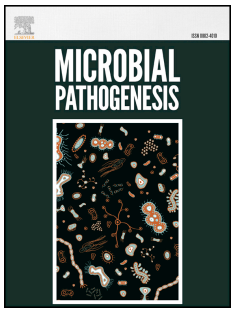

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The Critical Role of *Faecalibacterium prausnitzii* in Human Health: An Overview

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Abstract

Faecalibacterium prausnitzii (F. prausnitzii) is one of the most abundant bacterial species in the colon of healthy human adults and representing more than 5% of the total bacterial population. Recently, it has been known as a major actor in human intestinal health and a biosensor. Changes in this species population richness and quantity have been observed in many illnesses and several investigations have reported that abundance of *F. prausnitzii* is reduced in different intestinal disorders. In the current review, we aim to consider literature from various library databases and electronic searches (Science Direct, PubMed, and Google Scholar) which were randomly collected and serve as an overview of different features of *F. prausnitzii* including metabolites, anti-inflammatory action, and correlation of dysbiosis of this bacterium with various complications in human.

Keywords: *Faecalibacterium prausnitzii*, Anti-inflammatory, Microbiome, Gut Microbiota.

1. Introduction

The human gut microbiota consists of countless non-pathogenic microorganisms including bacteria and viruses [1]. The arrangement is affected by diverse elements including genotype, the sort of delivery, and early nourishment in addition to dietary components, age, antibiotic utilization, lifestyle, and miscellaneous metabolic issues [2, 3]. In recent years, it has been proven that the role of microorganisms community within the human gut is of utmost importance regarding the balance between health and disease [4]. Dysbiosis (imbalances in the microbial community) within the gut bacterial community and concomitant metabolic changes have an effect on human health [5]. The microbiome may affect the host metabolism through degrading non-enzymatically comestible foods, and synthesis of amino acids and short-chain fatty acids (SCFAs) [6]. Dysbiosis may have detrimental effects on host metabolism such as alterations in the abundance of nutrients crucial for homeostasis including butyrate [7].

Faecalibacterium prausnitzii (*F. prausnitzii*) is one of the most abundant anaerobic bacteria in the human gut microbiota, with a proportion of approximately 5% of total bacteria in feces according to the Meta-analysis of the Human Intestinal Tract project reports [8, 9]. Members of genus *Faecalibacterium* are considered as a commensal microorganism, ubiquitous within the gastrointestinal tracts (GIT) of animals and humans [10]. This taxon is the typical member of the *Clostridium leptum* cluster within the human colon, and known as the second-most common representative types in fecal samples, following the *Clostridium coccoides* [11]. The relative abundance of *F. prausnitzii* in animals and humans [12], reveals that this species is a functionally important member of the microbiota and presumably has a remarkable impact on the physiology and health of the host [13]. In that

context, changes in the abundance of *F. prausnitzii* related to various intestinal and metabolic diseases in humans have been widely described [14]. The expression of the relative abundances, which have been proposed as a possible indicator of gut dysbiosis in adult subjects, is considered as the ratio of *F. prausnitzii*/*E. coli* [15]. Based on the reported results in some studies, *F. prausnitzii* is an indicator and an active contributor to intestinal health and the maintenance of gut homeostasis due to its ubiquity and immunomodulatory properties [16]. In the current review, we aimed to investigate the impact of *F. prausnitzii* in human health according to the increasing number of studies, which have clearly described the importance of this highly metabolically active commensal bacterium and its relation with human health.

2. Energy producing and metabolites

Energy production is one of the crucial roles in *F. prausnitzii* to the colonocytes as well as anti-inflammatory metabolites cooperate for intestinal health [13]. The prebiotic fermentation process, as a nondigestible food component that stimulates and defines the health microbiota population, considered to the main contribution of *F. prausnitzii* metabolism [17]. The variation of *F. prausnitzii* population is related to modulation of eight urinary metabolites with diverse structures, which indicates highly functionally active members of the microbiome in this species [18]. This bacterium is one of the most well-known butyrate-producing bacteria (BPB) in the GIT [19]. Also, they can consume acetate and producing carbon dioxide, formate, and D-lactate, and hydrolyzing fructose, fructooligosaccharide, apple pectin, and starch, and some of them to hydrolyze inulin [20], although none of the strains isolated to date produce hydrogen [21]. However, it shows a narrow ability to utilize polysaccharides including arabinogalactan, xylan, and soluble starch that can be frequently encountered in the gut lumen

[22]. Although *F. prausnitzii* can ferment glucose to acetate, butyrate, D-lactate, and formate, probably, its modest received attention gives rise to an extreme oxygen-sensitivity and difficulties encountered in its cultivation. The majority of *F. prausnitzii* strains can grow on the host-derived sugar *N*-acetylglucosamine and some of them on D-glucosamine and D-glucuronic acid; has been reported in some *F. prausnitzii* isolates have B-glucuronidase activity as well [23]. The origin of most produced carbon from butyrate (around 85%) is external acetate [24].

Short-chain fatty acids (SCFAs) are considered as the main end products of the bacterial fermentation process in the human colon, which affect the host physiology widely and act as signaling molecules between gut microbiota and the host, with important implications for host health [25]. *F. prausnitzii* as an acetate consumer produces butyrate and bioactive anti-inflammatory molecules such as shikimic and salicylic acids [26] (Figure 1). The role of butyrate as an SCFA is very remarkable in gut physiology and the systemic functions and it has beneficial effects of the gut microbiota for human health [27]. *Eubacterium rectale* and *F. prausnitzii* are considered as two important butyrate producers in the human gut, which can degrade inulin and producing butyrate [27, 28]. Butyrate is produced abundantly in the human colon by *F. prausnitzii* [29]. The butyrate-producing has not affected by the metabolic activity of *F. prausnitzii*, and its potential for immunomodulation is also related to other molecules and/or metabolites; however, they have not yet been characterized [13]. Butyrate plays the main role in gut physiology and its pleiotropic effects in the intestinal cell life cycle and other numerous beneficial effects for health through the protection against pathogen invasion, modulation of the immune system and, reduction of cancer progression is of particular importance [27]. Butyrate production in the gut, by *F. prausnitzii* may affect the physiological functions and homeostasis to maintain health, however, most of the specific

physiological and health effects of butyrate production by this bacterium have not been displayed [13]. Butyrate represents the multiple pathways for electron disposal in the butyrogenic faecal bacteria, the concomitant generation of -NAD^+, reduced ferredoxin, facilitating immune response modulation. Also, it serves as a major energy source for colonocytes[13]. Butyrate is a key modulator of colonic health under the immune response aspect and appears to has both anti-inflammatory and cancer chemopreventive activities [30].

The metabolic activity of *F. prausnitzii* is not restricted to the production of butyrate, and its potential for immunomodulation is related to other molecules and/or metabolites as well, nevertheless, they have not yet been characterized [13]. However, it seems to necessarily investigate the role of *F. prausnitzii* metabolism on intestinal homeostasis, considering the crosstalk with the other members of the microbiota. *F. praunistzii* and *Bacteroides thetaiotaomicron* also are an acetate consumer and acetate producer respectively [31].

The intestinal mucus barrier has been modulated by *B. thetaiotaomicron* and *F. prausnitzii* through modifying goblet cells and mucin glycosylation. These bacteria are metabolically complementary in vivo [32]. Salicylic acid is another anti-inflammatory metabolite produced by *F. prausnitzii* [33]. Moreover, based on animal studies reports, *F. prausnitzii* can use the acetate, which is produced by *Bacteroides thetaiotaomicron* in vivo, the modulation of intestinal mucus barrier has been affected by this reaction significantly [32]. According to evidence in rodent studies, *F. prausnitzii* influences gut physiology through the production of mucus O-glycans and probably helps to maintain suitable proportions of different cell types of secretory lineage in the intestinal epithelium as well [32]. Nevertheless, *F. prausnitzii* is well adapted to the gut environment where it is possibly cross-fed by other members of the gut microbiota.

3. Mechanisms of anti-inflammatory effects

F. prausnitzii as a commensal bacterium has an anti-inflammatory property, it was identified based on human clinical data [26]. Reducing of epithelial signaling through the peroxisome proliferator-activated receptor γ (PPAR-γ) as a result of depletion of butyrate-producing bacteria (BPB) has been confirmed previously, therefore, dysbiotic expansion of potentially pathogenic Enterobacteriaceae (phylum Proteobacteria) has a significant role in the increasing of luminal oxygen bioavailability [34]. Several investigations revealed decreasing levels of *F. prausnitzii* in the gut gives rise to the reduced capacity of self-defense against inflammatory interactions. This protective mechanism presumably involves the inhibition of pro-inflammatory cytokines and has a key role in the stimulation procedure of anti-inflammatory cytokines secretion by active molecules [35]. *F. prausnitzii* anti-Inflammatory effects display both in vitro (cellular models) and in vivo (trinitrobenzene sulfonic acid (TNBS) colitis model), and one of the mechanisms performed to inhibition of *F. prausnitzii* and inflammation, it serves as secretion of bioactive molecules which can block activation of nuclear factor-kB (NF-κB) and production of interleukin (IL)-8 by intestinal epithelial cells [36]. *F. prausnitzii* also stimulates the high secretion levels of IL-10 through peripheral blood mononuclear cells, mucosal dendritic cells (DCs) and macrophages, it probably plays a role in contribution to intestinal homeostasis by inhibiting the production of the pro-inflammatory cytokines including Interferon-gamma (IFN- γ), Tumor necrosis factor-α (TNFα), IL- 6 and IL-12 and enhancement activity of the suppressive of forkhead box P3 ($FOXP3^+$) regulatory T cells (Tregs) in the mucosa [37]. The presentation of antigens in *F. prausnitzii* is performed by DCs in the colonic mucosa. Recognition process of mentioned antigens through the cluster of differentiation 4 (CD4) T cells equipped with a specific T-cell receptor (TCR), which participates in differentiation into Foxp3-lacking regulatory Treg characterized by the coexpression of CD4 and CD8a. The majority of

these Treg cells stay in the colonic mucosa and prevention of excessive inflammatory responses has been carried out by them. A fraction of these cells migrate into the blood and presumably contribute to the immune tolerance outside the intestine [38].

To exert anti-inflammatory effects, butyrate can work as a histone deacetylase (HDAC) inhibitor [39]. HDACs probably either promote or inhibit transcriptional activities [40]. A clear correlation between HDACs and Inflammatory bowel disease (IBD) has been understood in colitic animals. Of the 18 isoforms, HDAC1 was identified to inhibition of apoptosis in T cells and is containing pro-inflammatory effects [41]. Butyrate derived from *F. prausnitzii* has the ability to inhibition of HDAC1 activity, like that the inhibition of HDAC1 leads to preventing of interleukin (IL)-6/signal transducer, the pathway of transcription 3 (STAT3)/IL-17 activator and promoting Foxp3, therefore, these interactions lead to a reduction in inflammatory Th17 cell activation and the differentiation of anti-inflammatory Treg cells promotion. The cytokines are affected by the change in the ratio of Th17/Treg cell, in turn ameliorating colitis lesions in IBD [42].

Additionally, as mentioned *F. prausnitzii* has the secreting ability of the anti-inflammatory compounds including salicylic acid for its surrounding environment [26, 33]. It was reported that 10 mM salicylic acid, a similar concentration found in the colon, can decrease the level of in vitro IL-8 [26]. In the pharmaceutical industry, salicylic acid serves as the precursor of 5-aminosalicylic acid (5-ASA), and a drug prescribed in the treatment procedure of IBD [43]. Salicylic acid is effective as 20 mM 5-aminosalicylic acid (5-ASA) in vitro as well [44]. Quévrain declares another anti-inflammatory property for protein which is produced by *F. prausnitzii* as the anti-inflammatory molecule (MAM) [33], a remarkable decrease in the NF-κB pathway activation with a dose-dependent effect gives rise to the Complementary DNA (cDNA)

in epithelial cells because of the transfection of MAM. This protein has the ability to inhibition of the NF-κB pathway in gut epithelial cells and prevents colitis in an animal model. MAM is active in the levels of the central signaling molecule IκB kinase α (IKKα). Additional manipulation of signal transduction molecules upstream or downstream of IKKα probably potentiates the effect significantly. Overall, MAM might reach systemic body sites and plays a role in the control of inflammatory complications at anatomical locations other than the intestine. The action mechanism of *F. prausnitzii* showed in **figure2**.

4. *Faecalibacterium* in diseases

4.1 Gastrointestinal disorders

4.1.1. Inflammatory bowel disease

Inflammatory bowel disease (IBD) as a nonspecific chronic intestinal inflammatory complication with unknown etiology, comprises primarily 2 disorders: ulcerative colitis (UC) and Crohn's disease (CD) [45]. The hallmark of IBD, is uncontrolled inflammation of the intestinal mucosa, which can affect any part of the gastrointestinal tract [46]. It is generally believed that IBD in genetically susceptible individuals occurs because of an imbalance meant in the mucosal immune response to commensal bacteria [47]. The exact role of gut microbiota in IBD was the main target of numerous studies and microbial modulation becoming a major consideration in IBD management over the last decade. Until now, a wide variety of clinical and experimental studies revealed the microbial implication in IBD and revealed an imbalance between “anti-inflammatory” and “pro-inflammatory” bacteria in IBDs-suffering patients. Several investigations revealed that the abundance of *F. prausnitzii* can serve as an indicator or biomarker of intestinal health in adults relatively and low levels have predictive properties for

IBD [16]. The microbiota of patients with active CD and UC have increased the abundance of *Proteobacteria* and lower fecal counts of *Firmicutes* in comparison to healthy people [13], *F. prausnitzii*, as the most abundant gut bacteria in humans, has low quantity in CD and UC patients [48]. A significant inverse correlation between disease activity and the count of *F. prausnitzii* was found in UC patients, even with the quiescent disease [49]. According to Willing et al findings, *Faecalibacterium* populations and *Enterobacteriaceae* and *Ruminococcus gnavus* populations in ileal CD-suffering patients disappeared and increased respectively by using a pyrosequencing technique [50]. The depletion of *F. prausnitzii* was observed in patients with untreated CD but not in patients with chronic diarrhea, this point suggests a relationship in the pathomechanisms of CD [43]. The *F. prausnitzii* level was much lower in the intensive disease [51]. A possible protective benefit of *F. prausnitzii* against the development of IBD was suggested in Meta-analysis and systematic review [8]. A study by Lopez-Siles and et. al reveals that even though the main members of the *F. prausnitzii* population are present in both healthy subjects and individuals with gut diseases, richness is reduced in the latter and an altered phylotype distribution exists between diseases. This approach may serve as a basis for addressing the suitability of *F. prausnitzii* phylotypes to be quantified as a putative biomarker of disease and depicting the importance of the loss of these subtypes in disease pathogenesis [52]. An anti-inflammatory effect in IBD animal models has been shown in oral *F. prausnitzii* [53, 54]. The ratio of anti-inflammatory cytokine (IL-10) to pro-inflammatory cytokine (IL-12) secreted by the immunocytes, which are beneficial to declare from an anti-inflammatory (high ratio) versus pro-inflammatory (low ratio) capacity repeatedly, has been shown by this bacterium [55]. It is demonstrated that three effector $CD4^+$T lymphocytes including Th1, Th2, and Th17 cells can facilitate the initiation and development of IBD [56]. Treg cells are containing regulatory and

suppressive features, and their ability to restrain the progression of incidence of complication [57]. It is widely proven that immune responses drive the IBD through the Th1, Th2, or Th17 cells mediated [58]; however, the suppression process performed by the Treg [59]. IBD-suffering patients were proved to have an increased rate of the Th1, Th2 or, Th17 cells amount, while decreased in the Treg cells in their peripheral blood was observed as well [60]. Therefore, many researchers highlight the importance of reestablishment $CD4^{+}$T cell homeostasis in controlling the development of IBD [61]. Comparison of *F. prausnitzii* with *B. longum* and the role of both bacteria in accordance with the cellular and animal models showing a remarkably higher ratio of IL-10/IL-12p70 and attenuation of the TNBS-stimulated inflammation in comparison to the medium control was shown in a diligent study. The produced-butyrate by *F. prausnitzii* serves as to decrease Th17 differentiation and attenuate colitis through inhibiting HDAC3 and c-Myc-related metabolism in T cells [61]. *F. prausnitzii* also produces the ZP05614546.1 protein (15 kDa molecular weight), which is called MAM, including anti-inflammatory properties by in CD pathogenesis. This protein can inhibit the NF-κB pathway in gut epithelial cells and prevent colitis in an animal model [33]. In the subsequent in-vivo and in-vitro experiments, the MAM exhibits a significant function in decreasing the NF-KB pathway and alleviates chemically induced mouse colitis as well [33].

4.1.2. Irritable bowel syndrome

Irritable bowel syndrome (IBS) is the most prevalent gastrointestinal (GI) disorder in developed countries [62, 63]. It is estimated that IBS affects 10% to 15% of the adult population globally. According to a meta-analysis study, the global prevalence of IBS is 11.2%, with the lowest prevalence in South Asia and the highest prevalence in South America [64]. Traditionally, IBS has been considered as a multifactorial disorder associated with a misfunction in the brain-gut

axis causing GI sensory-motor abnormality. The etiology and the pathogenesis of IBS are still not clear. However, recent studies have shown new theories regarding the pathophysiology of IBS including; genetic pre-determinants, abnormal responses to dairy products, abnormalities of enteric immune responses and mucosal inflammation, and last but not least alterations of the gut microbiota mainly known as gut dysbiosis [14, 65]. Global and deep molecular analysis of fecal samples indicates that patients with IBS have a different composition of microbiota. This information might be used to develop better diagnostics and ultimately treatments for IBS [66]. The high heterogeneity of this syndrome makes it very difficult to make conclusions. An example of the heterogeneity of IBS is the diversity of the abundance of *F. prausnitzii*: its abundance is low in cases of IBS-A, unaffected in cases of IBS-D and may or may not be lower than in IBS-C patients than healthy controls [67]. An instance, a negative correlation between beneficial species of the gut and IBS symptoms have been demonstrated with Rajilić Stojanović et al. reporting a reduction in *Faecalibacterium* spp., in faecal samples, being associated with an increase in IBS symptoms [66]. *F. prausnitzii*, also, able to reduce visceral hypersensitivity induced by stress possibly through intestinal epithelial barrier enhancement [67]. A meta-analysis conducted on 13 studies in 2016 showed that there was a significant difference in the abundance of *Lactobacillus*, *Bifidobacterium*, and *F. prausnitzii* in IBS patients compared to healthy controls [68]. Therefore, the administration of a well-balanced gut microbiota from a healthy donor may have a great impact on the improvement of the gastrointestinal tract in patients with IBS. This commensal bacterium which presents a diminished prevalence in many patients suffering from different intestinal disorders could thus be considered as a keystone specie of intestinal health.

4.1.3. Colorectal cancer

Colorectal cancer (CRC) is considered as the most well-known malignant tumor types throughout the world. The gut microbiota and some specific gut bacteria have been related to the pathogenesis of CRC [69, 70]. The significant roles of specific pathogens in the CRC promoting through the pro-inflammatory reactions with host cells have been evaluated [71, 72], however, it has become increasingly evident that the collective activities related to resident gut microbiota (and not just specific pathogens) particularly the materials produced by metabolites influence protection against, and predisposition to the CRC development strongly [73, 74]. The significant changes have been observed in CRC patients in the composition of gut microbiota, like the growing rate in *Fusobacteria*, *Porphyromonadaceae*, *Staphylococcaceae*, *Akkermansia spp.* and Methane-bacterial and a decrease meant in *Bifidobacterium*, *Lactobacillus*, *Ruminococcus*, *Faecalibacterium spp.*, *Roseburia*, and *Treponema* in comparison with healthy controls [75, 76]. The production of SCFAs including butyrate is given rise to fermentation of lumen fiber. Butyrate has the ability to inhibit the development of CRC and promotion of intestinal health through the different mechanisms, BPB was shown to inhibition of CRC development as well [77]. Of note, butyrate is the significant energy source to the colonic mucosa and plays a remarkable role in the protection against CRC [78, 79]. *F. prausnitzii* decreased approximately four-fold in 20 CRC patients compared with 17 healthy volunteers based on Balamurugan et al findings through quantitative polymerase chain reaction (qPCR) assays [80]. *F. prausnitzii* has shown to be a very promising probiotic property as a partner with the gut commensals in inflammatory diseases and colon tumors [81].

4.2. Metabolic syndromes

4.2.1. Obesity

Genetics and environmental factors affect obesity as a complicated process. The involved pathways in metabolism cycles contribute to this procedure dramatically [81]. The increased oxidative stress and exacerbated inflammatory outcomes are typically characterizing factors of obesity through accompanying the infiltration of immune cells in adipocytes [82]. Obesity is associated with gut microbiota mainly *Firmicutes* and *Bacteroidetes*, which are involved in phylum abundances changes [83]. In obese individuals, the gut microbiota presumably has more efficiency in energy extracting from a given diet in comparison to the microbiota in lean individuals [83]. Obesity and metabolic disorders are affected by the mechanisms of the gut microbiota, which is the target to focus on intense research. The intestinal permeability in obese mice is affected by the gut microbiota, thereby promoting the translocation of bacterial products and stimulating the low-grade inflammation characteristic of obesity, and insulin resistance are related to gut microbiota [84]. Additionally, the alteration of microbiota composition in obesity-prone rats has been found to coincide with intestinal inflammation [85]. According to obtained results in a follow-up study, the microbial composition during childhood probably can predict the obesity process in adult individuals [86]. Gut microbiota influences energy extraction from nutrition and subsequent fat storage in adipose tissue as well [87]. Inconsistent results report the association between human colonic *F. prausnitzii* and obesity. A research reports that oral administration of butyrate reduces the production of macrophage chemoattractant protein-1 (MCP-1) by adipose tissue in diet-induced obese, also MCP-1 has an important role in macrophage recruitment and accumulation in the adipose tissue as an important factor for establishing insulin resistance in obese patients [88]. In comparison to lean mice, obese mice have fewer bacteria belong to the *Bacteroidetes* division, and more bacteria belonging to the *Firmicutes* division [89]. The increased quantity of *F. prausnitzii* in overweight people who

underwent a fasting program over 1-week followed by supplementation of a probiotic formula for 6-weeks has been described in some functional studies [90]. Other studies showed that *F. prausnitzii* increases in the non-obese cases and suggesting a pro-inflammatory effect on microbiota composition in obesity-related subjects [91]. Furet et al. reported a high level of *F. prausnitzii* in obese subjects, a representative of the *Firmicutes* that can ferment unabsorbed carbohydrates [37]. Dietary fibers can be converted to butyrate by the *F. prausnitzii* [90] using mainly the butyryl-CoA: acetate CoA-transferase (BUT) route [92]. In high levels, butyrate is considered to affect diet-induced [93]. It provides additional energy (5-15% of the total caloric intake) for gut epithelial cells and has a role in adipose tissue expansion [94]. An abundance of *F. prausnitzii* inconsistent results among overweight and obese patients showed in a systematic review, it is also observed an increasing trend in the relative abundances of *F. prausnitzii* [95]. Haro et al. reported a low fat/high carbohydrate diet increased *Prevotella spp.* and *F. prausnitzii* [96].

4.2.2. Type 2 Diabetes

Type 2 diabetes (T2D) is a complex and intensive metabolic disorder [97]. It resulted that the gut microbiota can alter the permeability of the intestinal lining and increasing the rate in the secretion of metabolic endotoxin. This situation may lead to chronic low-level inflammation, impaired insulin resistance, and T2D [98, 99]. This low-level inflammation serves as a trigger factor in the development of diabetes. It was demonstrated that the composition of gut microbiota probably is responsible for inducing a low-grade inflammatory state closely associated with T2D disorder directly [100]. The exact mechanism for how the gut microbiota can modulate the gut permeability is still unknown; however, a Glucagon-like Peptide-2 (GLP-2)-dependent mechanism has been proposed as a decreasing factor in permeability and reducing

Lipopolysaccharides levels after an increase in endogenous GLP2 [101]. Moderate butyrate levels can also prevent mitochondrial beta-oxidation and high-fat-diet-induced insulin insensitivity through epigenetic regulation [102].

Several studies have confirmed the microbiota shifts associated with T2D. The prevalence of *Firmicutes* as intestinal bacteria was significantly lower in patients with T2D compared to healthy controls (HC). Decreased glucose tolerance and T2D is related to *Bacteroidetes*/ *Firmicutes* ratio, which has often been related to a lower abundance of *Firmicutes*, while *Bacteroidetes* and *Proteobacteria* are more prone to be abundant [100]. Qin et al., after analyzing a cohort of Chinese, showed the diabetic microbiome is low in BPB such as *F. prausnitzii* and *Roseburia intestinalis* in patients with T2D [103]. Based on a report, a higher abundance of *F. prausnitzii* is linked with the reduction of a low-grade inflammatory state during the alleviation of diabetes in Roux-en-Y gastric bypass (RYGB) surgery-receiving patients [37]. An increase in *F. prausnitzii* was related to the alleviation of diabetes by another Chinese herbal formula, Gegen Qinlian Decoction (GQD), in a double-blinded, placebo-controlled clinical trial [104]. A significant decreased of *F. prausnitzii* in diabetic patients with a negative correlation to glycated hemoglobin A1c (HbA1c) values were had been reported previously [105]. Interestingly, the authors found that vancomycin treatment reduced levels of secondary bile acids (BA) and increased the pool of primary BA greatly, it shows the BA function as signaling molecules [106]. The consumption of low-fat, high complex carbohydrate diet (LFHc) increases the abundance of *F. prausnitzii* and protective effects against diabetes (evaluated with the Oral Glucose Tolerance Test), as suggested by the findings of an improvement in insulin sensitivity based on the results [107]. An effective therapeutic approach for diabetes and its complications is the transplantation of *F. prausnitzii*. It has also been proposed *F. prausnitzii* as potent probiotics

and consumption of these compositions probably helps prophylactic or therapeutic applications for diabetes [108].

4.2.3. Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) involves a spectrum of liver diseases including steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and, eventually hepatocellular carcinoma [109, 110]. Researches in both humans and animal models have demonstrated the role of the gut microbiota as an important factor in energy storage, which contributes to the development of NAFLD [111]. Several mechanisms including changing the permeability of the intestine, changing the amount of energy absorbed from the diet, altering the expression of genes in the de novo lipogenesis and choline and bile acid metabolic signaling pathways, producing ethanol in the intestine and interacting with the innate immunity pertinent to microbiota are able to improve or aggravate the NAFLD. Wong et al. realize that butyrate-producing *Faecalibacterium* in NASH patients had a lower prevalence [112]. Duarte et al. compared the gut microbiota from obese and lean patients with or without NASH to outline phenotypic differences. NASH patients displayed differences in *Faecalibacterium*, *Ruminococcus*, *Lactobacillus*, and *Bifidobacterium* abundance in comparison to the control group. A 3-fold lower abundance of *Faecalibacterium* and *Ruminococcus* was observed in lean NASH patients [113]. The lower abundance of *Faecalibacterium* in NAFLD was by following other investigations, for instance, Zhu et al. reported the greatest reduction in abundance *Faecalibacterium* in the obese group and the NASH group of patients [114]. Hannah et al. also, found a lower abundance of *F. prausnitzii* in NAFLD patients, in this research, measure some metabolites levels between groups and only propionate and isobutyric acid were higher in NAFLD in comparison to HC, however, any differences observed in concentrations of butyrate,

393 acetate, formate, and total SCFA [115]. According to investigations, the development of NAFLD
394 in humans is also related to changes in intestinal barrier function and higher endotoxin levels
395 [115, 116]. Recently, Kessoku et al. revealed an improvement of NASH pathogenesis via
396 ameliorating gut-permeability by inducing Treg in the colon *Faecalibacterium* administration
397 [117].

398 **4.3. Nervous System Diseases**

399 **4.3.1. Alzheimer's and Parkinson's disease**

400 The concept of the "gut-brain axis," which originated from behavioral investigations in
401 microbiome-reconstituted mice, has advanced the current research supporting the concept that
402 the microbiome probably is an account for some of the most devastating neurodegenerative
403 disorders, including Alzheimer's disease (AD). AD is the commonest neurodegenerative
404 disorder. In older people, it is the cause of dementia as the most common manifestations [118].
405 Abnormal extracellular accumulation of amyloid- peptide (A), senile plaques, and intracellular
406 neurofibrillary tangles are the neuropathological features of AD [119]. Age-related dysbiosis
407 such as the diminished presence of the suggestible anti-inflammatory *F. prausnitzii* might be
408 related to the cerebral accumulation of ß-amyloid in AD [120]. In comparison to HC, most
409 studies reported a major shift in the microbiota composition in AD patients. In a recent study
410 investigated numerous microbial taxa of AD dementia in comparison to elders without dementia
411 or with other dementia types, it was revealed that the way to characterized AD elders was by
412 lower proportions of key butyrate-producing species, such as members of the *Butyrivibrio,* and
413 *Eubacterium* genera, as well as species *Clostridium sp.* and *F. prausnitzii* [121]. Higher
414 abundance of pro-inflammatory bacteria (e.g. *Escherichia*/*Shigella*, *Pseudomonas aeruginosa*)
415 and lower distribution of anti-inflammatory bacteria (e.g. *Bacillus fragilis*, *Eubacterium rectale*,

Eubacterium hallii, *F. prausnitzii*, and Bacteroides fragilis) in amyloid-positive patients as compared to healthy subjects was recorded by Cattaneo et al. [122].

Other chronic, progressive, disabling neurodegenerative disorder that begins in mid to late life is Parkinson's disease (PD). The etiology of PD is not well understood, however, some genetic factors and interactive effects of environmental probably are involved in the PD procedure [123]; the potential contributions of gut microbiota and the enteric nervous system to aging and PD are becoming increasingly recognized as well and perhaps dysbiosis of gut microbiota has been involved in PD accompanied [124, 125]. One study has specifically compared mucosa-associated microbes in PD, identifying *Blautia,* and *Faecalibacterium* negatively correlated with PD duration [126]. Wei Li et al. analyzed the fecal bacterial composition belonged 24 PD patients and 14 healthy volunteers through the 16S rRNA sequencing, they reported that the bacteria from the genera *Blautia, Faecalibacterium* and *Ruminococcus* were significantly decreased in PD in comparison to HC [127].

4.3.2. Major depressive disorder and bipolar disorder

One of the most intriguing and controversial topics in microbiome research is the relationship between gut microbiota metabolism and mental health. Loss of interest in normally enjoyable activities, low self-esteem, and low energy are the main features to characterize major depressive disorder (MDD) as a mental disorder. Emerging evidence, suggests that gut microbiota can affect brain function and behavior through the 'microbiota-gut-brain axis' [128, 129]. The dysbiosis of the gut microbiota plays a role as a contributory factor in the development of MDD [130]. A diligent study confirmed differences between microbial composition in MDD patients from non-depressed individuals. Analyses of fecal samples from MDD patients reveal a weak negative correlation between the relative abundance of

Faecalibacterium and the severity of the depressive symptoms, also the MDD patients had increased levels of *Enterobacteriaceae* and *Alistipes*, however, reduced levels of *Faecalibacterium* was observed [131]. Butyrate-producing *Faecalibacterium* and *Coprococcus* bacteria showed a consistent association with a higher quality of life indicators based on a recent study; however, the health-associated *Faecalibacterium* negatively correlated with mood scores contrarily to the positive association to mental quality of life [132].

Bipolar disorder (BD) as another severe and persistent mental illness is associated with high morbidity and mortality rates. Many proof-of-concept clinical trial cases have shown a positive effect of anti-inflammatory agents in the BD treatment procedure [133]. Global gut microbiota community differences have been observed in BD, with the decreased fractional representation of *Faecalibacterium* and an unclassified member from the *Ruminococcaceae* family, both belonged the phylum *Firmicutes* as well. Also, increased *Faecalibacterium* was associated with improved physical health, reduced depressive symptoms, and better sleep in these patients [134]. According to the results in a cross-sectional study, which performed 16S rRNA gene sequencing of stool samples collected from 32 BD patients and 10 HC, finally identified that *Faecalibacterium* as a feature discriminating between BD patients and HC, given that HC had higher abundances of *Faecalibacterium* [135].

4.3.3. Multiple sclerosis

Multiple sclerosis (MS) is known as a chronic neuroinflammatory disease of the central nervous system [136], which was not a clear etiology, and both genetic and environmental factors are involved in to be susceptible versus the disease [137]. The colonic microbiome is thought to have a remarkable role in auto-immune MS [138]. The subsequent changes and alteration of the gut microbiota are involved in its metabolic network, which perturbs this homeostasis, it probably

462 leads to intestinal and systemic disorders such as MS [139]. In effector T cell development and
463 cytokine production, the gut microbiota is involving, it has a marked influence on Th17 cells and
464 Treg cells, which have a significant role in autoimmune response and its regulation [140]. As
465 such, it is involved in autoimmune diseases in general and MS in particular. Since butyrate
466 production is related to increased Treg cell populations, it is suggested that people are more
467 predisposed to MS by a mechanism in which gut microbiota alterations are involved in. More
468 evidence of a link between bacteria in the gut and MS is the decreased concentration of
469 *Faecalibacterium* in patients with MS in comparison to healthy subjects [49]. An alteration of
470 relative proportions of gut bacteria in MS has been reported in several studies. In a study of 20
471 MS patients versus 40 HC, *Faecalibacterium, Prevotella,* and *Anaerostipes* had low quantity in
472 MS patients, however, the connection between microbiota, treatment, and changes in immunity
473 was not evaluated [141]. The usefulness of vitamin D3 supplements in the treatment of MS was
474 demonstrated in a small pilot study published in 2015, it was also showed that *Faecalibacterium*,
475 was less abundant in patients with MS and increased after vitamin D3 supplementation in
476 patients who were not receiving glatiramer acetate. This study found some differences in
477 community composition (including *Bacteroidaceae*, *Faecalibacterium*, *Ruminococcus*,
478 *Lactobacillaceae,* and *Clostridium*) between untreated patients and glatiramer acetate receiving-
479 patients; these differences probably are linked to immune response modulation by the drug [142].
480 In an exploratory study, in a total of 15 fecal samples (seven samples belonged MS patients and
481 eight samples to HC), a decrease in *Faecalibacterium* abundance in MS patients was observed
482 compared to HC [143].

483 **4.4. Skin disease**

484 **4.4.1. Atopic dermatitis**

The commonest inflammatory skin disease in children is atopic dermatitis (AD), which poses a significant burden on healthcare resources [144]. The complex immune mechanisms are involved in AD. Details about the possible role of the gut microbiota in the aetiopathogenesis of AD and the role of the gut microbiota for the onset and severity of pre-existing AD remains controversial is incomplete and probably unknown. The use of new-generation pyrosequencing technology has already shown an association between low diversity of the infant gut microbiota in early life and an increase in AD risk during infancy, especially in high-risk children at the gut interface [145]. A systemic review investigated the role of the gut microbiota in AD, it showed that an altered gut microbiota colonization by the use of probiotics had a positive effect on the severity of AD [146]. An enrichment for *F. prausnitzii* and decreased levels of SCFAs in the gut was found in the initial study including 90 patients with established AD [147]. Analyzing the fecal microbiome in AD-suffering children with or without a concomitant diet allergy in a pilot study revealed a combination of 6 microbial species, including *E. coli*, *F. prausnitzii*, *A. muciniphila*, and 3 types of *Bifidobacteria*, is more probable between the presence and absence of food allergy in AD-suffering children [148]. Based on a suggestion, the feedback reactions of dysbiosis in *F.prausnitzii* and dysregulating of intestinal epithelial inflammation presumably underlie the progression of chronic in AD by resulting in impairment of the intestinal epithelial barrier, leads to Th2-type immune responses to allergens aberrantly in the skin [147].

4.5. Kidney disease

4.5.1. Chronic kidney disease

Chronic kidney disease (CKD) is a gradual loss of kidney function over for months or years [147]. CKD is a global health epidemic that accelerates cardiovascular disease, increases the risk of infection, and causes anemia and bone disease, among other complications that collectively

increase the risk of premature death. Diabetes and hypertension are the main causes of CKD in all high-income and middle-income countries, and also in many low-income countries [149, 150]. Dysbiotic gut microbiota has been manifested with an increase in pathogenic microbiota in comparison to symbiotic microbiota in CKD [151]. Preliminary evidence indicates the generation of toxic products by a dysbiotic gut microbiota probably contribute to progression to CKD and CKD-related complications [152, 153]. Alterations in the normal function of the neuroendocrine system due to gut dysbiosis probably has a critical role in the establishment and progression of kidney failure [154]. The activation of the hypothalamic-pituitary-adrenal (HPA) axis; increased serotonin via changes in tryptophan metabolism; the production of neurotransmitters, neuroactive compounds, and quorum sensing peptides; and decreased vagus nerve stimulation via decreased the production of SCFAs are affected by the altered gut microbiota. Concisely, the promotion of CKD progression depends on the HPA axis activation, chronic systemic inflammation, and alterations in sodium and blood pressure hemostasis [154].

The depletion of BPB probably has a role in inflammation and CKD progression based on some studies findings. According to the Jiang et al. report subpopulations of *Roseburia* and *F. prausnitzii* (butyrate-producing species) were reduced in the stool of 65 Chinese patients with CKD in comparison with 20 HC significantly, it suggests an association between these bacteria with CKD-related inflammation and CKD progression [155]. In a double-blind, parallel, randomized, placebo-controlled trial, which performed compared dietary supplementation of high-amylose maize resistant starch type 2 (HAM-RS2) with placebo in end-stage CKD-patients, it was reported that supplementation of amylose resistant starch, HAM-RS2, led to an elevation in *Faecalibacterium* and a decrease in systemic inflammation in patients with CKD [9].

4.6. Other diseases

The role of *Faecalibacterium* is investigated in some other diseases such as chronic heart failure [156], cardiometabolic diseases [157], children with enthesitis-related arthritis [158], rheumatoid arthritis [159], blood pressure [160], Sjögren syndrome [161], coeliac disease [162], psoriasis [163], attention-deficit/hyperactivity disorder [164], autism [165], prostate cancer [166], chronic pancreatitis [167] and healthy individuals as well. Other numerous studies investigate of gut microbiota with metagenomic performance. The interesting point in most studies is displaying a lower relative abundance in patients in comparison to HC.

5. Events that Alter an Individual's *Faecalibacterium* in microbiota

Despite the relative stability of gut microbiota in adults, it still presents susceptibility to change. Reductions in the *F. prausnitzii* level and anti-inflammatory relatives happen as young adults mature [168]. Some environmental factors including diet, exposure to toxic materials or antibiotic consumption alter microbiome composition either in a positive or negative route. Modulation of gut microbiota composition probably decreases the risk of many complications, it also can slow down the progression of these procedures. Accordingly, exert promote changes in microbiota composition to resemble a healthier profile would be feasible. The most influencing factor involved in the composition of gut microbiota is probably a type of diet. For instance, this effect depends on the different food supplies such as the presence of fat, vegetables, fruits, saturated and unsaturated fats, etc. A vegetarian diet has a relation to higher amounts of *Bacteroides thetaiotaomicron*, *Clostridium clostridioforme*, and *F. prausnitzii* in comparison to an omnivorous diet [169]. Although some investigations use various techniques and varying manipulations of diets that have comparability properties and generalization of the outcomes problematic, it seems to be clear that the different diets are important environmental factors that regulate and modify the gut microbiota. The in-vitro system in Crohn's disease patients can

simulate the mucus and lumen-associated microbiota, supplementation of either *F. prausnitzii* or *Butyricicoccus pullicaecorum* 25-3T and a mixture of the other six butyrate-producers, to the improve of epithelial barrier integrity, the fecal microbiota to increase the production of butyrate [170]. In recent years, a broader range of useful bacteria such as butyrate-producing indigenous types has been recognized, which are expected to be new probiotic strains. Of note, resident *F. prausnitzii* as a butyrate producer has significant anti-inflammatory properties, therefore, it can be considered useful and also as a next-generation probiotic (NGPs); however, it must be noted that *F. prausnitzii* as an extremely oxygen-sensitive bacterium has difficult criteria to grow industrially [171, 172]. Due to the difficulty in the mass-growing probiotic *F. prausnitzii*, the stimulation of resident *F. prausnitzii* using prebiotics probably is an alternative technique to capitalize on the useful impacts of this bacterium to human health. Based on the reports of Ramirez-Farias et al. inulin has remarkable effects on the number of *F. prausnitzii* in the intestine. In their results, fecal samples collected from healthy adults given 10 g/day inulin for 16 days displayed a major increase in the abundance of the bacterium in comparison to the baseline; nevertheless, the degree of increase was approximately 50% [22]. Another research reported the increasing number of *F. prausnitzii* as much as 10-fold in adults given 5 g/day 1-kestose for 8 weeks in contrast with a previous study [173]. Nowadays, *Faecalibacterium* inclusion on the QPS (for Qualified Presumption of Safety) list is difficult because of its lack of a history related to safe use. Additionally, full toxicology assays and characterization methods of the strain are needed for regulatory approval as well [174].

6. Conclusion

A wide range of disease states and complications correlate with the host microbiota. It can be concluded that the functions of the microbiota and intestinal health are associated with the

ubiquity and population level of *F. prausnitzii* and its frequent involvement in dysbiosis. Recently, the importance of *F. prausnitzii* in human health has been recognized by the research community. Existing evidence displays the relative abundance of *F. prausnitzii* function as an indicator or biomarker of intestinal health in humans. **Table 1** shows a summary of the microbiota changes detected in some diseases. A decreasing rate of *F. prausnitzii* in the GIT has been related to multiple complications and syndrome, however, cause or a consequence of them is not understood clearly. There is a lot of information still missing on which phylogroup is important under which conditions in the gut. As mentioned previously, these species are known as a unique bacterial sensor and actor in human health due to the special conditions, mainly associated with intestinal issues; however, it is not confined to this case. Which gut factors modulate *F. prausnitzii* presence in the gut and the extent of their influence, it remains problematic. As the depletion of this species is not homogeneous in all gut diseases however, the use of *F. prausnitzii* as a gold standard measure of healthy gut microbiota is limited. Nevertheless, it is a good biomarker of certain gut conditions. There is a need to conduct more studies to fully implement *F. prausnitzii* as a biomarker by defining in which medical condition it could be of assistance. It seems these studies should be conducted in larger independent patients groups that include individuals from different ethnicities.

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Compliance with ethical standards

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600 **Conflict of interest**

601 The authors declare that they have no conflict of interest.

602 **Ethical approval**

603 This is a literature review study and therefore ethical approval is not required.

604 **Informed consent**

605 For this type of study, formal consent is not required.

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Table1. Gut microbiota changes reported in some diseases

Condition	Main findings: microbiota variations	References
Type 2 diabetes	↓*Faecalibacterium prausnitzii* phylotypes	**[175]**
Type 2 diabetes	↑*Akkermansia muciniphila*, ↑*Faecalibacterium prausnitzii*, ↓*Bacteroides*	**[176]**
Type 2 diabetes	↑*Bifidobacterium*, ↑*Bacteroides*, ↑*Lactobacillus*, ↑*Lactococcus*, ↑*Streptococcus*, ↑*Veillonella*, ↑*Alistipes*, ↓*Subdoligranulum*, ↓*Faecalibacterium*	**[177]**
Type 1 diabetes	↑*Bacteroides*, ↑*Bacteroidesovatus*, ↑*Eubacterium*, ↓*Faecalibacterium*, ↓*Bacteroides vulgatus*, ↓*Bacteroidesfragilis*	**[178]**

Type 2 diabetes	↑*Lactobacillu*, ↓*Bifidobacterium*, ↓*Prevotella*, ↓*F. prausnitzii*, ↓*B. fragilis*	**[179]**
Inflammatory bowel diseases	↑ *F. prausnitzii*	**[180]**
Inflammatory bowel diseases associated with skin disorders	↓ *F. prausnitzii* and ↑ *E. coli*	**[163, 181]**
Crohn's disease	↑ *F. prausnitzii*	**[182]**
Crohn's disease	↓ *F. prausnitzii*	**[183-185]**
Crohn's disease	↓*F. prausnitzii*, ↓ *Roseburia* spp, ↓*Dialister* spp, ↓*Coprococcus* spp, ↑*Enterobacteriaceae*, ↑*Rumonococcus gnavus*	**[50]**
Colorectal cancer	↓ *F. prausnitzii*	**[186]**
Ulcerative colitis	↓ *F. prausnitzii*	**[186, 187]**
Ulcerative colitis	↓*F. prausnitzii*, ↓ *Roseburia* spp, ↓*Eubacterium rectale*, ↑*Fusobacterium* spp	**[49]**
Irritable bowel syndrome	↓ *F. prausnitzii*	**[52]**
Obesity	↓*Bacteroidetes*, ↓*Bifidobacterium* spp, ↓ *F. prausnitzii* ↓*Akkermansia muciniphila*, ↑*Bilophila wadsworthia*	**[188, 189]**
Multiple sclerosis	↓*Faecalibacterium*, ↓*Prevotella*, ↓*Anaerostipes*, ↑*Bifidobacterium* , ↑*Streptococcus*	**[141]**
Bipolar disorder	↓*Faecalibacterium*	**[134]**
Major depressive disorder	↓*Faecalibacterium*, ↑*Enterobacteriaceae*, ↑*Alistipes*	**[131]**
Parkinson's disease	↓*Faecalibacterium* , ↓*Ruminococcus*, ↓*Blautia*	**[127]**
Alzheimer's disease	↓*F. prausnitzii*, ↓*Butyrivibrio*, ↓*Eubacterium*, ↓*Clostridium sp.*	**[121]**
Chronic kidney disease	↓*F. prausnitzii*, ↓*Roseburia*	**[155]**
Non-alcoholic steatohepatitis	↓*Faecalibacterium* , ↓*Ruminococcus*, ↓*Lactobacillus*, ↓*Bifidobacterium*	**[190]**

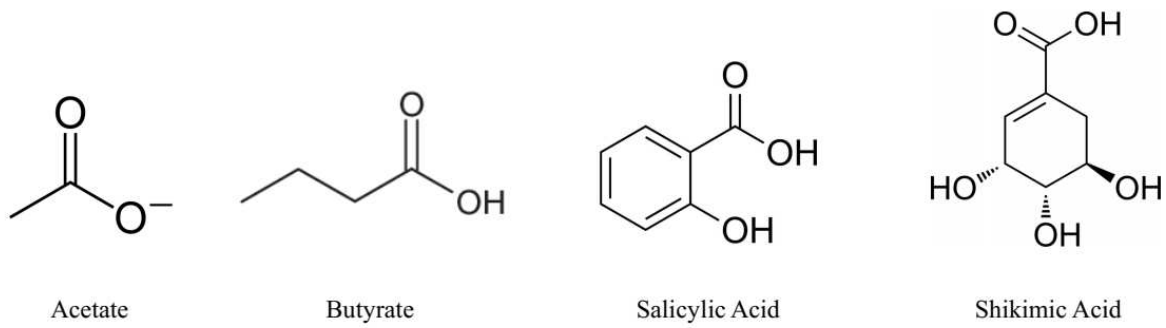

Fig.1. The molecular structure of the Acetate, Butyrate, Salicylic acid, and Shikimic Acid.

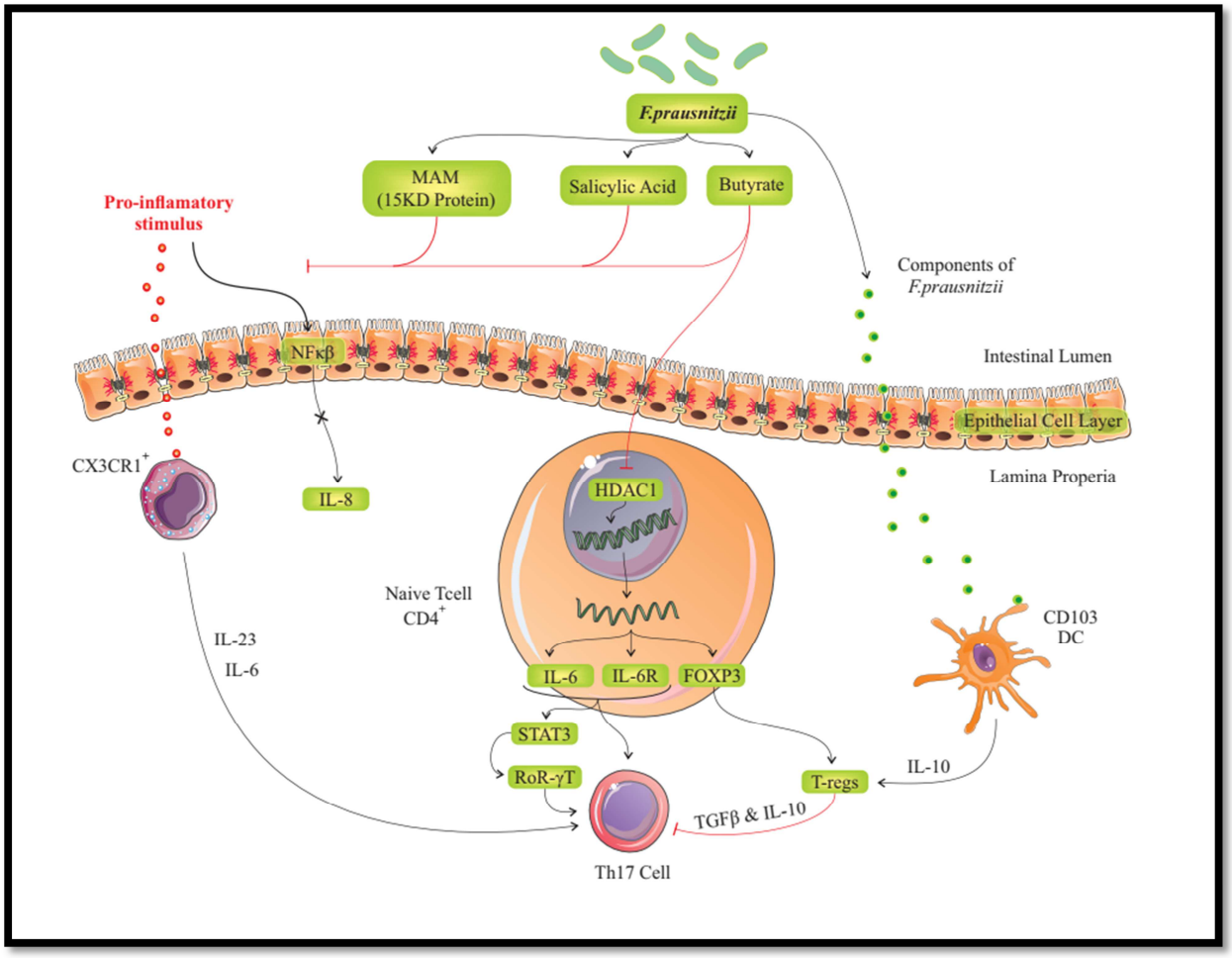

Fig.2. Overview of the mechanisms of Anti-inflammatory of *Faecalibacterium prausnitzii*.

NF-κB signaling and inflammation blockage by three bioactive molecules, named MAM, butyrate and salicylic acid from *F. prausnitzii*, followed it blocks the secretion of IL-8. *F. prausnitzii* components induce production of IL-10 by peripheral blood mononuclear cells and CD103+ dendritic cells, consequently, the synthesis of proinflammatory cytokines such as IL-6 and IL-12 is inhibited. *F. prausnitzii*–derived butyrate inhibits HDAC1 activity. The inhibition of HDAC1 leads to the downregulation of the IL-6/STAT3/IL-17 pathway and the induction of Foxp3 expression. **NF-κB,** nuclear factor kappa B; **MAM,** microbial anti-inflammatory molecule; **IL,** interleukin; **HDAC,** histone deacetylase; **STAT,** signal transducer and activator of transcription; **FOXP3,** forkhead box P3; **CX3CR1,** chemokine, CX3C motif, receptor 1; **TGF-β**, transforming growth factor beta; **RORγt,** related orphan nuclear receptor gamma, **Tregs,** regulatory T cells.

Highlights

- *F. prausnitzii* is one of the most abundant bacterial species in the colon of healthy human
- It has a major actor of human intestinal health and a biosensor.
- Changes in this species population quantity have been observed in many illnesses
- It has role by metabolites, anti-inflammatory action, and correlation of dysbiosis
- This bacterium is a good biomarker in the certain gut conditions.