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REVIEW

Disease-associated dysbiosis and potential therapeutic role of *Akkermansia muciniphila*, a mucus degrading bacteria of gut microbiome

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Abstract
The unique functionality of *Akkermansia muciniphila* in gut microbiota indicates it to be an indispensable microbe for human welfare. The importance of *A. muciniphila* lies in its potential to convert mucin into beneficial by-products, regulate intestinal homeostasis and maintain gut barrier integrity. It is also known to competitively inhibit other mucin-degrading bacteria and improve metabolic functions and immunity responses in the host. It finds a pivotal perspective in various diseases and their treatment. It has future as a promising probiotic, disease biomarker and therapeutic agent for chronic diseases. Disease-associated dysbiosis of *A. muciniphila* in the gut microbiome makes it a potential candidate as a biomarker for some diseases and can provide future theranostics by suggesting ways of diagnosis for the patients and best treatment method based on the screening results. Manipulation of *A. muciniphila* in gut microbiome may help in developing a novel personalized therapeutic action and can be a suitable next generation medicine. However, the actual pathway governing *A. muciniphila* interaction with hosts remains to be investigated. Also, due to the limited availability of products containing *A. muciniphila*, it is not exploited to its full potential. The present review aims at highlighting the potential of *A. muciniphila* in mucin degradation, contribution towards the gut health and host immunity and management of metabolic diseases such as obesity and type 2 diabetes, and respiratory diseases such as cystic fibrosis and COVID-19.

Keywords *Akkermansia muciniphila* · Biomarker · COVID-19 · Gut microbiome · Host immunity · Mucus degradation · Obesity · Probiotic · Therapeutic · Type 2 diabetes

Introduction

Akkermansia muciniphila (*A. muciniphila*) is a recently discovered member of commensal gut microbiota and constitutes a new genus of the phylum *Verrucomicrobia* (Derrien et al. 2004). It is oval, strictly anaerobic, non-motile and Gram-negative bacteria that do not form endospores. It has circular genome of 2,664,102 base pairs, sharing 29% gene similarity with phylum *Verrucomicrobia* (van Passel et al. 2011). As unveiled by whole-genome sequencing, its proteome consists of 5644 unique proteins (Guo et al. 2017). *A. muciniphila* colonizes the gastrointestinal tracts at an early stage through human milk and accounts for 1–4% of total gut microbiota (Collado et al. 2008). The abundance of *A. muciniphila* in caecum is ubiquitous in infants and healthy adults. Besides the large intestine, it is also found in the lining of the lungs and saliva.

The importance of *A. muciniphila* lies in its potential to degrade mucin, the significant component in mucus. It consumes mucin as a carbon and nitrogen source during its life cycle and metabolism. The optimum temperature and pH for its growth are 37 °C and 6.5 respectively. A recent study showed that despite being a strict anaerobe, it could sustain lower amounts of oxygen (Ouwerkerk et al. 2016). This property is quite similar to other microbes in the intestine, especially anaerobes, such as *Bifidobacterium adolescentis* and *Bacteroides fragilis*, which can tolerate ambient amounts of oxygen for 48 h (Ouwerkerk et al. 2016). *A. muciniphila* is known to competitively inhibit other mucin-degrading bacteria and improve metabolic functions and immunity responses in the host, making it a suitable candidate as a probiotic (Belzer and de Vos 2012). *A. muciniphila*

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was even found to be effective in treatment of inflammatory bowel diseases and cancer (Png et al. 2010; Chen et al. 2020a). The present review aims at studying the potential of *A. muciniphila* in mucin degradation, contribution towards the gut health and host immunity, and management of metabolic diseases such as obesity and type 2 diabetes, and respiratory diseases such as cystic fibrosis and COVID-19.

A. muciniphila in gut microbiome

The prevalence of *A. muciniphila* has been connected with a healthy gut, and therefore, its richness is inversely linked to numerous disease conditions (Jakobsson et al. 2015). An investigation of its relationships with the hosts revealed *A. muciniphila* to enhance the intestinal barrier function in mice (Shin et al. 2014). Colonization by *A. muciniphila* culminated in transcriptome alterations, leading to a rise in the genetic expression linked with immunogenicity. Outer membrane proteins of *A. muciniphila* were discovered to play a function in controlling immunological responses. One of the outer membrane proteins was recently discovered (Amuc-1100) (Ottman et al. 2017b). The work demonstrated that the outer membrane pili-like protein is essential in immunological modulation and the increase of trans-epithelial resistance. *A. muciniphila* performed a function in regulating metabolic endotoxemia and adipose tissue metabolism. Several investigations have consciously or inadvertently discovered the existence of *Akkermansia*-like spp. in regions of the human body other than the colon, where *A. muciniphila* could also have vital activities. The physiology and environmental factors of *Akkermansia*-like spp. in distinct anatomic locations of the digestive tract allow us to evaluate the ability of *A. muciniphila* to colonize and be productive at all these niches. Various beneficial effects of *A. muciniphila* in the human microbiome are presented in Fig. 1.

Mucin-degrading activity of *A. muciniphila*

Mucus consists of heavily glycosylated mucin-2 (MUC2), an oligosaccharide composed of various amino sugars and monosaccharide sugars, including *N*-acetyl-*D*-galactosamine (GalNAc), *N*-acetyl-*D*-glucosamine (GlcNAc), *D*-galactose

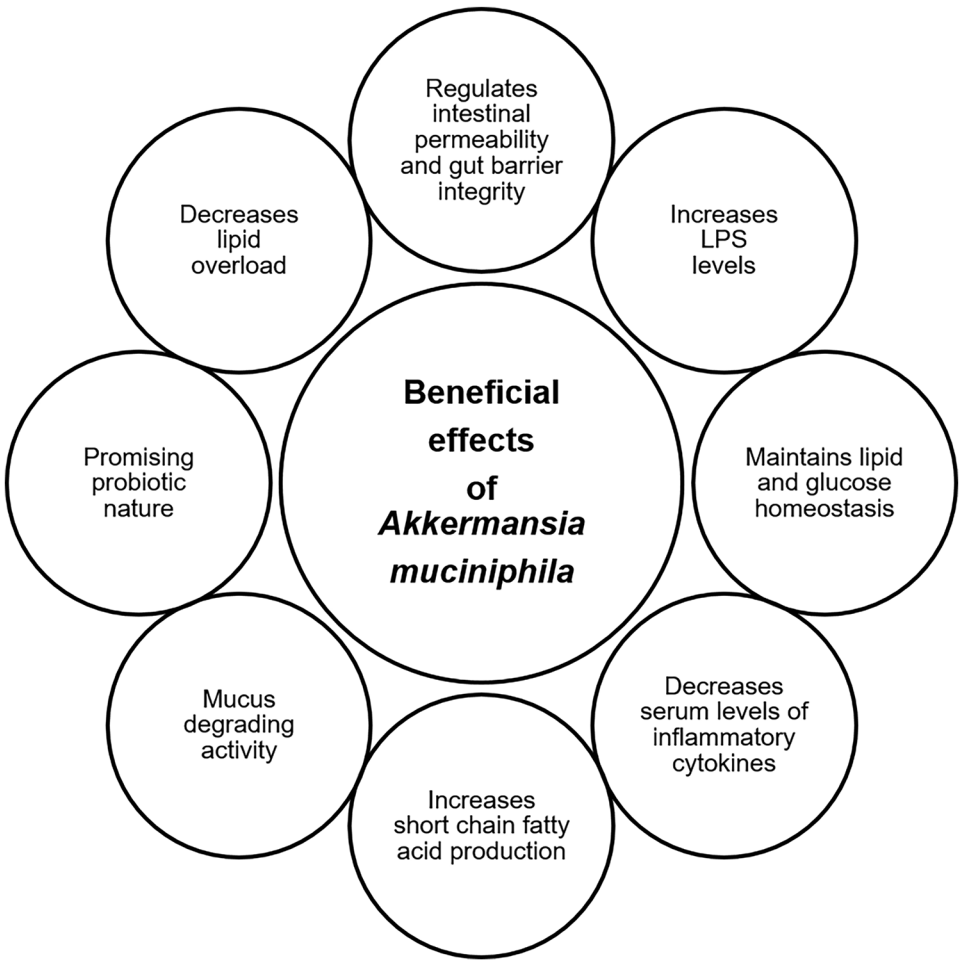

Fig. 1 Beneficial effects of *A. muciniphila* in human microbiome

and *L*-fucose (Ottman et al. 2017a). In many cases, these sugars are further substituted with acetate, phosphate and sulfate groups. Mucin has defining roles like a lubricant for food transport over membranes and provides selective permeability that allows the flow of nutrients to epithelial cells. It also acts as the first line of defence against mechanical damage, pathogens, and toxins and provides a surface layer to bacteria for its growth, adhesion and protection (Cone 2009; Johansson et al. 2013). However, some bacterial species of human microbiota release inflammatory toxins, which increase the permeability of the mucus layer and ultimately decrease its barrier property (Jakobsson et al. 2015). It has been concluded that bacterial colonies reside only at the outer layer of the intestinal tract. In contrast, the inner layer intends to keep the bacteria at bay from the epithelial cells to enforce immune tolerance to the guts by transporting IgA and antimicrobial proteins (Johansson et al. 2008, 2011).

It is observed that *A. muciniphila* can maintain an exciting microbial relationship in the host intestine by converting mucin into beneficial by-products (Ottman et al. 2017a, b). Recent studies showed that *A. muciniphila* could be grown on a synthetic medium where mucin can be replaced with media containing glucose, threonine, peptone and GlcNAc (Plovier et al. 2016). The amino group of sugars promotes the growth of bacteria in the presence of casitone, tryptone, yeast extract and peptone. One of the essential factors that account for the proliferation of *A. muciniphila* is glucose-6-phosphate, one of the constituents of mucin known to promote the adaptation of mucosal niche (van der Ark et al. 2018). In order to study substrate uptake abilities of *A. muciniphila*, few studies were conducted on a genome-scale metabolic model to demonstrate amino acids auxotrophy, sugar degrading capacities and vitamin biosynthesis (Ottman et al. 2017a). These experiments have also been validated through in vivo experiments in which *A. muciniphila* has been shown to proficiently utilize mucin-derived monosaccharide sugars and amino sugars. It has been found that the uptake of mucin-derived sugars and non-mucin sugar glucose by *A. muciniphila* is enhanced in a mucin-rich environment which indicates the need of mucin-derived components for the optimal growth of bacteria. In vivo experiments have also suggested that *A. muciniphila* may have galactose metabolism; however, mucin-derived components are necessary for its growth.

Transcriptomic analysis of *A. muciniphila* under mucin-rich and mucin-depleted conditions showed differential gene expression suggesting a global change in cellular functions (Shin et al. 2019). Out of 1126 differentially expressed genes (DEGs), 583 genes were upregulated while 543 were downregulated in mucin-rich conditions as compared to mucin-depleted conditions. The upregulated genes were significantly related to hydrolase activity acting on glycosidic bonds and their transporters, thereby confirming the activity of mucin-degrading genes under mucin-rich conditions. Thus, the genes that encode mucin-degrading enzymes, such as sulfatases, galactosidases, acetyl-glucosaminidase, neuraminidases and L-fucosidase transporters were upregulated in mucin-rich conditions. Furthermore, their downregulation in mucin-depleted medium determined the importance of its role in mucin-degradation. The catabolic glycolysis pathway is also correlated with mucin-degradation pathways (Shin et al. 2019). Thus, under mucin-depleted conditions, genes involved in glycolysis and energy metabolism, such as NADH dehydrogenase, succinate dehydrogenase and ATP synthase, either showed similar expression levels or were upregulated significantly. At the same time, there were few exceptions, including one ATP-dependent 6-phosphofructokinase gene (Amuc_1481), two enolase genes (Amuc_844, Amuc_1184) and one dihydrolipoyl dehydrogenase gene (Amuc_1689).

A. muciniphila in host immunity and probiotic nature

The symbiotic relationship between the gut microbiota and host determines the normal physiology, immunity and pathogen susceptibility of an individual. The interplay between host and gut microbiome that helps in pathogen displacement, regulating immune response and anti-inflammatory pathways, is a vital phenomenon. There is abundant evidence in the literature on mucin-utilizing *A. muciniphila* conferring immunity (Tummler and Puchelle 1997; Plovier et al. 2016; Ottman et al. 2017a). Many mucin degradation pathways regulate the host pathway by signalling through tumour necrosis factor α (TNF-α), interferon γ, interleukins-10 (IL-10) and interleukins-4 (IL-4) (Derrien et al. 2011; Andersson et al. 2012; Collado et al. 2012). Decreased levels of anti-inflammatory cytokines (IL-10 and IL-4) induced interleukins, while increased proinflammatory cytokines (TNF-α and IFN-γ) causing rapid proliferation of *A. muciniphila*. An increase in 2-arachidonoylglycerol levels was noted post *A. muciniphila* treatment, reducing inflammation (Gunderson and Kopito 1994; Everard et al. 2013). The secreted proteins from bacteria interact with host immune cells to induce signalling pathways that exhibit anti-inflammatory and immunomodulatory activity (Sánchez et al. 2008, 2010; Bernardo et al. 2012; Ruiz et al. 2014). The extracellular material secreted from it activates the downstream signalling pathway like toll-like receptors 2 (TLR2) (Ottman et al. 2017b). Amuc_110, a specific protein in the outer membrane, recapitulates the effect of bacteria on TLR2 activation and improves the barrier integrity of intestines (Dean and Annilo 2005; Belzer and de Vos 2012; Plovier et al. 2016; Ottman et al. 2017b). However, it is still unknown how Amuc_110 protein is regulated in the presence of a dynamic mucosal environment. The gene encoding

Amuc_110 protein is highly regulated in a mucin-depleted environment (Plovier et al. 2016). Amuc_110 has also shown its ability to exert a probiotic effect on diet-induced obesity and was present in the extracellular proteins of *A. muciniphila* as well (Plovier et al. 2016). To conclude, *A. muciniphila* is inversely correlated with inflammatory conditions and helps in epithelial barrier integrity by stimulating anti-inflammatory pathways (Gunderson and Kopito 1994; Shin et al. 2014; Cantarel et al. 2015; Caesar et al. 2015; Schneeberger et al. 2015).

The composition and functioning of the human gut microbiota are primarily proportional to nutritional accessibility of microbiota either obtained from a host or food (Zoetendal et al. 2012; Nicholson et al. 2012; Salonen and de Vos 2014). *A. muciniphila* is one of the good bacteria of the human gut microbiota. The presence of *A. muciniphila* in the intestinal mucus layer indicates it to be involved in gut regulation and host metabolism. It exists in a symbiotic relationship with the mucosal layer, and its abundance is greatly affected by the nutrients present in the mucus layer located around the intestinal epithelial cells. Its presence also supports other beneficial bacteria in the gut microbiome. *A. muciniphila* catabolizes mucins and turns them into short-chain fatty acids (SCFAs), including acetate, which other beneficial bacteria exploit, such as *Firmicutes*, to produce butyrate, a vital source of energy for the cells lining the gut. The production of SCFAs from the breakdown of mucin supplies energy to the goblet cells, which are responsible for secreting mucins. Furthermore, the consumption of specific dietary fibres can increase the abundance of this friendly bacteria, which helps thicken the mucus lining the gut. This strengthens the gut lining and improves gut barrier function and may, in turn, help in preventing weight gain. Chelakkot et al. demonstrated the role of Amuc_1100, isolated from *A. muciniphila*, in AMP-activated protein kinase (AMPK) activation mechanism, thereby improving gut integrity (Chelakkot et al. 2018). Amuc_1100 has been implicated in enhancing the expression of tight junction protein-1 (Tjp-1) and occludin (Li et al. 2016), thereby contributing to the gut barrier function. Thus, the presence of *A. muciniphila* in the mucus of the intestine regulates intestinal homeostasis and its integrity barrier through host signalling pathways (Derrien et al. 2004; Ottman et al. 2017a).

A. muciniphila dysbiosis associated with disease states and its management

The gut microbiome of healthy people is quite diverse. Gut microflora through microbial antigens and metabolites is the master regulator of innate and adaptive immunity. Disease associated dysbiosis results in induction, training and function of immune system. The disturbance of the mucus layer by any means may lead to inflammation and increase the risk of infection. Even slight variance in intestinal flora may be associated with sensitivity and severity of a disease. Therefore, gut microbes find use as potential diagnostic biomarkers by studying their abundance in different diseases.

A. muciniphila has been linked with wide range of diseases and disorders such as type 2 diabetes (Tilg and Moschen 2014), alcoholic steatohepatitis (ASH) (Grander et al. 2018), appendicitis (Swidsinski et al. 2011), obesity (Dao et al. 2016), atopic diseases (Drell et al. 2015), colorectal cancer (Weir et al. 2013), autism (Wang et al. 2011), inflammatory bowel disease (Png et al. 2010), cystic fibrosis (Hayden et al. 2019), and COVID-19 (Yeoh et al. 2021) (Table 1). Various studies demonstrated *A. muciniphila* to be negatively correlated with inflammatory bowel diseases (Png et al. 2010; Rajilić-Stojanović et al. 2013), appendicitis (Swidsinski et al. 2011), obesity (Karlsson et al. 2012; Dao et al. 2016) and type 2 diabetes (Tilg and Moschen 2014). Lower abundance of *A. muciniphila* is commonly observed in the majority of metabolic disorders while higher abundance is seen in few cases like colorectal cancer (Yu et al. 2017).

Recently, an association between *A. muciniphila* and metastasis of lymph nodes in lung adenocarcinoma was reported (Chen et al. 2020a). The relative abundance of *A. muciniphila* was observed to be greater in metastasis cohort (0.057) than the non-metastasis cohort (0.023) pointing towards its potential as a promising biomarker to predict lymph node metastasis. Likewise, a study to investigate whether *A. muciniphila* could enhance the antitumor effect of cisplatin (*cis*-diamminedichloroplatinum; CDDP) was conducted (Chen et al. 2020b). It was found that when *A. muciniphila* was combined with cisplatin, the growth of tumour volume slowed and the changes of tumour pathomorphology significantly improved. At molecular level, upregulation of factor-associated suicide (Fas) proteins and downregulation of p53, ki-67 and Fas ligand (FasL) proteins were also observed. Several proinflammatory factors (TNF-α, IFN-γ and IL-6) were induced while the expression of $CD4^+CD25^+Foxp3^+$ Treg was suppressed indicating the role of *A. muciniphila* in regulating immune inflammatory microenvironment in reversion of tumour growth and tumour immune escape. Also, the levels of IFI27l2 and IGFBP7, two most differentially expressed genes in lung cancer, were found to be increased because of the combined treatment with *A. muciniphila* and CDDP. Signalling pathways such as JAK-STAT, FOXO, cytokine-cytokine receptor interaction, PI3K-Akt, Th17 and cell differentiation were associated with the antitumor effect of *A. muciniphila* and CDDP. The study suggested that *A. muciniphila* combined with CDDP provides good symbiotic environment to achieve maximum therapeutic efficacy of antitumor drugs. The human gut microbiome could

Table 1 Altered abundance of *A. muciniphila* in various disease states in humans

Disease	*A. muciniphila* abundance	Detection method	Sample type	References
Allergic asthma	Reduced	qPCR	Faeces	(Demirci et al. 2019)
Asthma	Reduced	16S rRNA sequencing	Faeces	(Michalovich et al. 2019)
Alcoholic steatohepatitis (ASH)	Reduced	16S rRNA sequencing	Faeces	(Grander et al. 2018)
Atopy	Reduced	16S rRNA sequencing	Faeces	(Candela et al. 2012)
Atopy	Reduced	Pyrosequencing	Faeces	(Drell et al. 2015)
Autism	Elevated	bTEFAP	Faeces	(De Angelis et al. 2013)
Autism	Reduced	qPCR	Faeces	(Wang et al. 2011)
Clostridium difficile infection	Elevated	qPCR	Faeces	(Vakili et al. 2020)
Colorectal cancer	Elevated	16S rRNA sequencing	Faeces	(Weir et al. 2013)
Colorectal cancer	Elevated	qPCR	Tissue biopsy	(Mira-Pascual et al. 2015)
Crohn's disease	Reduced	qPCR	Tissue biopsy	(Png et al. 2010)
Crohn's disease	Reduced	16S rDNA pyrosequencing	Faeces	(Opstelten et al. 2016; Malham et al. 2019)
Cystic fibrosis	Reduced	16S-based tag-encoded FLX amplicon pyrosequencing (bTEFAP)	Faeces	(Hoffman et al. 2014)
Cystic fibrosis	Reduced	Metagenomic sequencing	Faeces	(Hayden et al. 2019)
COVID-19	Elevated	Shotgun sequencing	Faeces	(Yeoh et al. 2021)
Oesophageal cancer	Elevated	16S rRNA sequencing	Tissue biopsy	(Snider et al. 2019)
Hyperlipidaemia	Reduced	16S rRNA sequencing	Faeces	(Gargari et al. 2018)
Microscopic colitis	Reduced	16S rDNA pyrosequencing	Faeces	(Fischer et al. 2015)
Multiple system atrophy	Elevated	Metagenomic sequencing	Faeces	(Wan et al. 2019)
Obesity	Reduced	qPCR	Faeces	(Marvasti et al. 2020)
Obesity	Elevated	qPCR	Faeces	(Remely et al. 2015)
Parkinson's disease	Elevated	qPCR	Faeces	(Unger et al. 2016)
Parkinson's disease	Elevated	Shotgun sequencing	Faeces	(Bedarf et al. 2017)
Prediabetes	Reduced	16S rRNA sequencing	Faeces	(Allin et al. 2018)
Psoriasis	Reduced	16S rDNA pyrosequencing	Faeces	(Tan et al. 2018)
Pulmonary arterial hypertension	Reduced	Shotgun sequencing	Faeces	(Kim et al. 2020)
Pulmonary tuberculosis	Reduced	Metagenomic sequencing	Faeces	(Hu et al. 2019)
Schizophrenia	Elevated	16S rRNA sequencing	Faeces	(Xu et al. 2020a)
Schizophrenia	Elevated	Shotgun sequencing	Faeces	(Zhu et al. 2020)
Spleen deficiency syndrome	Reduced	qPCR	Faeces	(Peng et al. 2020)
Type 1 diabetes	Reduced	qPCR	Faeces	(Fassatoui et al. 2019)
Type 2 diabetes	Elevated	Metagenomic sequencing	Faeces	(Chelakkot et al. 2018)
Type 2 diabetes	Elevated	Shotgun sequencing	Faeces	(Qin et al. 2012)
Type 2 diabetes	Reduced	16S rRNA sequencing	Urine	(Liu et al. 2017)
Type 2 diabetes	Reduced	Metagenomic sequencing	Faeces	(Zhong et al. 2019)
Type 2 diabetes	Reduced	qPCR	Faeces	(Fassatoui et al. 2019)
Ulcerative colitis	Reduced	qPCR	Tissue biopsy	(Png et al. 2010)
Ulcerative colitis	Reduced	MiSeq sequencing	Faeces	(Bajer et al. 2017)
Ulcerative colitis	Reduced	16S rRNA sequencing	Faeces	(Malham et al. 2019)

therefore, be responsible for differences in drug response of individuals paving way for personalized therapeutics to significantly improve human health care. Thus, by regulating the abundance of *A. muciniphila* in the gut microbiome in a personalized manner, early treatment of related diseases may be facilitated. The microbiome in general, and *A. muciniphila* in particular, can act as a biomarker of these diseased states and provide future theranostics by suggesting ways of disease diagnosis and treatment (Morgan and Huttenhower 2012).

A. muciniphila and metabolic diseases

Decreased abundance of *A. muciniphila* in obesity

World Health Organization (WHO) defines obesity as abnormal fat accumulation leading to health implications like type 2 diabetes, fatty liver disease and hypertension. Being a multifactorial disorder, not only does it result in fatal complications like cardiovascular diseases and psychological effects but also challenges one to perform everyday tasks with ease. It is a low-grade inflammatory metabolic disorder resulting in higher levels of inflammatory cytokines such as IL-6, TNF-α and hypersensitive C-reactive protein (hs-CRP). Inflammation in obesity leads to significant changes in gut microbiota, for example, increase in the abundance of *Firmicutes, Bifidobacterium spp.* and *Lactobacillus gasseri* while decrease in the abundance of *Bacteroidetes* (Ley et al. 2005; Wang and Jia 2016). *A. muciniphila* was inversely associated with obesity and found to be more abundant in lean individuals than overweight individuals (Remely et al. 2016). The various mechanisms by which *A. muciniphila* helps in obesity management are shown in Fig. 2. *A. muciniphila* maintains the intestinal immunity, gut barrier integrity and permeability by reducing inflammatory cytokines, thereby achieving metabolic homeostasis (Ottman et al. 2017b). Also, lipopolysaccharide (LPS) found in cell wall of Gram-negative bacteria is a potential proinflammatory molecule and is associated with onset of inflammation. Imbalance in LPS levels leads to activation of proinflammatory signalling pathways causing increased secretion of IL-6 and TNF-α. The inherent property of *A. muciniphila* of SCFAs production signals G-protein coupled receptor (GPCR) activation and histone deacetylase (HDAC) inhibition to maintain energy homeostasis and appetite sensation (Lukovac et al. 2014). SCFAs production facilitate increased production of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulin tropic polypeptide (GIP) upon binding to GPR41/GPR43 receptors present in L-cells in the intestinal mucosa. This results in improvement in insulin resistance and glucose tolerance thereby, suppressing appetite through metabolic signalling. Furthermore, *A. muciniphila* decreases inflammation by increasing the levels of oleoylathanolamide (OEA), 2-palmitoylglycerol (2-PG), 2-acylglycerol (2-AG) and 2-oleoylglycerol (2-OG) which bind to GPR119 receptors, stimulating release of GLP-1 (Everard et al. 2013). In a recent study, oral supplementation of *A. muciniphila* in obese mice through high fat diet (HFD) has been demonstrated to reduce the intestinal endotoxin levels, hence reducing inflammation (Cani and de Vos 2017; Fuke et al. 2019). It helped restore gut barrier dysfunction through symbiotic relationships with other beneficial microbes like *Bacteroidetes*, *Euryarchaeota*, *Firmicutes* and *Actinobacteria* and improved intestinal permeability through the inhibition of claudin 3 (Cldn3), cannabinoid receptor 1 (Cnr1) and occludin like tight junction proteins or lowering of flavin-containing monooxygenase 3 (FMO3) expression (Dao et al. 2016).

In humans, both live and pasteurized *A. muciniphila* were found to be safe for oral consumption by heavy body weight individuals (Plovier et al. 2016). In a clinical trial (NCT02637115), oral administration of *A. muciniphila* in obese patients for 3 months was found to be an effective and safe treatment. Similarly, in a randomized, double-blind human study based on *A. muciniphila* supplementation, a decrease in body weight along with improvement in liver dysfunction and inflammation in patients was observed (Depommier et al. 2019). Also, supplementation with prebiotic containing oligofructose helped restore *A. muciniphila* abundance. But since *A. muciniphila* does not grow in vitro

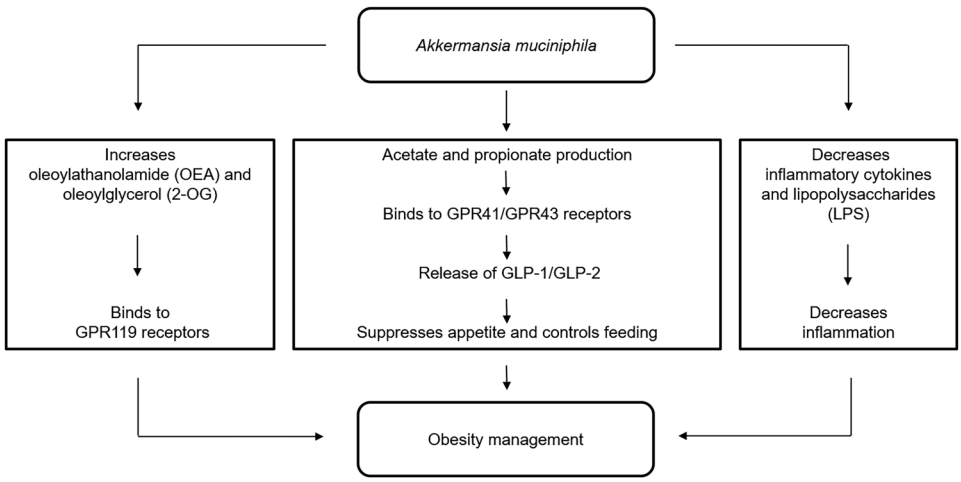

Fig. 2 Role of *A. muciniphila* in obesity management

on oligofructose-enriched media, it can be concluded that complex cross-feeding interactions might be involved. While it is clear that the human mucus colonizer maintains gut barrier integrity and homeostasis during obesity, the role of human gut microbiome on etiology of obesity remains to be investigated. The study of *Akkermansia*-obesity relationship could provide better insights to microbe-based treatments. Since *A. muciniphila* regulates the energy metabolism of host, its therapeutic intervention in obesity could be explored (Xu et al. 2020b). The reduction in fat-mass ratio in obesity can be studied by urinary metabolomics profile of *A. muciniphila*, making it a suitable biomarker for obesity (Png et al. 2010). Furthermore, the risk of obesity and associated metabolic diseases can be reduced by proper management of gut microbial profile.

Decreased abundance of *A. muciniphila* in type 2 diabetes

According to WHO, 1 out of 11 people suffer from diabetes with over 1.5 million deaths globally. Type 2 diabetes is a silent killer marked by the body's inability to utilize insulin produced by pancreatic β-cells. A study conducted by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) suggests that factors such as sedentary lifestyle and genetic conditions may contribute to early onset of type 2 diabetes. The increased levels of blood sugar, i.e. hyperglycaemia results in nervous, circulatory and immune system–related complications. Insulin resistance as a result of type 2 diabetes affects the gut microbial diversity and metabolite production. Alterations in the abundance of various gut microbes during the onset and progression of type 2 diabetes have also been observed. Many studies have reported negative correlation of genus *Akkermansia, Bacteroides, Faecalibacterium, Roseburia* and *Bifidobacterium*, while positive correlation of genus *Ruminococcus*, *Blautia* and *Fusobacterium* with type 2 diabetes (Sedighi et al. 2017; Gao et al. 2018). Patients with normal glucose tolerance exhibited higher abundance of *A. muciniphila* as compared to pre-diabetic or type 2 diabetes patients. Interestingly, several anti-diabetic drugs like metformin, dapagliflozin and liraglutide were found to favour the abundance of *A. muciniphila* (Shin et al. 2014; Wang et al. 2018; Lee et al. 2018). Furthermore, a study conducted on the administration of an antidiabetic drug, metformin revealed that *A. muciniphila* further enhanced its anti-diabetic effects (Shin et al. 2014). Mice fed on HFD, when treated with metformin, showed increased abundance of *A. muciniphila* and improved blood sugar levels. Moreover, improved tolerance to glucose was observed upon oral administration of *A. muciniphila* but not metformin.

A. muciniphila is known to protect the intestinal barrier function by maintaining normal blood sugar levels. The intrinsic ability of *A. muciniphila* to catabolize complex carbohydrates further assists in inhibition of α-glucosidase and reduction of postprandial hyperglycaemia (Everard et al. 2013). Both obesity and type 2 diabetes may be ameliorated by increasing fatty acid oxidation and energy expenditure but reducing fatty acid biosynthesis (Everard et al. 2013; Gurung et al. 2020). Thus, fatty acid oxidation in adipose tissues and adipocyte differentiation may be promoted by administration of *A. muciniphila*, and other bacteria such as *Lactobacillus gasseri*, *Bacteroides acidifaciens* and thus SCFAs. This is correlated to increased levels of 2-PG, 2-AG and 2-OG in the adipose tissue. Furthermore, *A. muciniphila* can be regulated by increasing circulation of tryptophan metabolites through dietary intake (Cronin et al. 2021). Interestingly, *A. muciniphila* positively influences the host's glucose metabolism by inducing IL-10, thus protecting from ageing-related insulin resistance (Wang et al. 2015; Greer et al. 2016). It fights against diabetic oxidative damage and improves resistance to gluco/lipotoxicity by decreasing hepatic glycogen levels and increasing HDL-C levels (Zhang et al. 2018). Moreover, it reduces inflammation by inhibiting the expression of TNF-α and lipid oxidative damage by lowering malondialdehyde levels in diabetic animals (Zhang et al. 2018). Increased paracellular gut permeability and gut barrier disruptions result in inflammation and metabolic diseases by increased absorption of LPS. *A. muciniphila* maintains glucose homeostasis and fat mass storage by controlling host mucus turnover and higher L-cell activity. Therefore, prebiotic treatment could help restore *A. muciniphila* abundance and counter metabolic endotoxemia in type 2 diabetes and obesity. Therefore, it becomes necessary to study the host-gut microbe interactions for better understanding of governing mechanisms in development of type 2 diabetes. *A. muciniphila*, through the alteration of the gut microbiota, could help to control and manage type 2 diabetes in the near future.

A. muciniphila and respiratory diseases

Decreased abundance of *A. muciniphila* in cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on chromosome 7. CFTR protein functions as an important anion-selective ion channel responsible for epithelial fluid secretion and intra-luminal hydration (Welsh and Smith 1993). Defective CFTR protein leads to accumulation of mucus in the lungs and intestine largely affecting the pulmonary and intestinal microbiota (Price and O'Toole 2021). As the mucus gets more and more viscous, the mucociliary clearance mechanism (MCC) becomes unable to clear the mucus resulting in manifestation of opportunistic microbial infections. Dysfunctional CFTR results in an altered intestinal condition including dysbiosis of gut

microbiota due to physiological and biochemical imbalance. It includes changes in intestinal pH, inflammation, malabsorption and gut barrier disruptions (Meeker et al. 2020). Various factors such as prolonged antibiotics intake, immunosuppressive mediations and high-calorie diet further shape the CFTR microbiome. Specifically, in delF508 mutations, bacteria such as *E. coli* and *Eubacterium biforme* were found in higher abundance while *Bifidobacterium* and *Faecalibacterium* species were in lower abundance (Schippa et al. 2013). Recent studies on the gut microbiota of CFTR-deficient mice reported an increase in abundance of *Enterobacteriaceae*, *Mycobacteria* and *Bacteroides* while a decrease in abundance of *Lactobacilli*, *Acinetobacter lwoffii* and *A. muciniphila* (Thomsson et al. 2002; Bazett et al. 2016). Through integrated metagenomics and metabolomics study on CFTR gut microbiota, an increase in the expression of associated metabolites such as propylbutyrate, γ-aminobutyric acid (GABA), ethanol, choline and pyridine was observed while there was reduction in expression levels of 4-methylphenol, methylacetate, uracil, sarcosine, acetate, phenol, benzaldehyde and glucose (Vernocchi et al. 2018). The multi-omics-based model pointed out the correlation of microbial and metabolite variations caused by CFTR functional defects. Therefore, it becomes important to study the relationship between host gut, microbes and associated metabolites to investigate CF and its biomarkers. Major evidence of their relationship is the study on the administration of CFTR potentiator Ivacaftor which resulted in an increase in *A. muciniphila*. It could be explained by the release of bicarbonates from CFTR post Ivacaftor treatment that provided the optimal environment for mucin degraders (Ambort et al. 2012; Schütte et al. 2014). Post treatment with Ivacaftor, a significant reduction in stool calprotectin, a protein released by neutrophils, but no change in M2 pyruvate kinase (M2-PK) was observed. The reduction of calprotectin indicated that intestinal inflammation could be improved in CF patients upon restoration of intestinal milieu. Also, there was selective loss of pathogens like those of *Enterobacteriaceae* family which was positively correlated with stool calprotectin level (Manor et al. 2016). It led to an increase in the expression of an antimicrobial peptide (Reg III), which has direct metabolic activity in the intestine against Gram positive bacteria. In CF, *A. muciniphila* accounted for normal stool M2-PK concentration and decreased amount of *Enterobacter.* Thus, the increased abundance of *A. muciniphila* supports its potential as a biomarker for the gut and it may be used for the microbe based therapy in CF (Pang et al. 2014). Many gut microbes including *A. muciniphila* could be associated with CF and hold future as its promising therapeutic intervention. By regulating the gut profile of *A. muciniphila* through personalized nutrition and supplementation, host immunity can be improved, which could serve as one of the prophylactic ways by which the severity of CF could be minimized.

Increased abundance of *A. muciniphila* in COVID-19

On 11th March 2020, COVID-19 caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was declared as a pandemic. Over 180 countries were affected globally leading to nationwide lockdowns. The virus primarily attacked the respiratory system causing high-grade fever, severe cough, shortness of breath and pneumonia in severe cases. Several people infected with the virus experienced neurological and gastrointestinal (GI) manifestations with or without respiratory symptoms. On the other hand, some people were asymptomatic or symptom-free. The viral infection was also correlated with gut-lung-brain axis and microbiome imbalance. Significant reduction in the abundance of beneficial microbes was associated with inflammation and pathogenesis in COVID-19 (Hussain et al. 2021). Altered microbiome composition could further weaken body's immunity and may play a role in SARS-CoV-2 infection. Recent studies have elucidated the relationship between gut and lung microbiota in COVID-19 and potential as prognostic markers (Wang et al. 2021). Although there is no direct evidence of specific interaction between resident gut microbe and COVID-19, some studies suggest that the gut microbiome in COVID-19 could be a key player in modulating host response and disease severity (Hussain et al. 2021; Yamamoto et al. 2021; Yeoh et al. 2021). GI symptoms were accompanied by gut dysbiosis during the early phase causing changes in gut microbiome and increase in inflammatory cytokines. Recently, proinflammatory cytokine storm due to significant increase in levels of IL-6 and IL-10 was reported to be predictive of COVID-19 severity (Han et al. 2020). Moreover, the presence of SARS-CoV-2 RNA was reported in faecal samples suggesting gut to be a viral replication site (Xiao et al. 2020). According to a study performed on SARS-CoV-2 recovered patients, *A. muciniphila* along with *B. dorei* was found to be elevated in the COVID-19 patients (Yeoh et al. 2021). Moreover, these bacteria were positively correlated with inflammatory cytokines, namely IL-1β and IL-6 and proinflammatory cytokine C-X-C motif ligand 8 (CXCL8). On the other hand, *Faecalibacterium prausnitzii*, *Eubacterium rectale* and some species of *Bifidobacteria* were found in lower abundance. A recent faecal metabolomics studies through machine learning approach suggested that particular set of gut microbiota could be used to predict proteomic risk score based on 20 blood proteomic biomarkers for COVID-19 severity (Gou et al. 2021). The gut microbial profile was used as a tool for prediction of the blood molecular signatures, indicating amino acid related pathways such as aminoacyl-tRNA biosynthesis, arginine biosynthesis

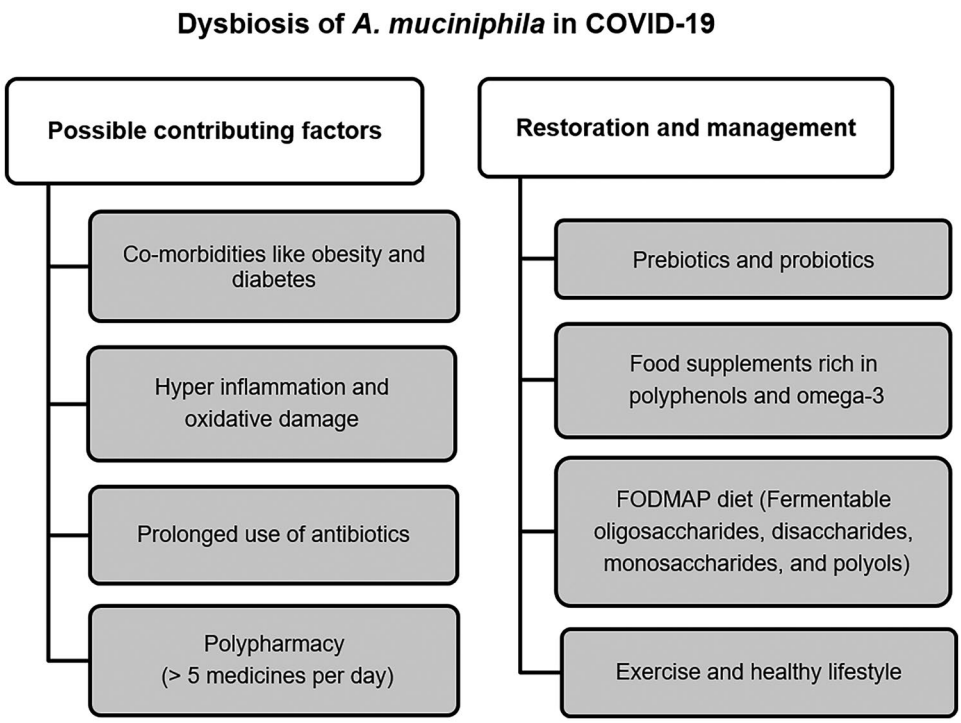

Fig. 3 Possible factors contributing to *A. muciniphila* dysbiosis in COVID-19 along with strategies to restore its normal abundance

and valine, leucine and isoleucine biosynthesis to be a possible link between inflammation and gut microbiota. It is well known that the gut microbiome renders beneficial effects on pulmonary mucosal immunity and host defence, thus safeguarding against respiratory infections (Gray et al. 2017). Downregulation of angiotensin-converting enzyme II (ACE2) involved in amino acid transport, tryptophan and antimicrobial peptide metabolism upon binding with viral spike protein might affect gut microbial ecology leading to dysbiosis in COVID-19 (Kuba et al. 2005). The possible factors contributing to *A. muciniphila* dysbiosis in COVID-19 along with strategies to restore its normal abundance are shown in Fig. 3. Co-morbidities such as diabetes, obesity and cardiovascular diseases largely influence the risk of infection and severity of disease. A lot of stress and consumption of fat and carbohydrate rich foods during the quarantine period was observed, leading to reduced CD8 + T cell response which could be linked to higher risk of infection (Mattioli et al. 2020). On the contrary, non-pharmacological measure such as reduction in consumption of fast food and increased emphasis on a healthy balanced diet also helped mitigate severe health conditions. Lifestyle habits, including diet and physical exercise, can profoundly influence the composition of the microbiome and consequently host metabolism and well-being. With the regulation of dietary habits, the optimum abundance of this friendly bacteria can be achieved in COVID-19 (Dhar and Mohanty 2020). Food supplements rich in polyphenols, omega-3 and FODMAP (Fermentable oligosaccharides, disaccharides, monosaccharides and polyols) are well known to increase *A. muciniphila*. Thus, by consuming polyphenol-rich foods, like fruits and vegetables, the abundance of *A. muciniphila* in the gut can be enhanced. Probiotic supplementations along with standard therapies as a prophylactic measure could also help mitigate the increased risk of comorbidities and move towards effective treatment. It becomes necessary to manage gut microbiome during and post disease recovery. The gut microbiome is asserted to critically impact the severity of infection as well as host immunity in COVID-19. By monitoring the GI symptoms, early diagnosis and treatment of COVID-19 can be facilitated. Therefore, it becomes important to study interaction between coronavirus and intestinal microbiome to develop novel treatment approaches.

Conclusion and future perspectives

A. muciniphila is a key mucus degrading bacteria in host immunity and infection response. The correlated metabolites and pathways are closely associated with inflammation, post-infection severity and recovery. *A. muciniphila* fortifying the intestinal mucus layer promotes several health-mediating effects. It regulates intestinal homeostasis and helps in maintaining epithelial barrier integrity by stimulating anti-inflammatory pathways. *A. muciniphila* presents itself as a powerful gut microbe having many metabolic interventions and as a promising therapeutic agent. The close relation of intestinal anti-inflammatory and protective effects of *A. muciniphila* emphasizes on its promising probiotic role (Neef and Sanz 2013). On the basis of

cross-talk elucidated across gut-lung axis, alterations in the gut microbiota through administration of SCFAs, probiotics or micronutrients could act as potential therapeutic strategies. A specific protein in the outer membrane of *A. muciniphila*, Amuc-110, which recapitulates the effect of bacteria on TLR2 activation and improves the barrier integrity of intestines, could serve as a strong candidate for drug production in future. Thus, by unveiling the interrelationships between host factors such as diet, lifestyle habits, clinical markers and *A. muciniphila* in the human gut microbiome, interventions and clinical trials may be designed. Through extensive investigation, new dimensions of the impact of *A. muciniphila* in the microbiome on human health may be explored in obesity, type 2 diabetes, cystic fibrosis and COVID-19 by examining its dysbiosis in patients as compared to healthy individuals and adopting suitable strategies for its restoration (Fig. 4). The study of the relationship between *A. muciniphila* in gut microbiome and personalized medicine can be one of the most attractive aspects of future research, which can provide significant perspectives for the treatment of metabolic diseases like type 2 diabetes and obesity, and even respiratory diseases such as cystic fibrosis and COVID-19. To conclude, potential opportunities exist for targeted interventions to modify the composition of *A. muciniphila* in the gut microbiome to improve host health.

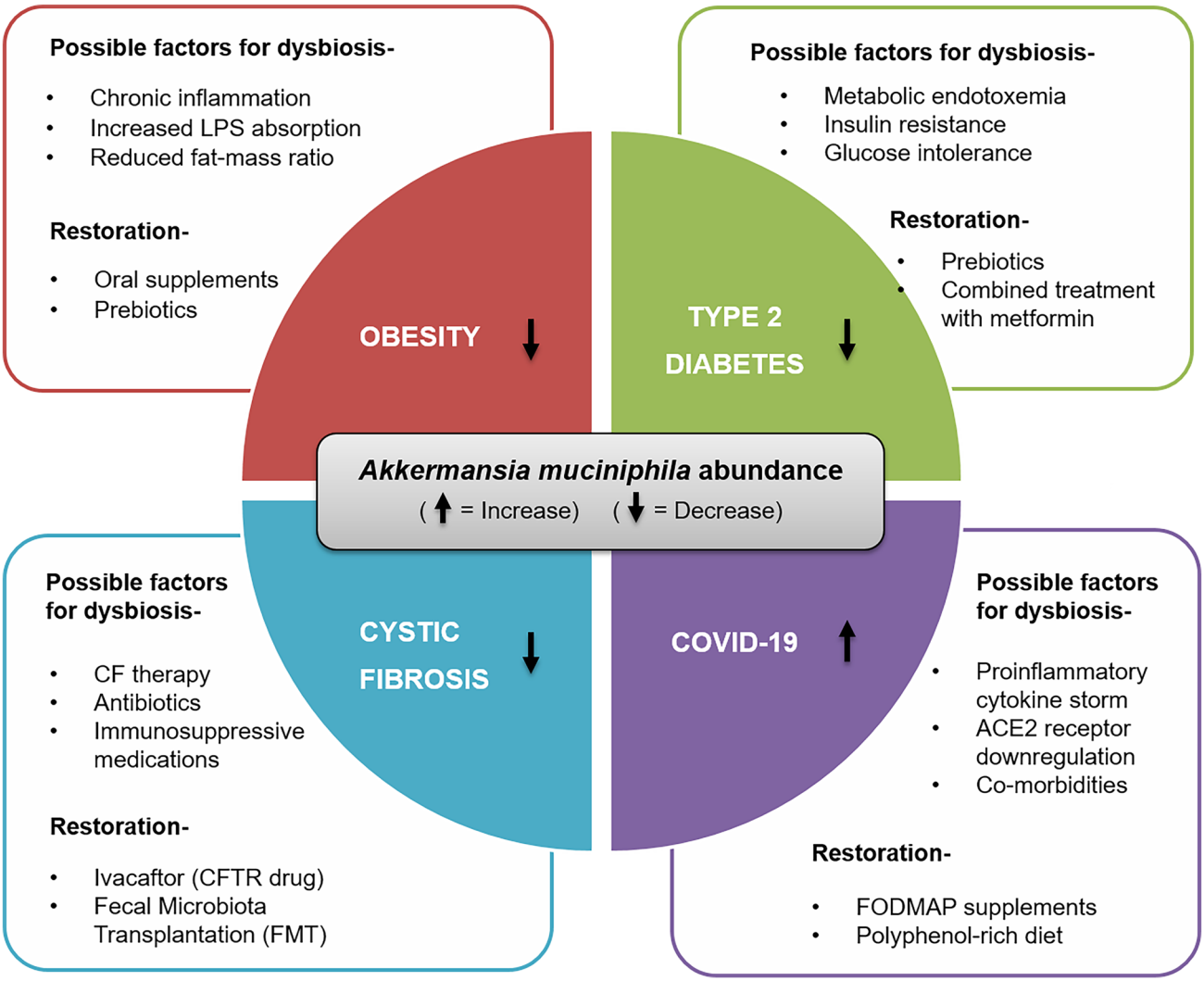

Fig. 4 Dysbiosis and restoration of *A. muciniphila* in obesity, type 2 diabetes, cystic fibrosis and COVID-19

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Declarations

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Consent to participate Not applicable.

Consent for publication Not applicable.

Conflict of interest The authors declare no competing interests.

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