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Review paper

Pharmacological modulation of mitochondrial function as novel strategies for treating intestinal inflammatory diseases and colorectal cancer

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic and recurrent intestinal disease, and has become a major global health issue. Individuals with IBD face an elevated risk of developing colorectal cancer (CRC), and recent studies have indicated that mitochondrial dysfunction plays a pivotal role in the pathogenesis of both IBD and CRC. This review covers the pathogenesis of IBD and CRC, focusing on mitochondrial dysfunction, and explores pharmacological targets and strategies for addressing both conditions by modulating mitochondrial function. Additionally, recent advancements in the pharmacological modulation of mitochondrial dysfunction for treating IBD and CRC, encompassing mitochondrial damage, release of mitochondrial DNA (mtDNA), and impairment of mitophagy, are thoroughly summarized. The review also provides a systematic overview of natural compounds (such as flavonoids, alkaloids, and diterpenoids), Chinese medicines, and intestinal microbiota, which can alleviate IBD and attenuate the progression of CRC by modulating mitochondrial function. In the future, it will be imperative to develop more practical methodologies for real-time monitoring and accurate detection of mitochondrial function, which will greatly aid scientists in identifying more effective agents for treating IBD and CRC through modulation of mitochondrial function.

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1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract, including Crohn's disease (CD) and ulcerative colitis (UC) [1]. The symptoms of IBD include vomiting, diarrhea, weight loss, nausea, occasional chills, and fever [2]. The risk of colorectal cancer (CRC) in people with UC is approximately 2–3 times higher than that in the general population, and patients with CD appear to have a similar increased risk [3]. In comparison, individuals with sporadic colon cancer who have a history of colon adenoma or adenocarcinoma exhibit an increasing propensity for the development of metachronous adenoma or adenocarcinoma [4].

Mitochondria, double-membrane organelles are found in the cytoplasm of almost all eukaryotic cells [5]. Mitochondrial reactive oxygen species (ROS) affects signaling pathways that govern cell proliferation and differentiation [6–8]. Mitochondria also act as calcium ion reservoirs and interact with the endoplasmic reticulum (ER), extracellular matrix, and other structures to maintain intracellular calcium ion levels [9]. In the case of viral or bacterial infection or cell damage, mitochondria are crucial for the response against pathogenic infections [10]. The accumulation of mitochondrial DNA (mtDNA) in the cytoplasm triggers immune system activation, leading to an antiviral immune response, while oxidative damage to mtDNA induces inflammasome activation [11]. Importantly, inflammation can arise not only from pathogen infections but also from tissue damage, which triggers inflammatory responses through the release of mitochondrial damage-associated molecular patterns (DAMPs) [10].

Mitochondrial dysfunction can impair the intestinal barrier, which is crucial in maintaining intestinal barrier homeostasis [12]. First, mitochondrial damage leads to energy depletion and induces

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susceptibility to cell death, influencing the secretory function and regenerative capacity of intestinal barrier [13]. Second, mitochondrial damage can alter the phenotype and function of immune cells through regulating metabolic pathways. In immune cells, energy is predominantly generated from glycolysis, and mitochondrial damage enhances and sustains a pro-inflammatory state [14]. Third, mitochondria serve as the primary cellular source of ROS, and excessive ROS accumulation leads to intestinal cell death [15].

In this review, we explore the relationships between mitochondria function and intestinal inflammation/CRC. This review also covers recent advancements in pharmacological modulation of mitochondrial dysfunction for treating IBD and CRC, primarily focusing on a range of natural compounds (such as flavonoids, alkaloids, and diterpenoids) and Chinese medicines that are capable of inducing intervention of mitochondrial function to alleviate intestinal inflammation/CRC. This review also introduces Chinese medicine with medication-food homologous properties that can influence mitochondrial function to treat IBD/CRC.

2. Mitochondria dysfunction in IBD

Genome-wide association studies (GWAS) have identified 242 loci associated with susceptibility to IBD [16]. Approximately 5% of these genes are involved in maintaining mitochondrial homeostasis, such as solute carrier family 25 member 28 (*SLC25A28*) encoding mitoferrin 2, valyl-transfer RNA (tRNA) synthetase (*VARS*) encoding valine-tRNA ligase, and ring finger protein 5 (*RNF5*) encoding E3 ubiquitin (Ub)-protein ligase RNF5 [15].

In colonic biopsy tissues from UC patients, a nonsignificant trend towards reducing the activity of mitochondrial electron transport chain complex I and complex II is observed [17]. Downregulation of mitochondria-encoding genes related to electron transport complexes (I, III, IV, and V), as well as peroxisome proliferator-activated receptor gamma (*PPARγ*), coactivator 1 alpha (*PPARGC1A*), and mitochondrial membrane potential (*MMP*), are significantly suppressed in the colon of IBD patients [17]. Many genes like GATA6 antisense RNA 1 (*GATA6-AS1*), mitochondrially encoded nicotinamide adenine dinucleotide (NADH):ubiquinone oxidoreductase core subunit 4 (*MT-ND4*), mitochondrial chaperone prohibitin (*PHB*)/*PHB1*, and respiratory chain proteins involve in IBD through their effects on mitochondrial function. *GATA6-AS1* is significantly downregulated in IBD patients, and it is associated with more severe UC cases and poor outcomes through inducing mitochondrial dysfunction [18]. *MT-ND4* was identified through a clinical study involving 2,687 German UC patients, and the gene has an important effect on mitochondrial respiratory chain function [19]. The decreasing expression of the mitochondrial chaperone *PHB*/*PHB1* and respiratory chain proteins destroy mitochondrial integrity, leading to increased ROS production and subsequent stimulation of mitophagy in intestinal epithelial cells of IBD patients [20].

Numerous animal and cell studies also indicate that mitochondrial dysfunction can modulate intestinal inflammation through mechanisms including mitochondrial damage, the release of mtDNA, mitochondrial oxidative stress, and mitophagy [21–24].

Mitochondrial damage can result in an energy deficit state by increasing cell death sensitivity, reducing secretory barrier function in IBD [13]. In UC, the interaction between Foxo and Notch signaling inhibits mitochondrial fission and subsequently suppresses stem cell differentiation into goblet cells [25]. Mitochondrial damage can also affect the phenotype and function of immune cells through regulating metabolic processes [26]. Pro-inflammatory cells, such as activated monocytes, T cells, and B cells, enhance cellular energy production via increasing glycolysis [15]. Various components and metabolites released from mitochondria, such as nucleic acids, proteins, and small molecule metabolites, can act as DAMPs, promoting inflammation when released into the cytosol or extracellular environment [27,28]. For example, cardiolipin, located within the inner mitochondrial membrane, can be presented by dendritic cells (DCs) on the major histocompatibility complex (MHC) class I-like molecule CD1d, thereby activating γδT cells [29]. Additionally, *N*-formyl peptides, another type of mitochondrial component, can bind to formyl peptide receptor 1 (FPR1) on neutrophils, functioning as activators of neutrophils [30].

Cell lines harboring mtDNA polymorphisms are associated with increased intestinal triphosphates resulting from more efficient oxidase activity, exhibiting enhanced protection against colitis induced by dextran sulfate sodium (DSS) [31]. The release of mtDNA has been observed to trigger an inflammatory response and impair the integrity of the intestinal barrier [32]. MtDNA accumulates in the extracellular milieu following programmed cell death, activating neutrophils via Toll-like receptor 9 (TLR9) or advanced glycosylation end-product specific receptor (AGER) [29]. Furthermore, the release of mtDNA can activate the cyclic cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) (cGAMP) synthase (cGAS)-stimulator of the interferon (IFN) genes 1 (STING1) pathway, leading to cytokine synthesis [33].

Mitochondrial ROS plays a crucial role in promoting intestinal inflammation [34]. Defects in the electron transport chain are observed in the colon, resulting in an increasing rate of mitochondrial ROS production, which further exacerbates disease progression in intestinal epithelial cells [35]. The ROS released from mitochondria stimulates the formation of the nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, subsequently promoting the production of interleukin (IL)-18 and IL-1β [33].

Changes in mitochondrial morphology are obvious manifestations of impaired mitophagy in CD, with MMP reduction, increase in mitochondrial ROS levels, and disruption of microtubule-associated protein 1A/1B-light chain 3 (LC3)-labeled autophagy [36]. During inflammation, autophagy-associated protein (ATG) recognizes LC3 and contributes to the degradation of inflammasomes activated by ROS [29]. Moreover, several genes are linked to mitophagy in IBD. CD-associated risk variants in autophagy related 16 like 1 (*ATG16L1*) lead to altered mitophagy, resulting in the accumulation of mitochondrial ROS [20]. Nuclear receptor subfamily 1 group D member 1 (*NR1D1*) regulates B-cell lymphoma 2 (Bcl-2)/adenovirus E1B 19 kDa interacting protein 3 (BNIP3)-mediated mitophagy [36], while immunity-related guanosine-triphosphate hydrolase (GTPase) M (*IRGM*) deletion is associated with defective mitophagy in Paneth cells [20].

3. Mitochondria dysfunction in CRC

In recent years, the relationship between mitochondria dysfunction and the development of CRC has been increasingly recognized. Here we mainly discuss the role of mitochondria function in CRC based on the following content.

Some target proteins localized in mitochondria have been shown in the development of CRC. Tumor necrosis factor type 1 receptor-associated protein (TRAP1) is an isoform of heat shock protein 90 (HSP90) predominantly localized in mitochondria. Its overexpression can promote CRC development through activating the cellular metabolism [37]. TRAP1 can influence mitochondrial structure and dynamics, leading to increased mitochondrial division [38]. NADH:ubiquinone oxidoreductase core subunit S1 (NDUFS1), by binding to PHB2 in mitochondria, can stabilize mitochondrial complex I, increase oxidative phosphorylation (OXPHOS) levels, and promote CRC cell growth [39].

Some proteins affecting mitochondrial dynamics are implicated in the regulation of CRC. For instance, Sirt3-mediated mitochondrial fragmentation modulates the cancer stress response in CRC by regulating the AKT serine/threonine kinase 1 (AKT1)/phosphatase and tensin homolog (PTEN) signaling pathway [40]. Ankyrin repeat domain 22 (ANKRD22) acts through the lipid transporter protein (extended synaptic binding protein-1 (E-Syt1) to facilitate lipid transport to mitochondria and reduce mitochondrial numbers, further promoting the reprogramming of cancer cells to meet their metabolic needs [41].

A specific metabolite in mitochondria is involved in the transition from colitis to cancer. D-2-hydroxyglutaric acid (D-2-HG), a metabolite in the tricarboxylic acid cycle (TCA) cycle, significantly increases during mice colitis [42]. The elevated D-2-HG levels promote the progression of intestinal epithelial cells to cancer and confer a hyperproliferative and non-apoptotic phenotype on these cells.

Besides the above, some proteins are involved in CRC by influencing mitochondrial function. For example, the mitochondrial calcium uniporter (MCU) aids in the proliferation of CRC cells by inhibiting the phosphorylation of mitochondrial transcription factor A (TFAM) [43]. Adenosine triphosphate (ATP)-binding cassette subfamily B member 7 (ABCB7), a mitochondrial iron transport protein regulating intracellular iron homeostasis, inhibits apoptosis by suppressing the expression of leucine zipper downregulated in cancer-1 (LDOC1), an inhibitor of nuclear factor-kappaB (NF-κB) [44]. The G-protein coupled receptor 176 (GPR176)/guanine nucleotide binding protein alpha stimulating activity polypeptide (GNAS) axis promotes CRC development by inhibiting mitophagy via the cyclic AMP (cAMP)/protein kinase A (PKA)/BNIP3-like (BNIP3L) pathway [45]. Cyclooxygenase-1 (COX-1) is involved in NF-κB-mediated mitochondrial dysfunction and CRC progression [46].

4. Pharmacological modulating mitochondrial dysfunction for treating IBD and CRC

4.1. Regulating mitophagy in the treatment of IBD and CRC

In 2005, Lemasters [47] proposed the term “mitophagy” to denote the process of selective autophagy of mitochondria. Subsequent studies found that PTEN induced kinase 1 (PINK1)-PRKN/parkin ring-between-ring (RBR) E3 Ub protein ligase (Parkin) dependent mitophagy are mediated by receptors including protein and lipid receptors (Fig. 1). Mechanisms of mitophagy can be divided into Ub-dependent pathway and Ub-independent pathway [20]. Ub-dependent pathways contain the PINK1/Parkin pathway [48]. In Ub-independent pathways, mitophagy receptors such as nineteen kDa interacting protein-3 (NIP3)-like protein X (NIX), BNIP3, and FUN14 domain-containing 1 (FUNDC1) bind directly to LC3 [48]. Mitophagy serves as a critical mechanism for autophagy to specifically eliminate dysfunctional or surplus mitochondria, thus exerting robust control over the immune system [20].

Andrographolide, labdane diterpenoid of the plant *Andrographis paniculata* belonging to the *Euphorbiaceous* family, is widely used in the treatment of viral and bacterial infections [49,50]. In the azomethane/DSS-induced colon carcinogenesis mouse model, andrographolide is demonstrated to induce mitophagy, leading to the inhibition of NLRP3 inflammasome activation and subsequent mitigation of intestinal inflammation and colon carcinogenesis [49]. Similarly, palmatine, a berberine and an organic heterotetracyclic compound isolated from *Fibraurea recisa Pierre*, has been found to inhibit NLRP3 inflammasome activation by promoting mitophagy in mice with DSS-induced colitis [51].

Sodium butyrate is a significant neuromodulator in the central nervous system, and it is a short-chain fatty acid (SCFA) primarily generated through the intestinal microbial fermentation of dietary fiber [52]. Sodium butyrate alleviates colitis severity in a mouse model by activating nuclear factor-erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) pathway. This activation reduces oxidative stress, suppresses NLRP3 inflammasome activation, and diminishes the secretion of related inflammatory factors [53]. Furthermore, sodium butyrate also promotes mitophagy by upregulating the expression of PINK1/Parkin [53].

Ginsenosides, crucial constituents derived from ginseng, a perennial deciduous plant of the *Acanthaceae* family [54]. Through the AMP-activated protein kinase (AMPK)/UNC-52-like kinase 1 (ULK1)/sequestosome-1 (p62) axis, ginsenosides promote mitophagy and concurrently induce the inacti1vation of the NLRP3 inflammasome, resulting in a reduction of IL-1β secretion by macrophages. This inhibition suppresses colitis in the DSS-induced mouse model [54].

Oxymatrine, a quinolizidine alkaloid, is one of the major matrine-type alkaloids extracted from *Sophora* medicinal plants and has been demonstrated to exert unique anti-CRC activity through the inhibition of leucine rich pentatricopeptide repeat containing (LRPPRC), the induction of mitophagy, and the inhibition of NLRP3 inflammatory vesicles [55].

4.2. Pharmacological modulating mitochondrial dynamics for treating IBD and CRC

Mitochondria undergo constant fission and fusion, influenced by numerous life processes or external stimuli, to maintain a dynamic equilibrium that regulates their form, function, and quantity. Nevertheless, specific physiological or pathological alterations might disturb this equilibrium, resulting in an escalation of fusion or fission occurrences, thereby impacting mitochondrial structure, performance, and abundance [56].

Aspartate, categorized as a non-essential amino acid in humans, inhibits mitochondrial destruction of colonic epithelial cells by regulating mitochondrial metabolism and enhancing mitochondrial dynamics. It promotes mitochondrial fusion, stimulates the proliferation of colonic stem cells, and ultimately alleviates intestinal epithelial cell damage in the DSS-induced colitis [57].

Matrine, an alkaloid compound, is obtained from the renowned Chinese herbal medicine *Sophora flavescens* Ait. [58]. Matrine can stimulate mitochondrial fission, which is linked to mitochondrial elongation factor 1 (MIEF1), and thereby effectively hinder the viability of CRC cells via the large tumor suppressor-2 (LATS2)-Hippo pathway [58].

Azelastine, an antihistamine that is often prescribed, effectively inhibits colon tumors and mitochondrial fission [59]. An instance of a molecular pathway implicated in the development of colon tumors is the interaction between Iq motif-containing GTPase-activating protein 1 (Iqgap1) and adenosine diphosphate (ADP)-ribosylation factor 1 (ARF1), which stimulates extracellular signal-regulated kinase (ERK) signaling and mitochondrial fission activation [59,60]. Through the facilitation of interactions among Iqgap1, mitogen-activated ERK (MEK), and ERK, ARF1 is implicated in the progression of colon malignancies. Azelastine inhibits the activity of ARF1 by binding to the threonine residue located at position 48, leading to a subsequent reduction in dynamin-related protein 1 (Drp1) phosphorylation [59].

4.3. Pharmacological modulating mitochondrial oxidative stress for treating IBD and CRC

Mitochondria play a crucial role in various metabolic pathways and the transfer of energy via OXPHOS [61,62]. Under normal physiological conditions, the production of ROS primarily occurs in

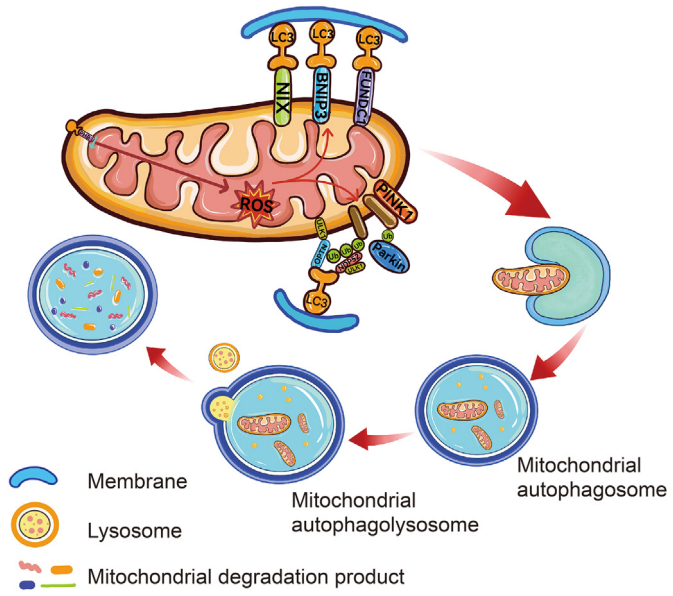

Fig. 1. The basic process of mitophagy. Mitochondrial damage undergoes a permeability transition leading to mitochondrial depolarization and loss of membrane potential, triggering the activation of mitochondrial autophagy-related proteins. Subsequently, autophagosomes envelop damaged mitochondria, forming mitochondrial autophagosomes. These autophagosomes then fuse with lysosomes to form mature mitochondrial autophagolysosomes, resulting in the degradation of mitochondria. LC3: microtubule-associated protein 1A/1B-light chain 3; NIX: nineteen kDa interacting protein-3 (NIP3)-like protein X; BNIP3: B-cell lymphoma 2 (Bcl-2)/adenovirus E1B 19 kDa interacting protein 3; FUNDC1: FUN14 domain-containing 1; ROS: reactive oxygen species; ULK1: UNC-52-like kinase 1; OPTN: optineurin; Ub: ubiquitin; NDP52: nuclear dot protein 52 kDa; PINK1: phosphatase and tensin homolog (PTEN) induced kinase 1; Parkin: parkin ring-between-ring (RBR) E3 Ub protein ligase.

mitochondria, making them the primary source of ROS in living cells [63]. Ferroptosis and apoptosis play significant roles in UC and are strongly associated with mitochondrial ROS [64]. In both UC and CD patients, apoptosis can be seen in various kinds of epithelial cells at the sites of inflammation [65]. The intestinal barrier is further compromised by pro-inflammatory tumor necrosis factor alpha (TNF-α) production by invading macrophages and excessive ER stress, which induces epithelial cell death, leading to the collapse of the intestinal barrier and exacerbating inflammation [65].

Farnesoid X receptor (FXR) agonists including GW4064 and nelumal A have been shown to regulate mitochondrial ROS production to exert anti-inflammation effects in mice models of UC and CRC [66]. Nrf2 agonists like cardamonin and schiandrin B can significantly ameliorate disease progression in the IBD model by decreasing mitochondrial ROS [67,68].

Some compounds can treat IBD/CRC by regulating mitochondrial ROS production such as triptolide, curcumin, melatonin, and artesunate. Triptolide, an abietane-type diterpenoid derived from *Tripterygium wilfordii* Hook. F., can alleviate IBD by inhibiting mitochondrial ROS production [69]. Curcumin can scavenge superoxide anions, peroxyates, hydroperoxide lipids, and hydroxyl radicals to interfere with lipid and protein oxidation within the lipid bilayer, thereby reactivating ROS detoxification mechanisms and replanting glutathione storage [70]. Curcumin aids in mitochondrial reconnection by quenching mitochondrial ROS, trapping hydrogen peroxide lipids around the respiratory body, and fine-adjusting mitochondrial permeability transition pore (mPTP) opening and physiological electron transport in the respiratory body [70]. Melatonin supplementation has been found to suppress oxidative stress and to activate the phosphoinositide 3-kinase (PI3K)/AKT/Nrf2/sirtuin 1 (SIRT1)/retinoic acid-related orphan receptor alpha (RORα) pathway and suppress NF-κB signaling pathway and mitochondrial dysfunction, leading to an improvement in DSS-induced intestinal mucosal injury (Fig. 2) [71]. Artesunate, derived from *Artemisia annua*, can specifically target mitochondria to induce mitochondrial dysfunction, consequently triggering the production of mitochondrial ROS. Thus, artesunate hampers the growth of CRC cells by promoting p16 (cyclin-dependent kinase inhibitor 2A (CDKN2A))- and p21 (CDKN1A)-dependent cellular senescence and inducing cell cycle arrest [72]. Resveratrol can increase ROS content through regulating mitochondrial pathway in human CRC cells to induced cancer cell apoptosis (Fig. 3) [73].

4.4. Pharmacological regulation of mtDNA for treating IBD and CRC

Mitochondria possess a small, distinct amount of DNA referred to as mtDNA, and excessive mutations in mtDNA can disrupt OXPHOS functionality, leading to disorders associated with mitochondrial dysfunction [74]. As we described above, the release of mtDNA has been identified as a contributing factor to the occurrence of inflammation. Fig. 4 shows how traditional Chinese medicine Huangqin decoction treat IBD via modulation of mtDNA [75,76].

In DSS-induced UC, dimethyl fumarate prevents mitochondrial perturbation and the release of mtDNA into the cytoplasm, which subsequently inhibits the activation of the NLRP3 inflammasome triggered by lipopolysaccharide (LPS) and ATP [77].

In DSS-induced UC, glucoraphanin can enhance AMPK activity and increase mtDNA, inhibit DRP1 protein responsible for regulating mitochondrial division, and maintain mitochondrial homeostasis [78].

Demethylberberine can effectively repair mitochondrial disorders, reduce the immune stimulation of mtDNA, inhibit the NF-κB signaling pathway, block the activation of NLRP3 inflammasome, and inhibit the excessive activation of TLR4-mitochondrial signaling pathway, thereby maintaining mitochondrial homeostasis. Demethylberberine has shown therapeutic potential in the treatment of IBD [79]. We summarized the advancements of pharmacological modulating mtDNA in Table 1 [80–89].

5. Mitochondria function regulated by intestinal microbiota

The intestinal microbes actively interact with each other and shape the host mucosal immune system, which plays a crucial role in regulating intestinal homeostasis and intestinal inflammation [90,91]. Mammalian microbiota is predominantly composed of five phyla: *Bacteroidetes*, *Firmicutes*, *Proteobacteria*, *Actinobacteria*, and *Verrucomicrobia* [92,93]. Bacteria occupy a leading position in the gastrointestinal microbial ecosystem, with more than 90% of the healthy intestinal microbiota belonging to the phylum *Bacteroidetes* and *Firmicutes*. Metabolites of intestinal bacteria, including SCFAs and hydrogen sulfide (H_2S), can regulate mitochondrial function involved in the development of colitis and associated CRC [94].

SCFAs play a pivotal role in maintaining colonic regulatory T (Treg) cell homeostasis by promoting Treg cell function in mice [93]. SCFAs, including acetate and butyrate, are encompassed within this group [95]. Inflammatory responses lead to increased oxygenation of epithelial cells, resulting in oxygen diffusion into the intestinal lumen. This process inhibits the growth of *Clostridium rodentium*, reduces the concentration of SCFA metabolites, and exacerbates the OXPHOS environment of mitochondria [96]. *Helicobacter pylori* secrete the pore-forming toxin vacuolating cytotoxin A (VacA), which acts on the mitochondrial membrane, inducing mitochondria outer membrane permeabilization

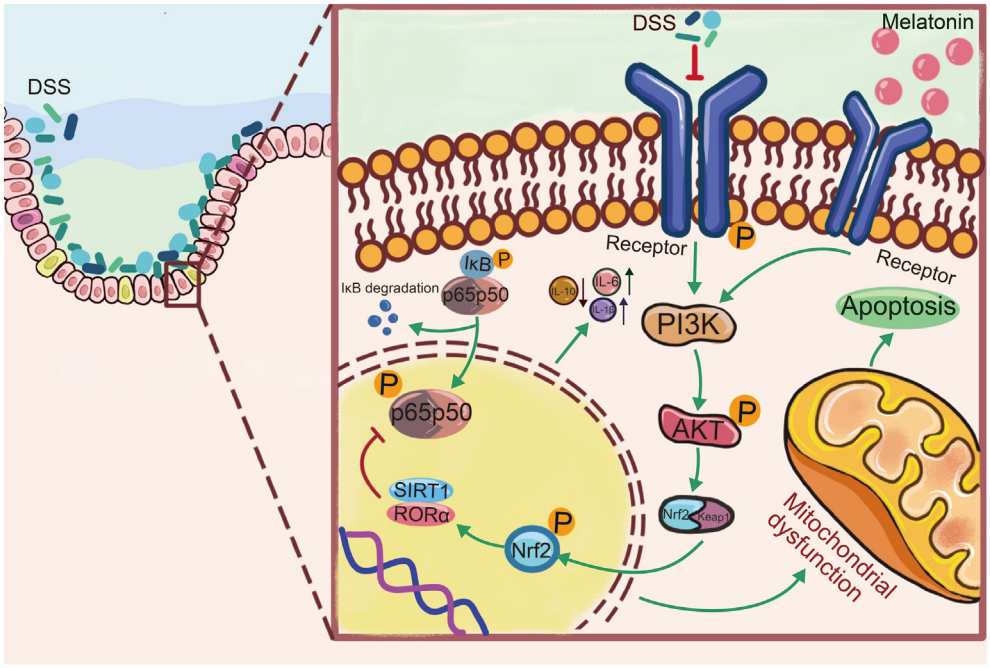

Fig. 2. Pharmacological modulation of inflammatory bowel disease (IBD) by regulating mitochondrial function. We selected melatonin as the representative drug to show its regulation of mitochondrial oxidative stress to treat IBD. DSS: dextran sulfate sodium; IL: interleukin; PI3K: phosphoinositide 3-kinase; AKT1: AKT serine/threonine kinase 1; Nrf2: nuclear factor erythroid 2-related factor 2; Keap1: Kelch-like ECH-associated protein 1; RORα: retinoic acid-related orphan receptor alpha; SIRT1: sirtuin 1. Reprinted from Ref. [71] with permission.

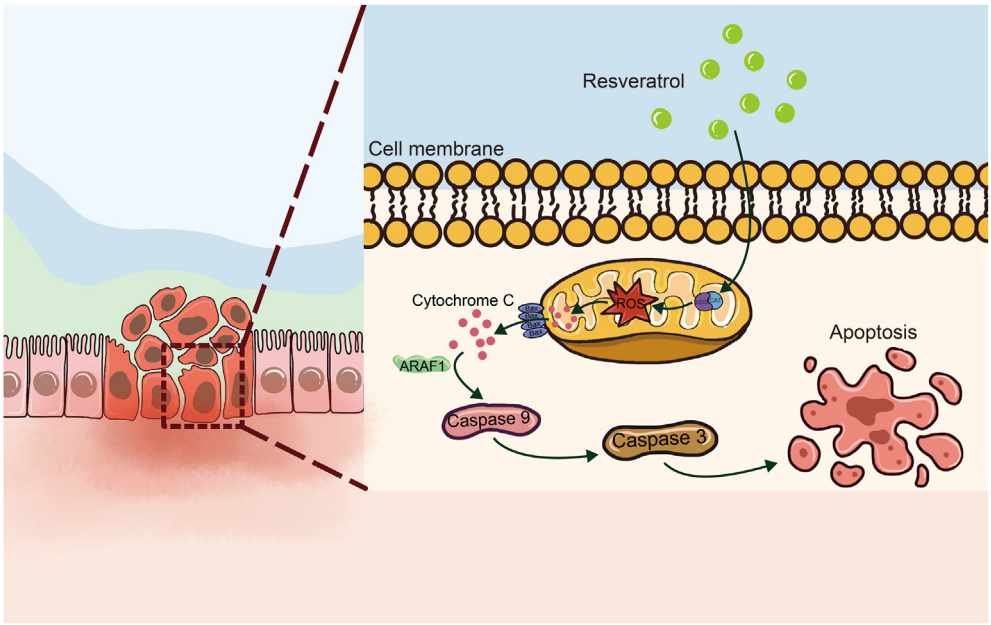

Fig. 3. Pharmacological modulation of colorectal cancer (CRC) by regulating mitochondrial function. Melatonin was selected as the representative drug to show its regulation of mitochondrial oxidative stress to treat CRC. CAT: catalase; SOD: superoxide dismutase; ROS: reactive oxygen species; Bax: B-cell lymphoma 2 (Bcl-2) associated X; ARAF1: A-Raf proto-oncogene, serine/threonine kinase 1. Reprinted from Ref. [73] with permission.

(MOMP). This action disrupts the proton concentration gradient of the electron transport chain and affects OXPHOS [97].

H_2S is the third gaseous signaling molecule, following both nitric oxide and carbon monoxide [98]. H_2S is primarily produced through luminal release by intestinal bacterial metabolism [99]. Due to its high membrane permeability, H_2S readily penetrates the biofilm in the intestinal lumen and enters colonic cells [100,101]. H_2S exhibits both anti-inflammatory and pro-inflammatory effects [102]. It protects mitochondria and their functions under hypoxic conditions by upregulating the Nrf2 stress response pathway, increasing detoxifying proteins and antioxidants [102]. At low concentrations, H_2S increases AKT phosphorylation and strengthens the localization of transcription factors Nrf1 and Nrf2, which enhance endogenous antioxidant levels, prevent cell apoptosis, and increase mitochondrial biogenesis [103]. However, H_2S can also exhibit cytotoxic effects by primarily inhibiting

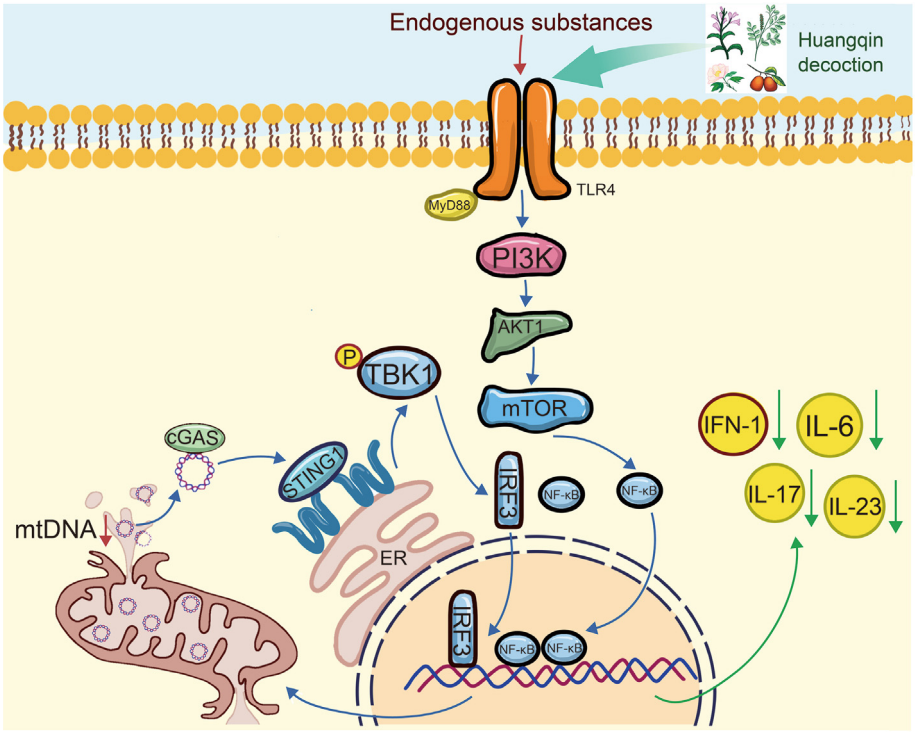

Fig. 4. Pharmacological modulation of inflammatory bowel disease (IBD) by regulating mitochondrial DNA (mtDNA). Huangqin decoction was selected as the representative traditional Chinese medicine to show its regulation of mtDNA to treat IBD. Huangqin decoction inhibits the expression of Toll-like receptor 4 (TLR4), phosphoinositide 3-kinase (PI3K), and AKT serine/threonine kinase 1 (AKT1) inflammatory signaling pathways and decreases the expression of interleukin 6 (IL-6), IL-17, and IL-23. It also causes a decrease in mtDNA content in the intestinal epithelium and reduces type 1 interferon (IFN-1) expression via cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS)-stimulator of IFN genes 1 (STING1). MyD88: myeloid differentiation factor-88; mTOR: mechanistic target of rapamycin; NF-κB: nuclear factor-kappa B; TBK1: TANK-binding kinase 1; IRF3: IFN regulatory factor 3; ER: endoplasmic reticulum.

mitochondrial complex IV, blocking mitochondrial electron transport, and impeding aerobic ATP production [104]. At lower concentrations, H_2S can also act as a metabolic substrate, stimulating the mitochondrial electron transport chain and promoting aerobic respiration and ATP synthesis [105]. Additionally, by stimulating mitochondrial ATP production, endogenous H_2S helps to maintain mitochondrial organization, prevent mitochondrial fission, and stimulate the assembly of mtDNA repair complexes responsible for repairing damaged mtDNA in cancer cells [104].

6. Additional strategies: seeking efficacious agents or herbal medicines with desirable mitochondrial function modulating effects

Medication-food homologous Chinese medicines refer to the concept that certain Chinese medicines can be utilized not only as drugs for treating a range of diseases but also as a source of nutrition and energy when consumed as food [106]. Some foods are believed to have a profound effect on human health and well-being

Table 1
The advancements of pharmacological modulating mitochondrial DNA (mtDNA).

Disease	Therapeutic agent	Pharmacological Mechanisms	Refs.
IBD	VBIT-4 and VBIT-12	Prevent apoptosis and mtDNA release by inhibiting VDAC1 oligomerization	[80]
	Vitamin A	Upregulate TFAMs, NFR-1, TFAM and prevent inflammatory and necrotic changes in colitis	[81]
	1′-Acetoxychavicol acetate	Inhibit mitochondrial ROS production, prevent the release of oxidized mtDNA, and prevent the activation of NLRP3 inflammatory vesicles *in vivo*	[82]
CRC	Tigecycline/tetracyclin	Reduce mtDNA content, increase mitochondrial biogenesis, ATP content, membrane potential and oxidative stress, and inhibit the assembly and activity of complex I in highly metastatic cells	[83]
	Ilimaquinone	Trigger mitochondria-mediated apoptosis as evidenced by DNA damage and a reduction in the proportion of Bcl-2 through the mitochondria-mediated apoptosis pathway	[84]
	3,3'-[(1,1′-Biphenyl)-4′,4′-diyl) bis(azo)]*bis*[4-amino-1-naphthalenesulfonic acid]	Inhibit Polγ activity and oxidative mtDNA damage repair and increase ROS production and oxidative mtDNA damage in MLH1-deficient cells, leading to mitochondrial dysfunction and cell death	[85]
	Marine invertebrate extracts	Intracellular ROS accumulation, mitochondrial depolarization, and DNA damage	[86]
	Aldose reductase inhibitor: fidarestat	Increase mitochondrial biogenesis via increasing the expression of Nrf2/HO-1/AMPK/p53 and decreasing the mtDNA damage	[87]
	Oroxylin A	Induce mitochondrial translocation of p53 and lead to mitochondrial dysfunction in human CRC cells	[88]
	Ciprofloxacin	Decrease proliferation and induce apoptosis of colon carcinoma cells by blocking mtDNA synthesis	[89]

IBD: inflammatory bowel disease; VDAC1: voltage-dependent-anion channel 1; NFR-1: nuclear respiratory factor 1; TFAM: mitochondrial transcription factor A; ROS: reactive oxygen species; NLRP3: NOD-like receptor thermal protein domain associated protein 3; CRC: colorectal cancer; ATP: adenosine triphosphate; Bcl-2: B-cell lymphoma 2; Polγ: polymerase gamma; MLH1: mutL homolog 1; Nrf2: nuclear factor-erythroid 2-related factor 2; HO-1: heme oxygenase-1; AMPK: adenosine monophosphate (AMP)-activated protein kinase.

because they support or counteract the body's internal balance. For example, some foods are thought to have warming or cooling properties, while others are believed to have moisturizing or drying properties [107]. Several medication-food homologous Chinese medicines can regulate mitochondrial function to treat IBD. In the 2,4,6-trinitrobenzenesulfonic acid solution (TNBS)-induced colitis rat model, supplementation of chlorogenic acid leads to improvements in mitochondrial ultrastructure while reducing mitochondrial damage [108]. Similarly, licorice has shown promising treatment efficacy in reducing inflammatory factors and oxidative stress in mice with UC, with possible activation of the Nrf2/PINK1 pathway to promote mitophagy [109]. *Securidaca longipedunculata*, a plant traditionally used to treat various diseases, has shown promising anti-inflammatory and antioxidant activity in both *in vivo* and *in vitro* studies. Exploring this potential therapeutic role for IBD is a promising direction for future research [110].

Several medication-food homologous Chinese medicines have demonstrated efficacy in treating CRC through the regulation of mitochondrial function. These Chinese medicines include *Houttuynia cordata* Thunb, *Alpiniae officinarum*, *Dendrobium officinale* Kimura et Migo, *Scutellaria baicalensis*, and *Dimocarpus longan* [111–114]. For instance, *Houttuynia cordata* Thunb. can increase the production of ROS in human primary colorectal adenocarcinoma cells, leading to a reduction in MMP and inducing apoptosis through mitochondria-dependent signaling pathways [115]. Similarly, treatment of human CRC HT-29 cells with piperine, an extract derived from black pepper, results in the loss of mitochondrial membrane integrity and exhibits anti-tumor effects [116]. Polysaccharides obtained from *Dendrobium officinale* Kimura et Migo have been found to inhibit the proliferation of CRC CT26 cells via the ROS-ATP-AMPK signaling pathway [113]. Magnolol, a compound found in the roots and stems of *Magnoliae officinalis cortex*, may combat CRC by triggering death receptors and mitochondria-dependent apoptotic mechanisms in CRC cells [117]. Specific medication-food homologous Chinese medicines that can be employed for the treatment of intestinal diseases are summarized in Table 2 [118–153].

Table 2
Medication-food homologous Chinese medicine that can treat intestinal diseases.

Disease	Name of the Chinese medicine	Refs.
Diarrhea	*Raphanus sativus* L.	[118]
	Lotus seed	[119]
	Kudzu root	[120]
	Piperis Fructus	[121]
	Allium macrostemon Bunge.	[122]
	Rubi Fructus	[123]
	Pogostemon cablin	[124]
	Astragalus mongholicus Bunge.	[125]
Constipation	*Raphanus sativus* L.	[126]
	Lotus seed	[127]
	Chrysanthemum morifolium	[128]
	Orange peel	[129]
	Codonopis bulleynana	[130]
	Cistanche deserticola	[131]
	Astragalus mongholicus Bunge.	[132]
Intestine ischemia reperfusion	*Pueraria*	[133]
	Propolis	[134]
	Ganoderma lucidum	[135]
IBD	*Ganoderma lucidum*	[136]
	Herba Andrographitis	[137]
	Ginger	[138]
	Ginseng	[139]
	Wheat germ	[140]
	Gardenia jasminoides Ellis	[141]
	Mulberry fruit	[142]
	Nelumbo nucifera Gaertn.	[143]
	Mulberry leaf	[144]
	Perilla frutescens leaf	[145]
	Pueraria lobate root	[146]
	Codonopsis pilosula	[147]
	Dendrobium officinale	[148]
	Licorice	[149]
	Honeysuckle (*Lonicerae Japonicae Flos*)	[150]
CRC	*Houttuynia cordata*	[151]
	Longan	[152]
	Scutellaria baicalensis Georgi.	[153]

IBD: inflammatory bowel disease; CRC: colorectal cancer.

7. Conclusions and future prospectives

This review has outlined how mitochondrial dysfunction can trigger IBD and CRC and has summarized various natural compounds, microbial metabolites, and Chinese medicines that can alleviate IBD or slow CRC progression by modulating mitochondrial function. Future research should focus on developing practical methodologies for real-time monitoring and accurate detection of mitochondrial function for a better understanding of its critical role in IBD and CRC. This will facilitate the identification of more effective agents to treat these conditions by modulating mitochondrial function. Additionally, the emerging feasibility of combining conventional drugs with Chinese medicines to modulate mitochondrial function offers a promising therapeutic strategy for the prevention and treatment of IBD and CRC.

CRediT authorship contribution statement

Boya Wang: Writing – original draft, Writing – review & editing, Project administration, Investigation, Data curation, Conceptualization. **Xinrui Guo:** Writing – original draft, Methodology, Investigation. **Lanhui Qin:** Writing – original draft, Methodology, Investigation. **Liheng He:** Writing – original draft, Supervision, Resources, Methodology. **Jingnan Li:** Writing – original draft, Supervision, Resources, Methodology. **Xudong Jin:** Writing – review & editing, Investigation. **Dapeng Chen:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Guangbo Ge:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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