AAPS PharmSciTech (2022) 23: 115
https://doi.org/10.1208/s12249-022-02268-y

REVIEW ARTICLE

Curcumin and Derivatives in Nanoformulations with Therapeutic Potential on Colorectal Cancer

Sourour Idoudi[1] · Takwa Bedhiafi[2] · Yousef Mohammad Hijji[3] · Nashiru Billa[1]

Received: 7 December 2021 / Accepted: 3 April 2022 / Published online: 19 April 2022

Abstract

There is growing concern in the rise of colorectal cancer (CRC) cases globally, and with this rise is the presentation of drug resistance. Like other cancers, current treatment options are either invasive or manifest severe side effects. Thus, there is a move towards implementing safer treatment options. Curcumin (CUR), extracted from *Curcuma longa*, has received significant attention by scientists as possible alternative to chemotherapeutic agents. It is safe and effective against CRC and nontoxic in moderate concentrations. Crucially, it specifically modulates apoptotic effects on CRC. However, the use of CUR is limited by its low solubility and poor bioavailability in aqueous media. These limitations are surmountable through novel approaches, such as nanoencapsulation of CUR, which masks the physicochemical properties of CUR, thus potentiating its anti-CRC effects. Furthermore, chemical derivatization of CUR is another approach that can be used to address the above constraints. This review spans published work in the last two decades, with key findings employing either of the two approaches, in addition to a combined approach in managing CRC. The combined approach affords the possibility of better treatment outcomes but not widely investigated nor yet clinically implemented.

KEY WORDS colorectal cancer · curcumin · derivatives · nanoformulations

INTRODUCTION

Globally, the incidences and mortality arising from colorectal cancer (CRC) have shot up sharply in the past decade, partly attributable to sedentary lifestyle or unhealthy eating habits. In 2020, the International Agency for Research on Cancer (IARC) recorded approximately 19.3 million new CRC cases, resulting in 10 million fatalities (1). The World Health Organization (WHO) has ranked CRC as the second leading cause of deaths in patients below 70 years (2). It is the third most frequent manifestation of cancer globally (3). Unsurprisingly, research has intensified toward evolving effective therapeutics to address this trend. CRC may manifest from genetic predispositions or non-permanent epigenetic aberrations within the colonic epithelium imposed by carcinogens in food. The latter also plays a central role in the pathogenesis of other types of cancers. Technically, therefore, it is possible to halt the progression to CRC if we are cognizant of the food content and avoid potentially carcinogenic material. Practically, however, this is not possible, and unfortunately, most interventions on CRC commence only after manifestation of the disease. Pathologically, CRC presents as abnormal growth of epithelial tissue within the colonic region of the gastrointestinal tract (4). When manifested in the colorectal epithelia, the tumor is referred to as sarcomas, while, within the interstitial cells of the Cajal, it is referred to as stromal tumors. Carcinoid tumors are cancer cells that grow in the hormone-producing intestinal cells (5). Several factors contribute to the pathogenesis of CRC, including environmental and genetic factors (6). Hereditary trajectory of CRC manifests as Lynch syndrome (a hereditary nonpolyposis CRC), MUTYH-associated polyposis (MAP), or familial adenomatous polyposis (FAP). Thus, there is a strong possibility of genetic transfer to later generations. Even in the absence of CRC gene codes within the family history, there is a 20% chance of developing the disease (7) through epigenetic aberrations, as stated earlier.

✉ Nashiru Billa
nbilla@qu.edu.qa

[1] Department of Pharmaceutical Sciences, College of Pharmacy, QU Health Qatar University, Doha, Qatar

[2] Translational Cancer Research Facility, Translational Research Institute, Hamad Medical Corporation, Doha, Qatar

[3] Department of Chemistry, College of Arts and Sciences, Qatar University, Doha, Qatar

Due to heterogeneity of CRC tissue like other cancers, and clonal growth patterns, CRC poses drug resistance (8, 9). Consequently, genetic phenotyping for somatic genetic changes is routine during CRC therapy. However, due to the molecular heterogeneity of metastatic cells and possible progression of cancer genomes, tissue sampling may not always be representative (8).

Drug delivery systems can be deployed to the colorectal region of the gastrointestinal tract either through oral administration or by rectal route. However, the oral route is favored because it is natural, safe, and promotes compliance to treatment. In contrast, rectal administration is unnatural, discomforting to patients and is opposed by the unidirectional movement of gastrointestinal content distally (10). However, deployment of drug delivery systems to the colon via the oral route faces several physiological and anatomical constraints. Fortunately, it is possible to formulate drug delivery systems destined for the colorectal region, but this requires extensive understanding of the physicochemical properties of both the active drug and the carrier system as well as the physiological and pathological dynamics within the gastrointestinal tract. There are several diagnostic tests available for screening CRC, including colonoscopy, sigmoidoscopy, computed tomography (CT) colonography, multitarget stool DNA (mt-sDNA) test, and fecal immunochemical tests (FITs) (10). A well-diagnosed CRC manifestation is key to successful implementation of treatment options, which include surgery, radiation, and chemotherapy, with the latter being the most viable treatment modality (23, 24). Chemotherapeutic agents approved for use in CRC include cetuximab, oxaliplatin, 5-fluorouracil, ipilimumab to name a few (11–13). However, the use of these drugs is associated with severe toxicity resulting in side effects that diminishes the quality of life of patients (12). Unselective targeting of tissue causes multi-drug resistance and cancer relapse (13). Researchers have sought to address these constraints through targeted delivery of the chemotherapeutic agents using novel formulation approaches, such as nanoformulations. On the other hand, the role of anticancer agents of plant origin are increasingly being recognized as safer options, especially when appropriately formulated in suitable delivery systems. Some anticancer agents of plant origin being investigated for use in CRC include soybean saponin, epigallocatechin gallate, curcumin (CUR), among others (14). Research on use of curcumin for CRC has received significant attention in recent years specifically because it modulates apoptotic effects in CRC (15). Indeed, epidemiological analyses on the low incidence of CRC in the Indian subcontinent is attributable to chemopreventive effects from consuming dietary CUR (16). However, CUR is poorly soluble and presents low systemic bioavailability following oral administration. It is possible improve the bioavailability of CUR through nanoencapsulation in a variety of carrier systems or through chemical derivatization. Application of both approaches appears to be the new frontier in the quest for better CRC treatment outcomes from CUR. Thus, the motivation for the present review is to discuss research findings and clinical studies conducted on CRC through use of CUR or CUR derivatives through nanoencapsulation. The review focuses on articles published in the last two decades since these capture the most recent development in the field.

BACKGROUND ON HISTORY AND CHEMICAL PROPERTIES OF CURCUMIN

CUR, chemically diferuloylmethane or 1,7-bis(4-hydroxy 3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a natural yellow compound extracted from *Curcuma longa* rhizomes (17). Although discovered in 1815, its chemical structure was only elucidated in 1973 by Roughley and Whiting (18). It was isolated in 1842 for the first time as a mixture of turmeric oil and resin by Vogel and Pelletier (19). It has molecular mass of 368.37 and is soluble in several organic solvents including acetone, ethanol, and DMSO. However, it is poorly soluble in water (20) and melts between 176 and 177 °C. It is a distinctive polyphenol that exhibit keto-enol tautomerism with the keto structure in acidic solutions and a stable enol form in basic media (21). The structure is symmetrical with four chemical units including aryl side chains linked through a methylene moiety hoisting a di-keto moiety.

CUR has been a major part of the early Chinese and Indian traditional lifestyle, used either as a spice (18) or medicinal agent in injury, depression, stress, infections, and skin diseases (19). There is growing interest in the discovery and utilization of anticancer agents of plant origin, largely driven by multidrug resistance observed from current chemotherapeutic agents (22). There is also a perceived acceptance by the public that anticancer agents of plant origin are safer treatment options than their chemotherapeutic cousins (23). Whether this perception is justified or not is dependent on the therapeutic evidence associated with the anticancer agent in question. Notwithstanding, intense research in the realm of plant-based anticancer agents has prompted the emergence of some exciting new compounds (19).

Extract from turmeric contains CUR as the main constituent with demethoxycurcumin and bisdemethoxycurcumin as sub-constituents (24). All three are collectively called "curcuminoids." CUR is considered safe, effective on CRC, and nontoxic when used in moderate concentrations (18). It has been shown to possess diverse biological activities including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, and anti-CRC activities in *in vitro* and *in vivo* study models (18, 25). Thus, CUR can potentially be used in infectious diseases, neurodegenerative diseases, cancer, and diabetes.

The anticancer effect of can be explained through its molecular structure, which is polyphenolic, and biophysical properties that permit interaction with various proteins during the induction of apoptosis. Through *in vivo* and *in vitro* studies selective toxicity of CUR towards colon cancer cell lines and tissue has been demonstrated (26–28).

CONSTRAINTS TO THERAPEUTIC USE OF CURCUMIN

Although CUR holds a wide range of pharmacological properties, its health benefits are still limited because of poor aqueous solubility (11 ng/mL) (29) and instability in alkaline conditions (17), resulting in poor cellular uptake (19) and low bioavailability. Furthermore, it is extensively metabolized and rapidly eliminated from the systemic circulation (29). These constraints hinder the clinical applications of CUR to its full potential. However, several studies have addressed these limitations, including chemical modification of existing structure or synthesis of new derivatives of CUR. Formulation approaches have also been adopted, all of which are geared toward providing better therapeutic performance on CRC than the ordinal CUR (Table I).

It is the view of the authors that a good balance between chemical modifications of CUR and formulation approach adopted be sought as a rational approach to addressing the aforementioned constraints.

CURCUMIN AND CRC

CUR has demonstrable chemo-preventive and anticancer properties on several types of cancers, specifically CRC (30). In CRC, CUR has been shown to play a major role in FAP and has been investigated in combined chemotherapy in an attempt to improve effectiveness and address resistance (25). Furthermore, some CUR derivatives inhibit cancer cell proliferation, growth, metastasis, invasion, angiogenesis with damaging propensity on apoptotic-resistant cells (18). In the "Curcumin Nanoformulations" section, we will discuss some key technologies, specifically nanotechnology, that have been employed to improve the physicochemical properties of CUR, thereby enhancing its therapeutic effects. Some of these novel formulations have demonstrated improved CUR delivery thus enhanced its therapeutic properties. Moreover, some CUR derivatives in nanoformulations showed enhanced anti-CRC properties compared to CUR only formulations or free CUR.

Anti-CRC Mechanisms of CUR

CUR exhibits anticancer properties through a variety of mechanisms at cellular levels, including inhibition of cell proliferation, apoptosis, and invasion of tumor cells by suppressing a range of cellular signaling pathways (31). Key signaling pathways disrupted include Wnt/β-catenin pathway; Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway; p53 pathway; phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway; mitogen-activated protein kinase (MAPK) pathway; and nuclear factor-κB (NF-κB) pathway. Activation of apoptosis is the key mechanism by which CUR impedes the progression of CRC. CUR modulates several molecular targets such COX-2 and superoxide dismutase (SOD) enzymes, through transcription factors peroxisome proliferator-activated receptor gamma (PPAR-γ), β-catenin, p53, and NF-κB, AP-1. Other targets include BH3 proteins through Bcl-2 family members and protease enzymes (caspase 8 and caspase 3), through death receptor 5 (DR5), Fig. 1 (32–34).

Table I Summary of Main CUR Clinical Trials

Reference	Number of patients	Formulation	Duration	Outcomes
(81)	15		4 months	Oral bioavailability of CUR was very low and mainly detected in the feces GST activity was not affected by free CUR doses
(85)	5		3–9 months	Decrease in number and size of rectal adenomas by 60.4% and 50.9% respectively, in all FAP patients
(82)	32		8 weeks	No dose-limiting toxicity was experienced in 26 patients Only one patient developed hemolysis Reduction in tumor marker responses noted in a patient with colon carcinoma metastasis
(83)	50		2 weeks	Liposomal CUR was well tolerated Liposomal CUR formulation was safe up to 120 mg/m^2
(84)	35		From 2011–2022	*

*Study on going

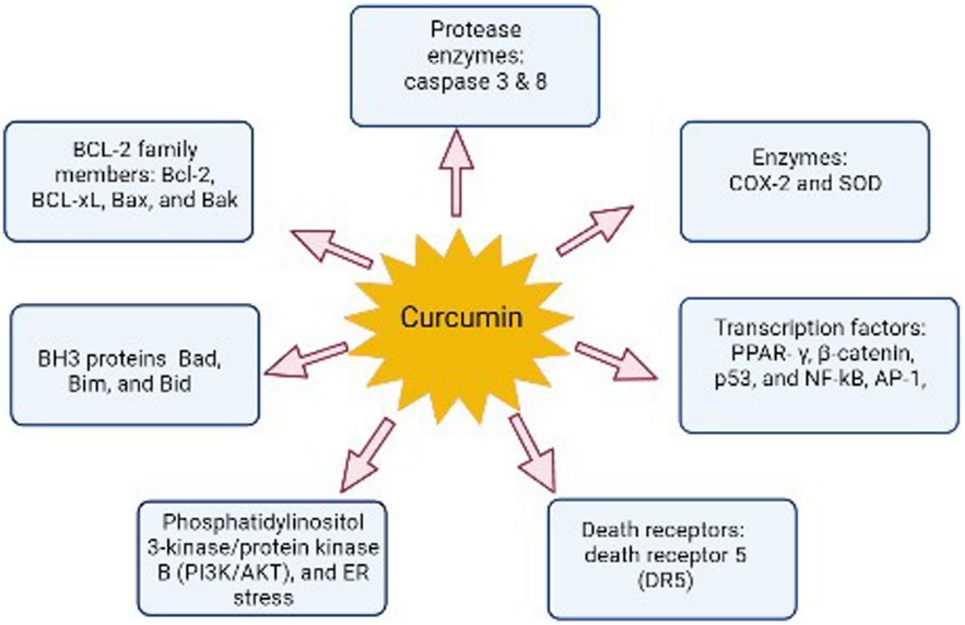

Fig. 1 Key apoptotic pathways induced by CUR on CRC

Curcumin Nanoformulations

Nanotechnology has been widely employed in drug delivery systems to improve the deployment of drugs at target sites (30). Encapsulation of CUR using various nanoformulation techniques have been used to improve its solubility and delivery to cancer tissue compared to free CUR (23, 30). Furthermore, nanoformulations provide improved stability of CUR, being less toxic to normal cells. In CRC treatment, several CUR nanoformulations have been studied including polymeric nanoparticles, polymeric nanocapsules, micelles, liposomes, nanogels, and gold nanoparticles (Fig. 2), each with their own unique features. The subsequent section captures key aspects of CUR nanoformulations as they relate to CRC treatment.

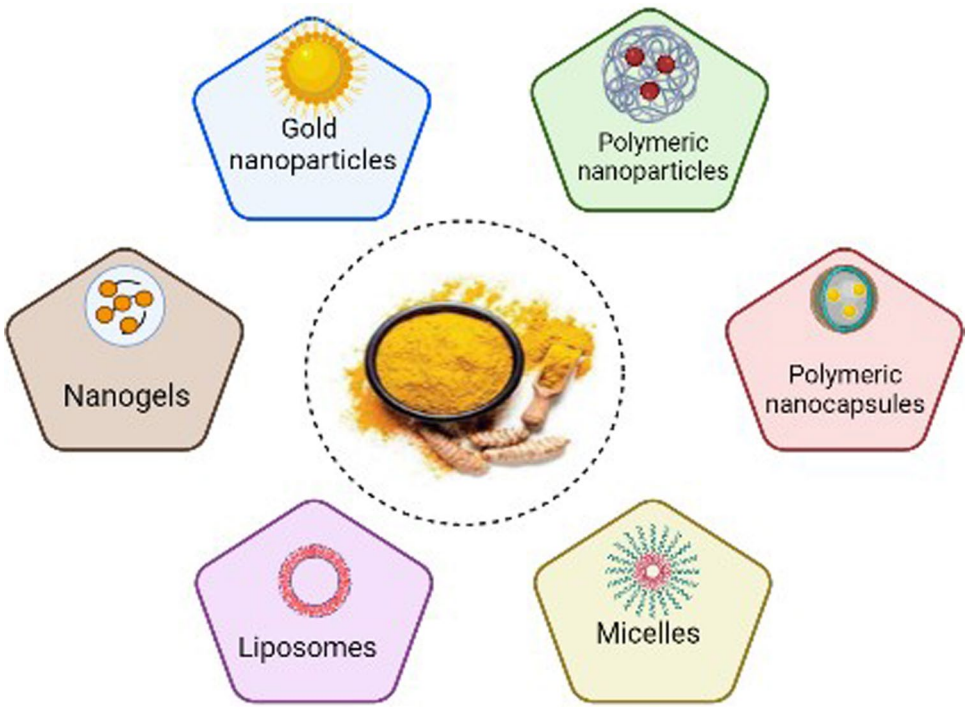

Fig. 2 CUR nanoformulations studied on CRC

Curcumin Polymeric Nanoparticles

Polymeric nanoparticles (PNPs) are composed of polymer-based formulations of 1–1000 nm size, with entrapped drug within the core or adsorbed to the surface of the particle (35). They present several advantages such as controlled drug release, protection of drug, modifying its physicochemical properties, thus potentially enhancing its bioavailability and therapeutic properties. Over the past decade, PNPs have been widely used for the delivery of CUR in CRC research. In a study on CUR containing hyaluronan (HA)-functionalized chitosan polymeric hybrid nanoparticulate system (CUR-HA NPs), fluorescence from CUR was used to quantify uptake by HT-29 cell lines (27). *In vitro* studies on enzymatic degradation of the nanoparticles displayed a suitable degradation profile; however, their morphology changed over time in simulated intestinal and gastric fluids. Furthermore, the CUR-HA NPs prevented fast release. Studies on HT-29 and Caco-2 cell lines showed that CUR-HA NPs did not affect metabolic activity or cell cytotoxicity; however, increase in cellular interactions and uptake was better than from uncoated nanoparticles (27).

In another study, CUR-loaded phenylboronic acid framboidal nanoparticles (CNPs) formulated through complexation exhibited enhanced stability for CUR, with sustained release profile obtained under physiological conditions. The CNPs inhibited HT29 cell proliferation with LC_{50} of 50 μM within 24 h. Furthermore, CNPs reduced cell viability to 65% at CUR concentration of 270 μM compared to free CUR. Finally, the CNPs showed strong antiangiogenic and anticancer activity *in ovo* compared to free CUR, which also signals improved CUR stability (36).

Polymeric nanoparticles of CUR formulated using cationic copolymer Eudragit E 100 (CENPs) by emulsification-diffusion-evaporation tested on C-26 cell lines and showed a 19-fold toxicity compared to free CUR. In addition, a 95-fold increase in $AUC_{(0–12\,h)}$ and 91-fold increase in C_{max} were observed in mice following oral administration of the CENP. The effectiveness of the CENPs on C-26 cancer-bearing mice was significantly increased in terms of reduction in tumor volume compared to free CUR (37), with good tolerability as evidenced by high survival rates and body weight from CENPs treated mice.

Chitosan-functionalized camptothecin (CPT)/CUR-loaded polymeric nanoparticles displayed sustained release pattern *in vitro* and cellular uptake by C-26 cell lines compared to free CUR, confirming that introduction of chitosan to the surface of the nanoparticles improved cellular uptake. Synergism was observed between CPT with CUR against C-26 cells, whereby CPT/CUR ratio of 4:1 showed the most effective anticancer properties (38). The fluorescence intensity from C-26 cells incubated with CPT/CUR nanoparticles was 2.1- and 2.8-fold higher than in cells incubated in free CPT and CPT only-loaded nanoparticles, respectively.

CUR loaded poly-lactic-co-glycolic acid (PLGA) nanoparticles fabricated by solvent evaporation and studied on SW480 cell lines revealed nuclear fragmentation within the cells (39). In addition, CUR nanoparticles formulated using chitosan and gum Arabic through emulsification solvent diffusion revealed that the nanoparticles arrived at the colon following oral administration without significant degradation in the upper gastrointestinal tract. Moreover, the nanoparticles showed higher anti-CRC properties than free CUR, which was also reflected by higher cellular uptake in HCT116 and HT-29 cancer cells followed by apoptosis (40).

Biodegradability and biocompatibility are desirable features associated with PNPs (41, 42). However, there is a limitation on the number of polymers with these features. Furthermore, PNP are prone to aggregation with only a few currently approved by the FDA and, hence their progression as drug carriers is somewhat impeded (43). There is also the issue of opsonization of circulating PNPs (35).

Curcumin Polymeric Nanocapsules

Polymeric nanocapsules in contrast to polymeric nanoparticles comprise of a core depot of active surrounded by layer(s) of typically, polymeric shell(s). Polymeric nanocapsules of CUR have been formulated using interfacial deposition, layer-by-layer, and nanoemulsion template methods (44).

CUR co-encapsulated with piperine (PIP) in polyallylamine hydrochloride (PAH) nanocapsules was formulated by nanoprecipitation and studied on Caco-2 cell line, where viability declined in proportion to PIP content. Moreover, PIP improved accumulation in colon cancer cells with enhanced cytotoxicity. Fluorescent images and percentage cell viability displayed localization of nanoparticles within cells with distorted morphologies indicative of apoptosis. Antiproliferation of tumor and inflammation in mice was via hindrance of COX-2 and iNOS enzymes in dimethylhydrazine (DMH)-induced CRC (28).

Long-circulating PLGA-based CUR-containing polymeric oil nanocapsules formulated by nanoprecipitation confirmed the delivery of CUR in CT26 cells and induction of apoptosis compared to free CUR. The nanocapsules displayed a prolonged blood circulation time compared to the free CUR and found to accumulate within CT26 tumor bearing mice, accompanied by a significant decrease in the tumor volumes (45).

In another study, CUR-loaded pH-sensitive hydroxy propylmethyl cellulose acetate succinate formulated by emulsion solvent diffusion and applied to HT29 cell lines showed a decrease in viability compared to the blank polymeric nanocapsules. Furthermore, the optimized formulation

showed a high cytotoxicity (IC50 value 20.32 μM) in HT 29 cell lines. Roentgenographic studies on Duncan Hartley guinea pigs indicated intact arrival at colonic region (46).

Although biocompatible polymers are primarily used their fabrication, some constraints related mainly to their instability in aqueous media promotes expulsion of encapsulated drug (44). Low encapsulation efficiencies of active contributes to the limitations of employing nanocapsules as drug carriers (47).

Curcumin Polymeric Micelles

Polymeric micelles are generally prepared using self-assembly of amphiphilic polymers, driven by van der Waals forces, electrostatic interactions, and intermolecular hydrogen bonds in selective solvents. Micelles potentially shield encapsulated cargo from surrounding milieu, improving the stability of the delivered drug and hence bioavailability (48).

CUR loaded in d-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) micellar nanoparticles was achieved through thin-film rehydration. The nanoparticles were stable with an average size of about 12 nm. The micelles were found to decrease ROS levels and induced apoptosis in HT-29 cell lines compared to free CUR. Following oral administration in rats, CUR-loaded TPGS micelles registered higher bioavailability compared to free CUR (49).

Reversible addition-fragmentation chain-transfer (RAFT) polymerization was used to assemble micelles comprising of poly (poly(ethylene glycol) methyl ether methacrylate)-block poly(styrene) (P(PEGMEMA)-b-PS) block copolymer in two average sizes: 16 nm and 46 nm. The CUR-loaded micelles showed significant cytotoxicity towards human colon carcinoma cells (WiDr) after 72 h of exposure compared to the unloaded micelles. Furthermore, rapid internalization of the micelles in cells occurred within minutes of exposure due to improved stability compared to the unloaded micelles. Surprisingly, larger micelles showed better internalization and well exocytosed compared to the smaller micelles (50).

In another study, biodegradable monomethoxy poly(ethylene glycol)poly(lactide) copolymer (MPEG-PLA) micelles containing CUR formulated via self-assembly was tested on CT26 cell lines, transgenic Tg(FLK-1:mCherry) zebrafish line, and female BALB/c mice. Compared to free CUR, the micelles were more potent at inhibiting cell growth, inducing cell apoptosis, and inhibiting colon tumor growth at the same dose. Moreover, immunofluorescent and immunohistochemical studies indicated that CUR/MPEG-PLA micelles induced cell apoptosis and inhibited angiogenesis than free CUR.

CUR encapsulated in monomethyl poly(ethylene glycol)-poly(ε-caprolactone)-poly(trimethylene carbonate) (MPEG-P(CL-co-TMC)) micelles in a single-step solid dispersion were tested on CT26 CRC cell lines and found to improve cellular uptake and induce apoptosis compared to free CUR. *In vivo* model comprising of tumor-bearing mice affirmed that CUR micelles was effective against cancer growth and suppression than free CUR. The micelles also inhibited cancer proliferation and angiogenesis with rising apoptosis level in the cancer cells. The side effects from the CUR micelles was also lesser than from free CUR, presumably because of the need to dissolve CUR in organic solvent (51).

Micelles are biocompatible and can be targeted to tumor (52); however, they may be unstable in physiological milieu (53). Furthermore, micelles are prone to premature release of active, thus precluding significant payload deployment at target (54).

Curcumin Liposomes

Liposomes are gradually gaining popularity as drug delivery vehicles for CUR because of their outstanding biocompatibility. They typically comprise of lipid molecules that are amphiphilic, such as phospholipids (55). β-Cyclodextrin-CUR (βCD-CUR) complex entrapped in liposomes via methanol refluxing was effective on CRC (SW-620) cell lines, inhibiting cell proliferation. Furthermore, the median effective dose (EC50) of the βCD-CUR liposomes was 3.25 μM, which is lower than in most studied CRC cell lines using CUR nanoformulations. Thus, including βCD complexes along with poorly water-soluble drugs such as CUR into liposomes appears to preserve the anticancer properties (56).

In another study, CUR entrapped in small unilamellar vesicular (SUVs) liposomes coated with a pH-responsive polymer (Eudragit S100) revealed no significant decrease in Caco-2 cell line viability after exposure to the liposomes with/without CUR, which confirms the safety profile of to the liposomes on intestinal tissue (57).

CUR liposomes with and without oxaliplatin tested on LoVo and Colo205 cells induced a dose-dependent growth inhibition as well as apoptosis in both cell lines. In addition, synergism was observed between CUR and oxalipatin at a ratio of 4:1 in LoVo cell lines. *In vivo* studies in nude mice with the same cells as xenografts showed significant inhibition of tumor growth from CUR-Liposomes compared to CUR + oxaliplatin liposomes, especially on Colo205 cells. Furthermore, antiangiogenic effect was noticed in tumors from animals treated with CUR liposomes as well as attenuation of CD31, which is an endothelial marker that reduces vascular endothelial growth factor and lowers expression of interleukin-8 (58).

The biocompatibility of liposomes is desirable (59) but high production costs (60), instability, and low drug encapsulation efficiencies hinder their clinical applications (61).

Curcumin Nanogels

Nanogels are cross-linked hydrophilic polymeric carriers typically with size in the order of 200 nm. Cellular uptake of

nanogels through receptor-mediated endocytosis is often facilitated, which makes them unique for the delivery of chemotherapeutics and active substances in the management of cancer (62).

CUR loaded in albumin-cored, folic acid functionalized amylopectin shell nanogels prevented the degradation of CUR in physiological milieu. An increased uptake of the nanogels by HT29 cell lines boosted by folate receptors was observed, with a retention of up to 60% compared to free CUR. This increased uptake led to early-stage apoptosis in the cell lines (63).

CUR-loaded nanogels formed through surfactant-free emulsion polymerization of N,N'-diethylaminoethyl methacrylate (DEAEM) with poly(ethyleneglycol) methacrylate (PEGMA) and CUR-loaded divinylacetal-cross-linked and N,N'-bis(acryloyl) cystamine (BAC)-cross-linked nanogels tested on HCT-116 cell lines yielded an IC_{50} of 1 μg/mL. However, both nanogels were nontoxic to female CD1 mice at concentrations of up to 40 mg/kg (64).

CUR-containing interpenetrating polymeric network of nanogels (IPN-NGs) formulated by free radical emulsion polymerization were evaluated on HCT-116 cell lines and found to demonstrate excellent anti-cancer activity (65). Furthermore, CUR and DOX loaded-non-toxic pH/thermo-responsive nanogels tested on HT-29 cell lines indicated efficient apoptosis compared to free CUR with an IC50 of 2.34 μg/mL in contrast to DOX alone (22.03 μg/mL) (66). Even though high drug loading capacities can be obtained from nanogels, coupled with biocompatibility and biodegradability (67, 68), they are relatively expensive and may be non-adherent to cancer tissue (67).

Curcumin Gold Nanoparticles

Gold nanoparticles are mostly used in cancer diagnosis but may serve as potential drug carriers due to inherent surface chemistry and multi-functionalization propensity, surface plasmon resonance, stability, and ease in formulation. Furthermore, they are considered non-toxic, non-immunogenic, highly retentive, and highly permeable, which facilitate good bioavailability of drug cargoes within tumors (69). CUR-loaded chitosan-graft-poly (N-vinyl caprolactam) gold nanoparticles formulated by ionic cross-linking and tested on CT26 xenografted Swiss albino mice was found to be in circulation after 7 days with no toxicity observed. Crucially, a significant concentration of CUR (3 μg/g) was localized within the CRC tumor sites. Moreover, the nanoparticles remained within the CRC tumor for up to 2 weeks, which affirms its high retention capacity (70). Gold nanoparticles can stimulate host immune response, which hinders their application as a drug carriers (71).

Recent Advancements in CRC Diagnosis via Nanotechnology

CRC diagnosis involving nanotechnology, specifically based on gold nanoparticles, have been successfully applied in early diagnosis of CRC through colonoscopy (72). Subject to clinical trials, this non-invasive technique can provide valuable insights on the progression of the tumor when visualized externally. For example, gold-loaded porous iron oxide nanocubes that is based on electrochemical detection of p53 autoantibodies against CRC has been developed for the detection of CRC (73).

Chemical Derivatives of Curcumin with CRC Activity

The key standing constraints limiting the therapeutic use of curcumin to its full potential is poor water solubility and low stability, which correlates with poor systemic bioavailability. As discussed in the "CONSTRAINTS TO THERAPEUTIC USE OF CURCUMIN" section, these constraints can be addressed through appropriate formulation techniques, whereby the physicochemical property of CUR is masked when cargoed in appropriate delivery systems. Indeed, the "Anti-CRC Mechanisms of Action of CUR" section captures a flavor of some CUR successful nanoformulations with potential use in CRC. On the other hand, there is intense interests in the synthesis of CUR analogues, in an attempt to not only address the above constraints but also to improve its therapeutic propensity. Some of these analogues demonstrate superior anticancer properties to CUR and comparable therapeutic effects to some established chemotherapeutic agents. In a recent study [15], CUR monocarbonyl analogs were synthesized and anticolon cancer properties investigated on SW620 cell line. Among the compounds synthesized, compound (i) (Fig. 3) displayed outstanding selectivity and significant antiproliferation activity towards SW620 cell lines compared to free CUR, with an IC_{50} of 9.36 μM, compared to CUR, with IC_{50} of 12 nM. This compound suppresses cell invasion, migration, and colony formation in SW620 with arrest of cell cycle in S and G2/M phases in addition to inducing cell apoptosis. The compound also downregulates the ATM gene. Thus, compound i represents a potential candidate for further investigation as an anti-CRC drug (74).

In another study, the anti-CRC activity of a CUR diarylheptanoid: 1,5-bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadiene-3-one (compound ii) (Fig. 4), showed higher cytotoxicity towards SW620 (IC_{50} = 5.7 μM) and SW480 (IC_{50} = 7.5 μM) compared to CUR (IC_{50} = 26.8 μM on SW620 and 30.6 μM on SW480). Moreover, compound (ii) effectively suppressed cell growth, with less cytotoxicity to normal cells at twice the IC_{50}. Anti-proliferative activity was demonstrable with the induction of apoptosis compared to free CUR. Furthermore, the activity of caspase-3 increased and Bcl-2 protein level was lowered in both tested cell lines. Thus, compound ii has potential for development as anti CRC agent (75).

A set of dimethylaminomethyl-substituted CUR analogues were studied on HCT-116 tumor cell lines (Fig. 5), where compounds (iii) and (v) displayed IC_{50s} of 3.7 and 10.9 μM respectively compared to 41.5 μM from CUR. On the other hand, the monoketone-linked CUR analogues (v) and (vi) were the most

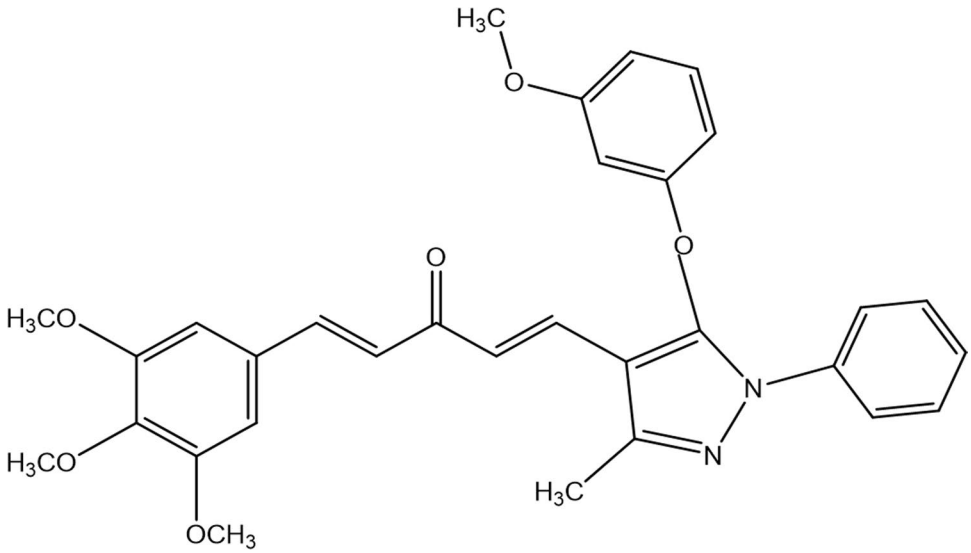

Fig. 3 CUR monocarbonyl analog (compound i)

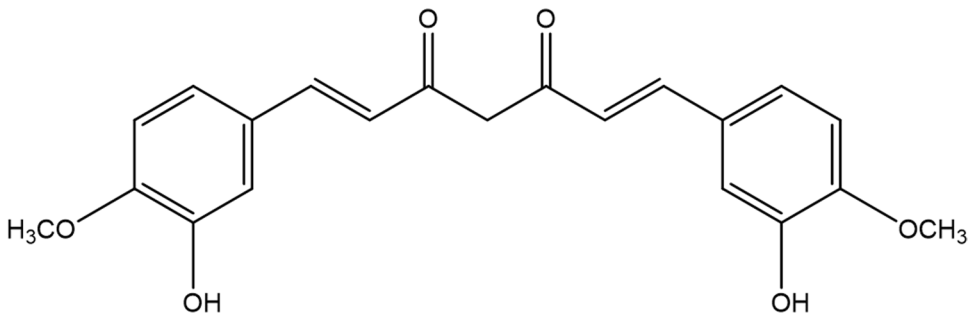

Fig. 4 CUR diarylheptanoid, MS13 (compound ii)

stable derivatives. The solubility values of the hydrochloride derivatives of (iv) and (v) were 367.88 and 302.96 mg/mL, respectively, in contrast to 0.1 mg/mL (76) for CUR.

Ester and acidic derivatives of CUR were synthesized in an attempt to enhance the chemical stability and anticancer activity of CUR (Fig. 6). Compounds (viii) and (x) were most stable, attributable to the absence of para substitution, which is critical to chemical stability. On the other hand, compound (xi) was most soluble due to partial dissociation of the enolic function. Excellent anti-proliferative activity was observed on HCT116 and LoVo cell lines from compounds vii and ix. After 24-h exposure to LoVo cell line, compound (vi) registered an IC_{50} of 4.1 μM, while compound (ix) had IC_{50} of 3 μM, compared to free CUR (IC_{50} = 13 μM). Compound (vi) registered an IC_{50} of 4.1 μM at 24 h on HCT116 cell line compared to free CUR (IC_{50} = 16 μM) (77).

A series of succinyl analogs of CUR were synthesized which showed varying degrees of anti-CRC properties on Caco-2 cell line (IC_{50} ranging from 1.8–9.6 μM) compared to CUR (3.3–4.9 μM). The diethyl disuccinate derivative (compound xii), Fig. 7, showed the highest anti-CRC potency (IC_{50} = 1.84 μM). Hydrolytic degradation studies at pH 7.4 showed that CUR succinylation significantly improved its chemical stability (78).

A CUR-glyco conjugate (Fig. 8) was synthesized and tested on Caco-2, HT29, and T84 cell lines for 96 h and yielded IC_{50} values of 10.3, 24.6, and 50.3 μM, respectively. Furthermore, apoptosis induction was observed to be through caspase-3 and caspase-9 proteins (79).

A CUR derivative, (1-(4-hy-droxy-3-methoxyphenyl)-5-(2-nitrophenyl) penta-1,4-dien-3 one) or WZ35 (compound xiv), Fig. 9, was synthesized and investigated on HCT116, SW620, and CT26 cell lines and *in vivo* on 5-week-old CT26 xenografted BalB/c female mice. *In vitro* study revealed that compound (xiv) successively reduced cell viability in the G2/M cell phase and induced apoptosis within the cell lines. The derivative was also effective at inhibiting growth of CT26 xenografted mice. Furthermore, generation of ROS and induction of ER stress within the CT26 cell line was demonstrable (15).

Nanoformulations of CUR Derivatives with Anti-CRC Effects

Nanoformulations are at the frontier in the quest for more effective formulations for delivering anticancer agents to tumor sites. Curcumin has potent anti-CRC activity; however, its use is limited due to its poor solubility and stability. Through appropriate nanoformulations, these constraints are being addressed, and as

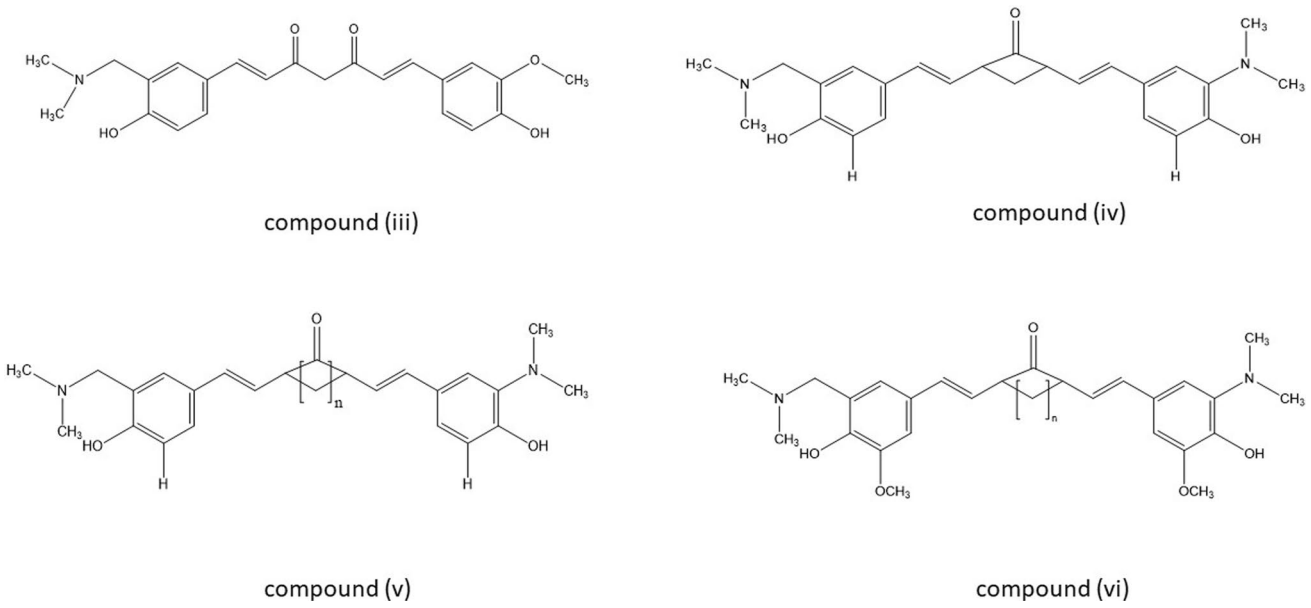

Fig. 5 Dimethylaminomethyl-substituted CUR analogues

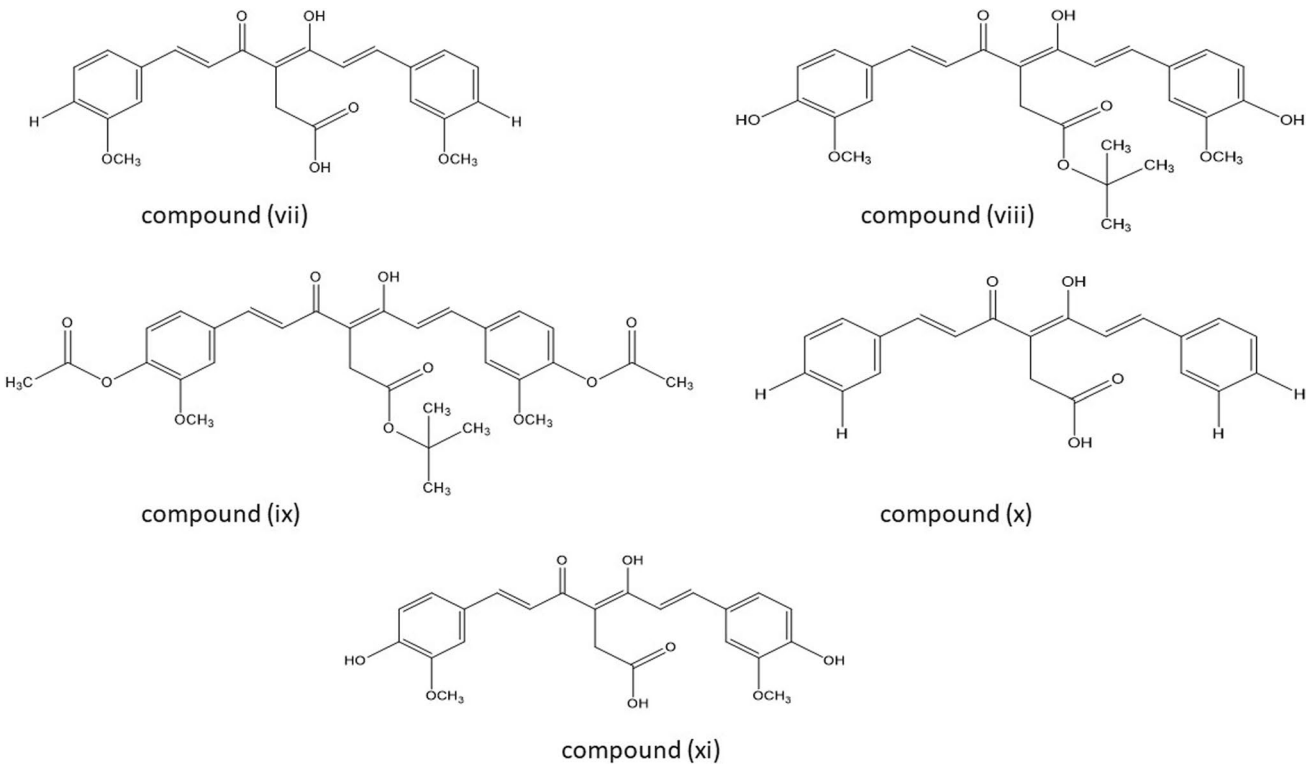

Fig. 6 Ester and acid derivatives of CUR

discussed in the "Anti-CRC Mechanisms of Action of CUR" section, viable curcumin formulations for use in CRC are beginning to emerge. Nevertheless, there is still scope for sorting the aforementioned solubility and stability issues akin with CUR. It is the view of the authors that nanoformulations comprising of CUR derivatives will represent a formidable approach to managing CRC with far-reaching therapeutic consequences. Imparting specificity to the nanoparticles toward cancer tissue,

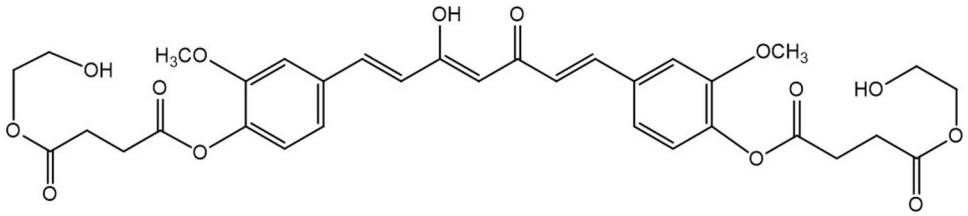

Fig. 7 Diethyl disuccinate derivative of CUR (compound xii)

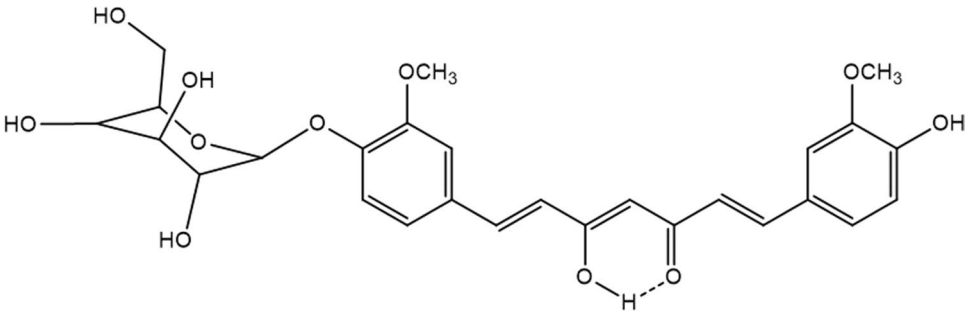

Fig. 8 CUR-glycoconjugate (79) (compound xiii)

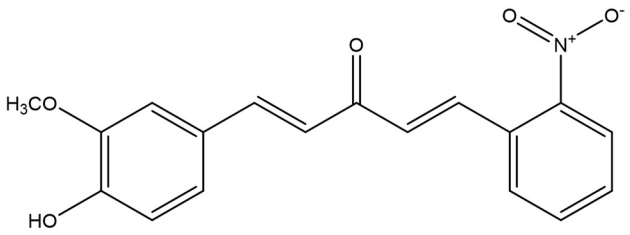

Fig. 9 CUR WZ35 derivative (compound xiv)

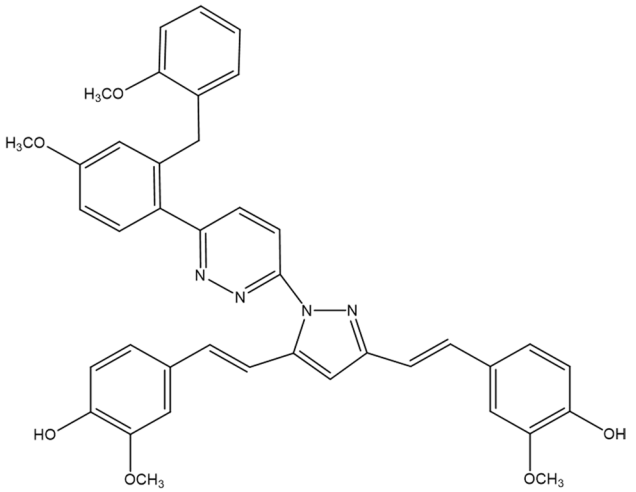

Fig. 10 Hydrazine-CUR derivative structure (26) (compound xv)

coupled with depolyability of the nanocarrier will significantly reduce side effects and improve therapy. Unfortunately, there is only a handful of such CUR derivatives formulated as nanoparticles with CRC activity. A hydrazine-CUR derivative: 4-((E)-2-(1-(4-methoxy benzyl)-6-p-tolylpyridazin-3-yl)-3-((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-5-yl) vinyl)-2-methoxyphenol (compound xv), Fig. 10, was encapsulated in nanoparticles using self-assembly process and were used to control drug release. Cell viability studies revealed that the hydrazine-CUR derivative formulations showed better activity towards HCT-116 cell line than free CUR, particularly in the prepared CUR-CS formulation (26).

CLINICAL TRIALS ON CURCUMIN IN NANOFORMULATIONS

From the preceding, it is conceivable that CUR or derivatives in nanoformulations will be the subject of future clinical investigations in the quest for safer and effective use of CUR in CRC (80). Clinical trials serve as a bridge from the bench the market and up to date, some clinical trials have evaluated the effectiveness of CUR or derivatives on CRC. In 2004, a phase I clinical trial was conducted to investigate the toxicity of high doses of free CUR after oral administration in order to ascertain pharmacokinetic and pharmacodynamic profiles that will inform dose appropriation in phase II chemotherapy or chemoprevention studies. Patients with advanced CRC were orally administered CUR doses ranging from 0.45–3.6 g daily for 4 months; however, the bioavailability was only 10 nmol/L, with significant recovery in feces. Furthermore, there was no reduction in CRC markers in patients following the treatment. However, 3.6 g of CUR consumed daily caused inhibition of prostaglandin E2 (PGE2) induction, but glutathione S-transferases (GST) activity was not affected at this CUR dose (81). Phase I investigation on CUR liposomal formulation was conducted on 32 patients with advanced or metastatic

cancer for safety and tolerability. The doses ranged between 100 mg/m^2 over 8 h until 300 mg/m^2 over 6 h. No dose-limiting toxicity was observed in 26 patients. Furthermore, one of six patients on 300 mg/m^2 over 6 h developed hemolysis, and other three patients showed decreases in hemoglobin levels without any signs of hemolysis. Tumor marker responses and reductions were noticed in a patient with colon carcinoma metastasis after administration of dose of 300 mg/m^2 liposomal CUR over 6 h (82).

A cohort of 50 healthy subjects involved in phase I clinical trial demonstrated tolerability of intravenously administered liposomal CUR 10–400 mg/m^2 or placebo over 2 h. The formulation was well tolerated with plasma CUR and metabolite tetrahydro-CUR (THC) increasing with increase in dose administered. Moreover, the mean urinary excretion was around 0.1% of total blood clearance. However, a transient red blood cell echinocyte was formed with a rise in mean cellular volume at dosages greater than 120 mg/m^2, which is considered a sign of toxicity (83).

Plant-based exosomes were used to deliver CUR to targeted sites within the colon in a phase I clinical trial conducted to examine effectiveness of exosomes as a CUR carrier to normal colon tissue or colon tumors. The clinical trial is still on going and obtained results are not published yet (84).

CONCLUSIONS AND FUTURE PROSPECTS

Evidence from the current review points to a strong therapeutic potential of CUR on CRC, which is best evidenced in nanoformulations. Some chemical modifications of CUR have also resulted in supra-therapeutic effects on CRC, compared to native CUR. This review also shows that there is only a handful of attempts at formulating derivatized CUR in nanocarriers and crucially no clinical study on nanoformulations of derivatized CUR. Although several CUR and CUR-derivatized nanoformulations show promising therapeutics on CRC, more research is needed especially aimed at safety concerns and meeting FDA regulations. It is the view of the authors that this space will be the next frontier in the search for the full therapeutic effects of CUR on not only CRC but other cancers as well.

Author Contribution Conceptualization: NB, SI; initial draft: SI, TB; review: NB, YMH, SI, TB; final draft: NB.

Funding Open Access funding provided by the Qatar National Library. This work was sponsored by the Qatar University International Research Collaboration Co-Fund (IRCC-2021–006).

Declarations

Conflict of Interest The authors declare no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al.* Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34.
4. Jahanafrooz Z, Mosafer J, Akbari M, Hashemzaei M, Mokhtarzadeh A, Baradaran B. Colon cancer therapy by focusing on colon cancer stem cells and their tumor microenvironment. J Cell Physiol. 2020;235(5):4153–66.
5. Selvam C, Prabu SL, Jordan BC, Purushothaman Y, Umamaheswari A, Hosseini Zare MS, *et al*. Molecular mechanisms of curcumin and its analogs in colon cancer prevention and treatment. Life Sci. 2019;239:117032.
6. Weitz J., Koch M., Debus J., Höhler T., Galle R. BM. Colorectal cancer. Lancet. 2005. p. 153–65.
7. Thanikachalam K, Khan G. Colorectal cancer and nutrition. Nutrients. 2019;11(1).
8. Osumi H, Shinozaki E, Yamaguchi K, Zembutsu H. Clinical utility of circulating tumor DNA for colorectal cancer. Cancer Sci. 2019;110(4):1148–55.
9. Patel SG, Ahnen DJ. Colorectal cancer in the young. Curr Gastroenterol Rep. 2018;20(4).
10. Simon K. Colorectal cancer development and advances in screening. Clin Interv Aging. 2016;11:967–76.
11. INSTITUTE NC. Drugs approved for colon and rectal cancer. NIH [Internet]. Available from: https://www.cancer.gov/about-cancer/treatment/drugs/colorectal
12. Ding L, Ma S, Lou H, Sun L, Ji M. Synthesis and biological evaluation of curcumin derivatives with water-soluble groups as potential antitumor agents: an *in vitro* investigation using tumor cell lines. Molecules. 2015;20(12):21501–14.
13. Baskaran R, Madheswaran T, Sundaramoorthy P, Kim HM, Yoo BK. Entrapment of curcumin into monoolein-based liquid crystalline nanoparticle dispersion for enhancement of stability and anticancer activity. Int J Nanomedicine. 2014;9(1):3119–30.
14. Page R and A. Natural products and colon cancer: current status and future prospects. Drug Dev Res. 2009;69(7):460–71.

15. Zhang J, Feng Z, Wang C, Zhou H, Liu W, Kanchana K, *et al.* Curcumin derivative WZ35 efficiently suppresses colon cancer progression through inducing ROS production and ER stress-dependent apoptosis. Am J Cancer Res. 2017;7(2):275–88.
16. Wilken R, Veena MS, Wang MBSE. Curcumin: a review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Mol Cancer. 2011;7(10):12.
17. Nair RS, Morris A, Billa N, Leong CO. An evaluation of curcumin-encapsulated chitosan nanoparticles for transdermal delivery. AAPS PharmSciTech. 2019;20(2):1–13.
18. Mbese Z, Khwaza V, Aderibigbe BA. Curcumin and its derivatives as potential therapeutic agents in prostate, colon and breast cancers. Molecules. 2019;24(23).
19. Yen P, Fadhlizil M, Mohd F, Rullah K, Wai K. Insights on the synthesis of asymmetric curcumin derivatives and their biological activities. Eur J Med Chem. 2019;183:111704.
20. Rodrigues FC, Anil Kumar NV, Thakur G. Developments in the anticancer activity of structurally modified curcumin: an up-to-date review. Eur J Med Chem. 2019;177:76–104.
21. Saranya TS, Rajan VK, Biswas R, Jayakumar R, Sathianarayanan S. Synthesis, characterisation and biomedical applications of curcumin conjugated chitosan microspheres. Int J Biol Macromol. 2018;110:227–33.
22. Aiello P, Sharghi M, Mansourkhani SM, Ardekan AP, Jouybari L, Daraei N, *et al*. Medicinal plants in the prevention and treatment of colon cancer. Oxid Med Cell Longev. 2019;2019.
23. Pricci M, Girardi B, Giorgio F, Losurdo G, Ierardi E, Di Leo A. Curcumin and colorectal cancer: from basic to clinical evidences. Int J Mol Sci. 2020;21(7).
24. Ma Z, Wang N, He H, Tang X. Pharmaceutical strategies of improving oral systemic bioavailability of curcumin for clinical application. J Control Release. 2019;316:359–80.
25. Willenbacher E, Khan SZ, Mujica SCA, Trapani D, Hussain S, Wolf D, *et al.* Curcumin: New insights into an ancient ingredient against cancer. Int J Mol Sci. 2019;20(8):1–13.
26. Kandile NG, Mohamed HM, Nasr AS. Novel hydrazinocurcumin derivative loaded chitosan, ZnO, and Au nanoparticles formulations for drug release and cell cytotoxicity. Int J Biol Macromol. 2020;158:1216–26.
27. Kotla NG, Burke O, Pandit A, Rochev Y. An orally administrated hyaluronan functionalized polymeric hybrid nanoparticle system for colon-specific drug delivery. Nanomaterials. 2019;9(9).
28. Slika L, Moubarak A, Borjac J, Baydoun E, Patra D. Preparation of curcumin-poly (allyl amine) hydrochloride based nanocapsules: piperine in nanocapsules accelerates encapsulation and release of curcumin and effectiveness against colon cancer cells. Materials Science & Engineering C. Elsevier B.V; 2019.
29. Liu W, Zhai Y, Heng X, Che FY, Chen W, Sun D, *et al.* Oral bioavailability of curcumin: problems and advancements. J Drug Target. 2016;24(8):694–702.
30. Wong KE, Ngai SC, Chan KG, Lee LH, Goh BH, Chuah LH. Curcumin nano-formulations for colorectal cancer: a review. Front Pharmacol. 2019;10.
31. Tomeh MA, Hadianamrei R, Zhao X. A review of curcumin and its derivatives as anticancer agents. Int J Mol Sci. 2019;20(1033).
32. Ismail NI, Othman I, Abas F, Lajis NH, Naidu R. Mechanism of apoptosis induced by curcumin in colorectal cancer. Vol. 20, International Journal of Molecular Sciences. 2019.
33. Jiang D, Rasul A, Batool R, Sarfraz I, Hussain G, Mateen Tahir M, *et al.* Potential anticancer properties and mechanisms of action of formononetin. Biomed Res Int. 2019;2019:645–51.
34. Park J. Anti-carcinogenic properties of curcumin on colorectal cancer. World J Gastrointest Oncol. 2010;2(4):169.
35. Zieli A., Carreiró F., Oliveira A. *et al*. Polymeric nanoparticles: production, characterization, toxicology and ecotoxicology. Molecules. 2020;25(3731).
36. Van Der Vlies AJ, Morisaki M, Neng HI, Hansen EM, Hasegawa U. Framboidal Nanoparticles containing a curcumin-phenylboronic acid complex with antiangiogenic and anticancer activities. Bioconjug Chem. 2019;30(3):861–70.
37. Chaurasia S, Chaubey P, Patel RR, Kumar N, Mishra B. Curcumin-polymeric nanoparticles against colon-26 tumor-bearing mice: cytotoxicity, pharmacokinetic and anticancer efficacy studies. Drug Dev Ind Pharm. 2016;42(5):694–700.
38. Xiaoa B., Sia X., Hanb M., Viennoisb E., Zhangb M. and MD. Co-delivery of camptothecin and curcumin by cationic polymeric nanoparticles for synergistic colon cancer combination chemotherapy†. J Mater Chem C. 2015;3(39):10715–22.
39. Sufi SA, Hoda M, Pajaniradje S, Mukherjee V, Coumar SM, Rajagopalan R. Enhanced drug retention, sustained release, and anticancer potential of curcumin and indole-curcumin analog-loaded polysorbate 80-stabilizied PLGA nanoparticles in colon cancer cell line SW480. Int J Pharm. 2020;588.
40. Udompornmongkol P, Chiang BH. Curcumin-loaded polymeric nanoparticles for enhanced anti-colorectal cancer applications. J Biomater Appl. 2015;30(5):537–46.
41. Anwar M, Muhammad F, Akhtar B. Biodegradable nanoparticles as drug delivery devices. J Drug Deliv Sci Technol. 2021;64:1–20.
42. Leyva-Gómez G, Piñón-Segundo E, Mendoza-Muñoz N, Zambrano-Zaragoza ML, Mendoza-Elvira S, Quintanar-Guerrero D. Approaches in polymeric nanoparticles for vaginal drug delivery: a review of the state of the art. Int J Mol Sci. 2018;19(6):1–19.
43. Mitchell MJ, Billingsley MM, Haley RM, Wechsler ME, Peppas NA, Langer R. Engineering precision nanoparticles for drug delivery. Nat Rev Drug Discov. 2021;20(2):101–24.
44. Deng S, Gigliobianco MR, Censi R, Martino P Di. Polymeric nanocapsules as nanotechnological alternative for drug delivery system : current status, challenges and opportunities. 2020;1–39.
45. Klippstein R, Wang JTW, El-Gogary RI, Bai J, Mustafa F, Rubio N, *et al.* Passively targeted curcumin-loaded PEGylated PLGA nanocapsules for colon cancer therapy in vivo. Small. 2015;11(36):4704–22.
46. Wadhwa J, Asthana A, Gupta S, Asthana GS, Singh R. Development and optimization of polymeric self-emulsifying nanocapsules for localized drug delivery : design of experiment approach. Sci World J. 2014;12.
47. Abu Abed OS, Chaw CS, Williams L, Elkordy AA. PEGylated polymeric nanocapsules for oral delivery of trypsin targeted to the small intestines. Int J Pharm. 2021;592.
48. Lin M, Dai Y, Xia F, Zhang X. Advances in non-covalent crosslinked polymer micelles for biomedical applications. Mater Sci Eng C. 2021;119.
49. Li H, Yan L, Tang EKY, Zhang Z, Chen W, Liu G, *et al.* Synthesis of TPGS/curcumin nanoparticles by thin-film hydration and evaluation of their anti-colon cancer efficacy *in vitro* and in vivo. Front Pharmacol. 2019;10:1–12.
50. Chang T, Trench D, Putnam J, Stenzel MH, Lord MS. Curcumin-loading-dependent stability of PEGMEMA-based micelles affects endocytosis and exocytosis in colon carcinoma cells. Mol Pharm. 2016;
51. Yang X, Li Z, Wang N, Li L, Song L, He T, *et al*. Curcumin-encapsulated polymeric micelles suppress the development of colon cancer *in vitro* and in vivo. Sci Rep. 2015;1–15.
52. Zhou Q, Zhang L, Yang TH, Wu H. Stimuli-responsive polymeric micelles for drug delivery and cancer therapy. Int J Nanomedicine. 2018;13:2921–42.
53. Lu Y, Zhang E, Yang J, Cao Z. Strategies to improve micelle stability for drug delivery. Nano Res. 2018;11(10):4985–98.

54. Wakaskar RR. Polymeric micelles and their properties. J Nanomed Nanotechnol. 2017;08(02).
55. Li M, Du C, Guo N, Teng Y, Meng X, Sun H, *et al.* Composition design and medical application of liposomes. Eur J Med Chem. 2019;164:640–53.
56. Rahman S, Cao S, Steadman KJ, Wei M, Parekh HS. Native and ß-cyclodextrin-enclosed curcumin: Entrapment within liposomes and their *in vitro* cytotoxicity in lung and colon cancer. Drug Deliv. 2012;19(7):346–53.
57. Process S, Leo V De, Id FM, Mancini E, Comparelli R, Id LG, *et al*. Encapsulation of curcumin-loaded liposomes for colonic drug delivery in a pH-responsive polymer cluster using a pH-driven and organic. Molecules. 2018;1–15.
58. Li L, Ahmed B, Mehta K, Li L, Ahmed B, Mehta K. Liposomal curcumin with and without oxaliplatin: effects on cell growth, apoptosis, and angiogenesis in colorectal cancer. Mol Cancer Ther. 2007;1276–82.
59. Shah S, Dhawan V, Holm R, Nagarsenker MS, Perrie Y. Liposomes: Advancements and innovation in the manufacturing process. Adv Drug Deliv Rev. 2020;154–155:102–22.
60. Daraee H, Etemadi A, Kouhi M, Alimirzalu S, Akbarzadeh A. Application of liposomes in medicine and drug delivery. Artif Cells, Nanomedicine Biotechnol. 2016;44(1):381–91.
61. Gyanani V, Haley JC, Goswami R. Challenges of current anticancer treatment approaches with focus on liposomal drug delivery systems. Pharmaceuticals. 2021;14(9):1–27.
62. Grimaudo MA, Concheiro A, Alvarez-Lorenzo C. Nanogels for regenerative medicine. J Control Release. 2019;313:148–60.
63. Kumar P, Sundar A, Mukhopadhyay R, Sarkar A, Kumar R. Macromolecular design of folic acid functionalized amylopectin–albumin core–shell nanogels for improved physiological stability and colon cancer cell targeted delivery of curcumin. J Colloid Interface Sci. 2020;580:561–72.
64. Manzanares-Guevara LA, Licea-Claverie A, Oroz-Parra I, Bernaldez-Sarabia J, Diaz-Castillo F, Licea-Navarro AF. Smart nano-formulation based on stimuli-responsive nanogels and curcumin: promising therapy against colon cancer. ACS Omega. 2020;5(16):9171–84.
65. Rao KM, Rao KSVK, Ramanjaneyulu G, Ha C. Curcumin encapsulated pH sensitive gelatin based interpenetrating polymeric network nanogels for anti cancer drug delivery. Int J Pharm. 2015;478(2):788–95.
66. Abedi F, Davaran S, Hekmati M, Akbarzadeh A, Baradaran B. An improved method in fabrication of smart dual - responsive nanogels for controlled release of doxorubicin and curcumin in HT - 29 colon cancer cells. J Nanobiotechnology. 2021;1–22.
67. Zarekar NS, Lingayat VJ, Pande V V. Nanogel as a novel platform for smart drug delivery system. Nanosci Nanotechnol Res Vol 4, 2017, Pages 25–31. 2017;4(1):25–31.
68. Suhail M, Rosenholm JM, Minhas MU, Badshah SF, Naeem A, Khan KU, *et al.* Nanogels as drug-delivery systems: a comprehensive overview. Ther Deliv. 2019;10(11):697–717.
69. Singh P, Pandit S, Mokkapati VRSS, Garg A, Ravikumar V, Mijakovic I. Gold nanoparticles in diagnostics and therapeutics for human cancer. Int J Mol Sci. 2018;19(1979).
70. SanojRejinold N, Thomas RG, Muthiah M, Chennazhi KP, Manzoor K, Park IK, *et al.* Anti-cancer, pharmacokinetics and tumor localization studies of pH-, RF- and thermo-responsive nanoparticles. Int J Biol Macromol. 2015;74:249–62.
71. Amina SJ, Guo B. A review on the synthesis and functionalization of gold nanoparticles as a drug delivery vehicle. Int J Nanomedicine. 2020;15:9823–57.
72. Research A in CC. Nanotechnology to improve early detection and treatment of colorectal cancer [Internet]. NIH. 2016. Available from: https://www.nih.gov/research-training/nanotechnology-improve-early-detection-treatment-colorectal-cancer
73. Yadav S, Masud MK, Islam MN, Gopalan V, Lam AKY, Tanaka S, *et al.* Gold-loaded nanoporous iron oxide nanocubes: a novel dispersible capture agent for tumor-associated autoantibody analysis in serum. Nanoscale. 2017;9(25):8805–14.
74. Hong X, Yu Z, Ye M, Yuan Q. Synthesis and biological evaluations of monocarbonyl curcumin inspired pyrazole analogues as potential anti-colon cancer agent. 2020;
75. Ismail N., Othman I., Abas F. LNNR. The curcumin analogue, MS13 (1,5-Bis(4-hydroxy-3- methoxyphenyl)-1,4-pentadiene-3-one), inhibits cell proliferation and induces apoptosis in primary and metastatic human colon cancer cells. Molecules. 2020;25:1–24.
76. Fang X, Fang L, Gou S, Cheng L. Design and synthesis of dimethylaminomethyl-substituted curcumin derivatives/analogues: potent antitumor and antioxidant activity, improved stability and aqueous solubility compared with curcumin. Bioorganic Med Chem Lett. 2013;23(5):1297–301.
77. Ferrari E, Pignedoli F, Imbriano C, Marverti G, Basile V, Venturi E, *et al.* Newly synthesized curcumin derivatives: crosstalk between chemico-physical properties and biological activity. J Med Chem. 2011;54(23):8066–77.
78. Wichitnithad W, Nimmannit U, Wacharasindhu S, Rojsitthisak P. Synthesis, characterization and biological evaluation of succinate prodrugs of curcuminoids for colon cancer treatment. Molecules. 2011;16(2):1888–900.
79. Arafa HMM. Possible contribution of β-glycosidases and caspases in the cytotoxicity of novel glycoconjugates in colon cancer cells. Invest New Drugs. 2010;28(3):306–17.
80. Shafei LKIA, Mohamed Ibrahim MI BN. Is curcumin at the threshold of therapeutic effectiveness on patients with colon cancer?-A systematic review. Front Pharmacol. 2021;2(12).
81. Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, *et al.* Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin Cancer Res. 2004;10(20):6847–54.
82. Greil R, Ressler SG, Weiss L, Schönlieb C, Magnes T, Radl B, *et al.* A phase 1 dose-escalation study on the safety, tolerability and activity of liposomal curcumin (Lipocurc ™) in patients with locally advanced or metastatic cancer. Cancer Chemother Pharmacol. 2018;0(0):0.
83. Storka A, Vcelar B, Klickovic U, Gouya G, Weisshaar S, Aschauer S, *et al.* Safety, tolerability and pharmacokinetics of liposomal curcumin in healthy humans. Int J Clin Pharmacol Ther. 2015;53(1):54–65.
84. Study investigating the ability of plant exosomes to deliver curcumin to normal and colon cancer tissue. NCT01294072 [Internet]. Available from: https://clinicaltrials.gov/ct2/show/NCT01294072
85. Cruz-Correa M, Shoskes DA, Sanchez P, Zhao R, Hylind LM, Wexner SD, *et al.* Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clin Gastroenterol Hepatol. 2006;4(8):1035–8.