Universal Library of Medical and Health Sciences Research Article

ISSN: 3064-6545 | Volume 4, Issue 1

Open Access | PP: 01-08

DOI: https://doi.org/10.70315/uloap.ulmhs.2026.0401001

Evaluation of the Health Benefits of Functional Protein Complex in Improving Intestinal Microbiota

Tzu-Chin Wu, BSs[1], Yi-Wen Chen, MS[2], Hui-Yu Huang, PhD[2], Jia-Xing Wang, MS[1]*, Yu-Jou Chien, PhD[1]*

[1]SummitBio Corporation, 3F., No. 192, Zhonggong 2nd Rd., Fuzhong Vil., Xitun Dist., Taichung City 407203, Taiwan (R.O.C.)

[2]Graduate Institute of Metabolism and Obesity Sciences, Taipei Medical University, No. 250, Wuxing St., Xinyi Dist., Taipei City 110301, Taiwan.

Abstract

Background: *The balance of intestinal microbiota plays a pivotal role in maintaining host health. Developing health supplements with the potential to modulate gut flora is of significant value for promoting gastrointestinal function and overall well-being.*

Methods: *In this study, forty 6-week-old male Sprague-Dawley (SD) rats were randomly assigned to four groups (n = 10 per group): a control group, a low-dose group (0.5X), a medium-dose group (1X), and a high-dose group (2X). The animals were administered the functional protein complex daily for eight consecutive weeks. Fecal samples were collected at weeks 0, 4, and 8 to analyze the counts of total anaerobes, Lactobacillus, and Bifidobacterium. Following sacrifice at week 8, the cecal microbiota was further analyzed.*

Results: *Compared with the control group, fecal analysis of the medium- and high-dose groups at weeks 4 and 8 showed a significant increase in the populations of total anaerobes, Lactobacillus, and Bifidobacterium ($p < 0.05$). Similar trends were observed in the cecal microbiota analysis of the medium- and high-dose groups.*

Conclusion: *This study demonstrates that the functional protein complex effectively increases the population of beneficial bacteria (Lactobacillus and Bifidobacterium) in the intestines of rats, thereby improving the balance of gut microbiota. Based on dose conversion, a daily intake of one sachet (20 g) for adults is suggested to enhance the count of beneficial intestinal bacteria and improve gastrointestinal function.*

INTRODUCTION

Diet is not only a fundamental requirement for human survival but also a profound factor in shaping the microbial communities residing in the digestive tract. The gut microbiome decomposes dietary carbohydrates and fibers to produce key metabolites, including short-chain fatty acids (SCFAs). These metabolites provide energy for colonic epithelial cells and exert systemic physiological effects by modulating immunity and influencing lipid and glucose metabolism (Makki et al., 2018; Holscher, 2017; den Besten et al., 2013). Consequently, the type, quality, and source of diet directly determine the composition and function of gut microbes, thereby affecting host-microbe interactions and health outcomes.

Recent epidemiological and mechanistic studies have revealed that intestinal dysbiosis is significantly associated with various chronic diseases, including obesity, metabolic syndrome, and colorectal cancer (Chiang et al., 2010; Derrien et al., 2004). Modern dietary patterns—characterized by high fat, high calories, and insufficient dietary fiber—often lead to a reduction in beneficial microbiota and the dominance of potential pathogens, increasing the risk of intestinal and systemic metabolic diseases.

Among strategies to improve gut microbiota, dietary intervention to increase fermentable fibers or prebiotics is a widely researched approach. These substances are metabolized by intestinal microbes, triggering fermentation pathways that produce SCFAs and other beneficial metabolites, which inhibit pathogens and enhance mucosal health (Holscher, 2017). In the cecum, anaerobic microbes ferment dietary fiber to produce SCFAs, which enter the bloodstream and influence lipid, glucose, and cholesterol metabolism via G protein-coupled receptors (den Besten et al., 2013).

Citation: Jia-Xing Wang, Yu-Jou Chien, et al., "Evaluation of the Health Benefits of Functional Protein Complex in Improving Intestinal Microbiota", Universal Library of Medical and Health Sciences, 2026; 4(1): 01-08. DOI: https://doi.org/10.70315/uloap.ulmhs.2026.0401001.

While various functional foods based on dietary fiber or prebiotics are available, their efficacy and mechanisms must be validated through rigorous experimental data. This study evaluates a functional protein complex primarily composed of total dietary fiber using an animal model. The research aims to explore its impact on functional indicators of gut microbiota composition, providing a scientific basis for its potential benefits in gastrointestinal health.

MATERIALS AND METHODS

Experimental Supplement

The functional protein complex was provided by SummitBio Co., Ltd. The formulation contains soy protein, corn-derived soluble fiber (Resistant Maltodextrin, RMD), calcium citrate, magnesium oxide, vitamin C, xanthan gum, zinc gluconate, vitamin E, ferrous glycinate, niacin, sucralose, vitamins D3, A, B2, B1, B6, K1, B12, folic acid, and biotin.

Animal and Study Design

Forty male Sprague-Dawley (SD) rats (5 weeks old, 190–200 g) were purchased from Lasco Biotechnology. After one week of acclimation, the intervention began at 6 weeks of age. Rats were housed individually in stainless steel cages under controlled conditions (23±2°C, 55±10% humidity, 12-h light/dark cycle). The product was dissolved in 12 mL of deionized water and administered via oral gavage twice daily (10:00 AM and 3:00 PM).

The dosage was calculated based on the human equivalent dose (HED) factor of 6.2 for a 200 g rat relative to a 60 kg human. The adult recommended intake is 1 sachet (20 g) per day. Protocol Approval: LAC-2022-0166 (Taipei Medical University).Groups were divided as follows (n=10):

- **Control (C):** Deionized water.
- **Low Dose (L, 0.5X):** 1.033 g/kg/day.
- **Medium Dose (M, 1X):** 2.067g/kg/day.
- **High Dose (H, 2X):** 4.133g/kg/day.

Fecal and Cecal Sampling

Fecal samples (1 g) were collected via anesthesia-induced rectal relaxation at weeks 0, 4, and 8. After 8 weeks, rats were sacrificed, and 1 g of cecal content was collected under anaerobic conditions for microbiota analysis. All samples were immediately placed in 9 mL of anaerobic diluent.

Preparation of Anaerobic Diluents and Culture Media

Preparation of Anaerobic Diluent

The anaerobic diluent was prepared by mixing 0.2 g gelatin, 50 mL distilled water, 50 mL salts solution, and 0.4 mL resazurin solution (25 mg/100 mL H_2O). The mixture was boiled, cooled, and supplemented with 0.05 g L-cysteine. Under anaerobic conditions, the solution was aliquoted into test tubes (9 mL per tube) and sterilized by autoclaving at 121°C for 15 minutes.

Medium for Total Anaerobic Bacteria Counts

Commercial CDC Anaerobe Blood Agar plates (BBL, B21734X) were utilized to determine total anaerobic bacteria counts.

Selective Medium for Lactobacilli

Lactobacillus species were cultured using a modified MRS agar (MRS + 0.5% $CaCO_3$). The composition per liter of distilled water included: 10 g peptone, 10 g beef extract, 5 g yeast extract, 20 g dextrose, 1 g Tween 80, 2 g K_2HPO_4, 5 g sodium acetate, 2 g ammonium citrate, 0.1 g $MgSO_4$, 0.05 g $MnSO_4$, 5 g $CaCO_3$, and 15 g agar. The basal medium was autoclaved and cooled to 50°C before being poured into Petri dishes and stored at 4°C.

Selective Medium for Bifidobacteria

Bifidobacteria iodoacetate medium-25 (BIM-25) was employed. The medium contained: 38 g Reinforced Clostridial Medium, 20 g agar, 0.02 g nalidixic acid, 0.0085 g polymyxin B sulfate, 0.05 g kanamycin sulfate, 0.0025 g iodoacetic acid, 0.025 g 2,3,5-triphenyltetrazolium chloride (TTC), and 1 L distilled water. The Reinforced Clostridial Medium was sterilized at 121°C for 15 minutes and cooled to 50°C. Antibiotics and chemicals were then added via membrane filtration (0.22 µm), mixed thoroughly, poured into plates, and stored at 4°C.

Microbial Cultivation and Enumeration

A 1 mL aliquot of fecal or cecal homogenate was added to 9 mL of anaerobic diluent for a ten-fold serial dilution series. Fifty microliters (50 µL) of the appropriate dilutions (three concentrations per medium) were inoculated onto the selective media using the spread plate method with a sterile glass spreader.

Plates were placed in an anaerobic jar containing anaerobic gas packs and indicators. Cultivation was performed at 35–37°C, and the colony-forming units (CFU) were counted. Specifically, total anaerobic organisms (white colonies) were grown on CDC Anaerobe Blood Agar; *Lactobacilli* (white colonies) on MRS agar; and *Bifidobacteria* (pink colonies) on BIM-25 medium.

Statistical analysis

The data are expressed as the mean ± standard deviation (SD). Statistical comparisons among groups were made using one-way analysis of variance (ANOVA), followed by Duncan's post hoc test. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were done using SAS software (SAS Institute, Cary, NC, USA).

RESULTS

Physiological Assessment

As shown in Table 1, which details the changes in body weight throughout the feeding period, no physiological abnormalities, illnesses, or fatalities were observed among the experimental animals during the 8-week study. Furthermore, there were no statistically significant differences in body weight between the groups ($p > 0.05$).

Table 1. Changes in body weight of rats in each group during the experimental period

Body weight (g)				
	Control	Low-dose	Medium-dose	High-dose
Week 0	191.8±3.4 a	192.1±3.8 a	193.7±4.6 a	194.4±5.5 a
Week 1	230.9±6.5 a	234.9±5.9 a	232.9±7.5 a	232.9±4.9 a
Week 2	272.7±6.5 a	278.9±8.4 a	276.3±9.8 a	274.9±8.4 a
Week 3	331.9±10.1 a	343.7±16.0 a	333.2±16.5 a	337.2±16.7 a
Week 4	376.8±22.2 a	384.8±21.0 a	376.4±20.6 a	383.2±18.5 a
Week 5	408.8±25.0 a	411.9±28.5 a	410.2±23.8 a	411.3±25.0 a
Week 6	441.2±28.2 a	448.8±27.7 a	439.8±24.7 a	444.7±23.5 a
Week 7	477.6±26.8 a	489.0±29.3 a	479.8±17.5 a	484.3±20.0 a
Week 8	505.7±30.1 a	520.0±24.5 a	509.1±24.4 a	512.4±25.3 a

Data are expressed as mean ±SD (n = 10). The test product was administered daily at 10:00 AM via oral gavage for 8 consecutive weeks. Values within the same column followed by different superscript letters (a, b, c) indicate significant differences compared to the control group ($p < 0.05$) based on one-way ANOVA and Duncan's post hoc test.

Dietary Intake Records

Throughout the experimental period, rats were given *ad libitum* access to a standard diet (LabDiet® 5001 Rodent diet). The dietary intake results (Table 2) indicate that there were no significant differences in food consumption between the groups throughout the study ($p> 0.05$).

Table 2. Dietary intake of rats in each group during the experimental period

Food (g/day)				
	Control	Low-dose	Medium-dose	High-dose
Week 1	25.1±0.4 a	25.4±0.6 a	25.4±0.7 a	25.6±1.1 a
Week 2	29.8±0.6 a	29.7±0.7 a	29.3±1.0 a	29.9±0.5 a
Week 3	29.9±0.6 a	30.2±0.6 a	30.2±0.6 a	30.2±0.5 a
Week 4	30.5±0.7 a	30.1±0.8 a	30.0±0.5 a	30.1±0.7 a
Week 5	29.8±0.6 a	30.2±0.7 a	30.1±0.7 a	30.4±0.6 a
Week 6	30.4±0.6 a	30.5±0.7 a	30.7±0.7 a	30.3±0.6 a
Week 7	30.7±0.6 a	30.6±0.5 a	30.8±0.6 a	30.6±0.6 a
Week 8	30.9±0.5 a	30.8±0.4 a	30.8±0.6 a	30.6±0.5 a

Data are expressed as mean ±SD (n = 10). The test product was administered daily at 10:00 AM via oral gavage for 8 consecutive weeks. Values within the same column followed by different superscript letters (a, b, c) indicate significant differences compared to the control group ($p < 0.05$) based on one-way ANOVA and Duncan's post hoc test.

Water Consumption Records

The results of water intake (Table 3) showed that the animals had regular access to water without any significant differences in consumption observed across all groups throughout the experimental period ($p> 0.05$).

Table 3. Water consumption of rats in each group during the experimental period

Water (g/day)				
	Control	Low-dose	Medium-dose	High-dose
Week 1	20.2±0.6 a	20.1±0.7 a	20.5±0.7 a	20.3±0.6 a
Week 2	24.1±0.8 a	24.4±0.8 a	24.3±1.0 a	24.2±0.7 a
Week 3	28.7±0.7 a	29.1±0.8 a	28.8±0.9 a	28.9±0.9 a
Week 4	34.5±0.8 a	35.0±0.7 a	34.9±0.9 a	35.1±0.6 a
Week 5	43.6±0.6 a	43.9±1.3 a	43.8±0.8 a	43.8±1.0 a
Week 6	45.9±1.1 a	45.6±1.1 a	46.1±0.8 a	46.0±1.2 a
Week 7	52.1±1.0 a	53.1±1.3 a	53.0±1.0 a	52.6±0.9 a
Week 8	54.3±0.5 a	54.6±0.6 a	54.3±0.7 a	54.8±0.6 a

Data are expressed as mean ±SD (n = 10). The test product was administered daily at 10:00 AM via oral gavage for 8 consecutive weeks. Values within the same column followed by different superscript letters (a, b, c) indicate significant differences compared to the control group ($p < 0.05$) based on one-way ANOVA and Duncan's post hoc test.

Analysis of Total Anaerobic Bacteria Counts

The analysis of total anaerobic bacteria counts (Figure 1) demonstrated that at week 0, there were no significant differences in fecal anaerobic bacteria between the low-, medium-, and high-dose groups compared to the control group ($p<0.05$). However, by week 4, total anaerobic bacteria counts in the medium- and high-dose groups increased significantly ($p<0.05$). At week 8, both groups continued to show a significant increase in fecal counts ($p<0.05$). Following sacrifice at week 8, analysis of the cecal content also revealed significantly higher anaerobic bacteria counts in the medium- and high-dose groups compared to the control ($p<0.05$).

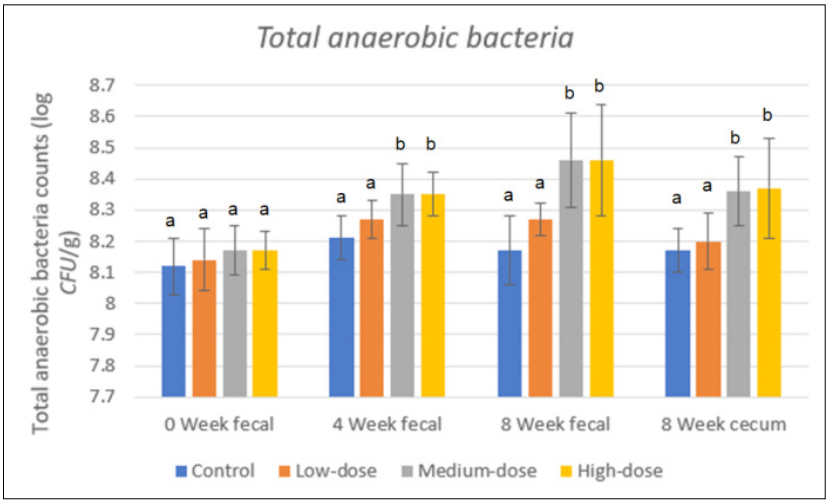

Figure 1. Analysis of Total anaerobic bacteria counts *s* counts in feces at weeks 0, 4, and 8, and in the cecum after sacrifice at week 8

Data are expressed as mean ±SD (n = 10). The test product was administered daily at 10:00 AM via oral gavage for 8 consecutive weeks. Values within the same column followed by different superscript letters (a, b, c) indicate significant differences compared to the control group ($p < 0.05$) based on one-way ANOVA and Duncan's post hoc test.

Analysis of Lactobacillus Counts

The results for *Lactobacillus* counts (Figure 2) indicated no significant baseline differences at week 0 across all groups ($p<0.05$). At weeks 4 and 8, the medium- and high-dose groups exhibited significant increases in fecal *Lactobacillus* counts compared to the control group ($p<0.05$). Consistent with the fecal results, cecal analysis at week 8 showed a significant increase in *Lactobacillus* populations in both the medium- and high-dose groups ($p<0.05$).

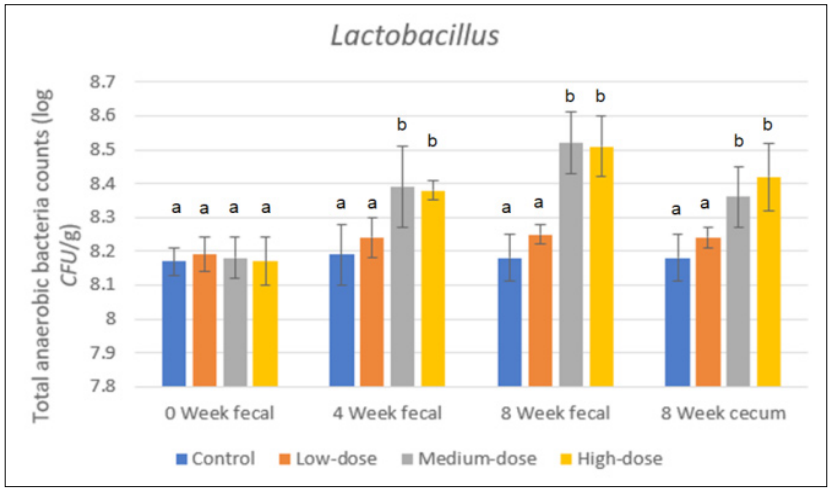

Figure 2. Analysis of *Lactobacillus* counts in feces at weeks 0, 4, and 8, and in the cecum after sacrifice at week 8

Data are expressed as mean ±SD (n = 10). The test product was administered daily at 10:00 AM via oral gavage for 8 consecutive weeks. Values within the same column followed by different superscript letters (a, b, c) indicate significant differences compared to the control group ($p < 0.05$) based on one-way ANOVA and Duncan's post hoc test.

Analysis of Bifidobacterium Counts

As illustrated in Figure 3, *Bifidobacterium* counts at week 0 showed no significant differences among the dose groups ($p<0.05$). At weeks 4 and 8, fecal *Bifidobacterium* counts were significantly elevated in the medium- and high-dose groups compared to the control ($p<0.05$). Similarly, cecal analysis after sacrifice at week 8 demonstrated that the medium- and high-dose groups achieved significantly higher *Bifidobacterium* counts than the control group.($p<0.05$).

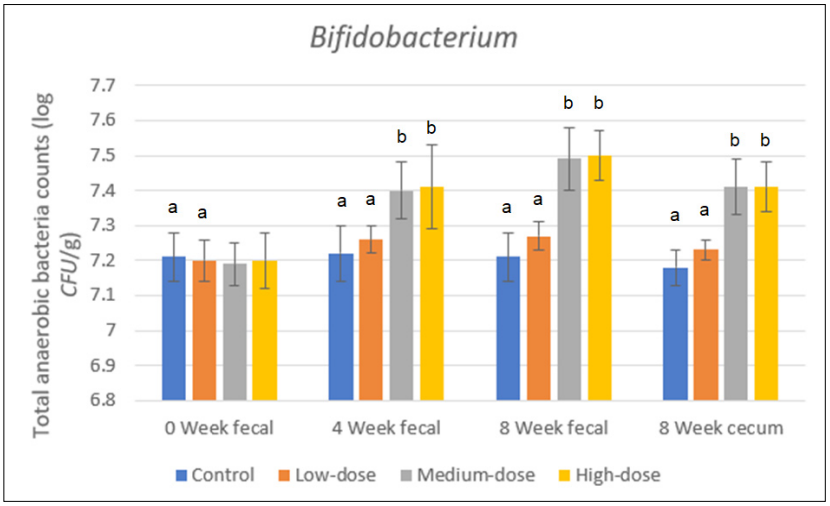

Figure 3. Analysis of Bifidobacterium counts in feces at weeks 0, 4, and 8, and in the cecum after sacrifice at week 8

Data are expressed as mean ±SD (n = 10). The test product was administered daily at 10:00 AM via oral gavage for 8 consecutive weeks. Values within the same column followed by different superscript letters (a, b, c) indicate significant differences compared to the control group ($p < 0.05$) based on one-way ANOVA and Duncan's post hoc test.

DISCUSSION

In this study, we evaluated the effects of a functional protein complex on intestinal microbiota by comparing SD rats administered different doses with a control group. Over the 8-week intervention, no significant differences were observed in body weight, water intake, or food consumption across groups. The rats exhibited normal behavior and physiological growth. Given that rats aged 6–8 weeks typically gain approximately 50 g per week and consume 10–12 mL/100g/day of water, our findings indicate that the supplement does not negatively impact basic growth parameters.

Our results demonstrate that daily intake of the supplement significantly increased the populations of total anaerobes, *Lactobacillus*, and *Bifidobacterium* in fecal samples starting from Week 4. Cecal microbiota analysis at Week 8 further confirmed that these bacterial counts remained significantly higher than those in the control group. These findings collectively suggest that the functional protein complex effectively promotes the proliferation of beneficial intestinal bacteria.

Total anaerobic bacteria constitute one of the primary microbial communities in the gut, encompassing beneficial genera such as Bacteroides, Clostridium, and *Lactobacillus* (Eckburg et al., 2005). These bacteria ferment dietary fibers to produce short-chain fatty acids (SCFAs), which maintain intestinal pH balance and epithelial barrier integrity (Louis & Flint, 2017). Changes in total anaerobic counts serve as a critical indicator of gut microbiota stability and host metabolic health (Rowland et al., 2018; Marchesi et al., 2016).

Similarly, *Bifidobacterium* and *Lactobacillus* are vital commensal probiotics. *Bifidobacterium* ferments dietary oligosaccharides to produce SCFAs, lowering intestinal pH and inhibiting pathogens while promoting immune stability (O'Callaghan & van Sinderen, 2016; Ruiz et al., 2017). *Lactobacillus* maintains the microbial balance by producing lactic acid, which enhances barrier integrity and digestive function (Marco et al., 2021; O'Toole et al., 2017).

The efficacy of the product is largely attributed to RMD, a corn-derived soluble fiber. RMD acts as a prebiotic, significantly increasing *Bifidobacterium* abundance and enhancing mucosal defense (Nishimoto et al., 2022). Furthermore, RMD has been shown to stimulate the production of IL-10 by intestinal cells, thereby reducing inflammation risks (Mai et al., 2022).

The inclusion of vitamins also plays a synergistic role in modulating the gut environment:Vitamin A: Supports mucosal immunity by promoting IgA secretion (Okayasu et al., 2016).Vitamin B complex: Supports bacterial metabolism and stabilizes beneficial microbial populations (Sharma et al., 2019).Vitamin C: Lowers fecal pH and redox potential, enhancing microbial diversity (Pham et al., 2021).Vitamin D: Promotes the abundance of healthy taxa such as *Akkermansia* and *Bifidobacterium* (Bashir et al., 2016).Vitamin E: Reduces inflammation by scavenging free radicals and modulating microbial composition (Wu et al., 2024).

In conclusion, our dose-response analysis over eight weeks

revealed that even the Medium Dose (equivalent to an adult intake of 20 g/day) is sufficient to significantly enhance *Lactobacillus*, *Bifidobacterium*, and total anaerobic counts in both feces and the cecum. Based on these data, a daily supplement of one sachet (20 g) is recommended for adults to improve intestinal microbiota composition and enhance gastrointestinal function.

CONCLUSION

In summary, the results of this study demonstrate that an 8-week intervention with the functional protein complex—at both medium and high doses—significantly increases the counts of total anaerobes, *Lactobacillus*, and *Bifidobacterium* in both the feces and cecum of Sprague-Dawley rats. Consequently, daily consumption of the functional protein complex provides the following health benefits. Enhancement of total anaerobic bacteria populations within the intestinal tract.Promotion of *Lactobacillus* proliferation, supporting a healthy microbial environment.Stimulation of *Bifidobacterium* growth, contributing to gut flora balance.

By modulating the composition of the intestinal microbiota, this supplement effectively improves gastrointestinal function and supports overall host health.

ACKNOWLEDGMENT

This research was founded by SummitBio Co., Ltd.

REFERENCES

1. Banach, M., Bruckert, E., Descamps, O. S., Ellegard, L., Ezhov, M., Foger, B., . . . Catapano, A. L. (2019). The role of red yeast rice (RYR) supplementation in plasma cholesterol control: A review and expert opinion. *Atheroscler Suppl, 39*, e1-e8. doi:10.1016/j.atherosclerosissup.2019.08.023

2. Banach, M., Catapano, A. L., Cicero, A. F. G., Escobar, C., Foger, B., Katsiki, N., . . . On Behalf of the International Lipid Expert Panel, I. (2022). Red yeast rice for dyslipidaemias and cardiovascular risk reduction: A position paper of the International Lipid Expert Panel. *Pharmacol Res, 183*, 106370. doi:10.1016/j.phrs.2022.106370

3. Banach, M., Penson, P. E., Farnier, M., Fras, Z., Latkovskis, G., Laufs, U., . . . Escobar, C. (2023). Bempedoic acid in the management of lipid disorders and cardiovascular risk. 2023 position paper of the International Lipid Expert Panel (ILEP). *Prog Cardiovasc Dis, 79*, 2-11. doi:10.1016/j.pcad.2023.03.001

4. Bashir, M., Prietl, B., Tauschmann, M., Mautner, S. I., Kump, P. K., Treiber, G., Wurm, P., Gorkiewicz, G., Högenauer, C., & Pieber, T. R. (2016). Effects of high doses of vitamin D3 on mucosa-associated gut microbiome vary between regions of the human gastrointestinal tract. *European journal of nutrition*, *55*(4), 1479–1489. https://doi.org/10.1007/s00394-015-0966-2

5. Brandts, J., & Ray, K. K. (2023). Novel and future lipid-modulating therapies for the prevention of cardiovascular disease. *Nat Rev Cardiol, 20*(9), 600-616. doi:10.1038/s41569-023-00860-8

6. Chang, H. H., Lan, Y. C., Chung, S. D., & Chien, C. T. (2021). Sweet Potato Leaf Feeding Decreases Cholesterol, Oxidative Stress and Thrombosis Formation in Syrian Hamsters with a High-Cholesterol Diet. *Life (Basel), 11*(8). doi:10.3390/life11080802

7. Derrien, M., & van Hylckama Vlieg, J. E. (2015). Fate, activity, and impact of ingested bacteria within the human gut microbiota. *Trends in microbiology*, *23*(6), 354–366. https://doi.org/10.1016/j.tim.2015.03.002

8. Dwivedi, S., Singh, V., Sharma, K., Sliti, A., Baunthiyal, M., & Shin, J. H. (2024). Significance of Soy-Based Fermented Food and Their Bioactive Compounds Against Obesity, Diabetes, and Cardiovascular Diseases. *Plant Foods Hum Nutr, 79*(1), 1-11. doi:10.1007/s11130-023-01130-1

9. *Eckburg, P. B., Bik, E. M., Bernstein, C. N., Purdom, E., Dethlefsen, L., Sargent, M., Gill, S. R., Nelson, K. E., & Relman, D. A. (2005). Diversity of the human intestinal microbial flora. Science (New York, N.Y.), 308(5728), 1635–1638. https://doi.org/10.1126/science.1110591*

10. Elmowafy, E., Pavoni, L., Perinelli, D. R., Tiboni, M., Casettari, L., Cespi, M., . . . Bonacucina, G. (2022). Hyperlipidemia control using the innovative association of lupin proteins and chitosan and α-cyclodextrin dietary fibers: food supplement formulation, molecular docking study, and in vivo evaluation. *European Food Research and Technology, 248*(12), 2977-2993. doi:10.1007/s00217-022-04105-9

11. Ferrarese, I., Giovanna Lupo, M., Rossi, I., Sut, S., Loschi, F., Allegrini, P., . . . Dall'Acqua, S. (2023). Bergamot (Citrus bergamia) peel extract as new hypocholesterolemic agent modulating PCSK9 expression. *Journal of Functional Foods, 108*. doi:10.1016/j.jff.2023.105724

12. Fogacci, F., Banach, M., Mikhailidis, D. P., Bruckert, E., Toth, P. P., Watts, G. F., . . . International Lipid Expert, P. (2019). Safety of red yeast rice supplementation: A systematic review and meta-analysis of randomized controlled trials. *Pharmacol Res, 143*, 1-16. doi:10.1016/j.phrs.2019.02.028

13. Fogacci, F., Di Micoli, V., Veronesi, M., & Cicero, A. F. G. (2023). Comparative effect of a nutraceutical compound based on a flavonoid complex from bergamot on plasma lipids, glucose metabolism, and liver enzymes: a 3-arm, double-blind, placebo-controlled, randomized clinical trial. *Arch Med Sci, 19*(5), 1180-1185. doi:10.5114/aoms/152791

14. Granito, M., Alvarenga, L., Ribeiro, M., Carvalhosa, P., Andrade, T., Mesquita, C. T., . . . Cardozo, L. F. (2024). Nattokinase as an adjuvant therapeutic strategy for non-communicable diseases: a review of fibrinolytic,

antithrombotic, anti-inflammatory, and antioxidant effects. *Expert Rev Cardiovasc Ther, 22*(10), 565-574. doi :10.1080/14779072.2024.2416663

15. Hill, C., Guarner, F., Reid, G., Gibson, G. R., Merenstein, D. J., Pot, B., Morelli, L., Canani, R. B., Flint, H. J., Salminen, S., Calder, P. C., & Sanders, M. E. (2014). Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nature reviews. Gastroenterology & hepatology*, *11*(8), 506–514. https://doi.org/10.1038/nrgastro.2014.66
16. Huang, C. H., Hsu, H. S., & Chiang, M. T. (2024). Influence of Varied Dietary Cholesterol Levels on Lipid Metabolism in Hamsters. *Nutrients, 16*(15). doi:10.3390/nu16152472
17. Huang, Y., Tocmo, R., Nauman, M. C., Haughan, M. A., & Johnson, J. J. (2021). Defining the Cholesterol Lowering Mechanism of Bergamot (Citrus bergamia) Extract in HepG2 and Caco-2 Cells. *Nutrients, 13*(9). doi:10.3390/nu13093156
18. Iqbal, I., Wilairatana, P., Saqib, F., Nasir, B., Wahid, M., Latif, M. F., . . . Mubarak, M. S. (2023). Plant Polyphenols and Their Potential Benefits on Cardiovascular Health: A Review. *Molecules, 28*(17). doi:10.3390/molecules28176403
19. Lee, J., Kang, M., & Park, Y. (2025). Exercise Training Enhances Brachial Artery Endothelial Function, Possibly via Improved HDL-C, not LDL-C and TG, in Patients with Coronary Artery Disease: A Systematic Review and Meta-analysis. *Am J Cardiovasc Drugs*. doi:10.1007/s40256-024-00716-7
20. Li, D., Hou, L., Hu, M., Gao, Y., Tian, Z., Fan, B., . . . Wang, F. (2022). Recent Advances in Nattokinase-Enriched Fermented Soybean Foods: A Review. *Foods, 11*(13). doi:10.3390/foods11131867
21. Li, H., Yu, X. H., Ou, X., Ouyang, X. P., & Tang, C. K. (2021). Hepatic cholesterol transport and its role in non-alcoholic fatty liver disease and atherosclerosis. *Prog Lipid Res, 83*, 101109. doi:10.1016/j.plipres.2021.101109
22. Liang, H., Jiang, F., Cheng, R., Luo, Y., Wang, J., Luo, Z., . . . He, F. (2021). A high-fat diet and high-fat and high-cholesterol diet may affect glucose and lipid metabolism differentially through gut microbiota in mice. *Exp Anim, 70*(1), 73-83. doi:10.1538/expanim.20-0094
23. Liang, Y. T., Chen, J., Jiao, R., Peng, C., Zuo, Y., Lei, L., . . . Chen, Z. Y. (2015). Cholesterol-lowering activity of sesamin is associated with down-regulation on genes of sterol transporters involved in cholesterol absorption. *J Agric Food Chem, 63*(11), 2963-2969. doi:10.1021/jf5063606
24. Louis, P., & Flint, H. J. (2017). Formation of propionate and butyrate by the human colonic microbiota. *Environmental microbiology*, *19*(1), 29-41.
25. Mai, V., Burns, A. M., Solch, R. J., Dennis-Wall, J. C., Ukhanova, M., & Langkamp-Henken, B. (2022). Resistant Maltodextrin Consumption in a Double-Blind, Randomized, Crossover Clinical Trial Induces Specific Changes in Potentially Beneficial Gut Bacteria. *Nutrients*, *14*(11), 2192. https://doi.org/10.3390/nu14112192
26. Marchesi, J. R., Adams, D. H., Fava, F., Hermes, G. D., Hirschfield, G. M., Hold, G., Quraishi, M. N., Kinross, J., Smidt, H., Tuohy, K. M., Thomas, L. V., Zoetendal, E. G., & Hart, A. (2016). The gut microbiota and host health: a new clinical frontier. *Gut*, *65*(2), 330–339. https://doi.org/10.1136/gutjnl-2015-309990
27. Marco, M. L., Sanders, M. E., Gänzle, M., Arrieta, M. C., Cotter, P. D., De Vuyst, L., Hill, C., Holzapfel, W., Lebeer, S., Merenstein, D., Reid, G., Wolfe, B. E., & Hutkins, R. (2021). The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on fermented foods. *Nature reviews. Gastroenterology & hepatology*, *18*(3), 196–208. https://doi.org/10.1038/s41575-020-00390-5
28. Nishimoto, Y., Mizuguchi, Y., Mori, Y., Ito, M., Miyazato, S., Kishimoto, Y., Yamada, T., & Fukuda, S. (2022). Resistant Maltodextrin Intake Reduces Virulent Metabolites in the Gut Environment: A Randomized Control Study in a Japanese Cohort. Frontiers in microbiology, 13, 644146.
29. Nogiec, C. D., & Kasif, S. (2013). To supplement or not to supplement: a metabolic network framework for human nutritional supplements. *PLoS One, 8*(8), e68751. doi:10.1371/journal.pone.0068751
30. O'Callaghan, A., & van Sinderen, D. (2016). Bifidobacteria and Their Role as Members of the Human Gut Microbiota. *Frontiers in microbiology*, *7*, 925. https://doi.org/10.3389/fmicb.2016.00925
31. O'Toole, P. W., Marchesi, J. R., & Hill, C. (2017). Next-generation probiotics: the spectrum from probiotics to live biotherapeutics. *Nature microbiology*, *2*, 17057. https://doi.org/10.1038/nmicrobiol.2017.57
32. Paci, P., Fiscon, G., Conte, F., Wang, R. S., Handy, D. E., Farina, L., & Loscalzo, J. (2022). Comprehensive network medicine-based drug repositioning via integration of therapeutic efficacy and side effects. *NPJ Syst Biol Appl, 8*(1), 12. doi:10.1038/s41540-022-00221-0
33. Pham, V. T., Fehlbaum, S., Seifert, N., Richard, N., Bruins, M. J., Sybesma, W., Rehman, A., & Steinert, R. E. (2021). Effects of colon-targeted vitamins on the composition and metabolic activity of the human gut microbiome- a pilot study. *Gut microbes*, *13*(1), 1–20. https://doi.org/10.1080/19490976.2021.1875774
34. Rashki, M., Ghasemzadeh Rahbardar, M., & Boskabady, M. H. (2025). Nutritional Advantages of Walnut (Juglans regia L.) for Cardiovascular Diseases: A Comprehensive Review. *Food Sci Nutr, 13*(1), e4526. doi:10.1002/fsn3.4526

35. Rondanelli, M., Peroni, G., Riva, A., Petrangolini, G., Allegrini, P., Fazia, T., . . . Perna, S. (2021). Bergamot phytosome improved visceral fat and plasma lipid profiles in overweight and obese class I subject with mild hypercholesterolemia: A randomized placebo controlled trial. *Phytother Res, 35*(4), 2045-2056. doi:10.1002/ptr.6950

36. Rowland, I., Gibson, G., Heinken, A., Scott, K., Swann, J., Thiele, I., & Tuohy, K. (2018). Gut microbiota functions: metabolism of nutrients and other food components. *European journal of nutrition*, *57*(1), 1–24. https://doi.org/10.1007/s00394-017-1445-8

37. Ruiz, L., Delgado, S., Ruas-Madiedo, P., Sánchez, B., & Margolles, A. (2017). Bifidobacteria and Their Molecular Communication with the Immune System. *Frontiers in microbiology*, *8*, 2345. https://doi.org/10.3389/fmicb.2017.02345

38. Sharma, V., Rodionov, D. A., Leyn, S. A., Tran, D., Iablokov, S. N., Ding, H., Peterson, D. A., Osterman, A. L., & Peterson, S. N. (2019). B-Vitamin Sharing Promotes Stability of Gut Microbial Communities. *Frontiers in microbiology*, *10*, 1485. https://doi.org/10.3389/fmicb.2019.01485

39. Su, C. H., Wang, H. L., Tsai, M. L., Lin, Y. C., Liao, J. M., Yen, C. C., . . . Yu, C. H. (2022). Protective effect of microorganism biotransformation-produced resveratrol on the high fat diet-induced hyperlipidemia, hepatic steatosis and synaptic impairment in hamsters. *Int J Med Sci, 19*(10), 1586-1595. doi:10.7150/ijms.59018

40. Teimouri, M., Homayouni-Tabrizi, M., Rajabian, A., Amiri, H., & Hosseini, H. (2022). Anti-inflammatory effects of resveratrol in patients with cardiovascular disease: A systematic review and meta-analysis of randomized controlled trials. *Complement Ther Med, 70*, 102863. doi:10.1016/j.ctim.2022.102863

41. Turroni, F., van Sinderen, D., & Ventura, M. (2009). Bifidobacteria: from ecology to genomics. *Frontiers in bioscience (Landmark edition)*, *14*(12), 4673–4684. https://doi.org/10.2741/3559

42. Wu, Q., Luo, Y., Lu, H., Xie, T., Hu, Z., Chu, Z., & Luo, F. (2024). The Potential Role of Vitamin E and the Mechanism in the Prevention and Treatment of Inflammatory Bowel Disease. *Foods (Basel, Switzerland)*, *13*(6), 898. https://doi.org/10.3390/foods13060898

43. Xu, C., Sun, R., Qiao, X., Xu, C., Shang, X., Niu, W., & Chao, Y. (2014). Effect of vitamin e supplementation on intestinal barrier function in rats exposed to high altitude hypoxia environment. *The Korean journal of physiology & pharmacology : official journal of the Korean Physiological Society and the Korean Society of Pharmacology*, *18*(4), 313–320. https://doi.org/10.4196/kjpp.2014.18.4.313

44. Yang, N.-C., Chou, C.-W., Chen, C.-Y., Hwang, K.-L., & Yang, Y.-C. Y. (2009). Combined nattokinase with red yeast rice but notnattokinase alone has potent effects on blood lipids inhuman subjects with hyperlipidemia. *Asia Pac J Clin Nutr, 18*(3), 310-317. doi:10.3316/ielapa.311419516442451

45. Yuan, R., Yuan, Y., Wang, L., Xin, Q., Wang, Y., Shi, W., . . . and, B. C. (2022). Red Yeast Rice Preparations Reduce Mortality, Major Cardiovascular Adverse Events, and Risk Factors for Metabolic Syndrome: A Systematic Review and Meta-analysis. *Front Pharmacol, 13*, 744928. doi:10.3389/fphar.2022.744928

46. Zou, J., Yan, C., & Wan, J. B. (2022). Red yeast rice ameliorates non-alcoholic fatty liver disease through inhibiting lipid synthesis and NF-kappaB/NLRP3 inflammasome-mediated hepatic inflammation in mice. *Chin Med, 17*(1), 17. doi:10.1186/s13020-022-00573-z