The Mechanisms and Clinical Potential of the Mediterranean Diet in the Management of Inflammatory Bowel Disease

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Abstract. Inflammatory bowel disease (IBD), including Crohn's disease (CD)and ulcerative colitis (UC), is a chronic, relapsing, immune-mediated disorder. With the increasing global incidence of IBD, traditional pharmacological therapies face limitations in both efficacy and safety, prompting growing interest in dietary interventions as adjunctive management strategies. The Mediterranean diet (MD), rich in plant-based foods, olive oil, fish, and natural antioxidants, has been shown to exert anti-inflammatory, immunomodulatory, and gut microbiota-regulating effects. This study explores the nutritional composition and anti-inflammatory mechanisms of the MD, its potential in modulating the gut microbiota, immune responses, and intestinal barrier function, and reviews clinical evidence from observational studies and randomized controlled trials. Although MD demonstrates promising effects in reducing disease activity and improving quality of life, the lack of standardized interventions, marked individual variability, and limited evidence on long-term efficacy remain challenges. Future research should focus on developing culturally adapted dietary protocols, elucidating individualized response mechanisms through multi-omics approaches, and integrating MD with functional nutrients or lifestyle interventions to promote its clinical translation and widespread application in IBD.

Keywords: Inflammatory bowel disease; Mediterranean diet; gut microbiota; immune modulation; intestinal barrier; anti-inflammatory diet; randomized controlled trial; nutritional therapy.

1. Introduction

Inflammatory bowel disease (IBD), mainly including Crohn's disease (CD) and ulcerative colitis (UC), is a group of chronic and relapsing inflammatory disorders of the intestine. In recent years, the global incidence of IBD has increased significantly, becoming an important public health issue in many regions worldwide [1,2]. Currently, IBD treatment relies primarily on immunosuppressants and biologics, but their long-term efficacy and safety remain challenging. Patients often face high relapse rates and impaired quality of life. Therefore, identifying safe and sustainable adjunctive management strategies is of great importance [3].

Among the modifiable lifestyle factors, diet, as a critical determinant of gut microbiota and immune responses, has gradually emerged as a novel focus in IBD management. Studies have shown that dietary patterns may influence the onset and remission of IBD by modulating gut microbiota composition, inflammatory status, and intestinal barrier function [4,5]. Thus, exploring dietary interventions with potential anti-inflammatory effects holds significant value for improving quality of life and reducing medication dependence in patients with IBD.

The Mediterranean diet (MD) is a traditional dietary pattern characterized by high intake of plant-based foods, olive oil, moderate consumption of fish, and red wine. A large body of evidence has demonstrated that MD exerts antioxidant, anti-inflammatory, and metabolic regulatory effects, and can modulate gut microbiota through multiple pathways. It is associated with a reduced risk of chronic diseases such as cardiovascular disease and metabolic syndrome. In recent years, research has also suggested that MD may confer benefits in immune-mediated conditions such as IBD [6].

This study examines the nutritional composition and potential anti-inflammatory mechanisms of the Mediterranean diet, summarizes recent clinical evidence on MD interventions in IBD, discusses its feasibility and limitations, and proposes directions for future research based on current findings.

2. Composition and Nutritional Characteristics of the Mediterranean Diet

The Mediterranean diet (MD) is a healthy dietary pattern derived from the traditional eating habits of Mediterranean countries. Its core feature is to ensure nutritional balance while emphasizing the intake of natural, unprocessed, and plant-rich foods. According to the modern MD pyramid model proposed by UNESCO and the international scientific community, the base of the pyramid includes the daily consumption of fresh vegetables, fruits, whole grains, legumes, nuts, and olive oil; the middle layer recommends moderate weekly intake of fish, poultry, eggs, and dairy products; the top layer suggests limiting the consumption of red meat, processed foods, and sweets. In addition, moderate red wine may be consumed as part of meals, while the model also highlights the integration of diet with physical activity and social interaction [7].

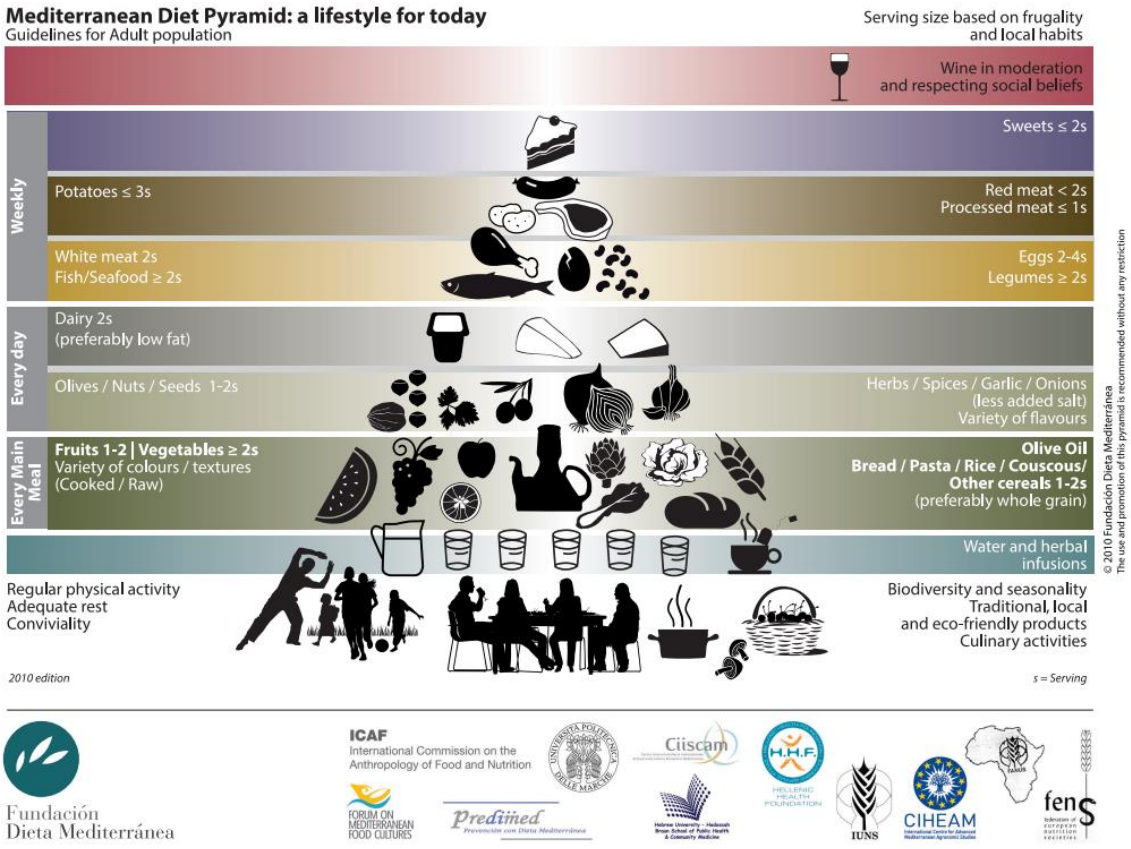

Fig. 1 The Mediterranean diet pyramid model (adapted from the MedDiet Foundation, revised 2010) [8]

In terms of nutritional composition, the MD is rich in monounsaturated fatty acids (MUFA), primarily derived from extra virgin olive oil. MUFAs possess strong antioxidant and anti-inflammatory properties, improve lipid metabolism, and modulate inflammatory signaling pathways (such as NF-κB and MAPK), thereby exerting protective effects against chronic inflammatory diseases [9]. Moreover, polyunsaturated fatty acids (PUFA), particularly omega-3 fatty acids mainly sourced from marine fish (such as salmon, sardines, and mackerel), have been shown to suppress the synthesis of pro-inflammatory mediators. In addition, dietary fiber from legumes, fruits, vegetables, and whole grains promotes the production of short-chain fatty acids (SCFAs), which in turn regulate immune responses and maintain intestinal barrier integrity [10,11].

The MD is also abundant in polyphenols (such as hydroxytyrosol, flavonoids, and resveratrol), as well as natural antioxidants including vitamins C and E and β-carotene. These compounds can scavenge free radicals, reduce oxidative stress, and protect the integrity of the intestinal mucosa [12]. Together, these components help maintain gut microbial diversity, reduce inflammation, and provide a nutritional foundation for the management of IBD [13].

In summary, through its unique nutritional profile, the MD provides a potential dietary intervention strategy for chronic inflammatory diseases such as IBD. It not only helps control inflammation and protect the intestinal barrier, but also offers clear mechanistic directions for subsequent intervention studies.

3. Mechanisms of the Mediterranean Diet in IBD

3.1 Improving Gut Microbiota Ecology and Metabolite Production

Gut dysbiosis is considered one of the key pathogenic factors in IBD, characterized by reduced beneficial bacteria, increased pathogenic species, and decreased microbial diversity [14]. The MD, being rich in both soluble and insoluble dietary fibers, provides fermentation substrates for probiotics and promotes the growth of anti-inflammatory bacteria such as Faecalibacterium prausnitzii, Bifidobacterium, and Akkermansia muciniphila [15,16].

The MD also significantly enhances the production of short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate. Among them, butyrate serves as the primary energy source for colonic epithelial cells, regulates Treg cell differentiation, suppresses pro-inflammatory cytokine expression, and strengthens intestinal epithelial barrier function [11,17,18].

3.2 Anti-inflammatory Effects and Immunomodulatory Mechanisms

The anti-inflammatory effects of the MD mainly stem from its abundance of natural anti-inflammatory components, such as polyphenols (hydroxytyrosol, tyrosol) from olive oil, omega-3 polyunsaturated fatty acids from fish, and flavonoids and antioxidant vitamins (vitamins C, E, β-carotene). These compounds downregulate inflammatory factor expression via multiple signaling pathways, including inhibition of NF-κB, p38 MAPK, and JAK-STAT, thereby reducing pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 [12, 19].

In terms of immune regulation, the MD helps restore the balance between Treg and Th17 cells, promoting immune tolerance. Studies have shown that IBD patients often exhibit reduced Treg counts and increased Th17 proportions, which is a critical mechanism underlying uncontrolled inflammation. Both polyphenols and SCFAs can induce Treg differentiation and inhibit IL-17A expression, thereby alleviating inflammation. López de las Hazas et al. reported that olive polyphenols enhance peripheral Treg function and demonstrate immunomodulatory potential in both in vivo and in vitro models [20]. SCFAs also promote Treg generation through HDAC inhibition and Foxp3 upregulation [18, 21].

3.3 Restoring Intestinal Barrier Function

The integrity of the intestinal barrier is essential for preventing pathogens and toxins from crossing the mucosal lining. Its disruption is considered a fundamental driver of persistent mucosal inflammation in IBD. The MD, by providing abundant SCFAs and antioxidants, promotes the expression of tight junction proteins (such as occludin, claudin-1, and ZO-1), thereby improving intestinal permeability (leaky gut) [18,22]. In a randomized controlled trial, Papada et al. found that MD intervention significantly reduced intestinal permeability and lowered serum LBP levels, suggesting decreased systemic endotoxin burden [23].

Furthermore, antioxidant components reduce ROS generation and apoptosis, thereby protecting mucosal barrier integrity [24].

Taken together, the Mediterranean diet intervenes in multiple pathogenic pathways of IBD, including improving gut microbiota ecology and metabolite production, inhibiting inflammatory signaling pathways, restoring immune regulation, and repairing intestinal barrier function. These mechanisms provide a theoretical basis for MD intervention studies and reinforce its potential as a nutrition-based, non-pharmacological strategy for IBD management.

4. Clinical Evidence of Mediterranean Diet Interventions

4.1 Observational and Cohort Studies

Multiple observational studies have shown a significant association between long-term adherence to the Mediterranean diet and reduced risk of developing IBD. Inoue et al., using data from the Dutch Lifelines prospective cohort, found that higher Mediterranean Diet Scores (MDS) were inversely associated with IBD risk, particularly in the UC subgroup [25]. The Nurses' Health Study in the United States also suggested that women with higher MD adherence had a significantly lower subsequent risk of both CD and UC [26].

Cross-sectional studies in IBD patients further indicate that MD adherence is negatively correlated with disease activity. For example, Chiba et al. evaluated dietary scores and clinical parameters in IBD patients, showing that higher MD adherence was associated with greater remission rates and lower serum CRP and fecal calprotectin levels [27].

However, observational studies are limited by weak control over interventions and multiple confounding factors, highlighting the need for high-quality randomized controlled trials (RCTs) for further validation.

4.2 Randomized Controlled Trials (RCTs)

In recent years, several RCTs have provided preliminary evidence of the therapeutic potential of MD in IBD. In 2023, Marino et al. conducted a single-center, 8-week prospective RCT in patients with active UC. Participants were randomized to an MD group or a control group. Results showed that the MD group had higher clinical remission rates at week 8, accompanied by increased microbial diversity and significant enrichment of Faecalibacterium prausnitzii. Additionally, inflammatory markers such as IL-6 and TNF-α decreased significantly, and the expression of barrier-related proteins was upregulated, suggesting systemic anti-inflammatory and mucosal healing potential of MD [28].

In 2024, Papada et al. conducted a multicenter RCT exploring the combined effects of MD and polyphenols (curcumin, resveratrol) in IBD. In this trial involving 108 patients with mild-to-moderate active UC, MD combined with polyphenols significantly improved CRP, calprotectin, and quality-of-life scores [23].

Furthermore, an Italian study by Barberio et al. followed IBD patients with high adherence to MD for six months. Findings indicated reduced disease activity, decreased medication use, and lower hospitalization rates, further supporting MD's potential as a long-term management strategy [29].

5. Advantages and Limitations of the Mediterranean Diet in IBD Treatment

5.1 Advantages

5.1.1 Natural Anti-inflammatory Effects

The MD includes foods rich in antioxidants and polyunsaturated fatty acids, such as olive oil, oily fish, nuts, fruits, vegetables, and whole grains. These components can inhibit inflammation through multiple pathways. For example, phenolic compounds in olive oil (such as hydroxytyrosol) downregulate the NF-κB pathway, thereby reducing the expression of pro-inflammatory cytokines such as TNF-α and IL-1β [30]. In a randomized controlled trial, UC patients in the MD intervention group exhibited lower mucosal inflammation scores and serum CRP levels [31]. In addition, the MD promotes the growth of beneficial gut microbes (e.g., Faecalibacterium prausnitzii) and increases the production of SCFAs (e.g., butyrate), further contributing to immune regulation [14].

5.1.2 Beneficial for Managing Metabolic Syndrome and Cardiovascular Risk

IBD patients often face increased metabolic disturbances and cardiovascular risk due to chronic inflammation, gut microbiota dysbiosis, and long-term medication use. Because of its high omega-3 fatty acid content, low saturated fat, and high dietary fiber, the MD has been shown to significantly improve insulin sensitivity, lower blood lipids, and reduce cardiovascular events [12]. In the PREDIMED study, MD effectively reduced the incidence of cardiovascular disease in high-risk populations, demonstrating broad protective effects against comorbidities [32]. Thus, MD may serve as a comprehensive long-term health intervention in IBD management.

5.1.3 High Dietary Sustainability and Good Adherence

Compared with restrictive dietary models such as low-FODMAP or specific carbohydrate diets, the MD offers more food choices and an overall balanced structure. Empirical studies show that IBD patients generally have high acceptance and adherence to MD, especially during remission or inactive phases, making it easier to maintain long-term [33]. For instance, an intervention study involving 75 UC patients found that over 80% of participants maintained MD eating habits after 12 weeks [31]. Moreover, MD has strong cultural adaptability, as its core nutritional characteristics can be preserved while tailoring food choices to local availability.

5.2 Limitations

5.2.1 Individual Patient Variability

IBD includes two subtypes, CD and UC, and patients exhibit substantial heterogeneity in disease activity, intestinal permeability, nutritional status, and microbiota composition. For example, in CD patients with strictures or malabsorption, a high-fiber diet may exacerbate symptoms [34]. Therefore, MD interventions should be adjusted according to individual disease conditions and nutritional tolerance.

5.2.2 Cultural Differences and Dietary Adherence

Although MD has an advantageous nutritional structure and health benefits, in non-Mediterranean countries, its core ingredients (such as olive oil, fresh seafood, and certain fruits and vegetables) may be relatively expensive or less accessible, which can hinder its implementation. A survey of Canadian IBD patients showed that only about 30% of respondents were able to fully adhere to the MD pattern, primarily due to cultural dietary habits and economic burden [35].

5.2.3 Lack of Standardization in Intervention Dosage and Duration

Currently, definitions of MD vary across studies. Some rely solely on MDS thresholds, while others employ structured dietary plans. Intervention durations range from several weeks to one year. This methodological heterogeneity limits comparability between studies and impedes clinical translation. Research has suggested that short-term (<6 weeks) MD interventions may have limited impact on gut microbiota, with at least 12 weeks required to observe significant changes [36].

6. Future Research

Although current evidence supports the potential benefits of the Mediterranean diet (MD) in the management of IBD, several limitations remain, including incomplete understanding of mechanisms, lack of standardized intervention protocols, and insufficient validation of long-term effects. These challenges restrict its widespread application in clinical practice. To further advance research and translation of MD in IBD management, future work may focus on the following aspects:

6.1 Establishing Standardized Dietary Intervention Protocols

At present, definitions and intervention methods for MD vary across studies. Some rely on subjective scoring systems (e.g., MDS), while others adopt structured meal plans, with inconsistent intervention content and duration, which compromises comparability and interpretation of results

[28,36]. Therefore, unified MD intervention protocols should be established, including recommended intake levels, food combinations, and culturally acceptable substitutes, in order to enhance research quality and facilitate clinical implementation.

6.2 Exploring Multi-omics Mechanisms and Individualized Responses

IBD patients show considerable individual variability in gut microbiota composition, host genomics, immune background, and dietary responses. With the development of multi-omics technologies (including metagenomics, metabolomics, and epigenomics), new insights into MD's mechanisms have emerged [37,38]. Future research should focus on multidimensional responses of the microbiota – immune – metabolism axis after MD intervention, with the aim of identifying personalized nutritional strategies and enabling precision nutrition in IBD management.

6.3 Conducting Long-term, Multicenter Randomized Controlled Trials

Most existing MD intervention studies are short-term, single-center, and with limited sample sizes, making it difficult to evaluate sustained effects on long-term remission, reduced drug dependence, relapse rates, and complications [23,28]. Future RCTs should be designed as multicenter studies with long-term follow-up, systematically assessing MD's efficacy and safety across different IBD subtypes (UC, CD) and disease stages (active, remission). Comprehensive evaluation should also include quality of life, nutritional status, and healthcare resource utilization [39].

6.4 Enhancing Cultural Adaptability and Patient Adherence

Although MD is widely accepted in its region of origin, its core ingredients (such as extra virgin olive oil, seafood, and fresh produce) may be difficult to access, economically burdensome, or culturally mismatched in non-Mediterranean regions [35]. Thus, culturally adapted MD protocols should be developed to retain its core nutritional characteristics while incorporating locally available foods and dietary habits. Coupling these with nutrition education and individualized guidance may further enhance feasibility and long-term adherence.

6.5 Exploring Combined Intervention Strategies

As a foundational dietary model, MD may exert synergistic effects when combined with other nutrients (such as probiotics, curcumin, or resveratrol) or lifestyle interventions (such as exercise or stress management) [23]. Future studies could investigate integrated "multi-dimensional intervention models" to more effectively reduce intestinal inflammation, regulate immune responses, and improve comprehensive treatment outcomes for IBD patients.

7. Summary

As a plant-based dietary pattern rich in anti-inflammatory and antioxidant components, the Mediterranean diet (MD) has been shown in multiple studies to regulate gut microbiota, suppress inflammatory responses, and improve intestinal barrier function through several mechanisms. These findings highlight its significant potential as a nutritional intervention in the management of IBD. Existing clinical evidence suggests that MD can serve as a safe and sustainable adjunctive therapy, providing benefits in reducing disease activity and improving quality of life.

However, current studies are limited by heterogeneous intervention methods, insufficient mechanistic exploration, and a lack of long-term evidence. Future research should prioritize standardized intervention designs, precision nutrition approaches, culturally adapted strategies, and integrated multidimensional interventions, thereby advancing the clinical translation and widespread application of MD in IBD management.

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