

Curcumin and colon cancer: from preclinical to clinical studies

Chong Li*

Department of Queen Mary, Nanchang University, Nanchang, China

*Corresponding author: jp4217120062@qmul.ac.uk

Abstract. In the US, colon cancer has the third most mortality. Though new managements have reported upgraded prognosis, the five-year survival rates of patients with general or metastatic colon cancer are still unsatisfied at 64.7% and 20%, respectively. As a result, more innovative therapies or drugs with high efficacy should be developed. Curcumin, a natural chemical compound, is now in the spotlight of both preclinical and clinical trials on colon cancer. It not only exerts exceptional anti-cancer effects, but also anti-inflammatory and antiviral bio-activities. However, curcumin shows low bioavailability when orally administered. To resolve this issue, nanoparticles have been widely utilized. In this review, we precisely summarize the effects of curcumin on colon cancer in both preclinical and clinical studies. In vitro studies, curcumin could arrest cell cycle at the G2/M phase as well as part of the G1 phase, and induce cell apoptosis by binding to targeted molecules. Except for this, epigenetic alterations could also induce colon cancer. Both in vitro and in vivo studies have proved that curcumin could remarkably influence the prognosis. Moreover, genetically designed murine models which were orally administered with curcumin demonstrated satisfactory effects on colon cancer induced by different factors. More importantly, curcumin alone or as an adjuvant showed satisfactory results in numerous clinical trials. In conclusion, curcumin demonstrated outstanding anti-cancer activity against colon cancer.

Keywords: colon cancer; curcumin; cell apoptosis; in vitro studies; in vivo studies.

1. Introduction

Colon cancer with extreme high mortality at advanced stage, has now become the third most prevalent cancer that affects both males and females in the US [1]. The mucosal of the colon, which is the deepest portion of the walls of the large intestine, is where colon cancer initially appeared. However, once this interior lining of cells mutates, polyps are created, and with time they may develop into malignant tumors [2]. Fortunately, cancerous tumors that have not yet developed can be surgically removed, however, with regard for both the stages of the cancer and the conditions of the patients, more complicated therapies should be used as the polyps grow larger. Furthermore, numerous follow-up studies have revealed that high-dosed and extended chemo-or immunotherapies not only target uncontrolled cancer cells, but also normal mucous cells in the mouth and gastrointestinal system, as well as hair follicles and bone marrows [2]. As a result, it's in urgent need to develop therapies with high effectiveness and low toxicity, in particularly without influencing the patients' quality of life [3].

In recent studies, orally administered curcumin, a kind of natural chemical compound extracted from turmeric, has been proved with remarkable effects on patients with colon cancer. Curcumin has already been utilized into many solid tumors as well as hematological malignancies. It has a promising future in colon cancer managements by stimulating cell apoptosis via mediating apoptosis-related molecular pathways [4]. This study outlines studies that examined the efficacy of curcumin's impacts on colon cancer in both in vitro and in vivo trials.

2. Bioavailability of Curcumin

In 1913, the structure of curcumin was first clarified (Figure 1), indicating its low solubility in water. Due to this hydrophobic feature, curcumin combined with serum albumin will be accurately transported to targeted cells, where curcumin could be accumulated in their membrane structures [5].

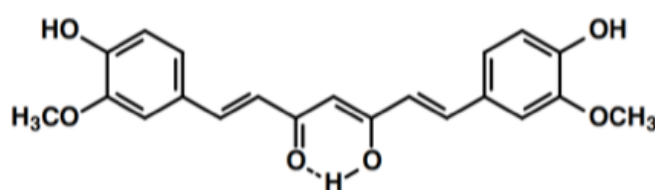


Fig. 1 Chemical structure of curcumin

Meanwhile, curcumin shows deficient absorption rates and will be promptly metabolized and eliminated both in plasma and gastrointestinal system [6]. In humans, orally administered curcumin at 8 g per day would be rapidly transformed into metabolism with extreme deficient plastic curcumin less than 2.5 ng/ml [7]. Despite the rapid internal metabolism of curcumin, nanotechnology using nanoparticles could be manually designed to resolve other limitations, such as hydrophobicity, instability and low bioavailability [6,8]. According to reliable results, this tailored therapy, utilizing nanoparticles to wrap curcumin has gained a promising future in cancer treatment, representing improved pharmacokinetics and pharmacodynamics, enhanced efficacy and less adverse, and precisely targeting at cancerous cells [8]. For instance, in a study by Li et al., PLGA-lecithin-PEG nanoparticles encapsulate curcumin could directly inhibit the HT-29 colon cancer cells with high bioavailability compared with oral administration [9].

3. Biological Activities of Curcumin

Numerous studies both in vitro or in vivo (including murine models and human clinical trials) have demonstrated curcumin's beneficial effects and therapeutic utilizations in various clinical trials [5]. Curcumin exhibits a wide range of biological properties, including impacts that target particular molecules to fight viruses, inflammation, and cancer (Figure 2) [7,10].

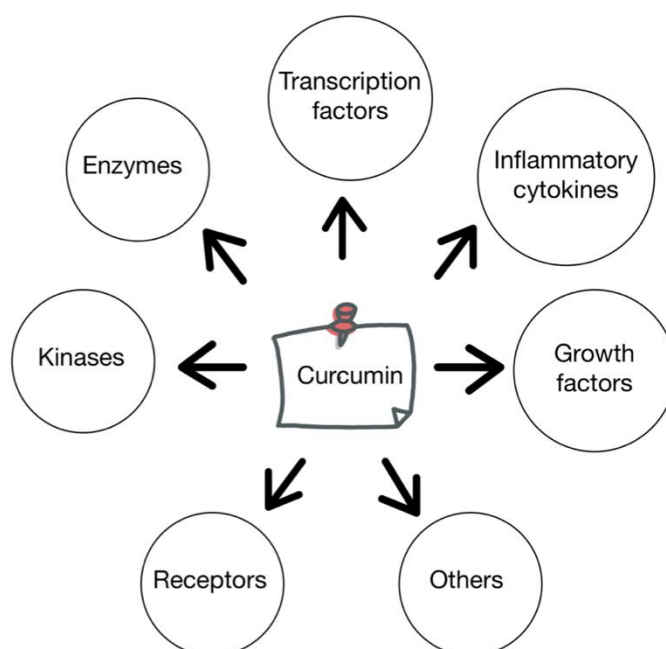


Fig. 2 Curcumin's negative regulations

3.1. Antioxidant and anti-inflammatory activities

Both oxidations and inflammations in our bodies contribute to various chronic diseases and dysfunctional metabolism, including cardiovascular diseases, obesity, type II diabetes. According to the results of a recent meta-analysis, which included sixty-six randomized controlled trials, that

curcumin and its analogues also showed the potential of enhancing the antioxidant and anti-inflammatory capabilities of humans via mediating particular oxidative and inflammatory markers. These chemical compounds could significantly decrease the levels of some inflammatory marker, such as C-reactive proteins (CRPs), tumor necrosis factor α (TNF- α), and interleukin-6 (IL-6). Meanwhile, curcumin also increased level of total antioxidant capacity (TAC) and alleviated levels of malondialdehyde (MDA) and superoxide dismutase (SOD), contributing to relieving oxidation stress. A recent meta-analysis that included sixty-six randomized controlled studies revealed that curcumin and its analogues also demonstrated the ability to improve human antioxidant and anti-inflammatory bio-activities by mediating specific oxidative and inflammatory markers. Some inflammation markers, such as C-reactive proteins (CRPs), tumor necrosis factor α (TNF- α), and interleukin-6 (IL-6), may be markedly reduced by these chemical substances. Curcumin also reduced amounts of malondialdehyde (MDA), superoxide dismutase (SOD), and total antioxidant capacity (TAC), which all helped to relieve oxidative stress [11].

3.2. Anticancer activity

Curcumin alone or combined with other substances to design efficient anticancer therapies is one of the most significant features in clinical trials [7]. Treatments with curcumin to different cancers (e.g., solid tumors and hematological malignancies) exhibited higher efficacy, less violent effects and cost-friendly benefit. These effects were achieved by negatively interacting with several extra- and intra-cellular molecules (Figure 3).

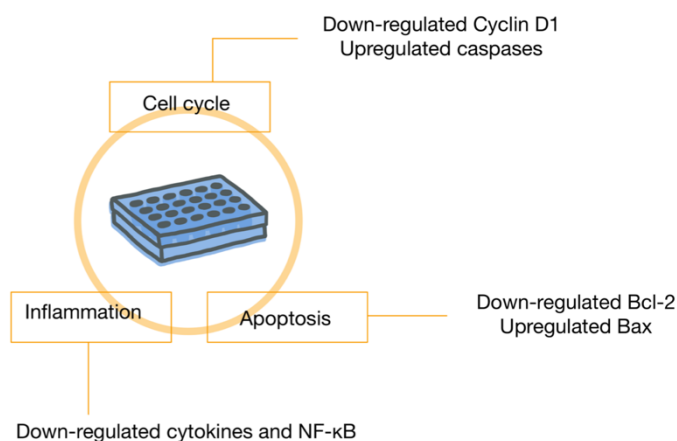


Fig. 3 Curcumin mediated molecules

Numerous clinical trials have proved that dysfunctional inflammatory pathways play significant roles in cancer. This mechanism is achieved by enhanced secretion of pro-inflammatory mediators, such as transcription factors, growth factors, inflammatory cytokines as well as particular proteins (including several enzymes, kinases and receptors) (Figure 2).

Take the expressions of NF- κ B and AP-1 for instances, these molecular signaling pathways are very common in different cancers. Curcumin could down-regulate their expression levels to activate cell apoptosis, resulting in abolished cancer cell proliferations [10].

3.3. Antiviral activity

According to numerous studies, curcumin has also represented excellent antiviral activity against different viruses [12]. For Zika and chikungunya viruses, both curcumin and its derivatives showed satisfactory antiviral activity by inhibiting the viral-cellular binding without damaging cell viabilities [13]. In a study by Balasubramanian et al., results demonstrated that curcumin and its analogues would potentially inhibit the replications and infectivity of dengue virus (DENV) in vitro. Additional analysis showed these chemical compounds would target intracellular pathways of both DENV proliferations by inhibiting polymerization of actions and expression of specific genes for lipid

synthesis [14]. Moreover, utilization of curcumin showed satisfactory effects against hepatitis B virus (HBV) by targeting NF- κ B, AP1, and Wnt/ β -catenin signaling pathways. According to the results, curcumin mainly controlled the HBV by suppressing the NF- κ B signaling pathway [15]. Recent epidemic induced by novel coronavirus, which significantly impacts both health of humans and animals, nevertheless, there is no effective therapeutics to effectively control this virus. In a study of Li et al., in Transmissible gastroenteritis virus (TGEV) alpha-corona viral models, curcumin firstly performed satisfactory antiviral activity and viral suppression against TGEVs, indicating the promising future of curcumin in treating virus-related diseases [12].

4. Curcumin in Colon (Colorectal) Cancer treatment

Numerous preclinical and clinical trials demonstrate that curcumin itself or combined with other therapies has the capability of anticancer by inhibiting various colon cancer related intracellular and extracellular pathways. According to the initiation of colon cancer, the expression of particular inflammatory molecules which could be precancerous factors in persistent development will be suppressed or enhanced (Figure 4). Moreover, curcumin can negatively control the anti-apoptotic genes/proteins and cancer cells' renewal in intestines [16].

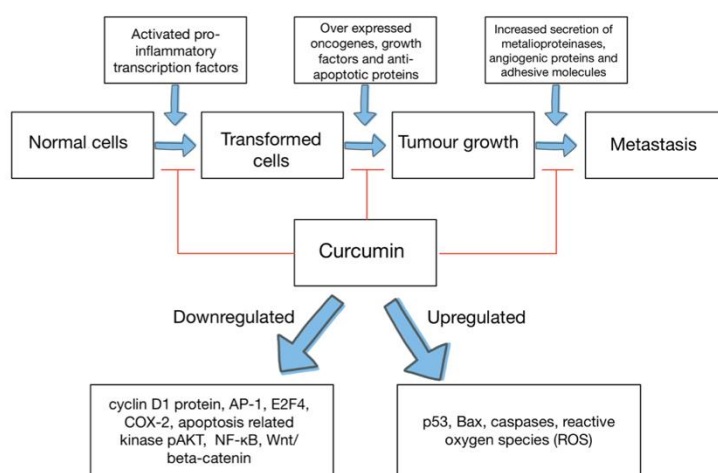


Fig. 4 Colon cancer initiation and curcumin targeted molecules

4.1. In vitro studies

Curcumin exerts its anticancer activity via arresting cell cycle and promoting cell apoptosis. Numerous in vitro studies have proved that this chemical compounds could interact with multiple molecules to modulate different cell signaling pathways [17]. Mosieniak and his colleagues discovered that the proliferation of HCT116 cell lines treated with curcumin were suppressed at the G2/M phase and part of the G1 phase [18]. Furthermore, Lim et al. performed curcumin on the same cell line found down-regulated cyclin D1 protein, which influences the phosphorylation of Rb protein, contributing to the difficulty in transition between G1 and S phases [19]. To figure out the mechanism of this cell cycle arrest, Kim and Lee examined the relationship between the E2F4 transcription factor and curcumin. The results proved that curcumin would suppress the expression of E2F4 and its targeted genes (e.g., cyclin A, p21 and p27) by inducing high level of reactive oxygen species (ROS) secretion. ROS could induce mitochondrial membranes lysis in cancer cells[20]. Also in a study by Watson et al., curcumin showed a satisfactory therapeutic potential in managing colon cancer, particularly in patients with resistance to traditional chemotherapies induced by p53 expressional or functional deficiencies [21]. Due to this, by enhancing the expression of p53, Bcl-2 family proteins'

ratios could be influenced. Curcumin could increase expression of Bax, while decrease Bcl-2 proteins, thus inducing HT-29 cell lines apoptosis [22].

To induce the mechanisms of cancerous cells apoptosis as the above mentioned studies, more targeted molecules are involved, such as cyclooxygenase-2 (COX-2) and transcription factors, death receptors (e.g., DR5 and Fas) and enzymes (e.g., caspase 3 and caspase 8) [17]. By Lee et al., curcumin could down-regulate expression of COX-2 and apoptosis related kinase pAKT, resulting in the induction of HT-29 cell lines apoptosis [23]. As for NF- κ B and beta-catenin, these transcription factors play significant roles in initiation of colon cancer. In a study on HCT-116 colon cancer cell lines by Collect and Campcell, curcumin could effectively promote the cell apoptosis by impressing the expression of NF- κ B [24]. Additionally, by Narayan, curcumin was reported to block HCT116 cell lines' cell cycle at G2/M phase by alleviating level of beta-catenin mediated c-myc gene [25].

Moreover, epigenetic changes brought on by environmental factors may also contribute to colon cancer [16]. Compared with both the negative and positive control groups, three groups of different cell lines (HCT116, HT29 and RKO) were managed with curcumin. The results showed reverse on partial DNA methylations, which indicated the chemo-preventive capability of curcumin [26].

4.2. In vivo studies

4.2.1 Animal models

Several in vivo studies demonstrated that curcumin showed satisfactory chemo-preventive capabilities against colon cancer [16]. In a study by Perkins et al., curcumin could greatly control the progression of adenomas in intestines of the C57Bl/6J Min/+ murine models, which simulated inheritable familial adenomatous polyposis (APC). Three groups of mice were orally administered curcumin at 0.1, 0.2 and 0.5% (corresponding to 150, 300, and 750 mg/kg), respectively. Compared with other group, curcumin at 0.1% showed ineffective reactions on adenomas, while at 0.2% and 0.5% the multi-complexity of the adenomas was reduced by approximately 40%. Moreover, part of orally administered curcumin could improve the hematocrit and alleviate the risks of bleeding induced by matured adenoma. Due to this study, daily intake of particular dose of curcumin has been highly recommended [27].

Moreover, colon cancer induced by imbalanced micro-bacterial intestinal environment could be determined by interventions of diets. In a study by McFadden et al., diets with curcumin prolonged the survival time. Compared with phosphate-buffered saline (PBS)/I110^{-/-} murine models, azoxymethane (AOM)/I110^{-/-} models could actively eliminate the effects of colon cancer via enhancement of intestinal microbial diversity [28].

Similar with the above mentioned in vitro studies, curcumin could control epigenetic alterations induced colon cancer [16]. Among all the diversely expressed and methylated genes, Tnf gene showed outstanding capability of decreasing the DNA CpG methylation levels in C57BL6 treated with AOM-dextran sulfate sodium (DSS) murine models. In a study by Guo et al., compared with the pure AOM-DSS, the group administered curcumin could reverse the levels of DNA methylation, indicating curcumin's preventive effects on colon cancer initiation and progression [29]. Later by Seiwert et al., nanotechnology was utilized in same groups of mice to enhance the low bioavailability of curcumin induced by intestinal inflammatory reactions [30]. Figure 4 has generally concluded the main mechanisms in colon cancer modulated murine models treated with curcumin.

4.2.2 Human bodies

Numerous clinical trials in different cell lines have proved that curcumin contains anticancer and therapeutic effects on colon cancer. By He et al., the tumor impressive mechanisms of curcumin were detailed examined. According to the results, curcumin could decrease the levels of TNF-alpha in serum, which intuitively improve the conditions of patients. As a result, curcumin could not only promote cell apoptosis, but also enhance the level of p53 molecules in colorectal tissues [31]. In familial adenomatous polyposis (FAP), which would eventually develop into colorectal cancer, both the conventional managements with non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2

showed severe adverse effects. Due to this, by Cruz Correa et al., a novel therapy with three times orally administered curcumin at 480 mg and quercetin at 20 mg daily was designed and evaluated. According to the results of 5 patients (after the colectomy) treated with new therapy, the number and sizes of polyps had been remarkably decreased 60.4% and 50.9%, respectively. Moreover, this clinical trial demonstrated no toxicity of curcumin or quercetin [32].

Also, curcumin combined with other conventional therapies could achieve better prognosis of advanced colon cancer and alleviate adverse effects or toxicity. To solve this issue, curcumin with safety has been proved to effectively manage the colon cancer with [17,33]. In a phase I clinical trial, patients with colon cancer were administered curcumin at 450-3,600 mg for 4 months, the results demonstrated that curcumin is safe for long-term treatment. To support this, another clinical study by James et al. proved that curcumin combined with FOLFOX therapy in 12 patients with metastatic colon cancer demonstrated safety and well-tolerated results [34]. Similarly, in a study by Howells et al., orally administered curcumin combined with FOLFOX chemotherapy also demonstrated remarkable and safe outcomes in controlling metastatic colon cancer, which demonstrated the enhanced survival rates of the patients treated with curcumin [35]. In the context of general colon cancer with no extreme effects, curcumin showed satisfactory and well-tolerated results with maximum doses at 8,000 mg daily [17,36].

5. Conclusion

In conclusion, different in vitro and in vivo studies have proved that curcumin features satisfactory anti-cancerous activity against colon cancer with different mechanisms. Also, curcumin exerts other beneficial anti-inflammatory and anti-viral bio-activities. The low bioavailability and cytotoxicities of orally administered curcumin could be relieved by nanotechnology like nanoparticles with lipid membranes, contributing to enhanced bioavailability and improved prognosis. Numerous studies have proved that curcumin is safety and well-tolerated with maximum dose at 8,000 mg in daily diet. It exerts its anticancer activity by regulating multiple molecular pathways related to colon cancer, leading to blocked cell cycles and promoted cell apoptosis. Both curcumins alone and combined with other conventional therapies show a promising future in colon cancer treatments, including reduced chemotherapies resistance and alleviated severe adverse effects. Nevertheless, more verified clinical trials should be performed to precisely evaluate other curcumin-related issues and resolve limitations, such as small sample populations, unsatisfactory bioavailability, patients' heterogeneities, optimal indications and other potential toxicities. Otherwise, novel curcumin delivery systems and curcumin formulations should be developed and performed in more clinical trials to promote efficient and safety utilization of curcumin in colon cancer managements.

References

- [1] Colorectal cancer statistics: How common is colorectal cancer? Colorectal Cancer Statistics | How Common Is Colorectal Cancer? (n.d.). Retrieved March 18, 2023, from <https://www.cancer.org/cancer/colon-rectal-cancer/about/key-statistics.html>
- [2] Colon cancer (colorectal cancer). Cleveland Clinic. (n.d.). Retrieved March 17, 2023, from <https://my.clevelandclinic.org/health/diseases/14501-colorectal-colon-cancer>
- [3] Fabregas, J. C., Ramnarain, B., & George, T. J. (2022). Clinical updates for colon cancer care in 2022. *Clinical Colorectal Cancer*, 21(3), 198–203. <https://doi.org/10.1016/j.clcc.2022.05.006>
- [4] Pricci, M., Girardi, B., Giorgio, F., Losurdo, G., Ierardi, E., & Di Leo, A. (2020). Curcumin and colorectal cancer: From basic to clinical evidences. *International Journal of Molecular Sciences*, 21(7), 2364. <https://doi.org/10.3390/ijms21072364>
- [5] Ali, B. H., Marrif, H., Noureldayem, S. A., Bakheit, A. O., & Blunden, G. (2006). Some biological properties of curcumin: A Review. *Natural Product Communications*, 1(6). <https://doi.org/10.1177/1934578x0600100613>

- [6] Villegas, C., Perez, R., Sterner, O., González-Chavarría, I., & Paz, C. (2021). Curcuma as an adjuvant in colorectal cancer treatment. *Life Sciences*, 286, 120043. <https://doi.org/10.1016/j.lfs.2021.120043>
- [7] Giordano, & Tommonaro. (2019). Curcumin and cancer. *Nutrients*, 11(10), 2376. <https://doi.org/10.3390/nu11102376>
- [8] de, V. M. H. van, & Müller, B. (2017). *Nanoscience and nanotechnology for human health*. Wiley-VCH Verlag GmbH & Co. KGaA.
- [9] Selvam, C., Prabu, S. L., Jordan, B. C., Purushothaman, Y., Umamaheswari, A., Hosseini Zare, M. S., & Thilagavathi, R. (2019). Molecular mechanisms of curcumin and its analogs in colon cancer prevention and treatment. *Life Sciences*, 239, 117032. <https://doi.org/10.1016/j.lfs.2019.117032>
- [10] Shanmugam, M., Rane, G., Kanchi, M., Arfuso, F., Chinnathambi, A., Zayed, M., Alharbi, S., Tan, B., Kumar, A., & Sethi, G. (2015). The multifaceted role of curcumin in cancer prevention and treatment. *Molecules*, 20(2), 2728–2769. <https://doi.org/10.3390/molecules20022728>
- [11] Dehzad, M. J., Ghalandari, H., Nouri, M., & Askarpour, M. (2023). Antioxidant and anti-inflammatory effects of curcumin/turmeric supplementation in adults: A grade-assessed systematic review and dose–response meta-analysis of randomized controlled trials. *Cytokine*, 164, 156144. <https://doi.org/10.1016/j.cyto.2023.156144>
- [12] Li, Y., Wang, J., Liu, Y., Luo, X., Lei, W., & Xie, L. (2020). Antiviral and virucidal effects of curcumin on transmissible gastroenteritis virus in vitro. *Journal of General Virology*, 101(10), 1079–1084.
- [13] Mounce, B. C., Cesaro, T., Carrau, L., Vallet, T., & Vignuzzi, M. (2017). Curcumin inhibits zika and chikungunya virus infection by inhibiting cell binding. *Antiviral Research*, 142, 148–157. <https://doi.org/10.1016/j.antiviral.2017.03.014>
- [14] Balasubramanian, A., Pilankatta, R., Teramoto, T., Sajith, A. M., Nwulia, E., Kulkarni, A., & Padmanabhan, R. (2019). Inhibition of dengue virus by curcuminoids. *Antiviral Research*, 162, 71–78. <https://doi.org/10.1016/j.antiviral.2018.12.002>
- [15] Hesari, A. R., Ghasemi, F., Salarinia, R., Biglari, H., Tabar Molla Hassan, A., Abdoli, V., & Mirzaei, H. (2018). Effects of curcumin on NF-KB, AP-1, and Wnt/ β -catenin signaling pathway in hepatitis B virus infection. *Journal of Cellular Biochemistry*, 119(10), 7898–7904. <https://doi.org/10.1002/jcb.26829>
- [16] Villegas, C., Perez, R., Sterner, O., González-Chavarría, I., & Paz, C. (2021). Curcuma as an adjuvant in colorectal cancer treatment. *Life Sciences*, 286, 120043. <https://doi.org/10.1016/j.lfs.2021.120043>
- [17] Pricci, M., Girardi, B., Giorgio, F., Losurdo, G., Ierardi, E., & Di Leo, A. (2020). Curcumin and colorectal cancer: From basic to clinical evidences. *International Journal of Molecular Sciences*, 21(7), 2364. <https://doi.org/10.3390/ijms21072364>
- [18] Mosieniak, G., Adamowicz, M., Alster, O., Jaskowiak, H., Szczepankiewicz, A. A., Wilczynski, G. M., Ciechomska, I. A., & Sikora, E. (2012). Curcumin induces permanent growth arrest of human colon cancer cells: Link between senescence and autophagy. *Mechanisms of Ageing and Development*, 133(6), 444–455. <https://doi.org/10.1016/j.mad.2012.05.004>
- [19] Lim, T.-G., Lee, S.-Y., Huang, Z., Lim, D. Y., Chen, H., Jung, S. K., Bode, A. M., Lee, K. W., & Dong, Z. (2014). Curcumin suppresses proliferation of colon cancer cells by targeting CDK2. *Cancer Prevention Research*, 7(4), 466–474. <https://doi.org/10.1158/1940-6207.capr-13-0387>
- [20] Kim, K.-C., & Lee, C. H. (2010). Curcumin induces downregulation of E2F4 expression and apoptotic cell death in HCT116 human colon cancer cells; involvement of reactive oxygen species. *The Korean Journal of Physiology and Pharmacology*, 14(6), 391. <https://doi.org/10.4196/kjpp.2010.14.6.391>
- [21] Watson, J. L., Hill, R., Yaffe, P. B., Greenshields, A., Walsh, M., Lee, P. W., Giacomantonio, C. A., & Hoskin, D. W. (2010). Curcumin causes superoxide anion production and p53-independent apoptosis in human colon cancer cells. *Cancer Letters*, 297(1), 1–8. <https://doi.org/10.1016/j.canlet.2010.04.018>
- [22] Song, G., Mao, Y. B., Cai, Q. F., Yao, L. M., Ouyang, G. L., & Bao, S. D. (2005). Curcumin induces human HT-29 colon adenocarcinoma cell apoptosis by activating p53 and regulating apoptosis-related protein expression. *Brazilian Journal of Medical and Biological Research*, 38(12), 1791–1798. <https://doi.org/10.1590/s0100-879x2005001200007>

- [23] Lee, Y.-K., Park, S. Y., Kim, Y.-M., & Park, O. J. (2009). Regulatory effect of the AMPK-COX-2 signaling pathway in curcumin-induced apoptosis in HT-29 colon cancer cells. *Annals of the New York Academy of Sciences*, 1171(1), 489–494. <https://doi.org/10.1111/j.1749-6632.2009.04699.x>
- [24] Collett, G. P., & Campbell, F. C. (2006). Overexpression of p65/RELA potentiates curcumin-induced apoptosis in HCT116 human colon cancer cells. *Carcinogenesis*, 27(6), 1285–1291. <https://doi.org/10.1093/carcin/bgi368>
- [25] Narayan, S. (2003). Curcumin, a multi-functional chemopreventive agent, blocks growth of colon cancer cells by targeting β -catenin-mediated transactivation and cell–cell adhesion pathways. *Journal of Molecular Histology*, 35(3), 301–307. <https://doi.org/10.1023/b:hijo.0000032361.98815.bb>
- [26] Link, A., Balaguer, F., Shen, Y., Lozano, J. J., Leung, H.-C. E., Boland, C. R., & Goel, A. (2013). Curcumin modulates DNA methylation in colorectal cancer cells. *PLoS ONE*, 8(2). <https://doi.org/10.1371/journal.pone.0057709>
- [27] Perkins, S., Verschoyle, R. D., Hill, K., Parveen, I., Threadgill, M. D., Sharma, R. A., Williams, M. L., Steward, W. P., & Gescher, A. J. (2002). Chemopreventive efficacy and pharmacokinetics of curcumin in the min/+ mouse, a model of familial adenomatous polyposis. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*, 11(6), 535–540.
- [28] McFadden, R.-M. T., Larmonier, C. B., Shehab, K. W., Midura-Kiela, M., Ramalingam, R., Harrison, C. A., Besselsen, D. G., Chase, J. H., Caporaso, J. G., Jobin, C., Ghishan, F. K., & Kiela, P. R. (2015). The role of curcumin in modulating colonic microbiota during colitis and colon cancer prevention. *Inflammatory Bowel Diseases*, 21(11), 2483–2494. <https://doi.org/10.1097/mib.0000000000000522>
- [29] Guo, Y., Wu, R., Gaspar, J. M., Sargsyan, D., Su, Z.-Y., Zhang, C., Gao, L., Cheng, D., Li, W., Wang, C., Yin, R., Fang, M., Verzi, M. P., Hart, R. P., & Kong, A.-N. (2018). DNA methylome and transcriptome alterations and cancer prevention by curcumin in colitis-accelerated colon cancer in mice. *Carcinogenesis*, 39(5), 669–680. <https://doi.org/10.1093/carcin/bgy043>
- [30] Seiwert, N., Fahrner, J., Nagel, G., Frank, J., Behnam, D., & Kaina, B. (2020). Curcumin administered as micellar solution suppresses intestinal inflammation and colorectal carcinogenesis. *Nutrition and Cancer*, 73(4), 686–693. <https://doi.org/10.1080/01635581.2020.1771384>
- [31] He, Z. Y., Shi, C. B., Wen, H., Li, F. L., Wang, B. L., & Wang, J. (2011). Upregulation of p53 expression in patients with colorectal cancer by administration of curcumin. *Cancer investigation*, 29(3), 208–213. <https://doi.org/10.3109/07357907.2010.550592>
- [32] Cruz-Correa, M., Shoskes, D. A., Sanchez, P., Zhao, R., Hyland, L. M., Wexner, S. D., & Giardiello, F. M. (2006). Combination treatment with curcumin and quercetin of adenomas in familial adenomatous polyposis. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*, 4(8), 1035–1038. <https://doi.org/10.1016/j.cgh.2006.03.020>
- [33] Weng, W., & Goel, A. (2022). Curcumin and colorectal cancer: An update and current perspective on this natural medicine. *Seminars in Cancer Biology*, 80, 73–86. <https://doi.org/10.1016/j.semcancer.2020.02.011>
- [34] James, M. I., Iwuji, C., Irving, G., Karmokar, A., Higgins, J. A., Griffin-Teal, N., Thomas, A., Greaves, P., Cai, H., Patel, S. R., Morgan, B., Dennison, A., Metcalfe, M., Garcea, G., Lloyd, D. M., Berry, D. P., Steward, W. P., Howells, L. M., & Brown, K. (2015). Curcumin inhibits cancer stem cell phenotypes in ex vivo models of colorectal liver metastases, and is clinically safe and tolerable in combination with Folfex chemotherapy. *Cancer Letters*, 364(2), 135–141. <https://doi.org/10.1016/j.canlet.2015.05.005>
- [35] Howells, L. M., Iwuji, C. O., Irving, G. R., Barber, S., Walter, H., Sidat, Z., Griffin-Teall, N., Singh, R., Foreman, N., Patel, S. R., Morgan, B., Steward, W. P., Gescher, A., Thomas, A. L., & Brown, K. (2019). Curcumin combined with Folfex Chemotherapy is safe and tolerable in patients with metastatic colorectal cancer in a randomized phase IIA trial. *The Journal of Nutrition*, 149(7), 1133–1139. <https://doi.org/10.1093/jn/nxz029>
- [36] Park, J. (2010). Anti-carcinogenic properties of curcumin on colorectal cancer. *World Journal of Gastrointestinal Oncology*, 2(4), 169. <https://doi.org/10.4251/wjgo.v2.i4.169>