsic pathways [111,119]. Intrinsic apoptosis is initiated by CUR through the activation of the tumor suppressor p53, leading to the up-regulation of pro-apoptotic proteins such as Bcl-2 and Bax. Extrinsic apoptotic pathways are activated by CUR through TNF receptor activation [95]. Furthermore, CUR regulates the expression of key proteins involved in cancer progression, including cyclin D1, MMPs, COX-2, and nuclear NF-κB, thereby inhibiting uncontrolled cell proliferation (see **fig.5**) [120]. Additionally, CUR disrupts cancer cell cycle progression, inhibiting uncontrolled growth [111,121], and suppresses angiogenesis, a process vital for tumor sustenance and metastasis [95]. Furthermore, CUR diminishes cell proliferation and migration by attenuating signaling molecules like STAT3 phosphorylation, consequently restraining downstream targets associated with metastasis [122]. Additionally, the modulation of pivotal signaling pathways including PI3K/Akt, MAPK, and Wnt/β-catenin contributes to the suppression of cancer cell survival and proliferation by CUR. Notably, CUR induces epigenetic alterations that intricately remodel gene expression patterns, exerting profound effects on tumor growth dynamics [111]. Recent research has uncovered CUR's anticancer efficacy through the inhibition of the Warburg effect, characterized by reduced glucose uptake and lactate production in cancer cells. This effect is achieved by downregulating pyruvate kinase M2 (PKM2) via suppression of the mammalian target of rapamycin-hypoxia-inducible factor 1α (TOR-HIF1α) pathway [14,94].

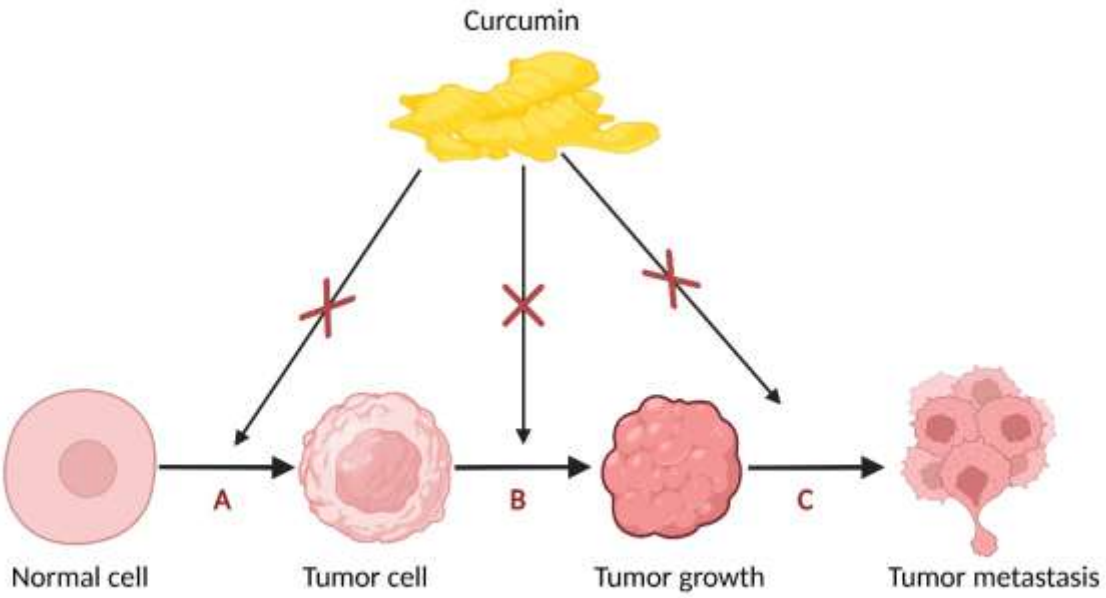

Figure 4. Mechanism of action of CUR as an anti-cancer molecule involving its ability to block or suppress various phases of tumor progression, including **[A]** transformation, **[B]** proliferation, and **[C]** invasion.

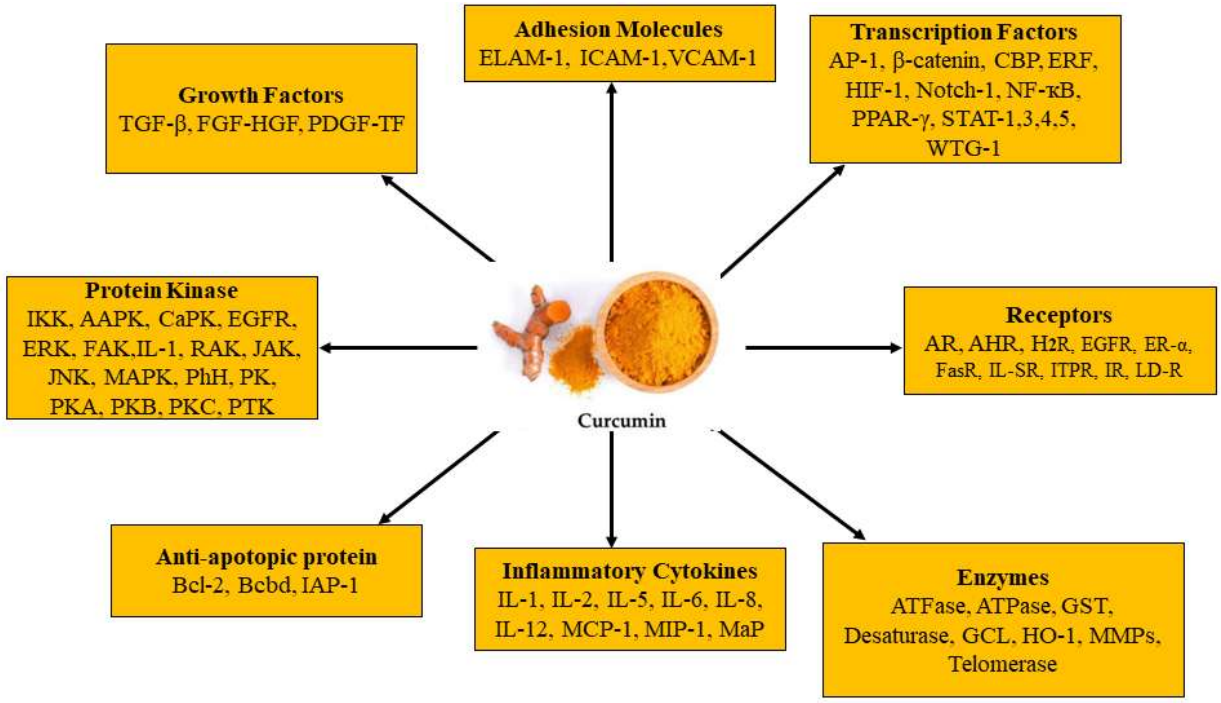

Figure 5. Pictorial representation of CUR inhibiting various factors, receptors, enzymes, and inflammatory mediators involved in cancer progression.

Nanotechnology-based delivery systems for Curcumin

Nanotechnology has significantly enhanced the safety and efficacy of cancer therapy through the development of drug delivery systems known as nanocarriers. These nanocarriers, owing to their minute size, are well-suited for passive targeting of chemotherapeutic agents via the enhanced permeability and retention (EPR) effect. Additionally, they have the capability to achieve active targeting through receptor-mediated uptake by specific cell types and host tissues [123]. encompass a range of structures, including liposomes, colloidal associations, small-scale emulsions, and others listed in **table.2**.

Table 2. A list detailing different nanoformulations containing CUR and the polymers/excipients commonly used in their composition.

S. No	**Curcumin nanoformulations**	**Description**	**Polymer/ Excipients**	**References**
1	Liposomes	Liposomes, spherical vesicles comprising single or multiple phospholipid bilayers surrounding aqueous units, closely mimic the structure of cell membranes. They effectively solubilize curcumin within the phospholipid bilayer, facilitating its distribution in aqueous media and enhancing its effectiveness.	Phosphatidylcholine, cholesterol, sodium cholate, span 60, span 80, tween 60, tween 80, Polyethylene glycol (PEG), hydrophilic polymers	[124,125]
2	Polymers	Polymers serve as an effective drug delivery system for CUR, significantly enhancing its oral bioavailability and solubility.	Poly(lactic acid), poly(glycolic) acid, chitosan, Hydroxypropyl methyl cellulose (HPMC), polycaprolactone, tween 80, lecithin, polyvinyl alcohol (PVA), polyvinylpyrrolidone (PVP), PEG	[126]
3	Gold nanoparticles	Gold nanoparticles possess distinct physical and chemical properties along with diverse	Sodium borohydride, sodium citrate, sodium dodecyl	[127,128]

		surface functionalities, making them a versatile platform for drug delivery, including CUR.	sulfate (SDS), cetyltrimethylammonium bromide (CTAB), PVA, PVP, Lipids, functionalized polymers	
4	Magnetic nanoparticles	Magnetic nanoparticles serve multiple purposes, including drug delivery, hyperthermia, and high-quality imaging, making them versatile tools in various biomedical applications, including the delivery of CUR.	SDS, CTAB, PVA, PEG, chitosan, dextran	[129,130]
5	Solid lipid nanoparticles (SLNs)	Solid lipid nanoparticles (SLNs) feature a lipid core matrix capable of solubilizing drugs such as CUR, stabilized by emulsifiers. Typically, SLNs exhibit a spherical shape, facilitating their application as drug delivery carriers.	Compritol 888, cetyl alcohol, stearic acid, glyceryl monooleate (GMO), tripalmitin, tristearin, poloxamer, tween 80, ethanol, propylene glycol, glycerol, PEG-400	[131,132]
6	Conjugates	A conjugate refers to the complex formed through the joining together of two or more molecules, often via covalent bonds. Conjugating CUR with small molecules and hydrophilic polymers enhances its solubility and oral bioavailability.	PEG, poly(lactic-co-glycolic acid), poly(ε-caprolactone), chitosan, phosphatidylcholine, cholesterol, SDS, CTAB	[133,134]
7	Cyclodextrins	Cyclodextrins are oligosaccharides with a-bucket-shaped structure, renowned for their solubilizing and stabilizing properties. They can solubilize CUR within their lipophilic cavity, while their outer hydrophilic surface aids in dispersing the formulation more effectively.	-	[135,136]
8	Solid dispersions	Solid dispersions involve one or more active components dispersed within a suitable matrix. They are effective in enhancing the bioavailability of poorly water-soluble drugs such as CUR.	PVP, copovidone, PEG, HPMC, hydroxypropyl methylcellulose acetate succinate (HPMCAS), polyvinyl caprolactam-	[137]

			polyvinyl acetate-polyethylene glycol	
9	Micelles	Micelles, typically ranging from 20 to 100 nm, are colloidal dispersions composed of amphiphilic molecules. They play a crucial role in improving the solubilization and targeted delivery of CUR.	PVP, copovidone, PEG, HPMC, HPMCAS	[138,139]
10	Nanospheres	Nanospheres refer to solid matrix particles where the main component (drug) is evenly dispersed, while microcapsules consist of an internal core encapsulated within an outer polymeric shell.	PVP, copovidone, PEG, HPMC, HPMCAS	[140,141]
11	Nanogels	A nanogel is a nanoparticle comprised of a hydrogel, synthesized through either physical or chemical cross-linking of polymers under controlled conditions. The cross-linked structure of nanogels provides a robust foundation for drug storage and release. This technique is viable for preparing and delivering active drugs such as CUR to cells, thereby preserving their activity, enhancing stability, and preventing drug immunogenicity.	Chitosan, hyaluronic acid, thiolated chitosan, thiolated hyaluronic acid	[142,143]
12	Nanodisks	Nanodisks are bilayers shaped like disks, stabilized and self-assembled by apolipoproteins. They enhance the solubility and enable targeted release of CUR.	Chitosan, hyaluronic acid, thiolated chitosan, thiolated hyaluronic acid	[144]

Nanoemulsions

Nanoemulsions are particles typically in the sub-micron range, often cited as being between 400 and 800 nm. However, particles within this size range are usually thermodynamically unstable and require mechanical energy input for formation. Additionally, they tend to be opaque [145]. NEs offer several benefits, including controlled release of drugs, enhanced drug stability, and resolution of water solubility issues associated with hydrophobic drugs [146]. Many nanotechnologists now align on the definition of a nanoemulsion as meeting specific criteria:

optical isotropy, thermodynamic stability, and a diameter less than 100 nm. Nanoemulsions, a form of nanoparticles, are typically dynamic structures formed from surfactants containing an encapsulated inner phase [147]. The integrity of these particles can be upheld by a complex blend of low molecular weight surfactants (emulsifiers) or polymers, including block copolymers and globular proteins. Some formulations may incorporate a synergistic mix of both polymer and emulsifier [148]. The overall characteristics of a nanoemulsion are influenced by factors such as individual particle size, shape (which may not be regular), surfactant residence time at the nanoemulsion surface, electrochemical properties, and interactions between particles and the dispersion medium components [145]. In contrast, the primary advantages of nanoemulsions lie in their composition. They are formulated using biocompatible components that are generally recognized as safe (GRAS), and their production is valuable to scalability and ease of manufacturing [149]. Furthermore, nanoemulsions offer additional advantages beyond those commonly associated with nanosystems. They boast a high encapsulation capacity for hydrophobic drugs, exceptional physicochemical stability, potentially heightened bioavailability, and reduced inter- and intra-individual variability in drug pharmacokinetics [150,151]. Notably, this versatile system is applicable across various administration routes. When orally administered, nanoemulsions shield drug molecules from degradation along the gastric and gut walls, thereby circumventing first-pass metabolism [152]. Nanoemulsions exhibit stability akin to liposomes, ethosomes, or microspheres, yet they possess the added benefit of enhancing the solubility and absorption of poorly bioavailable molecules. An in vivo study comparing the brain accumulation of lipid nanoparticles and nanoemulsions demonstrated that nanoemulsions significantly prolonged retention time compared to lipid nanoparticles [123]. Major components while manufacturing NE include:

Oil/lipids

The selection of oils in nanoemulsion (NE) development hinges significantly on the drug's solubility in the oil phase. Oils serve as pivotal excipients in NE formulation, not only for their capacity to solubilize substantial quantities of lipophilic drugs but also for their ability to enhance the transport of lipophilic drugs via the intestinal lymphatic system, thereby augmenting drug absorption from the gastrointestinal (GI) tract contingent upon the molecular properties of the oils [153]. Water-in-oil (w/o) NEs are deemed preferable for hydrophilic drugs, whereas oil-

in-water (o/w) NEs are more suitable for solubilizing lipophilic drugs. The loading of drugs in NE formulations emerges as a critical design parameter in the development of NEs for poorly soluble drugs, contingent upon the drug's solubility in various formulation components. Although edible oils are infrequently employed in NE development due to their limited capacity to dissolve large quantities of lipophilic drugs, formulating NEs with oils possessing low drug solubility would necessitate the incorporation of additional oil to achieve the target drug dose, thereby requiring higher surfactant concentrations to facilitate oil solubilization. This, in turn, could escalate system toxicity. Novel semi-synthetic medium-chain derivatives, acting as amphiphilic compounds, are progressively and effectively supplanting conventional medium-chain triglyceride oils in NE formulations [154].

Surfactants

Surfactants play a crucial role in the dispersion process by reducing interfacial tension to a minimal level and forming a flexible film that can easily conform around droplets. Their lipophilic nature ensures the appropriate curvature at the interfacial region, thereby facilitating the formation of the desired type of nanoemulsion, whether it be oil-in-water (o/w), water-in-oil (w/o), or bicontinuous [155]. Surfactants with low hydrophilic-lipophilic balance (HLB) values (ranging from 3 to 6), such as Spans, are typically employed in the development of w/o nanoemulsions. Conversely, surfactants with high HLB values (ranging from 8 to 18), such as Tweens, are favored for the creation of o/w nanoemulsion systems. Some of the commonly utilized surfactants and emulsifiers in the preparation include: Cationic surfactants, such as quaternary ammonium salts, represent a well-known class within this category. Hexadecyltrimethylammonium bromide (CTAB) and didodecylammonium bromide (DDAB) are among the commonly utilized cationic surfactants. These surfactants are primarily recognized for their applications as antiseptics or disinfectants and find widespread use in ophthalmic formulations [156], Anionic surfactants, on the other hand, find extensive use in topical routes, with sodium bis-2-ethylhexylsulphosuccinate (AOT) being the most prevalent. AOT, characterized by twin-tailed structure, is particularly adept at stabilizing water-in-oil (w/o) nanoemulsions [157], and In the realm of nonionic surfactants, sorbitan fatty acid esters like Spans and polyoxyethylene derivatives such as Tweens are predominant. These surfactants are frequently employed owing to their desirable properties in various applications [158].

Cosurfactants:

Achieving transient negative interfacial tension typically requires the incorporation of a cosurfactant in addition to a single surfactant. When a cosurfactant is absent, the surfactant alone forms a rigid film, limiting the formation of nanoemulsions to a narrow concentration range. However, the presence of cosurfactants imparts flexibility to the interfacial film, enabling it to adopt various curvatures necessary for nanoemulsion formation across a broader composition range [159]. Single-chain surfactants alone lack the ability to sufficiently reduce the interfacial tension in oil-in-water (o/w) systems to facilitate nanoemulsion formation. Medium-chain length alcohols, commonly employed as cosurfactants, play a pivotal role in further reducing interfacial tension while enhancing interface fluidity and increasing system entropy [160].

Aqueous Phase

The droplet size and stability of nanoemulsions are significantly influenced by the composition of the aqueous phase. Therefore, careful consideration must be given to the pH and ionic content of the aqueous phase during the design of nanoemulsions. The physiological environment encompasses diverse pH ranges, spanning from acidic conditions (pH 1.2 in the stomach) to neutral to slightly basic conditions (pH 7.4 and above in the blood and intestine). Additionally, the presence of various ions in the physiological milieu can exert a notable influence on the properties of nanoemulsions. Electrolytes, in particular, are known to impact nanoemulsion characteristics such as droplet size and physical stability. Consequently, it is recommended to assess nanoemulsions and their resulting characteristics in aqueous phases with varying pH and/or electrolyte concentrations, tailored to the specific application requirements [161].

Formulation of NEs

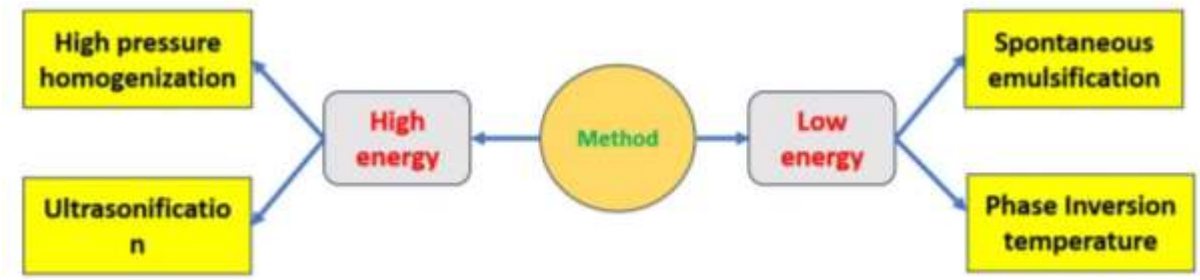

Figure 6. Diagrammatic representation of commonly employed method for development of NEs

Methods for producing nanoemulsions are typically categorized into high-energy and low-energy approaches. High-energy methods encompass techniques such as high-pressure homogenization and microfluidization, which are applicable at both laboratory and industrial scales. Additionally, ultrasonication is a high-energy method primarily utilized at the laboratory scale (see **fig.6**) [162,163]. High-energy methods, while effective in reducing droplet size, are not ideal for labile drugs and macromolecules such as proteins and nucleic acids due to the potential for degradation. In such cases, low-energy emulsification methods are preferred. These include spontaneous emulsification, the solvent-diffusion method, and the phase-inversion temperature (PIT) method [163,164]. Hydrophilic drugs can be solubilized in the aqueous phase, while lipophilic drugs can be incorporated into the oil phase during the formulation process. Co-solvents may also be employed, if necessary, to facilitate drug solubilization. During high-pressure homogenization, the initial coarse dispersion of the oil and aqueous phases is forced through a small inlet orifice under operating pressures ranging from 500 to 5000 psi. This process subjects the emulsion mixture to intense turbulence and hydraulic shear, resulting in the formation of a fine emulsion characterized by an extremely small droplet size [165]. In microfluidization, a high-pressure positive displacement pump is employed, operating at exceptionally high pressures of up to 20,000 psi. This pump drives the emulsion product through the interaction chamber, comprised of a series of microchannels. As the emulsion traverses these microchannels, it reaches an impingement area where it undergoes intense shearing forces, resulting in the formation of extremely fine emulsion droplets [166]. The particle size of the fine

emulsion in microfluidization is determined by the operating pressure and the number of passes of the coarse emulsion through the interaction chamber of the microfluidizer. Higher operating pressures and an increased number of passes result in smaller droplet sizes in the final emulsion. Subsequently, to eliminate any large particles present, the resulting nanoemulsion is filtered through a 0.2 μm filter under nitrogen, yielding a uniform nanoemulsion. High-energy emulsification methods are capable of producing both oil-in-water (o/w) and water-in-oil (w/o) nanoemulsions. Conversely, in low-energy emulsification methods, such as solvent diffusion and the phase-inversion temperature (PIT) method, o/w nanoemulsions are generated, while spontaneous emulsification yields w/o nanoemulsions [163]. Rapid cooling of the microemulsion in the phase-inversion zone or dilution with water, regardless of temperature, enables the production of highly stable oil-in-water (o/w) nanoemulsions. Dilution with water is considered more practical and adaptable, making it the preferred method for industrial and pharmaceutical applications. Recent studies have demonstrated that, under specific conditions, the phase-inversion temperature (PIT) method can also yield water-in-oil (w/o) nanoemulsions. This process involves incorporating a lipophilic polyethylene glycol (PEG) surfactant to generate a microemulsion within the phase-inversion zone, which, upon dilution with suitable oil, produces highly monodispersed w/o nanodroplets [163]. Nanoemulsions featuring an aqueous core are experiencing growing demand for the delivery and targeting of hydrophilic drugs, particularly peptides and proteins [9].

Patented, Clinical investigations, and commercially available curcumin-based formulations

Table 3 presents various patented nanotechnology-enabled formulations containing CUR as active ingredients, while Table 4 outlines the clinical trial status of commercial products in the drug discovery tunnel. Together, these tables offer insights into the current trends, progress, and significance of curcumin in the prevention and treatment of various types of cancer. Furthermore, Table 5 provides an overview of different preparations seeking approval from regulatory agencies.

Table 3. Table outlining various patents filed in the domain of CUR-based formulations for anticancer activities

S.no.	Patent No.	Invention's field	Year	Title	Ref.
1	**US10272053B2**	Method of delivering a compound to the lungs by *i.v.* injection	2019	Nanoparticle targeted drug delivery to the lungs using extra-testicular sertoli cells	[167]
2	**ES2885052T3**	Wound healing and anticancer	2021	Multifunctional formulation composed of natural ingredients and its preparation / manufacturing method	[168]
3	**US20230025663A1**	Herbal nanoformulations	2023	Nanoformulation with diverse functional molecules from turmeric and process for preparation of the same	[169]
4	**WO2013175507A1**	Novel highly bioavailable, water soluble, sustained release nanoformulation	2013	Novel highly bioavailable, water soluble and sustained release nanoformulations of hydrophobic plant derived compounds and extracts	[170]
5	**CN112469444A**	Solubilisate comprising curcumin	2021	Solubilizates containing curcumin and at least cannabinoid THC as other active substances	[171]
6	**US10485768B2**	Compositions and methods for treating glioblastomas	2019	Treatment for glioblastoma	[172]
7	**US10182997B2**	Cancer therapeutics	2019	Liposomal curcumin for treatment of cancer	[173]
8	**US7842705B2**	Compounds useful for the treatment of cancer	2010	Curcumin analogs with anti-tumor and anti-angiogenic properties	[174]
9	**US9775919B2**	curcumin coated magnetite nanoparticles	2016	Curcumin coated magnetite nanoparticles for biomedical applications	[175]

Table 4. List of clinical trials categorized as completed, active, or withdrawn, involving CUR or CUR-based formulations for cancer treatment.

Disease	Study Title	Voluntee	Study type,	Clinical trial	Status,

		rs enrolled	**location**	**no., Year**	**Ref**
Lung cancer	Phase II trial to modulate intermediate endpoint biomarkers in former and current smokers	75	Interventional, United states	NCT03598309, 2024	Recruiting, [176]
Gastrointestinal cancer	Curcumin in preventing gastric cancer in patients with chronic atrophic gastritis or gastric intestinal metaplasia	50	Interventional, (Honduras, Puerto Rico)	NCT02782949, 2024	Active, [177]
Breast cancer	Curcumin in reducing joint pain in breast cancer survivors with aromatase inhibitor-induced joint disease	42	Interventional, United states	NCT03865992, 2024	Active, [178]
Acute lymphoblastic leukemia, pediatric	Safety and efficacy of curcumin in children with acute lymphoblastic leukemia (CurcumPedALL)	30	Interventional, Egypt	NCT05045443, 2024	Completed, [179]
Glioblastoma	Study of liposomal curcumin in combination with RT and TMZ in patients with newly diagnosed high-grade gliomas	30	Interventional, United states	NCT05768919, 2023	Recruiting, [180]
Colon cancer	Study investigating the ability of plant exosomes to deliver curcumin to normal and colon cancer tissue	35	Interventional, United states	NCT01294072, 2023	Recruiting, [181]
Colon cancer	Curcumin in combination	13	Interventional,	NCT02724202,	Unknown,

	with 5FU for colon cancer		United states	2020	[182]
Breast cancer	Pilot study of curcumin for women with obesity and high risk for breast cancer	29	Interventional, United states	NCT01975363, 2019	Completed , [183]
Metastatic cancer	A phase IB dose escalation study of Lipocurc in patients with cancer	30	Interventional, Austria	NCT02138955, 2018	Completed , [184]
Colorectal cancer	Curcumin for the chemoprevention of colorectal cancer	56	Interventional, United states	NCT00118989, 2017	Terminate d, [185]
Colon cancer	Curcumin for the prevention of colon cancer	36	Interventional, United states	NCT00027495, 2012	Completed , [186]
Breast cancer	Curcumin for the prevention of radiation-induced dermatitis in breast cancer patients	35	Interventional, United states	NCT01042938, 2011	Completed , [187]
Colon cancer	The effects of curcuminoids on aberrant crypt foci in the human colon	60	Interventional, United states	NCT00176618, 2007	Completed , [188]

Table 5. Marketed preparations investigating the use of CUR-containing products in cancer prevention and treatment.

Sl. No.	**Product type**	**Description**	**Supplier**	**Ref.**
1.	**CEM**	Curcumin-containing product (480 mg) and quercetin (20 mg) using Oxy-Q tablets	Farr Laboratories (Santa Clarita, CA, USA)	[189]
2.	**CUR**	100% pure curcumin (CUR)	N/A	[190]

3.	**TE**	Pure curcumin (CUR) powder; 98.0% by HPLC	Sabinsa Corp. (East Windsor, NJ, USA)	[191]
4.	**TE**	C3 curcuminoid granule stick-packs (Allepey finger turmeric); each curcumin-containing product stick-pack contained 4,000 mg of curcuminoids (3,600 mg of curcumin [CUR], 320 mg of demethoxycurcumin, and 80 mg of bisdemethoxycurcumin)	Sabinsa Corp. (East Windsor, NJ, USA)	[192]
5.	**CEM**	Curcumin-containing product, reconstituted with turmeric oil and dispensed in capsules (BCM95–Biocurcumax)	Arjuna Natural Extracts Ltd. (Kerela, India)	[193]
6.	**CUR**	Curcumin-containing product (not further described)	Sigma Aldrich (Shanghai, China)	[194]
7.	**CEM**	Phytosomal preparation of curcuminoids	Meriva; Indena S.p.A (Milan, Italy)	[195]
8.	**TE**	A preparation containing CUR (87.2%); demethoxycurcumin (10.5%); and bisdemethoxycurcumin (2.3%)	Sabinsa Corp. (Piscataway, NJ, USA)	[196]
9.	**TE**	Curcumin-containing product in microbead form, containing a mixture of curcuminoids (Curcumin C3 Complex) that contains curcumin (CUR; 73%), demethoxycurcumin (22%), and bisdemethoxycurcumin (4%)	Sabinsa Corp. (Piscataway, NJ, USA)	[197]
10.	**TE**	Turmeric extract capsules (BCM-95/Curcugreen) containing essential oils of turmeric	Arjuna Natural, Aluva (India)	[198]

CEM= further processed curcuminoid-enriched materials, **CUR**= curcumin as a single-chemical entity, **TE**= hybrid of a CEM and Turmeric essential oil

Conclusions

This review delves into the dynamic landscape of cancer epidemiology, emphasizing the urgent need for innovative therapeutic approaches. It examines global cancer trends and highlights the pharmacological properties of curcumin, underscoring its potential in cancer management. Understanding the intricate mechanisms of curcumin's anticancer effects and the development of

advanced drug delivery platforms are essential for effective cancer treatment. Moreover, nanoemulsion-based drug delivery systems play a significant role in optimizing therapeutic outcomes. Recent research has focused on elucidating the kinetics and mechanisms of curcumin's actions, particularly in mitigating metal toxicity. However, the complexity of curcumin-metal complexes requires further investigation. Formulations incorporating natural biopolymers and nanotechnology-based delivery systems show promise in overcoming challenges in curcumin bioavailability. Nanoemulsions offer versatile capabilities, including cancer cell recognition and real-time efficacy assessment. Exploring different administration routes for nanoemulsions carrying cancer drugs holds potential for advancing anticancer drug delivery strategies. Additionally, vaccine carriers in nanoemulsion formulations targeting tumors represent a promising avenue for late-stage cancer therapeutics.

List of abbreviations

CUR- Curcumin

COX-2 - Cyclooxygenase-2

G2/M phase - Growth-2/Mitotic phase

STAT3 - signal transducer and activator of transcription 3

Bcl-2 - B-cell lymphoma 2

PAINS – Pan Assay interference compound

PIT - Phase-inversion temperature

HLB - Hydrophilic-lipophilic balance

O/W - Oil-in-water

W/O - Water-in-oil

HPMC - Hydroxypropyl methyl cellulose

HPMCAS - hydroxypropyl methylcellulose acetate succinate

PEG - Polyethylene glycol

PVP - Polyvinylpyrrolidone

SDS - Sodium dodecyl sulfate

TMZ - Temozolomide

RT - Radiotherapy

5FU - 5-fluorouracil

NF-kB - nuclear factor-kappa B

PI3K/Akt - Phosphatidylinositol 3-kinase/ protein kinase B

MAPK - Mitogen-activated protein kinases

MMPs - Matrix metalloproteinases

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Author contributions

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