MICROBIOME PLUS+™
ADVANCED DIABETES

Proviva Pharma
The healthy living company.

A MORE COMPLETE METABOLIC HEALTH SUPPLEMENT

Unique Probiotic Formulation

Herbal Sugar-Lowering Supplement

Consider the Role of MICROBIOME PLUS+ in your daily health regime today!

- Holistic approach to promote metabolic health
- Unique formulation of three scientifically-proven probiotics that reduce inflammation, oxidative stress and support metabolism
- Works in combination with *Gymnema* Leaf to reduce blood sugar levels and regulate insulin resistance

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WHAT IS MICROBIOME PLUS+?

Microbiome Plus+™ is an innovative new line of products that provide more complete dietary support for gastrointestinal and whole body health. All Microbiome Plus+ products and their components have been verified by doctors and optimized to treat specific physiological ailments.

Microbiome Plus+ supplements use professional grade and quality ingredients:

- Full recommended daily dose
- Sourced from nature and allergen free
- Bioavailable formats
- From renewable and sustainable sources
- Developed by doctors

WHAT IS MICROBIOME PLUS+ DIABETES?

Microbiome Plus+ Obesity is a more complete metabolic health dietary supplement that naturally heals the gut microbiota to support a lean phenotype while actively increasing the internal assimilation of fat and elimination of cholesterol.

Probiotic Formulation:

- *L. fermentum* PV6910
- *L. plantarum* PV2398
- *B. infantis* PV8712
- *B. bifidum* PV7761

Supplement:

- Gymnema Lead

WHY RECOMMEND MICROBIOME PLUS DIABETES?

Gastrointestinal health is critical for maintaining whole-body wellbeing. Imbalances in the gut microbiota living synergistically in the human gastrointestinal tract have been linked to many age-related chronic diseases including diarrhea, constipation, diabetes, obesity, metabolic syndrome, mood disorders, inflammation, allergies, irritable bowel syndrome, colon cancer, neurodegeneration and many more.

Many studies have shown that reinstating gastrointestinal homeostasis with dietary modifications, including probiotic and prebiotics, can prevent, reduce and/or alleviate symptoms of obesity by increasing the efficiency of fat assimilation and natural elimination of cholesterol. This is vital for whole-body health and longevity as obesity is linked to a host of diseases including cancer, neurodegeneration, diabetes and cardiovascular disease.

MICROBIOME PLUS DIABETES, combines gut-healing actions of probiotics with a potent regulator of insulin resistance with proven properties to lower blood glucose levels and heal pancreatic beta cells. The health of the gut microbiota has been shown to be intimately linked with diabetes and it is essential to regulate gastrointestinal health to control sugar and nutrient assimilation from foods. Further, to aid those already suffering from the disease, Gymnema Leads is added to reverse the effects of insulin resistance and bring balance to blood sugar levels.

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THE SCIENCE

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- Developed by doctors
- Produced and conceived in Canada

Gymnema Leaf

Gymnema sylvestre has been used for 3000 years in India to combat diabetes, high cholesterol and highglycemia (Nadkarni et al., 1954). It grows in the tropical areas of South India and Africa and is locally known in India as *Mesharinga.* The leaf extract contains several triterpene glycosides identified as gymnemoside-c, -d and –e that are accounting for its unique anti-diabetic effects (Kang et al., 2012) along with saponins, acidic glycosides and anthroquinones. The leaves are reported to lower blood sugar, stimulate the heart, uterus and circulatory systems (Rana et al. 1992).

Antidiabetic

- Leaf extract demonstrated hypoglycemic and subsequent blood cholesterol lowering property in streptozotocin-induced diabetic rats (Bishayee et al., 1991,)
- The same extract increased insulin production in diabetic rats (Shanmugasundaram et al., 1990) in addition to serum cholesterol, triglyceride and LDL levels (Kang et al., 2012)
- Genetically, Gymnema lead was also found to enhance the expresseion of the Glucose transporter (GLUT-4) and PPAR-gamma – a key factor for controlling energy levels and the diabetic state (Kumar PM et al. 2016).
- Another mechanism to induce anti-diabetic properties is to stimulate the secretion of insulin from the pancreas thereby encouraging regeneration of the pancreatic beta cells (Ahmed et al., 2010)
- Gymneic acid molecules can also bind to the receptors of the sodium—glucose transporter in the intestine to prevent the absorption of glucose (Pothuraju et al., 2013).

Anti-oxidant

- The Leaf extract has very strong anti-oxidant effects as attested by its TBA and SOD activity, both *in vitro* and *in vivo* (Kang et al., 2012)

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PROBIOTIC FORMULATION

Probiotic	CFU/capsule
L. fermentum PV6910	1.0 x 10^9
L. plantarum PV2398	1.0 x 10^9
B. Infantis PV8312	1.0 x 10^9
B. bifidum PV7761	1.0 x 10^9

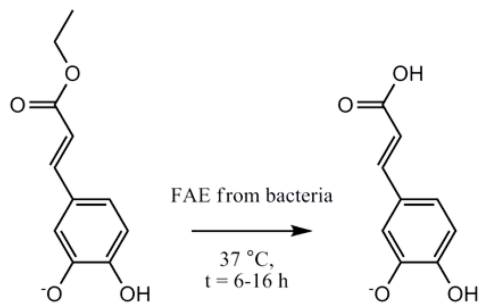
Probiotics are defined by the The Food and Agriculture Organization (FAO) of the United Nations and the WHO as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host". The administration of probiotics not only promote the growth of the administered bacterial species, but also creates a gastrointestinal microenvironment permissive to the growth of other beneficial bacterial species and non-favourable to the growth of pathogenic species. In the present formulation, the use of several species of aerobic *Lactobacillus* and anaerobic *Bifidobacteria* allows rapid development of a universally homeostatic system with complementary biological effects as outlined below.

L. fermentum PV6910

L. fermentum PV6910 is a human-derived aerobic bacterium with several active properties. Like other *Lactobacillus* species, *L. fermentum* has a good pH and bile-acid tolerance making it a practical probiotic species. Various species of *L. fermentum* have been shown to have immune-modulating, anti-aging, anti-oxidant and metabolic effects, though the specific characteristics of *L. fermentum* PV6910 will be outline below:

General Characteristics

- *L. fermentum* PV6910 has a potent intrinsic ferulic acid esterase (FAE) activity, producing large quantities of the phytochemical ferulic acid (Tomaro-Duchesneau et al., 2012)
- Traditionally, plants and herbs containing high levels of FA have been used in Chinese medicine for its potent inhibition of ROS generation and anti-inflammatory properties.
- In modern medicine, FA is recognized as a potent ROS scavenger with therapeutic potential in various chronic diseases including neurodegeneration, cancer, accelerated cell aging, obesity and diabetes (Hu et al., 2011)
- Potent antioxidant activity can be explained by its phenolic nucleus and unsaturated side chain which allow for the formation of a resonance-stabilized phenoxy radical since the unpaired electron may be present on the oxygen but also delocalized across the FA molecule (Srinivasan et al., 2007)
- Ferulic acid regulates oxidative stress through the regulation of peroxiredoxins and thioredoxins, key elements that provide neuro-protection and are correlated with aging (Patenaude et al., 2005)



- Ferulic acid also inhibits apoptosis through the upregulation of CRMP2 via the Akt/GSK3beta pathway (Gim et al., 2013)
- FA has been shown to regulate blood glucose levels by modulating insulin secretion, by promoting pancreatic beta-cell survival, and by reducing inflammatory markers linked to antioxidant activity (Adisakwattana et al., 2008)
- *L. fermentum* PV6910 has significant *in vitro* and *in vivo* cholesterol assimilation activity possible through affecting epithelial-cell surface hydrophobicity and cellular cholesterol uptake mechanisms (Tomaro-Duchesneau et al., 2014)
- In an *in vivo* study using a rat model of metabolic syndrome (ZDF rats), *L. fermentum* PV6910 reduced fasting insulin levels and insulin resistance, serum triglyceride levels, serum low-density lipoprotein cholesterol levels and the atherogenic and atherosclerosis indices (Tomaro-Duchesneau et al., 2014)

L. plantarum PV2398

L. plantarum species occupies a broad range of phenotypic properties due to its diverse range of environmental niches (Siezen et al., 2011). It is a facultative heterofermentative organism whose variety of species are able to ferment a diverse range of carbohydrates. In general, *L. plantarum* has a high acid tolerance making it an important component to food and health industries (Luxananil et al., 2008). As a probiotic, *L. plantarum* is superior at adapting to the host's colonic environment's metabolic capacity by expressing exopolysaccharide and proteinaceous cell-surface compounds (Marco et al., 2010). Of all the *L. plantarum* species, *L. plantarum* PV2398 is one of the most versatile and dynamic species with several prominent biological effects as detailed below:

Pharmacokinetics

- *L. plantarum* PV2398 has favourable pharmacokinetics in the body with a high survivability upto the ileum and through to the fecal matter (Vea et al., 2000)
- How? *L. plantarum* PV2398 has increased proton transport by F_0F_1-ATPase to retain proper intracellular pH and increased expression of the chaperone genes *dnaK, groEL, clpB and clpE, hsp1, hsp2, hsp3*
- Keen digester of a variety of plant-derived phenolics due to its intrinsic tannase, *p*-coumaric acid decarboxylase and benzyl alcohol dehydrogenase (Rodriguez et al., 2009)
- *L. plantarum* PV2398 has 4 bile-salt hydrolases to improves its integrity and anti-oxidant production in the colon compartments (van der Nieuboer er al., 2016)
- *L. plantarum* PV2398 also has some ferulic acid esterase activity for the liberation of methyl ferulate from plant lignins (Jimenez et al., 2013)
- *L. plantarum* PV2398 has a developed secretome, meaning it secretes several proteins mediating functional processes including bacteriocins (Bodaszewska-Lubas 2012), pSIP, mucus adhesion factors, mannose-specific adhesion molecules (Minic et al., 2015)

- Through the secretion of autoinducing peptides, there is are keen quorum-sensing and cross-feeding effects to promote a healthy gut environment (Sturme et al., 2005)
- *L. plantarum* PV2398 also secretes plantaricin A which triggers transcription of immune proteins (Rojo-Bezares et al., 2008) and has antimicrobial activity (Diep et al., 2009).
- In particular, *L. plantarum* PV2398's alanine-rich lipoteichoic acid moieties proves to be potently anti-inflammatory (Grangette er al., 2005)
- Indeed, it promotes secretion of anti-inflammatory cytokines by PBMCs and increases the number of regulatory dendritic cells and regulatory T cells in the spleen (Dong et al., 2012)
- *L. plantarum* PV2398 shown to increase the secretion of T cells, proportion of CD69+ on lymphocytes, NK cells and increased the production of IL-1, IL-6, IL-10 and TNFalpha and MIP1alpha (Dong et al., 2012)
- Secretion of bacteriocins inhibit the growth of pathogenic species including *Streptococcus* spp.
- *L. plantarum* PV2398 has enhanced efficiency for dealing with oxidative stress, especially in the production of the anti-oxidant thioredoxin (Serrano et al., 2007)
- Through its predicted 223 extracellular proteins, *L. plantarum* PV2398 can enhance intestinal cell wall integrity through TLR-2 activation and tight junction formation (Karczewski er al., 2010)
- Finally, in a human trials, after only 6h of exposure to *L. plantarum* PV2398, there was an upregulation of lipid and fatty-acid metabolic genes in addition to anti-oxidant molecules (Troost et al., 2008)

B. longum spp. infantis PV5553

Bifidobacteria spp. are a class of anaerobic bacteria… *B. longum spp. Infantis* PV5553 is an anaerobic bacteria derived from the infant's intestine that is prominently present in early life though levels are quickly lost in adolescence. *B. Infantis* thrives on human milk oligosacchrides and is highly beneficial at fighting off infections and invasion of pathogenic species in the gut. *B. infantis* significantly breaks down lactic acid thus modulating the pH of the intestines and controlling the growth of pathogenic species.

Gastrointestinal considerations

- *B. infantis* strains are experts at digesting long-chained complex carbohydrates and promoting cross-feeding growth of other health-promoting species in the gut.
- *B. infantis* sequenced to date contain a 43-kb gene cluster (HMO cluster I) that encodes a variety of oligosaccharide transport proteins and glycosyl hydrolases; this gene cluster is not found in other bifidobacterial species[53]
- *B. infantis* produces an endo-β-*N*-acetylglucosaminidase that is able to cleave the *N*-glycans associated with human glycoproteins like lactoferrin, IgA, and IgG[54]
- B. infantis strains have been shown to lower symptoms of irritable bowel syndrome in women, specifically the inflammatory and indigestion discomfort[55]

Immunity considerations

- *B. infantis* species have potent effects on the immune system.
- *B. infantis* produce exogenous substances that promote maturation of the immature innate immune response which attenuating IL-8 and IL-6 response to inflammatory stimuli, which explains the mechanism where *B. infantis* protects infants against necrotizing enterocolitis, an intestinal inflammatory disease[56]
- In normal BALB/c mice, a high dosage of *B. infantis* increased the number of T regulatory and Th17 cells and increased cytokine transcription in immunoregulatory cells. Further, such pretreatment for 3 weeks before the induction of colitis decreased inflammatory cell infiltration and restored the intestinal epithelium[57]
- *B. infantis* also decreases intestinal permeability increased stabilization of the tight junction proteins claudin 4 and occludin, and decreased the incidence of NEC[58]
- Finally, in F344 rats after 38 days of treatment, *B. infantis* has a significant decrease in Enterobacteriaceae compared to controls and reduced fecal and serum endotoxin levels[59]

B. bifidum PV7761

B. bifidum PV7761 is an anaerobic species derived from infant feces. In general, *B. bifidum* species are commonly used in yogurts and probiotic supplements due to their known effectiveness for supporting digestive health and the immune response. *B. bifidum* actually attached to the epithelial lining of the intestine and increases the integrity of the intestinal barrier thus prevents the infiltration of toxins, germs and unhealthy bacteria.

Immunity considerations

- The adherence of *B. bifidum* PV7761 to the intestinal cell wall was shown to be influences by the consumption of oligosacchrides (Altamimi et al., 2016)

Gastrointestinal considerations

- *B. bifidum* PV7761 significantly improved the gastrointestinal microflora ecosystem in BALC/c mice by increasing the amount of probiotics (*Lactobacillus intestinalis* and *Lactobacillus crispatus*) and by reducing unwanted bacterial populations (*Enterobacter, Escherichia coli*) (Wang et al., 2016)

Anti-oxidant considerations

- In BALB/c mice, *B. bifidum* PV7761 enhanced the rodent's free radical scavenging activity and microflora reducing power indicating beneficial effects and the anti-oxidant capacity (Medina et al., 2007)

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