Scientific Evidence of BellaVie GLUCO-----

The GLUCO Synbiotic from Bellavie is a broad-spectrum, high-CFU, multispecies probiotic supplement containing 7 probiotic microbial species, prebiotic, and supplement, each selected for well-documented supportive health benefits.

The formula has been developed with essential intestinal bacteria to support a more favourable balance of intestinal microbiota and reduce the risk of urinary tract infections.

The formula is completed with prebiotics and nutraceuticals which are working in synergy with probiotics and enhance their activity.

Background – Type 2 Diabetes

Being overweight or obese causes insulin resistance and is typically the main factor behind type 2 diabetes. The location of body fat also makes a difference. Extra belly fat is linked to insulin resistance, type 2 diabetes, and heart and blood vessel disease (1).

Type 2 is characterized by insulin resistance and linked more so with lifestyle factors rather than pancreatic islet cell dysfunction. Type 2 diabetes occurs due to the levels of blood sugar being too high and as a result the body doesn't produce enough insulin or may even become resistant to the effects insulin has on blood glucose. As type 2 diabetes is usually associated with being overweight or obese, it can be reversible with lifestyle changes and weight loss.

Signs and Symptoms of Type 2 diabetes (2)

- Urinating (pee) a lot, often at night
- Extreme thirst
- Extreme hunger
- Blurry vision
- Numb or tingling hands or feet
- Feeling very tired
- Having very dry skin
- Having sores that heal slowly
- Having more infections than usual

As type 2 diabetes is preventable, certain lifestyle factors may be modified to prevent or reverse this condition. Such lifestyle factors include;

- Level and intensity of physical activity
- Improvement of poor dietary habits
- Smoking
- High blood pressure
- The use of certain medications

Probiotics and Diabetes

Some variations of diabetes have unexplained causes and are irreversible but the most common form of diabetes - type 2 is mainly caused by excessive weight and accounts for up to 90% of all cases of diabetes worldwide. In the past three decades the prevalence of type 2 diabetes has risen dramatically in countries of all income level (3).

As diabetes is a rising phenomenon, it is very important to look for ways to decrease its effects and prevalence. Recently there has been emerging evidence towards the positive role of probiotics and type 2 diabetes and the link between the two.

Some of the following studies show the effects show the link between probiotics with type 2 diabetes and obesity:

- A diminished presence of Firmicutes and relatively higher levels of Bacteroidetes are found in type 2 diabetic patients, as compared to healthy individuals. That's why it could be very interesting to take certain prebiotics **(4).**

- A low diversity of microbes in microbiota has been linked to obesity and inflammatory bowel disease. Gut microbiota dysbiosis has been considered an additional factor in obesity and type II diabetes mellitus development (5).

- Kong et al. explored differences in host inflammatory variables and intestinal microflora in function of three distinct dietary clusters in overweight/obese subjects. An found that subjects who have a healthier dietary pattern (higher consumption of fruits, yogurt and soups and lower consumption of sweets, confectionary and table sugar and sugary drinks) showed less pronounced metabolic impairment and had the highest gene richness and diversity in their intestinal microflora, despite having no difference in total energy intake or bodyweight across dietary clusters (6).

- The ADA's expert panel estimates that up to 70% of prediabetic individuals will eventually be diagnosed with type two diabetes (T2D). Reduction in the abdominal adiposity and BMI; and probiotic supplementation produced an improvement in the metabolism of carbohydrates, as well as a reduction in the metabolic stress in patients with T2D and insulin resistance syndrome. So, supplementation of probiotics can help patients suffering from obesity, insulin resistance syndrome or T2D (7).

Benefits of probiotics for type 2 diabetes

<u>Intake of probiotics can positively:</u>

- Modulate the intestinal microbiota
- Resulting in increased production of saccharolytic fermentation and short chain fatty acids (SCFA),
- Improved function of the intestinal barrier.
- Increased SCFAs are implicated in the release of glucagonal peptide-1 (GLP-1), which have an important impact on satiety, hunger, insulin sensitivity, and improves intestinal barrier function (8).

Clinical Studies Demonstrating the Effects of Probiotics on Type 2 Diabetes Mellitus

- In a study evaluating the effect of the consumption of a symbiotic shake containing *Lactobacillus acidophilus, Bifidobacterium bifidum* and fructo-oligosaccharides on glycemia and cholesterol levels in elderly people, it was found that there was a significant reduction in glycemia over the course of the study in the individuals who consumed the symbiotic shake (9).

- In another study demonstrating the effects of synbiotic supplementation on insulin resistance in subjects with the metabolic syndrome, it was found that there was a significant reduction in fasting blood sugar and insulin levels, as also reflected by improvements in Homeostatic model assessment of insulin resistance (HOMA-IR) and QUICKI indices (measuring insulin sensitivity) (10).

- In another study investigating the effects of a hypocaloric diet supplemented with probiotic cheese (*L. plantarum TENSIA*), it was found that improvements in body mass index and blood pressure indices of Russian adults with obesity and hypertension. Overall, triglycerides were reduced only in probiotic cheese consumers (11).

Bellavie GLUCO Capsule Composition

Each Bellavie capsule contains a symbiotic element (Probiotic and Prebiotic) along with a nutraceutical element to give the overall term 'synbioceutical'. Within the probiotic element of the capsule, there are 7 specially selected microorganisms chosen based on scientific evidence outlining their many health benefits.

For the prebiotic element of the capsule, inulin from chicory is used based on its ability to stimulate growth and give a synergistic effect to the probiotics.

For the nutraceutical element of the capsule, Cactinea and Chromium Chloride are used for their well-documented benefits in weight management and stabilizing sugar and insulin levels in the blood.

Probiotics

Each probiotic contained within the Bellavie GLUCO capsule is based on scientific research that demonstrates how each probiotic makes a positive impact on weight management and stabilizing sugar and insulin levels in the blood. The following facts about each probiotic has been backed up by extensive research and clinical trials.

- ***Bacillus Coagulans***

- Bacillus Coagulans symbiotic supplementation could improve metabolic factors and inflammation in patients with type-2 diabetes (12).
- In a study investigating the effect of consumption of honey containing bacillus coagulans on inflammatory and oxidative stress factors in patients with diabetic nephropathy, serum insulin levels, HOMA-IR (Homeostatic Model Assessment for Insulin Resistance), serum high-sensitivity C-reactive protein and malondialdehyde (MDA)

levels significantly decreased in patients consumed probiotic honey compared to the patients in the control group after 3 months (13).

- In a study demonstrating the effect of UB0316, a multi-strain probiotic formulation containing *L. salivarius, L. casei, L. plantarum, L. acidophilus, B. breve, B. coagulans* (4/6 strains are included in BellaVie GLUCO) in patients with type 2 diabetes mellitus, it was found that that this probiotic (UB0316) significantly improved glycaemic control as indicated by the decrease in HbA1c levels. There was also a significant decrease in weight in the probiotic treated subjects and a reduction in HbA1c and fasting blood glucose levels as compared to baseline (14).

- ***Bifidobacterium animalis lactis***

- *Bifidobacterium lactis HY8101* can be used to moderate glucose metabolism, lipid metabolism and insulin sensitivity in mice and in cells (15).
- The presence of *Bifidobacterium Animalis* is linked to individuals who have a normal and healthy weight whereas low levels in the gut microbiome are associated with obesity (16).
- In a study to investigate the effects of daily consumption of the probiotic *Bifidobacterium animalis subsp. Lactis CECR 8145* on anthropogenic adiposity biomarkers in abdominally obese subjects, it was found that Ba8145 ingestion decreased waist circumference, waist circumference/height ratio, and Conicity index versus its baseline (17).
- In another study showing whether *Lactobacillus* or *Bifidobacterium* species are found in the human gut are associated with obesity or lean status, it was found that high levels of *Bifidobacterium* and *Lactobacillus* species were associated with normal weight (18).
- In a study investigating the effect of *Bifidobacterium animalis* ssp. *lactis* GCL2505 on visceral fat accumulation in healthy Japanese adults, it was discovered that ***B. lactis*** GCL2505 reduces abdominal visceral fat, a key factor associated with metabolic disorders (19).

- ***Lactobacilli***
  - Supplementation of overweight and obese adults with lactobacilli and *bifidobacteria* reduces bodyweight and improves well-being (20).
  - Lactobacillus genus acts upon mitochondria in the liver leading to the improvement of lipid metabolism which in turn may reduce the risk of type 2 diabetes (21).
  - *Lactobacillus acidophilus, L. casei, L. delbrueckii* were found to cause the biggest improvements on obesity, diabetes and non-alcoholic fatty liver disease related variables when tested against other probiotic strains (22).

- Multiple studies demonstrated the ability of lactobacilli to either reduce levels of cholesterol circulating in the plasma, levels of cholesterol in the liver, and/or increase levels excreted, mostly in response to treatment with *Lb. plantarum* strains (23).

- Probiotic powder containing *Lactobacillus plantarum Dad-13* caused the average body weight and BMI of overweight adults to decrease significantly over 9- days during a clinical trial (24).

- Upon comparing the gut microbiota of healthy individuals versus individuals with type 2 diabetes mellitus, it was found that *Lactobacillus acidophilus* count was lower among type 2 diabetic patients, which may show relationship of lactobacillus with type 2 diabetes mellitus (25).

- In a study of the impact of bacterial probiotics on obesity, diabetes, and non-alcoholic fatty liver disease related variables, it was found that in type 2 diabetics, probiotics reduced fasting glucose, glycated haemoglobin, insulin, and homeostatic model of insulin resistance. In overweight but not obese subjects, probiotics induced improvements in body weight, body mass index, waist circumference, body fat mass, and visceral adipose tissue mass (26).

- Another study investigated the effects of *Lactobacillus casei* on glycemic response, Serum Sirtuin1 and Fetuin-A Levels in Patients with Type 2 Diabetes Mellitus and found that consumption of *L. casei* for two months significantly decreased weight, BMI, and waist circumference in the probiotic group compared with the placebo group (27).

- In a trial where *Lactobacillus plantarum HAC01* Supplementation was investigated to see if it improves glycaemic control in prediabetic patients, the outcome was that supplementation significantly improved HbA1c and 2-hour post-prandial blood sugar levels relative to placebo in prediabetic subjects (28).

- The effects of a diet-based weight-reducing program with probiotic supplementation on satiety efficiency, eating behaviour traits, and psychosocial behaviours in obese individuals were tested and the outcome was that the biggest effect occurred in women, as they majorly benefited from an accentuation of body weight loss with LPR supplementation, also displayed concordant changes in satiety efficiency, eating behaviours, and mood when compared to men and women who received a placebo (29).

Prebiotics

Prebiotics are needed to provide nutrients to create an optimal environment and support the growth of the probiotics. Inulin was chosen as the prebiotic for this capsule as inulin increases the number of good bacteria in the gut, particularly bifidobacterial and lactobacilli.

The fibre in inulin is soluble, which means it dissolves in water and in the stomach and forms a gelatinous substance. Some of the functions of inulin include:

- Facilitates & slows digestion which enables the body to better absorb nutrients from the food.

-Helps modulate the immune system.

-Reduces cholesterol absorption as it passes through the digestive tract.

-Provides the body with nutrients and active elements.

-Facilitates the absorption of calcium and magnesium.

-Can be fermented into lactate and short chain fatty acids which impact the way energy is metabolised in the body and provides a protective effect against metabolic diseases and obesity.

Inulin and Type 2 Diabetes

- Inulin supplementation may control levels of glycaemic status and improve lipid profile in type 2 diabetic patients. These findings support the use of inulin as a safe treatment for managing diabetes (30).
- Supplementation of inulin type carbohydrate can ameliorate insulin resistance in type 2 diabetes, especially in obese type 2 diabetes mellitus patients (31).
- Both **IPE (inulin-propionate ester) and inulin supplementation improved insulin resistance** compared with a control – cellulose (32).

Nutraceutical

Nutraceuticals are natural health supplements recognized for their effects on targeted functions. The Bellavie GLUCO cap contains Cactinea and chromium chloride as they are known for the beneficial roles that they play in weight management and stabilizing sugar and insulin levels in the blood.

Effects of Chromium Chloride

- Trivalent chromium is one of the essential micronutrients; it **activates insulin receptors** through chromodulin to **increase insulin signal transduction and insulin sensitivity.**
- Other studies have also shown that, as diabetic patients age, loss of chromium increases. Therefore, it is possible that **chromium deficiency is associated with the development of diabetes.**
- Lower blood sugar
- Improves mood in people who only partially respond to antidepressant
- Lowers low-density lipoprotein (LDL or "bad") cholesterol and total cholesterol levels in people with slightly high or high cholesterol levels (33).

Effects of Cactinea

- Comes from *Opuntia Ficus Indica*
- Active ingredient from cactus fruit
- Anti-water retention properties,
- Highly bioavailable antioxidant
- Lowers glycemia

- The cactus fruit from which Cacti-Nea™ is derived is the richest vegetable source of indicaxanthin, the most bioavailable betalain pigment, with scientifically demonstrated properties:
    - Indicaxanthin is 20 times more bioavailable than betanin.
    - Cactus pears increase cells' antioxidant capacity (+50%).
    - Indicaxanthin protects LDL cholesterol from oxidation
- Cacti-Nea™ helps to significantly decrease the sensation of swollen feet / ankles / calves
- Cacti-Nea™ helps to significantly decrease the sensation of "heavy legs"

- Nopal has low glycemic, insulinemic, and GIP indexes and could be recommended for patients with type 2 diabetes (34).

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