



biombalance™

DISCOVER THE UNSUSPECTED
POWER OF POLYPHENOLS
FOR GUT HEALTH

Scientific report
authored by



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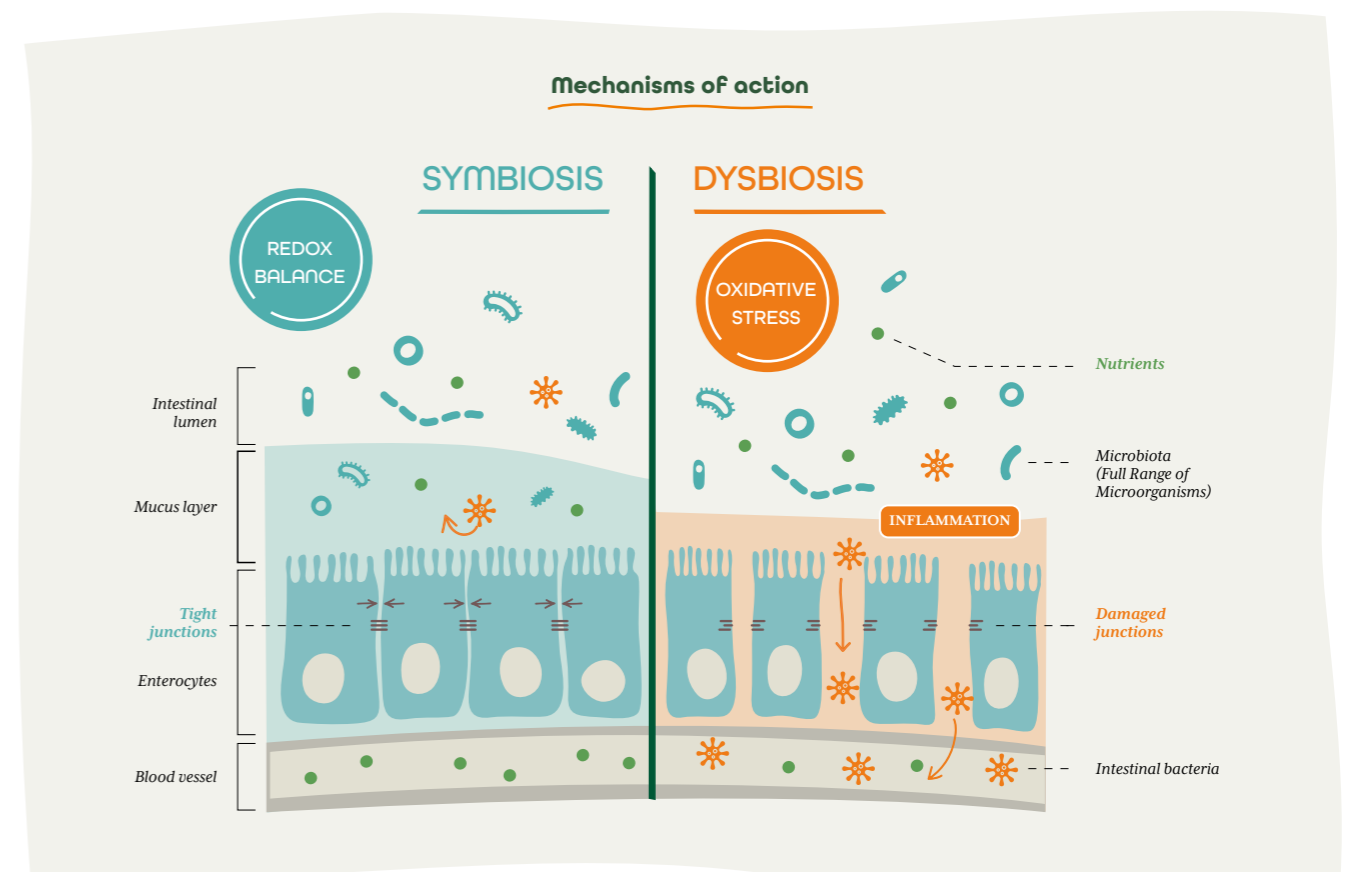
Gut health and beyond

With millions of people worldwide seeking support for gut health and documented links between gut, microbiota and overall health, polyphenols are an obvious answer for people searching for a holistic and efficient way to take care of themselves.

From the gut to the whole body.

Symbiosis and Dysbiosis

The main function of the intestinal tract is to digest food components and absorb nutrients and water. The intestine is also a physical barrier with selective permeability that protects the body from environmental insults, including dietary factors, stressors, and toxic compounds. Disturbances of the gut barrier function and microbiota can lead to an exaggerated immune response and oxidative stress, thus affecting intestinal permeability and compromising gut health. When the subtle equilibrium is broken, an imbalance in gut microbiota called dysbiosis may occur. This leads to harmful consequences, including increased oxidative stress and inflammation, which negatively impact the whole body. Proper nutrition, including supplementation, is important for helping to maintain a mutually beneficial symbiosis between our gut microbiota and our whole body. This symbiosis is crucial for overall health.



1. Prebiotic effect: a selective stimulation of good bacteria

Prebiotics are non-digestible food components which, through modulation of the gut microbiota, mediate an improvement of host health. A small portion of the flavan-3-ol and proanthocyanidin dimers contained in Biombalance™ may be absorbed in the upper part of the small intestine before reaching the bloodstream and acting globally throughout the body. The remaining unabsorbed larger oligomeric PACs reach the colon, where they are metabolized by gut microbiota. There, they exert prebiotic activity,

supporting a balanced gut microbiota and intestinal cells with proper barrier function (4). To evaluate the effect of Biombalance™ on both gut microbiota composition and activity, it was fermented by intestinal microbiota using an *ex vivo* approach. Additionally, the beneficial effects of fermented Biombalance for gut health were evaluated in human intestinal cells.

By mimicking colonic fermentation processes, we demonstrated that Biombalance™ may help maintain microbial abundance and species richness and may induce a selective stimulation of specific micro-organisms. Different species of the beneficial *Firmicutes* phylum, known to ferment polyphenols and to produce beneficial metabolites such as SCFA (Short Chain Fatty

Acids), were stimulated by Biombalance™ in our research on cultured human intestinal flora (Figure 1). Bacteroidetes were also promoted. Biombalance™ may be a cross-feeding effector: polyphenol metabolites produced by certain Bacteroidetes can be converted into SCFA (Short Chain Fatty Acids), such as butyrate, by Firmicutes.

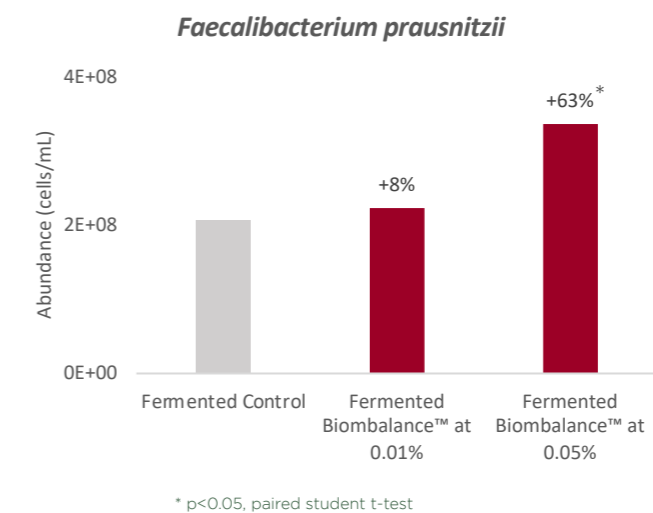


Figure 1. Biombalance™ impact on the abundance of the *Faecalibacterium prausnitzii* (*Firmicutes* phylum)

Through its prebiotic effects, Biombalance™ induces the modulation of the gut microbiota in favor of health-related micro-organisms.



biombalance™, our signature grape seed extract for gut health

Grape seed extract has been part of Groupe Berkem's DNA since the beginning, 60 years ago. This popular ingredient has been used for dozens of years in a number of indications, mainly as a global antioxidant and for cardiovascular health, among other benefits (1).

Thanks to our proprietary extraction and purification process, Biombalance™ is not just one more grape seed extract on the market: it exhibits a unique composition, high content of flavan-3-ols (monomers of catechin, epicatechin, and their gallates) and procyanidolic oligomers (OPCs) mainly dimers B1 and B2 (1). OPCs, also called proanthocyanidins or procyanidins, are commonly defined as oligomers (2 to 10 units) or polymers (>10 units) of monomeric units of flavan-3-ol (2,3).

This specific composition confers to Biombalance™ multiple beneficial effects on gut health and beyond.

2. Prebiotic effect: a positive impact on SCFA production

Activity of a healthy gut microbiota includes in the fermentation of carbohydrates (and to lesser extent proteins) by human colon bacteria, resulting in the formation of microbial end-products: short-chain fatty acids (SCFA), including acetate, propionate and butyrate. SCFA provide protective benefits for the lining of the gut, stimulating the formation of

tight junctions and improving gut barrier function (5). SCFA also decrease the pH of the colonic lumen which increases mineral absorption and inhibits growth of pathogens.

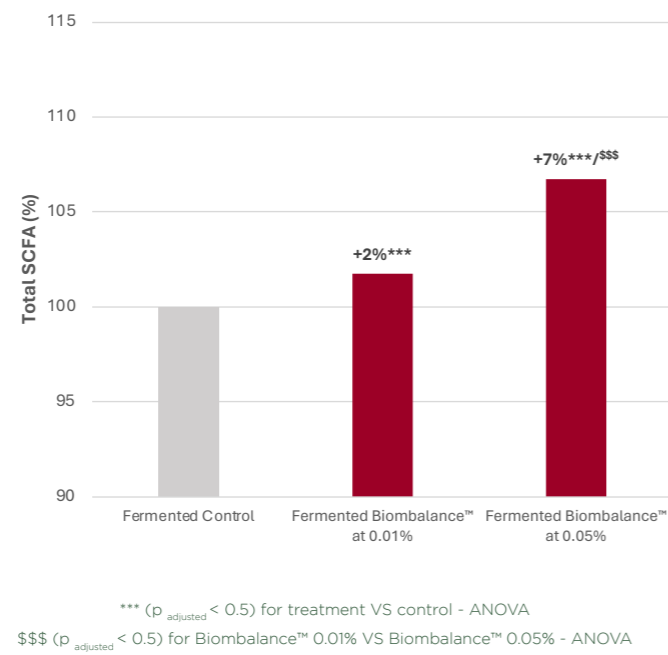


Figure 2. Impact of Biobalance™ on SCFA production.

Biobalance™ positively impact gut microbiota activity by increasing the production of healthy SCFA (Figure 2). Biobalance was also shown to support a healthy acidic pH.

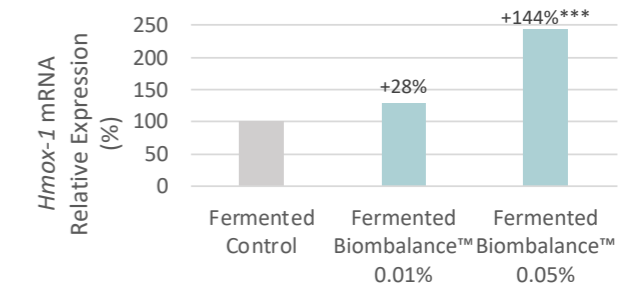
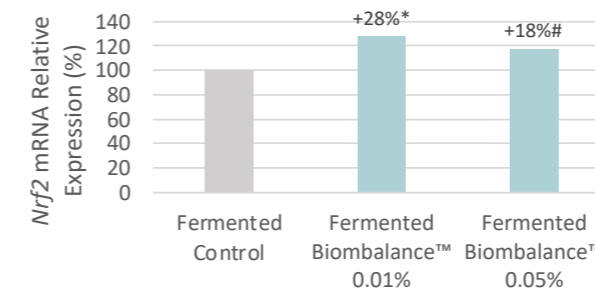
3. Protecting against free radicals

One of the main markers of dysbiosis is oxidative stress, which occurs when the production of reactive oxygen species (ROS) overcome the endogenous antioxidant defense system. The inevitable exposure to foreign substances and microbes results in the formulation of ROS. Disproportionate generation and long-term exposure to ROS causes damage to proteins, lipids and DNA, leading to damage of intestinal tissues and suboptimal functioning of the gut barrier (6). The epithelial cells' antioxidant activity is supported by an endogenous defense system that protects against

oxidative stress (10). One of the key regulators of this system is the stress inducible enzyme Hmox-1 which is activated by Nrf2 protein. Polyphenols, such as the proanthocyanidins in Biobalance™, contribute to antioxidant defense in multiple ways. They may activate the Nrf2 pathway or may contribute antioxidant activity directly. Such antioxidant activity is attributed to the numerous hydroxyl groups in proanthocyanidins which react with free radicals, scavenging them and protecting organelles, cells, and tissues from their harmful effects (7, 8).

Biobalance™ has a significant and dose-dependent free radicals scavenging activity. In addition, added to intestinal epithelial cells (IECS) in culture, Biobalance™ results in an increase in the antioxidant capacity. Polyphenols contained in Biobalance™ participate in the neutralization of ROS. We also observed that fermented

Biobalance™ enhanced endogenous antioxidant defenses in IECS. Fermented Biobalance™ increased Nrf2 expression by 28%*, and Hmox-1 expression by 144%*** in IECS compared to fermented control media (Figures 3 and 4).



#p<0.1; *p<0.05; ***p<0.001; Student's t test VS Fermented Control

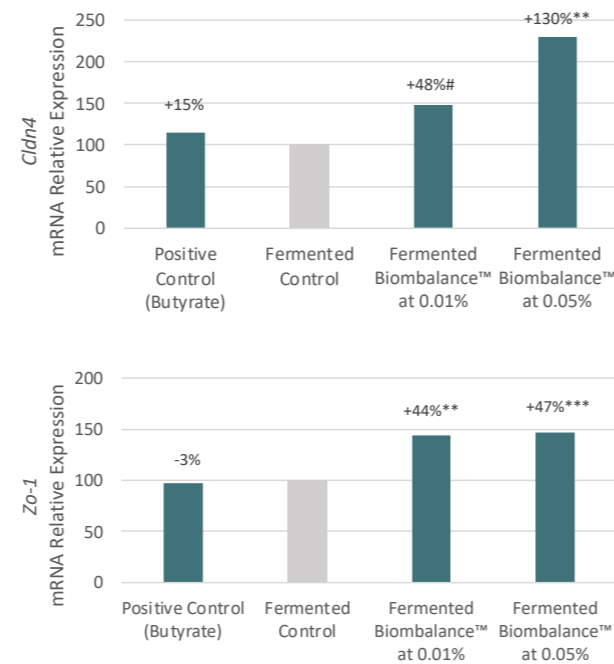
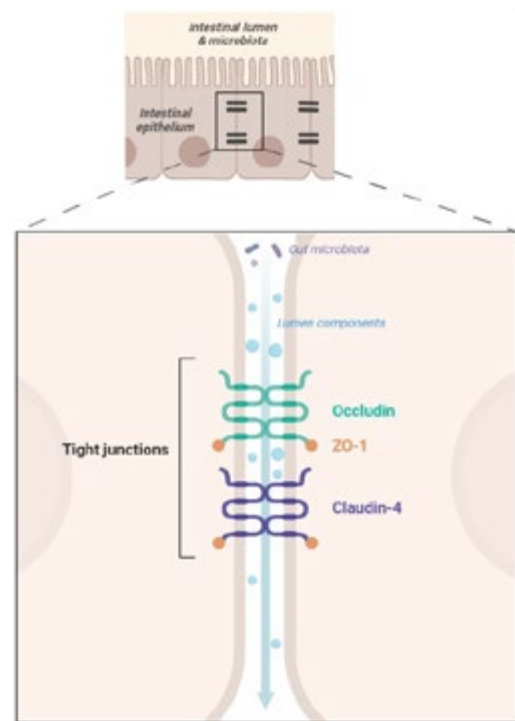
Figures 3 and 4. Biobalance™ impact on Nrf2 and Hmox-1 expression.

Biobalance™ possesses significant antioxidant activity and enhances endogenous antioxidant defenses to fight against oxidative stress.

4. Supporting intestinal wall barrier function

Increased permeability is a central hallmark of inflammation, observed in dysbiosis, which allows the infiltration of undesirable molecules, microbes and immune cells into inflamed tissues. This disturbed gut permeability is due to the disruption and widening of intercellular tight junctions. Intestinal epithelial cells serve as a barrier that segregates microorganisms and

components of the gut lumen from the sterile deep tissues and bloodstream (9). Intestinal cells are joined together thanks to tight junctions which are composed of proteins, including Claudin-4 (Cldn4), Occludin (Ocln) and Zonula Occludens-1 (ZO-1) (10).



p<0.1; **p<0.01; ***p<0.001 Student's t test VS Fermented Control

Figures 5 and 6. Impact of Biombalance™ on tight junction's gene expression, (Cldn-4 and Zo-1).

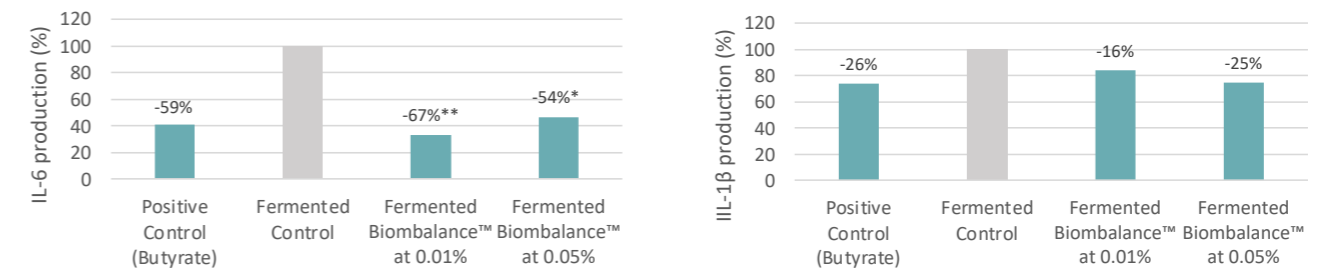
The expression of tight junction components - Claudin-4, and Zonula Occludens-1. Thus, in preliminary research, Biombalance™ appears to support intestinal barrier integrity through the enhancement of tight junctions between intestinal cells.

5. Supporting a healthy inflammatory response

A hallmark of gut dysbiosis is inflammation, which is characterized by immune cell infiltration triggered by intestinal cells producing pro-inflammatory cytokines, such as interleukin-6 (IL-6) and interleukin-1β (IL-1β) (11). This inflammatory

process can result in occasional gut discomfort, constipation and bloating. Supporting a healthy inflammatory response helps promote digestive health.

Biombalance™, after fermentation by gut microbiota, reduces the release of pro-inflammatory mediators IL-6 and IL-1β (Figures 7 and 8).



*p<0.05; **p<0.01; Student's t test VS Fermented Control

Figures 7 and 8. Impact of Biombalance™ on pro-inflammatory cytokines production.

(In cultured human intestinal cells), Biombalance significantly reduced the production of the inflammatory mediator, IL-6. This preliminary evidence suggests that Biombalance™ may help support a healthy inflammatory response and overall intestinal health.

What differentiates Biombalance™ from other grape extracts?

Biombalance™ is manufactured using a **specific proprietary process**, combining a step of extraction and a step of **purification**, leading to a **unique well-balanced composition**.

All steps are controlled from **sustainable sourcing** in the vineyards in the Champagne region of France, to **extraction and drying** in our facilities.

Biombalance™ contains **45% low molecular weight flavanols** (monomers and dimers).

Biombalance™ highlights the role of **polyphenols for gut health** with **proprietary findings** (*in vitro, ex vivo*).

5 main modes of action have been investigated revealing innovative key roles in supporting a healthy gut microbiota.

How to formulate Biombalance™?

Thanks to its powder form and waterdispersibility, Biombalance™ can be easily used in all conventional and innovative formulations including tablets, hardgel capsules, sachets, sticks, gummies, and one-shot drinks. Using a dispersing agent, Biombalance™ can be also used in lipid formulations (such as liquid capsules or softgel capsules).



Recommended dosage

We recommend using **Biombalance™** in the **500 mg/day** range, depending on the other ingredients in the formulation.

Why Groupe Berkem?



Our in-depth knowledge of plant chemistry. Our long standing relationships with sustainably managed farms within France, not only provide purity and quality of raw materials, but also ensure an uninterrupted, vertical supply chain.



We provide extensive complimentary services to our customers. We have teams of scientists dedicated to helping our customers: with private label manufacturing, custom extraction, and formulation of Groupe Berkem's ingredients into your end products, analytical chemistry (testing active content in your formulated end-product) and performing bioassays (evaluating the bioactivity of your end product containing our ingredients).



We have been a pioneer in plant extraction for over 60 years.



Our regulatory team is available for administrative, technical and regulatory compliance support.



References

- (1) Unusan, N., Proanthocyanidins in grape seeds: An updated review of their health benefits and potential uses in the food industry. *Journal of Functional Foods*, 2020, 67: p. 103861.
- (2) Gu, L.; Kelm, M.; Hammerstone, J.; Holden, J.; Haytowitz, D.; Beecher, G.; Prior, R. Development of a database of procyanidin profile and content in foods. International food database conference. 2003. Abstract p. B25.
- (3) Brunneton, J. *Pharmacognosie – Phytochimie, plantes médicinales*, 2è éd, entièrement refondue et augmentée, Paris, tech et doc, 1993, 915p. (ISBN 2-85206-911-3).
- (4) Keqin, O.; Liwei, G. Absorption and metabolism of proanthocyanidins. *Journal of functional foods*. 2014, 43-53.
- (5) Rivière, A.; Selak, M.; Lantin, D. ; Leroy, F. ; De Vuyst, L. Bifidobacteria and butyrate-producing colon bacteria : importance and strategies for their stimulation in the Human gut. *Frontiers in Microbiology*. 2016, 7, 979.
- (6) Vona, R.; Pallotta, L.; Cappelletti, M.; Severi, C.; Matarrese, P. The impact of oxidative stress in human pathology: Focus on gastrointestinal disorders. *Antioxidants*. 2021, 10, 2.
- (7) Bagchi, D.; Garg, A.; Krohn, R.L.; Bagchi, M.; Tran, M.X.; Stohs, S.J. Oxygen free radical scavenging abilities of vitamins C and E, and a grape seed proanthocyanidin extract in vitro. *Research communications in molecular pathology and pharmacology*. 1997, 95, 179-189.
- (8) Bagchi, D.; Garg, A.; Krohn, R.L.; Bagchi, M.; Bagchi, D.J.; Balmoori, J.; Stohs, S.J. Protective effects of grape seed proanthocyanidins and selected antioxidants against TPA-induced hepatic and brain lipid peroxidation and DNA fragmentation, and peritoneal macrophage activation in mice. *Gen. Pharmacol.* 1998, 30, 771-776.
- (9) Paradis, T.; Bègue, H. ; Basmacıyan, L. ; Dalle, F. ; Bon, F. *International journal of molecular sciences*. 2021, 22, 2506.
- (10) Meijers, B. ; Farré, R. ; Dejongh, S. ; Vicario, M. ; Evenepoel, P. *Toxins*. 2018, 10, 298.
- (11) Kang, L. ; Fang, X. ; Song, Y. ; He, Z. ; Wang, Z. ; Wang, S. ; Li, Z. ; Bai, Y. *Cellular and molecular gastroenterology and hepatology*. 2022, 14, 6.



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