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Review article

Molecular mechanisms of curcumin and its analogs in colon cancer prevention and treatment

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ABSTRACT

Colorectal cancer remains to be the most prevalent malignancy in humans and 1.5 million men and women living in the United States are diagnosed with colorectal cancer, with a predicted 145,600 new cases to be diagnosed in 2019. Curcuminoids and its synthetic analogs are now of interest due to their bioactive attributes, especially their action as anticancer activity in various cancer cell line models. Several *in vivo* and *in vitro* studies have substantially proved their anticancer activities against colon cancer cell lines. Curcumin analogues like IND-4, FLLL, GO-Y030 and C086 have demonstrated to produce greater cytotoxicity when experimentally studied and study results from many have been suggested to be the same. Combination of curcumin with therapeutic cancer agents like tolfenamic acid, 5-fluorouracil, resveratrol and dasatinib showed improved cytotoxicity and chemotherapeutic effect. The results propose that employment of curcumin with novel drug delivery systems like liposome, micelles and nanoparticle have been performed which could improve the therapeutic efficacy against colon cancer. The present review highlights the mechanism of action, synergistic effect and novel delivery methods to improve the therapeutic potential of curcumin.

1. Introduction

Colorectal cancer (CRC) a malignant tumor is recognized to be the third most common cancer worldwide with an array of high morbidity and mortality thereby fourth one to cause death. It is also one such cancer which could result from the accretion of genetic and epigenetic alterations. These alterations have been found to add an additional layer of complexity for the progression of CRC. Abnormal growth (noncancerous growth) of tissues known as polyp grows slowly over a period on the inner parts of rectum or colon which eventually becomes a tumor in colorectum region is referred to as colorectal cancer. Later it has the ability to spread and grow into the lymph and blood vessels which is quite difficult to be addressed in the initial stages. CRC is classified based on the region where the tumor cells had been observed in such a way that if the cancer cells grow in the hormone producing intestinal cell region it is referred to as carcinoid tumors; in interstitial cells of cajal region it is referred as gastrointestinal stromal tumors and in the colorectal walls it is referred to as sarcomas [1,2].

16.9 million Americans (8.1 million males and 8.8 million females) with a history of cancer are alive as reported on January 1, 2019; this number is further estimated to reach 22.1 million by January 1, 2030 based on the current generation health standards, growth and aging of the population alone [3]. Studies revealed 3 most prevalent cancers in 2019, they are prostate (3,650,030), colon and rectum (776,120), and melanoma of the skin (684,470) cancers among males, and breast (3,861,520), uterine corpus (807,860), and colon and rectum (768,650) cancers among females. As of now there are 1.5 million men and women living in the United States previously diagnosed with colorectal cancer and reports reveal that 145,600 new cases will be diagnosed in 2019 [3]. CRC is the third most commonly diagnosed cancer worldwide, 1.8 million new cases reported in 2018. Global burden of CRC is expected to be augmented more than 2.2 million new cases and 1.1 million deaths that is 60% rise in 2030 [4,5].

The incidence and mortality of CRC is more in Australia, New Zealand, Canada, United States and parts of Europe; with lowest incidence in China, India and parts of Africa, which could be due to the regular use of Curcumin in the diet. The profound incidence of CRC is mainly by westernized lifestyle culture which encompasses obesity,

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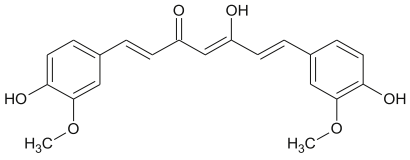
high-meat, high-calorie, diet with deficient fiber contents, rich fat and sedentary behavior [6–8]. Adolescence plays a major cause for CRC, where in 90% of cases were observed in people beyond 50 years of age [9,10]. In United States, CRC has set to be the most commonly diagnosed cancer among the other 10 main cancers types amongst the men and women in the age group ranging between 20 and 49 [11].

The molecular mechanism and targeted therapeutic approach emphasizes on proteins and different signaling pathways like mitochondria-dependent, PTEN-Akt [12], STAT3, p53 [13]; IGF-1R, Akt, Erk(s), PMPMEase, COX-2, NF-κB [14]; Akt, Erk(s) [15]; PMPMEase [16]; AMPK-COX-2 [17]; and Wnt [18] signaling are the dynamic targets identified as the therapeutic agents in the treatment and prevention of CRC. Terlikowska et al., have identified and reported twenty-six signaling pathways extensively like PPAR, COX-2, EGFR and NF-κB as medicated pathways for curcumin [19]. However, to date cancer therapeutic agents like avastin, 5-fluorouracil, cetuximab, elaxatin, erbitux etc, have been administered to treat CRC.

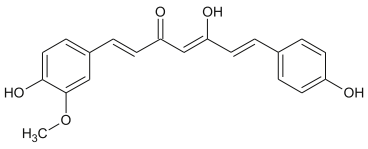
World Health Organization (WHO) assessed and reported that around 75–80% of the world population consumes medicinal plants as the primary requirement for their health care [20]. This is for the reason that natural compounds are having attractive strategy towards the target pathways and enzymes to express its anti-proliferation and cytotoxicity. Turmeric, a spice commonly utilized as a coloring agent in Southeast Asia and India. It has been estimated that turmeric powder contains 77% curcumin, 17% demethoxycurcumin and 5% bisdemethoxycurcumin (Fig. 1) [21,22]. Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a polyphenolic compound isolated from the plant rhizome called *Curcuma longa* Linn [21,22]. Curcumin has diverse pharmacological action towards several diseases which constructively dragged the attention and interest to the medicinal chemistry researchers to develop new analogs to address the therapeutic problems. Curcumin demonstrated to have antioxidant [23–26], anti-inflammatory [22,27], antibacterial [28–31], anti-rheumatoid arthritis [32–36], anti-diabetes [37–42], Alzheimer's [43–48] and psoriasis [49,50] activities. Curcumin has been investigated for its anti-cancer activity in various cancer cell lines such as breast [51–56], lung [57–62], ovarian [63–68], prostate [69–71], pancreatic [72–77], liver [78–80] and skin [81,82].

2. The effect of curcumin on various colon cancer signaling pathways: *In vitro* studies

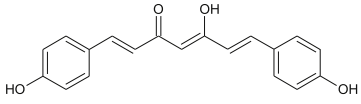
Reports suggest that modulation of different signaling pathways by curcumin leads to accelerated cytotoxicity, apoptosis and anti-proliferation in HCT-116, HT-29, SW620 cell lines shown with accordance in Table 1 and Fig. 2. Guo et al. [83] demonstrated that curcumin epigenetically upregulates the DLEC1 by methylation which has also been found to modify the protein expression in DNMTs and HDACs, in a concentration dependent manner thereby inhibiting the colony formation of HT29 cells at 2.5 and 5 μM for an uninterrupted 5 days. Mosieniak and team investigated the curcumin's anticancer activity in human colon cancer cells HCT116 and suggested certain outcomes that curcumin inhibits the cell proliferation by arresting the cells in the G2/M phase and partially in G1 phase of cell cycle at 10 μM. The study determined activation of SA-b-galactosidase, induction of cellular senescence with increased p53 level additionally increased cleavage of PARP by upregulation of p53 [84]. A study performed by Watson et al. on curcumin cytotoxicity in HCT-116 and HT29 cells revealed that when p53 was upregulated, it showed sequential inhibition of cell proliferation and induced superoxide anion level in HCT cells in a time and dose dependent manner which had been a result when exposed to 2.6–160 μM. It also exposed that curcumin induces apoptosis by reduction of pro-caspase 3 level [85]. Sandur et al. determined that curcumin inhibits the cell proliferation, reduces the ^{137}Cs induced NF-kB activation through the inhibition of phosphorylation thereby simultaneously degrading the inhibitor of kB alpha, inhibiting kB kinase activity, inhibiting Akt phosphorylation and also decreased the NF-kB regulated gene products in colorectal cancer cell line HCT116 and HT29 in a time and dose dependent mode when exposed at 10 and 25 μm concentrations [86]. Fenton and McCaskey investigated on insulin induced colon carcinoma cell (YAMC(Apcþ/þ) and MC38) proliferation with curcumin and docosahexaenoic (DHA) as dietary compounds and therefore the study result reveals that insulin induces cell proliferation by MAPK and MEK phosphorylation; curcumin and DHA inhibit the cell proliferation by down regulating p42/44 and MEK proteins [87]. Lee et al. [88] investigated the anti-metastatic properties of curcumin by proteomic analysis technique in SW480 and SW620. The study determined that curcumin exhibited suppressive effects on fatty acid synthase and histone H4 by reducing migratory effects. Amissah et al. [16] stated a hypothesis that curcumin is a cytotoxic agent in human colorectal adenocarcinomas (Caco-2). The team made a hypothesis and consolidated that curcumin inhibits the cell viability and suppresses the PMPMEase (Polyisoprenylated Methylated Protein Methyl Esterase) in polyisoprenylation pathway when exposed to 0–200 μM of curcumin in a concentration dependent manner. It has been clearly demonstrated that curcumin inhibits HT-29 by inducing G1-phase arrest in cell cycle and induces apoptosis through regulation of AMPK, downregulation of pAkt and COX-2 pathway in HT-29 [17]. Kim and Lee determined curcumin to be an apoptotic agent in colon cancer cells and inhibit the cell proliferation of HCT-116 through induction of ROS generation, downregulation of E2F4 and its related genes cyclin A, p21 and p27 [89]. Singh and team demonstrated the cell proliferation in HT29 cells and induced calpain and caspase-12 mediated apoptosis in a concentration dependent manner when exposed to 0–80 μM of curcumin



Curcumin



Demethoxycurcumin (DMC)



Bisdemethoxycurcumin (BDMC)

Fig. 1. Structures of natural curcumins.

Table 1
Effects of curcumin on colon cancer signaling pathways.

Curcumin on colon cancer signaling pathways	Mechanism of Action	Cell line: Cur Conc.	Ref
Curcumin enhances cytotoxic activity and alter tumor suppressor	↓ Colony Formation ↓ Cell viability ↓ Methylation of DLEC1 promoter ↓ DNMT1,3A and 3B expression ↓ HDAC 4,5,6,& 8 protein level	HT29: 1–25 μM	[83]
Curcumin induces cell cycle arrest, cellular senescence and downregulate autophagosome formation.	↓ ATG5 protein ↑ Cleavage of PARP ↓ Cell viability ↑ p53	HCT116: 10 μM	[84]
Curcumin decreases cell viability and induce apoptosis	↑ Cytotoxicity ↓ Pro-caspase 3 ↑ Superoxide anion level	2.5–160 μM	[85]
Curcumin inhibits radiation-induce protein expression	↓ Cell proliferation ↓ IKK activity ↓ Akt phosphorylation ↓ NF-kB	HCT116: 10 and 25 μM	[86]
Curcumin inhibits cell growth and MAPK cell signaling proteins	↓ p-p42/44 ↓ Cell proliferation	MC38: 50–100 μM	[87]
Curcumin enhances anti-metastatic activity	↓ Fatty acid Synthase ↓ Histone H4	SW620: 10,20,50 μM	[88]
Curcumin enhances cytotoxicity activity and inhibits polyisoprenylated proteins	↓ PMPMEase activity	Caco-2: 0–200 μM	[16]
Curcumin inhibits cell proliferation and induces apoptosis	↑ Chromatin condensation ↓ COX-2 and Akt phosphorylation Activate AMPKα1	HT-29 10–200 μmol/L	[17]
Curcumin induces ROS generation and inhibits E2F4 downstream genes	↓ Cell proliferation ↓ p27 and p21	HCT-116: 20 and 40 μM	[89]
Curcumin activates caspase expression and induces apoptosis	↓ Cell proliferation ↑ Caspase-12 expression	HT-29: 50 μM	[90]
Curcumin inhibits cell proliferation and increases ROS generation	↑ Apoptotis Fractional detachment ↓ p53 ↓ Prp4B expression	HCT-15: 30 and 50 μM	[91]
Curcumin inhibits cell proliferation and induces apoptosis	↓ GSH levels ↓ PKA activation ↓ p50 and p65	HCT-15: 20 μM	[92]
Curcumin synergize with FOLFOX, inhibits expression and activation of growth factor receptor	↓ Acitivation of EGFR, HER2 and IGF-1R ↓ COX-2 and Akt	HCT-116 and HT-29: 25 and 50 μM	[93]
Curcumin enhances cytotoxic activity and induces G1 cell cycle arrest	↓ Phosphorylation of Rb ↓ CDK2 kinase activity	HCT-116: 40 μM	[94]
Curcumin enhances cytotoxic activity and decreases Wnt signaling	↓ CXCR4 expression ↓ NKD2 expression ↑ Axin ↑ E-Cadherin	SW620: 10–40 μmol/L	[18]
Curcumin enhances anti-proliferation and induces apoptosis with 5-FU	↑ Caspase 8,9, and 3 ↑ Bax and PARP ↓ BCL-xL	HCT-116: 20 μM	[95]
Curcumin induces demethylation through CpG loci	↓ Colony formation	HCT-116: 7.5–10 μM	[96]
Curcumin enhances 5-FU activity	↓ Cell growth ↓ Colonspheres ↑ Apoptosis	HCT-116: 20 μM	[97]

[90]. The study significantly demonstrated that curcumin inhibited HCT-15 cell proliferation and rapid ROS generation. The study further proceeded to identify that curcumin showed multiple apoptotic signals by induced caspase-3, downregulated p53 and Prp4B expression in a time and dose dependent manner [91]. Curcumin performs an induced cell death and apoptosis in HCT-15 cells when exposed to 20 μM. Curcumin produced apoptosis by inducing ROS generation, reduced cellular GSH level, PARP and caspase-3 and furthermore reduced activation of NF-kB (blocking p50 and p65) [92]. Patel et al. [93], performed an investigation on curcumin with 5-Fluorouracil (5-FU) or 5-FU plus oxaliplatin as colorectal cancer chemotherapeutics. The study result revealed that curcumin inhibited the chemosurviving HCT-116 and HT-29 cells when exposed to 25 or 50 μM for a period of 48 h. In addition, curcumin apparently reduced the activation of EGFR, HER-2, IGF-1R and AKT, as well as expression of COX-2 and cyclin-D1. Lim et al. [94] investigated a new molecular target of curcumin. Curcumin reduced proliferation of HCT116, HCT15 and DLD-1, induced G1 cell cycle arrest and reduced the phosphorylation of Rb in colon cancer cells HCT116 and suppressed CDK2 kinase activity. Curcumin inhibited the colorectal cancer cells proliferation SW620 in a dose dependent manner and inhibit Wnt signaling pathway and EMT (epithelial-mesenchymal transition) by downregulation of β-catenin, TCF4 and vimentin protein expression and induce axin and E-cadherin protein expression in the concentration of 5–40 μmol/L. In addition, curcumin induced NKD2 (Naked cuticle homolog 2) mRNA in Wnt signaling pathway and therefore inhibited the chemokine receptor 4 (CXCR4) in cancer cells [18]. Shakibaei et al. [95] performed an investigation of curcumin and 5-FU apoptosis in HCT116 and HCT116 + ch3. The strategic study had determined and hypothesized that curcumin sensitizes the cells to 5-FU leads to proliferation inhibition, induces degenerative changes in mitochondria, enhances the cleavage of caspase-8, caspase-9, caspase-3, Bax, and PARP proteins and decreases the BCL-xL protein. Link et al. [96] demonstrated its chemoprotective effect in HCT116, HT29 and RKO when exposed to 7.5–10 μM of curcumin. The study further enlisted curcumin's anticancer effects by inducing demethylation in methylated CpG loci which lead them to have direct impact in genes that has important biological role. Shakibaei et al. [97] investigated the apoptosis effect of curcumin and 5-FU in HCT116, HCT116 + ch3 and DNA MMR deficient cell lines HCT116 and HCT116R. The study result reveals that curcumin induces apoptosis of 5-FU in HCT116,

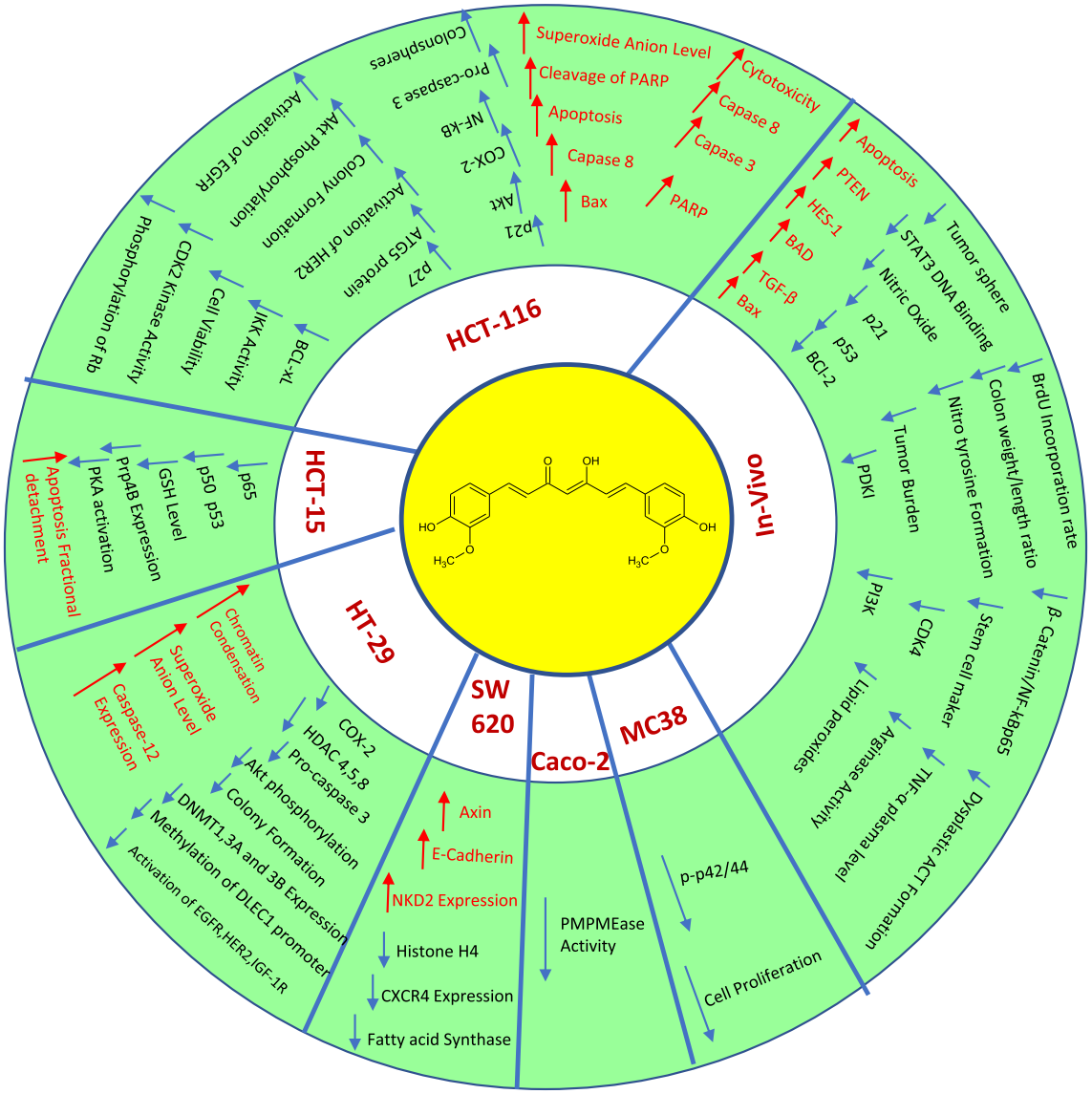


Fig. 2. Curcumin on colon cancer signaling pathways.

HCT116 + ch3 cells and DNA MMR deficient cell lines HCT116 and HCT116R by cleavage of PARP. In addition, the anticancer effect is more prominent in combination therapy than the individual.

3. Curcumin analogs on various colon cancer signaling pathways: *In vitro* studies

Various semisynthetic and synthetic curcumin analogs were synthesized and with the outcomes, the literature reported that curcumin analogs are tumor suppressive agents against liver, stomach, duodenal, colon, prostate, skin malignancies and that it is naturally found to possess anticancer properties both in-vivo and in-vitro. These analogues have drastically improved its efficacy as chemopreventive and therapeutic compounds in colorectal cancer. Certain analogues like IND-4, 1-aroyl-3,5-bis (benzylidene)-4-piperidone, dimeric 3,5-bis(arylidene)-4-piperidones, FLLL, GO-Y030, C-5 curcumin analogue, C086, curcumin diethyl disuccinate, dehydrozingerone, bis-dehydroxy-curcumin, difluorinated-curcumin and hexahydrocurcumin (Fig. 3) (Table 2) have demonstrated effectiveness against CRC. Zhou et al. investigated that curcumin analogue which consists inden-2-one has well addressed the prostate cancer PC-3 cells, pancreatic cancer BxPC-3 cells, colon cancer HT-29 cells, lung cancer cells H1299 and non-tumorigenic human prostate epithelial RWPE-1 cells. A methoxy group in the aromatic ring of inden-2-one core structure has attributed to the antiproliferative activity according to the study results. Among the several curcumin analogues, it has been revealed that analogue IND-4 showed potent cytotoxic effect against all cells lines and also suggested that cytotoxic as well as anti-proliferative properties were 20 times more potent than curcumin. In addition, studies determined that elevated interaction of curcumin analogue with the DNA of cancer cells by means of less steric hindrance showed the effective anticancer activity [98]. Helal and team performed a comparative study of curcumin analogue (3,5-bis(benzylidene)-4-piperidone derivatives) with 5-Fluorouracil for its anti-proliferative activity against colon HCT-116 cells. Due to increased ROS generation and decreased consumption of oxygen along with mitochondrial membrane potentials, 3,5-bis(benzylidene)-4-piperidone derivatives produced excellent anti-proliferative activity by interfering with mitochondrial functions [99]. A study performed by Das et al. [100] observed the effects of dimeric 3, 5-bis(arylidene)-4-piperidones as one among the curcumin analogues against HCT116, HT29 cell lines and performed a comparative analysis with 5-Fluorouracil and curcumin as references. The study result revealed that the curcumin analogues showed IC_{50} values with sub-micromolar to nano molar range and amidic carbonyl groups were to significantly contribute for their

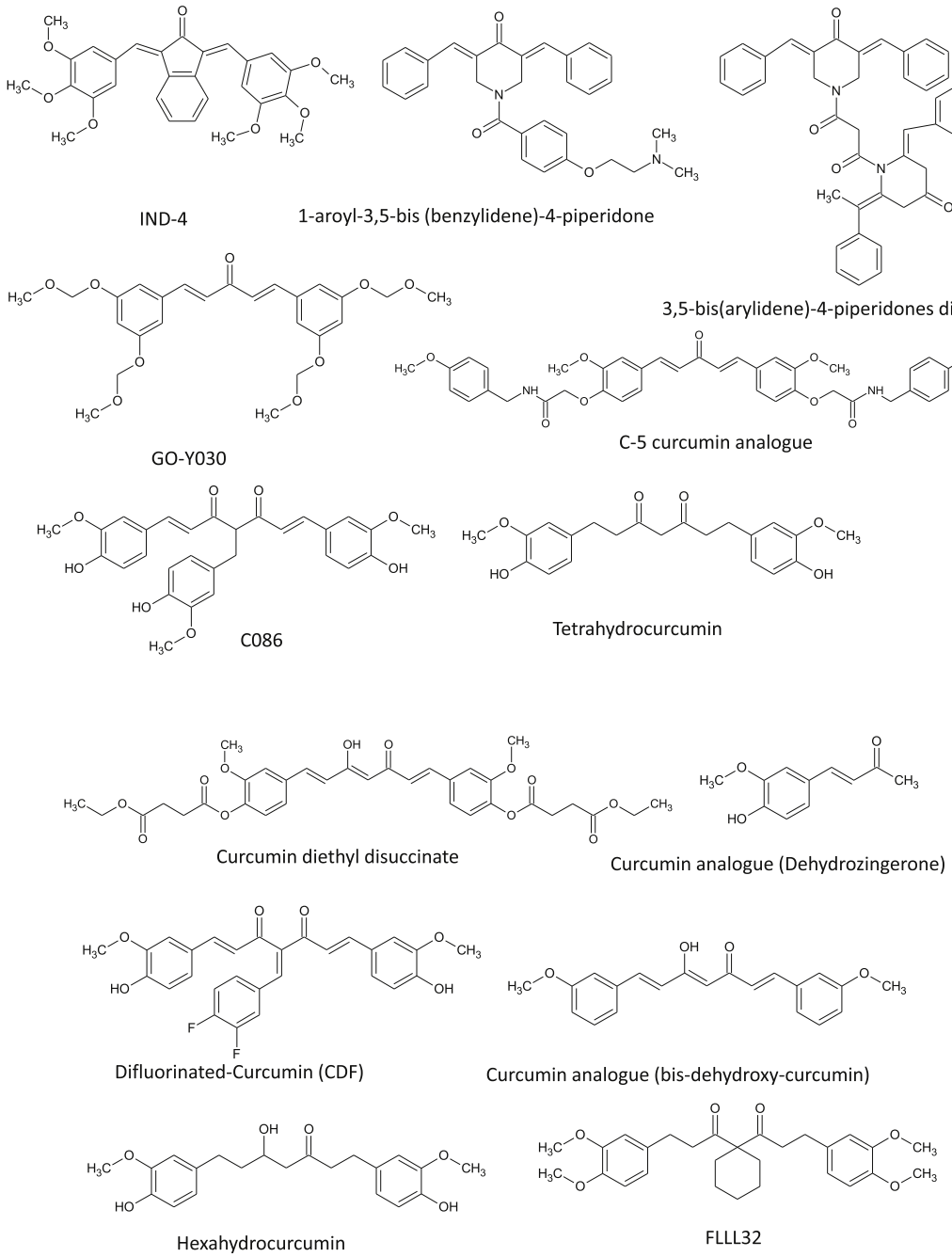


Fig. 3. Structures of semisynthetic and synthetic curcuminoids.

cytotoxic activities. However, it has been suggested that the efficiency of the curcumin analogue could be enhanced by introducing a strong electron withdrawing group in the aryl rings. Reportedly Kim and team synthesized curcuminoids (FLLL) as curcumin analogues and evaluated them against JMJD2C histone demethylase in HCT-116 colon cancer cells. It has been found that in colon cancer, histone demethylase JMJD2C is overexpressed which has an important role in the growth of cell HCT-116 and consequently the study revealed in which curcuminoids apoptosis induction can be done by enzymatic and catalytic activity of histone demethylase protein namely JMJD2C [101]. Lin et al. investigated the new curcumin analogue (GO-Y030) which served as an active agent against colon cancer cell line. The apoptosis efficiency of the analogue is induced by inhibiting the STAT3 phosphorylation by initiating the cleavages of PARP and caspase-3, decreasing cell viability and inhibiting the tumoursphere formation. In addition, the study result revealed that the targeted STAT3 analogue could provide promising apoptosis in colorectal cancer [102]. Anthwal and team [103] performed a comparative study of cytotoxicity between curcumin (standard) and C-5 curcumin analogues in chronic myeloid leukemia (KBM5) and colon cancer (HCT116) cell lines at 5 μM, which revealed that cytotoxic activity of the analogues are higher than curcumin, which also revealed that OMe substitution in aromatic ring enhances the efficiency of C-5 curcumin analogues.

Chen and team synthesized C086 as curcumin analogue and investigated its cytotoxicity activity against SW480, HT-29, SW1116, WiDr, KM12 and murine colon26 cell lines. The experimental demonstration suggested that analogue C086 showed dose and time dependent antiproliferative effect in KM12 and SW480. It is also reported that the antiproliferative activity of C086 is by downregulation of NF-κB activation through inhibition of IκBα phosphorylation and cell growth

Table 2
Effects of curcumin analogs on colon cancer signaling pathways.

Curcumin analogs on colon cancer signaling pathways	Mechanism of Action	IC_{50} (μM) Curcumin Vs Analogue	Ref
Curcumin analogue (IND-4) enhances cytotoxic activity	↓ Cell Viability	18.74 μM vs 0.98 μM	[98]
Curcumin analogue (1-aroyl-3,5-bis (benzylidene)-4-piperidone) inhibits cell growth and increase ROS production	↓ Cell proliferatoin ↓ MMP	Not Tested vs 0.49 μM	[99]
Curcumin analogue (1,3-bis-(3,5-bis(Benzylidene)-4-oxo-piperidin-1yl)propane-1,3-dione) demonstrate potent anti-proliferative activities	↑ Cytotoxicity	HCT116: 11.54 μM vs 0.02 μM HT29: 13.20 vs 0.003 μM	[100]
Curcumin analogue (FLLL) inhibits enzymatic and catalytic activity of histone demethylase proteins	↓ JMJD2C ↓ JMJD2A & JMJD2D	HCT116: Not Tested vs. 1 μM	[101]
Curcumin analogue (GO-Y030) inhibits STAT3 downstream target gene involved in apoptosis	Clevage PARP and Caspase 3 ↓ Tumor growth ↓ Notch 1 and 3 expression	Cell Viability: HCT116: 85% @25 μM vs. 90% @ 2.5 μM	[102]
C-5 curcumin analogue with –OMe substituent enhances intestinal absorption and cytotoxic activity	↓ Cell proliferation	Growth Inhibition: HCT116: 46.87% vs 60.72% @ 5 μM	[103]
Curcumin analogue (C086) inhibits TNF-α induced activation	↓ IkBα phosphorylation ↓ Protein binding ↓ NFkB translocation	HT29: 20.73 vs 5.41 μmol/L SW480: 17.94 vs 4.78	[104]
Curcumin metabolite Tetrahydrocurcumin exhibits decrease tumor incidence	↓ Polyp formation ↓ ERk ½ phosphorylation ↓ GSK phosphorylation ↓ Wnt-1 expression	Male ICR: THC and Cur (0.005 and 0.02%) diet	[105]
Curcumin diethyl disuccinate analogue exhibits anti-cancer activity	↓ Cell proliferation	Caco-2: Not tested vs 1.84 μM	[106]
Curcumin analogue (Dehydrozingerone) inhibits cell proliferation and induces cell cycle arrest	↑ Intracellular ROS ↑ G2/M phase	Growth Inhibition: HT-29: 84–94% @ 31.3 μM vs. 37% @ 1000 μM	[107]
Curcumin analogue, (bis-dehydroxy-curcumin) enhances growth suppressive activity and caspase-activating cell death pathways	↑ DNA fragmentation ↑ G2/M Phase ↓ Mitochrondrial transmembrane potential	HCT-116: Not test vs. 30 μM	[108]
Curcumin analogue (difluorinated-curcumin) alter activation of signaling pathway of miR2-overexpressing	↑ PTEN level ↓ Akt phosphorylation	HCT-116: Not test vs. 100 nM	[109]
Hexahydrocurcumin enhances cytotoxic activity with 5-FU	↓ COX-2 protein ↓ Cell proliferation	HT-29: Not test vs. 25 μmol/L	[110]
Hexahydrocurcumin combination therapy enhances apoptosis in dimethylhydrazine induced colon cancer	↓ ACF formation ↓ COX-2	Male Wistar: 50 mg/kg vs 50 mg/kg	[111]

suppression probably was five to seven times inordinate than curcumin [104]. Tetrahydrocurcumin, a curcumin metabolite, showed apoptosis activities via suppressing Wnt-1 and β-catenin protein expression and phosphorylation of GSK-3b in colonic tissue as well as reduced the connexin-43 protein level which leads to suppress the formation of colonic polyps by inhibiting gap junction formation [105]. Wichitnithad and team synthesized succinyl derivatives curcuminoids as prodrug and investigated its anticolon cancer activity against human epithelial colorectal adenocarcinoma cells (Caco-2 cells). The prodrugs induced anticolon cancer activity via decreasing cell proliferation with the IC_{50} values in the range between 1.8 and 9.6 μM and the cell proliferation effect was greater than curcumin [106]. Yogosawa and team investigated the dehydrozingerone as curcumin analogue for its antiproliferative activity in HT-29 Human colon cancer cells. The analogue demonstrated potent cytotoxicity and antiproliferative activity by the induction of cell cycle arrest at the G2/M Phase, significantly accumulated intracellular ROS and up-regulation of p21 [107]. Curcumin analogue bisdehydroxy curcumin noticed to be producing its apoptosis by reducing the sequential cell proliferation, cell cycle block, cell arrest in G2/M Phase and by decreasing mitochondrial transmembrane potential in mitochondria-dependent pathway [108]. Difluorinated curcumin (CDF) has demonstrated its potent cytotoxic effect in colon cancer cell lines HCT116 and HT29 by reduction of miR-21 (microRNA-21), increased PTEN (phosphatase and tensin homolog) levels and reduced phosphorylated form of Akt in PTEN-Akt pathway [109]. A study performed by Srimuangwong et al. observed the effect of a curcumin analogue hexahydrocurcumin against HT-29 cells and the study results concluded that hexahydrocurcumin inhibit the growth of HT-29 cells in a time and dose dependent fashion by down regulation of COX-2 mRNA production and protein expression [110,111].

4. In vivo studies of curcumin in colon cancer

Various *in vitro* cancer cell line studies have been successfully carried out and amongst them it has been demonstrated that curcumin has chemopreventive and chemotherapeutic effects (Fig. 2). Colorectal cancer activity of curcumin was investigated in various animal models (Table 3), the study results demonstrated that curcumin reduces the colorectal tumors and tumor size by exhibiting oxidative stress, alter homeostasis and tumor development in 1,2-dimethylhydrazine performed in induce colorectal *in-vivo* model. Bounaama et al. [112] investigated the effectiveness of curcumin in 1,2-dimethylhydrazine (DMH) colon carcinogenesis in mice administered with 60 mg/kg/day orally for 2 consecutive weeks. The study revealed and supported that curcumin inhibited aberrant crypt foci (ACF) formation in the DMH treated mice. A colon cancer was generated in mice which was induced intraperitonially by placing 25 mg/kg of azoxymethane in phosphate buffered saline. Curcumin was administered along with diet for 8 weeks resulting in 40% reduction of colorectal tumor multiplicity in the large intestine [113]. Xu et al. [114] investigated the effectiveness of curcumin in male Wister rats. These rats were further used for the experiments and therefore Colon carcinogenesis was induced by subcutaneously placing 20 mg/kg of 1,2-dimethylhydrazine for 18 weeks. Curcumin was administered along with normal rat chow for 32 weeks resulting in decreased total number of aberrant ACF, proliferation of cancer cells and thereby promoting the apoptosis. Apparently Kantara and team [115] investigated curcumin for its anticancer properties in xenografts by subcutaneously having placed at 5×10^6 HCT-116 cells. Curcumin (25 mmol/L) + DCLK-siRNA (100 nmol/L) were administered on ventral side of tumors every second day for 3 weeks, the study revealed significant loss of tumor mass, combination of curcumin with DCLK-siRNA produced synergistic activity in colon cancer cells. Also revealed that curcumin has both apoptotic cell death and autophagic survival whereas DCLK1-siRNA has only apoptotic cell death in colon

Table 3
In vivo curcumin colon cancer studies.

In vivo studies	Mechanism of Action	Curcumin (Dose)	Ref
Curcumin inhibits polyamines synthesis, morphological changes, oxidative stress and alter homeostasis and tumor development	↓ Arginase Activity ↓ Dysplastic ACF Formation ↓ Nitrotyrosine Formation ↑ Apoptosis ↑ HES-1 and TGF-β ↓ Lipid peroxides	60 mg/kg/day in 1% Tween	[112]
High protein and curcumin diet inhibits inflammatory proteins	↓ Nitric oxide ↓ TNF-α plasma level ↓ BrdU incorporation rate	HPDC diet (50% casein +0.02% curcumin)	[113]
Green tea catechin and curcumin diet inhibits ACF formation	↓ Cell proliferation ↑ Cell Apotosis	Cur: 0.2% per 173–180 g Combine: 0.1% Cur + 0.1% catechin per 173–180 g	[114]
Curcumin inhibits growth of spheroids and induces apoptosis	↓ B-catenin/NF-kBp65 ↓ Stem cell markers ↓ tumorosphere	Xenografts (100 μmol/L)	[115]
Curcumin diet enhances survival rate in AOM-induced colon cancer	↓ Tumor burden ↓ Colon weight/length ratio	8–162 mg/kg/day for 0.05% and 1% diet	[116]
Curcumin in combination with diclofenac therapy alter signaling transduction pathway	↓ PI3K and PDKI ↓ BCl-2 ↑ BAD and Bax ↑ PTEN	Male Sprague-Dawley rats (50 mg/kg/body wt.) Diclofenac (8 mg/kg/body wt.)	[117]
Curcumin inhibits cell cycle and upstream regulators	↓ p53 and p21 ↓STAT 3 DNA binding ↓CDK4	Male ICR mice (0.1 or 0.25 mmol/kg/body wt.)	[13]

cancer cell. A study with the tumorigenesis generated by intraperitoneal injection of azoxymethane (10 mg/kg) in specific pathogen-free wild-type (WT) 129/SvEv mice and germ-free Il10$^{-/-}$ mice were observed. Curcumin was administered along with the diet in the range of 8–162 mg/kg per day for 0.05% and 1% resulting decreased colonic tumor burden and increased colonic microbial ecology [116]. Rana and team investigated the chemopreventive effect of diclofenac and curcumin in colorectal carcinogenesis induced by subcutaneous injection of 1,2-dimethylhydrazine dihydrochloride for one week. Diclofenac (8 mg/kg b.w.) and curcumin (30 mg/kg b.w.) per day were administered for six weeks. The study had revealed suggesting that significant efficacy in down regulating the PI3–K and Akt expression subsequently increased the expression of proapoptotic Bcl-2 thereby upregulated the cysteine protease (caspase −3 and −9) and promoted the apoptotic mechanism by increasing reactive oxygen species and decreasing the mitochondrial membrane potential [117]. Yang and team investigated the curcumin chemoprotective effect on colitis induced by dextran sulfate sodium in ICR mice which involved curcumin dosage of 0.1 or 0.25 mmol/kg in 0.05% carboxymethyl cellulose was administered for a week resulting in regulated cyclin D1 and CDK4 expression, which decreased the p53 and its target protein p21 and suppressed the phosphorylation of STAT3 DNA binding [13].

5. Curcumin drug delivery in colon cancer

Oral administration of curcumin undergoes rapid metabolism in intestine and liver, 60–70% of the compound gets excreted in feces, so heavy dose of curcumin is required in order to produce therapeutic effects. Employment of curcumin with novel drug delivery systems like liposome, micelles and nanoparticle have been suggested which could improve the therapeutic efficacy against colorectal cancer (Table 4). Singh and team studied cytotoxicity of silica nanoparticle from curcumin, similarly silica nanoparticle curcumin complex with hyaluronic acid and compared with free curcumin in human colon carcinoma (colo-25). Silica nanoparticle of curcumin when complexed with hyaluronic acid demonstrated significant reduction of the cell viability, increased uptake of curcumin in intra cellular and in tumor spheroids when compared with silica nanoparticle curcumin as well as free curcumin. In the delivery system, hyaluronidase has a role in the release of curcumin from nanoparticle [118]. Alizadeh et al. [119] made a comparative investigation of polymeric nanocarrier curcumin (PNCC) and curcumin in azoxymethane induced colon carcinogenesis, resulted in PNCC showed 76.7% reduction of lesion size (mm), induced the proapoptotic protein Bax expression, reduced anti-apoptotic Bcl-2 expression and Bcl-2/Bax ratio than free curcumin. A comparison of nanoparticles curcumin/5-fluorouracil loaded thiolated chitosan nanoparticles (CRC-TCS-NPs/5-FU-TCS-NPs) with the free drug, states that curcumin can be released in time dependent manner with increased systemic circulation and improved half-life. Combination of curcumin and 5-FU in nanoparticles showed higher apoptosis effect by arresting the cells in the G2/M and S phase respectively [120]. N, O-carboxymethyl chitosan nanoparticles of curcumin and 5-fluorouracil are reported to inhibit the HT 29 cells in colon cancer. A comparison of N, O-carboxymethyl chitosan nanoparticles of curcumin and 5-fluorouracil showed prolonged plasma concentration than pure drugs. Combinatorial nanoparticle showed enhanced anticancer effect which leads to cell death through p53 and cytotoxic metabolites mediated pathways respectively by CUR and 5-FU [121]. Esmatabadi et al. [122] formulated dendrosome nanocarriers with curcumin, further reported that dendrosome increased the water solubility and penetrating ability of curcumin. In the delivery system DNC, inhibit the cell viability and adhesion of the SW480 cells to matrix in a dose and time dependent manner through reducing the expression of Hef 1, Zeb 1 and Claudin 1 genes. Chang and team synthesized Micelles, a curcumin encapsulated in PEGMEMA-Based micelles, by RAFT polymerization technique, which resulted internalization of curcumin into cells in a dose dependent manner. Micelles thermodynamic stability influences the cellular internalization and reduced the cell proliferation in Human colon carcinoma cell line WiDr [123]. PLGA-curcumin conjugate via ester linkage is reported to inhibit the cell proliferation in colon cancer cells. A comparison of free curcumin and PLGA-curcumin conjugates study demonstrated that PLGA-curcumin could improve the cellular uptake and controlled release, found to inhibit cell proliferation than free curcumin in HCT 116 and HT-29 cells in a time and dose dependent manner [124]. Li and team encapsulated the curcumin in PLGA-lecithin-PEG nanoparticles by nanoprecipitation technique, bioconjugated the aptamer with nanoparticle through amide linkage to form Apt-CUR-NP bioconjugates and is reported to inhibit human colorectal adenocarcinoma cells (HT29 cells). Bioconjugates resulted in sustained release, increased bioavailability, 64-fold cellular intakes in HT29 cells

Table 4
Curcumin drug delivery in colorectal cancer.

Curcumin drug delivery methods	Delivery Vessel	IC_{50}	Enhancement in Activity	Cell line	Ref
Curcumin in nanoparticle enhances cytotoxic activity	Hyaluronic acid-(silica nanoparticle)-Curcumin complex (HA-SiNp-Cur)	25 μM	Cellular Uptake: SiNP-Cur: 2.93x greater HA-SiNP-Cur: 4.5x greater Cell viability: Curcumin: 46% SiNP-Cur: 67% HA-SiNP-Cur: 88%	Colo-205	[118]
Curcumin in nanocarrier delivery system	Polymeric nanocarrier-Curcumin (PNCC)	2% Curcumin	Tumor Size: Curcumin: 20% PNCC: 76.7% Proapoptotic protein expression: Cur: 0.7 PNCC: 0.13	Male Wister Rats (100–120 g)	[119]
Curcumin in TCS-NP enhances cellular uptake and apoptosis	Curcumin loaded-thiolated chitosan nanoparticle (CRC-TCS-NP)	20 μM	Drug release: pH 7.4: 40% Acidic Cond.: 80% Cell Viability: Curcumin: 32.47% CRC-TCS-NP: 37.79%	HT29	[120]
Curcumin in N,O-CMC nanoparticle enhances cellular uptake and cytotoxic activity	Curcumin in N,O-carboxymethyl chitosan nanoparticle (CUR-N,O-CMC NP)	20 μM	Drug release: pH 7.4: 43.15% Acidic Cond.: 63.64% Cell Viability: 40.85%	HT29	[121]
Curcumin in Dendrosomal carrier inhibits cellular migration and adhesion	Dendrosomal 400 Curcumin (DNC) carrier	30 μM	Cell Viability: Cur: 60% DNC: 85%	SW480	[122]
Curcumin-loaded micelles enhances cytotoxic activity	Curcumin- poly(ethylene glycol) methyl ether methacrylate (PEGMEMA)	50 μg/ml	Cell proliferation: Cur: 25% Cur Loaded micelle: 45%	WiDr	[123]
Curcumin-loaded PLGA increases retention, inhibits colony formation and NF-kB activation	Curcumin-Poly(D,L-Lactic-co-glycolic acid) (PLGA)	8 μM	Drug release@ 24 h: Cur: 18 μg Cur-PLGA: 5 μg Cell Death: Cur @ 10 and 20 μM: 18 and 22% Cur-PLGA @ 10 and 20 μM: 38 and 40%	HCT116	[124]
Curcumin encapsulated bioconjugate enhances drug delivery and cytotoxic activity	Aptamer-Curcumin-PLGA-lecithin-PEG nanoparticle (Apt-Cur-	4 μg/ml and 8 μg/ml	Cell Viability: Cur: 35% Apt-Cur-NP: 40% Cellular uptake: Cur: 86.6 pmol Apt-Cur-NP: 138.0 pmol	HT-29	[125]
Curcumin/CPT PLGA-encapsulated enhances cellular uptake	Camptothecin and Curcumin -PLGA nanoparticle (CPT/CUR)-PLGA	25 μM	Bcl-2 mRNA expression: CPT/CUR-NP: 58.8% CPT-NP: 43.7%	Colon-26	[126]

than curcumin and delivering CUR via endocytosis into the HT29 cells [125]. Studies of CPT/CUR-NPs encapsulated curcumin and camptothecin by techniques like emulsion-solvent evaporation, functionalized with chitosan on colon-26 cells have observed increased cellular uptake efficiency and suppressed tumor cell growth by reducing Bcl-2 mRNA expression in a dose dependent manner. In addition, chitosan in the nanoparticle increased cellular uptake and simultaneously the concentration of drug in the intracellular region [126].

6. Curcumin synergistic combinations

Administration of curcumin along with therapeutic cancer agent *in vitro* and *in vivo* models demonstrated enhanced efficiency against colorectal cancer (Table 5). A combination of dasatinib and curcumin have synergistic effect in colon cancer cells. The combination therapy has been found to inhibit the cell growth, colonosphere formation and extracellular matrix invasion in HCT-116 and HT-29 cells [127]. The *in vitro* analysis of colon cancer cells (HCT116 and HT29) includes the treatment with a combination of curcumin and tolfenamic acid. The *in vitro* study revealed the synergistic combinations are effective in inhibiting cell growth, loss of mitochondrial membrane potential via mitochondrial pathways, increase in caspase 3/7 activity, down-regulating protein survivin, induction of ROS levels and inhibiting the translocation of NF-κB from the cytoplasm to nucleus [128]. Femia et al. [129] conducted an experiment consisting of the chemoprotective effect of sulindac, 3,3′-diindolylmethane and curcumin in Pirc rat having colon carcinogenesis. Eventually combinations showed its chemoprotective effect in Pirc rat by inhibition of cell proliferation and down regulates the anti-apoptotic gene survivin. Lu and team investigated the role of curcumin in multidrug resistance on colon cancer in female BALB/C nude mice & xenografted mice. Curcumin in combination with VCR, DDP, 5-FU and HCPT significantly decreased the IC_{50} than when they administered alone. Curcumin in MDR, induced cell apoptosis, suppressed the expression of surviving mRNA and finally reversed the drug resistance by decreasing the efflux of Pgp thereby blocking the mechanism of tumor cell resistance. The result discloses curcumin to be a counteract MDR in colon cancer [130]. Murakami et al. [131] created a curcumin and turmerones combination that demonstrated an ability to suppress COX-2 and iNOS mRNA expressions in concentration dependent manner and abolished at higher concentration in colon cancer induced by dimethylhydrazine or dextran sulfate sodium. In addition, CUR is potent suppresser of AP-1 and NF-κB.

Table 5
Curcumin synergistic combinations.

Synergistic combinations	Mechanism of Action	Cell line (curcumin IC_{50})	Combination Activity	Ref
Combination therapy with Src inhibitor enhances anti-cancer activity	↓ Cell growth ↓ Colonosphere formation ↓ Extracellular invasion	HCT-116 & HT-29 Curcumin (10 μM) Dasatinib (1 μM)	80–90% decrease of Cancer stem cell markers	[127]
Combination therapy with COX-2 inhibitor enhances inhibition of proliferation	↑ Caspase 3/7 activity ↑ ROS ↓ NF-kB levels	HCT-116 and H29 (7.5 μM) Tolfenamic Acid (50 μM)	Cell viability: HCT116: 58% H29: 51%	[128]
Combination therapy with COX-2 inhibitor and co-exposure to DIM inhibits tumor progression	↓ Anti-apoptotic gene	Pirc rats (2000 ppm) + DIM (250 ppm) SU (160 ppm)	Σ tumor volume: Cntrl: 52.4 mm^3 Cur: 20.0 mm^3	[129]
Combination therapy enhances inhibition of cell proliferation and tumor growth	↓ MDR1 expression ↓ Survivin ↓ Tumor weight	HCT-8/VCR (25 μM) Vincristine (0.5 μg/ml)	Σ tumor volume: Cur: 782.5 mm^3 Cur/VCR: 402 mm^3	[130]
Combination therapy enhances the synergistic effect	↓ iNOS and COX-2 ↓ AP-1 ↓ NF-kB	RAW 264.7 (20 μM) ATM (100 μM)	Inhibition: Cur: 59% Combine: 100%	[131]
Combination therapy enhances reduction in proliferation and stimulation of apoptosis	↓ DNA binding activity of NF-kB ↓ Tumor growth ↓ Acitivation of EGFRs and IGF-1R ↑ IGFBO-3 expression	HCT-116 (10 μM) Resveratrol (10 μM)	Growth Inhibition: Cur: 15–30% Combine: 40% Cell cycle Distr. (S phase) Cur: 35% Combine:122%	[14]
Combination therapy with Src inhibitor enhances inhibition of signal pathways	↓Activation of Akt and Erk ↓NF-kB Activity	HCT-116 (1 μM) Dasatinib (10 μM)	Growth Inhibition: Cur: 20–30% Combine: 81%	[15]

Resveratrol, a colorectal cancer drug, administered with curcumin showed synergistic activity in HCT-116 cells and female homozygous ICR SCID mice model than when administered alone. The combination results in reduction of cell proliferation, apoptosis by reduction of EGFRs, IGF-1R signaling pathways and NF-κB activity [14]. Nautiyal et al. [15] studied *in vitro* analysis of HCT-116 p53 wild type (wt), HT-29, and HCT-116 p53 null (HCT-116 p53−/−) and SW-620 colon cancer cells and *in vivo* analysis of C57BL/6J-$Apc^{Min+/-}$ mice treated with a combination of dasatinib and curcumin. The result reveals the combined therapy synergistic effect in inhibiting colony formation, invasion through extracellular matrix and tubule formation by endothelial cells. Apoptosis of this combination therapy is by reduction of Akt and Erk(s) signaling pathways and NF-κB activity.

7. Conclusion

Curcumin serves to be the best chemoprotective and chemotherapeutic agent amongst all. Furthermore, curcumin has been suggested for the treatment of liver, breast, ovarian, prostate, pancreatic and colorectal cancers so far. Inflection in the vital enzymes, transduction and inflammatory pathways, induction of cell cycle arrest and apoptotic nature have been emphasized for curcumin anticancer activity and have been found to serve better. Though on oral administration, it is chemically unstable, has poor aqueous solubility, undergoes rapid metabolism and tapered systemic distribution by conventional techniques like synthetic curcumin analogues, synergistic combination therapy and novel drug delivery system are a required system to be implemented to overcome the pharmacokinetic limitations of curcumin on oral administration. Curcumin analogue like IND-4, FLLL, GO-Y030 and C086 demonstrated to have greater cytotoxicity. Combination of curcumin with therapeutic cancer agent like tolfenamic acid, 5-fluorouracil, resveratrol and dasatinib showed enhanced cytotoxicity and chemotherapeutic effect when administered discretely. Encapsulation of curcumin in novel drug delivery systems like nanoparticle, liposome and micelles has been considered as an alternative strategy to oral administration and tumor targeted to release the curcumin over dose and time dependent manner, shows an enhanced cytotoxicity and chemotherapeutic effect in colon cancer. To further, these successful findings about curcumin provides valuable information for its future emphasis and development, also in preventing colon cancer to a greater extent.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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