triGUTTM

The world´s most well documented probiotic complex

Exclusively from Optiome

Trigut™ is a proprietary dietary supplement containing 3 selected, intensely studied probiotic strains with important health benefits.

Taken together the probiotic species included in the product has been published in more than 1200 scientific studies and studied in 350 clinical trials. They can all survive in low pH thus making a successful passage through the stomach and have been shown to establish in the human microbiota.

The strains included in the product have a history of being included in food products and supplements for more than 27 years. The species are included in the European Food Safety Authority (EFSA) list of microorganisms safe for human consumption and have obtained GRAS (Generally regarded as safe) by US FDA.

Clinical effectiveness

To be an effective probiotic, a clinically effective dose must be included in the supplement. Trigut has been formulated with a scientifically established clinically effective dose of each of the included strains. Thus, Trigut contains:

- 2 X 1010 Lactobacillus rhamnosus GG ATCC 53103
- 10 X 1010 Lactobacillus plantarum DSM 9843
- 1 X 1010 Bifidobacterium animalis spp lactis DSM 15954

Mechanism of action

The understanding of mechanism of action of probiotics is still unknown and despite the large number of studies have only partly been examined. The mechanism of actions discussed all evolve around the bacterias ability to colonize and establish itself as commensal bacteria in the gut. Examples of specific actions are:

- Production of biofilm that mechanically protects the mucosa and increases the longevity of the mocosa cells.
- Once established in the gastrointestinal tract the beneficial bacteria offer pathogen protection by secretion of biocide active proteins.
- Activation of immune response, again once established in the lumen , bacteria can contribute to an increased immune response by activating host cell immune cells by changes in signaling molecules such as SFCA or direct interaction, which are then transferred to systemic effect through circulation.
- Suppression of excessive inappropriate inflammation in the gut. Bacteria has been shown to increase IL-10 production in the immune system cells. IL-10 in turn suppresses excessive activation of Th1 cells which then suppress inflammation.
- Luminal interactions, there may be interactions between luminal content and the commensal bacteria or an effect of the luminal metabolism of nutrients.
- Intestine motility can be increased by Nitric Oxide. NO is generated as bacteria catabolize arginine which can have an effect on the motility of the large and small intestines.

Lactobacillus

Lactic acid bacteria are a functional group of bacteria. The term is used by Food microbiologists as a collective term for bacteria able to ferment carbohydrates in foods to lactic acid. They typically occur spontaneously in fermented foods and consist of several different bacterial families and genus such as the family Lactobacillaceae and the genus Lactobacillus.

Lactobacillus is a genus of bacteria consisting of more than 90 defined species, all able to ferment carbohydrates into carboxylic acids, mainly lactic acid. The Lactobacillus species have been divided into three functional groups based on fermentation function; Group I (obligate homofermentative) which ferments hexoses to lactic acid but cannot ferment gluconate or pentoses, Group II (facultative heterofermentative) which in addition to hexose also ferments pentoses and/or gluconate and finally Group III (obligate heterofermentative) which ferments hexoses to lactic acid, acetic acid and or ethanol and carbon dioxide.

Latobacillus rhamnosus

Lactobacillus rhamnosus is a species within the Lactobacillus genus with a wide variety of strains isolated from different environments including the human gastrointestinal tract. It belongs to group II of Lactobacillus and as such exclusively ferments hexoses into lactid acid but can also ferment pentoses and/or gluconates into lactic and acetic acid. Its pan-genome contains 4711 genes of which 2164 constitute its core genome. The accessory genome allows for wide strain specific functionalities and contains strain specific genes encoding for carbohydrate transport, extracellular polysaccharides, biosynthesis and pili production.

Lactobacillus rhamnosus GG ATCC 53103 - >800 scientific studies, >200 clinical trials (11), 7 ongoing clinical trials

The strain was isolated in 1983 from the intestinal tract. Since its discovery, the strain has been studied extensively on various health benefits and is claimed to the world's most studied probiotic bacterium with more than 800 studies. The bacteria display a specific pili (hair-like structure on bacterial surfaces important for adhesion) which has been shown to be important to adhesion to the human intestinal wall (1).

Example of studied health benefits:

- Immune function (11) (14)
- Normalizes intestinal permeability (6)
- Dysbiosis (11)
- Antibiotic-associated Diarrhea (AAD) (11)
- Functional GI disorders in children (4)
- IBS (5).
- Gawronska et al (4) found that RR was 33% compared with 5% in placebo in a 4-week study with 37 subjects. Francavilla et al found reduction of frequency and severity of abdominal pain in a 12-week study with 48 children. Kajander et al (7,8) found improvement in symptoms in two studies of 103 respective 86 subjects.
- Diarrhea (11),
- Allergy (17) and atopic disease (17).

Mechanism of action of L. rhamnosus GG

- Protection of the intestine mucosa (37). L. rhamnosus GG is able to produce a biofilm that mechanically protects the mucosa and different soluble factors that increase the health ang longevity of the mucosa cells
- Protection against pathogens (37). The bacteria secretes two proteins which inhibits certain Salmonella species.
- Immuno-responsiveness (37). L. rhamnosus GG reduce the expression of several activation and inflammation markers on monocytes and increases production of IL-10, IL-12 and TNF-α in macrophages.

Lactobacillus plantarum

Lactobacillus plantarum has one of the largest genomes, the type organism WCSF1 contains 3052 genes (9), known among lactic acid bacteria which makes it highly versatile for instance helping it to grow between pH 3.4-8.8 (2) and in temperatures from 12 to 40 degrees C (3). *L. plantarum* belongs to group II of *Lactobacillus* and is facultative heterofermentative which in addition to hexose also ferments pentoses and/or gluconate to Lactic acid (9). The organism is used commercially as silage inoculant where they quickly become dominant in culture and produce both lactic and acetic acid. It is commonly found in food products such as milk products and fermented foods such as kimchi, sauerkraut, and sourdough.

Lactobacillus plantarum DSM 9843 - >100 studies and >50 clinical studies, 6 ongoing studies.

L. plantarum DSM 9843 was isolated from human intestinal mucosa (12).

The strain is robust. It possesses wide pH tolerance and grows at pH between 4 and 8, it can survive down to pH2 and up to 9.0 (13). The strain can be considered halo-tolerant and can be grown in 6% NaCl and survive in 16% NaCl, it also grows in the presence of bile salts up to 2% (13).

L. plantarum attaches to human mucose cells in vitro depending on a mannose-binding adherence (15). In addition to being important for colonization this ability is also important for its immune modulating ability (16) and ability to decrease bacterial translocation through the intestinal wall (18).

Example of studied health effects:

IBS (19), (20), (21) . Nobaek et al found that administering a fruit drink containing L. plantarum DSM 9843 significantly reduced subjectively experienced bloating. Niedzelin et al, utilizing the same delivery format, found that IBS symptoms decreased. Finally, Ducrotte et al. found L. plantarum DSM 9843 to significantly decrease both pain severity and incidence as well as bloating.

Several mechanisms of action sources have been discussed for IBS.

- Luminal interactions (21). Since it has been observed that abdominal pain intensity is reduced more in vegetarians it suggests the symptomatic effect can be related to interactions between the luminal content or that the strain affects the luminal metabolism of nutrients.
- Nitric Oxide generates intestine motility (20). L. plantarum can catabolize arginine thus generating nitric oxide. It has been suggested that nitric oxide may exert a positive effect on the motility of the large and small intestines .
- Suppression of excessive inappropriate inflammation (36). L. plantarum increased IL-10 synthesis and secretion in macrophages and T-cells derived from the colon. IL-10 is a beneficial cytokine for inappropriate inflammation as it has immunosuppressive effects on Th1 cells. L. plantarum in the commensal gut flora could therefore reduce inflammatory responses in the colon. An environment with L. plantarum in the gut flora will be richer in IL-10 which contributes to amelioration of excessive inappropriate inflammation.
- Diarrhea, antibiotic and Clostridium difficile associated (22), 23). Lönnermark et al found that hospitalized patients on antibiotics drinking fruit drink containing L. plantarum DSM 9843 had significantly fewer loose or watery stools than a control group which received a placebo fruit drink. Wullt et al saw a trend that recurrence of infection episodes was lowered for patients receiving L. plantarum DSM 9843 as compared with a placebo group.
- Coronary artery disease (24). Bukowska et al found, In a human trial on men with slightly elevated cholesterol levels, that concentration of total cholesterol and LDL-cholesterol were deceased in the active L. plantarum DSM 9843 group as compared with placebo.
- Development of Immune system (25) and inflammation (36). Rask et al found that L. plantarum DSM 9843 seemed to activate acquired T-cell immunity by increasing expression on activation markers and memory cell markers. In the cholesterol level study by Bukowska it was also found that fibrinogen levels were significantly reduced in the active L. plantarum DSM 9843 group showing a lowered systemic inflammation status of the individuals.
- Antimicrobial property (23), (27)

Mechanistic explanations

Bifidobacterium

Bifidobacteria are gram-positive, nonmotile anaerobic bacteria. They are one of the major genera of bacteria that make up microbiota in mammals. The genus possesses a unique ability to pathway to ferment carbohydrates and are able to ferment human milk oligosaccharides as well as plant oligosaccharides.

Bifidobacterium animalis spp animalis and Bifidobacterium animalis spp lactis

Previously Bifidobacterium animalis and Bifidobacterium lactis were described as two separate species but are now both considered B. animalis with subspecies animalis and lactis respectively. The species grow well in milk and is resistant to acid and oxidative stress. Research has identified a number of species abilities such as immune modulation, epithelial adherence and enhancement of gut barrier function thus making it clinically relevant (28).

Bifidobacterium animalis spp lactis DSM 15954, >300 studies, > 100 clinical studies, 16 ongoing

The genome of B. animalis spp lactis DSM 15954 has been published and contains 1642 genes (29). It can survive down to pH 2, is able to grow in presence of bile salts and can grow on several carbohydrate sources (30).

Example of health benefits:

- Defecation frequency (34) In a study of 1248 individuals Eskesen et al found that the defecation frequency was significantly higher in the active group as compared with placebo.
- Immune function (35) Rizzardini et al studied immune function by measuring vaccine response in healthy volunteers. It was found that treatment with B. *animalis spp lactis* DSM 15954 resulted in increased vaccine specific antibodies as compared with the control group.
- Rizzardini discuss two possible mechanism of actions which both involve interactions with immune cells within the host’s gut-associated lymphoid tissue (35). First changes in the microbiota could result in altered concentrations of signaling molecules such as SCFA or peptides within the gut lumen that directly affects the host’s immune cells. Secondly, a direct contact could be made between the host’s immune cells and gut bacteria which can alter immune cell activity. Whichever mechanism, the altered immune cell activity must then be transferred systemically, which is possible because of recirculation of the bodys immune cells between body compartment.
- Children´s health – diarrhea (31) 55 infants aged 5-24 months were evaluated on diarrhea in a study by Saveedra et al, it was found that 7% developed diarrhea during the test period vs 31% of the control group.

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