Curcumin in Ulcerative Colitis

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Ulcerative colitis (UC) is one of the inflammatory bowel diseases (IBD). It is a chronic autoimmune inflammation of unclear etiology affecting the colon and rectum, characterized by unpredictable exacerbation and remission phases. Conventional treatment options for UC include mesalamine, glucocorticoids, immunosuppressants, and biologics. The management of UC is challenging, and other therapeutic options are constantly being sought. More attention is being paid to curcumin, a main active polyphenol found in the turmeric root, which has numerous beneficial effects in the human body, including anti-inflammatory, anticarcinogenic, and antioxidative properties targeting several cellular pathways and making an impact on intestinal microbiota.

Keywords: anti-inflammatory ; inflammatory bowel disease ; intestinal microbiota ; polyphenols

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) that affects the colon [1]. Typical mucosal inflammation involves the rectum but could continuously extend to proximal segments of the large intestine. Like other types of IBD, UC is classified as an autoimmune disease of unclear etiopathology characterized by phases of exacerbation and remission. Its symptoms consist mainly of abdominal pain and bloody diarrhea. The etiology and pathogenesis of UC are multifactorial and still not fully understood; it includes genetic predisposition, immunological dysregulation, intestinal dysbiosis, epithelial barrier dysfunction, and many potential environmental factors, which jointly lead to sustaining chronic inflammation [2].

The incidence of UC is rising around the world causing a global problem, and it is being diagnosed at an earlier age. It is estimated that at least a quarter of patients experience their first symptoms in childhood or adolescence [3][4]. Moreover, extensive colitis occurs in two-thirds of newly-diagnosed pediatrics patients versus in only 20–30% of adult patients [5]. The population-based studies of Ng et al. show that in adults the highest prevalence of UC is in Europe and in North America (505/100,000 in Norway and 286/100,000 in the USA) [4]. In the pediatric population, UC prevalence is estimated at 22/100,000 in most European and North American regions [6].

The main goal of UC management is to induce and maintain remission, defined as the resolution of symptoms with endoscopically confirmed mucosal healing, as long as possible. Long-term maintenance of IBD remission enables children to grow and develop properly, and adults to lead a normal personal and professional life. Pharmacological treatment for UC depends on the disease extent and the degree of its clinical activity and includes 5-aminosalicylic acid drugs, glucocorticoids, and immunomodulating, immunosuppressive, and biological drugs. Unfortunately, monotherapy is not always fully effective and the long-term combination of several drugs may be associated with the occurrence of side effects. Surgical management, with colectomy as the most common procedure, is sometimes the only solution in relapsed and severe disease and is usually being implemented in patients with pancolitis [1][7]. There is no fully effective, universal treatment as the etiology of the disease is complex. However, the therapy should aim to provide satisfactory quality of life for the affected individuals.

These days, more attention is being paid to the necessity of modifying the environmental factors, which includes, apart from the others, dietary aspects, as the so-called Western diet has been linked to the highest prevalence of IBD, including UC [8]. Such a strategy may improve clinical outcomes in UC patients while minimizing the risk of the occurrence of side effects. Recently, alternative therapeutic options that are being explored include specific dietary approaches or usage of nutraceuticals (e.g., polyphenols). A nutraceutical is “a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease” [9][10].

More research is focusing on the medicinal value of polyphenols to prevent immune-mediated intestinal chronic inflammation. Over the last few years curcumin, a natural polyphenol belonging to the curcuminoid family (compounds derived from *Curcuma longa* L. [turmeric root]), is of greater interest in the context of managing UC. It seems that

curcumin is a promising natural compound due to its widely described multi-beneficial effects on microbiota alteration and antioxidative, antitumor and—the most relevant—anti-inflammatory properties. The anti-inflammatory effect is mainly mediated via the regulation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which results in the inhibition of proinflammatory cytokines, such as IL-1, IL-6, and TNF-α expression [11][12][13].

2. Curcumin

Curcumin, also known as the 'golden spice of India', has been used for thousands of years as an essential medicinal, herbal ingredient that exhibits anti-inflammatory, antioxidant, or antimicrobial properties, mainly. It is also well-known in Chinese traditional medicine. Nowadays, curcumin, an orange-yellow crystalline powder, is widely used in the food industry mostly as a dye (E100) in foodstuffs and beverages processing. It is also a very popular dietary spice in many cuisines worldwide. It is extracted from the rhizomes of *Curcuma longa* L. from the ginger family *Zingiberaceae*. Curcumin comprises 2–5% of the rhizome content. Chemically, curcumin is a diferuloylmethane or 1,7-bis (4-hydroxy-3methoxyphenyl)-1,6-heptadiene-3,5-dione, with the molecular formula $C_{21}H_{20}O_6$ [14]. It is the principal curcuminoid, and the most active component of the total turmeric spice. It belongs to substances generally recognized as safe (GRAS), with its safety and tolerance confirmed in human clinical trials [14][15][16]. The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) and the European Food Safety Authority (EFSA) allocated an acceptable daily intake (ADI) for curcumin of 0–3 mg/kg body weight [17]. Commercial curcumin consists of three major compounds, which are referred collectively as curcuminoids: curcumin [diferuloylmethane] (82%), demethoxycurcumin (15%, DMC), and bisdemethoxycurcumin (3%, BDMC) [18].

Curcumin is a small molecular weight compound that is lipophilic, thereby nearly insoluble in aqueous physiologic media but is soluble in methanol, dimethylsufoxide, ethanol, and acetone, as well slightly soluble in benzene and ether. It is a very photosensitive compound [14][19]. This yellow-colored polyphenol is a small hydrophobic molecule that can accumulate in cell membranes, which are hydrophobic regions, and perform as an antioxidant, scavenging reactive oxygen species. It is stable in the range of pH between 2.5 and 6.5 and it remains quite stable at the low acidic pH of the stomach [20][21].

After oral administration, curcumin is rapidly metabolized via reduction, sulfation, and glucuronidation in the liver, kidneys, and intestinal mucosa with low absorption of accumulated curcumin from the intestine [22][23]. Phase I of curcumin metabolism consists of reduction of its double bonds in hepatocytes and enterocytes, transforming it to dihydrocurcumin, tetrahydrocurcumin, hexahydrocurcumin, and octahydrocurcumin [24][25]. Phase II consists of conjugation of glucuronide or sulfate to the curcumin and to its hydrogenated metabolites in the intestinal and hepatic cytosol [26]. Major curcumin metabolites in plasma, curcumin glucuronide and sulphate conjugate metabolites, are characterized by low activity [22]. There is a greater curcumin metabolic conjugation and reduction in the human models than in rat models. Therefore, human clinical trials are much more appropriate, and are constantly, highly needed to assess the real curcumin therapeutic potential [26]. The gut microbiome is considered capable of deconjugating phase II metabolites and converting them back to the metabolites of phase I. This process can also lead to the production of, for example, ferulic acid (4-hydroxy-3-methoxy-cinnamic acid) which is a phenolic antioxidant compound that has a high radical scavenger effect for free radicals [27][28]. Furthermore, it was found that commensal *Escherichia coli* had the highest metabolizing activity among curcumin-converting microorganisms via an enzyme called "NADPH-dependent curcumin/dihydrocurcumin reductase" (CurA). *E. coli* acts in a two-step reduction process, converting curcumin to dihydrocurcumin, and then to tetrahydrocurcumin [29]. In another study it was reported that *Blautia* sp. *MRG-PMF1* carries out an alternative metabolism of curcumin which is curcumin demethylation. This process led to the production of two metabolites, which were demethylcurcumin and bisdemethylcurcumin [30].

3. Curcumin, Anti-Inflammatory Effect, and Ulcerative Colitis

The significant anti-inflammatory properties of curcumin, being described over the years have attracted a lot of researchers' interest, especially in the context of treating diseases with a chronic inflammation basis. NF-κB is a multi-functional key nuclear transcription factor, involved in the development of inflammatory diseases. It is believed to strongly affect the progression of mucosal inflammation in ulcerative colitis. In many studies it has been shown that curcumin inhibits NF-κB expression by blocking IkappaB (IκB) kinase, that leads to the prevention of cytokine-mediated phosphorylation and the degradation of IκB, which is an NF-κB inhibitor. Hence, the expression of proinflammatory cytokines, such as IL-1, IL-6, IL-8, and TNF-α, is inhibited [31][32]. Furthermore, it was also reported that curcumin inhibited the activity of proinflammatory proteins (e.g., activated protein-1, peroxisome proliferator-activated receptor gamma, transcription activators, the expression of β -catenin) [33].

4. Curcumin, Intestinal Microbiota, and Ulcerative Colitis

As oral supplementation with curcumin leads to its high concentration in the gastrointestinal tract, studies have slowly focused on its impact on the intestinal microbiota. Via this mechanism, the problem of low systemic curcumin bioavailability probably is not a significant issue within the gastrointestinal tract, and curcumin may have a hypothetical beneficial influence on the gut microbiome [21][34]. A bidirectional interaction exists between curcumin and gut microbiota. Gut microbiota are actively involved in curcumin metabolism, which lead to curcumin biotransformation (demethylation, hydroxylation, demethoxylation) and the production of metabolites. Curcumin supplementation is effective in promoting the growth of beneficial bacterial strains, improving intestinal barrier functions, and counteracting the expression of pro-inflammatory mediators [35].

Only one study in healthy humans assessed microbiota alteration after oral curcumin administration. Peterson et al., in a double-blind, randomized, placebo-controlled pilot study with 30 healthy subjects, assessed changes in the gut microbiota using 16S rDNA sequencing after oral supplementation with turmeric 6000 mg with extract of piperine, curcumin 6000 mg with Bioperine (black pepper extract) tablets, or placebo, at baseline and after 4 and 8 weeks. They found that both turmeric and curcumin in a highly similar manner altered the gut microbiota. Participants who took turmeric supplementation displayed a 7% increase in observed microbial species post-treatment, and curcumin-treated subjects displayed an average increase of 69% in detected bacterial species. The authors indicated that the intestinal microbiota responses to such therapy were highly personalized. Subjects defined as “responders” showed uniform increases in most *Clostridium* spp., *Bacteroides* spp., *Citrobacter* spp., *Cronobacter* spp., *Enterobacter* spp., *Enterococcus* spp., *Klebsiella* spp., *Parabacteroides* spp., and *Pseudomonas* spp., with reduction in the relative abundance of several *Blautia* spp. and most *Ruminococcus* spp. [36].

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