SCIENCE PERFECTED IN MARKET

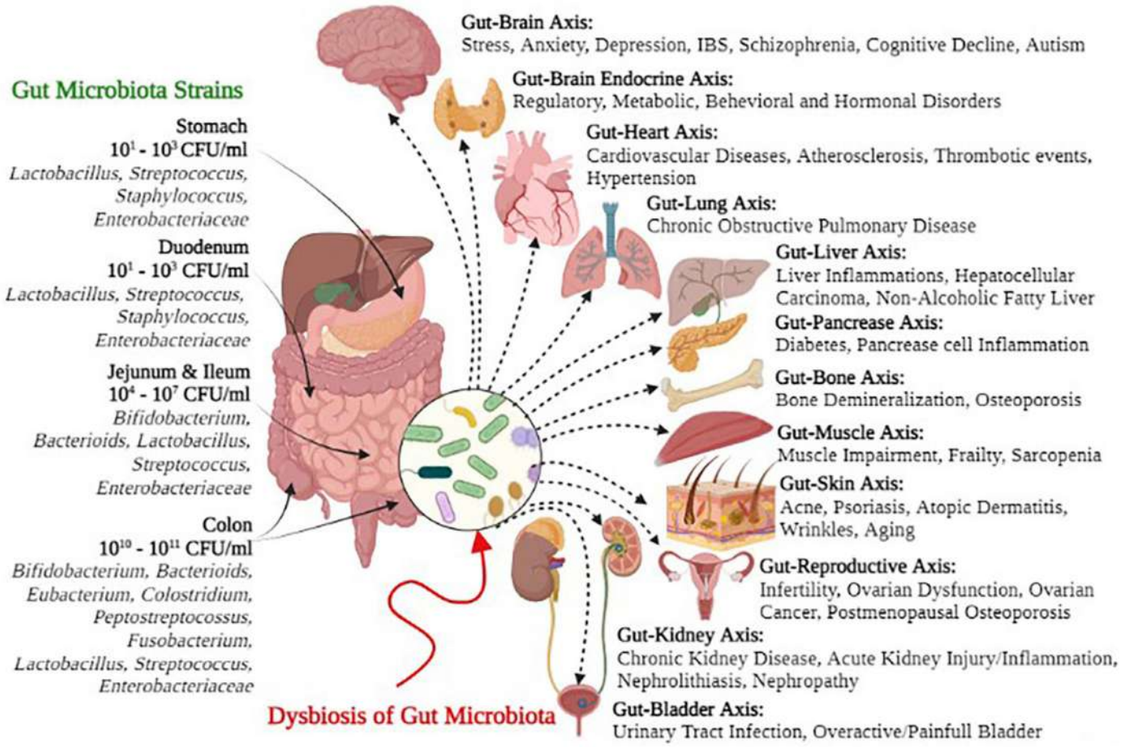
Livaux®

Formulate Next-Level Synbiotics with Livaux®

ANAGENIX

Synopsis

The human gut microbiota contains about 150x more genes than the entire human genome. As a result, they play a key role in maintaining our health and impact various physiological activities. Obviously, any alteration of its composition might lead to several undesirable outcomes. In recent years many of these mutual interactions have been defined as gut-brain, gut-skin axis, etc.



The alteration of the gut microbiota composition is called dysbiosis and is a cause or consequence of several disorders.

Several commercially available probiotics have clinically proven effects in restoring the human gut microbiota. Nevertheless, restoring the abundance of anaerobic bacteria, which are the main SCFA producers, is still problematic since they are sensitive to oxygen.

Faecalibacterium prausnitzii (F. prau) is one of the most abundant friendly anerobic bacteria and a major SCFA producer in the human gut microbiota.

Livaux®, a whole gold kiwifruit powder, has been clinically proven to significantly increase the abundance of F. prau. This promotes the necessary diversity and re-balances the disturbed microbiota. The increase of F. prau will also promote the production of SCFAs, particularly butyrate, which is considered as the biomarker of a health gut microbiota.

Livaux® as an active ingredient for synbiotic solutions.

Unique Value Proposition

- Livaux is proven to support the growth of *F. prausnitzii* at a low dose of 600mg.
- Livaux is effective in increasing SCFAs, particularly butyrate.
- Livaux promotes the diversity of the microbiota.
- Livaux promotes the growth of commercially available probiotics with a low dose of only 25 mg per billion cfu.
- The 600 mg effective dose of Livaux is convenient for formulating various synbiotic dosage forms.

The Human Microbiota

The human gut possesses millions of microbes that define a complex microbial community. The gut microbiota has been characterized as a vital organ forming its multidirectional connecting axis with other organs.

This gut microbiota axis is responsible for host-microbiome interactions and works by communicating with neural, endocrinal, humoral, immunological, and metabolic pathways. Dysbiosis of the gut microbiota is therefore linked to various human diseases, such as anxiety, depression, hypertension, cardiovascular diseases, obesity, diabetes, inflammatory bowel disease, and cancer[1].

The human gut microbiota carries about 150x more genes compared to the entire human genome. They are the primary mediators of body homeostasis, impacting various physiological activities, such as metabolism, barrier homeostasis, inflammation, and hematopoiesis through both intestinal and extra-intestinal actions. The gut microbiota has recently been classified as a "vital organ" because of its multidirectional and communicational connection or axis with other organs through neural, endocrine, humoral, immunological, and metabolic pathways. Any change in the microbial community not only causes gut-related issues, but also influences other organ related diseases (Fig. 1), though the actual interaction mechanism between the gut and the organs has yet to be fully understood.

Many research studies have supported the concept that gut microbiota plays a key role in modulating immunity, weight gain or loss, energy homeostasis, and obesity-related disorders. Likewise, gut microbiota and their metabolites are associated with various non-alcoholic fatty liver diseases (NAFLDs), inflammatory bowel diseases (IBDs), hepatocellular carcinoma, cardiovascular diseases (CVDs), alcoholic liver diseases (ALD), chronic kidney diseases (CKDs), and cirrhosis.

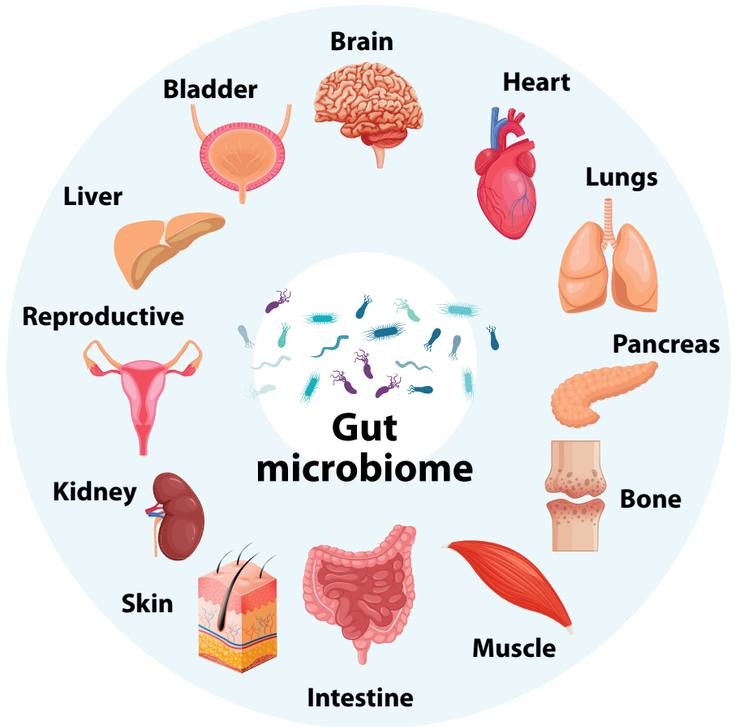


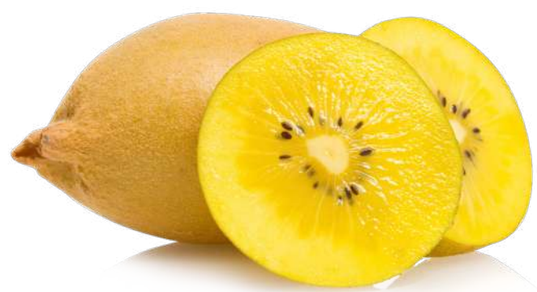
Figure 1 Gut microbiome is associated with disease through different axes.

A well-balanced gut microbial community is essential for the host and the microbiome to co-exist in a mutually beneficial relationship.

A healthy host-microorganism balance must be respected in order to optimally perform metabolic and immune functions and prevent disease development2. Understanding the cause or consequence of these gut microbiota balances in health and disease, and how to maintain or restore a healthy gut microbiota composition, should be useful in developing promising therapeutic interventions.

Gut bacteria are the key regulators of digestion along the gastrointestinal tract; commensal bacteria play an important role in the extraction, synthesis, and absorption of many nutrients and metabolites, including bile acids, lipids, amino acids, vitamins and short chain fatty acids (SCFAs).

The large intestine, which is characterized by slow flow rates and neutral to mildly acidic pH, harbors by far the largest microbial community (dominated by obligately anaerobic bacteria). We can observe a microbiota quantitative increasing gradient and a microbiota qualitative decreasing gradient with a progressive aerobic bacteria decrease for the benefit of strictly anaerobic bacteria.



Bottomline

The human microbiome and its relationship to disease is a new and rapidly evolving field of study.

Co-evolution of hosts and their microbiomes has led to cooperative interactions in metabolism and homeostasis.

Concepts from community ecology such as resilience, community disturbances and extinction are useful in understanding the microbiome.

New computational and statistical tools are being actively developed to analyze the large sequence datasets generated by the increasingly powerful technologies.

The taxonomic composition and functional characteristics of the microbiome may allow individuals to be categorized into different microbial patterns, called "enterotypes", in the gastrointestinal tract.

Many factors affect the composition of the microbiome over the course of a human lifetime. These include inheritance, mode of infant delivery, diet, and age-related changes in adults.

The relationships between the microbiome and several human diseases are being intensively studied for conditions that include colorectal cancer, inflammatory bowel disease, and immunologically-mediated skin diseases.

Causal relationships for many of the associations between the microbiome and disease states have yet to be proven.

Understanding the links between the microbiome and human disease may provide prophylactic or therapeutic tools to improve human health[3].

Factors Affecting the Composition of the Gut Microbiota

Several factors affect the composition of the gut microbiota (Fig. 2). Some of these factors are caused by short-term effects such as antibiotic use or exposure to short-term stress. Some of them might be due to longer-term effects such as lack of exercise or diet. Nevertheless, some of these appear to be more difficult to adjust since they might be based on criteria which are almost impossible to change like geographical location, host genetics or the mode of delivery.

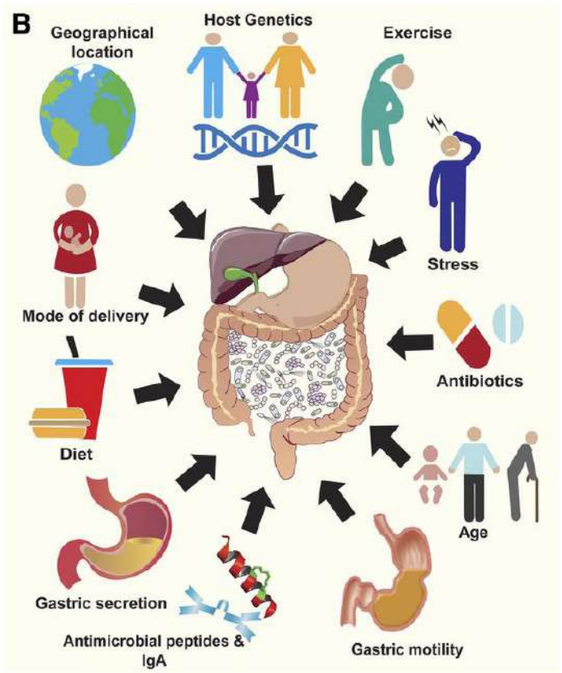


Figure 2: Factors affecting the composition of the human gut microbiota[4]

Gut Microbiota Variations in Health and Disease

Gut microbiota composition is highly variable. The variation itself is considered as physiological in the context of healthy gut microbiota, however these physiological gut microbiota variations have huge implications in intestinal and extra-intestinal disorders.

Dysbiosis is often defined as an alteration of gut microbiota composition and is a cause or consequence of disorders.

While the definition of a healthy gastrointestinal microbiome cannot be made precisely, features of a healthy gut microbiome include relatively greater biodiversity and relative abundance of specific phyla and genera[5].

The "Missing Microbe" hypothesis postulates that industrialization and current medical practices (e.g., vaccination, antibiotics) have diminished the prevalence of infectious diseases such as tuberculosis and malaria. However, access to healthcare and improved life expectancy has reduced gut microbial diversity. Urbanization is the main cause of major human microbiome shifts and microbial loss (Fig. 3), as documented by studies evaluating rural and urban lifestyles[6].

There is an increasing amount of evidence connecting dysbiosis to several health conditions as shown in Figure 4[1]. Correcting dysbiosis may therefore help to prevent or treat these conditions and there are many probiotics or other beneficial bacteria that show potential, although most of them cannot be cultivated at present (e.g., anaerobic bacteria). Some of these gut microbes belong to genera that contain many probiotics such as ***Lactobacillus*** and *Bifidobacterium*. Others are novel beneficial bacteria such as *Faecalibacterium prausnitzii*, which has potential for treating inflammatory bowel diseases (IBD) and irritable bowel syndrome (IBS)[7].

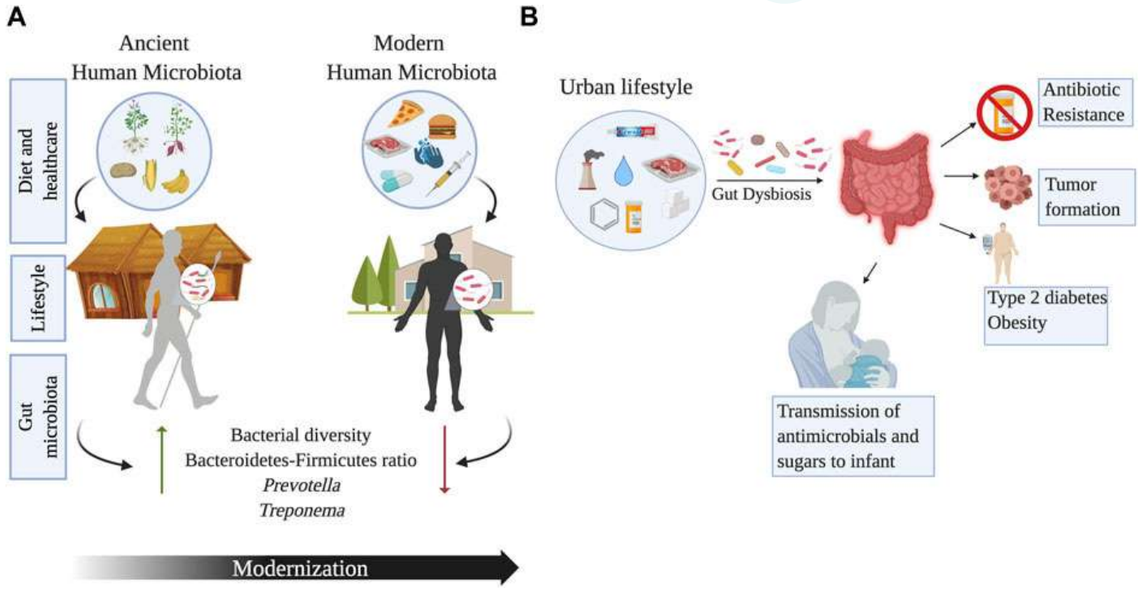


Figure 3: Changes in the gut microbiome across urbanization and human lifestyles[6].

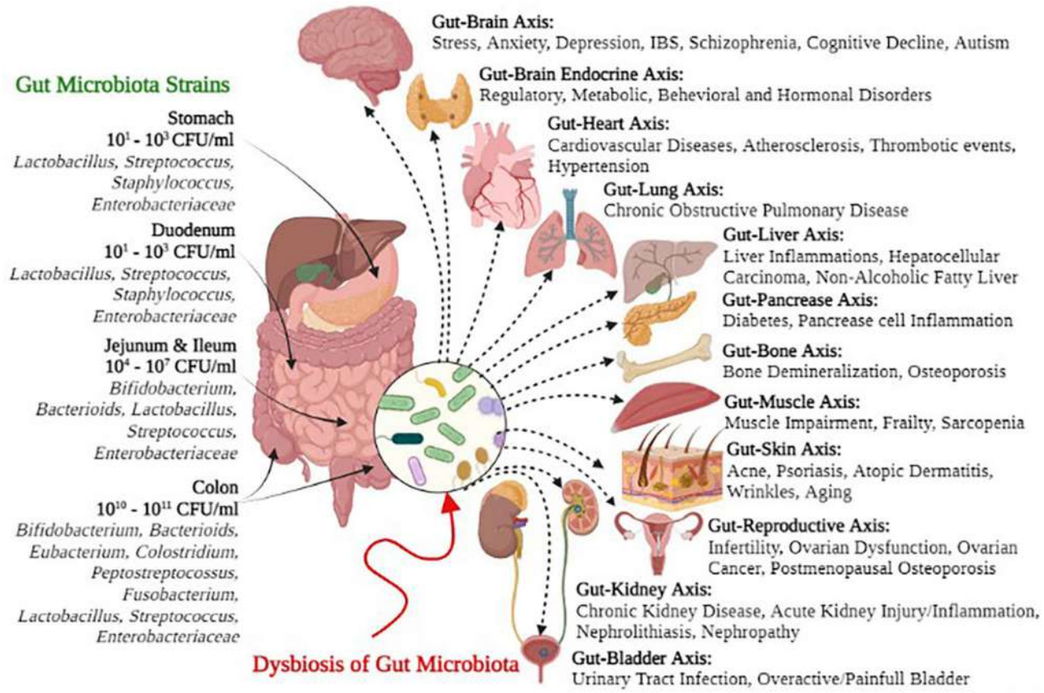


Figure 4: Gut microbial strains and negative health outcomes of gut dysbiosis[1]

Lactobacillus acidophilus NCFM®

There are many commercially available probiotics that have been shown in clinical studies to provide a beneficial effect in dysbiosis and related conditions. One such probiotic is *Lactobacillus acidophilus* NCFM®.

L. acidophilus NCFM®, was first isolated from a human source in the early 1970s. Since then, more than 370 scientific publications have reported on the functionality of *L. acidophilus* NCFM®, including more than 80 human clinical trials as a single entity and in combination with other probiotics and prebiotics[8].

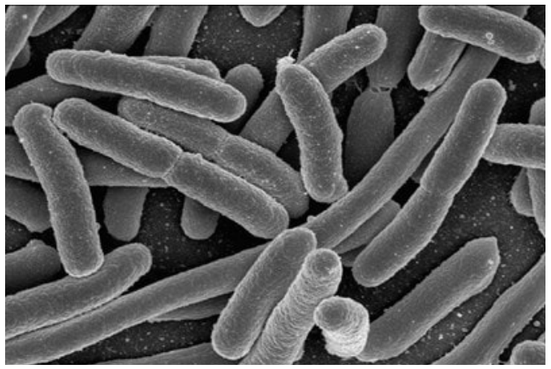


Figure 5: Lactobacillus acidophilus NCFM® under the microscope

Adhesion to intestinal mucosa

While adhesion is not a prerequisite for a strain to elicit probiotic properties, interaction with the intestinal mucosa is considered important for a number of reasons. Binding to the intestinal mucosa may prolong the time a probiotic strain can reside in the intestine. This interaction with the mucosa brings the probiotic in close contact with the intestinal immune system, giving it a better opportunity to modulate the immune response. It may also protect against enteric pathogens by limiting their ability to colonize the intestine. The ability of *L. acidophilus* NCFM® to adhere to different human epithelial cell lines has been confirmed in several studies[9,10].

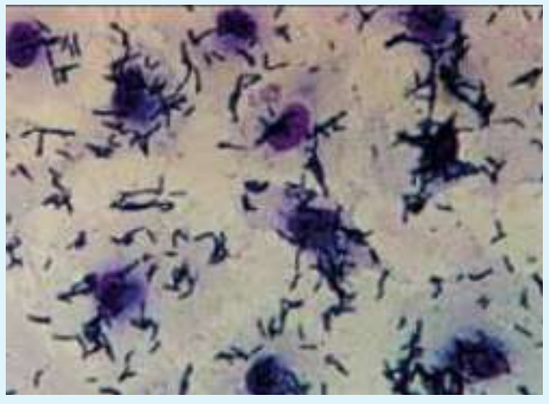


Figure 6: L. acidophillus NCFM shows strong adherence to human fetal intestinal epithelial cells[9]

Improving comfort

In a clinical trial published in 2016 by Lyra et al.[11], the effect of *L. acidophilus* NCFM® on IBS symptoms and quality of life was determined. 391 adults, 18 to 65 years old with IBS diagnosed per Rome III criteria, received the following treatment:

- Placebo

- NCFM® 1 billion CFU/day (low dose)

- NCFM® 10 billion CFU/day (high dose)

IBS Symptom Severity Score and individual symptoms plus quality of life among other outcomes were assessed at baseline, 4 and 12 weeks of intervention.

Table 1: Change in pain score for participants with moderate or severe abdominal pain at baseline

Treatment	n	Baseline mean ± SD	Week 12 mean ± SD	Change from baseline mean ± SD	Mean difference for combined active doses 95% CI	P value (combined active doses vs placebo)
Placebo	29	51.1 (9.3)	30.3 (22.9)	-20.8 (22.8)	-9.5 (-18.8; -0.17)	0.046
Low dose	36	53.6 (10.9)	24.4 (19.4)	-29.4 (17.9)		
High dose	34	52.1 (10.7)	21.9 (20.6)	-31.2 (21.9)		

Key Findings

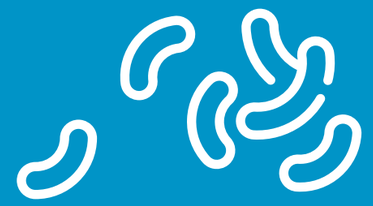
There was significant improvement in IBS symptom severity in both the probiotic and placebo groups.

For subjects experiencing moderate to severe pain, abdominal pain was significantly reduced in the NCFM groups compared to placebo.

Evidence from the more than 370 publications on the probiotic, supports the following health-related attributes for *L. acidophilus* NCFM®:

- **Long history of safe use**
- **Well suited for intestinal survival**
  - High tolerance of gastrointestinal conditions
  - Strong adhesion to intestinal cell lines
- **Improves gastrointestinal health and well-being**
  - May provide protection against pathogens
  - Utilizes prebiotics
  - Aids in lactose maldigestion
  - Maintains the balance of healthy microbiota
  - Aids digestion and well-being
  - Promotes gastrointestinal comfort
  - Induces human colonic mucosal opioid receptor expression
- **Beneficial modulation of immune functions**
  - May improve specific immune response, as demonstrated in human clinical studies
  - May influence immune regulation, as demonstrated by the induction of cytokines such as proinflammatory IL-12 and anti-inflammatory IL-10 in vitro
  - May reduce symptoms of respiratory tract infection

Meet *Faecalibacterium prausnitzii*



Clinical trials demonstrate that *Faecalibacterium prausnitzii* (*F. prausnitzii*), a beneficial bacterium in human inflammatory bowel disease, exerts anti-inflammatory effects and confirm that butyrate is largely responsible for this effect. This could be a useful point of intervention for reestablishing the proper interactions between the human colonic mucosa and microbiota[12].

As *F. prausnitzii* levels are decreased in various metabolic and digestive diseases, which are also characterized by a leaky gut, promoting *F. prausnitzii* abundance and/or metabolism by administration of prebiotics that favour *F. prausnitzii*, may support effective epithelial regeneration[13,14].

Therefore, *F. prausnitzii* is an attractive target of microbiomic reprogramming to restore intestinal homeostasis. Regretfully, *F. prausnitzii* is super-sensitive to oxygen[12]. However, prebiotic supplements can also be effective; for example, kiwifruit-based supplementation was noted to increase *F. prausnitzii* abundance in the gut as well as stool frequency in humans[15].

Bottomline; *F. prausnitzii* represents a Next Generation Probiotic in Gut Diseases[13], which requires a next level prebiotic that could increase the abundance of *F. prausnitzii* the gut.

Livaux® – the Next Generation Prebiotic

A next generation prebiotic should fulfil two challenges:

1. Increase diversity of the gut microbiota, particularly with anaerobic probiotics which are not manageable to be provided as food or food supplements.
2. Increase the amount of short chain fatty acids, particularly butyrate.

Livaux® is a wholefood-based nutritional ingredient crafted from the nutrient-dense New Zealand gold kiwifruit. It consists of a variety of bioactive components including fiber and polyphenolic compounds.

The wholefood concept provides a holistic use of this valuable fruit. While other dietary fibers are substances obtained by extraction from food sources, Livaux® represents a more diversified supplement including other valuable ingredients.

Summary of Livaux® Bioactive Nutrients

Livaux® as a whole kiwifruit powder provides the benefit of the "entourage" effect provided by several biological active compounds as follows:

- Dietary Fibers (soluble and insoluble)
  - Complex kiwifruit pectin - Prebiotic substrate to promote a diverse microbiota and increase butyrate
  - Hemicellulose
  - Cellulose
- Phytochemicals
  - Polyphenolic compounds providing direct and indirect antioxidant protection
- Vitamins
  - Antioxidant vitamins
    - Vitamin C
    - Vitamin E
- Minerals
  - Potassium

Livaux® is a gold kiwifruit powder. Whole kiwifruit is gently processed into a seedless, skinless puree which is then carefully dried into a powder. The gentle proprietary processing ensures levels of key nutrients and bioactives are maintained in the powdered form.

Complex Kiwifruit Pectin

One of the key benefits of Livaux® is its provision of complex dietary fiber to the colon. Simple structured prebiotics like FOS, GOS and inulin (Fig. 7) are easily and swiftly fermented by gut bacteria in the earlier parts of the colon. Unfortunately, this does not promote microbiota diversity.

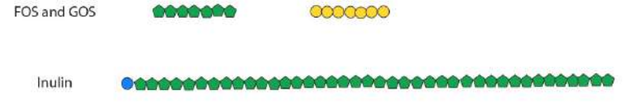


Figure 7: Simple structures of several known prebiotics

Whereas complex dietary fiber/prebiotics, such as the kiwifruit plant cell wall polysaccharides in Livaux®, require many different degradative enzymes to be digested. Such prebiotics should promote diversity and, being slower to ferment, should increase the levels of SCFA such as butyrate within the gut and right through the gut, not just in one place.

Kiwifruit dietary fiber mainly consists of pectic polysaccharides (pectin), hemicellulose and cellulose. The most fermentable of these polysaccharides is pectin. Pectin is amongst the most complex polysaccharides found in nature (Fig. 8)[16].

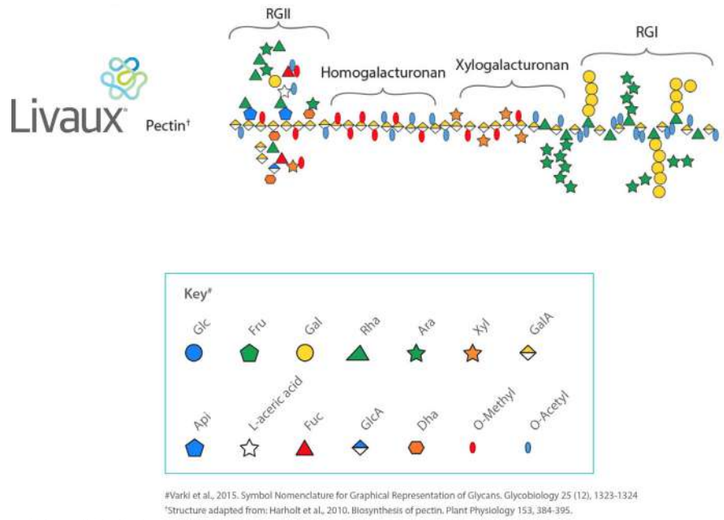


Figure 8: Complex structure of Livaux® kiwifruit pectin

This complex structure and commensurately slower fermentation allows Livaux® to reach deep into the colon, to be processed by a broad selection of bacteria, and to cause fewer undesirable effects like gas, bloating and discomfort.

Supporting the Growth of *F. prausnitzii* at a low dose of 600 mg

In a study performed by McKeen et al., 2023[17], there was a significant increase in the relative abundance of *F. prausnitzii* in healthy subjects with self-reported constipation who consumed 600 mg of Livaux® for 4 weeks (Fig. 9).

This supports an earlier study by Blatchford et al., 2017, which showed a significant increase in *F. prausnitzii* in functionally constipated individuals consuming 2.4 g of Livaux for 4 weeks (Fig. 10).[15]

The desired abundance of *F. prausnitzii* should be 5-15% and the average abundance in functionally constipated consumers was initially below these limits. After consumption of Livaux® for 4 weeks, there was a significant 2-fold increase in the average abundance of *F. prausnitzii* in the participants (Fig. 10).

As previously described, *F. prausnitzii* is one of the most important commensal bacteria responsible for the production of butyrate. The increase of *F. prausnitzii* abundance will lead to the augmented production of butyrate within the gut.

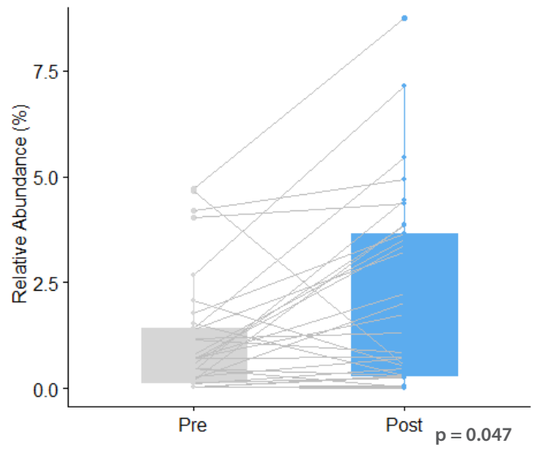


Figure 9: Increase in F. prausnitzii *relative abundance in healthy but self-reported constipated users after 600mg Livaux per day*

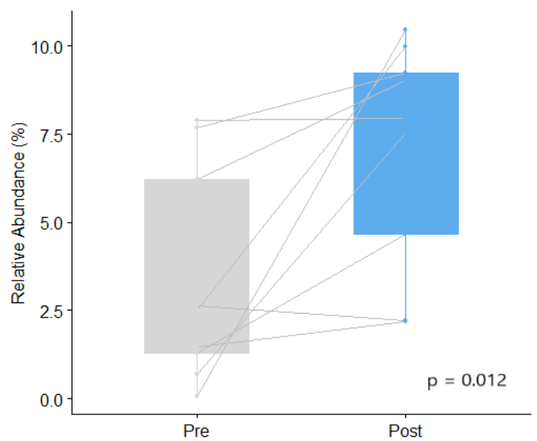


Figure 10: Increase in F. prausnitziii *relative abundance in functionally constipated users after 2.4g Livaux per day*

Additionally, Livaux® in a synbiotic formulation (a blend of Livaux®, other prebiotics and spore-forming probiotics) has been shown to increase *F. prausnitzii* relative abundance in an artificial gut system called M-SHIME® (Fig. 11)[18]. This supports the findings from the two clinical studies just described and was useful because it explained the clinical results using a simulation of the inner workings of our intestines, demonstrating that Livaux supports the growth of *F. prausnitzii* in regions of the colon not (normally) accessible for sampling without medical procedures.

The Livaux® synbiotic combination showed large and significant increases in butyrate in all three (proximal, transverse, and distal colonic) SHIME compartments. These increases are also difficult to measure without medical intervention, especially as butyrate is rapidly absorbed and used by the gut epithelia, so that little survives to the faeces[19]. Commensurate with these butyrate increases, there were significant increases in *F. prausnitzii* relative abundances (percentage of the total bacteria) in the second (transverse colon) and final (distal colon) vessels. Similar increases were not seen using the same probiotic mix in the absence of the prebiotic mix, proving these increases were due to the prebiotic being fermented.

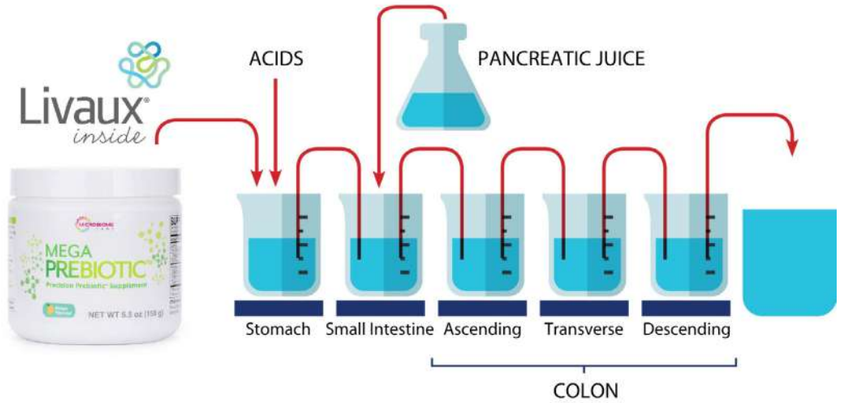


Figure 11: Livaux in the SHIME model of the gastrointestinal tract

These data collectively point to a multilayer effect of Livaux to increase microbial diversity, increase *F. prausnitzii* numbers, improve mucus barrier function, and improve tight junction integrity through the actions of the *F. prausnitzii* directly and through increased butyrate production.

Livaux Synbiotic Concepts

Synbiotics are defined by the International Scientific Association for Probiotics and Prebiotics (ISAPP)20 as:

"A mixture, comprising live microorganisms and substrate(s) selectively utilized by host microorganisms, that confers a health benefit on the host."

Synbiotics can be:

1. Complementary

- A mixture of probiotic(s) and prebiotic(s) where each works independently to achieve one or more health benefits.

2. Synergistic

- A mixture of probiotic(s) and prebiotic(s) where the substrate (prebiotic) is designed to be selectively utilized by the co-administered microorganisms (probiotics), and the components work together to bring about the health benefit(s).

At Anagenix we have developed Synbiotic Solutions with IFF strains and our kiwifruit powder.

How Livaux® can help provide a better environment for probiotics

- **Food for Probiotic to Grow**
  Kiwifruit pectin is a highly complex dietary fiber that is slowly fermented, increasing bacterial diversity and SCFA (inc. butyrate) production right through to the end of the colon, supporting a healthy microbiome.

- **Reduce Inflammation**
  Antioxidant vitamins C and E and polyphenols (e.g. epicatechin), neutralize reactive oxygen species to reduce inflammation.

- **Increase Mucus**
  Mucus production can be increased through the direct action of leucine and indirectly through increasing *F. prausnitzii* and butyrate.

Our Turnkey Solution – HOWARU GOLD

- Livaux® gold kiwifruit powder 600mg
- *Lactobacillus acidophilus* NCFM® 1B CFU

The scientific rational behind the product is based on the synergistic effect of the probiotics and prebiotic to promote the diversity of the microbiome, increase the abundance of *F. prausnitzii* and promote the production of SCFAs, particularly butyrate. Our Turnkey Solution is ready for use, with supporting stability data available.

***Lactobacillus acidophilus* NCFM® has been proven for significantly relieving the symptoms of IBS at a dose of 1B CFU per day.**

***F. prausnitzii* levels are know to be low in patients with IBS, IBD and Crohn's Disease.**

Other Livaux Synbiotic Concepts Starting with a Low Dose of 25 mg per Billion cfu of Probiotics

Beside the synergistic effect of *L. acidophilus* NCFM® and Livaux® we have also evaluated the prebiotic potential of Livaux® with other commercial probiotics.

Livaux supports the growth of probiotic strains, *Bifidobacterium*, *Lactobacillus* and *Bacillus* by up to 115% (Table 2) whilst not supporting the growth of the pathogenic bacteria, versus the control (Fig. 12). The observed effect is likely due to the presence of digestion-resistant carbohydrates (i.e. pectin) and one or more of the phytochemicals found in Livaux. As little as 25 mg of Livaux per billion cfu of probiotic is needed to promote the growth of the probiotics..

Table 2: Probiotic strains that grow on at least 25 mg of Livaux per billion cfu and their potential health benefits

Probiotic	% growth with Livaux[1]	Potential health benefits
Lactobacillus rhamnosus HN001	111%	Women's (maternal) health including immunity for mum and baby, postnatal mental health, vaginal health and protection against gestational diabetes
Bifidobacterium lactis HN019	115%	Gastrointestinal and immune health - improves intestinal transit time and reduces GI symptoms
Bifidobacterium lactis BB12	25%	One of the most clinically studied strains for constipation. Also evidence to support oral health, immune health and healthy cholesterol levels
Lactobacillus gasseri BN17	13%	Weight management (supports a healthy BMI) and provides digestive health support
Bacillus coagulans SC208	13%	Supports gastrointestinal and immune health

[1] *As shown in in vitro assays. Report available upon request.*

Unique Value Proposition

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Livaux is effective in increasing SCFAs, particularly butyrate.

Livaux promotes the diversity of the microbiota.

Livaux promotes the growth of commercially available probiotics with a low dose of only 25 mg per billion cfu.

The 600 mg effective dose of Livaux is convenient for formulating various synbiotic dosage forms.

Livaux® *inside*

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