



# Dietary Agents and Phytochemicals in the Prevention and Treatment of Experimental Ulcerative Colitis

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## ABSTRACT

Inflammatory bowel diseases (IBDs), consisting mainly of ulcerative colitis (UC) and Crohn's disease (CD), are important immune-mediated diseases of the gastrointestinal tract. The etiology of the disease includes environmental and genetic factors. Its management presents a constant challenge for gastroenterologists and conventional surgeon. 5-Aminosalicylates, antibiotics, steroids, and immune modulators have been used to reduce the symptoms and for maintenance of remission. Unfortunately, long-term usage of these agents has been found to lead to severe toxicities, which are deterrent to the users. Pre-clinical studies carried out in the recent past have shown that certain dietary agents, spices, oils, and dietary phytochemicals that are consumed regularly possess beneficial effects in preventing/ameliorating UC. For the first time, this review addresses the use of these dietary agents and spices in the treatment and prevention of IBD and also emphasizes on the mechanisms responsible for their effects.

**Key words:** Cancer, Colitis, Colon, Inflammation, Phytochemicals

## INTRODUCTION

Inflammatory bowel disease (IBD), manifested clinically by bloody diarrhea, abdominal cramps, and pain, is an immunologically mediated relapsing and chronic disease that affects the intestinal mucosa.<sup>[1]</sup> Patients with IBD are also at a higher risk to develop colorectal cancer, when compared to the average population.<sup>[2]</sup> Crohn's disease (CD) and ulcerative colitis (UC) represent the two most common forms of IBD.<sup>[1,2]</sup> These diseases mimic each other in symptoms and some mucosal pathology, but differ sufficiently to be considered as independent ailments.<sup>[1]</sup> The etiology and the exact disease mechanisms remain unknown despite much effort and research.<sup>[2]</sup> It is well known that the incidence of IBD is high in the

countries of North America, and northern and western Europe, while it is low in Africa, eastern Europe, South America, Asia, and the Pacific region. Conversely, recent studies indicate that the incidence has stabilized or slightly increased in countries with a high prevalence previously, while it is on the rise in countries with a low incidence previously. Jointly, these reports indicate that IBD could be a global health problem in the future and understanding its pathogenesis and developing affordable safe treatment is important.<sup>[3]</sup>

## CURRENT STATUS OF KNOWLEDGE

### Molecular events responsible for UC

From a clinical perspective, the central sign of UC is inflammation of the mucosal lining of the colon and mechanistically,

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this end event is a result of interplay between various molecular constituents of the cells. The inflammatory pathway in UC involves ubiquitous expression of proinflammatory eukaryotic transcription factors [activator protein (AP)-1 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B)],<sup>[4,5]</sup> which leads to the production of pro-inflammatory cytokines like tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, IL-1 $\beta$ , with T-helper (Th)-17 cytokines such as IL-23 and IL-17 predominating, and a concomitant decrease in the anti-inflammatory cytokines and proteins.<sup>[6,7]</sup> This surge in pro-inflammatory cytokines is followed by an increase in the production of cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), myeloperoxidase,<sup>[8]</sup> and signal transducer and activator of transcription<sup>[9]</sup> -3,<sup>[5,6]</sup> which further increases inflammation and leads to oxidative stress<sup>[10]</sup> and a concomitant decrease in the level of antioxidants.<sup>[10,11]</sup> All these events lead to an increase in cell inflammation, infiltration of the immune cells, especially the neutrophils, and culminate into epithelial cell damage and colonic barrier dysfunction. UC is also an established risk for colon cancer, which is caused due to the repeated cycle of inflammation leading to spontaneous mutation in the DNA repair mechanism, oncogenes, and tumor suppressor genes like p53.<sup>[4,5]</sup> Another factor responsible for the development of UC is the change in the constituent, number, and activity of the colon microflora, as studies with germ-free mice have conclusively shown less or no inflammation developing in chemical and genetic models of colitis.

### Conventional treatments in UC

Chemotherapy has been the mainstay of treatment of UC; in the event of a mild disease, anti-inflammatory drugs such as sulfasalazine and 5-aminosalicylic acid are given, while in severe and chronic cases, treatment with rectal and systemic corticosteroid and immunosuppressant is administered.<sup>[12]</sup> In most cases, the benefits are restricted to the reduction of inflammation and its complications.<sup>[1]</sup> However, in extreme conditions, surgery is the last solution to the patient's condition. Conversely, regular intake of these medications is unsafe as they may have severe side effects such as gastric ulcers, Cushing's habitus, hyperglycemia, muscle weakness, fragile skin, purple striae, flaring up of latent infections, delayed wound healing, cataract, osteoporosis, glaucoma and hypothalamic pituitary axis suppression with corticosteroids, and an increased risk of opportunistic infections and development of lymphomas.<sup>[1]</sup> In addition, some refractory condition can lead to severe morbidity and decrease in the quality of life.<sup>[1]</sup>

Recently, biologics such as anti-TNF- $\alpha$ , anti-alpha-4 integrin, as well as Peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ) ligand and probiotic therapy are being used, but their long-term benefits are unknown.<sup>[1]</sup> Importantly, reports suggest that the long-term use of biologics, especially infliximab, adalimumab, and certolizumab, may increase the risk of infections and malignancies, especially non-Hodgkin's lymphoma.<sup>[13]</sup> Drugs that block leukocyte adhesion such as natalizumab, those that target cytokines, like IL-12/23, and antibodies inhibiting T-cell signaling, such as IL-6 receptor antibodies, are also being studied. However, these drugs also have a number of contraindications and side effects, especially when used in combination with classical

immunosuppressive drugs. The major effects are opportunistic infections, malignancies, and diverse complications like injection/infusion reactions and autoimmunity, and contraindications such as heart failure and acute infectious diseases.<sup>[14]</sup>

The repeated relapses, surgery phobia, severe morbidity, and derisory response to conventional drugs make the patient to resort to unconventional treatments with a hope to decrease the symptoms of the disease and concomitantly perk up the quality of life.<sup>[15]</sup> Recent reports indicate that at least 40% of IBD patients have used complementary and alternative medicines, and that the botanicals constitute a major share of all these alternatives.<sup>[15]</sup>

Results from preclinical studies suggest the beneficial effect of medicinal plants including *Aloe vera* gel (蘆薈 Lú Hui), *Boswellia serrata* (乳香 Rǔ Xiāng), *Cassia fistula*, *Lepidium sativum*, *Bunium persicum*, *Plantago ovata*, *Pistacia lentiscus*, *Bunium persicum*, *Solanum nigrum*, *Commiphora mukul*, *Commiphora myrrha*, *Ocimum basilicum* (羅勒 Luó Lè), *Linum usitatissimum*, *Dracaena cinnabari*, *Plantago major*, *Lallemantia royleana*, and *Allium porrum*, which have been used since time immemorial in the various systems of traditional and folk medicine.<sup>[16,17]</sup>

From human perspective, it is always desirable to consume dietary agents that also possess medicinal value as their regular use can be achieved easily and regularly. This aspect was very well recognized by Hippocrates, the Father of Medicine, who proclaimed almost 25 centuries ago, "Let food be thy medicine and medicine be thy food." To further substantiate the importance and relevance of this adage, observations from around the world clearly indicate that the incidence of diet-related diseases is progressively increasing due to greater availability of hypercaloric food and a sedentary lifestyle, which cause low-grade inflammation in the individual.<sup>[18]</sup>

Recent reports also suggest that the functional foods and nutraceuticals rich in polyphenols and antioxidants are beneficial due to their intrinsic ability to scavenge free radicals, induce anti-inflammatory responses, maintaining a homeostatic regulation of the gut microbiota, and activate the intestinal T regulatory cells.<sup>[18]</sup> All these properties are extremely beneficial in the prevention and mitigation of the IBD. Studies have shown that the dietary agents like apple, bilberry, black raspberry, cocoa, bael, green tea (綠茶 Lǜ Chá); spices like garlic (大蒜 Dà Suàn), Malabar tamarind, saffron (番紅花 Fān Hóng Huā), fenugreek, ginger (生薑 Shēng Jiāng), turmeric (薑黃 Jiāng Huáng); oil of olive; nutraceuticals like grape seed polyphenols; and the dietary phytochemicals like resveratrol, ellagic acid, zerumbone, quercetin, kaempferol, rutoside, and rutin are consumed regularly and are commonly used. They will be addressed in detail by emphasizing on the mechanism of action.

## DIETARY AGENTS WITH ANTI-IBD EFFECTS

### Apple

Apple, known as *Malus malus*, belongs to the family Rosaceae and is an important dietary agent.<sup>[19-21]</sup> It has occupied a prime position in the dietary and nutritional requirements of humans and epidemiological studies have linked its consumption with reduced risk of certain cancers, cardiovascular diseases, asthma, and diabetes.<sup>[21]</sup> Apple is a good source of several flavonoids and certain phy-

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