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Review

Regulating arachidonic acid metabolism: a novel strategy to prevent colorectal inflammatory cancer transformation

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Abstract

Colorectal cancer (CRC) ranks among the leading causes of cancer-related morbidity and mortality worldwide, with colitis-associated colorectal cancer (CAC) driven by inflammatory cancer transformation. Arachidonic acid (AA), a key ω-6 polyunsaturated fatty acid, and its metabolites, including prostaglandins (PGs) and leukotrienes (LTs), play pivotal roles in this process by modulating inflammation, immune responses, and the intestinal microenvironment. Notably, a multi-enzyme co-expression nanoplatform integrating lipoxygenase (LOX) and phospholipase A_2 (PLA_2) has been developed, synergistically inducing immunogenic ferroptosis and upregulating AA expression to enhance $CD8^+$ T cell-mediated anti-tumor immunity. Additionally, dual COX-2/soluble epoxide hydrolase (sEH) inhibitors, such as PTUPB, demonstrate enhanced anti-tumor activity and reduced toxicity when combined with cisplatin, offering a promising approach to mitigate gastrointestinal side effects of nonsteroidal anti-inflammatory drugs (NSAIDs). Furthermore, natural products like ginsenoside Rk3 and berberine have been identified to regulate AA metabolism and gut microbiota, alleviating CAC by modulating lipid peroxidation and inflammatory pathways. This review synthesizes these innovative findings, highlighting the role of AA metabolism in maintaining intestinal homeostasis, promoting inflammatory cancer transformation, and serving as a therapeutic target to inhibit CAC progression, thus providing new insights into its prevention and treatment.

Keywords: colorectal cancer; arachidonic acid; gut microbiota; inflammatory cancer transformation; cancer therapy

1. Introduction

Colorectal cancer (CRC) is one of the most common malignant tumors of the digestive system [1]. According to the latest statistics from the National Cancer Center (NCC), CRC has the second highest incidence rate and the fourth highest mortality rate among all malignant tumors, and the incidence rate continues to increase [2]. Colitis-associated colorectal cancer (CAC) refers to CRC arising from chronic intestinal inflammation, primarily in ulcerative colitis (UC) and Crohn's disease (CD) patients. Clinically, CAC is characterized by earlier disease onset, multifocal lesions, and a higher likelihood of aggressive tumor behavior compared to sporadic CRC. The inevitable consequence of CAC is the

progression from chronic inflammation to dysplasia and malignancy, driven by persistent epithelial injury, immune dysregulation, and microbial dysbiosis, with potential outcomes including increased metastasis and reduced survival [3].

Polyunsaturated fatty acids (PUFAs) are essential fatty acids that may play a potential role in regulating inflammation, particularly in the pro-cancer inflammatory milieu of the colon. The two main types of PUFAs are omega-3 (ω-3) fatty acids and omega-6 (ω-6) fatty acids. A systematic review found that a high dietary intake of ω-3 fatty acids reduced the risk of CRC, and that the risk was higher with a high dietary ω-6/ω-3 ratio [4]. Furthermore, statistical analyses found that elevated hereditary PUFAs were strongly associated with CRC and emphasized the high expression of ω-6 as a potential mediator [5].

Arachidonic acid (AA) is one of the ω-6 fatty acids and one of the most abundant and widely distributed PUFAs in mammals. AA can be converted to various metabolites in the body, most of which have potent physiological effects and a wide range of actions and are important for cellular regulation. AA and its metabolites regulate inflammatory responses critical to CAC onset and progression [6, 7]. Given its wide range and importance, the functional study of AA metabolic pathways and metabolites has been highly valued by the life science and medical communities, and the present review will systematically elucidate the mechanism of AA and its metabolism in the inflammatory cancer transformation of CAC.

2. Metabolic pathways of arachidonic acid

AA, a 20-carbon ω-6 polyunsaturated fatty acid (20:4n-6), possesses four cis-double bonds at positions 5, 8, 11, and 14, conferring high flexibility and reactivity that facilitate its role as a substrate for enzymatic metabolism. Stored primarily as an esterified component of membrane phospholipids, AA is released by cytosolic phospholipase A_2 ($cPLA_2$), which is activated by calcium-dependent translocation to the membrane in response to inflammatory stimuli. The liberated AA undergoes metabolism via three primary pathways: cyclooxygenase (COX), lipoxygenase (LOX), and cytochrome P450 (CYP450), each catalyzed by enzymes with distinct kinetic properties (Figure 1). For instance, COX-2 exhibits a higher affinity for AA compared to COX-1, enabling rapid production of prostaglandin H_2 (PGH_2) under inflammatory conditions. Similarly, 5-LOX, activated by 5-lipoxygenase-activating protein (FLAP), converts AA into 5-hydroperoxyeicosatetraenoic acid (5-HPETE) with high specificity, subsequently forming leukotriene B_4 (LTB_4). These metabolites interact with G-protein-coupled receptors (such as EP1-4 for PGE_2, BLT_1 for LTB_4), triggering downstream signaling cascades such as cAMP/PKA and NF-κB, which are critical in CAC pathogenesis [8, 9].

The COX pathway comprises three isoforms: COX-1, COX-2, and COX-3, each with distinct expression patterns and functions. COX-1, constitutively expressed across most tissues, supports physiological processes such as promoting intestinal epithelial cell (IEC) proliferation and enhancing digestive juice secretion [10]. PGs produced by COX-1 maintain gastrointestinal and tissue homeostasis [11] and synergize with enzymes to regulate biological processes, including apoptosis and cell cycle progression [12]. In contrast, COX-2 is inducible, primarily expressed in response to inflammatory stimuli, and is rarely present in resting cells [13]. COX-3 is predominantly found in the cerebral cortex and heart, with its role less clearly defined. In the presence of COX enzymes, AA is converted into PGG_2 and PGH_2, and occasionally thromboxane A_2 (TXA_2), which has a short half-life and is rapidly converted to stable TXB_2. PGG_2 and PGH_2 are further transformed by isomerases into prostaglandins such as PGD_2, PGF_2, PGE_2, and PGI_2, which mediate inflammatory and homeostatic responses.

The LOX pathway involves four key enzymes—5-LOX, 8-LOX, 12-LOX, and 15-LOX—that metabolize AA into bioactive lipid mediators. The 5-LOX enzyme, activated by FLAP, is the primary producer of leukotrienes (LTs), which regulate both normal homeostasis and inflammatory responses [14]. LTs are categorized into LTB_4, a chemokine, and cysteinyl leukotrienes (LTC_4, LTD_4 and LTE_4). LTB_4 drives neutrophil recruitment, vascular leakage, and epithelial barrier function, while LTC_4 and LTD_4 modulate IEC proliferation and survival through effects on vascular permeability. LTE_4 serves as a clinical biomarker for asthma triggers [15, 16]. Additionally, 8-LOX, 12-LOX, and 15-LOX convert AA into 8-HPETE, 12-HPETE, and 15-HPETE, respectively, which are subsequently dehydrated to form 8-HETE, 12-HETE, and 15-HETE, contributing to inflammatory signaling.

In the CYP450 pathway, AA undergoes epoxidation to produce 5,6-, 8,9-, 11,12-, and 14,15-epoxyeicosatrienoic acids (EETs), which are hydrolyzed by soluble epoxide hydrolase (sEH) into biologically inactive dihydroxyeicosatrienoic acids (DHETs). Additionally, AA is metabolized via propylene oxidation to yield 5-, 8-, 9-, 11-, 12-, and 15-hydroxyeicosatetraenoic acids (HETEs) and via ω

-1 hydroxylation to produce 19- and 20-HETEs. These metabolites regulate vascular tone, inflammation, and cellular signaling, with emerging roles in the inflammatory microenvironment of CAC.

3. Arachidonic acid metabolism is involved in intestinal inflammation and tumorigenesis

The etiology of inflammatory bowel disease (IBD), encompassing UC and CD, remains multifactorial, involving genetic, environmental, and microbial factors. Central to IBD pathogenesis is chronic intestinal inflammation, characterized by epithelial damage and leukocyte infiltration, which is closely linked to the activation of AA metabolic pathways. Elevated AA levels have been observed in the inflamed mucosa of UC patients, with concentrations correlating strongly with the severity of inflammation [17]. Preclinical studies demonstrate that oral AA administration exacerbates inflammation in IBD mouse models, upregulating COX-2 and LTB_4 expression, while exerting no significant effect in healthy controls [18]. AA-derived metabolites, such as eicosanoids, activate transient receptor potential vanilloid 4, a calcium channel, leading to increased intracellular calcium and chemokine release, thereby amplifying IBD-associated inflammation [19]. Notably, PGE_2, a downstream AA metabolite, promotes Th17 cell-mediated inflammatory responses, further driving disease progression [20]. Clinical studies in adolescent IBD patients reveal significantly elevated levels of TXB_2, LTB_4, and 9S-HODE during active disease phases compared to remission, with 15S-HETE levels being markedly higher in CD than in UC [21, 22]. Additionally, lipoxygenases ALOX5 and ALOX15 exert proinflammatory effects, and their genetic inactivation confers protection in dextran sulfate sodium (DSS)-induced colitis models [23]. These findings underscore the pivotal role of AA metabolism in sustaining the inflammatory milieu of IBD, a key precursor to CAC.

The role of AA in CRC, particularly CAC, remains controversial, with evidence supporting both anti-tumorigenic and pro-tumorigenic activities. Some studies suggest that AA exerts anti-tumor effects by inhibiting cancer cell proliferation and promoting apoptosis. For instance, AA has been shown to activate neutral sphingomyelinase, increase β2-microglobulin exposure on cell surface membranes for antibody binding, and hydrolyze sphingomyelin to ceramide, a potent inhibitor of proliferation and inducer of apoptosis across various tumor cell lines [24, 25]. Furthermore, AA suppresses CRC cell proliferation by disrupting DNA replication and endogenous fatty acid synthesis, primarily through interference with the G1/S cell cycle transition and DNA repair processes, independent of reactive oxygen species production or caspase-3/7 activation [26, 27]. In contrast, other studies report that AA induces oxidative damage to DNA and proteins, activates caspase-3/7, and promotes apoptosis, thereby inhibiting CRC cell proliferation [28].

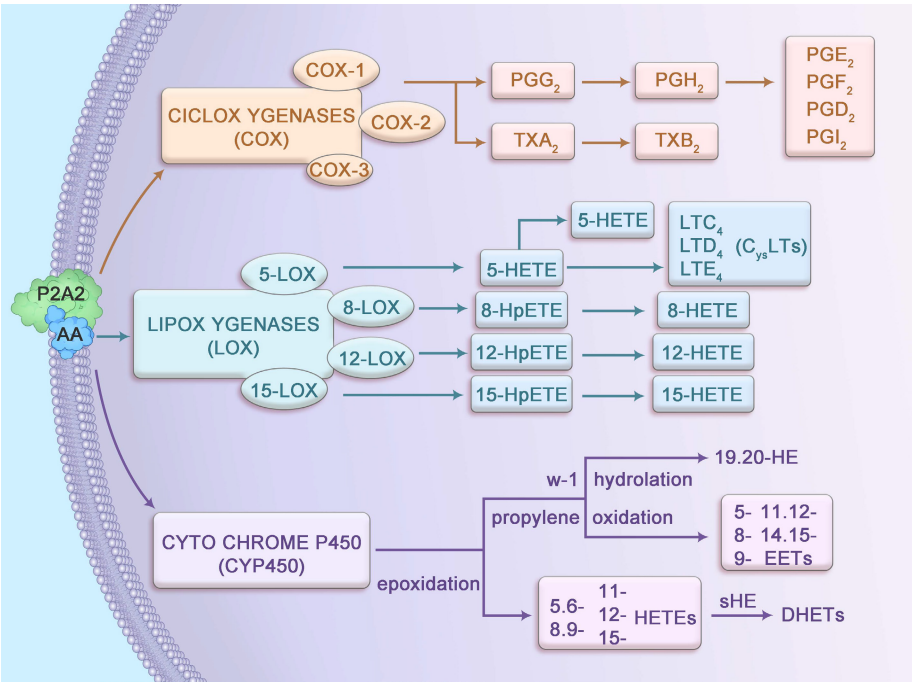

Figure 1: Metabolic pathways of arachidonic acid.

Conversely, substantial evidence supports a pro-tumorigenic role for AA and its metabolites. A Mendelian randomization study by Larsson *et al.* demonstrated a positive correlation between plasma phospholipid AA concentrations and increased risks of colorectal, lung, and esophageal cancers [29]. High dietary AA intake leads to the accumulation of prostaglandins, particularly PGE_2, which fosters a pro-inflammatory microenvironment conducive to cancer development [30]. PGE_2 enhances CRC cell proliferation, migration, and invasion in an autocrine manner and inhibits inflammasome complex formation (ASC/Caspase-1/NLRP3) in THP-1 cells, promoting a shift from pro-inflammatory M1 to pro-tumorigenic M2 macrophages in the presence of AA [31]. TXA_2, another AA metabolite, drives cell growth, migration, and angiogenesis, with elevated levels associated with poor prognosis, reduced survival, and metastatic disease in multiple cancers [32]. Overexpression of 5-LOX in the lipoxygenase pathway correlates strongly with risk factors for malignant transformation of adenomatous polyps [33]. Additionally, 12S-HETE, secreted by CRC cells, enhances cancer-associated fibroblast growth and angiogenesis, further promoting CRC invasiveness [34].

Chronic inflammation in IBD leads to repeated mucosal injury and repair, increasing the risk of dysplastic transformation and CAC development. Given the dual roles of AA in modulating inflammation and tumorigenesis, elucidating the intrinsic mechanisms of AA metabolism in the inflammatory-to-cancerous transition in CAC is critical. This review synthesizes global and domestic research to clarify the complex interplay of AA and its metabolites in driving CAC, providing a foundation for targeted therapeutic strategies to mitigate disease progression and improve clinical outcomes.

4. Mechanisms of Arachidonic acid involvement in inflammatory cancer transformation

CAC, primarily arising from UC and CD, represents a distinct paradigm of inflammatory cancer transformation driven by chronic intestinal inflammation. AA metabolism underpins this process through tightly regulated molecular mechanisms. $cPLA_2$, activated via phosphorylation at Ser505 by inflammatory cytokines (such as IL-1β, TNF-α), selectively hydrolyzes membrane phospholipids to release AA, a process amplified in UC and CD mucosa [35]. The liberated AA is metabolized by COX-2, induced by NF-κB, to produce PGE_2, which binds EP2/EP4 receptors to activate cAMP/PKA and PI3K/AKT pathways, promoting epithelial dysplasia [36]. Similarly, 5-LOX, stabilized by FLAP, generates LTB_4, which engages BLT_1 receptors to enhance NF-κB and STAT3 signaling, driving immune suppression and tumor progression [37]. Novel interventions, such as CRISPR/Cas9-mediated silencing of PLA2G4A, reduce AA availability, attenuating these oncogenic cascades in CAC models [38]. These molecular mechanisms link AA metabolism to the subsequent immune, epithelial, microbial, genetic, and epigenetic alterations driving CAC, as detailed below (Figure 2).

4.1 Tumor immune microenvironment

The tumor immune microenvironment (TIME) comprises immune cells, fibroblasts, blood vessels, signaling molecules, and the extracellular matrix, all of which shape tumor initiation, progression, and metastasis in CAC. AA metabolism influences the TIME by generating pro-inflammatory and immunosuppressive metabolites, such as PGE_2 and LTB_4, which foster a tumor-permissive environment [39]. Cytosolic PLA_2 promotes AA-derived PGE_2 production, driving lymphocyte infiltration and M1-to-M2 macrophage polarization, which protects the colon from excessive inflammation but promotes tumor tolerance [40]. Endogenous lipid mediators, formed via COX-2 and prostaglandin D synthase, reduce neutrophil and M2 macrophage polarization, facilitating IBD remission [41]. In trinitrobenzene sulfonic acid (TNBS)-induced colitis mouse models supplemented with AA, T cells increase interferon-gamma (IFN-γ) production in a COX-2-dependent manner, enhancing lymph node cell activation [42]. AA also mediates SLC3A2-dependent reprogramming of macrophage phenotypes, promoting M2 differentiation in both *in vitro* and *in vivo* settings [43]. Furthermore, the PLA2G4A/AA axis drives $CD39^{+}\gamma\delta$ T-regulatory cells (Tregs) polarization, exacerbating tumor progression and metastasis [44].

To counteract these effects, innovative approaches like a multi-enzyme co-expression nanoplatform integrating LOX and PLA_2 have been developed. This platform ind uces immunogenic ferroptosis—a form of programmed cell death—while upregulating AA expression to enhance ACSL4-mediated tumor cell death, synergizing with $CD8^{+}$ T cell-derived IFN-γ to boost anti-tumor immunity [45]. This strategy highlights the potential of targeting AA metabolism to reverse immunosuppression in CAC, offering a bridge to therapeutic interventions. In the $Apc^{Min/+}$ model of familial adenomatous polyposis, the amount of $CD25^{+}$ Treg increased with elevated COX-2

activity [46]. microsomal PGE_2 synthase 1 (mPGES-1), a terminal synthase that induces the formation of PGE_2, whose absence in tumors reduces collagen deposition and T-cell exhaustion and regulates the TIME [47].

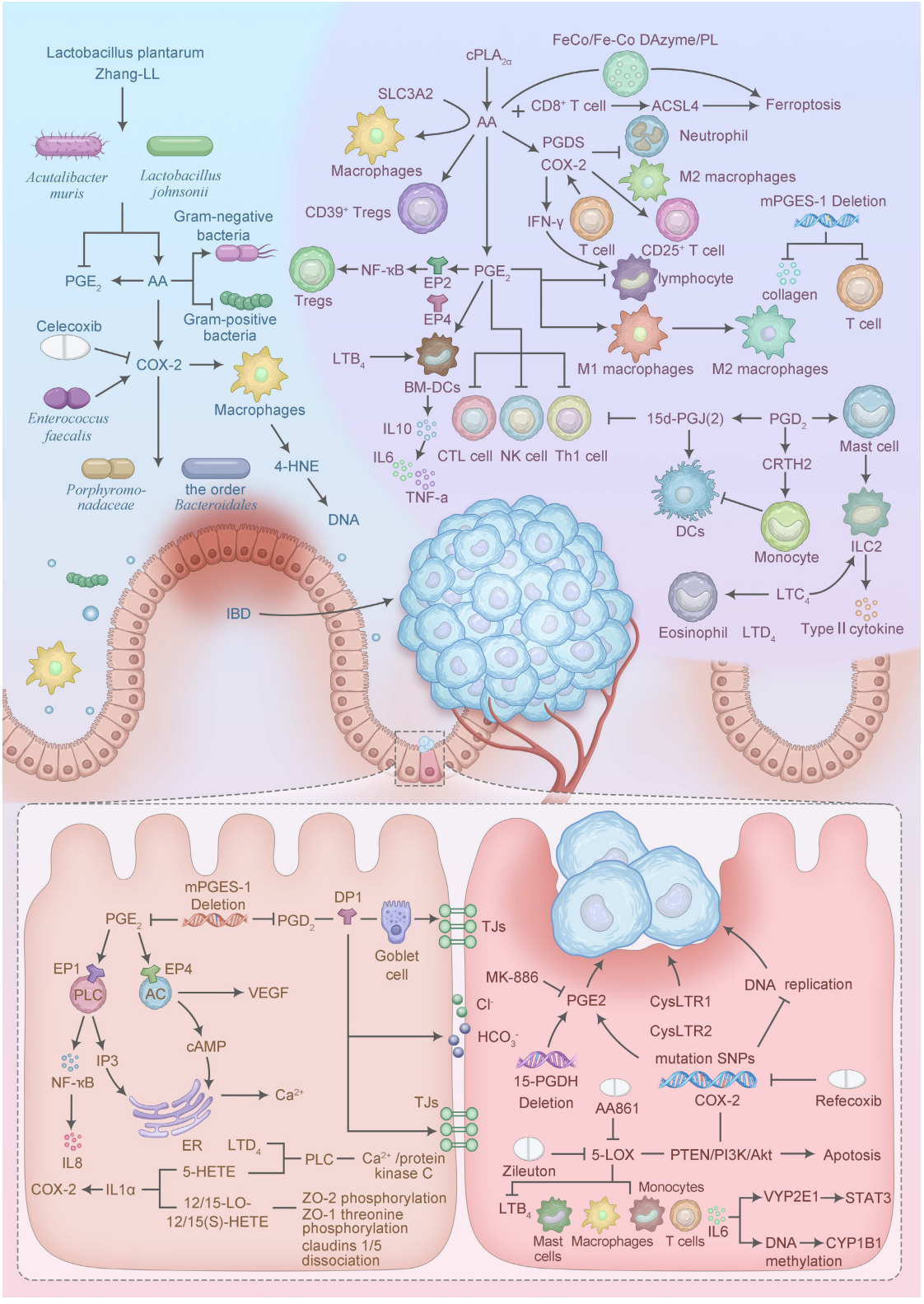

Figure 2: Mechanisms of AA involvement in inflammatory cancer transformation. The blue section in the upper left corner is the intestinal microbiota, the purple section in the upper right corner is the tumor immune microenvironment, the yellow section in the lower left corner is the intestinal barrier, and the pink section in the lower right corner is the Genetic, Epigenetic, and drug. IBD: Inflammatory bowel disease; PGE_2: prostaglandins E_2; AA: Arachidonic acid; COX-2: cyclooxygenase-2; NF-κB: Nuclear Factor Kappa-light-chain-enhancer of Activated B cells; LTB_4: Leukotriene B_4; IL10: Interleukin-10; IL6: Interleukin-6; TNF-a: Tumor Necrosis Factor-alpha; PGD_2: prostaglandins D_2; DCs: dendritic cells; ILC2: type 2 innate lymphoid cell; LTC_4: Leukotriene C_4; LTD_4: Leukotriene D_4; IL8: Interleukin-8; ER: Endoplasmic reticulum; TJs: Tight Junctions.

In general, PGE_2 promotes acute localized inflammatory responses and phagocyte-mediated immunity in response to the presence of pathogens. PGE_2-EP2/EP4 signaling has been reported to induce NF-κB gene expression to promote inflammation and cause immunosuppression through recruitment and activation of Tregs [48]. Selenoproteins in macrophages alleviate inflammation and protect DSS-induced IBD mice by enhancing 15-PGDH-dependent oxidation of PGE_2 [49]. And in the presence of PGE_2, it promotes IL-10 production by bone marrow-derived DCs (BM-DCs), which in turn down-regulates self-produced IL-6, TNF-a, and promotes immune homeostasis [50]. However, high expression of PGE_2 in tumor tissues suppresses cytotoxic immune responses in CTL, Th1, and NK cells, leading to immunosuppression [51]. The PGE_2 biosynthesis pathway correlates with $CD68^+$ macrophage infiltration and CRC tumor progression [52]. CAR-T therapy is a novel precision-targeted therapy for the treatment of tumors. PGE_2 is negatively correlated with memory T cells, and dual blockade of EP2 and EP4 receptors effectively reverses PGE_2-mediated inhibition of CAR T cells when it is applied to tumor tissues [53].

PGD_2 promotes type 2 immunity by activating the group 2 innate lymphoid cell (ILC2) to produce type 2 cytokines by affecting the supernatant of mast cells [54]. Meanwhile, PGD_2 inhibits the migration of monocyte-derived DCs through activation of CRTH2 and, together with the metabolite 15-deoxy-Delta (12,14)-PGJ(2) inhibits TH1 cell chemotaxis and reduces IL-12 secreted by TH1 cells [55].

LTs, as an important inflammatory mediator, play a key role in immune responses. The addition of exogenous LTB_4 promoted the proliferation of BM-DCs in *in vitro* experiments [56]. LTD_4 not only enhances the accumulation and proliferation of ILC2 and promotes the release of IL-5 and IL-13, but also induces increases of eosinophil [57]. In addition, LTC_4 also induces an increase in ILC2 inducing inflammation [58]. 5-LOX affects tumor immunity during CRC development and has a pro-tumorigenic role in the immune microenvironment [59]. The immunosuppressive TIME shaped by AA metabolites not only promotes tumor growth but also compromises intestinal epithelial integrity, setting the stage for barrier dysfunction.

4.2 Intestinal barrier

The maintenance of intestinal epithelial barrier (IEB) function is critical for intestinal homeostasis, and AA metabolites regulate intestinal electrolytes, epithelial cell proliferation, secretion, and tight junction (TJ) integrity. The COX pathway inhibits Cl^-/HCO_3^- exchange in chromaffin cells, decreasing affinity for Cl^- and causing NaCl malabsorption, leading to the development of diarrhea in IBD [60]. The secretion of HCO_3^- by the intestinal mucosa is also crucial for preventing acidic digestive damage. Studies have found that PGE_2 can stimulate the secretion of Cl^- and HCO_3^- in the intestines, which has a protective effect on IEB [61]. PGD_2 is able to induce Cl^- secretion from the human colonic mucosa by DP1 receptor-mediated means, causing an elevation of cAMP in epithelial cells [62].

In the intestinal mucosal epithelium of IBD patients, increased phospholipid content of AA contributes to the disruption of the intestinal barrier [63]. In animal experiments, the expression of AA and its metabolites (19H-PGF1α and 20H-PGF2α) progressively decreases with the decrease of inflammation, suggesting that mucosal healing is regulated by endogenous lipids [64]. COX-1 mainly produces endogenous PGs engaged in mucosal protection, while COX-2 mainly produces endogenous PGs engaged in ulcer and intestinal lesion healing. It has been shown that COX-2 expression is significantly elevated in the early stages of CRC development, which further affects epithelial cells by influencing the stromal microenvironment of the tumor [65].

PGs play an important role in maintaining intestinal mucosal integrity, especially PGE_2. PGE_2 is involved in stimulating mucus secretion and down-regulating the immune response through EP4 receptors and is protective against ischemic enteritis and DSS-induced colitis. And activation of EP4 receptors promotes healing of intestinal lesions and is associated with up-regulation of VEGF expression and stimulation of angiogenesis [66]. In addition, EP4 receptors are involved in colorectal homeostasis and cancer development [67]. However, it has also been suggested that PGE_2 contributes to the redistribution of intracellular calcium concentration and TJ proteins through multiple signaling pathways, including the PLC-IP 3-Ca^{2+} and cAMP-PKA pathways, that induces disruption of IEB function [68]. Ptgs2-expressing fibroblasts around intestinal crypts exert paracrine control of tumor-inducing stem cells through the PGE_2-Ptger4-Yap signaling axis, which helps drive tumorigenesis [69].

Prostaglandin homeostasis in the intestine is critical for maintaining intestinal homeostasis and influencing tumorigenesis. It was found that in DSS-induced mPGES-$1^{-/-}$ mice, this leads to a decrease in PGE_2 and PGD_2, resulting in more extensive acute injury affecting recovery. And in DSS-induced $Apc^{Min/+}$: *mPGES-*$1^{-/-}$ mice, the number of intestinal polyps was reduced [70]. Pharmacological studies

have found that PGD_2, through the DP1 receptor, is able to stimulate mucus secretion from goblet cells to reduce intestinal permeability and achieve protection of the IEB [71]. Moreover, PGD_2 promotes the regression of inflammation in the gastrointestinal mucosa [72].

PGE_2, LTB_4, and 5-, 12-, and 15-HETE can protect IECs by inducing proliferation and DNA synthesis in IECs [73]. BLT2, a receptor for LTB_4, is expressed only in IECs and epidermal keratinocytes. When BLT2 receptor is overexpressed in IECs it enhances epithelial drug resistance, suggesting that the LTB_4-BLT2 axis has a barrier function [74]. DSS-induced colitis in mice is exacerbated in the absence of BLT2 receptor, which may be correlated with the reduced intestinal barrier function [75]. LTD_4 and 5-HETE alter the proliferation and DNA synthesis of IECs by activating the phospholipase C/Ca^{2+}/protein kinase C pathway activation alters paracellular permeability and is involved in IEB disruption, a process that is not dependent on protein kinase A activation by cAMP [76]. In addition, LTD_4 is able to induce proliferation of Caco-2 cells by binding to the cysteinyl leukotriene receptor (CysLTR), which is dependent on PGE_2 [77].

Tight junctions (TJs) are multiprotein complexes composed of transmembrane proteins with cytoskeletal enclosing rings of actin and myosin, which are important components of the intestinal barrier [78]. It was found that 15-HETE regulates IEB permeability and homeostasis through inhibition of adenosine monophosphate-activated protein kinase and increased zonula occludens-1 (ZO-1) expression [79]. 12/15-LO-12/15(S)-HETE axis not only stimulates the phosphorylation of ZO-2, but also stimulates the phosphorylation of ZO-1 threonine and the dissociation of claudins 1/5, which mediates the disruption of endothelial TJs and disrupts the barrier function [80]. In addition, the COX pathway interacts with the LOX pathway; 5(S)-, 12(R)- and 15(S)-HETEs alone have little effect on COX-2 expression, but they synergize with IL-1α to cause increased COX-2 expression in human colonic myofibroblasts [81].

EETs exhibit anti-inflammatory effects and are elevated in UC patients, with reduced sEH expression in the intestinal mucosa [82]. sEH correlates with villin expression, a marker of intestinal cell differentiation [83]. Cyp4a14, a cytochrome P450 family member, promotes oxidative stress and exacerbates DSS-induced colitis, while its knockdown protects the colonic mucosa [84]. IEB disruption by AA metabolism facilitates microbial dysbiosis, amplifying inflammation and CAC risk.

4.3 Intestinal microbiota

The intestinal microbiota maintains immune homeostasis and protects against pathogen invasion, but chronic inflammation disrupts microbial balance, increasing CAC susceptibility [85]. AA metabolism interacts bidirectionally with the microbiota. For example, AA supplementation enhances lipid peroxidation by *adherent-invasive Escherichia coli*, exacerbating inflammation in CD patients [86]. In another study, AA was found to kill *S. aureus* through a lipid peroxidation mechanism, in which AA is oxidized to reactive electrophiles, which alters S. *aureus* macromolecules and produces toxicity [87].

Clinical studies have found that metabolites such as AA are increased in CRC patients, and the abundance of *Bacteroides fragilis* and *Prevotella* in the bacterial flora is elevated while the abundance of *Blautia* and *Lachnospiracaea* is reduced [88]. *ApoE*$^{-/-}$ mice not only have disturbed intestinal flora compared to wild-type mice (*Lachnospiraceae_FCS020*, *Ruminococcaceae_UCG-009*, *Acetatifactor*, *Lachnoclostridium*, and *Lactobacillus_gasseri* pathogenic bacteria were significantly increased), their metabolism was also significantly altered (AA metabolic pathways of 20-HETE, PGF2α and LTB_4 levels were significantly elevated) [89]. These results all indicate suggest a close link between gut flora imbalance and AA metabolism.

Lactobacillus plantarum Zhang-LL regulates the activity of *Acutalibacter muris* and *Lactobacillus johnsonii flora*, significantly reduces the expression of PGE_2, and promotes AA catabolism, which slows down the process of CRC [90]. Further studies have found that feeding AA significantly increases the number of Gram-negative bacteria such as *Escherichia coli* and *Enterobacter faecalis*, and decreases the the number of Gram-positive bacteria *Fusarium nucleatum*. The rich microecological environment of Gram-negative bacteria accelerated the conversion of AA to PGE_2 and promoted tumor growth in AOM/DSS and gut-specific *APC*$^{-/-}$ model mice. Notably, the pro-carcinogenic effect of AA was unaffected by the removal of Gram-positive bacteria, whereas the pro-carcinogenic effect of AA completely disappeared after the removal of Gram-negative bacteria. This evidence suggests that AA-regulated intestinal flora promote the development of CRC [91].

COX-2 is also closely related to the regulation of intestinal flora. *Enterococcus faecalis*, a human intestinal commensal, triggers the production of trans-4-hydroxy-2-nonenal (4-HNE) by macrophages via COX-2, which synergistically reinforces the damage of COX-2 to the DNA of the target cells through the bystander effect, leading to the development of CRC [92]. COX-2 inhibitors, such as

celecoxib, alter intestinal bacteria, such as *Porphyromonadaceae* family and the order *Bacteroidales*, whose metabolites inhibit the development of intestinal polyps in mice [93]. Gut microorganisms are also enriched in CYP450, and the solubility of bacterial CYPs, in contrast to the membrane-bound properties of mammalian CYPs, suggests that intestinal bacteria have a great potential to metabolize xenobiotic compounds.

4.4 Genetics

Genetic polymorphisms are strongly associated with CAC, and clinical studies have found that the COX-2 -765G > C polymorphism is associated with a reduced risk of CD in the Netherlands and an elevated risk of CRC in Asians, whereas the COX2 8473 T > C polymorphism interacts with NASID and is able to reduce the risk of CRC [94-97]. In order to explore the relationship between ALOX5, FLAP, ALOX12 and ALOX15 polymorphisms and CRC risk, a U.S. cohort analysis found that genetic variants in ALOXs may affect the risk of colorectal tumor development and alter the protective effect of NSAID use on CRC [98]. Clinical analyses in northeastern China showed that 12-LOX 261Arg > Gln polymorphisms are closely associated with the risk of CRC development and may serve as a potential marker of CRC prognosis [99].

Mutation or deletion of genes is one of the key factors affecting the number and size of tumors. It is generally accepted that COX-2 is overexpressed in tumors and polyps of CRC patients and CRC mouse models and is thought to promote tumor progression. Nevertheless, single nucleotide polymorphisms (SNPs) in the COX-2 gene may alter the function of the enzyme, thereby altering an individual's risk of developing CRC. Based on clinical cohorts, it has been found that carrying the COX-2 Val511Ala SNP is not associated with a risk of CRC, and that the use of NASID in combination can help reduce the risk of CRC in African Americans [100]. Animal studies have revealed that mice with mutations in the COX-2 gene significantly reduce the number and size of intestinal polyps [101]. The APC gene, a tumor suppressor, is mutated in >80% of sporadic CRC. sporadic CRCs with mutations. When rofecoxib, a COX-2 inhibitor, was used to treat APC mutant mice, the DNA replication rate of their polyps was significantly reduced and was effective in reducing the number and size of intestinal and colonic polyps [102]. In the familial adenomatous polyposis (MMR-proficient CRC) Apc^{Min+} mice and the $Apc^{\Delta 716}$ mice, COX-2 gene deletion resulted in reduced intestinal tumor formation [103]. In addition, *in vivo* and *in vitro* experiments have shown that knockdown of the COX-2 gene inhibits the proliferation and invasion of CRC cells [104]. In mouse models of Apc^{Min+} and AOM, the elevation of endogenous PGE_2 caused by deletion of the 15-PGDH gene promotes the growth of colonic tumors [105]. Interestingly, knockdown of Ptgs-1 and Ptgs-2 (encoding the COX-1 and COX-2 genes, respectively) greatly reduced the number and size of intestinal polyps in APC^{min+} mice [106].

mPGES-1 and mPGES-2 have been associated with poor prognosis in patients with CRC stages I-III [107]. Genetic deletion of mPGES-1 reduces tumor diversity and tumor load in the distal colon, and is significantly protective against carcinogen-induced CRC [108]. Compared with mutant APC, tumors with wild-type APC show higher expression of mPGES-1 [109]. Moreover, mPGES-1 deficiency enhances susceptibility to acute mucosal injury [110]. Genetic variants of LOX were found to be one of the risk factors affecting CRC based on a clinical control trial in the U.S., especially the ALOX15 allele variant [111]. In sporadic adenomas, genetic variants in the COX1, COX2, and ALOX12/15 genes were found to have a significant impact on CRC in recurrent adenomas [112]. Individuals with the ALOX5 VNTR variant genotype are linked to a reduced risk of CRC [98]. Additionally, the heterozygous mutant of ALOX12 is only associated with male CRC patients, revealing a gender bias in functional polymorphisms of ALOX12 in relation to CRC patients [113].

The CysLTR (containing CysLTR1 and CysLTR2) is a G-protein eurameric receptor that mediates the action of CysLT. patients with high expression of CysLTR1 and low expression of CysLTR2 have a poorer prognosis [114]. Animal experiments showed that AOM/DSS model mice had low-grade atypical hyperplasia of colon polyps and reduced inflammation levels in the $Cysltr1^{-/-}$ group compared with the wild-type group, supporting the important role of CysLTR1 in colon tumorigenesis [115]. In addition, based on the biosignature analysis CysLTR2 was positively correlated with immune cell infiltration and immune checkpoints, which could serve as a potential immune target for determining the CRC prognosis as a potential immune target [98].

CYP450 is overexpressed in CRC tissues and cells. Up-regulation of the CYP450 enzyme pathway in CRC plays a crucial role in its pathogenesis and may serve as a new direction for exploring preventive/therapeutic targets in colon cancer. When using pharmacological inhibitors or gene silencing of CYP450 enzymes, AOM/ DSS-induced CRC development can be inhibited [116]. Cytochrome P450 1A1 (CYP1A1) enzyme is one of the most important metabolic enzymes responsible for the metabolism of a wide range of xenobiotics [117]. Meta-analysis based

on the exploration of the relationship between genetic variants and CRC risk revealed that CYP1A1 rs1048943 A > G may increase susceptibility to CRC compared to rs4646903 T > C [118]. Overexpression of the CYP24A1 gene in a variety of cancers, including CRC, correlates with tumor invasion, lymph node metastasis, and decreased overall survival [119]. Therefore, investigating overexpression or silencing of a single target, or combining it with immunotherapy, may be a useful tool for chemoprevention of CRC proliferation, invasion, and metastasis as a viable option.

4.5 Epigenetic

Epigenetic changes, including DNA methylation, histone modifications, chromatin remodeling, and noncoding RNA, are significantly associated with colitis-associated cancer development and progression. The CpG-island methylation pathway (CIMP) is associated with KRAS/BRAF mutations, rewiring of cellular metabolism by two oncogenes, prognosis, and resistance to classical chemotherapy. Patients with high CIMP in CRC have activation of the AA metabolic pathway and exhibit hypermetabolism [120]. COX2 methylation in sporadic primary CRC is also closely related to the CpG island methylation phenotype [121]. Transcriptional silencing of 15-LOX-1 promotes CRC, and DNA methylation of the 15-LOX-1 promoter is independently of its transcriptional regulation [122]. However, the current studies on the association of ALOX15 and CRC epigenetic studies are scarce, and the underlying mechanisms can be further explored subsequently.

Clinical studies have revealed that CysLTR methylation and gene expression profiles are associated with progression, prognosis, and metastasis in patients with CRC [123]. Overexpression of IL6 in CRC induces CYP1B1 and CYP2E1 gene expression and alters the metabolic capacity of epithelial cells, with regulation of CYP2E1 expression occurring through a transcriptional mechanism involving STAT3. For CYP1B1 regulation, IL6 downregulates CYP1B1 targeting the microRNA miR27b through a mechanism involving DNA methylation [124]. Streptococcus gallolyticus induces CYP1A enzyme activity in an AhR-dependent manner to regulate expression of epithelial cell biotransformation pathways [125].

5. Arachidonic acid pathway as a target for drugs that inhibit inflammatory cancer transformation

The AA metabolism enzymes COXs and LOXs and their metabolites (such as, PGs and LTs) have been considered as novel targets for cancer prevention and treatment. Currently, many clinical trials and experimental studies have shown that some Nonsteroidal Anti-inflammatory Drugs (NSAIDs), inhibitors and natural products, etc. inhibit the occurrence and development of CRC by regulating AA metabolism.

5.1 Nonsteroidal anti-inflammatory drugs

NSAIDs are common anti-inflammatory drugs with antipyretic, analgesic, and anti-inflammatory effects, and are widely used in cardiovascular and cerebrovascular diseases as well as various types of cancers. There are two main types of NSAIDs, one type is non-selective inhibition of the COX pathway, which includes aspirin, naproxen, ibuprofen, and so on. naproxen, ibuprofen, etc. The other type is a selective COX-2 inhibitor, including celecoxib, refecoxib, etc. Acetylsalicylic acid (aspirin) was the first NSAIDs developed for commercial use in 1897 and was widely used for its anti-inflammatory effects. Epidemiology has found that aspirin reduces mortality and risk of distant metastasis in CRC [126]. Experimental studies have shown that aspirin induces apoptosis in enriched Cancer stem-like cells (CSCs), inhibits tumor progression, and enhances the antitumor effects of chemotherapeutic agents. In addition, aspirin directly interacts with p300 in the nucleus, promotes H3K9 acetylation, activates FasL expression, and induces apoptosis in colorectal CSCs [127].

Celecoxib competitively inhibit COX-2, reducing AA conversion to PGH_2 and subsequent PGE_2 synthesis, thereby attenuating EP2/EP4-mediated tumor proliferation [128]. Indomethacin, a commonly used potent NSAID, inhibits COX enzymes by reducing AA uptake, thereby inhibiting the malignant development of CRC [129]. Parecoxib, the only non-enteric administered COX-2 inhibitor among NSAIDs, is able to inhibit epithelial-mesenchymal transition and metastasis of human CRC cells by down-regulation of β-conjugated proteins, and inhibit CRC metastasis in combination with chemotherapeutic agents [130].

The selectivity of NSAIDs for COX-1 and COX-2 actions plays different pharmacological roles depending on their structures, and the effective therapeutic effects of NSAIDs on inflammation stem from the selective inhibition of COX-2 [131]. Studies have shown that the greater the selectivity of a drug for COX-2 inhibition, the fewer the gastrointestinal side effects it induces, with a good linear relationship. Currently, 1,3-diaryl pyrazole derivatives were found to have significant inhibitory power and sensitivity to

COX-2 enzyme and significant anti-inflammatory activity against COX-1 compared to celecoxib and indomethacin, and have dual anti-inflammatory and anti-cancer activity for the treatment of CRC [132].

Clinical trials, epidemiologic and experimental studies have shown that NSAIDs reduce the risk of CRC and mortality and prevent the progression of colitis to CRC. However, the major adverse effects of treatment with NSAIDs lead to gastrointestinal damage (including UC, bleeding, and even perforation) and cardiovascular side effects. Thus, the search for more effective improvements or combinations is an ongoing problem.

5.2 Single-target inhibitors

Currently, there are many inhibitors targeting metabolic enzymes or metabolites in the AA pathway, and the inhibitory effects of these inhibitors on CRC are mostly at the stage of experimental studies in animals. mPGES-1 enzyme, a COX downstream enzyme, is a membrane-associated protein with low expression in most tissues, and it can be induced to be produced by proinflammatory cytokines or tumorigenic conditions [133]. MK-886, target mPGES-1, a downstream enzyme in the COX pathway, reducing PGE_2 formation without affecting COX-1-mediated mucosal protection [134].

In addition to COX pathway inhibitors, there are also LOX pathway inhibitors such as Zileuton (5-LOX inhibitor) and PD146176 (15-LOX-1 inhibitor). Zileuton is used to treat asthma patients by inhibiting 5-LOX, blocking the production of LTB_4 and the BLT_1-driven inflammatory cascade reaction. Elias Gounaris *et al.* found that $APC^{\Delta 468/+}$ mice consuming food containing Zileuton for 12 consecutive weeks showed a decrease in serum LTB_4 concentration, as well as a significant reduction in tumor-infiltrating mast cells, macrophages, mature monocytes, and pro-inflammatory T-regs at the site of the polyp, which was effective in decreasing the tumors and polyp formation [135]. PD146176, a selective 15-LOX-1 inhibitor, significantly inhibited 13-HODE production to promote tumor growth in human CRC HCA-7 cells, while inhibiting 12-HETE production to inhibit tumor growth in mouse CRC MC38 cells [136].

Within the LOX pathway, LTs also have the potential to prevent CRC. A prospective study showed that montelukast targeting the leukotriene pathway by cysteinyl leukotriene receptor antagonist (LTRA) inhibited the formation of ACFs and cell proliferation in IECs, suggesting that LTRA has the potential to prevent CRC [137]. In addition, COX-2 inhibitor (NS-398) or 5-LOX inhibitor (AA861) inhibits CRC tumor invasion and proliferation by promoting apoptosis through modulation of the PTEN/PI3K/Akt pathway [138]. GSK2256294, an sEH inhibitor, reduces the production of IL2, IL12p70, IL10, and TNFα in IBD patients. Interestingly, GSK2256294 has different potential effects on UC and CD, reducing IL4 and IFNγ levels in the former and IL1β levels in the latter, respectively [139].

5.3 Dual Inhibitors

Frequent inhibition of either the COX or LOX pathway results in the conversion of AA metabolism from one to the other, which can lead to serious consequences. COX/LOX inhibitors inhibit both the COX pathway and the LOX pathway, inhibiting the production of their downstream products, improving therapeutic efficiency and reducing adverse effects associated with a single inhibitor. Meanwhile, dual COX/LOX inhibitors provide a safe and effective theoretical basis for the study of new anti-inflammatory drugs. Mukhopadhyay N *et al.* summarized plant-based natural products with dual inhibition of COX/LOX bioactivity in different species, including Tannins, Steroids, Flavonoids, Alkaloids, etc. emphasizing the importance of natural product derivatives [140]. Meshram MA *et al.* conducted a review of synthetic bis-COX-2/5-LOX inhibitors covering Thiazoles, 2,3,4-Trisubstituted thiophenes, Pyrazoloquinazolines and others. The design of these novel scaffolds retains the basic structural features of COX-2 and LOX-5 activity while synergizing or enhancing the activity of bis-COX-2/5-LOX, contributing to the discovery of molecules with superior anti-inflammatory activity [141].

sEH is the major epoxide hydrolase involved in the metabolism of EET and is encoded by the EPHX-2 gene on chromosome 8. sEH has been shown to be overexpressed in colitis and CRC [142]. Inhibition of sEH on the one hand increases EET to enhance the bioavailability of EET, which has significant anti-inflammatory effects and protective effects on the lungs, heart, gastrointestinal tract, and blood-brain barrier; and on the other hand, it reduces the product DHET, which is involved in monocyte chemoattractant protein-1 (MCP-1)-mediated monocyte chemotaxis [143].

When sEH inhibitors are co-administered with NASID, they are effective in treating cancer and reduce the side effects caused by NASID, and the underlying mechanisms may be related to decreasing monocyte recruitment and inflammation, blocking the endoplasmic reticulum (ER)/mitochondrial stress induced with NASID to reduce epithelial vascular barrier damage, or increase tissue repair and angiogenesis related [144]. 4-(5-phenyl-3-{3-[3-(4-trifluoromethyl-phenyl)-ureido]-propyl}-pyrazol-1-yl

)-benzenesulfonamide (PTUPB) is a dual COX-2/sEH inhibitor with antitumor activity and organ-protective effects. PTUPB, when used in combination with cisplatin, enhances antitumor properties without increasing toxicity [145]. The combination of sEH inhibitors with other drugs is an effective strategy in the transformation of inflammatory cancers, which can be further investigated in clinical trials.

3,3'-Diindolymethane (DIM) is a novel COX1/2 and ERK1/2 inhibitor derived from the derived from indole-3-carbinol found in broccoli and cabbage. In an *in vivo* mouse model, oral administration of DIM inhibits the growth of xenograft colon tumors and can be used in the chemotherapy of CRC [146]. Therefore, the design of simultaneous multi-target blockade can effectively overcome the side effects of the drug and suggest new ideas for the development of effective and safe new drugs.

5.4 Natural products

Most of the natural products used in the treatment of cancer are derived from plant extracts, and their derived drugs have the advantage of fewer residues and lower side effects (Table 1).

Table 1: Natural products that play a role in inflammatory cancer transformation in colorectal cancer

Ingredients	Origins	Experimental model	Cell lines/animals	Mechanisms	Anticancer/anticarcinogenic effects	References
Ginseng and Sinensis		*In vivo*	DSS-induced mice model	Regulation of metabolic pathways such as arachidonic acid metabolism Beneficial bacteria (such as *Muribaculaceae_norank*, *Lachnospiraceae* and *Akkermansia*)↑ Harmful bacteria (such as *Bacteroides*, *Parabacteroides* and *Desulfovibrio*)↓	Improvement of colitis	147
Ginsenoside Rk3	Ginseng	*In vivo*	High-fat diet-induced mice model	PGE_2, PGD_2, TXB_2, HETE, and HODE↓ EET and diHOME↑	Improve obesity-induced intestinal inflammation	148
Protopanaxatriol saponin	Ginseng	*In vivo*	DSS-induced mice model	TNF-α, IL-6, and IL-1↓ MPO and NO↓	Inhibit metabolic dysfunction Reversing abnormal metabolite changes Amelioration of pathological damage	149
Clinopodium chinense Kuntze		*In vitro* *In vivo*	Mouse macrophage RAW264.7 cell DSS-induced mice model	LPS-TLR_4-NF-κB-iNOS/COX-2 signaling pathway NO, PGE_2, IL-6, IL-10 and TNF-α↑	Reduces systemic inflammation Regulates metabolism	150
Jasminum elongatum		*In vivo*	DSS-induced mice model	IκB/p65/COX-2/arachidonic acid pathway	Improvement of UC mice	151
Chrysanthemum polysaccharides		*In vivo*	TNBS/ethanol induced rat model	P-p65, TLR_4, P-STAT3 and P-JAK2	Improvement of colitis rats	152
Pistacia lentiscus oil		*In vivo*	TNBS-induced rat model	Vesiculitis and cryptoinflammation↓	Protects against intestinal inflammation	153
Acacia saligna butanol extract and its nanoformulation		*In vivo*	Acetic acid-induced mice model	COX-2, PGE_2 and IL1β↓	Improvement of intestinal mucosal lesions and inflammatory infiltrates	154
6-Gingerol	Zingiber officinale Roscoe	*In vitro* *In vivo*	Human CRC cell lines Caco2 DSS-induced mice model	Iron load and MDA↓ GSSG↓ SOD, GSH↑	Anti-inflammatory, antioxidant	155
		In vitro *In vivo*	Human CRC cell lines HCT116 cells Xenograft mouse model	LTA_4 hydrolase↓ Proliferation↓	Inhibition of CRC progression	156
Berberine	Coptis chinensis and many other plants		DSS-induced mice model BBR-induced fecal microbiota transplantation model	AA metabolism pathway↓	Regulates the intestinal microbiome Improves serum metabolic balance	158
		In vitro *In vivo*	Human CRC cell lines SW620 and LoVo cells Xenograft mouse model	COX-2/PGE_2- JAK2/STAT3 signaling pathway↓	Inhibited CRC invasion and metastasis	159
		In vitro	Human CRC cell lines SW480 cell	Arrested SW480 cell cycle at G2/M phase Mitochondriamediated intrinsic apoptosis↑ Angiogenesis and inflammation markers↓	Chemopreventive effect on CRC	160
Emodin	Rheum officinale	*In vitro*	Human CRC cell lines SW620 and HCT116 cells AOM/DSS-induced mice model	Inflammatory cell, cytokine and pro-inflammatory enzymes↓ $CD3^+$ T lymphocytes↑	Inhibits cancer-associated intestinal inflammation and prevents CRC progression	161

Ingredients	Origins	Experimental model	Cell lines/animals	Mechanisms	Anticancer/anticarcinogenic effects	References
Inositol hexapphosphate		*In vitro*	Human CRC cell lines Caco2 cells	COX-2, 5-LOX, PGE_2 and LTB_4↓	Prevention of CRC	162
Celastrol	Tripterygium wilfordii Hook F	*In vitro*	Human CRC cell lines HCT116 and SW620	Cell apoptosis↑ Cell cycle arrest NF-κB/COX-2 pathway↓	Effective treatment of CRC	163
Ellagic acid	Ellagitannin	*In vivo*	1,2-dimethylhydrazine-induced mice model	NF-κB, COX-2, iNOS, TNF-α and IL-6↓ 5'-ND, gamma-GT, CEA, AFP, CD, ALP, LDH↓	Chemopreventive effect on CRC	165
Lycopene	Lycopersicum esculentum	*In vitro* *In vivo*	Human CRC cell lines HT29 cells Xenograft mouse model	p21(CIP1/WAF1) and p27(Kip1)↑ Proliferating cell nuclear antigen, β-catenin, cyclin D1 and c-Myc proteins↓ MMP-7, MMP-9, COX-2 and PGE_2↓	Synergistic fish oil inhibits CRC growth and progression	166
Lizhong Decoction (LZD)	Zingiberis Rhizoma, Radix Ginseng, Rhizoma Atractylodis Macrocephalae and Radix Glycyrrhizae	*In vivo*	DSS-induced mice	Improvement of metabolites in plasma and urine	Ameliorate of DSS-induced colitis mice	167
Zhilining Formula (ZLN)	Andrographis herba, Sophorae flavescentis radix and Aucklandia radix	*In vivo*	DSS-induced mice	MPO, IL1β, TNF-α, IL18↓ AHR↑, NF-κBp65 axis↓ COX-2↓	Repairing the intestinal mucosal barrier Reduce persistent inflammation	168
Yinhua Miyanling tablets	Lonicerae Japonicae Flos, Scu tellariae Barbatae Herba, Pol ygoni Avicularis Herba, Pyrrosiae Folium, Clematis Armandii Caulis, Lophatheri Herba, Plantaginis Semen, Dianthi Herba and Junci Medulla	*In vitro* *In vivo*	Human CRC cell lines Caco2 cell DSS-induced mice model	TNF-α, IL-6, iNOS↓ MPO, MDA, SOD↓	Improvement of colonic mucosal damage	169
Huang-lian-Jie-du decoction (HLJDD)	Copptidis Rhizoma, Scutellaria Radix, Phelodendri Chinensis Cortex and Gardenia Fructus	*In vivo*	DSS-induced mice model	COX-2, PLA_2 and 5-LOX↓	Reversing metabolite abnormalities Alleviates UC mice	170
Sanwu Baisan Decoction	Badoushuang, Zhebeimu and Jiegeng	*In vitro* *In vivo*	Mouse CRC cell line CT26 Xenograft mouse model	TLR_4/COX-2/PGE_2↓ Induces apoptosis	Inhibition of CRC progression	171

The gut microbiota-metabolite axis may be one of the important mechanisms for the treatment of IBD. The combination of ginseng and Sinensis effectively increases the abundance of beneficial bacteria and decreases the abundance of harmful bacteria through metabolic pathways such as AA metabolism [147]. ginsenoside Rk3, a natural anti-inflammatory active ingredient extracted from ginseng, can improve obesity-induced intestinal inflammation by regulating lipid metabolism [148]. Protopanaxatriol saponin is also a major active ingredient of ginseng, which can ameliorate pathological damage and reverse abnormal metabolite changes in UC mice through metabolic pathways such as AA [149]. Traditional Chinese medicine Clinopodium chinense Kuntze (CC) has anti-inflammatory, antidiarrheal, and hemostatic activities, and it was found that CC can reduce inflammation through the LPS-TLR4-NF-κB-iNOS/COX-2 signaling pathway, and regulate endogenous metabolites such as AA to alleviate UC [150]. Jasminum elongatum alleviates UC physiological and pathological symptoms and reverses DSS-induced UC mice via the IκB/p65/COX-2/AA pathway [151]. Also, Chrysanthemum polysaccharides ameliorate 2,4,6-trinitrobenzenesulfonic acid (TNBS)/ethanol-induced colitis in rats by adjusting multiple metabolites including AA [152]. Animal experiments in which the Pistacia lentiscus oil was administered first, and in which TNBS was given to induce UC, significantly reduced vesiculation and crypt inflammation [153]. Acacia saligna butanol extract and its nanoformulation can reduce COX-2, PGE_2 and IL1β levels, normalize metabolite levels, and ameliorate intestinal mucosal lesions and inflammatory infiltration in UC mice [154].

Some natural products have dual anti-inflammatory and cancer inhibiting activities for both IBD and CRC. natural phenolics, 6-Gingerol (6-G), one of the constituents of Zingiber officinale Roscoe, is able to inhibit ferrometabolism through AA metabolism, exerting anti-inflammatory and antioxidant effects to ameliorate UC [155]. 6-G also inhibits the growth of CRC by inhibiting LTA_4 hydrolase [156]. Berberine, an isoquinoline alkaloid, is

found in Coptis chinensis and many other plants [157]. Berberine has been found to be able to improve serum metabolic homeostasis by inhibiting the AA metabolic pathway and modulating the intestinal microbiome, thereby treating UC [158]. In CRC, berberine prevents the growth, migration and invasion of CRC cells *in vitro* and *in vivo* by targeting the COX-2/PGE_2-JAK2 and STAT3-MMP-2/MMP-9 signaling pathways [159]. Moreover, berberine is also able by targeting various pathways, such as the NF-κB/COX-2 pathway, to result in the cell cycle arrest, induction of apoptosis, and inhibition of inflammatory response in CRC cells [160]. Emodin, a plant root extract, reduces intestinal inflammation associated with carcinogenesis [161].

Inositol hexakisphosphate (IP6) is a natural phytochemical. Małgorzata Kapral *et al.* found that IP6 prevents CRC by limiting inflammatory events in the colon epithelium by regulating the expression of COX-2 and 5-LOX proteins, as well as by affecting the synthesis and secretion of PGE_2 and LTB_4 [162]. A natural product, Celastrol, isolated from Tripterygium wilfordii Hook F, can regulate the NF-κB/COX-2 pathway to block the cell cycle and induce apoptosis, and is a potent antitumor inhibitor [163]. Products present in some fruits, nuts and vegetables also have anticancer activity, such as ellagic acid, a hydrolyzed metabolite of ellagitannins [164]. Umesalma and sudhandiran found that ellagic acid prevented the development of CRC in rats induced by the chemical carcinogen 1,2dimethylhydrazine by targeting the NF-κB/COX-2 pathway [165]. lycopene is isolated from tomatoes. Using a mouse xenograft colon cancer model and *in vitro* experiments, Tang *et al.* found that lycopene and fish oil synergistically inhibited COX-2 and PGE_2, thereby inhibiting CRC development [166].

Chinese herbal formula is considered as one of the common protocols for effective treatment of CAC. Lizhong Decoction (LZD) improves UC by modulating endogenous metabolites such as AA [167]. Zhilining Formula (ZLN) repairs the intestinal mucosal barrier and attenuates persistent inflammation in UC mice by modulating AA metabolism [168]. Yinhua Miyanling tablets also has a favorable therapeutic effect on UC by ameliorating colonic mucosal damage through multiple endogenous metabolites and AA metabolic pathways, among others [169]. Also, Huang lian Jie du decoction (HLJDD) inhibited colonic pathological injury by regulating AA metabolism and alleviated UC in mice [170]. Sanwu Baisan Decoction exerts anti-CRC effects by inhibiting the TLR-4/COX-2/PGE-2 pathway, inhibiting the secretion of anti-tumor-promoting immune cytokines, inducing apoptosis of tumor cells, and maintaining intestinal flora [171].

6. Conclusions

AA metabolism drives the inflammatory cancer transformation in CAC through eicosanoid-mediated pathways. In CAC, novel insights highlight AA's role in epigenetic regulation, where COX-2 methylation correlates with CpG island methylation phenotypes, promoting KRAS/BRAF-driven oncogenesis. Additionally, 12S-HETE enhances cancer-associated fibroblast activity, fostering tumor invasiveness via stromal remodeling. A pioneering approach involves CRISPR-based ALOX5/15 gene editing, which suppresses LTB_4 production and inhibits tumor growth in preclinical CAC models, offering a targeted strategy to disrupt pro-tumorigenic inflammation. Furthermore, AA's interaction with the gut microbiota, particularly Gram-negative bacteria, amplifies PGE_2 production, accelerating CAC progression, while microbiota-modulating agents like berberine counteract this effect by reducing lipid peroxidation. Clinically, serum LTB_4 and urinary PGE-M levels serve as non-invasive biomarkers for CAC risk stratification. Dual COX/LOX inhibitors, such as licofelone, mitigate compensatory pathway shunting, enhancing therapeutic efficacy with reduced gastrointestinal toxicity compared to NSAIDs. Future research should leverage AI-driven profiling of AA metabolite signatures to guide personalized therapies and explore integration with immune checkpoint inhibitors to boost anti-tumor immunity in CAC. These advancements position AA metabolism as a transformative target for preventing and treating inflammation-driven colorectal cancer.

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Competing Interests

The authors have declared that no competing interest exists.

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