



# Nutritional Interventions for Managing Chronic Inflammation: A Comprehensive Review of Dietary Strategies and Their Impact on Gut Microbiota.

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## Abstract

**Background:** Chronic inflammatory disorders, including conditions such as metabolic syndrome, type 2 diabetes (T2DM), and cardiovascular disease (CVD), significantly impact global health, contributing to morbidity and mortality. This review investigates nutritional interventions aimed at managing inflammation associated with these chronic diseases.

**Methods:** A systematic search was performed across multiple electronic databases, including PubMed, Cochrane, Embase, and CINAHL, focusing on articles published until 2023.

**Results:** The review highlights that dietary patterns rich in fiber, particularly those resembling the Mediterranean diet and plant-based diets, are linked to lower levels of inflammation, as indicated by reduced C-reactive protein (CRP) levels. High-fiber diets enhance gut microbiota diversity and promote the proliferation of beneficial bacteria, which are instrumental in producing short-chain fatty acids (SCFAs) that have anti-inflammatory properties. Results demonstrate that dietary modifications leading to increased fiber intake can significantly improve clinical outcomes in individuals with chronic inflammatory conditions, particularly T2DM. However, the effectiveness of different dietary approaches varies, with plant-based diets often showing superior benefits compared to Mediterranean diets.

**Conclusion:** The study concludes that dietary strategies, particularly those increasing fiber intake, are promising adjuncts for managing chronic inflammation and improving health outcomes in affected populations. These findings underscore the importance of dietary interventions in public health strategies aimed at reducing the burden of chronic inflammatory diseases.

**Keywords:** Chronic inflammation, Nutritional interventions, Gut microbiota, Fiber intake, Chronic diseases.

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## 1. Introduction

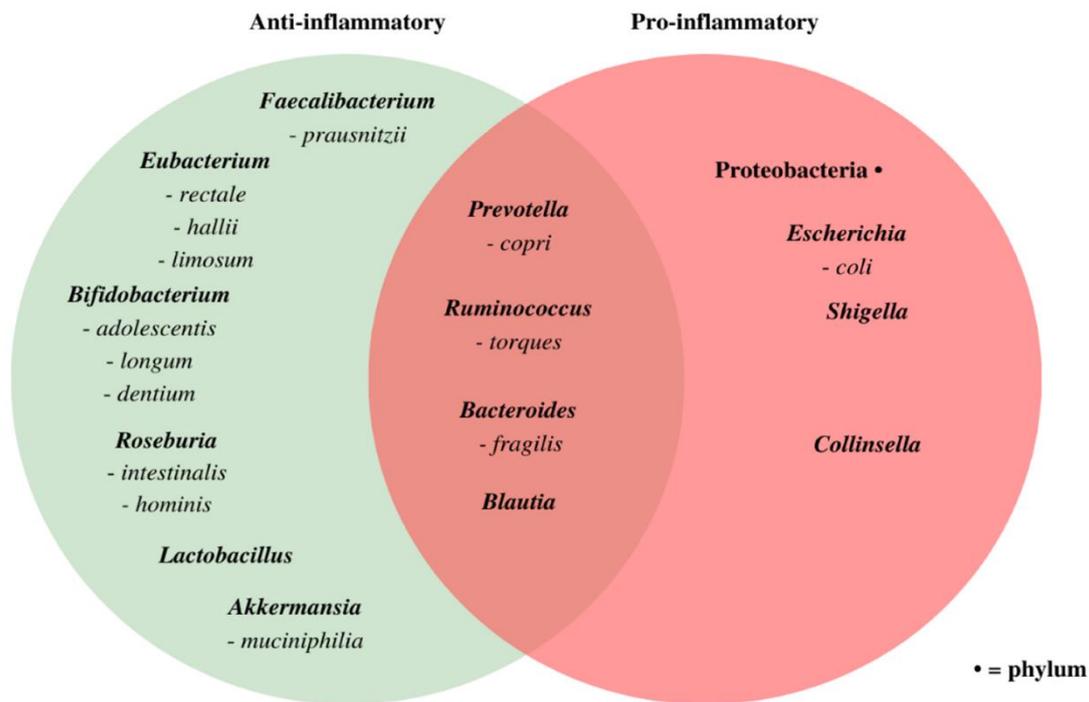
Chronic inflammatory disorders, characterized as non-infectious conditions in which chronic inflammation significantly contributes to their genesis and development, are a primary source of morbidity globally, diminishing both quality of life and lifespan [1]. Inflammation significantly contributes to metabolic syndrome, type 2 diabetes (T2DM), and cardiovascular disease (CVD) [1]. It is also essential to autoimmune illnesses like rheumatoid arthritis (RA), which are linked to a heightened risk of metabolic syndrome, type 2 diabetes mellitus (T2DM), and cardiovascular disease (CVD) [2-4]. C-reactive protein (CRP) serves as an inflammatory marker, with greater levels associated with a heightened risk of chronic diseases and overall mortality. Thus, mitigating inflammation results in a decrease in cardiovascular events and their risk factors [5-8].

Lifestyle variables, including smoking, poor food, and lack of physical exercise, are significant risk factors for chronic inflammation, and alterations in these areas might avert 70–90% of diverse chronic illnesses [1,9]. Among these risk variables, food behavior significantly contributes to mortality and disability-adjusted life years [10]. Mediterranean diets, characterized by high consumption of fruits, vegetables, and other plant-based foods, together with high-fiber diets (including fiber supplementation), are linked to decreased inflammatory levels [11,12].

A mechanism influencing the pro- or anti-inflammatory effects of food is its intermediary influence on the makeup and metabolic activity of the gut microbiota [13]. The gut microbiome comprises many species, including bacteria, viruses, protozoa, and fungi, found in the large intestine. The microbiome performs several activities, including digestion, metabolite production, and interaction with the immune system to facilitate its growth and regulate inflammatory responses [13-15]. The composition and ratio of bacterial species may vary considerably according to several circumstances, including health state, with a microbiome exhibiting more microbial diversity linked to improved health [14,16].

Moreover, gut microbiome dysbiosis, characterized by an imbalance in the composition and function of the gut microbial population, is associated with chronic inflammatory conditions, including autoimmune and metabolic illnesses [16,17]. Increasing data indicates that microbiome dysbiosis might compromise intestinal barrier integrity, affecting the mucus layer and epithelial cell junctions, hence leading to heightened intestinal permeability [13,18]. This enables the transport of detrimental microbiome-derived and environmental elements into the mucosal layer and systemic circulation, hence exacerbating host immune responses and chronic inflammatory conditions [13,18].

A healthy microbiome is defined by its richness and diversity; nevertheless, the ideal makeup of a healthy gut microbiome remains ambiguous and seems to differ across individuals [16,17]. Figure 1 summarizes particular bacterial genera and species typically linked to health, partly owing to their anti-inflammatory properties, contrasted with those recognized as opportunistic pathogens capable of eliciting pro-inflammatory responses [19-37]. A common trait of beneficial anti-inflammatory bacteria is their capacity to generate short-chain fatty acids (SCFA), including butyrate, acetate, and propionate [38]. In vitro and murine models have shown that short-chain fatty acids (SCFAs) regulate intestinal inflammation by enhancing transepithelial resistance, altering several signaling pathways, and suppressing pro-inflammatory cytokines while promoting anti-inflammatory cytokines [20]. Conversely, Proteobacteria, including *Escherichia coli*, *Shigella*, and *Collinsella* are linked to chronic inflammatory disorders [27,28]. For certain bacteria, shown in the intersecting region of the Venn diagram in Figure 1, the impact of their functions on the host—whether advantageous or detrimental—depends on variables such as their prevalence and environmental conditions [29].



**Figure 1. A Venn diagram categorizes different bacterial genera (bold) and species as anti-inflammatory (left circle), pro-inflammatory (right circle), or both (intersection of circles) based on their prevalence and environmental context.**

Diet is a significant factor in modifying the gut microbiota [17]. High-fiber diets, such as vegetarian, vegan, and Mediterranean, characterized by reduced red meat intake and elevated unsaturated fatty acids, correlate with more advantageous microbiome composition, enhanced microbial diversity, and an abundance of health-promoting bacteria, including *Bifidobacteria*, *Lactobacillus*, *Prevotella*, *Eubacterium*, and *Roseburia*, alongside increased levels of short-chain fatty acids (SCFAs) [39,40]. In contrast, Western diets, marked by elevated levels of animal fat and protein and decreased fiber content, exhibit a general reduction in total bacteria, Bifidobacteria, Lactobacillus, and Eubacterium, with an increase in pathogenic Proteobacteria [41]. Daily fiber consumption is crucial for the microbiome alterations linked to food [43]. In the gastrointestinal tract, non-digestible carbohydrates are fermented by the microbiome to produce short-chain fatty acids (SCFAs), whereas some dietary fibers, termed prebiotics, preferentially promote the proliferation of beneficial bacteria in the colon, enhancing host health [41,43,44].

Dietary therapies designed to mitigate inflammatory chronic illnesses and enhance the microbiota show promise. Nevertheless, the area continues to evolve, and the significant variety of research has made the formulation of definitive findings challenging in the past [45]. This comprehensive review seeks to assess the impact of dietary interventions on chronic inflammatory illnesses and the microbiome, as well as the degree to which the microbiome influences the link between these dietary interventions and chronic inflammatory diseases.

## 2. Methods

A comprehensive search was conducted in the electronic databases: PubMed, Cochrane, Embase, and CINAHL until July 2021, without any date constraints. Search phrases about food (e.g., “Diet,” “Nutrition,” “Fiber”), microbiome (e.g., “Microbiota,” “Gastrointestinal microbiome”), and chronic inflammatory disorders (e.g., “Autoimmune disease,” “Inflammation,” “Diabetes,” “heart disease”) were amalgamated. Refer to Supplement S1 for the comprehensive search technique for each database. Only articles in the English language were included, and duplicate items were omitted.

### 3. Clinical advantages seen with high-fiber diets

Dietary therapies that increase fiber intake seem to be most helpful in enhancing disease-specific outcomes and positively modifying the gut microbiota in individuals with chronic inflammatory illnesses, particularly type 2 diabetes mellitus (T2DM). Plant-based nutritional therapies, including vegetarian and vegan diets, have regularly shown superior efficacy in enhancing clinical and microbiome outcomes compared to other dietary interventions, such as Mediterranean dietary patterns. Moreover, increased fiber consumption resulting from a comprehensive dietary modification had greater advantageous benefits than fiber intake via supplementation. Moreover, a hypothesis may be proposed that modifications to the gut microbiota might serve as a mediating component in the observed variations in disease-specific outcomes after dietary treatments. Studies demonstrating a favorable disease response showed a more significant increase in short-chain fatty acid-producing bacteria, perhaps contributing to the anti-inflammatory benefits.

This comprehensive study underscores the advantageous impact of increased fiber consumption for individuals with chronic inflammatory conditions. The results align with epidemiological studies indicating that increased fiber intake and greater adherence to a plant-based dietary pattern correlate with a decreased risk and incidence of T2DM and CVD [46-51]. Fiber consumption progressively escalates from healthy omnivore diets to plant-based diets [52]. The augmentation of fiber may explain the documented clinical advantages of vegan and vegetarian diets on T2DM, CVD, and RA in this systematic review. Low-carbohydrate diets, which restrict the consumption of fiber-rich fruits, starchy vegetables, legumes, and whole grains, have been widely used in the management of T2DM. While these diets demonstrate efficacy in achieving T2DM remission after six months relative to other diets, their advantages wane by 12 months. Furthermore, largely animal-based diets correlate with an elevated risk of cardiovascular disease and death [53,54].

The Mediterranean diet, characterized by a mostly plant-based approach that prioritizes healthy fats and limited animal products, is recognized as a beneficial dietary pattern linked to a decreased risk of chronic illnesses, including cardiovascular disease, and lower all-cause mortality rates [55,56]. This analysis indicates that Mediterranean diets were successful in improving clinical outcomes for people with T2DM but had a limited or inconsistent impact on patients with RA and IBD. Furthermore, Candela et al. [57] demonstrated that a vegan macrobiotic diet yielded a higher daily fiber intake (+15 g/day) and was more efficacious in decreasing fasting blood glucose (FBG) and C-reactive protein (CRP) compared to a Mediterranean diet. Recent research by Barnard et al. indicated that a low-fat vegan diet was more effective in diminishing metabolic risk factors and insulin resistance than a Mediterranean diet [58]. The variable outcomes of Mediterranean diets may stem from significant discrepancies in their interpretation and implementation, with some iterations being more abundant in animal-based goods and deficient in fiber compared to others [59].

Among the 11 trials that used fiber supplementation, only two showed substantial clinical advantages [59,60]. Notably, the fiber interventions comprised supplementation with whole foods abundant in fiber (e.g., germinated barley foodstuff and a functional food supplement containing dehydrated nopal, chia seeds, and inulin), whereas the alternative fiber supplements consisted of isolated fibers (e.g., FOS, GOS, inulin, and psyllium). The comprehensive high-fiber dietary regimens were more efficacious in enhancing disease-specific outcomes compared to supplementation. Thus, substances other than fiber may also play a role in the therapeutic advantages of high-fiber diets. Conversely, King et al. demonstrated that a psyllium fiber supplementation of 25–30 g/day was as beneficial as a high-fiber diet in lowering CRP levels [12]. The trials mentioned may not have administered sufficiently large doses (ranging from 5.5 to 16.5 g/day) to demonstrate an impact. Moreover, different varieties of fiber have diverse biological consequences. Gel-forming fibers (e.g., beta-glucans, psyllium) enhance glycemic regulation and reduce serum cholesterol, whereas other fiber types, including insoluble fiber (e.g., wheat bran) and soluble, non-viscous fiber (e.g., inulin, wheat dextrin, oligosaccharides, and resistant starches), lack these attributes [61]. A varied whole-

food dietary regimen including different forms of fiber may potentially enhance the reported therapeutic outcomes.

While not covered in this review, more evidence exists on the impact of dietary treatments on chronic diseases in studies that did not assess changes in microbiome makeup. Mediterranean and other plant-based diets have shown a reduction in clinical outcomes for rheumatoid arthritis, type 2 diabetes mellitus, inflammatory bowel disease, and cardiovascular disease. Numerous studies demonstrate the advantages of low FODMAP dietary treatments for IBD [62].

#### 4. **High-fiber diets may enhance microbial diversity and the population of short-chain fatty acid-producing bacteria**

Overall, high-fiber whole-diet treatments yielded more advantageous microbiome results than low-fiber diets and fiber supplements. Seventy percent of high-fiber dietary treatments demonstrated a favorable alteration of the microbiome by enhancing variety, augmenting the prevalence of SCFA-producing bacteria, and/or reducing pathogenic bacteria [63-66]. Among the fiber supplement treatments, six out of the eleven studies showed a favorable alteration in the microbiome, three of which used synbiotic interventions. Both low-FODMAP trials adversely impacted the microbiota, although two other low-fiber diets showed some advantageous changes [52-55]. These results align with recent research indicating that high-fiber, low-fat plant-based diets might enhance the prevalence of advantageous polysaccharide-digesting bacterial species [41]. Nonetheless, given the established prebiotic properties of the several fiber supplements used in the included trials (GOS, FOS, and psyllium), a favorable alteration in the microbiota would have been anticipated in these investigations as well [43]. Differences in baseline individual microbiota makeup may influence the efficacy of dietary interventions or fiber supplements in individuals. Moreover, variables like age, physical activity, stress, and environmental conditions, together with dietary elements such as fat and protein consumption, might modify the microbiome and possibly affect the outcomes of the research analyzed [41].

Notwithstanding fiber consumption, the studies analyzed that assessed SCFAs indicated a general reduction in SCFA levels. Despite the surprising nature of these findings, the measurement of fecal amounts of SCFAs, as conducted in these investigations, is an imprecise procedure [43]. The rate of SCFA formation cannot be reliably measured due to many variables, including the absorption of SCFAs in the gut [67]. This evaluation indicated that trials with substantial therapeutic responses had enhanced alpha diversity and a tendency for more advantageous alterations in the microbiome compared to those lacking significant clinical benefits. Therefore, it may be inferred that the detected rise in SCFA-producing bacteria may have contributed to the reduction of inflammation, therefore facilitating the noted enhancements in disease-specific outcomes. Nevertheless, these discoveries are just trends and need more validation in further study. Other metabolites produced by microbes that provide a favorable benefit to the host, referred to as postbiotics, may have anti-inflammatory activity [108]. This study primarily focused on SCFAs; however, further research should explore other postbiotics and their possible mediatory function between the microbiome and host health.

The core microbiome is established early in childhood (between 4 to 36 months) and is regarded as highly stable but yet vulnerable to alterations from the age of two to three years forward [16]. The limited period of the research analyzed (median 12 weeks, range 2–107 weeks) might just reflect short-term impacts on the microbiota. The research does not ascertain whether dietary treatments may induce persistent alterations to the robust adult microbiome.

#### 5. **Methodological Considerations**

This systematic review has many strengths. Initially, it offers a comprehensive perspective on chronic inflammatory illnesses, facilitating a deeper comprehension of the impact of dietary treatments on the common pathophysiology of the affected disease groups. Comparing research on the relative change of disease-specific outcomes allows for a broad assessment of the impact of various dietary treatments on chronic inflammatory disorders, which could otherwise remain undetected. Sorting the studies into dietary

groups based on fiber intake provides an overview of the effects of various fiber treatments. Despite the absence of correlations, stratifying the research into "responder" and "non-responder" groups generates a hypothesis on the possible mediatory effects of the microbiota.

Although efforts have been made to provide a comprehensive perspective on chronic inflammatory illnesses, comparing research remains challenging owing to the many disease-specific outcomes and features used. While inflammation contributes to the pathophysiology of the specified disease categories, these diseases exhibit distinct features. T2DM is a metabolic illness characterized by inflammatory elements, while IBD and RA are autoimmune inflammatory diseases. This review's approach allows for the formulation of a general hypothesis on advantageous dietary patterns for chronic inflammatory illnesses; nevertheless, direct comparisons across disease types are now unfeasible.

The variability in outcomes extends beyond disease categories to include IBD research; for instance, a wide array of outcomes was used to measure disease activity. Given that drugs affect the microbiota variably and several medications were used in the studies, it is essential to interpret the results with care. Moreover, short-term fiber supplementation may exacerbate gastrointestinal symptoms and disease activity in individuals with inflammatory bowel disease (IBD), hence complicating the comparison of fiber intervention outcomes in IBD patients to those in other illnesses [60,61]. Therefore, in patients with IBD, high-fiber diets that include fiber gradually may be most advantageous, since this facilitates adaptation of the gut microbiota, therefore alleviating abdominal discomfort. Given that low-fiber diets, including low-FODMAP, adversely affect the microbiome without enhancing disease activity, IBD patients should approach these diets with care [52,53]. Finally, variations in group size among research should be acknowledged as a drawback. A total of 62% of the studies included had less than 50 enrolled people, 27% had between 50 and 100 participants, and 10% had more than 100 participants. Small research populations may be insufficient for microbiome analysis because of the considerable inter-individual variability of the microbiome [68].

## 6. Conclusion

Owing to the variability of the studies, only patterns can be seen between dietary treatments, disease-specific outcomes, and microbiome outcomes in comparative analyses. Moreover, the results should be evaluated judiciously and can only serve to generate supplementary hypotheses and stimulate further study.

This research was limited to dietary treatments including whole food modifications or fiber supplementation. Nonetheless, it is recognized that several dietary elements, including protein and fat, may similarly affect the microbiome [40,44]. Furthermore, not all research documented the changes in specific dietary components, such as fiber, complicating the correct comparison of dietary treatments.

Ultimately, the area of microbial science is very young and rapidly advancing. Consequently, there are several constraints associated with the methodologies used in microbiome research [66]. At present, 16S ribosomal RNA (16S rRNA) sequencing is the predominant technique for the analysis of bacterial species. This approach is superior, particularly in comparison to gas-liquid chromatography or FISH. This methodology exhibits flaws in species-level categorization; hence, future microbiome research should prioritize full metagenome sequencing methods [68].

Future research should use a comprehensive approach including several chronic inflammatory disorders to better understand the impact of dietary treatments. To do this with more precision, standardized outcomes must be used to quantify disease-specific results, and dietary evaluations should be utilized to provide data on changes in nutrient consumption. Additional dietary intervention studies are essential in chronic inflammatory illnesses (IBD, RA, and CVD) to ascertain if the observed patterns are universally relevant to chronic inflammatory diseases or are particular to individual conditions.

## References

1. Furman, D.; Campisi, J.; Verdin, E.; Carrera-Bastos, P.; Targ, S.; Franceschi, C.; Ferrucci, L.; Gilroy, D.W.; Fasano, A.; Miller, G.W.; et al. Chronic inflammation in the etiology of disease across the life span. *Nat. Med.* 2019, 25, 1822–1832.
2. Armstrong, A.W.; Harskamp, C.T.; Armstrong, E.J. Psoriasis and the risk of diabetes mellitus: A systematic review and meta-analysis. *JAMA Dermatol.* 2013, 149, 84–91.
3. Dregan, A.; Charlton, J.; Chowienczyk, P.; Gulliford, M.C. Chronic Inflammatory Disorders and Risk of Type 2 Diabetes Mellitus, Coronary Heart Disease, and Stroke. *Circulation* 2014, 130, 837–844.
4. Zhang, J.; Fu, L.; Shi, J.; Chen, X.; Li, Y.; Ma, B.; Zhnag, Y. The risk of metabolic syndrome in patients with rheumatoid arthritis: A meta-analysis of observational studies. *PLoS ONE* 2013, 8, e78151.
5. Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: An individual participant meta-analysis. *Lancet* 2010, 375, 132–140.
6. Proctor, M.J.; McMillan, D.; Horgan, P.G.; Fletcher, C.D.; Talwar, D.; Morrison, D. Systemic Inflammation Predicts All-Cause Mortality: A Glasgow Inflammation Outcome Study. *PLoS ONE* 2015, 10, e0116206.
7. Burska, A.N.; Sakthiswary, R.; Sattar, N. Effects of Tumour Necrosis Factor Antagonists on Insulin Sensitivity/Resistance in Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *PLoS ONE* 2015, 10, e0128889.
8. Ridker, P.M.; Everett, B.M.; Thuren, T.; MacFadyen, J.G.; Chang, W.H.; Ballantyne, C.; Fonseca, F.; Nicolau, J.; Koenig, W.; Anker, S.D.; et al. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. *N. Engl. J. Med.* 2017, 377, 1119–1131.
9. Willett, W.C. Balancing Life-Style and Genomics Research for Disease Prevention. *Science* 2002, 296, 695–698.
10. Murray, C.J.; Abraham, J.; Ali, M.K.; Alvarado, M.; Atkinson, C.; Baddour, L.M.; Bartels, D.H.; Birbeck, G.; Burstein, R.; Chou, D.; et al. The state of US health, 1990–2010: Burden of diseases, injuries, and risk factors. *JAMA* 2013, 310, 591–608.
11. Smidowicz, A.; Regula, J. Effect of Nutritional Status and Dietary Patterns on Human Serum C-Reactive Protein and Interleukin-6 Concentrations. *Adv. Nutr.* 2015, 6, 738–747.
12. King, D.E.; Egan, B.M.; Woolson, R.F.; Mainous, A.G., 3rd; Al-Solaiman, Y.; Jesri, A. Effect of a high-fiber diet vs a fiber-supplemented diet on C-reactive protein level. *Arch. Intern. Med.* 2007, 167, 502–506.
13. Zheng, D.; Liwinski, T.; Elinav, E. Interaction between microbiota and immunity in health and disease. *Cell Res.* 2020, 30, 492–506.
14. Valdes, A.; Walter, J.; Segal, E.; Spector, T.D. Role of the gut microbiota in nutrition and health. *BMJ* 2018, 361, k2179.
15. Blander, J.M.; Longman, R.S.; Iliev, I.D.; Sonnenberg, G.F.; Artis, D. Regulation of inflammation by microbiota interactions with the host. *Nat. Immunol.* 2017, 18, 851–860.
16. Rinninella, E.; Raoul, P.; Cintoni, M.; Franceschi, F.; Miggiano, G.A.D.; Gasbarrini, A.; Mele, M.C.; Rinninella, E.; Raoul, P.; Cintoni, M.; et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms* 2019, 7, 14.
17. Illiano, P.; Brambilla, R.; Parolini, C. The mutual interplay of gut microbiota, diet and human disease. *FEBS J.* 2019, 287, 833–855.
18. Allam-Ndoul, B.; Castonguay-Paradis, S.; Veilleux, A. Gut Microbiota and Intestinal Trans-Epithelial Permeability. *Int. J. Mol. Sci.* 2020, 21, 6402.
19. Ferreira-Halder, C.V.; Faria, A.V.D.S.; Andrade, S.S. Action and function of *Faecalibacterium prausnitzii* in health and disease. *Best Pr. Res. Clin. Gastroenterol.* 2017, 31, 643–648.
20. Mukherjee, A.; Lordan, C.; Ross, R.P.; Cotter, P.D. Gut microbes from the phylogenetically diverse genus *Eubacterium* and their various contributions to gut health. *Gut Microbes* 2020, 12.
21. Tamanai-Shacoori, Z.; Smida, I.; Bousarghin, L.; Loreal, O.; Meuric, V.; Fong, S.B.; Bonneure-Mallet, M.; Jolivet-Gougeon, A. *Roseburia* spp.: A marker of health? *Future Microbiol.* 2017, 12, 157–170.
22. Geerlings, S.Y.; Kostopoulos, I.; De Vos, W.M.; Belzer, C.; Geerlings, S.Y.; Kostopoulos, I.; De Vos, W.M.; Belzer, C. *Akkermansia muciniphila* in the Human Gastrointestinal Tract: When, Where, and How? *Microorganisms* 2018, 6, 75.

23. Ottman, N.; Reunanen, J.; Meijerink, M.; Pietilä, T.E.; Kainulainen, V.; Klievink, J.; Huuskonen, L.; Aalvink, S.; Skurnik, M.; Boeren, S.; et al. Pili-like proteins of *Akkermansia muciniphila* modulate host immune responses and gut barrier function. *PLoS ONE* 2017, 12, e0173004.
24. Karlsson, F.H.; Tremaroli, V.; Nookaew, I.; Bergström, G.; Behre, C.J.; Fagerberg, B.; Nielsen, J.; Bäckhed, F. Gut metagenome in European women with normal, impaired and diabetic glucose control. *Nature* 2013, 498, 99–103.
25. Shen, Z.; Zhu, C.; Quan, Y.; Yang, J.; Yuan, W.; Yang, Z.; Wu, S.; Luo, W.; Tan, B.; Wang, X. Insights into *Roseburia intestinalis* which alleviates experimental colitis pathology by inducing anti-inflammatory responses. *J. Gastroenterol. Hepatol.* 2018, 33, 1751–1760.
26. Round, J.L.; Mazmanian, S.K. The gut microbiota shapes intestinal immune responses during health and disease. *Nat. Rev. Immunol.* 2009, 9, 313–323.
27. Rizzatti, G.; Lopetuso, L.R.; Gibiino, G.; Binda, C.; Gasbarrini, A. Proteobacteria: A Common Factor in Human Diseases. *BioMed Res. Int.* 2017, 2017, 1–7.
28. Astbury, S.; Atallah, E.; Vijay, A.; Aithal, G.P.; I Grove, J.; Valdes, A.M. Lower gut microbiome diversity and higher abundance of proinflammatory genus *Collinsella* are associated with biopsy-proven nonalcoholic steatohepatitis. *Gut Microbes* 2019, 11, 569–580.
29. Zafar, H.; Saier, M.H., Jr. Gut *Bacteroides* species in health and disease. *Gut Microbes* 2021, 13, 1–20.
30. Heeney, D.D.; Gareau, M.G.; Marco, M.L. Intestinal *Lactobacillus* in health and disease, a driver or just along for the ride? *Curr. Opin. Biotechnol.* 2017, 49, 140–147.
31. O’Callaghan, A.; van Sinderen, D. Bifidobacteria and Their Role as Members of the Human Gut Microbiota. *Front. Microbiol.* 2016, 7, 925.
32. Precup, G.; Vodnar, D.-C. Gut *Prevotella* as a possible biomarker of diet and its eubiotic versus dysbiotic roles: A comprehensive literature review. *Br. J. Nutr.* 2019, 122, 131–140.
33. Vacca, M.; Celano, G.; Calabrese, F.M.; Portincasa, P.; Gobbetti, M.; De Angelis, M. The Controversial Role of Human Gut *Lachnospiraceae*. *Microorganisms* 2020, 8, 573.
34. Png, C.W.; Lindén, S.K.; Gilshenan, K.S.; Zoetendal, E.G.; McSweeney, C.S.; Sly, L.I.; McGuckin, M.A.; Florin, T.H. Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. *Am. J. Gastroenterol.* 2010, 105, 2420–2428.
35. Liu, X.; Mao, B.; Gu, J.; Wu, J.; Cui, S.; Wang, G.; Zhao, J.; Zhang, H.; Chen, W. *Blautia*—a new functional genus with potential probiotic properties? *Gut Microbes* 2021, 13, 1–21.
36. Benítez-Páez, A.; del Pugar, E.M.G.; López-Almela, I.; Moya-Pérez, A.; Codoñer-Franch, P.; Sanz, Y. Depletion of *Blautia* Species in the Microbiota of Obese Children Relates to Intestinal Inflammation and Metabolic Phenotype Worsening. *mSystems* 2020, 5, e00857-19.
37. Wexler, H.M. *Bacteroides*: The good, the bad, and the nitty-gritty. *Clin. Microbiol. Rev.* 2007, 20, 593–621.
38. Parada Venegas, D.; De la Fuente, M.K.; Landskron, G.; González, M.J.; Quera, R.; Dijkstra, G.; Harmsen, H.J.; Faber, K.N.; Hermoso, M.A. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. *Front. Immunol.* 2019, 10, 277.
39. De Filippo, C.; Cavalieri, D.; Di Paola, M.; Ramazzotti, M.; Poullet, J.B.; Massart, S.; Collini, S.; Pieraccini, G.; Lionetti, P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc. Natl. Acad. Sci. USA* 2010, 107, 14691–14696.
40. Tomova, A.; Bukovsky, I.; Rembert, E.; Yonas, W.; Alwarith, J.; Barnard, N.D.; Kahleova, H. The Effects of Vegetarian and Vegan Diets on Gut Microbiota. *Front. Nutr.* 2019, 6, 47.
41. Singh, R.K.; Chang, H.-W.; Yan, D.; Lee, K.M.; Ucmak, D.; Wong, K.; Abrouk, M.; Farahnik, B.; Nakamura, M.; Zhu, T.H.; et al. Influence of diet on the gut microbiome and implications for human health. *J. Transl. Med.* 2017, 15, 1–17.
42. De Filippis, F.; Pellegrini, N.; Vannini, L.; Jeffery, I.; La Stora, A.; Laghi, L.; Serrazanetti, D.I.; Di Cagno, R.; Ferracino, I.; Lazzi, C.; et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut* 2015, 65, 1812–1821.
43. Slavin, J. Fiber and Prebiotics: Mechanisms and Health Benefits. *Nutrients* 2013, 5, 1417–1435.
44. Holscher, H.D. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes* 2017, 8, 172–184.

45. Telle-Hansen, V.H.; Holven, K.B.; Ulven, S.M. Impact of a Healthy Dietary Pattern on Gut Microbiota and Systemic Inflammation in Humans. *Nutrients* 2018, 10, 1783.
46. Meyer, K.A.; Kushi, L.H.; Jacobs, D.R.; Slavin, J., Jr.; Sellers, T.A.; Folsom, A.R. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am. J. Clin. Nutr.* 2000, 71, 921–930.
47. E Threapleton, D.; Greenwood, D.C.; Evans, C.; Cleghorn, C.L.; Nykjaer, C.; Woodhead, C.; Cade, J.; Gale, C.P.; Burley, V.J. Dietary fibre intake and risk of cardiovascular disease: Systematic review and meta-analysis. *BMJ* 2013, 347, f6879.
48. Lie, L.; Brown, L.; Forrester, T.E.; Plange-Rhule, J.; Bovet, P.; Lambert, E.V.; Layden, B.T.; Luke, A.; Dugas, L.R. The Association of Dietary Fiber Intake with Cardiometabolic Risk in Four Countries across the Epidemiologic Transition. *Nutrients* 2018, 10, 628.
49. Satija, A.; Hu, F.B. Plant-based diets and cardiovascular health. *Trends Cardiovasc. Med.* 2018, 28, 437–441.
50. Satija, A.; Bhupathiraju, S.N.; Rimm, E.B.; Spiegelman, D.; Chiuve, S.; Borgi, L.; Willett, W.C.; Manson, J.E.; Sun, Q.; Hu, F.B. Plant-Based Dietary Patterns and Incidence of Type 2 Diabetes in US Men and Women: Results from Three Prospective Cohort Studies. *PLoS Med.* 2016, 13, e1002039.
51. Qian, F.; Liu, G.; Hu, F.B.; Bhupathiraju, S.N.; Sun, Q. Association Between Plant-Based Dietary Patterns and Risk of Type 2 Diabetes: A Systematic Review and Meta-analysis. *JAMA Intern. Med.* 2019, 179, 1335–1344.
52. Orlich, M.J.; E Fraser, G. Vegetarian diets in the Adventist Health Study 2: A review of initial published findings. *Am. J. Clin. Nutr.* 2014, 100, 353S–358S.
53. Goldenberg, J.Z.; Day, A.; Brinkworth, G.D.; Sato, J.; Yamada, S.; Jönsson, T.; Beardsley, J.; Johnson, J.A.; Thabane, L.; Johnston, B.C. Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: Systematic review and meta-analysis of published and unpublished randomized trial data. *BMJ* 2021, 372, m4743.
54. Seidelmann, S.B.; Claggett, B.; Cheng, S.; Henglin, M.; Shah, A.; Steffen, L.M.; Folsom, A.R.; Rimm, E.B.; Willett, W.C.; Solomon, S.D. Dietary carbohydrate intake and mortality: A prospective cohort study and meta-analysis. *Lancet Public Health* 2018, 3, e419–e428.
55. Martinez-Lacoba, R.; Pardo-Garcia, I.; Amo-Saus, E.; Sotos, F.E. Mediterranean diet and health outcomes: A systematic meta-review. *Eur. J. Public Health* 2018, 28, 955–961.
56. Lopez-Garcia, E.; Rodriguez-Artalejo, F.; Li, T.Y.; Fung, T.T.; Li, S.; Willett, W.C.; Rimm, E.B.; Hu, F.B. The Mediterranean-style dietary pattern and mortality among men and women with cardiovascular disease. *Am. J. Clin. Nutr.* 2013, 99, 172–180.
57. Candela, M.; Biagi, E.; Soverini, M.; Consolandi, C.; Quercia, S.; Severgnini, M.; Peano, C.; Turrone, S.; Rampelli, S.; Pozzilli, P.; et al. Modulation of gut microbiota dysbioses in type 2 diabetic patients by macrobiotic Ma-Pi 2 diet. *Br. J. Nutr.* 2016, 116, 80–93.
58. Barnard, N.D.; Alwarith, J.; Rembert, E.; Brandon, L.; Nguyen, M.; Goergen, A.; Horne, T.; Nascimento, G.F.D.; Lakkadi, K.; Tura, A.; et al. A Mediterranean Diet and Low-Fat Vegan Diet to Improve Body Weight and Cardiometabolic Risk Factors: A Randomized, Cross-over Trial. *J. Am. Coll. Nutr.* 2021, 1–13.
59. Nestle, M. Mediterranean diets: Historical and research overview. *Am. J. Clin. Nutr.* 1995, 61, 1313S–1320S.
60. Medina-Vera, I.; Sánchez-Tapia, M.; Noriega-López, L.; Granados-Portillo, O.; Guevara-Cruz, M.; Flores-López, A.; Avila-Nava, A.; Fernández, M.L.; Tovar, A.R.; Torres, N. A dietary intervention with functional foods reduces metabolic endotoxaemia and attenuates biochemical abnormalities by modifying faecal microbiota in people with type 2 diabetes. *Diabetes Metab.* 2018, 45, 122–131.
61. McRorie, J.W. Evidence-Based Approach to Fiber Supplements and Clinically Meaningful Health Benefits, Part 1. *Nutr. Today* 2015, 50, 82–89.
62. Philippou, E.; Petersson, S.D.; Rodomar, C.; Nikiphorou, E. Rheumatoid arthritis and dietary interventions: Systematic review of clinical trials. *Nutr. Rev.* 2020, 79, 410–428.
63. Klammer C, Schindler K, Bugl R, Plazek D, Vötter M, Kirchner T, Martino C, Klammer-Martin J, Brix J, Dämon S, Hoppichler F. Nutrition for diabetic patients (Update 2023). *Wiener Klinische Wochenschrift.* 2023 Jan 1;135(Suppl 1):62-77.
64. Neuenschwander, M.; Ballon, A.; Weber, K.S.; Norat, T.; Aune, D.; Schwingshackl, L.; Schlesinger, S. Role of diet in type 2 diabetes incidence: Umbrella review of meta-analyses of prospective observational studies. *BMJ* 2019, 366, l2368.

65. Pollakova, D.; Andreadi, A.; Pacifici, F.; Della-Morte, D.; Lauro, D.; Tubili, C. The Impact of Vegan Diet in the Prevention and Treatment of Type 2 Diabetes: A Systematic Review. *Nutrients* 2021, 13, 2123.
66. Popa, S.L.; Pop, C.; Dumitrascu, D.L. Diet Advice for Crohn's Disease: FODMAP and Beyond. *Nutrients* 2020, 12, 3751.
67. Sakata, T. Pitfalls in short-chain fatty acid research: A methodological review. *Anim. Sci. J.* 2018, 90, 3–13.
68. Cronin O, Lanham-New SA, Corfe BM, Gregson CL, Darling AL, Ahmadi KR, Gibson PS, Tobias JH, Ward KA, Traka MH, Rossi M. Role of the microbiome in regulating bone metabolism and susceptibility to osteoporosis. *Calcified tissue international*. 2022 Mar 1:1-2.

## التدخلات الغذائية لإدارة الالتهابات المزمنة : مراجعة شاملة لاستراتيجيات النظام الغذائي وتأثيرها على ميكروبات الأمعاء

### الملخص

**الخلفية:** تؤثر الاضطرابات الالتهابية المزمنة، بما في ذلك حالات مثل متلازمة الأيض، داء السكري من النوع 2 (T2DM)، وأمراض القلب والأوعية الدموية (CVD)، بشكل كبير على الصحة العالمية، مسببة مضاعفات ووفيات. تستعرض هذه المراجعة التدخلات الغذائية التي تهدف إلى إدارة الالتهابات المرتبطة بهذه الأمراض المزمنة.

**الطرق:** تم إجراء بحث منهجي عبر قواعد بيانات إلكترونية متعددة، بما في ذلك PubMed، وكوكرين، Embase، وCINAHL، مع التركيز على المقالات المنشورة حتى عام 2023.

**النتائج:** تبرز المراجعة أن أنماط النظام الغذائي الغنية بالألياف، لا سيما تلك المشابهة للنظام الغذائي المتوسطي والأنظمة الغذائية المعتمدة على النباتات، مرتبطة بمستويات منخفضة من الالتهابات، كما يتضح من انخفاض مستويات بروتين سي التفاعلي (CRP). تعزز الأنظمة الغذائية الغنية بالألياف تنوع ميكروبات الأمعاء وتقوي نمو البكتيريا المفيدة، التي تلعب دورًا أساسيًا في إنتاج الأحماض الدهنية قصيرة السلسلة (SCFAs) التي تتمتع بخصائص مضادة للالتهابات. تظهر النتائج أن تعديلات النظام الغذائي التي تؤدي إلى زيادة تناول الألياف يمكن أن تحسن بشكل كبير المخرجات السريرية لدى الأفراد الذين يعانون من حالات التهاب مزمن، خاصة داء السكري من النوع 2. ومع ذلك، تختلف فعالية الاستراتيجيات الغذائية المختلفة، حيث تُظهر الأنظمة الغذائية المعتمدة على النباتات فوائد أكبر مقارنةً بالأنظمة الغذائية المتوسطة.

**الاستنتاج:** تصل الدراسة إلى أن الاستراتيجيات الغذائية، لا سيما تلك التي تزيد من تناول الألياف، تمثل مضافات واعدة لإدارة الالتهابات المزمنة وتحسين النتائج الصحية في الفئات المتأثرة. تؤكد هذه النتائج على أهمية التدخلات الغذائية في استراتيجيات الصحة العامة الهادفة إلى تقليل عبء الأمراض الالتهابية المزمنة.

**الكلمات المفتاحية:** الالتهابات المزمنة، التدخلات الغذائية، ميكروبات الأمعاء، تناول الألياف، الأمراض المزمنة.