Lactiplantibacillus plantarum P8

Alleviates stress and anxiety and improves cognitive function

Stress is a psychological and physical response to challenges and demands that under some conditions can stimulate us and guide us in solving problems, known as eustress.
However, in many cases stress can come from emotionally challenging experiences or seemingly minor and routine everyday life events, from a traffic jam to tight work deadlines, that when accumulated can be detrimental to our health. Strong bouts of stress or prolonged stress can compromise our well-being and trigger anxiety that, if left untreated, can lead to more serious disturbances such as depression, which affects more than 300 million people worldwide.
Stress causes a prolonged rise in glucocorticoid levels, which progressively impairs the immune system and hippocampal structure, leading to alterations in neurogenesis and neuronal morphology. Furthermore, stress is also associated with increased risk of cardiovascular disease and metabolic and gastrointestinal pathologies.
Accumulating evidence on the role of gut bacteria on mental health has made scientists to start considering the gut microbiota as an "endocrine organ", leading to the concept of "gut-brain axis", a dynamic and bi-directional system of communication involved in maintaining homeostasis. For example, germ-free mice have higher levels of plasma corticosterone and anxiety behaviors, indicating the key role of the gut microbiota in mental health and host behaviors [1].
This binary interaction does not only impact our mental health, but also several other aspects of our physiology, such as glucose homeostasis, satiety, obesity, gastrointestinal and inflammatory disorders. Elements of the gut-brain-axis include signal molecules (cytokines, hormones, and neuropeptides) involved at nervous (central and enteric nervous system), hormonal and immune level.
Over the last years, there has been an increasing interest on the impact of probiotic intake in mental health: certain strains have shown potential as therapeutics or adjuvants in the treatment of stress and anxiety through the direct production of bioactive molecules, or through the modulation of specific pathways of the gut-brain axis.

***Lactiplantibacillus plantarum* P8** (basonym *Lactobacillus plantarum*) was isolated from a traditionally fermented sour milk in Inner Mongolia, China, and is produced by Sacco. **P8** has been deeply studied since 2005 for its excellent probiotic properties, including its effect on the gut-brain axis in adults, highlighting its significant benefits in reducing stress and anxiety, together with improving cognitive and memory functions.

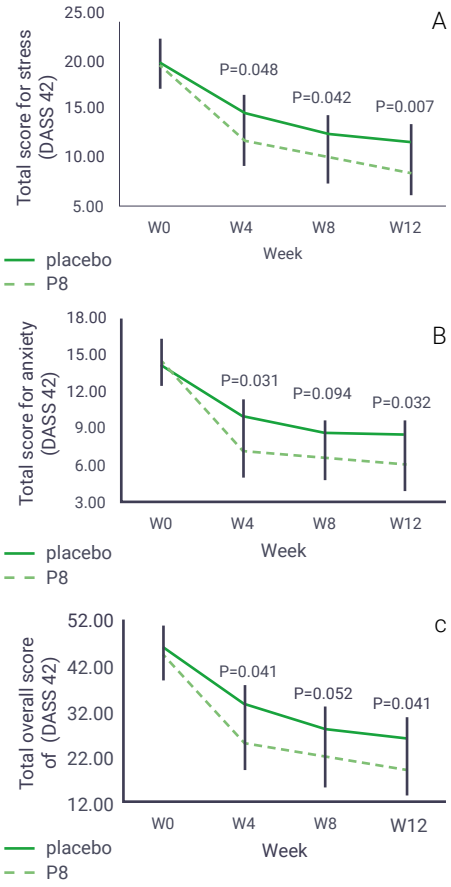

Figure 1. *Effects of 12-weeks administration of probiotic P8 (dashed line) or placebo (full line) on the DASS-42 score test: (A) stress score, (B) anxiety score and (C) total score of DASS-42 test. P-values indicated difference between treatment groups at individual time points. Results are expressed as mean; error bars (SEM); ANOVA test was used to evaluate the statistical significance (interval of confidence 95%) [2]*

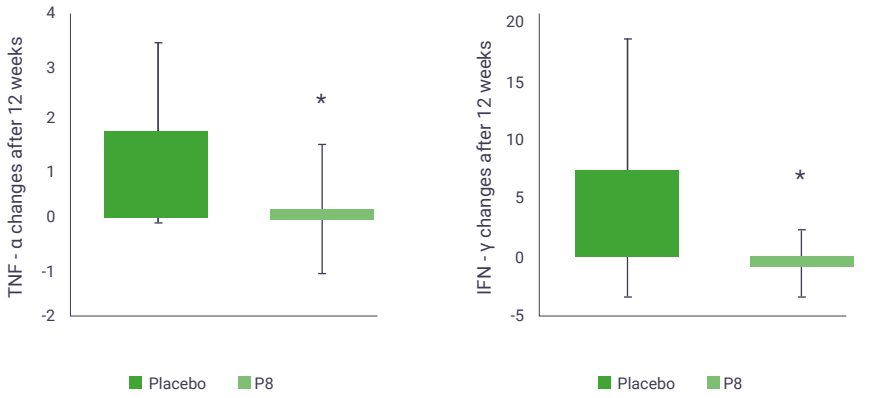

Figure 2. *IFN- γ and TNF- α changes after 12 weeks of P8 or placebo consumption (mean ± SEM. * p<0.05) [2]*

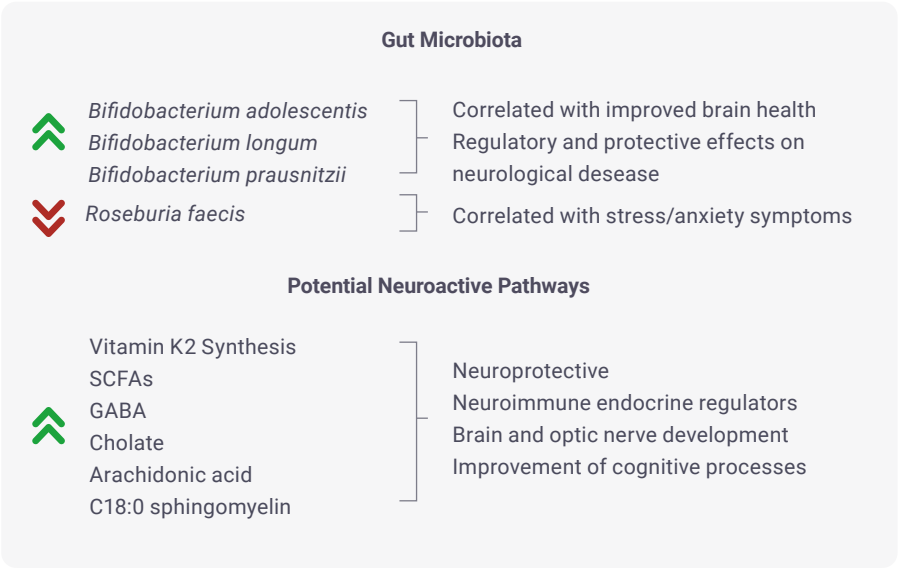

Figure 3. *Schematic overview of P8's supplementation effect on gut microbiota and neuroactive pathways [3].*

EFFICACY

Clinical Evidence of P8's effect on the Gut-Brain Axis

A 12-week randomized, double-blind and placebo-controlled study has been performed on 103 stress adults (mean age of 31.7 ± 11.1 years old) consuming 10^{10} CFU/day of P8 (or placebo) in sachets [2-3]. Psychological, memory and cognition parameters were investigated together with a metagenomic analysis of the gut microbiota. At the end of the study:

- Patients consuming P8 presented **reduced levels of stress and anxiety** (evaluated by the DASS-42 score test) with respect to the placebo group, in particular after 4 weeks of treatment (Figure 1).
- P8 helped to keep a stable and healthy inflammatory tone during the 12-weeks treatment: the pro-inflammatory cytokines (IFN-γ and TNF-α) levels did not change throughout the treatment period (Figure 2)
- Specific changes in the gut microbiota of stressed individuals consuming P8 correlated with improvements in neuroactive pathways related to the gut-brain axis (Figure 3) [3]
- These effects were associated with **improved social emotional cognition**
- In particular, **women** consuming P8 had **enhanced cognition** such as social emotional cognition (encoding, memory, and interpretation of social information) **and basic attention**, indicating better management of anxiety disorders, anxiety and mindful attention.
- **Men** consuming P8 **improved verbal memory functions and mental focus**

P8 mechanism of action is likely related to its effect on the anti-inflammatory response and on the modulation of the gut microbiota.

The clinical study on stressed adults revealed the possible mechanism of action of P8 [2-3]. Firstly, a correlation analysis revealed that a higher level of pro-inflammatory cytokines was associated to higher levels of stress and anxiety. These two psychological traits are in turn related to cognitive and memory deficiency. On the contrary, P8 administration alleviated stress, anxiety symptoms, and cognitive and memory capacity. These effects could be correlated to the activation of an anti-inflammatory response, in particular through the reduction of IFN-γ and TNF-α, two of the main biomarkers of inflammation [2].

Moreover, P8 showed a positive modulatory effect on the gut microbiota and of neuroactive potential-related pathways [3]:

- *Bifidobacterium adolescentis, Bifidobacterium longum*, and *Faecalibacterium prausnitzii,* positively correlated with mental health and with regulatory and protective effects on neurological diseases
- predicted levels of vitamin K2 synthesis, short-chain fatty acids (SCFAs), GABA, cholate, arachidonic acid, and C18:0 sphingomyelin increased significantly after probiotic treatment

Thus, the balancing effect on the intestinal microbiota may closely regulate host inflammatory response, activate intestinal and circulating immune pathways, and consequently influence the host's mood and brain function.

Additional clinical and pre-clinical evidence

The effect on the host's anti inflammatory response has been observed in separate clinical study performed by Xu et al. [4], where **P8** (in a blend with other probiotic bacteria) was administered as adjuvant to the classical therapy to patients with irritable bowel syndrome for 28 days (IBS): the outcome included a **reduction in inflammation**, specifically of **IL-6 and TNF-α, and of the symptoms**.

As observed in the clinical study on stressed individuals, P8 efficacy seems correlated to the modulation of the gut microbiota. Accordingly, another clinical study on subjects with different age (young, middle-age, elderly) revealed that 4-weeks consumption of **P8 led to significant changes in the gut microbiota** in the elderly population, with reduction of *Pseudomonas* and *Acinetobacter* genera (which include some opportunistic pathogen species associated to antibiotic-resistance), and of *Desulfovibrio* (potentially associated to inflammatory and chronic conditions as ulcerative colitis) [5]. Furthermore, **P8 consumption was correlated with higher levels of bifidobacteria**, which have a protective role against enteric infections, and are generally associated with beneficial effects on gut health.

Lastly, a pre-clinical study on hyperlipidemic rats [6] revealed that P8 had several **positive effects on lipid metabolism**: if compared to the control, the animals consuming **P8 presented reduced total cholesterol, in particular LDL, and triglycerides, and increased HDL levels**. Moreover, a reduction of the oxidative stress induced by the high-fat diet was observed, together with a decrease in lipid accumulation in the liver, indicating protection of hepatic function.

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