

# An Update on the Role and Potential Molecules in Relation to *Ruminococcus gnavus* in Inflammatory Bowel Disease, Obesity and Diabetes Mellitus

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**Abstract:** *Ruminococcus gnavus* (*R. gnavus*) is a gram-positive anaerobe commonly resides in the human gut microbiota. The advent of metagenomics has linked *R. gnavus* with various diseases, including inflammatory bowel disease (IBD), obesity, and diabetes mellitus (DM), which has become a growing area of investigation. The initial focus of research primarily centered on assessing the abundance of *R. gnavus* and its potential association with disease presentation, taking into account variations in sample size, sequencing and analysis methods. However, recent investigations have shifted towards elucidating the underlying mechanistic pathways through which *R. gnavus* may contribute to disease manifestation. In this comprehensive review, we aim to provide an updated synthesis of the current literature on *R. gnavus* in the context of IBD, obesity, and DM. We critically analyze relevant studies and summarize the potential molecular mediators implicated in the association between *R. gnavus* and these diseases. Across numerous studies, various molecules such as methylation-controlled J (MCJ), glucopolysaccharides, ursodeoxycholic acid (UDCA), interleukin(IL)-10, IL-17, and capric acid have been proposed as potential contributors to the link between *R. gnavus* and IBD. Similarly, in the realm of obesity, molecules such as hydrogen peroxide, butyrate, and UDCA have been suggested as potential mediators, while glycine ursodeoxycholic acid (GUDCA) has been implicated in the connection between *R. gnavus* and DM. Furthermore, it is imperative to emphasize the necessity for additional studies to evaluate the potential efficacy of targeting pathways associated with *R. gnavus* as a viable strategy for managing these diseases. These findings have significantly expanded our understanding of the functional role of *R. gnavus* in the context of IBD, obesity, and DM. This review aims to offer updated insights into the role and potential mechanisms of *R. gnavus*, as well as potential strategies for the treatment of these diseases.

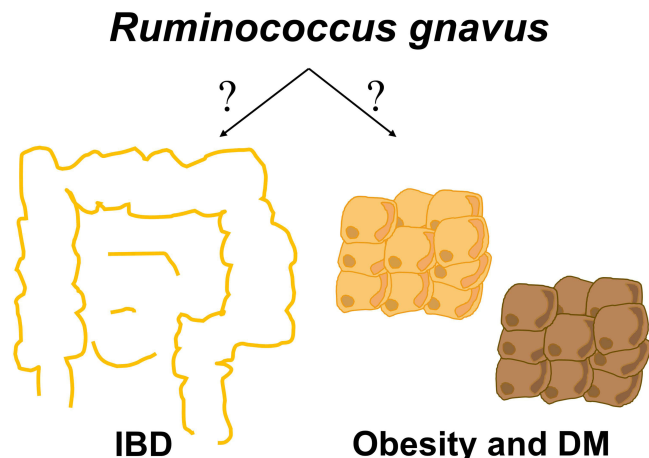
**Keywords:** *Ruminococcus gnavus*, inflammatory bowel disease, obesity, diabetes mellitus

## Background

The human gut microbiota is a complex ecosystem comprising bacteria viruses, fungi and other microbial and eukaryotic species.<sup>1</sup> With bacteria being the predominant taxonomic group, the microbiota comprises around 100 trillion microorganisms, classified into at least 1000 different species.<sup>2</sup> The medicinal fungus *Hericium erinaceus* as been shown to ameliorate gastrointestinal disorders through modulation of inflammatory processes.<sup>3,4</sup> The gut microbiota grows within the mucin layer and plays a crucial role in maintaining host homeostasis by offering protection to the gut barrier, shaping the immune system, and regulating human metabolism, nutrient absorption, and drug metabolism.<sup>5-9</sup>

Perturbations in gut microbiota have been implicated in the development of multiple diseases, including inflammatory bowel disease (IBD), obesity, and diabetes mellitus (DM).<sup>10</sup> In IBD patients, the most prominent changes in the microbiota

## Graphical Abstract



were the decreased diversity in bacteria species associated with decreased abundance of *Bacteroidetes* and *Firmicutes*,<sup>11,12</sup> alongside an increase in the abundance of *Proteobacteria*.<sup>11</sup> In addition, lower abundance of *Faecalibacterium prausnitzii* and *Roseburia* were recorded in patients with Crohn's disease (CD) and ulcerative colitis (UC).<sup>13</sup> There was also an enhancement of proteobacteria, *Neisseriaceae corrodens*, *Pasteurellaceae*, *Veillonella parvula* and *E. coli* in patients with CD.<sup>14</sup> Yeast and fungal taxa have also increased in CD patients such as *Cyberlindnera jadinii*, *Clavispora lusitanae*, *Candida albicans*, *Saccharomyces cerevisiae* and *Kluyveromyces marxianus*.<sup>12</sup> A systematic review on gut microbiota analysed sixty studies and concluded that the *Proteobacteria* phylum was most frequently associated with IBD<sup>15</sup> and obesity.<sup>16</sup> As seen in the animal model of obesity, the increased ratio *Firmicutes* to *Bacteroidetes* observed in individuals with obesity becomes a predisposing condition to excessive production of metabolites from nondigestible polysaccharides.<sup>17–20</sup> Observational studies in humans have shown that the genera of opportunistic pathogens were enriched in type 2 diabetes mellitus (T2DM) patients, while the genera *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, and *A. muciniphila* were negatively associated with T2DM.<sup>21</sup> Gut microbiota alternation in diseases have become a growing area of investigation.<sup>22</sup>

*Ruminococcus gnavus* (*R. gnavus*; family Lachnospiraceae) was first identified in 1974 as a strict anaerobe in the gut of healthy individuals.<sup>23</sup> It was reported to be one of the 57 species present in more than 90% of healthy North American and European adults, and in 65% of publicly available metagenomes of gut microbiota from healthy adults from China, Ethiopia, Spain, USA, and Sweden.<sup>24,25</sup> But recent evidence indicated that a disproportionate representation in the composition of *R. gnavus* can impact the pathophysiology of certain diseases, including IBD, obesity, DM, neurological disorders, and cancer.<sup>26</sup> While initial research generally examined the abundance of *R. gnavus* and its relation to disease presentation with various sample size, methods of sequencing and analysis, there has recently been a more prominent shift towards understanding the mechanisms by which *R. gnavus* can lead to disease manifestation.<sup>27</sup> Clarifying these mechanisms can inform the development of novel therapies and optimise clinical practice.<sup>22</sup> Therefore, through a critical review of current literature, we aim to provide an updated overview of the significant advancements made and summarize the potential mechanisms or the role of molecules in relation to *R. gnavus* in IBD, obesity, and DM.

## ***R. gnavus* and IBD**

### **Role of *R. gnavus* in IBD**

IBD is a complex immune-mediated inflammatory condition that affects the gastrointestinal tract, encompassing CD and UC.<sup>28</sup> It has been sporadically observed since ancient times, and has emerged as a growing problem in newly industrialized countries.<sup>29–31</sup> The prevalence of IBD has been increasing over the past decades in most regions.<sup>32</sup>

Accumulating evidence suggests that perturbations in the microbiota, particularly commensal flora, and host defensive responses at the mucosal frontier has been implicated in the initiation and pathogenesis of IBD.<sup>33–35</sup> An increasing number of studies show a positive association between *R. gnavus* and IBD, although a causal relationship remains to be demonstrated.<sup>36</sup> Active IBD often coincides with an increase in the abundance of *R. gnavus*, goes from an average of 0.1% in healthy controls (HC) to 69% in IBD patients with active disease.<sup>37</sup> This increase in *R. gnavus* abundance is associated with a decrease in *Akkermansia*, and this microbial shift has been proposed as a biomarker for mucosal integrity in IBD.<sup>38–40</sup> A study by Christine et al, analyzing fecal samples from children under 18 years old, found that the fecal microbiota profiles differentiated between IBD and non-IBD symptomatic children when compared to healthy children. However, both IBD and non-IBD symptomatic patients displayed similar dysbiosis.<sup>41</sup> Similarly, there was a more remarkable increase in the abundance of *R. gnavus* in the macroscopically and histologically normal intestinal epithelium of IBD, when compared to HC.<sup>38</sup>

*R. gnavus* has been implicated in the pathogenesis of CD.<sup>42</sup> By sequencing colonic biopsies from CD patients (undergoing colonoscopy or surgical resection) and HC with 16S rDNA, and detecting fecal samples with whole metagenome shotgun sequencing (WMGS), *R. gnavus* was remarkably enriched in CD patients when compared to HC.<sup>43</sup> Additionally, when comparing fecal samples from CD patients and their unaffected relatives, Joossens et al, found a higher abundance of *R. gnavus* in CD patients.<sup>44</sup> In IBD patients, the most distinctive feature between CD and UC was a significantly higher abundance of *R. gnavus* in CD.<sup>45</sup> Interestingly, studies on twins concordant or discordant for CD or UC have also demonstrated an increase in *R. gnavus* in CD patients.<sup>46</sup> A study of 56 mucosal microbiome samples from 28 Chinese UC patients and their healthy family partners showed an increase in *R. gnavus* in the mucosal microbiome of UC patients.<sup>47</sup> Consistently, furthermore, in UC patients who underwent fecal microbiota transplantation (FMT), the abundance of *R. gnavus* was found to be higher in donors of failed FMT and decreased after FMT.<sup>48,49</sup>

Pouchitis, a common complication following restorative proctocolectomy with ileal pouch-anal anastomosis for UC, is associated with increased levels of *R. gnavus* compared to UC and CD.<sup>50–52</sup> Additionally, in patients with *Clostridium difficile* infection (CDI), which can be a complication of IBD, *R. gnavus* has been found to be more abundant compared to HC and IBD patients without CDI.<sup>53,54</sup>

However, it is worth mentioning that some studies have reported decreased or even absent levels of *R. gnavus* in IBD patients, including those with UC and CD.<sup>55,56</sup> In a cohort study conducted in Korea, *R. gnavus* was found to be significantly more abundant in CD patients with a better prognosis, suggesting it may serve as a biomarker for favorable outcomes in CD.<sup>57</sup> Overall, the role of *R. gnavus* in the context of IBD remains unclear, but studies suggest that it plays a significant role in modulating the gut microbiota at the mucosal level. For a comprehensive summary of studies investigating the relationship between *R. gnavus* and IBD, please refer to [Supplementary Table 1](#).

## **Molecules in Relation to *R. gnavus* in IBD**

### **Methylation-Controlled J (MCJ)**

MCJ functions as an endogenous negative regulator of mitochondrial respiration.<sup>58</sup> Its absence can lead to increased activity of complex I and adenosine-triphosphate (ATP) synthesis, as well as the formation of respiratory supercomplexes, which helps to limit the production of reactive oxygen species (ROS).<sup>58–60</sup> In MCJ-deficient colitis-induced mice, it has been observed that *R. gnavus* levels are increased, along with higher expression of myeloid differentiation primary response gene (Myd) 88, toll-like receptor (TLR) 9, and immunoglobulin A (IgA).<sup>61</sup> *R. gnavus* is known to be highly IgA coated, regardless of the specific IgA target.<sup>62</sup> Furthermore, gene expression analyses in UC patients have shown decreased levels of MCJ and higher expression of tissue inhibitor of metalloproteinase 3 (TIMP3). This leads to the inhibition of tumor necrosis factor (TNF)  $\alpha$  converting enzyme (TACE) activity, which in turn inhibits the shedding of TNF from the cell membrane in the colon.<sup>61</sup> Anti-TNFs have been the first line of biologic therapies for IBD and have remained a cornerstone of IBD treatment in clinical practice over the past two decades, despite the emergence of numerous new therapies.<sup>63</sup> Therefore, the absence of MCJ may contribute to an altered gut microbiota composition, such as increased levels of *R. gnavus*, and dysregulated immune responses, which could have implications for the pathogenesis and treatment of IBD.

## Glucorhamnan and Ursodeoxycholic Acid

Glucorhamnan is primarily composed of a repeating unit of five sugars, with a linear backbone consisting of three rhamnose units and a short side chain made up of two glucose units.<sup>64</sup> *R. gnavus* has the ability to synthesize and secrete a complex glucorhamnan polysaccharide, which has been found to strongly induce the secretion of TNF- $\alpha$  through TLR4 activation.<sup>64,65</sup>

In addition to its polysaccharide synthesis capabilities, *R. gnavus* has also been reported as a producer of ursodeoxycholic acid (UDCA). It possesses an enzyme that can degrade 7-keto lithocholic acid (LCA) into UDCA.<sup>66</sup> Administration of UDCA has been shown to increase colonic LCA levels and inhibit caspase-3 cleavage.<sup>67</sup> Abnormal apoptosis in intestinal epithelial cells (IECs) can disrupt the integrity of the intestinal barrier, leading to bacterial infiltration and triggering an inflammatory cascade.<sup>68</sup> The dysregulated apoptosis also stimulates the production of TNF- $\alpha$  and interferon-gamma (IFN- $\gamma$ ), both of which further promote apoptosis.<sup>68</sup> Moreover, UDCA has been found to activate the epidermal growth factor receptor (EGFR)/ Raf-1/ extracellular regulating kinase (ERK) signaling pathway in colorectal cancer.<sup>67</sup>

## IL-10 and IL-17

Stimulation of mesenteric lymph node cells from IL-10<sup>-/-</sup> mice with *R. gnavus* lysate has been found to result in higher production of IL-17, indicating that *R. gnavus* can induce the secretion of IL-17.<sup>69,70</sup> IL-17 is a cytokine that is thought to contribute to the development of IBD, which expressed at higher levels in IBD patients compared to healthy controls.<sup>71,72</sup> Additionally, the non-inflamed mucosa of IBD patients exhibits significantly lower IL-17 levels compared to inflamed mucosa.<sup>73</sup> Furthermore, IL-17 has been shown to play a role in the progression of colorectal cancer through various signaling pathways, including signal transducer and activator of transcription 3 (STAT3), nuclear factor kappa B (NF- $\kappa$ B), and mitogen-activated protein kinase (MAPK) pathways.<sup>74,75</sup>

## Tryptamine

In patients with IBD, *R. gnavus* has been found to be highly abundant and positively correlated with tryptamine levels.<sup>65</sup> Specifically, *R. gnavus* is capable of producing tryptamine, which can affect gut motility through several mechanisms. First, tryptamine activates the serotonin receptor 4 (SR4) or 5-hydroxytryptamine receptor 4 (5-HT4R), leading to an increase in intracellular cyclic adenosine monophosphate (cAMP) concentration. This elevation in cAMP levels can enhance gut motility. Second, tryptamine can also increase fluid secretion by acting on the cystic fibrosis transmembrane regulator (CFTR). The activation of CFTR promotes the secretion of fluids into the gut, affecting gut motility.<sup>76–78</sup>

## Caprylic Acid

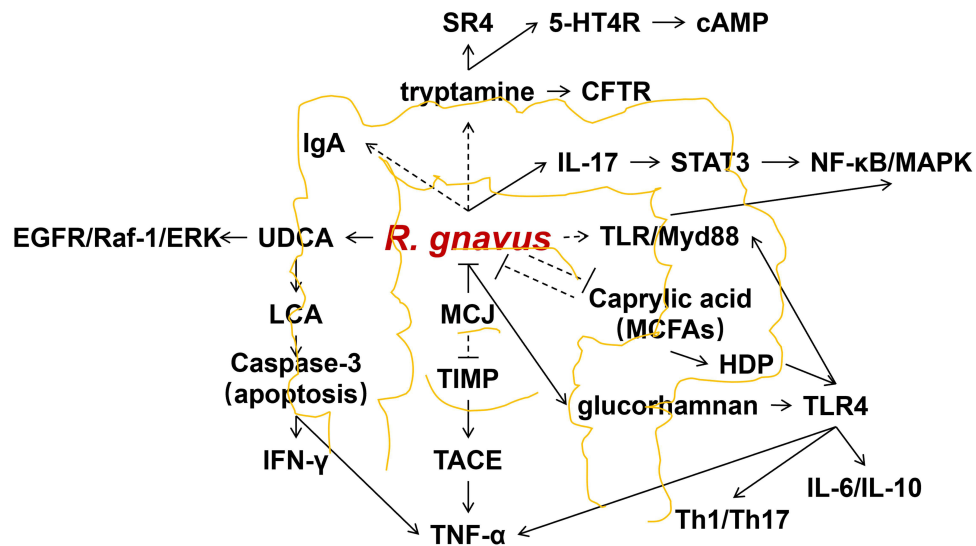
Caprylic acid, also known as octanoic acid, is a medium-chain fatty acid (MCFA) that possesses antibacterial and antiviral properties.<sup>79</sup> In the context of IBD, caprylic acid has been found to be enriched in non-IBD controls and negatively associated with the abundance of *R. gnavus*, which is consistent with previous observations of MCFA depletion in IBD.<sup>79,80</sup> This negative association suggests that *R. gnavus* may either take up and metabolize caprylic acid, leading to its depletion, or caprylic acid may possess inhibitory effects on the growth of *R. gnavus*.

Relative studies have indicated that MCFA can induce the production of host defense peptides (HDP) and activate TLR4.<sup>81,82</sup> Activation of TLR4 triggers the activation of NF- $\kappa$ B and MAPK pathways through the interaction between TLR4's toll-IL-1 receptor domain and Myd88.<sup>83,84</sup> Furthermore, TLR4 can mediate the production of interleukin(IL)-6 and IL-10.<sup>85,86</sup> and influences the balance of T helper (Th) 1 and Th17 cells.<sup>87</sup> Figure 1 provides a summary of the potential molecules in relation to *R. gnavus* in IBD.

## *R. gnavus* and Obesity

### Role of *R. gnavus* in Obesity

According to the World Obesity Atlas 2023, over 4 billion adults and nearly 3 million children will be overweight or obese by 2035, a significant global health concern.<sup>88</sup> *R. gnavus* has been found to be significantly more abundant in obese



**Figure 1** Molecules in relation to *R. gnavus* in IBD.

**Abbreviations:** *R. gnavus*, *Ruminococcus gnavus*; IL, Interleukin; SR4, serotonin receptor 4; 5-HT4R, 5-hydroxytryptamine receptor 4; cAMP, cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane regulator; STAT, signal transduction and activator of transcription; NF-κB, nuclear factors- kappa B; MAPK, mitogen-activated protein kinase; IgA, immunoglobulin A; MCFAs, medium-chain fatty acid; HDP, host defense peptides; TLR, toll-like receptor; Myd, myeloid differentiation primary response gene; Th, T helper; TNF, tumor necrosis factor; TACE, tumor necrosis factor  $\alpha$  converting enzyme; TIMP, tumor necrosis factor  $\alpha$  converting enzyme inhibitor tissue inhibitor of metalloproteinase; MCJ, Methylation-controlled J; UDCA, ursodeoxycholic acid; LCA, lithocholic acid; EGFR, epidermal growth factor receptor; ERK, extracellular regulating kinase; IFN- $\gamma$ , interferon-gamma.

individuals and decreases with weight loss.<sup>89,90</sup> Similar findings have been observed in obese dogs and rats.<sup>91</sup> Furthermore, there is a positive association between *R. gnavus* and body mass index (BMI),<sup>92</sup> as well as a strong correlation with fat mass.<sup>93</sup> However, a cross-sectional study involving 236 children reported a significantly negative relationship between the abundance of *R. gnavus* and BMI status, body fat distribution, and leptin levels.<sup>94,95</sup> A summary of studies investigating the relationship between *R. gnavus* and obesity can be found in [Supplementary Table 2](#).

## Molecules in Relation to *R. gnavus* in Obesity Haptoglobin (Hp)

Hp is an inflammation marker that plays a role in the interaction between obesity and inflammation.<sup>96</sup> Hp expression in white adipose tissue (WAT) is increased in obesity rodents,<sup>97</sup> and the level of Hp was found to be significantly correlated with the abundance of *R. gnavus* in individuals of normal weight and overweight.<sup>98</sup>

Hp binds to free hemoglobin (Hb) and inhibits oxidative tissue damage by reducing the release of heme iron and the generation of reactive oxygen species (ROS).<sup>99</sup> Hp has the ability to attract monocytes/macrophages through interaction with chemokine receptor 2 (CCR2), which is mediated by MAPK phosphorylation.<sup>100</sup> It has been observed that the MAPK p38 inhibitor down-regulates the phosphorylation of CCAAT/enhancer binding protein (C/EBP)- $\alpha$ , peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), STAT 3, fatty acid synthase (FAS), perilipin A, as well as its downstream effector activating transcription factor-2 (ATF-2).<sup>101</sup> Hp levels increase in WAT with weight gain, activate macrophages, and lead to the release of TNF- $\alpha$  and IL-6.<sup>102–104</sup>

## Butyrate

*R. gnavus* was initially characterized in 1976 as a bacterium capable of producing acetate, formate, ethanol, and a small quantity of lactate, but not butyrate, when cultured in peptone-yeast extract glucose broth.<sup>26</sup> However, a recent investigation on the dynamics of butyrate levels during the transition from an infant-like to an adult-like gut microbiota revealed a negative correlation between butyrate levels and the abundance of *R. gnavus*.<sup>105</sup> Given the observational nature of this study, further research focusing on the direct relationship between butyrate levels and *R. gnavus* is warranted.

Butyrate has been shown to play a role in energy homeostasis mediated by the gut microbiota, and it is found in higher amounts in obese individuals compared to lean individuals.<sup>106</sup> Butyrate is involved in the thermogenesis of adipose tissue.<sup>106</sup> Brown adipose tissue (BAT) is a key site of thermogenesis and energy expenditure, and butyrate can stimulate thermogenesis by up-regulating uncoupling protein (UCP) 1 and uncoupling mitochondrial respiration from ATP synthesis.<sup>107</sup> Additionally, butyrate has been shown to activate peroxisome proliferator-activated receptor coactivator-1 $\alpha$  (PGC-1 $\alpha$ ) through UCP1.<sup>108</sup> Butyrate supplementation has been found to increase PGC-1 $\alpha$  expression in BAT and is positively associated with GPCR43, suggesting a role for GPCR43 in activating PGC-1 $\alpha$ .<sup>109</sup> Moreover, butyrate stimulates PGC-1 $\alpha$  activity by activating AMP-activated protein kinase (AMPK) and inhibiting histone deacetylases (HDACs).<sup>110</sup> The knockout of lysine-specific demethylase 1 (LSD1) has been shown to block the butyrate-induced increase in thermogenesis and energy expenditure in BAT, suggesting LSD1 as a potential mediator of butyrate-induced thermogenesis.<sup>111,112</sup> Further studies have found that butyrate can activate LSD1 to increase UCP1 expression, and these effects are independent of AMPK.<sup>111</sup> Germ-free mice have been reported to have impaired thermogenic capacity in BAT due to decreased expression of UCP1.<sup>113</sup> Consistent with this, depletion of gut microbiota has been found to impair the thermogenesis of BAT, and butyrate supplementation partially rescues thermogenesis function.<sup>113</sup> This indicates that butyrate improves the function of BAT by regulating gut microbiota dysbiosis in obese mice.<sup>114,115</sup> Similar to BAT, beige adipocytes in WAT release energy as heat, and their thermogenesis is mediated by UCP1.<sup>116</sup> Butyrate supplementation has been shown to increase the expression of UCP1 and beige adipocyte markers to mediate thermogenesis in WAT, requiring GPCR43, GPCR41, and LSD1.<sup>111</sup> Butyrate acts as a ligand for metabolite-sensing GPCRs, mainly GPCR43, GPCR41, and GPCR109a.<sup>117,118</sup> Butyrate is the only SCFA that can bind to GPCR109a and regulate body energy expenditure to maintain metabolic homeostasis.<sup>118</sup> These mechanisms may be associated with the effects of butyrate on obesity.

Studies have shown that butyrate supplementation can lead to a reduction in body weight by decreasing lipogenesis in the liver and adipose tissue.<sup>119</sup> This effect is mediated by the activation of the PPAR $\gamma$ -mediated AMPK-acetyl-CoA carboxylase (ACC) pathway, which increases the expression of the glucagon-like peptide-1 receptor (GLP-1R).<sup>119,120</sup> Butyrate has also been found to modify histone acetylation on the promoter of the beta3-adrenergic receptors ( $\beta$ 3AR) gene and activate cAMP-dependent protein kinase A (PKA), leading to the phosphorylation of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL).<sup>121</sup> Additionally, butyrate supplementation can reverse the reduction of HDACs.<sup>122</sup>

Increasing fatty acid oxidation (FAO) can help reduce fat accumulation and improve obesity.<sup>123</sup> Butyrate has been shown to induce the expression of carnitine palmitoyltransferase-1 (CPT-1) in liver and adipose tissue,<sup>109</sup> which is the rate-limiting enzyme of FAO.<sup>124</sup> This effect is mediated by the AMPK/histone deacetylase inhibitor (HDACi)-PGC-1 $\alpha$  pathway.<sup>110</sup> Additionally, as an HDACi, butyrate activates AMPK by enhancing the expression of adiponectin receptors (adipoR)-1/2.<sup>125</sup> Butyrate also increases the expression of cytochrome c oxidase (COX-1), UCP2, and UCP3 in skeletal muscle.<sup>126</sup> Furthermore, butyrate has been found to significantly increase the levels of gut hormones such as glucagon-like peptide-1 (GLP-1) and polypeptide YY (PYY) in the colon and plasma, mediated by recombinant free fatty acid receptor 3 (FFAR3).<sup>127</sup>

## Ursodeoxycholic Acid (UDCA)

*R. gnavus* has been reported to produce UDCA.<sup>128</sup> In a mouse model of diet-induced obesity, UDCA treatment altered the profiles of bile acids and fatty acids.<sup>128</sup> UDCA down-regulated sterol regulatory element-binding protein 1c (SREBP1c), a transcription factor that promotes the expression of lipogenic genes such as fatty acid synthase (FAS) and SCD1.<sup>129</sup> Furthermore, UDCA reversed the inhibition of factors involved in FAO, including PPAR- $\alpha$ , CPT-1A, acyl-CoA oxidase (Aco), and down-regulated the expression of genes involved in fatty acid uptake in the liver, such as fatty acid transporter protein (FATP) and cluster of differentiation 36 (CD36).<sup>129</sup> These findings indicate that UDCA alters the profile of free fatty acids (FFAs) by inhibiting lipogenesis, promoting FAO, and reducing fatty acid uptake in adipose tissue.

Moreover, UDCA down-regulated the phosphorylation of NF- $\kappa$ B and STAT3 by negatively regulating the expression of suppressor of cytokine signaling (SOCS)-1 and SOCS3 signaling pathways.<sup>129</sup> These changes were accompanied by a decrease in angiogenesis, as evidenced by the down-regulation of vasoactive endothelial growth factor (VEGF), vascular cell adhesion molecule (VCAM), and transforming growth factor (TGF)- $\beta$  expression.<sup>129</sup> Additionally, UDCA significantly up-regulated adipose tissue browning, which was associated with the up-regulation of silent mating

type information regulation 2 homolog (SIRT)-1-PGC1- $\alpha$  signaling in epididymal adipose tissue.<sup>129</sup> Figure 2 provides a summary of the potential molecules in relation to *R. gnavus* in obesity.

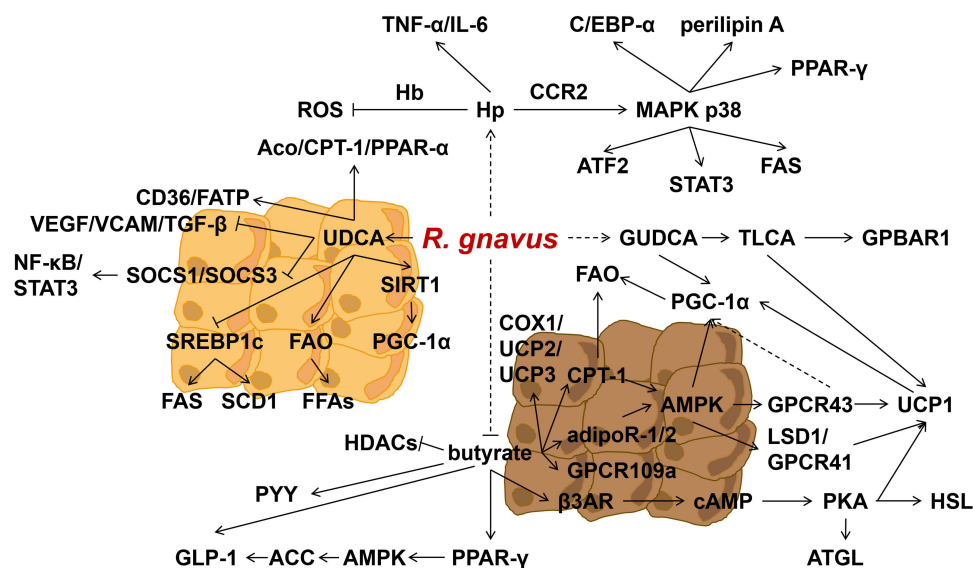
## *R. gnavus* and Diabetes Mellitus

### Role of *R. gnavus* in Diabetes Mellitus

Compared with HC, *R. gnavus* showed significantly higher abundance in patients with type 2 diabetes mellitus (T2DM) and prediabetes (PreDM).<sup>130,131</sup> Specifically, *R. gnavus* was found to be positively associated with the incidence of T2DM.<sup>132</sup> However, some studies have reported a reduction of *R. gnavus* in adults with PreDM-insulin resistance (IR), while it was found to be more enriched in a cluster characterized by moderate levels of blood glucose, severe IR, and hyperlipidemia. This was observed when compared to participants with the lowest blood glucose levels or participants with high blood glucose and insulin deficiency,<sup>133</sup> Supplementary Table 3 provides a summary of studies examining the relationship between *R. gnavus* and DM.

### Molecules in Relation to *R. gnavus* in Diabetes Mellitus

*R. gnavus* was found to have a positive correlation with glycine ursodeoxycholic acid (GUDCA) levels, which have been shown to improve metabolism by promoting fat thermogenesis.<sup>134</sup> Mammalian adipose tissue consists of WAT, BAT, and beige or brite adipose tissue.<sup>135</sup> WAT is characterized by single-locular lipid droplets and few mitochondria, while BAT has abundant mitochondria and multi-locular lipid droplets, and is highly vascularized.<sup>136</sup> Beige fat serves as an intermediary between BAT and WAT and can adapt to various environmental and pharmacological stimuli.<sup>136</sup> Notably, BAT possesses a unique capacity, distinct from other mitochondria-rich tissues, to induce energy futile cycling through the protein UCP1.<sup>137</sup> UCP1 can dissipate the mitochondrial membrane potential, resulting in the wastage of energy as heat.<sup>137</sup> This process leads to increased oxidation of glucose and fat to maintain ATP production.<sup>137</sup> However, in individuals with obesity and T2DM, the metabolic activity of BAT is suppressed.<sup>138,139</sup> GUDCA has the ability to



**Figure 2** Molecules in relation to *R. gnavus* in obesity and DM.

**Abbreviations:** *R. gnavus*, *Ruminococcus gnavus*; Hp, Haptoglobin; Hb, hemoglobin; ROS, reactive oxygen species; TNF- $\alpha$ , tumor necrosis factor alpha; IL-6, Interleukin-6; CCR2, chemokine (C-C motif) receptor 2; AMPK, AMP-activated protein kinase; MAPK, mitogen-activated protein kinase; C/EBP, CCAAT/enhancer binding protein; PPAR- $\gamma$ , peroxisome proliferator-activated receptor-gamma; ATF-2, activating transcription factor-2; STAT, signal transduction and activator of transcription 3; UDCA, ursodeoxycholic acid; Aco, acyl-CoA oxidase; SREBP1c, sterol regulatory element-binding protein 1c; FFA, free fatty acid; CPT-1, carnitine palmitoyltransferase-1; GUDCA, glycine ursodeoxycholic acid; GPBAR, G-protein-coupled bile acid receptor; FAS, fatty acid synthase; HDACs, histone deacetylases; UCP, uncoupling protein; COX, cytochrome c oxidase; GLP-1, glucagon-like peptide-1; ACC, AMP-activated protein kinase to phosphorylate acetyl-CoA carboxylase; PKA, cAMP-dependent protein kinase A; ATGL, adipose triglyceride lipase; CD36, cluster of differentiation 36; HSL, hormone-sensitive lipase;  $\beta$ 3AR, beta3-adrenergic receptors; FAO, fatty acid oxidation; GPCR, G protein-coupled receptors; PGC-1 $\alpha$ , peroxisome proliferator-activated receptor coactivator-1 $\alpha$ ; LSD 1, lysinespecificdemethylase1; TLCA, tauroolithocholic acid; cAMP, cyclic adenosine monophosphate; adipoR-1/2, adiponectin receptors-1/2; PYY, polypeptide YY; FATP, fatty acid transport protein; FAS, fatty acid synthase; SCD1, stearyl-CoA desaturase-1; FFAs, free fatty acids; SIRT, silent mating type information regulation 2 homolog; SOCS, cytokine signaling; STAT, signal transduction and activator of transcription; NF- $\kappa$ B, nuclear factors- kappa B; VEGF, vasoactive endothelial growth factor; VCAM, vascular cell adhesion molecule; TGF- $\beta$ , transforming growth factor beta.

regulate bile acid metabolism and induce the production of tauroolithocholic acid (TLCA), as well as activate the g-protein-coupled bile acid receptor (GPBAR)-1 and UCP1.<sup>140</sup> The deletion of the  $\beta$ 3AR receptor-cAMP-PKA-UCP1 cascade has been shown to reduce basal metabolic rate, making mice more prone to obesity.<sup>141</sup> GUDCA tends to increase the levels of PGC-1 $\alpha$ , although without a significant difference. Figure 2 provides a summary of the potential molecules in relation to *R. gnavus* in DM.

## Conclusions

*R. gnavus* was initially described as an important component of the human gut microbiota by Moore et al, in 1976 and was classified in the genus *Ruminococcus* within the family Ruminococcaceae. However, with the introduction of 16S rRNA analysis, it was reclassified as a species belonging to the phylum Firmicutes, class Clostridia, Clostridium cluster XIVa, and family Lachnospiraceae.<sup>142</sup> Across studies, gut dysbiosis, characterized by an imbalance in the abundance of *R. gnavus*, has been proposed to be associated with the development of inflammatory and metabolic diseases including IBD, obesity and DM. In this review, we provide an updated synthesis of the literature regarding *R. gnavus* in relation to IBD, obesity and DM in human subjects, and explore potential molecular mechanisms linking *R. gnavus* to these diseases through in vivo experiments. Despite variability in human metagenomic studies in terms of sample size, sequencing and analysis methods, and taxonomic classification, *R. gnavus* has been consistently reported to be more abundant in IBD, obesity, and DM compared to healthy individuals in most studies, although a few studies have reported contradictory results.

Regarding IBD, several molecules such as MCJ, glucorhamnan, UDCA, IL-10, IL-17, tryptamine, and caprylic acid, along with their related mechanisms, have been suggested as potential molecular mediators in the association between *R. gnavus* and IBD. In the context of obesity, molecules such as Hp, butyrate, and UDCA are proposed to be potential mediators in relation to *R. gnavus*, while GUDCA is implicated in the association between *R. gnavus* and DM. However, due to limited direct mechanistic studies on *R. gnavus* in these diseases, the proposed molecular relationships between *R. gnavus* and the diseases are predominantly derived from a combination of three types of research: animal studies investigating *R. gnavus* and molecules, correlation studies between *R. gnavus* and certain molecules in observational studies, and downstream effects of related molecules in disease pathogenesis. The latter two types of studies provide circumstantial evidence rather than direct proof, leading us to refer to these molecules as potential mediators in the interaction between *R. gnavus* and these diseases. This represents a limitation of our study.

Furthermore, it should be noted that the *R. gnavus* strain used in the research studies was ATCC 29149, which is strain-specific and may differ from *R. gnavus* as a species. Therefore, further intensive investigations are warranted to elucidate the direct effects of *R. gnavus* on the molecular pathways involved in IBD, obesity, and DM. It is essential to conduct additional research to determine whether targeting *R. gnavus*-related pathways could be an effective strategy in managing these conditions.

## Abbreviations

*R. gnavus*, *Ruminococcus gnavus*; IBS, irritable bowel syndrome; IBD, inflammatory bowel disease; DM, diabetes mellitus; NGS, next generation sequencing; WMGS, whole metagenome shotgun sequencing; CD, Crohn's disease; UC, ulcerative colitis; HC, healthy controls; FMT, fecal microbiota transplantation; CDI, Clostridium difficile infection; MCJ, Methylation-controlled J; SR4, serotonin receptor 4; ATP, adenosine-triphosphate; ROS, reactive oxygen species; Myd, myeloid differentiation primary response gene; TLR, toll-like receptor; IgA, immunoglobulin A; TNF, tumor necrosis factor; TACE, tumor necrosis factor  $\alpha$  converting enzyme; TIMP3, tumor necrosis factor  $\alpha$  converting enzyme inhibitor tissue inhibitor of metalloproteinase 3; UDCA, ursodeoxycholic acid; LCA, lithocholic acid; TLCA, tauroolithocholic acid; IECs, intestinal epithelial cells; IFN- $\gamma$ , interferon gamma; BAs, bile acids; EGFR, epidermal growth factor receptor; ERK, extracellular regulating kinase; STAT, signal transduction and activator of transcription; CCR2, chemokine (C-C motif) receptor 2; NF- $\kappa$ B, nuclear factors- kappa B; MAPK, mitogen-activated protein kinase; GPCR, epithelial G protein-coupled receptors; 5-HT4, 5-hydroxytryptamine receptor 4; cAMP, cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane regulator; MCFA, medium-chain fatty acid; HDP, host defense peptides; IL, Interleukin; BMI, body mass index; Hp, Haptoglobin; WAT, white adipose tissue; Hb, hemoglobin; ROS, reactive oxygen species; C/EBP, CCAAT/ enhancer-binding protein; PPAR, peroxisome proliferator-activated receptor; FAS, fatty acid synthase; ATF-2, activating transcription



factor-2; MCP-1, monocyte chemotactic protein 1; BAT, brown adipose tissue; UCP1, uncoupling protein-1; PGC-1 $\alpha$ , peroxisome proliferator-activated receptor coactivator-1 $\alpha$ ; AMPK, AMP-activated protein kinase; GLP-1R, glucagon-like peptide-1 receptor; ACC, AMP-activated protein kinase to phosphorylate acetyl-CoA carboxylase; ATGL, adipose triglyceride lipase; HSL, hormone-sensitive lipase;  $\beta$ 3AR, beta3-adrenergic receptors; PKA, protein kinase A; LPL, lipoprotein lipase; HDAC, histone deacetylase; HDACi, histone deacetylase inhibitor; FAO, fatty acid oxidation; CPT-1, carnitine palmitoyltransferase-1; adipoR, adiponectin receptors; COX-1, cytochrome c oxidase; FFAR3, free fatty acid receptor 3; SREBP1c, sterol regulatory element-binding protein 1c; SCD1, stearoyl-CoA desaturase-1; Aco, acyl-CoA oxidase; CD36, cluster of differentiation 36; PYY, polypeptide YY; FFAs, free fatty acids; FATP, fatty acid transport protein; CD 36, cluster of differentiation 36; SOCS, cytokine signaling; VEGF, vasoactive endothelial growth factor; VCAM, vascular cell adhesion molecule; SIRT, silent mating type information regulation 2 homolog; TGF, transforming growth factor; T2DM, type 2 diabetes mellitus; PreDM, prediabetes; IR, insulin resistance; GDM, gestational diabetes mellitus; HFD, high-fat diet; GUDCA, glycine ursodeoxycholic acid; TUDCA, tauroursodeoxycholic acid; TLCA, tauroolithocholic acid; GPBAR, G-protein-coupled bile acid receptor; LSD 1, lysinespecificdemethylase1.

## Data Sharing Statement

Data available on request from the first authors.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare no competing interests in this work.

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