MICROBIOME PLUS+™
ALZHEIMER'S

Proviva Pharma
The healthy living company.

A MORE COMPLETE HEALTHY AGING SUPPLEMENT

Probiotic FORMULATION

Unique Anti-Inflammatory Supplement

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

- Dynamic approach to promote healthy aging
- Unique formulation combining probiotics and sodium thiosulfate to reduce inflammation and oxidative stress
- Patented and approved by doctors

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WHAT IS MICROBIOME PLUS+?

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.

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

PRODUCT AVAILABILITY

Produced in Canada

- Labelled and manufactured locally
- Health Canada Safety Approved
- International trademarks
- Proprietary patent pending

Exclusive or Non-exclusive

WHY RECOMMEND MICROBIOME PLUS ALZHEIMER'S ?

Many studies have shown that reinstating gastrointestinal homeostasis with dietary modifications, including probiotics and other plant-derived dietary supplements is highly beneficial at maintaining a youthful glow. Oxidative stress, chronic inflammation, metabolic imbalances, insulin resistance and mental fatigue are just a few of the symptoms of aging that can be prevented, reversed and healed with probiotics and carefully selected herbal preparations.

MICROBIOME PLUS ALZHEIMER'S, combines gut-healing actions of probiotics with the neuroinflammatory reducing potential of sodium thiosulfate – a generic drug with innovative potential against neuroinflammation.

WHAT IS MICROBIOME PLUS+ ALZHEIMER'S ?

Microbiome PLUS+ Alzheimer's is a unique formulation containing the ferulic acid esterase-active probiotic *Lactobacillus fermentum* PV6910 (Lf6910) together with the inorganic chemical compound sodium thiosulfate (STS). The gut-health promoting action of Lf6910 together with the neuronal anti-inflammatory action of STS makes this synergistic product a superior preventative support for Alzheimer's disease and other age-related cognitive decline.

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THE SCIENCE

Alzheimer's disease is the most prevalent neurodegenerative disease affecting the global population today. It is characterized by the progressive degeneration of neurons throughout the brain, but specifically in the brainstem and locus coeruleus.. The etiology of AD is largely unknown except that the accumulation of aggregated amyloid(A)-beta plaques and tau proteins into neurofibrillary tangles causes an infiltration of inflammatory mediators that lead to neuronal cell death. There are a variety of life-style factors such as oxidative stress, chronic inflammation and metabolic syndrome that contribute to the increased pathogenicity of aggregating plaques, leaving much space for preventative therapies that protect neurons from the aforementioned insults.

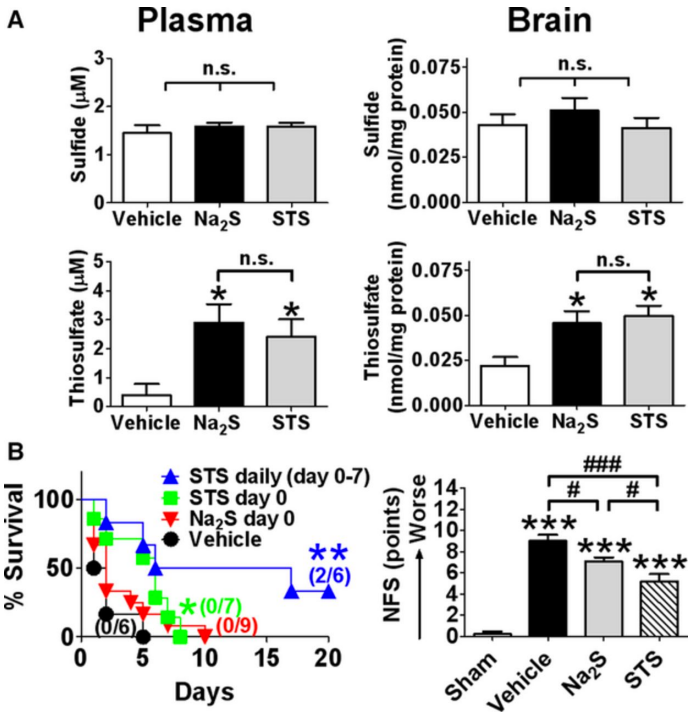
SODIUM THIOSULFATE

Sodium thiosulfate (STS) is an industrial inorganic chemical that has been successfully used in some rare diseases including cyanide poisoning (Hayden et al. 2010) and calciphylaxis in terminal kidney patients (Berlin et al., 2013). Further, STS is present in small amounts in salt and alcohol indicating that it is safe to consume by humans and could be used as a therapeutic agents at the appropriate concentration (Moonhee et al., 2016).

The anti-inflammatory action of STS is derived from its catabolic break-down product, hydrogen sulfide , a gasotransmitter with several biological effects. STS is a clinically applicable donor substance of hydrogen sulfide thus has great potential of holding the same clinically relevant properties of hydrogen sulfide.

Specially in the brain, hydrogen sulfide has been shown to attenuate ischemia-reperfusion injury (Marutani et al., 2015).

Hydrogen sulfide is relatively unstable in circulation as it is rapidly broken down by several endogenous enzymes. However thiosulfate remains more stable, can enter cells and has been proposed to elicit the protective effects of hydrogen sulfide. Indeed, administration of STS prevented *in vitro* and *in vivo* (see below) cerebral ischemia-reperfusion injury (Marutani et al., 2015).



Mechanistically, the protective effects of STS were attributed to inhibition of c-jun N-terminal kinase (JNK) and caspase-3 activation of extracellular signal-regulated kinase (Erk) 1/2. Further, this same compound protected against oxidative stress by increasing the concentration of glutathione and glutathione persulfide levels (see next page) (Marutani et al., 2015).

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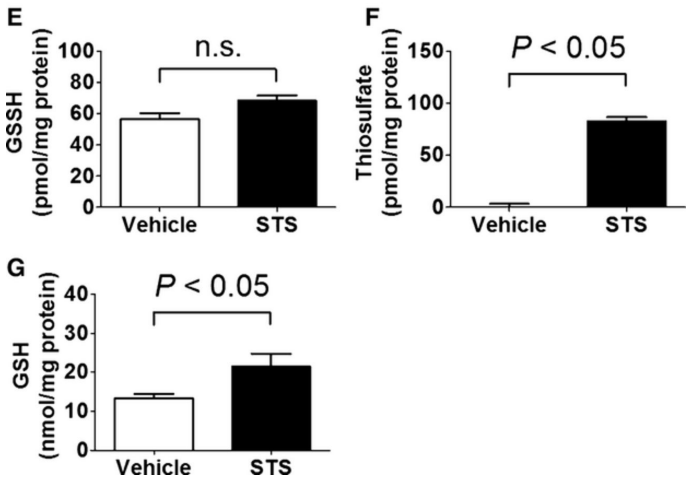
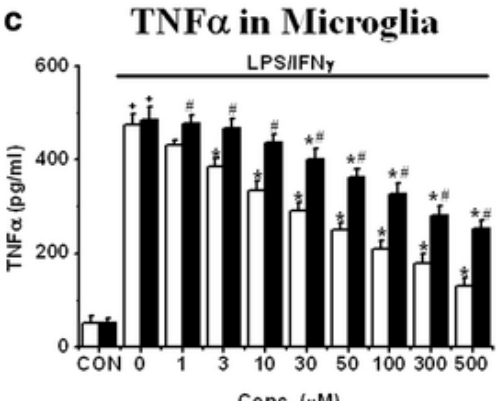
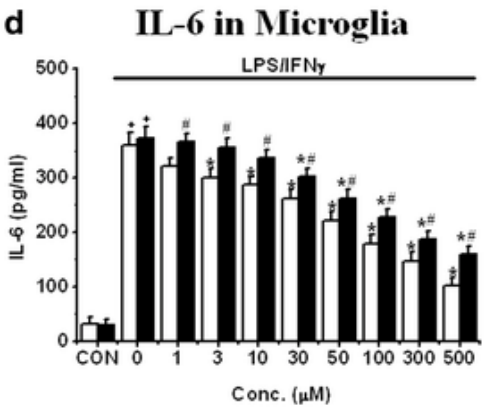
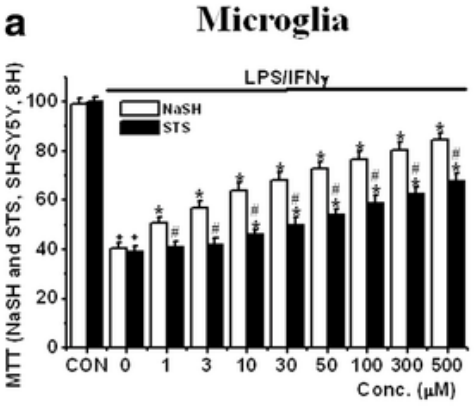


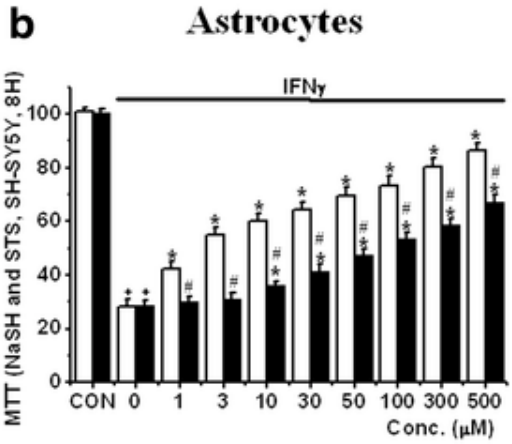
Specifically in brain microglial cells, STS is potently anti-inflammatory. As demonstrated below, microglia pre-exposed with STS (compared to NaSH - sodium hydrosulfide) attenuated TNFalpha and IL-6 release in a concentration dependent manner (Moonhee et al., 2016)





Further, a dose-dependent increase in survivability after exposure of neuroblasts to LPS, a strong proinflammatory agent was exhibited in cells pre-treated with STS indicating a direct application in neuronal survival to inflammatory stress (Moonhee et al., 2016)





Mechanistically, this group indicated that these anti-inflammatory effects could be due to the attenuation of the upstream inflammatory mediators phospho-P38 MAPK and phospho-P65-NFkB (Moonhee et al., 2016).

These results are highly significant as they indicate a direct mechanism of action that implicates STS in neuronal-specific anti-inflammatory action that could be beneficial in patients suffering from Alzheimer's disease.

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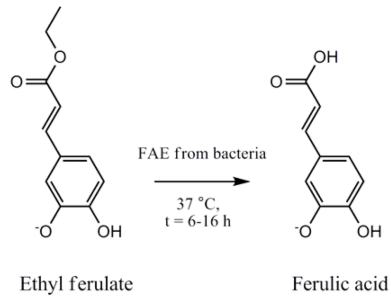
L. fermentum PV6910

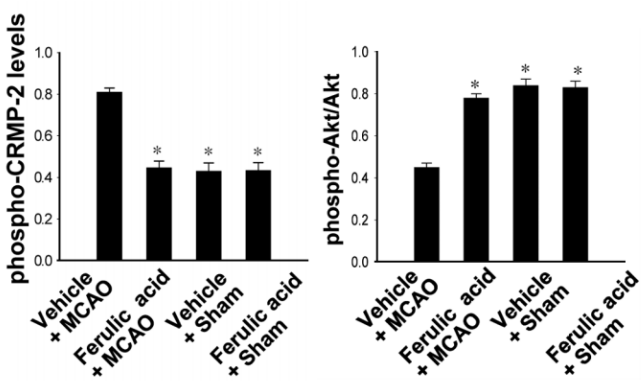
L. fermentum PV6910 is a human-derived aerobic bacterium with several active properties. Like other *Lactobacillus* species, *L. fermentum* has a good pH and bile-acid tolerance making it a practical probiotic species. Various species of *L. fermentum* have been shown to have immune-modulating, anti-aging,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

FERULIC ACID PRODUCTION

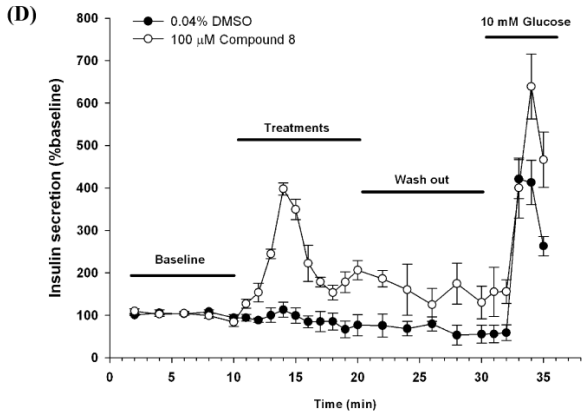
- *L. fermentum* PV6910 has a potent intrinsic ferulic acid esterase (FAE) activity, producing large quantities of the phytochemical ferulic acid (FA) (Tomaro-Duchesneau et al., 2012)



- Traditionally, plants and plants containing high levels of FA have been used in Chinese medicine for its potent inhibition of ROS generation and anti-inflammatory properties.
- 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 (Hu et al., 2011)
- 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 (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 in animals with middle cerebral artery occlusion (MCAO) 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 (Roy et al., 2013). Below, the levels of insulin secretion from perfused rat pancreata is depicted indicating a strong insulin response to ferulic acid administration.



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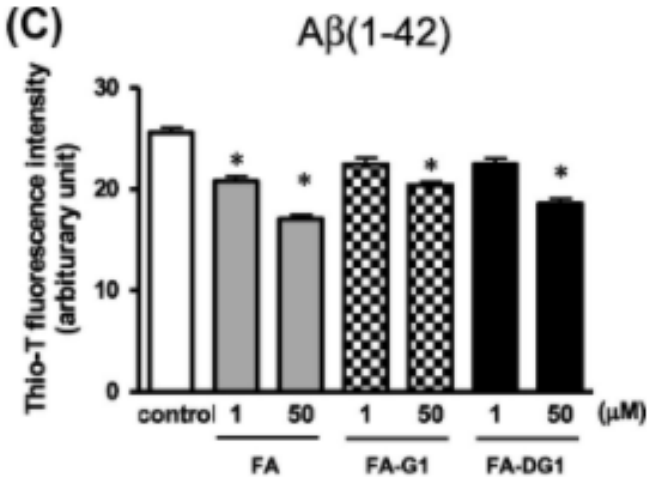
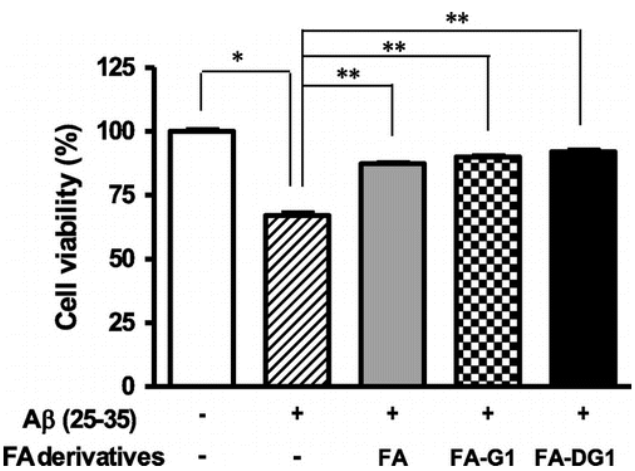
L. fermentum PV6910

FERULIC ACID PRODUCTION

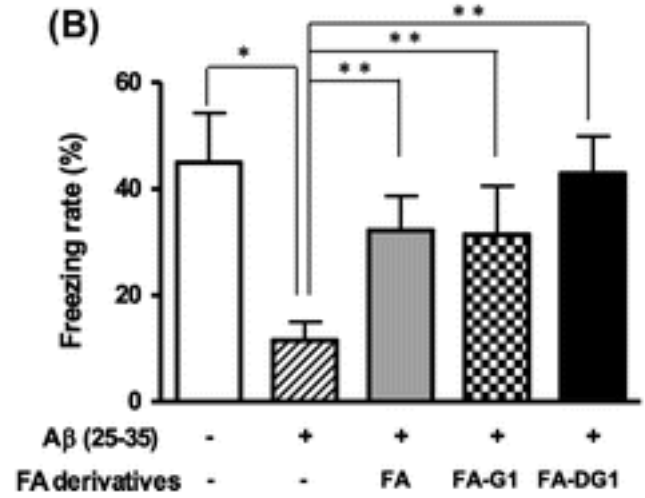
- Ferulic acid is actually specifically beneficial against the development of Alzheimer's disease. Ferulic acid (and some of its water-soluble derivaties) inhibit the aggregation of Abeta (1-42) pathogenic plaques, the plaque which are directly responsible for AD pathology (Kikugawa et al., 2015).



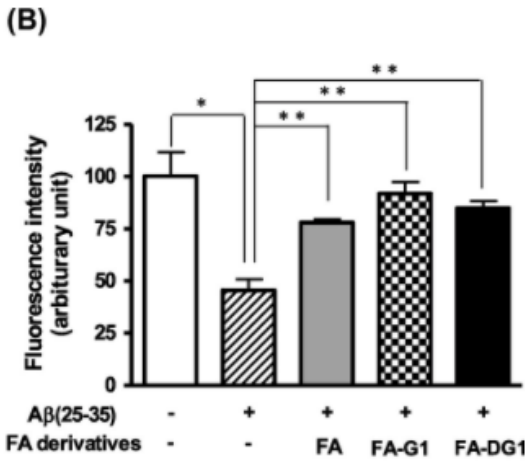
- Likewise, FA and its derivative were found to reduce cell death in cells exposed to pathogenic Abeta aggregates (Kikugawa et al., 2015).



- *In vivo*, FA was able to rescue some cognitive impairments in mice infused with Abeta (25-35) aggregates simulating AD:



- This was reflected in the *in vivo* rescue of neurons in Abeta treated mice indicating a direct implication of FA production on the treatment of AD (Kikugawa et al., 2015)



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