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REVIEW

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Analytical insights, modulation and compositional dynamics of the feline gut microbiota: a review

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Abstract

The gastrointestinal tract of felines is inhabited by an active and intricate population of microorganisms whose alteration creates disturbances in the immune response and can affect health and disease states. Studies using various analytical methods have identified peculiar trends in various illnesses, with Firmicutes being the most prevalent phylum, followed by Bacteroidetes, Proteobacteria, and Actinobacteria. However, more Firmicutes and fewer Bacteroidetes have been observed in cats infected with Feline coronavirus. Alterations in the composition of these gut microbiota can be solved by microbiota modification through dietary fiber, probiotics, and fecal microbiota transplantation. Therefore, it is critical to understand the composition of the gut microbiota, the changes in and roles of the gut environment, and the importance of these concepts for overall health while considering the exchange of microbes between humans and domestic animals. This review provides comprehensive information on feline gut microbiota composition, modulation, and analytic methods used for characterizing the gut microbiota.

Keywords Analytical methods, Bacteria, Disease, Dysbiosis, Gut microbiota

Introduction

The optimal functioning of the gut microbiota depends on its composition and diversity (Heiman and Greenway 2016), which can be disrupted in disease situations (Mosca et al. 2016). For this reason, interest in determining the makeup and variety of the microbiota in the gastrointestinal system has increased in recent years.

The whole genome of a population of microorganisms is referred to as its microbiome, and the composition of the microorganisms (bacteria, archaea, bacteriophages, bacteria, and fungi) present in a given environment is referred to as its microbiota (Shahi et al. 2019; Moszak et al. 2020; Berg et al. 2020). The term "intestinal microbiota" describes a complex community of microbiological communities living in the intestinal tract of mammals (Barko et al. 2018; Setubal and Dias-Neto 2022). The healthy gut microbiota is crucial for nutrition, metabolism, host immunity modulation, intestinal barrier

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maintenance, immunity to pathogens, and host defense (Thursby and Juge 2017; Gensollen et al. 2016; Scott and Charlene, 2016).

The microbiota counts in the stomach, small and large intestines vary due to disparities in intestinal physiology, including pH, oxygen concentrations, and antimicrobial agents. Firmicutes and Bacteroidetes are the primary phyla in the intestinal microbiota, alongside Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia (Laterza et al. 2016). According to Auchtung 2018, Candida, Malassezia, Saccharomyces and Cladosporium are the most prevalent fungi in the intestinal mycobiota (Auchtung et al. 2018).

Several factors, including nutrition, genetics, illness, lifestyle and aging, affect the makeup of the gut microbiota and can change it (Rothschild et al. 2018). Dysbiosis is often associated with reduced microbial diversity and immune-mediated inflammatory and autoimmune disorders (Wolter et al. 2021). Recently, advanced analytic methods such as next-generation sequencing (NGS) have significantly improved the accuracy of gut microbiome research by enabling precise evaluation of microbial components without the need for culture (Tang et al. 2020a, b). Several immune-mediated, metabolic, and neurological illnesses may be uncovered from a deeper knowledge of the gut microbiota, its metabolites, and its interaction with the host. Therefore, this review provides insights into feline gut microbiota composition, modulation, and analysis methods used for gut microbiota characterization.

Microbial composition in the healthy intestine

The various associations of bacteria, protozoa, viruses, fungi and archaea together with their genomes within and around the body constitute microbiomes (Barko et al. 2018). The diversity and variations in microbial growth rates (Kim et al. 2016), structural variations within genes (Huttenhower et al. 2012), and interindividual variability in host genetics and environmental exposures make the relative distributions of intestinal archaea and bacteria specific to each individual (Rothschild et al. 2018). However, a healthy gut microbial community is often characterized by a high diversity of taxa, high microbial gene richness, and stable, functional cores of the microbiome (Huttenhower et al. 2012).

Although dogs and cats have relatively simple gastrointestinal tracts compared with those of humans and most animal species, the feline and canine gastrointestinal tract microbial communities consist of hundreds of phylogenetic microbial species (Swanson et al. 2011) (Fig. 1).

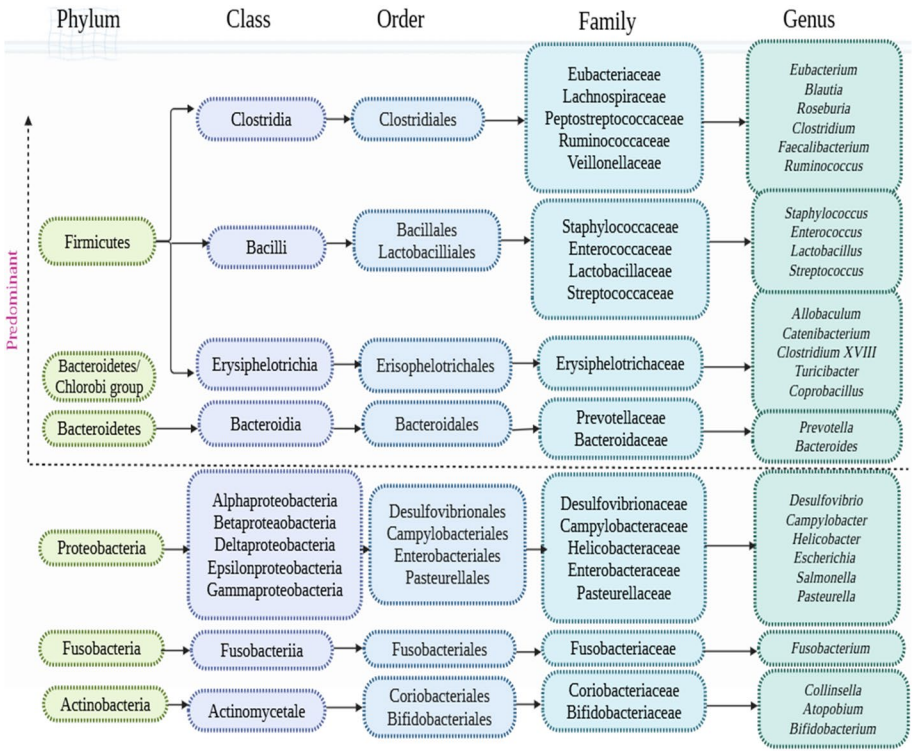

Fig. 1 Taxonomy and phylogeny of common feline gut microbiota (Minamoto et al. 2012a; Barko et al. 2018; Lyu et al. 2020). This figure provides a reference list of common intestinal microbes and their evolutionary relationships via DNA sequencing analysis and NCBI Taxonomy Browser data for taxonomic classification

The 16S rRNA analysis revealed that the feline GIT is primarily composed of five phyla: Firmicutes (68%), Proteobacteria (14%), Bacteroidetes (10%), Fusobacteria (5%), and Actinobacteria (4%) (Ritchie et al. 2008). However, the metagenomic approach revealed that Bacteroidetes/Chlorobi dominated the feline gut microbiota, accounting for 68% of the total diversity, followed by Proteobacteria and Firmicutes, with minor communities represented by viruses, Archaea, and fungi (Ascomycota) (Handl et al. 2011; Tun et al. 2012a). Nonetheless, compared with cats, dogs typically have a greater and more varied relative abundance of Proteobacteria (Barry et al. 2012).

Minamoto et al. (2012b) reported that the most common bacterial phyla in cat feces are Firmicutes, Betadactyloides, and Actinobacteria, whereas the most prevalent species are *Clostridium*, *Streptococcus*, *Bacteroides*, *Enterococcus*, *Eubacteria*, and *Fusobacteria*. *Clostridium* is the main abundant genus, and *Clostridiales* is the most abundant order among Firmicutes (Handl et al. 2011).

Microbial composition under disease conditions

Microbial changes in the guts of animals or differences in their function and structure have been linked to various diseases, ranging from intestinal inflammation to metabolic and respiratory diseases. There are numerous consequences of altering the intestinal microbiota environment, but two main ones are immunity, metabolic system imbalance, and disturbance of the intestinal barrier (Hrncir 2022).

Research on cats and dogs reveals that gut microbiome changes are not solely due to gastrointestinal diseases (Janeczko et al. 2008a, b; Blake et al. 2019) but are also associated with diseases of other organ systems (Table 1), including chronic kidney disease (CKD) (Summers et al. 2019), heart disease (Li et al., 2021a), diabetes mellitus (Kieler et al. 2019), obesity (Bermudez et al., 2020) and neurologic disorders (Jeffery et al. 2017). Cats with intestinal dysbiosis harbor enteric bacteria, streptococci, staphylococci, enterobacteria, Pseudomonas, and Citrobacter, in addition to fungi belonging to the genus Candida (Bugrov et al. 2022).

In helminth-infected felines, bacteria from the families Lactobacillales and Enterococcaceae, which are members of the phylum Firmicutes, are more prevalent. This study suggested that parasite-associated alterations in the composition of the gut flora may be associated with host malnutrition and immune modulation (Duarte et al. 2016). Research on bacteria that are differentially expressed at the genus level shows that certain pathogenic bacteria, such as *Clostridium* and *Staphylococcus*, are relatively common in the intestine of the host (Sieng et al. 2023). A study on stray cats revealed *Bacteroides* as the predominant bacterial genus, followed by *Prevotella* and *Collinsella*. However, the diversity and number of bacterial species decreased due to *Toxoplasma gondii* infection (Hong et al. 2023).

Studies suggest that the pathophysiology of inflammatory bowel disease in dogs, cats, and humans may involve the commensal gut microbiota (Suchodolski et al. 2009). Marsilio 2019 reported that overall bacterial diversity in feline inflammatory bowel disease (IBD) patients is lower than that in healthy cats (Marsilio et al. 2019). Feline feces analyzed by fluorescence in situ hybridization (FISH) revealed greater *Desulfovibrio* and lower *Bifidobacteria* and *Bacteroidetes* in colony cats with IBD than in healthy cats (Inness et al. 2007). Another FISH study revealed that cats with IBD had higher Enterobacteriaceae levels in their duodenal mucosa, indicating changes in mucosal architecture (Janeczko et al. 2008a, b). *Clostridium* and *E. coli* have been linked to intestinal

Table 1 Alterations in the feline gastrointestinal microbiome are linked with intestinal and extraintestinal diseases

Disease condition	Microbiota composition in number		References
	Decrease	Increase	
Chronic Enteropathies (CE)	*Bacteroides, Bifidobacterium, Chiranonis, Faecalibacterium, Turicibacter*	*Escherichia coli, Streptococcus*	Sung et al. 2022
Inflammatory bowel disease	*Bifidobacterium,* Bacteroides	*Enterobacteriaceae, Desulfovibrio*	Inness et al. 2007), (Janeczko et al. 2008a, b
Helminth infections	Firmicutes, Proteobacteria, Actinobacteria (*Collinsella*)	Bacteroides genera *Bulleidia, Jeotgalicoccus*	Duarte et al. 2016
Feline diabetes mellitus (FDM)	Bacteroidetes, Bacteroida, Bacteroidales, Prevotellaceae, *Prevotella, Anaerotruncus* (Firmicutes)	*Lachnospiraceae, Peptostreptococcaceae Incertae Sedis genus*	Kieler et al. 2019
Acute diarrhea	Firmicutes (*Solobacterium, Catenibacterium*), Actinobacteriota, *Collinsella*	Bacteroidota (*Prevotella, Muribaculaceae*)	Bai et al. 2023
Feline coronavirus	*Bacteroidia,* Proteobacteria	*Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria*	Meazzi et al. 2019

inflammation, suggesting that they may contribute to the pathophysiology of IBD in cats (Suchodolski 2022). A study revealed that, compared with cats with IBD, cats with small-cell intestinal lymphoma had more *Fusobacterium* adhering to the mucosa in the colon and ileum and increased expression of CD11b + myeloid cells and NF-κB (Garraway et al. 2018). This correlation suggests that bacteria may contribute to the development of small-cell GI lymphoma in cats, similar to human cases (Sun et al. 2019); however, further research and identification of specific *Fusobacterium* species are needed.

Cats with chronic diarrhea have different hindgut microbiota compositions, with the more prevalent bacterial phyla Bacteroidetes and Firmicutes (Ramadan et al. 2014). Recent research on cats infected with coronavirus has shown that Firmicutes and Bacteroidetes are present in relatively high proportions and relatively low proportions, respectively (Meazzi et al. 2019).

The proportions of Prevotella, Fusobacteria, Bacteroidales, Bacteroidetes, Bacteroida and Fusobacteriaceae are decreased in cats with diabetes mellitus (Kieler et al. 2019). Dogs with diabetes mellitus have been reported to have relatively high concentrations of *Phocaeicola plebeius, Clostridium difficile, Butyricicoccus pullicaecorum,* and *Lacrimispora indolis* (Kwong et al. 2023).

Microbial distribution across gastrointestinal segments

The microbiome in the mammalian gut comprises distinct microhabitats through the longitudinal axis of the intestinal lumen, including the colon, ileum, jejunum and cecum (Tropini et al. 2017) (Fig. 2). The gut segments display a compartmentalized microbiota distribution due to variations in intestinal physiology, including pH, oxygen concentration, intestinal motility, and antimicrobial compounds. Compared with the colon, which has slower flow rates and a gentler pH, the small intestine typically

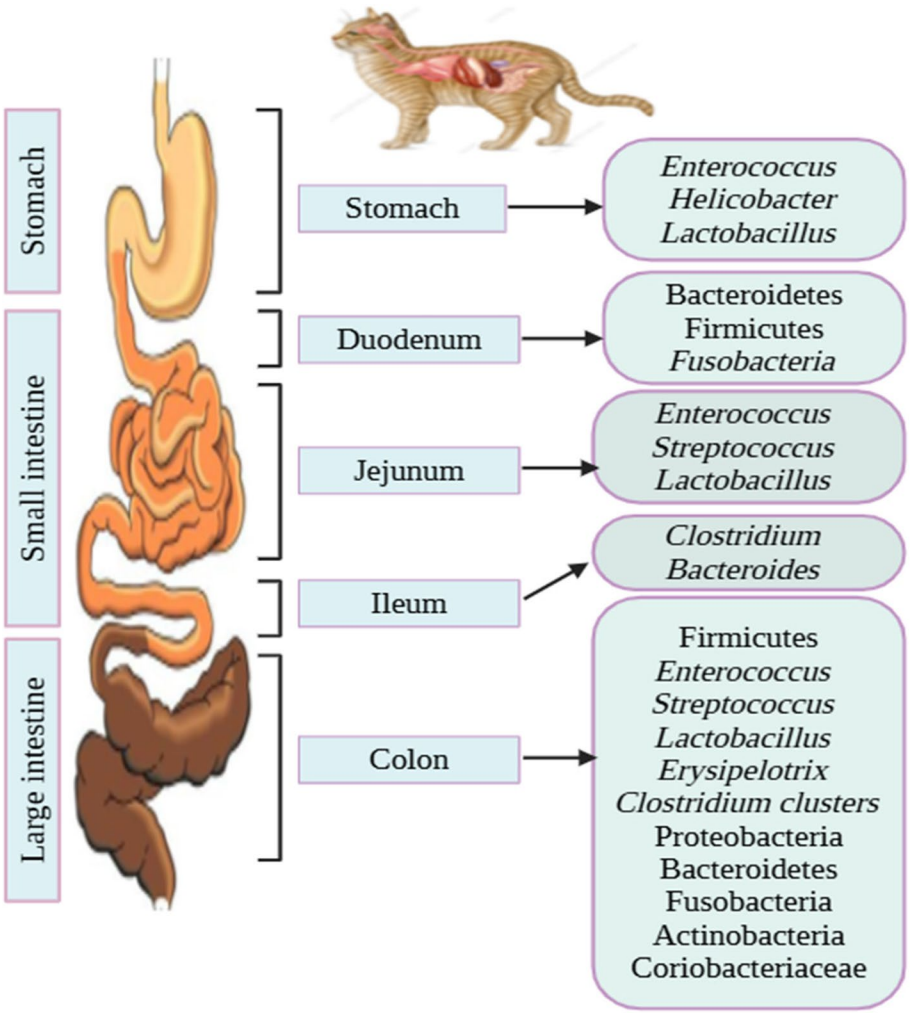

Fig. 2 Variations in bacterial colonization along the gastrointestinal tract in healthy cats (stomach, small intestine and large intestine)(Deng and Swanson 2015)

contains higher acidity levels, high concentrations of oxygen and antimicrobials, and a shorter transit time (Donaldson et al. 2015). These characteristics prevent bacteria from growing, so only facultative anaerobic bacteria that can grow rapidly and adhere to mucus or epithelia can persist (Donaldson et al. 2015). Aerobic bacterial groups are evenly distributed throughout the proximal intestine, whereas anaerobic bacterial groups are located primarily in the distal parts of the gut (Minamoto et al. 2012a). As a result, the small intestine has less bacterial diversity than the colon does and has a high concentration of *Clostridium* species and Proteobacteria (Zoetendal et al. 2012). Eckburg 2005 reported that Bacteroidetes are more prevalent in fecal and luminal samples than in mucosa samples (Eckburg et al. 2005). These findings underscore the necessity of exercising attention when selecting sampling techniques for analysis.

The normal makeup and organization of the microbiota lengthwise in a segment may represent how the gastrointestinal system functions and can be used to assess a patient's health or establish a diagnosis (Kundu et al. 2017). The gastrointestinal tract produces and consumes various metabolites, indicating variations in taxonomic abundance. These metabolites can be used as metabolomics data inputs to analyze metabolite metabolic exchange between the microbiome and host (Pilla and Suchodolski 2020).

Research has indicated that the composition of the gut microbiota varies spatially according to location (Ma et al. 2022a, b). The concentration and percentage of exclusively anaerobic bacteria increased from the duodenum to the colon, reaching a peak of 10^{11} CFU/g of feces. The small intestine of healthy cats has diverse bacteria counts ranging from less than 10^2 to more than 10^8 CFU/mL, often exceeding the upper limit of the normal level, which is reported to be 10^5 CFU/mL (Johnston 1999). The feline gut microbiota grows along the gut, from the stomach to the colon, similar to humans and other species (Handl et al. 2011; Deng and Swanson 2015) (Fig. 2). For example, *Lactobacillales* are found throughout the intestine of cats, particularly in the colon and jejunum (Ritchie et al. 2008). Firmicutes and Bacteroides dominate the microbiome of the feline small intestine, whereas Proteobacteria and Actinobacteria dominate the ileum, and Fusobacteria, Proteobacteria, and Firmicutes are more prevalent in the colon (Ritchie et al. 2008; Suchodolski 2011).

Identification/analysis of the gut microbiota

Trillions of bacteria reside in the stomachs of both humans and animals and perform physiological tasks. Several variables, including genetic and environmental variables, may impact the composition of these bacteria. Thus, the first stage in appreciating the microbiome's function in healthy and disease states should involve identifying these microbial communities (Shahi et al. 2019). More recently, researchers have discovered the importance of diagnostic procedures and microbial analysis techniques in this field (Yu et al. 2021; Bugrov et al. 2022; Suchodolski 2022; Bai et al. 2023; Ko et al. 2023; Wang et al. 2023; Wiredu et al. 2023). The most popular technique in microbiome-based research is the identification of certain taxa, usually at the species or strain level (Damhorst et al. 2021). Although many methods exist to identify the microbiome, they do not have a standard. Therefore, it is useful to define the microbiome metrics that can be used in research and clinical diagnosis.

Several methods are available for studying microbial communities, including bacterial culture, next-generation sequencing (DNA shotgun sequencing/metagenomics, 16S rRNA gene sequencing), and quantitative PCR (q-PCR) metatranscriptome sequencing (Fig. 3), all of which have the potential to produce transformative results (Sarangi et al. 2019). Every widely used method has advantages and disadvantages; thus, when selecting a method, the questions, presumptions, sample types, budgets, specificities and sensitivities for the examined bacterial groups and the study goals should all be considered (Knight et al. 2018). Researchers have investigated the bacterial community in healthy cats and dogs via bacterial culture or next-generation approaches (Honneffer et al. 2014). The mechanism of this research context has completely changed due to the current development of high-throughput methods for sequencing DNA and innovative bioinformatic advances that characterize bacteria and genes inside and on the body's surface (Deng and Swanson 2015). While microbiome data analysis approaches have broad applicability to various sample types and habitats, sample type specificity necessitates careful consideration of experimental design and method selection. Since the growth of some microorganisms during room temperature storage may alter the sample composition, the collection, preservation, and storage techniques used in a study must always be the same for all samples to prevent confounding variations (Knight et al. 2018).

Culture-based methods

Cultivating bacteria for experimental testing and using bacterial sequence references for metagenome dataset interpretation and functional analysis are crucial steps toward understanding the role and diversity of the gut microbiome (Forster et al. 2019). The bacterial species most frequently isolated from the feline gastrointestinal tract are *Clostridium*, *Bacteroides, Streptococcus*, *Enterococcus, Fusobacteria* and *Eubacteria* (Johnston 1999;

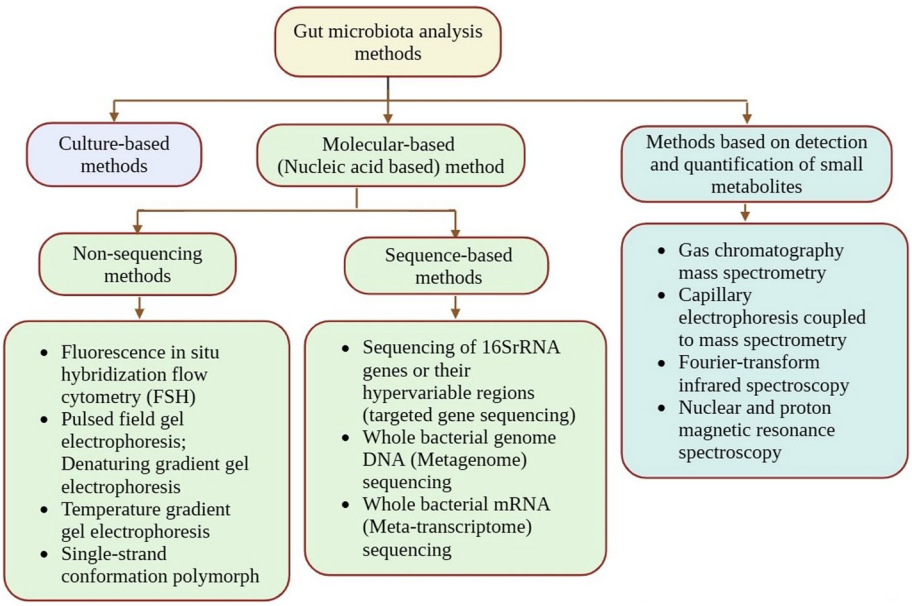

Fig. 3 Various analytical methods used to characterize the gut microbiota (Sarangi et al. 2019). These techniques identify the microbial composition in the feline intestinal tract, revealing previously unidentified bacterial phylotypes

Johnston et al. 2000). A culture-based study revealed that cats have more total bacteria [10105–108] 10^5-10^8 CFU/mL) in their small intestines, including obligate anaerobic bacteria, than dogs and humans do (Johnston et al. 2001). Clinical microbiology has employed culture-based techniques for nearly a century (Suchodolski 2022). These methods are widely available in the clinical setting but are semiquantitative and labor intensive because of their large-scale use in microbiome characterization. Furthermore, although the results of hypothesis-based diagnosis of particular taxa or antibiotic resistance can be interpreted semiquantitatively, broad measurements of richness and abundance are not appropriate because of the difficulty of cultivating obligate anaerobic species and low-abundance bacteria (Damhorst et al. 2021).

However, a bacterial culture is needed to assess the antibiotic susceptibility of cultivable organisms (Salmonella) linked to bowel illnesses, enabling validation and experimental testing on various bacteria and enhancing our understanding of microbial communities (Suchodolski 2022). This has enabled validation and experimental testing on various bacteria, enhancing our knowledge of significant microbial communities. However, modern molecular tools have largely supplanted conventional bacterial culture methods in characterizing the intestinal microbiota, and multiple species of bacteria have been identified through 16S ribosomal RNA gene sequence analysis (Sarangi et al. 2019).

Molecular-based (nucleic acid-based) methods

Until recently, classical bacterial culture was the most widely utilized technique for characterizing the bacterial groups found in cats' gastrointestinal tracts. However, cultivation-based methods underestimate the GI tract bacterial count and fail to identify most bacterial families because most intestinal bacteria are nonculturable (Minamoto et al. 2012b). Recent molecular technologies have significantly improved the understanding of the gut microbiota, becoming the gold standard for microbial ecology research and replacing traditional bacterial culture methods (Suchodolski et al. 2008). Figure 3 summarizes recent molecular techniques, including shotgun sequencing, PCR/DGGE, qPCR, and fluorescence in situ hybridization (Paul and Stayt 2019). These methods can also characterize the functional potential of the microbiome when combined with metagenomics tools (Tun et al. 2012a).

Nonsequencing methods

Fluorescence in situ hybridization

Fecal microbiota analysis in clinical settings requires more information on the makeup, number, and potential presence of enteroinvasive or mucous membrane-adhering bacteria of the small intestinal microbiota. Mucosa-adherent bacteria differ from luminal populations, and fluorescence in situ hybridization (FISH) may address specific issues (Garraway et al. 2018). FISH, a technique using fluorescently labeled oligonucleotide probes

targeting 16S rRNA, is widely recognized for accurately quantifying bacterial groups and identifying their shape and spatial distribution (Minamoto et al. 2012a). A study using FISH and over 1000 microscopic fields in canine duodenal biopsies reported a median of zero bacteria per field (Garcia-Mazcorro et al. 2012). FISH revealed *Helicobacter* bacteria in the deep colonic crypts of healthy dogs, whereas dogs with chronic inflammatory enteropathy presented increased mucosa-adherent bacteria levels (Giaretta et al. 2020). A study using FISH on intestinal tissue revealed that cats with IBD had relatively high levels of Enterobacteriaceae adhering to the duodenal mucosa, which was linked to alterations in the mucosal structure (Janeczko et al. 2008a, b).

Nonetheless, investigations employing FISH yield important data regarding the abundance of total and particular bacterial groups in the feline gut. These investigations revealed that lactic acid bacteria, which include Bifidobacteria, the Atopobium group (probe Ato291), which includes Coriobacteriaceae, and the Clostridium cluster XIVa, are the most prevalent groups in the intestines of kittens and elderly cats (Abecia et al. 2010; Jia et al. 2011). FISH-based research has shown that healthy cats have increased total bacteria, *Bacteroides* and *Bifidobacterium*, whereas cats with IBD have increased *Desulfovibrio*, which are toxic sulfide producers, and decreased Bacteroides and Bifidobacteria (Inness et al. 2007).

FISH allows visualization of bacterial locations but is labor intensive owing to the limited number of probes per tissue slide, and unique probes must be created for the microorganisms of interest. Healthy cat duodenums contain only 6% bacteria hybridizing to EUB-338 probes against *Bacteroides*, *Clostridium*, *Streptococcus*, *E. coli*, and *Enterobacteria* (Janeczko et al. 2008a, b). Furthermore, costly microscopy equipment is needed, which restricts FISH to a few specialized laboratories (Suchodolski 2022).

Quantitative PCR

Quantitative PCR (qPCR), also called real-time PCR, is a valuable technique for quantifying specific taxa or the total amount of bacteria present. qPCR is a quick, affordable, and highly repeatable method for quantifying particular clinically significant products taxa (Kurina et al. 2020). It is used in many clinical settings and has become a reliable technique for quantifying the amount of DNA present and amplifying it (Fraher et al. 2012). qPCR has been widely employed to evaluate the impact of various therapies on the quantity of the gut microbiota in cats, dogs, and humans (Garcia-Mazcorro et al. 2011; Larsen et al. 2011). The fecal abundance of total bacteria was assessed via qPCR, and it was discovered that cats with chronic enteritis presented significantly higher levels of *E. coli* and *Streptococcus* than significantly lower levels of *Bacteroides*, *Bifidobacterium*, *Faecalibacterium*, *Clostridium hiranonis*, and *Turicibacter* (Sung et al. 2022). According to a recent qPCR-based feline dysbiosis index study, the fecal bile acid profile was strongly correlated with the abundance of *C. hiranonis*, indicating that the latter plays a role as a bile acid converter in cats. The study also revealed that, in healthy adult cats, the feline dysbiosis index exhibited temporal stability in the absence of disturbances (Sung et al. 2024).

The number of bacterial cells cannot be directly determined from the qPCR data in one section because of variations in the cell genome content and 16S rRNA gene copies (Garcia-Mazcorro and Minamoto 2013). qPCR can enhance the understanding of gut microbiota diversity and abundance when used alongside semiquantitative methods such as microarrays or denaturing gradient gel electrophoresis (DGGE), which are not suitable for the numerical assessment of gut microbiota components (Ponnusamy et al. 2011). Jian 2020) suggested that combining qPCR-based quantitative microbiome profiling with standard NGS-based microbiome analysis may yield better results (Jian et al. 2020).

Sequence-based methods

Thus far, the analysis of underexamined bacterial groups has been achieved through sequencing techniques such as 16S rRNA gene clone libraries or contemporary high-throughput techniques such as Illumina sequencing or 454-pyrosequencing (Lyu et al. 2020). Conventional Sanger sequencing identified five distinct bacterial phyla in the stomach and intestines of healthy cats: Firmicutes (68%), Proteobacteria (14%), Bacteroidetes (10%), Fusobacteria (5%), and Actinobacteria (4%) (Minamoto et al. 2012a). High-throughput sequencing methods such as Illumina sequencing or 454-pyrosequencing can efficiently sequence many base pairs, enabling precise amplicon quantification and in-depth microbiome studies. Using these methods, the most frequent phyla of bacteria found in cat fecal samples were Firmicutes (92%) and Actinobacteria (7.3%) (Handl et al. 2011). A 454-pyrosequencing study revealed that the Bacteroidetes/Chlorobi group (68%), Firmicutes (13%), Proteobacteria (6%), Actinobacteria (1.2%), and Fusobacteria (0.7%) were the most common phyla in the cat fecal microbiota (Tun et al. 2012a).

A study using 454 pyrosequencing of the 18S rRNA gene revealed four fungal phyla in cat feces, with Ascomycota (> 90%) and Neocallimastigomycota (> 5%) being the most prevalent phyla. Ascomycota was the sole and most prevalent phylum of fungi, dominated by the genera *Saccharomyces* and *Aspergillus*, accounting for 58.31% and 11%, respectively, of the total (Suchodolski 2011).

Shotgun sequencing of viral dsDNA identified Caudovirales as the only order of bacteriophages (Barry 2010). Sabatino 2019, with viruses comprising 0.07% of all sequences, primarily belonging to this unclassified order (Sabatino 2019). This study provided an explanation for 18 families and 42 genera, including the first report of Archaea. This domain comprises twelve classes and five phyla, Euryarchaeota, Korarchaeota, Crenarchaeota, Thaumarchaeota, and Nanoarchaeota, accounting for 0.77% of the sequences.

Next-generation sequencing (NGS) methods include 16S rRNA gene sequencing, DNA shotgun sequencing, and metatranscriptomics (Suchodolski 2022), with most studies assessing the gut microbiota of cats via 16S rRNA gene sequencing (Ma et al. 2022a, b). Figure 4 presents a comprehensive analysis of various microorganisms, including fungi, protozoa, viruses, and archaea, via molecular tools.

Bacterial 16S ribosomal RNA

Nucleotide sequence-based bacterial detection methods do not require bacterial culture and, therefore, can detect both culturable and poorly growing bacteria. Furthermore, regardless of the ability and rate of growth of the individual bacterial groups in culture, the findings of these approaches applied to bacterial mixtures provide an unbiased estimate of the number of various bacterial groups (Sarangi et al. 2019). Therefore, the 16S rRNA gene, owing to its global distribution and gradual changes in base pair composition over evolution, is frequently utilized for bacterial identification. This gene contains a region containing phylogenetic information at the group and species levels and a highly conserved nucleotide base sequence exclusive to bacteria (Tannock 2005). According to Sun2021, most research evaluating variation by biospecimen type has focused on taxonomic makeup, as determined by 16S rRNA gene amplicon sequencing (Sun et al. 2021).

16S rRNA gene sequencing is the gold standard for microbial research, providing detailed information on bacterial groups and communities in animal species and their response to therapeutic interventions. 16S rRNA gene sequencing is suitable for identifying general variations in microbiome composition but is not trustworthy for detecting the particular bacterial species causing these changes (Suchodolski 2022). This method identified the main bacterial groups in healthy dog and cat feces, with investigations suggesting that the phylum Firmicutes contains numerous genomic sequences (Handl et al. 2011). Researchers have utilized 16S rRNA gene amplicon sequencing to investigate the microbiome's effect on *Toxoplasma gondii* in cats (Hong et al. 2023).

16S-based studies on cat feces have shown that the GI tract is dominated by the bacterial phylum Firmicutes, most of which are gram-positive bacteria. The two most common orders are Clostridiales, which is dominated by Lactobacillales, and the Clostridium cluster XIVA, which comprises the Lactobacillaceae, Enterococcaceae

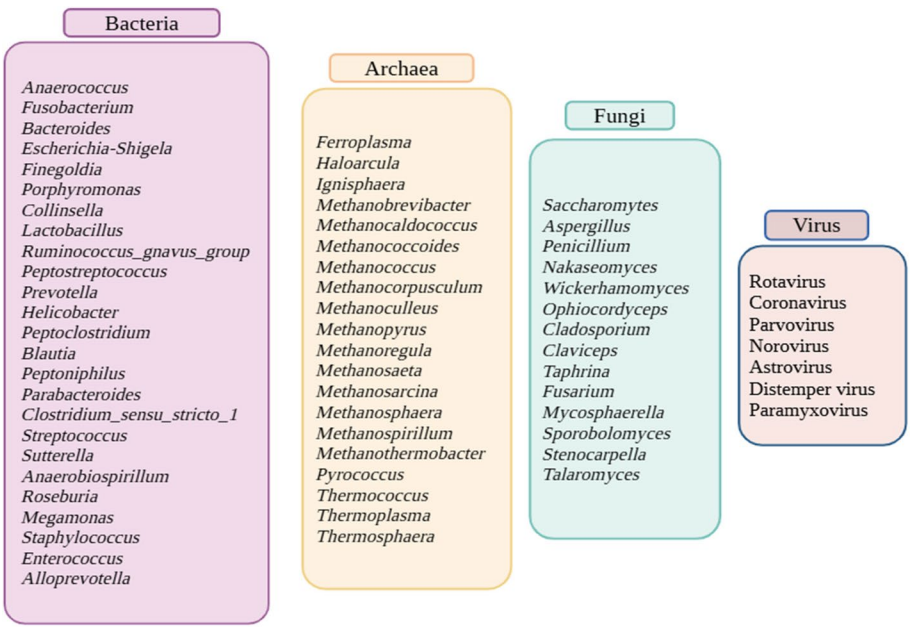

Fig. 4 Predominant bacterial archaeal, fungal and viral genera were identified in the feces of cats through 16S rRNA gene sequencing or metagenomic approaches (Suchodolski 2011)

and Streptococcaceae families (Minamoto et al. 2012a; Ritchie et al. 2010). Studies using cultures have shown that *Clostridium* sp. accounts for more than 90% of duodenal aspirates from cats, which is consistent with these findings (Johnston 1999; Johnston et al. 2001). Thus far, 16S-based research has indicated that individual microbiota are generally more similar than the same intestinal area is among many cats (Ritchie et al. 2008).

16S rRNA gene sequencing methods often lack the ability to identify all bacteria due to varied gut microbiota, particularly species and strains, causing biases in the interpretation and comparability of studies (Johnson et al. 2019). There is no optimal method for microbiome 16S rRNA gene sequencing; consistent methodologies and techniques such as metabolomics, quantitative qPCR, and NGS can be used for fundamental scientific inquiries. For example, more repeatable techniques, such as qPCR, can be used to validate the discovered taxa of interest (Suchodolski 2022).

Metagenomics-based metabolic profiles

Metagenomics is a technique of sequencing whole microbial genomes from a sample, enabling taxonomic resolution and computing of all microbial genomes from short DNA sequence reads with full sequencing depth (sequencing reads per sample) (Scholz et al. 2016; Mukherjee et al. 2017). Although the preparation, sequencing and analysis of materials for metagenomic sequencing are expensive, they provide more precise taxonomic resolution and genomic information than does marker gene sequencing alone (Knight et al. 2018). Metagenomics has been employed extensively to identify microbes linked to an illness or a physiological state. In the same way, metagenomic data can be combined with metaproteomic, metabolomic, and culture data to explain the role of gut bacterial communities (Lagier et al. 2018).

Swanson 2011 conducted the first study assessing the metabolic potential of the gut microbiota and the impact of dietary fiber on dogs by pyrosequencing and metagenomics (Swanson et al. 2011). This metagenomics data collection included the phylogeny and functional capacity of the canine gastrointestinal microbiome, revealing that the predominant bacterial phyla (Bacteroidetes; Firmicutes) are comparable to those in rodent and human models. While making up a small percentage of all sequences, viral, fungal, and archaeal sequences were present in comparable quantities to those observed in other mammalian biomes (Swanson et al. 2011). A study involving 152,494 sequences was conducted on fecal samples from five healthy domestic cats. The study revealed that the Bacteroides/Chlorobi group (68%) was the most prevalent phylum, followed by Firmicutes (13%), Proteobacteria (6%), Actinobacteria (1.2%), and Fusobacteria (0.7%). The most common bacterial order in the phylum Bacteroides/Chlorobi was Bacteroidetes, and the most common bacterial class in Firmicutes was Clostridia (65%), followed by Bacilli and Mollicutes (Tun et al. 2012b). A study examined 4,192,192 sequences from 12 fecal samples from four healthy research colony cats fed three diets (Barry 2010). The MG-RAST metagenomics platform revealed that Firmicutes (36.3%) and the Bacteroidetes/Chlorobi group (36.1%) were the leading phyla, followed by Proteobacteria (12.4%) and Actinobacteria (7.7%). Whole-genome shotgun (WGS) metagenomic sequencing revealed *Prevotella* to be the most abundant genus. It increased the number of Bacteroides in obese cats, significantly altering the *Lactimicrobium* and *Phascolarctobacterium* genera in the gut microbiome (Ma et al. 2022a, b).

Metabolomic analysis

Metabolomics studies small nonprotein molecules, such as metabolic products, constituting an interesting developing field directly linked with community function (Allaband et al. 2019). Metabolomics research has revealed that interactions between the host and the gut microbiota and between small molecule metabolites influence the host metabolome and biochemical functions (Chow et al. 2014).

Metabolomic techniques can identify clinical and physiological biomarkers that specific methods cannot obtain (Weckwerth and Morgenthal 2005). Three effective techniques for investigating interactions between the intestinal microbiota and host are liquid chromatography–mass spectrometry (LC–MS), gas capillary electrophoresis–mass spectrometry (CE–MS), and chromatography–mass spectrometry (GC–MS) (Chen et al. 2019). GC–MS was used to analyze the fecal metabolome qualitatively and quantitatively to identify potential biomarkers for human gastrointestinal disorders (Garner et al. 2007). LC–MS-based metabolomics analysis of patients with retinopathy linked to type 2 diabetes mellitus revealed a reduced abundance of *Pantoea*, *Bacillus*, and *Veillonella* and a high abundance of *Olsenella*, *Prevotella*, *Subdoligranulum*, *Agathobacteria* and *Faecalibacterium*. Furthermore, when diabetic patients were compared with healthy controls, there was a genus-level depletion of *Lachnospira* and *Faecalibacterium* and an enrichment of *Enterococcus* and *Klebsiella* (Zhou et al. 2021). CE-MS techniques successfully identified 352 typical molecules from established metabolic pathways and analyzed 1,692 compounds from *B. subtilis* extracts, revealing the relationship between metabolite changes and sporulation (Soga et al. 2003).

Metabolomics in gut microbiota–host health studies faces challenges because individual lifestyles affect the

composition of the microbiota and its metabolic products, which can originate from the microbiota and host. Identifying functional microbial metabolites that can alter the host phenotype is also challenging owing to the difficulty in connecting the unique characteristics of metabolites to their respective microorganisms. Therefore, to assess the effects of microbial metabolites on the host's phenotype, the use of synthesized pure molecules or supplementation with metabolite precursors is recommended (Yu et al. 2021).

In recent years, matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) has emerged as a widely used tool for single microbial identification because of its specificity, sensitivity, speed, and affordability (Singhal et al. 2015). It generates mass spectra of ribosomal proteins and peptides, providing species-specific fingerprints for precisely identifying purified strains at both the genus and species levels (Prod'hom et al., 2010).

The gram-negative bacteria *Yersinia* (Stephan et al. 2011) and *Vibrio* (Singhal et al. 2015) were identified via MALDI-TOF MS via direct cell profiling, whereas the gram-positive bacteria *Staphylococcus* were identified *via* preparatory extraction of microbes with formic acid (Dubois et al. 2010). The MALDI-TOF MS process identifies microbes *via* intact cells or cell extracts, but identifying and classifying specific microbiota remains challenging (Chen et al. 2023).

Modification of the intestinal microbiota

Nutrition/diet

Dietary fibers (DFs), prebiotics, and probiotics are among the several nutritional compounds associated with effects on the immune system and host microbiota (Wiertsema et al. 2021). Prebiotics and DFs serve as fermentation substrates, promoting the growth of beneficial bacteria in the intestine while preventing the growth of pathogens through appropriate exclusion. The primary byproducts of fermentation are short-chain fatty acids (SCFAs), which prevent the spread of infectious diseases by blocking histone deacetylases and stimulating G protein-coupled receptors, thereby promoting anticancer, antibacterial, and anti-inflammatory effects (Li et al. 2018). As strict carnivores, cats consume significantly more protein than other mammals do despite being less susceptible to the cancer-causing effects of protein fermentation (Rissetto et al. 2011). Research suggests that severe clinical outcomes in COVID-19 patients may be attributed to decreased SCFA-producing bacteria in their gut microbiota (Tang et al. 2020a, b; Hirayama et al. 2021). In addition to SCFAs, dietary fiber and prebiotics can also directly prevent gastrointestinal infections through their elimination and antimicrobial activities (Asadpoor et al. 2020). It has been demonstrated that DFs such as Arabinoxylans and beta-glucans activate CLR dectin-1, a crucial receptor in trained immunity development, enhancing the immune response against secondary infections (Divangahi et al. 2021).

Additionally, Arabinoxylans, human milk oligosaccharides, and pectins interact with Toll-like receptors (TLRs) to promote inflammation resolution, increase dendritic cell efficacy, induce tolerogenic DCs, and shield the gastrointestinal tract from excessive TLR signaling (Wang et al. 2019; Wiertsema et al. 2021). Fermentation of prebiotic carbohydrates such as inulin and fructo-oligosaccharides promotes the growth of important microbes in the gastrointestinal system, primarily *Lactobacillus* and *Bifidobacterium* species (Hemarajata and Versalovic 2013). Dogs fed a weight loss diet presented a significant increase in the prevalence of the SCFA producers Faecalibacterium, Prevotella, and Bacteroides, with Faecalibacterium being more prevalent in low-fat diets (Pilla and Suchodolski 2021). Prebiotic fiber also increases Bifidobacterium (Young et al. 2016) and SCFA-producing bacterial species in dogs (Rochus et al. 2014). Prebiotic supplements in cats show potential benefits, including increased concentrations of fecal butyrate and Bifidobacteria, reduced *E. coli*, and increased *Lactobacillus* and fecal SCFA levels (Barry et al. 2010).

High-fiber diets alleviate COVID-19 gastrointestinal symptoms by increasing the number of SCFA-producing bacteria in the gut, including *Bifidobacterium*, *Lactobacillus*, *Sellimonas*, *Oscillibacter*, *Faecalitalea, Blautia*, *Eubacterium* and *Anaerofustis* (Wang et al. 2022). In contrast, dietary components such as vegetables, fruits, dairy products, medicinal herbs, spices, prebiotics (dietary fiber and alpha-lactalbumin), probiotics (*Bifidobacterium* and *Lactobacillus*), postbiotics, and synbiotics may exert a protective effect on mental illnesses by promoting beneficial effects on the gut microbiota and preventing detrimental bacteria (Xiong et al. 2023). Furthermore, vitamin D supplementation ameliorates clinical symptoms by lowering inflammatory cytokine levels (Ohaegbulam et al. 2020). Research has revealed promising anti-inflammatory benefits in animal models of colitis, with potential future applications in dogs and cats (Cervenka et al. 2017). Dietary exposure significantly alters fecal bacterial populations, potentially affecting the functional capacity and host–microbiota interactions of the microbiota and affecting a cat's ability to process macronutrients. Furthermore, a metagenomic study suggested that diet-based microbiome manipulation could improve companion animal nutrition; however, additional investigations are needed to understand the health implications of these modifications and novel dietary formulations (Lyu et al. 2020).

Probiotics

Antibiotics, which are prescribed for gastrointestinal conditions such as bacterial infections, chronic enteropathy, gastroenteritis, and acute diarrhea, can cause unintended modifications in the gut flora (Igarashi et al. 2014), potentially leading to long-lasting detrimental effects on the host (Becattini et al. 2016). Recent research suggests that probiotic supplements can moderate antibiotic-induced damage to the gut microbiota (Neveling and Dicks 2021), increasing their use in human and veterinary medicine for treating and preventing gastrointestinal and extragastrointestinal diseases (Rijkers et al. 2010; Roberfroid et al. 2010).

Probiotics are live microorganisms that, when properly administered, can provide health benefits to the host (Ahn et al. 2022); typically, they belong to the *Bifidobacterium*, *Saccharomyces* and *Lactobacillus* genera. Conversely, "prebiotics are components of selective fermented elements that change the activity and composition of the gastrointestinal microbiota" (Valcheva and Dieleman 2016). Probiotics, primarily *Lactobacillus*, *Bifidobacterium* and *Enterococcus*, have been studied for improving pet health, with *Bifidobacterium* and other lactic acid-producing bacteria found in cat feces being potential sources for selection (Jugan et al. 2017; Sanders et al. 2019). A study revealed that various bacterial strains from healthy cats, including *L. plantarum*, *L. rhamnosus*, *L. acidophilus*, *B. adolescentis* (Rudenko et al. 2021), *L. reuteri*, *L. fermentum*, *E. faecium* and *Pediococcus pentosaceus* (Kim et al. 2021) *Bacteroides* sp. CACC 737 (Kim et al. 2020), have potential probiotic properties.

Probiotics, prebiotics, or their combination (symbiosis) can alter the gut microbiota and impact the host immune response (Valdes et al. 2018). Probiotics work by producing antimicrobial peptides, enhancing the growth of beneficial microorganisms that suppress harmful bacterial growth (Hemarajata and Versalovic 2013), producing metabolites that change the gut microbiota composition, regulating the immune response, and protecting intestinal barrier integrity (Valdes et al. 2018; Schmitz and Suchodolski 2016), competing for epithelial invasion sites and promoting immunomodulation functions (Collado et al. 2007). The colonization of *Salmonella Enteritidis* and *Campylobacter jejuni* is reduced by a combination of *Enterococcus faecium*, *Bacillus animalis, Pediococcus acidilactici, Lactobacillus reuteri,* and *Lactobacillus salivarius*, decreasing the colonization of *Salmonella Enteritidis* and *Campylobacter jejuni* (Ghareeb et al. 2012). Probiotics have been found to improve the intestinal health of cats suffering from diarrhea (Lee et al. 2022), chronic constipation, and idiopathic megacolon (Rossi et al. 2020).

However, there is a hesitation to prescribe probiotics because concerns that probiotics might eventually change the composition of the gut microbiota. Additionally, research investigating the effects of simultaneous probiotic delivery on antibiotic-induced gut microbiota modifications has yielded conflicting findings (Fernández-Alonso et al. 2022).

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a procedure in which a patient with a disease receives an infusion of feces from a healthy donor (Garcia-Mazcorro et al. 2016). FMTs can improve the fecal microbiome composition by increasing beneficial microbe numbers and metabolites, increasing diversity, promoting synergistic interactions, or outcompeting pathogens (Zheng et al. 2022; Tuniyazi et al. 2022). Fecal suspension therapy (FMT) was initially demonstrated to be clinically successful in treating refractory *C. difficile* infection in humans by introducing healthy donor feces to restore the gut microbiome of diseased individuals (Nood et al. 2013). FMT is a potentially effective microbiota-modifying treatment for illnesses linked to HCV. Patients with HC-derived cirrhosis infection treated with broad-spectrum antibiotics for five days have shown that administering a fecal suspension containing Ruminococcaceae and Lachnospiraceae reduces severe side effects and restores bacterial diversity and function in the gut (Wang et al. 2020). Because FMT can restore the prevalence of specific bacteria in the intestine, it is a viable novel therapy for disorders related to HBV (Yang et al. 2021). FMT may be a prospective therapy for restoring the homeostasis of T-cell subsets in HIV patients, as evidenced by a pilot study showing that this treatment was associated with high peripheral Th17 and Th22 cell levels and promoted by intestinal T-cell activation without hostile effects (Hensley-McBain et al. 2016).

Since the eighteenth century, they have been utilized in veterinary practice to treat animals such as horses, cattle, and sheep suffering from inappetence, rumen dysfunction, indigestion, and colitis (DePeters and George 2014; Mandal et al. 2017). Recent studies have used FMTs to treat relapsing chronic diarrhea, acute diarrhea, chronic enteropathies, and canine parvovirus in dogs (Sugita et al. 2021; Chaitman et al. 2020). FMT effectively treats chronic ulcerative colitis in domestic cats (*Felis catus*) (Furmanski and Mor 2017). A study on cats revealed that the fecal microbiomes of FMT recipients varied with host clinical signs and dry kibble consumption, with changes in *Clostridium*, *Collinsella*, *Megamonas*, *Desulfovibrio*, and *Escherichia* abundances noted following FMT. These findings indicate that the microbiome response to FMT may be influenced by the recipient's initial clinical signs, diet, and donor's microbiome (Rojas et al. 2023).

Although FMT is important for gut microbiota modification, it may not cause long-lasting microbiome remodeling, indicating that further strategies may be needed to sustain gut microbiota remodeling and facilitate the colonization of exotic bacteria (Yang et al. 2021).

Conclusions

A wide variety of microorganisms, including bacteria, fungi, archaea, viruses and protozoa, inhabit the gastrointestinal tract of cats. These microbial communities can be altered in gastrointestinal disorders and may also contribute to extraintestinal disorders. Dietary supplements, probiotics, and fecal microbiota transplantation could modulate gut microbiota dysbiosis. Recent molecular techniques have been used to analyze the gut microbiota, aiding in understanding the pathophysiology of diverse animal gut-associated diseases and contributing to improving general health. Nonetheless, the role of the feline gut microbiota in disease prevention and therapy still needs to be explored, necessitating future studies to explore the relevance of the gut microbial community to health and disease conditions.

Abbreviations

CFU	Colony-forming units
DFs	Dietary Fibers
FCoV	Feline coronavirus
FMT	Fecal Microbiota Transplantation
SCFA	Short-Chain Fatty Acids
TLRs	Toll-Like Receptors
16S rRNA	16S ribosomal Ribonucleic Acid

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