MICROBIOME PLUS+™
ARTHRITIS

Proviva Pharma
The healthy living company.

A MORE COMPLETE METABOLIC HEALTH SUPPLEMENT

Unique Probiotic Formulation

Anti-inflammatory Herbal Support

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+ ARTHRITIS?

Microbiome Plus+ Arthritis is a wholistic anti-inflammatory treatment that reduces inflammation both directly and indirectly. This synergistic formula targets both the local inflammatory response with the herbal anti-inflammatory *Boswellia* and through fundamental inflammatory routes in the gut.

Probiotic Formulation:

- *L. rhamnosus* PV3188
- *L. casei* PV7005
- *B. infantis* PV5553
- *B. bifidum* PV7761
- *B. longum* PV8312

Supplement:

- *Boswellia Serrata*

WHY RECOMMEND MICROBIOME PLUS ARTHRITIS?

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 arthritis by reducing inflammation. Recent studies have found that the foundation of many low-grade chronic inflammatory conditions resides in the gut and from imbalances in the gut microbiota.

MICROBIOME PLUS ARTHRITIS, combines gut-healing actions of probiotics with an active anti-inflammatory agent, *Boswellia Serrata. Boswellia Serrata* has been verified over the centuries in India as a potent anti-inflammatory agent with positive effects on osteoarthritis, rheumatoid arthritis, bronchial asthma, joint function, ulcerative colitis and Crohn's disease (Ammon 2010). The effects are similar to many common NSAIDs providing a safer alternative for common inflammatory conditions.

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THE SCIENCE

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- Produced and conceived in Canada

BOSWELLIA SERRATA

Boswellia serrata has been used for centuries in India and China as a folk remedy for various inflammatory conditions. The resinous part of *Boswellia serrata* possesses monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids and four major pentacyclic triterpenic acids i.e. β-boswellic acid, acetyl-β-boswellic acid, 11-keto-β-boswellic acid and acetyl-11-keto-β-boswellic acid, responsible for inhibition of pro-inflammatory enzymes (Siddiqui, 2011).

In particular, acetyl-11-keto-β-boswellic acid was shown to potently and specifically inhibit 5-lipoxygenase (5-LO), an enzyme responsible for inflammation (Ammon et al., 1991, Ammon, 2006, Schweizer, S. et al., 2000). 5-LO generates inflammatory leukotrienes, which cause inflammation by promoting free radical damage, calcium dislocation, cell-adhesion and migration of inflammation-producing cells to the inflamed body area (Ammon, 1996). With such a clear mechanism of action, it is clear that *Boswellia serrata* has great potential to be used as a wide-spread anti-inflammatory therapeutic.

THE FACTS

Anti-inflammatory Effects

- In rats and mice, *Boswellia serrata* induced a 25-46 % inhibition of paw oedema and a 45-67% inhibition of formaldehyde-induced arthritis (Singh & Atal, 1984)
- Clinical trials of gum-resin of *Boswellia* alone was shown to improve symptoms in patients with osteroarthritis and rheumatoid arthritis (Murray & Rocklin, 1995)
- Another clinical trials showed that *Boswellia serrata* can reduce pain and considerable improve knee-joint functions (Anonymous, 2011)
- In collagen-induced arthritis, *Boswellia serrata* rescued several anti-oxidant enzymes including LPO, GSH, catalase and SOD while reducing arthritis scoring and bone histology (Umar et al., 2014)
- Mechanistically, it was shown in human PBMCs that *Boswellia serrata* pure extracts exhibited its anti-inflammatory effects through the inhibition of TNF-alpha, IL-1beta, NO and MAP kinases (Gayathri et al., 2007)
- More recently, it was shown that *Boswellia serrata* administered to rats with induced ulcerative colitis (inflammation and infiltration of leukocytes into the colon and rectum) reduced the anal sphincter pressure, lipid peroxidation and iNOS levels, potently increased in ulcerative colitis models (Hartmann et al., 2014).

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THE FACTS, Continued

- *Boswellia serrata* also showed promise in the preservation of intestinal epithelial barrier from oxidative and inflammatory damage proving its potential to be used as a therapeutic in inflammatory bowel disease (IBD). Specifically, *Boswellia serrata* extracts significantly rescued the reduction in trans-epithelial resistance, prevented functional and morpholigcail alterations induced by the IBD and prevented NF-kB phosphorylation and ROS stimulation (Catanzaro et al., 2015).
- *Boswellia serrata* is so promising that industries have begun to further develop its capacity as a therapeutic by increasing its bioavailability through isolating the non-volatile portion of the gum resin. This manipulation increased the bioavilability of the active ingredient 3-O-acetyl-11-keto-beta-bowellic acid (AKBA) by 52 %. This formulation reared better anti-inflammatoory efficacy in the Freund's Complete Adjuvant induced inflammation model in rats and also has superior protection against IL-1beta induced death of human primary chondrocyte (Sengupta et al., 2011)

PROBIOTIC FORMULATION

Probiotic	CFU/capsule
L. rhamnosus PV3188	1.0 x 10^9
B. infantis PV5553	1.0 x 10^9
B. bifidum PV7761	1.0 x 10^9
B. longum PV8312	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. rhamnosus PV3188

L. rhamnosus is an abundant bacteria found in the female genito-urinary tract and often used in un-pasteurized milk and semi-hard cheese. *L. rhamnosus* GG is a strain isolated in the 1980s has been extensively studied and is known to have acid- and bile-resistant properties which alleviates dysbiosis, reduce allergic reactions, alleviate bursts of diarrhea, protect the female urogenital tract from infections and many more. Despite the popularity of *L. rhamnosus* GG, *L. rhamnosus* PV3188 is another powerful strain with the following properties:

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- *L. rhamnosus* PV3188 has been shown to be protective against trichinellosis, a parasite present in undercooked meats (Costamagne et al., 2005)
- Mechanistically, it was found that *L. rhamnosus* PV3188 colonized the intestines after prolonged treatment and achieved competitive adhesion and/or blockage of the penetration of pathogens by competing for the glycoconjugate receptors (Ramiah et al., 2008; Thirabunyanon, et al., 2011)
- Immunologically, *L. rhamnosus* PV3188 increased the production of IFN-gamma from both Peyer's patches and spleen cells (Aattouri et al., 2002) and IFN-gamma induces parasite-killing through the activation of macrophages (Helmby and Grencis 2003). Henceforth, the activated macrophages induce nitric oxide-dependent inflammatory response which interrupts the establihsment of female trichinella worms in the intestinal mucosa (Randazzo and Costamagne 2005)

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 (LoCascio et al., 2010)
- *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 (Whorwell et al., 2006)
- B. infantis strains have been shown to lower symptoms of irritable bowel syndrome in women, specifically the inflammatory and indigestion discomfot (Garrido et al., 2012)

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 (Ganguli et al., 2013)
- 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 (Zuo et al., 2014)
- *B. infantis* also decreases intestinal permeability increased stabilization of the tight junction proteins claudin 4 and occludin, and decreased the incidence of NEC (Bergmann et al., 2013)
- 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 (Rodes et al., 2014)

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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)

B. longum PV8312

B. longum PV8312 is another commensal anaerobic gut bacteria derived from infant's stool. Its presence is often limited in the adult gastrointestinal tract and is a potent produced of lactic acid, which prevents the growth of pathogenic organisms. Like *B. infantis, B. longum* species have a broad array of enzymes for the breakdown of prebiotic species, thus enhance the gut microflora overall environment through cross-feeding mechanisms. It is immuno-protective through increasing the integrity of the gut epithelial barrier and produces several enzymes that digest proteins to prevent the putrification of proteins in the gut.

Immunity considerations

- There have been several indications that *B. longum* PV8312 modulates the host immune system (Caracciolo et al., 2014)
- *B. longum* PV8312 produces antimicrobial substances and was shown to antagonize the growth of *Listeria innocua, L. bulgaricus, Stapphylococcus, Clostridium tyrobutrricum* (Sanchez et al., 2007)
- In isolated PBMCs (human blood cells), *B. longum* PV8312 stimulated IL-10, IFNgamma and TNFalpha levels, a trait produced by cell surface signaling factors (Medina et al., 2007)

Gastrointestinal Considerations

- *B. longum* PV8312 is bile- and acid-tolerant (Sanchez et al., 2007)
- After exposure to bile, *B. longum* PV8312 showed differential regulation of 34 proteins, notably ones related to stress response including chaperones, transcription, translation and the metabolism of amino acids and nucleotides. There was also variations in the metabolic end-products, notably acetate and lactate (Sanchez et al., 2005)

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