Current Cancer Research

https://ccr.cultechpub.com/ccr

Cultech Publishing

Article

Targeting IL-17A: A New Frontier in the Treatment of Colitis-Associated Cancer

Ashok Kumar Pandurangan*

School of Life Sciences, B.S. Abdur Rahman Crescent Institute of Science and Technology, Vandalur, Chennai, India

*Corresponding author: Ashok Kumar Pandurangan, panduashokkumar@gmail.com

Abstract

Ulcerative colitis (UC) is characterized by chronic inflammation in the colon that can lead to the development of colitis-associated cancer if left untreated. Interleukin-17A (IL-17A), an inflammatory cytokine produced by Th17 cells, plays a crucial role in mediating inflammatory reactions in autoimmune diseases like inflammatory bowel disease and has been implicated in colitis associated cancer development. This review discusses the importance of IL-17A in colitis associated cancer pathogenesis and examines novel therapies targeting IL-17A as potential treatments. Evidence from animal studies demonstrates that inhibition of IL-17A signaling can suppress intestinal inflammation and tumor development in colitis associated cancer models. Several natural compounds like cocoa, embelin, β-carotene, and melatonin have shown promise in reducing IL-17A expression and colitis associated cancer progression in preclinical studies. Additionally, administration of IL-17A antibodies has been found to decrease tumor formation in mouse models of colitis associated cancer. Recent research has also revealed the role of microRNAs like microRNA-146a in modulating IL-17 responses and limiting tumorigenic inflammation. While further research is needed, targeting the IL-17A pathway represents a promising therapeutic approach for preventing and treating colitis associated cancer. This review summarizes the current evidence supporting IL-17A as a key mediator of colitis associated cancer and highlights potential strategies to inhibit this pathway for therapeutic benefit.

Keywords

Colitis associated cancer, Cytokines, IL-17A, Cocoa, Embelin

Article history

Received: 4 June 2025
Revised: 20 August 2025
Accepted: 13 October 2025
Available Online: 24 October 2025

1. Introduction

Chronic inflammation is a recognized risk factor for the development of carcinogenesis, with accumulated evidence indicating that up to 15% of human cancer incidence is associated with inflammation [1,2]. Specifically, chronic inflammatory bowel diseases, such as ulcerative colitis and Crohn's disease, are known to promote colorectal carcinogenesis (CRC), which correlates with the duration, extent, and severity of the inflammation [3,4]. The molecular mechanisms underlying this neoplastic transformation remain poorly understood. However, immune cells infiltrating the tumor and producing tumor-promoting cytokines are implicated in colon cancer growth [2]. The mouse model of colitis-associated cancer, induced by the administration of azoxymethane followed by repeated oral administration of dextran sulfate sodium , has provided significant insights [5,6]. The interleukin (IL)-6/STAT3 signaling pathway plays a crucial role in Ulcerative colitis and the development of colitis associated cancer, regulating IL-17A [7-9].

The pathogenesis of colitis associated cancer is characterized by a dynamic interplay among chronic inflammation, genetic instability, and dysregulation of cellular processes. The molecular events leading to the development of colitis associated cancer (Figure 1) include the following: Chronic inflammation in the colon creates a conducive environment for cancer development. This inflammation enhances the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), resulting in DNA damage and genomic instability. Furthermore, inflammation compromises the integrity of the intestinal epithelial barrier, facilitating bacterial translocation and exacerbating inflammation [10]. Chronic inflammation promotes mutations in target genes (e.g., p53, adenomatous polyposis coli, K-ras) and induces epigenetic modifications, contributing to dysregulated cell growth and survival. Pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-1β) activate oncogenic signaling pathways such as NF-κB and STAT3, thereby enhancing cell survival and proliferation. Defects in apoptosis and increased cell survival lead to the accumulation of aberrant cells [11]. Chronic inflammation also promotes angiogenesis, favoring tumor growth and metastasis. The inflammatory microenvironment can suppress anti-tumor immune responses, allowing cancer cells to evade immune surveillance. Additionally, epithelial-mesenchymal transition induced by inflammation stimulates cancer cell invasion and metastasis. Collectively, these processes contribute to the transformation of normal colonic epithelium into dysplastic and ultimately cancerous tissue [12,13].

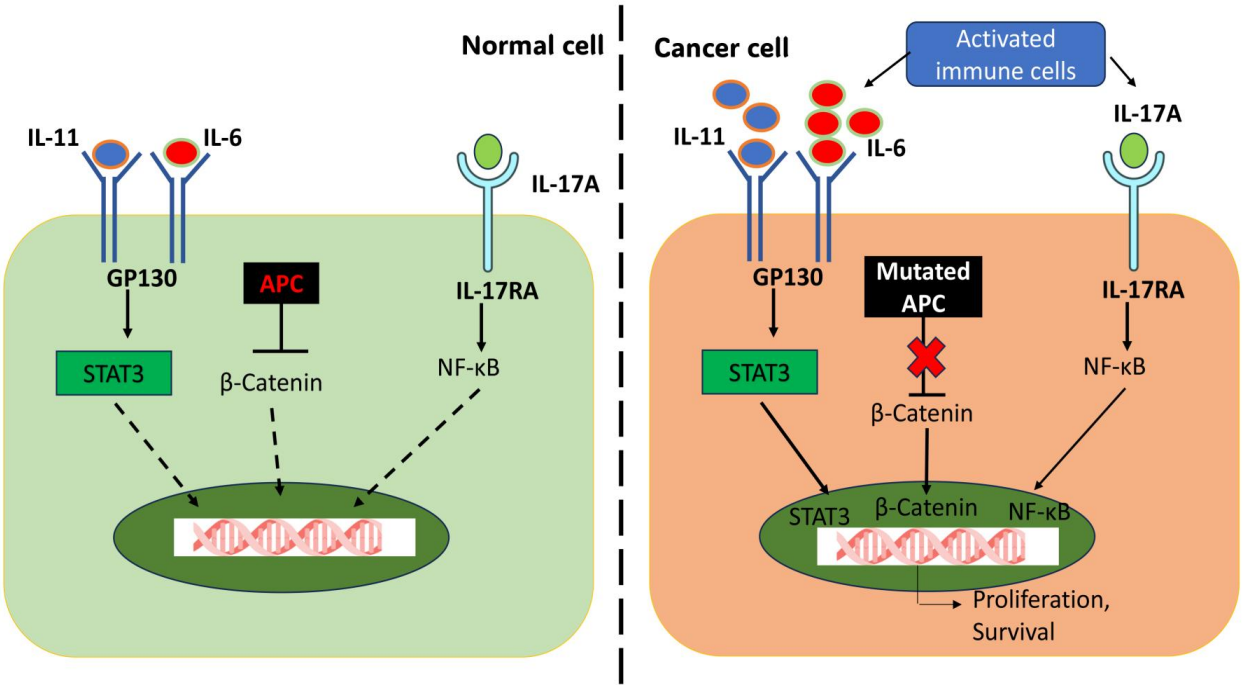

Figure 1. Involvement of IL-17A in normal and cancer cell. The activation of NF-κB through the receptors of IL-17 and leads to the activation of inflammatory mediators.

2. Functions of IL-17 Family

Cytokines are small peptide proteins that are produced mainly by immune cells (i.e. dendritic cells and macrophages) which facilitate communication between cells, stimulate the proliferation of antigen specific effector cells and mediate the local and systemic inflammation in an autocrine, paracrine and endocrine pathways [14]. They play an important role in the intestinal immune system. Among other cytokines IL-17 family of cytokines plays a crucial role in the inflammation. The IL-17 family of cytokines contains six members, IL-17 (also called IL-17A), IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25) and IL-17F. The IL-17 family of polypeptides consist of 163-202 amino acids with molecular masses of 20-30 kDa. In particular, they share four conserved cysteine residues at C-terminal region that may participate in the formation of intermolecular disulfide linkages [15]. While little is known about IL-17B, IL-17C and

IL-17D, IL-25 has the least sequence identity with IL-17. The IL-17 family has been shown to regulate innate and adaptive allergic responses [16-18]. In particular, IL-17A is an inflammatory mediator of Th17 cells, which is derived from naive CD^{4+} cells, essentially mediating inflammatory reactions in autoimmune diseases, such as inflammatory bowel disease, rheumatoid arthritis and autoimmune myelo-encephalitis [19,20].

IL-17A and other IL-17 cytokines are different in the downstream signaling pathways they utilize. Whereas IL-17A signals mainly through the IL-17RA/RC receptor complex to activate the NF-κB and MAPK pathways, other members of the IL-17 family use alternative receptor combinations and activate different signaling cascades. For example, IL-17E (also IL-25) signals via IL-17RA/RB to activate STAT6 and induce Th2 responses. IL-17C directly interacts with IL-17RA/RE, which activates the same pathways as IL-17A but with distinct patterns of gene expression. The differences in receptor usage and subsequent signaling are responsible for the varied biological activities of IL-17 family cytokines from pro-inflammatory reactions to mucosal immunity and tissue homeostasis [21-23]. In this review, the role of IL-17A in CAC was discussed in detail.

3. IL-17A and Colitis Associated Cancer

The IL-23/Th17 pathway is recognized as one of the most important etiological factors in inflammatory bowel disease, and studies evaluating the pro-inflammatory or anti-inflammatory roles of IL-17A are ongoing [24-26]. Few reports showed that [27,28], a relationship between IL-17A and tumor formation was identified using a spontaneous intestinal tumorigenesis mouse model. Wu et al. [28] reported that intestinal tumor formation was promoted upon stimulation of the intestine in multiple intestinal neoplasia (Min) mice with enterotoxigenic Bacteroides fragilis, a human intestinal commensal bacterium and that tumor formation was inhibited when the IL-17A receptor was blocked. Similarly, Chae et al. [27] reported that intestinal tumor formation was inhibited when IL-17A signaling was blocked in the Min mouse model. Xie et al. [29] reported that human colon adenocarcinomas contained the highest levels of IL-17A cytokine, which was significantly higher than the IL-17A levels in the adenomas, UC, and normal colon tissues. The levels of IL-17 receptor A (IL-17RA) were also the highest in human colon adenocarcinomas, followed by adenomas and UC. The findings also revealed that the increased levels of IL-17A and IL-17RA were accompanied with increased IL-17-driven inflammatory responses, including activation of extracellular signal-regulated kinase (ERK)1/2 and c-Jun N-terminal kinase (JNK) pathways, increase in expression of matrix metalloproteinase (MMP)-9, MMP-7, MMP-2, B-cell lymphoma (Bcl-2), and cyclin D1, decrease in Bcl-2-associated X protein (Bax) expression, and increase in vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR) expression that were associated with increased angiogenesis. Hyun et al. [30] revealed that the role of IL-17A during the developmental process of colitis associated cancer using an IL-17A knockout mouse model. The study revealed that selective inhibition of IL-17A in a mouse model of colitis associated cancer inhibits intestinal inflammation and tumor development. The mechanism behind this process is a decrease in inflammation through the blockage of IL-17A, which ultimately leads to inhibition of the initiation of tumor development. Therefore, they concluded that small molecule inhibitors of IL-17A may be excellent candidates for the treatment and prevention of colon cancer. Qi et al. [31] reported that therapeutic IL-17A antibody injection prevents the development of colitis associated carcinogenesis in mice. They also stated that the administration of anti-IL-17A antibody in mice with colitis associated cancer will result in a reduced inflammation and proliferation labeling index in the colonic mucosa. They observed that a significant reduced proliferation labeling index was observed in the colitis associated cancer mice after anti-IL-17A antibody injection for 2 weeks. The results of the study confirms that IL-17A plays a vital role in mediating the process of colitis associated cancer. The administration of anti-IL-17A antibody for 2 weeks in colitis associated cancer mice also result in a reduction of inflammation severity, but not totally dismissed and the possible explanation for this phenomenon may be that the chronic inflammation in colitis associated cancer mice was induced by both the carcinogen DMH and chemical inflammation inducer dextran sodium sulfate. Finally, they concluded that the dose and duration of anti-IL-17A antibody injection used in this study may not be enough to induce the complete remission of inflammation. Another explanation could be that, except IL-17A, many other cytokines (i.e. IL-17F, IL-8, and TNF-α) are also involved in the stimulation of chronic inflammation [32]. Girondel et al. [33] reported that, the deficiency of IL-17RD is implicated in the progression of tumors within a model of colitis-associated cancer, that is associated with an exacerbated inflammatory response. In IL-17RD-deficient mice, colonic tumors demonstrate a significant enrichment of inflammation-related gene signatures, elevated expression of pro-inflammatory tumorigenic cytokines, such as IL-17A and IL-6, and increased STAT3 tyrosine phosphorylation.

4. miRNA and IL-17A

microRNAs are small, non-coding RNA molecules approximately 22 nucleotides in length that play crucial roles in post-transcriptional gene regulation. These molecules function by binding to complementary sequences in the 3' untranslated regions of target messenger RNAs (mRNAs), leading to mRNA degradation or translational repression. miRNAs are involved in various biological processes, including cell proliferation, differentiation, apoptosis, and development. They can act as fine-tuners of gene expression, often regulating multiple genes simultaneously and participating in complex regulatory networks. Dysregulation of miRNA expression has been implicated in numerous diseases, including cancer, cardiovascular disorders, and neurodegenerative conditions, making them potential targets for therapeutic interventions and biomarker development. Garo et al. [34] reported the role of microRNA-146a in

limiting tumorigenic inflammation in colorectal cancer. The researchers identified microRNA-146a as a major negative regulator of colonic inflammation and associated tumorigenesis by modulating IL-17 responses. The study found that miR-146a-deficient mice were more susceptible to both colitis-associated and sporadic colorectal cancer, presenting with enhanced tumorigenic IL-17 signaling. The research revealed two interlinked mechanisms by which miR-146a prevents intestinal inflammation and colorectal cancer. First, within myeloid cells, miR-146a targets RIPK2, a NOD2 signaling intermediate, to limit myeloid cell-derived IL-17-inducing cytokines and restrict colonic IL-17. Second, within intestinal epithelial cells, microRNA-146a targets TRAF6, an IL-17R signaling intermediate, to restrict IEC responsiveness to IL-17. Additionally, miR-146a within Intestinal epithelial cells suppresses colorectal cancer by targeting PTGES2, a PGE2 synthesis enzyme. The study demonstrated that mice deficient in micorRNA-146a either globally, specifically within myeloid cells, or specifically within intestinal epithelial cells, presented with enhanced IL-17 signaling and severe colorectal cancer. Importantly, the researchers found that preclinical administration of miR-146a mimic, or small molecule inhibition of the microRNA-146a targets, TRAF6 and RIPK2, ameliorated colonic inflammation and colorectal cancer. These findings suggest that miR-146a overexpression or microRNA-146a target inhibition represent potential therapeutic approaches to limit pathways converging on tumorigenic IL-17 signaling in colorectal cancer. This research provides unique insights into the molecular mechanisms underlying the protective role of microRNA-146a in colorectal cancer. It highlights the potential of microRNA-146a as a single powerful target in colorectal cancer that modulates multiple pathways converging on tumorigenic IL-17 signaling. The study's findings not only enhance our understanding of colorectal cancer pathogenesis but also open up new avenues for therapeutic interventions. The dual action of microRNA-146a in limiting both IL-17 production and IL-17 responsiveness makes it an attractive alternative to current treatments, potentially offering a more comprehensive approach to managing colorectal cancer.

5. Inhibitors of IL-17A in Inflammation Associated Cancer

There are few inhibitors of different class was shown to inhibit the IL-17 production in the colitis associated cancer. The structures of the inhibitors were represented in Figure 2 and their mechanisms of action in Table 1.

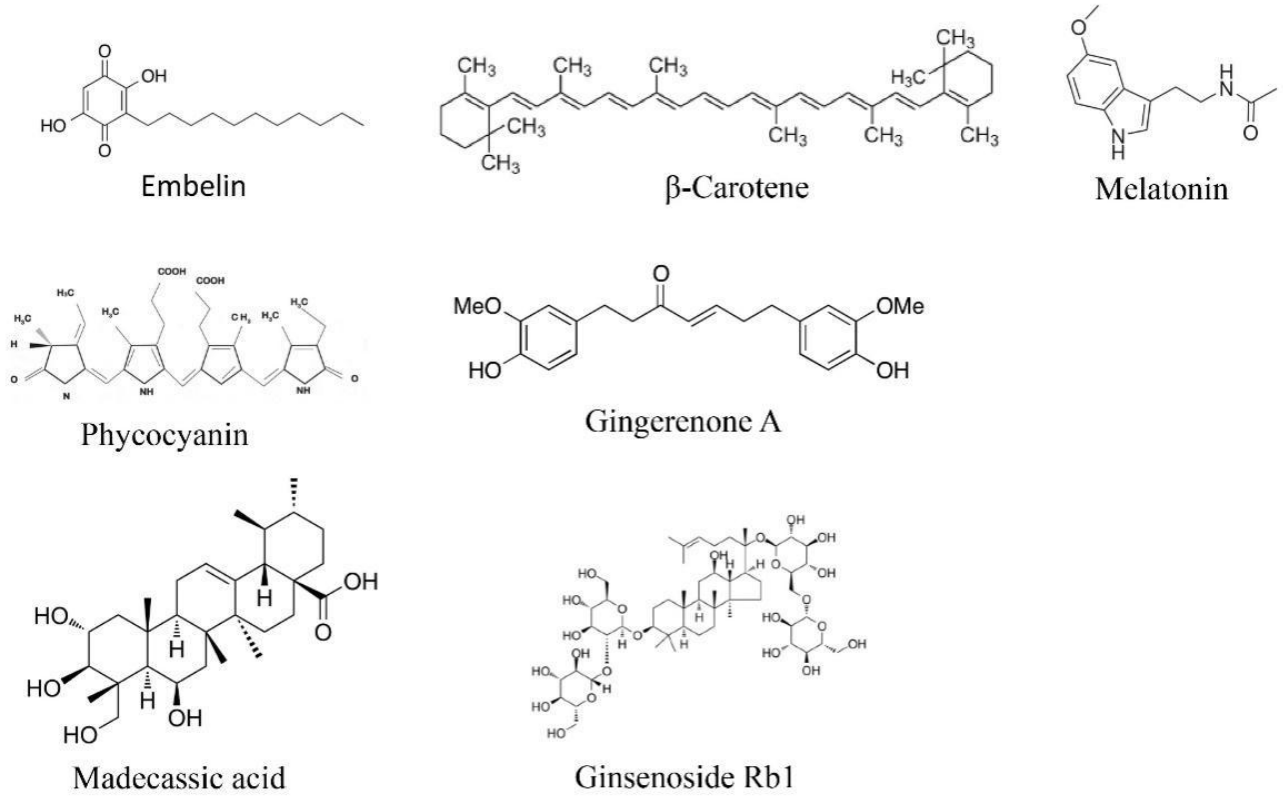

Figure 2. The structure of various natural agents that modulate the expression of IL-17A in colitis associated cancer.

Table 1. The possible role of compounds/drugs that target IL-17A in colitis associated cancer.

S. No	Treatment	Mechanism of Action	References
1	Cocoa	Reduces the IL-17 expression in the colon Reduces tumor number and size Downregulates the expression of STAT3	[35]
2	Embelin	Reduces the IL-17A expression in the colon Reduces tumor number and size Downregulates the expression of STAT3	[36]
3	β-Carotene	Reduces the IL-17A expression in the colon Protects colon by upregulating Nrf2 expression	[37]
4	Melatonin	Reduces the IL-17A expression in the colon Protects colon by upregulating Nrf2 expression Suppress autophagy by downregulating Beclin 1, LC3 II and p62	[38]
5	IL-17A antibody	Reduces the IL-17A and IL-6 expressions in the colon Reduces the inflammation and cell proliferation	[31]
6	Phycocyanin	Reduces the expressions of tumor necrosis factor-α, IL-1β and IL17 Reduces the levels of COX-2 in colitis associated cancer	[39]
7	Chang qing formula	inhibited NF-κB/IL-6/STAT3 signaling cascade, suppressed MMP9 expression Suppress pro-inflammatory cytokines including IL-17	[40]
8	Madecassic acid	Maecassic acid alleviates colitis associated cancer by blocking the recruitment of Myeloid-derived suppressor cells to increase the population of anti-tumor immune cells	[41]
9	Qingre Huayu Jianpi	Qingre Huayu Jianpi inhibits colitis-associated cancer by inhibiting the IL-17RA/ACT1/NF-κB axis	[42]
10	Gingerenone A	Gingerenone A inhibits colitis-associated cancer by inhibiting the IL-17RA/ACT1 axis	[43]
11	Ginsenoside Rb1	Ginsenoside Rb1 inhibits IL-17A expression along with other cytokines in azoxymethane/dextran sodium sulfate -induced colitis associated cancer	[44]
12	Purple Yam Polyphenol Extracts	Purple Yam Polyphenol Extracts inhibits IL-17A and inactivated NF-κB and STAT3 signaling to exert anti-inflammatory and anticancer effects	[45]
13	Huoxiang Zhengqi	Huoxiang Zhengqi activated the nuclear factor-erythroid factor 2-related factor 2 signaling pathway and increased the levels of antioxidants	[46]
14	Jacalin	Jacalin reduced the tumor number and tumor size. Jacalin reduced the inflammation by controlling the levels IL-1β, IL-17 and IL-23	[47]
15	Caffeic Acid Phenethyl Ester (CAPE)	CAPE-induced protection against ETBF-mediated tumorigenesis is mediated by IL-17A/CXCL1, and by NF-κB activity in intestinal epithelial cells	[48]

Abbreviations: STAT3, Signal transducer and activator of transcription 3; CXCL1, Chemokine (C-X-C motif) ligand 1; NF-κB, Nuclear factor kappa-B; CAPE, CAPE; MMP9, Matrix metalloproteinase-9; IL-6, Interleuckin-6; ETBF, Enterotoxigenic Bacteroides fragilis; COX-2, Cyclooxygenase-2.

Cocoa, a natural product historically utilized for medicinal purposes, has garnered significant attention due to its phenolic compounds, including flavanols such as epicatechin, catechin, quercetin, naringenin, luteolin, apigenin, and procyanidins, which may serve as effective chemo-prophylaxis agents. Saadatdoust et al. [35] demonstrated that a cocoa-enriched diet reduces IL-17A gene expression in colitis-associated cancer. Their findings also indicated that the reduction in tumor number is linked to the downregulation of the IL-6/STAT3 pathway.

Embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone), a potent, nonpeptidic, cell-permeable small molecule inhibitor of the X-linked inhibitor of apoptosis protein, was shown to decrease the expression of IL-1β, IL-17a, and IL-23a, as well as the infiltration of CD^{4+} T cells and macrophages in colonic tissues. Embelin suppresses colitis associated cancer tumorigenesis, with its antitumor effects partially mediated by limiting IL-6/STAT3 activation and the Th17 immune response. Consequently, embelin may be a promising agent for the prevention and treatment of colitis associated cancer[36].

β-Carotene, a vitamin A precursor, has a number of pharmacological advantages. It is a very effective antioxidant that can neutralize free radicals, possibly lowering oxidative damage and cell damage. This properties may be beneficial in reducing its carcinogenic and cardiovascular disease effects [49]. β-Carotene also acts as a key component for having healthy eyes, immune function, and healthy skin [50]. There is evidence that it can be anti-inflammatory, affecting the production of pro-inflammatory cytokines such as IL-17. The conversion of β-carotene to vitamin A in the body supports various physiological activities, including cell growth, differentiation and immune response. Yet, even though these advantages look promising, one should be aware that too much supplementation can be harmful, and the best beneficial intake is usually accomplished with a balanced diet supplemented with lots of fruits and vegetables. Beta carotene has also been studied for its possible impact on IL-17 levels in colitis associated cancer. Research has indicated that β-carotene could regulate the inflammatory response by affecting the synthesis of IL-17, a pro-inflammatory cytokine that plays a role in the pathogenesis of colitis-associated cancer. Evidence indicates that supplementation with β-carotene would likely decrease IL-17 levels, thus reduce the inflammation and potentially delay the progression of colitis associated cancer. The mechanisms underlying how β-carotene acts in this regard are not yet fully understood and need further study. The interplay between β-carotene, IL-17, and the colitis associated cancer microenvironment is an ongoing area of study with implications for prevention and therapy [37].

Melatonin (N-acetyl-5-methoxytryptamine), a secretory product of the pineal gland and an evolutionarily conserved molecule, has been associated with numerous health benefits. Melatonin has been reported to reduce IL-17A expression in colitis associated cancer, and its treatment decreased colitis associated cancer progression by downregulating autophagy, as evidenced by the expression patterns of autophagy markers, such as Beclin-1, the LC3B-II/LC3B-I ratio, and p62 [38].

The research proves the inhibitory therapeutic effect of anti-IL-17A antibody injection in barring the onset of colitis associated cancer in mice. Qi and colleagues [31] employed a revised colitis associated cancer mouse model in which mice were permanently exposed to DMH and DSS during the experiment, more accurately reflecting the natural course of colitis associated cancer development. The research validates that IL-17A is a critical driving force for the onset of dysplastic lesions, as reported earlier. Possible mechanisms of IL-17A's tumor-promoting action are addressed, such as its function as a proangiogenic factor and interaction with tumor-initiating cells. The research demonstrated that IL-6 expression was elevated in colitis associated cancer lesions and reduced following IL-17A antibody injection, and therefore IL-6 may serve as an important intermediate for IL-17A's promoting effect on colitis associated cancer. Injection with anti-IL-17A antibody led to decreased proliferation labeling index in CAC mice, attesting to the essential role of IL-17A in mediating the process of colitis associated cancer. Additionally, the inflammation was decreased but not abolished following treatment with anti-IL-17A, potentially because other cytokines also participate in chronic inflammation. It was hypothesized that using combined anti-IL-17A and anti-IL-17F antibodies might be more effective in treating experimental colitis and subsequently preventing the development of colitis associated cancer.

Gingerenone A protective mechanisms are directly related to preventing intestinal mucosal inflammation and improving intestinal barrier integrity. Gingerenone A treatment, therefore, substantially reduced the expression of pro-inflammatory cytokines including IL-1β, IL-6, TNF-α, and IL-17 in colonic tissues. It also enhanced the expression of tight junction proteins including Zonula Occludens (ZO)-1 and Occludin and the mucus barrier protein Muc-2, thus restoring intestinal barrier function. GA acts directly on the IL-17RA protein, a critical member of the IL-17 signaling pathway. The interaction inhibits IL-17RA signaling and downstream inflammatory pathways such as NF-κB and Mitogen-activated protein kinase (MAPK) signaling. The researchers validated this mechanism using a range of methods, including pull-down assays, surface plasmon resonance analysis, and molecular dynamics simulations. Notably, IL-17RA or Act1 knockdown drastically inhibited GA's protective activity, emphasizing the key role of IL-17RA signaling in GA-mediated protection against ulcerative colitis. This research reveals new perspectives into the therapeutic potential of natural compounds for inflammatory bowel diseases. Discovery of GA as a direct inhibitor of IL-17RA signaling provides a novel therapeutic strategy for ulcerative colitis treatment. The study also sheds light on the complex interplay between inflammation, intestinal barrier integrity, and ulcerative colitis pathogenesis, further enhancing our understanding of the disease process. In addition, the application of both in vivo and in vitro models, such as intestinal organoids, to the study further enhances the strength of its findings and shows the translational potential of GA as a therapeutic agent for ulcerative colitis [43].

Huoxiang Zhengqi (HXZQ) (藿香正气), is a traditional Chinese herbal medicine, that was tested against CAC in mice model. [please write the Chinese name here for the benefit of Chinese readers who can do more research on this useful drug.] The study used an azoxymethane/dextran sulfate sodium -induced colitis associated cancer mouse model to explore HXZQ's anti-CAC activity. The study discovered that HXZQ greatly alleviated colonic inflammation, inhibited tumor growth, and regulated the levels of multiple inflammatory cytokines and oxidative stress markers in colitis associated cancer mice. It was reported that HXZQ changed the gut microbial structure and influenced the abundance of 29 serum metabolites in colitis associated cancer mice. HXZQ was also found to stimulate the Nrf2 signaling pathway, elevating the expression levels of antioxidants like Catalase, Hemooxygenase-1, NQO-1, and SOD-1. The research also revealed that HXZQ suppressed the NF-κB signaling pathway activation and reduced the NLRP3 expression through suppressing phosphorylation of IκB, IKK, and NF-κB. One of the most fascinating revelations in this research is the multi-pronged strategy of HXZQ in mitigating colitis associated cancer. The herbal medicine not only exhibited anti-

inflammatory and antioxidant activities but also displayed the potential to modulate the gut microbiome and serum metabolites. This holistic effect indicates that HXZQ may have the potential to serve as a therapeutic agent or used in combination with other treatments for colitis associated cancer. [to emphasize this important potential clinical implication by italics]. The research offers a scientific foundation for the conventional application of HXZQ against intestinal diseases and suggests new directions in research on the treatment of colitis associated cancer by traditional Chinese medicine [46].

Veronez et al., [47] reported, Jacalin administration alleviated the azoxymethane/dextran sodium sulfate -induced colitis associated cancer in mice model. Jacalin is a lectin that derived from the jackfruit seed. In general, the plant derived lectins are carbohydrate binding proteins proven to have anticancer potential. Jacalin reduced the tumor number and size and controls inflammation by modulating the levels of proinflammatory cytokines such as IL-1β, IL-23, and IL-17 [47].

CAPE is a polyphenol that possess different varieties of biological activity [51]. Pandurangan et al. [52] reported that-CAPE protects the colon from the damage induced with. In addition, CAPE treatment leads to the reduced expressions of intercellular adhesion molecules (ICAM)-1 and vascular cell adhesion molecules (VCAM), both are key cell adhesion molecules. Enterotoxigenic Bacteroides fragilis (ETBF) is a pathogenic commensal bacterium in humans that induces colonic inflammation in murine models. Treatment with CAPE has demonstrated protective effects against ETBF-enhanced colon tumorigenesis in a mouse model of colitis-associated colon cancer, which is induced by azoxymethane and dextran sodium sulfate. The observed reduction in colon tumorigenesis following CAPE administration is associated with decreased expression of IL-17A and CXCL1 in the gastrointestinal tract. The molecular mechanism underlying CAPE-induced protection against ETBF-mediated tumorigenesis involves modulation of IL-17A/CXCL1 and NF-κB activity in intestinal epithelial cells [51].

In summary, this report covers a range of natural compounds and their possible impacts on colitis associated cancer and accompanying inflammatory processes, paying special attention to IL-17. The report points out several compounds and how they work. The phenolic compounds in cocoa inhibit the IL-17A gene expression and suppress the IL-6/STAT3 pathway in colitis associated cancer. Embelin is an XIAP inhibitor that reduces the expression of inflammatory cytokines and inhibits colitis associated cancer tumorigenesis. β-Carotene can modulate inflammatory reactions by influencing IL-17 production. Melatonin suppresses IL-17A expression and inhibits colitis associated cancer progression by suppressing autophagy. Injection of anti-IL-17A antibody suppresses colitis associated cancer onset in mice, highlighting the role of IL-17A in tumor promotion. Gingerenone A suppresses pro-inflammatory cytokines, improves intestinal barrier function, and blocks IL-17RA signaling. HXZQ, a traditional Chinese medicine, exerts anti-colitis associated cancer effects by mitigating inflammation, suppressing tumor growth, and regulating gut microbiota. Jacalin, a lectin isolated from jackfruit seeds, inhibits tumor growth and modulates inflammation in colitis associated cancer mouse models. CAPE exhibits protective effects on colon injury. The findings provide suggestions for potential therapeutic strategies for colitis associated cancer prevention and cure.

6. Challenges in Targeting IL-17A in Colitis Associated Cancer

IL-17A plays both pro-inflammatory and protective roles in the gut. It induces inflammation and tumor growth, as well as preserves intestinal barrier function. Total blockade of IL-17A might create unintended adverse effects. Other IL-17 family cytokines such as IL-17F can substitute when IL-17A is inhibited. Inhibiting several family members at the same time may be required but will have more adverse effects. The best time for IL-17A blockade during the development of colitis to cancer is unknown. Early treatment may block cancer formation but potentially disrupt normal immune mechanisms. IL-17A blockade alone is unlikely to cure established CAC. Adding complexity to that is combination with other immunotherapies or traditional treatments.

7. Conclusion

This review concludes by highlighting the crucial role that IL-17A plays in mediating inflammation and tumor development in cancers linked to colitis. According to the evidence, a promising therapeutic strategy for both preventing and treating this illness is to target the IL-17A pathway. In preclinical research, a number of natural substances and antibodies have demonstrated promise in lowering IL-17A expression and inhibiting the development of cancer linked to colitis. The intricate roles of IL-17A in gut homeostasis and the possibility of compensatory effects from other cytokines are two obstacles that still need to be overcome before these findings can be applied in clinical settings. To improve IL-17A-targeted treatments and identify the best times and combinations for intervention, more study is required. All things considered, altering the IL-17A pathway presents a fascinating new avenue for creating better therapies for patients with cancer linked to colitis.

Conflict of Interest

The authors declare no conflict of interest.

Generative AI Statement

The authors declare that no Gen AI was used in the creation of this manuscript. For proof reading, Paperpal was used.

References

[1] Shah SC, Itzkowitz SH. Colorectal cancer in inflammatory bowel disease: mechanisms and management. Gastroenterology, 2022, 162(3), 715-730. e3. DOI: 10.1053/j.gastro.2021.10.035

[2] Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. Nature, 2008, 454(7203), 436-444. DOI: 10.1038/nature07205

[3] Gupta RB, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, et al. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. Gastroenterology, 2007, 133(4), 1099-1105; quiz 1340-1. DOI: 10.1053/j.gastro.2007.08.001

[4] Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology, 2004, 126(2), 451-459. DOI: 10.1053/j.gastro.2003.11.010

[5] Pandurangan AK, Saadatdoust Z, Esa NM, Hamzah H, Ismail A. Dietary cocoa protects against colitis-associated cancer by activating the Nrf2/Keap1 pathway. Biofactors, 2015, 41(1), 1-14. DOI: 10.1002/biof.1195

[6] Stolfi C, Rizzo A, Franzè E, Rotondi A, Fantini MC, Sarra M, et al. Involvement of interleukin-21 in the regulation of colitis-associated colon cancer. The Journal of experimental medicine, 2011, 208(11), 2279-2290. DOI: 10.1084/jem.20111106

[7] Pandurangan AK, Esa NM. Signal transducer and activator of transcription 3-a promising target in colitis-associated cancer. Asian Pacific journal of cancer prevention, 2014;15(2):551-560. DOI: 10.7314/apjcp.2014.15.2.551

[8] Pandurangan AK, Ismail S, Saadatdoust Z, Esa NM. Allicin Alleviates dextran sodium sulfate-(DSS-) induced ulcerative colitis in BALB/c mice. Oxidative Medicine and Cellular Longevity, 2015, 2015, 605208. DOI: 10.1155/2015/605208

[9] Pandurangan AK, Mohebali N, Mohd Esa N, Looi CY, Ismail S, Saadatdoust Z. Gallic acid suppresses inflammation in dextran sodium sulfate-induced colitis in mice: Possible mechanisms. International immunopharmacology, 2015, 28(2), 1034-1043. DOI: 10.1016/j.intimp.2015.08.019

[10] Hisamatsu T, Miyoshi J, Oguri N, Morikubo H, Saito D, Hayashi A, et al. Inflammation-associated carcinogenesis in inflammatory bowel disease: Clinical features and molecular mechanisms. Cells, 2025, 14(8), 567. DOI: 10.3390/cells14080567

[11] Koyyala VPB, Kantharia C, Darooka N, Kumar M, Ranjan P, Anikhindi S, et al. Inflammatory bowel disease and colorectal cancer: An eternal fire in a beautiful garden. South Asian Journal of Cancer, 2025, 13(4), 300-304. DOI: 10.1055/s-0045-1802335

[12] Liu M, Yang C, Peng X, Zheng S, He H, Wang W, et al. Formononetin suppresses colitis-associated colon cancer by targeting lipid synthesis and mTORC2/Akt signaling. Phytomedicine, 2025, 142, 156665. DOI: 10.1016/j.phymed.2025.156665

[13] Yamamoto-Furusho JK, Gutierrez-Herrera FD. Molecular mechanisms and clinical aspects of colitis-associated cancer in ulcerative colitis. Cells, 2025, 14(3), 162. DOI: 10.3390/cells14030162

[14] Neuman MG. Immune dysfunction in inflammatory bowel disease. Translational Research: The Journal of Laboratory and Clinical Medicine, 2007, 149(4), 173-186. DOI: 10.1016/j.trsl.2006.11.009

[15] Moseley TA, Haudenschild DR, Rose L, Reddi AH. Interleukin-17 family and IL-17 receptors. Cytokine Growth Factor Reviews, 2003, 14(2), 155-174. DOI: 10.1016/s1359-6101(03)00002-9

[16] Fallon PG, Ballantyne SJ, Mangan NE, Barlow JL, Dasvarma A, Hewett DR, et al. Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. Journal of Experimental Medicine, 2006, 203(4), 1105-1116. DOI: 10.1084/jem.20051615

[17] Fort MM, Cheung J, Yen D, Li J, Zurawski SM, Lo S, et al. IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies in vivo. Immunity, 2001, 15(6), 985-995. DOI: 10.1016/s1074-7613(01)00243-6

[18] Owyang AM, Zaph C, Wilson EH, Guild KJ, McClanahan T, Miller HR, et al. Interleukin 25 regulates type 2 cytokine-dependent immunity and limits chronic inflammation in the gastrointestinal tract. Journal of Experimental Medicine, 2006, 203(4), 843-849. DOI: 10.1084/jem.20051496

[19] Abraham C, Cho J. Interleukin-23/Th17 pathways and inflammatory bowel disease. Inflammatory Bowel Diseases. 2009, 15(7), 1090-1100. DOI: 10.1002/ibd.20894

[20] Koenders MI, van den Berg WB. Translational mini-review series on Th17 cells: are T helper 17 cells really pathogenic in autoimmunity? Clinical and Experimental Immunology, 2010, 159(2), 131-136. DOI: 10.1111/j.1365-2249.2009.04039.x

[21] Brown J, Martin M, Wang H, Hajishengallis GN. TLR-signaling networks: an integration of adaptor molecules, kinases, and cross-talk. Journal of Dental Research, 2010, 90(4), 417-427. DOI: 10.1177/0022034510381264

[22] Che KF, Sun J, Lindén A, Lappi-Blanco E, Levänen B, Sköld CM, et al. Interleukin-26 production in human primary bronchial epithelial cells in response to viral stimulation: Modulation by Th17 cytokines. Molecular Medicine, 2017, 23(1), 247-257. DOI: 10.2119/molmed.2016.00064

[23] Jiang R, Sun B. IL-22 Signaling in the tumor microenvironment. Advances in Experimental Medicine and Biology, 2021, 1290, 81-88. DOI: 10.1007/978-3-030-55617-4_5

[24] Brand S. Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. Gut, 2009, 58(8), 1152-1167. DOI: 10.1136/gut.2008.163667

[25] Ito R, Kita M, Shin-Ya M, Kishida T, Urano A, Takada R, et al. Involvement of IL-17A in the pathogenesis of DSS-induced colitis in mice. Biochemical and Biophysical Research Communications, 2008, 377(1), 12-16. DOI: 10.1016/j.bbrc.2008.09.019

[26] Chae WJ, Gibson TF, Zelterman D, Hao L, Henegariu O, Bothwell AL. Ablation of IL-17A abrogates progression of spontaneous intestinal tumorigenesis. Proceedings of the National Academy of Sciences of the United States of America, 2010, 107(12), 55405544. DOI: 10.1073/pnas.0912675107

[27] Tâlvan ET, Budișan L, Mohor CI, Grecu V, Berindan-Neagoe I, et al. Interleukin dynamics and their correlation with tumor aggressiveness in colorectal carcinoma. International Journal of Molecular Sciences, 2025, 26(14), 7027. DOI: 10.3390/ijms26147027
[28] Wu S, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, Huso DL, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nature Medicine, 2009, 15(9), 1016-1022. DOI: 10.1038/nm.2015
[29] Xie Z, Qu Y, Leng Y, Sun W, Ma S, Wei J, et al. Human colon carcinogenesis is associated with increased interleukin-17-driven inflammatory responses. Drug Design, Development and Therapy, 2015, 9, 1679-1689. DOI: 10.2147/DDDT.S79431
[30] Hyun YS, Han DS, Lee AR, Eun CS, Youn J, Kim HY. Role of IL-17A in the development of colitis-associated cancer. Carcinogenesis, 2012, 33(4), 931-936. DOI: 10.1093/carcin/bgs106
[31] Qi H, Yang H, Xu G, Ren J, Hua W, Shi Y, et al. Therapeutic efficacy of IL-17A antibody injection in preventing the development of colitis associated carcinogenesis in mice. Immunobiology, 2015, 220(1), 54-59. DOI: 10.1016/j.imbio.2014.09.002
[32] Fantini MC, Pallone F. Cytokines: from gut inflammation to colorectal cancer. Curr Drug Targets, 2008, 9(5), 375-380. DOI: 10.2174/138945008784221206
[33] Girondel C, Lévesque K, Langlois MJ, Pasquin S, Saba-El-Leil MK, Rivard N, et al. Loss of interleukin-17 receptor D promotes chronic inflammation-associated tumorigenesis. Oncogene, 2021, 40(2), 452-464. DOI: 10.1038/s41388-020-01540-4
[34] Garo LP, Ajay AK, Fujiwara M, Gabriely G, Raheja R, Kuhn C, et al. MicroRNA-146a limits tumorigenic inflammation in colorectal cancer. Nature Communications, 2021, 12(1), 2419. DOI: 10.1038/s41467-021-22641-y
[35] Saadatdoust Z, Pandurangan AK, Ananda Sadagopan SK, Mohd Esa N, Ismail A, Mustafa MR. Dietary cocoa inhibits colitis associated cancer: a crucial involvement of the IL-6/STAT3 pathway. Journal of Nutritional Biochemistry, 2015, 26(12), 1547-1558. DOI: 10.1016/j.jnutbio.2015.07.024
[36] Dai Y, Jiao H, Teng G, Wang W, Zhang R, Wang Y, et al. Embelin reduces colitis-associated tumorigenesis through limiting IL-6/STAT3 signaling. Molecular Cancer Therapeutics, 2014, 13(5), 1206-1216. DOI: 10.1158/1535-7163.MCT-13-0378
[37] Trivedi PP, Jena GB. Mechanistic insight into beta-carotene-mediated protection against ulcerative colitis-associated local and systemic damage in mice. European Journal of Nutrition, 2015, 54(4), 639-652. DOI: 10.1007/s00394-014-0745-5
[38] rivedi PP, Jena GB, Tikoo KB, Kumar V. Melatonin modulated autophagy and Nrf2 signaling pathways in mice with colitis-associated colon carcinogenesis. Molecular Carcinogenesis, 2016, 55(3), 255-267. DOI: 10.1002/mc.22274
[39] Pan D, Huang B, Gan Y, Gao C, Liu Y, Tang Z. Phycocyanin Ameliorates Colitis-Associated Colorectal Cancer by Regulating the Gut Microbiota and the IL-17 Signaling Pathway. Marine Drugs, 2022, 20(4), 260. DOI: 10.3390/md20040260.
[40] Luo Q, Huang S, Zhao L, Liu J, Ma Q, Wang Y, et al. Chang qing formula ameliorates colitis-associated colorectal cancer via suppressing IL-17/NF-κB/STAT3 pathway in mice as revealed by network pharmacology study. Frontiers in Pharmacology, 2022, 13, 893231. DOI: 10.3389/fphar.2022.893231
[41] Yun X, Zhang Q, Fang Y, Lv C, Chen Q, Chu Y, et al. Madecassic acid alleviates colitis-associated colorectal cancer by blocking the recruitment of myeloid-derived suppressor cells via the inhibition of IL-17 expression in γδT17 cells. Biochemical Pharmacology, 2022, 202, 115138. DOI: 10.1016/j.bcp.2022.115138
[42] Duan Y, Lu Y, Liu Z, Zhang J, Yang Z, Guo Y, et al. Qingre Huayu Jianpi prescription alleviates the inflammatory transformation of colitis-associated colorectal cancer by inhibiting the IL-17RA/ACT1/NF-κB axis. Journal of Ethnopharmacology, 2025, 345, 119554. DOI: 10.1016/j.jep.2025.119554
[43] Liang J, Dai W, Liu C, Wen Y, Chen C, Xu Y, et al. Gingerenone A attenuates ulcerative colitis via targeting IL-17RA to inhibit inflammation and restore intestinal barrier function. Advanced science (Weinheim, Baden-Wurttemberg, Germany), 2024, 11(28), e2400206. DOI: 10.1002/advs.202400206
[44] Wang L, Zhang QQ, Xu YY, Zhang R, Zhao Q, Zhang YQ, et al. Ginsenoside Rb1 suppresses AOM/DSS-induced colon carcinogenesis. Anti-cancer Agents in Medicinal Chemistry, 2023, 23(9), 1067-1073. DOI: 10.2174/1871520623666230119092735
[45] Yang X, Wang Q, Zhang X, Li L, Cao X, Zhou L, et al. Purple yam polyphenol extracts exert anticolitis and anticolitis-associated colorectal cancer effects through inactivation of NF-κB/p65 and STAT3 signaling pathways.Journal of Agricultural and Food Chemistry, 2023, 71(32), 12177-12189. DOI: 10.1021/acs.jafc.3c00346
[46] Dong M, Liu H, Cao T, Li L, Sun Z, Qiu Y, et al. Huoxiang Zhengqi alleviates azoxymethane/dextran sulfate sodium-induced colitis-associated cancer by regulating Nrf2/NF-κB/NLRP3 signaling. Frontiers in Pharmacology, 2022, 13, 1002269. DOI: 10.3389/fphar.2022.1002269
[47] Veronez LC, Silveira DSCD, Lopes-Júnior LC, Dos Santos JC, Barbisan LF, Pereira-da-Silva G. Jacalin attenuates colitis-associated colorectal carcinogenesis by inhibiting tumor cell proliferation and intestinal inflammation. Inflammatory Bowel Diseases, 2025, 31(5), 1344-1354. DOI: 10.1093/ibd/izae303
[48] Hwang S, Jo M, Hong JE, Kim WS, Kang DH, Yoo SH, et al. Caffeic acid phenethyl ester administration reduces enterotoxigenic bacteroides fragilis-induced colitis and tumorigenesis. Toxins, 2024, 16(9), 403. DOI: 10.3390/toxins16090403
[49] Pinos I, Coronel J, Albakri A, Blanco A, McQueen P, Molina D, et al. β-Carotene accelerates the resolution of atherosclerosis in mice. Elife, 2024, 12, RP87430. DOI: 10.7554/eLife.87430
[50] von Lintig J. Eat your carrots! β-Carotene and cholesterol homeostasis. The Journal of Nutrition, 2020, 150(8), 2003-2005. DOI: 10.1093/jn/nxaa189
[51] Shih YH, Chen CC, Kuo YH, Fuh LJ, Lan WC, Wang TH, et al. Caffeic acid phenethyl ester and caffeamide derivatives suppress oral squamous cell carcinoma cells. International Journal of Molecular Sciences, 2023, 24(12), 9819. DOI: 10.3390/ijms24129819
[52] Pandurangan AK, Mohebali N, Hasanpourghadi M, Esa NM. Caffeic acid phenethyl ester attenuates dextran sulfate sodium-induced ulcerative colitis through modulation of NF-κB and cell adhesion molecules. Applied Biochemistry and Biotechnology, 2022, 194(3), 1091-1104. DOI: 10.1007/s12010-021-03788-2