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Review Article

Antioxidant therapy for treatment of inflammatory bowel disease: Does it work?

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ABSTRACT

Oxidative stress (OS) is considered as one of the etiologic factors involved in several signals and symptoms of inflammatory bowel diseases (IBD) that include diarrhea, toxic megacolon and abdominal pain. This systematic review discusses approaches, challenges and perspectives into the use of non-traditional antioxidant therapy on IBD, including natural and synthetic compounds in both human and animal models. One hundred and thirty four papers were identified, of which only four were evaluated in humans. Some of the challenges identified in this review can shed light on this fact: lack of standardization of OS biomarkers, absence of safety data and clinical trials for the chemicals and biological molecules, as well as the fact that most of the compounds were not repeatedly tested in several situations, including acute and chronic colitis. This review hopes to stimulate researchers to become more involved in this fruitful area, to warrant investigation of novel, alternative and efficacious antioxidant-based therapies.

Contents

1. Introduction

Inflammatory bowel diseases (IBD) are most commonly represented by Crohn's disease (CD), which involves any segment of the gastrointestinal tract, and ulcerative colitis (UC), that occurs in the inner lining of the colon (large intestine) or rectum. IBD is characterized by chronic or relapsing immune activation and

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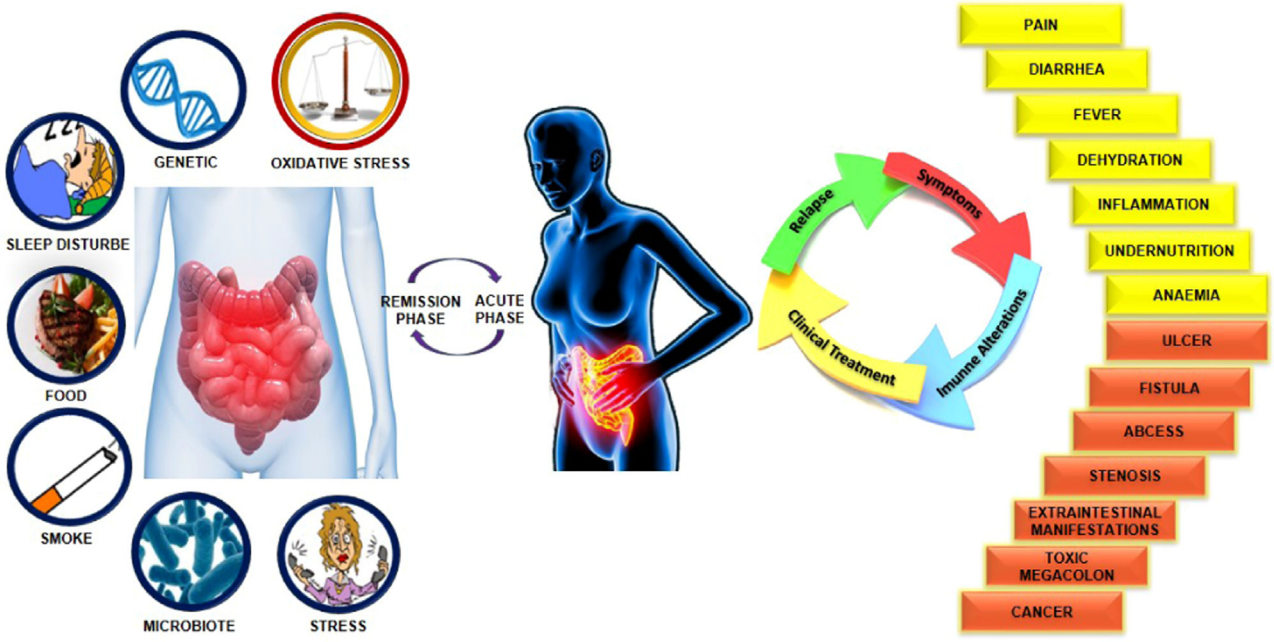

Fig. 1. Important risk factors associated with inflammatory bowel diseases and immunological changes.

inflammation within the gastrointestinal tract [1]. The etiology of IBD remains unclear but environmental factors, as well as infectious, immunological, and psychological ones, together with genetic susceptibility could be the major causes for the onset of UC [2] (Fig. 1). Although the prevalence and incidence of IBD is increasing (150–250/100,000 population), especially in developed countries, it is rarely fatal. It can however, greatly diminish the quality of life because of the pain, vomiting, diarrhea and other socially unacceptable symptoms it causes. The increased risk of colorectal cancer (from 0.5% up to 20% per year) is a serious complication of IBD, particularly in the case of UC [3].

The current therapy for IBD relies on the use of sulfasalazine, corticosteroids, immunosuppressive agents, such as azatriopine, and biological therapy (Fig. 2) represented by the anti-TNFα (tumor necrosis factor alpha) antibody as the mainstream treatment for down-regulating aberrant immune responses and inflammatory cascades [4]. However, the adverse effects associated with these drugs over prolonged treatment periods and the high relapse rate limit their use [5]. Sulfasalazine, for instance, can exacerbate colitis, resulting in diarrhea, abdominal cramps and discomfort [6]. Antibiotics, one of the commonly used therapies, could adversely change the environmental conditions of microbiota and trigger resistance. Moreover, immunosuppressant and anti-inflammatory drugs (such as corticosteroids) have many undesirable side effects [7] and the combined therapy, using corticosteroids plus infliximab does not appear to provide any additional benefit over infliximab monotherapy [8]. Furthermore, these drugs display limited beneficial actions. In the long term, $\leq$25–33% of patients with UC will require surgery if pharmacological treatments are not successful, or in the case of complications such as fistulae, stenosis, or abscesses (particularly in Crohn's patients) [9]. The potential of these drugs when used over a long period of time, to induce severe side effects, together with the high costs of the therapy for patients, warrant investigation of novel and alternative pharmacological approaches [10].

In recent years, several studies had focused on reactive oxygen species (ROS) and reactive nitrogen species (RNS) as the etiologic factors for IBD [11–14]. The gastrointestinal tract is a major site for generation of pro-oxidants, whose production is primarily due to the presence of a plethora of microbes, food ingredients and interactions between immune cells [15]. Furthermore, the antioxidant capacity of patients with IBD is reduced, even in the asymptomatic phase of the disease [16]. To scavenge RONS, intestinal cells have several enzymatic and non-enzymatic antioxidants, including superoxide dismutase (SOD), reduced glutathione (GSH) and catalase (CAT), but excessive generation of RONS enhances lipid peroxidation (LP) and could deplete antioxidant defenses [17].

It should be noted that OS is clearly involved in IBD, once immune activation such as inflammation [18] occurs and could be a major contributing factor to tissue injury and fibrosis that characterize CD [19]. In this regard, reduction of plasma antioxidants and total intestinal antioxidant capacity has been observed in CD [20]. Like in CD, several studies have shown oxidative stress in UC. Patients with UC often have antioxidant nutrient deficiencies at the time of diagnosis [21–23] and that could suggest an increase of OS.

In this context, recent studies have suggested that the administration of antioxidants, from different sources, with additional anti-inflammatory action may be beneficial in the treatment of IBD because inflammation is caused by OS and leads to the increase of OS that contributes to tissue damage [24–26].

Several reports on non-traditional therapy for IBD have been published. However, those publications put special emphasis on antioxidant and/or anti-inflammatory activity [25–27] or regulation of gut microbiota [28, 29]. Unlike other published approaches, this review is broader and aims to describe and analyze the effect of functional foods and isolated nutrients, probiotics, natural active compounds from vegetal sources, drugs, hormones and other synthetic substances, all of them reported as antioxidants, in IBD.

2. Methods

In 2009, Rahimi et al. [30] published a systematic review on the use of herbal medicines for the treatment of IBD [31]. These