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REVIEW

Treatment of inflammatory bowel disease via green tea polyphenols: possible application and protective approaches

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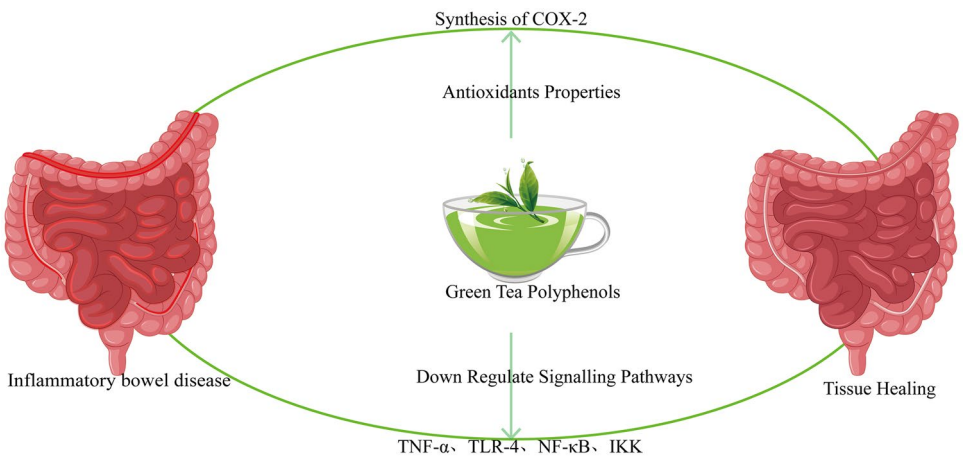
Abstract

Inflammatory bowel disease (IBD) is a collection of inflammatory conditions of colon and small intestine which affect millions of individuals worldwide and the prevalence amount is on the rise. The organ failure as well as loss of tissue function is because of the inflammatory reaction which is the major contributor of tissue healing leading to lifelong debilitation. To stop the tough consequences of inflammation every patient pursues alternative therapy to relieve symptoms. Green tea polyphenols (GTPs) play significant roles in down regulating signaling pathways because GTPs exert effective antioxidant properties and regulate Toll-like receptor 4 (TLR4) expression via certain receptor, inhibited endotoxin-mediated tumor necrosis factor alpha (TNF-α) production by blocking transcription nuclear factor-kappa B (NF-kB) activation and upstream of mediated I kappa B kinase complex pathway activities, as well as intrusion with the flow of cytokines and synthesis of cyclooxygenase-2 (COX-2). This article highlights the green approach regarding the defensive effects of GTP review-related studies concerning the contrary effects and the key therapeutic targets application of GTPs in biomedical field to treat inflammatory bowel disease (IBD) and its complications.

Graphical abstract



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Keywords Inflammatory conditions · Crohn's diseases · Green tea polyphenols · Signaling pathways · Treatment

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Abbreviations

GTPs	Green tea polyphenols
TLR4	Toll-like receptor 4
COX-2	Cyclooxygenase-2
IBD	Inflammatory bowel disease
CED	Celiac disease
CAM	Complementary and alternative medicine

UC	Ulcerative colitis
CD	Crohn's disease
TNF-α	Tumor necrosis factor alpha
NSAIDs	Non-steroidal anti-inflammatory drugs
IKK	I kappa B kinase complex
NF-kB	Nuclear factor-kappa B
NPCs	Neural progenitor cells
EGCG (−)	Epigallocatechin gallate
EGC (−)	Epigallocatechin
ECG (−)	Epicatechin gallate
EC (−)	Epicatechin
LPL	Lamina propria lymphocytes
APAP	Acetaminophen [*N*-acetyl-p-aminophenol]
C. diff	*Clostridium difficile*
Nrf2	Nuclear factor erythroid 2-related factor
NO	Nitric oxide
NOS	Nitric oxide synthases
iNOS	Inducible nitric oxide synthase
cNOS	Catalytic nitric oxide synthase
MMP-9	Matrix metalloproteinase-9

Introduction

Inflammatory bowel disease (IBD) is a long-lasting idiopathic inflammatory disorder with intestinal and additional intestinal manifestations. Medications are the foundation of handling IBD, i.e., the role of nutrition like GTPs is essential which involves in both pathogenesis and in treatment of these diseases (Wędrychowicz et al. 2016). However, patients frequently follow medication poorly. Treatment non-adherence is a common problem among persistent infections, averaging 50% in developed countries and is even poorer in developing countries (Webber et al. 2017). Recently, these diseases are affecting more people while the reason and mechanism are still unfound. The two main forms of Crohn's disease (CD) manifest in small and large intestine while ulcerative colitis (UC) is limited to colon. The signs comprise weight loss, abdominal pain, diarrhea, fever, wasting and finally cancer. Normally, it establishes itself before 28–30 years of age and most likely by autoimmune responses but the authentic reasons are still to be assumed. In IBD, the gut epithelial lining or some portion is damaged which disturbed the absorbency of the mucosal obstacle and the absorption of the compounds by passing through the enterocytes starting some allergic responses which are scientifically described as "leaky gut syndrome" (Michielan and Inca 2015; Odenwald and Turner 2013). The pro-inflammatory cytokines called tumor necrosis factor (TNF-α) begin the chronic and acute stages of inflammation by stimulating numerous chemokines and cytokines, linked with inflammation and pain-associated feeling in patients with inflammatory illnesses such as neuropathic complications, pancreatitis, hepatitis and inflammatory bowel disease.

The first difference between UC and CD is UC affects the colon but CD can distress the distal ileum (lower part) and upper part of the colon. Second difference is that CD may affect certain areas and leave intermittent parts ("skip areas") intact, which is not detected in UC, and the third difference is UC normally affects the epithelium but CD affects the whole gut wall. Some ecological aspects play an important role in the increased prevalence of IBD but actually are still to be discussed. The main features are changes of the gut microflora (Uceyler et al. 2009; Beers et al. 2006), ambient air pollution, nonsteroidal anti-inflammatory drugs (NSAIDs), breast feeding, use of excessive antibiotics, hygiene such as smoking (Jostins et al. 2012; Frolkis et al. 2013) and other microorganisms like pathogenic bacteria such as salmonella and campylobacter as well as acute gastroenteritis have been implicated in IBD pathogenesis. Certain *Escherichia coli* (EC) were also linked with the ileal phenotype of CD (Gracia et al. 2006; Gradel et al. 2009). Some similarity between CD and UC also exists with the etiology of celiac disease (CED) but the difference is that people stay without showing any symptoms of the disease with CED (Pascual et al. 2014). The main features and some possible mechanisms which are involved in the onset of IBD are discussed in Table 1.

Nutritional involvements allow for easier combination treatments, with fewer side effects, and also allow for longer term treatment. Entire body approach is required which involves weight loss and use of anti-inflammatories, insulin sensitizers and antioxidants to fully combat obesity and inflammatory bowel diseases (Lyons et al. 2016). GTPs are known to have many health-promoting functions such as increasing immunity, anti-carcinogenicity, antimicrobial action as well as anti-inflammation and act as potent antioxidants (Oz et al. 2004, 2005). GTPs play an important role to deactivate certain signaling pathways which are mostly involved in the onset of inflammation. These include TNF-α (Oz et al. 2013) down-regulation of cyclooxygenase (Cox-2) (Oz and Chen 2008)-mediated I kappa B kinase complex (IKK) and transcription nuclear factor-kappa B (NF-kB) pathways (Yang et al. 2001). GrTPs are shown to also have valuable properties including anti-colorectal cancer possibly through reducing the serum levels of triglyceride (Shimizu et al. 2008) as well as helpful in promotion of apoptosis (Shirakami et al. 2008). About 70–90% polyphenols is excreted into bowls and urine when it is broken down by gut microbiota. Due to its anti-inflammatory, antioxidant effect and alteration of cell signaling properties, polyphenols are one of the utmost used herbal treatments accessible. In addition, GTPs have been described to have antimicrobial properties and to interrupt microbial development (Steinmann et al. 2013).

Table 1 The main features and possible mechanisms for the onset of IBD

MF	Mechanisms	Effect	Refs.
GM	Manufacturing of anti-inflammatory mixtures with immunomodulatory properties. Negative and positive strains of bacteria such as Clostridia and Bifidobacteria	Both positive and negative	Kostic et al. 2014)
AAE	Still unclear	Maybe negative	Gracia et al. (2006)
Diet	Immunomodulatory properties	Positive	Guandalini (2014)
DP	Reduce PH, production of anti-inflammatory SCFA	Positive	Guandalini(2014)
IH	Reduced exposure initially in life to microorganisms, decrease IBD incidence existing in farms, living in over-crowded families, consuming unpasteurized milk	Negative	Gracia et al. (2006)
Smoking	Making of cytokines, enhanced mucus production and transformed air blood flow	Negative	Gracia et al. (2006)
GP	Histocompatibility complex, genes involved in inflammation and oxidative pressure responses and in protected purpose	Both positive and negative	(Jostins et al. (2012); Cho and Brant (2011)

MF main features, *REF* references, *GM* gut microflora, *AAE* ambient air effluence, *DP* diet probiotics, *SCFA* short-chain fatty acids, *IH* improved hygiene, *GP* genetic predisposition

The main purpose of this review is to understand relevant findings concerning defensive effects of GTPs and their possible application for the treatment of IBD and related diseases. Moreover, we review existing information about nitric oxide's (NO) role in IBD and CVD as well protective, arbitrary actions and possible side effects due to the usage of polyphenols (Table 1).

Green tea polyphenols and different disorders

Tea is the utmost popular beverage consumed all over the world, which accounts for about three billion kilograms produced and consumed per year. Tea is derived from plant *Camellia sinensis* in the form of green, black and oolong tea. Green tea is most popular and favored in China and Japan. In western countries, people mostly like and consume black tea which is about 78% worldwide but the countries in Asia mostly like green tea which accounts for about 20% and oolong tea which is very rare, about 2%. A combination of green tea catechins and caffeine has a useful effect on body weight management, specifically by sustained energy spending, fat oxidation, and protection of fat-free body mass, after energy restriction induced body weight loss, when taking the limitations into account (Janssens et al. 2016). GTPs also called as catechins are characterized by di- or tri-hydroxyl group replacement of the B ring and the meta-5,7-dihydroxy substitution of the A ring. The four key catechins shown in Fig. 1, (−) epigallocatechin gallate (EGCG), (−) epigallocatechin (EGC), (−) epicatechin gallate (ECG), and (−) epicatechin (EC), typically account for 30–42% of the dry weight of the solids in brewed green tea (Naghma and Mukhtar 2007). The compositions of polyphenols and their catechins are shown in Table 2 (Lin et al. 2003; Vuong et al. 2010).

Cardiovascular disease (CVD) restrained by constituents in the nutrition mostly depends on many factors. On the coronary, heart sickness, atherosclerotic plaques knob from the internal surface of the arteries, thin the lumen and reduced blood flow (Sosnowska et al. 2017) indicated that nutraceuticals are natural nutritional compounds, which have been shown to be efficacious in preventative medicine or in the treatment of CVD, but the use of GTPs has been inversely related to the expansion and progression of atherosclerosis and it has been stated that nutritional green tea consumption preserves and develops arterial compliance and endothelial function (Murakami and Oshato 2003). GTPs also affect the metabolism of lipid which can be helpful in the appearance of atherosclerotic plaque by different pathways. Tea polyphenols decline the absorption of cholesterol and persuade elimination of fat as well as reduce absorption of triglycerides (Raederstorff et al. 2003). Investigation finds that EGCG, polyphenols and catechin cholesterol related to events that may lead to CVD. The proper use of GTPs can regulate obesity and hypertension which may also have influence on the prevalence of CVD. Some investigations also suggested that increasing GTPs may have reduced the rate of CVD outcomes (Peters et al. 2001). An opposite association of green tea consumption and myocardial infarction and its genetic deviation has also been described.

Parkinson's and Alzheimer disease are the central nervous system (CNS) disorders commonly related to neurodegeneration. These ailments are triggered by numerous hereditary and ecological factors. Neuroinflammation is a hallmark for Alzheimer's disease. The pro-inflammatory cytokines (TNF-α) and neurotoxins which are released by microglia contribute to neuroinflammation (Gregersen

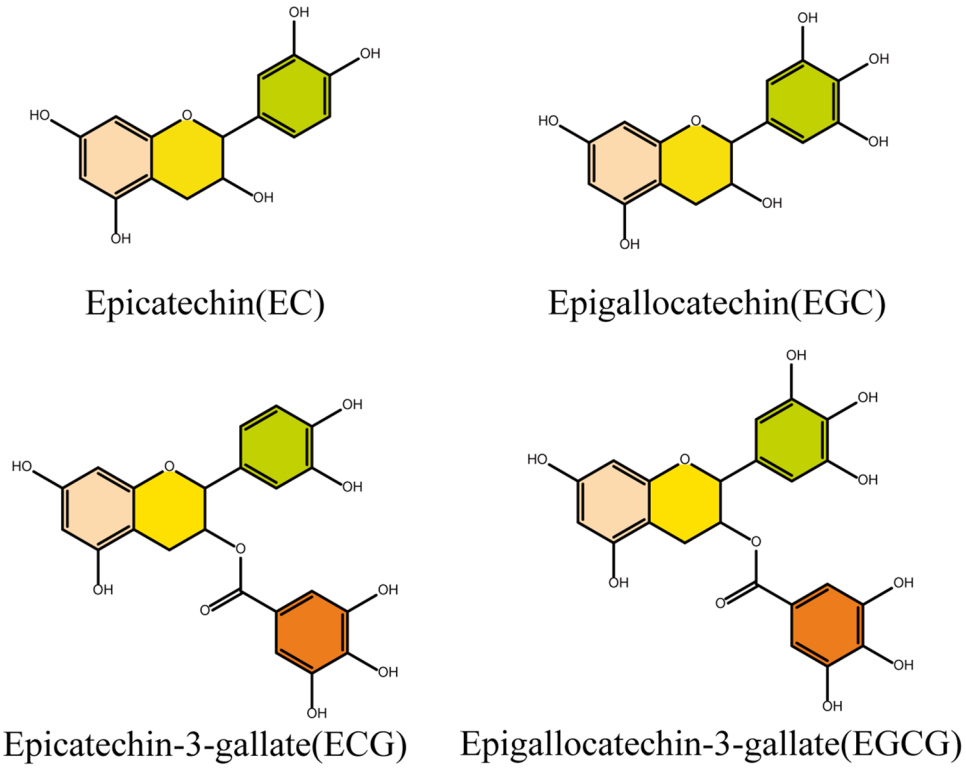

Fig. 1 Main catechin components of green tea polyphenols (chemical structure)

Table 2 Composition of key polyphenols originating in green tea

Major polyphenols	Percent of total polyphenol
Catechin	2
Epicatechin	6
EG	8–12
Epigallocatechin	18–28
EGG	32–46 or 50

MP major polyphenols, *EG* epicatechin gallate, *EGG* epigallocatechin gallate

et al. 2000). GTPs protect neural cells from microglia which induced cytotoxicity to increase TNF-α release as well as avoid microglial stimulation which may be beneficial in the treatment of Alzheimer's (Schwartz and Deczkowska 2016). GTPs are known to enhance cerebral dysfunction by anti-inflammatory and anti-oxidant properties. The second most important disease is Parkinson disease which occurs with the loss of neuronal degeneration and neurotransmitter dopamine in substantial nigra pars compacta. EGCG is known to recover dopamine degeneration which may be helpful for the patient with Parkinson's disease (Renaud et al. 2015). EGCG and GTPs have anti-angiogenic properties and a possible protective outcome against ischemic stroke through the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway. Stroke is also a major CNS disease which results in death. Some therapeutic therapies such as EGCG used against acute ischemic stroke may decrease the side effects and improve the outcomes (Zhang et al. 2017). Moreover, EGCG also enlarges neural progenitor cells (NPCs) after the ischemic stroke which are isolated from sub-ventricular region with successive unprompted recovery. GTPs are shown to have also a positive effect against different CNS diseases such as inflammatory-neurodegenerative disease (Yang et al. 2016), intra-cerebral hemorrhage, autism spectrum disease (Banji et al. 2011), prenatal and postnatal toxin contact with new born, neurogenesis and cognitive function (Ide et al. 2016). The antioxidants' fortune of GTPs recommends a possible treatment and application against these chronic inflammatory diseases.

GTPs can also have a beneficial impact on viral and bacterial infection. GTPs toughly prevent rotavirus propagation in monkey cell culture and influenza A virus in animal cell culture. It is stated that numerous flavonoids comprising EGCG and ECG prevent retrovirus human immunodeficiency virus (HIV) propagation by inhibiting reverse transcriptase, an enzyme allowing the establishment of the virus in host cells (Yamamoto et al. 1997). GTPs reduce entero-bacteria which mainly produce harmful amines and ammonia. It can also induce the percent of bifido-bacteria and lacto-bacteria which are useful for lowering the pH of intestines (Weisburger 1999). The anti-bacterial action of tea extract was also confirmed in vivo. It protected the Swiss strain of white mice challenged with *Salmonella typhimurium* at dissimilar

quantities (Bandyopadhyay et al. 2005). EGCG can also influence the inhibition of HIV infection and *Staphylococcus aureus* infections.

Since 1955, a drug named acetaminophen [N-acetyl-p-aminophenol] (APAP) is mostly used as analgesic and antipyretic but sometimes due to overdose it causes hepatic problems which may lead to death. APAP overdose is designated in 50% of acute hepatic failures and about 20% of the liver transplant cases in the USA (Yoon et al. 2016). This drug increases the toxicity of liver through many factors such as glutathione reduction (GSH), Cox-2 generation, up-regulation of apoptosis and inflammatory cytokine production. GTPs have been reported to show recognized effects including protection against obesity and inflammation. Liu et al. (2017) indicated that tea polyphenols could significantly protect rats from the fatigue, inflammation and tissue damage persuaded by severe exhaustive exercise. In recent decades, unhealthy diet including metabolic syndrome and fatty liver inflammation is the socio-economic problem. In a dose-dependent study, insertion of high-dose (1.3 mg/g) EGCG in everyday foods initiated weight loss in DSS-treated BALB/c mice (Oz et al. 2013). It has been suggested that use high dose of EGCG may require safety trials because when consumed in high amount it may have different effects, including lowering of digestion with possible application in obesity and reduction of weight. GTPs protected against hepatic injury induced by a high-fat diet in obese rats (Chung et al. 2015). Using of GTPs (10–20 mg/g) regulated liver malondialdehyde deprived of affecting cytochrome P450 2E1 mRNA expression, and reduced up-regulated hepatic Cox-2 activity and PGE2 raised levels provoked by the high-fat diet. In addition, GTPs attenuated upsurges in total hepatic short-chain fatty acids without affecting the n-6/n-3 ratio and decreased total liver arachidonic acid (Chung et al. 2015). Several studies indicated that EGCG has numerous benefits in fighting cancer, heart diseases, diabetes, and obesity, among others. Nevertheless, the poor intestinal absorbance and variability of EGCG establish the key disadvantage to use this molecule in prevention and therapy. The encapsulation of EGCG in nanocarriers leads to its improved stability and advanced therapeutic effects (Granja et al. 2017) (Fig. 1).

Possible contribution and role of nitric oxide in IBD and CVD (highlights)

Nitric oxide (NO) is a lipophilic free radical which plays a key role in regulating the homeostasis of many pharmacological, physiological and biological systems. NO is derived from L-arginine, an amino acid of nitric oxide synthase (NOS) enzyme family. Evidence from different studies suggests and found a core relation between increased concentration of NO and severity of disease especially IBD (Predonzani et al. 2015). In treating IBD, the important function of NO was proposed when a first clinical study reported by Cross and Wilson (2003) and Rachmilewitz et al. (1998) stated increased level of nitrite/nitrate in the lumen of colon, urine and plasma. When the level of NO decreases it will initiate and maintain inflammation as well as experimental IBD. Recent studies on animal models of experimental IBD have shown that constitutive and inducible NO production is useful during acute colitis (Larussa et al. 2017), constant up-regulation of NO is harmful but NO per se is not dangerous and cytotoxic for intestinal tissues (Kubes et al. 1995).

The effects of NO vary on its amount, period, and place of production as well as the nature of the target particles or molecules (Bogdan 2001). Inducible nitric oxide synthase (iNOS) produces high levels of NO which facilitates antimicrobial and antitumor activities but under normal condition catalytic nitric oxide synthase (cNOS) generates low level of NO which regulates the blood vessels but when NO is combined with superoxide anion it forms peroxynitrite which could induce colonic inflammation when administered intracolonically (Rachmilewitz et al. 1995). In a study conducted by Gawronska et al. (2017) it is proposed that high amounts of nitric oxide inhibit platelet activation in severe form of UC. In patients with UC, low platelet activation may be a result of the inhibitory action of NO. They also found that increased concentrations of IL-6, matrix metalloproteinase-9 (MMP-9) and NO may designate exacerbation of inflammation during UC. NO also stops activation of platelets and chemotaxis of neutrophils. Pro-inflammatory cytokines, IL-6, IL-17, TNF-α and IFNγ, increase production and release of NO which is considered as the indicator of inflammation in the course of IBD (Soufli et al. 2016; Rafa et al. 2013; Avdagic et al. 2013; Szypuła et al. 2009). Rectal NO is a biomarker of treatment response in IBD. Ljung et al. (2006) found that active UC and CD are associated with highly increased rectal NO levels. They also found association between TNF-α and IL-1β expression as well as iNOS expression which supports the concept that these cytokines may have a role in inducing NO production which plays a key role in the onset of IBD. The NOS2 gene encodes for the iNOS, responsible for NO production, which contributes to antimicrobial and anti-pathogenic actions. Higher levels of both iNOS- and NO-induced impairment have been detected in IBD patients. NOS2 may also have a role in a specific subset of IBD patients with severe and/or extensive colitis. A study conducted by Dhillon et al. (2014) proposes that NOS2 variants prompting higher activity of iNOS contribute to the genetic predisposition to earlier onset of IBD due to NO-induced tissue impairment and intestinal inflammation.

Arterial dysfunction in IBD patients is related to the increased production of nitric oxide, which is a well-known indicator of inflammation. The dysfunctional endothelial

system in patients with UC and CD has been observed as a sign of endothelial function (Wu et al. 2017). NO formed in the endothelium plays an important role in regulating local vasomotor as well as different vascular roles. NO plays an important role as vasoconstrictor as well as vasodilator. It has been thought that decreased bioavailability of NO is the common factor of cardiovascular disease. Local disturbance in NO bioavailability may lead to loss of heart actions as well as higher disease progression (Naseem 2005). When bioavailability of NO is impaired it can also characterize endothelial dysfunction due to decreased production of NO or increased reactive oxygen species breakdown in the earlier stages of atherosclerosis (Dobutovic et al. 2011). Three different isoforms of NOS produce NO which is mostly expressed in vascular cells where it plays an important role in structure regulation and vascular tone. The endothelium consists of all three isoforms, eNOS, nNOS and iNOS, but during inflammatory condition it has the capability to express iNOS (Tsutsui et al. 2010). Tsutsui et al. also found that eNOS system contributes to the endothelial-derived factor and H_2O_2 responses in minor vessels while serving as a NO-producing system in large arteries. Lack of NO leads to endothelial dysfunction but higher concentration of NO may lead to failure of myocardium that can cause myocyte loss which will impede myocyte contractility (Anker and Haehling 2004). The cells of the vascular endothelium transduce circulatory stimuli to the arterial wall leading to the regulation of vessel tone, hemostasis, blood pressure and vascular remodeling. The endothelium manufactures and releases NO which regulates these physiological processes. These studies have confirmed that NO has many vaso-protective functions and significant loss in availability of NO could increase the progression of cardiovascular diseases (Stephani et al. 2017; Shaparoodi et al. 2016; Hsu et al. 2017). Cumulative information of the role of iNOS in heart has motivated efforts to target NO pathway pharmacologically because NO is a key messenger molecule so far as its variety of action is concerned. The production, metabolism and functional targets of NO are shown in Fig. 2.

Green tea polyphenols attenuate inflammatory bowel disease

There is rising attention in the role of complementary and alternative medicine (CAM) in health and disease. Mostly IBD patients use CAM as a therapy. It has been found that 15% of IBD patients sought out complementary consultants for treatment associated with only 8% of those with other gastrointestinal disorders (Verhoef and Sutherland 1990). Patients inclined to practice CAM as well as traditional therapy. Herbal products and vitamins are the common agents used. Probiotics may be helpful in UC but not CD, especially in children where the adverse consequences of steroid therapy are proportionally greater (Frobes et al. 2016). CAM usages may show beneficial effects for patients with IBD. These therapies have anti-inflammatory properties, alter gut microbiota, or reduce responses to psychosocial stresses. Unfortunately, the study root for the use of these modalities often is deficient, and safety has not been assessed.

The treatment of IBD is difficult but medications are the basis for handling IBD. These are called multifactorial

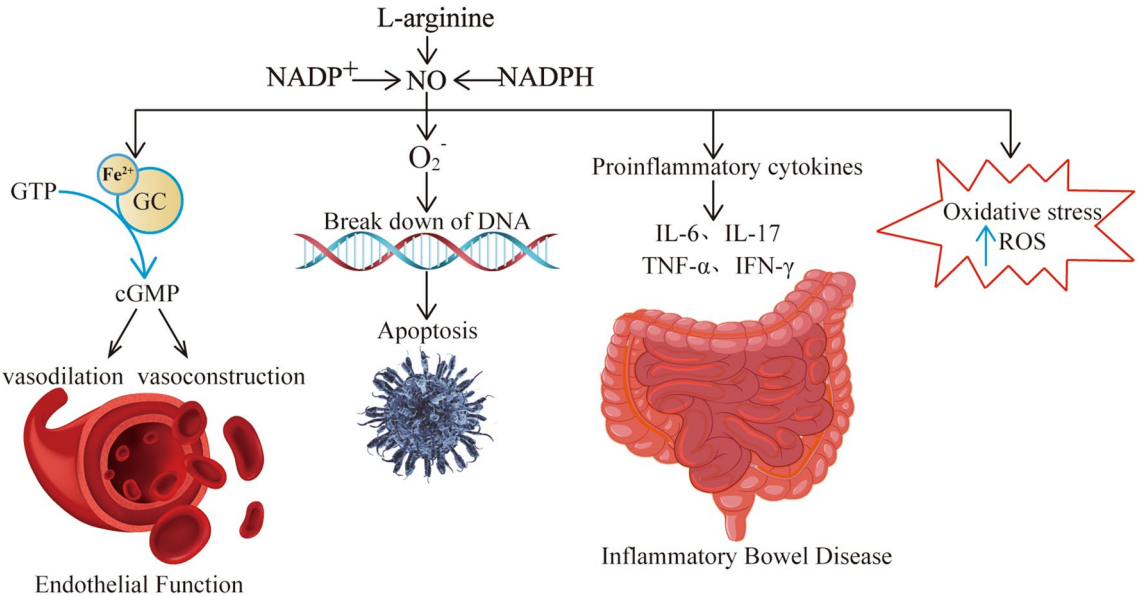

Fig. 2 The production metabolism and effective targets of NO. *NADP* nicotinamide adenine dinucleotide phosphate, *NADPH* nicotinamide adenine dinucleotide phosphate hydrogen, *cGMP* cyclic guanosine monophosphate, *ROS* reactive oxygen species

diseases mainly resulting from dysfunctional epithelial, adaptive and innate immune reaction to the microorganisms existing in the intestine (Kleinman et al. 2004). In normal gut, intestinal epithelial cells (IEC) are controlled to shelter the surface of crypts and villi. Thus, the percentage of villus height in crypt stays in a constant state as it is controlled by the apoptosis (death) pathways (Oz and Ebersole 2010). The function of intestinal epithelial barrier harms by defective apoptosis which stimulates macrophages and immune system as well as induce TNF-α production which finally leads to the disorder IBD. In Crohn's disorder patient, the mucosa is chronically stimulated because of the lamina propria lymphocytes which increase the expression of anti-apoptotic molecules. This apoptotic dysregulation activated lamina propria lymphocytes (LPL) in IEC which is a key mechanism for onset of IBD (Doering et al. 2004; Strober et al. 2002). Crohn's disease patients need enteral nutrition as well as low-quantity parenteral nutrition to improve metabolism and growth because the enteral nutrition is an effective treatment to uphold remission. Patients with CD having short bowel syndrome after wide resection of the intestines frequently depend on non-natural nutrition as a source of nutrients. Thus, benefit of dietary provision in UC is less supported and is currently not being given much attention.

The IBD patients are commonly treated with Sulfasalazine but it has many and diverse side effects, mainly lack of response, infertility and fibrosis which may lead to intestinal resection. In wild-type mice study, when comparing both the GTPs and Sulfasalazine for showing their anti-inflammatory responses, the GTPs developed less severe symptoms compared to sulfasalazine by provoking enterocolitis a disease similar Crohn's disorders (Oz et al. 2005). GTPs reduced disease action and reserved inflammatory responses in interleukin-2-deficient (IL-2) mouse models for chronic inflammatory disease. GTPs and EGCG significantly restored antioxidant concentrations and reduced colitis signs related to sulfasalazine management (Oz et al. 2013). In a rat model study, treatment with GTPs significantly attenuated diarrhea and loss of body weight, which were related to a significant amelioration of the interruption of the colonic architecture, substantial reduction of colonic myeloperoxidase (MPO) and tumor necrosis factor-α (TNF-α) production. Green tea extract also reduced the entrance of nitrotyrosine immuno-reactivity in the colon and reduced the up-regulation of intercellular adhesion molecule 1 (ICAM-1) (Mazzon et al. 2005). In another bold animal study, interleukin-2-deficient IL-2(-/-) mice fed nonpurified diet were randomly assigned to take water with GTPs (5 g/L), culture supernatants from GTP-treated mice indicated reduced unprompted interferon-gamma and TNF-α secretion and the GTPs showed less severe colitis. GTPs attenuated inflammation and intend a role for treating chronic inflammatory ailments such as IBD (Varilek et al. 2001).

GTPs had shown in in vitro studies a series of anti-inflammatory properties through inactivation of I-kB kinase complex in epithelial cells by inhibiting NF-kB pathways. EGCG downregulates TLR-4 expression through 67LR (67-kDa laminin receptor) that may be effective in treating both chronic and inflammatory diseases. Pretreatment of intestinal cells with GTPs (0.4 mg/mL) reduced TNF-α-induced IKK and NF-kB action. Gallate was required to stop IKK stimulation and TNF-α initiation. When intestinal epithelial cells were rapidly transfected with NF-kB-inducing kinase (NIK) for nonstop IKK stimulation, EGCG ominously declined IKK action in these NIK-transfected epithelia (Yang et al. 2001). Thus, GTPs and definitely EGCG, but not any other polyphenols compounds such as (EC, EGC, ECG), were stated as active inhibitors of IKK action and as natural anti-inflammatory agents (Fig. 3).

Flavonoids have antioxidant properties and have been described to suppress inflammation in vivo and in vitro so it may also reduce the severity of IBD (Mizoguchi 2012; Cano et al. 2014). (-)-Epigallocatechin-3-gallate (EGCG) has been shown to have cancer-preventive affect in vitro and in vivo. Catechins may stabilize the structure of the gastrointestinal micro-ecological environment via promoting the proliferation of beneficial intestinal bacteria and regulating the balance of intestinal flora, so as to relieve the IBD (Fan et al. 2017). These studies support possible beneficial properties of GTP addition in diets for IBD patients.

Green tea polyphenols: a prescribed therapy for intestinal cancer (IC)

Intake of GTPs (*Camellia sinensis*) has been suggested to have useful health effects, including cancer prevention. Many studies have recognized that the active cancer-preventive ingredients in green tea are a group of polyphenols. GTPs have been shown to induce apoptosis in numerous cancer cells and stop experimental carcinogenesis in many animal models. A study conducted by Mbuthia et al. (2017) found that green, black and purple tea induced anti-cancer responses by the induction of caspases which induced the apoptotic pathway. Further, the outcomes of some epidemiological studies have recommended that GTP intake has an inverse association with cancer occurrence in humans. Extensive studies have proven that there are two kinds of substances in green tea, polyphenols and caffeine, which are responsible for cancer-defensive actions (Conney et al. 2007). It has been described that GTPs improved colon carcinogenesis in rat prototypes. Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) of unknown cause, which may grow to colorectal cancer in chronic and persistent

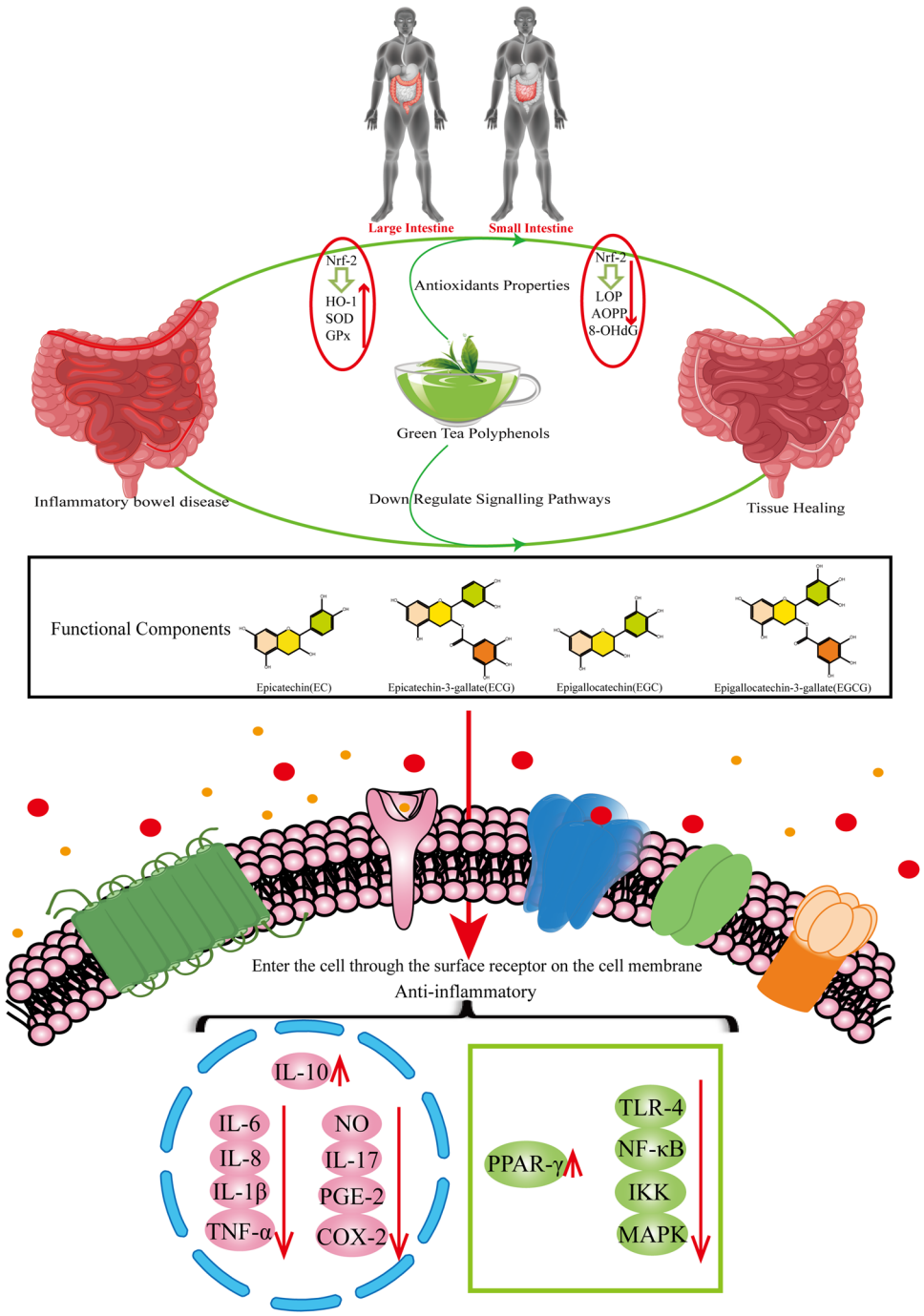

Fig. 3 The mechanisms through which green tea polyphenols may positively or negatively inhibit the development of inflammatory bowel disease. *AOPP* advanced oxidation protein end-products, *COX-2* cyclooxygenase 2, *GPx* glutathione peroxidase, *IL* interleukin, *IKK* nuclear factor-κB (IκB) kinase, *MAPK* mitogen-activated protein kinase, *Nrf-2* nuclear factor (erythroid-derived 2)-like 2, *NF-B* nuclear factor kappa B, *OHdG* 8-hydroxy-2-deoxyguanosine, *PPARγ* peroxisome proliferator-activated receptor gamma, *SOD* superoxide dismutase, *TNF-* tumor necrosis factor alpha, *TLR-4* Toll-like receptor-4

cases. GTPs show carcinogenic properties in animal models and many organs, including stomach, skin, prostate, colon, small intestine, lungs and bladder (Yang and wang 2011). Further studies have identified EGCG in GTPs, as the most strong chemoprotective mediator that can induce apoptosis, defeat the creation and development of human cancers including colorectal cancers (CRC). For CRC, the most effective drugs are aspirin and NSAIDS but also carry some significant risk of toxicity like intestinal hemorrhage, dyspepsia and ulcers (Silagy et al. 1993). In a mouse model study, synergistic chemo-preventive outcome of GTPs directed with sulindac against intermediate and late stages of colon cancer, which directly effects on the betacatenin/Tcf signaling pathway (Orner et al. 2002). Further, GTPs also inhibit stimulation of RTKs EGFR, HER2 and HER3, which are downstream signaling pathways and play important role in the onset of CRC. EGCG also inhibited this critical RTK pathway involved in cell propagation (Shimizu et al. 2005). Stimulation of apoptosis in colon cancer cells has also been detected via the TGF-beta superfamily protein, NAG-1

(NSAIDS activated gene). In colon epithelial cells, EGCG downregulated the genes which are involved in inflammatory pathways which comprise reduction of chemokine production (Porath et al. 2005). Intake of GTPs using the model of rats and mice has shown a positive effect by inhibiting lung carcinogenesis (Ju et al. 2007). Further, apoptosis exact in tumors and not in typical lung tissues were induced by EGCG action while pro-proliferation signaling (i.e., c-Jun and phospho-ERK1/2) in tumors were decreased (Lu et al. 2006). Multiple studies on lung cancer show that GTPs inhibit lung carcinogenesis in diverse aspects.

There is indication from epidemiological and preclinical research that precise components of GTPs such as EGCG are linked to CRC, lung and inhibition of other cancers, but the specific mechanisms are still indescribable. It has been shown that dietary polyphenolic compounds act at numerous key steps in carcinogenesis and, therefore, a role in colorectal cancer prevention (Little et al. 2017). EGCG regulates cancer development; prevention of cancer through nutrients needs still more effort because this is the best and easy way of therapy. Table 2 demonstrates cancer in different organs and their possible inhibition by GTPs.

Possible adverse effects of green tea polyphenols

The intake of green tea has been shown to have many physiological and pharmacological health benefits; however, there are also some harmful effects. Recently, a increased growth of recurrent *Clostridium difficile* (C. diff) is shown, which is known to be related to the intake of GTPs. In some clinical cases many hospitals show that patients with C. diff who drank GTPs with regular infection may be exposed to antimicrobial effects of tea. The facultative pathogens may be increased and the normal microbiome will be reduced in the gut of those patients with frequent use of tea (Evans et al. 2016). Further research is needed to confirm these findings as a future goal.

Tea is a diuretic agent. In a mice model when fed high-cholesterol diets, the GTPs intake for long time may increase hepatic oxidative stress with alters bile acid production resulting in inflammatory hepatic injury (Hirsch et al. 2016). Weight loss may be considered a useful as well as an unsafe effect of high-dose GTPs 2.6 mg/g and 1.3 mg/kg (Oz et al. 2013), and 3.2 mg/kg (Bitzer et al. 2016). Tea also has antimicrobial and antifungal properties but bacterial contamination occurs from unpasteurized GTPs (Ting et al. 2013).

Prolonged consumption of tea enhanced the psychomotor and cognitive performance of adults but disrupts sleep quality at night like intake of coffee (McKay and Blumberg 2002; Lin et al. 2003). The patients with heart problems, breast feeding and pregnant women have been advised not to drink more than two cups of tea (GTPs) daily as it causes increased rhythm of heart. Due to its diuretic effect it is useful to control its high consumption (Bruneton 2001).

Conclusions and future perspectives

In summary, we propose that GTPs are potentially effective for use in ameliorating IBD and associated abnormal conditions, with its recognized anti-inflammatory, antioxidative, and anti-bacterial properties. GTPs are shown to have reduced inflammatory reactions in signaling pathways, by downregulating IKK, NF-kB and cytokines like TNF-α, inflammatory markers, Cox-2 and Bcl-2, to protect against hepatic and many other chronic and inflammatory disorders. GTPs also have shown to reduce metabolic syndrome and obesity. Moreover, several studies suggested that GTPs have prebiotic effects which developed strong and healthy microbiota (i.e., Bacteroidetes) that may exert anti-inflammatory effects through short-chain fatty acid production or via direct effect on occludin and claudin proteins. Finally, GTPs maybe also stabilize intestinal flora and help in the recovery of IBD.

Additionally, animal and human experiments are required to explore the exact activities and possible mechanisms, even down to the molecular level that GTPs could in fact establish a defensive approach and complementary treatment for suffering from IBD or associated diseases and whether individual polyphenols or rather composite combinations such as extracts are also effective and promising to ameliorate this ailment.

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Compliance with ethical standards

Conflict of interest No potential conflict of interest was reported by the authors.

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