HHS Public Access

Author manuscript

Mol Carcinog. Author manuscript; available in PMC 2021 February 01.

Published in final edited form as:

Mol Carcinog. 2020 February ; 59(2): 227–236. doi:10.1002/mc.23146.

Epigenetics/epigenomics and prevention by curcumin of early stages of inflammatory-driven colon cancer

Renyi Wu[1], **Lujing Wang**[1,2], **Ran Yin**[1], **Rasika Hudlikar**[1], **Shanyi Li**[1], **Hsiao-Chen Dina Kuo**[1,2], **Rebecca Peter**[1,2], **Davit Sargsyan**[1,2], **Yue Guo**[3], **Xia Liu**[1,4], **Ah-Ng Kong**[1]

[1]Department of Pharmaceutics, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA

[2]Graduate Program in Pharmaceutical Science, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscataway, NJ 08854, USA

[3]Janssen Research & Development, Spring House, PA 19002, USA

[4]Department of Pharmacology, School of Basic Medical Science, Lanzhou University, Lanzhou 730000, China

Abstract

Colorectal cancer (CRC) is associated with significant morbidity and mortality in the US and worldwide. CRC is the second most common cancer related death in both men and women globally. Chronic inflammation has been identified as one of the major risk factors of CRC. It may drive genetic and epigenetic/epigenomic alterations such as DNA methylation, histone modification, and noncoding RNA regulation. Current prevention modalities for CRC are limited and some treatment regimens such as use the NSAID aspirin may have severe side effects, namely gastrointestinal ulceration and bleeding. Therefore, there is an urgent need of developing alternative strategies. Recently, increasing evidence suggests that several dietary cancer chemopreventive phytochemicals possess anti-inflammation and anti-oxidative stress activities, and may prevent cancers including CRC. Curcumin is the yellow pigment that is found in the rhizomes of turmeric (*Curcuma longa)*. Many studies have demonstrated that curcumin exhibits strong anticancer, anti-oxidative stress and anti-inflammatory activities by regulating signaling pathways such as Nrf2, NF-κB, and epigenetics/epigenomics pathways of histones modifications, and DNA methylation. In this review, we will discuss the latest evidence in epigenetics/epigenomics alterations by curcumin in CRC and their potential contribution in the prevention of CRC.

Keywords

colon cancer; inflammation; epigenetics; curcumin

Correspondence Professor Ah-Ng Tony Kong, Rutgers, the State University of New Jersey, Ernest Mario School of Pharmacy, Room 228, 160 Frelinghuysen Road, Piscataway, NJ 08854, Phone: +1-848-445-6369/8, Fax: +1 732 445 3134, kongt@pharmacy.rutgers.edu.

Conflict of Interest

The authors declare no conflicts of interest.

1. Introduction

Curcumin is a polyphenolic derivative produced from turmeric (*Curcuma longa*) (1). It is the main active ingredient in turmeric and gives turmeric its yellow color. The IUPAC name for curcumin is (1*E*, 6*E*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, and its molecule structure contains a symmetric structure of two aromatic o-methoxy phenolic groups, linked by a diketone unsaturated carbon bridge (2). Previous reports have demonstrated that the curcumin content in turmeric are significantly different and affected by geology and environment, among other factors (3). For example, curcumin content reaches as high as 3.14% by weight in both turmeric and curry powders purchased from South California (4), while in Japan, fertilizing the plant with nitrogen, phosphorus and potassium in greenhouses, the content of curcumin in turmeric yields in the range of 0.12% to 0.21 % by weight (5). Regional similarity also found that the curcumin content grown in Japan, Indonesia and Vietnam is around 0.18% to 0.44%, 2.3%, and 3.2% by weight, respectively (6). Due to curcumin's hydrophobic structure, rapid metabolism and systemic elimination occurs upon entering the human body and the bioavailability of curcumin is considered very poor (7). In vivo studies in rats show that oral administration of curcumin (500 mg/kg body weight) leads to a maximum serum concentration of 0.06 ± 0.01 μg/mL at 41.7 ± 5.4 min. In addition, the elimination half-life for curcumin oral administration (500 mg/kg) and IV injection (10 mg/kg) are 28.1 ± 5.6 and 44.5 ± 7.5 min, respectively (8). To improve the bioavailability of curcumin, piperine has been used in combination with curcumin, and the bioavailability could be increased by 20-fold in human clinical trials (9). Curcumin-loaded nanoparticles have also been developed to improve curcumin's bioavailability (10). Lipidated curcumin was shown to increase the bioavailability and promote human health by decreasing the plasma triglyceride and increasing the free radical scavenging ability (11). While multiple delivery systems are designed to reach superior curcumin bioavailability, the mechanisms of curcumin metabolism and bioactivity are not fully understood.

Chronic inflammation is highly related to human digestive tract disorders including ulcerative colitis, Crohn's disease and colon cancer. Risk factors such as oxidative stress, cytokines, duration of colon inflammation and family history are all associated with colon cancer incidence (12). The possible genetic mechanisms of colon cancer induced by inflammation include loss of function of tumor suppressor genes such as adenomatous polyposis coli (Apc) and p53, and elevated expression of the inflammatory genes such as cyclooxygenase-2 (COX-2) and nitric oxide synthase-2 (NOS-2) (13, 14). In addition, accumulating evidence has revealed that epigenetic mechanisms, heritable alterations that are not caused by changes to the DNA sequence, could play an important role in colon carcinogenesis (15). DNA methylation, with the addition of a methyl group to 5-cytosine in the CpG dinucleotide, is one of the common epigenetic mechanisms associated with aberrant gene expression in cancer. Specifically, CpG hypermethylation in promoter regions is believed to play a crucial role in suppressing gene expression, perhaps by blocking transcription factor binding (16). Grimm et al. and our group identified aberrant methylation in a well-established Apc(min/+) intestinal tumorigenesis model using methylated DNA immunoprecipitation (MeDIP) and next-generation sequencing approaches (17, 18).

Katsurano et al. observed that aberrant DNA methylation accumulates in epithelial cells during DSS-induced inflammation (19). More recently, Abu-Remaileh et al. used whole-genome bisulfite sequencing to demonstrate that inflammatory signals establish a novel epigenetic landscape that silences gene sets important for cellular transformation in an AOM/DSS-induced CRC model (20). Current studies suggest that gut microbiota also plays important roles during the development of colon cancer (21, 22). To reduce colon cancer rate by anti-inflammatory intervention, therapeutic treatments including utilizing bioactive phytochemicals appears to be logical. Curcumin has been demonstrated to reduce colitis-accelerated colon cancer in both in vitro and in vivo models (23-25). More details regarding colon cancer carcinogenesis and its prevention by curcumin will be discussed subsequently.

2. Epigenetics/epigenomics of colon cancer carcinogenesis

Alterations in epigenetics have been reported for several age-related diseases, including CRC (26). The estimated loss of epigenetic control may be one to two fold higher than that of somatic DNA mutations in colon cancer (27). The NF-κB and STAT3 signaling pathways play particularly important roles in the transformation of inflammation into cancer, and both are critical in cellular signal transduction and appears to be constitutively activated in cancer by abnormal changes including epigenetics. The NF-κB and STAT3 signaling pathways contribute to the microenvironment for tumorigenesis through secretion of a large number of pro-inflammatory cytokines and their crosstalk in the nucleus makes it even more difficult to treat colon cancer (28).

In CRC, three molecular carcinogenesis pathways have been identified; (1) chromosomal instability (CIN), (2) microsatellite instability (MSI), and (3) CpG island methylator phenotype (CIMP), each account for ~85%, 15%, and 17%, respectively (29, 30). Around 30–40% of proximal site colon tumors and 3–12% of distal colon and rectal tumors are characterized by high CIMP, in which numerous CpG islands are methylated and several tumor suppressor genes or ncRNA are inactivated (31). Based on CIMP profiles, primary CRC may be clustered into three distinct but relatively homogeneous subclasses: CIMP1, characterized by intense methylation of multiple genes, MSI and BRAF mutations; CIMP2, including methylation of a limited group of genes, increased methylation level for age-related genes, and mutation in KRAS; and CIMP negative, characterized by rare methylation with p53 mutation (29). CIMP1 and CIMP2 phenotypes are more often expressed in the proximal colon; CIMP1 has a good prognosis, whereas CIMP2 has a poor prognosis (32). Lind and colleagues found frequent promoter hypermethylation of CNRIP1, FBN1, INA, MAL, SNCA, and SPG20 in both CRCs (65–94%) and adenomas (35–91%), whereas normal mucosa samples were rarely (0–5%) methylated (33).

Chromatin remodeling together with DNA CpG methylation, are two of the key mechanisms of regulating gene expression (34, 35). Chromatin remodeling consists of modifications at conserved lysine residues on the tails of histone proteins. Lysine acetylation generally enhances transcription by weakening the association of the histones with DNA and permitting the accessibility of transcription factors to bind to promoter/enhancer regions and subsequent transcriptional activation. SOCSs and SHP1 genes play an important role as tumor suppressors in CRC cells (36-38). Xiong and colleagues reported that trichostatin A

(TSA), a histone deacetylase inhibitor (HDACi), increased the mRNA levels of SOCS1 and SOCS3. The induction of SOCS1 and SOCS3 expression by TSA in human CRC cells was due to increased acetylation of histone H3 and H4 in their promoter regions (39).

Chromosomal anomalies (deletions, translocations, copy number alterations), DNA mutations and epigenetic dysregulation of the miRNAs or genes involved in their biogenesis have been found during tumor progression (40-43). The best-characterized miRNAs dysregulated by DNA hypermethylation in tumors including CRC, and the functional consequences in tumor cells have been reviewed recently (44). Loss of miR-133a and gain of miR-224 are associated with CRC tumorigenesis. Reduced expression of miR-143 and miR-145 were found in CRC and adenomatous polyps (45). The level of miR92 and miR173p has been reported to be significantly higher in the plasma of colon cancer patients compared with healthy controls, and is implicated as potential markers for CRC (46). The expression of the miR-17-92 cluster, which encodes for a total of fifteen miRNAs, and miR135 are also significantly increased in CRC patients (47).

3. Colon cancer prevention by curcumin via non-epigenetic and epigenetic mechanisms

Curcumin has many biological anti-cancer activities in colon cancer, including induction of apoptosis, anti-oxidation and anti-inflammation. In this section, we will highlight the potential mechanisms of CRC prevention by curcumin, focusing on apoptosis, antioxidative, anti-inflammatory and epigenetic regulation in *in vitro* studies.

3.1 Cancer prevention through non-epigenetic pathways

A number of studies have demonstrated that curcumin can induce apoptosis and cell cycle arrest in many colon cancer cell lines, including human colon cancer HT-29 (48, 49), SW480 (50, 51), CT26 (52), HCT-116 (53-56), HCT-15 (57), COLO 205 (58, 59), LoVo (60) and DLD-1 cells (61). The molecular mechanisms by which curcumin induces apoptosis or cell cycle arrest vary, depending on the cell type and the doses of curcumin. Generally, curcumin-induced apoptosis or suppressed proliferation involves inhibition of Wnt/β-Catenin pathways (50, 62), mitochondria-mediated apoptotic pathway (60, 63), oxidative stress (53), accumulation in G2/M phase (64, 65), targeting CDK2 (54), modulating EGFR and IGF-1R (66) and activation of Caspase-3, −7 and −9 (55, 59, 67).

High expression of NADPH oxidase 1 (NOX1) promotes proliferation of colon cancer cells by regulating ROS-dependent signal transduction (68). Curcumin possesses antioxidant and radical scavenging properties (69, 70). Curcumin may protect colon cells from oxidative stress by free radical scavenging and colon repair mechanism (52). Curcumin also is a fairly strong Nrf2 activator, resulting in induction of Nrf2-mediated antioxidant and detoxifying enzymes (71-75). Many studies have also shown that curcumin and its derivatives possess great anticancer effects in colon cancer, due to induction of ROS production, ROS-dependent mitochondrial dysfunction, and ER stress-dependent apoptosis accompanied with cell cycle arrest (56, 76-78). This latter phenomenon is probably due to much higher doses as compared to the lower doses needed to activate the Nrf2 mediated anti-oxidative stress

pathway (79). In addition, curcumin as a well-known anti-inflammatory agent, possesses very strong anti-inflammatory activities (80, 81). Curcumin regulates its anti-inflammatory effects by downregulating inflammatory transcription factors, cytokines and redox states (82), as well as interrupting the NF-κB signaling pathway, a major transcription factor in inflammation (83-85). Curcumin could also exhibit its anti-inflammatory activities through Nrf2-mediated pathways, since in LPS-stimulated Nrf2−/− macrophages curcumin's inhibition of cyclooxygenase-2 (COX-2), interleukin-6 (IL-6) and inducible nitric oxidte (iNOS) mRNA was dampened as compared to the LPS-stimulated Nrf2+/+ macrophages (86).

3.2 Cancer prevention through epigenetic regulations

We have previously reported that curcumin reduced the CpG methylation in the promoter of DLEC1 (Deleted in lung and esophageal cancer 1), a tumor-suppressor gene, with corresponding increase in mRNA expression in human colon HT29 cells (87). The demethylation was associated with reduced protein expression of DNMTs and HDACs and this was similarly observed in another study using in DNMT1 and DNMT3B knockout HCT116 cells (88). Microsatellite instability, a hypermutable phenotype, is observed in 15% of CRCs, out of which 12% are resulted from hypermethylation of the promoter of MLH1 (mutL homolog 1) (89). Clinical tissues with sporadic deficient mismatch repair in colorectal cancer have hypermethylation in MLH1 promoter, which may cause microsatellite instability, leading to BRAF mutations and double-hit somatic mutations of MSH2 and MSH6 (90). Curcumin abrogates G2/M arrest and enhances apoptosis in MLH1- or MSH2-knockdown HCT116 cells and RKO cells (91). In this context, the apoptosis inductive mechanism of curcumin may be associated with hypomethylation of MLH1 promoter and disruption of microsatellite instability (89-91). Combination of curcumin with UCN-01, an inhibitor of the cell cycle check point kinase Chk1, increases apoptosis even in MLH1+ and MSH2+ cells, potentially via epigenetic mechanism, which could be a promising treatment modality for CRC (91).

Decreased expression of miR-491 and increased expression of PEG10 (paternally expressed gene), β-catenin, and Wnt have been identified in colon cancer tissues (92). In HCT116 cells, it has been reported that curcumin increases miR-491 expression, suppressed PEG10 expression and consequently silences the Wnt/β-catenin signaling pathway as a mechanism of inducing apoptosis and inhibiting cells proliferation (92). Curcumin can also inhibit the AP-1 transcription factor components c-Jun and c-Fos, and bind to the promoter of pri-miR-21 which arrests cells in the G2/M phase, inhibits cell migration/invasion in vitro (HCT116 and RKO cells), and suppresses tumor growth and metastasis in vivo (93). Through inhibition of miR-21, curcumin could increase the protein expression of Pdcd4 (colorectal tumor suppressor programmed cell death protein 4) (93).

Study by Roy et al. showed that difluorinated curcumin (CDF), a synthetic analog of curcumin, demethylated miR-34a and miR-34c promoter, restoring the expression of miR-34a and miR-34c that were down-regulated in colon cancer cell lines (HCT116 and SW620) and colon cancer tissues (94). The up-regulation of miR-34 by CDF resulted in decreased expression of its target gene Notch-1. Elevated Notch-1 expression in CRCs

inhibits apoptosis (95, 96) while promoting epithelial to mesenchymal transition and stemness (97, 98). Another study showed that CDF could inhibit miR-21and restore expression of PTEN (phosphatase, and tensin homolog), normalizing the dysregulated miR-21-PTEN-Akt axis in chemo-resistant HCT116 and HT29 cells (99). In RKO and SW480 cells, curcumin and curcumin analog, RL197, have been shown to inhibit cell growth and induce apoptosis through suppressing miR-27a and miR-20a/miR-17-5p and downregulating the specificity protein transcription factors (Sp1, Sp3, and Sp4) (100). The proposed mechanisms include induction of reactive oxygen species (ROS) (100).

4. Colon cancer prevention by curcumin in *in vivo* animal studies: epigenetics/epigenomics

Curcumin's preventive effects against inflammation-associated colorectal carcinogenesis have been widely studied in various animal models, among which azoxymethane (AOM) and/or dextran sulfate sodium (DSS) induced mouse model is one of most commonly used animal model to recapitulate the pathogenesis of CRC in patients (101-103). This multistep carcinogenesis process usually involves a single AOM injection (an initiation factor that induces aberrant crypt foci (ACF) by causing DNA damage) and DSS in the drinking water (a promotion factor that induces colitis by imposing inflammatory damage in the epithelial lining of the colon). We have recently reported using this model the molecular mechanisms of inflammation-associated colon carcinogenesis utilizing next generation RNA sequencing (RNA-seq) and its prevention by combination of curcumin and aspirin in C57BL/6 mice (104). In the study, diets supplemented with 0.02% aspirin (ASA), 2% curcumin (CUR) or 0.01% ASA+1% CUR were given to mice from 1 week prior to AOM initiation through the end at 22 weeks post AOM initiation. The results showed that CUR had a superior inhibitory effect in colon carcinogenesis compared to that of ASA. Additionally, the combination of CUR and ASA at a lower dose level exhibited similar efficacy to that of a higher dose of CUR at 2%. RNA-seq analysis revealed that the low-dose combination of ASA and CUR modulated a larger set of genes than the single treatment of ASA or CUR. Pathway analysis showed these differentially expressed genes were found in several cellular functions which are specifically in the inflammatory networks and liver metastasis in CRC. We also identified a small subset of genes as potential molecular targets involved in the preventive action of the combination of ASA and CUR. This study provides the first evidence in support of the chemopreventive effect of a low-dose combination of ASA and CUR in CRC, and a framework for identifying the mechanisms underlying the carcinogenesis process from normal colonic tissue to tumor development. Surprisingly, when we conducted a second study of CUR and ASA in CF-1 mice, the results show that only aspirin but not curcumin inhibited DSS-induced inflammation and AOM+DSS induced carcinogenesis (unpublished results). The different results between CF1 versus C57BL/6 mice are not clear, however, could be due to differences in genetic background and or obesity (CF-1 mice are generally inactive and obese as compared to C57BL/6) or other factors, and further study would be needed.

In a similar follow-up study, we focused on the epigenetic/epigenomic mechanisms of colon cancer prevention by curcumin in AOM-DSS-induced CRC in C57BL/6 mice (23). We

performed RNA-seq and DNA CpG methyl-seq and identified lists of differentially expressed and differentially methylated genes in pairwise comparisons and several pathways involved in the potential cancer prevention effects of curcumin were uncovered. These pathways include LPS/IL-1-mediated inhibition of RXR function, Nrf2-mediated oxidative stress response, production of NO and ROS in macrophages and IL-6 signaling. Among the differentially expressed and methylated genes, Tnf (also known as Tnf-α) stood out with decreased DNA CpG methylation of Tnf in the AOM-DSS group and reversal of the AOM-DSS-induced Tnf demethylation by curcumin. These observations of Tnf methylation correlated with increased and decreased Tnf expression in RNA-seq. In addition, the DNA methylation level of a group of inflammatory genes was decreased in the AOM+DSS group but restored by curcumin and the results were validated by pyrosequencing. Our study shows for the first time that global epigenomic changes in DNA CpG methylation particularly in the inflammatory response from colitis-associated colon cancer and the reversal of their CpG methylation alterations by curcumin, which could potentially contribute to the overall cancer chemopreventive effect of curcumin in this CRC mouse model.

Other investigators in the past decades also performed several *in vivo* studies of cancer prevention effects of curcumin with the AOM/DSS model. As early as in 1994, a study by Huang et al. showed that administration of 0.5-4% curcumin in the diet decreased the number of AOM-induced colon tumors by 51-66% when fed during the initiation period (105). Other forms of curcumin such as tetrahydrocurcumin and phytosomal curcumin also have the ability of preventing AOM/DSS induced colon carcinogenesis (106, 107). As for the mechanisms of action, it has been reported that curcumin prevents colon carcinogenesis through decreasing the expression of Tnf-α, NF-κB, IL-6, COX-2, NOS, and IFN-γ (102, 106, 108, 109). Other studies suggest that curcumin, in combination with turmeric oils, have superior cancer preventive effects than curcumin alone (110, 111). MaFadden et al. reported that curcumin reduced colonic tumor burden, in association with increased colon bacteria richness and relative abundance of *Lactobacillales*, and decreased *Coriobacterales* order (112).

5. Colon cancer prevention by curcumin: clinical studies

Curcumin as the treasure of the dietary supplement world has been studied for its potential health benefits primarily in cell culture and animal models. Although the therapeutic use of curcumin was studied as early as 1748 (113), the first study referring to the use of curcumin for human disease was published in 1937 (114). Over the past quarter century, many scientists performed clinical studies with curcumin in both healthy humans and in patients, in the management of oxidative and inflammatory conditions, anxiety, metabolic syndrome, hyperlipidemia, ulcerative colitis and some other digestive disorders, as well as arthritis (115). As discussed above, curcumin's pleiotropic activities emanate from its capability of modulating many signaling molecules such as pro-inflammatory cytokines, adhesion molecules, apoptotic proteins, C-reactive protein, NF–κB, 5-LOX, prostate-specific antigen, phosphorylase kinase, Tgf-β, triglyceride, ET-1, creatinine, HO-1, AST, and ALT in human participants (116). However, the poor bioavailability of curcumin appears to be the most challenging barrier for advancing to human studies due to its poor absorption, rapid metabolism, and fast systemic elimination (7).

Most recently, we performed a simple pharmacokinetics (PK)-pharmacodynamics (PD) acute study with health human subjects (117). We found that the plasma levels of curcumin were below our LCMS detection limit (0.1 ng/ml) and only curcumin glucuronide, a metabolite of curcumin, was detected (117). Similar observations were reported in other studies (118). However, we also found that curcumin administration increased the mRNA expression of antioxidant genes NRF2, HO-1 and NQO1 while suppressing the expression of epigenetic gene histone deacetylases including HDAC1, HDAC2, HDAC3 and HDAC4 in leucocytes. HDACs are a class of epigenetic enzymes that remove the acetyl groups from an ε-*N*-acetyl lysine amino acid on a histone protein. And histone modifications are among the most important epigenetic changes, because it can alter gene expression and modify cancer risks (119). This result suggests that curcumin can elicit the *in vivo* biological responses like antioxidant and epigenetic effects which could contribute to the overall beneficial effects of curcumin in normal healthy population, despite the very low blood levels of curcumin (117). Bora-Tatar et al. reported that among 33 carboxylic acid derivatives, curcumin was the most effective HDAC inhibitor, and that it was even more potent than valproic acid and sodium butyrate, which are well-known HDAC inhibitors (120). In another study, it was reported that the protein levels HDACs 1, 3, and 8 were significantly decreased by curcumin, resulting in increased levels of histone H4 acetylation (121). Similarly, Chen et al. reported significant decrease in the expression of HDAC1 and HDAC3 were also detected after treatment with curcumin (122).

To date, majority of curcumin studies in humans have been in populations with existing health problems, especially some inflammatory related diseases such as Crohn's disease, ulcerative colitis, ulcerative proctitis, and colon cancer. Perhaps this is because studies with healthy people can be challenging where the benefits may not be as immediate and measurable if biomarkers are normal at baseline. Some promising effects have been observed in patients with various pro-inflammatory diseases including ulcerative colitis, ulcerative proctitis, irritable bowel syndrome, Crohn's disease, gastric inflammation and even colorectal cancer (116, 123-126). The biological effects of curcumin in healthy volunteers, CRC patients, Crohn's disease, ulcerative proctitis, ulcerative colitis, inflammatory bowel disease, irritable bowel syndrome and the potential molecular targets are summarized in Table 1. As shown in Table 1, the clinical trials conducted thus far indicate the potential therapeutic benefits of curcumin against a wide range of human inflammatory-driven diseases including colon cancer. Moreover, these human studies indicate curcumin's ability to modulate multiple biomarkers such as tumor necrosis factor (TNF-α), interleukin [IL]-1β, IL-6, IL-10, among others. Some of the potential pitfalls of performing the anti-cancer treatment studies of CRC patients with curcumin could be due to the advanced stages of CRC with many genetic mutations, epigenetics changes and chromosomal instability, the doses selected, the curcumin products used with varied curcumin content, and the etiology/genetic background of the patients, among others. Nevertheless, in summary, curcumin has shown promising beneficial effects from clinical trials and most of these effects can be attributed to its anti-oxidative, anti-inflammatory, epigenetic/epigenomic and other signaling modulating properties, which would contribute to the overall cancer chemopreventive effects of curcumin in early stages of inflammatory-mediated CRC (115, 116).

6. Conclusion

Colon cancer continues to be a major public health burden. Several factors from genetics to diets contribute to the incidence of this malignancy. Although there have been significant advances in the development of targeted therapies, the 5-year prognosis for distant CRC is about 15% (135). With our increased understanding of the molecular and epigenetic/epigenomic changes during CRC development, we will be able to develop new and more precise therapies, including relatively non-toxic dietary cancer chemopreventive regimens including curcumin either with individual therapy or in combination with other relatively non-toxic drugs such as NSAIDs (aspirin with lower doses), to prevent early stages, and or treat newly diagnosed inflammatory-mediated colon cancers in humans.

Acknowledgments

We thank all members of Dr. Ah-Ng Tony Kong's lab for helpful discussions and preparation of the manuscript.

Funding

This work was supported in part by Institutional Funds, by R01 CA200129, from the National Cancer Institute (NCI), R01 AT007065 and R01 AT009152 from National Center for Complementary and Integrative Health (NCCIH) of the National Institute of Health (NIH) awarded to Dr. Ah-Ng Tony Kong.

References

1. Esatbeyoglu T, Huebbe P, Ernst IM, Chin D, Wagner AE, Rimbach G. Curcumin--from molecule to biological function. Angew Chem Int Ed Engl. 2012;51(22):5308–32. Epub 2012/05/09. doi: 10.1002/anie.201107724. PubMed PMID: 22566109. [PubMed: 22566109]
2. Priyadarsini KI. The Chemistry of Curcumin: From Extraction to Therapeutic Agent. Molecules. 2014;19(12):20091–112. doi: 10.3390/molecules191220091. PubMed PMID: WOS: 000346793200046. [PubMed: 25470276]
3. Anandaraj M, Prasath D, Kandiannan K, Zachariah TJ, Srinivasan V, Jha AK, Singh BK, Singh AK, Pandey VP, Singh SP, Shoba N, Jana JC, Kumar KR, Maheswari KU. Genotype by environment interaction effects on yield and curcumin in turmeric (Curcuma longa L.). Ind Crop Prod. 2014;53:358–64. doi: 10.1016/j.indcrop.2014.01.005. PubMed PMID: WOS:000338612500045.
4. Tayyem RR, Heath DD, Al-Delaimy WK, Rock CL. Curcumin content of turmeric and curry powders. Nutr Cancer. 2006;55(2):126–31. doi: DOI 10.1207/s15327914nc5502_2. PubMed PMID: WOS:000241899500002. [PubMed: 17044766]
5. Castro FC, Magre A, Cherpinski R, Zelante PM, Neves LM, Esquisatto MA, Mendonca FA, Santos GM. Effects of microcurrent application alone or in combination with topical Hypericum perforatum L. and Arnica montana L. on surgically induced wound healing in Wistar rats. Homeopathy. 2012;101(3):147–53. Epub 2012/07/24. doi: 10.1016/j.homp.2012.05.006. PubMed PMID: 22818231. [PubMed: 22818231]
6. Difference of Curcumin Content in Curcuma longa L. (Zingiberaceae) Caused by Hybridization with Other Curcuma Species Hayakawa Hiroshi, Minaniya Yukio, Katsura Ito, Yoshinori Yamamoto, Tatsuya Fukuda
7. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007;4(6):807–18. Epub 2007/11/15. doi: 10.1021/mp700113r. PubMed PMID: 17999464. [PubMed: 17999464]
8. Yang KY, Lin LC, Tseng TY, Wang SC, Tsai TH. Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci. 2007;853(1-2):183–9. Epub 2007/04/03. doi: 10.1016/j.jchromb.2007.03.010. PubMed PMID: 17400527.

9. Shoba G, Joy D, Joseph T, Majeed M, Rajendran R, Srinivas PS. Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. Planta Med. 1998;64(4):353–6. Epub 1998/06/10. doi: 10.1055/s-2006-957450. PubMed PMID: 9619120. [PubMed: 9619120]
10. Sasaki H, Sunagawa Y, Takahashi K, Imaizumi A, Fukuda H, Hashimoto T, Wada H, Katanasaka Y, Kakeya H, Fujita M, Hasegawa K, Morimoto T. Innovative preparation of curcumin for improved oral bioavailability. Biol Pharm Bull. 2011;34(5):660–5. Epub 2011/05/03. doi: 10.1248/bpb.34.660. PubMed PMID: 21532153. [PubMed: 21532153]
11. DiSilvestro RA, Joseph E, Zhao S, Bomser J. Diverse effects of a low dose supplement of lipidated curcumin in healthy middle aged people. Nutr J. 2012;11:79. Epub 2012/09/28. doi: 10.1186/1475-2891-11-79. PubMed PMID: 23013352; PMCID: PMC3518252. [PubMed: 23013352]
12. Triantafillidis JK, Nasioulas G, Kosmidis PA. Colorectal cancer and inflammatory bowel disease: epidemiology, risk factors, mechanisms of carcinogenesis and prevention strategies. Anticancer Res. 2009;29(7):2727–37. Epub 2009/07/15. PubMed PMID: 19596953. [PubMed: 19596953]
13. Hussain SP, Amstad P, Raja K, Ambs S, Nagashima M, Bennett WP, Shields PG, Ham AJ, Swenberg JA, Marrogi AJ, Harris CC. Increased p53 mutation load in noncancerous colon tissue from ulcerative colitis: a cancer-prone chronic inflammatory disease. Cancer Res. 2000;60(13):3333–7. Epub 2000/07/26. PubMed PMID: 10910033. [PubMed: 10910033]
14. Itzkowitz SH, Yio X. Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. Am J Physiol Gastrointest Liver Physiol. 2004;287(1):G7–17. Epub 2004/06/15. doi: 10.1152/ajpgi.00079.2004. PubMed PMID: 15194558. [PubMed: 15194558]
15. Lao VV, Grady WM. Epigenetics and colorectal cancer. Nat Rev Gastroenterol Hepatol. 2011;8(12):686–700. doi: 10.1038/nrgastro.2011.173. PubMed PMID: 22009203; PMCID: 3391545. [PubMed: 22009203]
16. Robertson KD. DNA methylation and human disease. Nat Rev Genet. 2005;6(8):597–610. doi: 10.1038/nrg1655. PubMed PMID: 16136652. [PubMed: 16136652]
17. Guo Y, Lee JH, Shu L, Huang Y, Li W, Zhang C, Yang AY, Boyanapalli SS, Perekatt A, Hart RP, Verzi M, Kong AN. Association of aberrant DNA methylation in Apc(min/+) mice with the epithelial-mesenchymal transition and Wnt/beta-catenin pathways: genome-wide analysis using MeDIP-seq. Cell & bioscience. 2015;5:24. Epub 2015/06/24. doi: 10.1186/s13578-015-0013-2. PubMed PMID: 26101583; PMCID: PMC4476183. [PubMed: 26101583]
18. Grimm C, Chavez L, Vilardell M, Farrall AL, Tierling S, Bohm JW, Grote P, Lienhard M, Dietrich J, Timmermann B, Walter J, Schweiger MR, Lehrach H, Herwig R, Herrmann BG, Morkel M. DNA-methylome analysis of mouse intestinal adenoma identifies a tumour-specific signature that is partly conserved in human colon cancer. PLoS Genet. 2013;9(2):e1003250. doi: 10.1371/journal.pgen.1003250. PubMed PMID: 23408899; PMCID: 3567140. [PubMed: 23408899]
19. Katsurano M, Niwa T, Yasui Y, Shigematsu Y, Yamashita S, Takeshima H, Lee MS, Kim YJ, Tanaka T, Ushijima T. Early-stage formation of an epigenetic field defect in a mouse colitis model, and non-essential roles of T- and B-cells in DNA methylation induction. Oncogene. 2012;31(3):342–51. doi: 10.1038/onc.2011.241. PubMed PMID: 21685942. [PubMed: 21685942]
20. Abu-Remaileh M, Bender S, Raddatz G, Ansari I, Cohen D, Gutekunst J, Musch T, Linhart H, Breiling A, Pikarsky E, Bergman Y, Lyko F. Chronic inflammation induces a novel epigenetic program that is conserved in intestinal adenomas and in colorectal cancer. Cancer research. 2015;75(10):2120–30. doi: 10.1158/0008-5472.CAN-14-3295. PubMed PMID: 25808873. [PubMed: 25808873]
21. Sears CL, Garrett WS. Microbes, microbiota, and colon cancer. Cell Host Microbe. 2014;15(3):317–28. Epub 2014/03/19. doi: 10.1016/j.chom.2014.02.007. PubMed PMID: 24629338; PMCID: PMC4003880. [PubMed: 24629338]
22. Arthur JC, Perez-Chanona E, Muhlbauer M, Tomkovich S, Uronis JM, Fan TJ, Campbell BJ, Abujamel T, Dogan B, Rogers AB, Rhodes JM, Stintzi A, Simpson KW, Hansen JJ, Keku TO, Fodor AA, Jobin C. Intestinal inflammation targets cancer-inducing activity of the microbiota. Science. 2012;338(6103):120–3. Epub 2012/08/21. doi: 10.1126/science.1224820. PubMed PMID: 22903521; PMCID: PMC3645302. [PubMed: 22903521]

23. Guo Y, Wu R, Gaspar JM, Sargsyan D, Su ZY, Zhang C, Gao L, Cheng D, Li W, Wang C, Yin R, Fang M, Verzi MP, Hart RP, Kong AN. DNA methylome and transcriptome alterations and cancer prevention by curcumin in colitis-accelerated colon cancer in mice. Carcinogenesis. 2018;39(5): 669–80. Epub 2018/03/17. doi: 10.1093/carcin/bgy043. PubMed PMID: 29547900. [PubMed: 29547900]

24. Guo Y, Su ZY, Zhang CY, Gaspar JM, Wang R, Hart RP, Verzi MP, Kong ANT. Mechanisms of colitis-accelerated colon carcinogenesis and its prevention with the combination of aspirin and curcumin: Transcriptomic analysis using RNA-seq. Biochem Pharmacol. 2017;135:22–34. doi: 10.1016/j.bcp.2017.02.021. PubMed PMID: WOS:000403133300003. [PubMed: 28267439]

25. Guo Y, Shu LM, Zhang CY, Su ZY, Kong ANT. Curcumin inhibits anchorage-independent growth of HT29 human colon cancer cells by targeting epigenetic restoration of the tumor suppressor gene DLEC1. Biochem Pharmacol. 2015;94(2):69–78. doi: 10.1016/j.bcp.2015.01.009. PubMed PMID: WOS:000351479500003. [PubMed: 25640947]

26. Liu L, Wylie RC, Andrews LG, Tollefsbol TO. Aging, cancer and nutrition: the DNA methylation connection. Mech Ageing Dev. 2003;124(10-12):989–98. Epub 2003/12/09. PubMed PMID: 14659588. [PubMed: 14659588]

27. Bennett-Baker PE, Wilkowski J, Burke DT. Age-associated activation of epigenetically repressed genes in the mouse. Genetics. 2003;165(4):2055–62. Epub 2004/01/06. PubMed PMID: 14704185; PMCID: PMC1462878. [PubMed: 14704185]

28. Yang ZH, Dang YQ, Ji G. Role of epigenetics in transformation of inflammation into colorectal cancer. World J Gastroenterol. 2019;25(23):2863–77. Epub 2019/06/30. doi: 10.3748/wjg.v25.i23.2863. PubMed PMID: 31249445; PMCID: PMC6589733. [PubMed: 31249445]

29. Harada S, Morlote D. Molecular Pathology of Colorectal Cancer. Adv Anat Pathol. 2019. Epub 2019/09/11. doi: 10.1097/PAP.0000000000000247. PubMed PMID: 31503031.

30. Zeng Q, Lei F, Chang Y, Gao Z, Wang Y, Gao Q, Niu P, Li Q. An oncogenic gene, SNRPA1, regulates PIK3R1, VEGFC, MKI67, CDK1 and other genes in colorectal cancer. Biomed Pharmacother. 2019;117:109076. Epub 2019/06/17. doi: 10.1016/j.biopha.2019.109076. PubMed PMID: 31203132. [PubMed: 31203132]

31. Carmona FJ, Esteller M. Moving closer to a prognostic DNA methylation signature in colon cancer. Clin Cancer Res. 2011;17(6):1215–7. Epub 2011/03/18. doi: 10.1158/1078-0432.CCR-10-3446. PubMed PMID: 21411436. [PubMed: 21411436]

32. Migheli F, Migliore L. Epigenetics of colorectal cancer. Clin Genet. 2012;81(4):312–8. Epub 2012/01/24. doi: 10.1111/j.1399-0004.2011.01829.x. PubMed PMID: 22263639. [PubMed: 22263639]

33. Lind GE, Danielsen SA, Ahlquist T, Merok MA, Andresen K, Skotheim RI, Hektoen M, Rognum TO, Meling GI, Hoff G, Bretthauer M, Thiis-Evensen E, Nesbakken A, Lothe RA. Identification of an epigenetic biomarker panel with high sensitivity and specificity for colorectal cancer and adenomas. Mol Cancer. 2011;10:85. Epub 2011/07/23. doi: 10.1186/1476-4598-10-85. PubMed PMID: 21777459; PMCID: PMC3166273. [PubMed: 21777459]

34. Sarkar D, Leung EY, Baguley BC, Finlay GJ, Askarian-Amiri ME. Epigenetic regulation in human melanoma: past and future. Epigenetics. 2015;10(2):103–21. Epub 2015/01/15. doi: 10.1080/15592294.2014.1003746. PubMed PMID: 25587943; PMCID: PMC4622872. [PubMed: 25587943]

35. Youn A, Kim KI, Rabadan R, Tycko B, Shen Y, Wang S. A pan-cancer analysis of driver gene mutations, DNA methylation and gene expressions reveals that chromatin remodeling is a major mechanism inducing global changes in cancer epigenomes. BMC Med Genomics. 2018;11(1):98. Epub 2018/11/08. doi: 10.1186/s12920-018-0425-z. PubMed PMID: 30400878; PMCID: PMC6218985. [PubMed: 30400878]

36. Takahashi T, Shivapurkar N, Riquelme E, Shigematsu H, Reddy J, Suzuki M, Miyajima K, Zhou X, Bekele BN, Gazdar AF, Wistuba, II. Aberrant promoter hypermethylation of multiple genes in gallbladder carcinoma and chronic cholecystitis. Clin Cancer Res. 2004;10(18 Pt 1):6126–33. Epub 2004/09/28. doi: 10.1158/1078-0432.CCR-04-0579. PubMed PMID: 15447999. [PubMed: 15447999]

37. Xiong H, Chen ZF, Liang QC, Du W, Chen HM, Su WY, Chen GQ, Han ZG, Fang JY. Inhibition of DNA methyltransferase induces G2 cell cycle arrest and apoptosis in human colorectal cancer cells

via inhibition of JAK2/STAT3/STAT5 signalling. J Cell Mol Med. 2009;13(9B):3668–79. Epub 2010/03/04. doi: 10.1111/j.1582-4934.2009.00661.x. PubMed PMID: 20196786; PMCID: PMC4516515. [PubMed: 20196786]

38. Oh J, Hur MW, Lee CE. SOCS1 protects protein tyrosine phosphatases by thioredoxin upregulation and attenuates Jaks to suppress ROS-mediated apoptosis. Oncogene. 2009;28(35): 3145–56. Epub 2009/06/30. doi: 10.1038/onc.2009.169. PubMed PMID: 19561639. [PubMed: 19561639]
39. Xiong H, Du W, Zhang YJ, Hong J, Su WY, Tang JT, Wang YC, Lu R, Fang JY. Trichostatin A, a histone deacetylase inhibitor, suppresses JAK2/STAT3 signaling via inducing the promoter-associated histone acetylation of SOCS1 and SOCS3 in human colorectal cancer cells. Mol Carcinog. 2012;51(2):174–84. Epub 2011/04/27. doi: 10.1002/mc.20777. PubMed PMID: 21520296. [PubMed: 21520296]
40. Smit KN, Jager MJ, de Klein A, Kili E. Uveal melanoma: Towards a molecular understanding. Prog Retin Eye Res. 2019:100800. Epub 2019/09/30. doi: 10.1016/j.preteyeres.2019.100800. PubMed PMID: 31563544. [PubMed: 31563544]
41. Rode A, Maass KK, Willmund KV, Lichter P, Ernst A. Chromothripsis in cancer cells: An update. Int J Cancer. 2016;138(10):2322–33. Epub 2015/10/13. doi: 10.1002/ijc.29888. PubMed PMID: 26455580. [PubMed: 26455580]
42. Yang JJ, Park TS, Wan TS. Recurrent Cytogenetic Abnormalities in Acute Myeloid Leukemia. Methods Mol Biol. 2017;1541:223–45. Epub 2016/12/03. doi: 10.1007/978-1-4939-6703-2_19. PubMed PMID: 27910027. [PubMed: 27910027]
43. Levine MS, Holland AJ. The impact of mitotic errors on cell proliferation and tumorigenesis. Genes Dev. 2018;32(9-10):620–38. Epub 2018/05/29. doi: 10.1101/gad.314351.118. PubMed PMID: 29802124; PMCID: PMC6004076. [PubMed: 29802124]
44. Lopez-Serra P, Esteller M. DNA methylation-associated silencing of tumor-suppressor microRNAs in cancer. Oncogene. 2012;31(13):1609–22. Epub 2011/08/24. doi: 10.1038/onc.2011.354. PubMed PMID: 21860412; PMCID: PMC3325426. [PubMed: 21860412]
45. Michael MZ, OC SM, van Holst Pellekaan NG, Young GP, James RJ. Reduced accumulation of specific microRNAs in colorectal neoplasia. Mol Cancer Res. 2003;1(12):882–91. Epub 2003/10/24. PubMed PMID: 14573789. [PubMed: 14573789]
46. Zhang H, Zhu M, Shan X, Zhou X, Wang T, Zhang J, Tao J, Cheng W, Chen G, Li J, Liu P, Wang Q, Zhu W. A panel of seven-miRNA signature in plasma as potential biomarker for colorectal cancer diagnosis. Gene. 2019;687:246–54. Epub 2018/11/21. doi: 10.1016/j.gene.2018.11.055. PubMed PMID: 30458288. [PubMed: 30458288]
47. Koga Y, Yasunaga M, Takahashi A, Kuroda J, Moriya Y, Akasu T, Fujita S, Yamamoto S, Baba H, Matsumura Y. MicroRNA expression profiling of exfoliated colonocytes isolated from feces for colorectal cancer screening. Cancer Prev Res (Phila). 2010;3(11):1435–42. Epub 2010/10/21. doi: 10.1158/1940-6207.CAPR-10-0036. PubMed PMID: 20959518.
48. Agarwal A, Kasinathan A, Ganesan R, Balasubramanian A, Bhaskaran J, Suresh S, Srinivasan R, Aravind KB, Sivalingam N. Curcumin induces apoptosis and cell cycle arrest via the activation of reactive oxygen species-independent mitochondrial apoptotic pathway in Smad4 and p53 mutated colon adenocarcinoma HT29 cells. Nutrition research (New York, NY). 2018;51:67–81. Epub 2018/04/21. doi: 10.1016/j.nutres.2017.12.011. PubMed PMID: 29673545.
49. Du B, Jiang L, Xia Q, Zhong L. Synergistic inhibitory effects of curcumin and 5-fluorouracil on the growth of the human colon cancer cell line HT-29. Chemotherapy. 2006;52(1):23–8. [PubMed: 16340194]
50. Dou H, Shen R, Tao J, Huang L, Shi H, Chen H, Wang Y, Wang T. Curcumin Suppresses the Colon Cancer Proliferation by Inhibiting Wnt/beta-Catenin Pathways via miR-130a. Front Pharmacol. 2017;8:877. Epub 2017/12/12. doi: 10.3389/fphar.2017.00877. PubMed PMID: 29225578; PMCID: PMC5705620. [PubMed: 29225578]
51. Radhakrishnan VM, Kojs P, Young G, Ramalingam R, Jagadish B, Mash EA, Martinez JD, Ghishan FK, Kiela PR. pTyr421 cortactin is overexpressed in colon cancer and is dephosphorylated by curcumin: involvement of non-receptor type 1 protein tyrosine phosphatase (PTPN1). PLoS One. 2014;9(1):e85796. [PubMed: 24465712]

52. Marjaneh RM, Rahmani F, Hassanian SM, Rezaei N, Hashemzehi M, Bahrami A, Ariakia F, Fiuji H, Sahebkar A, Avan A. Phytosomal curcumin inhibits tumor growth in colitis-associated colorectal cancer. Journal of cellular physiology. 2018;233(10):6785–98. [PubMed: 29737515]
53. Watson JL, Hill R, Yaffe PB, Greenshields A, Walsh M, Lee PW, Giacomantonio CA, Hoskin DW. Curcumin causes superoxide anion production and p53-independent apoptosis in human colon cancer cells. Cancer letters. 2010;297(1):1–8. [PubMed: 20472336]
54. Lim T-G, Lee S-Y, Huang Z, Chen H, Jung SK, Bode AM, Lee KW, Dong Z. Curcumin suppresses proliferation of colon cancer cells by targeting CDK2. Cancer Prevention Research. 2014;7(4): 466–74. [PubMed: 24550143]
55. Sankpal UT, Nagaraju GP, Gottipolu SR, Hurtado M, Jordan CG, Simecka JW, Shoji M, El-Rayes B, Basha R. Combination of tolfenamic acid and curcumin induces colon cancer cell growth inhibition through modulating specific transcription factors and reactive oxygen species. Oncotarget. 2016;7(3):3186. [PubMed: 26672603]
56. Wang J, Zhang J, Zhang C-J, Wong YK, Lim TK, Hua Z-C, Liu B, Tannenbaum SR, Shen H-M, Lin Q. In situ proteomic profiling of curcumin targets in HCT116 colon cancer cell line. Scientific reports. 2016;6:22146. [PubMed: 26915414]
57. Shehzad A, Lee J, Huh TL, Lee YS. Curcumin induces apoptosis in human colorectal carcinoma (HCT-15) cells by regulating expression of Prp4 and p53. Molecules and cells. 2013;35(6):526–32. Epub 2013/05/21. doi: 10.1007/s10059-013-0038-5. PubMed PMID: 23686430; PMCID: Pmc3887881. [PubMed: 23686430]
58. Su C-C, Chen G-W, Lin J-G, WU L-T, CHUNG J-G. Curcumin inhibits cell migration of human colon cancer colo 205 cells through the inhibition of nuclear factor kappa B/p65 and down-regulates cyclooxygenase-2 and matrix metalloproteinase-2 expressions. Anticancer research. 2006;26(2A):1281–8. [PubMed: 16619535]
59. Su C-C, Lin J-G, Li T-M, Chung J-G, Yang J-S, Ip S-W, Lin W-C, Chen G-W. Curcumin-induced apoptosis of human colon cancer colo 205 cells through the production of ROS, Ca2+ and the activation of caspase-3. Anticancer research. 2006;26(6B):4379–89. [PubMed: 17201158]
60. Ld Guo, Xj Chen, Yh Hu, Zj Yu, Wang D Liu Jz. Curcumin inhibits proliferation and induces apoptosis of human colorectal cancer cells by activating the mitochondria apoptotic pathway. Phytotherapy Research. 2013;27(3):422–30. [PubMed: 22628241]
61. Liang HH, Huang CY, Chou CW, Makondi PT, Huang MT, Wei PL, Chang YJ. Heat shock protein 27 influences the anti-cancer effect of curcumin in colon cancer cells through ROS production and autophagy activation. Life sciences. 2018;209:43–51. Epub 2018/07/30. doi: 10.1016/j.lfs.2018.07.047. PubMed PMID: 30056019. [PubMed: 30056019]
62. Vallee A, Lecarpentier Y, Vallee JN. Curcumin: a therapeutic strategy in cancers by inhibiting the canonical WNT/beta-catenin pathway. Journal of experimental & clinical cancer research : CR. 2019;38(1):323. Epub 2019/07/25. doi: 10.1186/s13046-019-1320-y. PubMed PMID: 31331376. [PubMed: 31331376]
63. Agarwal A, Kasinathan A, Ganesan R, Balasubramanian A, Bhaskaran J, Suresh S, Srinivasan R, Aravind K, Sivalingam N. Curcumin induces apoptosis and cell cycle arrest via the activation of reactive oxygen species–independent mitochondrial apoptotic pathway in Smad4 and p53 mutated colon adenocarcinoma HT29 cells. Nutrition Research. 2018;51:67–81. [PubMed: 29673545]
64. Moragoda L, Jaszewski R, Majumdar A. Curcumin induced modulation of cell cycle and apoptosis in gastric and colon cancer cells. Anticancer research. 2001;21(2A):873–8. [PubMed: 11396178]
65. Chen H, Zhang Z, Zhang Y, Zhou D. Curcumin inhibits cell proliferation by interfering with the cell cycle and inducing apoptosis in colon carcinoma cells. Anticancer research. 1999;19(5A): 3675–80. [PubMed: 10625938]
66. Patel BB, Sengupta R, Qazi S, Vachhani H, Yu Y, Rishi AK, Majumdar AP. Curcumin enhances the effects of 5-fluorouracil and oxaliplatin in mediating growth inhibition of colon cancer cells by modulating EGFR and IGF-1R. International journal of cancer. 2008;122(2):267–73. [PubMed: 17918158]
67. Rashmi R, Santhosh Kumar TR, Karunagaran D. Human colon cancer cells differ in their sensitivity to curcumin-induced apoptosis and heat shock protects them by inhibiting the release of apoptosis-inducing factor and caspases. FEBS letters. 2003;538(1-3):19–24. Epub 2003/03/14. doi: 10.1016/s0014-5793(03)00099-1. PubMed PMID: 12633846. [PubMed: 12633846]

68. Juhasz A, Markel S, Gaur S, Liu H, Lu J, Jiang G, Wu X, Antony S, Wu Y, Melillo G, Meitzler JL, Haines DC, Butcher D, Roy K, Doroshow JH. NADPH oxidase 1 supports proliferation of colon cancer cells by modulating reactive oxygen species-dependent signal transduction. The Journal of biological chemistry. 2017;292(19):7866–87. Epub 2017/03/24. doi: 10.1074/jbc.M116.768283. PubMed PMID: 28330872; PMCID: Pmc5427267. [PubMed: 28330872]

69. Jayaprakasha G, Rao LJ, Sakariah K. Antioxidant activities of curcumin, demethoxycurcumin and bisdemethoxycurcumin. Food chemistry. 2006;98(4):720–4.

70. Ak T, Gülçin İ. Antioxidant and radical scavenging properties of curcumin. Chemico-biological interactions. 2008;174(1):27–37. [PubMed: 18547552]

71. Kunnumakkara AB, Bordoloi D, Padmavathi G, Monisha J, Roy NK, Prasad S, Aggarwal BB. Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases. Br J Pharmacol. 2017;174(11):1325–48. Epub 2016/10/23. doi: 10.1111/bph.13621. PubMed PMID: 27638428; PMCID: PMC5429333. [PubMed: 27638428]

72. Dong W, Yang B, Wang L, Li B, Guo X, Zhang M, Jiang Z, Fu J, Pi J, Guan D, Zhao R. Curcumin plays neuroprotective roles against traumatic brain injury partly via Nrf2 signaling. Toxicology and applied pharmacology. 2018;346:28–36. Epub 2018/03/25. doi: 10.1016/j.taap.2018.03.020. PubMed PMID: 29571711. [PubMed: 29571711]

73. Yan C, Zhang Y, Zhang X, Aa J, Wang G, Xie Y. Curcumin regulates endogenous and exogenous metabolism via Nrf2-FXR-LXR pathway in NAFLD mice. Biomed Pharmacother. 2018;105:274–81. Epub 2018/06/04. doi: 10.1016/j.biopha.2018.05.135. PubMed PMID: 29860219. [PubMed: 29860219]

74. Hassan FU, Rehman MS, Khan MS, Ali MA, Javed A, Nawaz A, Yang C. Curcumin as an Alternative Epigenetic Modulator: Mechanism of Action and Potential Effects. Front Genet. 2019;10:514. Epub 2019/06/20. doi: 10.3389/fgene.2019.00514. PubMed PMID: 31214247; PMCID: PMC6557992. [PubMed: 31214247]

75. Shen G, Xu C, Hu R, Jain MR, Gopalkrishnan A, Nair S, Huang MT, Chan JY, Kong AN. Modulation of nuclear factor E2-related factor 2-mediated gene expression in mice liver and small intestine by cancer chemopreventive agent curcumin. Molecular cancer therapeutics. 2006;5(1):39–51. doi: 10.1158/1535-7163.MCT-05-0293. PubMed PMID: 16432161. [PubMed: 16432161]

76. Zhang J, Feng Z, Wang C, Zhou H, Liu W, Kanchana K, Dai X, Zou P, Gu J, Cai L, Liang G. Curcumin derivative WZ35 efficiently suppresses colon cancer progression through inducing ROS production and ER stress-dependent apoptosis. American journal of cancer research. 2017;7(2):275–88. Epub 2017/03/25. PubMed PMID: 28337376; PMCID: Pmc5336501. [PubMed: 28337376]

77. Zhang T, Zheng P, Shen X, Shao R, Wang B, Shen H, Zhang J, Xia Y, Zou P. Curcuminoid WZ26, a TrxR1 inhibitor, effectively inhibits colon cancer cell growth and enhances cisplatin-induced cell death through the induction of ROS. Free radical biology & medicine. 2019;141:93–102. Epub 2019/06/10. doi: 10.1016/j.freeradbiomed.2019.06.005. PubMed PMID: 31176737. [PubMed: 31176737]

78. He G, Feng C, Vinothkumar R, Chen W, Dai X, Chen X, Ye Q, Qiu C, Zhou H, Wang Y, Liang G, Xie Y, Wu W. Curcumin analog EF24 induces apoptosis via ROS-dependent mitochondrial dysfunction in human colorectal cancer cells. Cancer chemotherapy and pharmacology. 2016;78(6):1151–61. Epub 2016/10/28. doi: 10.1007/s00280-016-3172-x. PubMed PMID: 27787644. [PubMed: 27787644]

79. Ramirez CN, Li W, Zhang C, Wu R, Su S, Wang C, Gao L, Yin R, Kong A-NT. In Vitro-In Vivo Dose Response of Ursolic Acid, Sulforaphane, PEITC, and Curcumin in Cancer Prevention. The AAPS journal. 2017;20(1):19. doi: 10.1208/s12248-017-0177-2. [PubMed: 29264822]

80. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research. Alternative medicine review. 2009;14(2).

81. Menon VP, Sudheer AR. Antioxidant and anti-inflammatory properties of curcumin. The molecular targets and therapeutic uses of curcumin in health and disease: Springer; 2007 p. 105–25.

82. Shehzad A, Rehman G, Lee YS. Curcumin in inflammatory diseases. Biofactors. 2013;39(1):69–77. [PubMed: 23281076]

83. Lin C-L, Lin J-K. Curcumin: a potential cancer chemopreventive agent through suppressing NF-κB signaling. J Cancer Molecules. 2008;4:11–6.

84. Katta S, Srivastava A, Thangapazham RL, Rosner IL, Cullen J, Li H, Sharad S. Curcumin-Gene Expression Response in Hormone Dependent and Independent Metastatic Prostate Cancer Cells. Int J Mol Sci. 2019;20(19). Epub 2019/10/05. doi: 10.3390/ijms20194891. PubMed PMID: 31581661.
85. Ghasemi F, Shafiee M, Banikazemi Z, Pourhanifeh MH, Khanbabaei H, Shamshirian A, Amiri Moghadam S, ArefNezhad R, Sahebkar A, Avan A, Mirzaei H. Curcumin inhibits NF-kB and Wnt/beta-catenin pathways in cervical cancer cells. Pathol Res Pract. 2019;215(10):152556. Epub 2019/07/31. doi: 10.1016/j.prp.2019.152556. PubMed PMID: 31358480. [PubMed: 31358480]
86. Boyanapalli SS, Paredes-Gonzalez X, Fuentes F, Zhang C, Guo Y, Pung D, Saw CL, Kong AN. Nrf2 knockout attenuates the anti-inflammatory effects of phenethyl isothiocyanate and curcumin. Chemical research in toxicology. 2014;27(12):2036–43. doi: 10.1021/tx500234h. PubMed PMID: 25387343; PMCID: 4269407. [PubMed: 25387343]
87. Guo Y, Shu L, Zhang C, Su ZY, Kong AN. Curcumin inhibits anchorage-independent growth of HT29 human colon cancer cells by targeting epigenetic restoration of the tumor suppressor gene DLEC1. Biochem Pharmacol. 2015;94(2):69–78. doi: 10.1016/j.bcp.2015.01.009. PubMed PMID: 25640947. [PubMed: 25640947]
88. Ying J, Poon FF, Yu J, Geng H, Wong AHY, Qiu GH, Goh HK, Rha SY, Tian L, Chan ATC, Sung JJY, Tao Q. DLEC1 is a functional 3p22.3 tumour suppressor silenced by promoter CpG methylation in colon and gastric cancers. Br J Cancer. 2009;100:663. doi: 10.1038/sj.bjc.6604888. [PubMed: 19156137]
89. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology. 2010;138(6): 2073–87. e3. [PubMed: 20420947]
90. Westwood A, Glover A, Hutchins G, Young C, Brockmoeller S, Robinson R, Worrilow L, Wallace D, Rankeillor K, Adlard J, Quirke P, West N. Additional loss of MSH2 and MSH6 expression in sporadic deficient mismatch repair colorectal cancer due to MLH1 promoter hypermethylation. Journal of Clinical Pathology. 2019;72(6):443. doi: 10.1136/jclinpath-2018-205687. [PubMed: 30723092]
91. Jiang Z, Jin S, Yalowich JC, Brown KD, Rajasekaran B. The mismatch repair system modulates curcumin sensitivity through induction of DNA strand breaks and activation of G2-M checkpoint. Molecular cancer therapeutics. 2010;9(3):558–68. [PubMed: 20145018]
92. Li B, Shi C, Li B, Zhao JM, Wang L. The effects of Curcumin on HCT-116 cells proliferation and apoptosis via the miR-491/PEG10 pathway. J Cell Biochem. 2018;119(4):3091–8. Epub 2017/10/24. doi: 10.1002/jcb.26449. PubMed PMID: 29058812. [PubMed: 29058812]
93. Mudduluru G, George-William JN, Muppala S, Asangani IA, Kumarswamy R, Nelson LD, Allgayer H. Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. Biosci Rep. 2011;31(3):185–97. Epub 2010/09/08. doi: 10.1042/BSR20100065. PubMed PMID: 20815812. [PubMed: 20815812]
94. Roy S, Levi E, Majumdar AP, Sarkar FH. Expression of miR-34 is lost in colon cancer which can be re-expressed by a novel agent CDF 2012;5(1):58. doi: 10.1186/1756-8722-5-58.
95. Wu WK, Wang XJ, Cheng AS, Luo MX, Ng SS, To KF, Chan FK, Cho CH, Sung JJ, Yu J. Dysregulation and crosstalk of cellular signaling pathways in colon carcinogenesis. Critical reviews in oncology/hematology. 2013;86(3):251–77. [PubMed: 23287077]
96. Zhang Y, Li B, Ji ZZ, Zheng PS. Notch1 regulates the growth of human colon cancers. Cancer. 2010;116(22):5207–18. [PubMed: 20665495]
97. Becker KF, Rosivatz E, Blechschmidt K, Kremmer E, Sarbia M, Hofler H. Analysis of the E-cadherin repressor Snail in primary human cancers. Cells Tissues Organs. 2007;185(1-3):204–12. Epub 2007/06/26. doi: 10.1159/000101321. PubMed PMID: 17587826. [PubMed: 17587826]
98. Fender AW, Nutter JM, Fitzgerald TL, Bertrand FE, Sigounas G. Notch-1 promotes stemness and epithelial to mesenchymal transition in colorectal cancer. J Cell Biochem. 2015;116(11):2517–27. Epub 2015/04/29. doi: 10.1002/jcb.25196. PubMed PMID: 25914224. [PubMed: 25914224]
99. Roy S, Yu Y, Padhye SB, Sarkar FH, Majumdar APN. Difluorinated-Curcumin (CDF) Restores PTEN Expression in Colon Cancer Cells by Down-Regulating miR-21. PLOS ONE. 2013;8(7):e68543. doi: 10.1371/journal.pone.0068543. [PubMed: 23894315]

100. Gandhy SU, Kim K, Larsen L, Rosengren RJ, Safe S. Curcumin and synthetic analogs induce reactive oxygen species and decreases specificity protein (Sp) transcription factors by targeting microRNAs. BMC Cancer. 2012;12:564. Epub 2012/12/01. doi: 10.1186/1471-2407-12-564. PubMed PMID: 23194063; PMCID: PMC3522018. [PubMed: 23194063]

101. Murphy EA, Davis JM, McClellan JL, Gordon BT, Carmichael MD. Curcumin's effect on intestinal inflammation and tumorigenesis in the ApcMin/+ mouse. J Interferon Cytokine Res. 2011;31(2):219–26. Epub 2010/10/19. doi: 10.1089/jir.2010.0051. PubMed PMID: 20950131; PMCID: PMC3064532. [PubMed: 20950131]

102. Kubota M, Shimizu M, Sakai H, Yasuda Y, Terakura D, Baba A, Ohno T, Tsurumi H, Tanaka T, Moriwaki H. Preventive effects of curcumin on the development of azoxymethane-induced colonic preneoplastic lesions in male C57BL/KsJ-db/db obese mice. Nutr Cancer. 2012;64(1): 72–9. Epub 2011/12/17. doi: 10.1080/01635581.2012.630554. PubMed PMID: 22172229. [PubMed: 22172229]

103. De Robertis M, Massi E, Poeta ML, Carotti S, Morini S, Cecchetelli L, Signori E, Fazio VM. The AOM/DSS murine model for the study of colon carcinogenesis: From pathways to diagnosis and therapy studies. J Carcinog. 2011;10:9. Epub 2011/04/13. doi: 10.4103/1477-3163.78279. PubMed PMID: 21483655; PMCID: PMC3072657. [PubMed: 21483655]

104. Guo Y, Su ZY, Zhang C, Gaspar JM, Wang R, Hart RP, Verzi MP, Kong AN. Mechanisms of colitis-accelerated colon carcinogenesis and its prevention with the combination of aspirin and curcumin: Transcriptomic analysis using RNA-seq. Biochem Pharmacol. 2017;135:22–34. Epub 2017/03/08. doi: 10.1016/j.bcp.2017.02.021. PubMed PMID: 28267439; PMCID: PMC5541256. [PubMed: 28267439]

105. Huang MT, Lou YR, Ma W, Newmark HL, Reuhl KR, Conney AH. Inhibitory effects of dietary curcumin on forestomach, duodenal, and colon carcinogenesis in mice. Cancer research. 1994;54(22):5841–7. Epub 1994/11/15. PubMed PMID: 7954412. [PubMed: 7954412]

106. Lai CS, Wu JC, Yu SF, Badmaev V, Nagabhushanam K, Ho CT, Pan MH. Tetrahydrocurcumin is more effective than curcumin in preventing azoxymethane-induced colon carcinogenesis. Mol Nutr Food Res. 2011;55(12):1819–28. Epub 2011/09/03. doi: 10.1002/mnfr.201100290. PubMed PMID: 21887819. [PubMed: 21887819]

107. Marjaneh RM, Rahmani F, Hassanian SM, Rezaei N, Hashemzehi M, Bahrami A, Ariakia F, Fiuji H, Sahebkar A, Avan A, Khazaei M. Phytosomal curcumin inhibits tumor growth in colitis-associated colorectal cancer. J Cell Physiol. 2018;233(10):6785–98. Epub 2018/05/09. doi: 10.1002/jcp.26538. PubMed PMID: 29737515. [PubMed: 29737515]

108. Villegas I, Sanchez-Fidalgo S, de la Lastra CA. Chemopreventive effect of dietary curcumin on inflammation-induced colorectal carcinogenesis in mice. Mol Nutr Food Res. 2011;55(2):259–67. Epub 2010/09/18. doi: 10.1002/mnfr.201000225. PubMed PMID: 20848615. [PubMed: 20848615]

109. Girardi B, Principi M, Pricci M, Giorgio F, Iannone A, Losurdo G, Ierardi E, Di Leo A, Barone M. Chemoprevention of inflammation-related colorectal cancer by silymarin-, acetyl-11-keto-beta-boswellic acid-, curcumin- and maltodextrin-enriched dietetic formulation in animal model. Carcinogenesis. 2018;39(10):1274–82. Epub 2018/08/08. doi: 10.1093/carcin/bgy104. PubMed PMID: 30084990. [PubMed: 30084990]

110. Murakami A, Furukawa I, Miyamoto S, Tanaka T, Ohigashi H. Curcumin combined with turmerones, essential oil components of turmeric, abolishes inflammation-associated mouse colon carcinogenesis. Biofactors. 2013;39(2):221–32. Epub 2012/12/13. doi: 10.1002/biof.1054. PubMed PMID: 23233214. [PubMed: 23233214]

111. Toden S, Theiss AL, Wang X, Goel A. Essential turmeric oils enhance anti-inflammatory efficacy of curcumin in dextran sulfate sodium-induced colitis. Sci Rep. 2017;7(1):814. Epub 2017/04/13. doi: 10.1038/s41598-017-00812-6. PubMed PMID: 28400554; PMCID: PMC5429743. [PubMed: 28400554]

112. McFadden RM, Larmonier CB, Shehab KW, Midura-Kiela M, Ramalingam R, Harrison CA, Besselsen DG, Chase JH, Caporaso JG, Jobin C, Ghishan FK, Kiela PR. The Role of Curcumin in Modulating Colonic Microbiota During Colitis and Colon Cancer Prevention. Inflamm Bowel Dis. 2015;21(11):2483–94. Epub 2015/07/29. doi: 10.1097/MIB.0000000000000522. PubMed PMID: 26218141; PMCID: PMC4615313. [PubMed: 26218141]

113. Loeber C De curcuma officinarum. diss Inaug Halae. 1748.

114. Oppenheimer A TURMERIC (CURCUMIN) IN BILIARY DISEASES. The Lancet. 1937;229(5924):619–21. doi: 10.1016/S0140-6736(00)98193-5.

115. Hewlings SJ, Kalman DS. Curcumin: A Review of Its' Effects on Human Health. Foods. 2017;6(10):92. doi: 10.3390/foods6100092. PubMed PMID: 29065496.

116. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J. 2013;15(1):195–218. Epub 11/10. doi: 10.1208/s12248-012-9432-8. PubMed PMID: 23143785. [PubMed: 23143785]

117. Cheng D, Li W, Wang L, Lin T, Poiani G, Wassef A, Hudlikar R, Ondar P, Brunetti L, Kong AN. Pharmacokinetics, Pharmacodynamics, and PKPD Modeling of Curcumin in Regulating Antioxidant and Epigenetic Gene Expression in Healthy Human Volunteers. Mol Pharm. 2019;16(5):1881–9. Epub 2019/03/13. doi: 10.1021/acs.molpharmaceut.8b01246. PubMed PMID: 30860383; PMCID: PMC6710832. [PubMed: 30860383]

118. Vareed SK, Kakarala M, Ruffin MT, Crowell JA, Normolle DP, Djuric Z, Brenner DE. Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. Cancer Epidemiol Biomarkers Prev. 2008;17(6):1411–7. Epub 2008/06/19. doi: 10.1158/1055-9965.epi-07-2693. PubMed PMID: 18559556; PMCID: PMC4138955. [PubMed: 18559556]

119. Gibbons RJ. Histone modifying and chromatin remodelling enzymes in cancer and dysplastic syndromes. Hum Mol Genet. 2005;14 Spec No 1:R85–92. Epub 2005/04/06. doi: 10.1093/hmg/ddi106. PubMed PMID: 15809277. [PubMed: 15809277]

120. Bora-Tatar G, Dayangac-Erden D, Demir AS, Dalkara S, Yelekci K, Erdem-Yurter H. Molecular modifications on carboxylic acid derivatives as potent histone deacetylase inhibitors: Activity and docking studies. Bioorg Med Chem. 2009;17(14):5219–28. Epub 2009/06/13. doi: 10.1016/j.bmc.2009.05.042. PubMed PMID: 19520580. [PubMed: 19520580]

121. Liu HL, Chen Y, Cui GH, Zhou JF. Curcumin, a potent anti-tumor reagent, is a novel histone deacetylase inhibitor regulating B-NHL cell line Raji proliferation. Acta Pharmacol Sin. 2005;26(5):603–9. Epub 2005/04/22. doi: 10.1111/j.1745-7254.2005.00081.x. PubMed PMID: 15842781. [PubMed: 15842781]

122. Chen Y, Shu W, Chen W, Wu Q, Liu H, Cui G. Curcumin, both histone deacetylase and p300/CBP-specific inhibitor, represses the activity of nuclear factor kappa B and Notch 1 in Raji cells. Basic Clin Pharmacol Toxicol. 2007;101(6):427–33. Epub 2007/10/12. doi: 10.1111/j.1742-7843.2007.00142.x. PubMed PMID: 17927689. [PubMed: 17927689]

123. Lahiff C, Moss AC. Curcumin for clinical and endoscopic remission in ulcerative colitis. Inflamm Bowel Dis. 2011;17(7):E66. Epub 2011/04/13. doi: 10.1002/ibd.21710. PubMed PMID: 21484966. [PubMed: 21484966]

124. Hanai H, Iida T, Takeuchi K, Watanabe F, Maruyama Y, Andoh A, Tsujikawa T, Fujiyama Y, Mitsuyama K, Sata M, Yamada M, Iwaoka Y, Kanke K, Hiraishi H, Hirayama K, Arai H, Yoshii S, Uchijima M, Nagata T, Koide Y. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. Clin Gastroenterol Hepatol. 2006;4(12):1502–6. Epub 2006/11/15. doi: 10.1016/j.cgh.2006.08.008. PubMed PMID: 17101300. [PubMed: 17101300]

125. Holt PR, Katz S, Kirshoff R. Curcumin therapy in inflammatory bowel disease: a pilot study. Dig Dis Sci. 2005;50(11):2191–3. Epub 2005/10/22. doi: 10.1007/s10620-005-3032-8. PubMed PMID: 16240238. [PubMed: 16240238]

126. Chandran B, Goel A. A randomized, pilot study to assess the efficacy and safety of curcumin in patients with active rheumatoid arthritis. Phytother Res. 2012;26(11):1719–25. Epub 2012/03/13. doi: 10.1002/ptr.4639. PubMed PMID: 22407780. [PubMed: 22407780]

127. Sharma RA, McLelland HR, Hill KA, Ireson CR, Euden SA, Manson MM, Pirmohamed M, Marnett LJ, Gescher AJ, Steward WP. Pharmacodynamic and pharmacokinetic study of oral Curcuma extract in patients with colorectal cancer. Clin Cancer Res. 2001;7(7):1894–900. Epub 2001/07/13. PubMed PMID: 11448902. [PubMed: 11448902]

128. Sharma RA, Euden SA, Platton SL, Cooke DN, Shafayat A, Hewitt HR, Marczylo TH, Morgan B, Hemingway D, Plummer SM, Pirmohamed M, Gescher AJ, Steward WP. Phase I clinical trial of oral curcumin: biomarkers of systemic activity and compliance. Clin Cancer Res. 2004;10(20):

6847–54. Epub 2004/10/27. doi: 10.1158/1078-0432.ccr-04-0744. PubMed PMID: 15501961. [PubMed: 15501961]

129. Garcea G, Berry DP, Jones DJ, Singh R, Dennison AR, Farmer PB, Sharma RA, Steward WP, Gescher AJ. Consumption of the putative chemopreventive agent curcumin by cancer patients: assessment of curcumin levels in the colorectum and their pharmacodynamic consequences. Cancer Epidemiol Biomarkers Prev. 2005;14(1):120–5. Epub 2005/01/26. PubMed PMID: 15668484. [PubMed: 15668484]
130. Cruz-Correa M, Shoskes DA, Sanchez P, Zhao R, Hylind LM, Wexner SD, Giardiello FM. Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. Clin Gastroenterol Hepatol. 2006;4(8):1035–8. Epub 2006/06/08. doi: 10.1016/j.cgh.2006.03.020. PubMed PMID: 16757216. [PubMed: 16757216]
131. Carroll RE, Benya RV, Turgeon DK, Vareed S, Neuman M, Rodriguez L, Kakarala M, Carpenter PM, McLaren C, Meyskens FL, Jr., Brenner DE. Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. Cancer Prev Res (Phila). 2011;4(3):354–64. Epub 2011/03/05. doi: 10.1158/1940-6207.capr-10-0098. PubMed PMID: 21372035; PMCID: PMC4136551. [PubMed: 21372035]
132. He ZY, Shi CB, Wen H, Li FL, Wang BL, Wang J. Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin. Cancer Invest. 2011;29(3):208–13. Epub 2011/02/15. doi: 10.3109/07357907.2010.550592. PubMed PMID: 21314329. [PubMed: 21314329]
133. Epstein J, Docena G, MacDonald TT, Sanderson IR. Curcumin suppresses p38 mitogen-activated protein kinase activation, reduces IL-1beta and matrix metalloproteinase-3 and enhances IL-10 in the mucosa of children and adults with inflammatory bowel disease. Br J Nutr. 2010;103(6):824–32. Epub 2009/11/03. doi: 10.1017/s0007114509992510. PubMed PMID: 19878610. [PubMed: 19878610]
134. Bundy R, Walker AF, Middleton RW, Booth J. Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: a pilot study. J Altern Complement Med. 2004;10(6):1015–8. Epub 2005/01/28. doi: 10.1089/acm.2004.10.1015. PubMed PMID: 15673996. [PubMed: 15673996]
135. N H AM M K N, A B DM, J R MY, A M ZT, HS C DRL, KA C EJF. SEER Cancer Statistics Review, 1975-2016 Bethesda, MD: National Cancer Institute; 2019 [cited 2019].

Table 1.

Pharmacological effects of curcumin in clinical studies.

Diseases	Dosage; duration	Outcome (reference)	Molecular targets
Healthy volunteer	4 g/person; 1 single dose	Upregulated Nrf2/ARE genes; Downregulated HDACs (117)	NRF2 ↑, HO1 ↑, NQO1 ↑, HDAC 1, 2 & 3↓
	0.036–0.18 g/day; 4 mo	Reduced glutathione S-transferase activity (127)	GST ↓(127)
	0.45–3.6 g/day; 4 mo	Reduced PGE2 production (128)	PGE2 ↓ (128)
	0.45–3.6 g/day; 7 d	Reduced the levels of M1G (129)	M1G ↓ (129)
Colorectal cancer	1.44 g/day; 6 mo	Reduced the number and size of polyps without any appreciable toxicity (130)	
	2 or 4 g/day; 1 mo	Reduced ACF formation in smokers (131)	
	1.08 g/day; 10–30 d	Improved body weight, reduced serum TNF-α, and induced p53 expression (132)	TNF-α↓, Bcl-2 ↓ p53 ↑, Bax ↑(132)
Crohn's disease	1.08 g/day, 1 mo 1.44 g/day, 2 mo	Significant reductions in CDAI and inflammatory indices in patients (125)	
Ulcerative proctitis	1.1 g/day; 1 mo 1.65 g/day; 1 mo	Significant reduction in symptoms as well as inflammatory indices in patients (125)	
Ulcerative colitis	2 g/day; 6 mo	Prevented relapse of disease (124)	
	0.5 g/day; 2-10 mo	Associated with clinical and endoscopic remission of the disease (123)	
Inflammatory bowel disease	5-20 μM; 0.5-24 h	Suppressed p38 MAPK activation, reduced IL-1β, and enhanced IL-10 levels in mucosal biopsies; suppressed MMP-3 in colonic myofibroblasts (133)	CRP ↓, ESR ↓, CDAI ↓ (125) p38 MAPK ↓, IL-1β↓, MMP-3↓, IL-10↑(133)
Irritable bowel syndrome	0.072 or 0.144 g STE/d; 8 wk	Produced significant reduction in the prevalence of symptoms (134)	
	0.5 g in food	Increased bowel motility and activated hydrogen producing bacterial flora in the colon (126)	

↓, Downregulation; ↑, upregulation; mo, month; d, day; wk. week; h, hour.