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New Insights Into the Anticancer Effects of *p*-Coumaric Acid: Focus on Colorectal Cancer

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Abstract

Colorectal cancer is considered the second most deadly cancer in the world. Studies have indicated that diet can prevent the risk of developing colorectal cancer. Recently, there has been an increasing interest in polyphenols due to their plausible effect on cancer prevention and treatment. *p*-Coumaric acid (*p*-CouA), a phenolic compound, is a cinnamic acid derivative found in several fruits, vegetables, and herbs. A growing body of evidence suggests that *p*-CouA may be an effective agent for preventing and managing colorectal cancer. In this current review, we briefly highlight the bioavailability of *p*-CouA. We also provide an up-to-date overview of molecular mechanisms underlying its anticancer effects, focusing on anti-inflammatory and antioxidant potentials, apoptosis induction, and cell cycle blockade. Finally, we discuss the impact of *p*-CouA on clonogenicity and multidrug resistance of colorectal cancer cells.

Keywords

Colorectal cancer, *p*-coumaric acid, COX-2, Nrf-2, apoptosis, cell cycle

Introduction

Colorectal cancer (CRC) has been estimated to be the second most deadly cancer and the third most widespread malignancy of the digestive system tumor worldwide.[1] Carcinoid tumors and adenocarcinoma are the main histological subtypes contributing to the onset of CRC incidence in the United States.[2] Carcinoid tumors can arise anywhere in the digestive tract; however, 60% are found in the appendix.[3] Adenocarcinomas usually emerge from glandular epithelial cells such as those that line the inside of the colon and rectum.[4] According to Thanikachalam and Khan, about 41% of colorectal cancers arise in the proximal colon and 22% in the distal colon, and around 28% in the rectum.[5] In 2018, nearly 2 million new CRC cases and about 1 million deaths were signalized. This number amounts to almost 10% of new cancer cases and deaths worldwide,[6] and the number of new cases may reach 2.5 million in 2035.[7]

CRC is more frequent in men than in women and is 3-4 times more common in developed nations than in underdeveloped countries.[4] It has been reported that the highest number of new CRC cases in 2020 is in China and the United States.[8] The same authors reported that the countries with the highest incidence of CRC per 100,000 population are Hungary (45.3) and Slovakia (43.9). The incidence rates of CRC are the lowest in Africa and South Asia; nevertheless, the survival rate in African countries was reported to be less than 8%.[4,9]

Several factors, including genetic and inflammatory bowel disease (IBD), play a significant role in the pathogenesis of CRC. Moreover, environmental factors and nutrition are closely related to the incidence and the progression of CRC.[5] Indeed, a growing body of evidence shows that western dietary pattern, with a predominance of high red meat and

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alcohol consumption at the expense of vegetable intake, is prospectively associated with CRC risk.[10,11] On the other hand, it has been suggested that adherence to the Mediterranean diet (MedDiet) is associated with a lower risk for cancers, including CRC.[12] Polyphenols are the most prevalent antioxidants among MedDiet nutraceuticals and have a wide variety of pharmacological actions such as anti-inflammatory and antitumorigenic properties.[13,14] *p*-CouA is a hydroxycinnamic acid widely found in the MedDiet pattern, mainly whole cereal grains, fruit, and vegetables.[13,15,16] This hydroxycinnamic acid has been shown to exert antiproliferative and pro-apoptotic effects on several colon cancer cells and to exhibit chemopreventive effects in a short-term preclinical model of colon cancer.[17–25] To the best of our knowledge, no study has summarized *p*-CouA action with respect to its anti-inflammatory and therapeutic implications in colorectal cancer. Therefore, this review aims to elucidate the plausible mechanisms involved in the chemopreventive and therapeutic effect of dietary *p*-CouA against CRC with a focus on its anti-inflammatory and pro-apoptotic signaling pathways.

Bioavailability and Pharmacological Proprieties of *p*-CouA

Phenolic compounds are one of the most influential and ubiquitous plant secondary metabolites.[26] Coumaric acids are natural metabolites belonging to the family of hydroxycinnamic acids, and *p*-CouA (4-hydroxycinnamic acid) (Figure 1) is the most abundant isomer. *p*-CouA is a yellowish-green crystalline powder with a molecular formula of $C_9H_8O_3$.[27,28] In plants, *p*-CouA exists in free or conjugated forms and is a precursor of other phenolic compounds.[16] *p*-CouA is widely found in edible plants, mushrooms, vegetables (eg, tomatoes, carrots, garlic, onions, and potatoes), fruits (eg, grapes, apples, and pears), grains (eg, wheat, oats, rice, corn, and peanuts), and in beverages (eg, teas, coffee, and wines).[16,19,28–30]

p-CouA has attracted a great deal of attention due to its pharmacological and biological proprieties (Figure 2), including cardioprotective, antioxidant, neuroprotective, anti-ulcer, antiplatelet, antimicrobial, chemoprotective, and anticancer activities.[16,31] It has been demonstrated that *p*-CouA is a potential anticancer agent with less toxicity in human health.[20,32]

Bioavailability is the key to the bioefficiency of dietary nutraceuticals such as polyphenols.[33] As far as hydroxycinnamic acids are concerned, the physiological importance of *p*-CouA lies in its availability for intestinal absorption and further interaction with target tissues.[34] Interestingly, the transepithelial transport rate of *p*-CouA is about 100 times higher than that of gallic acid in Caco-2 cell monolayers.[34] *In vivo* studies showed that *p*-CouA could be absorbed via the stomach, jejunum, ileum, and colon.[15,35] Moreover, *p*-CouA is much more bioavailable than caffeic, ferulic, rosmarinic, and chlorogenic acids.[15,36] Similarly, another study using the gastrointestinal sac technique demonstrated that *p*-CouA might be absorbed in all parts of the gastrointestinal tract, with the highest absorption rate in the jejunum.[37] In addition to the diffusional uptake, Garrait et al. noted that *p*-CouA absorption across the brush-border membrane of the jejunum involved an Na^+-dependent transport process.[37] Konishi et al. showed an active absorption of *p*-CouA across Caco-2 cell monolayers via proton-coupled monocarboxylic acid transporter (MCT).[34] Rats absorb and remove *p*-CouA as a metabolite more slowly (t_{max}, 1, 2 h; t1/2, 1, 3 h), likely due to the hydrolyzed E-6-O-p-coumaroyl scandoside methyl ester *in vivo* diffusion.[38] Moreover, a randomized controlled trial revealed that a total polyphenols intake of 837 mg/day, containing 5.5 mg *p*-CouA, for eight weeks increases *p*-CouA plasma concentration of 40% and a concomitant increase in its urinary excretion (18%) compared to the baseline values of the experimental group.[39] Yet, cumulative evidence from multiple studies showed that conjugated forms of p-CouA are less available but more bioactive than free p-CouA, which is relatively low in the plant kingdom.[16]

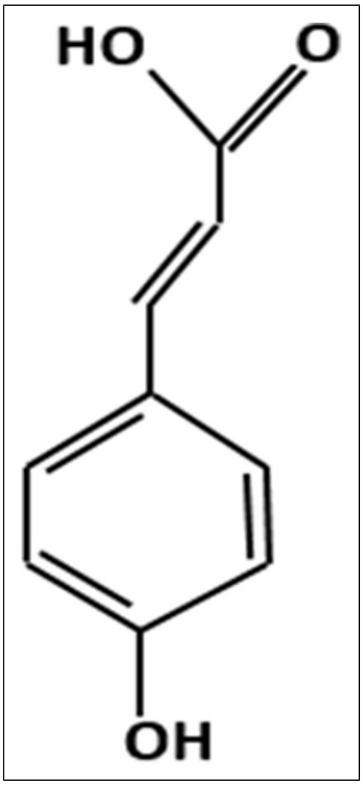

Figure 1. Chemical structure of *p*-CouA acid.

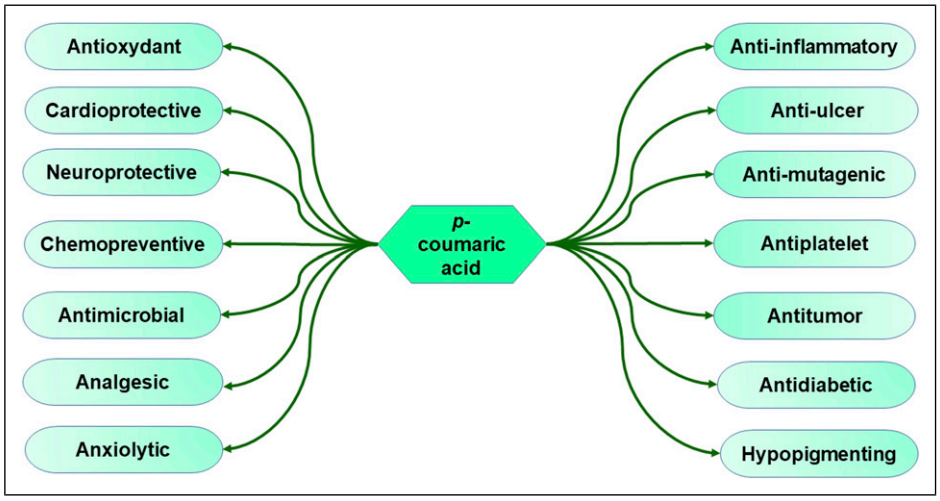

Figure 2. Pharmacological activities of *p*-CouA acid.

Molecular Mechanisms Targeted by *p*-CouA in Colorectal Cancer

Modulating Inflammation

Mechanisms of inflammation-mediated tumorigenesis and tumor-promoting inflammation have been extensively reviewed elsewhere.[40,41] Therefore, modulating inflammation can be an excellent strategy to prevent cancer development and progression.[42] Nuclear factor kappa B (NF-κB) is a key transcriptional regulator of several genes involved in oxidative stress and inflammatory responses. The activated NF-κB induces the expression of various enzymes, which catalyze inflammatory mediator biosynthesis, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and pro-inflammatory cytokines such as interleukins (ILs) and tumor necrosis factor-alpha (TNF-α).[43,44] Importantly, *p*-CouA has been shown to inhibit NF-κB expression and activation and to counteract a myriad of molecules, involved in different inflammatory response processes, expression, production, and secretion, including TNFα, IL-1β, IL-6, IL-8, COX-2, and prostaglandin E2 (PGE2).[43,45–47] COX-2 is an enzyme that plays an important role in inflammatory responses through PGE2 synthesis from arachidonic acid, and it is selectively overexpressed in colon tumors.[43,48,49] Hence, COX-2 selective pharmacological inhibition may reduce the incidence of CRC. According to the American Cancer Society, there is a high prevalence of CRC in IBD patients, and *p*-CouA alleviates DSS-induced intestinal inflammation by suppressing the expression of COX-2.[48,50] Moreover, *in vivo* studies on transplantable tumors in mice showed that a panoply of hydroxycinnamic acids reduce COX-2 expression and modulate tumor growth.[43] Indeed, HT-29 colon cancer cells treatment with *p*-CouA has been shown to decrease COX-2 expression.[43]

Antioxidant Activity

In addition to inflammation, oxidative stress has been known to cause malignant disorders, including CRC.[50] Oxidative stress can lead to unchecked cell proliferation associated with resistance to apoptotic signals resulting in cancer initiation, progression, and metastasis.[51] For this reason, boosting antioxidant systems may be a prominent strategy for cancer management. The transcription factor nuclear factor erythroid 2-related factor 2 (Nrf-2) is regarded as a master modulator of the intracellular antioxidant response by regulating numerous antioxidants and detoxifying enzymes' gene expression. Therefore, there has been a significant focus on Nrf-2 as an emerging target against oxidative stress-associated disorders, including cancers.[52–54] Nevertheless, Nrf-2 appears to be a double-edged sword in cancer biology.[53–56] Nrf-2 binds to its negative regulator Kelch-like ECH-related protein 1 (keap1) under resting conditions.[57] Several kinases can directly regulate Nrf-2, including phosphatidylinositol 3-kinase (PI3-K), protein kinase B (PKB, also known as AKT), mitogen-activated protein kinase (MAPK), protein kinases, and tyrosine kinases.[52,57] In response to disrupted redox homeostasis, Nrf-2 dissociates from its cytoplasmic inhibitor, keap1, and translocates to the nucleus where it binds to the antioxidant responsive element (ARE) in their promoter regions. This leads to the gene expression of several enzymes known for their reactive oxygen species (ROS)-detoxifying activity such as glutathione peroxidase 2 (GPx2), glutathione reductase-1 (GSR1), and glutathione S-transferases (GST).[56–59] A research by Sharma et al. on a short-term preclinical model of colon cancer showed that *p*-CouA treatment prevents DMH-induced colorectal carcinogenesis mainly through the Nrf2–ARE pathway.[23] Indeed, these authors observed that *p*-CouA treatment induced Nrf2-mediated upregulation of phase II detoxifying enzyme genes, namely, GPx2, GST, and UDP-glucuronosyltransferase (UGT) in DMH-administered albino

Wistar rats. Another *in vivo* study confirmed the anti-preneoplastic proprieties of *p*-CouA against experimental colon carcinogenesis in a dose-dependent manner, which was associated with an increase in SOD, CAT, and GPx antioxidant enzymes and decreased thiobarbituric acid reactive substance (TBARS), lipid peroxidation by-products, levels.[21]

Apoptosis Induction

Apoptosis is a distinctive and highly regulated program of cell death. It represents a propitious mechanism of conventional chemotherapeutic strategies and phytotherapeutic approaches. Most chemotherapeutic drugs and plant-derived anticancer agents induce cysteine-aspartic-proteases (caspases)-dependent apoptosis.[60] The so-called "effector" caspases (Casp-3 and -7) are activated in both extrinsic (death receptors) and intrinsic (also called "classical" or "mitochondrial") apoptotic pathways.[61] The mitochondrial pathway is the major route to apoptotic death in mammalian cells.[62] A decrease in mitochondrial membrane potential ($\Delta\Psi$) and increased ROS generation are collectively seen as early signs of intrinsic apoptosis.[63] Moreover, BAK and BAX, Bcl-2 protein family members, induction of mitochondrial outer membrane permeabilization is a hallmark of this apoptotic pathway.[62,64] Altogether, these events lead to cytochrome *c* (cyt-*c*) release from mitochondria to form with apoptotic protease-activating factor-1 (Apaf-1) a complex called the native apoptosome, which, in turn, regulates caspase-9-dependent apoptosis.[60,62,65–67] Previous studies demonstrated that *p*-CouA induces mitochondrial-dependent apoptosis in a series of colorectal cancer cell lines, including DLD-1, HT-29, SW480, HCT-15, SW-620, and Caco-2.[11,19,22,68] Conversely, *p*-CouA was not found to be toxic on intestinal epithelial cells (IEC), even at a higher concentration, nor on healthy colon epithelial cells (CCD-18Co).[11,19] It is well established that the pro-survival mediators Bcl-2 and Bcl-xL, Bcl-2 protein family members, abrogate the mitochondrial apoptotic pathway by preventing BAK and BAX activation.[62] A study performed by Sharma et al. revealed that *p*-CouA decreases the expression of the antiapoptotic Bcl-xL concomitant with cyt-*c* release from mitochondria resulting in caspase-dependent apoptosis in HT-29 and SW480 human colon cancer cell lines.[22] Similarly, Jaganathan et al. suggested that HCT-15 and HT-29 treatment with *p*-CouA upregulates BAX and downregulates Bcl-2 associated with a decrease in mitochondrial membrane potential in these cells.[19] The pro-apoptotic effect of *p*-CouA was confirmed in animal models of colon carcinogenesis. Indeed, Sharma et al. found that *p*-CouA supplementation triggers mitochondrial apoptosis by increasing Bax/Bcl-2 ratio in adult Wistar rats.[23] Cellular Bax/Bcl-2 ratio can be controlled by the well-known pro-apoptotic p53, whose loss occurs in many cancers, including colon cancer.[69] Interestingly, the upregulation of p53 expression in DLD-1 colon cancer cell lines treated with *p*-CouA-rich extract of *Viburnum opulus* L. (EVO) led to the p53/Bax/Bcl-2 apoptotic pathway in these cells.[11]

Besides the mitochondrial apoptotic pathway, researchers highlighted endoplasmic reticulum stress (ERS) as a new signaling mechanism that mediates apoptosis. Disruption of calcium homeostasis and unfolded/misfolded proteins accumulation in the endoplasmic reticulum (ER) lumen underlie the onset of ERS. Unfolded protein response (UPR) is consequently activated to restore ER homeostasis; however, persistent ERS commonly triggers apoptosis.[63,70,71] Glucose-regulated protein 78 (GRP78; also known as BIP and HSPA5) is a chaperone heat shock protein that plays a central role in UPR to promote cell survival. Indeed, GRP78 is overexpressed in various cancer cells leading to an increase in the aggressiveness of the disease.[72] In basal conditions, GRP78 complexes to three ER transmembrane protein stress sensors, namely, activating transcription factor 6 (ATF6), inositol requiring kinase 1 (IRE1), and protein kinase R-like ER kinase (PERK). The latter phosphorylates eukaryotic translation initiation factor 2 (eIF2α), which favors the expression of activating transcription factor 4 (ATF4) as an adaptive mechanism to restore ER equilibrium.[71,73] Nevertheless, the overexpression of ATF4 results in the expression of the apoptotic C/EBP homologous protein (CHOP) transcription factor that mediates ER-initiated apoptosis.[71,74] Therefore, there has been an increasing interest in GRP78 in the last two decades to develop new strategies for cancer treatment.[72] A study by Sharma et al revealed that *p*-CouA mitigates GRP78 upregulation in the colon tissue of DMH-treated rats. Moreover, *p*-CouA downregulated GRP78 activation *in vitro* as assessed on HT-29 and SW480 cells.[22] According to the findings of these authors, *p*-CouA exhibits pro-apoptotic effects through GRP78 downregulation associated with PERK-eIF2α-ATF4-CHOP pathway activation in cancer cells.[22] Another study found a moderate inhibitory effect of *p*-CouA on the activation of NF-κB, a downstream target of PERK-eIF2α signaling, which exacerbated inflammatory status once activated in response to UPR.[71]

Cell Cycle Arrest

Normal cell division is controlled, thanks to the so-called cell cycle regulatory machinery. The coordination of many molecules, such as cyclins, cyclin-dependent kinases (Cdks), $p21^{WAF1}$, $p27^{kip1}$, and p53, is required for cell cycle progression and regulation. Uncontrollable cell division due to aberrant proliferative signaling is a common feature of cell malignancy. For over two decades, there has been an increasing interest in drugs targeting cell cycle phases and checkpoints as a prominent cancer prevention and treatment strategy.[75–77] Phytochemicals may also exhibit chemopreventive effects because of their ability to induce cancer cell cycle arrest.[78–80] It has been demonstrated that *p*-CouA exerts an apoptotic effect associated with a cell cycle arrest in

colorectal cancer cells.[11,18,23] Indeed, *p*-CouA induced cell cycle blockade in the G2/M phase through downregulating cdc2 (a putative homolog of Cdk1)/cyclin B activity. Moreover, it mitigated the expression of *c-myc*, *c-jun,* and *c-fos* oncoproteins, which play a pivotal role in proliferation and differentiation, in the colon tissue of DMH-treated rats.[23] The *p*-CouA-induced cell cycle arrest was associated with apoptosis through the abrogation of mdm2, a negative regulator of the tumor suppressor p53.[23] In line, *p*-CouA treatment resulted in cell cycle arrest in the G2/M phase in Caco-2 cells.[18] Consistent with these findings, *p*-CouA-rich EVO induced cell cycle blockade in the G2/M phase and increased p53 expression in DLD-1 colon cancer cells.[11] The same authors reported that *p*-CouA halts HT-29 and Caco-2 cell cycle in the sub-G1 (apoptosis region) and G2 phases. Although *p*-CouA (1400 µM) treatment halted cell cycle progression at the sub-G1 phase and induced apoptosis HT-29 and HCT-15 cells, *p*-CouA-induced cell cycle arrest in sub-G1 phase was not associated with evidenced apoptosis in Caco-2 cells at nearly the same dose (1500 µM).[19,27] These discrepancies could be explained by different cancer cell sensitivities toward a single compound. For this reason, there has been a widespread opinion that argues the combination of phytochemicals for better preventive and therapeutic efficacies.[81]

Effect of p-CouA on Clonogenicity and Multidrug Resistance

The epidermal growth factor receptor (EGFR) plays a central role in colon cancer initiation, progression, and metastasis. Indeed, EGFR is an essential upstream effector of mitogenic signaling networks, including PI3K/AKT/mammalian target of rapamycin (mTOR) and RAS/RAF/MEK/ERK pathways.[20,82] *In vitro* studies showed *p*-CouA efficiency against tumor initiation and progression.[17,20] In addition to its antiproliferative effect, *p*-CouA has been shown to suppress

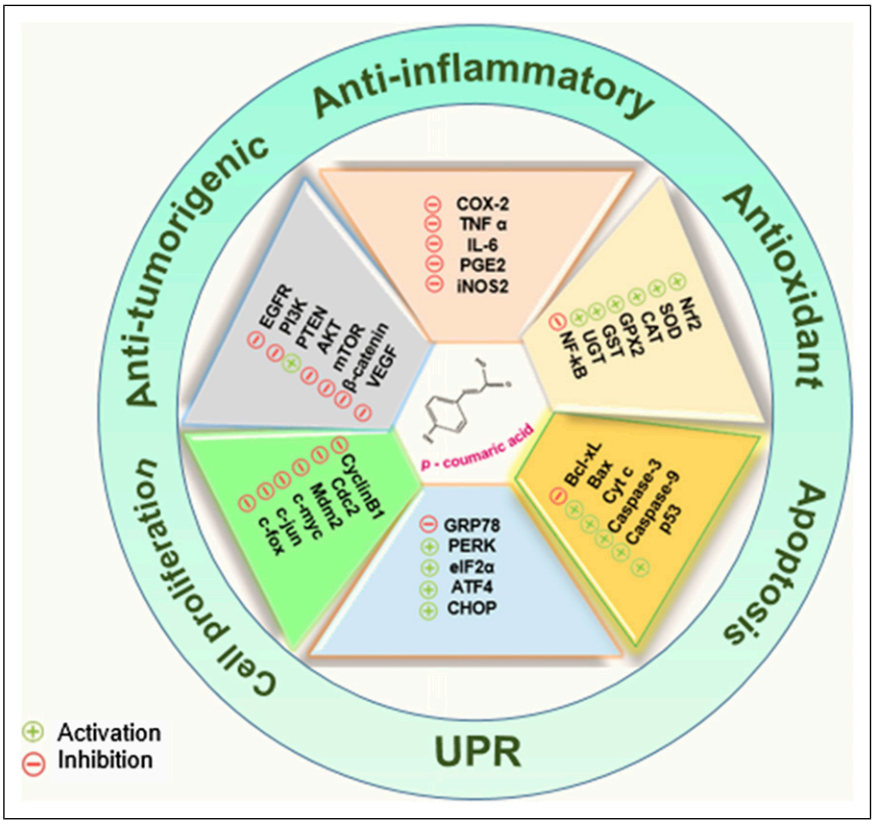

Figure 3. Main potential protective effects of *p*-CouA against CRC trough anti-inflammatory, antioxidant, pro-apoptotic, antiproliferative, and antitumorigenic mechanisms. Cyclooxygenase-2 (COX-2), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS2), nuclear factor erythroid-2-related factor 2 (Nrf2), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase 2 (GPx2), glutathione S-transferase (GST), UDP-glucuronosyltransferase (UGT), nuclear factor-kappa B (NF-κB), B-cell lymphoma-extra large (Bcl-xL), Bcl-2-associated x protein (Bax), cytochrome c (Cyt c), caspase-3, caspase-9, p53, unfolded protein response (UPR), glucose-regulated protein 78 (GRP78), protein kinase R-like ER kinase (PERK), eukaryotic translation initiation factor 2 (eIF2α), activating transcription factor 4 (ATF4), C/EBP homologous protein (CHOP), cyclin-B1, cyclin-dependent kinases (Cdc2), murine double minute 2 (Mdm2), cellular myelocytomatosis (c-*myc*), c-*jun*, c-*fox*, epidermal growth factor receptor (EGFR), phosphoinositide 3-kinase (PI3K), phosphatase and tensin homolog (PTEN), protein kinase B (AKT), mammalian target of rapamycin (mTOR), β-actin, and vascular endothelial growth factor (VEGF).

EGFR gene expression in HCT-15 cells.[20] While *p*-CouA had been identified as an antiproliferative compound at 50 µM, it exerted an anticlonogenic effect, at 200 µM, in three human colon-derived cell types (immortalized HCEC, tumorigenic SW-480, and HT-29 cells).[17] The anticarcinogenic activity of *p*-CouA was confirmed by *in vivo* studies.[21,22,43] Sharma et al found that the supplementation of *p*-CouA suppresses colonic polyp formation by improving the detoxification process in DMH-treated rats.[23] Another study reported that *p*-CouA induces a significant dose-dependent reduction of polyp incidence in the colon of rats exposed to the procarcinogen DMH and suppresses the formation of preneoplastic lesions.[21] The same study demonstrated the antitumorigenic effect of *p*-CouA through the immunoreactivity reduction of β-catenin, a proto-oncogene, in the colonic crypts. Moreover, *p*-CouA co-administration decreased the expression of angiogenic proteins (VEGF, PDGF, and bFGF) in the colon tissue of DMH-treated rats.[22] Furthermore, Ferguson et al research revealed that *p*-CouA exerts a protective activity against the hydrogen peroxide-induced DNA damage and modulates the activity of enzymes that were shown to be associated with the risk of colon carcinogenesis such as COX-2.[43]

Since resistance to chemotherapy is a big concern, there is a growing interest in dietary polyphenols, including *p*-CouA, as adjuvants in therapeutic cancer treatment.[25,81,83] A previous investigation showed that *p*-CouA-rich bound polyphenols of inner shell (BPIS) extract improves drug-resistant HCT-116/L-OHP cells sensitivity to oxaliplatin.[25] In line, BPIS co-treatment with chemotherapeutic drugs (5-fluorouracil "5-Fu", oxaliplatin, and vincristine) reversed the multidrug resistance of colorectal cancer in human HCT-8/Fu cells.[83]

Taken together, various mechanisms can underlie the protective role of *p*-CouA against CRC development (Figure 3).

Conclusion

Out of coumaric acids, *p*-CouA is the most abundant isomer. The present review discussed the molecular mechanisms involved in *p*-CouA potential in CRC prevention and treatment. *In vitro* and *in vivo* studies reveal a high bioavailability of *p*-CouA as compared to other phenolic acids. *p*-CouA can exert anticancer activity by different mechanisms: modulating inflammation and oxidative stress, inducing apoptosis, halting cell cycle progression, altering cellular proliferation pathways, and enhancing sensitivity to chemotherapeutic drugs. Collectively, these properties make *p*-CouA a promising nutraceutical candidate for phytochemical-based strategies to reduce CRC incidence and morbidity.

Declaration of Conflicting Interests

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