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Dietary polyphenols in the treatment of inflammatory bowel diseases

Açelya Gül Koyuncu [1], Elvan Yılmaz Akyüz [2]

[1] Yeditepe University, Faculty of Health Sciences, Department of Nutrition and Dietetics İstanbul, Turkey
[2] University of Health Sciences, Hamidiye Faculty of Health Sciences, Department of Nutrition and Dietetics, İstanbul, Turkey

ORCID ID of the author(s)
AGK: 0000-0003-1776-1829
EYA: 0000-0002-1878-9412

Corresponding Author
Açelya Gül Koyuncu
Yeditepe University, Faculty of Health Sciences, Department of Nutrition and Dietetics
İstanbul, Turkey
E-mail: acelya.gul@yeditepe.edu.tr

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Abstract

Ulcerative colitis and Crohn's disease, caused by chronic inflammation in the digestive tract, are inflammatory bowel diseases and have similar symptoms. Abnormal immune responses play a pretty important role in the pathogenesis of the disease. Proinflammatory mediators trigger inflammation, stimulate cell signaling molecules, and induce disease onset. Corticosteroids, anti-tumor necrosis factor-α antibodies, and immunosuppressants are some drugs used to treat the disease. However, these drugs have some side effects. In addition, surgical methods might be used in the treatment, but these methods may have some complications. Due to the negative impact on treatment options, alternative methods for reliable, inexpensive, and effective treatment are being sought. Secondary plant compounds with an aromatic or phenolic ring structure, so-called polyphenols or phenolic compounds, may modulate cellular signaling pathways and reduce intestinal inflammation due to their antioxidant and anti-inflammatory effects. Polyphenols may be evaluated as alternative methods for inflammatory bowel disease based on these properties. This review aims to investigate the effect of some polyphenols on inflammatory bowel disease.

Keywords: Inflammatory bowel diseases, Ulcerative colitis, Crohn's disease, Polyphenols

Introduction

Inflammatory bowel disease (IBD) is a condition characterized by chronic inflammation in the gastrointestinal tract. It usually displays involvement in the bowel [1]. The disease includes phases of relapse and remission. It is also considered a progressive disease in recent years [2].

IBD is mainly classified as ulcerative colitis (UC) or Crohn's disease (CD) based on clinical and pathological features [1]. CD and UC cause indigestion and inflammation in the gastrointestinal tract [3]. CD may occur anywhere from the mouth to the anus and is characterized by transmural inflammation [4]. It is usually seen in the terminal ileum, cecum, perianal region, and colon, but intermittent lesions may be seen in any part of the intestine [5]. On the other hand, UC originates in the rectum and involves the entire colon. It also causes superficial damage to the intestinal wall by leading to mucosal inflammation [6].

The incidence of IBD has been increasing day by day in recent years [7]. While the incidence of IBD in developed Western countries has been high in the past, it has recently increased in developing countries such as Asia and South America [7–9]. This increase is considered to be due to changes in lifestyle and eating habits due to industrialization and Westernization [10].

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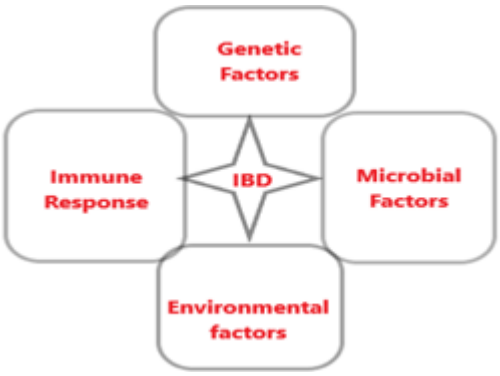
Etiology and symptoms of IBD

The disease is associated with immune system dysregulation, altered gut microflora, disrupted digestive mucosal barrier, altered oxidative stress, and increased permeability [11]. Figure 1 shows these factors that affect the etiology of IBD [8].

Figure 1: Factors affecting the etiology of IBD



Dysfunction of the mucosal barrier induces intestinal permeability and causes luminal contents to leak into underlying tissues [12]. In addition, there is an increase in free radicals, proteolytic enzymes, and cytokines in IBD. This condition causes inflammation, abdominal pain, bloody stools, weight loss, diarrhea, and ulcers [5]. Meanwhile, the adaptive immune response triggers chronic inflammation in the colon, leading to the formation of IBD lesions [12].

Unlike other inflammatory diseases, IBD may not be quickly suppressed because the immune system is stimulated and part of the intestine is destroyed. This condition may cause pain, diarrhea, fever, and other symptoms [13]. Bloody diarrhea is a common symptom in most patients with UC, and the severity of the bleeding depends on its location in the colon. Weight loss is common in CD patients. Weight loss in these patients is thought to be due to chronic diarrhea, malabsorption, and fear of food [14]. In addition, the inflammatory effects of the disease may pass through the intestinal lumen and affect the extraintestinal organs, forming abscesses, fissures, and fistulas. Extraintestinal symptoms are common, especially in the eyes, hematologic system, joints, and skin [15]. Moreover, these symptoms may vary from person to person and can reduce normal daily activities, absenteeism, eating disorders, and psychological effects [16].

Treatment of IBD

Clinical, endoscopic, histologic, and radiologic tests diagnose IBD [17]. After diagnosis, the disease's severity and location are critical in determining treatment strategies and evaluating possible side effects. The main goal of diagnosis and treatment of the disease is to reduce the symptoms and improve the patient's health, eliminate the symptoms of the disease or keep the disease in a sound stage and avoid surgical treatment [13]. Remission, known as mucosal healing and normalization of blood biomarkers, is critical for the maintenance of therapy [18].

Treatment options for the disease include nutrition, medication, or surgical interventions [16]. Recently, drugs such as immunosuppressants, anti-tumor necrosis factor (TNF)-α antibodies, and corticosteroids have been used as drug therapy. These drugs are associated with an increased risk of opportunistic infections and malignancies [11]. It is also one of the treatment options in surgical methods, but it can cause some complications [19]. In addition to the negative aspects of treatments, the cost of health care services in treatment, and social costs such as lost work and daily activities impose a significant economic burden. This economic burden ranges from $8.1 billion to $14.9 billion in the United States [20].

Because of these adverse effects in treatment, alternative methods are being sought for reliable, inexpensive, and effective treatment [11]. Recently, some nutraceutical compounds, such as bioactive peptides and phytochemicals, have been investigated as alternative methods to treat IBD [21]. Therefore, this review aims to examine the effects of some polyphenol components on IBD.

Polyphenols

Polyphenols, known as secondary plant metabolites, contain more than 7000 compounds [22, 23]. These compounds are classified according to the bonds that connect the rings and the number of rings [22]. They are grouped into flavonoids such as isoflavonoids, anthocyanins, and non-flavonoids such as stilbenes, phenolic acids, tannins, and coumarins [23]. Polyphenols with these components are found in different amounts in different foods [22]. For example, flavonols are commonly found in fruit, apples, and red onions, while flavanols are mainly in tea, cocoa, and chocolate. Isoflavones are also in soybeans, while flavones are in thyme and rosemary. Furthermore, grapes and wine are rich in resveratrol [24].

The relationship between polyphenols and IBD

Polyphenols modulate cellular signaling pathways and have antioxidant and anti-inflammatory effects [22]. Due to these effects, polyphenols are thought to be effective in treating IBD [25]. These compounds may regulate the intestinal immune response and the production of molecular mediators involved in inflammation [26]. These components limit the production of cytokines such as interleukin-8, interleukin-1β, and TNF-a and increase the activities of intracellular antioxidants such as superoxide dismutase and glutathione peroxidase. Moreover, these components act as antioxidants and scavenge free radicals. In addition, intestinal inflammation is reduced by interrupting redox signaling pathways [24, 27]. It has been reported that flavonoids protect the cell against oxidative stress and the epithelial mucosal layer of the intestine in vivo and in vitro [28]. Curcumin, a component of Indian curry spices, has been reported to inhibit the proinflammatory transcription factor Nuclear Factor Kappa B due to its anti-inflammatory effects. Curcumin has also improved symptoms in patients with reduced corticosteroid therapy [29]. Another study investigated the protective effects of Curcumin (50 mg/kg/day) and resveratrol (80 mg/kg/day) and the underlying mechanisms in colitis-induced mice. As a result of the study, it was reported that mice treated with Curcumin or resveratrol decreased weight loss, disease severity, and proinflammatory cytokine production and prolonged life span compared to the colitis group. In addition, Curcumin and resveratrol were found to suppress inflammation in the gut, reduce autophagy, and have a protective effect against colitis by regulating sirtuin 1/mTOR signaling [30]. In another study, the therapeutic effects of pretreatment with 10 mg/kg/day of resveratrol were investigated in colitis-induced rats. It was found that resveratrol treatment increased glutathione peroxidase and catalase activities, while the microscopic score and

malondialdehyde levels were decreased. As a result of the study, it was emphasized that resveratrol had a beneficial effect on colitis in rats [31]. Similarly, in another study, 56 patients with ulcerative colitis received 500 mg of resveratrol daily for six weeks. It was found that resveratrol treatment in these patients increased total antioxidant capacity, serum superoxide dismutase, and quality of life while decreasing serum malondialdehyde levels and disease activity [32].

In the study examining the effect of grape seed polyphenol on colitis, 500mg/kg and 750mg/kg grape seed polyphenol were given orally to colitis-induced mice, respectively. As a result of the study, it was determined that grape seed polyphenol reduced diarrhea, mucosal damage, weight loss, bloody stool, inflammatory infiltration, and mRNA expression of interleukin-6, interleukin-1β, and TNF-a and signal converter and transcription 3 phosphorylation activator [33].

Luteolin is a flavonoid with anti-inflammatory properties. In a study aimed to qualify the anti-inflammatory property of luteolin against intestinal inflammation and its effect on the underlying molecular mechanisms, it was observed that luteolin negatively regulates inflammatory pathways by decreasing the expression of interleukin-8, cyclooxygenase-2, nitric oxide, and inducible nitric oxide synthase. It was also concluded that luteolin may be effective against intestinal inflammation and could be considered a therapeutic option for IBD [34]. A study investigating the protective effect of lycopene against colitis found that treatment with 10 mg/kg of lycopene increased superoxide dismutase levels and total antioxidant levels in colitis-induced rats. As a result, it was found that treatment with lycopene improved biochemical and pathological outcomes in rats with colitis [35]. In another study, the effects of tomatoes called Bronz, enriched with three different classes of polyphenols, on the microbiota, inflammatory responses, and chronic IBD symptoms were investigated, and as a result, Bronz tomatoes were found to reduce IBD symptoms significantly [26].

Another animal study examining the effects of gallotannin-rich mango and ellagitannin-rich pomegranate found that mango and pomegranate drinks reduced intestinal inflammation, mucosal damage, and proinflammatory cytokines [36]. In a different study on pomegranate polyphenols, the effects of purified punicalagin and pomegranate juice on nuclear factor kappa B signaling pathways and its expression in colitis were studied in rats with experimental colitis. It was concluded that the severity of the disease decreased, and the levels of TNF-a, interleukin-18, and interleukin-1 B mRNA decreased. It was concluded that pomegranate juice and its main ingredient, punicalagin, may be used to control inflammatory diseases such as IBD and to inhibit nuclear factor kappa B directly [37].

In another study investigating the anti-inflammatory properties of flavonoid compounds, eupatilin and quercetin were administered to rats 48 hours before colitis was induced. Rats receiving flavonoid extracts had fewer mucosal lesions, nitric oxide production, and TNF-α levels. Higher glutathione levels have also been reported. Finally, it was observed that these compounds improved the inflammatory response and colon damage in colitis by reducing oxidative stress and neutrophil activation [38]. Dönder et al. [4] studied the effects of quercetin on bacterial translocation in IBD in an experimental colitis model and reported that quercetin has a substantial therapeutic effect. In addition, histopathologic improvement, inflammation reduction, and bacterial translocation were observed in the treatment group.

In the study, which investigated the effect of epigallocatechin gallate (EGCG) in green tea, rats were given 20 mg/kg and 50 mg/kg EGCG orally daily. Different doses of EGCG therapy were found to reduce weight loss and clinical manifestations of the disease. It also prevented colon shortening, decreased intestinal permeability, reduced colon inflammation, and provided histopathological improvements[39]. Zhao et al. concluded that different doses of magnolol (5 mg/kg, 10 mg/kg, and 15 mg/kg) reduced myeloperoxidase activity, colon lesions, proinflammatory cytokines, and disease activity index in colitis-induced mice [40]. In the study evaluating the protective effect of different doses of gallic acid treatment (25 mg/kg, 50 mg/kg, 75 mg/kg, and 100 mg/kg), it was concluded that treatment with 100 mg/kg gallic acid reduced disease activity index, macroscopic and microscopic colon damage, and myeloperoxidase activity. This effect is believed to be due to the gallic acid's anti-inflammatory and antioxidant properties [41].

Conclusion

Dietary polyphenols have several health benefits, such as protecting against chronic diseases and supporting healthy aging. The main problems of therapeutic approaches to the disorder are limited benefits, side effects, and poor response in patients taking anti-inflammatory drugs. Polyphenols modulate cellular signaling pathways and exert antioxidant and anti-inflammatory effects. Polyphenols are believed to have beneficial effects on reducing the severity of IBD and slowing its progression. For these reasons, dietary polyphenols are now complementary to treating IBD.

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