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Green tea: A possibility in the therapeutic approach of inflammatory bowel diseases?
Green tea and inflammatory bowel diseases

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ABSTRACT

Objective: this review aimed to investigate the effects of green tea polyphenols (GTP) in Ulcerative colitis and Crohn´s Disease.
Materials and Methods: The databases used were MEDLINE–and EMBASE (October 2009 to September 2018). Studies that reported the use of green tea and its effects on IBD were included.
Results: Ten articles were included in this review.
Discussion: GTP play a role in reducing TNF-α, Interleukin 1β (IL-1β), IL-6, IL-8, and 17; downregulate cyclooxygenase-mediated I kappa B kinase and transcription of NFκB. They regulate the pathways mediated by the Nuclear erythroid 2-related factor 2, mitogen-activated protein kinases, and signal transducer and the activator of transcription 1/3, and also minimize the lipid peroxidation. Furthermore, GTP can stimulate antioxidant enzymes. These actions reduce inflammatory and oxidant patterns in IBD resulting in improvement of the disease scores.
Conclusions: We suggest that professionals and researchers take into account the use of GTP in further researches and in clinical practice in order to verify the real effects in humans.

1. Introduction

There is a growing interest in natural polyphenols obtained from plants due to their therapeutic properties. Polyphenols are compounds that result from secondary metabolism and hold significant potential for human health. Green tea (GT) is a worldwide consumed beverage produced with the leaves of *Camellia sinensis* and its polyphenols (GTP) have been reputable in the prevention or treatment of several diseases (Fig. 1).[1,2]

GT represents a rich source of flavonoids, also named catechins, that also include phenolic acid, theobromine, theophylline, theanine, and caffeine. Epigallocatechin-3-gallate (EGCG) is the most relevant catechin (32–50%) found in green tea leaves, but others such as epicatechin (EC) (6%), epigallocatechin (EGC) (18–28%), and epicatechin-3-gallate (ECG) (8–12%) are also present. These constituents, that may represent 30% of the dry weight of the leaves, have been considered to promote significant antioxidant and anti-inflammatory properties and can help in the prevention and the treatment of pathologies such as diabetes, obesity, heart diseases, cancer and inflammatory diseases.[3–6]

Inflammatory processes are biological responses to chemical, mechanical, or infectious stimuli with the aim of localized protection. Depending on the characteristics and type of the response and mediators that are involved, the inflammatory process is designated to be acute or chronic. Some conditions such as Inflammatory Bowel Diseases (IBD) are related to longstanding exposure to inflammatory cytokines such as Interleukin-1 β (IL-1 β), IL-6, IL-8, Tumor Necrosis Factor-α (TNF-α), and Interferon Gamma (IFN- γ). These cytokines lead to an unbalanced inflammatory status resulting in a chronic inflammatory process that interferes with the homeostasis of the gastrointestinal tract leading to diarrhea, bloating, gas, bleeding, abdominal pain, and increased risk of cancer.[7,8]

Oxidative stress is also associated with inflammatory responses and thus, with IBD. This oxidative process results from the increase of free radicals in relation to the antioxidant mechanisms. It is capable of

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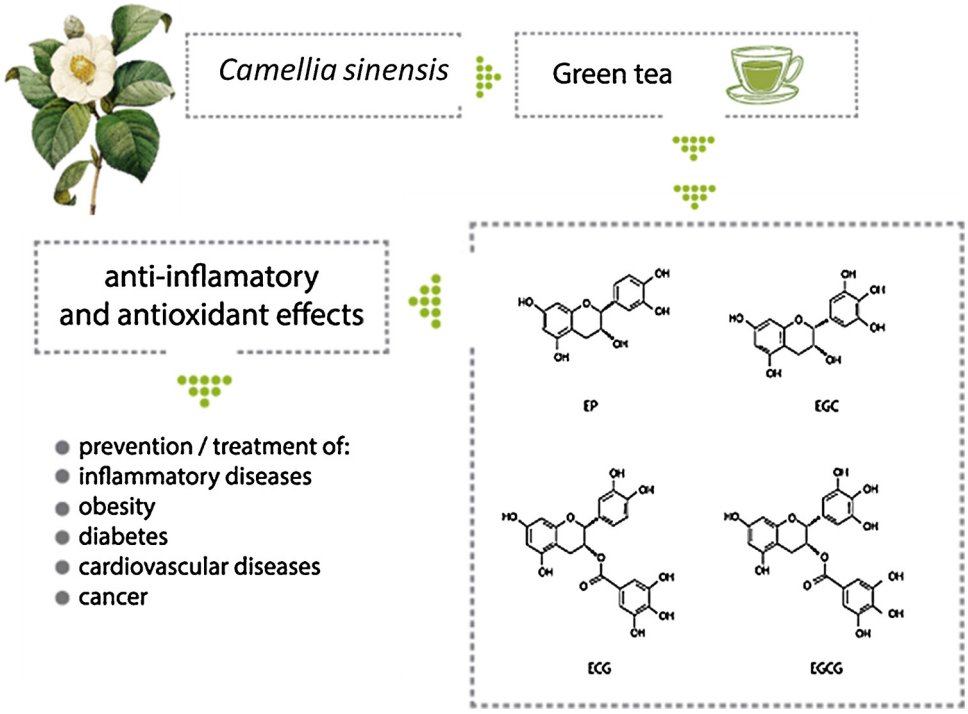

Fig. 1. Structure of the main compounds found in *Camellia sinensis* (green tea) and its effects in human health. EP: epicatechin; ECG: Epicatechin-3-gallate; EGC: Epigallocatechin; EGCG: Epigallocatechin-3-gallate (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

altering lipids, proteins and DNA ensuing injury via their oxidation. It can as well interfere with apoptosis and carcinogenic cell transformation. Studies have shown that oxidative stress is one of the most important factors that are envolved in the pathophysiology of IBD due to several mechanisms. Damages to the mucosal layer and increases pathogen invasion, stimulating inflammatory responses and initiates the disease. Furthermore, free radicals are capable of accelerating cell damages due to modifications in the functions of proteins and lead to lipid peroxidation. They are also related to intestinal dysbiosis.[9,10]

The scientific literature shows that GTP has been reported to exhibit both anti-inflammatory and antioxidant properties. This review aims to evaluate the effects of this plant in Ulcerative colitis (UC) and Crohn´s Disease (CD), that represent the main entities of the IBD.

2. Methods

2.1. Data sources

The authors of this review have searched the MEDLINE–PubMed (National Library of Medicine, National Institutes of Health) and EMBASE (from October 2009 to September 2018) following PRISMA (Preferred Reporting Items for a Systematic Review and Meta-Analysis) guidelines. This review was performed to answer the following focused question: *Can green tea offer a novel therapeutic approach for IBD?*

2.2. Search

The search included randomized placebo-controlled trials, controlled clinical trial, double-blind, randomized controlled study, retrospective case-controlled study, prospective cross-sectional study, and case report. The combination of terms that we used for this search was *green tea* and *IBD*, *Camellia sinensis* and *IBD*." We also combined the terms *green tea* and *C. sinensis* with *Ulcerative colitis* and *Crohn´s Disease.*

Based on the list of references that resulted from the combination of these terms, we selected 10 articles that included animal and human models to build Table 1. The flow diagram shows the selection of the articles and the inclusion and exclusion studies (Fig. 2). Other studies on IBD, inflammation, green tea composition and effects were used in the discussion section.

2.3. Eligible criteria and study selection

Our search included quantitative and qualitative studies that reported the use of GT and its effects on IBD. All articles associating green tea and IBD (in the last ten years) were included, except reviews, communication letters, and articles not in English.

2.4. Data extraction

Independent extraction of articles was carried out by two authors that used the above described predefined data. Data were extracted from eligible articles that included date, author, study design, sample size, gender, symptoms-related to IBD and use of GT.

Only original articles were selected. The exclusion criteria for this search were reviews, studies not in English, case reports, editorials, and poster presentations (Reviews were used to help in the discussion but were not included in Table 1).

3. Results

In the past ten years, nine studies showed the potential role of GT or its compounds in IBD. All of these studies were summarized in Table 1.[11–20]

4. Discussion

4.1. Pathophysiological aspects of IBD

IBD is an idiopathic inflammatory alteration of the gastrointestinal tract that may profoundly interfere with quality of life. The inflammatory pathways may be associated with the hypersensitive response of the system to the intestinal microbiota, and the course of the disease consists in remitting and relapsing phases.[21,22]

There is a growing consensus that IBD incidence is increasing in incidence globally. Although the causes are not entirely understood, abnormal gut microbiota, environment, genetic susceptibility,

Table 1
Properties of green tea or its derivatives in the therapeutic approach of inflammatory bowel disease.

Reference	Model	Major findings	Conclusions
Shapira et al.[11]	Wistar rats with colitis (induction by TNBS) and 20 UC subjects that received combined therapy.	GT did not promote significant modifications in colitis score in the rats. Substantial improvement was observed in the overall assessment of the patients: improvement of the symptoms, reduction in the in abdominal pain, amount of blood in stool/number of weekly stools. There was an endoscopic improvement, and many patients achieved complete remission (combined therapy with curcumin, GT and selenium)	The combined therapy may be useful as a first-line or as adjuvant therapy in patients with mild-to-moderate UC. No substantial adverse events were observed with the use of the combined therapy.
Gerges et al. [12]	Sprague-Dawley rat model of colitis (induction by TNBS).	Epigallocatechin-3-gallate (EGCG) was used daily for one week after the induction of UC. Treated animals showed a significant improvement in the histological parameters and strong anti-oxidant and anti-inflammatory effects (due to the reduction of inflammatory cytokines), and improved UC and stabilized the mast cells.	The actions of EGCG occurred mainly through the NF-kB pathway.
Bitzer et al. [13]	Mice model of UC (induced by DSS).	EGCG reduced colitis induced spleen enlargement and colon shortening and reduced colonic levels of IL-1β, IL-6, TNF-α, and colonic lipid peroxides. It also decreased gastrointestinal permeability induced by colitis but promoted higher body weight loss.	EGCG promotes anti-inflammatory and antioxidant actions, but it also may promote weight loss.
Yeoh et al [14]	C57BL/6 J mice model for colitis (DSS).	EGCG inhibited the activity of MPO activity in vitro and inhibited the activity of LPO; led to a reduction of pro-inflammatory mediators related to gut inflammation; decreased MPO (muco-protective effects) + H2O2-mediated bacterial killing.	The actions of EGCG depend on the environment in the gut. Due to the anti-inflammatory effects of EGCG, it can be considered in the treatment of IBD.
Panduragan et al. [15]	BALB/c mice model for colitis (induced by DSS).	GA attenuated the colon shortening and the disease activity index; decreased histopathological injury and significantly reduced IL-21 and IL-23. GA upregulated the synthesis of Nrf2 and its targets.	GA showed promising results in the treatment of UC and can be a new therapeutic adjuvant to immunosuppressants, corticosteroids, and anti-TNF-α agents.
Dryden et al.[16]	Twenty UC patients.	UC patients treated with a pharmaceutical therapeutic agent with well-characterized levels of catechins (*Polyphenon E*®) showed significant improvement in the disease activity. The response rate was 66.7% in the treated group and 0% in the placebo group.	*Polyphenon E*® may be a viable therapy for UC patients who were refractory to azathioprine and 5-aminosalicylic with low side effects.
Oz et al. [17]	BALB/c mice with colitis (induced by DSS) and IL-10 deficient mice exposed to normal microbiota.	Both groups (UC and DC mimic group) showed a significant reduction in colonic and hepatic antioxidants. GTP, EGCG, and SF decreased injury in colon and in histological scores for IBD. The reduction was also observed in serum amyloid A, IL-6, and TNF-α. GTP and EGCG induced restoration of antioxidants levels.	GTP and EGCG increased antioxidants levels and decreased inflammatory cytokines and attenuated the colitis similarly to SF.
Barnett et al [18]	24 male Mdr1a−/− mice (treatment with GTP).	The colonic histological injury score of animals treated with GTP was significantly inferior to the control group. There was a reduced abundance of transcripts and proteins related to the inflammatory process. There was an increase in xenobiotic metabolism in the treated group.	The use of GTP may improve intestinal inflammation in the colon and reduce symptoms of IBD.
Brückner et al. [19]	Female C57BL/6 mice (DSS-model of colitis) treated with EGCG + piperine.	EGCG plus piperine reduces the weight loss, increase survival rates, and improve the clinical course of colitis (due to less histological alterations in the colon, a decrease of MAL and MPO in colon tissue, and an increase in the activity of antioxidant enzymes such as SOD and GSH). Similar results were found *in vitro*.	EGCG produces anti-inflammatory effects and may bring benefits in colitis due to the antioxidative potential.
Byrav et al [20]	Wistar rats (GT / SF).	The use of GT alone and in combination with sulfasalazine decreased inflammation due to the decrease of lipid peroxidation and TNF-α. There was an improvement in the morphological and histopathological scores.	The combination of GT plus sulfasalazine showed higher efficiency compared to the single drug treatment.

UC: Ulcerative colitis; CD: Chron´s Disease; TNBS: 2.4.6 trinitrobenzene sulfonic acid; GT: Green Tea; GTP: Green Tea polyphenols; IBD: inflammatory bowel disease; EGCG: Epigallocatechin-3-gallate; DSS: dextran sulfate sodium; IL: Interleukin; TNF-α: tumor necrosis factor-α; MPO: myeloperoxidase; LPO: lactoperoxidase; GA: Gallic acid; Nrf: Nuclear erythroid 2-related factor 2; MAL: malondialdehyde; PPAR-α: Peroxisome proliferator-activated receptor-α; SOD: superoxide dismutase; GSH: glutathione peroxidase; SF: sulfasalazine.

disruption in the consumption of fats, sugar, and additives, insufficiency of vitamin D, and oxidative stress are possibly related to the development of IBD.[23]

CD and UC may be distinguished by pathological and histological dissemblance. In UC a stratified pattern of inflammation from the colon to rectum can be observed. This pattern is limited to mucosal layer progressing up the colon from the rectum continuously, and the terminal ileum is commonly not affected. On the other hand, the inflammatory pattern in CD occurs in skipped areas from mouth to anus (*cobblestone* pattern), with transmural inflammation. In CD patients, the terminal ileum is usually affected. Both UC and CD may present with periods of remission and flares.[23],[24]

Some studies have shown that there is an association between modification in the microbiome and IBD. Also, IBD patients present a defective epithelial barrier increasing the intestinal permeability and a reduction in the release of antimicrobial peptides. The mucus layer covering the epithelium and the intestinal epithelium in which enterocytes, goblet cells and Paneth cells reside, act as a physical barrier against intestinal bacteria and food antigens.[25]

Innate and adaptative immunity is also involved with the

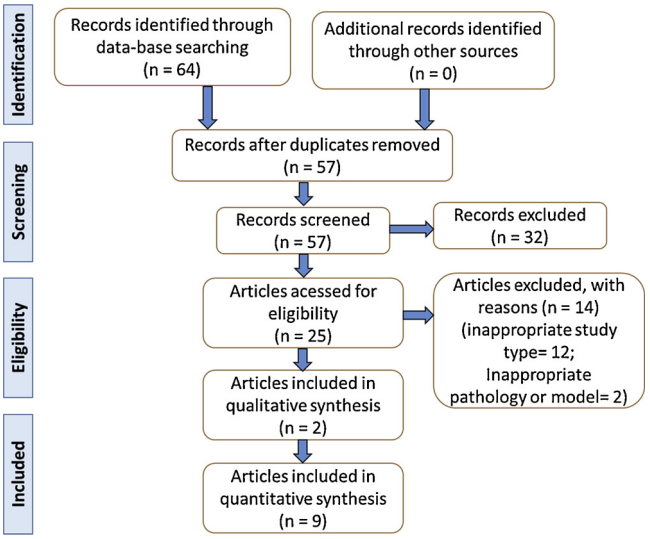

Fig. 2. Literature search Flow diagram (based on PRISMA, 2009).

inflammatory events in IBD. Innate immunity represents the first and non-specific line of defense against the pathogen and is mediated by epithelial and dendritic cells, neutrophils, macrophages, monocytes, and natural killer cells (NKT). This mechanism of defense is initiated after the recognition of microbial antigens by pattern recognition receptors such as NOD-like (NOD) and Toll-like receptors (TLR) that are both modified in IBD patients. Mutations of NOD2 results in inappropriate activation of NFκB.[26]

IBD is possibly related to a reduction or loss in the adaptative immune tolerance to antigens in the colon. This intolerance triggers the release of cytokines resulting in the influx of immune cells. T helper cells such as Th1, Th2, Th9, Th17 and a loss of T regulatory cells (Treg) are normally linked to IBD (Fig. 3). Th1 and Th17 are generally activated in CD patients and TH2 and Th9 in UC patient. Furthermore, innate lymphoid cells and NKT may also contribute to IBD consequences.[27]

The activation of Th1 triggered by IL-12 and IL-18 is related to the release of TNF-α, IFN-γ, and IL-2.[28] NKT-cells mediate the disrupted activation of Th2 through the release of IL-4, IL-5, IL-10, and IL-13. Th9 activation culminates with the release of IL-9 through transforming growth factor β (TGF-β) and IL-4, leading to the impairment of the intestinal permeability, barrier function, and wound healing. The activation of Th17 occurs by IL-6 and TGF-β and results in the production of IL-17 A, IL-17 F, IL-21, and IL-22. IL-17 A and IL-17 F induce the recruitment, activation, and migration of granulocytes and activation of epithelial and endothelial cells, and macrophages. Tregs are associated with the expression of Foxp3 and immune homeostasis due to the release of IL-10 and TGF-β that exhibit anti-inflammatory properties.[29]

The understanding of the role of the above-described cells is crucial for the therapeutic approach of the IBD.

4.2. GT and IBD

The standard drugs used in the treatment of IBD are generally associated with many side effects, lack of response in many patients and can be related to other comorbidities. Several authors have shown that some compounds may be useful in improving the quality of life of the IBD patients once they reduce the inflammation (Fig. 3) and oxidative stress. GTP may be involved with health benefits such as anti-inflammatory, antioxidant, and anticarcinogenic effects. These molecules exhibit a role in reducing TNF-α, downregulating cyclooxygenase (Cox-2)-mediated I kappa B kinase (IKK) and transcription of NFκB. They also regulate the pathways mediated by the Nuclear erythroid 2-related factor 2 (Nrf2), mitogen-activated protein kinases (MAPKs), and signal transducer and the activator of transcription 1/3 (STAT1/3). They also promote benefical roles as inhibitors of colorectal cancer and inducers of apoptosis.[1,18]

Furthermore, GTP may diminish serum levels of triglycerides. EGCG promotes downregulation of TLR-4 expression. Catechins are capable of stabilizing the structure of the gastrointestinal microbiota due to the stimulation of beneficial bacteria environment. Furthermore, GTP may also promote prebiotic effects which can induce the development of a healthy microbiota or may act on the regulation of occludin and claudin. Beyond the actions mentioned above, GTP may also positively interfere in cell signaling, infiltration and proliferation, and in the gap and tight junctions in the epithelium.[2,30,31]

EGCG significantly improves antioxidant levels and diminishes colitis signs associated with sulfasalazine 20 and is an antagonist of oxidative stress in lymphocytes of both IBD and healthy individuals.[32]

This review sheds light the main effects of GT on IBD are related to antioxidant, anti-inflammatory, in cell signaling, infiltration, and proliferation. (Table 1). Shapira et al.[11] showed that the use of GT ameliorates IBD symptoms in Wistar rats model of colitis and in UC patients (most of them were already receiving mesalamine). They observed that in 70% of the patients, 45% went into total remission, 20% experienced remarkable improvement and 5% experienced moderate amelioration at the end of the trial. Byrav et al.[20] also used Wistar rats to evaluate the effects of GT and showed that the concentration of 70 mg/kg improved IBD and the combination with sulfasalazine was more efficient than the use of a single-drug treatment.

Dryden et al.[16] investigated the effects of GT (pharmaceutical agent named Polyphenon E®) in the first randomized, placebo-controlled trial in UC patients and observed that this therapy produced a 66.7% of response according to improvement in the UC disease activity index and 0% in the placebo group. They concluded that *Polyphenon E®* provided convincing initial evidence for an effective treatment for IBD patients.

In another study, authors investigated the effect of EGCG in Sprague-Dawley rats with colitis and found significant histological improvement, less expression of IL-6, TNF-α, and NFkB, and anti-oxidant compounds improved colitis and led to stabilization of mast cells.[12] In a mouse model, Bitzer et al.[13] showed that EGCG significantly prevented colon shortening and inflammation and reduced levels of IL-1β, IL-6, TNF-α, monocyte chemotactic protein-1 (MCP-1).

Brucker et al.[19] and Yeoh et al.[14] studied the effects of EGCG in C57BL/6 mice model. In the research performed by Brucker et al.[19] ECGC was co-administered with the alkaloid piperine increasing the bioavailability of the first component. This combination also led to a significant reduction in body weight loss and improved inflammation and oxidative stress due to a reduction in IL-8, malondialdehyde, and myeloperoxidase, and an increase in the expression of superoxide dismutase and glutathione peroxidase. Yeoh et al.[14] demonstrated that EGCG could reduce the activity of myeloperoxidase in vitro and in vivo, and inhibited the peroxidase-catalyzed reaction due to the reversion of the reactive peroxidase heme, indicating that EGCG may exert mucoprotection and counter-regulatory factors.

Panduragan et al.[15] evaluated the effects of galic acid in a BALB/c mice model of colitis and observed that GA significantly reduced the disease activity index, colon shortening, injury, and inflammatory process due to the reduction in the release of IL-21 and IL-23. On the other hand, GA stimulated the expression of Nrf2, Superoxide dismutase, Catalase, glutathione peroxidase, and glutathione reductase, indicating it has protected effect in colitis.

Oz et al.[17] compared the effects of GT, ECGC, and sulfasalazine in a BALB/c mice model and observed that both GTP and sulfasalazine might play a parallel role as an anti-inflammatory in colitis due to the reduction in IL-6, TNF-α, and serum amyloid A.

In another study, a multidrug resistance targeted mutation (Mdr1a−/−) mouse model for IBD was evaluated after a treatment with a diet rich in GTP. The diet promoted a significant improvement in the histological injury score and could inhibit the fibrogenesis pathways

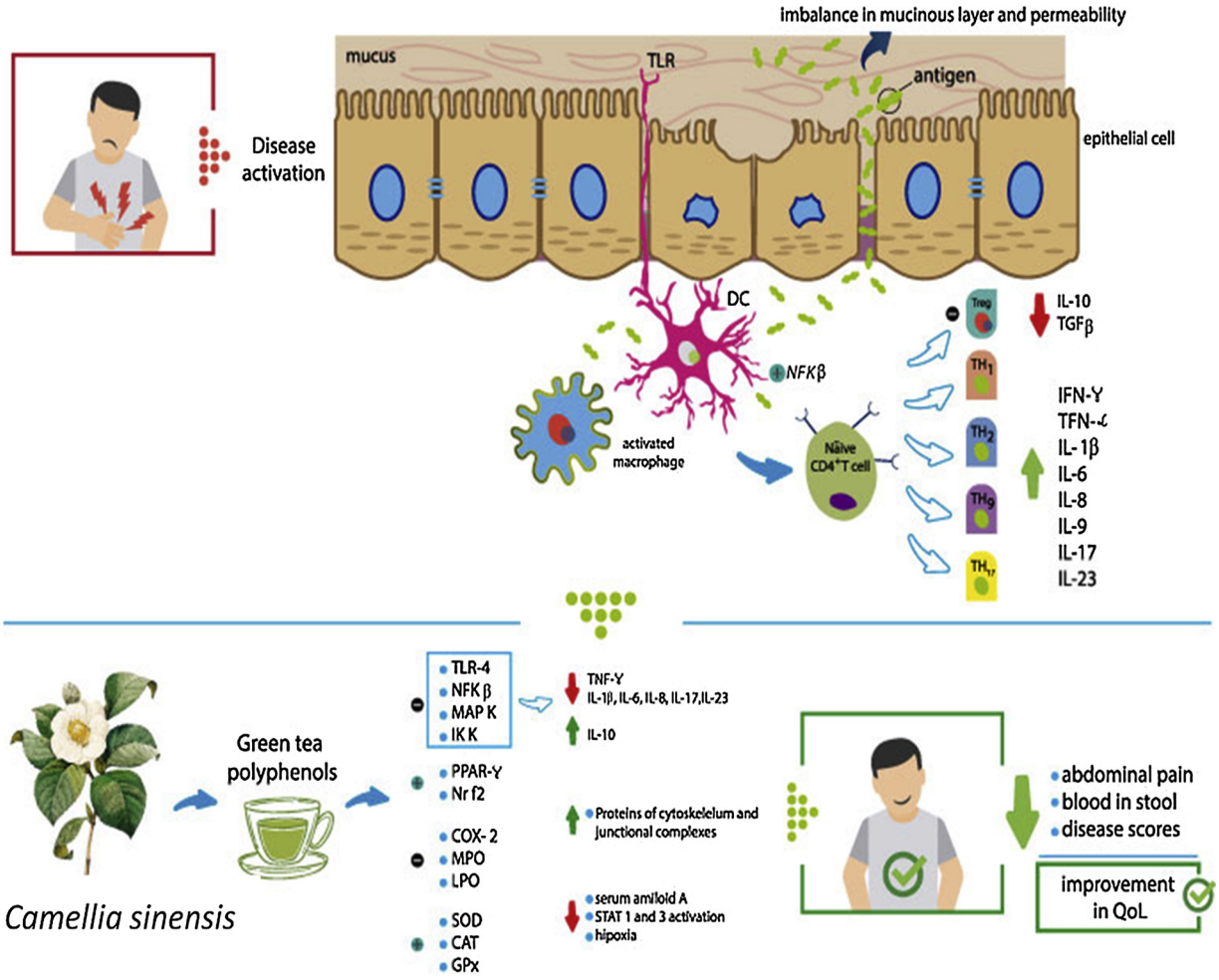

Fig. 3. In the IBD flares, the inadequate activation of the immune system leads to decrease in the expression of Treg cells and increase in the expression of TH1, TH2, TH9 and TH17, resulting in augmented release of IFN-γ, TNF-α and pro-inflammatory interleukins such as IL-1β, IL-6, IL-8, IL-9 and IL-17.

in colon tissue and affected the stimulation of many pathways associated with the activation of the peroxisome proliferator-activated receptor (PPAR)α/retinoid X receptor. Modulation of several proteins related to the immune response, inflammation and cellular stress was also reported. Up-regulation of proteins related to junctional complexes was also observed, as well as the downregulation of proteins linked to hypoxia in the cardiovascular system, tight junction, and calcium signaling. These results suggested that the use of GT may be helpful in the treatment of IBD (Barnett et al.[18]).

The above results indicate that the use of GT and EGCG, alone or co-administered with other compounds, has potential to be used in the therapeutic approach of IBD patients,[33] but appropriate nutrient support is necessary to mitigate the reduction in food intake.

5. Conclusion

A plethora of Complementary Alternative Medicines is currently being studied to manage IBD. GTP are implicated in many aspects of the inflammatory processes and severity of symptoms that afflict patients once can promote antioxidant and anti-inflammatory effects. These properties occur due to the downregulation of NFkB, IKK, TNF-α, IL-1β, and other cytokines, and due to the prebiotic effects.

For these reasons, we suggest that health professionals and researches in the field take into account the use of these compounds in clinical practice and further researches in order to verify their effect clinically.

Moreover, other investigations are necessary to establish the safe doses of GT that should be used in the remission or during the flares with the purpose of constructing an ideal protocol of supplementation.

Disclosure statement

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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