Escola Superior
de Tecnologia
da Saúde
Politécnico de Coimbra

Carolina Matias Bernardes

POLYPHENOLS DUPLIBIOTIC ROLE IN INTESTINAL INFLAMMATORY DISEASE: FOCUS ON NEXT-GENERATION *AKKERMANSIA MUCINIPHILA*

Dissertação no âmbito do Mestrado em Farmácia - Especialização em Farmacoterapia Aplicada, orientada pelo Doutor Flávio Nelson Fernandes Reis, pela Doutora Sara Raquel Nunes e pelo Mestre André Filipe Alves e apresentada na Escola Superior de Tecnologia da Saúde do Politécnico de Coimbra para obtenção do grau de Mestre.

Setembro de 2024

Escola Superior
de Tecnologia
da Saúde
Politécnico de Coimbra

Escola Superior
de Tecnologia
da Saúde
Politécnico de Coimbra

POLYPHENOLS DUPLIBIOTIC ROLE IN INTESTINAL INFLAMMATORY DISEASE: FOCUS ON NEXT-GENERATION *AKKERMANSIA MUCINIPHILA*

Carolina Matias Bernardes

Dissertação no âmbito do Mestrado em Farmácia - Especialização em Farmacoterapia Aplicada, orientada pelo Doutor Flávio Nelson Fernandes Reis, pela Doutora Sara Raquel Nunes e pelo Mestre André Filipe Alves e apresentada na Escola Superior de Tecnologia da Saúde do Politécnico de Coimbra para obtenção do grau de Mestre.

Setembro de 2024

Escola Superior
de Tecnologia
da Saúde
Politécnico de Coimbra

Escola Superior
de Tecnologia
da Saúde
Politécnico de Coimbra

1 2 9 0 FACULDADE DE MEDICINA
UNIVERSIDADE D
COIMBRA

iCBR Coimbra Institute for Clinical and Biomedical Research
Faculty of Medicine – University of Coimbra

cibb
CENTRE FOR INNOVATIVE
BIOMEDICINE
AND BIOTECHNOLOGY

This work was performed at the Institute of Pharmacology and Experimental Therapeutics and at the Coimbra Institute for Clinical and Biomedical Research (iCBR), from the Faculty of Medicine of the University of Coimbra.

This work was supported by the European Regional Development Fund (ERDF) through the Operational Program for Competitiveness Factors (COMPETE) and by National funds via Portuguese Science and Technology Foundation (FCT) through strategic projects UIDB/04539/2020 and UIDP/04539/2020.

fct Fundação
para a Ciência
e a Tecnologia

COMPETE
PROGRAMA OPERACIONAL FACTORES DE COMPETITIVIDADE

REPÚBLICA
PORTUGUESA

UNIÃO EUROPEIA
Fundo Europeu
de Desenvolvimento Regional

Acknowledgments

Esta dissertação é o culminar de uma jornada académica muito importante, que não teria sido possível sem a orientação e o apoio de pessoas muito especiais, às quais quero expressar a minha gratidão.

Em primeiro lugar, gostaria de exprimir o meu mais sincero agradecimento aos meus orientadores, o Dr. Flávio Reis e a Prof. Dra. Sofia Viana, pela sua orientação ao longo desta jornada.

Agradeço aos meus coorientadores Sara Nunes e André Alves, pela colaboração, ajuda, dedicação e paciência durante todo este processo. As vossas orientações foram fundamentais para o desenvolvimento deste trabalho e para o meu crescimento tanto a nível pessoal como a nível académico. Agradeço também pelo tempo que despenderam, pelas críticas construtivas e sugestões de melhoria que foram sucessivamente tecendo, contribuindo assim para a superação deste desafio. O apoio de ambos, em momentos de dúvida e incerteza, foi determinante para que eu pudesse concluir esta etapa tão importante da minha vida, sem vocês não teria sido possível. Muito obrigada.

Gostaria de deixar um agradecimento especial à minha melhor amiga, Sara Umbelino. A tua amizade, apoio incondicional e palavras de encorajamento nos momentos mais difíceis foram essenciais para que eu me mantivesse motivada e focada. Obrigada por estares sempre ao meu lado, por me ouvires e por acreditares em mim, mesmo quando eu própria duvidava. Sem ti, esta jornada teria sido muito mais difícil.

Quero agradecer também aos meus colegas de trabalho, por me terem ajudado sempre que foi necessário efetuar alguma troca ou ajustar o horário para que pudesse assistir às aulas.

Gostaria também de deixar um agradecimento a todos os professores deste mestrado que ao longo desta jornada, contribuíram de maneira significativa para minha formação académica.

Por fim, agradeço a todos os que, de alguma forma, contribuíram para a realização deste trabalho. O meu mais sincero obrigada.

Resumo

As doenças inflamatórias intestinais (DII), que incluem a doença de Crohn (DC) e a colite ulcerosa (CU), representam uma condição inflamatória crónica do trato digestivo. A patogénese da DII é complexa e multifatorial, resultando da interação de fatores ambientais, predisposição genética, disbiose intestinal e desregulação do sistema imunológico; contudo, a etiologia exata da doença permanece desconhecida. A redução da abundância de Akkermansia muciniphila foi observada em doentes com DII, sugerindo um possível papel na progressão da doença e um potencial alvo para estratégias terapêuticas. A. muciniphila é uma bactéria degradadora de mucina, que exibe efeitos protetores na integridade da barreira intestinal e propriedades anti-inflamatórias, sendo reconhecida como um probiótico de última geração pelo seu potencial benefício na saúde intestinal. No entanto, o seu papel exato e os mecanismos subjacentes na DII requerem mais investigação.

Os polifenóis (PPs) são compostos bioativos encontrados em alimentos de origem vegetal, com propriedades prebióticas, anti-inflamatórias, antioxidantes e antimicrobianas. Evidências emergentes sugerem um efeito "duplibiótico" onde os PPs aumentam a abundância de A. muciniphila e simultaneamente beneficiam a saúde intestinal, principalmente devido aos seus efeitos antimicrobianos. Esta tese investiga a interação entre PPs e A. muciniphila, explorando os seus potenciais efeitos benéficos na modulação da microbiota intestinal, na integridade da mucosa e na redução da inflamação na DII.

Esta revisão seguiu as diretrizes PRISMA-ScR. A pesquisa bibliográfica, realizada entre 2012 e 2023 (outubro) na PubMed, focou-se em estudos quase experimentais e experimentais usando modelos in vitro, modelos animais e humanos. A estratégia de pesquisa incluiu palavras-chave como "Polifenóis", "Doença Inflamatória Intestinal", "Microbiota Intestinal" e "Akkermansia muciniphila", e os estudos foram analisados utilizando o software Covidence. Apenas foram incluídos artigos originais que reportavam efeitos dos PPs na abundância de A. muciniphila na DII. As principais descobertas relacionadas com classe de polifenóis, modulação da microbiota intestinal e resultados clínicos foram sintetizadas em tabelas para avaliar o seu potencial papel terapêutico na DII.

Num total de 47 artigos incluídos nesta revisão, analisou-se o impacto de classes específicas de PPs (flavonoides, ácidos fenólicos e outros) na abundância de A. muciniphila, na diversidade e composição da microbiota intestinal (nomeadamente em bactérias aeróbicas e anaeróbicas), e em outros parâmetros relacionados com a DII.

As evidências destacam a capacidade de classes distintas de PPs, particularmente flavonoides, de restaurar a função da barreira intestinal, reduzir a inflamação e promover a regulação imunológica, particularmente em modelos animais, bem como a capacidade de estimular a abundância de A. muciniphila e aumentar os seus efeitos benéficos. As descobertas sugerem que dietas ricas em PPs podem servir como uma terapia coadjuvante promissora para a DII, promovendo uma mudança em direção à eubiose e melhorando a função da barreira intestinal. A existência de um efeito duplibiótico dos PPs na DII devido à modulação específica de A. muciniphila merece investigação adicional, de forma a elucidar os mecanismos moleculares subjacentes, com vista a desenvolver estratégias terapêuticas direcionadas capazes de melhorar a qualidade de vida de doentes com DII.

Palavras-chave: Doença inflamatória intestinal, *Akkermansia muciniphila*, Polifenóis, Microbiota intestinal, Saúde intestinal

Abstract

Inflammatory bowel diseases (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), represents a chronic inflammatory condition of the digestive tract. The pathogenesis of IBD is complex and multifactorial, resulting from an intricate interplay of environmental factors, genetic predisposition, gut dysbiosis, and immune system dysregulation; however, the exact etiology of the disease remains unknown. Reduction of *Akkermansia muciniphila* abundance has been observed in IBD patients, suggesting a possible role in disease progression and a potential target for therapeutic strategies. *A. muciniphila*, a mucin-degrading bacteria, exhibits protective effects on gut barrier integrity and has anti-inflammatory properties, being recognized as a next-generation probiotic for its potential to benefit gut health. However, the precise role and underlying mechanisms in IBD require further investigation.

Polyphenols (PPs), bioactive compounds found in plant-based foods, exhibit prebiotic, anti-inflammatory, antioxidant, and antimicrobial properties. Emerging evidence suggests a novel "duplibiotic" effect where PPs enhance the abundance of *A. muciniphila* while simultaneously benefiting gut health, namely by having antimicrobial effects. This thesis investigates the interplay between PPs and *A. muciniphila*, exploring their potential beneficial effects in modulating gut microbiota, improving intestinal mucosal integrity, and reducing inflammation in IBD.

This scoping review was conducted following the PRISMA-ScR guidelines. The literature search, performed from 2012 to 2023 (October) in PubMed, focused on quasi-experimental and experimental studies using in vitro models, animal models, and human participants. The search strategy incorporated keywords like "Polyphenols," "Inflammatory Bowel Disease," "Gut Microbiota," and "*Akkermansia muciniphila*," and studies were screened using Covidence software. Only original research exploring the effects of polyphenols on *A. muciniphila* abundance in IBD was included. Key findings related to polyphenol class, gut microbiota modulation, and clinical outcomes were synthesized and presented in tables to evaluate their potential therapeutic role in IBD management.

Through a comprehensive analysis of a final number of 47 articles included in this scoping review, the impact of specific PPs classes (flavonoids, phenolic acids, and others) on *A. muciniphila* abundance, gut microbiota diversity and composition (namely on aerobic and anaerobic bacteria), as well as on IBD-related outcomes.

Evidence from the literature highlights the capacity of distinct PPs classes, particularly flavonoids, to restore intestinal barrier function, reduce inflammation, and promote immune regulation, particularly in animal models, as well as the ability to stimulate *A. muciniphila* abundance and enhance its beneficial effects. The findings suggest that PP-rich diets could serve as a promising co-adjuvant therapy for IBD, promoting a shift towards eubiosis and improving gut barrier function. The existence of a duplibiotic effect of PPs on IBD due to specific modulation of *A. muciniphila* deserve further clarification. In particular, further research is required to elucidate the precise molecular mechanisms underlying this interaction between PPs and *A. muciniphila*, in order to develop targeted therapeutic strategies able to improve IBD patients' quality of life.

Keywords: Inflammatory bowel disease, *Akkermansia muciniphila*, Polyphenols, Gut Microbiota, Gut health.

List of Abbreviations

ADME – Absorption, distribution, metabolism and excretion

A. muciniphila – Akkermansia muciniphila

AmEVS – *A. muciniphila* extracellular vesicles

CAT – Catalase

CD – Crohn's disease

CRP – C-reactive protein

DAI – Disease activity index

DAMPs – Damage-associated molecular patterns

DNA – Deoxyribonucleic acid

DSS – Dextran sulfate sodium

FMT – Fecal microbiota transplantation

HFD – High-fat diet

HO-1 – Heme-oxygenase 1

IBD – Inflammatory bowel disease

IECs – Intestinal epithelial cells

Ig – Immunoglobulin

IgG1 – Immunoglobulin G1

IL – Interleukin

LPS – Lipopolysaccharides

MDA – Malondialdehyde

MPO – Myeloperoxidase

NF-κB – Nuclear factor kappa-light-chain-enhancer of activated B cells

NGPs – Next-generation probiotics

NLRs – Nod-like receptors

Nrf2 – Nuclear factor erythroid 2-related factor 2

PAMPs – Pathogen-associated molecular patters

PAZymes – Polyphenol-associated enzymes

PCR – Polymerase chain reaction

PPs – Polyphenols

PRRs – Pattern recognition receptors

QS – Quorum sensing

ROS – Reactive oxygen species

SCFAs – Short-chain fatty acids

SOD – Superoxide dismutase

TFA – Total flavone of Abelmoschus Manihot

TFH – T-follicular helper

Th17 – T-helper 17

TLRs – Toll-like receptors

TNF – Tumor necrosis factor

Tregs – Regulatory T cells

UC – Ulcerative colitis

WMT – Washed microbiota transplantation

List of Figures

List of Tables

Contents

CHAPTER I – INTRODUCTION

1.1. Inflammatory Bowel Disease (IBD): An overview

1.1.1. Definition and clinical diagnosis

Inflammatory bowel disease (IBD) encompasses a subset of inflammatory diseases involving the small intestine and the colon. IBD primary types are Ulcerative Colitis (UC) and Crohn's Disease (CD) (Bruner et al., 2023; Hussein et al., 2023).

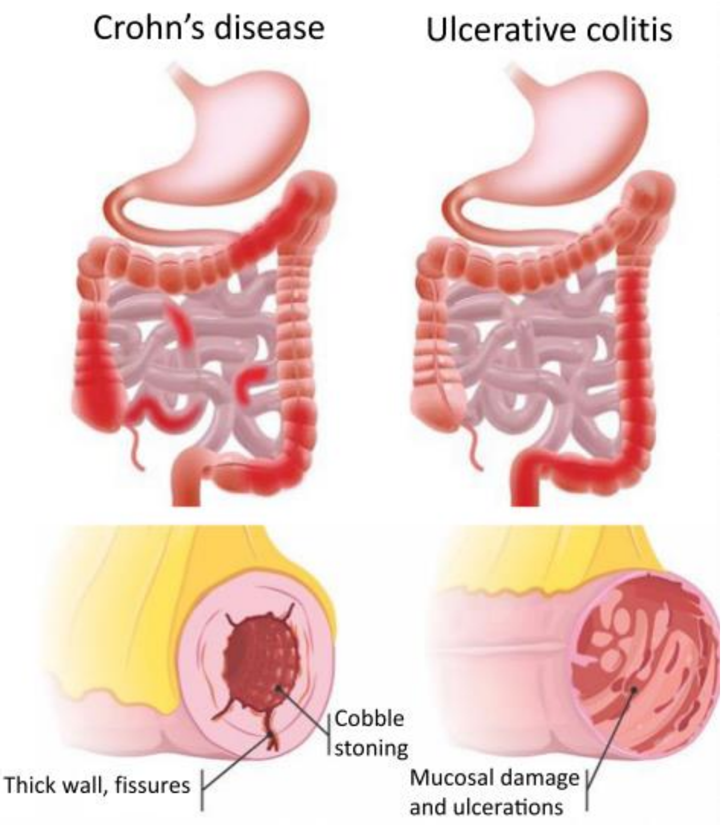

Figure 1. Inflammatory bowel disease types. Taken from (Kotla & Rochev, 2023).

UC and CD differ in key features like location and patterns of inflammation, patient symptoms, and histopathological conditions.

CD can cause transmural inflammation along the gastrointestinal tract, with the terminal ileum or the perianal region being the most affected regions. CD results in extensive inflammation, often leading to deep ulcerations and formation of fistulas, and submucosal fibrosis. Conversely, the pathology of UC involves mucosal inflammation limited to the colon and the rectum and sometimes may extend proximally up to the caecum (**Figure 1**) (Bruner et al., 2023; Saez et al., 2023; Zhang & Li, 2014).

The most common symptoms of IBD patients are persistent abdominal pain, diarrhea, rectal bleeding, fatigue, and weight loss. Disease symptomatology has a significant impact on patient's life quality, work productivity and health outcomes (Bruner et al., 2023; Saez et al., 2023). Currently, there isn't a standardized diagnostic method for IBD. Still, it often relies on a full approach that combines medical history, endoscopic findings, histopathological examination, and imaging studies (Bruner et al., 2023; Farrell, 2000).

Laboratory tests, including blood tests to assess inflammation markers such as C-reactive protein (CRP), calprotectin and lactoferrin levels, hold prognostic and diagnostic value in IBD (Seyedian et al., 2019). Endoscopy coupled with biopsy remains the gold standard for definitively diagnosing IBD and distinguishing between CD and UC. Computed tomography and magnetic resonance imaging are two of the most used imaging techniques and provide complementary information regarding the extent and intensity of intestinal inflammation. Clinical eye examinations and rectal examinations are also utilized for diagnosis (Seyedian et al., 2019).

Even though all the above methods are available for diagnosis, it can be challenging due to its nonspecific symptoms and the potential overlay with other gastrointestinal disorders, like infectious colitis or irritable bowel syndrome, leading to a wrong diagnosis. Consequently, a thorough clinical evaluation, involving multidisciplinary collaboration between gastroenterologists, radiologists, and pathologists, is crucial to establish an accurate diagnosis and initiate timely and tailored management strategies for individuals affected by IBD (Farrell, 2000).

1.1.2. Epidemiology and prevalence

Previously thought to primarily impact Western nations, the epidemiological landscape of IBD is witnessing significant changes on a global scale and experiencing exponential growth, particularly among the pediatric population (Borowitz, 2023; Ng et al., 2017).

IBD is an emerging global health concern that greatly spread in the last 50 years across developing regions, garnering significant attention from medical and scientific communities who aim to deepen the knowledge about its pathophysiology and therapeutics, with the overarching goal of enhancing the life quality of these patients (Bruner et al., 2023).

Globally, there is some scarcity of epidemiological data that accurately reflects IBD reality (**Figure 2**). Despite IBD challenges such as diagnostic complexities, disparities in healthcare accessibility, varying lifestyle and risk factors, trends suggest a consistent rise in both incidence (new cases) and prevalence (number of total cases) of both CD and UC over time (Burisch & Munkholm, 2015; Kaplan, 2015; Ng et al., 2017).

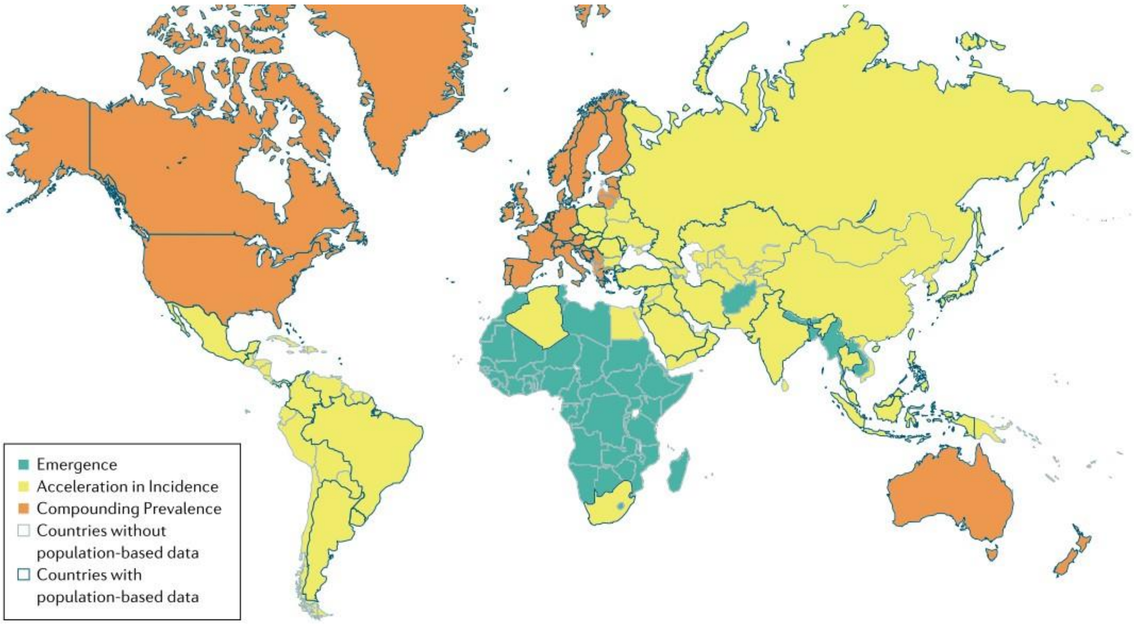

Figure 2. Distribution of IBD epidemiological stages in 2020. Taken from (Kaplan & Windsor, 2021).

While the onset of this pathology is commonly observed among young adults (20-30 years), a significant proportion of patients, approximately 25%, exhibit symptoms before 20 years of age (Borowitz, 2023; Bruner et al., 2023).

Recent studies suggest a rising incidence of IBD in regions like South America, Eastern Europe, Asia, and Africa. This shift is also evident in newly industrialized countries and among Asian immigrants to the Western countries, mirroring patterns observed in the Western world over 50 years ago, which aligned with rapid socioeconomic growth (Ng et al., 2017).

Traditionally, North America and Europe have the highest occurrence of both UC and CD. In Europe, it is estimated that 2.5–3 million people are affected by IBD, with a direct healthcare expenditure ranging from 4.6 to 5.6 billion euros annually (Burisch et al., 2013).

In the Western world, IBD is associated with major health challenges, including illness, death, with considerable costs for healthcare systems. The increasing occurrence of this disease in newly industrialized countries suggests a potential global epidemic of IBD beyond Western nations. This pattern indicates that the impact of IBD on healthcare systems needs to be reevaluated to revert the epidemiological patterns worldwide. Understanding the geographical distribution and trends of the disease will enable researchers and policy makers to anticipate and address the healthcare infrastructure and resource requirements necessary to lessen the burden of IBD (Ng et al., 2017).

In the year 2023, in Portugal, the IBD population was estimated to comprise 24,069 patients with approximately 11,866 individuals diagnosed with UC and 12,203 with CD. The total annual cost associated with IBD patients in Portugal was estimated to be 146,293 euros, with an average annual cost of 6,075 euros per patient. These costs are further categorized into direct costs amounting 86,834 euros direct and indirect costs totaling 59,459 euros (Magro et al., 2023).

Understanding the worldwide epidemiological patterns of IBD, both prevalence and incidence rates, it’s essential to manage the burden of IBD over time, developing effective strategies to control this disease (Kaplan, 2015).

1.1.3. Pathogenesis of IBD

Although IBD remains etiologically unclear, some theories suggests that IBD arises from an abnormal immune response in genetically susceptible individuals. In addition, it appears evident that individuals with IBD exhibit an imbalance or disrupted intestinal microbiota.

Besides an imbalanced microbiota, the intestinal barrier function is also impaired in IBD. It displays less mucus secretion by goblet cells, reduced antimicrobial peptides’ production by Paneth cells and several mutations in genes coding tight junction proteins, resulting in their dysfunction and consequent loss of barrier integrity (Ferreira et al., 2024).

Nowadays, the most accepted theory suggests that IBD arises from a complex interaction between four main components: microbial and environmental factors, immune responses and genetic predisposition (**Figure 3**) (Borowitz, 2023; Bruner et al., 2023; Zhang & Li, 2014).

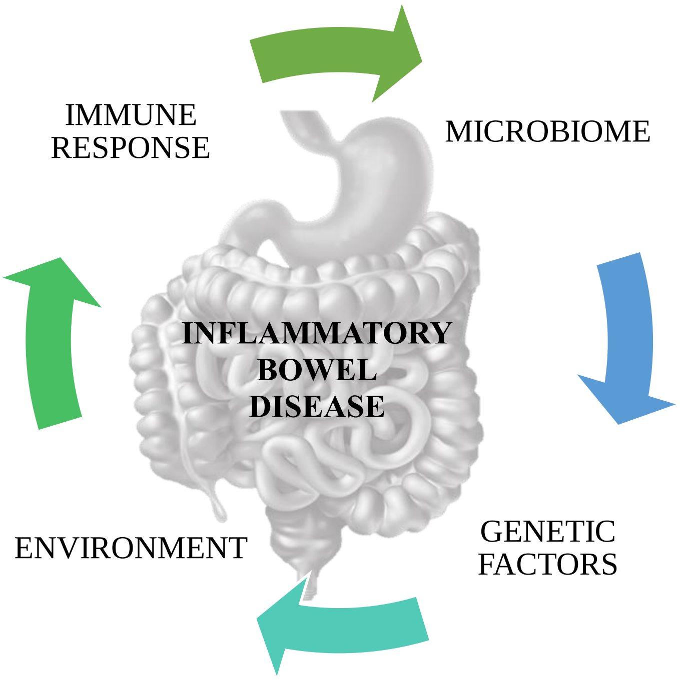

Figure 3. Understanding the multifactorial etiology of inflammatory bowel disease (IBD). Adapted from (Zhang & Li, 2014)

Genetic susceptibility, intestinal microbiota composition, external environment influences and immune dysregulation all play integral roles in the IBD development and progression, as underscored by several studies. The abnormal immune responses are linked with dysregulation of both adaptive and innate immune responses (Kotla & Rochev, 2023; Saez et al., 2023; Zhang & Li, 2014).

1.1.3.1. Genetic predisposition

Extensive investigations were conducted to elucidate the genetic basis of IBD. Through them it was possible to understand that genetic predisposition and family history are important determinants of disease's phenotype, as well as the degree of irritability associated to IBD (Hussein et al., 2023).

Having a close family member with IBD is the best known risk factor (Borowitz, 2023). It was documented that first-degree family members have an increased risk of developing IBD, and that 12% of IBD patients have someone in the family suffering from this disease.

Researchers have identified over 240 risk variants associated with IBD through genome-wide association studies (GWAS) (Saez et al., 2023). These genetic variants span pathways involved in bacteria recognition (e.g., NOD2), autophagy (e.g., ATG16L1 and IRGM), regulation of epithelial barrier (e.g., ECM1), and innate and adaptive immunity (e.g., IL-23R, IL-10, ITGAL, and ICAM1 variants) (Saez et al., 2023). Other susceptibility genes implicated in the pathogenesis of IBD are CARD9, IL1R2, REL, SMAD3 and PRDM1(Zhang & Li, 2014).

Despite all these breakthroughs, further research is needed to pinpoint more clinically significant associations between genetic loci and IBD susceptibility as they exhibit only modest effect sizes (Zhang & Li, 2014).

1.1.3.2. Environmental factors

Environmental factors represent another key component proved to have a major impact on the development of IBD. Certain factors have been identified as either protective or predisposing to the disease. For instance, a plant-based or a Mediterranean diet and breastfeeding have been associated with reduced risk, whereas oral contraceptive use, highly processed diets, as well as early life antibiotic misuse have been associated with the development of IBD (Hussein et al., 2023).

Vitamin D has garnered attention of researchers due to its immunological role in IBD’s pathogenesis. In a study carried out by Leslie et al. it was observed that low Vitamin D levels were common amongst diagnosed IBD patients, suggesting a potential link between vitamin D deficiency and disease risk (Leslie et al., 2008).

Infectious gastroenteritis episodes can also induce an abnormal immune response and increase the risk of IBD up to 40% (Hussein et al., 2023).

Some studies have reported that breastfeeding has protective effects against the development of IBD, corroborating the probiotic and prebiotic effects of breast milk described in the literature (Moossavi et al., 2018).

In a study carried to assess the impact of diet on the risk of developing IBD, it was verified that diets high in total fats, omega-6 fatty acids, and meat correlates to increased risk to IBD, while a higher fruit intakes decreases the risk for CD and a high intake of vegetables decreases the risk for UC (Hussein et al., 2023).

Furthermore, the excessive use of antibiotics, particularly in early childhood, has been associated with IBD development. Despite the paradoxical nature of this association given the efficacy of antibiotics in certain IBD patients, it may be justified by impaired commensal microbiota and immune dysregulation in genetically susceptible subjects (Glassner et al., 2020). Nevertheless, much remains to be understood about the complex interplay between antibiotics, microbiota, and IBD pathogenesis.

1.1.3.3. Immune system dysregulation

The immune system performs a wide number of vital functions for our body´s defense, including the recognition and identification of invading agents, phagocytosis, innate and adaptive immune responses along with inflammatory reactions, antibody production, among others. It comprises both the innate and adaptative arms, representing our body's frontline defense mechanism against foreign invaders. Innate immunity acts as the first line of defense against pathogens, eliciting rapid responses primarily through myeloid cells among other essential components. In turn, adaptative immunity develops over time as we are exposed to pathogens throughout our lives.

From an early age, we are taught that the immune system exists to protect the body from external threats. However, the immune system can also fail, resulting in the erroneous targeting of the body's own cells, leading to an auto-immune pathological condition, like IBD. Herein, the immune system becomes dysregulated, resulting in the erroneous targeting of the body's own cells in the digestive tract, leading to a generalized inflammatory environment and tissue damage.

Dysregulated immune responses lie at the core of IBD pathogenesis and understanding their impact has been a primary focus of research. In IBD context, the innate immune system takes precedence, promptly responding to pathogen-associated molecular patterns (PAMPs) and to molecules released from damaged or dying cells, known as damage-associated molecular patterns (DAMPs) through pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) and Nod-like receptors (NLRs). Components of the innate immune system, including granulocytes (neutrophils, eosinophils, and basophils), monocytes, macrophages, and dendritic cells, alongside non-immune cells like intestinal epithelial cells (IECs) and myofibroblasts, detect these patterns, thereby triggering responses aimed at enhancing the protection of epithelial barrier and mitigating inflammation (Saez et al., 2023).

In acute inflammatory responses, granulocytes are rapidly recruited to the inflammatory site with the aim to neutralize and remove DAMPs and PAMPs, and for defense against microbial invasion. After that, neutrophils secrete antibacterial proteins, myeloperoxidase, tissue-degrading enzymes, and reactive oxygen species (ROS), leading to an oxidative burst reaction to destroy microbes. However, these processes inadvertently induce local tissue damage and foster additional inflammation, characterized by edema, hyperemia, and further epithelial damage (Rogler, 2017). The development of chronic inflammation in IBD is posited by some theories as a failure to resolve acute inflammation, although the intricacies of this phenomenon are far from linear and underscore the multifactorial nature of IBD (**Figure 4**) (Rogler, 2017). Thus, it appears unlikely that IBD arises solely from a failure to resolve acute inflammation, as the disease process is influenced by a multitude of complex factors. As previous evidenced, IBD is a multifactorial disease, suggesting a more complex etiology beyond merely unresolved acute inflammation.

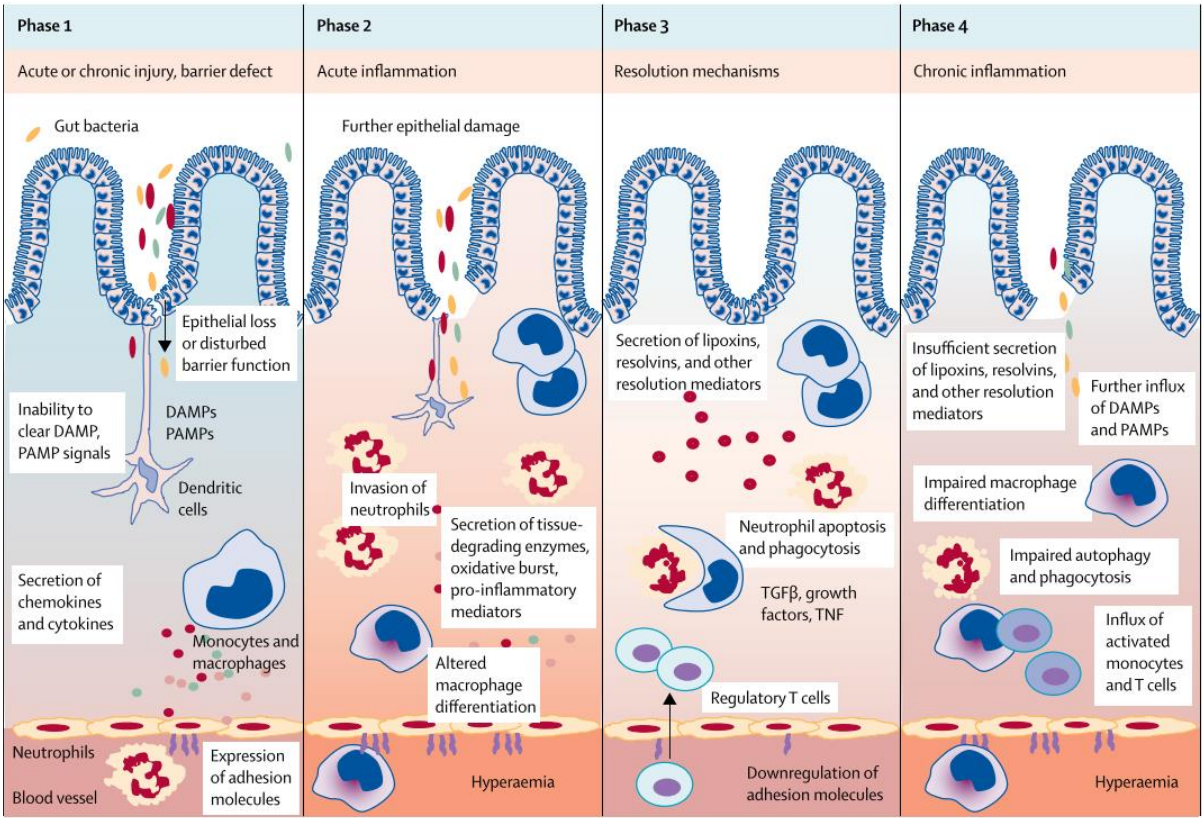

Figure 4. The four phases leading to chronic inflammation in IBD. Taken from (Rogler, 2017).

1.1.3.4. Gut microbiota dysbiosis

The gut microbiota is a complex and dynamic ecosystem characterized by wide inter and intra-individual variability based on factors such as diet, genetics, age, and overall health. The gut microbiota community plays a pivotal role in host susceptibility responsible for several diseases, including IBD (Caruso et al., 2020).

Within the human intestinal tract resides an impressively diverse array of microorganisms, numbering around one hundred trillion and encompassing at least 15,000 to 36,000 bacterial species, alongside viruses, fungi and other microbes (Hussein et al., 2023). These symbionts microorganisms coexist in a balanced relationship, contributing to crucial physiological processes such as the regulation of the epithelial barrier, modulation of the host immune system, digestive and metabolic functions, and protection against pathogen colonization.

Changes in the composition and/or function of the microbiota are known as dysbiosis. Dysbiosis refers to a disruption in the normal balance of microorganisms in the gut, characterized by changes in their types and numbers, which can lead to an imbalance between beneficial and harmful bacteria (Santana et al., 2022). The reduced gut microbiota diversity is also referrer as dysbiosis. These alterations are associated with various health conditions, including metabolic syndrome, IBD, allergies and autoimmune diseases (Hussein et al., 2023). Numerous studies have highlighted that individuals with IBD exhibit an imbalance or disrupted intestinal microbiota, underscoring its importance in the pathogenesis (Hussein et al., 2023). These changes in microbiota composition include reductions in beneficial bacteria, increases in harmful bacteria, and alterations in the abundance and activity of certain bacterial strains (Qiu et al., 2022). Each microbiota is unique, therefore there are clearly differences between patients with UC and CD. Qiu et al, reviewed that in UC there's a reduction in beneficial bacteria like *Bifidobacterium longum* and *Akkermansia muciniphila* (*A. muciniphila*), along with an increase in harmful bacteria like *Bacteroides fragilis* and *Escherichia coli.* Conversely, in CD patients, reductions in beneficial bacteria, *Eubacterium rectal*, *Faecalibacterium prausnitzii*, *Roseburia intestinalis* were observed, while harmful bacteria like *Bacteroides fragilis*, *Ruminococcus torques*, and *Ruminococcus* were increased.

Nevertheless, the causal relationship between this dysbiosis and the disease remains ambiguous – is it a cause or a consequence of IBD? (Borowitz, 2023).

1.1.3.5. Disruption of mucosal barrier integrity

The dysregulation of the immune system in IBD individuals can compromise the integrity of the intestinal barrier, leading to increased permeability and subsequent bacteria and antigens translocation. This, in turn, triggers an exaggerated immune response.

The intestinal epithelium act as a protective barrier, preventing the passage of bacteria and antigens into circulation through tightly sealed intercellular epithelial junctions. However, in a IBD condition, these junctions can become compromised and defective due to either a failure in primary barrier function or as a result of severe inflammation (Hussein et al., 2023). The compromised integrity of the intestinal barrier, arising from defective intercellular junctions, and immune dysregulation can lead to persistent tissue damage in individuals with IBD. This sustained immune response against gut antigens fuels chronic inflammation, facilitating the production of inflammatory mediators such as cytokines and ROS, thereby exacerbating tissues damage over time (Hussein et al., 2023).

Moreover, mucosal barrier defects and alterations can arise from a multifactorial interplay involving dietary, environmental, genetic and microbial factors. Recent evidence suggests that damage to the mucosal lining may culminate in compromised barrier function and increased permeability (Kotla & Rochev, 2023). Additionally, the inflamed mucosal barrier releases ROS and metalloproteinases, further exacerbating tissue damage and necrosis (Kotla & Rochev, 2023). These factors can disturb the balance within the mucosa and alter gut microbiota composition, ultimately contributing to adverse outcomes, such as colorectal cancer and associated neurological diseases (Kotla & Rochev, 2023).

Therefore, ensuring healthy and functional mucosal barrier is paramount to prevent the onset and progression of such diseases.

1.1.4. Current therapeutic approaches for IBD

Current treatments for IBD aim not only to reduce inflammation, relieve symptoms such as rectal bleeding, bloody diarrhea, abdominal cramps and pain but also to enhance the patient's quality of life and address dysbiosis to restore microbiota balance (Hussein et al., 2023; Kotla & Rochev, 2023).

The current treatment options usually involve a combination of lifestyle habits modification, pharmacotherapy and in some cases surgical interventions.

1.1.4.1. Lifestyle modification

a) **Exercise:** exercise helps to mitigate the cardiovascular risk and the elevated rates of anxiety/depression often seen in IBD patients and is considered a crucial strategy to improve overall health (Bruner et al., 2023);

b) **Healthy dietary patterns**: nutritional deficiencies can arise due to the disease symptomatology as well as some treatment interventions. Some individuals find symptoms relief by avoiding certain foods, such as spicy foods, dairy, or high-fiber foods. Meanwhile, the Mediterranean diet, known for its health benefits and diverse food options, may be reasonable for IBD patients (Bruner et al., 2023);

c) **Smoking cessation**: patients should be advised to stop smoking to improve treatment outcomes (Bruner et al., 2023);

d) **Stress management**: stress can exacerbate IBD symptoms, so techniques like mindfulness, meditation, and counselling can be helpful (Bruner et al., 2023).

1.1.4.2. Surgery

In some cases of IBD presentations, surgery becomes an inevitable recommendation (Farrell, 2000). The purpose of the surgery is to relieve symptoms and improve the patient's quality of life. Collaboration with healthcare professionals, including nutritionists, psychologists, and gastroenterologists, is essential for developing personalized treatment plans tailored to individual needs, ensuring optimal outcomes for patients with IBD.

1.1.4.3. Pharmacotherapy

a) **Anti-inflammatory drugs**: these include aminosalicylates (e.g., 5-aminosalicylic acid and its prodrugs), corticosteroids (e.g., prednisone, budesonide) and immunomodulators (e.g., azathioprine, 6-mercaptopurine) which primary inhibit local colonic inflammation and immune system hyperreactivity (Kotla & Rochev, 2023);

b) **Antibiotics**: considered for IBD treatment due to the microbial abnormalities and the presence of known pathogens, antibiotics are used to address bacterial overgrowth or infections in the gut (Santana et al., 2022);

c) **Probiotics**: strains such as *E. coli* Nissle 1971, *Bacillus subtilis*, and VSL#3 are used to reduce luminal pH and normalize intestinal flora (Kotla & Rochev, 2023);

d) **Biologic therapies**: novel therapeutic agents such as anti-tumor necrosis factor (TNF) agents (e.g., infliximab, adalimumab), JAK inhibitors (e.g., tofacitinib), anti-interleukin (IL) agents (e.g., Ustekinumab) and anti-adhesion agents (e.g., natalizumab) target specific molecules involved in the inflammatory process (Kotla & Rochev, 2023).

Since current therapeutic interventions mainly target established chronic inflammation (phase 4), future approaches should also focus on resolving of acute inflammation (phase 3), currently a hot topic of research (Rogler, 2017).

1.1.4.3.1. Gut microbiota as an amenable target for therapeutic modulation

Given that current therapies achieve complete remission in fewer than 50% of patients, the development of new therapeutic approaches targeting intestinal microorganisms hold promise for treating IBD. The effectiveness of fecal microbiota transplantation (FMT) in treating recurrent *C. difficile* infection by restoring the gut microbial diversity underscored the potential of microbiota-modulating therapies, both pre-, pro- and symbiotics (Caruso et al., 2020). Accordingly, the nutraceutical potential of *A. muciniphila* in IBD will be underscored in the next sections.

1.2. *Akkermansia muciniphila*: a next-generation probiotic

1.2.1. Impact of *A. muciniphila* on gut health

Akkermansia muciniphila, a bacterium with an oval shape, is strictly anaerobic, non-motile, gram-negative, and it does not form endospores. Its discovery dates back to 2004 at Wageningen University of the Netherlands during the quest for a new mucin-degrading microorganism in human feces (Derrien et al., 2004). Notably, *A. muciniphila* stands as the inaugural member and sole representative of the phylum Verrucomicrobia within the human gut (Derrien et al., 2010; Hoskins et al., 1985), rendering it relatively straightforward to detect (Rajili C-Stojanovi & De Vos, 2014).

A. muciniphila thrives within the host's intestinal mucosal layer, most notably in the caecum, and is widely distributed in the intestine of both healthy adults and infants, constituting 1–4% of the total gut microbiota from early life (Ghotaslou et al., 2023). Initially categorized as a strict anaerobe (Derrien et al., 2004), *A. muciniphila* has recently been found to exhibit tolerance to small quantities of oxygen, leading to its reclassification as an aerotolerant anaerobe (Machado et al., 2020; Reunanen et al., 2015).

Throughout our lifespan, *A. muciniphila* remains a stable gut symbiont (Collado et al., 2007). This bacterium establishes its presence in the human gut within the first-year post-birth, eventually attaining similar abundance levels to those found in healthy adults, albeit diminishing gradually in the elderly (Collado et al., 2007; Derrien et al., 2008).

Numerous phylogenetic and metagenomic investigations involving hundreds of subjects have consistently identified *A. muciniphila* as one of the top 20 most prevalent species in the human gut (Collado et al., 2007; Drell et al., 2015; Thomas et al., 2014). Moreover, research indicates the presence of *A. muciniphila* in human milk (Collado et al., 2008), suggesting that it may serve as a conduit for the transmission of *A. muciniphila* from mothers to infants, thereby explaining its colonization in the gastrointestinal tract of newborns (Collado et al., 2007). During the developmental stage, *A. muciniphila* successfully establishes itself in the gastrointestinal tract, aided by an active acid resistance system and the capability to degrade human milk oligosaccharides present in the newborn's stomach (Bosscher et al., 2001). In adulthood, the abundance of *A. muciniphila* varies across the gastrointestinal tract, as shown in **Figure 5**.

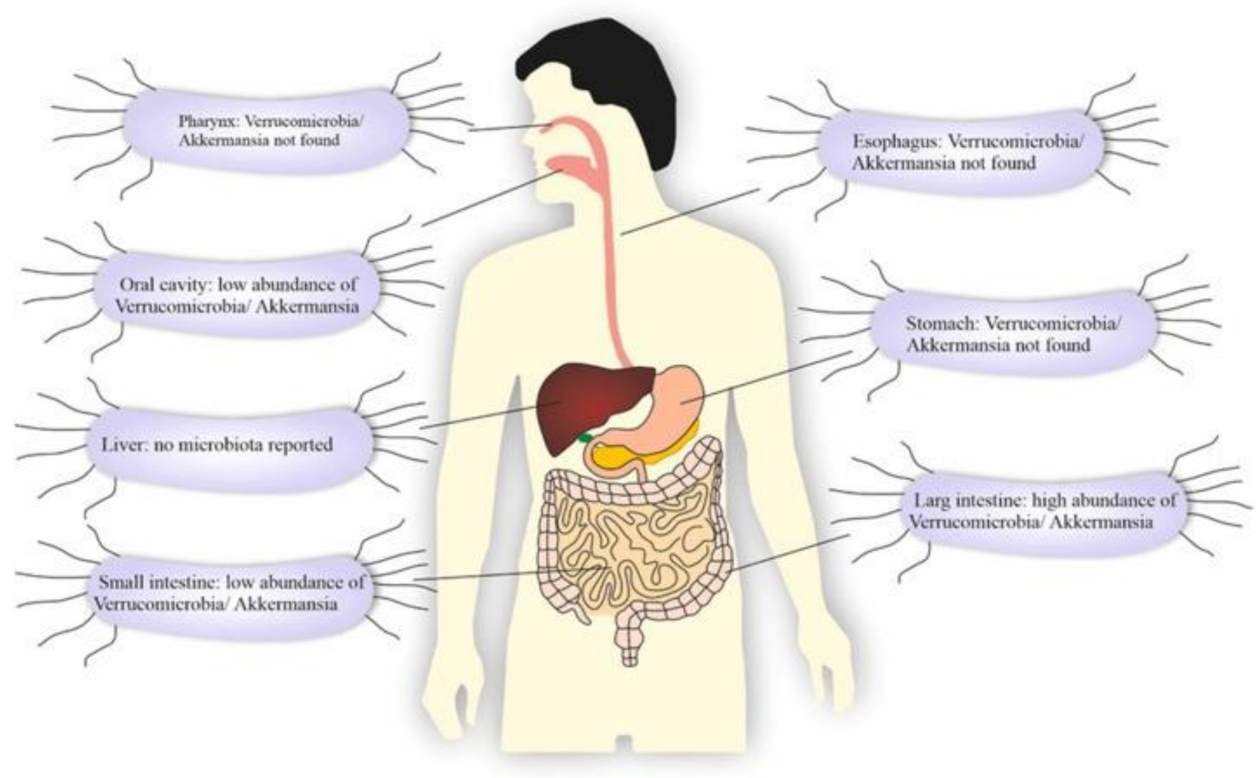

Figure 5. The distribution and abundance of *A. muciniphila* throughout the gastrointestinal tract. Taken from (Ghotaslou et al., 2023).

A. muciniphila has a significant role in regulating host metabolic processes (Cani & Knauf, 2021; Everard et al., 2013; Katiraei et al., 2020; Yang et al., 2019). Its capacity to reduce gut permeability has emerged as a key mechanism through which it influences host metabolism (Chelakkot et al., 2018; Rao et al., 2021). While the gut mucus serves as an initial line of defense by capturing bacteria and preventing epithelial damage, the tight junction barrier prevents the escape of bacterial antigens from the lumen into epithelial tissues (Ermund et al., 2013; Jiang et al., 2014). Despite its well-known role in mucin degradation, *A. muciniphila* also stimulates mucin production by augmenting both the number and density of goblet cells in mice induced with a high-fat diet (HFD), thus restoring mucus layer thickness and fortifying the intestinal barrier (Everard et al., 2013; Shin et al., 2014). Additionally, Amuc_1100, an outer membrane protein of *A. muciniphila*, has been shown to reduce body weight and fat mass while enhancing epithelial tight junctions in HFD-induced obese mice (Plovier et al., 2017). Meanwhile, advances have been made on the underlying molecular mechanisms through which *A. muciniphila* ameliorates metabolic diseases (Everard et al., 2013; Shin et al., 2014).

1.2.1.1. Features and Next-Generation potential of *A. muciniphila*

The term "probiotic" originates from a Greek word meaning "for life” (Sankarapandian et al., 2022). The FAO/WHO group defines probiotics as “living microorganisms that, when administered in sufficient quantities, offer a health benefit”(Binetti et al., 2020).

Currently, next-generation probiotics (NGPs) are classified through the 5W1H (Which, Where, When, How, What, and Why) method, to provide an overall perspective on their features and properties.

Succinctly, this perspective is based on clarifying *Which* microorganisms are involved (bacteria like *A. muciniphila*; *Faecalibacterium prausnitzii*), *Where*: the ecological niche (gastrointestinal tract), *When* they are implemented (prevention, maintenance, therapeutic intervention), *How* they are formulated in terms of production and delivery (O2 exclusion, animal component avoidance), in *What* processes they might interact or promote health improvement (gut barrier integrity; anti-inflammatory; insulin regulation; adiposity reduction), and *Why* they are used and which emerging diseases (such as metabolic and inflammatory disorders) these probiotics are intended to target (Almeida et al., 2020).

The International Scientific Association of Probiotics and Prebiotics, in 2019, convened a panel of experts specialized in nutrition, microbial physiology, gastroenterology, pediatrics, food science and microbiology to review the definition and scope of the non-viable microorganisms or their cell fragment and metabolites that had health benefits – hitherto known as inactivated probiotics, heat-inactivated probiotics, non-viable probiotics, dead probiotics, tyndallized probiotics, ghost probiotics, paraprobiotics, postbiotics, cell fragments, and cell lysates (Salminen et al., 2021; Vinderola et al., 2023). The need to convene this panel arose due to the lack of uniform terminology, which represented several inconveniences for the field, so standardizing the language used became urgent (Salminen et al., 2021). Later on, international scientific associations and key-industrial stakeholders advance a set of criteria that probiotic strains must meet the following criteria to be qualified in foods or dietary supplements, namely: (i) be thoroughly characterized; (ii) be safe for their intended use; (iii) be backed by at least one positive human clinical trial conducted according to accepted scientific standards or local/national authority recommendations; and (iv) remain alive in the product at an effective dose throughout its shelf life.

The concept of traditional probiotics stems from ancestral knowledge that regular consumption of lactic acid bacteria fermented dairy products was associated with improved health and longevity among the elderly in Bulgaria. This association led to the term “probiotics” being linked to beneficial bacteria for health promotion, although its precise definition has evolved over time (Azad et al., 2018; Chang et al., 2019; Tsai et al., 2019). Current understanding suggests that chronic inflammation-related diseases are primarily due to gut microbiota dysbiosis, which is characterized by altered composition, reduced diversity and stability, and increased levels of lipopolysaccharide-containing, proinflammatory bacteria (Chang et al., 2019). These chronic inflammations can develop locally in the intestine and systemically throughout the host. Factors such as abnormal diet intake, antibiotic use, and changes in sanitation can contribute to this dysbiosis. To combat diseases related to gut microbiota dysbiosis and leaky gut syndrome, probiotics are considered an optimal choice. Probiotics can influence nutrition, metabolism, physiology, and immunity, thereby alleviating diseases and maintaining the host's health. Among traditional probiotics, several *Lactobacillus spp*. (belonging to Firmicutes) and *Bifidobacterium spp*. (Actinobacteria) are dominant (Chang et al., 2019; Tsai et al., 2019).

However, most microorganisms inhabiting the human gut have remained unidentified due to their anaerobic nature, making them difficult to cultivate. Advances in modern microbiology, particularly polymerase chain reaction (PCR) of the 16S rRNA gene, next-generation sequencing, and bioinformatics, have enabled the precise identification and detection of various bacterial strains in the gut. Recent developments in complete genome sequencing and culture techniques have facilitated the isolation and characterization of numerous novel microbes from the human microbiome with promising health benefits, leading to the concept of next-generation probiotics (Abouelela & Helmy, 2024). NGPs are defined as “living microbes identified through comparative microbiome investigations that confer health advantages to their host when consumed in appropriate amounts” (Morelli & Capurso, 2012). The term "probiotic" now includes more species beyond the well-recognized lactic acid bacteria and bifidobacteria. NGPs, which include species with no history of use as probiotics, show potential in managing inflammatory diseases, cancer, and metabolic disorders and are likely to be regulated under drug frameworks (Cunningham et al., 2021). Examples of NGPs include *A. muciniphila*, *Roseburia intestinalis*, *Eubacterium* spp., *Faecalibacterium prausnitzii*, and *Bacteroides* spp. (Abouelela & Helmy, 2024).

Unlike traditional probiotics, NGPs offer physiological benefits, such as the production of folate, serotonin, indoles, and short-chain fatty acids (SCFAs) like butyrate, propionate, and acetate, all of which play significant roles in regulating the host's physiological phenotype. Transforming these novel species into industrially beneficial probiotics poses significant challenges due to their need for expensive, complex rich culture media and anaerobic conditions. Therefore, research in defining optimal fermentation and industrial processes for these species is a critical challenge(Cunningham et al., 2021).

A. muciniphila, a symbiont microbe that lives in the human intestinal mucosal layer, is a promising next-generation probiotic. *A. muciniphila* plays a crucial role in boosting metabolic functions and strengthening immune responses. Additionally, *A. muciniphila* is garnering increasing attention, with numerous animal experiments corroborating its beneficial effects in multiple diseases. **Figure 6** pinpoints a chronologic workflow *of A. muciniphila*, from its isolation to characterization and health-related outcomes.

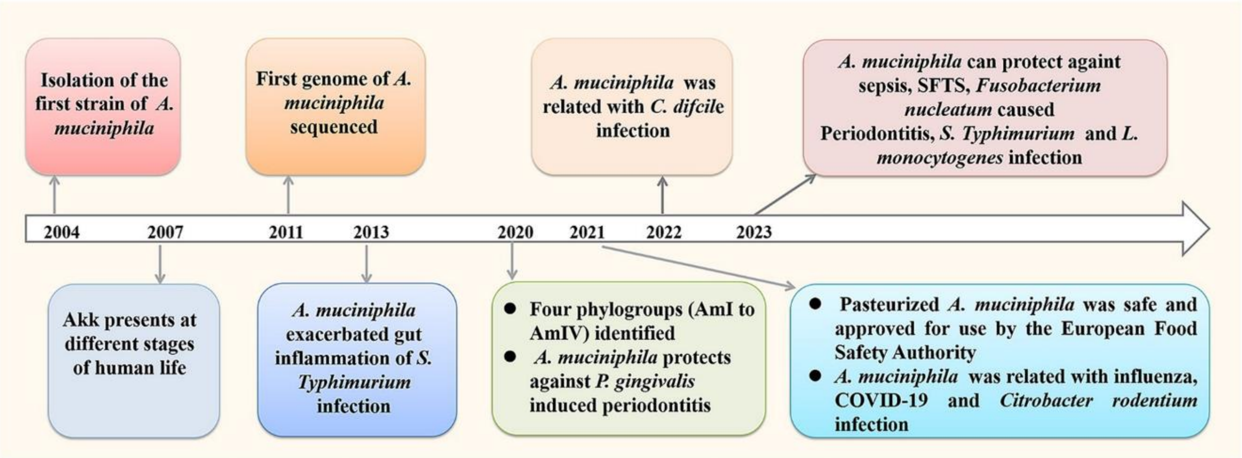

Figure 6. The research process of *A. muciniphila* focusing on infectious diseases. Taken from (Li et al., 2024).

1.2.1.2. *A muciniphila* and gut microbiota ecosystem

Various gut bacteria, including *A. muciniphila*, reside within the mucus layer and engage in intricate interactions. While some bacteria lack the ability to degrade mucin, they benefit from the presence of mucin-degrading bacteria. *A. muciniphila* generates sugars derived from mucus and short-chain fatty acids (SCFAs) like acetate and propionate. Non-mucus-degrading bacteria such as *Anaerostipes caccae, Eubacterium hallii, and Faecalibacterium prausnitzii* utilize sugars degraded from mucin by *A. muciniphila for* their growth. Mucin degradation by *A. muciniphila* supports the growth of *A. caccae* and enhances butyrate production (Chia et al., 2018).

A. muciniphila modulates the gut microbiota, fostering a more balanced microbial environment. It accomplishes this by lowering the abundance of *Alistipes, Lactobacilli*, *Tyzzerella*, *Butyricimonas*, and *Blautia*, while enhancing the populations of *Ruminiclostridium*, *Oscillibacter*, *Allobaculum, Anaeroplasma*, and *Rikenella* (Wu et al., 2023). This modulation is driven by its capacity to use mucin as a nutrient source, which provides *A. muciniphila* with a competitive edge over other gut microbes and suppresses host genes associated with sterol (Davey et al., 2022). As a crucial regulator of microbiota homeostasis, the depletion of *A. muciniphila* during extended antibiotic use can lead to notable shifts in microbiota composition, specifically altering the *A. muciniphilaceae*/*Lachnospiraceae* ratio and impairing microbiome functionality (Chen et al., 2023). Furthermore, *A. muciniphila* positively influences the gut microbiome by decreasing the abundance of *Enterobacteriaceae* and *Enterococcaceae*, enhancing SCFAs production, and maintaining bile acid levels, which collectively contribute to mitigating *Clostridioides difficile* infection (Wu et al., 2022). It further encourages the growth of beneficial bacteria like *Muribaculaceae* while simultaneously decreasing harmful bacteria such as *Escherichia_Shigella* (Xu et al., 2023).

1.2.1.3 *A. muciniphila* and intestinal mucosal barrier

The thickness of the mucus layer in the intestine serves as a crucial gauge of intestinal permeability, which tends to decrease in cases of diet-induced obesity and IBD. Goblet cells secrete intestinal mucus, comprising roughly 20% protein and 80% carbohydrates, thereby acting as a substrate and nutrient source for *A. muciniphila*. This mucus can be categorized into two layers: an inner layer devoid of bacteria and a thicker layer inhabited by commensal bacteria (Johansson et al., 2008). Functioning as a physical barrier, the mucus prevents harmful agents and microorganisms from directly contacting epithelial cells and potentially entering circulation.

Thinner mucus layers and heightened gut permeability facilitate the translocation of lipopolysaccharide (LPS) from the intestine into circulation, consequently leading to inflammation and metabolic endotoxemia. Various studies indicate that *A. muciniphila* can enhance mucus thickness, thereby fortifying gut barrier integrity. Previous research unveiled that *A. muciniphila* colonization in mice fosters goblet cells, which were notably diminished due to colitis induced by C. rodentium infection (Mao et al., 2021). Additionally, studies have demonstrated that oral administration of viable or pasteurized *A. muciniphila* significantly increases the population of mucin-secreting goblet cells, thereby replenishing lost mucus during obesity (Everard et al., 2013). This increase in goblet cells is attributed to *A. mucini*phila stimulating mucus turnover rate (Everard et al., 2013). As *A. muciniphila* breaks down mucin into SCFAs, which are the preferred energy source for goblet cells, mucin synthesis can experience a significant boost. Conversely, the quantity of mucin can impact the abundance of *A. muciniphila*. Earley et al. proposed that the reduced presence of *A. muciniphila*, as observed in patients with UC, may be due to a deficiency in sulphomucin, a substrate utilized by *A. muciniphila*. This theory was supported by the correlation observed between inflamed mucosa and diminished sulphomucin levels in acute UC patients (Earley et al., 2019). However, the absence of sulphomucin is unlikely to be the sole contributing factor, as changes in glycosylation and reduced MUC2 mucin levels may also influence microbial survival (Larsson et al., 2011). Consistent with these findings, a prior study conducted by their team demonstrated that mice colonized with *A. muciniphila* exhibited significantly increased goblet cell numbers in the colon, leading to upregulated expression of genes encoding mucin, including muc1, muc5, and muc13. These findings suggest a protective role of *A. muciniphila* against colitis by regulating the mucus barrier in the gut (Everard et al., 2013).

Furthermore, *A. muciniphila* extracellular vesicles (AmEVs), composed of lipid, protein, lipopolysaccharides, and other molecules, have been shown to regulate intestinal barrier permeability by modulating tight junction protein expression. Administration of AmEVs promotes the expression of major tight junction proteins responsible for maintaining barrier integrity, thus mitigating reductions observed during HFD treatment (Everard et al., 2013). This improvement is likely mediated by Amuc_1100 activating TLR2, a receptor responsible for regulating tight junction proteins such as occludin (Everard et al., 2013). In vitro studies indicate that AmEVs enhance Caco-2 cell barrier integrity via AMPK activation, possibly facilitated by increased SCFA levels (Gonzalez et al., 2019). Additionally, *A. muciniphila* has been observed to up-regulate occludin and ZO-1 in Apoe-/- mice, thereby mitigating inflammation and endotoxemia induced by a Western diet (Li et al., 2016).

1.2.1.4. *A. muciniphila* and gut mucosal immunity

The intestinal barrier comprises both physical diffusion and immunological components that contribute to maintain gut health (Söderholm & Perdue, 2001). *A. muciniphila* plays a significant role not only in maintaining the physical barrier but also modulates immune responses within the gut.

Adaptive immune cells, particularly through immunoglobulin (Ig) A, play a crucial role for preserving the integrity of the intestinal mucosal barrier and the immune homeostasis in the gut (Belkaid & Harrison, 2017). While T cells can recognize a broad spectrum of intestinal microorganisms independently of IgA activity, they rely on IgA activity to identify a specific subset of microbes (Bunker & Bendelac, 2017). Traditionally, IgG activity was thought to restricted to instances of compromised mucosal barriers or the presence of pathogens (Zeng et al., 2016). However, recent *in vivo* research has unveiled that T cells are broadly activated in response to gut microbiota through pathways independent of anti-IgG2b and IgG3, predominantly reliant on the presence of TLRs (Kristi et al., 2017). Certain gut microbes strains can elicit antigen-specific T cell responses despite the myriad of foreign bacterial antigens encountered during intestinal equilibrium (Xu et al., 2018). Emerging evidence suggests that abnormal T cell responses are implicated in IBD (Noble et al., 2019), and it is believed that anti-commensal T cell responses play a critical role in controlling intestinal infections (Castro-Dopico et al., 2019).

A. muciniphila has been shown to induce immunoglobulin G1 (IgG1) and specific T cell-related responses in mice. These T-cell-dependent responses occur independently of follicular T-cells, highlighting the crucial interaction between the microbiota and host immunity during gut homeostasis (Ansaldo et al., 2019). Additionally, *A. muciniphila* triggers the production of specific IgG1 antibodies through B cells, aided by T-follicular helper (TFH) cells induced in mesenteric lymph nodes that migrate to the lamina propria (Ansaldo et al., 2019). This bacterium also promotes the differentiation of CD4+ T cells into the TFH lineage, supports the *in vivo* expansion of regulatory T cells (Tregs), and prevents colitis in mice (Kuczma et al., 2020). Furthermore, *A. muciniphil*a abundance correlates positively with an expansion of the T-helper 17 (Th17) cells in the caecal and colonic mucosa, as well as with IgA-coated bacteria in fecal contents of spondylarthritis rat models (Asquith et al., 2016).

Recent studies have explored the interaction between *A. muciniphila* and macrophages, which are essential for pathogen destruction and tissue repair in inflammation. *A. muciniphila* can modulate macrophage polarization, a process in which these cells exhibit remarkable plasticity depending on local signals cells (Shapouri-Moghaddam et al., 2018). Macrophages are typically classified into two phenotypes: pro-inflammatory M1 macrophages, polarized by LPS or Th1 cytokines (e.g. IFN-γ) which produce pro-inflammatory mediators (e.g. IL-1β, IL-6, IL-12, IL-23, and TNF-α); and anti-inflammatory M2 macrophages, and polarized by Th2 cytokines (e.g. IL-4 and IL-13) which release anti-inflammatory cytokines (e.g. IL-10 and TGF-β) (Shapouri-Moghaddam et al., 2018).

An outer protein membrane of *A. muciniphila* called Amuc has been the focus of experimental studies. In a study exploring its role in modulating the immune microenvironment for gastric cancer treatment, Fang and colleagues reported that Amuc promoted the expression of macrophage proinflammatory factors such as IL-23 and TNF-α and inhibited the expression of TGF-β, ultimately promoting M1 polarization and inhibited M2 polarization (Fang et al., 2024). Another recent study supported this finding by showing that the acute stimulation of macrophages with live *A. muciniphila* induced a pro-inflammatory M1 phenotype (Peña-Cearra et al., 2024). However, contradictory results have emerged regarding the macrophage phenotypes influenced by *A. muciniphila* in different IBD contexts. In one study, IL-10 knockout mice gavaged with a daily dose of $2x10^8$CFUs of *A. muciniphila* showed increased IL-6 production in bone marrow-derived macrophages, indicative of an M1 response (Zheng et al., 2023). In contrast, another study found that oral administration of an *A. muciniphila*-secreted protein (P9) for 8 weeks led to an increased number of M2 macrophages in C57BL/6J mice (Zheng et al., 2023). These findings suggest that *A. muciniphila'*s influence on macrophage polarization depends on the context of immune stimulation. Further studies are needed to understand in which contexts the M1 and M2 phenotypes are favored.

Overall, previous studies have demonstrated that *A. muciniphila* enhances gut health by improving by intestinal barrier integrity, increasing mucus layer thickness, and promoting epithelial connectivity. These immunomodulatory effects highlight the critical role of *A. muciniphila* to maintain gut homeostasis and protect against various diseases.

1.2.2. *A. muciniphila* and inflammatory bowel disease

The gut microbiota plays an indisputable role in the development of IBD, making the modulation of gut microbiota one of the most promising challenges within IBD therapy (Lee & Chang, 2021; Liu et al., 2020).

Numerous case-control studies have consistently shown a significant decrease in the relative abundance of *A. muciniphila* in both UC and CD patients compared to healthy controls, although one study reported an opposite trend in a subset of CD patients (Abdulkhakov et al., 2021; Png et al., 2010; Presti et al., 2019; Zhang et al., 2020).

A. muciniphila demonstrates anti-inflammatory properties within the intestinal microenvironment, an area of active exploration within IBD research. Among the proposed mechanisms, the production of SCFAs has been extensively investigated. SCFAs have been shown to mitigate colitis by increasing the population of regulatory T cells expressing forkhead box P3 (Foxp3+) in the colon and by activating the G-protein coupled receptor 43 (GPR43) present on immune cells and colonic epithelium (Kim et al., 2019; Maslowski et al., 2009). Studies by Wang et al. and Bian et al. demonstrated that administration of *A. muciniphila* could ameliorate dextran sulfate sodium (DSS)-induced colitis in mice by reducing levels of macrophages and CD8+ cytotoxic T lymphocytes in the colon and downregulating pro-inflammatory cytokines and chemokines, respectively (Masotti et al., 2019; Wang et al., 2020; Bian et al., 2019). Additionally, *A. muciniphila* administration has been shown to enhance intestinal stem cell proliferation and promote differentiation of Paneth and goblet cells in both healthy mice and those with gut damage (Kim et al., 2021).

A. muciniphila also reinstated the mRNA expression of tight junction proteins such as zonulin-1, occludin, and claudin-1 in mouse models of DSS-induced colitis. This restoration led to a reduction in gut permeability and a reshaping of the intestinal microbiota towards eubiosis. These beneficial effects were attributed to the administration of Amuc:2109, a β-acetylaminohexosidase secreted by this microorganism (Qian et al., 2022).

Conversely, an increased abundance of *A. muciniphila* has been reported in preclinical models of IBD. Intriguingly, administration of *A. muciniphila* to mice with non-DSS-induced colitis exacerbated symptoms. Similarly, in a mouse model with a background microbiota of eight bacterial species, *A. muciniphila* administration worsened symptoms of *Salmonella-typhimurium*-induced gut inflammation. Additionally, *A. muciniphila* may have contributed to the worsening of colitis in IL10$^{-/-}$ mice (Ganesh et al., 2013). The varied effects of *A. muciniphila* could be interpreted in multiple ways, potentially influenced by the different mouse models used. It can be speculated that the increased abundance of *A. muciniphila* in colitis models might represent either a causative factor or a reactive response. Interestingly, *when A. muciniphila* was administered in IL-10 $^{-/-}$ mice colonized with a simplified human gut microbiota, it did not promote inflammation, suggesting the involvement of other environmental conditions (Ring et al., 2019; Seregin et al., 2017).

Lastly, there is limited research on the predictive effect of *A. muciniphila* after FMT in IBD patients. Zhang et al. demonstrated that washed microbiota transplantation (WMT) significantly increased the colonization rate of *A. muciniphila*. Moreover, there was a positive correlation between the abundance of *A. muciniphila* in patients and donors after WMT, suggesting its potential role as a predictive factor of WMT efficacy. Similar findings were reported by Kump et al. in treatment-refractory UC patients, where donors with higher bacterial richness and relative abundance of *A. muciniphila*, *Ruminococcaceae*, and *Ruminococcus* spp. were more likely to induce remission. Particularly, *A. muciniphila* was nearly absent in baseline samples but significantly increased the day after FMT in patients achieving remission (Kump et al., 2017; Zhang et al., 2020).

In conclusion, although current evidence presents conflicting findings to some extent, it suggests a potential role for *A. muciniphila* in the treatment of IBD (Zhang et al., 2021).

1.2.3. Challenges of *A. muciniphila* culture and delivery methods

While *A. muciniphila* holds promise as a potential therapeutic agent for various health conditions, there are several challenges associated with its culture and delivery methods, including:

Culturing difficulties: *A. muciniphila* can be challenging to culture in laboratory settings due to its fastidious growth requirements and sensitivity to oxygen. Maintaining optimal culture conditions to ensure viability and purity is essential but can be technically demanding (Diaferia et al., 2023; Meng et al., 2024).

Limited viability: *A. muciniphila* may have limited viability outside its natural habitat in the gut, particularly during storage, transportation, and manufacturing processes. Ensuring the viability and stability of live cultures in formulations presents a significant challenge for the development of probiotic products (Diaferia et al., 2023; Ouwerkerk et al., 2017).

Specific growth substrate: *A. muciniphila* primarily feeds on mucin, the glycoprotein present in the gut mucosal layer. Mimicking this complex substrate in laboratory media or designing delivery vehicles that effectively deliver mucin-like compounds can be challenging and may impact the growth and viability of the bacterium (Diaferia et al., 2023; Ropot et al., 2020).

Gut colonization: Delivering *A. muciniphila* to the gut and ensuring its successful colonization poses a challenge. Factors such as competition with resident microbiota, host immune response, and environmental conditions within the gastrointestinal tract can influence the colonization efficiency of exogenously administered bacteria (Diaferia et al., 2023; Ropot et al., 2020).

Delivery methods: Identifying effective delivery methods to ensure the targeted delivery of live *A. muciniphila* to the gut is crucial. Various delivery vehicles, such as capsules, powders, beverages, or food matrices, need to be optimized to protect the bacteria from gastric acidity and bile salts and facilitate their release in the intestine (Diaferia et al., 2023; Druart et al., 2021; Ropot et al., 2020).

Regulatory considerations: Regulatory requirements for the development and commercialization of live biotherapeutic products, including probiotics containing *A. muciniphila*, can be stringent. Meeting safety, efficacy, and quality standards established by regulatory agencies adds complexity and costs to the development process. In 2021, the

European Food Safety Authority verified the safety of pasteurized *A. muciniphila* and granted approval for its utilization as a novel food source (Turck et al., 2021).

Addressing these challenges requires interdisciplinary efforts involving microbiologists, bioengineers, clinicians, regulatory experts, and industry partners. Advanced technologies, such as synthetic biology, microencapsulation, and targeted drug delivery systems, may offer innovative solutions to overcome these hurdles and harness the therapeutic potential of *A. muciniphila* for improving human health.

1.2.4. Strategies to enhance *A. muciniphila* abundance

1.2.4.1. Supplementation with viable *A. muciniphila*

Supplementing with viable *A. muciniphila* has been a subject of research for nearly two decades, yet there is a scarcity of direct human studies on *A. muciniphila* supplementation, particularly for patients with IBD. Nevertheless, numerous intervention studies on mice have shown significant protective effects of *A. muciniphila* against intestinal inflammation. Bian et al. conducted a study focusing on viable *A. muciniphila*, dividing mice into three groups: the control group (CP), experimental group (DP), and *A. muciniphila* group (AKK). In this study, 2% (wt/vol) DSS was administered in the drinking water of DP and AKK groups for 7 days (day 0-6) before returning to normal water. *A. muciniphila* was exclusively administered to the AKK group through oral gavage for 14 consecutive days (day -7 to day 7). Their findings supported the modulatory role of *A. muciniphila* in barrier function, demonstrating the alleviation of DSS-induced colitis symptoms (e.g., weight loss, colon shortening) following *A. muciniphila* administration in mice (Bian et al., 2019; Turck et al., 2021). Moreover, *A. muciniphila* improved gut microbial composition by promoting species such as *A. muciniphila* and *Rikenellaceae*, although some studies yielded inconsistent results regarding changes in gut microbiota profile (aside from *A. muciniphila* itself) (He et al., 2022). Similar experimental designs were employed to assess the effects of varying concentrations of *A. muciniphila* on different mice models: a lower daily dose of *A. muciniphila* (1×10^9 - 2×10^9 CFU) was found to alleviate colitis in BALB/c and AAA mice, respectively (He et al., 2022; Mao et al., 2021). Additionally, APOE$^{-/-}$ and E3L.CETP mice fed a Western diet experienced reduced intestinal permeability and systemic inflammation after 8 weeks and 4 weeks of *A. muciniphila* supplementation, respectively, as demonstrated by studies conducted by Li et al. and Katiraei et al (Katiraei et al., 2020; Li et al., 2016).

1.2.4.2. Supplementation with pasteurised or heat-killed *A. muciniphila*

In addition to live *A. muciniphila*, there is growing interest in researching pasteurized and heat-killed forms of *A. muciniphila*, along with Amuc_1100, to assess their abilities in regulating gut microflora and mucosal functions. In a study by Everard et al., mice fed either a standard or HFD were administered either live *A. muciniphila* MucT (ATTC BAA-835, 2.10^8 cfu/0.2mL) or heat-killed *A. muciniphila* via oral gavage. The group treated with live *A. muciniphila* exhibited a significantly higher abundance of viable bacteria of interest in their caecal and colonic content compared to counterparts in the HFD and heat-killed bacteria group. Furthermore, heat-killed *A. muciniphila* was unable to restore colonic mucus impairments or metabolic defects induced by a HFD and obesity. While live *A. muciniphila* mitigated HFD-induced metabolic endotoxemia and reduced mucus layer thickness, heat-killed *A. muciniphila* did not yield significant improvements, suggesting the necessity of *A. muciniphila* being alive to exert its regulatory effect on the mucosal barrier (Everard et al., 2013).

Wang et al. investigated the effects of pasteurization-inactivated *A. muciniphila* on attenuating colitis development and associated tumorigenesis. They administered 1.5×10^8 CFU of pasteurized *A. muciniphila* to mice models of colitis or colorectal cancer induced by DSS and azoxymethane. Results from qPCR, 16S rRNA sequencing, and flow cytometry confirmed that pasteurized *A. muciniphila* positively influenced the host's immune system by reducing infiltrating macrophages and decreasing proportions of CD8+ cytotoxic T lymphocytes in the colon, ultimately ameliorating colitis in mice. These findings suggest that pasteurized *A. muciniphila* holds promise as a preventive and therapeutic strategy for IBD (Wang et al., 2020).

1.2.4.3. Supplementation with probiotics

Administering various strains of probiotics has been shown to promote the abundance of *A. muciniphila*. Alongside direct administration of *A. muciniphila*, a single probiotic treatment with *Lactobacillus pentosus* in mice with DSS-induced colitis increased *A.*

muciniphila abundance. This treatment also alleviated inflammatory cell infiltration, and colonic injuries caused by colitis, thereby impeding disease progression (Ma et al., 2020). Similarly, other members of the *Lactobacillus species* have been extensively researched as promising probiotics to regulate gut microbiota and enhance intestinal health, although not all strains have been directly associated with promoting *A. muciniphila* or improving IBD. For instance, *Lactobacillus plantarum* strain WCFS1 has been found to enhance TLR2 signaling activities and bolster mucosal barrier integrity in the gut (Karczewski et al., 2010). This modulation could potentially correlate with an increase in *A. muciniphila* levels. Recent research supported this notion by demonstrating that four weeks of daily administration of 3×10^{10} CFU of *Lactobacillus plantarum* to healthy triathletes significantly boosted *A. muciniphila* abundance (Huang et al., 2020).

Several probiotic combinations have also been identified as capable of restructuring gut microbiota composition and consequently ameliorating IBD. A combination of *Bifidobacterium infant*is, *Lactobacillus acidophilus*, *Enterococcus faecalis*, and *Bacillus cereus* collectively enhances *A. muciniphila* abundance, nearly restoring gut microflora to a normal state (Chen et al., 2020). Another study revealed that administering *Bifidobacterium animalis subsp. lactis* LMG P-28149 or a mixture with *Lactobacillus rhamnosus* for 14 weeks can rebalance host gut microbiota composition and significantly elevate *A. muciniphila* abundance. Furthermore, this mixture enhances the production of SCFAs like butyrate and acetate, which may promote mucin growth and consequently contribute to an increase of *A. muciniphila* levels, bringing favorable changes to host intestinal immunity. It's noteworthy that the protective effect of the mixture is likely attributed to *Bifidobacterium animalis subsp. lactis*, as administering *Lactobacillus rhamnosus* alone decreased *A. muciniphila* abundance (Alard et al., 2016).

1.2.4.4. Supplementation with prebiotics

Prebiotics are dietary substances that stimulate the growth or activity of specific species in the gut microbiota, leading to beneficial effects for the host. Bu et al. investigated the effects of 7-day prebiotic administration on the gut microbiota of mice. Interestingly, mice treated with the total flavone of Abelmoschus Manihot (TFA), a prebiotic of *A. muciniphila*, exhibited a direct dose-dependent promotion of *A. muciniphila* within a certain range.

Moreover, the inhibitory effect on pro-inflammatory cytokines was enhanced with increased concentrations of TFA, consequently contributing to improved gut barrier permeability and immunity. Notably, experimental colitis reduced the mRNA expression of KLF4, MUC2, and ZO-1. KLF4 is a transcription factor associated with intestinal cell proliferation, especially goblet cells. Mucin MUC2 blocks pathogens in the gut lumen, and deficiency in MUC2 leads to the destruction of the symbiotic bacterial habitat. ZO-1 is involved in maintaining the integrity of the gut barrier and contributes to the recruitment of other components during the assembly of tight junctions. Treatment with TFA improved the expression of KLF4, MUC2, and ZO-1 (Bu et al., 2021).

Hyaluronan, a glycosaminoglycan polymer, has also demonstrated prebiotic properties by maintaining gut homeostasis and ameliorating IBD symptoms. Previous studies have shown that hyaluronan attenuates C. rodentium-induced colitis by increasing *A. muciniphila* abundance, promoting the expression of antimicrobial peptides, restoring gut microbiota composition, and subsequently protecting against C. rodentium infection (Bu et al., 2021).

Dietary supplements of prebiotics have been extensively investigated for their effects on promoting *A. muciniphila*. For instance, vitamin D3 supplementation has been found to promote *A. muciniphila*, along with other beneficial probiotics such as *Bifidobacterium*, in healthy human participants. Additionally, intake of inulin, a fermentable fructo-oligosaccharide, has been associated with increased levels of *A. muciniphila* in both healthy and obese individuals. Another study revealed that anthocyanin-containing purple potatoes in the diet alleviated DSS-induced colitis, significantly increasing *A. muciniphila* abundance (Roopchand et al., 2015; Wu et al., 2021).

Administration of dietary polyphenols, natural antioxidants with significant antimicrobial properties, has yielded inconsistent results in mice studies. While some polyphenols like those found in Concord grapes and green tea promoted *A. muciniphila* abundance and attenuated colitis symptoms, others did not induce significant changes (Axling et al., 2012). These results suggest that the effects of dietary PPs may depend on their sources, doses and presentations (Zhang et al., 2020).

1.3. Polyphenols and A*. muciniphila* modulation: A novel approach for IBD management?

1.3.1. Polyphenols: Chemistry and dietary sources

The health benefits of natural food products have long been recognized, but given their increasing importance, studies on plant's secondary metabolites have significantly rise over the last decade, and they are drawing attention for their capacity to improve human health (Rasouli et al., 2017).

Polyphenols (PPs) are bioactive compounds found in fruits and vegetables (plant-based foods) contributing to their colour, flavour and pharmacological activities (Yahfoufi et al., 2018). These phytochemicals are recognized for their pivotal role in plant adaptation to the natural environment facilitating essential life functions such as growth, development, respiration, storage, and reproduction(Rasouli et al., 2017). Briefly, PPs constitute a large group of bioactive phytochemicals and include multiple sub-classes such as flavonoids, phenolic acids, stilbenes, lignans, curcuminoids, coumarins and tannins, as presented in **Figure 7** (Jamieson et al., 2023).

PPs are characterized by multiple phenolic units, comprising over 8000 structural varieties identified, ranging from small molecules like coumarins to larger ones like tannins (Jamieson et al., 2023). Although simple phenolic acids technically do not qualify as PPs due to their single phenol group, their structural resemblance and abundance alongside PPs in nature and human metabolism justify their inclusion in discussions about PPs (Jamieson et al., 2023).

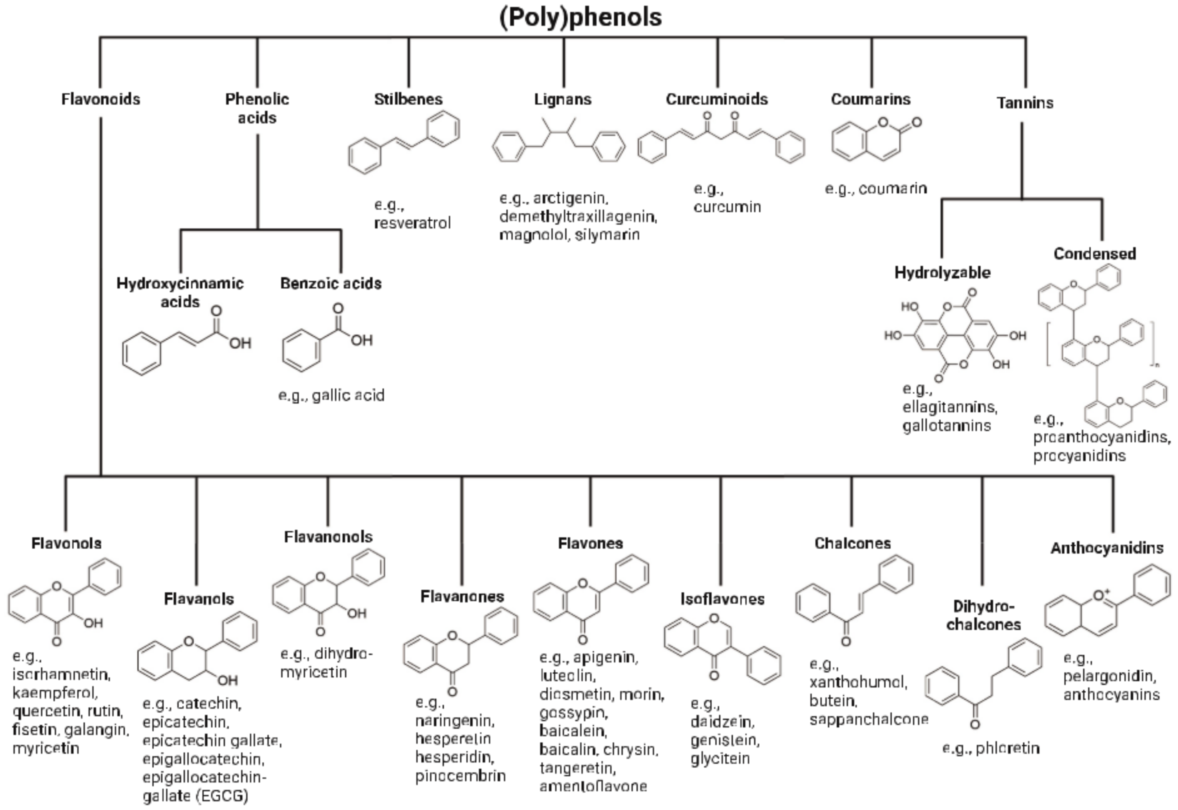

Figure 7. Classification and chemical structures of (poly)phenols. Taken from (Jamieson et al., 2023).

Phenolic compounds can be broadly categorized into two main groups: flavonoids and non-flavonoids. The distinctive feature of phenolic compounds is the presence of one or more aromatic rings with hydroxyl groups attached to them (Rasouli et al., 2017).

The dietary sources of polyphenol vary depending on the specific compound, as outlined in the examples provided below and detailed in the **Table 1**.

Table 1. Main dietary sources of polyphenols by specific compound. Adapted from *(Luca et al., 2020)*

POLYPHENOL	SUBCLASS	MAIN DIETARY SOURCES
RESVERATROL	Stilbene	Specific fruits: grapes, berries and peanuts (high variability of its content)
CURCUMIN	Curcuminoid	Turmeric rhizome
QUERCETIN	Flavonoid (Flavonols)	Lettuce, pepper, onion, black chokeberry, tomato, broccoli and apple
RUTIN	Flavonoid (Flavonols)	Fruits and vegetables, namely buckwheat, grapes, apples, berries, citrus fruits, capers, onions, asparagus and rooibos tea
DAIDZEIN **GENISTEIN**	Flavonoids (Isoflavones)	Soy (daidzin and genistin)
ELLAGITANNINS	Tannins (hydrolyzable)	Fruits (pomegranate, raspberry, blueberry, blackberry), nuts (walnuts, hazelnuts, pecans), honey and certain medicinal plants (geranium, oak)
PROANTHOCYANIDINS	Tannins (condensed)	Cinnamon bark, sorghum grains, grape seeds, baking chocolate, chokeberries and hazelnuts, blueberries, apples, pears and red wine

.

1.3.2. Polyphenols: ADME and biological activities

The absorption, distribution, metabolism and excretion (ADME) of PPs is a complex but vital field for understanding the biological effects of each polyphenol.

The absorption and metabolism of PPs are conditioned by their chemical structure including glycosylation or degree of polymerization, molecular size, and solubility. Unlike PPs administered as supplements that are likely to have greater bioavailability, PPs present in foods are usually present as complex mixtures and exist mainly as esters, glycosides or polymers, which are not easily absorbed. The majority of PPs are hydrolytically converted into their matching aglycone in the stomach or small intestine where they are absorbed by passive diffusion. Once the absorption has occurred, the metabolic transformation is driven by phase I and II detoxifying enzymes with the purpose of producing glucuronides and sulfates. Lastly, a variable proportion of conjugated PPs is eliminated through urine or bile, where they re-enter the small intestine (Jamieson et al., 2023).

The bioavailability of PPs depends on their transformation in the gastrointestinal tract and their bioaccessibility. The first refers to the amount of compound that remains bioactive in the intestinal phase after the digestive process, whereas bioaccessibility is the amount of the active compound available for absorption. The PPs bioavailability varies significantly among their different classes and ranks as follows, from the highest to the lowest bioavailability: phenolic acids > isoflavones > flavonols > catechins > flavanones, proanthocyanidins > anthocyanins (Lorenzo et al., 2021).

Curcumin is known for its poor solubility in water, chemical instability and low pharmacokinetic profile. Although being recognized as effective and safe, its therapeutic potential is still up for debate due to its poor bioavailability in humans, even at high doses (up to 12g/day). The major factors contributing to the low bioavailability of curcumin are the limited absorption in the small intestine, extensive metabolism in the liver and elimination through the gall bladder (Lorenzo et al., 2021). Curcumin undergoes extensive phase I and II biotransformation, primary in the liver but also in the intestine, namely by gut microbiota. Even though it presents poor oral bioavailability, curcumin can cross the blood-brain barrier due to its lipophilicity. Therefore, is able to reach the brain in biologically effective concentrations promoting neuroprotection (Lorenzo et al., 2021).

Research acknowledges that a PP-rich diet protects against chronic pathologies by modulating numerous physiological processes, such as cellular redox potential, enzymatic activity, cell proliferation and signaling transduction pathways (Luca et al., 2020). There is a comprehensive list of the various ways polyphenols can impact human health, highlighting their versatility and potential therapeutic benefits across different physiological systems. This list includes immunologic modulation and anti-inflammatory properties, antioxidant and free radical scavenging properties, anti-atherosclerosis and cardio protection, neuroprotective effects on anti-aging and neurodegenerative diseases, antimutagenic/anticarcinogenic properties, improvement of endothelium functions, protective effect on immune cell functions, antiallergic activity, antidiabetic effects, regulation of cell cycle progression, modulation of hormonal effects and contraceptive activity (Fraga et al., 2019).

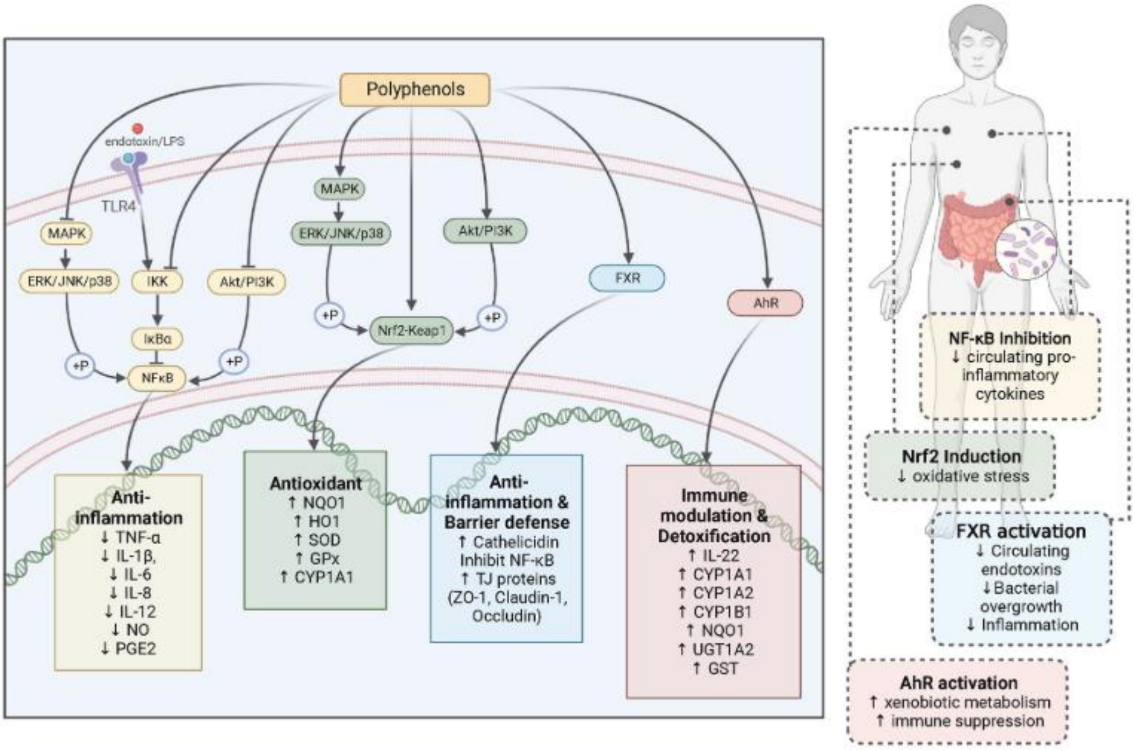

Figure 8. Key molecular targets of polyphenols important in IBD and proposed systemic effects. Taken from (Jamieson et al., 2023).

As demonstrated by several studies, PPs exhibit immune-modulating effects through diverse mechanisms. Some PPs can impact immune cells population, modulate the expression of inflammatory genes and affect cytokine production, while others can scavenge radicals, chelate metal ions, inhibit ROS production and promote ROS detoxification, promoting an anti-inflammatory effect (Yahfoufi et al., 2018), as presented in **Figure 8**.

1.3.3. Polyphenols and inflammatory bowel disease

By reducing oxidative stress and inflammation, PPs may lower the risk of chronic diseases such as cardiovascular disease, cancer or chronic inflammatory conditions such as IBD. Quercetin, for instance, regulates gene expression, has anti-proliferative and antiallergy effects and fights influenza A virus, among other well-known health-benefits (Rasouli et al., 2017). Dabeek & Marra reviewed a great number of studies regarding the effectiveness of quercetin on hypertension, inflammation, and cardiovascular risk. They found out that quercetin supplements as low as 150mg of aglycone were effective in reducing blood pressure in individuals, as well as oxidative stress and vascular damage markers. Moreover, they concluded that the most effective dose in lowering inflammatory markers, TNF-α and IL-6 was 500 mg of aglycone (flavonols in their free forms) (Dabeek & Marra, 2019).

Cytokines are important cellular mediators with pro and anti-inflammatory effects. Both *in vivo* and *in vitro* studies demonstrated that PPs affect macrophages through inhibition of multiple key regulators of inflammatory response such as TNF-α, IL-1-β, and IL-6 (pro-inflammatory cytokines), reducing inflammatory states (Yahfoufi et al., 2018).

The antioxidant properties of PPs are mainly mediated by ability to down-regulate the nuclear factor NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells), modulating crucial cell signaling pathways involved in inflammation and cancer (Mileo et al., 2019). NF-κB is a complex protein that plays a key role in deoxyribonucleic acid (DNA) transcription, cytokine production and cell survival. It controls immune responses, inflammation, cellular stress, proliferation and apoptosis. A great number of studies have reported that NF-κB signaling pathways are closely related to cancer metastasis. PPs have been shown to inhibit NF-kB, disrupting the metastatic potential of cancer, possibly offering huge benefits in controlling inflammatory condition (Yahfoufi et al., 2018).

Given their broad biological activity and minimal side effects, PPs have emerged as promising therapeutic agents for IBD, being a hot topic in biomedical research. They possess the capacity to alleviate inflammation, shield cells from damage, alter cellular communication, and influence factors implicated in IBD progression (Jamieson et al., 2023; Niedzwiecki et al., 2016; Yahfoufi et al., 2018).

1.3.4. Bilateral relationship between polyphenols and gut microbiota

Research over the years has led to the conclusion that PPs and the gut microbiota share a bilateral relationship. PPs can modulate the composition and activity of gut microbiota (Bao et al., 2020), bolstering beneficial bacteria and inhibiting harmful ones (Makarewicz et al., 2021). In exchange, gut microbiota can metabolize PPs into bioactive compounds that praise their health benefits, for example, their antioxidant and anti-inflammatory effects (Fraga et al., 2019). This reciprocal relationship is crucial for maintaining gut health and the general well-being of individuals.

1.3.4.1. Polyphenols and bacterial catabolic pathways

Undigested and unabsorbed PPs are thought to reach the large intestine and impact the bacteria inhabiting there and only these can undergo enzymatic biotransformation (Makarewicz et al., 2021). This biotransformation process results in metabolites with greater bioavailability and variable pharmacological properties compared to the parent compound (Jamieson et al., 2023).

Gut microbiota transformations can be grouped into three major catabolic pathways: hydrolysis (O-deglycosylations and ester hydrolysis), cleavage (C-ring cleavage; delactonization, demethylation), and reductions (dehydroxylation and double bond reduction) (Espín et al., 2017; Makarewicz et al., 2021):

a) Hydrolysis – Gut microbiota can deconjugate the native PPs releasing the corresponding aglycones that are better absorbed (Espín et al., 2017). Anthocyanidins, plant pigments responsible for flower, fruit and vegetable color are an important class of flavonoids. Anthocyanidins are generally present in the form of glycosides, called anthocyanins, and then suffer hydrolytic conversion into their corresponding anthocyanidins (Makarewicz et al., 2021).

Some dietary polyphenols, like isoflavones, can suffer glycosylation. Generally, the first step in isoflavones' biotransformation is glycoside hydrolysis by the bacteria in the gut, which release the aglycon fraction, improving the absorption rate. For example, daidzin (daidzein 7-O-glycoside) can be hydrolyzed to daidzein by *Eubacterium ramulus* (Makarewicz et al., 2021).

b) Ring-cleavage and carbon removal from side chains A – These catabolic reactions are carried out under the anaerobic conditions of the gut by the enzymatic activities of bacteria such as *Clostridium* and different *Coriobacteriaceae*. The aglycones released by the hydrolases are then catabolized through C-ring cleavage, in the case of flavonoids (Espín et al., 2017).

c) Reductions – Gut microbes also catalyze different reduction reactions of PPs, including hydrogenation of double bonds, carbonyl reductions and specific dehydroxylations (Espín et al., 2017). The conversion of caffeic acid into 3',4'-dihydroxyphenyl propionic acid is an emblematic hydrogenation reaction (Espín et al., 2017).

Another catabolic pathway is metabolic activation, which consists in breaking down PPs into bioactive metabolites, as the case of isoflavones (Steinert et al., 2016). Daidzein and genistein, isoflavones, are bioactivated through *Slackia isoflavoniconvertens,* which is responsible for the formation of EQUOL (bioactive metabolite) and 5-hydroxy-equol, respectively (Makarewicz et al., 2021).

1.3.4.2. Polyphenols and prebiotic effects

Polyphenols can trigger significant ecological shifts, resulting in major changes to the structure and functions of microbial ecosystems, thereby leading to the reconfiguration of alternative states (Costello et al., 2012). The polyphenol-induced shifts are evident in the formation of enterotype-like clusters within the gut microbiota.

PPs possess the capacity to: i) open up ecological niches by inhibiting potential opportunistic pathogens; ii) restore the proper functioning of the mucosal epithelial barrier along with its immunological response; iii) decrease oxidative agents such as ROS and free radicals (Magrone et al., 2019). These three actions promote the proliferation of beneficial gut bacteria that confer health benefits to the host, thereby showcasing their indirect prebiotic-like effect. A notable instance of this phenomenon is observed in the case of *A. muciniphila*.

Similar to carbohydrate-associated enzymes utilized by prebiotic-stimulated bacteria, many beneficial bacterial genomes encode a variety of polyphenol-associated enzymes (PAZymes) specifically involved in metabolizing PPs (Arumugam et al., 2011; Ley et al., 2008). When PPs are present, bacteria producing PAZymes can utilize these compounds to enhance their fitness and persistence in intestinal environments (Bäckhed et al., 2007; Shin et al., 2015). Accordingly, PPs have been shown to increase the growth and settlement of the probiotic bacterial families such as *Bifidobacteriaceae* and *Lactobacillaceae,* to name just a few (Plamada & Vodnar, 2022). In addition, they can also stimulate the production of mucus by Paneth cells, maintaining or improving the mucosal lining (Qiu et al., 2022; Ray & Mukherjee, 2021). *In vitro* cultures with PPs also showcase the ability of PPs to enhance total and individual SCFAs, end products of bacterial catabolism (Qiu et al., 2022)**.** Notably, recent studies demonstrated the beneficial effect of PPs by stimulating bacteria such as *A. muciniphila*, in mice under diet supplemented with red grapes (Plamada & Vodnar, 2022).

Such a case may result from a reduced competition caused by PPs inhibitory action on opportunistic microbes. As such, it is an indirect stimulation and may not be considered a prebiotic effect, as its (poly)phenol-degrading ability has not been established (Rodríguez-Daza et al., 2021a).

One can consider that PPs exert their beneficial effects as prebiotic substrate, on the one hand, by increasing the growth and settlement of the probiotic bacterial families such as *Bifidobacteriaceae* and *Lactobacillaceae* and, on the other hand, by reducing the number of pathogenic bacteria such as *Escherichia coli*, *Clostridium perfringens*, and *Helicobacter pylori*, with subsequent health benefits. This mechanism is associated with modification in the permeability and the rigidity of the bacterial membrane through modifications of the bacteria ratio (beneficial/pathogenic), leading to a change in the composition of SCFAs, thus decreasing inflammation (Plamada & Vodnar, 2022).

1.3.4.3. Polyphenols and antimicrobial effects

The use of herbs dates to antiquity, when plants were recognized as having great healing properties and were widely spread within folk medicine, and well as used as natural food preservatives (Makarewicz et al., 2021). Studies in literature prove that herbs such as thyme, oregano, rosemary, sage and mint, and spices can inhibit Gram-positive and Gram-negative bacteria, including pathogens (Makarewicz et al., 2021).

Polyphenols grant the plants their antimicrobial activity. The antimicrobial mechanisms of PPs against bacteria depend on the polyphenol structure, the dosage assigned and the strain of microorganism (Makarewicz et al., 2021). Moreover, differences in cell wall composition render Gram-positive bacteria more sensitive to polyphenols (Corrêa et al., 2019).

PPs can exert their antimicrobial effects through several mechanisms, including the below detailed as the most important ones (highlighted in **Figure 9**):

a) **Reaction with proteins:** PPs can bind to bacterial proteins and form soluble or insoluble complexes. Such bonds affect the function of both the polyphenol and the protein, causing changes in the protein structure, solubility, hydrophobicity, thermal stability, which can lead to the inactivation of essential enzymes and proteins, hindering the bacteria's ability to survive and reproduce (Makarewicz et al., 2021).

b) **Inhibition of nucleic acid synthesis by bacterial cells or DNA damage:** Flavonoids are inhibitors of topoisomerases, enzymes crucial for DNA replication and transcription, and play an important role in their antimycobacterial activity. By blocking topoisomerase, PPs inhibit the synthesis of nucleic acids leading to inhibition of bacteria functions and, ultimately, death (Makarewicz et al., 2021). Furthermore, PPs can damage bacterial DNA, leading to mutation or ultimately death (Makarewicz et al., 2021).

c) **Interaction with the bacterial cell wall or inhibition of cell wall formation:** Differences in cell surface structures between positive and negative Gram species may affect their susceptibility to antimicrobial agents, therefore impacting on their antimicrobial activity strength. Gram-positive bacteria appear to be more sensitive to the action of phenolic acids than Gram-negative bacteria, as they lack an outer membrane, which smooths phenolic acid diffusion through cell wall, leading to intracellular acidification. The hyper acidification, alters the membrane permeability and potential disrupting the sodium-potassium ATPase pump resulting into cell death (Makarewicz et al., 2021). Regarding the inhibition of cell wall formation, has already been demonstrated that quercetin and apigenin inhibit D-alanine ligase, a crucial enzyme for bacterial wall synthesis. In addition, they can inhibit the FabZ enzyme in *H. pylori* (Makarewicz et al., 2021).

d) Alteration of cytoplasmic membrane function: PPs can alter the properties of the bacterial cell membrane, such as permeability and fluidity. They have the ability to cause membrane dysfunction/damage, increase cell permeability and fluidity, which causes leakage of small intracellular constituents and eventual cell death (Makarewicz et al., 2021)

e) **Inhibition of energy metabolism:** Many cellular metabolic processes count on ATP production and consumption, the universal energy exchange factor facilitates catabolism, anabolism, motile contraction, phosphorylation and active nutrients transport. The ATP production through phosphorylation or photophosphorylation depends on membrane bound F1F0ATP synthase, an enzyme from bacteria. Research has shown that morin, baicalein and epicatechin completely inhibit ATPase activity. Meanwhile, hesperidin, chrysin, kaempferol, diosmin, apigenin, genistein, and rutin partially inhibit ATPase activity by about 40-60% (Makarewicz et al., 2021).

f) **Changes in cell attachment and inhibition of biofilm formation:** Biofilm is a collection of microbial cells attached to a surface, with bacteria integrated in a selfproduced extracellular matrix of biopolymers. Its formation is crucial for most pathogenic bacteria and is linked to quorum sensing (QS) or cell-to-cell communication (Makarewicz et al., 2021). Curcumin acts as an anti-QS agent inhibiting biofilm formation of pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa PAO1*, *Proteus mirabilis* and *Serratia marcescens*. It possibly interferes with their QS systems, disrupting biofilm maturation (Makarewicz et al., 2021).

g) **Substrate and metal deprivation:** PPs, like proanthocyanidins, can chelate essential metal ions, and deprive the bacteria of the substrate required for their growth, especially essential mineral micronutrients such as iron and zinc. Both processes end up removing the nutrients and cofactors crucial to bacteria, impairing their metabolic functions and growth (Makarewicz et al., 2021).

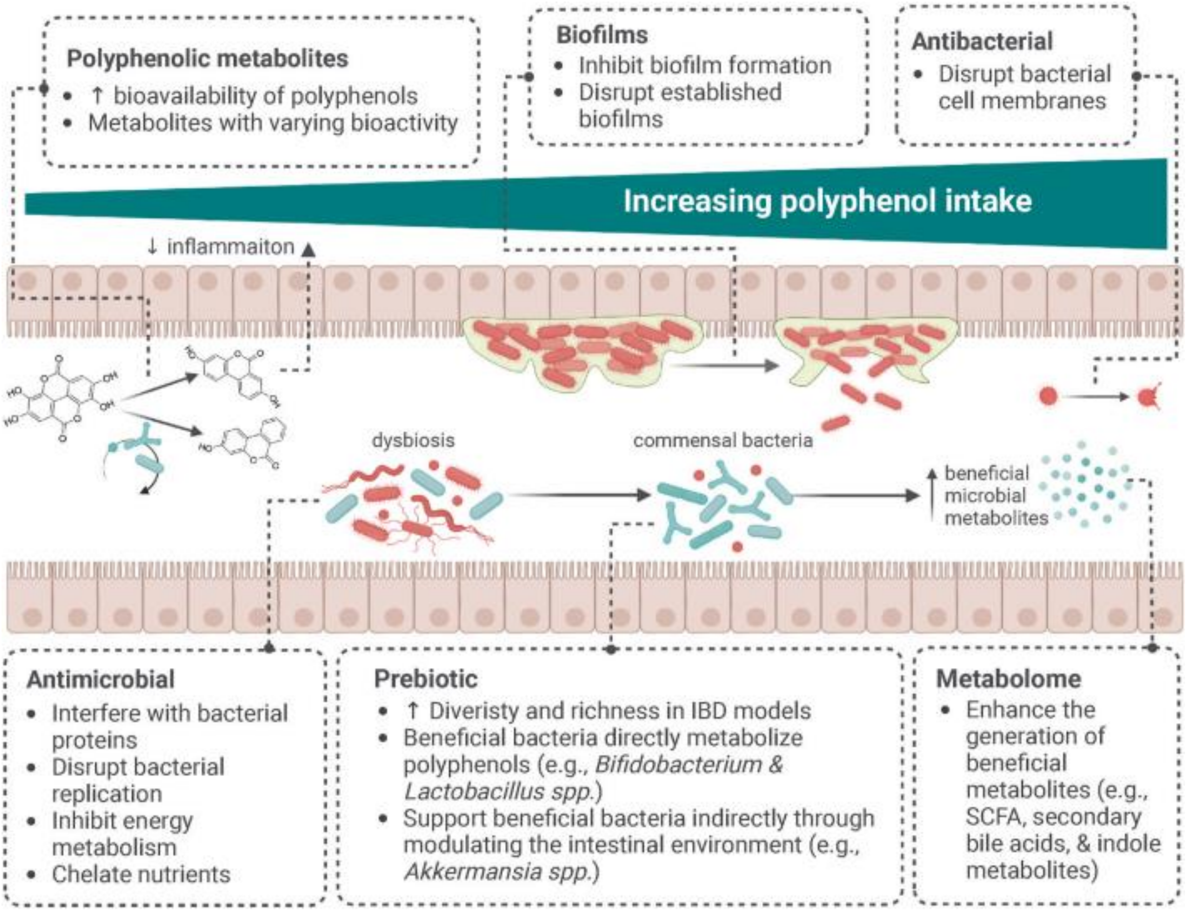

Figure 9. Modulation of gut microbiome by polyphenols: putative mechanisms. Taken from (Jamieson et al., 2023).

1.3.5. Polyphenols-mediated *A. muciniphila* modulation: Unveiling a putative duplibiotic effect in inflammatory bowel disease

The direct actions of PPs on the microbiota induce shifts in bacterial ecology and promote symbiotic relationships that further shape the composition and function of the microbiota. Through successive catabolic processes, intestinal PAZymes-producing bacteria generate phenolic metabolites that can be utilized by other beneficial bacterial species in intricate trophic cross-feeding networks. Recent findings suggest that certain PPs can be metabolized and transformed by beneficial gut microbes, such as *Lactobacillus plantarum* (Jiang et al., 2015; Reverón et al., 2015), into bioactive phenolic metabolites that readily traverse cell membranes, reaching target tissues where they exert localized anti-inflammatory effects. These metabolites have the potential to modulate the immune system, inhibit the growth of pro-inflammatory gut bacteria, and induce ecological shifts within the gut microbiota. Thus, the changes brought about by PPs in the microbiome highlight their duplibiotic nature, an elegant term proposed by Rodríguez-Daza et al. aimed to provide a complete description of the dual effects of certain PPs, promoting the growth of symbionts that are less metabolically adapted for PPs catabolization through concomitant prebiotic and antimicrobial effects (Rodríguez-Daza et al., 2021). Such bacteria resistant to PPs, as is the case of A. *muciniphila*, thrive following dietary intake of PPs, demonstrating their ability to withstand the antimicrobial effects and opportunistically occupy available ecological niches (Reverón et al., 2015).

Several studies have reported the reduced colonization of the mucin-degrading A. *muciniphila* anaerobic bacteria in IBD patients that appear to correlate with poor clinical outcomes. Accordingly, pharmacological and nutraceutical strategies to boost *A. muciniphila* abundance has been in the spotlight.

Polyphenols, phytochemicals with well-demonstrated prebiotic effects, confer benefits to intestinal dysbiosis and have been associated to improvements of IBD clinical scores. Strikingly, they combine direct prebiotic effects by promoting beneficial (poly)phenol-transforming bacteria abundance with an antimicrobial action, more pronounced against oxygen-dependent (aerobic) bacteria, allowing beneficial anaerobic bacteria to thrive given the reduced competition from aerobic species (Imlay, 2013), as is the case of *A. muciniphila*. Accordingly, exploring the duplibiotic nature of PPs and *A. muciniphila* abundance remodeling is promising to advance innovative IBD therapies.

CHAPTER II – AIMS

A wealth of evidence highlights polyphenol's ability to improve anaerobic *A. muciniphila* abundance and ameliorate IBD progression. However, it is still unclear whether this effect may parallel a *duplibiotic* behavior on IBD ecological niches. Moreover, a differential effect of polyphenols based on their chemical classes may occur, even though there is scarce information on this topic. In this work, we seek to:

1. Scrutinize polyphenols *duplibiotic* behavior through the simultaneous characterization of *A. muciniphila* abundance and aerobic/anaerobic bacterial communities remodeling in IBD upon polyphenols supplementation, as well as on α and β gut microbiota diversity.
2. To unveil the therapeutic potential of polyphenols supplementation on 3 key-features of gut health and IBD physiopathology, namely gut barrier permeability, mucus balance, and immune response, as well as on inflammatory and oxidative stress markers and disease activity index (DAI) score.

CHAPTER III – METHODS

This study is a scoping review conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) and guided by the PRISMA-ScR checklist (Tricco et al., 2018). The protocol for this review was registered with the Open Science Framework (https://doi.org/10.17605/OSF.IO/ZQHCS).

3.1. Research Question

The research question for this scoping review was: "**Can polyphenols improve intestinal *A. muciniphila* abundance in a *duplibiotic* fashion in IBD?**".

3.2. Search Strategy

The search strategy will be designed using the Participants-Concept-Context (PCC) framework, using keywords such as "Polyphenols", "Phenolic", "Flavonoids", "Anthocyanin", "Inflammatory bowel disease", "Colitis" "Crohn", "Gut microbiota" and "Microbiome", combined with Boolean operators and the following syntax: **(Polyphenols OR Phenolic OR Flavonoids OR Anthocyanin) AND (Inflammatory bowel disease OR Colitis OR Crohn) AND (Gut microbiota OR Microbiome)**. The literature search was conducted from 2012 to 2023 (October) in the PubMed.

3.3. Eligibility criteria

Only quasi-experimental and experimental studies published in English were considered, limited to those utilizing in vitro models, animal models and human participants to explore the mechanistic pathways involved.

Studies not focusing on the effect of polyphenols in the inflammatory bowel disease, or not related to gut microbiota composition in particularly on the *A. muciniphila* abundance were excluded. Additionally, non-original research articles, such as systematic reviews, meta-analyses, and other review articles, were not included in the analysis.

3.4. Study Selection

The screening process was managed using Covidence software (https://www.covidence.org/). All retrieved records were imported into Covidence, where duplicate entries were automatically removed. Title and abstract screenings were conducted independently by two reviewers (Carolina Matias and André Alves), with any disagreements resolved through discussion with a third reviewer (Sara Nunes). Articles that passed the initial screening were subjected a full-text review based on the inclusion criteria detailed above. The results of the search and reasons for exclusion at the full-text review stage are presented in **Figure 10**.

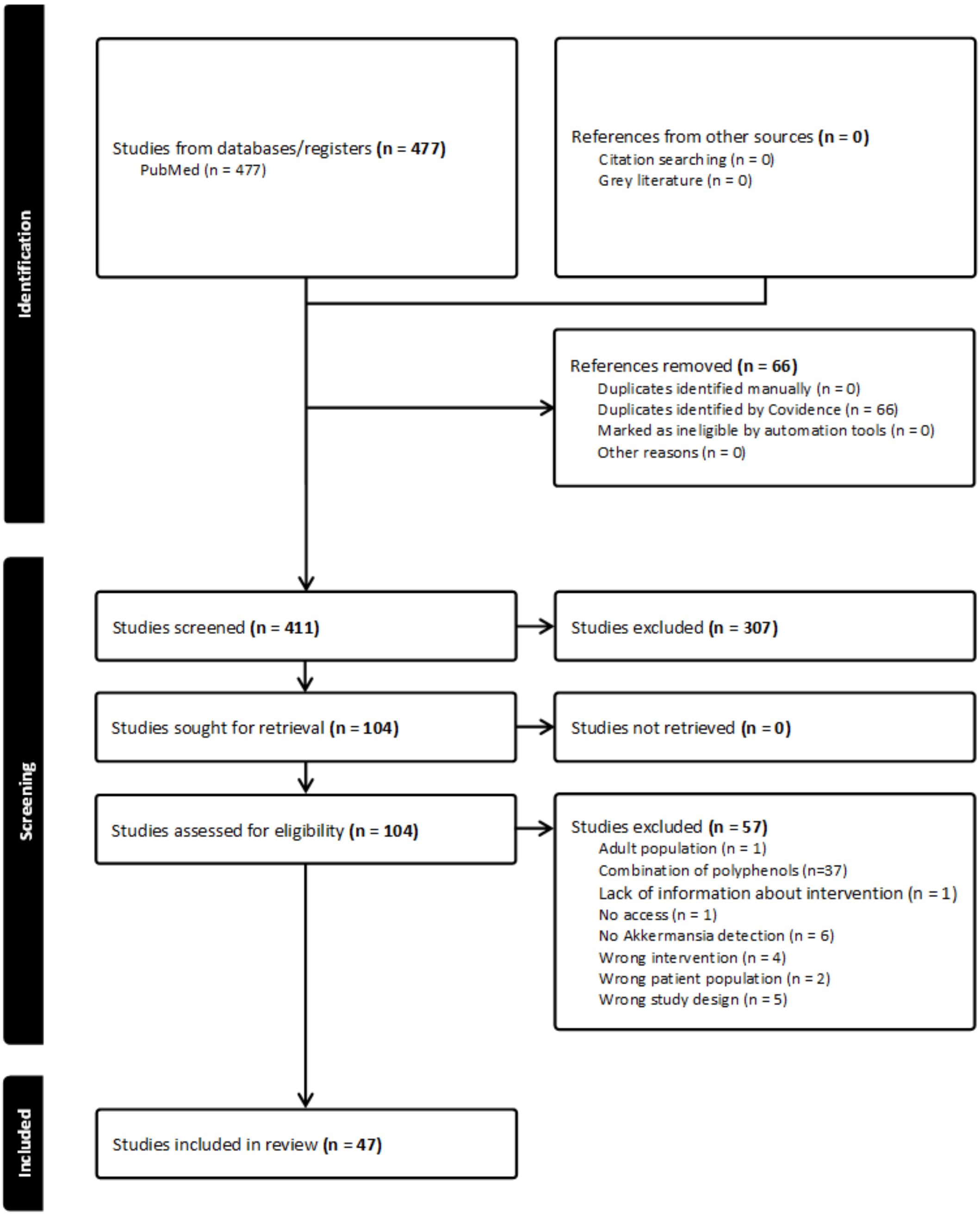

Figure 10. The flow chart of study selection.

3.5. Synthesis of results

Key findings from the included studies were analyzed to evaluate polyphenols class-*A. muciniphila* abundance, focusing on microbiota modulation. Polyphenols class, A. muciniphila abundance, microbiota composition, gut barrier permeability, mucus balance, immune system homeostasis, inflammatory and oxidative stress markers, along with relevant clinical outcomes, were synthesized and organized into tables.

CHAPTER IV – RESULTS

4.1. Literature search overview

Through the search strategy, we have retrieved 477 articles in PubMed Medline. After removing duplicate documents, 411 articles remained. Upon screening the title and abstract, 307 articles were excluded due to being reviews and unrelated topics. The remaining 104 articles were carefully analyzed and 57 were further excluded for following reasons: 1 was focused on adult population, 1 lacked sufficient information about the intervention, 1 was inaccessible, 2 had the wrong patient population, 4 used incorrect intervention, 5 had inappropriate study designs, 6 did not detect *A. muciniphila*, and 37 included PPs mixtures. In the end, 47 articles met the inclusion criteria and were included. The detailed processes of literature selection are illustrated in **Figure 10.**

The main representative classes of PPs on the included studies were flavonoids (28 articles; 56%), phenolic acids (12 articles; 24%) and other PPs (10 articles; 20%), including curcuminoids, tannins, and stilbenes (**Figure 11**).

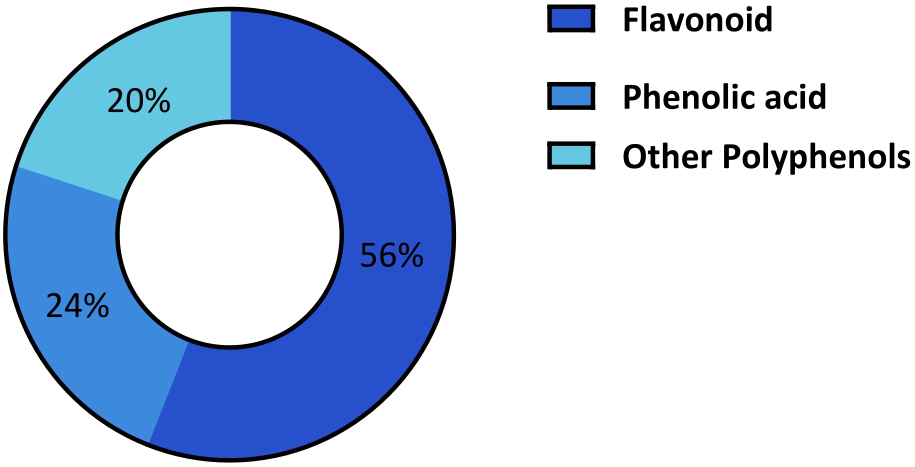

Figure 11. Main representative class of polyphenols in the included studies.

Through the analysis of the included articles, it was possible to understand the modulation of different polyphenol classes on *A. muciniphila* abundance in the context of IBD. Among the studies focused on flavonoids as the therapeutic approach, 64.3% articles showed an increase in *A. muciniphila* abundance, 21.4% articles reported a decrease and 14.3% showed no significant *A. muciniphila* modulation. Studies using phenolic acids have similar results: 66.7% of the articles reported an increase in *A. muciniphila* abundance, 25%

observed a decrease and 8.3% did not report any change. Lastly, among the studies focused on other PPs, such as curcuminoids, tannins, and stilbenes, 60% of the articles showed an increase in *A. muciniphila* abundance, 30% reported a decrease while 10 % showed no significant *A. muciniphila* modulation (**Figure 12**).

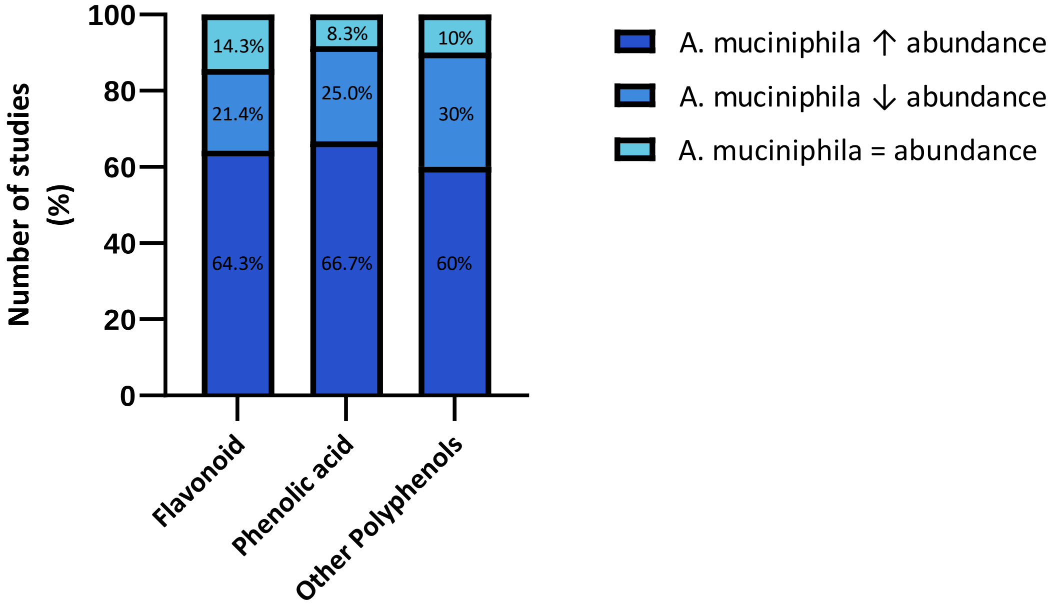

Figure 12. Number (and percentage) of studies reporting impact of distinct PPs classes on the *A. muciniphila* abundance (increased, reduced or unchanged).

4.1.1. Flavonoids' impact on gut microbiota

Table 2 details the effects of various flavonoids on gut microbiota, focusing on how these PPs impact the abundance of *A. muciniphila*, microbial diversity (α- and β-diversity), and their specific impact/modulation on different bacterial populations, such as anaerobic and aerobic bacteria.

In general, flavonoids promote an increase in *A. muciniphila* abundance, with a total of 18 studies showing positive effects. However, in a few studies, such as those reporting the use of quercetin, dihydroquercetin and EGCG, a decrease in the *A. muciniphila* abundance was observed (Guo et al., 2021; Liu et al., 2022; Han, et al., 2021). This variability in microbial composition reflects the complex role of flavonoids on the gut microbiota composition modulation and suggest their potential to influence the growth of beneficial bacteria.

Regarding microbial diversity, α-diversity, which reflects the diversity of species within a microbial community, tends to increase with the majority of flavonoids studied. Only a few flavonoids, such as 4′,5,6,7,8-pentamethoxyflavone and EGCG, showed no significant effect on this parameter. In contrast, β-diversity, which measures the differences in microbial community composition between different environments, was increased in many studies, suggesting that flavonoids promote substantial shifts in the gut microbiota structure.

Flavonoids also impact the abundance of facultative anaerobic bacteria, including *Enterobacteriaceae*, *Lactobacillaceae*, and *Streptococcaceae families*. Increases in *Lactobacillaceae,* a bacterial family associated with the gut health promotion, where commonly observed with flavonoids like apigenin, astragalin and icariin (Fu et al., 2022; Peng et al., 2020; Zhang et al., 2023; Zhang et al., 2021). On the other hand, a reduction of *Enterobacteriaceae*, a bacterial family often associated with inflammatory conditions and intestinal infections, was a positive outcome observed with flavonoids like 4′,5,6,7,8-pentamethoxyflavon, apigenin, astragalin (Chen et al., 2021; Fu et al., 2022; Peng et al., 2020).

In contrast, the modulation of flavonoids on anaerobic bacterial abundance, particularly on the Bacteroidaceae family is less consistent, with both increases and decreases observed in the analyzed studies (**Table 2**). Flavonoids such as icariin and TFA promoted a reduction of the facultative anaerobic bacteria like those of the *Helicobacteraceae* family (Wang et al., 2021; Zhang et al., 2023; Zhang et al., 2021). Despite this, a consistent improvement in *A. muciniphila* abundance along with a modulation in the abundance of anaerobic and facultative anaerobic bacteria, more precisely with a decrease in the *Bacteroidaceae* and an increase in *Lactobacillaceae*, was observed upon supplementation with icariin (Wang et al., 2021; Zhang et al., 2023; Zhang et al., 2021). Regarding the evidence reporting the effects of quercetin and dihydroquercetin, it was reported an inconsistent pattern of microbial composition, with conflicting result on the abundance of *A. muciniphila* and anaerobic bacteria families such as *Bacteroidacea*e and *Ruminococcaceae* (Li et al., 2022; Han, et al., 2021). EGCG demonstrated an ability to enhance both α- and β-diversity, as well as modify bacterial composition by promoting the growth of beneficial bacteria (Liu et al., 2022; Wu et al., 2021). Moreover, this flavonoid showed variable effects on the *Bacteroidacea*e abundance, with both increases and decreases reported.

Table 2. Impact of flavonoids on gut microbiota composition and diversity.

Flavonoid	*A. muciniphila* abundance	α-diversity	β-diversity	Anaerobic bacteria abundance	Facultative anaerobic abundance	Aerobic bacteria abundance	Refs
4′,5,6,7,8-pentamethoxyflavone	↑	=	↑	↑ *Lachnospiraceae;* ↓*Marinifilaceae;* ↓*Rikenellaceae*	↓*Enterobacteriaceae;* ↑*Lactobacillacea*	___	(Chen et al., 2021)
Apigenin	↑	↑	___	↓*Bacteroidaceae;* ↑*Erysipelotrichaceae;* ↓*Peptostreptococcaceae;* ↓*Turicibacteraceae*	↓*Enterobacteriaceae;* ↑*Lactobacillaceae*	___	(Fu et al., 2022)
Astragalin	↑	↑	↑	↓*Bacteroidaceae;* ↓*Erysipelotrichaceae;* ↑*Lachnospiraceae;* ↓*Peptostreptococcaceae;* ↓*Prevotellaceae;* ↑*Ruminococcaceae*	↓*Coriobacteriaceae;* ↓*Enterobacteriaceae;*	___	(Peng et al., 2020)
Dihydromyricetin	↑	↑	↑	↓*Bacteroidaceae;* ↓*Lachnospiraceae;* ↓*Peptostreptococcaceae;*	↑*Lactobacillaceae;* ↓*Streptococcaceae*	___	(Dong et al., 2021)
Dihydroquercetin	↑	↑	↑	↑ *Bacteroidaceae;* ↑*Eubacteriaceae;* ↑*Ruminococcaceae;* ↑*Turicibacteraceae*	↑*Lactobacillaceae*	___	(Li et al., 2022)
Epigallocatechin-3-gallate	↑	=	↑	↑*Bacteroidaceae;* ↑ *Enterococcaceae;* ↓*Erysipelotrichidae;* ↓*Odoribacteraceae;* ↓*Peptostreptococcaceae;* ↓*Turicibacteraceae;*	↑*Enterobacteriaceae;* ↑*Lactobacillaceae*	___	(Wu et al., 2021)
Genistein	↑	↑	↑	↓ *Deferribacteraceae;* ↓*Lachnospiraceae;* ↑*Odoribacteraceae;* ↑ *Oscillospiracea;* ↑*Rikenellaceae;* ↓*Ruminococcaceae*	___	↓*Sphingomonadaceae*	(Fan et al., 2021)
Icariin	↑	___	___	↓*Bacteroidaceae;* ↑*Lachnospiraceae;* ↓*Turicibacteraceae;*	↓*Helicobacteraceae;* ↑*Lactobacillaceae;*	___	(Zhang et al., 2021)
Icariin-1	↑	↑	↑	↓*Bacteroidaceae;* ↑*Desulfovibrionaceae;* ↑*Erysipelotrichaceae;* ↑*Eubacteriaceae;* ↑*Lachnospiraceae;* ↓*Odoribacteraceae;* ↓*Oscillospiraceae;* ↓*Rikenellaceae*	↓*Helicobacteraceae;* ↑*Lactobacillaceae*	___	(Zhang et al., 2023)
Licochalcone A	↑	___	___	↑*Bacteroidaceae;* ↑*Bifidobacteriaceae;* ↓*Defluviitaleaceae;* ↑*Erysipelotrichidae;* ↓ *Prevotellaceae;* ↑*Ruminococcaceae*	↓*Bacillaceae;* ↓*Enterococcaceae;* ↑*Streptococcaceae*	↑*Moraxellaceae*	(Zhang et al., 2021)

Legend: ↑-increased; ↓ - decreased; = - equal; ___ - no data

Table 2. Impact of flavonoids on gut microbiota composition and diversity (continued).

Flavonoid	*A. muciniphila* abundance	α-diversity	β-diversity	Anaerobic bacteria abundance	Facultative anaerobic abundance	Aerobic bacteria abundance	Refs
Luteolin	↑	↑	↑	↑*Bacteroidaceae;* ↑*Clostridiaceae;* ↑*Lachnospiraceae;* ↑*Prevotellaceae*	↑*Lactobacillaceae;*	___	(Li et al., 2021)
Myricetin and myricetin-3-O-b-D-lactose sodium	↑	↑	↑	↓*Bacteroidaceae;* ↓*Clostridiaceae;* ↓*Coriobacteriaceae;* ↓*Desulfovibrionaceae;* ↓*Eggerthellaceae;* ↓*Oscillospiraceae;* ↓*Peptostreptococcaceae;* ↓*Ruminococcaceae;* ↓*Sutterellaceae*	↓*Lactobacillaceae*	___	(Miao et al., 2021)
Phloretin	↑	=	=	↑ *Bacteroidaceae;* ↓*Hungateiclostridiaceae;* ↓*Lachnospiraceae;* ↓*Oscillospiraceae;* ↑*Rikenellaceae*	↑*Lactobacillaceae*	___	(Wu et al., 2019)
Proanthocyanidins	↑	↑	___	↓*Bacteroidaceae;* ↑*Bifidobacteriaceae;* ↑*Erysipelotrichaceae;*	↑*Lactobacillaceae;* ↓*Straphylococcaceae;*	___	(Chen et al., 2023)
Puerarin	↑	___	___	↓*Lachnospiraceae;* ↓*Prevotellaceae;* ↓*Rikenellaceae;* ↓*Ruminococcaceae*	___	___	(Wu et al., 2020)
Quercetin	↑	=	=	↓*Bacteroidaceae;* ↓*Oscillospiraceae;* ↓*Ruminococcaceae;* ↓*Tannerellaceae*	↓*Enterobacteriaceae;* ↑*Flavobacteriaceae;*	___	(Liso et al., 2018)
Total flavone of Abelmoschus manihot	↑	↑	↑	↑*Bacteroidaceae;* ↑*Hungateiclostridiaceae;* ↑*Oscillospiraceae;* ↑*Prevotellaceae;* ↑*Rikenellaceae*	↓*Enterococcaceae;* ↓*Helicobacteraceae;* ↓*Lactobacillaceae*	___	(Wang et al., 2021)
Vitexin	↑	___	___	↓*Bacillaceae;* ↑*Clostridiaceae;* ↑*Erysipelotrichidae*	↓ *Enterobacteriaceae;* ↓*Vibrionaceae*	___	(Zhang et al., 2022)
Quercetin	↓	___	___	↓*Bacteroidaceae;* ↑*Clostridiaceae;* ↑*Lachnospiraceae;* ↓*Paraprevotellaceae;*	↑*Lactobacillaceae*	___	(Guo et al., 2021)
Baicalin	↓	↑	↑	↑*Eubacteriaceae;* ↑*Lachnospiraceae;* ↑*Odoribacteraceae;* ↑*Ruminococcaceae*	___	___	(Zhu et al., 2020)
Dihydroquercetin	↓	=	=	↓*Bacteroidaceae;* ↑*Erysipelotrichidae;* ↑*Muribaculaceae;* ↓*Prevotellaceae*	↑*Enterobacteriaceae;* ↑*Lactobacillaceae*	___	(Han, et al., 2021)

Legend: ↑-increased; ↓ - decreased; = - equal; ___ - no data

Table 2. Impact of flavonoids on gut microbiota composition and diversity (continued).

Flavonoid	*A. muciniphila* abundance	α-diversity	β-diversity	Anaerobic bacteria abundance	Facultative anaerobic abundance	Aerobic bacteria abundance	Refs
Epigallocatechin-3-gallate	↓	↑	___	↓*Bacteroidaceae;* ↑*Bifidobacteriaceae;* ↑*Clostridiaceae;* ↑*Coriobacteriaceae;* ↑*Desulfovibrionaceae;* ↑*Rikenellaceae;* ↓*Sutterellaceae;*	↑*Lactobacillaceae*	___	(Liu et al., 2022)
Galangin	↓	↑	↑	↓*Bacteroidaceae;* ↑*Deferribacteraceae;* ↑*Odoribacteraceae*	↓*Enterobacteriaceae;* ↑*Lactobacillaceae*	___	(Xuan et al., 2020)
Total Flavonoids of Glycyrrhiza uralensis	↓	↑	↑	↑*Bacteroidaceae;* ↑*Lachnospiraceae;* ↑*Muribaculaceae;* ↑*Oscillospiraceae;* ↑*Rikenellaceae*	↑*Lactobacillaceae*	___	(Yue et al., 2021)
Diosmetin	=	↑	↑	↑*Bacteroidaceae;* ↓*Coriobacteriaceae;* ↓*Clostridiaceae;* ↑*Cyanobacteriaceae;* ↑*Lachnospiraceae;* ↑*Odoribacteraceae;* ↑*Oscillospiraceae;* ↑*Prevotellaceae;* ↑*Rikenellaceae;* ↑*Ruminococcaceae;* ↑*Synergistaceae*	↑ *Anaeroplasmataceae*	↓*Flavobacteriaceae*	(long Li et al., 2022)
Linarin	=	↑	↑	↑*Bacteroidaceae;* ↓*Clostridiaceae;* ↑*Erysipelatoclostridiaceae;* ↓*Erysipelotrichidae;* ↑*Lachnospiraceae;* ↓*Rikenellaceae;* ↑*Paraprevotellaceae;*	↑*Lactobacillaceae;* ↑ *Enterobacteriaceae*	___	(Jin et al., 2022)
Rutin	=	↑	↑	↓*Bacteroidaceae;* ↑*Bifidobacteriaceae;* ↑*Clostridiaceae;* ↓*Deferribacteraceae;* ↓*Prevotellaceae;* ↑*Ruminococcaceae*	↓*Enterococcaceae;* ↑*Lactobacillaceae*	___	(Power et al., 2016)
Taxifolin	=	↑	___	↑*Anaeroplasmataceae;* ↓*Bacteroidaceae;* ↓*Clostridiaceae* ↑*Desulfovibrionaceae;* ↑*Erysipelotrichidae;* ↑*Hyphomicrobiaceae;* ↑ *Sutterellaceae;*	↑*Alcaligenaceae;* ↑*Burkholderiaceae;* ↓*Coprobacillaceae*	↓*Sphingobacteriaceae*	(Hou et al., 2021)

Legend: ↑-increased; ↓ - decreased; = - equal; ___ - no data

4.1.2. Phenolic acids' impact on gut microbiota

Table 3 show the influence of different phenolic acids on intestinal microbiota. Phenolic acids have varying effects on gut microbiota, particularly on *A. muciniphila* abundance and microbial diversity. Notably, phenolic acids (e.g. acteoside, caffeic acid, chlorogenic acid, gallic acid, p-hydroxybenzoic acid and salvianolic acid A) showed an increase in the abundance of *A. muciniphila* (Chen et al., 2023; Han et al., 2022; Liu et al., 2022; Wan, Zhong, et al., 2021; Wang et al., 2018; Xie et al., 2022; Zhang et al., 2017). Conversely, compounds like 6-gingerol, paeonol, and rosmarinic acid reduced its abundance (Li et al., 2023; Tian et al., 2022; Zheng et al., 2022).

Most phenolic acids (e.g. caffeic acid, chlorogenic acid, gallic acid, salvianolic acid A, and 6-gingerol) tend to increase α-diversity and β-diversity, suggesting enhanced microbial richness and variation in microbial community. However, the impact on *Bacteroidaceae* abundance remains inconsistent across studies (Chen et al., 2023; Tian et al., 2022; Wan, Zhong, et al., 2021; Wang et al., 2018; Xie et al., 2022; Zhang et al., 2017).

Several phenolic acids, such as acteoside, caffeic acid, gallic acid, and paenol, significantly reduced the abundance of pro-inflammatory bacterial families like *Desulfovibrionaceae* and *Turicibacteraceae*, indicating their potential anti-inflammatory effects (Chen et al., 2023; Y. Liu et al., 2022; Wan, Zhong, et al., 2021; Zheng et al., 2022).

Remarkably, gallic acid, salvianolic acid A and paeonol significantly promoted the growth of the beneficial *Lactobacillaceae* family, known for its role in maintaining gut health (Chen et al., 2023; Wang et al., 2018; Zheng et al., 2022). In contrast, chlorogenic acid and rosmarinic acid effectively reduced the abundance of *Enterobacteriaceae*, a bacterial family frequently linked to dysbiosis and inflammation, highlighting their potential to mitigate gut imbalances and inflammatory conditions (Li et al., 2023; Xie et al., 2022).

4.1.3. Other polyphenols' impact on gut microbiota

Table 4 provides a comparative analysis of the effects of other distinct PPs, such as curcumin, resveratrol, and tannic acid on the gut microbiota composition and diversity.

Curcumin has been widely studied and consistently shown to increase in the abundance of *A. muciniphila*. Regarding α-diversity, curcumin generally tends to increase diversity, suggesting a greater species richness within the gut ecosystem. However, finding related to β-diversity are less consistent, with some studies indicating an increase and others providing insufficient data (Guo et al., 2022; Ye et al., 2023; Zhou et al., 2023). In terms of its effects on anaerobic bacteria, curcumin fosters the growth of several bacterial families, such as *Lachnospiraceae*, *Muribaculaceae* and *Odoribacteraceae* (Guo et al., 2022; Zhang et al., 2022; Zhou et al., 2023). Moreover, curcumin shows a trend to reduce the abundance of the Bacteroidaceae family (Guo et al., 2022; Ye et al., 2023; Zhang et al., 2022; Zhou et al., 2023). For facultative anaerobic bacteria, curcumin demonstrates a notable reduction in pathogenic families like *Enterobacteriaceae* and *Enterococcaceae*, while increasing *Lactobacillaceae*, a family known for its probiotic properties and positive role in maintaining gut health (Guo et al., 2022; Zhang et al., 2022; Zhou et al., 2023).

Resveratrol has also exhibited similarly positive effects on the gut microbiota, not only increasing the abundance of *A. muciniphila but also enhancing α*- and β- diversity. Resveratrol fosters the growth of anaerobic bacteria, including Bacteroidaceae and Ruminococcaceae, and improves the abundance of *Bifidobacteriaceae*, a family critical for gut health (Alrafas et al., 2019). Additionally, resveratrol reduces the abundance of harmful bacteria, such as *Desulfovibrionaceae* and Lachnospiraceae, both of which are often associated with inflammatory and metabolic disorders (Singh et al., 2023; Teffera et al., 2024; Vacca et al., 2020). Resveratrol also decreases the *Enterococcaceae* (facultative anaerobes) and reduces the abundance of aerobic bacteria like *Xanthomonadaceae* and *Moraxellaceae* (Xu et al., 2023).

Tannins, another polyphenol, mirrors these beneficial effects. It has been associated with an enhancement of *A. muciniphila* abundance and *α*-diversity, promoting a richer microbial environment. Furthermore, tannin acid promotes the growth of beneficial bacteria like *Bifidobacteriaceae* and *Lactobacillaceae*, while simultaneously reducing the population of the pathogenic microorganisms, including *Staphylococcaceae* (Chen et al., 2023; He et al., 2023).

Regarding the impact of PPs in the aerobic bacteria modulation, despite the limited data on the specific effects, available evidence suggests that polyphenols supplementation, in general, tends to reduce their abundance. This reduction could further contribute to a healthier microbial balance in the gut (Imlay, 2013).

Table 3. Impact of phenolic acids on gut microbiota composition and diversity.

Phenolic acid	*A. muciniphila* abundance	α-diversity	β-diversity	Anaerobic bacteria abundance	Facultative anaerobic abundance	Aerobic bacteria abundance	Refs
Acteoside	↑	=	___	↑*Bacteroidaceae;* ↓*Desulfovibrionaceae;* ↑*Odoribacteraceae;*	___	___	(Liu et al., 2022)
Caffeic Acid	↑	↑	↑	↓*Bacteroidaceae;* ↑*Erysipelotrichidae;* ↑*Rikenellaceaeceae;* ↓*Turicibacteraceae*	↓*Lactobacillaceae*	___	(Zhong, et al., 2021)
Chlorogenic acid	↑	=	↑	↑*Clostridiaceae;* ↑*Coprobacillaceae;* ↓*Lachnospiraceae*	↓ *Enterococcaceae;* ↑*Coriobacteriaceae;* ↑*Corynebacteriaceae*	___	(Xie et al., 2022)
Chlorogenic acid	↑	↑	___	↑*Bacteroidaceae;* ↑*Cyanobacteriaceae*	___	___	(Zhang et al., 2017)
Gallic acid	↑	↑	___	↓*Bacteroidaceae;* ↑*Bifidobacteriaceae;* ↑*Erysipelotrichaceae*	↑ *Lactobacillaceae;* ↓*Straphylococcaceae*	___	(Chen et al., 2023)
P-Hydroxybenzoic acid	↑	↑	=	↓ *Clostridiaceae;* ↓*Oscillospiraceae;* ↓*Prevotellaceae;* ↓*Rhodospirillales;*	___	___	(Han et al., 2022)
Salvianolic Acid A	↑	↑	↑	↓*Bacteroidaceae;* ↑*Lachnoclostridiaceae;* ↓*Ruminiclostridiaceae*	↑*Lactobacillaceae*	___	(Wang et al., 2018)
6-gingerol	↓	↑	↑	↑*Desulfovibrionaceae;* ↑*Erysipelotrichaceae;* ↑*Oscillospiraceae*	___	___	(Tian et al., 2022)
Paeonol	↓	↑	___	↑ *Bacteroidaceae;* ↓*Peptostreptococcaceae;* ↓ *Turicibacteraceae*	↓*Enterobacteriaceae;* ↑*Lactobacillaceae;* ↓*Streptococcaceae*	___	(Zheng et al., 2022)
Rosmarinic acid	↓	↓	↑	↓*Bifidobacteriaceae;* ↑*Clostridiaceae;* ↓*Peptostreptococcaceae*	↓*Enterobacteriaceae;* ↑*Lactobacillaceae*	___	(Li et al., 2023)
Gallic acid	=	↑	↑	↑ *Bacteroidaceae;* ↓ *Erysipelotrichidae;* ↓*Lachnospiraceae;* ↓*Prevotellaceae;* ↓*Sutterellaceae;* ↓*Turicibacteraceae*	↓ *Streptococcaceae* ↑*Lactobacillaceae*	___	(Li et al., 2019)

Legend: ↑-increased; ↓ - decreased; = - equal; ___ - no data.

Table 4. Effects of other polyphenols on gut microbiota composition and diversity.

Other PPs	PP class	*A. muciniphila* abundance	α-diversity	β-diversity	Anaerobic bacteria abundance	Facultative anaerobic abundance	Aerobic bacteria abundance	Refs
Curcumin	Curcuminoid	↑	↑	___	↓*Aerococcaceae;* ↑*Comamonadaceae;* ↑ *Coprobacillaceae;* ↑*Lachnospiraceae;* ↑*Odoribacteraceae;* ↓*Turicibacteraceae;*	↓*Enterobacteriaceae;* ↓*Enterococcacea;* ↓*Planococcaceae*	___	(Guo et al., 2022)
Curcumin	Curcuminoid	↑	↑	↑	↓*Bacteroidaceae*	___	___	(Ye et al., 2023)
Curcumin	Curcuminoid	↑	=	↑	↑ *Bacteroidaceae;* ↓*Deferribacteraceae;* ↓ *Erysipelotrichaceae;* ↑*Lachnospiraceae;* ↑*Muribaculaceae*	↑*Lactobacillaceae*	___	(Zhou et al., 2023)
Resveratrol	Stilbenes	↑	↑	↑	↑*Bacteroidaceae;* ↑*Ruminococcaceae*	______	_____	(Alrafas et al., 2019)
Tannic acid	Tannins	↑	↑	___	↓*Bacteroidaceae;* ↑*Bifidobacteriaceae;* ↑*Erysipelotrichaceae*	↓ *Straphylococcaceae;* ↑ *Lactobacillaceae*	___	(Chen et al., 2023)
Tannin acid	Tannins	↑	=	___	↑*Bifidobacteriaceae;* ↑*Erysipelotrichaceae;* ↑*Muribaculaceae;* ↑*Turicibacteraceae*	↓*Enterococcaceae;* ↑*Lactobacillaceae*	___	(He et al., 2023)
Curcumin	Curcuminoid	↓	↓	↑	___	___	___	(Wen et al., 2023)
Curcumin	Curcuminoid	↓	___	↑	↓*Bacteroidaceae;* ↑*Cyanobacteriaceae;* ↑*Muribaculaceae;* ↑*Odoribacteraceae;* ↓*Sutterellaceae*	↓ *Enterobacteriaceae*	___	(Zhang et al., 2022)
Resveratrol	Stilbenes	↓	↑	↑	↑*Bacteroidaceae;* ↑ *Bifidobacteriaceae;* ↓ *Desulfovibrionaceae;* ↓*Lachnospiraceae;* ↓*Sutterellaceae*	___	___	(Li et al., 2020)
Resveratrol	Stilbenes	=	↑	↑	↓*Bacteroidaceae;* ↓*Lachnoclostridiaceae;* ↓*Lachnospiraceae;* ↓*Prevotellaceae;* ↓*Ruminoclostridiaceae;* ↓*Ruminococcaceae;*	↓ *Enterobacteriaceae*	↓ *Xanthomonadaceae;* ↓*Moraxellaceae*	(Xu et al., 2023)

Legend: PPs, polyphenols; ↑-increased; ↓ - decreased; = - equal; ___ - no data.

4.1.4. Impact of flavonoids on gut health

Table 5 provides a comprehensive overview of various flavonoids and their impact on gut health, particularly focusing on key markers such as the abundance of *A. muciniphila*, gut permeability, mucus layer integrity, immune system homeostasis, inflammatory and oxidative stress markers, as well as on the DAI score.

Several flavonoids, including tangeretin, dihydromyricetin, genistein, apigenin, phloretin, puerarin, and vitexin were found to improved gut permeability. This was evidenced by increased expression of tight junction proteins such as Claudin-1, Occludin, and ZO-1, indicating their role in strengthening the intestinal barrier and preventing the "*leaky gut*". Furthermore, certain flavonoids (e.g., apigenin, phloretin, and vitexin) have also been shown to enhance the mucus layer, by promoting goblet cells proliferation and increasing levels of proteins like MUC2, which serves as a protective barrier in the gut (Fu et al., 2022; Wu et al., 2019; Zhang et al., 2022).

The immune-modulating effects of flavonoids were reflected in the increased prevalence of Treg cells, reduction of pro-inflammatory Th17 cells, and shifts from M1 (pro-inflammatory) to M2 (anti-inflammatory) macrophages. Icariin-1, phloretin, and baicalin were particularly noted for their effects on immune cell populations, suggesting their role in attenuate inflammation while fostering a balanced immune response (Wu et al., 2019; Zhang et al., 2023; Zhu et al., 2020).

Most flavonoids listed in **Table 5** significantly reduced inflammatory markers such as IL-1β, IL-6, TNF-α, NF-κB, as well as oxidative stress markers like malondialdehyde (MDA) and myeloperoxidase (MPO). Additionally, flavonoids were also found to increase anti-inflammatory cytokines like IL-10 and enhance antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), along with activate pathways like Nrf2 (Nuclear factor erythroid 2-related factor 2) that provide cellular defense against oxidative stress. The DAI score showed improvement with all flavonoids assessed.

While the majority of flavonoids exhibited beneficial effects on increasing the *A. muciniphila* abundance, notable exceptions were detected. For instances, baicalin and dihydroquercetin were found to reduce *A. muciniphila* abundance while still improve gut permeability and reduce inflammation (Han, et al., 2021; Zhu et al., 2020). Similarly, compounds like diosmetin and taxifolin did not significant alter *A. muciniphila* levels but nonetheless positively impact gut permeability and inflammation markers.

4.1.5. Impact of phenolic acids on gut health

Table 6 illustrates the effects of various phenolic acids on different aspects of gut health. Several phenolic acids, including acteoside, caffeic acid, gallic acid, salvianolic acid A, 6-Gingerol, Paeonol, and rosmarinic acid, improve gut permeability by increasing markers like ZO-1, Occludin, and Claudin-1/2, which are integral proteins associated with tight junctions responsible to maintain the gut barrier integrity (Chen et al., 2023; Li et al., 2023; Liu et al., 2022; Tian et al., 2022; Wan, Zhong, et al., 2021; Wang et al., 2018; Zheng et al., 2022).

Notable, chlorogenic acid and p-hydroxybenzoic acid did not show a direct impact on gut permeability but contributed positively to other facets of gut health (Han et al., 2022; Xie et al., 2022; Zhang et al., 2017).

Several compounds, such as acteoside, caffeic acid, chlorogenic acid, p-Hydroxybenzoic acid, and gallic acid were found to enhance the mucus layer by the increasing the goblet cells proliferation and MUC2 levels (Han et al., 2022; Li et al., 2019; Liu et al., 2022; Wan, Zhong, et al., 2021; Zhang et al., 2017).

Interestingly, although 6-Gingerol decreased *A. muciniphila* levels, it still promoted goblet cells activity and MUC2 production, indicating its protective role for the mucus layer through alternative mechanisms (Tian et al., 2022).

Chlorogenic acid contributed to immune system homeostasis by reducing pro-inflammatory markers, such as M1 macrophages, and enhancing markers associated with tissue repair and anti-inflammatory markers, such as M2 macrophages (Zhang et al., 2017). Additionally, gallic acid was shown to increase Treg cells populations (Chen et al., 2023).

Compounds such as acteoside, caffeic acid, chlorogenic acid, ellagic acid, gallic acid, p-hydroxybenzoic acid, salvianolic acid a, tannin acid, 6-gingerol, paeonol, and rosmarinic acid effectively decreased inflammatory markers, including IL-1β, TNF-α, IL-6, and ROS while boosting antioxidant defenses, such as SOD, CAT and quinone oxidoreductase 1 (**Table 6**).

Table 5. Impact of flavonoid on gut barrier permeability, mucus balance, and immune response.

Flavonoid	*A. muciniphila* abundance	Gut permeability	Mucus layer (Markers)	Immune system homeostasis	Inflammatory and Oxidative stress markers	DAI score	Refs
Apigenin	↑	↗	↑	___	↘	↗	(Fu et al., 2022)
Astragalin	↑	↗	↑	___	↘	↗	(Peng et al., 2020)
Dihydromyricetin	↑	↗	___	___	↘	↗	(Dong et al., 2021)
Dihydroquercetin	↑	___	___	___	↘	↗	(Li et al., 2022)
Epigallocatechin-3-gallate	↑	___	↑	___	↘	↗	(Wu et al., 2021)
Genistein	↑	↗	___	___	↘	↗	(Fan et al., 2021)
Icariin	↑	___	___	___	↘	↗	(Zhang et al., 2021)
Icariin-1	↑	↗	↑	+	↘	↗	(Zhang et al., 2023)
Licochalcone A	↑	↗	___	___	↘	↗	(Zhang et al., 2021)
Luteolin	↑	___	___	___	↘	↗	(Li et al., 2021)
Myricetin myricetin-3-O-b-D-lactose sodium	↑	___	___	___	___	↗	(Miao et al., 2021)
Phloretin	↑	↗	↑	+	↘	↗	(Wu et al., 2019)
Proanthocyanidins	↑	↗	___	+	↘	↗	(Chen et al., 2023)
Puerarin	↑	↗	↑	___	↘	↗	(Wu et al., 2020)
Quercetin	↑	___	___	+	↘	↗	(Liso et al., 2018)
Tangeretin	↑	↗	↑	___	↘	↗	(Chen et al., 2021)
Total flavone of Abelmoschus manihot	↑	↗	↑	___	↘	↗	(Wang et al., 2021)
Vitexin	↑	↗	↑	___	↘	↗	(Zhang et al., 2022)

Legend: ↑-increased; ↓ - decreased; = - equal; ___ - no data; ↗ - improvement; ↘ - reduction.

Table 5. Impact of flavonoid on gut barrier permeability, mucus balance, and immune response (continued).

Flavonoid	*A. muciniphila* abundance	Gut permeability	Mucus layer (Markers)	Immune system homeostasis	Inflammatory and Oxidative stress markers	DAI score	Refs
Baicalin	↓	↗	↑	+	↘	↗	(Zhu et al., 2020)
Dihydroquercetin	↓	___	↑	___	↘	↗	(Han, et al., 2021)
Epigallocatechin-3-gallate	↓	___	___	___	↘	↗	(Liu et al., 2022)
Galangin	↓	___	___	___	↘	↗	(Xuan et al., 2020)
Quercetin	↓	↗	___	___	↘	↗	(Guo et al., 2021)
Total Flavonoids of Glycyrrhiza uralensis	↓	___	___	___	↘	↗	(Yue et al., 2021)
Diosmetin	=	↗	___	___	↘	↗	(Li et al., 2022)
Linarin	=	___	↑	___	↘	↗	(Jin et al., 2022)
Rutin	=	↗	↑	___	↘	↗	(Power et al., 2016)
Taxifolin	=	↗	___	___	↘	↗	(Hou et al., 2021)

Legend: ↑-increased; ↓ - decreased; = - equal; ___ - no data; ↗ - improvement; ↘ - reduction.

4.1.6. Impact of other polyphenols on gut health

Table 7 outlines the effects of other additional PPs on markers of gut health. Curcumin and tannic acid are particularly effective in improving gut permeability, as evidenced by increased expression of proteins such as claudin-1/3, occludin, and ZO-1 (Chen et al., 2023; Guo et al., 2022; Ye et al., 2023). Resveratrol also enhances gut permeability, as indicated by elevated claudin-1 and occludin expression, despite having no significant effect on *A. muciniphila* abundance (Xu et al., 2023).

Resveratrol contributes to an improvement in mucus balance by increasing the number of goblet cells, a finding also observed with the supplementation of curcumin (Alrafas et al., 2019; Guo et al., 2022). Additionally, resveratrol reduces the number of pro-inflammatory immune cells such as T helper cells (CD4+) and cytotoxic T cells (CD8+) while promoting an increase in anti-inflammatory markers such as CD4+FOXP3+ T cells and CD4+IL-10+ T cells (Alrafas et al., 2019). Tannic acid similarly increases Treg cells populations, also by reducing pro-inflammatory markers, such as M1 macrophages, and enhancing anti-inflammatory markers, such as M2 macrophages (Chen et al., 2023; He et al., 2023).

Resveratrol has been shown to reduce levels of IL-2, IFN-γ, and other pro-inflammatory markers like serum amyloid A, MPO, and TNF-α, while elevating anti-inflammatory markers like IL-10 (Alrafas et al., 2019; Li et al., 2020; Xu et al., 2023).

Curcumin exhibits anti-inflammatory effect by reducing cytokines, like IL-1β, IL-6, TNF-α, and inhibiting pathways, namely NF-kB (Guo et al., 2022; Wen et al., 2023; Ye et al., 2023). Tannic acid and tannin acid enhances antioxidant responses by increasing markers like Nrf2 and heme-oxygenase 1 (HO-1), while reducing pro-inflammatory markers like IL-6 (Chen et al., 2023; He et al., 2023).

Most PPs, including curcumin, resveratrol, and tannic acid, demonstrates improvements in the DAI score. However, in one study, curcumin did not yield a significant improvement in the DAI score, which may be attributable to variables such as dosage or formulation.

Table 6. Impact of phenolic acids on gut barrier function, mucus balance and immune response.

Phenolic acid	*A. muciniphila* abundance	Gut permeability	Mucus balance	Immune system homeostasis	Inflammatory and Oxidative stress markers	DAI score	Refs
Acteoside	↑	↗	↑	___	↘	↗	(Liu et al., 2022)
Caffeic Acid	↑	↗	↑	___	↘	↗	(Zhong, et al., 2021)
Chlorogenic acid	↑	___	___	___	↘	↗	(Xie et al., 2022)
Chlorogenic acid	↑	___	↑	↗	↘	↗	(Zhang et al., 2017)
Ellagic acid	↑	___	___	___	↘	↗	(Chen et al., 2023)
Gallic acid	↑	↗	___	↗	↘	↗	(Chen et al., 2023)
P-Hydroxybenzoic acid	↑	___	↑	___	↘	↗	(Han et al., 2022)
Salvianolic Acid A	↑	↗	___	___	↘	↗	(Wang et al., 2018)
6-gingerol	↓	↗	↑	___	↘	↗	(Tian et al., 2022)
Paeonol	↓	↗	___	___	↘	↗	(Zheng et al., 2022)
Rosmarinic acid	↓	↗	___	___	↘	↗	(Li et al., 2023)
Gallic acid	**nd**	___	↑	___	↘	↗	(Li et al., 2019)

Legend: ↑-increased; ↓ - decreased; = - equal; ___ - no data; ↗ - improvement; ↘ - reduction**.**

Table 7. Impact of other polyphenols on gut barrier function, mucus balance and immune response.

Other PPs	PP class	*A. muciniphila* abundance	Gut permeability	Mucus balance	Immune system homeostasis	Inflammatory and Oxidative stress markers	DAI score	Refs
Curcumin	Curcuminoid	↑	↑	↑	___	↘	↗	(Guo et al., 2022)
Curcumin	Curcuminoid	↑	↑	___	___	↘	↗	(Ye et al., 2023)
Curcumin	Curcuminoid	↑	___	___	___	___	↗	(Zhou et al., 2023)
Resveratrol	Stilbenes	↑	___	↑	↗	↘	↗	(Alrafas et al., 2019)
Tannic acid	Tannins	↑	↑	___	↗	↘	↗	(Chen et al., 2023)
Tannin acid	Tannins	↑	___	___	↗	↘	↗	(He et al., 2023)
Curcumin	Curcuminoid	↓	___	___	↗	↘	↗	(Wen et al., 2023)
Curcumin	Curcuminoid	↓	___	___	___	___	↘	(Zhang et al., 2022)
Resveratrol	Stilbenes	↓	___	___	___	↘	↗	(Li et al., 2020)
Resveratrol	Stilbenes	**nd**	↑	___	___	↘	↗	(Xu et al., 2023)

Legend: PPs, polyphenols; ↑-increased; ↓ - decreased; = - equal; ___ - no data; ↗ - improvement; ↘ - reduction.

CHAPTER V – DISCUSSION AND CONCLUDING REMARKS

One of the most pressing challenges in IBD therapy has been the modulation of the intestinal microbiota. This issue has emerged due to the growing recognition that in some diseases, like IBD, certain bacteria are drastically depleted while others proliferate excessively, causing a dysbiotic gut environment. Studies have consistently shown a marked decrease in the relative abundance of *A. muciniphila* in both UC and CD patients compared to healthy controls, which appears to correlate with poor clinical outcomes (Abdulkhakov et al., 2021; Png et al., 2010; Presti et al., 2019; Zhang et al., 2020).

The potential role of *A. muciniphila* in the IBD treatment has attracted significant attention of the scientific community not only due to the anti-inflammatory properties within the intestinal microenvironment, but also due to its ability to modulate immune responses, together with its well-recognized ability to strength the mucus layer of IECs. In particular, administration of *A. muciniphila* has been shown to enhance intestinal stem cell proliferation, promote the differentiation of Paneth and goblet cells, reduce colonic macrophages and CD8+ cytotoxic T lymphocytes and suppress pro-inflammatory cytokines (Kim et al., 2021; Masotti et al., 2019; Wang et al., 2020). Additionally *A. muciniphila* plays a key role in maintaining a balanced gut microbiome that promotes SCFA production, which contribute significantly to microbial balance and play a crucial role in regulating immune responses which are known to mitigate colitis (Akhtar et al., 2022).

Polyphenols (PPs) – bioactive compounds found in fruits, vegetables and other plant-based foods – are known for their ability to protect against chronic diseases, like IBD, by modulating numerous physiological processes (mentioned in 1.3.2.) (Yahfoufi et al., 2018; Luca et al., 2020). It is now well established that PPs and the gut microbiota engage in a bilateral relationship. While PPs influence the composition and activity of the gut microbiota, including of *Akkermansia muciniphila*, the gut microbiota metabolizes PPs into bioactive compounds that praise their health-promoting benefits (Bao et al., 2020). This expanding research highlights the potential of PPs-based therapies as a complementary treatment for IBD, especially due to their modulatory effects on microbial communities, including *A. muciniphila*. PPs have been described as having a putative duplibiotic effect on gut microbiota regarding their ability to concomitantly exert prebiotic properties and antimicrobial effects (Rodríguez-Daza et al., 2021). However, this effect remains to be described in IBD, namely concerning the impact of distinct classes of PPs on A. *muciniphila,* which was the main goal of the current thesis, using the scoping review approach.

Of the 47 studies included in this thesis – focusing primarily on flavonoids and phenolic acids, two majors PPs classes included in the articles analyzed – most reported a significant increase in *A. muciniphila*. The aforementioned reinforces the promising potential of fully exploring *A. muciniphila´*s health benefits and possible therapeutic applications. Interestingly, this bacterium was found to be increased in studies where the following PPs were used: apigenin, astragalin, epigallocatechin-3-gallate, genistein, icariin, quercetin, phloretin, proanthocyanidins, as well as some others. Conversely, PPs like quercetin, baicalin, dihydroquercetin, epigallocatechin-3-gallate, galangin reported a decrease in *A. muciniphila* abundance. The antagonistic effect observed for quercetin and epigallocatechin-3-gallate in *A. muciniphila* abundance (increase and decrease, respectively) in different studies, could be seen as a paradox, at least at first glance. However, the lack of standardization of these studies might explained the opposite effects; in fact, there are several variables that may have contributed to the difference in the outcome, namely the duration of the study, specific health conditions of the animal model, the bacterial profile analyzed, diet and other environmental factors, the polyphenols formulation (pure, in extract or in food) and corresponding bioavailabilities, the dose used, as well as the study design (namely population enrolled, control groups used, and other conditions under which the study was conducted). This diversity of conditions is a common challenge in studies intended to compare the effect of PPs in disease conditions.

PPs are not fully absorbed in the small intestine, with a substantial amount reaching the colon, where they are metabolized by intestinal bacteria into bioactive compounds with different bioactivities, thus increasing their bioavailability. This metabolic interaction further underscores the intricate relationship between PPs and gut microbiota. Regarding microbial diversity, previous studies suggest that most of the flavonoids generally increase α- and β-diversity, increasing the microbial diversity and richness of species existing in the intestinal microbiota, with only a few flavonoids not following this trend. This finding suggests that this class of PPs can alter the microbial composition, promoting gut health by fostering beneficial bacterial populations and suppressing harmful ones. For instance, flavonoids such as icariin and TFA demonstrated beneficial effects in reducing pathogens, like *Helicobacteraceae* family (table 2). *Helicobacter pylori* is one of the most studied and well-known bacteria of this family and is recognized as a pathogen linked to serious gastrointestinal diseases such as chronic gastritis (Mitchell et al., 2014). Leveraging PPs to reduce the population of this bacterial family could significantly help mitigate the risk of infections and related complications.

Other examples of PP's beneficial effect includes the reduction of the *Peptostreptococcaceae* family, microorganisms mainly found in polymicrobial and scarcely in bacterial infections such as prosthetic and native endocarditis (Legaria et al., 2021). Epigallocatechin-3-gallate, a flavonoid found in green-tea and rosmarinic acid, a phenolic acid constituent of many culinary herbs, are a couple of examples of PPs capable of achieving this reduction.

As previously stated, PPs not only are able to suppress pathogens but also to directly promote the expansion of beneficial bacteria, such as *Bifidobacterium* genera and *Lactobacillus* family, both of which are recognized for their health benefits in treatment and prevention of many pathological conditions, promoting gut and immune health (Mitchell et al., 2014). In addition, they could support beneficial bacteria indirectly though modulating the intestinal environment, namely by affecting *Akkermansia spp.* (Jamieson et al., 2023). It has been reported in almost all studies that PPs increase the *Lactobacillus* family; among them, epigallocatechin-3-gallate appears as having the double role of simultaneously reduce pathogens and increase *Bifidobacterium* and *Lactobacillus*, which makes it a very interesting flavonoid for future studies. Tannin acid and gallic acid (phenolic acids) have both been reported to increase these two families, as well as rutin and proanthocyanidins (flavonoids) (tables 2 and 3). Interestingly, this profile found in some PPs of the flavonoids class, compatible with a duplibiotic effect, was accompanied by increased abundance of A. muciniphila and/or an increase in bacterial diversity.

Research has demonstrated the different ways in which PPs modulate the microbiota. Another mechanism important to highlight is the enhancement of SCFA production. By favoring the growth of beneficial/probiotic bacteria, the production of SCFA, such as butyrate, propionate and acetate, its indirectly favored because some of these beneficial bacteria are simultaneously SCFA producers, such as *Bifidobacterium* (Ghamry Abdelhamid et al., 2019).

The evidence that many beneficial bacteria use enzymes – PAZymes - that metabolize polyphenols, comes from some studies on the interaction between the microbiota and the polyphenols found in food (Arumugam et al., 2011; Ley et al., 2008). When in the presence of PPs, these PAZymes producing bacteria can provide phenolic metabolites used by other beneficial bacterial species in complex trophic crossfeeding chains (Rodríguez-Daza et al., 2021). In this sense, emerging reports suggest that certain PPs can be utilized and transformed by beneficial gut microbes, belonging for example to *Bifidobacteriaceae* and *Lactobacillae* families or Bacteroides, Eubacterium and Ruminococcus genus, into bioactive phenolic metabolites that are later freely absorbed and transported to target organs, with the capacity to impact both the commensal microbiota and the host health (Luo et al., 2022; Rodríguez-Daza et al., 2021).

This knowledge is corroborated with some examples presented in tables 2, 3 and 4. It was observed that Linarin achieved a simultaneously increase in proportion of both *Lactobacillaceae* and *Bacteroidaceae* (Jin et al., 2022). Supplementation with Dihydroquercetin, Epigallocatechin-3-gallate, Licochalcone A, and Luteolin also increase the *Bacteroidaceae* family (Li et al., 2021; Wan, Han, et al., 2021; Wu et al., 2021; Zhang et al., 2021). *Lactobacillaceae* and *Bacteroidaceae* presented a joint increase in their proliferation, with the supplementation of Phloretin, Total Flavonoids of Glycyrrhiza uralensis and Paeonol (Wu et al., 2019; Yue et al., 2021; Zheng et al., 2022). The abundance of *Bifidobacteriaceae and Bacteroidaceae* also increased upon Resveratrol supplementation (Xu et al., 2023). Supplementation with the aforementioned PPs may have stimulated the growth of bacteria from the *Bifidobacteriaceae*, *Lactobacillaceae* and *Bacteroidaceae* families because they can metabolize polyphenolic compounds by expressing PAZymes that facilitate this biotransformation.

Mucus balance was also a parameter analyzed in the selected articles. PP supplementation also positively influenced mucus production, increasing the size and number of goblet cells, and enhancing mucin thickness—crucial for protecting the epithelial lining from pathogens and inflammation. Even in cases where *A. muciniphila* abundance decreased, improvements in mucus secretion were observed, demonstrating a robust benefit from PPs supplementation independent of *Akkermansia* modulation.

Ideally the gut barrier should be intact to prevent the passage of bacteria and antigens into circulation through tightly sealed intercellular epithelial junctions (tight junctions). However, in conditions of IBD, these junctions can become compromised and defective, causing increased intestinal permeability, allowing the passage of molecules and microorganisms into the bloodstream, thus leading to persistent tissue damage an inflammation in individuals with this disorder. This inflammation caused by intestinal permeability becomes chronic and contributes to ongoing damage of the intestinal barrier. IBD is also characterized by deficient protective mucus production, leaving the epithelium more exposed to the attack of pathogens and inflammatory substances (Hussein et al., 2023).

Most studies that reported an increase in *Akkermansia* also reported an improvement in intestinal permeability (decreased permeability), making the epithelium more selective and restricted to the passage of molecules and microorganisms. However, it is not possible to establish a direct causal relationship, since even in studies where the *Akkermansia* population was reduced, the permeability of the barrier decreased. There were no studies reporting an increase in intestinal permeability, thus suggesting that PPs protect the barrier from passage of deleterious bacterial components and other pro-inflammatory compounds that will cause endotoxemia. Furthermore, most studies demonstrated that PPs improved gut barrier integrity by increasing the expression of proteins like Claudin-3, Occludin, and ZO-1, which are essential for the function of tight junctions that control the passage of molecules between adjacent cells. This enhancement of the gut barrier contributes to better overall gut health, especially in conditions like IBD where permeability is often compromised.

All reviewed studies, except one, reported a reduction in inflammatory markers and attenuation of oxidative stress, along with downregulation of the proinflammatory cytokines (e.g. TNF-α, IL-6 and IFN-γ) and upregulation of anti-inflammatory cytokines (e.g. IL-10). These anti-inflammatory effects of PPs resulted in significant improvements in clinical symptoms and disease outcomes in animal models of IBD.

In summary, the increase in tight junctions, contributes to the reduction of intestinal permeability, which is one of the major problems in IBD. The balance between pathogens and beneficial bacteria and the increase in mucin, also contributes to intestinal homeostasis and to an eubiotic gut microbiota. The reduction in excessive activation of the immune system through the decrease of inflammatory markers and increase in anti-inflammatory markers, also plays a crucial role in decreasing intestinal inflammation (characteristic of IBD), improving intestinal and general health, positively impacting quality of life.

Disease activity index (DAI) score, used to assess the severity of the disease, is based on weight loss, stool consistency, fecal bleeding and general health status. All studies included in this scoping review that mentioned this parameter reported a decrease in it. Together with the reduction of this “disease marker” there was a significant improvement in other parameters of animals’ welfare and disease amelioration, namely weight gain and colon length, which reinforces the favorable effects of PP’s supplementation. While the evidence supports the beneficial effects of PPs on gut microbiota modulation in IBD, these effects do not appear to be solely dependent on the modulation of *A. muciniphila*. Future research should explore these effects in more detail, especially regarding the independent benefits of PPs on gut health beyond *A. muciniphila* modulation. Only then will it be possible to take advantage of and fully harness the therapeutic potential of PPs and *A. muciniphila.*

Certain polyphenols exhibit prebiotic properties, fostering the growth of *A. muciniphila*, which in turn enhances the integrity of the intestinal lining, reduces inflammation, and promotes overall gut health. This dynamic interaction between PPs and *A. muciniphila* can be characterized as a "duplibiotic effect." However, a deeper analysis of the available studies shows that this effect may not be directly attributable to *A. muciniphila*. Instead, these effects seem to be mediated indirectly through the activity of other PAZymes-producing bacteria. Evidence supporting this conclusion shows that even when *A. muciniphila* abundance decreases, improvements in intestinal health markers are still observed, suggesting that other bacterial communities also play a crucial role in driving these health benefits. This highlights the complex interplay of microbial populations within the gut and the multifaceted mechanisms underlying polyphenol-induced health effects.

In conclusion, these findings suggest that PPs may positively influence *A. muciniphila* abundance and foster a balanced microbial environment by promoting a favorable ratio of anaerobic to aerobic bacteria, thus contributing significantly to gut health. Combined with their well-documented anti-inflammatory effects, PPs could serve as an effective dietary intervention for preventing gut dysbiosis and associated health issues. The therapeutic potential of polyphenols in promoting gut health through microbial modulation remains a promising area for further exploration, particularly in clinical contexts of gut inflammatory diseases

CHAPTER VI – REFERENCES

Abdulkhakov, and R., Lo Sasso, G., Khachatryan, L., Kondylis, A., Battey, J. N., Sierro, N., Danilova, N. A., Grigoryeva, T. V, Markelova, M. I., Khusnutdinova, D. R., Laikov, A. V, Salafutdinov, I. I., Romanova, Y. D., Siniagina, M. N., Yu Vasiliev, I., Boulygina, E. A., Solovyeva, V. V, Garanina, E. E., Kitaeva, K. V, … Abdulkhakov, S. R. (2021). Inflammatory Bowel Disease-Associated Changes in the Gut: Focus on Kazan Patients. *Inflamm Bowel Dis •*, *27*(3). https://doi.org/10.1093/ibd/izaa188

Abouelela, M. E., & Helmy, Y. A. (2024). Next-Generation Probiotics as Novel Therapeutics for Improving Human Health: Current Trends and Future Perspectives. *Microorganisms*, *12*(3). https://doi.org/10.3390/microorganisms12030430

Akhtar, M., Chen, Y., Ma, Z., Zhang, X., Shi, D., Khan, J. A., & Liu, H. (2022). Gut microbiota-derived short chain fatty acids are potential mediators in gut inflammation. *Animal Nutrition*, *8*, 350–360. https://doi.org/10.1016/J.ANINU.2021.11.005

Alard, J., Lehrter, V., Rhimi, M., Mangin, I., Peucelle, V., Abraham, A. L., Mariadassou, M., Maguin, E., Waligora-Dupriet, A. J., Pot, B., Wolowczuk, I., & Grangette, C. (2016). Beneficial metabolic effects of selected probiotics on diet-induced obesity and insulin resistance in mice are associated with improvement of dysbiotic gut microbiota. *Environmental Microbiology*, *18*(5), 1484–1497. https://doi.org/10.1111/1462-2920.13181

Almeida, D., Machado, D., Andrade, J. C., Mendo, S., Gomes, A. M., & Freitas, A. C. (2020). Evolving trends in next-generation probiotics: a 5W1H perspective. *Critical Reviews in Food Science and Nutrition*, *60*(11), 1783–1796. https://doi.org/10.1080/10408398.2019.1599812

Alrafas, H. R., Busbee, P. B., Nagarkatti, M., & Nagarkatti, P. S. (2019). Resveratrol modulates the gut microbiota to prevent murine colitis development through induction of Tregs and suppression of Th17 cells. *Journal of Leukocyte Biology*, *106*(2), 467–480. https://doi.org/10.1002/JLB.3A1218-476RR

Ansaldo, E., Slayden, L. C., Ching, K. L., Koch, M. A., Wolf, N. K., Plichta, D. R., Brown, E. M., Graham, D. B., Xavier, R. J., Moon, J. J., & Barton, G. M. (2019). *R ES E A RC H*. *01*(June), 1–7. https://doi.org/10.1126/science.aaw7479

Arumugam, M., Raes, J., Pelletier, E., Paslier, D. Le, Yamada, T., Mende, D. R., Fernandes,

G. R., Tap, J., Bruls, T., Batto, J. M., Bertalan, M., Borruel, N., Casellas, F., Fernandez, L., Gautier, L., Hansen, T., Hattori, M., Hayashi, T., Kleerebezem, M., … Zeller, G. (2011). Enterotypes of the human gut microbiome. *Nature*, *473*(7346), 174–180. https://doi.org/10.1038/NATURE09944

Asquith, M., Stauffer, P., Davin, S., Mitchell, C., Lin, P., & Rosenbaum, J. T. (2016). *Perturbed Mucosal Immunity and Dysbiosis Accompany Clinical Disease in a Rat Model of Spondyloarthritis, Arthritis Rheumatol; 68(9): 2151-62*. https://doi.org/10.1002/art.39681

Axling, U., Olsson, C., Xu, J., Fernandez, C., Larsson, S., Ström, K., Ahrné, S., Holm, C., Molin, G., & Berger, K. (2012). Green tea powder and Lactobacillus plantarum affect gut microbiota, lipid metabolism and inflammation in high-fat fed C57BL/6J mice. *Nutrition and Metabolism*, *9*(1), 1–18. https://doi.org/10.1186/1743-7075-9-105

Azad, M. A. K., Sarker, M., Li, T., & Yin, J. (2018). Probiotic Species in the Modulation of Gut Microbiota: An Overview. *BioMed Research International*, *2018*. https://doi.org/10.1155/2018/9478630

Bäckhed, F., Manchester, J. K., Semenkovich, C. F., & Gordon, J. I. (2007). Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(3), 979–984. https://doi.org/10.1073/PNAS.0605374104

Bao, N., Chen, F., & Dai, D. (2020). The Regulation of Host Intestinal Microbiota by Polyphenols in the Development and Prevention of Chronic Kidney Disease. *Frontiers in Immunology*, *10*(January), 1–13. https://doi.org/10.3389/fimmu.2019.02981

Belkaid, Y., & Harrison, O. J. (2017). Homeostatic immunity and the microbiota. I*mmunity*., 46(4), 562-576. https://doi.org/10.1016/j.immuni.2017.04.008

Bian, X., Wu, W., Yang, L., Lv, L., Wang, Q., Li, Y., Ye, J., Fang, D., Wu, J., Jiang, X., Shi, D., & Li, L. (2019). Administration of Akkermansia muciniphila Ameliorates Dextran Sulfate Sodium-Induced Ulcerative Colitis in Mice. *Frontiers in Microbiology*, *10*(October), 1–18. https://doi.org/10.3389/fmicb.2019.02259

Binetti, A. G., Gómez, E. M., Pulgar, D., Fiocco, D., Ouwehand, A. C., Binda, S., Hill, C., Johansen, E., Obis, D., Pot, B., Sanders, M. E., & Tremblay, A. (2020). *Criteria to Qualify Microorganisms as ``Probiotic'' in Foods and Dietary Supplements*. https://doi.org/10.3389/fmicb.2020.01662

Borowitz, S. M. (2023). The epidemiology of inflammatory bowel disease: Clues to pathogenesis? *Frontiers in Pediatrics*, *10*(January), 5–9. https://doi.org/10.3389/fped.2022.1103713

Bosscher, D., Lu, Z., Janssens, G., Van Caillie-Bertrand, M., Robberecht, H., De Rycke, H., De Wilde, R., & Deelstra, H. (2001). *In vitro availability of zinc from infant foods with increasing phytic acid contents*. https://doi.org/10.1079/BJN2001384

Bruner, L. P., White, A. M., & Proksell, S. (2023). Inflammatory Bowel Disease. *Primary Care - Clinics in Office Practice*, *50*(3), 411–427. https://doi.org/10.1016/j.pop.2023.03.009

Bu, F., Ding, Y., Chen, T., Wang, Q., Wang, R., Zhou, J. yong, Jiang, F., Zhang, D., Xu, M., Shi, G., & Chen, Y. (2021). Total flavone of Abelmoschus Manihot improves colitis by promoting the growth of Akkermansia in mice. *Scientific Reports 2021 11:1*, *11*(1), 1–12. https://doi.org/10.1038/s41598-021-00070-7

Bunker, J. J., & Bendelac, A. (2018). *IgA responses to microbiota*. Immunity, 50 Cell Press https://doi.org/10.1016/j.immuni.2018.08.011

Burisch, J., Jess, T., Martinato, M., & Lakatos, P. L. (2013). The burden of inflammatory bowel disease in Europe. *Journal of Crohn’s and Colitis*, *7*(4), 322–337. https://doi.org/10.1016/j.crohns.2013.01.010

Burisch, J., & Munkholm, P. (2015). The epidemiology of inflammatory bowel disease. *Scandinavian Journal of Gastroenterology*, *50*(8), 942–951. https://doi.org/10.3109/00365521.2015.1014407

Cani, P. D., & Knauf, C. (2021). A newly identified protein from Akkermansia muciniphila stimulates GLP-1 secretion. *Cell Metabolism*, *33*(6), 1073–1075. https://doi.org/10.1016/j.cmet.2021.05.004

Caruso, R., Lo, B. C., & Núñez, G. (2020). Host–microbiota interactions in inflammatory bowel disease. *Nature Reviews Immunology*, *20*(7), 411–426. https://doi.org/10.1038/s41577-019-0268-7

Castro-Dopico, T., Dennison, T. W., Ferdinand, J. R., Mathews, R. J., Fleming, A., Clift, D., Stewart, B. J., Jing, C., Strongili, K., Labzin, L. I., Monk, E. J. M., Saeb-Parsy, K., Bryant, C. E., Clare, S., Parkes, M., & Clatworthy, M. R. (2019). Anti-commensal IgG Drives Intestinal Inflammation and Type 17 Immunity in Ulcerative Colitis. *Immunity*, *50*(4), 1099-1114.e10. https://doi.org/10.1016/j.immuni.2019.02.006

Chang, C. J., Lin, T. L., Tsai, Y. L., Wu, T. R., Lai, W. F., Lu, C. C., & Lai, H. C. (2019). Next generation probiotics in disease amelioration. *Journal of Food and Drug Analysis*, *27*(3), 615–622. https://doi.org/10.1016/j.jfda.2018.12.011

Chelakkot, C., Choi, Y., Kim, D.-K., Park, H. T., Ghim, J., Kwon, Y., Jeon, J., Kim, M.-S., Jee, Y.-K., Gho, Y. S., Park, H.-S., Kim, Y.-K., & Ryu, S. H. (2018). Akkermansia muciniphila-derived extracellular vesicles influence gut permeability through the regulation of tight junctions. *Nature Publishing Group*, *50*, 450. https://doi.org/10.1038/emm.2017.282

Chen, B., Luo, J., Han, Y., Du, H., Liu, J., He, W., Zhu, J., Xiao, J., Wang, J., Cao, Y., Xiao, H., & Song, M. (2021). Dietary Tangeretin Alleviated Dextran Sulfate Sodium-Induced Colitis in Mice via Inhibiting Inflammatory Response, Restoring Intestinal Barrier Function, and Modulating Gut Microbiota. *Journal of Agricultural and Food Chemistry*, *69*(27), 7663–7674. https://doi.org/10.1021/ACS.JAFC.1C03046

Chen, H., Li, Y., Wang, J., Zheng, T., Wu, C., Cui, M., Feng, Y., Ye, H., Dong, Z., & Dang, Y. (2023). Plant Polyphenols Attenuate DSS-induced Ulcerative Colitis in Mice via Antioxidation, Anti-inflammation and Microbiota Regulation. *International Journal of Molecular Sciences*, *24*(13). https://doi.org/10.3390/IJMS241310828

Chen, P. C., Lin, M. S., Lin, T. C., Kang, T. W., & Ruan, J. W. (2023). The Alteration of Akkermansiaceae/Lachnospiraceae Ratio Is a Microbial Feature of Antibiotic-Induced Microbiota Remodeling. *Bioinformatics and Biology Insights*, *17*. https://doi.org/10.1177/11779322231166229

Chen, Y., Zhang, L., Hong, G., Huang, C., Qian, W., Bai, T., Song, J., Song, Y., & Hou, X. (2020). Probiotic mixtures with aerobic constituent promoted the recovery of multi-barriers in DSS-induced chronic colitis. *Life Sciences*, *240*. https://doi.org/10.1016/J.LFS.2019.117089

Chia, L. W., Hornung, B. V. H., Aalvink, S., Schaap, P. J., de Vos, W. M., Knol, J., & Belzer, C. (2018). Deciphering the trophic interaction between Akkermansia muciniphila and the butyrogenic gut commensal Anaerostipes caccae using a metatranscriptomic approach. *Antonie van Leeuwenhoek, International Journal of General and Molecular Microbiology*, *111*(6), 859–873. https://doi.org/10.1007/s10482-018-1040-x

Collado, M. C., Derrien, M., Isolauri, E., De Vos, W. M., & Salminen, S. (2007). Intestinal Integrity and Akkermansia muciniphila, a Mucin-Degrading Member of the Intestinal Microbiota Present in Infants, Adults, and the Elderly. *APPLIED AND ENVIRONMENTAL*

MICROBIOLOGY, *73*(23), 7767–7770. https://doi.org/10.1128/AEM.01477-07

Collado, M. C., Isolauri, E., Laitinen, K., & Salminen, S. (2008). Distinct composition of gut microbiota during pregnancy in overweight and normal-weight women. *American Journal of Clinical Nutrition*, *88*(4), 894–899. https://doi.org/10.1093/ajcn/88.4.894

Corrêa, T. A. F., Rogero, M. M., Hassimotto, N. M. A., & Lajolo, F. M. (2019). The Two-Way Polyphenols-Microbiota Interactions and Their Effects on Obesity and Related Metabolic Diseases. Frontiers In Nutrition, 6. https://doi.org/10.3389/fnut.2019.00188

Costello, E. K., Stagaman, K., Dethlefsen, L., Bohannan, B. J. M., & Relman, D. A. (2012). The Application of Ecological Theory Toward an Understanding of the Human Microbiome. *Science*, *336*(6086), 1255–1262. https://doi.org/10.1126/SCIENCE.1224203

Cunningham, M., Azcarate-Peril, M. A., Barnard, A., Benoit, V., Grimaldi, R., Guyonnet, D., Holscher, H. D., Hunter, K., Manurung, S., Obis, D., Petrova, M. I., Steinert, R. E., Swanson, K. S., Van Sinderen, D., Vulevic, J., & Gibson, G. R. (2021). Shaping the Future of Probiotics and Prebiotics. *Trends in Microbiology*, *29*, 667–685. https://doi.org/10.1016/j.tim.2021.01.003

Dabeek, W. M., & Marra, M. V. (2019). Dietary quercetin and kaempferol: bioavailability in humans. *Nutrients*, *11*, 3–19. https://doi.org/10.3390/nu11102288

Davey, L., Malkus, P., Villa, M., Dolat, L., Holmes, Z., Letourneau, J., Ansaldo, E., David, L., Barton, G., & Valdivia, R. (2022). Mucin foraging enables Akkermansia muciniphila to compete againstother microbes in the gut and to modulate host sterolbiosynthesis. *Research Square, 2022. DOI: 10.21203/rs.3.rs-1475049/v1.*.

Derrien, M., Collado, M. C., Ben-Amor, K., Salminen, S., & De Vos, W. M. (2008). The mucin degrader Akkermansia muciniphila is an abundant resident of the human intestinal tract. *Applied and Environmental Microbiology*, *74*(5), 1646–1648. https://doi.org/10.1128/AEM.01226-07

Derrien, M., van Passel, M. W. J., van de Bovenkamp, J. H. B., Schipper, R. G., de Vos, W. M., & Dekker, J. (2010). Mucin-bacterial interactions in the human oral cavity and digestive tract. *Gut Microbes*, *1*(4), 254–268. https://doi.org/10.4161/gmic.1.4.12778

Derrien, M., Vaughan, E. E., Plugge, C. M., & De Vos, W. M. (2004). *Akkermansia muciniphila gen. nov., sp. nov., a human intestinal mucin-degrading bacterium*. *Int J Syst Evol Microbiol.*, 54(Pt 5),1469-1476. doi: 10.1099/ijs.0.02873-0

Diaferia, C., Machado, D., Fonseca, M., Vedor, R., Sousa, S., Barbosa, J. C., & Gomes, A. M. (2023). *Akkermansia muciniphila Encapsulated in Calcium-Alginate Hydrogelated Matrix: Viability and Stability over Aerobic Storage and Simulated Gastrointestinal Conditions, GEls, 9(11):869*. https://doi.org/10.3390/gels9110869

Dong, S., Zhu, M., Wang, K., Zhao, X., Hu, L., Jing, W., Lu, H., & Wang, S. (2021). Dihydromyricetin improves DSS-induced colitis in mice via modulation of fecal-bacteria-related bile acid metabolism. *Pharmacological Research*, *171*. https://doi.org/10.1016/J.PHRS.2021.105767

Drell, T., Larionova, A., Voor, T., Simm, J., Julge, K., Heilman, K., Tillmann, V., Štšepetova, J., & Sepp, E. (2015). Differences in Gut Microbiota Between Atopic and Healthy Children. *Current Microbiology*, *71*(2), 177–183. https://doi.org/10.1007/s00284-015-0815-9

Druart, C., Plovier, | Hubert, Van Hul, M., Brient, | Alizée, Kirt, |, Phipps, R., De Vos, W. M., & Cani, P. D. (2021). Toxicological safety evaluation of pasteurized Akkermansia muciniphila. *J Appl Toxicol*, *41*, 276–290. https://doi.org/10.1002/jat.4044

Earley, H., Lennon, G., Balfe, Á., Coffey, J. C., Winter, D. C., & Ronan O'connell, P. (2019). *the abundance of Akkermansia muciniphila and its relationship with sulphated colonic mucins in health and ulcerative colitis*. *Sci Rep.*, 9(1), 15683. https://doi.org/10.1038/s41598-019-51878-3

Ermund, A., Schütte, A., Johansson, M. E. V., Gustafsson, J. K., & Hansson, G. C. (2013). Studies of mucus in mouse stomach, small intestine, and colon. I. Gastrointestinal mucus layers have different properties depending on location as well as over the Peyer's patches. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *305*(5), 341–347. https://doi.org/10.1152/ajpgi.00046.2013

Espín, J. C., González-Sarrías, A., & Tomás-Barberán, F. A. (2017). The gut microbiota: A key factor in the therapeutic effects of (poly)phenols. *Biochemical Pharmacology*, *139*, 82–93. https://doi.org/10.1016/j.bcp.2017.04.033

Everard, A., Belzer, C., Geurts, L., Ouwerkerk, J. P., Druart, C., Bindels, L. B., Guiot, Y., Derrien, M., Muccioli, G. G., Delzenne, N. M., De Vos, W. M., & Cani, P. D. (2013). Cross-talk between Akkermansia muciniphila and intestinal epithelium controls diet-induced obesity. *Proceedings of the National Academy of Sciences of the United States of America*, *110*(22), 9066–9071. https://doi.org/10.1073/pnas.1219451110

Fan, W., Zhang, S., Wu, Y., Lu, T., Liu, J., Cao, X., Liu, S., Yan, L., Shi, X., Liu, G., Huang, C., &

Song, S. (2021). Genistein-Derived ROS-Responsive Nanoparticles Relieve Colitis by Regulating Mucosal Homeostasis. *ACS Applied Materials and Interfaces*, *13*(34), 40249–40266. https://doi.org/10.1021/ACSAMI.1C09215

Fang, J., Zhang, H., Zhang, X., Lu, X., Liu, J., Li, H., & Huang, J. (2024). Akkermansia muciniphila improves gastric cancer treatment by modulating the immune microenvironment. *Future Microbiology*, *19*(6), 481–494. https://doi.org/10.2217/FMB-2023-0210

Farrell, R. J. (2000). Inflammatory Bowel Disease: Clinical Diagnosis and Management,. *Journal of Clinical Gastroenterology*, *31*(2), 185–186. https://doi.org/10.1097/00004836-200009000-00025

Ferreira, C., Vieira, P., Sá, H., Malva, J., Castelo-Branco, M., Reis, F., & Viana, S. (2024). Polyphenols: immunonutrients tipping the balance of immunometabolism in chronic diseases. *Frontiers in Immunology*, *15*(March), 1–26. https://doi.org/10.3389/fimmu.2024.1360065

Fraga, C. G., Croft, K. D., Kennedy, D. O., & Tomás-Barberán, F. A. (2019). The effects of polyphenols and other bioactives on human health. *Food & Function*, *10*(2), 514–528. https://doi.org/10.1039/c8fo01997e

Fraga, C. G., Croft, K. D., Kennedy, D. O., & Tomás-Barberán, F. A. (2019). The effects of polyphenols and other bioactives on human health. *Food & Function*, *10*(2), 514–528. https://doi.org/10.1039/C8FO01997E

Fu, R., Wang, L., Meng, Y., Xue, W., Liang, J., Peng, Z., Meng, J., & Zhang, M. (2022). Apigenin remodels the gut microbiota to ameliorate ulcerative colitis. *Frontiers in Nutrition*, *9*. https://doi.org/10.3389/FNUT.2022.1062961

Ganesh, B. P., Klopfleisch, R., Loh, G., & Blaut, M. (2013). Commensal Akkermansia muciniphila Exacerbates Gut Inflammation in Salmonella Typhimurium-Infected Gnotobiotic Mice. *PLoS ONE*, *8*(9), 74963. https://doi.org/10.1371/journal.pone.0074963

Ghamry Abdelhamid, A., El-Masry, S. S., & El-Dougdoug, N. K. (2019). Probiotic Lactobacillus and Bifidobacterium strains possess safety characteristics, antiviral activities and host adherence factors revealed by genome mining. *EPMA Journal*, *10*, 337–350. https://doi.org/10.1007/s13167-019-00184-z

Ghotaslou, R., Nabizadeh, E., Memar, M. Y., Law, W. M. H., Ozma, M. A., Abdi, M., Yekani, M., Kadkhoda, H., hosseinpour, R., Bafadam, S., Ghotaslou, A., Leylabadlo, H. E., & Nezhadi, J. (2023). The metabolic, protective, and immune functions of Akkermansia muciniphila. *Microbiological Research*, *266*(June 2022), 127245. https://doi.org/10.1016/j.micres.2022.127245

Glassner, K. L., Abraham, B. P., Quigley, E. M. M., & Houston, M. (2020). The microbiome and inflammatory bowel disease. *Journal of Allergy and Clinical Immunology*, *145*, 16–27. https://doi.org/10.1016/j.jaci.2019.11.003

Gonzalez, A., Krieg, R., Massey, H. D., Carl, D., Ghosh, S., Gehr, T. W. B., & Ghosh, S. S. (2019). Sodium butyrate ameliorates insulin resistance and renal failure in CKD rats by modulating intestinal permeability and mucin expression. *Nephrol Dial Transplant*, *34*, 783–794. https://doi.org/10.1093/ndt/gfy238

Guo, F., Tsao, R., Li, C., Wang, X., Zhang, H., Jiang, L., Sun, Y., & Xiong, H. (2021). Green Pea (Pisum sativum L.) Hull Polyphenol Extracts Ameliorate DSS-Induced Colitis through Keap1/Nrf2 Pathway and Gut Microbiota Modulation. *Foods (Basel, Switzerland)*, *10*(11). https://doi.org/10.3390/FOODS10112765

Guo, X., Xu, Y., Geng, R., Qiu, J., & He, X. (2022). Curcumin Alleviates Dextran Sulfate Sodium-Induced Colitis in Mice Through Regulating Gut Microbiota. *Molecular Nutrition & Food Research*, *66*(8), 2100943. https://doi.org/10.1002/MNFR.202100943

Hajj Hussein, I., Dosh, L., Al Qassab, M., Jurjus, R., El Masri, J., Abi Nader, C., Rappa, F., Leone, A., & Jurjus, A. (2023). Highlights on two decades with microbiota and inflammatory bowel disease from etiology to therapy. *Transplant Immunology*, *78*(April), 101835. https://doi.org/10.1016/j.trim.2023.101835

Han, X., Li, M., Sun, L., Liu, X., Yin, Y., Hao, J., & Zhang, W. (2022). p-Hydroxybenzoic Acid Ameliorates Colitis by Improving the Mucosal Barrier in a Gut Microbiota-Dependent Manner. *Nutrients*, *14*(24). https://doi.org/10.3390/NU14245383

He, H., Qin, Q., Xu, F., Chen, Y., Rao, S., Wang, C., Jiang, X., Lu, X., & Xie, C. (2023). Oral polyphenol-armored nanomedicine for targeted modulation of gut microbiota-brain interactions in colitis. *Science Advances*, *9*(21). https://doi.org/10.1126/SCIADV.ADF3887

He, X., Bai, Y., Zhou, H., & Wu, K. (2022). Akkermansia muciniphila Alters Gut Microbiota and Immune System to Improve Cardiovascular Diseases in Murine Model. *Frontiers* *in Microbiology*, *13*, 906920. https://doi.org/10.3389/FMICB.2022.906920/BIBTEX

Hoskins, L. C., Agustines, M., Mckee, W. B., Boulding, E. T., Krians, M., & Niedermeyer, G. (1985). Mucin Degradation in Human Colon Ecosystems Isolation and Properties of Fecal Strains that Degrade ABH Blood Group Antigens and Oligosaccharides from Mucin Glycoproteins. *J. Clin. Invest*, *75*, 944–953. https://doi.org/10.1172/JCI111795

Hou, J., Hu, M., Zhang, L., Gao, Y., Ma, L., & Xu, Q. (2021). Dietary Taxifolin Protects Against Dextran Sulfate Sodium-Induced Colitis via NF-κB Signaling, Enhancing Intestinal Barrier and Modulating Gut Microbiota. *Frontiers in Immunology*, *11*, 631809. https://doi.org/10.3389/FIMMU.2020.631809/BIBTEX

Huang, W. C., Pan, C. H., Wei, C. C., & Huang, H. Y. (2020). Lactobacillus plantarum PS128 Improves Physiological Adaptation and Performance in Triathletes through Gut Microbiota Modulation. *Nutrients 2020, Vol. 12, Page 2315*, *12*(8), 2315. https://doi.org/10.3390/NU12082315

Imlay, J. A. (2013). The molecular mechanisms and physiological consequences of oxidative stress: lessons from a model bacterium. *Nature Reviews. Microbiology*, *11*(7), 443–454. https://doi.org/10.1038/NRMICRO3032

Jamieson, P. E., Carbonero, F., & Stevens, J. F. (2023). Dietary (poly)phenols mitigate inflammatory bowel disease: Therapeutic targets, mechanisms of action, and clinical observations. *Current Research in Food Science*, *6*(May), 100521. https://doi.org/10.1016/j.crfs.2023.100521

Jiang, Y., Chen, B., Duan, C., Sun, B., Yang, J., & Yang, S. (2015). Multigene editing in the Escherichia coli genome via the CRISPR-Cas9 system. *Applied and Environmental Microbiology*, *81*(7), 2506–2514. https://doi.org/10.1128/AEM.04023-14

Jiang, Y., Guo, C., Zhang, D., Zhang, J., Wang, X., & Geng, C. (2014). *The Altered Tight Junctions: An Important Gateway of Bacterial Translocation in Cachexia Patients with Advanced Gastric Cancer*. *Interferon Cytokine Res.*, 34(7), 518-25. https://doi.org/10.1089/jir.2013.0020

Jin, C., Liu, J., Jin, R., Yao, Y., He, S., Lei, M., & Peng, X. (2022). Linarin ameliorates dextran sulfate sodium-induced colitis in C57BL/6J mice via the improvement of intestinal barrier, suppression of inflammatory responses and modulation of gut microbiota. *Food & Function*, *13*(20), 10574–10586. https://doi.org/10.1039/D2FO02128E

Johansson, M. E. V, Phillipson, M., Petersson, J., Velcich, A., Holm, L., Hansson, G. C., &

Greenberg, E. P. (2008). *The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria*. https://doi.org/10.1073pnas.0803124105

Kaplan, G. G. (2015). The global burden of IBD: From 2015 to 2025. *Nature Reviews Gastroenterology and Hepatology*, *12*(12), 720–727. https://doi.org/10.1038/nrgastro.2015.150

Karczewski, J., Troost, F. J., Konings, I., Dekker, J., Kleerebezem, M., Brummer, R.-J. M., & Wells, J. M. (2010). Regulation of human epithelial tight junction proteins by Lactobacillus plantarum in vivo and protective effects on the epithelial barrier. *Am J Physiol Gastrointest Liver Physiol*, *298*, 851–859. https://doi.org/10.1152/ajpgi.00327.2009

Katiraei, S., de Vries, M. R., Costain, A. H., Thiem, K., Hoving, L. R., van Diepen, J. A., Smits, H. H., Bouter, K. E., Rensen, P. C. N., Quax, P. H. A., Nieuwdorp, M., Netea, M. G., de Vos, W. M., Cani, P. D., Belzer, C., van Dijk, K. W., Berbée, J. F. P., & van Harmelen, V. (2020). Akkermansia muciniphila Exerts Lipid-Lowering and Immunomodulatory Effects without Affecting Neointima Formation in Hyperlipidemic APOE*3-Leiden.CETP Mice. *Molecular Nutrition and Food Research*, *64*(15), 1–10. https://doi.org/10.1002/mnfr.201900732

Kim, C. H., Schroeder, B. O., Zhang, C., Zhai, R., Xue, X., Zhang, L., Yang, X., & Zhao, L. (2019). Strain-Specific Anti-inflammatory Properties of Two Akkermansia muciniphila Strains on Chronic Colitis in Mice. *Frontiers in Cellular and Infection Microbiology | Www.Frontiersin.Org*, *1*, 239. https://doi.org/10.3389/fcimb.2019.00239

Kim, S., Shin, Y. C., Kim, T. Y., Kim, Y., Lee, Y. S., Lee, S. H., Kim, M. N., O, E., Kim, K. S., & Kweon, M. N. (2021). Mucin degrader Akkermansia muciniphila accelerates intestinal stem cell-mediated epithelial development. *Gut Microbes*, *13*(1), 1–20. https://doi.org/10.1080/19490976.2021.1892441

Kotla, N. G., & Rochev, Y. (2023). IBD disease-modifying therapies: insights from emerging therapeutics. *Trends in Molecular Medicine*, *29*(3), 241–253. https://doi.org/10.1016/j.molmed.2023.01.001

Kristi L. Stringer, Bulent Turan, Lisa McCormick, Modupeoluwa Durojaiye, Laura Nyblade, Mirjam-Colette Kempf, Bronwen Lichtenstein, and J. M. T. (2017). Public Access. *Physiology & Behavior*, *176*(3), 139–148. https://doi.org/10.1002/hep.30150

Kuczma, M. P., Szurek, E. A., Cebula, A., Chassaing, B., Jung, Y.-J., Kang, S.-M., Fox, J. G., Stecher, B., & Ignatowicz, L. (2020). Commensal epitopes drive differentiation of colonic T regs. *Sci. Adv*, *6*, 3186–3203. https://doi.org/10.1126/sciadv.aaz3186

Kump, P., Wurm, P., Gr, H. P., Wenzl, H., Petritsch, W., Halwachs, B., Wagner, M., Stadlbauer, V., Eherer, A., Hoffmann, K. M., Deutschmann, A., Reicht, G., Reiter, L., Slawitsch, P., & Gorkiewicz, G. (2017). *The taxonomic composition of the donor intestinal microbiota is a major factor influencing the efficacy of faecal microbiota transplantation in therapy refractory ulcerative colitis*. https://doi.org/10.1111/apt.14387

Larsson, J. M. H., Karlsson, H., Crespo, J. G., Johansson, M. E. V., Eklund, L., Sjövall, H., & Hansson, G. C. (2011). Altered O-glycosylation profile of MUC2 mucin occurs in active ulcerative colitis and is associated with increased inflammation. *Inflammatory Bowel Diseases*, *17*(11), 2299–2307. https://doi.org/10.1002/ibd.21625

Lee, M., & Chang, E. B. (2021). *Inflammatory Bowel Diseases and the Microbiome: Searching the Crime Scene for Clues*. https://doi.org/10.1053/j.gastro.2020.09.056

Legaria, M. C., Nastro, M., Camporro, J., Heger, F., Barberis, C., Stecher, D., Rodriguez, C. H., & Vay, C. A. (2021). Peptostreptococcus anaerobius: Pathogenicity, identification, and antimicrobial susceptibility. Review of monobacterial infections and addition of a case of urinary tract infection directly identified from a urine sample by MALDI-TOF MS. *Anaerobe*, *72*, 102461. https://doi.org/10.1016/J.ANAEROBE.2021.102461

Leslie, W. D., Miller, N., Rogala, L., & Bernstein, C. N. (2008). Vitamin D status and bone density in recently diagnosed inflammatory bowel disease: The Manitoba IBD Cohort Study. *American Journal of Gastroenterology*, *103*(6), 1451–1459. https://doi.org/10.1111/j.1572-0241.2007.01753.x

Ley, R. E., Hamady, M., Lozupone, C., Turnbaugh, P. J., Ramey, R. R., Bircher, J. S., Schlegel, M. L., Tucker, T. A., Schrenzel, M. D., Knight, R., & Gordon, J. I. (2008). Evolution of mammals and their gut microbes. *Science (New York, N.Y.)*, *320*(5883), 1647–1651. https://doi.org/10.1126/SCIENCE.1155725

Li, B., Du, P., Du, Y., Zhao, D., Cai, Y., Yang, Q., & Guo, Z. (2021). Luteolin alleviates inflammation and modulates gut microbiota in ulcerative colitis rats. *Life Sciences*, *269*. https://doi.org/10.1016/J.LFS.2020.119008

Li, F., Han, Y., Cai, X., Gu, M., Sun, J., Qi, C., Goulette, T., Song, M., Li, Z., & Xiao, H. (2020). Dietary resveratrol attenuated colitis and modulated gut microbiota in dextran sulfate sodium-treated mice. *Food & Function*, *11*(1), 1063–1073. https://doi.org/10.1039/C9FO01519A

Li, H. long, Wei, Y. ying, Li, X. he, Zhang, S. shan, Zhang, R. tong, Li, J. he, Ma, B. wei, Shao, S. bo, Lv, Z. wei, Ruan, H., Zhou, H. gang, & Yang, C. (2022). Diosmetin has therapeutic efficacy in colitis regulating gut microbiota, inflammation, and oxidative stress via the circ-Sirt1/Sirt1 axis. *Acta Pharmacologica Sinica*, *43*(4), 919–932. https://doi.org/10.1038/S41401-021-00726-0

Li, J., Lin, S., Vanhoutte, P. M., Woo, C. W., & Xu, A. (2016). Akkermansia muciniphila protects against atherosclerosis by preventing metabolic endotoxemia-induced inflammation in Apoe-/- Mice. *Circulation*, *133*(24), 2434–2446. https://doi.org/10.1161/CIRCULATIONAHA.115.019645

Li, J., Lin, S., Vanhoutte, P. M., Woo, C. W., & Xu, A. (2016). Akkermansia muciniphila protects against atherosclerosis by preventing metabolic endotoxemia-induced inflammation in Apoe-/- Mice. *Circulation*, *133*(24), 2434–2446. https://doi.org/10.1161/CIRCULATIONAHA.115.019645

Li, K., Wu, J., Xu, S., Li, X., Zhang, Y., & Gao, X. (2023). Rosmarinic acid alleviates intestinal inflammatory damage and inhibits endoplasmic reticulum stress and smooth muscle contraction abnormalities in intestinal tissues by regulating gut microbiota. *Microbiology Spectrum*, *11*(5). https://doi.org/10.1128/SPECTRUM.01914-23

Li, W., Zhang, L., Xu, Q., Yang, W., Zhao, J., Ren, Y., Yu, Z., & Ma, L. (2022). Taxifolin Alleviates DSS-Induced Ulcerative Colitis by Acting on Gut Microbiome to Produce Butyric Acid. *Nutrients*, *14*(5), 1069. https://doi.org/10.3390/NU14051069

Li, Y., Xie, Z., Gao, T., Li, L., Chen, Y., Xiao, D., Liu, W., Zou, B., Lu, B., Tian, X., Han, B., Guo, Y., Zhang, S., Lin, L., Wang, M., Li, P., & Liao, Q. (2019). A holistic view of gallic acid-induced attenuation in colitis based on microbiome-metabolomics analysis. *Food & Function*, *10*(7), 4046–4061. https://doi.org/10.1039/C9FO00213H

Liso, M., De Santis, S., Scarano, A., Verna, G., Dicarlo, M., Galleggiante, V., Campiglia, P., Mastronardi, M., Lippolis, A., Vacca, M., Sobolewski, A., Serino, G., Butelli, E., De Angelis, M., Martin, C., Santino, A., & Chieppa, M. (2018). A Bronze-Tomato Enriched Diet Affects the Intestinal Microbiome under Homeostatic and Inflammatory Conditions. *Nutrients 2018, Vol. 10, Page 1862*, *10*(12), 1862. https://doi.org/10.3390/NU10121862

Liu, S., Cao, Y., Ma, L., Sun, J., Ramos-Mucci, L., Ma, Y., Yang, X., Zhu, Z., Zhang, J., & Xiao, B. (2022). Oral antimicrobial peptide-EGCG nanomedicines for synergistic treatment of ulcerative colitis. *Journal of Controlled Release : Official Journal of the Controlled Release Society*, *347*, 544–560. https://doi.org/10.1016/J.JCONREL.2022.05.025

Liu, S., Zhao, W., Lan, P., & Mou, X. (2020). *The microbiome in inflammatory bowel diseases: from pathogenesis to therapy. Protein Cell ;12(5):331-345*. https://doi.org/10.1007/s13238-020-00745-3

Liu, Y., Huang, W., Zhu, Y., Zhao, T., Xiao, F., Wang, Y., & Lu, B. (2022). Acteoside, the Main Bioactive Compound in Osmanthus fragrans Flowers, Palliates Experimental Colitis in Mice by Regulating the Gut Microbiota. *Journal of Agricultural and Food Chemistry*, *70*(4), 1148–1162,https://doi.org/10.1021/acs.jafc.1c07583

Lorenzo, C. Di, Colombo, F., Biella, S., Stockley, C., & Restani, P. (2021). *Polyphenols and Human Health: The Role of Bioavailability*. Nutrients. 19;13(1):273. https://doi.org/10.3390/nu13010273

Luca, S. V., Macovei, I., Bujor, A., Miron, A., Skalicka-Woźniak, K., Aprotosoaie, A. C., & Trifan, A. (2020). Bioactivity of dietary polyphenols: The role of metabolites. *Critical Reviews in Food Science and Nutrition*, *60*(4), 626–659. https://doi.org/10.1080/10408398.2018.1546669

Luo, C., Wei, X., Song, J., Xu, X., Huang, H., Fan, S., Zhang, D., Han, L., & Lin, J. (2022). Interactions between Gut Microbiota and Polyphenols: New Insights into the Treatment of Fatigue. *Molecules 2022, Vol. 27, Page 7377*, *27*(21), 7377. https://doi.org/10.3390/MOLECULES27217377

Ma, Y., Hu, C., Yan, W., Jiang, H., & Liu, G. (2020). Lactobacillus pentosus Increases the Abundance of Akkermansia and Affects the Serum Metabolome to Alleviate DSS-Induced Colitis in a Murine Model. *Frontiers in Cell and Developmental Biology*, *8*. https://doi.org/10.3389/FCELL.2020.591408

Machado, D., Almeida, D., Seabra, C. L., Andrade, J. C., Gomes, A. M., & Freitas, A. C. (2020). Uncovering Akkermansia muciniphila resilience or susceptibility to different temperatures, atmospheres and gastrointestinal conditions. *Anaerobe*, *61*. https://doi.org/10.1016/j.anaerobe.2019.102135

Magro, F., Portela, F., Lago, P., Chagas, C., Moreira, F., Pereira, F., Rodrigues, B., Pedrosa, H., & Correia, L. (2023). Burden of Disease and Cost of Illness of Inflammatory Bowel

Diseases in Portugal. *GE Portuguese Journal of Gastroenterology*, *30*(4), 283–292. https://doi.org/10.1159/000525206

Magrone, T., Magrone, M., Russo, M. A., & Jirillo, E. (2019). Recent Advances on the Anti-Inflammatory and Antioxidant Properties of Red Grape Polyphenols: In Vitro and In Vivo Studies. *Antioxidants 2020, Vol. 9, Page 35*, *9*(1), 35. https://doi.org/10.3390/ANTIOX9010035

Makarewicz, M., Drożdż, I., Tarko, T., & Duda-Chodak, A. (2021). The interactions between polyphenols and microorganisms, especially gut microbiota. *Antioxidants*, *10*(2), 1–70. https://doi.org/10.3390/antiox10020188

Mao, T., Su, C. W., Ji, Q., Chen, C. Y., Wang, R., Vijaya Kumar, D., Lan, J., Jiao, L., & Shi, H. N. (2021). Hyaluronan-induced alterations of the gut microbiome protects mice against Citrobacter rodentium infection and intestinal inflammation. *Gut Microbes*, *13*(1). https://doi.org/10.1080/19490976.2021.1972757

Maslowski, K. M., Vieira, A. T., Ng, A., Kranich, J., Sierro, F., Di Yu, Schilter, H. C., Rolph, M. S., MacKay, F., Artis, D., Xavier, R. J., Teixeira, M. M., & MacKay, C. R. (2009). Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature*, *461*(7268), 1282–1286. https://doi.org/10.1038/nature08530

Masotti, A., Gesù Children Hospital, B., Vaziri, F., Del Chierico, F., Bambino Gesu, O., Julio Galvez, I., Li, L., Bian, X., Wu, W., Yang, L., Lv, L., Wang, Q., Li, Y., Ye, J., Fang, D., Wu, J., Jiang, X., & Shi, D. (2019). *Administration of Akkermansia muciniphila Ameliorates Dextran Sulfate Sodium-Induced Ulcerative Colitis in Mice*. https://doi.org/10.3389/fmicb.2019.02259

Meng, X., Xv, C., Lv, J., Zhang, S., Ma, C., & Pang, X. (2024). *microorganisms Optimizing Akkermansia muciniphila Isolation and Cultivation: Insights into Gut Microbiota Composition and Potential Growth Promoters in a Chinese Cohort*. https://doi.org/10.3390/microorganisms12050881

Miao, R. R., Zhan, S., Hu, X. T., Yuan, W. M., Wu, L. J., Cui, S. X., & Qu, X. J. (2021). Myricetin and M10, a myricetin-3-O-β-d-lactose sodium salt, modify composition of gut microbiota in mice with ulcerative colitis. *Toxicology Letters*, *346*, 7–15. https://doi.org/10.1016/J.TOXLET.2021.03.009

Mileo, A. M., Nisticò, P., & Miccadei, S. (2019). Polyphenols: Immunomodulatory and therapeutic implication in colorectal cancer. *Frontiers in Immunology*, *10*(APR), 1–9. https://doi.org/10.3389/fimmu.2019.00729

Mitchell, H. M., Rocha, G. A., Kaakoush, N. O., O'Rourke, J. L., & Queiroz, D. M. M. (2014). The Family Helicobacteraceae. *The Prokaryotes: Deltaproteobacteria and Epsilonproteobacteria*, *9783642390449*, 337–392. https://doi.org/10.1007/978-3-642-39044-9_275

Moossavi, S., Miliku, K., Sepehri, S., Khafipour, E., & Azad, M. B. (2018). The prebiotic and probiotic properties of human milk: Implications for infant immune development and pediatric asthma. *Frontiers in Pediatrics*, *6*, 392513. https://doi.org/10.3389/FPED.2018.00197

Morelli, L., & Capurso, L. (2012). FAO/WHO Guidelines on Probiotics. *Journal of Clinical Gastroenterology*, *46*(October), S1–S2. https://doi.org/10.1097/mcg.0b013e318269fdd5

Ng, S. C., Shi, H. Y., Hamidi, N., Underwood, F. E., Tang, W., Benchimol, E. I., Panaccione, R., Ghosh, S., Wu, J. C. Y., Chan, F. K. L., Sung, J. J. Y., & Kaplan, G. G. (2017). Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *The Lancet*, *390*(10114), 2769–2778. https://doi.org/10.1016/S0140-6736(17)32448-0

Niedzwiecki, A., Roomi, M., Kalinovsky, T., & Rath, M. (2016). Anticancer Efficacy of Polyphenols and Their Combinations. *Nutrients*, *8*(9), 552. https://doi.org/10.3390/nu8090552

Noble, A., Durant, L., Hoyles, L., Mccartney, A. L., Man, R., Segal, J., Costello, S. P., Hendy, P., Reddi, D., Bouri, S., Lim, D. N. F., Pring, T., O'connor, M. J., Datt, P., Wilson, A., Arebi, N., Akbar, A., Hart, A. L., Carding, S. R., & Knight, S. C. (2019). Deficient Resident Memory T Cell and CD8 T Cell Response to Commensals in Inflammatory Bowel Disease. *Journal of Crohn's and Colitis*, *2020*, 525–537. https://doi.org/10.1093/ecco-jcc/jjz175

Ouwerkerk, J. P., Aalvink, S., Belzer, C., & De Vos, W. M. (2017). Preparation and preservation of viable Akkermansia muciniphila cells for therapeutic interventions. *Beneficial Microbes*, *8*(2), 163–170. https://doi.org/10.3920/BM2016.0096

Peña-Cearra, A., Palacios, A., Pellon, A., Castelo, J., Pasco, S. T., Seoane, I., Barriales, D., Martin, J. E., Pascual-Itoiz, M. Á., Gonzalez-Lopez, M., Martín-Ruiz, I., Macías-Cámara, N., Gutiez, N., Araujo-Aris, S., Aransay, A. M., Rodríguez, H., Anguita, J., & Abecia, L. (2024). Akkermansia muciniphila-induced trained immune phenotype increases bacterial intracellular survival and attenuates inflammation. *Communications Biology*, *7*(1). https://doi.org/10.1038/s42003-024-05867-6

Peng, L., Gao, X., Nie, L., Xie, J., Dai, T., Shi, C., Tao, L., Wang, Y., Tian, Y., & Sheng, J. (2020). Astragalin Attenuates Dextran Sulfate Sodium (DSS)-Induced Acute Experimental Colitis by Alleviating Gut Microbiota Dysbiosis and Inhibiting NF-κB Activation in Mice. *Frontiers in Immunology*, *11*, 566952. https://doi.org/10.3389/FIMMU.2020.02058

Plamada, D., & Vodnar, D. C. (2022). Polyphenols—gut microbiota interrelationship: A transition to a new generation of prebiotics. *Nutrients*, *14*(1), 1–27. https://doi.org/10.3390/nu14010137

Plovier, H., Everard, A., Druart, C., Depommier, C., Van Hul, M., Geurts, L., Chilloux, J., Ottman, N., Duparc, T., Lichtenstein, L., Myridakis, A., Delzenne, N. M., Klievink, J., Bhattacharjee, A., Van Der Ark, K. C. H., Aalvink, S., Martinez, L. O., Dumas, M. E., Maiter, D., … Cani, P. D. (2017). A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. *Nature Medicine*, *23*(1), 107–113. https://doi.org/10.1038/nm.4236

Png, C. W., Lindén, S. K., Gilshenan, K. S., Zoetendal, E. G., McSweeney, C. S., Sly, L. I., McGuckin, M. A., & Florin, T. H. J. (2010). Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. *American Journal of Gastroenterology*, *105*(11), 2420–2428. https://doi.org/10.1038/ajg.2010.281

Power, K. A., Lu, J. T., Monk, J. M., Lepp, D., Wu, W., Zhang, C., Liu, R., Tsao, R., Robinson, L. E., Wood, G. A., & Wolyn, D. J. (2016). Purified rutin and rutin-rich asparagus attenuates disease severity and tissue damage following dextran sodium sulfate-induced colitis. *Molecular Nutrition & Food Research*, *60*(11), 2396–2412. https://doi.org/10.1002/MNFR.201500890

Presti, A. Lo, Chierico, F. Del, Altomare, A., Zorzi, F., Cella, E., Putignani, L., Luca Guarino, M. P., Monteleone, G., Cicala, M., Angeletti, S., & Ciccozzi, M. (2019). Exploring the genetic diversity of the 16S rRNA gene of Akkermansia muciniphila in IBD and IBS. *Future Microbiology*, *14*(17), 1497–1509. https://doi.org/10.2217/fmb-2019-0175

Qian, K., Chen, S., Wang, J., Sheng, K., Wang, Y., & Zhang, M. (2022). A β-Nacetylhexosaminidase Amuc_2109 from Akkermansia muciniphila protects against dextran sulfate sodium-induced colitis in mice by enhancing intestinal barrier and modulating gut microbiota. *Food and Function*, *13*(4), 2216–2227. https://doi.org/10.1039/D1FO04094D

Qiu, P., Ishimoto, T., Fu, L., Zhang, J., Zhang, Z., & Liu, Y. (2022). The Gut Microbiota in Inflammatory Bowel Disease. *Frontiers in Cellular and Infection Microbiology*, *12*(February), 1–14. https://doi.org/10.3389/fcimb.2022.733992

Rajili C-Stojanovi, M., & De Vos, W. M. (2014). *The first 1000 cultured species of the human gastrointestinal microbiota*. *FEMS Microbiol Rev*., 38(5), 996-1047. https://doi.org/10.1111/1574-6976.12075

Rao, Y., Kuang, Z., Li, C., Guo, S., Xu, Y., Zhao, D., Hu, Y., Song, B., Jiang, Z., Ge, Z., Liu, X., Li, C., Chen, S., Ye, J., Huang, Z., & Lu, Y. (2021). Gut Akkermansia muciniphila ameliorates metabolic dysfunction-associated fatty liver disease by regulating the metabolism of L-aspartate via gut-liver axis. *Gut Microbes*, *13*(1), 1–19. https://doi.org/10.1080/19490976.2021.1927633

Rasouli, H., Farzaei, M. H., & Khodarahmi, R. (2017). Polyphenols and their benefits: A review. *International Journal of Food Properties*, *20*(2), 1–42. https://doi.org/10.1080/10942912.2017.1354017

Ray, S. K., & Mukherjee, S. (2021). Evolving Interplay Between Dietary Polyphenols and Gut Microbiota—An Emerging Importance in Healthcare. *Frontiers in Nutrition*, *8*(May), 1–18. https://doi.org/10.3389/fnut.2021.634944

Reunanen, J., Kainulainen, V., Huuskonen, L., Ottman, N., Belzer, C., Huhtinen, H., de Vos, W. M., & Satokaria, R. (2015). Akkermansia muciniphila adheres to enterocytes and strengthens the integrity of the epithelial cell layer. *Applied and Environmental Microbiology*, *81*(11), 3655–3662. https://doi.org/10.1128/AEM.04050-14

Reverón, I., de las Rivas, B., Matesanz, R., Muñoz, R., & López de Felipe, F. (2015). Molecular adaptation of Lactobacillus plantarum WCFS1 to gallic acid revealed by genome-scale transcriptomic signature and physiological analysis. *Microbial Cell Factories*, *14*(1). https://doi.org/10.1186/S12934-015-0345-Y

Ring, C., Klopfleisch, R., Dahlke, K., Basic, M., Bleich, A., & Blaut, M. (2019). Akkermansia muciniphila strain ATCC BAA-835 does not promote short-term intestinal inflammation in gnotobiotic interleukin-10-deficient mice. *Gut Microbes*, *10*.

https://doi.org/10.1080/19490976.2018.1511663

Rodríguez-Daza, M. C., Pulido-Mateos, E. C., Lupien-Meilleur, J., Guyonnet, D., Desjardins, Y., & Roy, D. (2021). Polyphenol-Mediated Gut Microbiota Modulation: Toward Prebiotics and Further. *Frontiers in Nutrition*, *8*, 689456. https://doi.org/10.3389/FNUT.2021.689456

Rodríguez-Daza, M. C., Pulido-Mateos, E. C., Lupien-Meilleur, J., Guyonnet, D., Desjardins, Y., & Roy, D. (2021). Polyphenol-Mediated Gut Microbiota Modulation: Toward Prebiotics and Further. *Frontiers in Nutrition*, *8*, 689456. https://doi.org/10.3389/FNUT.2021.689456

Rogler, G. (2017). Resolution of inflammation in inflammatory bowel disease. *The Lancet Gastroenterology and Hepatology*, *2*(7), 521–530. https://doi.org/10.1016/S2468-1253(17)30031-6

Roopchand, D. E., Carmody, R. N., Kuhn, P., Moskal, K., Rojas-Silva, P., Turnbaugh, P. J., & Raskin, I. (2015). Dietary Polyphenols Promote Growth of the Gut Bacterium Akkermansia muciniphila and Attenuate High-Fat Diet-Induced Metabolic Syndrome. *Diabetes*, *64*(8), 2847–2858. https://doi.org/10.2337/DB14-1916

Ropot, A. V., Karamzin, A. M., & Sergeyev, O. V. (2020). Cultivation of the Next-Generation Probiotic Akkermansia muciniphila, Methods of Its Safe Delivery to the Intestine, and Factors Contributing to Its Growth In Vivo. *Current Microbiology*, *77*(8), 1363–1372. https://doi.org/10.1007/S00284-020-01992-7

Saez, A., Herrero-Fernandez, B., Gomez-Bris, R., Sánchez-Martinez, H., & Gonzalez-Granado, J. M. (2023). Pathophysiology of Inflammatory Bowel Disease: Innate Immune System. *International Journal of Molecular Sciences*, *24*(2). https://doi.org/10.3390/ijms24021526

Salminen, S., Carmen Collado, M., Endo, A., Hill, C., Lebeer, S., M Quigley, E. M., Ellen Sanders, M., Shamir, R., Swann, J. R., Szajewska, H., & Vinderola, G. (2021). *The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics*. *Nat Rev Gastroenterol Hepatol.,* 18(9), 649-667. https://doi.org/10.1038/s41575-021-00440-6

Sankarapandian, V., Alagar, B., Maran, V., Rajendran, R. L., Jogalekar, M. P., Gurunagarajan, S., Krishnamoorthy, R., Gangadaran, P., & Ahn, B.-C. (2022). *An Update on the Effectiveness of Probiotics in the Prevention and Treatment of Cancer*. Life (Basel), 2;12(1):59. https://doi.org/10.3390/life12010059

Santana, P. T., Rosas, S. L. B., Ribeiro, B. E., Marinho, Y., & de Souza, H. S. P. (2022). Dysbiosis in Inflammatory Bowel Disease: Pathogenic Role and Potential Therapeutic Targets. *International Journal of Molecular Sciences*, *23*(7). https://doi.org/10.3390/ijms23073464

Seregin, S. S., Golovchenko, N., Schaf, B., Chen, J., Pudlo, N. A., Mitchell, J., Baxter, N. T., Zhao, L., Schloss, P. D., Martens, E. C., Eaton, K. A., & Chen, G. Y. (2017). NLRP6 protects IL10 −/− mice from colitis by limiting colonization of Akkermansia muciniphila HHS Public Access. *Cell*, *19*(4), 733–745. https://doi.org/10.1016/j.celrep.2017.03.080

Seyedian, S. S., Nokhostin, F., & Dargahi Malamir, M. (2019). A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. *Journal of Medicine and Life*, *12*, 113–122. https://doi.org/10.25122/jml-2018-0075

Shapouri-Moghaddam, A., Mohammadian, S., Vazini, H., Taghadosi, M., Esmaeili, S. A., Mardani, F., Seifi, B., Mohammadi, A., Afshari, J. T., & Sahebkar, A. (2018). Macrophage plasticity, polarization, and function in health and disease. In *Journal of Cellular Physiology* (Vol. 233, Issue 9). https://doi.org/10.1002/jcp.26429

Shin, N. R., Lee, J. C., Lee, H. Y., Kim, M. S., Whon, T. W., Lee, M. S., & Bae, J. W. (2014). An increase in the Akkermansia spp. population induced by metformin treatment improves glucose homeostasis in diet-induced obese mice. *Gut*, *63*(5), 727–735. https://doi.org/10.1136/gutjnl-2012-303839

Shin, N. R., Whon, T. W., & Bae, J. W. (2015). Proteobacteria: microbial signature of dysbiosis in gut microbiota. *Trends in Biotechnology*, *33*(9), 496–503. https://doi.org/10.1016/J.TIBTECH.2015.06.011

Singh, S. B., Carroll-Portillo, A., & Lin, H. C. (2023). Desulfovibrio in the Gut: The Enemy within? *Microorganisms*, *11*(7). https://doi.org/10.3390/MICROORGANISMS11071772

Söderholm, J. D., & Perdue, M. H. (2001). Stress and the gastrointestinal tract II. Stress and intestinal barrier function. *American Journal of Physiology - Gastrointestinal and Liver Physiology*, *280*(1 43-1). https://doi.org/10.1152/AJPGI.2001.280.1.G7

Steinert, R. E., Sadaghian Sadabad, M., Harmsen, H. J. M., & Weber, P. (2016). The prebiotic concept and human health: A changing landscape with riboflavin as a novel prebiotic candidate. *European Journal of Clinical Nutrition*, *70*(12), 1348–1353.

https://doi.org/10.1038/ejcn.2016.119

Teffera, M., Veith, A. C., Ronnekleiv-Kelly, S., Bradfield, C. A., Nikodemova, M., Tussing-Humphreys, L., & Malecki, K. (2024). Diverse mechanisms by which chemical pollutant exposure alters gut microbiota metabolism and inflammation. *Environment International*, *190*, 108805. https://doi.org/10.1016/J.ENVINT.2024.108805

Thomas, L. V, Ockhuizen, T., & Suzuki, K. (2014). *Exploring the influence of the gut microbiota and probiotics on health: a symposium report*. *Br J Nutr.,* 112 Suppl 1(Suppl 1), S1-18. https://doi.org/10.1017/S0007114514001275

Tian, W., Wang, H., Zhu, Y., Wang, Q., Song, M., Cao, Y., & Xiao, J. (2022). Intervention effects of delivery vehicles on the therapeutic efficacy of 6-gingerol on colitis. *Journal of Controlled Release*, *349*, 51–66. https://doi.org/10.1016/J.JCONREL.2022.06.058

Tsai, Y. L., Lin, T. L., Chang, C. J., Wu, T. R., Lai, W. F., Lu, C. C., & Lai, H. C. (2019). Probiotics, prebiotics and amelioration of diseases. *Journal of Biomedical Science*, *26*(1), 1–8. https://doi.org/10.1186/s12929-018-0493-6

Turck, D., Bohn, T., Castenmiller, J., De Henauw, S., Ildico Hirsch-Ernst, K., Maciuk, A., Mangelsdorf, I., McArdle, H. J., Naska, A., Pelaez, C., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Cubadda, F., Frenzel, T., Heinonen, M., Marchelli, R., … Katrine Knutsen, H. (2021). Safety of pasteurised Akkermansia muciniphila as a novel food pursuant to Regulation (EU) 2015/2283. *Journal*, *19*(7), 6780. https://doi.org/10.2903/j.efsa.2021.6780

Vacca, M., Celano, G., Calabrese, F. M., Portincasa, P., Gobbetti, M., & De Angelis, M. (2020). The Controversial Role of Human Gut Lachnospiraceae. *Microorganisms*, *8*(4). https://doi.org/10.3390/MICROORGANISMS8040573

Vinderola, G., Druart, C., Gosálbez, L., Salminen, S., Vinot, N., & Lebeer, S. (2023). Postbiotics in the medical field under the perspective of the ISAPP definition: scientific, regulatory, and marketing considerations. *Frontiers in Pharmacology*, *14*. https://doi.org/10.3389/FPHAR.2023.1239745

Wan, F., Han, H., Zhong, R., Wang, M., Tang, S., Zhang, S., Hou, F., Yi, B., & Zhang, H. (2021). Dihydroquercetin supplement alleviates colonic inflammation potentially through improved gut microbiota community in mice. *Food & Function*, *12*(22), 11420–11434. https://doi.org/10.1039/D1FO01422F

Wan, F., Zhong, R., Wang, M., Zhou, Y., Chen, Y., Yi, B., Hou, F., Liu, L., Zhao, Y., Chen, L., &

Zhang, H. (2021). Caffeic Acid Supplement Alleviates Colonic Inflammation and Oxidative Stress Potentially Through Improved Gut Microbiota Community in Mice. *Frontiers in Microbiology*, *12*. https://doi.org/10.3389/FMICB.2021.784211

Wang, K., Yang, Q., Ma, Q., Wang, B., Wan, Z., Chen, M., & Wu, L. (2018). Protective Effects of Salvianolic Acid A against Dextran Sodium Sulfate-Induced Acute Colitis in Rats. *Nutrients*, *10*(6). https://doi.org/10.3390/NU10060791

Wang, L., Tang, L., Feng, Y., Zhao, S., Han, M., Zhang, C., Yuan, G., Zhu, J., Cao, S., Wu, Q., Li, L., & Zhang, Z. (2020). Gut microbiota A purified membrane protein from Akkermansia muciniphila or the pasteurised bacterium blunts colitis associated tumourigenesis by modulation of CD8 + T cells in mice. *Gut*, *69*, 1988–1997. https://doi.org/10.1136/gutjnl-2019-320105

Wang, R., Chen, T., Wang, Q., Yuan, X. M., Duan, Z. L., Feng, Z. Y., Ding, Y., Bu, F., Shi, G. P., & Chen, Y. G. (2021). Total Flavone of Abelmoschus manihot Ameliorates Stress-Induced Microbial Alterations Drive Intestinal Barrier Injury in DSS Colitis. *Drug Design, Development and Therapy*, *15*, 2999–3016. https://doi.org/10.2147/DDDT.S313150

Wen, Z., Kang, L., Fu, H., Zhu, S., Ye, X., Yang, X., Zhang, S., Hu, J., Li, X., Chen, L., Hu, Y., & Yang, X. (2023). Oral delivery of porous starch-loaded bilayer microgels for controlled drug delivery and treatment of ulcerative colitis. *Carbohydrate Polymers*, *314*. https://doi.org/10.1016/J.CARBPOL.2023.120887

Wu, M., Li, P., An, Y., Ren, J., Yan, D., Cui, J., Li, D., Li, M., Wang, M., & Zhong, G. (2019). Phloretin ameliorates dextran sulfate sodium-induced ulcerative colitis in mice by regulating the gut microbiota. *Pharmacological Research*, *150*. https://doi.org/10.1016/J.PHRS.2019.104489

Wu, W., Kaicen, W., Bian, X., Yang, L., Ding, S., Li, Y., Li, S., Zhuge, A., & Li, L. (2023). Akkermansia muciniphila alleviates high-fat-diet-related metabolic-associated fatty liver disease by modulating gut microbiota and bile acids. *Microbial Biotechnology*, *16*(10), 1924–1939. https://doi.org/10.1111/1751-7915.14293

Wu, Y., Li, Y., Ruan, Z., Li, J., Zhang, L., Lu, H., & Xu, Z. (2020). Puerarin Rebuilding the Mucus Layer and Regulating Mucin-Utilizing Bacteria to Relieve Ulcerative Colitis. *Journal of Agricultural and Food Chemistry*, *68*(41), 11402–11411. https://doi.org/10.1021/ACS.JAFC.0C04119

Wu, Z., Huang, S., Li, T., Li, N., Han, D., Zhang, B., Xu, Z. Z., Zhang, S., Pang, J., Wang, S., Zhang, G., Zhao, J., & Wang, J. (2021). Gut microbiota from green tea polyphenol-dosed mice improves intestinal epithelial homeostasis and ameliorates experimental colitis. *Microbiome*, *9*(1), 1–22. https://doi.org/10.1186/S40168-021-01115-9

Wu, Z., Xu, Q., Gu, S., Chen, Y., Lv, L., Zheng, B., Wang, Q., Wang, K., Wang, S., Xia, J., Yang, L., Bian, X., Jiang, X., Zheng, L., & Li, L. (2022). Akkermansia muciniphila Ameliorates Clostridioides difficile Infection in Mice by Modulating the Intestinal Microbiome and Metabolites. *Frontiers in Microbiology*, *13*(May), 1–15. https://doi.org/10.3389/fmicb.2022.841920

Xie, M., Zhang, X., Wang, X., Chen, G., Liu, J., Zeng, X., & Yang, W. (2022). Effects of arabinoxylan and chlorogenic acid on the intestinal microbiota in dextran sulfate sodium–treated mice. *Frontiers in Nutrition*, *9*, 950446. https://doi.org/10.3389/FNUT.2022.950446

Xu, M., Pokrovskii, M., Ding, Y., Yi, R., Au, C., Harrison, O. J., Galan, C., Belkaid, Y., Bonneau, R., & Littman, D. R. (2018). C-MAF-dependent regulatory T cells mediate immunological tolerance to a gut pathobiont. *Nature*, *554*(7692), 373–377. https://doi.org/10.1038/nature25500

Xu, X., Ocansey, D. K. W., Pei, B., Zhang, Y., Wang, N., Wang, Z., & Mao, F. (2023). Resveratrol alleviates DSS-induced IBD in mice by regulating the intestinal microbiota-macrophage-arginine metabolism axis. *European Journal of Medical Research*, *28*(1), 1–18. https://doi.org/10.1186/S40001-023-01257-6/FIGURES/9

Xu, Y. ;, Duan, J. ;, Wang, D. ;, Liu, J. ;, Chen, X. ;, Qin, X.-Y. ;, & Yu, W. (2023). Akkermansia muciniphila alleviates persistent inflammation, immunosuppression, and catabolism syndrome in mice. *Metabolites., 13(2), 194.* https://doi.org/10.3390/metabo13020194

Xuan, H., Ou, A., Hao, S., Shi, J., & Jin, X. (2020). Galangin Protects against Symptoms of Dextran Sodium Sulfate-induced Acute Colitis by Activating Autophagy and Modulating the Gut Microbiota. *Nutrients*, *12*(2). https://doi.org/10.3390/NU12020347

Yahfoufi, N., Alsadi, N., Jambi, M., & Matar, C. (2018). The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. *Nutrients*, *10*(11), 1618. https://doi.org/10.3390/nu10111618

Yang, Y., Zhong, Z., Wang, B., Xia, X., Yao, W., Huang, L., Wang, Y., & Ding, W. (2019). *Early-*

life high-fat diet-induced obesity programs hippocampal development and cognitive functions via regulation of gut commensal Akkermansia muciniphila. Neuropsychopharmacology, (12):2054-2064. https://doi.org/10.1038/s41386-019-0437-1

Ye, N., Zhao, P., Ayue, S., Qi, S., Ye, Y., He, H., Dai, L., Luo, R., Chang, D., & Gao, F. (2023). Folic acid-modified lactoferrin nanoparticles coated with a laminarin layer loaded curcumin with dual-targeting for ulcerative colitis treatment. *International Journal of Biological Macromolecules*, *232*. https://doi.org/10.1016/J.IJBIOMAC.2023.123229

Yue, S. J., Qin, Y. F., Kang, A., Tao, H. J., Zhou, G. S., Chen, Y. Y., Jiang, J. Q., Tang, Y. P., & Duan, J. A. (2021). Total Flavonoids of Glycyrrhiza uralensis Alleviates Irinotecan-Induced Colitis via Modification of Gut Microbiota and Fecal Metabolism. *Frontiers in Immunology*, *12*, 628358. https://doi.org/10.3389/FIMMU.2021.628358

Zeng, M. Y., Cisalpino, D., Varadarajan, S., Hellman, J., Warren, H. S., Cascalho, M., Inohara, N., & Núñez, G. (2016). Gut Microbiota-Induced Immunoglobulin G Controls Systemic Infection by Symbiotic Bacteria and Pathogens. *Immunity*, *44*(3), 647–658. https://doi.org/10.1016/j.immuni

Zhang, C., Cao, Z., Lei, H., Chen, C., Du, R., Song, Y., Zhang, C., Zhou, J., Lu, Y., Huang, L., Shen, P., & Zhang, L. (2023). Discovery of a novel small molecule with efficacy in protecting against inflammation in vitro and in vivo by enhancing macrophages activation. *Biomedicine & Pharmacotherapy*, *165*, 115273. https://doi.org/10.1016/J.BIOPHA.2023.115273

Zhang, F., Zhou, Y., Chen, H., Jiang, H., Zhou, F., Lv, B., & Xu, M. (2022). Curcumin Alleviates DSS-Induced Anxiety-Like Behaviors via the Microbial-Brain-Gut Axis. *Oxidative Medicine and Cellular Longevity*, *2022*(1), 6244757. https://doi.org/10.1155/2022/6244757

Zhang, H., Zhuo, S., Song, D., Wang, L., Gu, J., Ma, J., Gu, Y., Ji, M., Chen, M., & Guo, Y. (2021). Icariin Inhibits Intestinal Inflammation of DSS-Induced Colitis Mice Through Modulating Intestinal Flora Abundance and Modulating p-p65/p65 Molecule. *The Turkish Journal of Gastroenterology : The Official Journal of Turkish Society of Gastroenterology*, *32*(4), 382–392. https://doi.org/10.5152/TJG.2021.20282

Zhang, J., Li, N., Cao, L., Sun, Y., Qing, D. G., Xu, X. Q., Wang, J. C., & Si, J. Y. (2021). The Regulatory Effects of Licochalcone A on the Intestinal Epithelium and Gut Microbiota in Murine Colitis. *Molecules 2021, Vol. 26, Page 4149*, *26*(14), 4149. https://doi.org/10.3390/MOLECULES26144149

Zhang, J., Liang, F., Chen, Z., Chen, Y., Yuan, J., Xiong, Q., Hou, S., Huang, S., Liu, C., & Liang, J. (2022). Vitexin Protects against Dextran Sodium Sulfate-Induced Colitis in Mice and Its Potential Mechanisms. *Journal of Agricultural and Food Chemistry*, *70*(38), 12041–12054. https://doi.org/10.1021/ACS.JAFC.2C05177

Zhang, T., Ji, X., Lu, G., & Zhang, F. (2021). The potential of Akkermansia muciniphila in inflammatory bowel disease. *Applied Microbiology and Biotechnology*, *105*(14–15), 5785–5794. https://doi.org/10.1007/S00253-021-11453-1

Zhang, T., Li, P., Wu, X., Lu, G., Marcella, C., Ji, X., Ji, G., & Zhang, F. (2020). Alterations of Akkermansia muciniphila in the inflammatory bowel disease patients with washed microbiota transplantation. *Applied Microbiology and Biotechnology*, *104*(23), 10203–10215. https://doi.org/10.1007/s00253-020-10948-7

Zhang, Y.-Z., & Li, Y.-Y. (2014). Inflammatory bowel disease: Pathogenesis. *World J Gastroenterol*, *20*(1), 91–99. https://doi.org/10.3748/wjg.v20.i1.91

Zhang, Z., Wu, X., Cao, S., Cromie, M., Shen, Y., Feng, Y., Yang, H., & Li, L. (2017). Chlorogenic Acid Ameliorates Experimental Colitis by Promoting Growth of Akkermansia in Mice. *Nutrients*, *9*(7). https://doi.org/10.3390/NU9070677

Zheng, J., Li, H., Zhang, P., Yue, S., Zhai, B., Zou, J., Cheng, J., Zhao, C., Guo, D., & Wang, J. (2022). Paeonol Ameliorates Ulcerative Colitis in Mice by Modulating the Gut Microbiota and Metabolites. *Metabolites*, *12*(10). https://doi.org/10.3390/METABO12100956

Zheng, M., Han, R., Yuan, Y., Xing, Y., Zhang, W., Sun, Z., Liu, Y., Li, J., & Mao, T. (2023). The role of Akkermansia muciniphila in inflammatory bowel disease: Current knowledge and perspectives. *Frontiers in Immunology*, *13*(January), 1–19. https://doi.org/10.3389/fimmu.2022.1089600

Zhou, F., Mai, T., Wang, Z., Zeng, Z., Shi, J., Zhang, F., Kong, N., Jiang, H., Guo, L., Xu, M., & Lin, J. (2023). The improvement of intestinal dysbiosis and hepatic metabolic dysfunction in dextran sulfate sodium-induced colitis mice: effects of curcumin. *Journal of Gastroenterology and Hepatology*, *38*(8), 1333–1345. https://doi.org/10.1111/JGH.16205

Zhu, L., Xu, L. Z., Zhao, S., Shen, Z. F., Shen, H., & Zhan, L. Bin. (2020). Protective effect of baicalin on the regulation of Treg/Th17 balance, gut microbiota and short-chain fatty acids in rats with ulcerative colitis. *Applied Microbiology and Biotechnology*, *104*(12), 5449–5460. https://doi.org/10.1007/S00253-020-10527-W