

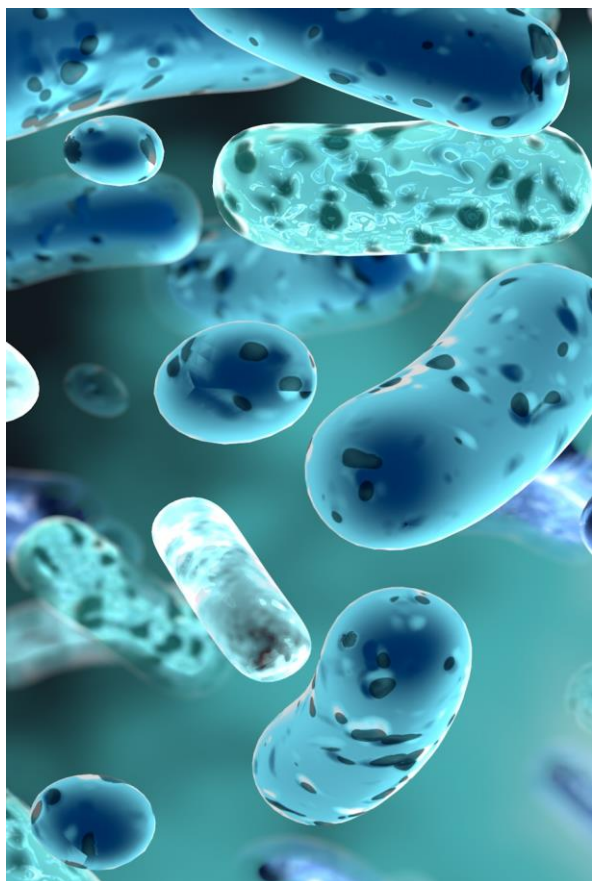


Probiotics - metabolic health and weight management



The potential of the Microbiome

Microbiome research has shown it is possible to affect outcomes in numerous diagnoses by modulating the microorganisms of the gut, and much research interest has been focused on the role of the microbiome in helping to tackle obesity. By first characterizing and understanding the microbial changes present in overweight and obese populations, researchers are then able to progress to interventional trials in order to understand how modulating the microbiome can affect obesity outcomes.



ADM'S INNOVATIVE MICROBIOME RESEARCH

ADM has a long history of conducting proprietary microbiome research, with an extensive library of pre-clinical and clinical trials to support our growing range of cutting-edge microbiome solutions.

Game Changer Probiotic Solutions

BPL1: A Cutting-Edge Biotic Solution

BPL1 (*Bifidobacterium animalis subsp. lactis* CECT 8145) is ADM's proprietary, award-winning probiotic strain with clinically documented results in improving body mass index (BMI), waist circumference (WC), and visceral fat area.



WINNER: NutraIngredients Awards in 2020 as Ingredient of the Year in Weight Management

BPL1 at a Glance

Clinical trials have demonstrated beneficial effects of BPL1 in metabolic balance, metabolic health, better body shape, reduced waist circumference, decreased visceral fat area and reduced BMI

More than 9 years of R&D, including proprietary, patent protected science and human clinical trials

Cutting-edge pre-clinical and clinical Research, product Development and commercialization capabilities

Human origin strain protected by patent

More Applications. More Benefits

BPL1 is ideal for use in **dietary supplements** including drops, capsules, sachets and sticks, **and dairy products**, such as fresh milk and fermented milk.

BPL1 can also be incorporated into the following applications, under certain manufacturing and preservation conditions:



sports
nutrition



clinical
nutrition



better-for-you
snacks



beverages



infant
nutrition

CLAIMS AND CERTIFICATIONS

- FDA Approved
- EU Approved | QPS list
- GRAS
- Non-GMO
- Organic
- Clean Label
- Gluten Free
- Kosher
- Vegan

Probiotic - metabolic health and weight management: Executive summary

ADM offers an effective, scientifically-validated metabolic health and body composition intervention. Our solution is not only focused in fat loss but also addresses various obesity-related factors, as oxidative stress and inflammation that act as a link to other pathologies.

Our strains...

Bifidobacterium lactis BPL1

→ Research suggest positive results on reduction of BMI, waist circumference and abdominal visceral fat

Lactobacillus rhamnosus
CNCM I-4036

→ Research suggest positive anti-inflammatory properties

Lactobacillus rhamnosus
CECT 8361 (BPL15)

→ Research suggests positive antioxidant properties

Lactobacillus casei
CECT 9104 (BPL4)

→ Complementary and enhancing properties

Introduction

According to the World Health Organization, an escalating global epidemic of obesity – globesity – is taking over in many parts of the world. Continued growth in the number of people who are overweight or obese is driving the need for effective, scientifically-validated interventions focused weight management and improving metabolic health.

The causes of obesity are complex and multifactorial – and the treatments and solution options available are similarly diverse and wide ranging. In recent years, consumer trends have started shifting toward the implementation of adjunct therapies like probiotics. Current consumer insights show a clear need and demand for the development of new and innovative solutions to drive positive metabolic health outcomes & to assist with maintaining a healthy weight. Modulation of the microbiome offers consumers an exciting opportunity to influence health outcomes through every day choices. Therefore, microbiome modulation for improved metabolic health, body composition & weight management has the potential to represent a key breakthrough for today’s consumers.

The probiotic industry can address this need but has been slow to develop condition-specific strains and show probiotics can drive improvements in meaningful endpoints. To fill this gap in the market, ADM offers an effective, scientifically-researched metabolic health and body composition intervention with its probiotic *Bifidobacterium lactis* BPL1.

In addition, **we have added 3 different strains (*Lactobacillus rhamnosus* CECT8361, *Lactobacillus rhamnosus* CNCM I-4036 and *Lactobacillus casei* CECT 9104)** in order to act as an adjuvant together with BPL1 to deal with the complications associated with obesity, as inflammation, oxidative stress and dysbiosis (Figure 1)

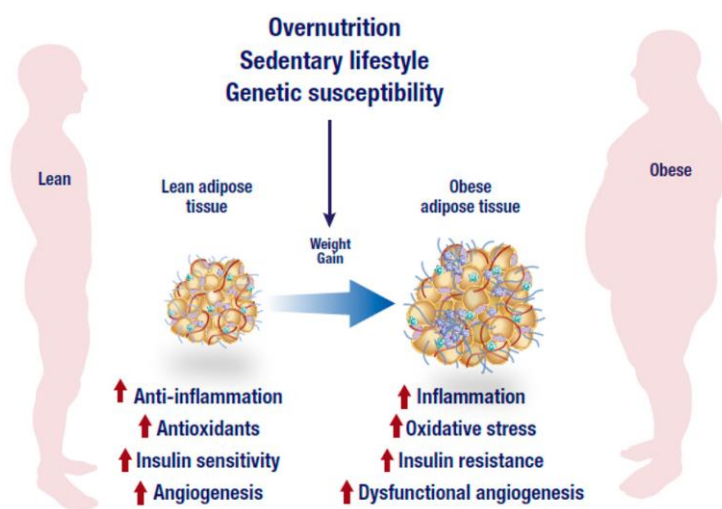


Fig1: Overnutrition, sedentary lifestyle and genetic susceptibility are the leading factors associated with the development of obesity. In addition to dysfunctional angiogenesis, **an obese state is characterized by an abnormal inflammatory response, low antioxidant capacity and reduced insulin sensitivity** that may eventually lead to the generation of inflammation, oxidative stress and insulin resistance. From: [1]

ADM Biopolis' support for metabolic health and weight management

Bifidobacterium lactis BPL1:

BPL1 is the ADM Biopolis probiotic strain with published clinical data showing improvements BMI, waist circumference and visceral fat area. Several studies, including in vitro tests, *C.elegans* and murine models, and a human clinical trial in abdominally obese individuals demonstrated the effects of BPL1 on anthropometric adiposity biomarkers [2-5]. After 12 weeks of BPL1 treatment, participants saw a statistically **significant reduction in BMI** compared to baseline and placebo. The results also showed a **significant reduction in waist circumference** (WC) against baseline (1.4 cm) after 6 weeks of treatment with BPL1. This decrease reached 1.75 cm at the end of the treatment [5].

Abdominal visceral fat area also decreased compared to baseline. Overall, 56% of patients in the BPL1 arm had more than a 3cm² reduction in visceral fat area. In a recent systematic review and meta-analysis of clinical trials examining the effect of exercise and pharmacological interventions on visceral adiposity, the authors concluded that **losing 3cm² of visceral fat was equivalent to 14kg of weight loss from exercise or 18kg of weight loss using pharmacological interventions** [6].

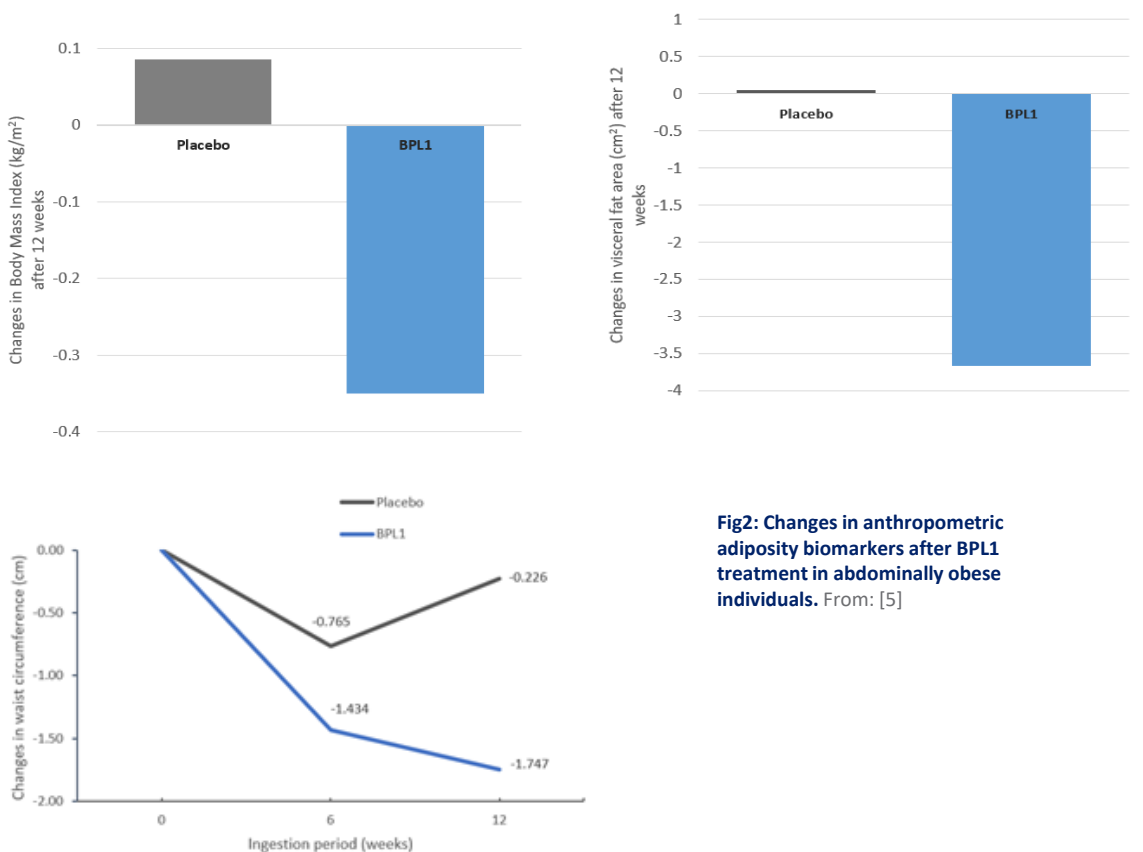


Fig2: Changes in anthropometric adiposity biomarkers after BPL1 treatment in abdominally obese individuals. From: [5]

ADM Biopolis' support for metabolic health and weight management

What other strains do we add that promote metabolic balance?

***Lactobacillus rhamnosus* CNCM I-4036: with anti-inflammatory support**

Obesity is associated with alterations in immunity, a chronic low-grade inflammation in which there are elevated circulating pro-inflammatory cytokines. The excess of macronutrients in the adipose tissues stimulates them to release inflammatory mediators such as tumor necrosis factor α and interleukin 6 (IL-6), and reduces production of adiponectin, predisposing to a pro-inflammatory state and oxidative stress [7]. It has been calculated that one third of total circulating concentrations of IL-6 originate from adipose tissue. Ellulu et al. **linked abdominal obesity with metabolic abnormalities via the inflammatory process** [8]. ; Figure 3 presents their illustration of it:

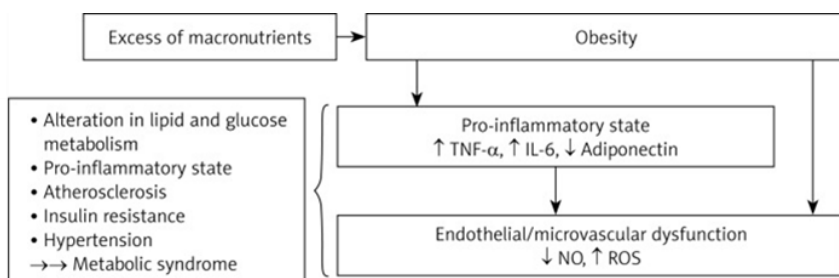


Fig3: Mechanisms linking abdominal obesity and metabolic syndrome via inflammatory mediators. TNF- α – tumor necrosis factor α , IL-6 – interleukin 6, NO – nitric oxide, ROS – reactive oxygen species. – adapted from: [8]

***Lactobacillus rhamnosus* CNCM I-4036** was selected within a large collection of strains isolated from exclusively breastfed babies as the best performant in anti-inflammatory and immune support characteristics. **This strain increased anti-inflammatory cytokines as IL-4 and IL-10 and decreased IL-12 (a pro-inflammatory cytokine)** after 4 weeks of treatment in healthy volunteers. *L. rhamnosus* CNCM I-4036 also significantly improved the IL-10/TNF- α ratio [9]. IL-10 inhibits inflammatory reactions, while TNF- α activates inflammatory reaction locally and systemically. Thus, this ratio is a marker of inflammatory response, and its increase by *L. rhamnosus* CNCM I-4036 indicates an anti-inflammatory effect. Moreover, This strain was seen to reduce serum lipopolysaccharides (LPS), (a factor associated with hepatic steatosis) and diminished the serum profile of proinflammatory cytokines, as TNF- α of obese Zucker rats [10].

In addition, *Lactobacillus rhamnosus* CNCM I-4036 has showed protection against *Clostridium difficile* [9], one the most common cause of infectious nosocomial diarrhoea among adults and strongly related with obesity.

ADM Biopolis' support for metabolic health and weight management

What other strains do we add that promote metabolic balance?

Lactobacillus rhamnosus CECT 8361 (BPL15): demonstrates antioxidant activity

In addition to driving an enhanced pro-inflammatory response, adipose tissue expansion during the progression of obesity can result in excess production of toxic radical species that can cause generation of oxidative stress. Oxidative stress plays an important role in the development of co-morbidities in obesity, including insulin resistance and diabetes, cardiovascular complications, sleep disorders, asthma, oncological problems, reproduction, rheumatological problems, and liver failure (Figure 4). Moreover, oxidative stress could trigger obesity by stimulating the deposition of white adipose tissue (WAT) and altering food intake [11].



Fig4: Conditions generating oxidative stress in the pathogenesis of obesity and the role of oxidative stress in the development of obesity associated health risks. From: [11]

Lactobacillus rhamnosus CECT 8361 (BPL15) significantly increases the survival of the *Caenorhabditis elegans* model organism by more than 30% under oxidative stress compared to control without the strain and its antioxidant activity has been tested on sperm quality from males suffering asthenozoospermia [12]. In this study a decrease in DNA fragmentation and intracellular H₂O₂ levels in spermatozoa due to an antioxidant effect from *Lactobacillus rhamnosus* CECT8361 (BPL15) was observed.

ADM Biopolis' support for metabolic health and weight management

What other strains do we add that promote metabolic balance?

***Lactobacillus casei* CECT 9104 (BPL4): a strain that enhances the effectiveness of the probiotic mixture**

Internal analyses performed on the *C. elegans* animal model showed a percentage of fat reduction of 28.8% with respect to standard feeding conditions, as well as an increase in the survival of this model after acute oxidative stress. Thus, the addition of this strain strengthens and enhances the qualities of this probiotic mixture to obtain an adequate metabolic balance. In addition, *Lactobacillus casei* CECT 9104 (BPL4) presents antagonism against the pathogenic bacterium *Listeria monocytogenes*, one of the most common foodborne pathogen. Recently has been demonstrated that short-term consumption of a westernized diet has the capacity to significantly alter host susceptibility to oral *L. monocytogenes* infection [13].

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