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Beyond the Bacterial Microbiome: Exploring the Gut Virome and Mycobiome in Health and Disease

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Abstract

The gut microbiome encompasses not only bacteria but also viruses (the virome) and fungi (the mycobiome), which play crucial roles in gut homeostasis and host health. However, research has predominantly focused on the bacterial component, with the virome and mycobiome remaining comparatively underexplored due to their lower abundance and the challenges associated with their detection. Emerging evidence indicates that these components significantly contribute to mucosal barrier integrity, metabolic processes, and immune modulation and that disturbances in the gut virome or mycobiome (dysbiosis) are associated with various diseases, including inflammatory bowel disease, metabolic disorders, and autoimmune conditions. In this review, we examine the composition and functions of the gut virome and mycobiome in both healthy and diseased contexts, highlighting their interactions with each other and with bacterial communities. We discuss how bacteriophages shape bacterial populations and how fungi such as Candida influence metabolism and immunity. We also address recent advances in viral and fungal metagenomics that have begun to illuminate the extensive "dark matter" of the gut virome and the diversity of the mycobiome. Finally, this review identifies critical gaps in current knowledge and outlines future directions for integrating virome and mycobiome insights into microbiome research and therapeutic strategies.

Keywords: Gut Microbiome, Bacteria, Gut virome, Clinical Significance, Disease, dysbiosis, mycobiome, Bacteroides

Introduction

Over the past decade, our understanding of the human gastrointestinal (GI) microbiome has expanded significantly, with new insights into the trillions of microorganisms residing in the gut [1]. These microbes, including bacteria, viruses, and fungi, interact closely with the host environment and are essential to human health, participating in digestion, breakdown of polysaccharides, vitamin synthesis, and protection against pathogens [2,3]. They also play a significant role in immune regulation and communication with host cells [4,5]. Disruption of the gut microbiome (dysbiosis) is now recognized as a key factor in many diseases, not only in classic infections but also in obesity, diabetes, liver disorders, and cancer [2,4,6]. Consequently, the gut microbiota has emerged as a promising target for new diagnostic and therapeutic approaches. While bacteria are the most abundant and well-studied constituents of the microbiome, the gut also harbors important populations of viruses (the virome) and fungi (the mycobiome), both of which contribute to mucosal barrier function and gut homeostasis [7-9]. Research has focused predominantly

on the bacterial fraction, largely because viruses and fungi are less abundant and more complex to identify using standard laboratory methods [10-12]. However, advances in sequencing and bioinformatics are beginning to shed light on the roles of these previously overlooked communities. This review examines the current understanding of the gut virome and mycobiome in human health and disease, with an emphasis on their roles in gut homeostasis, immune modulation, and disease mechanisms. This study precisely reviewed publications addressing the composition, function, or clinical implications of the intestinal virome or mycobiome, prioritizing recent and mechanistic work.. This synthesis highlights key knowledge gaps, advances in methodology, and future directions for research and clinical application.

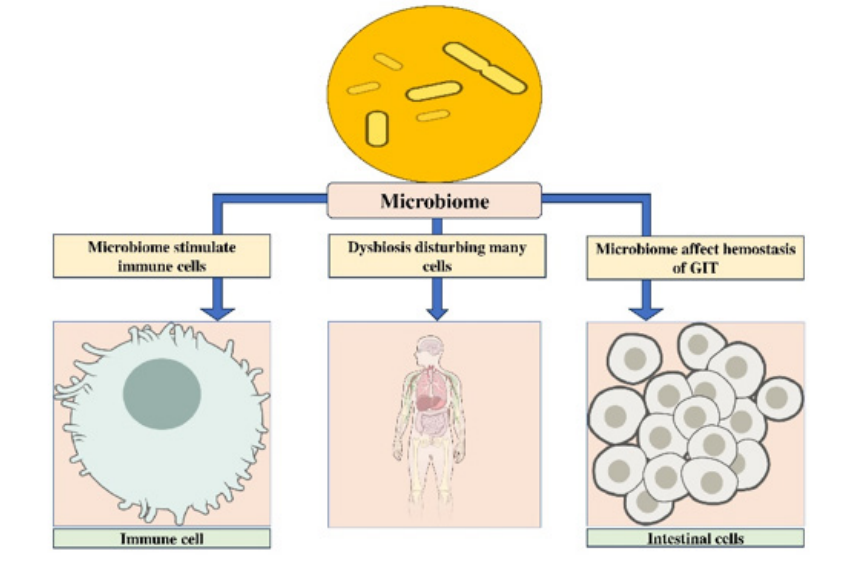

Figure 1: Influence of the microbiome on immune and intestinal cells.

Methodology

In this review, a narrative search of PubMed, Scopus, and Google Scholar using the terms "gut virome", "gut mycobiome", "viral microbiome", "fungal microbiome", and "microbiome dysbiosis in health and disease" was performed. Additionally, other information with respect to study aims was also collected. No date limits were imposed to capture both foundational and contemporary work; however, preference was given to studies published within the past decade and those offering mechanistic insights or clinically applicable findings, and pros and cons were discussed accordingly.

Gut virome: composition, function, and clinical significance

Definition and components of the Gut Virome

The gut virome often described as the "dark matter" of the gut microbiome [13], is a genetically diverse and complex microbial community. Various body sites, including the blood, nasal passages, skin, conjunctiva, oral cavity, vagina, and gastrointestinal (GI) tract, each harbor their own distinct populations of viruses [14] The virome comprises eukaryotic viruses that primarily infect human cells, prokaryotic viruses known as bacteriophages (phages), and archaeal viruses [15,16]. In the human gut, bacteriophages are by far the most abundant, outnumbering eukaryotic viruses, and are the predominant viral group present [17,18]. Fecal samples contain between 10^9 and 10^{10} viral particles per gram, reflecting the remarkable density and persistence of these phages within the gut environment [13]. Although eukaryotic viruses are less prevalent, they have been the focus of significant research due to their role in intestinal diseases. Additionally, the human genome contains rare endogenous retroviruses, which can influence disease processes by altering gene expression and immune regulation [19].

Role in Gut Homeostasis The human gut virome plays a vital role in both human health and ecological biology [20]. Colonization of the gut virome begins at birth. It gradually stabilizes into adulthood, with each individual developing a unique virome profile influenced by factors such as age, antibiotic use, and underlying health conditions [21]. Even the mode of delivery can shape the initial virome composition: newborns delivered vaginally have a more diverse gut virome compared to those delivered by cesarean section, with Caudoviricetes, Microviridae, and Anellovi-

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ridae among the most abundant viruses detected [22]. Moreover, specific changes in the virome have been linked to various disease states, including inflammatory bowel disease, diabetes, hypertension, AIDS, colorectal cancer, and acute malnutrition [17]. These associations reflect the complex, multifaceted interactions between the virome, particularly bacteriophages, and the gut bacteriome, which together contribute to microbial colonization, ecological balance, and host health through dynamic host-pathogen interactions [23].

Gut virome in Disease

Although research into the gut virome remains in its early stages, emerging evidence reveals that disruptions in viral community composition and reduced diversity can impair intestinal barrier function. A notable pathogenic mechanism involves viruses crossing the gut epithelium, especially in conditions with increased permeability, which may trigger immune responses and contribute to autoimmune, infectious, and inflammatory diseases such as inflammatory bowel disease (IBD) [14,24]. The pathogenesis of IBD is multifactorial, involving genetic susceptibility, immune activation, and environmental influences—including the gut microbiota [25,26]. Animal studies further suggest that certain eukaryotic viruses can interact with host genetic risk factors to modify intestinal disease risk [27]. In healthy individuals, the dominant gut phages are double-stranded DNA (dsDNA) Caudovirales and single-stranded DNA (ssDNA) Microviridae [28]. When exposed to environmental stressors like nitric oxide or antibiotics, phages may switch to the lytic cycle, causing bacterial lysis and spreading infectious virions within the gut [29]). Increased Caudoviricetes abundance has been observed in both ulcerative colitis and Crohn's disease, while overall phage diversity is lower in Crohn's [30,31]. Distinct virome changes are also noted in metabolic and inflammatory diseases. For example, shifts in the gut phagosome have been reported in obesity, type 1 and type 2 diabetes [32,33] though whether these are causal or simply reflect broader dysbiosis is unclear. Notably, the human gut microbiome accounts for a significant portion of resting energy expenditure, and disturbances in its composition may contribute to metabolic dysfunction [34]. In pregnant women with early-onset diabetes, increased levels of tobamoviruses and picobirnaviruses have been detected; these changes may serve as biomarkers of immune alterations, though their precise roles and host targets remain uncertain [21]. COVID-19, caused by SARS-CoV-2, further illustrates the clinical relevance of the gut virome. The virus infects the gastrointestinal tract via the ACE2 receptor, and patients even those with mild disease show reduced virome diversity and an increase in inflammation-associated viral genes [21,35]. While short-term changes are well described, the long-term impact on gut health requires further study. Ultimately, the virome, along with the bacteriome and mycobiome, forms a tightly interconnected network in the gut. Disruptions in one component can reshape the entire microbial ecosystem and influence host immunity and disease risk. For example, changes in phage populations can affect bacterial evolution, while virome alterations have been implicated in autoimmunity, such as rheumatoid arthritis, where distinct shifts in specific bacteriophages have been observed in at-risk individuals [7,8].

Challenges and advances in virome research

Bioinformatics challenges in viral metagenomics stem primarily from the phenomenon known as "viral dark matter," which refers to the 40–90% of gut viruses in a sample that remains unidentified and unexplored [36]. This uncharacterized genetic material holds substantial potential for discoveries; for instance, analysis of this dark matter led to the identification of crAssphage, now known as one of the most common bacteriophages in the human gut. Addressing this gap requires the development of improved computational tools. Methods such as hidden Markov models, which detect distant similarities in viral proteins, are being used to classify unknown viruses. Advances in machine learning and artificial intelligence, including neural networks, further improve classification accuracy. Experimentally, culturing more viruses in the laboratory will generate valuable reference data and help reduce the number of unclassified sequences [37]. As a result, advancing our understanding of the gut virome is crucial for uncovering its role in human health. Research on the gut virome remains limited, mainly due to incomplete reference libraries and technological hurdles [38]. Many intestinal viruses remain unclassified, but ongoing improvements in metagenomic technologies, including the combination of short-read and long-read sequencing, are expected to overcome these barriers [39]. Enhanced, cost-effective, and sensitive sequencing methods now allow for more comprehensive characterization of the human virome, encompassing double-stranded DNA (dsDNA), single-stranded DNA (ssDNA), and RNA virus-like particles [14]. This progress supports the exploration of diverse gut bacteriophage populations and aids in the discovery of novel viral genomes [40]. To support these efforts, several human gut virome databases have been established, including the Gut Virome Database (GVD), the Cenote Human Virome Database (CHVD), the Metagenomic Gut Virus Database (MGV), and the Gut Phage Database (GPD) [41]. Most well-known databases encompass the Gut Virome Database (GVD), Cenote Human Virome Database (CHVD), Metagenomic Gut Virus Database (MGV), and Gut Phage Database (GPD). These resources have significantly expanded our understanding of gut viral diversity, providing accurate and informative datasets that serve as guidelines for future studies [42].

The Gut Mycobiome: Diversity, Function, and Pathogenic Potential

The human gut microbiome the collection of microorganisms in the gastrointestinal tract - is increasingly recognized as a key player in the pathogenesis of various diseases, including inflammatory bowel disease (IBD) [43], type 2 diabetes [44], hypertension [45], and colorectal cancer [46]. Both bacteria and fungi contribute to host metabolism, with research highlighting asso-

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ciations between microbial populations and metabolic outcomes in conditions like diabetes [47] and cholesterol metabolism [48]. Lifestyle factors such as diet and physical activity substantially influence the gut microbial community, as demonstrated in animal models and human cohort studies [49,50].

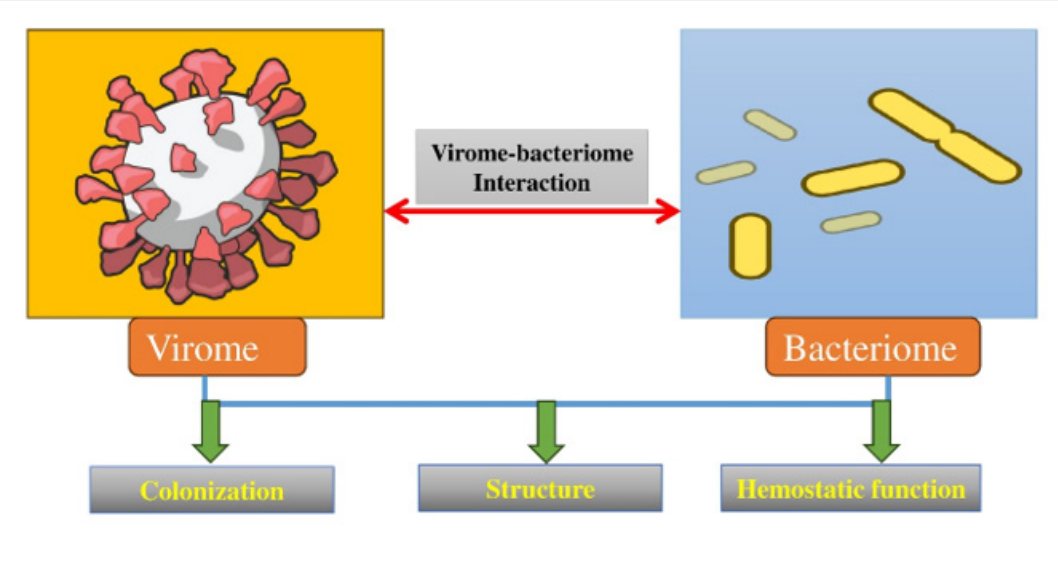

Figure 2: Virome and bacteriome interaction in Gut hemostasis.

The gut microbiota behaves in a metabolically active manner, operating symbiotically with the gut mucosa to contribute to metabolic, immunological, and protective functions [51]. Current research no longer focuses solely on enumerating the abundance and diversity of gut microbes but rather on how they contribute to overall health. Most nutrients for the gut microbiota are derived from dietary carbohydrates, fermented by colonic bacteria such as *Bacteroides*, *Roseburia*, *Bifidobacterium*, *Fecalibacterium*, and *Enterobacteria* to produce short-chain fatty acids (SCFAs) [52,53]. The microbiota also synthesizes essential vitamins (K and B groups) and conjugated linoleic acid (CLA), which have anti-inflammatory, antiatherogenic, and immunomodulatory effects [54]. Additionally, specific bacteria, including *Bacteroides intestinalis*, *Bacteroides fragilis*, and *E. coli*, transform primary bile acids into secondary bile acids, such as deoxycholic and lithocholic acid [55]. The gut microbiome's influence on drug metabolism has long been recognized; for example, the microbial metabolite p-cresol inhibits acetaminophen metabolism, and microbial activities can increase toxicity from drugs like irinotecan, resulting in side effects such as diarrhea and inflammation [56-58].

Maintaining the balance of the gut microbiota requires the mucosal immune system to tolerate commensals while preventing the overgrowth of pathogens. This is achieved through a dual-layer mucus barrier produced by goblet cells, which shields the epithelium from microbes. The inner mucus layer is dense and typically free from microorganisms, while the outer layer provides nutrients and stability to the mucin polymers, thereby supporting barrier integrity [59-61]. Both innate and adaptive immune components, including gut-associated lymphoid tissues, effector T cells, and innate lymphoid cells, work in conjunction with the microbiota to modulate [62] immune responses [63].

Currently, there is a convincing body of evidence that supports the role of the gut microbiota in maintaining the structure and function of the gastrointestinal tract. *Bacteroides thetaiotaomicron* is reported to induce expression of the small proline-rich protein 2A (sprr2A), which is required to maintain desmosomes at the epithelial villus [64]. External and host factors can induce dysbiosis in the gut microbiome, impairing host wellness and potentially leading to harmful microbial-derived products or metabolites, causing various diseases in local, systemic, or remote organs, and requiring microbiome-based therapy [65].

Clostridium difficile, a Gram-positive anaerobe and member of the *Firmicutes*, produces toxins A and B that damage colonic epithelial barrier integrity, causing an inflammatory response and cell death [66,67]. C. difficile infection (CDI)-associated symptoms include diarrhea, pseudomembranous colitis, sepsis, and death in severe cases [68].

Another example of gut microbiome-associated disease is IBD. IBD is a group of multifactorial, idiopathic, persistent, and recurring gastrointestinal inflammations. Two common forms of IBD are celiac Disease (CD) and ulcerative colitis (UC) [69]. CD and UC inflammations, causing relapsing diarrhea, fever, and abdominal pain, are increasing globally, affecting 1.4 million and 2.2 million individuals in America and Europe, respectively [70]. IBD is a complex disease influenced by host and environmental factors, with gut microbiota and host factors potentially intertwining to contribute to its development [65].

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The gut microbiome, a key factor in host metabolism regulation, has been linked to obesity, a global health hazard affecting over 600 million people. Obesity is associated with high energy intake, metabolic syndrome, obesity-related disorders, low-grade inflammation, and premature mortality [71].

Composition of the Gut Mycobiome Common Fungal Species

Animal models reveal the role of intestinal fungi, particularly *Candida*, in energy harvest and host metabolism. *Candida albicans and Candida parapsilosis* have been studied extensively, showing contrasting effects on metabolic hormones and obesity development, highlighting the need for further research [62,72,73].

The human gut mycobiome is typically dominated by commensal yeasts such as *Saccharomyces cerevisiae*, *Malassezia restricta*, and *Candida albicans*, which coexist with bacteria to support digestion, modulate immune function, and prevent the overgrowth of pathogens. Analysis of stool samples from healthy individuals in the Human Microbiome Project showed that fungal diversity is lower than bacterial diversity, with yeast, particularly *Saccharomyces*, *Malassezia*, and *Candida,* being the most prevalent genera. The persistence of particular fungal species across multiple individuals suggests the existence of a core gut mycobiome [62,74].

Mycobiome-Host Interactions Cross-talk between fungi, bacteria, and immune system

Role in digestion and metabolism

Bacterial-fungal interactions in the host are shaped by immune responses, with certain microbial colonizers inducing significant immunological changes that influence the balance of other microbes [75]. For example, *Bacteroides thetaiotaomicron* activates innate immune genes in mice, which suppresses colonization by *Candida albicans*. Overall, studies indicate that both bacterial and fungal species can have important effects on the host immune system [76].

Recognition of fungi by the immune system

The host's immune response to fungi relies on immune cells detecting molecular patterns through pattern recognition receptors (PRRs), including Toll-like receptors, C-type lectin receptors, and NOD-like receptors. Phagocytosed fungi can activate NOD-like receptors (NLRs), triggering inflammation [77,78]. Mutations in the Dectin-1 gene increase susceptibility to *Candida tropicalis* invasion and worsen colitis in both mice and humans, while mutations in Dectin-2 are linked to higher rates of *Candida glabrata* infection [79]. deficiencies in TLR4 and TLR2 signaling impact systemic candidiasis outcomes. Specifically, TLR4 deficiency leads to an increased *C. albicans* burden in the kidneys, while blocking TLR2 reduces inflammatory cytokine production, including TNF-α and IL-1β [80,81]. Other receptors, including MelLec, pentraxins, MBL, and MDA5, are also involved in fungal recognition, such as binding to *Aspergillus fumigatus* conidia, recognizing galactomannan and mannan, and mediating immune responses to systemic *Candida albicans* infection [82,83].

Immune system-mycobiota interaction

Research indicates that fungi play a crucial role in immune system maturation, as their presence enhances circulating granulocyte levels in mice residing in natural environments [84]. This builds on earlier work indicating that mice colonized with a "wild-mouse microbiota" exhibit immune responses to immunotherapy that more closely resemble those of humans [85]. Fungi, and the mycobiome in general, are vital for immune system development and homeostasis but can also play a role in inflammatory and pathogenic conditions. For example, *Candida* and *Malassezia*, especially *C. albicans*, can exacerbate gut inflammation [86]. Fungal dysbiosis and increased colonization by *C. albicans* have been linked to IBD in humans, underscoring the importance of understanding the mycobiome's role in immune system development [87].

Gut Mycobiome in Disease

Crohn's disease

Crohn's disease (CD) is a chronic, severe inflammatory condition that most often affects the terminal ileum and can cause irreversible damage throughout the gastrointestinal tract, leading to significant reductions in quality of life [88]. Its pathogenesis involves a combination of genetic, epigenetic, immunological, and microbiological factors, as well as environmental triggers like smoking, diet, stress, and infections. Overgrowth of microbes, such as *Mycobacterium avium* and adherent-invasive *Escherichia coli* (AIEC), may also play a role [89]. Current evidence suggests that dysbiosis—an alteration in the gut microbiome may be either a cause or a consequence of CD, with affected patients displaying reduced microbial community complexity compared to healthy individuals [90]. *Faecalibacterium prausnitzii*, a Firmicutes bacterium with proposed anti-inflammatory effects, has been found at lower levels in CD patients and may be linked to a higher risk of disease recurrence [91,92].

Irritable bowel syndrome (IBS)

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder that, although rarely life-threatening, imposes a substantial socioeconomic burden and significantly reduces quality of life [93]. IBS is diagnosed based on persistent and recurrent symptoms, and while treatment focuses on symptom relief, atypical presentations can complicate management over time [94]. The pathogenesis of IBS is increasingly linked to micro-dysbiosis alterations in the gut microbial community with more than 70% of patients showing reduced diversity and distinct microbial profiles compared to healthy controls. Notably, IBS is often associated with increased levels of facultative anaerobes, such as *Streptococcus* species, and decreased *levels of Lactobacilli* and *Bifidobacteria*. Many studies also report an elevated fecal Firmicutes/Bacteroidetes ratio among IBS patients [95].

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Colorectal cancer (CRC)

Colorectal cancer (CRC) ranks as the fourth leading cause of cancer mortality worldwide. It arises from a combination of genetic and environmental influences, with the gut microbiota playing a key role in promoting a tumor-friendly environment. Experimental models, such as those using APC mutations, demonstrate the role of the microbiome in colorectal carcinogenesis [96]. There is a complex, bidirectional relationship between the gut microbiome and CRC: gut fungi interact with the host immune system, modulating immunity and potentially contributing to conditions such as IBD, asthma, and cancer [97]. The bacterial microbiome also influences host metabolism by shaping immune cell populations and inflammatory tone, with intestinal fungi potentially affecting host energy balance through their immunomodulatory properties [98].

Challenges and Future Directions in Mycobiome Research Fungal metagenomics and biomarker discovery

While advances in metagenomics and experimental techniques have expanded our understanding of the mycobiome, significant technical and conceptual challenges remain. Low fungal biomass and lack of control over data sources contribute to variability in study results, particularly when investigating the mycobiome's role in cancer [99]. Many studies do not provide detailed protocols for sample contamination control, highlighting the need for more rigorous sample collection and larger, well-defined cohorts. Current fungal databases are limited by inconsistent species nomenclature and insufficient data; therefore, harmonization of bioinformatics analysis tools is necessary for improved data comparability [100]. The reproducibility and accuracy of pan-cancer mycobiome analyses have not been fully validated, making future research with improved coordination, robust data sharing, and standardized denoising procedures essential for their validation. Study design, specimen source, population characteristics, cancer type, pathological subtype, and environmental factors can all affect study outcomes and interpretations [62]. High inter-individual variability is common in mycobiome studies and may contribute to immune-mediated disorders driven by rare fungal species. However, this variability could also offer insights for predicting individualized disease changes [101]. Future cancer mycobiome research should prioritize causality, collaborative work, and mechanistic understanding. While correlation studies are valuable, experimental validation through controlled experiments and extensive model validation is essential for establishing causal links between fungi and cancer [102]. Animal models and other experimental systems can help simulate cancer environments, validate microbiome profiles, and assess the effects of fungi on tumor development. New technologies also allow the spatial distribution of fungal communities within tumor tissues to be studied [103]. Inter-kingdom interactions between fungi and bacteria have been documented in cancer, suggesting that communities of multiple microbial species, rather than individual ones, may collectively drive ecological dysbiosis [104]. Most research to date relies on metagenomics, but integrating meta-transcriptomics and meta-proteomics in a multi-omics approach could lead to the identification of more reliable biomarkers [105]. Clinical studies indicate that combining chemotherapy or immunotherapy with microbiome modulation may enhance cancer management. However, mycobiome research has yet to be translated into clinical therapeutic interventions for humans [106].

Gut Virome-Mycobiome Interactions: The Unexplored Cross-Talk

Influence on bacterial microbiome

The gut virome, particularly bacteriophages, interacts with gut bacteria, shaping the gut microbiota [107] and altering bacterial gene expression, impacting the host's immune response [108]. This interaction also leads to microbial imbalances, such as in IBD [109]. Although the gut mycobiome is significantly smaller than the bacterial population, it has a substantial impact on bacterial colonies by producing metabolites that inhibit bacterial growth and by competing with bacteria for nutrients and space [110]. The virome can also transfer antimicrobial resistance genes to bacterial pathogens, enabling them to develop drug resistance [111]. Interactions between the virome and mycobiome can be either synergistic or antagonistic. For example, phage-induced bacterial lysis, supported by fungal metabolites, releases nutrients that may promote fungal growth, illustrating the complex dynamics that shape gut ecology [112]. These multi-kingdom interactions among viruses, fungi, and bacteria are essential for maintaining the structure and function of the gut microbiome. Disruptions in these interactions can lead to microbial imbalances, which in turn affect host health and increase disease susceptibility [111].

Implications for gut inflammation and systemic diseases

Imbalance in the gut microbiota including disruptions in the virome and mycobiome-can drive systemic inflammation and is implicated in diseases such as rheumatoid arthritis and systemic lupus erythematosus [113]. Dysbiosis of the virome can trigger immune responses that promote gut inflammation and contribute to IBD, characterized by a loss of microbial diversity and the accumulation of specific bacterial groups, such as the *Ruminococcus gnavus* clade and *E. coli* [109,114,115]. Alterations in the mycobiome, particularly the overgrowth of *Candida*, can further escalate gut inflammation and disease by stimulating the host immune system [116]. The virome and mycobiome also regulate the production of microbial-derived metabolites, which can affect host metabolism. Their dysbiosis can lead to chronic low-grade inflammation, contributing to metabolic syndromes such as obesity and type 2 diabetes mellitus [117]. Additionally, the gut microbiota influences lung diseases-for example, lipopolysaccharide stimulation in atopic asthma and gut injury or inhibited epithelial growth in pneumonia. Recent findings suggest that altering the

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gut microbiota can lead to metabolites that promote inflammation in distant organs such as the lungs and bone marrow. The mycobiome not only affects local gut inflammation but can also contribute to systemic inflammation by releasing metabolites that impact distant tissues and organs.

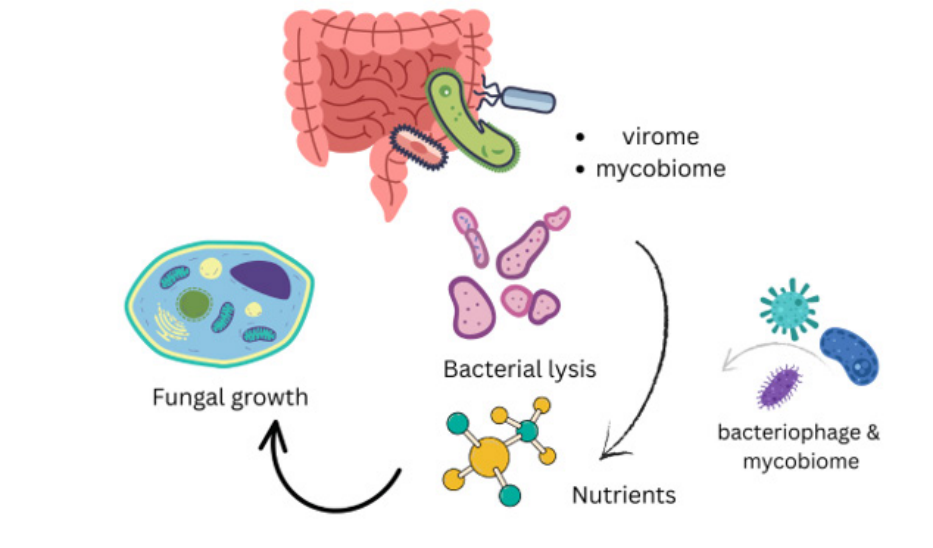

Figure 3: Gut Virome-Mycobiome Interactions and Their Impact on Gut Microbial Dynamics: This diagram illustrates how interactions between the gut virome and mycobiome influence bacterial populations. Bacteriophage-mediated bacterial lysis releases nutrients that promote fungal growth, while fungal metabolites further modulate bacterial dynamics.

Potential therapeutic targets

Emerging therapeutic strategies now focus on developing microbiome-modulating drugs, such as those targeting bacteriophage-host interactions, as new treatments for chronic gastrointestinal diseases [108]. Diet remains a central factor in regulating the gut microbiome; for example, a fiber-rich diet in patients with type 2 diabetes mellitus (T2DM) has been shown to improve insulin sensitivity by promoting beneficial gut fermenters and enhancing glucose metabolism. Similarly, supplementation with flaxseed mucilage in obese women resulted in changes to the gut microbiome and improvements in glycemic control [118]. Bacteriophage therapy represents another promising approach, demonstrating efficacy in treating antibiotic-resistant bacterial infections in clinical settings [119]. Modulating the gut mycobiome with antifungal agents has also been shown to reduce inflammation in conditions such as Crohn's disease and ulcerative colitis [109]. Targeting the virome, particularly bacteriophages, to restore microbial ecosystem balance has been linked to symptom improvement in inflammatory bowel disease [107]. Microbiota transplantation is another strategy, with evidence showing that transferring gut microbiota from healthy donors can alleviate both gastrointestinal and behavioral symptoms in patients with autism spectrum disorder [118]. Combining virome and mycobiome modulation therapies offers a synergistic approach to reestablishing microbial balance and treating inflammatory conditions [120].

Current and future therapeutic approaches.

Virome-Based Therapies

The "human virome" encompasses all viruses present on or within the human body, including those responsible for acute, persistent, or latent infections, as well as endogenous retroviruses integrated into the genome [121]. While microbiome research has historically centered on bacterial communities due to well-established techniques for bacterial study, the archaeal, eukarya, and viral components have received less attention [122]. Recent advancements in high-throughput sequencing and bioinformatics have expanded and standardized virome research, bringing new insight into the gut virome's role in health and disease [123,124].

As the relationship between gut dysbiosis and disease becomes clearer, targeted manipulation of the gut virome is emerging as a therapeutic focus. Approaches such as prebiotics, probiotics, synbiotics, fecal microbiota transplantation (FMT), phage therapy, and fecal virome transplantation (FVT) are increasingly explored. Phage therapy stands out for its ability to specifically target and eliminate pathogenic bacteria, making it especially valuable for infections caused by invasive or drug-resistant organisms [123]. Phage therapy and FVT are now being studied as promising alternatives for treating *Clostridioides difficile* infections, particularly those involving resistant strains. Given the risks associated with broad-spectrum antibiotic therapy, complementary strategies such as FMT, FVT, and phage-based interventions are being adopted to treat, prevent, and reduce the recurrence of CDI [125].

As virome research and bioinformatics advance, improved databases and analytical tools are enabling the achievement of strain-level resolution, thereby facilitating more accurate identification of dysbiosis-associated viral communities [124]. Thus,

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virome-based therapies represent a rapidly growing frontier in microbiome interventions, with significant potential for treating a broad range of diseases

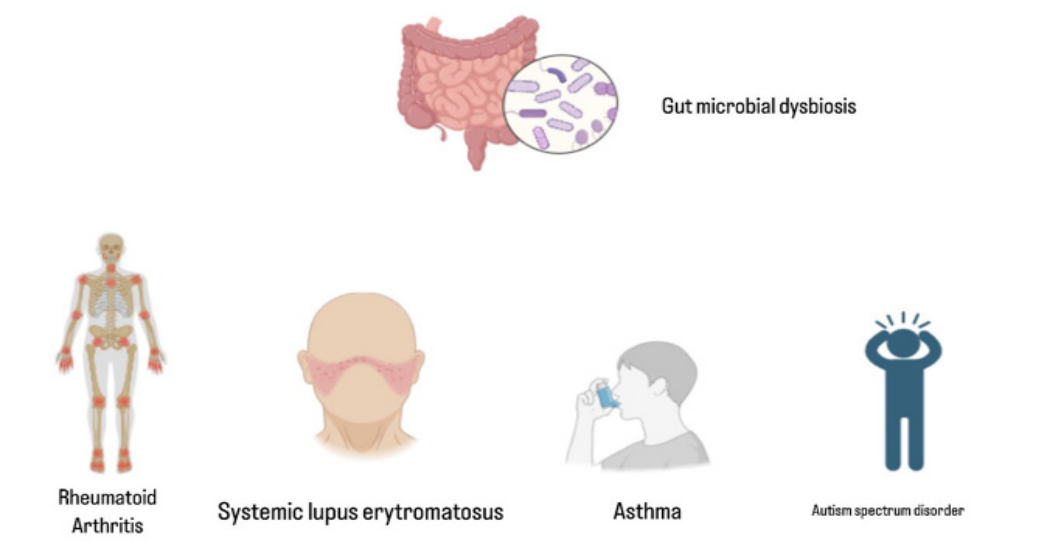

Figure 4: Impact of Gut Microbial Dysbiosis on Systemic and Neurological Diseases: Gut microbial dysbiosis is linked to systemic diseases like rheumatoid arthritis and systemic lupus erythematosus. It also contributes to respiratory conditions such as asthma and neurodevelopmental disorders like autism spectrum disorder.

Phage therapy for gut dysbiosis

A balanced gut microbiome is essential for maintaining intestinal barrier integrity and preventing pathogenic invasion [126]. Dysbiosis-disruption of microbial composition and function-may result from various factors, including diet, toxins, drugs, and pathogens [127]. This imbalance alters microbial populations and metabolism, disrupts the gut barrier [128] and can lead to various inflammatory and systemic diseases [129]. Phage therapy, which utilizes bacteriophages to target specific harmful bacteria, has emerged as a promising strategy for restoring microbial balance [129]. Phages are highly specific to their bacterial hosts, replicate using bacterial machinery, and do not persist outside their target bacteria [130]. Therapeutic approaches include conventional and engineered phages, as well as phage-derived enzymes [131]. The gut virome predominantly includes ssDNA phages (Microviridae) and dsDNA phages [132].

Metagenomic studies have identified crAssphage, a dsDNA phage, as highly prevalent in the human gut, present in approximately half of individuals, and constituting up to 90% of viral DNA in stool [133]. Healthy adults tend to share a core set of bacteriophages, forming the healthy gut phagosome (HGP), which is notably reduced in diseases such as ulcerative colitis and Crohn's disease (by up to 42–54%) [134].

Phage therapy aims to modulate the phageome to beneficially influence the bacteriome. This involves selecting or engineering phages for specific bacterial targets, preparing effective phage formulations, and establishing appropriate dosing strategies [135]. While the introduction of antibiotics historically overshadowed phage therapy, the rise of antibiotic resistance has renewed interest in these targeted interventions [136]. Phages offer strain specificity, which reduces the risk of complications like antibiotic-associated diarrhea and *Clostridium difficile* infection [137]. Their ability to replicate within the host also enables sustained therapeutic activity at the site of infection [138]. Recent research highlights the potential of phage therapy. For instance, a five-phage cocktail targeting *Klebsiella pneumoniae* in IBD models reduced inflammation and disease severity [139]. Furthermore, the selection of bacteriophages from families such as Leviviridae, Microviridae, and Caudovirales (Myoviridae, Siphoviridae, and Podoviridae) underlines their broad applicability in clinical contexts [140]. Clinical applications use phages from families such as Leviviridae, Microviridae, and Caudovirales. Phages can also work synergistically with antibiotics, disrupting bacterial biofilms and improving antibiotic penetration 140,141,142. Safety and efficacy have been demonstrated in human trials. Oral administration of T4-like phage cocktails in children with acute bacterial diarrhea confirmed the safety of phages [143]. The PHAGE study in healthy adults found a four-strain phage cocktail to be safe and well-tolerated [144]. Another trial demonstrated that phage supplementation selectively reduced fecal *E. coli* without affecting overall microbiota diversity and was associated with favorable shifts, including increased butyrate-producing *Eubacterium* and reduced *Clostridium perfringens* [145]. Animal studies also confirm the efficacy of phages in reducing pathogenic bacteria in vivo [146]. Phage therapy can selectively eliminate pathogenic species using lytic phages or potentially induce temperate phages in commensals; however, the latter approach is limited by an

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incomplete understanding of phage induction mechanisms [147]. Targeted phage therapies have shown success in models of IBD; for example, a seven-lytic-phage cocktail targeting adherent invasive *Escherichia coli* (AIEC) reduced inflammation and preserved non-target commensal strains [148]. Collectively, these studies demonstrate the promise of phage therapy as a precise and effective tool for modulating the gut microbiota and addressing dysbiosis. Further research is needed to optimize dosing and better understand phage-immune system interactions, but phage therapy is an emerging alternative to antibiotics for gut health.

Antiviral Interventions for Gut Health

Recent research suggests that antiviral treatments can decrease viral loads and have a positive impact on the gut microbiota. Direct-acting antiviral agents (DAAs), for example, are effective in eradicating viruses and have been linked to a partial restoration of α-diversity and a reduction in potentially pathogenic species; however, these benefits are less evident in patients with cirrhosis [149]. In inflammatory bowel disease, particularly Crohn's disease, an increase in Caudovirales has been linked to reduced bacterial diversity, suggesting that virome alterations may contribute to intestinal inflammation and dysbiosis [150]. During viral infections, epithelial and innate immune cells recognize pathogens via pattern recognition receptors, activating inflammatory cascades that generate type I and III interferons, IL-6, IL-1β, IL-18, and TNF-α—key mediators in antiviral defense and leukocyte recruitment [151]. Beyond antiviral drugs, immune modulation with probiotics offers additional benefits. Probiotic supplementation can strengthen the gut's antiviral defenses by influencing microbial composition and stimulating interferon production, potentially supporting longer-term resistance to infections like COVID-19 [152]. In HIV, INSTI-based antiretroviral regimens promote better recovery of gut microbiota diversity compared to NNRTI-based therapies, underscoring the relationship between antiviral treatment and microbiome restoration [153]. Vitamin A supplementation has also been shown to inhibit murine norovirus replication and increase *the* abundance of Lactobacillus, further enhancing antiviral protection [154]. Collectively, these findings highlight the multifaceted impact of antiviral interventions not only in reducing viral pathogens directly but also in supporting a healthier and more resilient gut microbiota.

Mycobiome-Targeted Interventions

The healthy gut mycobiome, primarily composed of commensal fungi such as *Saccharomyces cerevisiae*, *Malassezia restricta*, and *Candida albicans*, is essential for intestinal homeostasis—supporting digestion, modulating immunity, and preventing pathogenic overgrowth [101]. Disruption of the mycobiome, or fungal dysbiosis, has been increasingly linked to a range of diseases, including gastrointestinal, metabolic, neurological, and cardiovascular disorders [155]. Recognizing its importance, the mycobiome is now viewed as a promising target for diagnostics and therapy in precision medicine. Strategies to restore mycobiome balance include the use of probiotic fungi, antifungal medications, dietary modifications, and fecal microbiota transplantation (FMT) all of which have shown potential to re-establish a healthy gut environment [155,156]. Ongoing research into these interventions may yield new treatments for mycobiome-associated diseases.

Antifungal Strategies and Probiotics

Fungal infections cause over 1.5 million deaths globally each year, particularly in individuals with weakened immune systems [157]. The increasing incidence of these infections, combined with rising resistance and side effects from conventional antifungal drugs, highlights the urgent need for safer, broad-spectrum alternatives [158,159]. Probiotics live microorganisms that confer health benefits when administered in adequate amounts have emerged as promising antifungal agents by boosting host immunity and preventing pathogen colonization [159]. Research has demonstrated that specific probiotic strains can inhibit the growth of pathogenic fungi. For example, certain probiotics are effective in preventing and treating dermatophyte infections [160]. *Lactobacillus reuteri* R2, in particular, showed potent antifungal activity: its freeze-dried supernatant, at concentrations above 1%, completely inhibited the growth and germination of *Trichophyton tonsurans* [161]. Another study found that combining probiotics with seaweed extract (*Ascophyllum nodosum*) produced significant in vitro antifungal effects against *Trichophyton mentagrophytes* and *Candida albicans* [162].

Additional investigations have highlighted the efficacy of various probiotic bacteria, including *Streptococcus salivarius* K12, *Lactobacillus rhamnosus* GR-1, *Lactobacillus reuteri* RC-14, and clinical *Lactobacillus* isolates, against *Candida* species [163]. Clinical studies support these findings: In preterm infants, supplementation with *Lactobacillus* species has been shown to reduce gastrointestinal *Candida* colonization, decrease late-onset sepsis, and improve neurological outcomes [164]. Similarly, a randomized, double-blind trial found that probiotic supplementation reduced rates of fungal colonization and invasive fungal sepsis, promoted earlier initiation of full enteral feeds, and shortened hospital stays compared with the placebo [165]. These results support the use of probiotics as an antifungal strategy either alone or in combination with traditional agents—to control fungal infections and help maintain a balanced mycobiome.

Holistic Microbiome Modulation

Fecal Microbiota Transplantation (FMT), Including Virome and Fungi

Fecal microbiota transplantation (FMT) involves transferring the microbiota from the stool of a healthy donor to a patient with gut dysbiosis. In addition to bacteria, the human gut contains a diverse virome and mycobiome-collections of viruses and fungi, respectively [166]. While FMT is primarily used to treat *Clostridioides difficile* infection (CDI), recent research highlights the critical role of the virome and mycobiome in its efficacy.

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CDI patients exhibit an enrichment of bacteriophage Caudovirales, characterized by reduced viral diversity compared to healthy individuals. Successful FMT reduces the abundance of Caudovirales, and the presence of donor-derived Caudovirales in recipients correlates with clinical cure [167]. Donor-derived bacteriophages can persist in recipients for up to a year, with long-term outcomes influenced by the compatibility between the donor and recipient [168]. Refined approaches such as fecal viral transfer (FVT) and fecal filtrate transplantation (FFT) aim to transfer virome components without bacteria, potentially reducing infection risks. However, the persistence of eukaryotic viruses and prophage-encoded virulence factors requires caution [169]. Animal studies suggest that FVT can help restore gut homeostasis after antibiotics, with recipient mice regaining pre-antibiotic bacteriome profiles more effectively when given viable virome transplants [170]. Fungal constituents of FMT are also gaining attention for their immunomodulatory and therapeutic roles. In patients with ulcerative colitis (UC), FMT-induced remission was associated with an increase in beneficial fungi (e.g., *Kazachstania naganishii*, *Schizosaccharomyces pombe*) and a decrease in pathogenic fungi, such as *Candida* [171]. In CDI, the overrepresentation of *Candida albicans* and reduced fungal diversity are common, while FMT responders tend to gain donor-derived *Saccharomyces* and *Aspergillus* species; non-responders, on the other hand, retain high *Candida* levels [172]. The pre-FMT abundance of *Candida* spp. in recipients may predict FMT success, and donor feces enriched in fungi, such as *Filobasidium*, are associated with better outcomes, possibly due to enhanced anti-inflammatory effects [173]. Experimental models further demonstrate that antibiotic-induced dysbiosis promotes fungal overgrowth, which can be suppressed by fecal microbiota transplantation (FMT) highlighting the interplay between bacteria and fungi in colonization resistance [174]. These findings underscore the importance of considering both the virome and mycobiome in FMT. Incorporating their dynamics into future FMT strategies may improve therapeutic outcomes, reduce recurrence, and enable more personalized microbiota-based interventions.

Personalized Medicine Approaches

Personalized medicine is emerging as a powerful strategy for addressing microbiome-related health conditions by tailoring interventions to an individual's specific microbial and clinical profile. Advances in metagenomics and sequencing technologies now enable comprehensive analysis of the gut microbiota, making it possible for clinicians to design targeted treatments that consider factors such as diet, ancestry, physiology, and microbial signatures [175]. These individualized approaches bridge microbiome research and clinical practice, allowing for precise dietary and therapeutic recommendations based on both host and microbial metabolic profiles [176,177]. A personalized strategy typically involves a detailed analysis of a patient's clinical data, gut microbiome, and metabolome, identifying shifts in microbial diversity and function. This is crucial given the significant intra-individual variability in microbiota, which can influence therapeutic responses and create drug response biases [178,179]. For example, personalized probiotic regimens based on stool analysis and health history have demonstrated increased beneficial bacterial populations and microbial diversity, resulting in improved outcomes in conditions such as diarrhoea and constipation [180]. As omics data are increasingly integrated into clinical care, advances in bioinformatics and machine learning are essential for interpreting complex datasets. These tools support the development of precision probiotics, next-generation prebiotics, and tailored dietary therapies [181]. Ultimately, the integration of microbiome-based diagnostics and therapeutics with pharmacogenomics and epigenomics marks a new frontier in patient care, moving healthcare toward truly personalized medicine [182].

Conclusion and Future Perspectives

A balanced interplay among gut bacteria, viruses, and fungi is fundamental to maintaining gut homeostasis and overall human health. Disruption of these interactions, through virome or mycobiome dysbiosis, leads to microbial imbalances that contribute to the development of disease. Indeed, shifts in virome or mycobiome composition are linked to a range of conditions, from chronic gut inflammation (e.g., IBD) and autoimmune disorders (such as rheumatoid arthritis) to metabolic diseases (obesity and type 2 diabetes). Such disturbances compromise mucosal barrier integrity, disrupt immune responses, and alter metabolic pathways, leading to both local and systemic effects. Looking ahead, the gut virome and mycobiome remain less well-characterized than the bacteriome, primarily due to persistent technical challenges. Advances in metagenomic sequencing and bioinformatics are beginning to illuminate the vast "viral dark matter" and reveal greater fungal diversity. However, incomplete reference databases and high inter-individual variability still hinder progress. Future studies should prioritize integrated multi-omics approaches to decipher multi-kingdom interactions and their impacts on the host, complemented by targeted experiments to establish causative mechanisms in disease. On the therapeutic front, targeting the virome and mycobiome is a promising strategy. Bacteriophage therapy and microbiome-modulating drugs are being investigated for the treatment of antibiotic-resistant infections and chronic gastrointestinal disorders. Antifungal treatments have shown benefits in alleviating gut inflammation (as in IBD). Additionally, tailored high-fiber diets can beneficially reshape gut microbial communities to improve metabolic outcomes. Ultimately, incorporating virome and mycobiome insights into microbiome-based diagnostics and personalized medicine holds promise for more effective disease prevention and treatment.

Author contribution

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