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Minireview

Phytochemical Regulation of RNA in Treating Inflammatory Bowel Disease and Colon Cancer: Inspirations from Cell and Animal Studies[S]

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ABSTRACT

Recent studies suggest an important role for RNA, especially noncoding RNA, in inflammatory bowel disease (IBD) and colon cancer. Drug development based on regulating RNA rather than protein is a promising new area. Phytochemicals are naturally occurring plant-derived compounds with chemical diversity, biologic activity, easy availability, and low toxicity. Many phytochemicals have been shown to exert protective effects on IBD and colon cancer through modulation of RNAs. The aim of this study was to summarize the advancements of phytochemicals in regulating RNA for the treatment of IBD and colon cancer. This review involves many phytochemicals, including polyphenols, flavones, and alkaloids, which can influence various types of RNAs, including microRNA, long noncoding RNA, as well as messenger RNA, by influencing a variety of upstream molecules or regulating epigenetic processes. The limitation for many current studies is that the specific mechanisms of phytochemicals regulating RNA have not been fully uncovered. Accompanied by more identified functions of RNAs, especially noncoding RNA functions, the screening of RNA-regulating phytochemicals has presented challenges as well as opportunities for the prevention and treatment of IBD and colon cancer.

SIGNIFICANCE STATEMENT

Noncoding RNAs, which constitute the majority of the human transcriptional genome, play a key role in the disease state and are considered as important therapeutic targets in inflammatory bowel disease (IBD) and colon cancer. Recent studies have shown that phytochemicals regulate the expression of many noncoding RNAs involved in IBD and colon cancer. Therefore, identifying the specific molecular mechanism of phytochemicals regulating noncoding RNA in disease models may result in novel and effective therapeutic opportunities.

Introduction

Inflammatory bowel disease is a chronic, recurrent bowel disease that includes ulcerative colitis (UC) and Crohn disease (Xiao et al., 2013). The main clinical symptoms of inflammatory bowel disease (IBD) include recurrent diarrhea, mucous purulent stool, abdominal pain (Pepin et al., 2005), and various extraintestinal manifestations, such as blurred vision, joint pain, and rash (Afif et al., 2010). Worldwide, the incidence of IBD fluctuates between 0.5 and 24.5 per 100,000 people, and in China, the prevalence of UC is 11.6 per 100,000 people, and that of Crohn disease is 1.4 per 100,000 people (Sugimoto et al., 2008). Colon cancer is the third most common malignancy and fourth most common cause of cancer mortality worldwide, and more than 1 million new cases of colon cancer are diagnosed worldwide each year (Macarulla et al., 2014; Taieb et al., 2019). Clinically relevant assessments suggest that in patients with UC the cumulative risk of colitis-related cancer (a type of colon cancer) is 1.6% at 10 years, 8.3% at 20 years, and 18.4% at 30 years (Lukas, 2010). Physical pain and psychologic pressure afflict patients, and families and society also bear a huge burden (Dong et al., 2019).

Conventional therapies for IBD include anti-inflammatory drugs such as 5-aminosalicylic acid, corticosteroids, antibiotics, and biologicals, as well as immunosuppressive drugs such as anti–TNF-α antibodies (Sałaga et al., 2014). Traditional therapies have potential drawbacks, whereas the safety

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ABBREVIATIONS: AKT, protein kinase B; ASO, antisense oligonucleotide; CDF, difluorocurcumin; circRNA, circular RNA; DSS, dextran sodium sulfate; HIF-1, hypoxia inducible factor-1; IBD, inflammatory bowel disease; lncRNA, long noncoding RNA; miRNA, microRNA; MALAT, metastasis-associated lung adenocarcinoma transcript; PI3K, phosphatidylinositol-3-kinase; PTEN, phosphatase and tensin homolog; PXR, pregnane X receptor; SOCS-1, signal transduction inhibitor-1; Sp, specificity protein; UC, ulcerative colitis.

and clinical effects of newly marketed drugs are controversial, and the cost is expensive (Bonovas et al., 2018; Hirten et al., 2018). The available treatments for colon cancer include surgery, cryosurgery, chemotherapy, radiation therapy, and targeted therapy (Kim, 2015; Zhang et al., 2017). Conventional chemotherapy delivers drugs in a nontargeted way, so patients may ultimately suffer from unwanted side effects (Ades, 2009), and it can easily lead to the development of drug resistance (Son et al., 2009). As the primary treatment, surgery can cure about 50% of patients, but relapse is common (Banerjee et al., 2017). Therefore, it is urgent to find new effective treatment strategies and drugs for the treatment of IBD and colon cancer.

RNAs are potential candidate drug targets when it is not possible to identify proteins as drug targets in some complicated diseases. For example, the structures of some proteins are very unstable and difficult to be targeted; some proteins are closely related or similar, so drugs cannot show sufficient selectivity to the target; and for protein complexes, targeting a single protein may be ineffective (Dang et al., 2017; Matsui and Corey, 2017). Therefore, upstream regulation of undruggable targets could be a more effective choice. Antisense oligonucleotides (ASOs) and RNA interference strategies targeting RNA have been clinically tested in the treatment of IBD and colon cancer, with preliminary results showing great potential (Scarozza et al., 2019). Because the advantages of small-molecule drugs in absorption, distribution, and oral bioavailability are more significant, RNA-based small-molecule therapy is worth further exploration in IBD and colon cancer ((Persidis, 2000); Warner et al., 2018). Many phytochemicals can regulate mRNA and various noncoding RNAs to participate in various biologic activities and exert pharmacological effects, raising the question of how phytochemicals could affect RNA to play a therapeutic role.

Perspectives of RNA Regulation in Drug Design

The precursor of mRNA is transcribed by RNA polymerase II. The precursor RNA needs to be processed into mature mRNA to enter the cytoplasm for protein synthesis (Percipalle, 2014). MicroRNAs (miRNAs), a type of widely studied noncoding RNA, target mRNAs and induce their translational repression or deadenylation and degradation (Krol et al., 2010). lncRNAs can also influence the fate of target proteins. Different kinds of RNA, including mRNAs, miRNAs, and lncRNAs, form into a regulation net, which is also very important for biologic processes, disease development, and drug design.

With the development of technology and the improvement of experimental techniques, new approaches have been introduced for the design of targeted RNA molecules: 1) Alternative splicing compounds based on the abnormal structure of RNA involves small-molecule selective shearing agents based on the RNA G quadruplex structure. Abnormal repeating amplification sequences of RNA have been screened and developed (Angelbello et al., 2019; Zhang et al., 2019a). 2) Some drugs intervene in the process of RNA generation and modification. For example, only for the design of small molecules targeting miRNA, endoribonuclease Dicer, Argonaute 2 protein, miRNA-Argonaute 2 protein complex, or highly structured miRNA precursor hairpin structure may be effective (Velagapudi et al., 2014; Herrera-Carrillo and Berkhout, 2017). 3) The establishment of RNA binding scaffolds can be used to screen small-molecule ligands. This method is used to verify that the triple helix structure of lncRNA metastasis-associated lung adenocarcinoma transcript (MALAT) can specifically bind small molecules (Donlic et al., 2018).

Classifications of Phytochemicals That Regulate RNA

Phytochemicals may have specific advantages in regulating RNA because of their complicated structures. For example, natural alkaloids have a high affinity for transfer RNA, RNA double-stranded structures, and triplet structures (Islam and Suresh Kumar, 2009; Tiwari et al., 2017). Alkaloids, including berberine, palmitine, and coralline, can interact and bind to two double-stranded RNA homopolymers of the cytidine-guanosine and inosine-cytidine sequences (Islam and Suresh Kumar, 2009). In another experiment in which phytochemicals target miRNA, the specific chemical groups of resveratrol and epigallocatechin gallate can directly bind miR-33a and miR-122 via ^{1}H nuclear magnetic resonance spectroscopy (Baselga-Escudero et al., 2014). In fact, many studies have indicated the therapeutic effects of phytochemicals regulating RNA function on IBD and colon cancer; however, it is not clear whether the phytochemicals can directly bind to RNA. Basic information about phytochemicals that can treat IBD and/or colon cancer through regulating RNA is shown in Fig. 1.

Phytochemicals that regulate RNAs to treat IBD/colon cancer mainly include polyphenols, flavonoids, terpenoids, alkenes, and alkaloids. Polyphenols are chemically characterized as compounds with phenolic structural characteristics. The orthophenolic hydroxyl groups in the phenolic hydroxyl structure of plant polyphenols (catechol or pyrogallol) are easily oxidized to a quinone structure, which has strong oxidative properties (Tsao, 2010). Flavonoids possess a 2-phenyl-4H-chromen-4-one skeleton and exist in mono-, di-, tri-, tetra-, or polymeric forms through C-C or C-O-C linkages (Guan and Liu, 2016). Terpenoids are compounds whose molecular skeleton consists of isoprene units (C5 units) as the basic structural unit, with their derivatives derived from mevalonic acid. According to the number of ring structures they contain, terpenoids can be classified as hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, ester terpenes, triterpenes, tetraterpenes, and polyterpenes (Yang and Dou, 2010). Alkaloids, a kind of nitrogen-containing basic organic compound, exist extensively in nature. Most alkaloids have a common complexed ring structure that consists of primarily nitrogen molecules and has significant biologic activities (Cordell, 2008). Organic substances containing only hydrocarbon and hydrogen are called hydrocarbons, and the organic substances derived from the substitution of hydrogen atoms in hydrocarbon molecules by other atoms or atomic groups are derivatives of hydrocarbons.

Phytochemicals Treat IBD and Colon Cancer by Regulating miRNA

miRNA, a 21- to 23-nucleotide noncoding single-stranded RNA, can reduce the translation or degradation of mRNA by targeting the 3′ untranslated region of the transcribed mRNA (Rupaimoole and Slack, 2017). A single miRNA can target

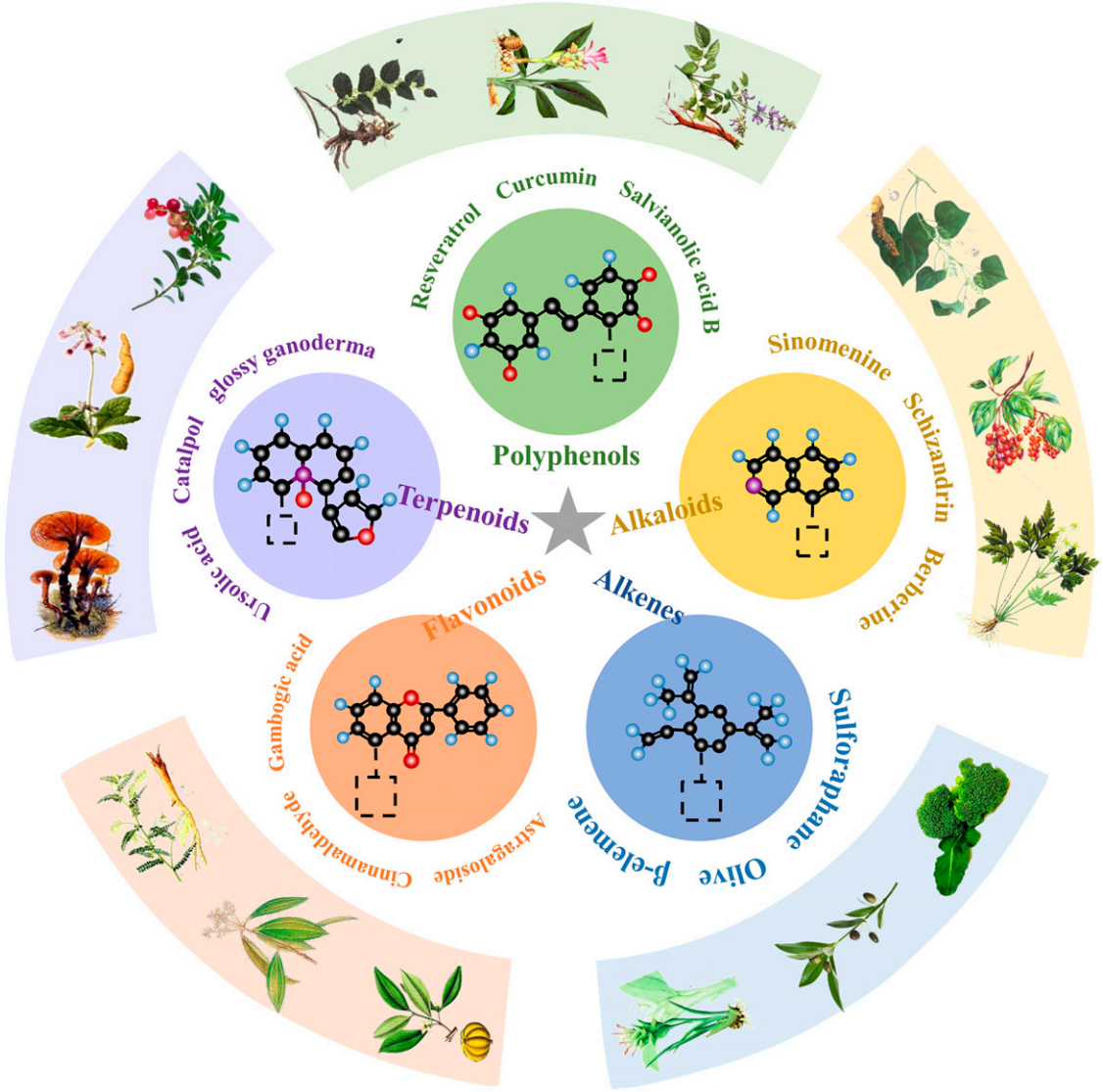

Fig. 1. Basic information about phytochemical-regulating RNA in the treatment of IBD and colon cancer. The classifications, major plant sources, and representative structural formulas are shown. The dashed boxes denote basic nuclear structures of phytochemicals. There are five main kinds of phytochemicals discussed in this review: polyphones, alkaloids, alkenes, flavonoids, and terpenoids.

hundreds of mRNAs and affect the expression of many genes involved in functional interaction pathways (Lu and Rothenberg, 2018). miRNA, a key mediator of inflammatory signaling pathways and regulators, is closely associated with IBD, disorders of the intestinal mucosal barrier, intestinal epithelial cell apoptosis, oxidative stress, immune homeostasis, and intestinal flora imbalances (Grivennikov, 2013). miRNA also participates in the regulation of apoptosis, cell migration, proliferation, and metastasis (Tili et al., 2007), as well as tumor epithelial-mesenchymal transition, tumor angiogenesis, and tumor resistance (Acunzo et al., 2015; Wang et al., 2015; Xuan et al., 2015; Vu and Datta, 2017). Therefore, miRNA is a new and promising target for precise and specific treatment of IBD and colon cancer. Detailed information about phytochemical-regulating miRNAs in the treatment of IBD and colon cancer is shown in Supplemental Table 1.

Polyphenols. Polyphenols are widely found in many foods, including fruits, vegetables, and herbs, and many polyphenols are considered as potential candidates for the treatment and prevention of IBD and colon cancer (Kaulmann and Bohn, 2016; Mileo et al., 2019). The potential of polyphenols to regulate miRNAs to regulate target proteins has been fully demonstrated in various colon cancer cell lines. Resveratrol can inhibit the proliferation of HT29 and HCT116 cells by partially upregulating miR-34c to reduce the protein expression of its target, stem cell factor. The study also showed that under the action of p53, cells may enhance this effect by inhibiting the phosphatidylinositol-3-kinase (P13K)/Akt pathway and sensitize colon cancer cells to oxaliplatin by modulating miR-34c (Yang et al., 2015). Meanwhile, the downregulation of miR-34c may be related to its own methylation. However, resveratrol may not upregulate miR-34c through direct demethylation but instead indirectly promote miR-34c demethylation by acting on p53 protein (Yang et al., 2015). Rosmarinic acid is a phenol that is commonly found in *Boraginaceae* and *Lamiaceae*. It can inhibit the expression of miR-155-5p in three colon cancer cell lines, including HCT-8, HCT-116, and Ls174-T. Rosmarinic acid inhibits the /STAT3 pathway through lowering levels of miR-155-5p to inhibit the glycolysis process of cancer cells and inhibit the proliferation

of tumor cells (La et al., 2019). Piceatannol is a natural analog of resveratrol and has the effect of upregulating miR-129 in HCT-116 and HT-9 cells. I addition, after upregulating miR-129, piceatannol downregulates Bcl-2 protein while upregulating Bax protein, ultimately promoting cancer cell apoptosis (Zhang et al., 2014). Curcumin is a polyphenol in turmeric that has antioxidant, anti-inflammatory, and anticancer properties (Yang et al., 2015; Girardi et al., 2018). Curcumin can significantly inhibit the growth of colon cancer cells by inhibiting the Wnt/β-catenin pathway and downregulating miR-130a in SW480 colon cancer cells, thereby inhibiting the expression of naked cuticle *Drosophila* 2 (Dou et al., 2017). Difluorocurcumin (CDF) can downregulate miR-21 in drug-resistant HCT116 and HT-29 cells to restore phosphatase and tensin homolog (PTEN) levels and reduce Akt phosphorylation (Roy et al., 2013). In addition, CDF can demethylate the miR-34a promoter and restore the normal expression of miR-34a in SW620 and HCT116 colon cancer cells. CDF is considered to be a new type of demethylating agent that restores miR expression and is expected to play a critical role as a new therapeutic agent (Roy et al., 2012).

Polyphenols have also been shown to exert prevention/treatment effects on IBD and colon cancer in animal models. Pomegranate polyphenolics can downregulate the expressions of p70 S6 kinase 1 and hypoxia inducible factor-1 (HIF-1) by upregulating the expression of miR-145. In both dextran sodium sulfate (DSS)-induced rat colitis and in lipopolysaccharide-treated CCD-18Co colon-myofibroblastic cells, pomegranate polyphenolics were shown to exert a significant effect by reducing colitis symptoms (Kim et al., 2017).

Flavonoids. Natural flavones include apigenin, baicalein, chrysin, luteolin, scutellarein, tangeritin, and 6-hydroxyflavone (Zakaryan et al., 2017). Flavonoids can exert multiple effects, including anti-inflammatory, antiviral, antibacterial, and antioxidant activities (Pietta, 2000; Serafini et al., 2010; Xie et al., 2015; Rengasamy et al., 2019).

A large number of studies have demonstrated the potential of flavonoids to regulate miRNA in colon cancer cells. In SW480 cells, miR-134 expression levels were significantly reduced after astragaloside IV treatment, leading to inhibition of tumor cell proliferation and migration (Ye et al., 2017). The presence of gambogic acid significantly reduced the expression of miR-21 in HT-29 cells and affected the expression of PTEN to exert an inhibitory effect on cell growth (Gao et al., 2018). In addition, calycosin can downregulate miR-17 in HCT-116 cells and upregulate PTEN to induce apoptosis. This may be caused by estrogen receptor β mediated by calycosin (Chen et al., 2015). Skullcap flavone I can downregulate the level of miR-107 in HCT116 and promote the expression of its target protein, tropomyosin 1, in colon cancer cells, thereby affecting the proliferation and viability of cancer cells (Zhang et al., 2019b). α-Mangostin can increase the expression of miR-143 in colorectal cancer DLD-1 cells to influence its cell cycle by targeting extracellular regulated protein kinases 5 (Nakagawa et al., 2007).

In in vivo experiments, genistein could significantly reduce the symptoms of colon cancer after xenograft in nude xenograft mice. Meanwhile, in in vitro experiments, genistein reduced the expression of miR-95 in HCT-116 colon cancer cells and inhibited the phosphorylation of Akt. Ultimately, genistein inhibits the proliferation of cancer cells and promotes their apoptosis (Qin et al., 2015). In the colitis model, a flavonoid compound, pineal hormone, restores the T helper type 17/Regulatory T balance in DSS-induced colitis mice by regulating Aryl Hydrocarbon Receptor/miR-302/DNA-methyltransferase 1/cAMP Response Element-Binding Protein signaling. In colitis mice, pineal hormone can upregulate the expression of miR-302, downregulate the expression of DNA methyl-1, promote the association of cAMP Response Element-Binding protein and forkhead box P3 protein promoter region, and effectively alleviate colitis symptoms (Lv et al., 2018). miR-191a can downregulate mRNA and protein levels of its target gene, zonula occludes 1. Together with TNF-α, baicalin can inhibit miR-191a and act as an efficient remission pathway for UC (Wang et al., 2017).

Terpenoids. Terpenoids widely exist in fruits, vegetables, and medicinal plants. In vitro and in vivo human epidemiologic trials have suggested an antiproliferative role of terpenoids in various kinds of cancers (Huang et al., 2012). Terpenoids show great potential in regulating miRNAs to induce apoptosis and inhibit proliferation in cancer cells. Catalpol can promote apoptosis by promoting the expression of miR-200 in HCT116 cells. Additionally, it can reduce the expression of PI3K, phosphorylated protein kinase B, and Akt and enhance the activity of caspase-3 and caspase-9 to influence cancer cell apoptosis (Liu et al., 2017). Ursolic acid can increase the expression of miR-4500 in HCT116 and HT29 cell lines, attenuating STAT3 phosphorylation and inhibiting the proliferation of colon cancer cells (Kim et al., 2018). Betulinic acid can decrease miR-27a promoter activity and its expression in cancer cells, and downregulation of miR-27a is associated with reactive oxygen species–dependent destruction of the specificity protein (Sp) repressor gene zinc finger and BTB domain containing 10. This may be related to betulinic acid inhibiting the growth of RKO and SW480 cells and promoting apoptosis by inhibiting the expression of Sp1, Sp3, and Sp4 transcription factors (Chintharlapalli et al., 2011). *Antrodia cinnamomea* was found to induce the expression of miR-142-3p and downregulate the target protein ATP-binding cassette superfamily G (White) member 2 in three cell lines (SW480, SW620, and HCT116), thereby increasing the sensitivity of colon cancer cells to the chemical agent 5-fluorouracil (Huang et al., 2019b).

Terpenoids also have therapeutic effects in animal models of colitis and colon cancer. Limonin, a type of triterpenoid extracted from citrus, can regulate the STAT3/miR-214 signaling pathway to alleviate inflammation. Limonin has been shown to have notable therapeutic effects on DSS-induced experimental colitis, including a significant reduction in the disease activity index, intestinal damage, and proinflammatory cytokine levels (Liu et al., 2019a). In 2,4,6-trinitrobenzenesulfonic acid–induced colitis in mice, a polyphenol, catalpol, alleviated colitis by downregulating miRNA-132 expression (Xiong et al., 2017).

Alkenes and Their Derivatives. Sulforaphane can be produced in the human body by ingesting cruciferous vegetables and hydrolyzing glucosides. A variety of evidence suggests that sulforaphane can be genetically regulated, including histone deacetylase inhibition, overall demethylation, and miRNA regulation acting to reverse abnormal changes in gene transcription (Tortorella et al., 2015). In colon cancer cells, sulforaphane can downregulate carcinogenic miR-21 in RKO colorectal cancer (CRC) cells, which may have the effect of preventing and delaying CRC (Martin et al.,

2018). β-Elemene can increase the sensitivity of colon cancer cells to 5-fluorouracil by downregulating miR-191 and key kinases such as Wnt3a and β-catenin (Guo et al., 2018). In animal models of colitis, cinnamaldehyde, the main active compound of cinnamon, can ameliorate DSS-induced colitis through affecting miR-21 and miR-155 levels in the colon and in macrophages (Qu et al., 2019).

Alkaloids. Alkaloids, important chemical compounds that are a source for drug discovery, have a wide distribution in the plant kingdom and largely exist in plants belonging to the *Leguminosae*, *Menispermaceae*, *Ranunculaceae*, *Loganiaceae*, and *Papaveraceae* families (Benyhe, 1994; Huang et al., 2007; Li et al., 2007). Recent studies on colon cancer cells showed that alkaloids can regulate miRNA. In the human colon cancer HCT116 cell line, berberine can promote the expression of Integrin β4 and programmed cell death 4 proteins by inhibiting miR-21 and inducing apoptosis of cancer cells (Lü et al., 2018). Schisandrin A upregulates miR-195 in the SW480 colon cancer cell line to inhibit the PI3K/AKT and the nuclear factor kappa-B pathways (Kong et al., 2018). Using in vitro cultures of colorectal tissues, berberine inhibited the epithelial-mesenchymal transition by downregulating miR-429 (Liu et al., 2016).

Beneficial effects of alkaloids on IBD and colon cancer have also been demonstrated in animal studies. Nicotine plays a protective role in DSS-induced colitis by upregulating miR-124, which can inhibit STAT3 expression in macrophages (Qin et al., 2017). Both activated mature B and T lymphocytes express miR-155, and one of the known targets in $CD4^+$ T cells is the transcription factor cellular-macrophage activating factor. Sinomenine can downregulate the expression of miR-155, as well as cellular-macrophage activating factor, TNF-α, and Interferon-γ mRNA in 2,4,6-trinitrobenzenesulfonic acid–induced colitis in mice, possessing an anti-inflammatory effect (Yu et al., 2013).

Butyrate. In addition to the anticancer effects of natural dietary ingredients, some metabolites produced by dietary fiber undergoing anaerobic bacterial fermentation in the large intestine may have anticancer effects. One of them is butyrate, a short-chain fatty acid that is a metabolite of normal colonic epithelial cells (Gonçalves and Martel, 2013). Dual luciferase reporter gene shows that neural precursor cell-expressed, developmentally downregulated 9 is a target gene of miR-203. Butyrate can induce apoptosis of colon cancer cells by regulating miR-203 (Han et al., 2016). Butyrate was also shown to increase miR-200 expression and mediate downregulation of B-lymphoma Mo-MLV insertion region 1 to inhibit colon cancer cell migration, which promoted apoptosis and cell cycle arrest in HCT116 and LoVo CRC cells (Xu et al., 2018).

Phytochemicals Treat IBD and Colon Cancer by Regulating lncRNA and circRNA

lncRNA, a type of RNA, does not translate into polypeptides and, at >200 nucleotides in length, it plays a crucial role in transcriptional silencing, transcriptional activation, chromosome modification, and nuclear transport (Wang and Chang, 2011). Recently, the function of lncRNA molecules gradually has been revealed in IBD and colon cancer and is considered to be an important anti-inflammatory and anticancer target in the future (Yarani et al., 2018; He et al., 2020). Phytochemicals can directly or indirectly regulate lncRNA to affect key proteins in signaling pathways, and they are part of a significant strategy for the treatment of colon cancer (Mishra et al., 2019). No phytochemicals have been reported to regulate lncRNA against IBD, but many phytochemicals, including sinomenine, emodin, and baicalin, have been reported to regulate lncRNA to exert anti-inflammatory effects in other diseases (Liang and Ren, 2018; Huang et al., 2019a; Liu et al., 2019b). Detailed information about some phytochemical-regulating lncRNAs in the treatment of colon cancer is shown in Supplemental Table 2.

MALAT1 and Its Regulation by Phytochemicals. MALAT1 is overexpressed in colon cancer, and one of the five fragments of the 3′ end of MALAT1 influences the biologic processes of cancer cell proliferation, migration, and invasion (Kan et al., 2015). In LoVo cells, resveratrol can downregulate lncRNA MALAT1 expression in a dose-dependent manner, significantly reducing promoter activity. At the same time, the expression of c-Myc and Matrix metalloproteinase-7, the downstream target genes of β-catenin, was also significantly reduced. In general, resveratrol may play a biologic role by inhibiting MALAT1 and then inhibiting the Wnt/β-catenin signaling pathway (Ji et al., 2013).

The lncRNA Promoter of cyclin dependent kinase inhibitor 1A Antisense DNA Damage–Activated RNA and Its Regulation by Phytochemicals. The synergy between the silencing of the lncRNA promoter of cyclin dependent kinase inhibitor 1A antisense DNA damage–activated RNA and curcumin may enhance the inhibition of colon cancer cell growth and promote it to a greater extent than tumor apoptosis. After curcumin treatment, silencing lncRNA promoter of cyclin dependent kinase inhibitor 1A antisense DNA damage–activated RNA may stimulate p53-upregulated modulator of apoptosis expression and promote apoptosis in three colon cancer cell lines: DLD-1, SW620, and HCT116 (Chen et al., 2017).

The lncRNA Cancer Susceptibility Candidate 2 and Its Regulation by Phytochemicals. The lncRNA cancer susceptibility candidate 2 can inhibit the proliferation of colon cancer cells. It can be used as a competitive endogenous RNA for Adenine Uracil-binding factor 1 (AUF1) to isolate the binding of AUF1 and Bcl-2, thereby inducing the binding of AUF1 and Bcl-2 and finally inactivating Bcl-2 (Dai et al., 2019a). Currently, berberine has been shown to downregulate lncRNA cancer susceptibility candidate 2, and BCL-2 has been shown to downregulate tumor cell apoptosis in colon cancer cell lines such as HT29 and HCT116 (Dai et al., 2019b).

The lncRNA Colon Cancer Associated Transcript-1 and Its Regulation by Phytochemicals. The lncRNA cancer susceptibility candidate 1 is consistently upregulated in and is closely related to the development of colon cancer (Chen et al., 2019). Ginsenoside (R)-ginsenoside 3 can negatively regulate lncRNA cancer susceptibility candidate 1 and inhibit the PI3K/AKT signaling pathway, thereby inhibiting colon cancer Caco-2 cell growth, migration, and invasion and promoting their apoptosis (Li and Qi, 2019).

circRNA and Its Regulation by Phytochemicals. circRNA is a type of single-stranded molecule with tissue-specific expression patterns. Unlike linear RNA, circRNA forms a covalent closed loop that is inherently resistant to degradation of exonucleic RNA (Li et al., 2020). circRNA can be used as endogenous competitive RNAs to weaken the activity of miRNA through chelation. Compared with exogenous linear transcripts (e.g., antisense oligonucleotides,

small interfering RNA), circRNA is more stable and effective in inhibiting miRNA activity (Thomson and Dinger, 2016). The latest research in related disease models demonstrates that curcumin, berberine, martini, and naringenin have been shown to influence the level of target miRNA by regulating circRNA (Lin et al., 2020b; Tan et al., 2020; Yang et al., 2020; Zhang et al., 2020b). Theoretically, the strategy of regulating miRNA by phytochemicals through affecting circRNA may be more advantageous than targeting exogenous nucleic acid sequences directly. In addition, in view of the fact that multiple circRNAs have been proven to be vital mediators in the development of IBD and colon cancer (Zheng et al., 2019; Lin et al., 2020a), compounds such as rutin and ergometrine have been identified to regulate lncRNA/circRNA/miRNA/mRNA networks to inhibit colon cancer, implying that RNA-based networks can also be used as effective treatments in the future (Lin et al., 2020b; Xu et al., 2020).

Phytochemicals Treat IBD and Colon Cancer by Modulating mRNA

The screening of drugs regulating mRNA has achieved preliminary results. Some phytochemicals that can treat colon cancer by modulating mRNA are shown in Supplemental Table 3.

CYP3A4 mRNA and Its Regulation by Phytochemicals. Pregnane X Receptor (PXR) is a transcription factor that can bind to specific PXR response elements such as CYP3A4 on the promoter of the *PXR* target gene after activation (Liu et al., 2018). PXR plays a protective role in IBD, and identifying reliable PXR agonists has become a potential IBD treatment strategy (Liu et al., 2018). Piperine is a potential activator of PXR, which may reduce DSS-induced colitis by inducing expression of the *CYP3A4* gene at the mRNA and protein levels (Hu et al., 2015). In the nuclear factor kappa-B–mediated intestinal inflammation, patchouli alcohol, a natural tricyclic sesquiterpene, can decrease intestinal inflammation by activating PXR. The CYP3A4 promoter activity and levels of PXR, CYP3A4, and multidrug resistance 1 mRNA are significantly increased in this study (Zhang et al., 2020a).

HIF-1α mRNA and Its Regulation by Phytochemicals. Tumor cells consume glucose and produce lactic acid instead of breaking down glucose through the Krebs' cycle, which is called the Warburg effect. Targeting HIF-1α to inhibit the Warburg effect in human cancers has become a promising anticancer treatment strategy (Hong et al., 2019). Using colon cancer cell lines HCT116 and SW620, an alkaloid extracted from the roots of *Sophora flavescens* can significantly suppress cell proliferation by inhibiting HIF-1α mRNA (Hong et al., 2019). In human colon cancer cells, evodiamine exerts an antiproliferative effect through Insulin-like growth factor-1/HIF-1α inhibition (Huang et al., 2015). Phytochemicals regulating RNA also play a role in chemotherapy. Ursolic acid (a triterpene acid) significantly increases the sensitivity to chemotherapy by inhibiting HIF-1α (Shan et al., 2016).

Phytochemicals Regulate the mRNA of Suppressor of Cytokine Signaling-1. Janus kinase/STAT/suppressor of cytokine signaling-1 (SOCS-1) signal transduction is involved in regulation of both cytokine expression and epithelial barrier integrity in IBD (Zundler and Neurath, 2016). In the IBD model induced by 2,4,6-trinitrobenzene sulfonic acid, curcumin has a time-dependent effect on Janus kinase/STAT pathway–mediated SOCS-1, and a significant degree of down-regulation on the mRNA levels of SOCS-1, to improve a series of 2,4,6-trinitrobenzene sulfonic acid–induced colitis symptoms (Zhang et al., 2016).

Phytochemicals Regulating the mRNA of Specific Protein 1. SP1 is a transcription factor that can drive tumor progression and metastatic oncogene activation. High SP1 levels in colorectal cancers suggest a poor prognosis. Baicalin can reduce the expression of SP1 mRNA, thus inducing apoptosis of SW480 cells (Ma et al., 2019). Besides baicalin, curcumin and cannabinoids can also reduce Sp1, Sp3, and Sp4 mRNA levels to limit the proliferation of tumor cells (Noratto et al., 2013; Sreevalsan and Safe, 2013).

Limitations and Challenges of Regulating RNA Therapy

A clinical study demonstrated that patients with UC who received curcumin had an improved therapeutic effect compared with the placebo group (Salehi et al., 2019). Curcumin intake causes a decrease in polyp number and size and aberrant crypt foci (Salehi et al., 2019). Other phytochemicals such as berberine and resveratrol have performed well in clinical trials in a variety of diseases including intestinal inflammation and colon cancer (Imenshahidi and Hosseinzadeh, 2019; Singh et al., 2019). Although it is not confirmed that regulating RNA is the main mechanism underlying these phytochemical-induced treatment effects, a preclinical study has suggested the potential for regulating RNA function. The mechanisms for the effects of phytochemical-regulating RNAs on IBD and colon cancer have been summarized in Fig. 2.

RNA-based treatments of IBD/colon cancer by small-molecule drugs also come with many problems, such as toxicity, lack of tissue-specific targeting, and drug failure (Rupaimoole and Slack, 2017). The performance of RNA-based ASOs for drugs entering clinical trials is not always optimal (Scarozza et al., 2019; Liu and Guo, 2020). Alicaforsen is a phosphorothioate ASO that can hybridize with vascular cell adhesion molecule 1 mRNA and induce DNA-RNA complex degradation by the RNase enzyme (Scarozza et al., 2019). In 2001 and 2007, two independent clinical trials on alicaforsen showed that there were no treatment effects observed statistically (Schreiber et al., 2001; Yacyshyn et al., 2007). Another problem is that it is difficult to classify these phytochemicals according to their structural basis in regulating RNA function because, compared with protein-based therapies, RNA-based therapies have increased challenges, and current knowledge is limited.

In recent decades, many natural phytochemicals that can regulate RNA have been screened and found with low toxicity, high bioavailability, and low price. Phytochemicals can mediate a single RNA molecule or the entire RNA regulatory network to regulate the level of single or multiple target genes to rescue abnormal signaling pathways. Moreover, the structure and specific classes of phytochemicals are conducive to the design and development of a new generation of RNA-targeted small molecules. However, because of the complexity, diversity, and variability of RNA structures, the development

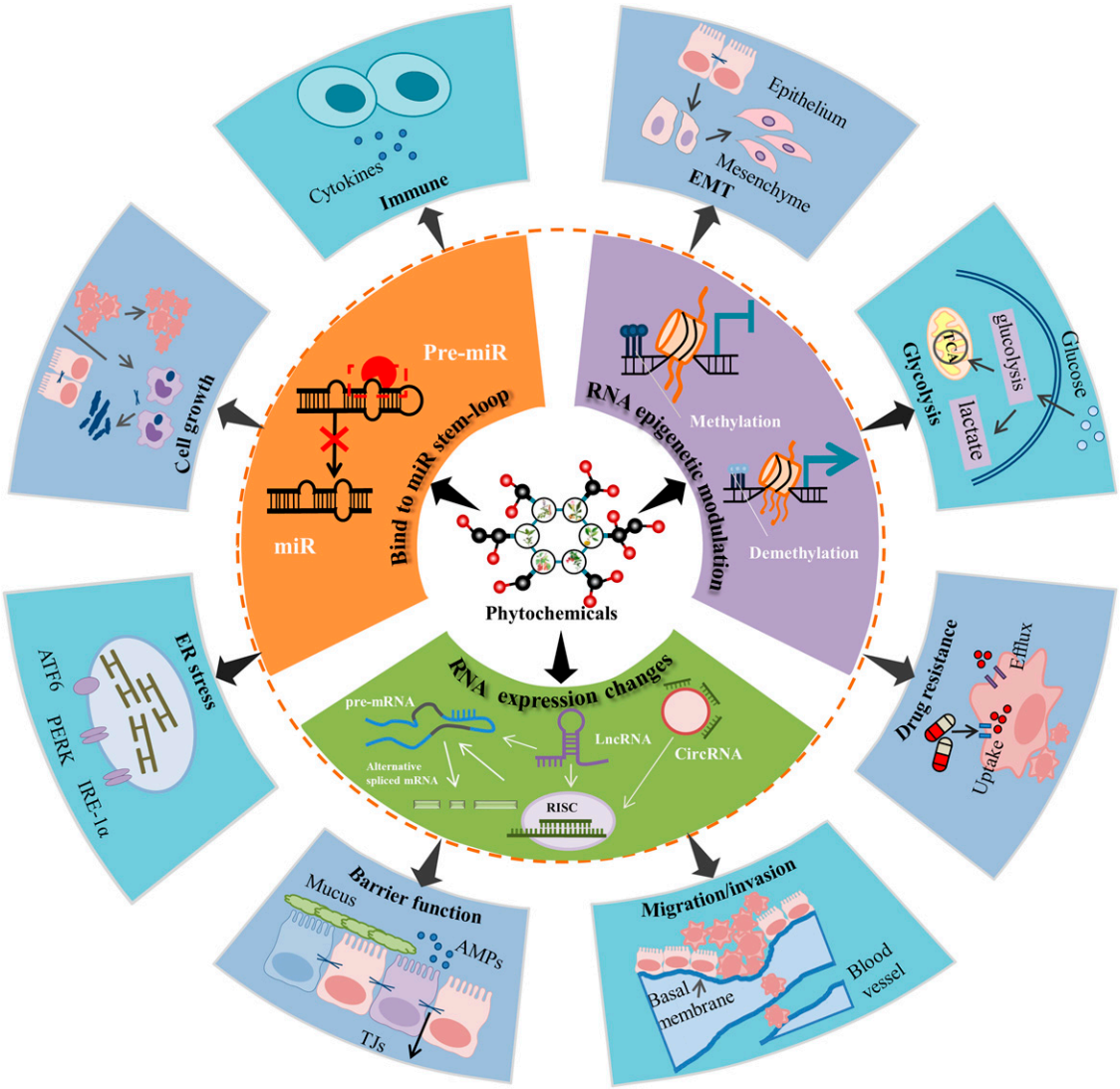

Fig. 2. Phytochemical-regulating RNAs affect the biologic process in IBD and colon cancer. Three main mechanisms of phytochemical-regulating RNAs involve 1) affecting RNA expression through the interaction between mRNA and noncoding RNA, 2) epigenetic modulation of RNAs, and 3) directly binding to the RNA structure. The biologic function of drugs regulating RNAs affects the following processes: immune function, cell growth, ER stress, epithelial barrier function, cell migration/invasion, drug resistance, glycolysis, and epithelial-to-mesenchymal transition and finally affects IBD and colon cancer development. ER, endoplasmic reticulum; ATF6, activating transcription factor 6; IRE-1α, inositol-requiring enzyme-1α; AMP, adenosine monophosphate; TJ, tight junction; EMT, epithelial mesenchymal transition; RISC, RNA-induced silencing complex.

of drugs that target RNA based on existing technologies has a long way to go.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: G. Zhang, C. Zhang, Sun, Xiong, Wang, Chen.

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