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The Role of Human Gut Microbe *Ruminococcus gnavus* in Inflammatory Diseases

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Abstract: Dysbiosis is a prominent factor in numerous inflammatory conditions, with *Ruminococcus gnavus*, a prevalent gut microbe, implicated in inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), eczema, metabolic disorders, and rheumatic diseases. *R. gnavus* contributes to inflammation by producing an inflammatory polysaccharide and degrading mucin. The increasing evidence of elevated *R. gnavus* abundance in various inflammatory conditions suggests its potential as a therapeutic target. Despite this, there are limited studies on treatment strategies targeting *R. gnavus*. This article provides a comprehensive overview of the association between *R. gnavus* and diverse inflammatory conditions, highlighting the need for further research to explore effective treatment options against this bacterium.

Keywords: *Ruminococcus gnavus*; gut microbiome; inflammatory diseases; probiotics; SDG 3 Good health and well-being

1. Introduction

The human microbiota consists of different types of microbes like bacteria, viruses, fungi, and protozoa, which colonise the surfaces of the human body, ranging from the oral cavity to the skin and the gut [1]. The gut microbiota is the largest, consisting of a diverse microbial consortium with a plethora of bacterial species. The two common phyla found in the gut are the *Bacteroidetes* and the *Firmicutes* [2]. The gut microbiome plays an important role in developing a symbiotic relationship in humans, but they are also the causative factor in certain diseases [3, 4]. One of the important members present in the gut microbiome is *Ruminococcus gnavus*, which can be found within the gut of most individuals. *R. gnavus* is a Gram-positive, anaerobic bacterium that belongs to the *Firmicutes* phylum, *Clostridia* class. Colonisation of *R. gnavus* in the gut begins during the first days of the life of newborns [5]. It plays a vital role in the human gut and is present within the mucus layer of the gastrointestinal mucosa. Moreover, *R. gnavus* has an advantage in colonising the gut because of its capability to degrade mucosal mucus for utilisation as an energy source and bacteriocin production for protection and colonisation [2, 5, 6].

Dysbiosis is when a disruption to the homeostatic microbiome is caused by perturbation in the microbiota composition or changes in metabolic activities [2]. Dysbiosis has been reported in certain inflammatory conditions like inflammatory bowel disease (IBD), eczema and spondyloarthritis [2]. Several studies have found an increased abundance of *R. gnavus* in these inflammatory conditions due to its proinflammatory mechanism. Multiple studies have aimed to develop therapeutic strategies against *R. gnavus*, but its efficacy is still

not clear [7-10]. Thus, this review aims to provide an overview and update regarding the current link between *R. gnavus* and various inflammatory diseases.

2. *Ruminococcus gnavus* in inflammatory conditions involving the gastrointestinal system

2.1. Inflammatory bowel disease

IBD is a term used to describe inflammatory conditions that involve the gastrointestinal (GI) tract. IBDs are composed principally of Crohn's disease (CD), involving any segment of the GI tract, and ulcerative colitis (UC), which occurs in the inner lining of the colon or rectum. CD and UC share some symptoms, including diarrhoea and abdominal pain [11]. Although the aetiology of IBDs remains unknown, epidemiological and genetic data suggest that IBD is triggered by environmental factors in genetically predisposed individuals, such as individuals with defective immune responses to certain antigens of the intestinal microbiome [12]. Besides, gut dysbiosis is also found to be associated with the pathogenicity of IBD. In normal circumstances, the well-controlled mucosal immune system protects the intestines from harmful bacterial infections and also maintains the immune system to benefit the gut microflora. Disruption of this immune system against the commensal bacteria can cause continuous microbial antigenic stimulation, leading to gut inflammation [13].

Multiple studies looking at the role of *R. gnavus* in IBD have been done [14-17]. In CD patients, they found an inflammatory polysaccharide synthesised by *R. gnavus* that plays an important role in the pathogenesis of IBD. Henke and colleagues found that the polysaccharide is made up of glucorhamnan, which consists of a rhamnose backbone and short glucose sidechains, and this was identified by culturing *R. gnavus* in a defined medium [14]. They also discovered that glucorhamnan could cause inflammation by inducing tumour necrosis factor-alpha (TNFα), a proinflammatory cytokine released by dendritic cells, which relies on the toll-like receptor (TLR4) [14].

Furthermore, the role of the capsule in causing a proinflammatory response has been analysed. Capsules are defined as a mesh of proteins and polysaccharides that cover the outermost part of the bacteria [15]. The bacterial strains that have capsules were found to have a gene cluster which encodes a capsular polysaccharide (CPS). *R. gnavus* strains that have a capsule were ATCC 29149, RJX1120, RJX1121, and RJX1123, while the strains that lack a capsule were RJX1128 and RJX1124. To test the role of capsule in inducing proinflammatory cytokines, murine bone-marrow-derived dendritic cells (mBMDCs) were used, and cytokines secretion was detected by enzyme-linked immunosorbent assay (ELISA). Henke and

colleagues have identified that *R. gnavus* strains with capsules (encapsulated) induced hardly any to no TNF-α whereas strains that lack a capsule (unencapsulated) with uncovered cell wall, did induce a large amount of TNF-α. This indeed led to increased inflammation in the gut by the unencapsulated strain compared to the encapsulated strain of *R. gnavus* [15].

Studies have also shown that the mucin degrader, *R. gnavus* strain ATCC 29149 contains a complete Nan cluster, a cluster of genes required in the metabolism of sialic acid and putative transporters. Bacteria that have the Nan cluster have the ability to colonise areas that are rich in mucus and sialic acid, like the gut, bladder, lung and oral region, where the sialic acid can act as a source of energy, carbon and nitrogen and also protect the bacteria from the continuous mucus turnover [16, 18]. For *R. gnavus* strains to make complete use of mucin as a source of nutrients, the metabolism of sialic acid is very important. Even though *R. gnavus* is able to use mucin as a source of carbon which could lead to gut barrier disruption, exposing the body's immune system to harmful triggers like the glucorhamnan produced by it. Studies also found that *R. gnavus strains* (ATCC 29149 and E1) are not able to use sialic acid as the only carbon source [5, 17]. This is because *R. gnavus* synthesises an intramolecular trans-sialidase (IT-sialidase) that splits off from terminal a2-3-linked sialic acid, and instead of releasing sialic acid, they release 2,7-anhydro-Neu5Ac. This actually gives a nutritional competitive benefit to *R. gnavus*, which lets it bloom within the intestinal mucosa by scavenging sialic acid in the form of 2,7-anhydro-Neu5Ac because other gut microflora does not encode IT-sialidase, making them hard to adapt to the sialoglycan-rich mucosal niche, thus contributing to the overabundance of *R. gnavus* in the gut of IBD patients [17].

In patients with IBD, gut dysbiosis has been identified as one of the causes, but the underlying mechanism of provoking dysbiosis is still elusive. Several human studies have found that *R. gnavus* is one of the gut bacteria involved in IBD, and they have proved the association between *R. gnavus* and IBD. As shown in Table 1, all the studies done showed an increased abundance of *R. gnavus* in UC [7, 8, 12, 19-22] and CD [23-34] patients compared to the healthy controls. Some studies showed increased *R. gnavus* in IBD patients because it expresses a high amount of beta-glucuronidase, which can release toxic substances in the gut, leading to local inflammation [21, 32]. It also consists of a complex polysaccharide and acts as a proinflammatory bacterium with the ability to degrade mucin, thus resulting in the inflammation seen in CD patients [23, 27]. Hall et al. [28] found the enrichment of *R. gnavus* in IBD was surprising because *R. gnavus* is an obligate anaerobe, so they tested its ability to bloom in the presence of oxygen. They discovered that *R. gnavus* had a higher tolerance to atmospheric oxygen, which led to its increased abundance in the IBD gut [28]. Moreover, another study found that after faecal microbiota transplantation (FMT), *R. gnavus* was

decreased in UC patients [7]. In a nutshell, there is an association between *R. gnavus* and IBD based on the findings from human clinical studies.

Table 1. Association between *Ruminococcus gnavus* and IBD in humans.

Inflammatory diseases	Study group	Sample	Findings	Ref.
IBD	- UC: n = 15 twin pairs - CD: n = 23 twin pairs - Control: n = 2 twin pairs	Faeces	Increased abundance of *R. gnavus* seen in ileal CD patients.	[33]
Paediatric IBD	- IBD: n = 110 - Non-IBD symptomatic: n = 50 - Healthy: n = 75	Faeces	*R. gnavus* was seen more in patients with ileo-colitis or total colitis compared to those with colonic CD or left-sided UC. *R. gnavus* that also consist of beta-glucuronidase which could lead to inflammation, was said to show a wide distribution of IBD in patients.	[21]
IBD	- IBD: n = 20 - Healthy: n = 12	Faeces	Increased abundance of *R. gnavus* was found in IBD patients. Even though *R. gnavus* is an obligate anaerobe, it was found to have higher tolerance to atmospheric oxygen leading to its increased abundance in IBD gut.	[28]
Pouchitis	- Normal pouch: n = 16 - Recurrent acute pouchitis: n = 6 - Chronic pouchitis: n = 27	Faeces	*R. gnavus* was decreased after antibiotic treatment. Treatment with Ciprofloxacin and Metronidazole did reduce the levels of *R. gnavus* that were said to be linked with a greater risk of developing pouchitis.	[25]
Pouchitis	- UC and undergoing pouch surgery: n = 20	Faeces	The genus *Ruminococcus* was reduced in the pre-pouchitis group patients compared to patients in the normal-pouch sustained group. The presence of *R. gnavus* in UC patients prior to pouch surgery could be used as a predictor for the development of pouchitis.	[22]

Pouchitis, IBD	- Healthy: n = 80 - UC: n = 43 - CD: n = 57 - Normal pouch: n = 35 - Pouchitis: n = 34	Faeces	Increased abundance of *R. gnavus* was noted in patients with pouchitis. Not much mucus was used or degraded in IBD but changes were noted in the constitution of mucolytic bacteria, mainly shown by *R. gnavus* strains that consist of fucosidases and this is seen in pouchitis.	[12]
Pouchitis, UC	- UC undergoing IPAA: n = 21	Faeces	Presence of *R. gnavus* in patients with UC prior to colectomy was said to have a higher risk of pouchitis post-IPAA. They also found that patients who did not have *R. gnavus* in their gut microbiome had higher pouchitis-free survival compared to patients who have the bacteria.	[20]
UC	- Active UC: n = 34 - Healthy: n = 6	Faeces	*R. gnavus* was enriched in donors of failed FMT. It was found to be greater in relapse patients compared to those who had continuous remission. Relapse was also seen in patients who received donor microbiota consisting of increased levels of *R. gnavus.* Thus, it was mentioned that *R. gnavus* could be a useful predictor for failed donors.	[8]
UC	- Active UC: n = 31	Faeces	Proinflammatory bacteria like *R. gnavus* was enriched in UC patients compared to the donor. They also found that after FMT, *R. gnavus* did decrease. The findings from the study showed that single donor FMT treatment turned out to be effective for UC patients and repeated process of FMT also have its benefits in improving the condition.	[7]
UC	- Healthy: n = 28 - UC: n = 28	Intestinal mucosa	Particularly done on Chinese population. Findings showed an increase in *R. gnavus* in the mucosal microbiome of patients with UC.	[19]
CD	- Healthy: n = 14 - CD: n = 39	Faeces and blood serum	*R. gnavus* was increased in patients with CD and also in CD patients with psychological conditions. Bloom of *R. gnavus* in CD patients can cause psychological conditions as it is said to affect the	[24]

			gut–microbiota–brain axis via different mechanisms.	
CD	- Healthy: n = 25 - CD: n = 25	Faeces and saliva	*R. gnavus* was found to be enriched in CD patients compared to control. The polysaccharide produced by *R. gnavus* is said to be the cause of inflammation in CD.	[23]
CD	- CD: n = 27 - Non-CD: n = 17	Jejunal and ileal mucosa	Increased abundance of *R. gnavus* was found in CD patients regardless of the route of insertion or sampling procedure. It was enriched in the small intestine mucus layer.	[26]
IBD and CDI	- IBD: n = 56 - Healthy: n = 24	Faeces	Dysbiosis with *R. gnavus* was increased in IBD patients with CDI compared to IBD patients without CDI. In conclusion, they found that IBD patients with CDI had a marked intestinal dysbiosis but the cause of it is still unknown.	[30]
CD	- Active CD: n = 20	Faeces	*R. gnavus* was found to have high bile acid 7α-dehydroxylating activity which leads to secretion of secondary bile acids. Pathogenesis of CD and colon cancer have been associated with high levels of secondary bile acids. Moreover, increased abundance of *R. gnavus* was also reported in CD patients.	[31]
CD	- CD: n = 68 - Unaffected relatives: n = 84 - Healthy control: n = 55	Faeces	An increased abundance of *R. gnavus* was seen in CD patients. *R. gnavus* is said to express high levels of b-glucuronidase which can release some toxic substance in the gut leading to inflammation. In this study, they also found that the unaffected relatives of CD patients had different microbiome composition compared to the controls.	[32]
CD	- CD patients undergoing colonoscopy or surgical resection: n = 25	Biopsy	*R. gnavus* was increased in CD patients especially in the small bowel. It was highly significant because all the CD patients in the subgroup did have an increase in *R. gnavus* making the result reliable even though the sample size was small.	[34]
IBD	- CD: n = 64 - UC: n = 84	Faeces	The fluorescent signals (FSSs) for *R. gnavus* was higher in patients with CD compared to the healthy controls. *R. gnavus* was also said to have	[27]

	- Symptomatic non-IBD: n = 116 - Healthy: n = 44		proinflammatory actions and was able to degrade mucin, which was also shown in other studies.	
IBD	- CD: n = 26 - UC: n = 43 - Non-IBD: n = 14	Mucosa	*R. gnavus* was increased in CD patients compared to the non-IBD control group. When compared between CD and UC patients, more inflammatory bacteria like *R. gnavus* was seen in CD patients and protective bacteria were seen in UC patients. This shows that the gut environment is more inflammatory in CD patients compared to UC patients.	[29]
PI-IBS	- PI-IBS: n = 11 - Healthy: n = 10	Colonic mucosal biopsy	Study was done *ex vivo* where cytokine response was observed using some anaerobic bacteria including *R. gnavus*. Usage of *R. gnavus* in PI-IBS patients did show a decrease in cytokine (IL-1β), however there were no difference in the release of other cytokines.	[35]

2.2. Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a chronic gastrointestinal condition which causes symptoms like abdominal discomfort, pain and changes in bowel habits (diarrhoea or constipation) [35]. The prevalence of IBS and IBD has been increasing worldwide in the Western population [36]. The cause of IBS is also not really known, but there are several factors said to be associated with IBS, like changes in the gut microbiome, low levels of inflammation in the mucosa, genetic susceptibility, and diet [37, 38]. Some studies have also been done to look at the association between *R. gnavus* and IBS. Baumgartner et al. [36] found that biofilms were very prevalent in IBS compared to IBD and *R. gnavus* was identified in increased abundance in colonic biopsies with biofilms (BF+). Biofilms have the ability to destroy the mucus layer, leading to activation of the immune system through the release of proinflammatory polysaccharides by *R. gnavus* [36]. Another study was done *ex vivo* where cytokine response was observed using some anaerobic bacteria, including *R. gnavus*. Stimulation with *R. gnavus* in post-infectious irritable bowel syndrome (PI-IBS) patients resulted in a decrease of interleukin-1β (IL-1β) [35]. As changes in the gut microbiome are one of the causes of IBS, a study was done to find the effect of FMT in IBS patients. The bacterial strains that were found before FMT, like *R. gnavus*, became insignificant 3 weeks post-FMT [37].

2.3. Pouchitis

For patients with UC, the main surgical option would be restorative proctocolectomy and ileal pouch anal-anastomosis (IPAA), where the procedure involves resecting the colon and rectum, and a pouch is created from the healthy small intestine [22]. Most of the patients, unfortunately, might develop inflammation of the pouch (pouchitis) created during the procedure normally within 1 year post-surgery [20]. The pathogenesis of pouchitis is still unclear, however several causes have been found, such as defective immune system and gut dysbiosis seen in genetically predisposed individuals [25]. Maharshak et al. [22] and Machiels et al. [20] found an abundance of *R. gnavus* in patients with pouchitis. These studies also found that the existence of *R. gnavus* prior to the surgery was associated with a greater risk of developing pouchitis after IPAA. Thus, the composition of the gut microbiota of UC patients prior to the surgery, especially the presence of *R. gnavus*, could be used as a predictor of developing pouchitis [20, 22]. Pouchitis is said to be responsive to antibiotics; however, certain patients might have developed resistance to the antibiotics or have recurrent flares where they need longer periods of antibiotics [25]. A study found that antibiotic treatment with ciprofloxacin and metronidazole had an impact on the levels of *R. gnavus* where there was a decrease in the bacteria in patients with pouchitis [25].

2.4. Animal models examining roles of Ruminococcus gnavus in the gastrointestinal tract

As shown in Table 2, several studies have been done using mouse models to identify the association between *R. gnavus* and IBD and related inflammatory diseases. Studies found that an increased abundance of R. gnavus was observed in murine colitis models. This finding was similar to the human studies [39, 40]. Paneth cell metaplasia which is normally present in the bowel, and abnormal production of lysozyme are features of IBD. When the Paneth cell lysozyme was disrupted, the mice were protected from experimental colitis; however, an increased abundance of *R. gnavus* was observed in mice with lysozyme deficiency [41]. *R. gnavus*, which is a mucin degrader and a tryptamine producer, can affect the gut microbiome in the release of mucus by producing tryptamine. This makes *R. gnavus* less protective and also leads to exacerbation of IBD [42]. Several other studies were done to check for therapeutic options against *R. gnavus* that were tested in murine models.

Table 2. Association between *Ruminococcus gnavus* and various murine models.

Murine model	Subject	Study group	Sample	Findings	Ref.
Colitis in MCJ-deficient mice	C57BL/6 mice	MCJ-deficient mice vs wild-type B6 mice	Colon	Increased abundance of *R. gnavus* was detected in MCJ-deficient colitis-induced mice. *R. gnavus* was also found to play an important role in gut dysbiosis that can adapt with increase oxidative stress.	[39]
Colitis	C57BL/6 mice	Wild type (WT) and lysozyme deficient mice	Colon	Expansion of *R. gnavus* was seen in Lyz1-deficient mice due to reduced intestinal immune responses. However, decreased abundance of *R. gnavus* was seen in Lyz1-deficient mice after FMT.	[41]
DSS-induced colitis	Germ-free mice	Tryptamine (Trp D+) mice vs Trp D- mice	Faeces	R. gnavus have been found to be one of the species that expresses tryptophan decarboxylase. As a mucin degrader and tryptamine producer, R. gnavus may be harmful and lead to progression of IBD.	[42]
DSS-induced colitis	C57BL/6J male mice	Normal vs DSS-induced colitis vs DSS colitis mice with malvidin 3-glucoside (MV)	Colon	*R. gnavus* was decreased in colitis mice with MV. MV is also able to improve symptoms of colitis by regulating the presence of *R. gnavus* and its adaptation to oxidative stress.	[9]
4,6-trinitrobenzen esulfonic acid (TNBS)-induced colitis	Female BALB/c mice	Vehicle vs Resveratrol vs TNBS+Vehicle vs TNBS+Resveratrol	Colon and faeces	TNBS administration caused a decrease in *R. gnavus*. However, an increased abundance of *R. gnavus* was detected in the groups that were treated with Resveratrol compared to those treated with vehicle.	[43]

Colitis	Interleukin-10 null ($Il10^{-/-}$) mice	($Il10^{-/-}$) vs weaned wildtype (WT) mice	Faeces and colon	In $Il10^{-/-}$ mice, oligosaccharide 2-fucosyllactose (2FL) and 3FL led to an increased abundance of *R. gnavus* thus also reducing the progression of colitis after weaning especially 2FL. After treated with antibiotic, *R. gnavus* was enriched in $Il10^{-/-}$ mice and helped reduce inflammation.	[44]
IBD	Female C3H/HeN mice	Bacterial vs yeast suspension vs control	Faeces and colon	Increased abundance of *R. gnavus* was found in the colon. They also found that *R. gnavus* showed some effects on metabolism. Bacteria that were found to be enriched in IBD patients like *R. gnavus* showed a proinflammatory mechanism.	[40]
DSS-induced colitis	Male C57BL/6 mice	Darkening vs non-darkening cranberry beans vs basal diet control	Colon and faeces	Beans help reduce the abundance of *R. gnavus* which was seen during faecal analysis compared to the basal diet control group.	[10]
Colitis	129S6/SvEv (129) and C57BL/6 (B6) mice	Germfree (GF) interleukin-10-deficient ($IL\text{-}10^{-/-}$) vs wild-type (WT) mice	Colon and faeces	In mice colonised with *R. gnavus*, increased levels of IL-17 were produced by the mesenteric lymph node (MLN) cells. Increased abundance of *R. gnavus* was noticed in the 129 WT, 129 $IL\text{-}10^{-/-}$, and B6 $IL\text{-}10^{-/-}$ mouse groups. *R. gnavus* was also found to express proinflammatory cytokines from *ex vivo*-stimulated MLN cells.	[45]
NAFLD	Male and female C57BL/6 mice	Control diet vs HFD	Blood and tissue	In PXR-KO mice, decrease in *R. gnavus* was observed and it led to higher resistance to NAFLD in females. Thus, it shows that PXR plays a role in down-regulating proinflammatory bacteria like *R.*	[46]

				gnavus and this was specifically seen in females.	
NAFLD	Healthy male Sprague-Dawley rats	Normal, model, pioglitazone hydrochloride (PH), Shuganlidan, Jianpihuatan, Tongfuxiezhuo, and dachaihu decoction (DD)	Faeces	*R. gnavus* was found to play an important role in the model group, however not much information was given about it. They found that "Tongfuxiezhuo" element improved the gut microflora of the NAFLD rats.	[47]
n.a.	C57Bl/6 J male mice	Total Western Diet (TWD) vs Prebiotics (PRE) vs Probiotics (PRO) vs Tri-Factor and COM (prebiotics, probiotics and Tri-Factor)	Faeces and colon	In prebiotic fed mice, an increased abundance of *R. gnavus* was found in the gut microbiota. There was an increase in the COM group and PRE group but a significant increase was seen in PRE group. However, there was no effect seen on gut inflammation.	[48]
Humanised mouse model	C57BL/6 J female mice	Fucosyl-α1,3-GlcNAc (3FN), fucosyl-α1,6-GlcNAc (6FN), lacto-N-biose (LNB) and galacto-N-biose (GNB)	Faeces	*R. gnavus* was not seen in the control group but after disaccharide supplementation it was present showing that its survival is dependent on disaccharide. An increased abundance of *Ruminococcus* genus specifically *R. gnavus* was seen in all 4 disaccharide groups.	[49]

n.a. – not applicable

3. *Ruminococcus gnavus* in skin-related inflammatory conditions

3.1. Dermatitis

Dermatitis is an inflammatory condition of the skin. Among the different types of dermatitis, atopic dermatitis, commonly known as eczema, is the most common type and usually starts in early childhood. It is a common disorder affecting 60% of children in the first year of their lives, and it has been rising worldwide [50]. Eczema is the initial step of an atopic diathesis, which represents a sequence of atopic diseases from childhood till later in

life [51]. It starts with atopic dermatitis, followed by allergic rhinitis and asthma. Symptoms seen in these patients are skin patches that are dry, itchy, and red, which are seen on the flexor regions, and they get worse at night [52]. Even though several studies have been done regarding eczema, the pathogenesis of this disease is still unclear [53, 54]. Some associations between the gut microbiome with atopic sensitisation, IgE-mediated eczema, and the development of asthma are currently being studied. As the microbiome is associated with immune development, it is sensible to hypothesise that the gut microbiota can play a vital role in the development of allergic conditions [55, 56].

Several studies have investigated the role of *R. gnavus* in patients with atopic dermatitis [51, 55]. Zheng et al. [51] found an increased abundance of *R. gnavus*, which is linked with atopy and inflammation, in infants with eczema. It is said to be related to the expression of beta-glucuronidase by *R. gnavus*, which could lead to inflammation. They also suggest that the abundant taxa can be used to differentiate the gut microbiome of healthy infants compared to infants with eczema [51]. Another study found that the presence of *R. gnavus* was linked with changes in functional genes in relation to the development of the host immune system. Stimulation by the gut microbiota antigens is needed to improve the gut immune system further. *R. gnavus*, a mucin degrader, is said to supply nutrients that allow the colonisation of different gut microbes and is also involved in immune development. Thus, the colonisation of the gut microbiome by mucin-degrading bacteria, such as *R. gnavus*, and the contribution of mucin-degrading bacteria to the host's innate immune development in the gut, which plays an important role in atopic dermatitis [55].

Furthermore, De Filippis et al. [57] did a study to understand the importance of gut microbiota in the treatment and prevention of allergies. They found that *R. gnavus* was enriched in the gut microbiota of allergic children compared to the healthy controls. The *R. gnavus* strains found in those with food or respiratory allergies showed reduced capacity to break down fibre and had genes required in the secretion of proinflammatory polysaccharides. *R. gnavus* strains in allergy showed an increased ability to attach to the gut mucosa and colonise the area, which might be associated with the pathogenesis of the disease [57].

3.2. Hidradenitis Suppurativa

Hidradenitis suppurative (HS) is a long-term, painful skin condition that presents with inflammatory lumps, usually around the axilla, groin, and breast area. It is said to be predominantly seen in females compared to males [58]. There have been several comorbidities found in HS patients, which include spondyloarthritis, metabolic syndrome, and IBD,

especially Crohn's disease (CD). The pathogenesis of HS is still unclear, but it might be due to blocked hair follicles, impaired release of inflammatory cytokines (such as TNF-α, IL-1β, and IL-17), and dysbiosis. Some studies found that HS might be associated with smoking, obesity, and genetic susceptibility [58]. In a study by McCarthy et al. [58], they investigated the association between dysbiosis of the skin, nasal mucosa, and faeces with the manifestation of HS. The proinflammatory polysaccharide secreted by the *R. gnavus* causes the release of cytokines like TNF-α through toll-like receptor 4 of the innate immune system and this polysaccharide has shown significant association with the pathogenesis of HS. Besides, comorbidities associated with HS could have the same aetiology due to the presence of *R. gnavus.* They have postulated the possible therapeutic target for HS where the selective reduction of microbes, such as *R. gnavus*, could help in improving the condition [58].

4. *Ruminococcus gnavus* in metabolic inflammatory syndrome

4.1. Diabetes mellitus

Type 1 diabetes (T1D) is a chronic condition that is usually seen more in children, teens, and young adults. It is due to the destruction of insulin-making cells in the pancreas called β-cells by the body's immune system via self-reactive T cells. However, the main pathogenesis of this condition remains unclear. It could be owing to the genetic predisposition of T1D or environmental triggers that disrupt gut microbiota composition, which may be involved in T1D [59, 60]. Unlike T1D, the more prevalent type 2 diabetes (T2D) is a long-term metabolic condition described by high glucose levels and insulin resistance. T2D is more commonly seen in adults but can also affect any other age group [61].

A study by Abdellatif et al. [59] examined the role of specific gut bacteria like *R. gnavus* in the development of T1D. Disruption to the gut microbiota and gut permeability are characteristics of T1D. They found that *R. gnavus* was enriched before the development of autoimmunity. This is because it could pass through the disrupted gut barrier, and the components released by it trigger a response from the islets that leads to metabolic problems and inflammation. They also found that *R. gnavus* was one of the bacteria that increased at the time of onset of T1D [59]. Another study was done to identify the role of gut microbiome in the development of T2D. The study found an increased abundance of *R. gnavus* in the faecal samples of T2D patients compared to the healthy controls. The development of T2D could also be linked with increased levels of proinflammatory cytokines, chemotactic cytokines, and inflammatory proteins found in the circulation [61, 62].

4.2. Obesity

With the advancement of microbiome studies, the definition of obesity is no longer just about the excessive accumulation of fat that could result in serious health issues that are potentially life-threatening, such as diabetes mellitus, hypertension, and hyperlipidaemia. A growing number of studies have suggested that obesity is a chronic, low-grade, and systemic inflammation of various tissues [63]. Proinflammatory diets like high amounts of carbohydrates, fried food, and meat with low intake of fruits and vegetables have been linked with obesity, including truncal obesity and other abnormalities in the liver [64]. Even though a clear causal link between proinflammatory diet and obesity is not found, the impact of diet on gut microbiota could be a possible link leading to long-term systemic inflammation and developing adiposity [65, 66]. Lozano et al. [65] investigated the role of diet in the gut microbiota that could lead to obesity. They found that eating a proinflammatory diet was linked to greater total fat mass, visceral adipose tissue, and liver fat when compared with an anti-inflammatory diet. As *R. gnavus* is a mucin-degrading bacteria that uses mucin as a source of carbon, this can lead to the disruption of the gut barrier and a surge of metabolite translocation into the circulation. In conclusion, having an anti-inflammatory diet that favours fruits and vegetables is recommended as it helps reduce inflammation and fat accumulation, resulting in a healthier gut microbiome [65].

During pregnancy, obesity is quite common, and it can lead to increased birth weight and a greater risk of childhood obesity, adding up to the risk of developing other chronic diseases. Obesity is also associated with systemic inflammation [67]. Another study was done to determine the association between pregestational body mass index (pre-BMI) status and inflammatory biomarkers, especially in the third trimester and the link with the gut microbiome. They found that greater levels of high-sensitive C-reactive protein (hs-CRP) and haptoglobin were associated with reduced microbiome diversity, and the values of these biomarkers were related to *R. gnavus*, particularly in mothers who were normoweight and overweight. They also found a positive association between haptoglobin and *R. gnavus* [67].

Obesity is not only commonly seen in humans but also in animals like dogs. An animal study was done to analyse the impacts of restricted feeding, weight loss, and the faecal microbiome of overweight dogs. They found a decreased abundance of *R. gnavus* with restricted feeding (high protein, high fibre diet) in dogs that lost weight. Strong associations between biological variables and gut microbiome were seen. Some studies show that some bacteria could aggravate obesity and its comorbidities and the other way around [68]. Another study on mice tested the effects of arachidonic acid (AA) on obesity via microbiome-guided

inflammation with the hypothalamus-adipose-liver axis. The mice were fed a high-fat diet (HFD), and another group was fed a low-fat diet as a control. The HFD mice group was divided into two groups; one group was fed with AA-enriched HFD and the other with HFD only. In the HFD and AA male mice group, an increased abundance of *R. gnavus* was found, and it was also linked with obesity, whereas a decreased abundance of *R. gnavus* was noted in female mice [69]. Pekkala et al. [70] conducted a study to identify if rats selectively bred for high capacity running (HCR) and low capacity running (LCR), their aerobic capacity had different age-dependent microbiota, and which bacterial taxa were involved in metabolism. They found that the LCR rats had a higher abundance of *Ruminococcus* genus compared to the HCR rats, which have been associated with obesity [70].

On the other hand, a study was done on malnourished Malawian children by transplanting their microbiome into germ-free mice which were fed with a Malawian diet [71]. This study aimed to test the relationship between gut microbiome and undernutrition. The results showed that *R. gnavus* (isolated from the faecal microbiota of healthy Malawian infants) improves the stunted growth phenotype transmitted by an immature and undernourished donor's microbiota [71].

5. Role of *Ruminoccous gnavus* in neurological and psychological disorders

Exploring the gut microbiome has also led to a deepened understanding of the gut-brain axis, a complex bidirectional communication network that integrates the gut, the central nervous system and various regulatory systems [72-74]. Metabolites produced through microbial activity in the gut can impact the brain, exerting influence indirectly by activating the enteric nervous and immune systems and directly through molecules that enter the bloodstream and pass through the blood-brain barrier [75, 76]. The altered composition of human gut microbiota has been associated with extraintestinal diseases such as neurodegenerative diseases [73, 77], stress, depression [78], anxiety and trauma-related disorders [79, 80], and neurodevelopmental dysfunctions. Although a causal effect of specific microbiota remains to be elucidated, studies in gnotobiotic mouse models have increasingly identified the role of the gut microbiota in the communication between the gut and the brain [81, 82]. One example is that a germ-free mice study found that monocolonisation of *R. gnavus* influenced the development and function of microglia and granule cells in the hippocampus and the integrity of the blood-brain barrier, leading to improved spatial memory via the increased production of specific metabolites such as tryptamine, indole and choline metabolites [83].

5.1. Autism spectrum disorder and attention deficit hyperactive disorder

In association studies, patients suffering from general anxiety disorders, depression [84], autism spectrum disorder (ASD) and attention deficit hyperactive disorder (ADHD) [85] have been reported to have altered levels of *R. gnavus*. The existing research on the associations between *R. gnavus* and the pathophysiology of ADHD and ASD has yielded inconsistent findings across studies [85, 86]. Despite some inconsistency in previous association studies, the role of *R. gnavus* has been getting clearer with the increasing number of studies on the two neurodevelopmental disorders. For ADHD, Wan et al. [86] revealed a significant reduction in the abundance of *R. gnavus* in the faecal samples from children with ADHD compared to the age-matched healthy controls. Meanwhile, a more recent study demonstrated that *R. gnavus* is associated with externalizing behaviour in children with ADHD [85]. For ASD, reported in 2013, there was no significant difference in the faecal samples between children with ASD and healthy controls [87]. Meanwhile, a recent study by Fujishiro et al. [88] showed a significantly increased abundance of *R. gnavus* in children with ASD who had been born preterm compared to typically developing children who had been born preterm. In another recent study, a longitudinal study design [89], *R. gnavus* has been shown to be positively correlated to the elevated likelihood of ASD infants together with the reduced availability of GABA, which may interfere with neurodevelopment and contribute to the development of ASD. A recent study from Denmark, for the first time, showed that children and adolescents with ADHD and ASD share gut microbiota signatures different from controls [90]. *R. gnavus* was found to be increased in abundance together with elevated plasma lipopolysaccharide-binding protein and proinflammatory cytokine levels, suggesting increased gastrointestinal permeability and translocation described in the development of both ADHD and ASD.

5.2. Cognitive function and neurodegenerative diseases

The elderly population in the world is increasing faster as the years pass. The gut microbiome has been the main therapeutic target for a healthy ageing process. During the ageing process, there are changes in their lifestyle and function of the gastrointestinal tract, increased levels of inflammation, and changes in their diet, which could all affect the gut microbiome. Changes in the gut microbiome can affect age-related functions like cognitive decline [91], leading to the risk of developing age-related diseases, including Alzheimer's disease [92, 93] and Parkinson’s disease [77]. In the animal model, Park and Wu [92] showed that the abundance of *R. gnavus* was higher in the scopolamine-induced memory deficit mice than in the normal mice group. Interestingly, a recent study discovered a significant negative

association between *R. gnavus* and cognitive scores from a large cohort of healthy and neurotypically developing children by analysing the relationship between the gut microbial taxa and their gene functions and the overall cognitive function and brain regions [94]. The study indicated that *R. gnavus* could be a potential biomarker of neurocognition and brain development, acting as a target for early detection and intervention.

Based on a study conducted by van Soest et al. [91], the association between diet, gut microbiome, and cognitive function was observed in older Dutch adults. They found that diets rich in animal products were linked with proinflammatory bacteria, such as *R. gnavus*, where the increased intake of such diets leads to a greater abundance of *R. gnavus*. Conversely, diets rich in plant products, such as fruits, nuts, and seeds, had anti-inflammatory properties that were associated with a higher anti-inflammatory gut microbiome. However, they did not identify the link between cognitive function and gut microbiome, even though inflammation has a role in cognitive decline [91]. Another recent study revealed that *R. gnavus* is associated with cognition in vascular cognitive impairment (VCI) [95]. The study showed a negative association between the abundance of *R. gnavus* with the Montreal Cognitive Assessment scores and cerebral blood flow in the bilateral hypothalamus and left amygdala in VCI patients, suggesting the involvement of nutrition and metabolic pathways in VCI.

6. Role of Ruminococcus gnavus in rheumatic disorders

6.1. Spondyloarthritis

Spondyloarthritis (SpA) is defined as a group of inflammatory conditions that have similar clinical features and pathogenesis but different outcomes [96]. It is a multifactorial disorder that could be associated with genetic predisposition and other environmental triggers; however, the exact pathogenesis is still unclear. SpA is a diverse disorder that includes axial and peripheral joint arthritis along with extra-articular manifestations comprising psoriasis, IBD, and uveitis. Genetics plays an important role in SpA, as a study has found that the human leukocyte antigen (HLA)-B27 is the important gene involved in SpA [97]. Breban et al. [97] investigated the association between gut dysbiosis and SpA, and they found that *R. gnavus* was enriched in SpA patients compared to those with rheumatoid arthritis and healthy controls. The abundance of R. gnavus also increased in SpA patients with no history of IBD and also in those with a history of IBD compared to the controls. This shows the role of *R. gnavus* as a proinflammatory bacteria and further provides evidence regarding the possible association between SpA and IBD [97].

Ankylosing spondylitis (AS), which is a subtype of SpA, involves mainly the sacroiliac joints and the spine, causing inflammation [96]. Chen et al. [96] conducted a study to determine the association between the gut, and they found a decreased abundance of *R. gnavus* in AS patients, especially in axial AS patients. There are contradictory results seen between these two studies, where Breban et al. [97] reported an increased abundance of *R. gnavus* in SpA patients. The discrepancy between them is assumed to be due to the gut inflammatory status, so further studies have to be done on this [96].

6.2. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is an autoimmune condition that causes multisystem inflammation due to dysfunction of B cells, autoantibodies production directed towards nuclear components, and immune complex deposition. The pathogenesis of SLE is still unclear. However, it is assumed to be associated with genetic and environmental factors [98]. A study was done to find if any pathogen was associated with the development of SLE. They found that SLE patients had higher levels of *R. gnavus* compared to the controls. The abundance of *R. gnavus* was directly proportional to the disease activity. The faecal samples of SLE patients had an increased amount of sIgA-coated *R. gnavus*. Moreover, SLE patients with nephritis had an increased abundance of *R. gnavus* with increased serum IgG levels to its cell wall lipoglycan antigens [98, 99].

7. Association of *Ruminococcus gnavus* with respiratory-related diseases

Acute respiratory distress syndrome (ARDS) is a severe type of lung injury that could lead to respiratory failure due to lung inflammation. It is caused by various causative agents, and one of them is staphylococcal enterotoxin-B (SEB). SEB is a potent bacterial toxin produced by *Staphylococcus aureus* that can induce the production of cytokines. SEB that is inhaled could lead to ARDS, which has a high mortality rate [100]. There are no proper treatments for ARDS, so a study was conducted to investigate the effects of Δ9-tetrahydrocannabinol (THC) in a murine model of SEB-mediated ARDS [100]. They found an increased abundance of beneficial bacteria like *R. gnavus* in mice treated with THC. THC increased the amount of *R. gnavus* in the lungs, colon, and blood of ARDS mice. *R. gnavus* was viewed as a beneficial bacterium because of its role in regulating mucin in the mucus. THC was found to suppress the expression of mucin Muc5ac, which is linked with inflammation and obstruction of airways, but boosted the expression of mucin Muc5b, which helps in mucociliary clearance, managing infections in the airways, and preserving the immune system in mouse lungs. Thus, treatment with THC helps reverse dysbiosis and other changes caused by SEB, which helps in the survival of the mice [100].

Severe COVID-19 patients have also been known to develop ARDS, cytokine storm, and lung failure, which have been increasing due to the pandemic [101-106]. The SARS-CoV-2 virus is found to infect and replicate in human small intestine enterocytes and alter the gut microbiota composition in COVID-19 patients. With that, substantial studies have demonstrated the close relationship of gut microbiota with host inflammatory immune responses in COVID-19 [107, 108]. Dotan et al. [109] described in a recent article that the lung and gut microbiomes could have an immense role in the pathogenesis, clinical severity, outcomes, and treatment of COVID-19.

In a cohort study, Yeoh et al. [110] found that the gut microbiome of COVID-19 patients was enriched with taxa associated with immune dysfunction, including *R. gnavus*, while depleted with gut commensal microbes that are known to play immunomodulatory roles in the human gut. The study also corroborated with Gou et al. [111], which showed that *R. gnavus* is more prevalent in COVID-19 patients and correlated with inflammatory markers. The study employed a multi-omics approach to demonstrate the positive correlation between *R. gnavus* and proinflammatory cytokines from a large healthy human cohort based on a constructed blood proteomic risk score derived from COVID-19 patient data, serving as valuable tools for prognosis as well as potential preventive or therapy for COVID-19 [111]. With the latest findings, six months after the clearance of the SARS-CoV-2 virus, long-COVID patients still presented gut dysbiosis, which is characterized by a higher number of specific species of harmful bacteria, including *R. gnavus* [112]. The study highlighted that gut dysbiosis is strongly associated with persistent symptoms in patients after recovering from COVID-19 infection. Given the available approaches for modulating gut microbiota, including probiotics, prebiotics, and synbiotics, there is potential for easing and alleviating the burden of long-COVID syndrome [113-115].

Smoking has been increasing among the population in recent times, and it is leading to more deaths due to the diseases caused by smoking itself. Smokers have a higher risk of developing many diseases like heart disease, respiratory diseases, and cancer compared to non-smokers. The harmful substances found in cigarette smoke can alter the microbiome by inducing cytokine release, mucin production, and reactive oxygen species in the blood. Smoking can also cause inflammation by producing more proinflammatory bacteria in the body [116]. Yan et al. [116] conducted a study to determine the effects of smoking on certain diseases through alteration in the gut microbiome. Faecal samples were collected from smokers and non-smokers for this study. They found an increased abundance of *R. gnavus* in smokers compared to non-smokers. This is because of the production of certain antigens and stimulation of the immune system by *R. gnavus* to release antibodies, leading to more

inflammation. Conversely, in non-smokers an increased abundance of anti-inflammatory bacteria was observed [116].

8. Role of *Ruminococcus gnavus* in cardiovascular diseases

Coronary artery disease (CAD) is one of the most common cardiovascular diseases seen in the adult population in recent years, and it has been increasing as well. Disruption in the gut microbiota has been associated with cardiovascular diseases [117-119]. A case-control study investigated the association between certain bacterial species and CAD. Stool samples were collected from CAD patients and healthy controls to compare the gut microbiota between the two groups. After analysing, they found an increased abundance of *R. gnavus* in patients with advanced CAD, even after adjusting for diabetes mellitus and dyslipidaemia. They also identified that an increase in *R. gnavus* could be used as a predictor of CAD after adjusting for cardiovascular risk factors. Besides, they also found that inflammation and mucin metabolisation cause gut barrier disruption, leading to exposure to certain foreign substances that could be associated with *R. gnavus* and the development of CAD [117].

Another study was done to explore the link between gut dysbiosis, some proinflammatory substances, and osteocalcin (OCN) expressing endothelial progenitor cells (EPC) in CAD and control patients. Osteogenic EPCs can cause damage to endothelial repair and develop CAD with calcification of vascular cells. Unstable CAD has been associated with the immature release of OCN-expressing EPCs [120]. In this study, stool samples were collected from CAD and non-CAD patients for analysis. They found an increased abundance of *R. gnavus* which was associated with immature OCN expressing EPCs, particularly in diabetic patients. A weak but positive link was found between *R. gnavus* and the immature OCN-expressing EPCs, which were more notable in diabetic patients. However, further studies are needed to look at the role of *R. gnavus* in atherosclerosis [120].

R. gnavus is also linked to the increased production of trimethylamine N-oxide (TMAO), a proatherogenic metabolite associated with increased risk for cardiovascular diseases [121]. Using both metagenomic and metabolomic analyses of faecal and plasma samples, Cui et al. [122] investigated the gut microbiota dysbiosis in chronic heart failure (CHF) patients. The study found that CHF patients had a distinct gut microbiota composition from controls, particularly characterised by an increase of *R. gnavus*. Furthermore, the study discovered a positive correlation between the abundance of *R. gnavus* and the level of TMAO in plasma samples of CHF patients, suggesting that *R. gnavus* may contribute to the elevated TMAO production in CHF.

9. Role of *Ruminococcus gnavus* in other conditions

9.1. Bilateral tubo-ovarian abscess

Currently, there are more studies about the role of *R. gnavus* in inflammatory conditions like IBD, SLE, and SpA. However, there are fewer studies regarding the role of *R. gnavus* in the genital tract. A case report described a patient who presented with bilateral tubo-ovarian abscess (TOA), where *R. gnavus* was detected from the abscess fluid via computed tomography-guided drainage. Based on this case report, the usage of amoxicillin/clavulanic acid stabilised the patient who remained afebrile, which shows that it can be a therapeutic option in treating *R. gnavus* [123]. The vagina, which is said to be colonised by *R. gnavus*, could be a possible entry route for this bacterium through ascending infection. As mentioned earlier, the role of *R. gnavus* in the urogenital tract is still not known, and this case of bilateral TOA could be useful for further investigation of the nature of this bacteria [123].

9.2. Tic disorder

Tics are sudden, repeated movements that people involuntarily do when they are not able to stop themselves from doing it. Different terms are used for tic disorders (TD) based on the type of tic (either motor or vocal or a combination of both) [124]. There are different terms, such as provisional tic disorder (PTD), Tourette syndrome (TS), and chronic motor or vocal tic disorder (CTD). These are disorders involving neurodevelopment that are commonly seen in childhood or teenagers. The pathogenesis of TD is not completely understood; however, it might be associated with genetic predisposition and environmental triggers [125]. After faecal microbiota transplantation, there was some improvement noticed in children with TD, which led Xi et al. [125] to investigate the role of the gut microbiome in children with TD by examining the bacterial taxa involved with the severity of TD and observing the effect of dopamine receptor antagonist (DRA) drugs on the gut microbiome. They found that TD children treated with DRA drugs showed an increased abundance of *R. gnavus*. This suggested that the abundance of this bacteria could be a possible side effect of DRA drugs [125].

9.3. Exercise-induced stress

During vigorous exercise, the demands required can start a stress response and activate the sympathetic-adrenomedullary and hypothalamus-pituitary-adrenal (HPA) axes, causing the release of stress hormones, proinflammatory cytokines, and other molecules. Moreover, the gut microbiota can affect the host's behaviour, gut barrier, and immune system,

which are said to be the main features of the brain-gut axis [126]. As there is an association between the gut microbiome and gut-brain axis on stress and food intake, a systematic review was done to find the role of gut microbiome in exercise-induced stress and its impact on the health and performance of athletes. They found that in exercise-induced stress murine models, there was an increased abundance of *R. gnavus* and its role in immune function. It was increased in the forced treadmill running group compared to the sedentary group. This shows that exercise plays a role in altering the gut microbiota seen in the murine models [126].

10. Discussions

To date, comprehensive studies have established the involvement of *R. gnavus* in various inflammatory conditions, positioning it as a possible causative factor in the pathogenesis of these disorders. Considering its role, therapeutic interventions aimed at targeting *R. gnavus*, particularly strategies to reduce its abundance, hold promise for enhancing gut health. Previous case reports have identified *R. gnavus* as susceptible to a spectrum of antibiotics, including penicillin and amoxicillin/clavulanic acid, meropenem, imipenem, cefotaxime, ceftriaxone, minocycline, tetracycline, metronidazole, clindamycin, vancomycin and piperacillin/tazobactam [2, 127, 128]. However, the exploration of conventional antibiotics as a viable option presents substantial challenges, primarily owing to the escalating threat of antibiotic resistance. The indiscriminate use of antibiotics significantly contributes to the emergence of resistant strains [129-132], undermining the efficacy of these agents and posing a public health concern. Addressing these challenges requires a paradigm shift towards innovative antimicrobial strategies that selectively target *R. gnavus*.

Natural sources, such as plants and animals, offer a rich reservoir of bioactive compounds with potential antimicrobial properties [133-136]. For instance, the vast biodiversity of plant secondary metabolites and animal-derived peptides [137] holds promise for identifying specific molecules capable of modulating *R. gnavus* abundance without inducing resistance mechanisms [138]. Moreover, integrating plant-based compounds and animal-derived peptides aligns with the burgeoning field of nutraceuticals, emphasizing the potential health benefits derived from natural sources [139, 140]. Investigations into the anti-inflammatory and antimicrobial properties of such bioactive molecules can contribute to the development of precision nutrition, where tailored dietary approaches aim to optimize individual health [141, 142]. Dietary modifications can influence the abundance of specific microbial taxa, contributing to shifts in the overall gut microbiome profile [143, 144]. Studies showed certain diets or dietary components might help reduce the pathogenic microorganisms and restore dysbiosis [145, 146]. In a study conducted on murine colitis model, researchers found that

ingestion of malvidin 3-glucoside (MV), which is found in blueberries, reduced the amount of *R. gnavus* in colitis mice due to its anti-inflammatory properties, thus improving gut inflammation and the integrity of the colon [9]. Monk et al. [10] also found that cranberry beans reduced the abundance of *R. gnavus* in dextran sulfate sodium-induced colitis mice. The beans helped decrease the severity of the disease and damage to the colon, thus improving its condition [10]. This shows that diet-induced changes can alter the gut microbiome and help with the disease process.

Microorganisms have historically been prolific sources of bioactive compounds with antimicrobial properties [147-150]. These compounds, often produced as secondary metabolites, may exhibit specific activities against pathogenic bacteria [151-155]. Exploring microbial biodiversity and isolating novel compounds offer potential avenues for developing targeted interventions [156-160]. Furthermore, bacterial-derived therapeutics have been gaining attention in the last decade. Bacteria strains from specific genera, such as *Lactobacillus* sp., *Bifidobacterium* sp., *Streptomyces* sp. and *Bacillus* sp., are classified as probiotics that can exert beneficial effects on the host by modulating the gut microbiota [161-164]. There is growing interest in the potential role of probiotics in managing inflammatory diseases due to their influence on the gut microbiota and the immune system [165-168]. While research is ongoing and the field is evolving, some studies suggest that certain probiotic strains may have anti-inflammatory effects and could be beneficial for inflammatory conditions [169-172]. Toscano et al. [173] have found that oral intake of probiotics consisting of *Lactobacillus rhamnosus* HN001 and *Bifidobacterium longum* BB536 reduce the abundance of certain bacteria, including *R. gnavus* [173]. However, in another study, an increase in *R. gnavus* was found in mice's gut microbiomes after prebiotic supplementation and when given in combination with probiotics. In addition, the treatments did not affect gut inflammation [48]. These studies show various degrees of efficacy and contradictory results, so further studies should be conducted. Nevertheless, the use of probiotics in managing inflammatory diseases requires careful consideration, especially in vulnerable populations, and their efficacy as a monotherapy continues to be explored in a wide range of diseases [174, 175]. Future research is warranted to elucidate the specific mechanisms, advancing towards personalized applications of specific probiotic strains tailored to individual microbiota profiles. Interestingly, a recent study by Chua et al. [176] demonstrated that *Akkermansia muciniphila* exerted an antagonistic effect towards *R. gnavus* via the secretion of small molecules, structurally similar to apigenin, lovastatin and ribavirin, ameliorating the burden of *R. gnavus* outgrowth associated to chronic hepatitis B. Ultimately, the probiotic applications into inflammatory disease management should be conducted under the guidance of healthcare professionals,

considering factors such as the strain specificity, disease types, patient history, and the latest scientific evidence [177].

Faecal microbiota transplantation (FMT) is the transfer of a healthy microbiome from a donor to a recipient, which aims to restore microbial balance and alleviate diseases due to gut dysbiosis [178]. FMT has shown promising results in improving inflammatory conditions, especially in IBD [179, 180]. Ren et al. [7] found a decrease in *R. gnavus* in patients with UC after FMT, where there were changes seen in the gut composition post-FMT treatment [7]. In another study, they found that the different bacterial strains like *R. gnavus* seen in IBS patients and donors prior to FMT became insignificant 3 weeks post-FMT, showing some positive results after FMT treatment [37].

Taken together, future research for *R. gnavus* should encompass a broader range of inflammatory conditions and delve deeper into mechanistic pathways through which *R. gnavus* contributes to the underlying inflammatory immune responses, potentially paving the way for targeted therapeutic interventions. Further investigation is also needed to elucidate these interventions' efficacy, safety, and long-term impacts on human subjects [181-183]. Clinical trials and longitudinal studies could provide valuable insights into the feasibility and potential risks associated with those aforementioned treatments [182, 184].

11. Conclusions

The involvement of *R. gnavus* in inflammatory conditions has been extensively examined through human studies and murine models. Elevated levels of *R. gnavus* have been observed in various inflammatory conditions such as IBD, IBS, eczema, spondyloarthritis, SLE, ARDS, metabolic inflammatory syndrome and coronary artery disease. The consistent association between an increased abundance of *R. gnavus* and diverse inflammatory disorders suggests its potential utility as a potential biomarker for both prognosis and diagnosis in various inflammatory diseases. Furthermore, an enrichment of *R. gnavus* is also evident in COVID-19 patients as well as smokers as opposed to non-smokers. Moreover, the mechanistic link between *R. gnavus*, mucin utilization, and the production of the inflammatory polysaccharide glucorhamnan provides insight into the specific pathways through which *R. gnavus* may exacerbate inflammation, thereby influencing the severity of these conditions. Future research should delve deeper into understanding these mechanisms to implement targeted therapeutic strategies aimed at mitigating the impact of *R. gnavus* on disease severity, ultimately offering new avenues for improving patient outcomes in the context of inflammatory diseases.

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