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COVID-19 AND GUT MICROBIOME DYSBIOSIS – Low Levels of *Faecalibacterium prausnitzii* Linked to Covid-19 Infection Severity and Duration

Maintain a healthy gut microbiome and boost *Faecalibacterium prausnitzii* (F. prau) by consuming **Livaux®**. A high level of F. prau may help to reduce the risk of developing severe and long-lasting Covid-19 infection symptoms upon exposure to the virus.

Livaux® is novel, targeted prebiotic powder, derived entirely from New Zealand gold kiwifruit, and has been clinically shown to increase F. prau numbers in individuals with low F. prau levels (1). Recent studies have found that low levels of F. prau are associated with increased SARS-CoV-2 (Covid-19) virus symptom severity and duration (2).

Covid-19 Infection – How the Gut Microbiome is Involved

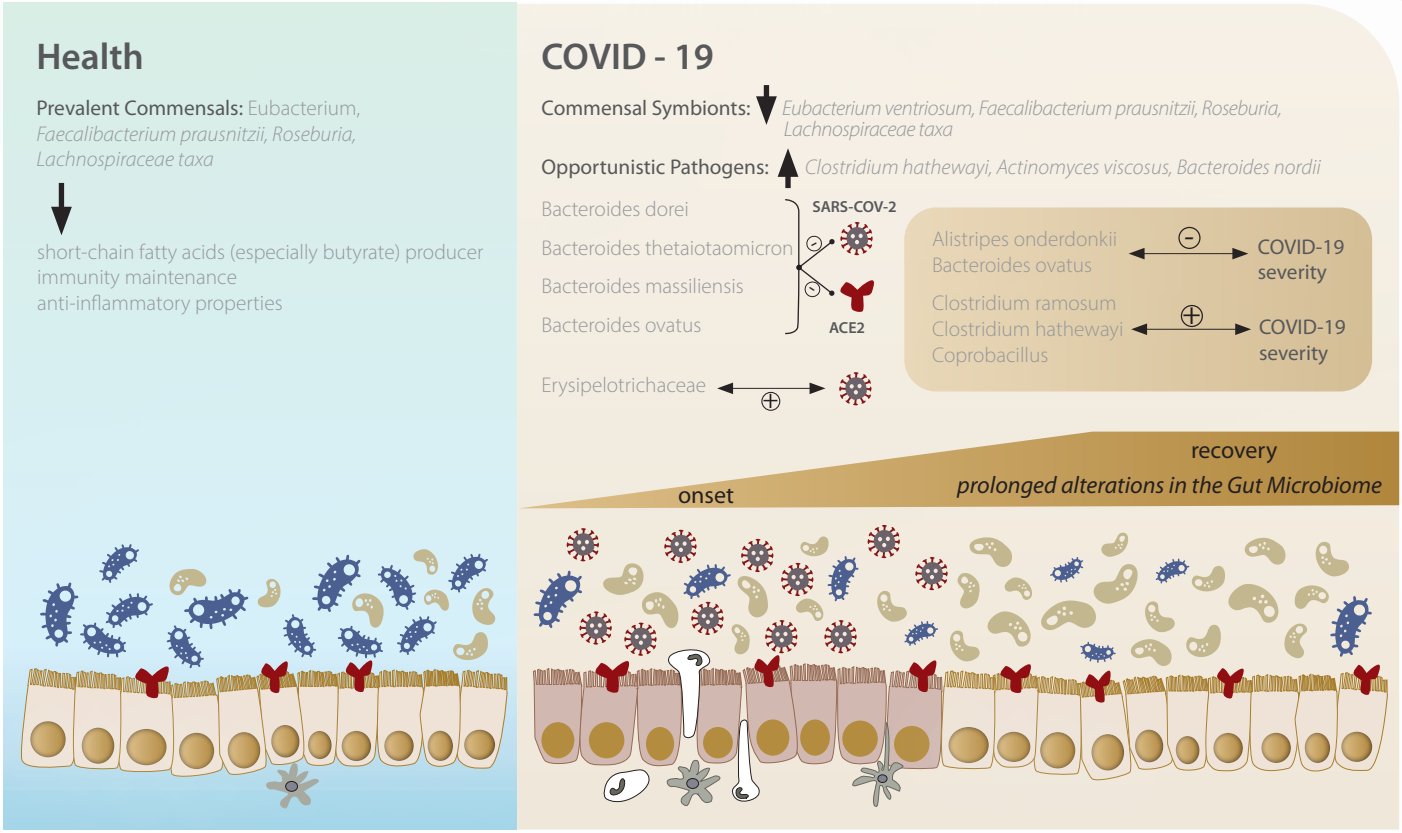
Covid-19 invades cells by a process starting with binding the ACE2 receptor (3). This receptor is found in highest levels on the surfaces of cells of the lungs, and on the surfaces of the cells lining the intestines (4). In the intestines, ACE2 is linked to inflammation and the gut microbiome (5). Covid-19 is known to cause gastrointestinal disturbances, with a high incidence of diarrhoea and microbiome dysbiosis (3-9). Viral material has been detected in faeces, even after the respiratory tract tests negative, illustrating the risk of faecal-oral transmission (3) and an urgent need to address these gastrointestinal issues (10).

In order for the Covid-19 virus to invade intestinal epithelial cells, it must survive transit through the stomach acid. Indeed, individuals on proton pump inhibitors (which reduce stomach acidity) are at risk of increased Covid-19 symptom severity and duration (11-13). Similarly, susceptibility to the virus is age-related (14), and increased age is associated with decreased stomach acidity (4), as well as decreased overall immune function and microbial dysbiosis (15).

The microbial dysbiosis associated with Covid-19 is well documented, and the bacteria most commonly inversely correlating with presence or severity of Covid-19 symptoms is F. prau.

Livaux®

Livaux®



Adapted from Zuo et al. Alterations in gut microbiota of patients with Covid-19 during time of hospitalisation. Gastroenterology. 2020. 159: 944-955

For example, recently patients with Covid-19 were shown to have significantly underrepresented F. prau, *Eubacterium rectale* and *Bifidobacterium adolescentis,* with the strongest inverse correlations with severity being numbers of F. prau and *Bifidobacterium bifidum* (16).

A previous study showed Covid-19 patients had lower numbers of *Eubacterium rectale, Ruminococcus obeum, Lachnospiraceae* bacterium 1_1_57FAA and F. prau (17). Again, F. prau most strongly negatively correlated with severity, in addition to *Alistipes* (17). These patients were also shown to have greater numbers of opportunistic pathogens known to cause bacteraemia such as *Clostridium hathewayi, Actinomyces viscosus, Bacteroides nordii*, and *Coprococcus* species known to upregulate ACE2 in the gut (17).

The depletion of key bacterial species in the gut microbiota of Covid-19 patients was also associated with increased concentrations of inflammatory cytokines (16), suggesting the gut microbiome is influencing the immune system's response to the Covid-19 infection.

A similar association of increased viral disease severity with lower F. prau has been seen in flu (H1N1) patients (18).

Decreases in F. prau numbers have not been shown to be associated with infectivity. In another study, individuals with high Covid-19 infectivity had lower abundances of *Parabacteroides merdae, Bacteroides stercoris, Alistipes onderdonkii* and *Lachnospiraceae* bacterium 1_1_57FAA (19). However, given that lower numbers of F. prau, *Alistipes* and *Lachnospiraceae* bacterium 1_1_57FAA were common across multiple independent studies, this suggests these bacteria occupy guilds that are relevant to mitigating the severity of Covid-19 symptoms.

Benefits of Healthy F. prau Levels

Of the thousand or so bacterial species that reside in the human gut, only a few are very special. F. prau is one of those very special bacterial species (20, 21). F. prau accounts for ~5% of the total faecal microbiota in healthy individuals but can increase to ~20% in some, making it one of the most abundant bacterium in the healthy human intestinal microbiota (22, 23).

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).

The major end products of fermentation by F. prau are formate, lactate and significant amounts of butyrate (> 10 mM in vitro). 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 (22).

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 (23, 24).

In *in vitro* and *in vivo* studies, F. prau and the molecules it secretes has been found to have potent anti-inflammatory action, affecting cytokine levels and intestinal permeability (22, 25, 26).

Over the last decade, an increasing number of studies have reported on F. prau depletion in various diseases/health concerns, including inflammatory bowel disease (IBD, i.e. Crohn's disease and ulcerative colitis), irritable bowel syndrome (IBS), colorectal cancer, diabetes, psoriasis, atopy, multiple sclerosis, Parkinson's disease and depression. The findings of these studies indicate that F. prau has a crucial role to play in maintaining gut physiology and overall host wellbeing.

Possible Solution to Improving Covid-19 Infection Outcomes Through Microbiome Modulation

Modulating the gut microbiome to help it maintain healthy levels of key bacteria like F. prau, may be a solution to decrease the risk and severity of Covid-19 infection should exposure to the virus occur (27, 28).

What can be done to address microbiome dysbiosis and increase F. prau numbers? Decreased hygiene and cleanliness has been associated with an increased microbial diversity and decreased Covid-19 susceptibility (29). Conversely, social distancing and its commensurate decrease in microbial transfer and acquisition has been posited to lead to a dangerous decrease in microbial diversity (30). However, decreasing hygiene and social distancing are dangerous, as they are associated with other larger risks (29, 30). A more viable alternative to increase microbial diversity for decreased Covid-19 symptom severity is through food (27).

The use of probiotics, live microorganisms that confer health benefits when consumed, has been suggested as a viable strategy (27). Indeed, The Natural Health Committee of China has promoted this course of action (27). Similarly, some of the researchers who first definitely established the link between Covid-19 severity and gut microbiota have attempted to create probiotic supplements for this purpose (31). However, F. prau is highly oxygen sensitive and cannot be viably delivered for consumption in adequate live numbers.

Prebiotics, food which survives digestion and reaches our large intestine to selectively increase the numbers of gut bacteria that confer health benefits, are a better proposition. Diet has been shown to increase F. prau numbers (32), particularly high carbohydrate/low glycemic impact diets (33). In terms of selectively increasing F. prau, Livaux® from New Zealand gold kiwifruit is a natural prebiotic clinically shown to increase F. prau levels in individuals with low baseline levels (1). This effect has also been demonstrated in vitro (34). Livaux contains high methoxy pectin, and high methoxy pectic galacturonic acid is a substrate used by F. prau (35).

Livaux®

More About Livaux®

Livaux® is a high-quality powdered ingredient derived entirely from New Zealand Gold3 (Zesy002) kiwifruit. The proprietary processing technology gently converts the nutrient-dense gold kiwifruit into a free-flowing powder which is packed full of the key bioactives from the whole fruit.

The key bioactives from gold kiwifruit include (but are not limited to):

VITAMINS C, E AND FOLATE

- Folate and vitamin C can increase antibody production (36).
- Vitamin C, E and polyphenols are antioxidants which help to mop up the damaging reactive oxygen species generated during inflammation (36).

POLYPHENOLS

- Apart from their antioxidant action, the polyphenols in Livaux can also inhibit pro-inflammatory cytokine production (36).

DIETARY FIBRE – PECTIN (HIGH METHOXY), HEMICELLULOSE AND CELLULOSE

- The high methoxy pectin in Livaux is a food source for the beneficial gut bacteria, F. prau (35).
- Fermentation of dietary fibre by gut bacteria generates short chain fatty acids which have anti-inflammatory and other health benefits.

The bioactives in **Livaux®** work together to support gastrointestinal and immune health. Clinical research has shown that daily consumption of Livaux increases the relative abundance of F. prau in individuals with low baseline levels. A significant 2-fold increase in F. prau was observed, bringing the relative abundance from 3.4% to a healthy 7% (1). And studies on gold kiwifruit have shown the fruit's bioactives help to reduce the duration and severity of upper respiratory tract infections, particularly in susceptible individuals such as the elderly and preschool children (36, 37).

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