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FAECALIBACTERIUM PRAUSNITZII & HUMAN HEALTH

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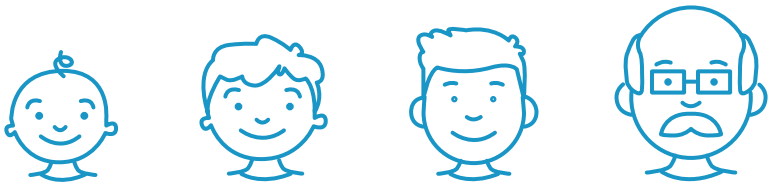
F. PRAU PROPERTIES/ HISTORY



What is *F. prau?*

Faecalibacterium prausnitzii (F. prau) is a member of the Firmicutes phylum. Initially it was classified as *Fusobacterium prausnitzii,* but genome sequencing in 1996 revealed the bacterium was more closely related to members of the *Clostridium leptum* group (*Clostridium* cluster IV). *F. prau* is a dominant member of the *C. leptum* group. *F. prau* accounts for ~5% of the total faecal microbiota in healthy individuals but can increase to ~15% in some, making it one of the most abundant bacterium in the healthy human intestinal microbiota (Miquel, et al., 2013) (Martin, Bermudez-Humaran, & Langella, 2018).

It is not limited to humans, but is also found in other mammals, for example, pigs, mice and calves, as well as in poultry and cockroaches (Miquel, et al., 2013).

Within the gastrointestinal tract, *F. prau* is present in higher amounts in the proximal colon than the terminal ileum (Miquel, et al., 2014).

F. prau establishment & growth

Although *F. prau* is dominant in healthy adults, numbers can vary depending on the age of the host (Miquel, et al., 2014). For example, no detectable *F. prau* has been found in stool from babies up to 6 months of age; numbers then increase between 6 and 24 months (Hopkins, Macfarlane, Furrie, Fite, & Macfarlane, 2005); peak at 2 – 3 years; then decline in the elderly (van Tongeren, Slaets, Harmsen, & Welling, 2005).

Low *F. prau* numbers in infancy suggests initial colonisers may facilitate the subsequent arrival and implantation of *F. prau.* Establishment of *F. prau* in the gut may result from a combination of environmental factors, e.g. other commensal species, redox mediators, oxygen concentration, mucus layer, bile salt concentrations and pH (Martin, Bermudez-Humaran, & Langella, 2018). *F. prau* is an extremely oxygen sensitive (EOS) bacterium and difficult to grow, but it is capable of withstanding the low levels of oxygen that is found in the intestinal mucosa by using extracellular electron transfer in the presence of flavin and cysteine or glutathione (Khan, et al., 2012).

The optimal pH for *F. prau* growth is between 5.7-6.7, the range of the pH in the colon. At lower pH (3.5 and 4.5) *F. prau* will not grow (Lopez-Silas, Duncan, Garcia-Gill, & Martinez-Medina, 2017). Its growth is also compromised by the presence of bile salts at 0.5% (w/v). Various IBD treatments have been shown to have a positive effect on *F. prau* populations. However, xenobiotics, antibiotics, chemotherapy, isoflavones and essential oils can reduce *F. prau* populations.

In terms of the substrates that *F. prau* can utilise to grow:

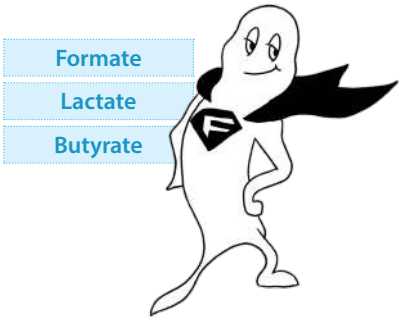
- It has limited ability to utilise arabinogalactan, xylan and soluble starch (Ferreira-Halder, de Sousa Faria, & Andrade, 2017).
- Flavins and cysteine or glutathione has been shown to support the growth of *F. prau* (Khan, et al., 2012).
- *F. prau* can hydrolyse fructose, fructooligosaccharides, apple pectin, starch and inulin. *F. prau* is not able to exploit as a **sole** energy source however arabinose, melibiose, raffinose, rhamnose, ribose, xylose, citrus pectin or peptides.
- Most strains will grow well on pectin and pectin derivatives such as galacturonic acid (Lopez-Siles, et al., 2012), and pectinolytic enzymes have been encoded in the *F. prau* reference genome (Heinken, et al., 2014). It appears to prefer high methoxy pectin from apple to low methoxy pectin from citrus, signifying that it utilises high methoxy esterified galacturonic acid as a substrate. Kiwifruit contains high methoxy pectin.

- It can grow on host-derived N-acetylglucosamine (a constituent of the glycoproteins in the gut mucosa), D-glucosamine and D-glucuronic acid (Lopez-Silas, Duncan, Garcia-Gill, & Martinez-Medina, 2017). It can switch between substrates derived from the diet or the host.
- *F. prau* may rely on other species like *Bacteroides* or *Bifidobacteria* for cross-feeding, particularly from acetate producers, which *F. prau* feeds on. Other bacteria feeding on pectin may also help to release pectin derivatives that *F. prau* can utilise. For example, inulin at 10 g/day for 16 days resulted in an increase in *F. prau* and Bifidobacterium. Bifidobacteria probiotics also appear to increase *F. prau*. This may be due to Bifidobacteria producing acetate which *F. prau* can feed on. Acetate is the precursor for butyrate production. (Miquel, et al., 2014) (Ferreira-Halder, de Sousa Faria, & Andrade, 2017).
- Increased consumption of dietary fibre has been linked to increased *F. prau*.

Properties

Two of the key properties of *F. prau* is that it is a major butyrate-producer and has anti-inflammatory effects (directly and indirectly via butyrate and other metabolites).

Major end products of fermentation by *F.prau*



The major end products of fermentation by *F. prau* is formate, lactate and significant amounts of butyrate (> 10mM *in vitro*). It is one of the most abundant butyrate-producing bacteria in the gastrointestinal tract. As butyrate plays a major role in gut physiology (it serves as the major energy source for colonocytes), intestinal cell lifecycle (stimulates growth and apoptosis) and immunity (anti-inflammatory, induces apoptosis in cancer cells), it follows that *F. prau* may impact on these functions (Miquel, et al., 2013).

Other metabolites produced either by or in the presence of *F. prau* include salicylic acid, shikimic acid and raffinose. Salicylic acid and shikimic acid are anti-inflammatory molecules. Shikimate is a precursor for folate and aromatic amino acids (tyrosine etc). Raffinose plays a role in maintaining gut permeability (Martin, Bermudez-Humaran, & Langella, 2018) (Ferreira-Halder, de Sousa Faria, & Andrade, 2017).

In *in vitro* and *in vivo* studies, *F. prau* has been found to:

- Secrete a compound(s) that inhibits NF-κB activation and IL-8 secretion (Miquel, et al., 2013).
  - One of these compounds is a protein of 15 kDa named MAM (microbial anti-inflammatory molecule). MAM has been found to inhibit the NF-κB pathway and is able to alleviate colitis in mice. (Martin, Bermudez-Humaran, & Langella, 2018).
- Induce secretion of IL-10 and low amounts of IL-12, potentially inhibiting pro-inflammatory cytokines and enhancing Foxp3+ Treg cells.
  - *F. prau* and *Bifidobacteirum longum* were studied in both cellular and animal experiments. Human peripheral blood mononuclear cells (PBMCs) and TNBS-induced colitis rats were treated with *F. prau, B. longum, F. prau* supernatant or control medium (Qiu, Zhang, Yang, Hong, & Yu, 2013)
  - *F. prau, B. longum* and *F. prau* supernatant all induce IL-10 and TGF-β1 – the supernatant exhibited the strongest anti-inflammatory capacity (as determined by IL-10/IL-12p70 ratio). *F. prau, B. longum* and the *F. prau* supernatant also induced Foxp3 and Treg production and ameliorated TNBS-induced colitis.
- Reduce intestinal permeability, pro-inflammatory cytokine levels and serotonin levels.
  - Chronic low-grade inflammation and gut dysfunction was induced in mice using dinitro-benzene sulfonic acid (DNBS). The effects of *F. prau* and its supernatant on markers of inflammation, gut permeability, colonic serotonin and cytokine levels were investigated (Martin, et al., 2015).
  - Gut permeability, colonic serotonin and cytokines IL-6, IFN-γ, IL-4 and IL-22 were higher in the DNBS treated mice compared to the controls. Following treatment with *F. prau* or its supernatant, there were significant decreases in intestinal permeability, cytokines and serotonin levels.

F. prau is also metabolically complementary to another major commensal bacteria, *Bacteroides thetaiotaomicron*. In an *in vivo* study, *B. thetaiotaomicron,* an acetate producer, was found to increase goblet cell differentiation, the expression of mucus-related genes and the ratio of sialylated to sulphated mucins in rats, showing that it favours mucus production. When *F. prau,* an acetate consumer and butyrate producer, was introduced the effects on goblet cells and mucin were diminished. This effect may help to maintain colonic epithelial homeostasis (Wrzosek, et al., 2013).

Relationship to health

Over the last decade, an increasing number of studies have reported on *F. prau* depletion in various diseases/health concerns, with the list growing year by year. The findings of these studies indicate that *F. prau* has a crucial role to play in maintaining gut physiology and overall host wellbeing.

The following is a summary of some of the literature on *F. prau,* particularly as it relates to human health.

Gastrointestinal Conditions

Inflammatory Bowel Disease (IBD)

IBD is a group of disorders characterised by chronic and relapsing inflammation. The two most common forms are ulcerative colitis (UC) and Crohn's disease (CD). In CD in particular, the intestinal microbiota is believed to play a role in initiating and triggering the immune system, resulting in the characteristic inflammation.

The ileal mucosa-associated microbiota of CD patients was analysed at the time of surgical resection for active disease and 6 months later (Sokol, et al., 2008). *F. prau* was significantly lower at the time of surgery, consistently associated with endoscopic relapse, and there was a lower proportion of *F. prau* 6 months after surgery in CD patients with endoscopic recurrence compared to those still in remission (Figure 1).

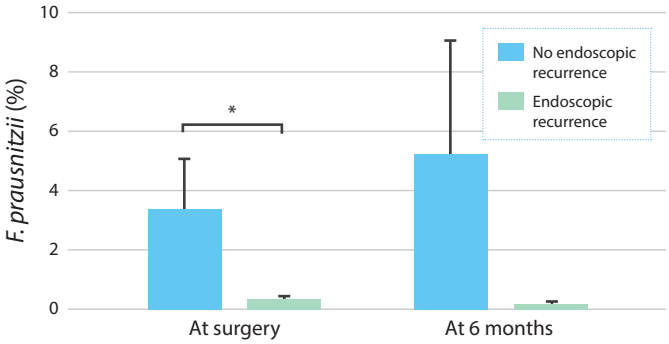


Fig. 1. *F. prausnitzii* proportions in the ileal MAM using FISH at the time of surgery and at 6 months according to the endoscopic recurrence status. *, Significant difference, P= 0.03.

The authors hypothesised that remission might be associated with the presence of *F. prau* and probably its anti-inflammatory effects. They then conducted a series of *in vitro* and *in vivo* studies to test and prove their hypothesis and found:

- *F. prau* exerts anti-inflammatory effects in peripheral blood mononuclear cells (PBMCs) by inducing IL-10 production (an anti-inflammatory cytokine).
- *F. prau* supernatant reduced IL-8 secretion by Caco-2 cells.
- *F. prau* supernatant inhibited NF-κB activation by IL-1β in Caco-2 cells.
- *F. prau* supernatant did not exhibit any antibacterial effect.
- *F. prau* and its supernatant reduced the severity of TNBS-induced colitis in mice.
- *F. prau* and its supernatant increased secretion of IL-10 and decreased secretion of TNF-α and IL-12 in TNBS-induced colitis in mice.
- *F. prau* was diminished in the TNBS-induced colitis control mice and a higher amount of bacteria from the *C. leptum, C. coccoides* and *Bacteroides* groups was observed. Following treatment with *F. prau* or its supernatant, this dysbiosis was counterbalanced, with *F. prau* nearly normalised in the *F. prau* treated group.
- *F. prau* and its supernatant significantly decreased the mortality rate of TNBS-induced colitis mice. This effect was not due to butyrate presence, as a group of mice treated with butyrate (at the same concentration as in the supernatant) had a similar mortality rate to the colitis control group.

The abundance of *F. prau* in the gut microbiota of Japanese CD patients has also been investigated (Fujimoto, et al., 2012). Faecal samples from 47 CD patients and 20 healthy controls were tested. The abundance of *F. prau* was significantly decreased in the CD patients compared to the healthy group ($P = 0.0004$).

Sokol and colleagues conducted a further study on IBD patients, this time including both those in remission and those with active symptoms. Faecal samples from 22 active CD patients, 10 CD patients in remission, 13 active ulcerative colitis (UC) patients, 4 UC patients in remission, 8 infectious colitis (IC) patients and 27 healthy subjects were analysed (Sokol, et al., 2009). Significantly lower counts of *F. prau* was found in **active** IBD and IC patients compared to healthy subjects ($p < 0.01$). Those in remission had lower levels of *F. prau* than the healthy group, however the difference was not significant.

Further studies in UC patients have also shown significant reductions in *F. prau.*

Machiels et al., 2014 analysed the predominant microbiota from 127 UC patients and 87 healthy controls. A lower abundance of *F. prau* was observed in UC patients compared to controls ($P < 0.0001$) (Machiels, et al., 2014).

In 2013, total bacteria and abundance of *F. prau* was measured in 116 UC patients in remission, 29 first-degree relatives and 31 healthy controls (Varela, et al., 2013).

It was found that *F. prau* was reduced both in the UC patients and their healthy relatives compared to the healthy controls ($P < 0.0001$). Low levels of *F. prau* were also associated with less than 12 months of remission and more than 1 relapse per year. Upon follow-up, those patients with persistent remission has steadily increasing *F. prau* until reaching similar levels to the controls.

The low levels of *F. prau* in the healthy relatives indicates that shared genetic and/or environmental factors contribute to this change.

Potential link to IBD – the anti-inflammatory action of *F. prau* and its supernatant are likely to play a role in the management of IBD with reduced abundance contributing to the pathophysiology of the disease.

Irritable Bowel Syndrome (IBS)

IBS is a common functional intestinal disorder defined by symptoms of abdominal pain, bloating or discomfort, and altered bowel habits. The etiology of IBS is not yet known, but several mechanisms have been proposed including low-grade inflammation, impaired mucosal barrier function, or visceral hypersensitivity. These mechanisms could be influenced by the intestinal microbiota.

The microbiota composition of fecal samples from 62 people with IBS were compared to that from 46 healthy individuals (Rajilic-Stojanovic, et al., 2011). The intestinal microbiota of the IBS patients differed significantly to the healthy group. In particular, there was a 1.5-fold decrease in the numbers of *Faecalibacterium* spp. in IBS-A patients ($P < 0.05$). There was also a notably lower level of *Faecalibacterium* spp. in IBS-C patients, but this did not reach significance. Further, a negative correlation between *Faecalibacterium* abundance and IBS symptoms was observed ($P = 0.0004$).

In a rodent study, the effects of *Faecalibacterium prausnitzii* was investigated in two models of colonic hypersensitivity (CHS) induced by chronic or acute stress, namely Neonatal Maternal Separation (NMS) in mice or partial restraint stress in rats (Miquel, et al., 2016). The study found that *F. prau* significantly decreased CHS, which is considered a major factor in IBS physiopathology.

Potential link to IBS – As with IBD, inflammation appears to play a role in IBS and therefore the anti-inflammatory properties of *F. prau* and the butyrate produced by it, could affect the symptoms of IBS.

Colorectal Cancer (CRC)

CRC is one of the most common malignant cancers in the world and an important factor associated with CRC is the intestinal microbiota.

In several studies, dysbiosis with reduced *F. prau* has been observed:

- The microbiota composition of patients with colorectal cancer ($n = 46$) were compared to healthy controls ($n = 56$) (Chen, Liu, Ling, Tong, & Xiang, 2012). Stool, swab (of the gut) and cancerous tissue (CRC patients only) samples were collected and analysed. *Faecalibacterium* was significantly lower in CRC patients compared to the healthy controls ($p < 0.05$).
- DNA was extracted from the faeces of 20 patients with colorectal cancer, 9 patients with upper gastrointestinal cancer and 17 healthy volunteers (Balamurugan , et al., 2008). Levels of *F. prau* were significantly reduced in CRC patients compared to healthy (4-fold decrease, $P = 0.0028$).
- The faecal microbiota of 19 patients with CRC were compared to 20 healthy controls. *Faecalibacterium* was found to be significantly less abundant in patients with CRC (Wu, et al., 2013)

Potential link to CRC – butyrate, a short chain fatty acid generated in the colon by bacterial fermentation of undigested carbohydrate, provides energy for colonic epithelial cells, promotes epithelial cell differentiation, ameliorates inflammation, and hastens tissue repair in the colon. It can also induce apoptosis of cancer cells (Bultman, 2014). Therefore, butyrate has the potential to protect against the development of colorectal cancer. As a major-butyrate producer, *F. prau* could subsequently play an important role in the development/progression of colorectal cancer.

Systemic Conditions

Diabetes & Obesity

Obesity is characterised by increased fat mass and the development of other metabolic and cardiovascular diseases. Diabetes is a complex metabolic disorder affecting glucose regulation in the body. Inflammation has been found to play a role in both conditions as has the gut microbiota.

While there has been variable data relating to *F. prau* levels and obesity **without** concomitant diabetes (Miquel, et al., 2013) (Balamurugan, et al., 2010), several studies have found *F. prau* to be reduced in diabetics including obese diabetics and pre-diabetics.

Furet et al., 2010, profiled the gut microbiota from 13 lean controls and 30 obese (including 7 type-2 diabetics) subjects (Furet, et al., 2010). One key finding from the study was that *F. prau* was lower in the obese subjects with diabetes and negatively associated with inflammatory markers.

Later, Zhang et al, 2013, explored the relationship of the gut microbiota and the development of type 2 diabetes by analysing 121 subjects who had been divided into 3 groups based on their glucose intolerance status: normal glucose tolerance type 2 diabetics (T2DM; n = 13), prediabetes (Pre-DM; n= 64) and new diagnosed T2DM (n = 13). *F. prau* was found to be in higher abundance in the NGT group than the pre-DM group (Zhang, et al., 2013).

In 2015, 24 type-2 diabetics under GLP-1 Agonist therapy, 14 obese participants (without established insulin resistance) and a lean control group were recruited (Remely, et al., 2015). The differences in the gut microbiota of these groups were investigated over a 4-month intervention period whereby the diabetics and obese participants received nutritional counselling concerning weight reduction. Faecal samples were taken at the beginning and end of the 4-month period. The abundance of *F. prau* increased in the type 2 diabetics over the study period. This increase correlated positively with the loss of weight in the type 2 diabetics. No significant differences were observed in the obese patients or lean group, or between groups.

Stool samples collected from 18 lean, 24 diabetic and 26 obese subjects were analysed for *F. prau* (Hippe, et al., 2016). The lean control group had the highest abundance of *F. prau* with the diabetic group showing significantly lower levels compared to the lean control. The obese group had a lower abundance of *F. prau* than the lean control, however this was not statistically significant.

Possible link to obesity/diabetes – dysbiosis and a lack of *F. prau* and the associated butyrate can contribute to the onset of low-grade inflammation associated with gut barrier dysfunction (increased permeability/'leaky gut'). With increased permeability, bacterial pathogens containing lipopolysaccharide (LPS) can enter into the bloodstream and directly damage pancreatic β-cells, influencing insulin resistance.

Other Inflammatory/Auto-Immune/Allergic Conditions - Psoriasis, Atopy

Other conditions in which inflammation plays a role have also been found to be associated with reduced *F. prau*.

For example, psoriasis can co-occur with IBD, due to shared pathogenic and genetic features. As *F. prau* is known to be decreased in IBD patients, a study was conducted to determine if it was also depleted in patients with psoriasis, with and without concomitant IBD (Eppinga, et al., 2016).

Levels of *F. prau* in the faecal samples of healthy controls (n = 33), people with psoriasis (n = 29), IBD (n = 31), and concomitant IBD and psoriasis (n = 13) were analysed. Compared to the healthy controls, the abundance of *F. prau* was significantly lower in the psoriasis, IBD, and psoriasis with concomitant IBD groups ($p < 0.001$).

Intestinal microbiota has also been implicated as playing a role in atopy. Stool samples from 19 atopic children and 12 healthy controls were collected and the faecal microbiota was characterised. The intestinal microbiota of the atopic children showed a significant depletion of *F. prau* (Candela, et al., 2012).

Neurological Conditions

There is a significant and growing amount of literature on how the gut microbiota influences mental health and brain function via the microbiome/microbiota-gut-brain axis. Microbial dysbiosis has been associated with many health issues, including neurological conditions, such as autism, attention deficit hyperactivity disorder (ADHD), depression, anxiety, Parkinson's disease and multiple sclerosis. These disorders are associated with elevated levels of proinflammatory cytokines, increased oxidative stress, altered gastrointestinal function, and lowered micronutrient and omega-3 fatty acid status (Slykerman, et al., 2017).

Multiple Sclerosis

MS is an autoimmune disease affecting the brain and spinal cord. To investigate whether the gut microbiota in patients with MS is altered, the gut microbiota of 20 Japanese patients with relapsing-remitting MS was compared to 58 healthy subjects (Miyake, et al., 2015). The analysis showed that *Faecalibacterium* were less abundant in the gut microbiota of the MS patients than the healthy subjects.

In a second 2015 study (Cantarel, et al., 2015), women with or without relapsing-remitting multiple sclerosis were recruited. Stool samples were collected at baseline and again after 90 days of vitamin D supplementation.

The abundance of *Faecalibacterium* was significantly lower in multiple sclerosis patients at baseline compared to the healthy controls. Supplementation with vitamin D led to an increase in the abundance of *Faecalibacterium*.

Depression

Depression has also been linked to gut microbiota dysbiosis.

Faecal samples from 46 patients with depression (major depressive disorder, MDD) and 30 healthy controls were analysed. *Faecalibacterium* was reduced in the MDD group compared to the controls and a negative correlation was observed between *Faecalibacterium* and the severity of depressive symptoms (Jiang, et al., 2015).

Given the association between reduced *F. prau* and depression, a recent study tested *F. prau* as a potential psychobiotic with anxiolytic and antidepressant-like effects examined in rats (Hao, Wang, Guo, & Liu, 2019). Administration of *F. prau* had preventive and therapeutic effects on chronic unpredictable mild stress (CUMS)-induced depression-like and anxiety-like behaviour.

Possible link to neurological conditions - A pro-inflammatory microbiota may lead to increased gut permeability (leaky gut) which allows for easier passage of bacterial products and inflammatory mediators through the gut mucosa and into the blood (Gerhardt & Mohajeri, 2018).

Parkinson's Disease

Parkinson's disease (PD) is a neurodegenerative disease, which has been postulated to be influenced by changes in the gut. Several studies have therefore examined the microbial composition of PD patients.

- Sigmoid mucosal biopsies and faecal samples were collected from 38 PD patients and 34 healthy controls. The mucosal and faecal microbial composition of PD patients was significantly different to the controls. *Faecalibacterium* was significantly more abundant in the mucosa of the controls than in the PD patients (Keshavarzian, et al., 2015).
- Short chain fatty acid concentrations and microbiota composition was investigated in the faecal samples of 34 PD patients and 34 age-matched healthy controls (Unger, et al., 2016). *F. prau* was significantly reduced in the PD patients compared to the healthy controls. Further, there was a significant decrease in the absolute concentrations of acetate, propionate and butyrate and a significant reduction in the relative concentration of butyrate in PD patients compared to controls.
- Gut microbiota of patients with PD and healthy controls was analysed. In the PD patients, *Faecalibacterium* was reduced (Petrov, et al., 2016).
- The faecal bacterial composition of 24 PD patients and 14 healthy controls was determined (Li, et al., 2017). There were significant differences between the two groups as well as among the difference PD stages. *Faecalibacterium* was significantly reduced in PD patients and was negatively associated with disease severity and duration.

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For more information, please contact:

Email: info@anagenix.com
Tel: +64 9 520 0831
www.anagenix.com

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