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REVIEW

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Curcumin and its anti-colorectal cancer potential: From mechanisms of action to autophagy

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Abstract

Colorectal cancer (CRC) development and progression, one of the most common cancers globally, is supported by specific mechanisms to escape cell death despite chemotherapy, including cellular autophagy. Autophagy is an evolutionarily highly conserved degradation pathway involved in a variety of cellular processes, such as the maintenance of cellular homeostasis and clearance of foreign bodies, and its imbalance is associated with many diseases. However, the role of autophagy in CRC progression remains controversial, as it has a dual function, affecting either cell death or survival, and is associated with cellular senescence in tumor therapy. Indeed, numerous data have been presented that autophagy in cancers serves as an alternative to cell apoptosis when the latter is ineffective or in apoptosis-resistant cells, which is why it is also referred to as programmed cell death type II. Curcumin, one of the active constituents of *Curcuma longa*, has great potential to combat CRC by influencing various cellular signaling pathways and epigenetic regulation in a safe and cost-effective approach. This review discusses the efficacy of curcumin against CRC in vitro and in vivo, particularly its modulation of autophagy and apoptosis in various cellular pathways. While clinical studies have assessed the potential of curcumin in cancer prevention and treatment, none have specifically examined its role in autophagy. Nonetheless, we offer an overview of potential correlations to support the use of this polyphenol as a prophylactic or co-therapeutic agent in CRC.

KEYWORDS

apoptosis, autophagy, colorectal cancer, curcumin, senescence

Abbreviations: 5-FU, 5-fluorouracil; AKBA, acetyl-11-keto-beta-boswellic acid; Akt, protein kinase B; AMPK, AMP-activated protein kinase; AP-1, activating protein-1; ATG, autophagy-related protein; Bcl-2, B-cell lymphoma 2; CDK, cyclin-dependent kinase; CHOP, C/EBP homologous protein; COX, cyclooxygenase; CRC, colorectal cancer; CSC, cancer stem cell; CXCL, C-X-C-motif ligand; DR5, death receptor 5; EMT, epithelial-mesenchymal transition; ER, endoplasmatic reticulum; HCQ, hydroxychloroquine; HDAC, histone deacetylase; HIF, hypoxia inducible transcription factor; HSPs, heat shock proteins; IAP, inhibitor of apoptosis protein; IL, interleukin; JAK, Janus kinase; LC3, light chain 3; MACC1, metastasis-associated in colon cancer 1; MCP-1, monocyte chemoattractant protein-1; MET, mesenchymal-epithelial transition; miRNAs, microRNAs; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B-cells; NRF2, nuclear factor erythroid 2-related factor 2; PGE, prostaglandin E; PI3K, phosphoinositide-3-kinase; PTEN, phosphatase and tensin homolog; ROS, reactive oxygen species; STAT, signal transducer and activator of transcription; TFEB, transcription factor EB; TGF, transforming growth factor; TME, tumor microenvironment; TNF, tumor necrosis factor; UPR, unfolded protein response; YAP, Yes-associated protein.

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1 | INTRODUCTION

Compared with the 19th century, statistical data on causes of death have changed significantly. While infectious diseases dominated in the past, nowadays most people die as a result of cardiovascular diseases or cancer. With regard to cancer, a rising trend in prevalence and mortality can be observed, so that this will be the most common cause of death worldwide in the near future (Bray et al., 2021). One of the top places is occupied by malignant neoplasms of rectum or colon, summarized as colorectal cancer (CRC). Although it is well established that genetic and epigenetic factors, including alterations in key genes like *APC*, *KRAS*, *BRAF*, *PI3K*, *DCC*, *SMAD2*, *SMAD4*, and *TP53*, are pivotal in the development of CRC (Raskov et al., 2014), the emergence of these tumors is further exacerbated by demographic change and factors related to an increasingly unhealthy lifestyle (Sung et al., 2021).

Epigenetic influences such as tobacco smoke, alcohol consumption, obesity, lack of exercise, but also chronic inflammatory bowel diseases cause an imbalance in the interaction between the different cell types of the intestinal environment (Muthusami et al., 2021). Subsequently, the secretion of pro-inflammatory enzymes and cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β, or IL-6 is stimulated, resulting in chronic inflammation and metabolic imbalances up to the development and progression of CRC (Muthusami et al., 2021). In these circumstances, an uncontrolled inflammatory, pro-carcinogenic cascade entails systemic disturbances including a dysregulation of autophagic processes.

Autophagy means an intracellular cleaning and defense mechanism that keeps cells healthier by breaking down damaged organelles or proteins (Majeed et al., 2022). For example, it is known that cell damage by ultraviolet radiation triggers cascades surrounding multifunctional proteins such as p62, nuclear factor erythroid 2-related factor 2 (NRF 2) and nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB). Interestingly, autophagy plays a central role in preventing these pro-inflammatory and thus pro-tumorigenic mechanisms involved in the transformation of cells into malignancy (Zhong et al., 2022). This autophagic machinery is closely connected with the induction of cell senescence, characterized by irreversible cessation of cell division, and with apoptosis, a programmed cell death. Together, these mechanisms constitute a triad of defense against metabolic disruptions (Patschan et al., 2008). Their intact interplay is particularly crucial in the intestine to prevent a degeneration of healthy cells despite rapid renewal cycles. Whenever these self-protective functions are disrupted, the gut homeostasis is no longer synchronized and a pathological switch in the intestinal cells can no longer be prevented (P. Zhang et al., 2019).

If a cancerous disease has already occurred, autophagy takes on a completely different perspective since malignant tumor cells have also developed the ability to use these mechanisms. Overall, autophagic processes represent a double-edged sword, the balance of which can determine physiology or pathology. Related to CRC, maintaining a controlled, canonical mammalian target of rapamycin (mTOR) pathway including its phosphoinositide-3-kinase (PI3K)/protein kinase B (Akt) signaling seems of central importance, because it has been shown both in vitro as well as in vivo, that a modulation of mTOR/PI3K/Akt has considerable effects on growth, morphology and metastasis of CRC cells (Francipane & Lagasse, 2014). Additionally, the mTOR pathway can be regulated by a noncanonical pathway independent of Akt (Majeed et al., 2021; Majeed et al., 2023; Napolitano et al., 2022). Furthermore, even the development of chemoresistance is closely linked to autophagic dysregulation, leading to tumor growth despite cytostatic therapy (Hussain et al., 2016; Wei et al., 2019). From a clinical perspective, the significance of autophagic malfunction has also already been noted, so that treatment of CRC patients with autophagy-inhibitors in addition to standardized chemotherapy or radiotherapy has been attempted (Z. Li, Si, et al., 2022). However, these treatments can induce severe side effects, such as a rapid deterioration in overall health characterized by severe tiredness and weight loss (Karasic et al., 2022). Moreover, their use is limited to treatment and they cannot be used to prevent cancer. Given these conditions, the proactive modulation of autophagy has emerged as an appealing strategy for cancer prevention.

Hence, nature-derived substances may well be a viable option for a cost-effective and well-tolerated long-term CRC prophylaxis. In this review, we present the qualities of the natural polyphenol curcumin, based on its well-established role as both a preventive and therapeutic agent in cancer, along with its ability to modulate autophagy. This phytotherapeutic agent has been extracted from the plant *Curcuma longa* and is used as turmeric powder by traditional medicine for thousands of years on the basis of a variety of health-promoting effects (Brockmueller et al., 2022). Meanwhile, a wide range of protecting effects has been proven, for example pathogen elimination (Kudva et al., 2012), pain as well as fatigue reduction (K. A. Agarwal et al., 2011). Especially in the intestine, curcumin relieves inflammation impeding the damage of the gut barrier (Szymanski et al., 2018) and preventing colon cell dysplasia by modulating inflammatory and metabolic markers of CRC carcinogenesis (Macis et al., 2023). Moreover, the plant substance shows extensive antiproliferative, antimetastatic, proapoptotic, and even chemosensitizing effects on CRC cells (Buhrmann et al., 2014; Shakibaei et al., 2015).

To date, the mechanisms of curcumin's modulation of autophagic processes are controversially discussed in the literature, because autophagy can ensure either the survival or death of a cell. In general, most authors consider curcumin to be an inducer of senescence-associated loss of proliferation (Galluzzi et al., 2018), autophagy or apoptosis in CRC cells (Kantara et al., 2014; Mosieniak et al., 2016). In this way, the phytopharmaceutical unfolds both a prophylactic and therapeutic effect on CRC. Therefore, in the following chapters, this review summarizes our current knowledge and presents the CRC-modulating qualities of the phytopharmaceutical in vitro, in vivo, and in clinical trials, with special consideration of the connection between autophagy and cell senescence. Finally, the resulting conclusions are discussed, giving an outlook of curcumin's perspective relevance as co-therapeutic agent in CRC treatment.

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2 | FRAMEWORK OF THIS REVIEW

2.1 | Aim of this review

This review was initiated after identifying a gap in the international literature summarizing curcumin's modulation of autophagy in CRC cells. Therefore, the aim was to present the known connections between CRC, autophagic processes, and the influence of the natural substance curcumin on both entities.

2.2 | Database of this review

For this manuscript, the following keywords were chosen, combined according to the respective chapter focus and entered into the PubMed database for search: "curcumin," "turmeric," "curcuminoid," "colorectal cancer," "CRC," "colon cancer," "autophagy," "senescence," "apoptosis," "programmed cell death," "mTOR," "PI3K," "Akt," "inflammation," "NF-κB," "in vitro," "in vivo," "clinical trial."

3 | ROLE OF CURCUMIN IN CRC

Curcumin, a hydrophobic polyphenol commonly known as *diferuloylmethane*, is the predominant curcuminoid present in the spice turmeric and this bioactive compound is sourced from the rhizome of the *Curcuma longa* plant. Over the past few decades, a plethora of in vitro and in vivo studies have demonstrated the potential of curcumin as a protective and antitumor agent that acts against CRC by influencing several cellular signaling pathways or by epigenetically regulating gene expression (Ruiz de Porras et al., 2020; Selvam et al., 2019; Weng & Goel, 2022). These anticancer properties are often attributed to curcumin's anti-inflammatory and antioxidant effects, as well as to its capacity to regulate processes related to cell proliferation, death, migration and invasion, angiogenesis, metastasis, and even gut microbiota composition (Giordano & Tommonaro, 2019; Weng & Goel, 2022). Furthermore, numerous investigators, including our own team, have shown that curcumin enhances chemosensitivity to drugs currently used in the treatment of CRC (Brockmueller, Samuel, et al., 2023; Ruiz de Porras et al., 2020). In this section, we aim to elucidate the molecular mechanisms underlying the interaction between curcumin and key biological processes associated with CRC prevention, development, progression and treatment (Figure 1).

3.1 | Curcumin as a preventive and anti-inflammatory agent for CRC

The molecular carcinogenesis of CRC is characterized by a series of intricate events ultimately resulting in the malignant transformation of colon or rectal epithelial cells. This transformation leads to the formation of dysplastic adenomas, widely recognized as the primary precursor lesions of CRC development. Subsequently, these adenomas progress to early and advanced stages of CRC. Throughout these processes, various chromosomal alterations, along with genetic mutations and epigenetic modifications, may occur in key genes that regulate cell proliferation, differentiation, angiogenesis and apoptosis, including tumor suppressor genes, such as *APC*, *TP53*, *DCC*, and *SMAD4*, and oncogenes, such as *KRAS*, *NRAS*, and *BRAF*. Additionally, deregulation of downstream signaling pathways, such as Wnt/β-catenin, RAS/RAF/MAPK, PI3K/Akt, and transforming growth factor (TGF)-β/SMAD, plays a central role in promoting CRC tumorigenesis (Raskov et al., 2014; Tariq & Ghias, 2016). CRC carcinogenesis and new preventive strategies have been studied in spontaneous, induced, genetically engineered, xenograft, and syngeneic mouse models (Burtin et al., 2020; Nascimento-Goncalves et al., 2021). For example, a recent study demonstrated that the synthetic hybrid derivative PQM-162, which combines curcumin and resveratrol, reduces the formation of aberrant crypt foci—the earliest identifiable neoplastic lesions in the colon carcinogenic model—by acting on anti-inflammatory, antioxidant, and cell proliferation pathways in Wistar rats in which preneoplastic lesions were induced with 1,2-dimethylhydrazine treatment (Baptistella et al., 2023). Similarly, in the ApcMin/+ mouse model associated with colitis-induced CRC, mice receiving a diet enriched with a nutritional blend of curcumin, silymarin, and acetyl-11-keto-beta-boswellic acid (AKBA) demonstrated a notable decrease in both the number and size of polypoid lesions compared to the control group (Girardi et al., 2020). Interestingly, similar results were observed when maltodextrins, polymers derived from starch hydrolysis with anti-oxidative properties, were added to this enriched nutritional formulation (Girardi et al., 2018). In the same line, theracurmin, a highly bioavailable formulation of curcumin, suppresses intestinal polyp development in Apc-mutant mice through the inhibition of inflammation-related factors such as NF-κB, monocyte chemoattractant protein-1 and IL-6 (Adachi et al., 2020). In addition, a diet supplemented with curcumin prevented and improved histopathological signs of colonic inflammation induced by trinitrobenzene sulfonic acid in mice. The beneficial effects of the phytopharmaceutical were associated with the suppression of $CD4^+$ T-cell infiltration, inhibition of NF-κB activation, and reduced expression of pro-inflammatory cytokines in colonic mucosa (Sugimoto et al., 2002). Furthermore, in mouse models of CRC induced by azoxymethane-dextran sodium sulfate, a diet enriched with curcumin was shown to reverse DNA methylation and, consequently, the suppression of the expression of genes associated with inflammation and cancer progression (Y. Guo et al., 2018).

Inflammation in the intestine is increasingly recognized as a pivotal factor in the initiation and progression of CRC (Schmitt & Greten, 2021; Terzic et al., 2010). Indeed, chronic inflammation, often resulting from conditions such as inflammatory bowel disease, Crohn's disease or ulcerative colitis creates a microenvironment rich in pro-inflammatory cytokines and immune cells (Hemminki et al., 2009; Lucafo et al., 2021), which can lead to genomic instability, DNA damage, enhanced cell proliferation, and evasion of apoptosis, representing hallmark characteristics of cancer. In particular, the activation of

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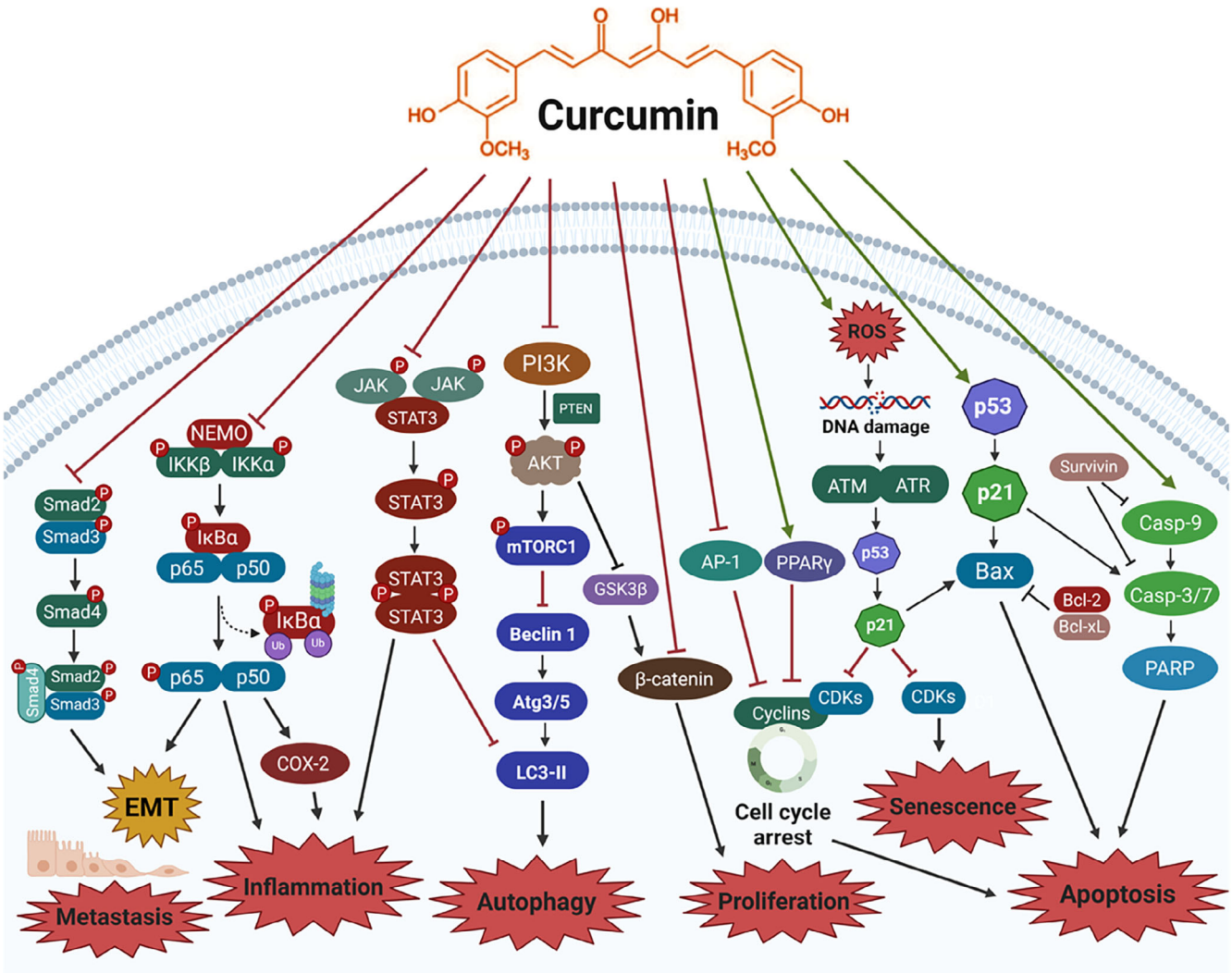

FIGURE 1 The major effects and modes of action of curcumin in colorectal cancer (CRC). Illustration of the activating (green arrows) or inhibitory effects (red line with a dash) of curcumin on various signaling pathways and molecular targets involved in inflammation, reactive oxidative species (ROS) production, cell proliferation, apoptosis, autophagy, senescence, migration and invasion, angiogenesis, metastasis, and epithelial-mesenchymal transition (EMT) in CRC cells. Created with Biorender.com.

key signaling pathways in response to chronic inflammation contributes to the transformation of normal colorectal epithelial cells into their malignant counterparts (Schmitt & Greten, 2021; Terzic et al., 2010). Especially, the NF-κB transcription factor, a central regulator of inflammation and immune response, is commonly upregulated in CRC cells, playing a prominent role in promoting cell proliferation and metastasis, angiogenesis, therapy resistance, evasion of apoptosis, and the establishment of a pro-tumorigenic microenvironment (Chaturvedi et al., 2011; Karin & Greten, 2005; Kojima et al., 2004; Sakamoto et al., 2009; H. G. Yu et al., 2004). Curcumin has been extensively studied for its ability to modulate NF-κB activity, thereby mitigating inflammation-associated development of CRC (Figure 1). In addition, curcumin also interferes with the activation of the TNF-α/NF-κB pathway by suppressing the phosphorylation and degradation of its inhibitory protein IκBα, thereby blocking the nuclear translocation of this transcription factor (Anthwal et al., 2014; Jobin et al., 1999; Rajitha et al., 2016; Ruiz de Porras et al., 2016; Shakibaei et al., 2013). Consequently, the natural polyphenol has been shown to downregulate the expression of NF-κB target genes, including pro-inflammatory cytokines and chemokines, such as C-X-C-motif ligand (CXCL) 8, CXCL1, or CXCL2, which are crucial contributors to CRC development, progression, angiogenesis and therapy resistance (Ruiz de Porras et al., 2016). Another well-known NF-κB target is cyclooxygenase (COX)-2 (J. W. Lim et al., 2001), a pro-inflammatory enzyme that is overexpressed in almost 80% of CRC patients, especially those with advanced disease (Elzagheid et al., 2013; Roelofs et al., 2014) and curcumin downregulates COX-2 expression in in vitro (Goel et al., 2001; Y. K. Lee et al., 2009; Plummer et al., 1999) as well as in vivo models of CRC (Villegas et al., 2011) (Figure 1).

Additionally, the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is an essential modulator of cellular inflammatory processes that contributes to CRC development and

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progression (Sabaawy et al., 2021; Slattery et al., 2013). Furthermore, several preclinical studies have demonstrated curcumin's anti-inflammatory activity through the inhibition of the JAK/STAT3 signaling cascade (Hashemi et al., 2023) (Figure 1). In this regard, in a recent work, Li and colleagues demonstrated that the anticancer activities of curcuminoids, including curcumin, desmethoxycurcumin, and bisdesmethoxy-curcumin, against CRC are due to the modulation of the IL-6/JAK/STAT3 pathway (Q. Li et al., 2023).

Altogether, chronic inflammation leads to the activation of key signaling pathways, particularly the upregulation of NF-κB and JAK/STAT3, promoting CRC development, progression, and therapy resistance. Through the downregulation of crucial target genes and anti-inflammatory activity, curcumin exhibits significant potential as a preventive and therapeutic agent against CRC.

3.2 | The interplay of curcumin, gut microbiota, and CRC

The gut microbiome also plays a fundamental role in CRC development through its influence on host metabolism, immunity, and inflammation (Omar Al-Hassi et al., 2018). Hence, disruptions in the balance or unhealthy changes in the composition of the gut microbiome, a process known as dysbiosis, can significantly increase an individual's susceptibility to CRC. Specific bacterial strains, such as *Fusobacterium nucleatum* and their metabolites can contribute to CRC development, progression and prognosis through the activation of β-catenin signaling and the expression of pro-inflammatory cytokines and chemokines, including TNF-α, IL-17, CXCL8, and CXCL1 (Casasanta et al., 2020; Mima et al., 2016; Rubinstein et al., 2013). Similarly, *Bacteroides fragilis* triggers CRC by instigating an inflammatory cascade that supports carcinogenesis (Chung et al., 2018). Interestingly, curcumin reduces significantly intestinal inflammation, at least in part, by regulation of gut microbiota in mice models (McFadden et al., 2015) and in humans (Peterson et al., 2018). Moreover, the phytopharmaceutical can eliminate intestinal microflora dysbiosis by normalizing colonic microbial ecology and bacteria-associated enzymatic modifications (McFadden et al., 2015; Pluta et al., 2020). For instance, Ohno and colleagues demonstrated that curcumin ameliorated colitis symptoms in a dextran sodium sulfate-colitis mouse model by increasing the abundance of butyrate-producing bacteria, thereby ameliorating Treg-associated inflammation and fecal butyrate level. This effect was accompanied by increased expansion of $CD4^+$ $Foxp3^+$ regulatory T-cells and $CD103^+$ $CD8\alpha^-$ regulatory dendritic cells in the colonic mucosa (Ohno et al., 2017).

In conclusion, the intricate interplay among gut microbiota, inflammation, and CRC underscores the complexity of their relationships and the potential impact on cancer development. The multifaceted nature of these interactions emphasizes the need for continued research in this field to unravel the specific mechanisms by which curcumin influences the gut microbiota, modulates inflammatory responses, and ultimately affects CRC development and progression.

3.3 | Curcumin in CRC cell proliferation and metastasis

One of the key aspects contributing to the anticancer potential of curcumin is its ability to inhibit the proliferation of CRC cells. Curcumin has been shown to induce cell cycle arrest at different phases, such as G0/G1 or G2/M, through the upregulation of critical cyclin-dependent kinase (CDK) inhibitors like p16, p21, and p27, while concurrently inhibiting the activity of CDK2, CDK4, Cyclin D1, B, and E (Choudhuri et al., 2005; Dasiram et al., 2017; T. G. Lim et al., 2014; Moragoda et al., 2001; Ruiz de Porras et al., 2016; C. C. Su, Lin, Chen, et al., 2006) in CRC cells. In particular, the natural polyphenol was found to regulate Cyclin D1 expression, a key regulator of the transition from G1 to S phase, via activation of peroxisome proliferator-activated receptor gamma (A. Chen & Xu, 2005), as well as inhibition of activating protein-1 (AP-1) (Jeong et al., 2004) and NF-κB transcription factors (Mukhopadhyay et al., 2002; Ruiz de Porras et al., 2016) (Figure 1). Interestingly, similar results were observed when CRC cells were treated with calebin A, a compound derived from turmeric (Buhrmann et al., 2020).

In fact, in addition to its role in inflammation, NF-κB plays a pivotal role in the proliferation of CRC cells. Thus, curcumin also exerts its antiproliferative effects by inhibiting the NF-κB pathway at several molecular levels (Ruiz de Porras et al., 2016). Moreover, the phytotherapeutic can suppress CRC cell proliferation by repressing the expression of COX-2 through NF-κB inhibition (Goel et al., 2001; Plummer et al., 1999) or through the attenuation of the AMP-activated protein kinase (AMPK)—Akt signaling pathway (Y. K. Lee et al., 2009). Similarly, Johnson and colleagues reported that curcumin inhibits CRC proliferation by inhibiting Akt/mTOR signaling (Johnson et al., 2009) (Figure 1). In addition, curcumin has demonstrated antiproliferative activity through the suppression of the Wnt/β-catenin (Dou et al., 2017) and Notch (Howells et al., 2011) pathways, which are altered in almost all CRCs, leading to their hyperactivation (Tariq & Ghias, 2016; Vinson et al., 2016).

Of note, the uncontrolled proliferation of CRC cells establishes a critical connection to the metastatic process, underscoring the intricate relationship between tumor growth and the potential dissemination of malignancy. In fact, about 20% of patients with CRC present with metastases at the time of diagnosis. Furthermore, 20–50% of patients with localized disease have distant recurrence within 5 years of surgery. The most common sites for metastasis of CRC are the liver and lungs and these metastases are by far the most frequent cause of CRC-related death (Cervantes et al., 2023; Dekker et al., 2019). Therefore, understanding the molecular mechanisms that drive metastasis in CRC is of paramount importance for developing effective therapeutic strategies and improving patient outcome. Among these mechanisms, the process known as EMT plays a pivotal role. EMT is a dynamic cellular program by which epithelial cells lose their characteristics and acquire a mesenchymal phenotype, which enhances their motility and invasive properties as well as their resistance to chemotherapy (H. Cao et al., 2015; Y. Lu, Wu, et al., 2020; Shibue & Weinberg, 2017; Thiery et al., 2009). Several key molecular events

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contribute to EMT, including the downregulation of epithelial markers like E-cadherin and the upregulation of mesenchymal markers like N-cadherin, vimentin, and fibronectin. These alterations can lead to reduced cell adhesion, disruption of tight junctions, and the loss of cellular polarity (Kalluri & Weinberg, 2009; Lamouille et al., 2014; J. Lu et al., 2023; Tsai & Yang, 2013). Curcumin has been shown to reverse EMT (Figure 1) by downregulating vimentin and N-cadherin levels and increasing E-cadherin protein levels (C. Zhang et al., 2018). NF-κB and TGF-β are well known activators of EMT in CRC, especially after chemotherapy treatment (J. Li, Liu, et al., 2015; Y. Li et al., 2017; Singh et al., 2023). Particularly, TGF-β stimulates EMT through SMAD activity by upregulating the synthesis of E-cadherin transcriptional repressors such as SNAIL, TWIST, and ZEB (Lamouille et al., 2014). A growing body of evidence suggests curcumin as regulator of TGF-β in several diseases, including CRC (Ashrafizadeh et al., 2020; Ramamoorthi & Sivalingam, 2014). Furthermore, Yin and colleagues demonstrated that curcumin suppresses EMT through the downregulation of the canonical TGF-β/Smad2/3 signaling pathway, resulting in a reduction in CRC cell migration and proliferation (Figure 1). Moreover, this inhibition was associated with overcoming oxaliplatin resistance (Yin et al., 2019). In the same line, our group found a suppression of TME-induced EMT in CRC cells by calebin A through the NF-κB/Slug axis, TGF-β1, and FAK signaling inhibition (Buhrmann et al., 2021). On the other hand, overactivation of the Wnt/β-catenin pathway promotes EMT by inducing the expression of EMT-related transcription factors, such as SNAIL, which represses E-cadherin, thereby promoting cell invasion in CRC (Yook et al., 2005; H. Zhao et al., 2022). Curcumin reversed 5-fluorouracil (5-FU) resistance by regulating the ten-eleven translocation1 (TET1)-naked cuticle homolog-Wnt signal pathway to prevent EMT progress in CRC cells (Y. Lu, Zhang, et al., 2020).

Remarkably, noncoding RNAs, such as microRNAs (miRNAs), play a critical role in the regulation of EMT and CRC metastasis (Osei et al., 2023) and curcumin was shown to affect the expression of miRNAs associated with tumor growth, chemoresistance, and metastasis in CRC cells (J. Li, Chai, et al., 2022; Toden, Okugawa, Jascur, et al., 2015; Zhou et al., 2017). In a recent study, Liu and colleagues demonstrated that the natural substance promotes mesenchymal-epithelial transition (MET) and prevents the formation of lung metastases in mice by inducing miR-34a and miR-34b/c expression in a ROS/NRF2-dependent and p53-independent manner (C. Liu et al., 2023). Additionally, curcumin has been found to decrease the transcriptional expression of miR-21, a key tumor-promoting factor in CRC (Asangani et al., 2008; Y. Yu et al., 2012), through the inhibition of the AP-1 transcription factor (Mudduluru et al., 2011). In the same line, difluorinated curcumin, an analogue of curcumin, downregulates miR-21 in chemoresistant CRC cells and restores phosphatase and tensin homolog (PTEN) levels, thus reducing Akt phosphorylation (Roy et al., 2013). In addition, the antimetastatic effects of curcumin were also linked to the upregulation of miR-200c (H. Wang et al., 2020). miR-200c, a tumor-suppressive miRNA, belongs to the miR-200 family, which plays a crucial role in the post-transcriptional inhibition of the EMT-related transcription factors ZEB1, ZEB2, SNAIL, and SLUG, resulting in the repression of the mesenchymal phenotype of CRC cells (Brabletz & Brabletz, 2010; Guan et al., 2018). In this vein, Toden and colleagues demonstrated that curcumin upregulates multiple EMT-suppressive miRNAs, such as miR-200c, miR-200b, miR-141, miR-429, miR-101, and miR-34, thereby restoring 5-FU sensitivity in 5-FU-resistant CRC cells by upregulating E-cadherin and downregulating ZEB1 (Toden, Okugawa, Jascur, et al., 2015). Moreover, combination of curcumin and AKBA induces miR-27a downregulation and miR-34a upregulation, leading to cell cycle arrest as well as apoptosis in CRC cells, along with a reduction in tumor growth in xenograft mice (Toden, Okugawa, Buhrmann, et al., 2015).

Hypoxia promotes metastasis in CRC through the activation of the hypoxia inducible transcription factors (HIFs), HIF-1α, and HIF-2α, which regulate genes associated with tumor growth, invasion, angiogenesis, glucose metabolism, EMT, and treatment resistance (Ioannou et al., 2015; X. Lu & Kang, 2010). Several studies suggested curcumin and its analogs as reducers of HIF activity in several human tumor cell lines. Curcumin acts on HIFs through various mechanisms, including degradation of HIF-1α and HIF-2α, disruption of the microtubule cytoskeleton, and inhibition of HIF-1α transcriptional activity (Bahrami et al., 2018). Interestingly, our team demonstrated that calebin A also inhibits tumor microenvironment (TME)-induced expression of the NF-κB/HIF-1α/VEGF axis. This, in turn, affects CRC cell viability, proliferation, and metastatic capacity in a manner similar to that of a specific inhibitor targeting HIF-1α (Brockmueller, Girisa, et al., 2023). Altogether, turmeric compounds are able to limit the proliferation as well as metastasis of CRC cells through modulation of a numerous signaling pathways. Curcumin in particular has already been demonstrated multifunctional qualities in suppressing CRC-expansion as summarized in Figure 1.

3.4 | Curcumin and CRC cancer stem cells

A growing body of evidence indicates a strong correlation between EMT and the development of properties associated with cancer stem cells (CSCs), which leads to increased treatment resistance and a higher likelihood of tumor recurrence (Mani et al., 2008). While constituting only a small subpopulation (<1%) of the total number of tumor cells, CSCs are believed to possess enhanced self-renewal and differentiation capabilities, as well as resistance mechanisms, thereby contributing to treatment failure and the progression of metastasis (Du & Shim, 2016; Hervieu et al., 2021; Najafi et al., 2019). Several preclinical studies have demonstrated the potential of curcumin to target CSCs mainly by modulating the Wnt/β-catenin, Sonic Hedgehog, PI3K/Akt/mTOR and Notch pathways—key signaling pathways involved in the growth and survival of CSCs (Ramasamy et al., 2015). In fact, the phytotherapeutic curcumin enhances the sensitivity of chemoresistant colon CSCs to 5-FU, FOLFOX (5-FU + oxaliplatin), and irinotecan, both in vitro (Fan et al., 2020; Shakibaei et al., 2014; P. Su et al., 2018; Y. Yu et al., 2009) and ex vivo (James et al., 2015). This activity of curcumin ultimately results in the elimination of colorectal CSCs, as evidenced by the decreased expression of CD44, CD166, and CD133 CSC markers. Interestingly, curcumin structural

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analogs with enhanced bioavailability, stability, and pharmacokinetic profiles have demonstrated a higher ability to target colorectal CSCs than curcumin itself. For instance, Kanwar and colleagues demonstrated that difluorinated-curcumin induces a more substantial reduction in the expression of colorectal CSC markers, including CD44, CD166, and ABCG2, compared to curcumin, indicating that it inhibits the growth of FOLFOX-resistant colon CSCs more effectively (Kanwar et al., 2011). In a similar vein, the curcumin analogue GO-YO30 has been shown to be more effective than curcumin in suppressing STAT3 activation, inducing apoptosis and causing cell cycle arrest in colorectal CSCs and suppressing tumor growth in NOD/SCID xenograft mouse models (Lin et al., 2011).

In addition to being involved in EMT, TGF-β also contributes to the maintenance and self-renewal of CSCs (Singh et al., 2023). Using high-density monolayer co-cultures, our group found that curcumin interferes with the TGF-β-mediated crosstalk between tumor cells and stromal fibroblasts in the TME, inhibiting EMT and sensitizing CSCs to 5-FU (Buhrmann et al., 2014). Additionally, Toden and colleagues demonstrated that curcumin downregulates the polycomb group of epigenetic gene silencers, including BMI-1, SUZ12, and EZH2 (Toden, Okugawa, Jascur, et al., 2015), which are a series of chromatin-modifying enzymes that regulate stem cell renewal and pluripotency as a consequence of EMT activity (Boyer et al., 2006). Another important regulator of stemness, migration, invasion, and metastasis in CRC is metastasis-associated in colon cancer 1 (MACC1) (Radhakrishnan et al., 2018). Gullu and colleagues showed that curcumin reduces MACC1 expression in CRC cells, thereby inhibiting proliferation, clonogenicity and cell motility. These findings provide evidence for targeting MACC1 with curcumin as a potential treatment strategy for MACC1-driven tumor progression and metastasis in CRC (Gullu et al., 2022). Overall, curcumin and its analogues reduce the progression of CRC by effectively suppressing CSC development, which is reflected in measurable downregulation of CSC-specific markers such as CD44, CD133, CD166, and ABCG2.

3.5 | Curcumin in CRC cell death

Cell death encompasses various mechanisms, of which apoptosis, necrosis, ferroptosis, pyroptosis, and autophagy have been extensively studied (Nirmala & Lopus, 2020).

Apoptosis is a tightly regulated biological process essential for maintaining tissue homeostasis and eliminating damaged or unwanted cells. Additionally, it plays a pivotal role in orchestrating intricate cellular processes crucial for embryonic development, such as tissue remodeling, morphogenesis, and the precise regulation of cell numbers to establish tissue architecture (Voss & Strasser, 2020). The progression from colorectal epithelium to carcinomas was linked to a gradual suppression of apoptosis. This inhibition of apoptosis in CRC might play a role in fostering tumor growth, promote neoplastic progression, and confer resistance to cytotoxic anticancer agents (Bedi et al., 1995).

Triggered by various intrinsic signals, such as DNA damage or cellular oxidative stress, and extrinsic signals, including death ligands binding to cell surface receptors, apoptosis is initiated through the activation of specific initiator caspases. These initiator caspases, such as caspase-8 and caspase-9, then activate downstream effector caspases, including caspase-3. Activation of these proteins orchestrates the cleavage of crucial cellular substrates, such as DNA repair enzymes and structural proteins, ultimately leading to cell death. Concurrently, the B-cell lymphoma 2 (Bcl-2) protein family plays a critical role in apoptosis modulation by regulating the permeability of the mitochondrial outer membrane and inhibiting the release of cytochrome c, thereby blocking the activation of the intrinsic apoptotic cascade. Hence, the Bcl-2 family consists of both proapoptotic members, such as Bax and Bak, and anti-apoptotic members, such as Bcl-2 and Bcl-XL, in addition to proteins with dual functions. The dynamic balance between these proteins precisely regulates cellular life and death, and their dysfunction can contribute to various pathologies, including various types of cancer. Related to CRC, the majority of tumors, has been associated with an impaired expression of Bcl-2 family molecules (Watson, 2004) (Figure 2).

The anticancer effects of curcumin in CRC are associated with its ability to activate both intrinsic and extrinsic apoptosis through regulating multiple molecular targets and signaling pathways. In particular, curcumin's multifaceted mechanisms involve the activation of caspase cascades, disruption of mitochondrial membrane potential, and the regulation of apoptotic regulatory proteins (Ismail et al., 2019). For instance, several studies have shown that this natural polyphenol promotes Bax and Bak expression and downregulates Bcl-2 and Bcl-xL, increasing the release of cytochrome c from mitochondria and inducing the intrinsic apoptotic pathway in CRC cells (L. D. Guo et al., 2013; Moragoda et al., 2001; C. C. Su, Lin, Li, et al., 2006), at least in part through the inhibition of the NF-κB (Ruiz de Porras et al., 2016; Sandur et al., 2009) or the PI3K/Akt pathway (Jiang et al., 2014) (Figure 2).

On the other hand, an important mechanism of mitochondria-independent/extrinsic induction of apoptosis involves the impact of curcumin on death receptors, members of the TNF receptor superfamily, such as death receptor 5 (DR5) or Fas. Both DR5 and Fas play crucial roles in transmitting death signals from the cellular membrane to the cytoplasmic signaling pathways. Binding of "death" ligands to DR5 or Fas triggers the formation of death-inducing signaling complexes, leading to the activation of caspase-8, which activates caspase-3 and consequently initiates apoptosis (Danial & Korsmeyer, 2004; Wajant, 2002). In a study in HT29 and HCT116 CRC cells, Jung and colleagues demonstrated that curcumin enhances TNFα-related apoptosis-inducing ligand-induced apoptosis through ROS-mediated upregulation of DR5 (E. M. Jung et al., 2005). Furthermore, the phytopharmaceutical has been found to enhance caspase-8 activation, initiating the Fas-mediated extrinsic apoptotic pathway, which in turn leads to the activation of caspase-3 and caspase-7 and the cleavage of Bid, a proapoptotic member of the Bcl-2 protein family, thus facilitating the release of cytochrome c and subsequently inducing apoptosis (A. Cao et al., 2013) (Figure 2). Additionally, it has been reported that another mitochondria-independent apoptotic pathway includes endoplasmic reticulum (ER) stress-induced apoptosis that triggers the unfolded protein response (UPR) aimed at

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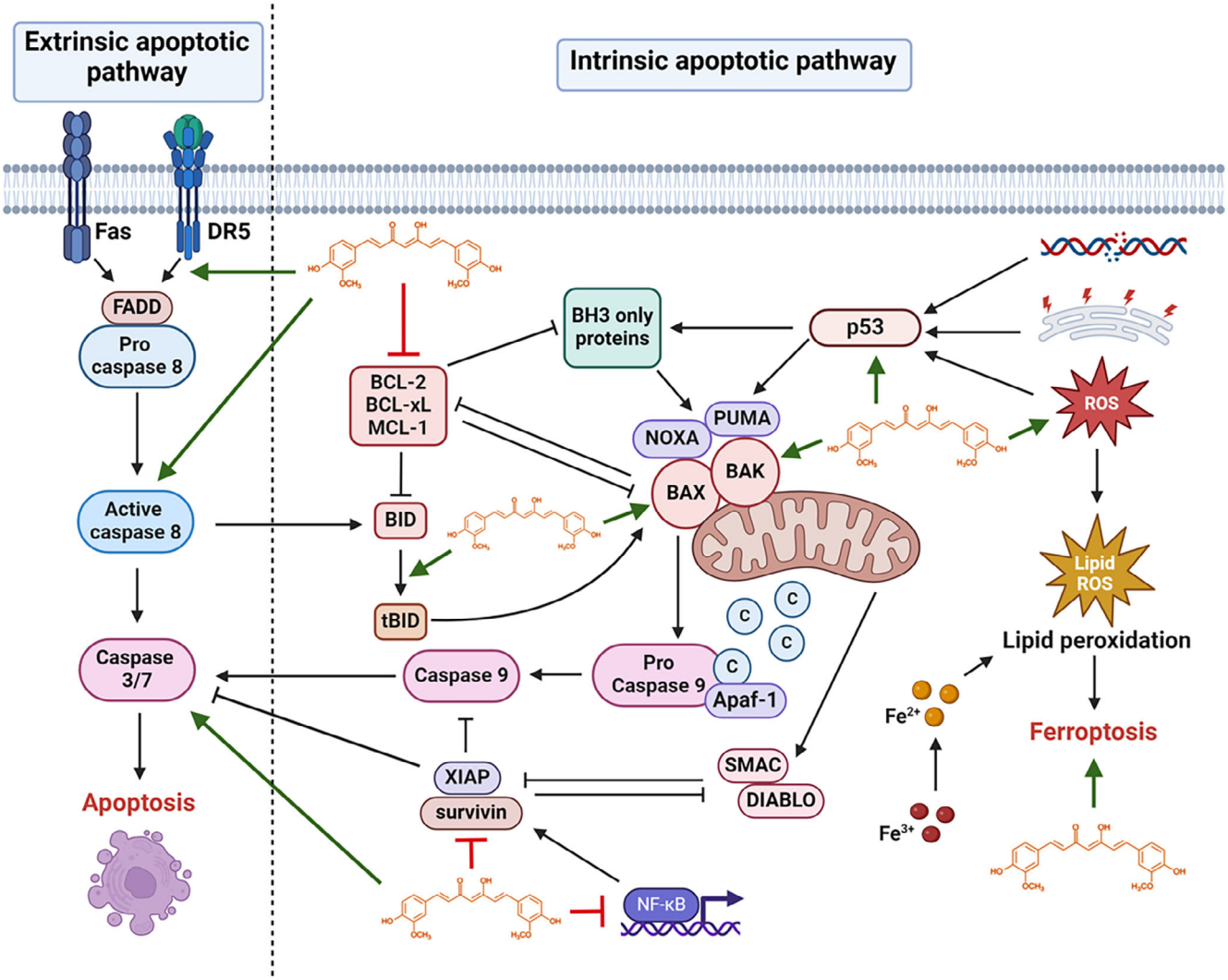

FIGURE 2 Overview of the modulation of intrinsic and extrinsic apoptosis pathways by curcumin in colorectal cancer (CRC). Curcumin triggers apoptosis in CRC by either inducing (green arrows) or inhibiting (red line with a dash) several target molecules and modulating associated signaling pathways. It downregulates anti-apoptotic proteins of the Bcl-2 family and inhibitors of apoptosis proteins, including Survivin and XIAP. Additionally, the polyphenol enhances the production of reactive oxygen species (ROS) and proapoptotic proteins that facilitate the release of mitochondrial cytochrome c (C). Moreover, curcumin upregulates Fas and the death receptor 5 (DR5) receptor, thereby activating the extrinsic apoptotic pathway. Finally, curcumin has also been shown to trigger ferroptosis thereby reducing CRC cell proliferation. Created with Biorender.com.

restoring protein homeostasis (Sano & Reed, 2013). In this context, Cao and colleagues found that curcumin induces ER-stress-mediated apoptosis in HT29 CRC cells (A. Cao et al., 2013).

Inhibitor of apoptosis proteins (IAPs), such as cIAP1/2, XIAP and survivin, also suppress apoptosis by directly inhibiting caspase-3, caspase-7, and caspase-9 (Schimmer, 2004) and dysregulation of IAPs has been associated with CRC cell survival as well as tumor progression (Gullulu et al., 2021). In this scenario, curcumin (L. D. Guo et al., 2013; Ruiz de Porras et al., 2016) and calebin A (Buhrmann et al., 2020) have been shown to downregulate survivin expression in a NF-κB-dependent manner in CRC cells (Figure 2).

The role of ROS in cellular physiological processes depends on its concentration: excessive ROS production promotes apoptosis (Pelicano et al., 2004). Paradoxically, although curcumin's antioxidant potential is widely known, several studies have demonstrated its induction of ROS production, thus promoting apoptosis in CRC (Bhaumik et al., 1999; C. C. Su, Lin, Li, et al., 2006) (Figure 2). Interestingly, Agarwal et al. suggested that curcumin-mediated ROS ascent promoted a ROS-independent mitochondrial apoptotic pathway in cells harboring mutations in both p53 and Smad2, a key mediator of TGF-β cellular response in CRC (A. Agarwal et al., 2018) (Figure 1).

Mutations in the tumor suppressor p53 are common in sporadic CRC (Cancer Genome Atlas, 2012) and although the critical function of p53 in the induction of intrinsic and the extrinsic apoptosis pathway is well known (G. Song et al., 2005; Vazquez et al., 2008), studies on the role of p53 in curcumin-mediated apoptosis induction have

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yielded contradictory results. While some studies have found that curcumin promotes an increase in p53 levels and also induces p53 activation through phosphorylation at Ser15 in vitro (L. D. Guo et al., 2013; G. Song et al., 2005) and in CRC tissues (He et al., 2011), others have reported that curcumin downregulates p53 protein levels (Shehzad et al., 2013). Remarkably, Howells and colleagues observed the proapoptotic effects of curcumin in CRC cells with either wild-type or mutant p53, suggesting that the natural substance induces apoptosis through both p53-dependent and p53-independent pathways (Howells et al., 2007).

In addition to apoptosis, ferroptosis, a regulated form of cell death characterized by iron-dependent lipid peroxidation, has emerged as a compelling area of investigation in the context of CRC. The intricate interplay between cellular iron homeostasis, lipid metabolism, and redox signaling pathways contributes to the susceptibility of CRC cells to ferroptosis (Y. Q. Song et al., 2023). Recent studies have highlighted the dual role of ferroptosis in CRC, acting as both a potential therapeutic target and a mechanism employed by cancer cells to evade conventional treatments (Yan et al., 2023). For example, in a study of CRC cell lines and patient-derived organoids, Miyakazi and colleagues recently demonstrated that the combination of curcumin with *andrographis*, an active compound derived from the Chinese herbal medicine *andrographis paniculate*, promotes ferroptosis through the dual suppression of the ferroptosis regulators glutathione peroxidase-4 and ferroptosis suppressor protein 1 (Miyazaki et al., 2023). Curcumin has also been shown to trigger ferroptosis (Figure 2) and reduce CRC cell proliferation by inhibiting the PI3K/Akt/mTOR signaling pathway (M. Chen et al., 2023) (Figure 1). However, despite these promising preclinical results, further exploration of the relationship between ferroptosis, CRC, and curcumin is essential if these findings are to be translated into effective clinical interventions.

In conclusion, a treatment with curcumin triggers numerous cell death as well as cell arrest cascades in CRC cells. While the involvement of curcumin in activating apoptosis in CRC cells stands out as a crucial mechanism for its antitumoral activity in the scope of our current review, we particularly focus on exploring the role of autophagy and senescence in CRC. The subsequent sections delve into the intricate interplay between curcumin and these specific cellular processes, as understanding curcumin's modulation can provide valuable insights into potential therapeutic applications of curcumin in CRC.

4 | AUTOPHAGY AND SENESCENCE IN CRC CELLS

Autophagy represents a big term with a lot of explanatory potential, as its balance determines whether a cell is protected or destroyed. During embryonic development, autophagic processes are involved in cell growth management and differentiation via regulation of the EMT (Gugnoni et al., 2016). This phenomenon is crucial for the phenotype as well as distribution ability of cells, whereby epithelialization ensures that cells remain in a certain place or mesenchymalization enables their migration (Ranieri et al., 2021).

In terminally differentiated cells, autophagy guarantees a proper degradation and replacement of damaged proteins or cell organelles (Figure 3). To manage this turnover, unusable cellular components are encapsulated in double-membraned vesicles called autophagosomes. Subsequently, autophagosomes fuse with lysosomes, leading to the formation of autolysosomes, specialized compartments where the contents of the autophagosomes are degraded and recycled (Majeed et al., 2022; Patschan et al., 2008). Furthermore, autophagy contributes to the functioning of healthy cell's metabolism. In the intestine (Figure 3), a constant synthesis of the autophagy-specific protein Beclin-1 enables a permanently activated recycling cascade to reduce ER stress and, at the same time, maintain a gut-buffering mucus production (Naama et al., 2023).

Cancer cells, including CRC cells, are permanently exposed to cellular stress due to increased metabolic activity with an increased nutrient requirement, leading to a reprogramming of the cellular metabolism. In this context, intact autophagic processes appear to play an important role in the maintenance of mitochondrial metabolites that are necessary for tumor cell growth (Devenport et al., 2021). Instabilities of cellular metabolism could explain why, depending on the stage of oncogenesis, both repression or promotion of autophagy can contribute to antitumor therapy, since, the autophagy machinery exerts both pro-tumorigenic and tumor-suppressive effects in CRC (Figure 3). This dual role affects a fragile balance that significantly influences cancer initiation, progression, and response to therapy. On the one hand, autophagy acts as a pro-survival mechanism in all cell types, including cancer cells, by promoting the degradation of damaged organelles and misfolded proteins, thereby mitigating cellular stress and fostering cell survival (Dalby et al., 2010; S. Y. Wang et al., 2011). On the other hand, autophagy exhibits tumor-suppressive properties by facilitating the removal of damaged cellular components and preventing the accumulation of genomic aberrations (S. Y. Wang et al., 2011; White & DiPaola, 2009). In relation to intestinal epithelial cells, this means that a promotion of autophagy is beneficial to prevent healthy cell's degeneration and to protect them from cancer initiation (S. Y. Wang et al., 2011). Therefore, autophagy is considered as a tumor suppressor mechanism in early stages of tumorigenesis (Chavez-Dominguez et al., 2020).

However, these survival mechanisms are also used by cancer cells in the early stages of CRC resulting in a pro-tumorigenic aspect, because autophagy can contribute to the maintenance of cellular homeostasis and the sustenance of cancer cell viability under adverse conditions (S. Y. Wang et al., 2011). Hence, inhibition of autophagy in early tumor cells can reduce their metabolism and thus proliferation as well as EMT capacity (Manzoor et al., 2022).

Especially, the role of autophagy in advanced tumor stages is controversially discussed in the literature. On the one hand, there is evidence of a cancer-promoting effect of autophagic processes through stress reduction in the TME (Chavez-Dominguez et al., 2020). But, on the other hand, autophagy is also known to act as a safeguard against uncontrolled CRC cell proliferation, supporting the elimination of malignant cells (Mahgoub et al., 2022). Given this context, the advanced promotion or progression stage of CRC can be disrupted by

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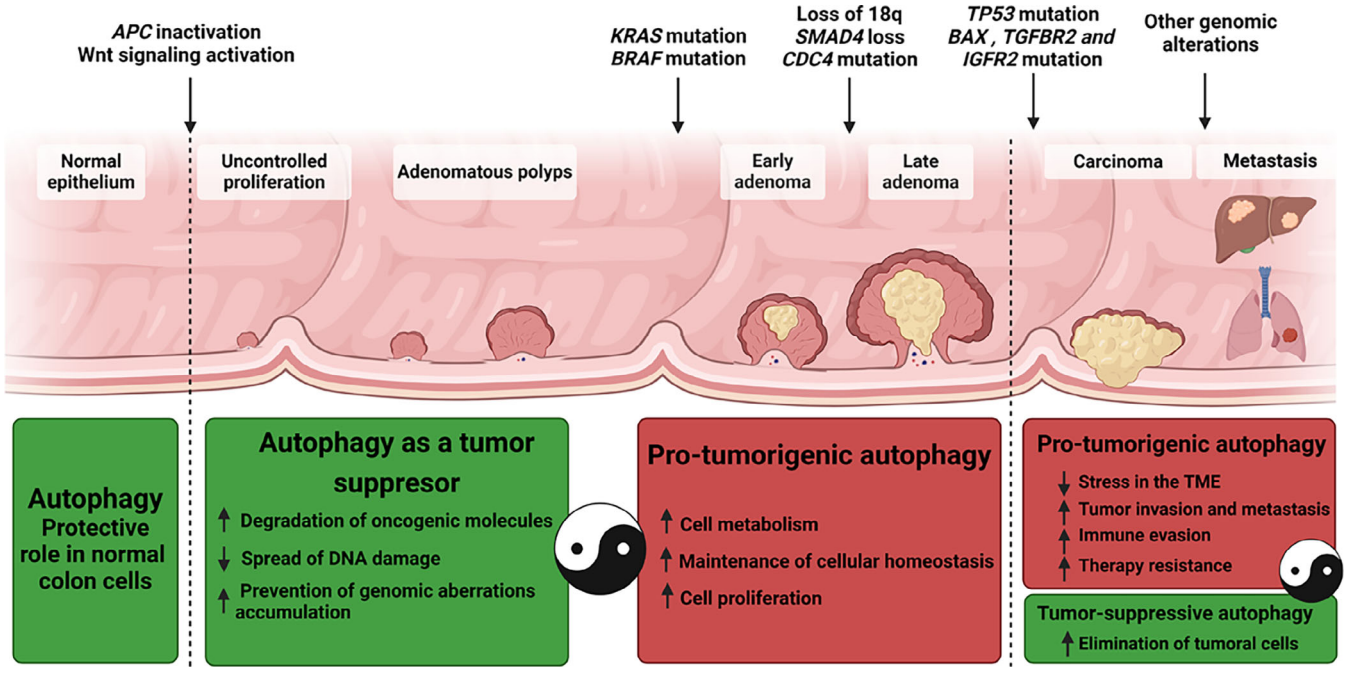

FIGURE 3 Pro-tumorigenic or tumor-suppressive role of autophagy depending on colorectal cancer (CRC) progression stage. Autophagy plays a dual role in CRC progression. In early stages, autophagy demonstrates tumor-suppressive properties by aiding in the elimination of damaged cellular components and preventing the accumulation of genomic aberrations. However, these survival mechanisms are also exploited by cancer cells during the early stages of CRC, leading to a pro-tumorigenic activity. On the other hand, in advanced stages, autophagy serves a dual role, acting as both a tumor promoter by reducing stress in the TME and as a tumor suppressor by eliminating tumoral cells. APC: adenomatous polyposis coli; BAX: Bc-l2-associated X, apoptosis regulator; BRAF: v-raf murine sarcoma viral oncogene homolog B; CDC4: cell division control protein 4; IGFR2: insulin-like growth factor 2 receptor; KRAS: Kirsten rat sarcoma; SMAD4: SMAD family member 4; TGFBR2: transforming growth factor beta receptor 2. Created with Biorender.com.

over-activation of autophagy (Figure 3), which triggers pro-death signaling leading to an apoptosis-like cell elimination (S. Y. Wang et al., 2011). While apoptosis is called programmed cell death type I, autophagy in cancer cells is therefore also known as programmed cell death type II (Dalby et al., 2010; Thorburn, 2008). This systematic division shows that lysosome-related autophagy and caspase-dependent apoptosis occur as separate mechanisms, but they are closely related and can induce each other.

In addition to apoptosis and autophagy, cellular senescence represents a third barrier mechanism against carcinogenesis. Despite cellular senescence acting hand in hand with apoptotic as well as autophagic cascades to prevent promotion and progression of neoplastic cancer cells (Kuilman & Peeper, 2009), it must be clearly distinguished from these cell death mechanisms according to the Nomenclature Committee on Cell Death 2018, because this term describes an irreversible loss of proliferation capacity while maintaining the viability of a cell (Galluzzi et al., 2018). Specifically, this state of irreversible cell cycle arrest is assumed in response to cellular stress caused by epigenetic or DNA damages (Young et al., 2009). Alongside several subgroups, replicative senescence and stress-induced premature senescence are known as major subtypes. Similar to autophagy, a two-sided regulation must also be considered in the context of senescence, because while replicative senescence is involved in cancer prevention, stress-induced senescence can promote inflammation by inducing the senescence-associated secretory phenotype, thereby contributing to cancer development. Due to this complexity, it is the subject of current research to identify how health-promoting senescence can be initiated or health-damaging senescence can be eliminated in cancer patients (Galluzzi et al., 2018). Through the connection via numerous commonly used signaling pathways, autophagy can be activated during senescence and can mediate it (Cassidy & Narita, 2022; Kang & Elledge, 2016; Young et al., 2009). Moreover, autophagy is now recognized as a switchover between apoptosis and cellular senescence. In this context, Patschan et al. demonstrated that pharmacological inhibition of autophagy prevented the development of premature senescence but resulted in an increased rate of apoptosis in human umbilical vein endothelial cells (Patschan et al., 2008). Overall, a functional triangle of tumor control appears here with extensive regulatory significance in CRC cells (Figure 3).

Due to its double-edged sword properties, there are reports of successful suppression of tumor cells through both inhibition or induction of autophagy. The clinical studies with CRC patients have so far mainly examined the effects of suppressing autophagic processes (Mahalingam et al., 2014). Such a pharmacological intervention appears to prevent early senescence but leads to a noticeable increase in apoptosis (Patschan et al., 2008). From the perspective of preclinical research, the focus is currently on the induction of autophagic

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cascades, which can be triggered, for example, by phytopharmaceuticals such as curcumin.

Autophagy is related to the modulation of several signaling pathways, where mTOR/PI3K/Akt plays a central role. Negative feedback in the mTOR pathway correlates with autophagy induction during stress-induced senescence, suggesting a mechanistic link between mTOR signaling and autophagy induction (Young et al., 2009). Especially for CRC, different genes such as *ULK3*, *DAPK1*, *ATG101*, *TSC1*, *MAP1LC3C*, and *SERPINA1* are associated with a poor outcome prognosis through their immunosuppressive influence on the intestinal TME (Y. Wang et al., 2021), but their overexpression is able to induce autophagy (Young et al., 2009). Furthermore, Beclin-1 as well as light chain 3 (LC3) proteins that correlate with advanced CRC disease and influence the response to chemotherapeutic agents (G. F. Guo et al., 2011), are known as parameters for autophagosome formation (Patschan et al., 2008).

Balancing the intricate processes of senescence induction and autophagy could prevent tumor initiation or trigger self-destruction in CRC cells (Figure 3). It is therefore a challenge to establish a modulating medical agent that can be used both prophylactically as well as cotherapeutically and is also well tolerated. Natural substances are offered in this context and several studies in recent years have assessed the potential of curcumin to regulate autophagy in several tumor types, including CRC, but results have been controversial. In the following section, we therefore summarize the trigger or inhibitory effect of curcumin on several key autophagy-related pathways of cell death.

5 | CURCUMIN AS MODULATOR OF AUTOPHAGY IN CRC CELLS: A DOUBLE-EDGED SWORD?

While autophagy is in general a double-edged sword, capable of either causing cell death or promoting cell survival (White & DiPaola, 2009), the majority of studies suggests that curcumin-induced autophagy acts as a pro-death signal in several tumor types, with the PI3K/Akt/mTOR and MAPK pathways playing a central role (Shinojima et al., 2007). mTOR is a serine/threonine kinase that interacts with several proteins to form mTOR complexes (mTORC) 1 and 2. mTORC1 deactivates the established autophagy-regulatory complex via phosphorylation, thereby impacting autophagosome production and suppressing autophagy (C. H. Jung et al., 2010; Zou et al., 2020). Interestingly, Aoki et al. demonstrated that curcumin inhibits the Akt/mTOR/p70S6K pathway and activates the MEK/ERK1/2 signaling, resulting in induction of autophagy in in vitro and in vivo models of malignant glioma (Aoki et al., 2007). Similar results have been demonstrated in thyroid cancer (L. Zhang et al., 2022) and lung cancer cells (F. Liu et al., 2018). Consistent with these findings, co-treatment with curcumin and resveratrol, a stilbene phytoalexin, inhibited the PI3K/Akt/mTOR pathway, thereby promoting autophagy in breast and salivary cancer cells (Arena et al., 2021). In contrast, curcumin has been reported to function as a MEK inhibitor, enhancing apoptosis and autophagy specifically in KRAS-mutant CRC cells treated with regorafenib, a potent multikinase inhibitor, while showing no significant effects in KRAS-wild-type cells (Wu et al., 2019). Although these findings are preliminary, they suggest that the natural polyphenol could induce synthetic lethality with regorafenib in KRAS-mutant cells (Wu et al., 2019). Furthermore, the combination of curcumin and crocin, a hydrophilic carotenoid from *Crocus Sativus Linnaeus*, induced autophagy in SW480 CRC cells by modulating the expression of several autophagy-related genes, such as Akt1, JAK2 and STAT3 (Hosseini et al., 2022). Taken together, the results of these studies reinforce the idea that curcumin induces autophagy by inhibiting PI3K/Akt and activating MAPK pathways (Figure 4 and Table 1).

Although in normal cells, the wild-type p53 protein acts as a tumor suppressor, in tumor cells, the mutated variant may exhibit oncogenic properties (X. Chen et al., 2022). The p53 transcription factor plays a dual role in autophagy. Within the nucleus, it activates the transcription of several genes involved in cell cycle arrest, apoptosis, and autophagy. However, under various conditions that induce cell death, p53 translocates to the cytoplasm, where it triggers outer mitochondrial membrane permeabilization, leading to apoptosis. Additionally, cytoplasmic p53, but not its nuclear counterpart, can suppress autophagy by inhibiting AMPK, a positive regulator of autophagy, and activating the mTOR pathway. It is worth noting that both the activation of apoptosis and the inhibition of autophagy contribute to the effectiveness of p53 as a tumor suppressor (Green & Kroemer, 2009). At transcriptional level, p53 can concurrently regulate autophagy and apoptosis by upregulating genes associated with apoptosis and modulating AMPK-mTORC1 signaling (J. Xu et al., 2020). Specifically, p53 promotes the activation of AMPK, a recognized repressor of mTORC1, thus inducing autophagy in CRC cells (X. Song et al., 2014). Curcumin acts as a direct AMPK agonist, enhancing AMPK phosphorylation and activation (Z. Liu et al., 2017). In this context, it was found that the phytopharmaceutical induced autophagy in Caco-2 cells by the repression of the insulin receptor substrate-1/Akt/PRAS40/mTOR signaling cascade and the activation of the AMPK and MAPK pathways (Kaur & Moreau, 2021). Similarly, curcumin induced autophagy in human lung adenocarcinoma cells through AMPK phosphorylation together with an increase in microtubule-associated protein 1 LC3-II levels (Xiao et al., 2013) (Table 1). Moreover, due to its ability to elevate p53 expression (L. D. Guo et al., 2013; G. Song et al., 2005), the turmeric-compound can indirectly stimulate AMPK, leading to the promotion of autophagy. Importantly, the AMPK/mTOR signaling pathway has been demonstrated to be activated in response to ROS production (G. H. Li, Lin, et al., 2015), and curcumin has been shown to induce this ROS generation, thereby promoting apoptosis in CRC (Bhaumik et al., 1999; Su, Lin, Li, et al., 2006) (Figure 2). Nevertheless, it is widely acknowledged that ROS, as well as reactive nitrogen species, can also initiate and sustain autophagic processes in tumor cells (Azad et al., 2009; Filomeni et al., 2015; L. Li, Tan, et al., 2015). The production of ROS plays a pivotal role in inducing ER stress, a cellular condition associated with the disruption of ER homeostasis. The accumulation of misfolded or unfolded proteins within the ER triggers the

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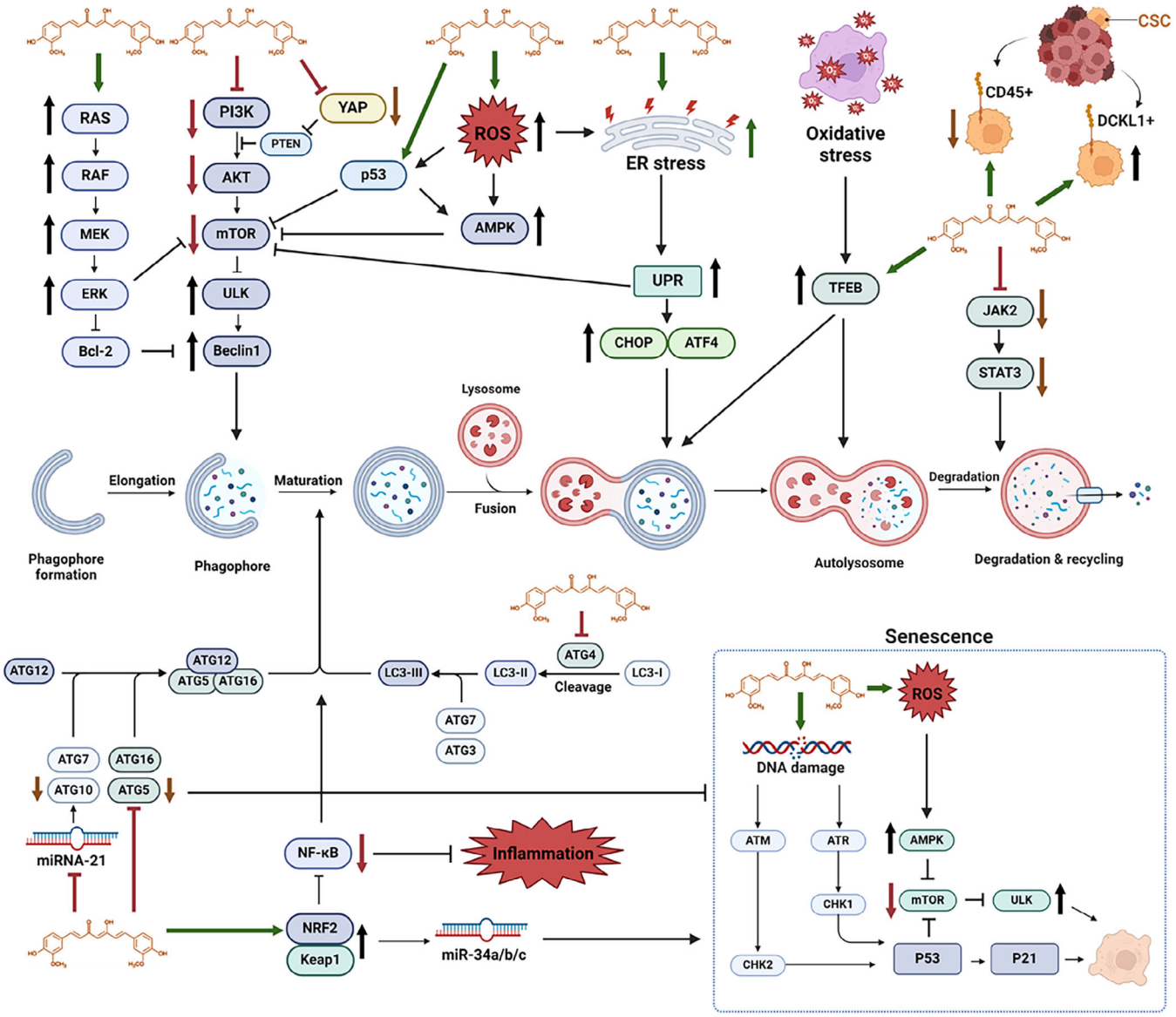

FIGURE 4 An overview of curcumin-modulated signaling pathways in autophagy and senescence. Multiple pathways such as PI3K/Akt and RAS/MEK/ERK signaling can regulate mTORC1, an inhibitor of autophagy, or directly influence autophagy-associated factors. In cancer cells, curcumin suppresses PI3K/Akt/mTOR signaling, inducing autophagy, with p53 activation recognized as a potential initiator. By upregulating p53 expression after DNA damage or ROS production, curcumin may trigger autophagy and senescence induction. AMPK activation is crucial for inducing autophagy in CRC, and its expression is intricately regulated by reactive oxygen species (ROS) or p53. Curcumin activates AMPK, promoting autophagy induction in CRC. Additionally, curcumin induces endoplasmic reticulum (ER) stress, leading to unfolded protein response (UPR) and autophagy. Curcumin induces autophagy in CRC cells by inhibiting the JAK2/STAT3 pathway. Additionally, it promotes autophagy in CRC CSCs and enhances autophagic activity in CRC cells by inhibiting several miRNAs. Notably, autophagic mechanisms can be activated during senescence induction and play a critical role in establishing senescence. Finally, curcumin triggers the NRF2 signaling pathway, leading to the induction of cellular senescence. CSC: cancer stem cells. Green arrows: curcumin activating effects. Red arrows: curcumin inhibitory effects. Created with Biorender.com.

UPR, a cellular mechanism aimed at restoring ER function and maintaining proteostasis (L. Zhao & Ackerman, 2006). The redox-independent interplay between autophagy and the antioxidant response, facilitated via the p62/Kelch-like ECH-associated protein 1 (Keap1)/NRF2 axis, is also a crucial regulatory mechanism in cellular homeostasis. Under conditions of oxidative stress, the accumulation of p62 promotes its interaction with Keap1, disrupting the Keap1-mediated degradation of NRF2. Consequently, stabilized NRF2 translocates to the nucleus, where it orchestrates the transcriptional activation of antioxidant and stress response genes, bolstering the cell's defense against oxidative damage (Filomeni et al., 2015). Curcumin-associated ROS trigger the conversion of LC3-I to LC3-II, leading to autophagy activation and cell death in HCT116 CRC cells (Basile et al., 2013; Y. J. Lee et al., 2011) (Figure 4 and Table 1).

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TABLE 1 Curcumin's autophagy modulation in cancer cells in vitro and in vivo.

Experimental model	Treatment and dose	Mechanisms of action	Reference
U87-MG and U373-MG malignant glioma cell lines Subcutaneous xenograft model of U87-MG cells	Curcumin (20 and 40 μM in vitro/100 mg/kg in vivo)	Akt/mTOR/p70S6K signaling inhibition ERK1/2 signaling activation	(Aoki et al., 2007)
BCPAP thyroid carcinoma cell line	Curcumin (0–50 μM)	PI3K/Akt/mTOR/p70S6K signaling inhibition ERK1/2 signaling activation	(L. Zhang et al., 2022)
A549 non-small cell lung cancer cell line	Curcumin (0-40 μM)	PI3K/Akt/mTOR signaling inhibition	(F. Liu et al., 2018)
HCT116 and HT29 CRC cell lines	Curcumin (0–30 μM)	MEK inhibition	(Wu et al., 2019)
SW480 CRC cell line	Curcumin (6.29 μM) + Crocin (6.29 μM)	JAK2/STAT3 signaling inhibition Akt1 signaling inhibition	(Hosseini et al., 2022)
SALTO-5 salivary gland cancer cell line TUBO mammary cancer cell line	Curcumin (15 μM) + Resveratrol (15 μM)	PI3K/Akt/mTOR signaling inhibition ER-stress induction	(Arena et al., 2021)
Caco-2 CRC cell line	Curcumin (20 μM)	Akt/mTORC1 signaling inhibition AMPK signaling activation IRS-1 inhibition	(Kaur & Moreau, 2021)
A549 lung adenocarcinoma cell line	Curcumin (50 μM)	AMPK signaling activation	(Xiao et al., 2013)
HCT116 CRC cell line	Curcumin (0–40 μM)	ROS production	(Y. J. Lee et al., 2011)
HCT116 CRC cell line	Bis-DeHydroxy Curcumin (30 μM)	ER-stress induction	(Basile et al., 2013)
PC3 prostate cancer cell line	Curcumin (5 μg/ml)	ROS production ER-stress induction UPR activation	(Rivera et al., 2017)
HT29 and DLD-1 CRC cell line DLD-1 HSP27-KD CRC cell line	Curcumin (0–20 μM)	ROS production	(Liang et al., 2018)
HCT116 CRC cell line	Curcumin (0–20 μM)	TFEB activation, nuclear translocation and transcriptional activity increase Akt/mTOR signaling inhibition	(J. Zhang et al., 2016)
N2a and SH-SY5Y neuroblastoma cell lines Adult male Sprague–Dawley rats	Curcumin (10 μM) C1 curcumin derivative (1 μM in vitro/25-mg/kg in vivo)	TFEB activation	(J. X. Song et al., 2016)
HCT116 and SW620 CRC cell lines	Curcumin (0–30 μM)	Inhibition of YAP expression	(Zhu et al., 2018)

Abbreviations: Akt: protein kinase B; AMPK: AMP-activated protein kinase; mTOR: mammalian target of rapamycin; p70S6K: p70S6 kinase; ERK1/2: extracellular signal-regulated kinase 1/2; PI3K: phosphoinositide-3-kinase; MEK: mitogen-activated protein kinase; JAK2: Janus kinase 2; STAT3: signal transducer and activator of transcription 3; ER: endoplasmatic reticulum; mTORC1: mammalian target of rapamycin complex 1; IRS-1: insulin receptor substrate 1; ROS: reactive oxygen species; UPR: unfolded protein response; TFEB: transcription factor EB; YAP: yes-associated protein.

Additionally, several studies have suggested that the UPR may promote autophagy by inhibiting mTOR and upregulate the expression of pro-autophagic genes, including Activating transcription factor 4 and C/EBP homologous protein (CHOP) (Senft & Ronai, 2015). In this context, Rivera and colleagues demonstrated that curcumin induces ER stress-mediated apoptosis in PC3 prostate cancer cells, in a process involving cell cycle arrest, increased ROS levels, autophagy, and UPR induction (Rivera et al., 2017). Here, the induction of autophagy after curcumin treatment was demonstrated by an increased expression of LC3B, a common autophagic marker. In fact, Sala de Oyanguren et al. have shown that the pharmaceutical primarily localizes at the ER and lysosomes, destabilizing these compartments and triggering stress responses, including the UPR and lysosomal stress (Sala de Oyanguren et al., 2020). Interestingly, in breast and salivary cancer cell lines, the combination of curcumin and resveratrol promoted cytotoxic effects by forcing ROS production, stronger ER stress and upregulation of CHOP, the pro-death UPR molecule, leading to autophagy (Arena et al., 2021) (Figure 4 and Table 1). Under oxidative stress conditions, heat shock proteins (HSPs) have been reported to work hand in hand with the antioxidant system to inhibit or neutralize the cellular effects of ROS. They not only assist in the proper folding of proteins affected by oxidative damage but also participate in the clearance of damaged cellular components through chaperone-mediated autophagy (Ikwegbue et al., 2017). Notably, HSP27 knockdown contributes to curcumin resistance in CRC cells by decreasing the production of ROS after treatment and consequently reducing apoptosis and autophagy. In fact, CRC cells exhibiting elevated levels of HSP27 expression demonstrate greater sensitivity to curcumin treatment compared to cells with lower HSP27 expression. These results suggest that HSP27 may be a promising selective target

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in patients with CRC undergoing curcumin treatment (Liang et al., 2018). Additionally, under stress conditions or upon mTOR inhibition, transcription factor EB (TFEB) is activated and translocated to the nucleus, promoting the transcription of several genes related to autophagy induction and lysosome activation (Settembre et al., 2012). Curcumin directly binds to this transcription factor, increasing its activity and thereby enhancing lysosomal function in either a mTOR-dependent (J. Zhang et al., 2016) or -independent manner (J. X. Song et al., 2016).

Curcumin's influence on the NF-κB-NRF2 interplay is also interesting, as the modulation of this signaling pathway is involved in the regulation of inflammation as well as autophagy. In this context, a downregulated NRF2 can activate the pro-inflammatory NF-κB cascade (Wardyn et al., 2015), which is particularly relevant in tumor cells. However, the natural substance curcumin can have a health-promoting effect by inducing the expression of NRF2 in cancer cells, thereby suppressing a cytokine storm and the resulting inflammatory reaction. Ultimately, this regulation contributes to the initiation of cancer cell death (Garufi et al., 2020). Additionally, curcumin has been shown to reverse cytostatic-induced neurotoxicity by balancing NRF2 signaling, autophagic processes and suppressing oxidative as well as ER stress (Liao et al., 2023). Especially for CRC cells, it is further known that curcumin also uses the NRF2 signaling pathway to induce cellular senescence, leading to a reduced proliferation and metastasis capacity (C. Liu et al., 2023). CSCs play a key role in treatment resistance, as well as in the progression, metastasis, and EMT of CRC (Du & Shim, 2016; Hervieu et al., 2021; Najafi et al., 2019). Mao and colleagues demonstrated that a suppression of the proliferation of rapidly cycling LGR5(+) CRC CSCs by curcumin-related autophagy (Mao et al., 2021). In contrast, Kantara et al. had previously found that curcumin unexpectedly promoted the survival of a subset of DCLK1-positive CSCs by the induction of autophagy, suggesting that the combination of curcumin with RNA interference-mediated silencing of DCLK1 (DCLK1-siRNA) demonstrates synergistic inhibitory effects on both apoptotic and autophagic pathways. In conclusion, the study proposes a strategy using a combination of curcumin and DCLK1-siRNA to effectively target CSCs positive for Lgr5/DCLK1/CD44 (Kantara et al., 2014) (Figure 4).

miRNAs also play a crucial role in the regulation of autophagic machinery (J. Li, Chai, et al., 2022), and curcumin has been shown to promote the activation of autophagy in HCT116 CRC cells by inhibiting miR-21-3p and miR-21-5p, which increased the levels of autophagy-related protein (ATG) 10 (J. Li, Chai, et al., 2022). In contrast, a recent study demonstrated a curcumin-associated inhibition of the proliferation of renal cell carcinoma cells by regulating the miR-148/ADAMTS18 axis through the suppression of autophagy (B. Xu et al., 2023).

Finally, the natural polyphenol reduced proliferation and promoted autophagy in CRC cells, as evidenced by increased levels of LC3-II and p62, through the inhibition of Yes-associated protein (YAP) (Zhu et al., 2018), a negative regulator of autophagy in CRC (Jin et al., 2021). Mechanistically, YAP induces activation of the Akt/mTOR signaling pathway by suppressing PTEN in a Hippo-pathway-dependent manner, which corresponds to autophagy in lung adenocarcinoma cells (W. Xu et al., 2021). Moreover, YAP also upregulates the transcription of the apoptosis-inhibitory protein Bcl-2, which may subsequently facilitate cell survival by suppressing autophagy-related cell death in CRC cells (Jin et al., 2021). Interestingly, Bcl-2 has been found to exert a complex role in autophagy regulation. In certain cellular contexts, Bcl-2 can inhibit autophagy by sequestering Beclin-1, a key autophagy regulator, thereby preventing the formation of the Beclin-1-VPS34 complex, which is essential for autophagosome nucleation (H. D. Xu & Qin, 2019) (Figure 4).

It is important to highlight that curcumin-induced autophagy also allows tumor-initiating cells to survive and either differentiate (Zhuang et al., 2012) or become senescent (Mosieniak et al., 2012). In CRC, the crosstalk between autophagy and senescence is multifaceted and context-dependent, as it is influenced by genetic alterations, microenvironmental cues, and therapeutic interventions (Ma et al., 2023). Autophagic mechanisms could be activated during the induction of senescence and, in turn, play a critical role in the establishment of senescence. Indeed, a subset of autophagy-related genes is upregulated during senescence, including ULK3, which induces both autophagy and senescence (Cassidy & Narita, 2022; Rajendran et al., 2019; Young et al., 2009). In this context, Moseniak et al. elegantly demonstrated that curcumin-induced cell senescence and growth inhibition in both p53-positive and p53-negative HCT116 cells were preceded and accompanied by autophagy. Moreover, decreased expression of ATG5, a gene involved in autophagy, inhibited senescence in curcumin-treated cells (Mosieniak et al., 2012). The same research group has shown that this phenomenon could be, at least in part, attributed to the fact that CRC cells treated with curcumin acquire double-strand DNA breaks due to mitotic disturbances. These disruptions, in turn, activate the DNA damage response pathway and induce senescence (Mosieniak et al., 2016). Similarly, in accordance with findings by Young and colleagues, the inhibition of autophagy delays senescence and senescence-associated secretion (Young et al., 2009) (Figure 4). In addition, Chen et al. showed that low-dose curcumin (5 μM) induces senescence in CRC cells without affecting apoptosis. Furthermore, silencing the long noncoding RNA PANDAR in curcumin-treated cells enhanced apoptosis and reduced senescence, possibly through PUMA proapoptotic gene expression stimulation (T. Chen et al., 2017).

Compelling evidence indicates that many chemotherapeutic drugs currently used in clinical practice can induce cellular senescence. Although senescence can be triggered in response to treatment designed to hinder the spread of cancer cells through cell cycle arrest, numerous studies have found that persistent populations can utilize senescence as an adaptive pathway to reinitiate proliferation and assume a more aggressive drug-resistant phenotype (Guillon et al., 2019). Hence, eliminating senescent tumor cells may be a promising therapeutic strategy to prevent tumor recurrence in patients. In this regard, it has been shown that curcumin can induce apoptosis in HCT116 CRC cells with doxorubicin-induced senescence (El-Far et al., 2020). In particular, the curcumin analog EF24 was identified as a potent and broad-spectrum senolytic agent that can selectively eliminate senescent cells (W. Li et al., 2019).

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In conclusion, the findings from all these studies confirm the intricate role of curcumin in regulating autophagy in CRC cells (Figure 4 and Table 1). The collective evidence suggests that the ability of curcumin to stimulate an autophagic cascade adds another layer to its potential as an agent of cancer prevention. Nevertheless, we must acknowledge that our current understanding is based only on preclinical studies, and further preclinical and clinical investigation is imperative to validate these findings and translate them to human applications. Specifically, there is a need for comprehensive studies that corroborate the role of curcumin in inducing autophagy in CRC. Additionally, the potential capacity of curcumin to eliminate senescent cells warrants further attention. This dual focus on autophagy induction and senolysis could pave the way for innovative therapeutic strategies in CRC, highlighting the importance of continued research in this promising area.

6 | AUTOPHAGY-RELATED CLINICAL TRIALS WITH CRC PATIENTS

By harnessing the dual nature of autophagy, researchers can design interventions that either stimulate or inhibit autophagy based on the specific stage of CRC progression (Z. Li, Si, et al., 2022). The role of autophagic processes in CRC has been investigated in six clinical trials since 2009 (Table 2).

Initially, a histological examination (Table 2) demonstrated damage to the liver tissue caused by anti-CRC standard chemotherapeutic agents and an associated inhibition of the self-renewal activities in hepatocytes, noticeable through altered expression of the autophagy markers Beclin-1 and LC3-II as well as the apoptosis-regulatory Bcl-2 protein (Domart et al., 2009). Then, a first trial investigated the effectiveness of a combined vorinostat/hydroxychloroquine (HCQ) treatment in patients with solid malignant tumors, including 12 CRC affected (Table 2). HCQ is a well-known autophagy-suppressor commonly used in the treatment of rheumatoid arthritis, malaria or HIV (M. B. Carroll et al., 2016; Lukas et al., 2019) and represents the currently most favored chemically substance to achieve a pharmacological control in this regard (Karasic et al., 2022). Moreover, vorinostat is the first inhibitor of histone deacetylases (HDACs) approved for cancer therapy. Although adverse effects such as nausea, diarrhea and fatigue were registered, more in-depth research into this drug combination was recommended especially in CRC patients, after observing a successful tumor response (Mahalingam et al., 2014). On the other hand, considering the side effects of standard CRC therapy, an additional study found that patients with mutations/polymorphisms in the autophagy gene FIP200 had an elevated risk of developing high blood pressure in response to 5-fluorouracil + folinic acid + irinotecan (FOLFIRI)/bevacizumab treatment (Berger et al., 2017). Interestingly, in blood samples of patients with KRAS-mutated CRC tumors, an increase in LC3 levels was found after co-infection with oncolytic reovirus (Jiffry et al., 2021).

In recent years, research has focused on supplementation with the autophagy-inhibitory drug HCQ. On this occasion, the previously mentioned combination of vorinostat and HCQ was confirmed for its effectiveness against CRC with a favorable safety profile. However, this combination, when compared to regorafenib a multikinase inhibitor with autophagy-repressor properties presented an inferior progression-free survival (Arora et al., 2022). However, the proposal of a triple combination containing HCQ, regorafenib, and entinostat, an HDAC-inhibitor, failed because the CRC patients developed unbearable side

TABLE 2 Clinical trials (phase I-III) with CRC patients considering autophagy.

CRC patients	Therapy selection	Main results	Study phase	Publication year	Reference
$n = 20$	HCQ/regorafenib/entinostat	The triple therapy scheme was accompanied by severe side effects and no benefit for CRC patients.	I	2022	(Karasic et al., 2022)
$n = 42$	400 mg vorinostat/day and 600 mg HCQ/day or 160 mg regorafenib/day	Both autophagy-targeting therapy schemes improved the anti-CRC immunity.	II	2022	(Arora et al., 2022)
$n = 8$	Pelareorep hijacks	Oncolytic reovirus infection promoted autophagy in KRAS-mutated CRC cells.	I	2021	(Jiffry et al., 2021)
$n = 234$	FOLFIRI and bevacizumab	Polymorphisms in the autophagy-associated FIP200 gene at CRC patients led to hypertension.	III	2017	(Berger et al., 2017)
$n = 12$	200–400 mg vorinostat/day and 400–1000 mg HCQ/day	CRC was receptive to therapy with this drug combination despite observation of side effects.	I	2014	(Mahalingam et al., 2014)
$n = 61$	Conventional chemotherapy	CRC chemotherapy led to liver damage and suppressed the autophagy of hepatocytes resulting in unbalanced expression of Beclin-1, LC3-II, and Bcl-2.	?	2009	(Domart et al., 2009)

Abbreviations: Bcl-2, B-cell lymphoma 2; CRC, colorectal cancer; FOLFIRI, 5-fluorouracil + folinic acid + irinotecan; HCQ, hydroxychloroquine; *n*, number.

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effects such as severe fatigue and rapid weight loss, so that they could not benefit from the therapy (Karasic et al., 2022). Overall, these clinical studies highlight the importance of autophagy regulation in CRC and at the same time show the dose limitation in the use of chemical substances due to intense adverse effects (Table 2).

To the best of our knowledge, although clinical studies have explored the potential of curcumin in cancer prevention and treatment, our literature search did not yield any clinical trials specifically targeting curcumin to investigate autophagy metabolism, either in CRC or in other physiological or pathological health conditions. Nonetheless, it is noteworthy that certain trials indirectly showcased evidence of curcumin's impact on autophagy, despite this not being the primary focus of the studies.

In humans, several clinical trials have evaluated the efficacy of curcumin in suppressing the development of colon premalignant lesions (Table 3). Interestingly, curcumin (480 mg) combined with quercetin (20 mg) orally three times a day for 6 months was associated with a 60% reduction in the number and size of polyps in patients with familial adenomatous polyposis (Cruz-Correa et al., 2006). However, in a double-blind randomized trial of patients with this disease, no difference was found in the mean number or size of lower intestinal tract adenomas between patients given curcumin (3.000 mg/day) and those given placebo for 12 weeks (Cruz-Correa et al., 2018). A further interesting study showed a reduction of aberrant crypt foci, early microscopic lesions in the colon and rectum that serve as precursors to CRC, by 40% in the intestine of healthy subjects after a 30-day intake period of 4 g curcumin daily (Table 3), resulting in a significant decrease in precancerous lesions without any signs of toxic side effects (R. E. Carroll et al., 2011). Moreover, curcumin as a single agent has also been shown to inhibit the recurrence of ulcerative colitis, thereby preventing the development of CRC (Hanai et al., 2006). In the context of chemotherapy, two early phase trials performed by Howells' team reported that the addition of curcumin, at doses of up to 2 g daily, is a secure and well-tolerated complement to FOLFOX chemotherapy in CRC patients with liver metastases (Howells et al., 2019; James et al., 2015).

The possibility of biomonitoring patients, analysis of biomedical material to determine hazardous substances, their metabolites or their biochemical or biological effect parameters, serves as a basis for the following clinical investigations into the effects of curcumin on CRC patients. Thereby, those patients affected from therapy-refractory advanced disease tolerated well a daily intake of 3.6 g of the phytopharmaceutical for 4 months. In addition (Table 3), a reduction of inflammation-related prostaglandin E (PGE) 2 in blood serum was observed and metabolites in both blood and urine emerged as suitable biomarkers for the systemic activity of curcumin (Sharma et al., 2004).

As clinical research into curcumin's influences on CRC began over 20 years ago, the initial focus was on its anti-inflammatory and thus autophagy-related tumor-inhibiting effect, which had been identified in in vitro experiments. In fact, inflammation and autophagy are closely interconnected processes. Autophagy regulates inflammation by removing damaged cellular components and pathogens, thereby controlling the inflammatory response. Conversely, inflammation can impact autophagy by interfering with its normal function, leading to the exacerbation of inflammatory diseases and contributing to cancer progression (Qian

TABLE 3 Clinical trials (phase I-III) with patients at CRC-risk or CRC-disease receiving curcumin-supplementation with a possible autophagy-modulating effect.

Study participants	Therapy selection	Main results	Study phase	Publication year	Reference
$n = 5$, advanced CRC-disease	0.45–3.6 g curcumin/day for 4 months + standard chemotherapy	Inflammatory blood parameters were decreased by curcumin co-treatment.	I	2004	(Sharma et al., 2004)
$n = 5$, CRC-risk: familial adenomatous polyposis	480 mg curcumin + 20 mg quercetin/day for 6 months	Both the size and number of polyps were reduced by polyphenol-therapy.	?	2006	(Cruz-Correa et al., 2006)
$n = 19$, CRC-risk: colitis ulcerosa	Sulfasalazine or mesalamine + 2 g curcumin or placebo/day for 6 months	The maintenance of remission was promoted by curcumin supplementation.	?	2006	(Hanai et al., 2006)
$n = 19$, CRC-risk: smoking + aberrant crypt foci in colonoscopy	2 g or 4 g curcumin/day for 30 days	Precancerous crypt lesions were suppressed in patients who consumed 4 g curcumin/day.	IIa	2011	(R. E. Carroll et al., 2011)
$n = 126$, CRC-disease	360 mg/day for 30 days + surgery	Inflammatory blood levels as well as general quality of health were improved by co-administration of curcumin.	?	2011	(He et al., 2011)
$n = 67$, CRC-disease	500 mg curcuminoids or placebo/day for 8 weeks + surgery + standard chemotherapy	Inflammatory blood parameters as well as quality of life were improved by curcuminoid capsules.	?	2021	(Panahi et al., 2021)

Note: ? - There is no information about the study phase in this manuscript.
Abbreviations: CRC, colorectal cancer; *n*, number.

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et al., 2017). An initial study confirmed that curcumin treatment reduced the levels of COX-2 and PGE2 in the blood of healthy subjects (Plummer et al., 2001). Furthermore, patients with advanced CRC were orally supplemented with Curcuma extracts and here too, the PGE2 levels in the blood were reduced in a dose-dependent manner, though without clear signs of significance (Plummer et al., 2001). The interpretability of these results remained questionable, as pure curcumin was used during the in vitro tests, but only weakly concentrated Curcuma extract was used in the patient trial.

In the meantime, as part of a new study (Table 3), patients were treated with curcuminoid capsules (500 mg daily intake) over a period of 8 weeks and their effects were compared with those in a placebo group. Alongside an improved erythrocyte sedimentation rate, the curcuminoids provided a significant reduction of inflammation represented by a decrease in the serum levels of IL-1α as well as C-reactive protein. Interestingly, the treatment also resulted in increased functional and overall quality of life for CRC patients (Panahi et al., 2021). In addition, it should be mentioned that very recent studies indicate a complex modulation induced by curcumin in the interaction between biomarkers of inflammation and metabolism, which are related with CRC oncogenesis including autophagic processes (Macis et al., 2023).

Ultimately, a goal of every cancer treatment is to induce a senescence-related cell cycle arrest as well as controlled cell death in tumor cells and this is also the focus in rapidly proliferating CRC. A clinical examination (Table 3) demonstrated the anti-inflammatory and apoptosis-inducing regulatory ability of curcumin via downregulation of TNF-α levels in the blood serum and simultaneous induction of the p53 signaling pathway (He et al., 2011).

Taken together, these results underline the importance of early and CRC-preventive modulation by natural polyphenols such as curcumin and it seems sensible to investigate the role of senescence as well as apoptosis induction in this context against the background of a successful influence on autophagy-associated signaling pathways by this phytotherapeutic. The fact that autophagic processes have numerous health-promoting functions in normal cells and the entire body, the fulfillment of which must not be negatively influenced by CRC treatment, should be taken into account as a major challenge of cancer therapy.

7 | DISCREPANCIES AND SUGGESTED SOLUTIONS

The detailed mechanisms of autophagic cascades in CRC cells are a subject of the current research at both the preclinical as well as the clinical level. Due to the complexity of this topic, there are different findings that could lead to confusion and in order to organize them, it is advisable to consider different perspectives.

On the one hand, a reduced autophagic effectiveness is known to favor a malignant degeneration of healthy cells with the consequence of cancer development. On the other hand, an autophagic machinery is able to support CRC cells to become resilient and resistant against classical chemotherapeutic agents. Therefore, a pharmacological inhibition of autophagy was initially investigated in patients suffering from advanced CRC and this was accompanied by therapy-limiting side effects (Karasic et al., 2022).

Very interestingly, the phytopharmaceutical curcumin is well tolerated by humans. To the best of our knowledge, only few side effects and no toxic doses are described so far. Multiple antitumor effects of curcumin against CRC have been demonstrated in vitro and also a significant tumor reduction in clinical settings (Brockmueller, Samuel, et al., 2023). Its induction of apoptosis is undisputed in this regard, but while an initiation of caspase-dependent programmed cell death type I is illuminated in quite detail (W. Xu & Shen, 2024), curcumin's mechanisms of autophagy modulation are discussed contradictorily (Mahalingam et al., 2014). In contrast to clinical trials investigating the antitumor effects of autophagy inhibitors such as HCQ (Mahalingam et al., 2014), the majority of preclinical authors detected a curcumin-related promotion of autophagy in CRC cells in vitro. Furthermore, a treatment with curcumin can induce DNA damages in cancer cells leading to a senescence-associated interruption of the cell cycle (Mosieniak et al., 2016).

After summarizing the current literature, we believe that these opposing views can be reconciled by taking the different metabolic states of the oncogenic stages (initiation, promotion, progression) into account. Against this background, we advocate for an identification of the phase examined as accurately as possible in future publications as this would enable better comparison of their conclusive statements.

The majority of observations about autophagy promotion by curcumin is consistent with the fact that most studies examine advanced CRC situations and is strongly supported by the proven tumor-inhibiting induction of autophagy by curcumin in other types of cancer such as glioma (Aoki et al., 2007), prostate (Rivera et al., 2017), breast, and salivary cancer (Arena et al., 2021). Through the knowledge of the sensitively balanced regulation of autophagy processes, targeted pharmacological autophagy acceleration has so far been avoided in clinical studies for understandable reasons. The use of modulatory phytopharmaceuticals could represent a safe and cost-effective bridge for the co-treatment of different cancer types including CRC. However, it is important to highlight that the poor absorption and water solubility of curcumin, as well as its rapid metabolism and systemic elimination, limits its bioavailability and makes its clinical use a therapeutic challenge. That is why the optimization options for these parameters have been investigated for years. First of all, it has been shown that the addition of piperine, the main component of pepper, increases curcumin's bioavailability in humans by up to 2000%, for example when 2 g curcumin were combined with 20 mg piperine (Shoba et al., 1998). In the meanwhile, several strategies have been explored to overcome this low bioavailability, such as the use of new bioavailable formulations as well as curcumin analogues and derivatives (Dei Cas & Ghidoni, 2019; Stohs et al., 2020). Especially nano-formulations and a new γ-cyclodextrin curcumin appear to lead to a strong improvement in bioavailability, which is reflected in a significant increase in blood plasma levels (Purpura et al., 2018; Sasaki et al., 2011). Overall, the presented and summarized data in this review emphasized the benefit of curcumin as a co-therapeutic agent for CRC. In comparison to other authors who have already reviewed the relevant findings on the

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general mechanisms of action of the natural product (Ojo et al., 2022), this review incorporates the previous findings on curcumin's autophagy modulation from the current literature. Despite the euphoria due to confident future prospects, it should be considered that a plant compound can never be used to cure cancer as a single substance. Rather, the focus is on its importance as a continuous prophylactic or complementary supplement to cytostatic therapy. To ensure that a patient or even a healthy person takes a phytotherapeutic regularly, a high level of compliance is required. For this reason and in order to establish this, a great deal of understanding and the imparting of knowledge within the framework of educational courses would be necessary among the affected population.

8 | SUMMARY AND CONCLUSION

The clinical trials of autophagy regulation underscore its central importance for cancer treatment at all stages of CRC. After reviewing the current literature, curcumin's multifunctional CRC-inhibiting potential was described. Regarding this, the striking qualities of the natural polyphenol against inflammation, proliferation, metastasis, CSC development and imbalances in the gut microbiota as well as cell death mechanisms were particularly noticeable. The previous findings can be expanded to emphasize the significance of curcumin treatment in autophagy modulation, as the phytopharmaceutical is able to maintain self-renewal processes in healthy intestinal cells but also to interrupt it in CRC affected cells. Thus, influencing the autophagic balance leading to the initiation of senescence as well as programmed cell death seems to crystallize as a key mechanism. Although both the clinical relevance of autophagy and the autophagy-regulating effect of curcumin on CRC cells are already known, this knowledge has not yet been combined in clinical studies. This opens up a wide potential for future investigations into a possible co-therapeutic and autophagy-targeting property of the phytotherapeutic agent. Specifically, curcumin could be used as a natural dietary supplement in the daily lifestyle to maintain a healthy gut and counteract the development of tumor cells. Another vision would be to administer the phytopharmaceutical in addition to chemical autophagy modulators or classic cancer therapeutics to CRC patients in order to support their effectiveness on the one hand and mitigate their limiting side effects on the other. Overall, it could be worthwhile to expand future research questions in this regard, especially by transferring the preclinical knowledge from bench to bedside, to establish the clinical efficacy of curcumin.

AUTHOR CONTRIBUTIONS

Aranka Brockmueller: Conceptualization; data curation; investigation; methodology; writing – original draft; writing – review and editing. **Vicenç Ruiz de Porras:** Data curation; methodology; visualization; writing – original draft; writing – review and editing. **Mehdi Shakibaei:** Conceptualization; data curation; investigation; project administration; supervision; visualization; writing – original draft; writing – review and editing.

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The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data are available in the manuscript.

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REFERENCES

Adachi, S., Hamoya, T., Fujii, G., Narita, T., Komiya, M., Miyamoto, S., Kurokawa, Y., Takahashi, M., Takayama, T., Ishikawa, H., Tashiro, K., & Mutoh, M. (2020). Theracurmin inhibits intestinal polyp development in Apc-mutant mice by inhibiting inflammation-related factors. *Cancer Science*, *111*(4), 1367–1374. https://doi.org/10.1111/cas.14329

Agarwal, A., Kasinathan, A., Ganesan, R., Balasubramanian, A., Bhaskaran, J., Suresh, S., Srinivasan, R., Aravind, K. B., & Sivalingam, N. (2018). 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*, *51*, 67–81. https://doi.org/10.1016/j.nutres.2017.12.011

Agarwal, K. A., Tripathi, C. D., Agarwal, B. B., & Saluja, S. (2011). Efficacy of turmeric (curcumin) in pain and postoperative fatigue after laparoscopic cholecystectomy: A double-blind, randomized placebo-controlled study. *Surgical Endoscopy*, *25*(12), 3805–3810. https://doi.org/10.1007/s00464-011-1793-z

Anthwal, A., Thakur, B. K., Rawat, M. S., Rawat, D. S., Tyagi, A. K., & Aggarwal, B. B. (2014). Synthesis, characterization and in vitro anticancer activity of C-5 curcumin analogues with potential to inhibit TNF-alpha-induced NF-kappaB activation. *BioMed Research International*, *2014*, 524161. https://doi.org/10.1155/2014/524161

Aoki, H., Takada, Y., Kondo, S., Sawaya, R., Aggarwal, B. B., & Kondo, Y. (2007). Evidence that curcumin suppresses the growth of malignant gliomas in vitro and in vivo through induction of autophagy: Role of Akt and extracellular signal-regulated kinase signaling pathways. *Molecular Pharmacology*, *72*(1), 29–39. https://doi.org/10.1124/mol.106.033167

Arena, A., Romeo, M. A., Benedetti, R., Masuelli, L., Bei, R., Gilardini Montani, M. S., & Cirone, M. (2021). New insights into curcumin- and resveratrol-mediated anti-cancer effects. *Pharmaceuticals (Basel)*, *14*(11), 1068. https://doi.org/10.3390/ph14111068

Arora, S. P., Tenner, L., Sarantopoulos, J., Morris, J., Liu, Q., Mendez, J. A., Curiel, T., Michalek, J., & Mahalingam, D. (2022). Modulation of autophagy: A phase II study of vorinostat plus hydroxychloroquine versus regorafenib in chemotherapy-refractory metastatic colorectal cancer (mCRC). *British Journal of Cancer*, *127*(6), 1153–1161. https://doi.org/10.1038/s41416-022-01892-6

Asangani, I. A., Rasheed, S. A., Nikolova, D. A., Leupold, J. H., Colburn, N. H., Post, S., & Allgayer, H. (2008). MicroRNA-21 (miR-21) post-

10991573, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.8220, Wiley Online Library on [15/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

transcriptionally downregulates tumor suppressor Pdcd4 and stimulates invasion, intravasation and metastasis in colorectal cancer. *Oncogene*, *27*(15), 2128–2136. https://doi.org/10.1038/sj.onc.1210856

Ashrafizadeh, M., Zarrabi, A., Hushmandi, K., Zarrin, V., Moghadam, E. R., Hashemi, F., Makvandi, P., Samarghandian, S., Khan, H., Hashemi, F., Najafi, M., & Mirzaei, H. (2020). Toward regulatory effects of curcumin on transforming growth factor-beta across different diseases: A review. *Frontiers in Pharmacology*, *11*, 585413. https://doi.org/10.3389/fphar.2020.585413

Azad, M. B., Chen, Y., & Gibson, S. B. (2009). Regulation of autophagy by reactive oxygen species (ROS): Implications for cancer progression and treatment. *Antioxidants & Redox Signaling*, *11*(4), 777–790. https://doi.org/10.1089/ars.2008.2270

Bahrami, A., Atkin, S. L., Majeed, M., & Sahebkar, A. (2018). Effects of curcumin on hypoxia-inducible factor as a new therapeutic target. *Pharmacological Research*, *137*, 159–169. https://doi.org/10.1016/j.phrs.2018.10.009

Baptistella, M. M., Assuncao, R. R. S., Sales de Oliveira, C., Siqueira, A. P., Goncalves Dos Santos, E., de Freitas Silva, M., Lima, E. T. F., Caixeta, E. S., Novaes, R. D., Ferreira, E. B., Ionta, M., Viegas, C., Jr., & Francielli de Oliveira, P. (2023). A synthetic resveratrol-curcumin hybrid derivative exhibits chemopreventive effects on colon pre-neoplastic lesions by targeting Wnt/beta-catenin signaling, anti-inflammatory and antioxidant pathways. *The Journal of Pharmacy and Pharmacology*, rgad077. https://doi.org/10.1093/jpp/rgad077

Basile, V., Belluti, S., Ferrari, E., Gozzoli, C., Ganassi, S., Quaglino, D., Saladini, M., & Imbriano, C. (2013). Bis-dehydroxy-curcumin triggers mitochondrial-associated cell death in human colon cancer cells through ER-stress induced autophagy. *PLoS One*, *8*(1), e53664. https://doi.org/10.1371/journal.pone.0053664

Bedi, A., Pasricha, P. J., Akhtar, A. J., Barber, J. P., Bedi, G. C., Giardiello, F. M., Zehnbauer, B. A., Hamilton, S. R., & Jones, R. J. (1995). Inhibition of apoptosis during development of colorectal cancer. *Cancer Research*, *55*(9), 1811–1816.

Berger, M. D., Yamauchi, S., Cao, S., Hanna, D. L., Sunakawa, Y., Schirripa, M., Matsusaka, S., Yang, D., Groshen, S., Zhang, W., Ning, Y., Okazaki, S., Miyamoto, Y., Suenaga, M., Lonardi, S., Cremolini, C., Falcone, A., Heinemann, V., Loupakis, F., … Lenz, H. J. (2017). Autophagy-related polymorphisms predict hypertension in patients with metastatic colorectal cancer treated with FOLFIRI and bevacizumab: Results from TRIBE and FIRE-3 trials. *European Journal of Cancer*, *77*, 13–20. https://doi.org/10.1016/j.ejca.2017.02.020

Bhaumik, S., Anjum, R., Rangaraj, N., Pardhasaradhi, B. V., & Khar, A. (1999). Curcumin mediated apoptosis in AK-5 tumor cells involves the production of reactive oxygen intermediates. *FEBS Letters*, *456*(2), 311–314. https://doi.org/10.1016/s0014-5793(99)00969-2

Boyer, L. A., Plath, K., Zeitlinger, J., Brambrink, T., Medeiros, L. A., Lee, T. I., Levine, S. S., Wernig, M., Tajonar, A., Ray, M. K., Bell, G. W., Otte, A. P., Vidal, M., Gifford, D. K., Young, R. A., & Jaenisch, R. (2006). Polycomb complexes repress developmental regulators in murine embryonic stem cells. *Nature*, *441*(7091), 349–353. https://doi.org/10.1038/nature04733

Brabletz, S., & Brabletz, T. (2010). The ZEB/miR-200 feedback loop—A motor of cellular plasticity in development and cancer? *EMBO Reports*, *11*(9), 670–677. https://doi.org/10.1038/embor.2010.117

Bray, F., Laversanne, M., Weiderpass, E., & Soerjomataram, I. (2021). The ever-increasing importance of cancer as a leading cause of premature death worldwide. *Cancer*, *127*(16), 3029–3030. https://doi.org/10.1002/cncr.33587

Brockmueller, A., Girisa, S., Motallebi, M., Kunnumakkara, A. B., & Shakibaei, M. (2023). Calebin a targets the HIF-1alpha/NF-kappaB pathway to suppress colorectal cancer cell migration. *Frontiers in Pharmacology*, *14*, 1203436. https://doi.org/10.3389/fphar.2023.1203436

Brockmueller, A., Mueller, A. L., Kunnumakkara, A. B., Aggarwal, B. B., & Shakibaei, M. (2022). Multifunctionality of calebin A in inflammation, chronic diseases and cancer. *Frontiers in Oncology*, *12*, 962066. https://doi.org/10.3389/fonc.2022.962066

Brockmueller, A., Samuel, S. M., Mazurakova, A., Busselberg, D., Kubatka, P., & Shakibaei, M. (2023). Curcumin, calebin A and chemosensitization: How are they linked to colorectal cancer? *Life Sciences*, *318*, 121504. https://doi.org/10.1016/j.lfs.2023.121504

Buhrmann, C., Brockmueller, A., Harsha, C., Kunnumakkara, A. B., Kubatka, P., Aggarwal, B. B., & Shakibaei, M. (2021). Evidence that tumor microenvironment initiates epithelial-to-mesenchymal transition and calebin A can suppress it in colorectal cancer cells. *Frontiers in Pharmacology*, *12*, 699842. https://doi.org/10.3389/fphar.2021.699842

Buhrmann, C., Kraehe, P., Lueders, C., Shayan, P., Goel, A., & Shakibaei, M. (2014). Curcumin suppresses crosstalk between colon cancer stem cells and stromal fibroblasts in the tumor microenvironment: Potential role of EMT. *PLoS One*, *9*(9), e107514. https://doi.org/10.1371/journal.pone.0107514

Buhrmann, C., Shayan, P., Banik, K., Kunnumakkara, A. B., Kubatka, P., Koklesova, L., & Shakibaei, M. (2020). Targeting NF-kappaB signaling by calebin A, a compound of turmeric, in multicellular tumor microenvironment: Potential role of apoptosis induction in CRC cells. *Biomedicine*, *8*(8), 236. https://doi.org/10.3390/biomedicines8080236

Burtin, F., Mullins, C. S., & Linnebacher, M. (2020). Mouse models of colorectal cancer: Past, present and future perspectives. *World Journal of Gastroenterology*, *26*(13), 1394–1426. https://doi.org/10.3748/wjg.v26.i13.1394

Cancer Genome Atlas, N. (2012). Comprehensive molecular characterization of human colon and rectal cancer. *Nature*, *487*(7407), 330–337. https://doi.org/10.1038/nature11252

Cao, A., Li, Q., Yin, P., Dong, Y., Shi, H., Wang, L., Ji, G., Xie, J., & Wu, D. (2013). Curcumin induces apoptosis in human gastric carcinoma AGS cells and colon carcinoma HT-29 cells through mitochondrial dysfunction and endoplasmic reticulum stress. *Apoptosis*, *18*(11), 1391–1402. https://doi.org/10.1007/s10495-013-0871-1

Cao, H., Xu, E., Liu, H., Wan, L., & Lai, M. (2015). Epithelial-mesenchymal transition in colorectal cancer metastasis: A system review. *Pathology, Research and Practice*, *211*(8), 557–569. https://doi.org/10.1016/j.prp.2015.05.010

Carroll, M. B., Fields, J. H., & Clerc, P. G. (2016). Rheumatoid arthritis in patients with HIV: Management challenges. *Open Access Rheumatology: Research and Reviews*, *8*, 51–59. https://doi.org/10.2147/oarrr.S87312

Carroll, R. E., Benya, R. V., Turgeon, D. K., Vareed, S., Neuman, M., Rodriguez, L., Kakarala, M., Carpenter, P. M., McLaren, C., Meyskens, F. L., Jr., & Brenner, D. E. (2011). Phase IIa clinical trial of curcumin for the prevention of colorectal neoplasia. *Cancer Prevention Research*, *4*(3), 354–364. https://doi.org/10.1158/1940-6207.Capr-10-0098

Casasanta, M. A., Yoo, C. C., Udayasuryan, B., Sanders, B. E., Umaña, A., Zhang, Y., Peng, H., Duncan, A. J., Wang, Y., Li, L., Verbridge, S. S., & Slade, D. J. (2020). Fusobacterium nucleatum host-cell binding and invasion induces IL-8 and CXCL1 secretion that drives colorectal cancer cell migration. *Science Signaling*, *13*(641), eaba9157. https://doi.org/10.1126/scisignal.aba9157

Cassidy, L. D., & Narita, M. (2022). Autophagy at the intersection of aging, senescence, and cancer. *Molecular Oncology*, *16*(18), 3259–3275. https://doi.org/10.1002/1878-0261.13269

Cervantes, A., Adam, R., Roselló, S., Arnold, D., Normanno, N., Taïeb, J., Seligmann, J., De Baere, T., Osterlund, P., Yoshino, T., Martinelli, E., & ESMO Guidelines Committee. (2023). Metastatic colorectal cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Annals of Oncology*, *34*(1), 10–32. https://doi.org/10.1016/j.annonc.2022.10.003

Chaturvedi, M. M., Sung, B., Yadav, V. R., Kannappan, R., & Aggarwal, B. B. (2011). NF-kappaB addiction and its role in cancer: 'One size does not

10991573, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.8220, Wiley Online Library on [15/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

fit all'. *Oncogene*, *30*(14), 1615–1630. https://doi.org/10.1038/onc.2010.566

Chavez-Dominguez, R., Perez-Medina, M., Lopez-Gonzalez, J. S., Galicia-Velasco, M., & Aguilar-Cazares, D. (2020). The double-edge sword of autophagy in cancer: From tumor suppression to pro-tumor activity. *Frontiers in Oncology*, *10*, 578418. https://doi.org/10.3389/fonc.2020.578418

Chen, A., & Xu, J. (2005). Activation of PPARgamma by curcumin inhibits Moser cell growth and mediates suppression of gene expression of cyclin D1 and EGFR. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, *288*(3), G447–G456. https://doi.org/10.1152/ajpgi.00209.2004

Chen, M., Tan, A. H., & Li, J. (2023). Curcumin represses colorectal cancer cell proliferation by triggering ferroptosis via PI3K/Akt/mTOR signaling. *Nutrition and Cancer*, *75*(2), 726–733. https://doi.org/10.1080/01635581.2022.2139398

Chen, T., Yang, P., Wang, H., & He, Z. Y. (2017). Silence of long noncoding RNA PANDAR switches low-dose curcumin-induced senescence to apoptosis in colorectal cancer cells. *Oncotargets and Therapy*, *10*, 483–491. https://doi.org/10.2147/OTT.S127547

Chen, X., Zhang, T., Su, W., Dou, Z., Zhao, D., Jin, X., Lei, H., Wang, J., Xie, X., Cheng, B., Li, Q., Zhang, H., & Di, C. (2022). Mutant p53 in cancer: From molecular mechanism to therapeutic modulation. *Cell Death & Disease*, *13*(11), 974. https://doi.org/10.1038/s41419-022-05408-1

Choudhuri, T., Pal, S., Das, T., & Sa, G. (2005). Curcumin selectively induces apoptosis in deregulated cyclin D1-expressed cells at G2 phase of cell cycle in a p53-dependent manner. *The Journal of Biological Chemistry*, *280*(20), 20059–20068. https://doi.org/10.1074/jbc.M410670200

Chung, L., Thiele Orberg, E., Geis, A. L., Chan, J. L., Fu, K., DeStefano Shields, C. E., Dejea, C. M., Fathi, P., Chen, J., Finard, B. B., Tam, A. J., McAllister, F., Fan, H., Wu, X., Ganguly, S., Lebid, A., Metz, P., Van Meerbeke, S. W., Huso, D. L., … Housseau, F. (2018). *Bacteroides fragilis* toxin coordinates a pro-carcinogenic inflammatory cascade via targeting of colonic epithelial cells. *Cell Host & Microbe*, *23*(2), 203–214 e205. https://doi.org/10.1016/j.chom.2018.01.007

Cruz-Correa, M., Hylind, L. M., Marrero, J. H., Zahurak, M. L., Murray-Stewart, T., Casero, R. A., Jr., Montgomery, E. A., Iacobuzio-Donahue, C., Brosens, L. A., Offerhaus, G. J., Umar, A., Rodriguez, L. M., & Giardiello, F. M. (2018). Efficacy and safety of curcumin in treatment of intestinal adenomas in patients with familial adenomatous polyposis. *Gastroenterology*, *155*(3), 668–673. https://doi.org/10.1053/j.gastro.2018.05.031

Cruz-Correa, M., Shoskes, D. A., Sanchez, P., Zhao, R., Hylind, 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*, *4*(8), 1035–1038. https://doi.org/10.1016/j.cgh.2006.03.020

Dalby, K. N., Tekedereli, I., Lopez-Berestein, G., & Ozpolat, B. (2010). Targeting the prodeath and prosurvival functions of autophagy as novel therapeutic strategies in cancer. *Autophagy*, *6*(3), 322–329. https://doi.org/10.4161/auto.6.3.11625

Danial, N. N., & Korsmeyer, S. J. (2004). Cell death: critical control points. *Cell*, *116*(2), 205–219. https://doi.org/10.1016/s0092-8674(04)00046-7

Dasiram, J. D., Ganesan, R., Kannan, J., Kotteeswaran, V., & Sivalingam, N. (2017). Curcumin inhibits growth potential by G1 cell cycle arrest and induces apoptosis in p53-mutated COLO 320DM human colon adenocarcinoma cells. *Biomedicine & Pharmacotherapy*, *86*, 373–380. https://doi.org/10.1016/j.biopha.2016.12.034

Dei Cas, M., & Ghidoni, R. (2019). Dietary curcumin: Correlation between bioavailability and health potential. *Nutrients*, *11*(9), 2147. https://doi.org/10.3390/nu11092147

Dekker, E., Tanis, P. J., Vleugels, J. L. A., Kasi, P. M., & Wallace, M. B. (2019). Colorectal cancer. *Lancet*, *394*(10207), 1467–1480. https://doi.org/10.1016/S0140-6736(19)32319-0

Devenport, S. N., Singhal, R., Radyk, M. D., Taranto, J. G., Kerk, S. A., Chen, B., Goyert, J. W., Jain, C., Das, N. K., Oravecz-Wilson, K., Zhang, L., Greenson, J. K., Chen, Y. E., Soleimanpour, S. A., Reddy, P., Lyssiotis, C. A., & Shah, Y. M. (2021). Colorectal cancer cells utilize autophagy to maintain mitochondrial metabolism for cell proliferation under nutrient stress. *JCI Insight*, *6*(14), e138835. https://doi.org/10.1172/jci.insight.138835

Domart, M. C., Esposti, D. D., Sebagh, M., Olaya, N., Harper, F., Pierron, G., Franc, B., Tanabe, K. K., Debuire, B., Azoulay, D., Brenner, C., & Lemoine, A. (2009). Concurrent induction of necrosis, apoptosis, and autophagy in ischemic preconditioned human livers formerly treated by chemotherapy. *Journal of Hepatology*, *51*(5), 881–889. https://doi.org/10.1016/j.jhep.2009.06.028

Dou, H., Shen, R., Tao, J., Huang, L., Shi, H., Chen, H., Wang, Y., & Wang, T. (2017). Curcumin suppresses the colon cancer proliferation by inhibiting Wnt/beta-catenin pathways via miR-130a. *Frontiers in Pharmacology*, *8*, 877. https://doi.org/10.3389/fphar.2017.00877

Du, B., & Shim, J. S. (2016). Targeting epithelial-mesenchymal transition (EMT) to overcome drug resistance in cancer. *Molecules*, *21*(7), 965. https://doi.org/10.3390/molecules21070965

El-Far, A. H., Darwish, N. H. E., & Mousa, S. A. (2020). Senescent colon and Breast cancer cells induced by doxorubicin exhibit enhanced sensitivity to curcumin, caffeine, and thymoquinone. *Integrative Cancer Therapies*, *19*, 1534735419901160. https://doi.org/10.1177/1534735419901160

Elzagheid, A., Emaetig, F., Alkikhia, L., Buhmeida, A., Syrjanen, K., El-Faitori, O., Latto, M., Collan, Y., & Pyrhonen, S. (2013). High cyclooxygenase-2 expression is associated with advanced stages in colorectal cancer. *Anticancer Research*, *33*(8), 3137–3143.

Fan, X., Zhu, M., Qiu, F., Li, W., Wang, M., Guo, Y., Xi, X., & Du, B. (2020). Curcumin may be a potential adjuvant treatment drug for colon cancer by targeting CD44. *International Immunopharmacology*, *88*, 106991. https://doi.org/10.1016/j.intimp.2020.106991

Filomeni, G., De Zio, D., & Cecconi, F. (2015). Oxidative stress and autophagy: The clash between damage and metabolic needs. *Cell Death and Differentiation*, *22*(3), 377–388. https://doi.org/10.1038/cdd.2014.150

Francipane, M. G., & Lagasse, E. (2014). mTOR pathway in colorectal cancer: An update. *Oncotarget*, *5*(1), 49–66. https://doi.org/10.18632/oncotarget.1548

Galluzzi, L., Vitale, I., Aaronson, S. A., Abrams, J. M., Adam, D., Agostinis, P., Alnemri, E. S., Altucci, L., Amelio, I., Andrews, D. W., Annicchiarico-Petruzzelli, M., Antonov, A. V., Arama, E., Baehrecke, E. H., Barlev, N. A., Bazan, N. G., Bernassola, F., Bertrand, M. J. M., Bianchi, K., … Kroemer, G. (2018). Molecular mechanisms of cell death: Recommendations of the nomenclature committee on cell death 2018. *Cell Death and Differentiation*, *25*(3), 486–541. https://doi.org/10.1038/s41418-017-0012-4

Garufi, A., Baldari, S., Pettinari, R., Gilardini Montani, M. S., D'Orazi, V., Pistritto, G., Crispini, A., Giorno, E., Toietta, G., Marchetti, F., Cirone, M., & D'Orazi, G. (2020). A ruthenium(II)-curcumin compound modulates NRF2 expression balancing the cancer cell death/survival outcome according to p53 status. *Journal of Experimental & Clinical Cancer Research*, *39*(1), 122. https://doi.org/10.1186/s13046-020-01628-5

Giordano, A., & Tommonaro, G. (2019). Curcumin and cancer. *Nutrients*, *11*(10), 2376. https://doi.org/10.3390/nu11102376

Girardi, B., Pricci, M., Giorgio, F., Piazzolla, M., Iannone, A., Losurdo, G., Principi, M., Barone, M., Ierardi, E., & Di Leo, A. (2020). Silymarin, boswellic acid and curcumin enriched dietetic formulation reduces the growth of inherited intestinal polyps in an animal model. *World Journal of Gastroenterology*, *26*(14), 1601–1612. https://doi.org/10.3748/wjg.v26.i14.1601

Girardi, B., Principi, M., Pricci, M., Giorgio, F., Iannone, A., Losurdo, G., Ierardi, E., Di Leo, A., & Barone, M. (2018). Chemoprevention of inflammation-related colorectal cancer by silymarin-, acetyl-11-keto-

10991573, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.8220, Wiley Online Library on [15/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

beta-boswellic acid-, curcumin- and maltodextrin-enriched dietetic formulation in animal model. *Carcinogenesis*, *39*(10), 1274–1282. https://doi.org/10.1093/carcin/bgy104

Goel, A., Boland, C. R., & Chauhan, D. P. (2001). Specific inhibition of cyclooxygenase-2 (COX-2) expression by dietary curcumin in HT-29 human colon cancer cells. *Cancer Letters*, *172*(2), 111–118. https://doi.org/10.1016/s0304-3835(01)00655-3

Green, D. R., & Kroemer, G. (2009). Cytoplasmic functions of the tumour suppressor p53. *Nature*, *458*(7242), 1127–1130. https://doi.org/10.1038/nature07986

Guan, T., Dominguez, C. X., Amezquita, R. A., Laidlaw, B. J., Cheng, J., Henao-Mejia, J., Williams, A., Flavell, R. A., Lu, J., & Kaech, S. M. (2018). ZEB1, ZEB2, and the miR-200 family form a counterregulatory network to regulate CD8(+) T cell fates. *The Journal of Experimental Medicine*, *215*(4), 1153–1168. https://doi.org/10.1084/jem.20171352

Gugnoni, M., Sancisi, V., Manzotti, G., Gandolfi, G., & Ciarrocchi, A. (2016). Autophagy and epithelial-mesenchymal transition: An intricate interplay in cancer. *Cell Death & Disease*, *7*(12), e2520. https://doi.org/10.1038/cddis.2016.415

Guillon, J., Petit, C., Toutain, B., Guette, C., Lelievre, E., & Coqueret, O. (2019). Chemotherapy-induced senescence, an adaptive mechanism driving resistance and tumor heterogeneity. *Cell Cycle*, *18*(19), 2385–2397. https://doi.org/10.1080/15384101.2019.1652047

Gullu, N., Smith, J., Herrmann, P., & Stein, U. (2022). MACC1-dependent antitumor effect of curcumin in colorectal cancer. *Nutrients*, *14*(22), 4792. https://doi.org/10.3390/nu14224792

Gullulu, O., Hehlgans, S., Rodel, C., Fokas, E., & Rodel, F. (2021). Tumor suppressor protein p53 and inhibitor of apoptosis proteins in colorectal cancer-a promising signaling network for therapeutic interventions. *Cancers (Basel)*, *13*(4), 624. https://doi.org/10.3390/cancers13040624

Guo, G. F., Jiang, W. Q., Zhang, B., Cai, Y. C., Xu, R. H., Chen, X. X., Wang, F., & Xia, L. P. (2011). Autophagy-related proteins Beclin-1 and LC3 predict cetuximab efficacy in advanced colorectal cancer. *World Journal of Gastroenterology*, *17*(43), 4779–4786. https://doi.org/10.3748/wjg.v17.i43.4779

Guo, L. D., Chen, X. J., Hu, Y. H., Yu, Z. J., Wang, D., & Liu, J. Z. (2013). Curcumin inhibits proliferation and induces apoptosis of human colorectal cancer cells by activating the mitochondria apoptotic pathway. *Phytotherapy Research*, *27*(3), 422–430. https://doi.org/10.1002/ptr.4731

Guo, Y., Wu, R., Gaspar, J. M., Sargsyan, D., Su, Z. Y., Zhang, C., Gao, L., Cheng, D., Li, W., Wang, C., Yin, R., 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

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. (2006). Curcumin maintenance therapy for ulcerative colitis: Randomized, multicenter, double-blind, placebo-controlled trial. *Clinical Gastroenterology and Hepatology*, *4*(12), 1502–1506. https://doi.org/10.1016/j.cgh.2006.08.008

Hashemi, M., Abbaszadeh, S., Rashidi, M., Amini, N., Talebi Anaraki, K., Motahhary, M., Khalilipouya, E., Harif Nashtifani, A., Shafiei, S., Ramezani Farani, M., Nabavi, N., Salimimoghadam, S., Aref, A. R., Raesi, R., Taheriazam, A., Entezari, M., & Zha, W. (2023). STAT3 as a newly emerging target in colorectal cancer therapy: Tumorigenesis, therapy response, and pharmacological/nanoplatform strategies. *Environmental Research*, *233*, 116458. https://doi.org/10.1016/j.envres.2023.116458

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

Hemminki, K., Li, X., Sundquist, J., & Sundquist, K. (2009). Cancer risks in Crohn disease patients. *Annals of Oncology*, *20*(3), 574–580. https://doi.org/10.1093/annonc/mdn595

Hervieu, C., Christou, N., Battu, S., & Mathonnet, M. (2021). The role of cancer stem cells in colorectal cancer: From the basics to novel clinical trials. *Cancers (Basel)*, *13*(5), 1092. https://doi.org/10.3390/cancers13051092

Hosseini, S. S., Reihani, R. Z., Doustvandi, M. A., Amini, M., Zargari, F., Baradaran, B., Yari, A., Hashemi, M., Tohidast, M., & Mokhtarzadeh, A. (2022). Synergistic anticancer effects of curcumin and crocin on human colorectal cancer cells. *Molecular Biology Reports*, *49*(9), 8741–8752. https://doi.org/10.1007/s11033-022-07719-0

Howells, L. M., Iwuji, C. O. O., Irving, G. R. B., 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 FOLFOX 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

Howells, L. M., Mitra, A., & Manson, M. M. (2007). Comparison of oxaliplatin- and curcumin-mediated antiproliferative effects in colorectal cell lines. *International Journal of Cancer*, *121*(1), 175–183. https://doi.org/10.1002/ijc.22645

Howells, L. M., Sale, S., Sriramareddy, S. N., Irving, G. R., Jones, D. J., Ottley, C. J., Pearson, D. G., Mann, C. D., Manson, M. M., Berry, D. P., Gescher, A., Steward, W. P., & Brown, K. (2011). Curcumin ameliorates oxaliplatin-induced chemoresistance in HCT116 colorectal cancer cells in vitro and in vivo. *International Journal of Cancer*, *129*(2), 476–486. https://doi.org/10.1002/ijc.25670

Hussain, A., Qazi, A. K., Mupparapu, N., Kumar, A., Mintoo, M. J., Mahajan, G., Sharma, P. R., Singh, S. K., Bharate, S. B., Zargar, M. A., Ahmed, Q. N., Mondhe, D. M., Vishwakarma, R. A., & Hamid, A. (2016). A novel PI3K axis selective molecule exhibits potent tumor inhibition in colorectal carcinogenesis. *Molecular Carcinogenesis*, *55*(12), 2135–2155. https://doi.org/10.1002/mc.22457

Ikwegbue, P. C., Masamba, P., Oyinloye, B. E., & Kappo, A. P. (2017). Roles of heat shock proteins in apoptosis, oxidative stress, human inflammatory diseases, and cancer. *Pharmaceuticals*, *11*(1), 2. https://doi.org/10.3390/ph11010002

Ioannou, M., Paraskeva, E., Baxevanidou, K., Simos, G., Papamichali, R., Papacharalambous, C., Samara, M., & Koukoulis, G. (2015). HIF-1alpha in colorectal carcinoma: Review of the literature. *J BUON*, *20*(3), 680–689.

Ismail, N. I., Othman, I., Abas, F., Lajis N. H., & Naidu, R. (2019). Mechanism of apoptosis induced by curcumin in colorectal cancer. *International Journal of Molecular Sciences*, *20*(10), 2454. https://doi.org/10.3390/ijms20102454

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 FOLFOX chemotherapy. *Cancer Letters*, *364*(2), 135–141. https://doi.org/10.1016/j.canlet.2015.05.005

Jeong, W. S., Kim, I. W., Hu, R., & Kong, A. N. (2004). Modulation of AP-1 by natural chemopreventive compounds in human colon HT-29 cancer cell line. *Pharmaceutical Research*, *21*(4), 649–660. https://doi.org/10.1023/b:pham.0000022412.69380.d7

Jiang, Q. G., Li, T. Y., Liu, D. N., & Zhang, H. T. (2014). PI3K/Akt pathway involving into apoptosis and invasion in human colon cancer cells LoVo. *Molecular Biology Reports*, *41*(5), 3359–3367. https://doi.org/10.1007/s11033-014-3198-2

Jiffry, J., Thavornwatanayong, T., Rao, D., Fogel, E. J., Saytoo, D., Nahata, R., Guzik, H., Chaudhary, I., Augustine, T., Goel, S., & Maitra, R. (2021).

10991573, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.8220, Wiley Online Library on [15/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Oncolytic reovirus (pelareorep) induces autophagy in KRAS-mutated colorectal cancer. *Clinical Cancer Research*, *27*(3), 865–876. https://doi.org/10.1158/1078-0432.Ccr-20-2385

Jin, L., Chen, Y., Cheng, D., He, Z., Shi, X., Du, B., Xi, X., Gao, Y., & Guo, Y. (2021). YAP inhibits autophagy and promotes progression of colorectal cancer via upregulating Bcl-2 expression. *Cell Death & Disease*, *12*(5), 457. https://doi.org/10.1038/s41419-021-03722-8

Jobin, C., Bradham, C. A., Russo, M. P., Juma, B., Narula, A. S., Brenner, D. A., & Sartor, R. B. (1999). Curcumin blocks cytokine-mediated NF-kappa B activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappa B kinase activity. *Journal of Immunology*, *163*(6), 3474–3483.

Johnson, S. M., Gulhati, P., Arrieta, I., Wang, X., Uchida, T., Gao, T., & Evers, B. M. (2009). Curcumin inhibits proliferation of colorectal carcinoma by modulating Akt/mTOR signaling. *Anticancer Research*, *29*(8), 3185–3190.

Jung, C. H., Ro, S. H., Cao, J., Otto, N. M., & Kim, D. H. (2010). mTOR regulation of autophagy. *FEBS Letters*, *584*(7), 1287–1295. https://doi.org/10.1016/j.febslet.2010.01.017

Jung, E. M., Lim, J. H., Lee, T. J., Park, J. W., Choi, K. S., & Kwon, T. K. (2005). Curcumin sensitizes tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis through reactive oxygen species-mediated upregulation of death receptor 5 (DR5). *Carcinogenesis*, *26*(11), 1905–1913. https://doi.org/10.1093/carcin/bgi167

Kalluri, R., & Weinberg, R. A. (2009). The basics of epithelial-mesenchymal transition. *The Journal of Clinical Investigation*, *119*(6), 1420–1428. https://doi.org/10.1172/JCI39104

Kang, C., & Elledge, S. J. (2016). How autophagy both activates and inhibits cellular senescence. *Autophagy*, *12*(5), 898–899. https://doi.org/10.1080/15548627.2015.1121361

Kantara, C., O'Connell, M., Sarkar, S., Moya, S., Ullrich, R., & Singh, P. (2014). Curcumin promotes autophagic survival of a subset of colon cancer stem cells, which are ablated by DCLK1-siRNA. *Cancer Research*, *74*(9), 2487–2498. https://doi.org/10.1158/0008-5472.CAN-13-3536

Kanwar, S. S., Yu, Y., Nautiyal, J., Patel, B. B., Padhye, S., Sarkar, F. H., & Majumdar, A. P. (2011). Difluorinated-curcumin (CDF): A novel curcumin analog is a potent inhibitor of colon cancer stem-like cells. *Pharmaceutical Research*, *28*(4), 827–838. https://doi.org/10.1007/s11095-010-0336-y

Karasic, T. B., Brown, T. J., Schneider, C., Teitelbaum, U. R., Reiss, K. A., Mitchell, T. C., Massa, R. C., O'Hara, M. H., DiCicco, L., Garcia-Marcano, L., Amaravadi, R. K., & O'Dwyer, P. J. (2022). Phase I trial of regorafenib, hydroxychloroquine, and Entinostat in metastatic colorectal cancer. *The Oncologist*, *27*(9), 716-e689. https://doi.org/10.1093/oncolo/oyac078

Karin, M., & Greten, F. R. (2005). NF-kappaB: Linking inflammation and immunity to cancer development and progression. *Nature Reviews. Immunology*, *5*(10), 749–759. https://doi.org/10.1038/nri1703

Kaur, H., & Moreau, R. (2021). Curcumin represses mTORC1 signaling in Caco-2 cells by a two-sided mechanism involving the loss of IRS-1 and activation of AMPK. *Cellular Signalling*, *78*, 109842. https://doi.org/10.1016/j.cellsig.2020.109842

Kojima, M., Morisaki, T., Sasaki, N., Nakano, K., Mibu, R., Tanaka, M., & Katano, M. (2004). Increased nuclear factor-kB activation in human colorectal carcinoma and its correlation with tumor progression. *Anticancer Research*, *24*(2B), 675–681.

Kudva, P., Tabasum, S. T., & Gupta, S. (2012). Comparative evaluation of the efficacy of turmeric and curcumin as a local drug delivery system: A clinicomicrobiological study. *General Dentistry*, *60*(5), e283–e287.

Kuilman, T., & Peeper, D. S. (2009). Senescence-messaging secretome: SMS-ing cellular stress. *Nature Reviews. Cancer*, *9*(2), 81–94. https://doi.org/10.1038/nrc2560

Lamouille, S., Xu, J., & Derynck, R. (2014). Molecular mechanisms of epithelial-mesenchymal transition. *Nature Reviews. Molecular Cell Biology*, *15*(3), 178–196. https://doi.org/10.1038/nrm3758

Lee, Y. J., Kim, N. Y., Suh, Y. A., & Lee, C. (2011). Involvement of ROS in curcumin-induced autophagic cell death. *Korean Journal of Physiology & Pharmacology*, *15*(1), 1–7. https://doi.org/10.4196/kjpp.2011.15.1.1

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*, 489–494. https://doi.org/10.1111/j.1749-6632.2009.04699.x

Li, G. H., Lin, X. L., Zhang, H., Li, S., He, X. L., Zhang, K., Peng, J., Tang, Y. L., Zeng, J. F., Zhao, Y., Ma, X. F., Lei, J. J., Wang, R., Wie, D. H., Jiang, Z. S., & Wang, Z. (2015). Ox-Lp(a) transiently induces HUVEC autophagy via an ROS-dependent PAPR-1-LKB1-AMPK-mTOR pathway. *Atherosclerosis*, *243*(1), 223–235. https://doi.org/10.1016/j.atherosclerosis.2015.09.020

Li, J., Chai, R., Chen, Y., Zhao, S., Bian, Y., & Wang, X. (2022). Curcumin targeting non-coding RNAs in colorectal cancer: Therapeutic and biomarker implications. *Biomolecules*, *12*(10), 1339. https://doi.org/10.3390/biom12101339

Li, J., Liu, H., Yu, J., & Yu, H. (2015). Chemoresistance to doxorubicin induces epithelial-mesenchymal transition via upregulation of transforming growth factor beta signaling in HCT116 colon cancer cells. *Molecular Medicine Reports*, *12*(1), 192–198. https://doi.org/10.3892/mmr.2015.3356

Li, L., Tan, J., Miao, Y., Lei, P., & Zhang, Q. (2015). ROS and autophagy: Interactions and molecular regulatory mechanisms. *Cellular and Molecular Neurobiology*, *35*(5), 615–621. https://doi.org/10.1007/s10571-015-0166-x

Li, Q., Ding, Y., Ou, Y., Li, M., Jithavech, P., Buranasudja, V., Sritularak, B., Xu, Y., Rojsitthisak, P., & Han, J. (2023). Curcuminoids modulated the IL-6/JAK/STAT3 signaling pathway in LoVo and HT-29 colorectal cancer cells. *Current Pharmaceutical Design*, *29*, 2867–2876. https://doi.org/10.2174/0113816128263974231029180947

Li, W., He, Y., Zhang, R., Zheng, G., & Zhou, D. (2019). The curcumin analog EF24 is a novel senolytic agent. *Aging (Albany NY)*, *11*(2), 771–782. https://doi.org/10.18632/aging.101787

Li, Y., Lin, Z., Chen, B., Chen, S., Jiang, Z., Zhou, T., Hou, Z., & Wang, Y. (2017). Ezrin/NF-kB activation regulates epithelial-mesenchymal transition induced by EGF and promotes metastasis of colorectal cancer. *Biomedicine & Pharmacotherapy*, *92*, 140–148. https://doi.org/10.1016/j.biopha.2017.05.058

Li, Z., Si, W., Jin, W., Yuan, Z., Chen, Y., & Fu, L. (2022). Targeting autophagy in colorectal cancer: An update on pharmacological small-molecule compounds. *Drug Discovery Today*, *27*(8), 2373–2385. https://doi.org/10.1016/j.drudis.2022.05.011

Liang, H. H., Huang, C. Y., Chou, C. W., Makondi, P. T., Huang, M. T., Wei, P. L., & Chang, Y. J. (2018). Heat shock protein 27 influences the anti-cancer effect of curcumin in colon cancer cells through ROS production and autophagy activation. *Life Sciences*, *209*, 43–51. https://doi.org/10.1016/j.lfs.2018.07.047

Liao, D., Shangguan, D., Wu, Y., Chen, Y., Liu, N., Tang, J., Yao, D., & Shi, Y. (2023). Curcumin protects against doxorubicin induced oxidative stress by regulating the Keap1-Nrf2-ARE and autophagy signaling pathways. *Psychopharmacology*, *240*(5), 1179–1190. https://doi.org/10.1007/s00213-023-06357-z

Lim, J. W., Kim, H., & Kim, K. H. (2001). Nuclear factor-kappaB regulates cyclooxygenase-2 expression and cell proliferation in human gastric cancer cells. *Laboratory Investigation*, *81*(3), 349–360. https://doi.org/10.1038/labinvest.3780243

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 (Philadelphia, Pa.)*, *7*(4), 466–474. https://doi.org/10.1158/1940-6207.CAPR-13-0387

10991573, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.8220, Wiley Online Library on [15/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Lin, L., Liu, Y., Li, H., Li, P. K., Fuchs, J., Shibata, H., Iwabuchi, Y., & Lin, J. (2011). Targeting colon cancer stem cells using a new curcumin analogue, GO-Y030. *British Journal of Cancer*, *105*(2), 212–220. https://doi.org/10.1038/bjc.2011.200

Liu, C., Rokavec, M., Huang, Z., & Hermeking, H. (2023). Curcumin activates a ROS/KEAP1/NRF2/miR-34a/b/c cascade to suppress colorectal cancer metastasis. *Cell Death and Differentiation*, *30*(7), 1771–1785. https://doi.org/10.1038/s41418-023-01178-1

Liu, F., Gao, S., Yang, Y., Zhao, X., Fan, Y., Ma, W., Yang, D., Yang, A., & Yu, Y. (2018). Antitumor activity of curcumin by modulation of apoptosis and autophagy in human lung cancer A549 cells through inhibiting PI3K/Akt/mTOR pathway. *Oncology Reports*, *39*(3), 1523–1531. https://doi.org/10.3892/or.2018.6188

Liu, Z., Cui, C., Xu, P., Dang, R., Cai, H., Liao, D., Yang, M., Feng, Q., Yan, X., & Jiang, P. (2017). Curcumin activates AMPK pathway and regulates lipid metabolism in rats following prolonged clozapine exposure. *Frontiers in Neuroscience*, *11*, 558. https://doi.org/10.3389/fnins.2017.00558

Lu, J., Kornmann, M., & Traub, B. (2023). Role of epithelial to mesenchymal transition in colorectal cancer. *International Journal of Molecular Sciences*, *24*(19), 14815. https://doi.org/10.3390/ijms241914815

Lu, X., & Kang, Y. (2010). Hypoxia and hypoxia-inducible factors: Master regulators of metastasis. *Clinical Cancer Research*, *16*(24), 5928–5935. https://doi.org/10.1158/1078-0432.CCR-10-1360

Lu, Y., Wu, S., Xiang, B., Li, L., & Lin, Y. (2020). Curcumin attenuates oxaliplatin-induced liver injury and oxidative stress by activating the Nrf2 pathway. *Drug Design, Development and Therapy*, *14*, 73–85. https://doi.org/10.2147/DDDT.S224318

Lu, Y., Zhang, R., Zhang, X., Zhang, B., & Yao, Q. (2020). Curcumin may reverse 5-fluorouracil resistance on colonic cancer cells by regulating TET1-NKD-Wnt signal pathway to inhibit the EMT progress. *Biomedicine & Pharmacotherapy*, *129*, 110381. https://doi.org/10.1016/j.biopha.2020.110381

Lucafo, M., Curci, D., Franzin, M., Decorti, G., & Stocco, G. (2021). Inflammatory bowel disease and risk of colorectal cancer: An overview from pathophysiology to pharmacological prevention. *Frontiers in Pharmacology*, *12*, 772101. https://doi.org/10.3389/fphar.2021.772101

Lukas, C., Mary, J., Debandt, M., Daïen, C., Morel, J., Cantagrel, A., Fautrel, B., & Combe, B. (2019). Predictors of good response to conventional synthetic DMARDs in early seronegative rheumatoid arthritis: Data from the ESPOIR cohort. *Arthritis Research & Therapy*, *21*(1), 243. https://doi.org/10.1186/s13075-019-2020-x

Ma, T. F., Fan, Y. R., Zhao, Y. H., & Liu, B. (2023). Emerging role of autophagy in colorectal cancer: Progress and prospects for clinical intervention. *World Journal of Gastrointestinal Oncology*, *15*(6), 979–987. https://doi.org/10.4251/wjgo.v15.i6.979

Macis, D., Briata, I. M., D'Ecclesiis, O., Johansson, H., Aristarco, V., Buttiron Webber, T., Oppezzi, M., Gandini, S., Bonanni, B., & DeCensi, A. (2023). Inflammatory and metabolic biomarker assessment in a randomized presurgical trial of curcumin and anthocyanin supplements in patients with colorectal adenomas. *Nutrients*, *15*(18), 3894. https://doi.org/10.3390/nu15183894

Mahalingam, D., Mita, M., Sarantopoulos, J., Wood, L., Amaravadi, R. K., Davis, L. E., Mita, A. C., Curiel, T. J., Espitia, C. M., Nawrocki, S. T., Giles, F. J., & Carew, J. S. (2014). Combined autophagy and HDAC inhibition: A phase I safety, tolerability, pharmacokinetic, and pharmacodynamic analysis of hydroxychloroquine in combination with the HDAC inhibitor vorinostat in patients with advanced solid tumors. *Autophagy*, *10*(8), 1403–1414. https://doi.org/10.4161/auto.29231

Mahgoub, E., Taneera, J., Sulaiman, N., & Saber-Ayad, M. (2022). The role of autophagy in colorectal cancer: Impact on pathogenesis and implications in therapy. *Front Med (Lausanne)*, *9*, 959348. https://doi.org/10.3389/fmed.2022.959348

Majeed, S. T., Batool, A., Majeed, R., Bhat, N. N., Zargar, M. A., & Andrabi, K. I. (2021). mTORC1 induces eukaryotic translation initiation factor 4E interaction with TOS-S6 kinase 1 and its activation. *Cell Cycle*, *20*(9), 839–854. https://doi.org/10.1080/15384101.2021.1901038

Majeed, S. T., Majeed, R., & Andrabi, K. I. (2022). Expanding the view of the molecular mechanisms of autophagy pathway. *Journal of Cellular Physiology*, *237*(8), 3257–3277. https://doi.org/10.1002/jcp.30819

Majeed, S. T., Majeed, R., Malik, A. A., & Andrabi, K. I. (2023). MTORC2 is a physiological hydrophobic motif kinase of S6 kinase 1. *BBA Molecular Cell Research*, *1870*(4), 119449. https://doi.org/10.1016/j.bbamcr.2023.119449

Mani, S. A., Guo, W., Liao, M. J., Eaton, E. N., Ayyanan, A., Zhou, A. Y., Brooks, M., Reinhard, F., Zhang, C. C., Shipitsin, M., Campbell, L. L., Polyak, K., Brisken, C., Yang, J., & Weinberg, R. A. (2008). The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell*, *133*(4), 704–715. https://doi.org/10.1016/j.cell.2008.03.027

Manzoor, S., Muhammad, J. S., Maghazachi, A. A., & Hamid, Q. (2022). Autophagy: A versatile player in the progression of colorectal cancer and drug resistance. *Frontiers in Oncology*, *12*, 924290. https://doi.org/10.3389/fonc.2022.924290

Mao, X., Zhang, X., Zheng, X., Chen, Y., Xuan, Z., & Huang, P. (2021). Curcumin suppresses LGR5(+) colorectal cancer stem cells by inducing autophagy and via repressing TFAP2A-mediated ECM pathway. *Journal of Natural Medicines*, *75*(3), 590–601. https://doi.org/10.1007/s11418-021-01505-1

McFadden, R. M., 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

Mima, K., Nishihara, R., Qian, Z. R., Cao, Y., Sukawa, Y., Nowak, J. A., Yang, J., Dou, R., Masugi, Y., Song, M., Kostic, A. D., Giannakis, M., Bullman, S., Milner, D. A., Baba, H., Giovannucci, E. L., Garraway, L. A., Freeman, G. J., Dranoff, G., … Ogino, S. (2016). *Fusobacterium nucleatum* in colorectal carcinoma tissue and patient prognosis. *Gut*, *65*(12), 1973–1980. https://doi.org/10.1136/gutjnl-2015-310101

Miyazaki, K., Xu, C., Shimada, M., & Goel, A. (2023). Curcumin and andrographis exhibit anti-tumor effects in colorectal cancer via activation of ferroptosis and dual suppression of glutathione peroxidase-4 and ferroptosis suppressor protein-1. *Pharmaceuticals (Basel)*, *16*(3), 383. https://doi.org/10.3390/ph16030383

Moragoda, L., Jaszewski, R., & Majumdar, A. P. (2001). Curcumin induced modulation of cell cycle and apoptosis in gastric and colon cancer cells. *Anticancer Research*, *21*(2A), 873–878.

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

Mosieniak, G., Sliwinska, M. A., Przybylska, D., Grabowska, W., Sunderland, P., Bielak-Zmijewska, A., & Sikora, E. (2016). Curcumin-treated cancer cells show mitotic disturbances leading to growth arrest and induction of senescence phenotype. *The International Journal of Biochemistry & Cell Biology*, *74*, 33–43. https://doi.org/10.1016/j.biocel.2016.02.014

Mudduluru, G., George-William, J. N., Muppala, S., Asangani, I. A., Kumarswamy, R., Nelson, L. D., & Allgayer, H. (2011). Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. *Bioscience Reports*, *31*(3), 185–197. https://doi.org/10.1042/BSR20100065

Mukhopadhyay, A., Banerjee, S., Stafford, L. J., Xia, C., Liu, M., & Aggarwal, B. B. (2002). Curcumin-induced suppression of cell proliferation correlates with down-regulation of cyclin D1 expression and

10991573, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.8220, Wiley Online Library on [15/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

CDK4-mediated retinoblastoma protein phosphorylation. *Oncogene*, *21*(57), 8852–8861. https://doi.org/10.1038/sj.onc.1206048

Muthusami, S., Ramachandran, I. K., Babu, K. N., Krishnamoorthy, S., Guruswamy, A., Queimado, L., Chaudhuri, G., & Ramachandran, I. (2021). Role of inflammation in the development of colorectal cancer. *Endocrine, Metabolic & Immune Disorders Drug Targets*, *21*(1), 77–90. https://doi.org/10.2174/1871530320666200909092908

Naama, M., Telpaz, S., Awad, A., Ben-Simon, S., Harshuk-Shabso, S., Modilevsky, S., Rubin, E., Sawaed, J., Zelik, L., Zigdon, M., Asulin, N., Turjeman, S., Werbner, M., Wongkuna, S., Feeney, R., Schroeder, B. O., Nyska, A., Nuriel-Ohayon, M., & Bel, S. (2023). Autophagy controls mucus secretion from intestinal goblet cells by alleviating ER stress. *Cell Host & Microbe*, *31*(3), 433–446.e434. https://doi.org/10.1016/j.chom.2023.01.006

Najafi, M., Mortezaee, K., & Majidpoor, J. (2019). Cancer stem cell (CSC) resistance drivers. *Life Sciences*, *234*, 116781. https://doi.org/10.1016/j.lfs.2019.116781

Napolitano, G., Di Malta, C., & Ballabio, A. (2022). Non-canonical mTORC1 signaling at the lysosome. *Trends in Cell Biology*, *32*(11), 920–931. https://doi.org/10.1016/j.tcb.2022.04.012

Nascimento-Goncalves, E., Mendes, B. A. L., Silva-Reis, R., Faustino-Rocha, A. I., Gama, A., & Oliveira, P. A. (2021). Animal models of colorectal cancer: From spontaneous to genetically engineered models and their applications. *Veterinary Sciences*, *8*(4), 59. https://doi.org/10.3390/vetsci8040059

Nirmala, J. G., & Lopus, M. (2020). Cell death mechanisms in eukaryotes. *Cell Biology and Toxicology*, *36*(2), 145–164. https://doi.org/10.1007/s10565-019-09496-2

Ohno, M., Nishida, A., Sugitani, Y., Nishino, K., Inatomi, O., Sugimoto, M., Kawahara, M., & Andoh, A. (2017). Nanoparticle curcumin ameliorates experimental colitis via modulation of gut microbiota and induction of regulatory T cells. *PLoS One*, *12*(10), e0185999. https://doi.org/10.1371/journal.pone.0185999

Ojo, O. A., Adeyemo, T. R., Rotimi, D., Batiha, G. E., Mostafa-Hedeab, G., Iyobhebhe, M. E., Elebiyo, T. C., Atunwa, B., Ojo, A. B., Lima, C. M. G., & Conte-Junior, C. A. (2022). Anticancer properties of curcumin against colorectal cancer: A review. *Frontiers in Oncology*, *12*, 881641. https://doi.org/10.3389/fonc.2022.881641

Omar Al-Hassi, H., Ng, O., & Brookes, M. (2018). Tumour-associated and non-tumour-associated microbiota in colorectal cancer. *Gut*, *67*(2), 395. https://doi.org/10.1136/gutjnl-2017-314219

Osei, G. Y., Adu-Amankwaah, J., Koomson, S., Beletaa, S., Asiamah, E. A., Smith-Togobo, C., & Razak, S. R. A. (2023). MicroRNAs and colorectal cancer: Clinical potential and regulatory networks. *Molecular Biology Reports*, *50*(11), 9575–9585. https://doi.org/10.1007/s11033-023-08810-w

Panahi, Y., Saberi-Karimian, M., Valizadeh, O., Behnam, B., Saadat, A., Jamialahmadi, T., Majeed, M., & Sahebkar, A. (2021). Effects of curcuminoids on systemic inflammation and quality of life in patients with colorectal cancer undergoing chemotherapy: A randomized controlled trial. *Advances in Experimental Medicine and Biology*, *1328*, 1–9. https://doi.org/10.1007/978-3-030-73234-9_1

Patschan, S., Chen, J., Polotskaia, A., Mendelev, N., Cheng, J., Patschan, D., & Goligorsky, M. S. (2008). Lipid mediators of autophagy in stress-induced premature senescence of endothelial cells. *American Journal of Physiology. Heart and Circulatory Physiology*, *294*(3), H1119–H1129. https://doi.org/10.1152/ajpheart.00713.2007

Pelicano, H., Carney, D., & Huang, P. (2004). ROS stress in cancer cells and therapeutic implications. *Drug Resistance Updates*, *7*(2), 97–110. https://doi.org/10.1016/j.drup.2004.01.004

Peterson, C. T., Vaughn, A. R., Sharma, V., Chopra, D., Mills, P. J., Peterson, S. N., & Sivamani, R. K. (2018). Effects of turmeric and curcumin dietary supplementation on human gut microbiota: A double-blind, randomized, placebo-controlled pilot study. *Journal of Evidence-Based Integrative Medicine*, *23*, 2515690X18790725. https://doi.org/10.1177/2515690X18790725

Plummer, S. M., Hill, K. A., Festing, M. F., Steward, W. P., Gescher, A. J., & Sharma, R. A. (2001). Clinical development of leukocyte cyclooxygenase 2 activity as a systemic biomarker for cancer chemopreventive agents. *Cancer Epidemiology, Biomarkers & Prevention*, *10*(12), 1295–1299.

Plummer, S. M., Holloway, K. A., Manson, M. M., Munks, R. J., Kaptein, A., Farrow, S., & Howells, L. (1999). Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex. *Oncogene*, *18*(44), 6013–6020. https://doi.org/10.1038/sj.onc.1202980

Pluta, R., Januszewski, S., & Ulamek-Koziol, M. (2020). Mutual two-way interactions of curcumin and gut microbiota. *International Journal of Molecular Sciences*, *21*(3), 1055. https://doi.org/10.3390/ijms21031055

Purpura, M., Lowery, R. P., Wilson, J. M., Mannan, H., Münch, G., & Razmovski-Naumovski, V. (2018). Analysis of different innovative formulations of curcumin for improved relative oral bioavailability in human subjects. *European Journal of Nutrition*, *57*(3), 929–938. https://doi.org/10.1007/s00394-016-1376-9

Qian, M., Fang, X., & Wang, X. (2017). Autophagy and inflammation. *Clinical and Translational Medicine*, *6*(1), 24. https://doi.org/10.1186/s40169-017-0154-5

Radhakrishnan, H., Walther, W., Zincke, F., Kobelt, D., Imbastari, F., Erdem, M., Kortüm, B., Dahlmann, M., & Stein, U. (2018). MACC1-the first decade of a key metastasis molecule from gene discovery to clinical translation. *Cancer Metastasis Reviews*, *37*(4), 805–820. https://doi.org/10.1007/s10555-018-9771-8

Rajendran, P., Alzahrani, A. M., Hanieh, H. N., Kumar, S. A., Ben Ammar, R., Rengarajan, T., & Alhoot, M. A. (2019). Autophagy and senescence: A new insight in selected human diseases. *Journal of Cellular Physiology*, *234*(12), 21485–21492. https://doi.org/10.1002/jcp.28895

Rajitha, B., Belalcazar, A., Nagaraju, G. P., Shaib, W. L., Snyder, J. P., Shoji, M., Pattnaik, S., Alam, A., & El-Rayes, B. F. (2016). Inhibition of NF-kappaB translocation by curcumin analogs induces G0/G1 arrest and downregulates thymidylate synthase in colorectal cancer. *Cancer Letters*, *373*(2), 227–233. https://doi.org/10.1016/j.canlet.2016.01.052

Ramamoorthi, G., & Sivalingam, N. (2014). Molecular mechanism of TGF-beta signaling pathway in colon carcinogenesis and status of curcumin as chemopreventive strategy. *Tumour Biology*, *35*(8), 7295–7305. https://doi.org/10.1007/s13277-014-1840-1

Ramasamy, T. S., Ayob, A. Z., Myint, H. H., Thiagarajah, S., & Amini, F. (2015). Targeting colorectal cancer stem cells using curcumin and curcumin analogues: Insights into the mechanism of the therapeutic efficacy. *Cancer Cell International*, *15*, 96. https://doi.org/10.1186/s12935-015-0241-x

Ranieri, D., Nanni, M., Guttieri, L., Torrisi, M. R., & Belleudi, F. (2021). The aberrant expression in epithelial cells of the mesenchymal isoform of FGFR2 controls the negative crosstalk between EMT and autophagy. *Journal of Cellular and Molecular Medicine*, *25*(8), 4166–4172. https://doi.org/10.1111/jcmm.16309

Raskov, H., Pommergaard, H. C., Burcharth, J., & Rosenberg, J. (2014). Colorectal carcinogenesis—Update and perspectives. *World Journal of Gastroenterology*, *20*(48), 18151–18164. https://doi.org/10.3748/wjg.v20.i48.18151

Rivera, M., Ramos, Y., Rodriguez-Valentin, M., Lopez-Acevedo, S., Cubano, L. A., Zou, J., Zhang, Q., Wang, G., & Boukli, N. M. (2017). Targeting multiple pro-apoptotic signaling pathways with curcumin in prostate cancer cells. *PLoS One*, *12*(6), e0179587. https://doi.org/10.1371/journal.pone.0179587

Roelofs, H. M., Te Morsche, R. H., van Heumen, B. W., Nagengast, F. M., & Peters, W. H. (2014). Over-expression of COX-2 mRNA in colorectal

10991573, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.8220, Wiley Online Library on [15/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

cancer. *BMC Gastroenterology*, *14*, 1. https://doi.org/10.1186/1471-230X-14-1

Roy, S., Yu, Y., Padhye, S. B., Sarkar, F. H., & Majumdar, A. P. (2013). Difluorinated-curcumin (CDF) restores PTEN expression in colon cancer cells by down-regulating miR-21. *PLoS One*, *8*(7), e68543. https://doi.org/10.1371/journal.pone.0068543

Rubinstein, M. R., Wang, X., Liu, W., Hao, Y., Cai, G., & Han, Y. W. (2013). Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/beta-catenin signaling via its FadA adhesin. *Cell Host & Microbe*, *14*(2), 195–206. https://doi.org/10.1016/j.chom.2013.07.012

Ruiz de Porras, V., Bystrup, S., Martinez-Cardus, A., Pluvinet, R., Sumoy, L., Howells, L., James, M. I., Iwuji, C., Manzano, J.L., Layos, L., Bugés, C., Abad, A, & Martinez-Balibrea, E. (2016). Curcumin mediates oxaliplatin-acquired resistance reversion in colorectal cancer cell lines through modulation of CXC-chemokine/NF-kappaB signalling pathway. *Scientific Reports*, *6*, 24675. https://doi.org/10.1038/srep24675

Ruiz de Porras, V., Layos, L., & Martinez-Balibrea, E. (2020). Curcumin: A therapeutic strategy for colorectal cancer? *Seminars in Cancer Biology*, *73*, 321–330. https://doi.org/10.1016/j.semcancer.2020.09.004

Sabaawy, H. E., Ryan, B. M., Khiabanian, H., & Pine, S. R. (2021). JAK/STAT of all trades: Linking inflammation with cancer development, tumor progression and therapy resistance. *Carcinogenesis*, *42*(12), 1411–1419. https://doi.org/10.1093/carcin/bgab075

Sakamoto, K., Maeda, S., Hikiba, Y., Nakagawa, H., Hayakawa, Y., Shibata, W., Yanai, A., Ogura, K., & Omata, M. (2009). Constitutive NF-kappaB activation in colorectal carcinoma plays a key role in angiogenesis, promoting tumor growth. *Clinical Cancer Research*, *15*(7), 2248–2258. https://doi.org/10.1158/1078-0432.CCR-08-1383

Sala de Oyanguren, F. J., Rainey, N. E., Moustapha, A., Saric, A., Sureau, F., O'Connor, J. E., & Petit, P. X. (2020). Highlighting curcumin-induced crosstalk between autophagy and apoptosis as supported by its specific subcellular localization. *Cells*, *9*(2), 361. https://doi.org/10.3390/cells9020361

Sandur, S. K., Deorukhkar, A., Pandey, M. K., Pabon, A. M., Shentu, S., Guha, S., Aggarwal, B. B., & Krishnan, S. (2009). Curcumin modulates the radiosensitivity of colorectal cancer cells by suppressing constitutive and inducible NF-kappaB activity. *International Journal of Radiation Oncology, Biology, Physics*, *75*(2), 534–542. https://doi.org/10.1016/j.ijrobp.2009.06.034

Sano, R., & Reed, J. C. (2013). ER stress-induced cell death mechanisms. *Biochimica et Biophysica Acta*, *1833*(12), 3460–3470. https://doi.org/10.1016/j.bbamcr.2013.06.028

Sasaki, H., Sunagawa, Y., Takahashi, K., Imaizumi, A., Fukuda, H., Hashimoto, T., Wada, H., Katanasaka, Y., Kakeya, H., Fujita, M., Hasegawa, K., & Morimoto, T. (2011). Innovative preparation of curcumin for improved oral bioavailability. *Biological & Pharmaceutical Bulletin*, *34*(5), 660–665. https://doi.org/10.1248/bpb.34.660

Schimmer, A. D. (2004). Inhibitor of apoptosis proteins: Translating basic knowledge into clinical practice. *Cancer Research*, *64*(20), 7183–7190. https://doi.org/10.1158/0008-5472.CAN-04-1918

Schmitt, M., & Greten, F. R. (2021). The inflammatory pathogenesis of colorectal cancer. *Nature Reviews. Immunology*, *21*(10), 653–667. https://doi.org/10.1038/s41577-021-00534-x

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

Senft, D., & Ronai, Z. A. (2015). UPR, autophagy, and mitochondria crosstalk underlies the ER stress response. *Trends in Biochemical Sciences*, *40*(3), 141–148. https://doi.org/10.1016/j.tibs.2015.01.002

Settembre, C., Zoncu, R., Medina, D. L., Vetrini, F., Erdin, S., Erdin, S., Huynh, T., Ferron, M., Karsenty, G., Vellard, M. C., Vellard, M. C., Sabatini, D.M., & Ballabio, A. (2012). A lysosome-to-nucleus signalling mechanism senses and regulates the lysosome via mTOR and TFEB. *The EMBO Journal*, *31*(5), 1095–1108. https://doi.org/10.1038/emboj.2012.32

Shakibaei, M., Buhrmann, C., Kraehe, P., Shayan, P., Lueders, C., & Goel, A. (2014). Curcumin chemosensitizes 5-fluorouracil resistant MMR-deficient human colon cancer cells in high density cultures. *PLoS One*, *9*(1), e85397. https://doi.org/10.1371/journal.pone.0085397

Shakibaei, M., Kraehe, P., Popper, B., Shayan, P., Goel, A., & Buhrmann, C. (2015). Curcumin potentiates antitumor activity of 5-fluorouracil in a 3D alginate tumor microenvironment of colorectal cancer. *BMC Cancer*, *15*, 250. https://doi.org/10.1186/s12885-015-1291-0

Shakibaei, M., Mobasheri, A., Lueders, C., Busch, F., Shayan, P., & Goel, A. (2013). Curcumin enhances the effect of chemotherapy against colorectal cancer cells by inhibition of NF-kappaB and Src protein kinase signaling pathways. *PLoS One*, *8*(2), e57218. https://doi.org/10.1371/journal.pone.0057218

Sharma, R. A., Euden, S. A., Platton, S. L., Cooke, D. N., Shafayat, A., Hewitt, H. R., Marczylo, T. H., Morgan, B., Hemingway, D., Plummer, S. M., Pirmohamed, M., Gescher, A. J., & Steward, W. P. (2004). Phase I clinical trial of oral curcumin: Biomarkers of systemic activity and compliance. *Clinical Cancer Research*, *10*(20), 6847–6854. https://doi.org/10.1158/1078-0432.CCR-04-0744

Shehzad, A., Lee, J., Huh, T. L., & Lee, Y. S. (2013). Curcumin induces apoptosis in human colorectal carcinoma (HCT-15) cells by regulating expression of Prp4 and p53. *Molecules and Cells*, *35*(6), 526–532. https://doi.org/10.1007/s10059-013-0038-5

Shibue, T., & Weinberg, R. A. (2017). EMT, CSCs, and drug resistance: The mechanistic link and clinical implications. *Nature Reviews. Clinical Oncology*, *14*(10), 611–629. https://doi.org/10.1038/nrclinonc.2017.44

Shinojima, N., Yokoyama, T., Kondo, Y., & Kondo, S. (2007). Roles of the Akt/mTOR/p70S6K and ERK1/2 signaling pathways in curcumin-induced autophagy. *Autophagy*, *3*(6), 635–637. https://doi.org/10.4161/auto.4916

Shoba, G., Joy, D., Joseph, T., Majeed, M., Rajendran, R., & Srinivas, P. S. (1998). Influence of piperine on the pharmacokinetics of curcumin in animals and human volunteers. *Planta Medica*, *64*(4), 353–356. https://doi.org/10.1055/s-2006-957450

Singh, S., Gouri, V., & Samant, M. (2023). TGF-beta in correlation with tumor progression, immunosuppression and targeted therapy in colorectal cancer. *Medical Oncology*, *40*(11), 335. https://doi.org/10.1007/s12032-023-02204-5

Slattery, M. L., Lundgreen, A., Kadlubar, S. A., Bondurant, K. L., & Wolff, R. K. (2013). JAK/STAT/SOCS-signaling pathway and colon and rectal cancer. *Molecular Carcinogenesis*, *52*(2), 155–166. https://doi.org/10.1002/mc.21841

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

Song, J. X., Sun, Y. R., Peluso, I., Zeng, Y., Yu, X., Lu, J. H., Xu, Z., Wang, M. Z., Liu, L. F., Huang, Y. Y., Chen, L. L., Durairajan, S. S., Zhang, H. J., Zhou, B., Zhang, H. Q., Lu, A., Ballabio, A., Medina, D. L., Guo, Z., & Li, M. (2016). A novel curcumin analog binds to and activates TFEB in vitro and in vivo independent of MTOR inhibition. *Autophagy*, *12*(8), 1372–1389. https://doi.org/10.1080/15548627.2016.1179404

Song, X., Kim, S. Y., Zhang, L., Tang, D., Bartlett, D. L., Kwon, Y. T., & Lee, Y. J. (2014). Role of AMP-activated protein kinase in cross-talk between apoptosis and autophagy in human colon cancer. *Cell Death & Disease*, *5*(10), e1504. https://doi.org/10.1038/cddis.2014.463

Song, Y. Q., Yan, X. D., Wang, Y., Wang, Z. Z., Mao, X. L., Ye, L. P., & Li, S. W. (2023). Role of ferroptosis in colorectal cancer. *World Journal of Gastrointestinal Oncology*, *15*(2), 225–239. https://doi.org/10.4251/wjgo.v15.i2.225

10991573, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.8220, Wiley Online Library on [15/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Stohs, S. J., Chen, O., Ray, S. D., Ji, J., Bucci, L. R., & Preuss, H. G. (2020). Highly bioavailable forms of curcumin and promising avenues for curcumin-based research and application: A review. *Molecules*, *25*(6), 1397. https://doi.org/10.3390/molecules25061397

Su, C. C., Lin, J. G., Chen, G. W., Lin, W. C., & Chung, J. G. (2006). Down-regulation of Cdc25c, CDK1 and cyclin B1 and up-regulation of Wee1 by curcumin promotes human colon cancer Colo 205 cell entry into G2/M-phase of cell cycle. *Cancer Genomics Proteomics*, *3*(1), 55–61.

Su, C. C., Lin, J. G., Li, T. M., Chung, J. G., Yang, J. S., Ip, S. W., Lin, W. C., & Chen, G. W. (2006). Curcumin-induced apoptosis of human colon cancer colo 205 cells through the production of ROS, Ca2+ and the activation of caspase-3. *Anticancer Research*, *26*(6B), 4379–4389.

Su, P., Yang, Y., Wang, G., Chen, X., & Ju, Y. (2018). Curcumin attenuates resistance to irinotecan via induction of apoptosis of cancer stem cells in chemoresistant colon cancer cells. *International Journal of Oncology*, *53*(3), 1343–1353. https://doi.org/10.3892/ijo.2018.4461

Sugimoto, K., Hanai, H., Tozawa, K., Aoshi, T., Uchijima, M., Nagata, T., & Koide, Y. (2002). Curcumin prevents and ameliorates trinitrobenzene sulfonic acid-induced colitis in mice. *Gastroenterology*, *123*(6), 1912–1922. https://doi.org/10.1053/gast.2002.37050

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/caac.21660

Szymanski, M. C., Gillum, T. L., Gould, L. M., Morin, D. S., & Kuennen, M. R. (2018). Short-term dietary curcumin supplementation reduces gastrointestinal barrier damage and physiological strain responses during exertional heat stress. *Journal of Applied Physiology (Bethesda, MD: 1985)*, *124*(2), 330–340. https://doi.org/10.1152/japplphysiol.00515.2017

Tariq, K., & Ghias, K. (2016). Colorectal cancer carcinogenesis: A review of mechanisms. *Cancer Biology & Medicine*, *13*(1), 120–135. https://doi.org/10.28092/j.issn.2095-3941.2015.0103

Terzic, J., Grivennikov, S., Karin, E., & Karin, M. (2010). Inflammation and colon cancer. *Gastroenterology*, *138*(6), 2101–2114 e2105. https://doi.org/10.1053/j.gastro.2010.01.058

Thiery, J. P., Acloque, H., Huang, R. Y., & Nieto, M. A. (2009). Epithelial-mesenchymal transitions in development and disease. *Cell*, *139*(5), 871–890. https://doi.org/10.1016/j.cell.2009.11.007

Thorburn, A. (2008). Apoptosis and autophagy: Regulatory connections between two supposedly different processes. *Apoptosis*, *13*(1), 1–9. https://doi.org/10.1007/s10495-007-0154-9

Toden, S., Okugawa, Y., Buhrmann, C., Nattamai, D., Anguiano, E., Baldwin, N., Shakibaei, M., Boland, C. R., & Goel, A. (2015). Novel evidence for curcumin and boswellic acid-induced chemoprevention through regulation of miR-34a and miR-27a in colorectal cancer. *Cancer Prevention Research (Philadelphia, Pa.)*, *8*(5), 431–443. https://doi.org/10.1158/1940-6207.CAPR-14-0354

Toden, S., Okugawa, Y., Jascur, T., Wodarz, D., Komarova, N. L., Buhrmann, C., Shakibaei, M., Boland, C. R., & Goel, A. (2015). Curcumin mediates chemosensitization to 5-fluorouracil through miRNA-induced suppression of epithelial-to-mesenchymal transition in chemoresistant colorectal cancer. *Carcinogenesis*, *36*(3), 355–367. https://doi.org/10.1093/carcin/bgv006

Tsai, J. H., & Yang, J. (2013). Epithelial-mesenchymal plasticity in carcinoma metastasis. *Genes & Development*, *27*(20), 2192–2206. https://doi.org/10.1101/gad.225334.113

Vazquez, A., Bond, E. E., Levine, A. J., & Bond, G. L. (2008). The genetics of the p53 pathway, apoptosis and cancer therapy. *Nature Reviews. Drug Discovery*, *7*(12), 979–987. https://doi.org/10.1038/nrd2656

Villegas, I., Sanchez-Fidalgo, S., & de la Lastra, C. A. (2011). Chemopreventive effect of dietary curcumin on inflammation-induced colorectal carcinogenesis in mice. *Molecular Nutrition & Food Research*, *55*(2), 259–267. https://doi.org/10.1002/mnfr.201000225

Vinson, K. E., George, D. C., Fender, A. W., Bertrand, F. E., & Sigounas, G. (2016). The notch pathway in colorectal cancer. *International Journal of Cancer*, *138*(8), 1835–1842. https://doi.org/10.1002/ijc.29800

Voss, A. K., & Strasser, A. (2020). The essentials of developmental apoptosis. *F1000Res*, *9*, F1000. https://doi.org/10.12688/f1000research.21571.1

Wajant, H. (2002). The Fas signaling pathway: More than a paradigm. *Science*, *296*(5573), 1635–1636. https://doi.org/10.1126/science.1071553

Wang, H., Cai, X., & Ma, L. (2020). Curcumin modifies epithelial-mesenchymal transition in colorectal cancer through regulation of miR-200c/EPM5. *Cancer Management and Research*, *12*, 9405–9415. https://doi.org/10.2147/CMAR.S260129

Wang, S. Y., Yu, Q. J., Zhang, R. D., & Liu, B. (2011). Core signaling pathways of survival/death in autophagy-related cancer networks. *The International Journal of Biochemistry & Cell Biology*, *43*(9), 1263–1266. https://doi.org/10.1016/j.biocel.2011.05.010

Wang, Y., Lin, K., Xu, T., Wang, L., Fu, L., Zhang, G., Ai, J., Jiao, Y., Zhu, R., Han, X., & Cai, H. (2021). Development and validation of prognostic model based on the analysis of autophagy-related genes in colon cancer. *Aging (Albany NY)*, *13*(14), 19028–19047. https://doi.org/10.18632/aging.203352

Wardyn, J. D., Ponsford, A. H., & Sanderson, C. M. (2015). Dissecting molecular cross-talk between Nrf2 and NF-κB response pathways. *Biochemical Society Transactions*, *43*(4), 621–626. https://doi.org/10.1042/bst20150014

Watson, A. J. (2004). Apoptosis and colorectal cancer. *Gut*, *53*(11), 1701–1709. https://doi.org/10.1136/gut.2004.052704

Wei, R., Xiao, Y., Song, Y., Yuan, H., Luo, J., & Xu, W. (2019). FAT4 regulates the EMT and autophagy in colorectal cancer cells in part via the PI3K-AKT signaling axis. *Journal of Experimental & Clinical Cancer Research*, *38*(1), 112. https://doi.org/10.1186/s13046-019-1043-0

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

White, E., & DiPaola, R. S. (2009). The double-edged sword of autophagy modulation in cancer. *Clinical Cancer Research*, *15*(17), 5308–5316. https://doi.org/10.1158/1078-0432.CCR-07-5023

Wu, C. S., Wu, S. Y., Chen, H. C., Chu, C. A., Tang, H. H., Liu, H. S., Hong, Y. R., Huang, C. F., Huang, G. C., & Su, C. L. (2019). Curcumin functions as a MEK inhibitor to induce a synthetic lethal effect on KRAS mutant colorectal cancer cells receiving targeted drug regorafenib. *The Journal of Nutritional Biochemistry*, *74*, 108227. https://doi.org/10.1016/j.jnutbio.2019.108227

Xiao, K., Jiang, J., Guan, C., Dong, C., Wang, G., Bai, L., Sun, J., Hu, C., & Bai, C. (2013). Curcumin induces autophagy via activating the AMPK signaling pathway in lung adenocarcinoma cells. *Journal of Pharmacological Sciences*, *123*(2), 102–109. https://doi.org/10.1254/jphs.13085fp

Xu, B., Yuan, C. W., & Zhang, J. E. (2023). Curcumin inhibits proliferation of renal cell carcinoma in vitro and in vivo by regulating miR-148/ADAMTS18 through suppressing autophagy. *Chinese Journal of Integrative Medicine*, *29*(8), 699–706. https://doi.org/10.1007/s11655-022-3690-9

Xu, H. D., & Qin, Z. H. (2019). Beclin 1, Bcl-2 and autophagy. *Advances in Experimental Medicine and Biology*, *1206*, 109–126. https://doi.org/10.1007/978-981-15-0602-4_5

Xu, J., Patel, N. H., & Gewirtz, D. A. (2020). Triangular relationship between p53, autophagy, and chemotherapy resistance. *International Journal of Molecular Sciences*, *21*(23), 8991. https://doi.org/10.3390/ijms21238991

Xu, W., & Shen, Y. (2024). Curcumin affects apoptosis of colorectal cancer cells through ATF6-mediated endoplasmic reticulum stress. *Chemical Biology & Drug Design*, *103*(1), e14433. https://doi.org/10.1111/cbdd.14433

10991573, 2024, 7, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/ptr.8220, Wiley Online Library on [15/11/2024]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Xu, W., Zhang, M., Li, Y., Wang, Y., Wang, K., Chen, Q., Zhang, R., Song, W., Huang, Q., Zhao, W., & Wu, J. (2021). YAP manipulates proliferation via PTEN/AKT/mTOR-mediated autophagy in lung adenocarcinomas. *Cancer Cell International*, *21*(1), 30. https://doi.org/10.1186/s12935-020-01688-9

Yan, H., Talty, R., Aladelokun, O., Bosenberg, M., & Johnson, C. H. (2023). Ferroptosis in colorectal cancer: A future target? *British Journal of Cancer*, *128*(8), 1439–1451. https://doi.org/10.1038/s41416-023-02149-6

Yin, J., Wang, L., Wang, Y., Shen, H., Wang, X., & Wu, L. (2019). Curcumin reverses oxaliplatin resistance in human colorectal cancer via regulation of TGF-beta/Smad2/3 signaling pathway. *Oncotargets and Therapy*, *12*, 3893–3903. https://doi.org/10.2147/OTT.S199601

Yook, J. I., Li, X. Y., Ota, I., Fearon, E. R., & Weiss, S. J. (2005). Wnt-dependent regulation of the E-cadherin repressor snail. *The Journal of Biological Chemistry*, *280*(12), 11740–11748. https://doi.org/10.1074/jbc.M413878200

Young, A. R., Narita, M., Ferreira, M., Kirschner, K., Sadaie, M., Darot, J. F., Tavaré, S., Arakawa, S., Shimizu, S., Watt, F. M., & Narita, M. (2009). Autophagy mediates the mitotic senescence transition. *Genes & Development*, *23*(7), 798–803. https://doi.org/10.1101/gad.519709

Yu, H. G., Zhong, X., Yang, Y. N., Luo, H. S., Yu, J. P., Meier, J. J., Schrader, H., Bastian, A., Schmidt, W. E., & Schmitz, F. (2004). Increased expression of nuclear factor-kappaB/RelA is correlated with tumor angiogenesis in human colorectal cancer. *International Journal of Colorectal Disease*, *19*(1), 18–22. https://doi.org/10.1007/s00384-003-0494-z

Yu, Y., Kanwar, S. S., Patel, B. B., Nautiyal, J., Sarkar, F. H., & Majumdar, A. P. (2009). Elimination of colon cancer stem-like cells by the combination of curcumin and FOLFOX. *Translational Oncology*, *2*(4), 321–328. https://doi.org/10.1593/tlo.09193

Yu, Y., Kanwar, S. S., Patel, B. B., Oh, P. S., Nautiyal, J., Sarkar, F. H., & Majumdar, A. P. (2012). MicroRNA-21 induces stemness by downregulating transforming growth factor beta receptor 2 (TGFbetaR2) in colon cancer cells. *Carcinogenesis*, *33*(1), 68–76. https://doi.org/10.1093/carcin/bgr246

Zhang, C., Xu, Y., Wang, H., Li, G., Yan, H., Fei, Z., Xu, Y., & Li, W. (2018). Curcumin reverses irinotecan resistance in colon cancer cell by regulation of epithelial-mesenchymal transition. *Anti-Cancer Drugs*, *29*(4), 334–340. https://doi.org/10.1097/CAD.0000000000000599

Zhang, J., Wang, J., Xu, J., Lu, Y., Jiang, J., Wang, L., Shen, H. M., & Xia, D. (2016). Curcumin targets the TFEB-lysosome pathway for induction of autophagy. *Oncotarget*, *7*(46), 75659–75671. https://doi.org/10.18632/oncotarget.12318

Zhang, L., Xu, S., Cheng, X., Wu, J., Wu, L., Wang, Y., Wang, X., Bao, J., & Yu, H. (2022). Curcumin induces autophagic cell death in human thyroid cancer cells. *Toxicology in Vitro*, *78*, 105254. https://doi.org/10.1016/j.tiv.2021.105254

Zhang, P., Holowatyj, A. N., Ulrich, C. M., & Edgar, B. A. (2019). Tumor suppressive autophagy in intestinal stem cells controls gut homeostasis. *Autophagy*, *15*(9), 1668–1670. https://doi.org/10.1080/15548627.2019.1633863

Zhao, H., Ming, T., Tang, S., Ren, S., Yang, H., Liu, M., Tao, Q., & Xu, H. (2022). Wnt signaling in colorectal cancer: Pathogenic role and therapeutic target. *Molecular Cancer*, *21*(1), 144. https://doi.org/10.1186/s12943-022-01616-7

Zhao, L., & Ackerman, S. L. (2006). Endoplasmic reticulum stress in health and disease. *Current Opinion in Cell Biology*, *18*(4), 444–452. https://doi.org/10.1016/j.ceb.2006.06.005

Zhong, Q. Y., Luo, Q. H., Lin, B., Lin, B. Q., Su, Z. R., & Zhan, J. Y. (2022). Protective effects of andrographolide sodium bisulfate on UV-induced skin carcinogenesis in mice model. *European Journal of Pharmaceutical Sciences*, *176*, 106232. https://doi.org/10.1016/j.ejps.2022.106232

Zhou, S., Zhang, S., Shen, H., Chen, W., Xu, H., Chen, X., Sun, D., Zhong, S., Zhao, J., & Tang, J. (2017). Curcumin inhibits cancer progression through regulating expression of microRNAs. *Tumour Biology*, *39*(2), 1010428317691680. https://doi.org/10.1177/1010428317691680

Zhu, J., Zhao, B., Xiong, P., Wang, C., Zhang, J., Tian, X., & Huang, Y. (2018). Curcumin induces autophagy via inhibition of yes-associated protein (YAP) in human colon cancer cells. *Medical Science Monitor*, *24*, 7035–7042. https://doi.org/10.12659/MSM.910650

Zhuang, W., Long, L., Zheng, B., Ji, W., Yang, N., Zhang, Q., & Liang, Z. (2012). Curcumin promotes differentiation of glioma-initiating cells by inducing autophagy. *Cancer Science*, *103*(4), 684–690. https://doi.org/10.1111/j.1349-7006.2011.02198.x

Zou, Z., Tao, T., Li, H., & Zhu, X. (2020). mTOR signaling pathway and mTOR inhibitors in cancer: Progress and challenges. *Cell & Bioscience*, *10*, 31. https://doi.org/10.1186/s13578-020-00396-1

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