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Modulation of Gut-Brain Axis Improves Microbiome, Metabolism, and Mood

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ABSTRACT

Objective: There is a close bidirectional relationship between overweight/obesity and depression, which may be largely modified through the microbiome and the gut-brain axis. Previous research has shown targeted weight loss effects and anti-depressive benefits of diets high in fiber and phytonutrients and low in sugar and processed foods. Thus, our objective was to determine changes in parameters common to both obesity and depression (e.g., microbiome balance, metabolic biomarkers, and psychological mood state) following a coordinated supplementation regimen combining probiotics, prebiotics, and phytonutrients ("phytobiotics").

Methods: Thirty-three (33) healthy subjects participated in a 6-week supplementation trial (Amare "Project b3") containing a targeted blend of probiotics, prebiotics, and phytobiotics. Microbiome balance was assessed in fecal samples using a novel PCR-based analysis (BiomeTracker) that has previously compared favorably to 16S sequencing. Biomarkers, including blood lipids, glucose, cortisol, and butyrate kinase, were assessed as indicators of effects on cardiovascular, inflammatory, and energy metabolism. Psychological mood state was assessed using the validated Profile of Mood States survey (POMS) to generate scores for Global Mood State and six sub-scales (Depression, Tension, Fatigue, Anger, Confusion, and Vigor).

Results: Following supplementation, there was a significant increase in populations of "good" bacteria (+8% Bifidobacterium, +33% Lactobacillus, +62% S. Thermophilus, +90% Akkermansia) as well as bacterial ratios associated with a healthier "obesity-resistant" metabolism (+6% composite score, -11% Firmicutes, +6% Bacteroidetes, -14% F/B ratio). Metabolites associated with stress and glycemic control improved post-supplementation (-11% cortisol; +89% butyrate kinase, -6% glucose), as did body fat (-2%) and blood lipids (-8% total cholesterol, -5% LDL, +3% HDL, -23% triglycerides, -7% TC/HDL). Psychological indices were significantly improved post-

supplementation for both positive (+17% Global Mood; +23% Vigor) and negative mood states (-38% Depression; -41% Tension; -42% Fatigue; -31% Confusion; -39% Anger).

Conclusions: These results demonstrate the close relationship between microbiome balance, systemic metabolism, and psychological parameters – and the utility of targeted supplementation to optimize gut-brain-axis balance for both improved metabolism and enhanced mental wellness.

Keywords: Obesity; Depression; Anxiety; Stress; Probiotics; Prebiotics; Diet; Supplement

INTRODUCTION

Globally, more than 1.9 billion people struggle with overweight, while depression affects over 350 million people [1]. More than a decade has passed since the initial discovery of the close link between the gut microbiota and obesity [2, 3]. One of the predominant mechanisms underlying the microbiome/obesity relationship is the metabolic endotoxemia hypothesis, whereby an impaired or permeable gut barrier allows translocation of endotoxins from the gut lumen into systemic circulation, thereby leading to low-grade inflammation and metabolic disorders including obesity and diabetes.The gut microbiome is also closely linked to psychological mood states, including depression and anxiety, through multiple communication pathways, including neurotransmitters, the immune system, and the inflammatory cascade via the gut-brain axis [4]. Indeed, a close bi-directional relationship between overweight and depression has repeatedly been established, whereby being overweight increases the risk of developing depression, and having depression increases the risk of becoming overweight [5, 6]. In addition, antidepressant medications often lead to weight gain [7], and dietary restriction for weight loss often exacerbates depression [8].

Probiotics are live micro-organisms that confer health benefits to the host [9], whereas prebiotics are fibers that selectively improve the growth of beneficial gut microbes [10]. An emerging class of functional foods, termed "psychobiotics," encompasses probiotics (bacteria), prebiotics (fibers), and phytobiotics (phytonutrients) that additionally confer psychological benefits related to mood and cognition [11]. A number of recent clinical trials have shown promising weight management benefits of probiotics [12-15] and prebiotics [16, 17], as well as reductions in anxiety and depression with specific probiotic strains [18] and prebiotic fibers [19].

Because many prior studies in this area have examined "diseased" subjects (e.g., those with diagnosed "gut problems" such as irritable bowel syndrome, "metabolic problems" such as obesity or diabetes, or "psychological problems" such as major depressive disorder or generalized anxiety disorder), this study aimed to determine the holistic benefits of a multi-ingredient functional food on microbiome balance, metabolic markers, and mood state in a population of normal weight, "healthy-stressed" adults.

METHODS

Study design

This study was done in accordance with the Helsinki Declaration, as revised in 1983, for clinical research involving humans, and all procedures, measurements, and informed consent processes were reviewed and approved by an external third-party review board (Aspire IRB; Santee, CA).

Thirty-three (33) volunteers, free of prescription medications for depression, anxiety, diabetes, or obesity, signed informed consent documents after the study details were explained. Subjects self-administered the supplements daily (*Project b3*; Amare Global, Irvine, CA) for 6-weeks and were contacted weekly to remind them to take their supplement daily (**Table 1**). The 6-week duration was selected as more representative of persistent changes in mood state that may result from microbiome modulation and superior neurotransmitter balance, as opposed to short-term changes in emotions that may be more closely linked with stressors of daily living. Unfortunately, 6-weeks is often not a sufficient duration of time to observe significant changes in body weight, but since our main objective was not overt weight loss, but rather to assess obesity-related metabolic traits (e.g., microbiome, cholesterol, cortisol, etc.), the 6-week duration was judged to be sufficient to evaluate changes in these aspects of metabolism.

Table 1. Key Bioactive Ingredients in Supplement (*Project b3, Amare Global*)

Ingredient	**Purpose/Effect**	**Supplier**
Lactobacillus helveticus R0052 [20-22]	Serotonin/Depression	Lallemand Health Solutions, Montreal, Canada
Bifidobacterium longum R0175 [22-24]	GABA/Anxiety	Lallemand Health Solutions, Montreal, Canada
Lactobacillus rhamnosus R0011 [20, 25-26]	Cortisol/Stress	Lallemand Health Solutions, Montreal, Canada
Bimuno GOS [27-29]	Microbiome/Resilience	Clasado BioSciences, UK
Sunfiber Guar Gum Galactomannan [30-32]	Microbiome/Resilience	Taiyo, Minneapolis, MN, USA
Suntheanine L-theanine [33-35]	Stress/Tension	Taiyo, Minneapolis, MN, USA
Applephenon Asian Apple Polyphenols [36-38]	Gut-Brain Axis Signaling	BGG, Beijing, China
Enovita French Grape Seed Polyphenols [39-41]	Gut-Brain Axis Signaling	Indena, Milan, Italy
Enzogenol New Zealand Pine Bark Polyphenols [42-44]	Gut-Brain Axis Signaling	Enzo, Auckland, New Zealand
Pomma+ Pomegranate Extract [45-47]	Brain Activation	Stauber, Fullerton, CA, USA
ProDigest Artichoke Leaf Extract plus Ginger Root Extract [48-50]	Gut Motility	Indena, Milan, Italy

Wellmune Baker's Yeast Beta 1,3/1,6 Glucan [51-53]	Immune Priming	Kerry Group, Tralee, Ireland
MycoFusions high-polyphenol purple mushrooms (Maitake, Shiitake, Agaricus, Chaga) [54-56]	Immune Priming	NutraGenesis, Brattleboro, VT, USA
FucoMax Fucoidan [57-59]	Gut integrity	BGG, Beijing, China
Calcium/Magnesium Butyrate (short-chain fatty acid) [60-62]	Gut integrity	Phoenix Formulations, Tempe, AZ
Zinc Carnosine Complex [63-65]	Gut integrity	Phoenix Formulations, Tempe, AZ
Artesa Chickpea Protein [66-68]	Gut Integrity	PLT Health, Morristown, NJ
ETAS Japanese Asparagus Extract [69-71]	Stress / Heat Shock Proteins	AminoUp, Sapporo, Japan
AHCC Shiitake Mycelia Extract [72-74]	Anxiety / microRNA Signaling	AminoUp, Sapporo, Japan

Dietary supplement

All subjects consumed one serving daily of a natural multi-ingredient targeted mental wellness supplement regimen (*Project b3*, Amare Global, Irvine, CA, USA) containing probiotic bacteria, prebiotic fibers, and phytobiotic plant extracts and phytonutrients (**Table 1**). In recognition of the recently demonstrated strain-specific benefits of probiotics and structure-specific benefits of prebiotics, the Supplement contained research-validated bacterial strains (e.g., Lactobacillus helveticus R0052 for serotonin/depression; Bifidobacterium longum R0175 for GABA/anxiety; and Lactobacillus rhamnosus R0011 for cortisol/stress); clinically-proven prebiotic fibers (galactooligosaccharides, GOS, Bimuno, Clasado BioSciences, UK; and galactomannan, partially hydrolyzed guar gum, PHGG, Sunfiber, Taiyo International, Minneapolis, MN USA); and selected nutrients with demonstrated mental wellness functional benefits across the gut-brain-axis, including L-theanine (Suntheanine, Taiyo International); Asian Apple Polyphenols (Applephenon, BGG, Beijing, China); French Grape Seed Polyphenols (Enovita, Indena, Milan, Italy); New Zealand Pine Bark Polyphenols (Enzogenol, Enzo, Auckland, New Zealand); Artichoke Leaf Extract plus Ginger Root Extract (ProDigest, Indena, Milan, Italy); Chickpea protein (Artesa, PLT Health, Morristown, NJ); Japanese Asparagus extract (ETAS, AminoUp, Sapporo, Japan); and Shiitake mushroom mycelia (AHCC, AminoUp, Sapporo, Japan).

Microbiome Assessment

Microbiome analysis of fecal samples was carried out using the complete *BiomeTracker* system (Wasatch Scientific, Murray, UT). Briefly, fecal samples were obtained by nylon swab and placed

into a preservative binding buffer to lock the composition of bacteria in place. DNA was then purified by following the recommended procedure and using the provided DNA columns. Reaction mixtures were set up as recommended with the components provided (WS#1- WS#8), and ~20ng of DNA from each sample was added to the reaction mixtures. Samples were processed using the recommended conditions on an ABI 7500 Fast (Applied Biosystems) instrument in duplicate. Threshold values were input into the normalization/quantification template provided.

Metabolic Assessments

Lipid Profile (including total cholesterol/TC, low-density lipoproteins/LDL, high-density lipoproteins/HDL, TC/HDL ratio) and blood glucose were assessed by fingerstick with all subjects in an overnight fasted condition (Cholestech LDX Analyzer, Abbott/Alere, Charlottesville, VA). Cortisol was measured as free cortisol in first-morning saliva samples (Salimetrics, Carlsbad, CA). Body fat percentage was assessed by bioelectrical impedance analysis (BIA) in a fasted condition before and after 6-weeks of supplementation (InBody, Seoul, South Korea).

Psychological Mood Assessment

We employed the Profile of Mood States (POMS) questionnaire to measure six primary psychological factors (tension, depression, anger, fatigue, vigor, or confusion) plus the combined global mood state as an indication of subjective well-being. The POMS methodology has been used in ~3,000 studies, and its validity is well established [75]. The POMS profile uses 65 adjective-based intensity scales scored on a 0–4 hedonic scale (e.g., “not at all” to “extremely”). The 65 adjective responses are categorized into the six mood factors (tension, depression, anger, fatigue, vigor, or confusion), tabulated, scored, and analyzed. The output of the POMS questionnaire is an assessment of the positive and negative moods of each subject at baseline and post-supplementation (6 weeks).

Data Management and Analysis

All questionnaires were collected and stored in a central location and transcribed to a central database. Data were identified by subject number and examined for accuracy and completeness. Tabulated data were analyzed with JMP 14.0 (SAS Institute, Cary, NC) using standard parametric paired t-tests, and significance was assessed with a 2-tailed alpha level set at 0.05.

RESULTS

Body Composition

As expected, following the short 6-weeks of dietary supplementation, with no major alterations in dietary intake or physical activity patterns, there was no significant change in average body weight (~176 lbs) or muscle mass (~71 lbs), but there was a surprising and meaningful drop of 2% in total body fat levels from 27% to 25% ($p<0.05$; **Figure 1**).

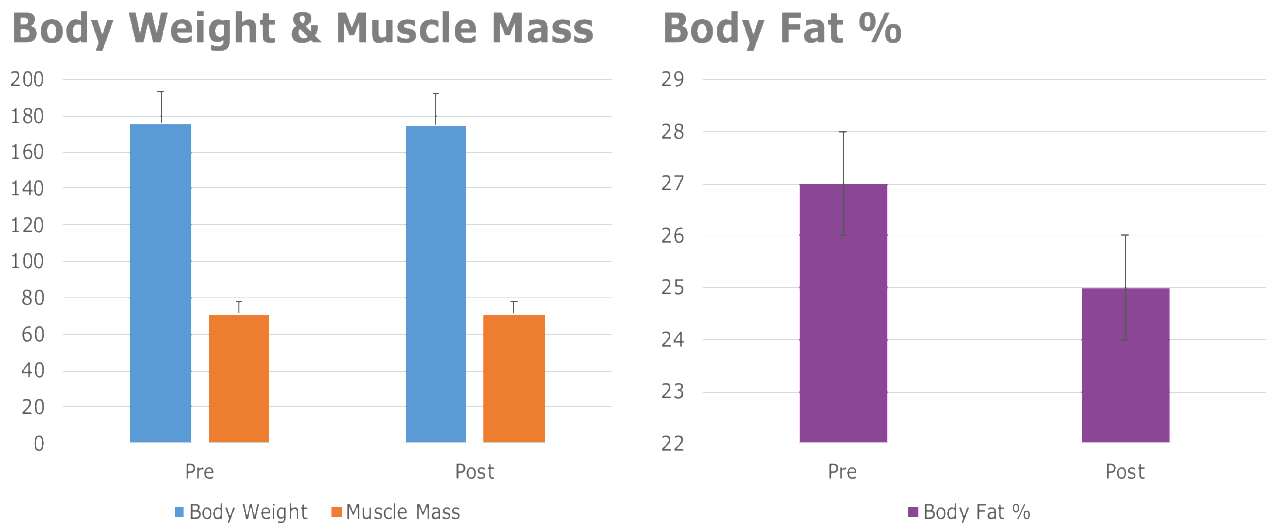

Figure 1. Body Composition

Microbiome Balance

Following 6 weeks of dietary supplementation, there was a significant increase (relative units) in populations of "good" bacteria (+8% Bifidobacterium, +33% Lactobacillus, +62% S. Thermophilus, +90% Akkermansia; all $p<0.05$; **Figure 2A**) as well as bacterial ratios associated with metabolism (+6% composite score, -11% Firmicutes, +6% Bacteroidetes, -14% F/B ratio, all $p<0.05$; **Figure 2B**).

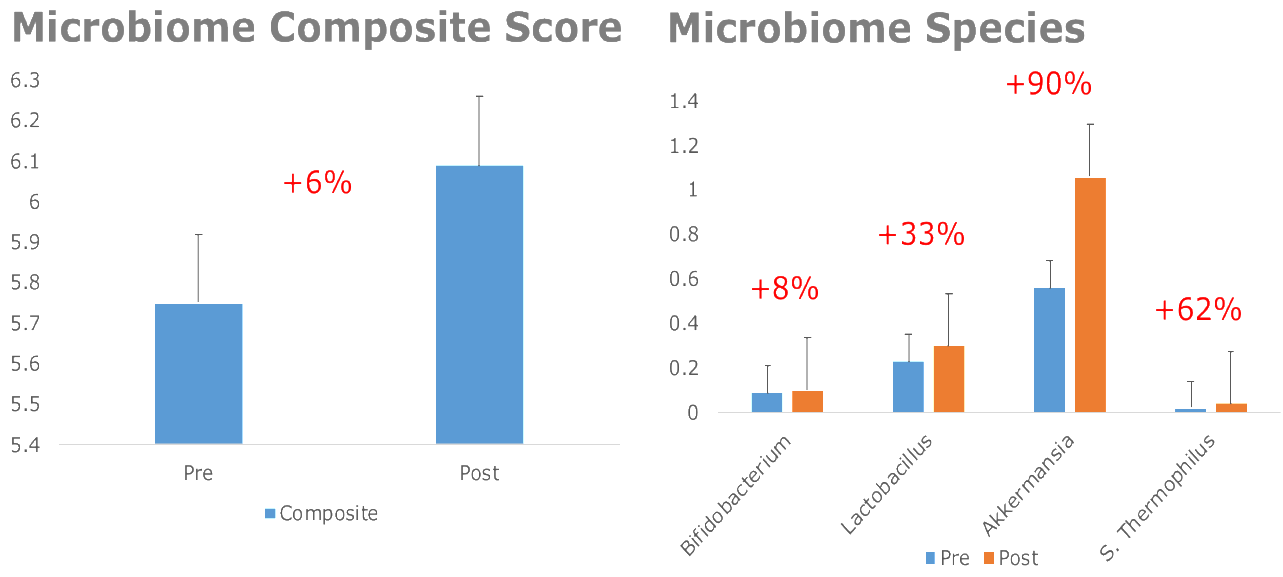

Figure 2A. Microbiome Composition

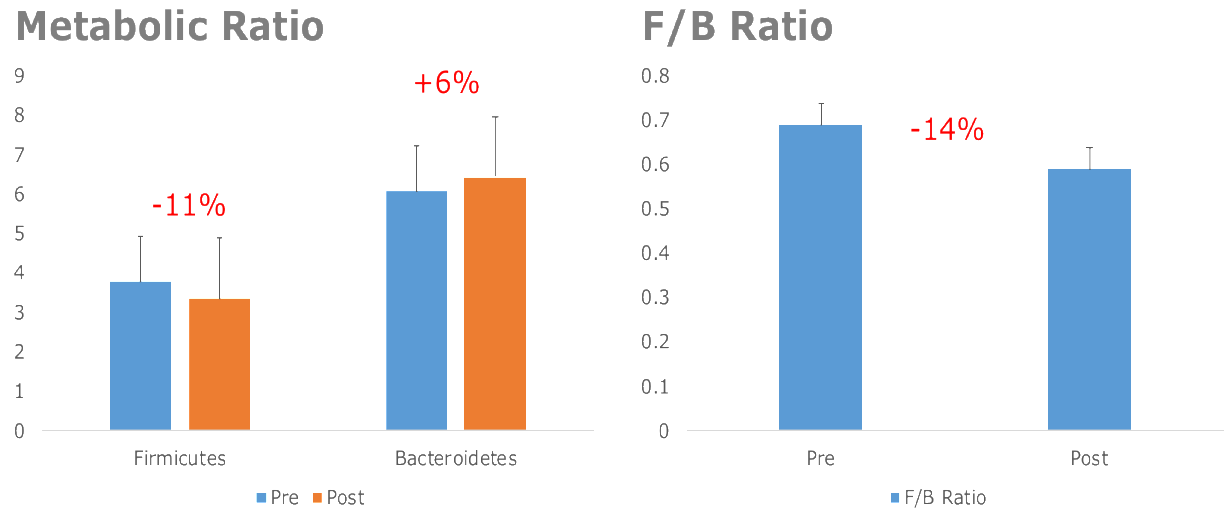

Figure 2B. Microbiome Composition

Metabolic and Cardiovascular Parameters

Post-supplementation improvements were observed for a variety of metabolites associated with stress, inflammation, and glycemic control (-11% cortisol (ng/dl), +89% butyrate kinase, -6% glucose (mg/dl), all $p<0.05$; **Figure 3A**), and for blood lipids (-8% total cholesterol (mg/dl), -5% LDL (mg/dl), -23% triglycerides (mg/dl), all $p<0.05$; **Figure 3B**). The promising 3% improvement in HDL cholesterol did not reach statistical significance, but that fact that HDL was maintained helped to improve the cardiac risk profile (TC/HDL, $p<0.05$; **Figure 3B**).

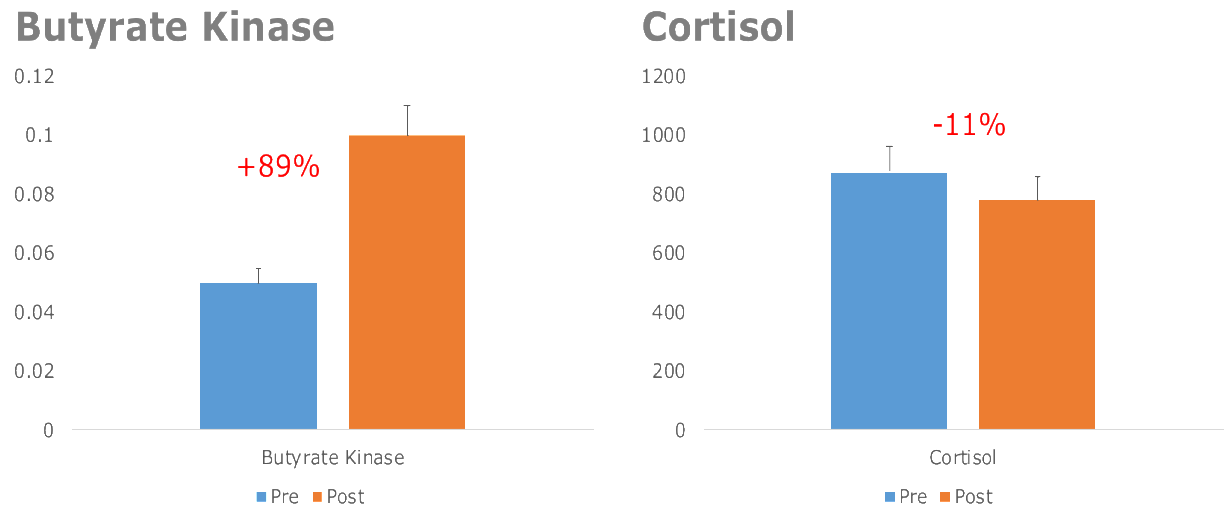

Figure 3A. Metabolic Parameters

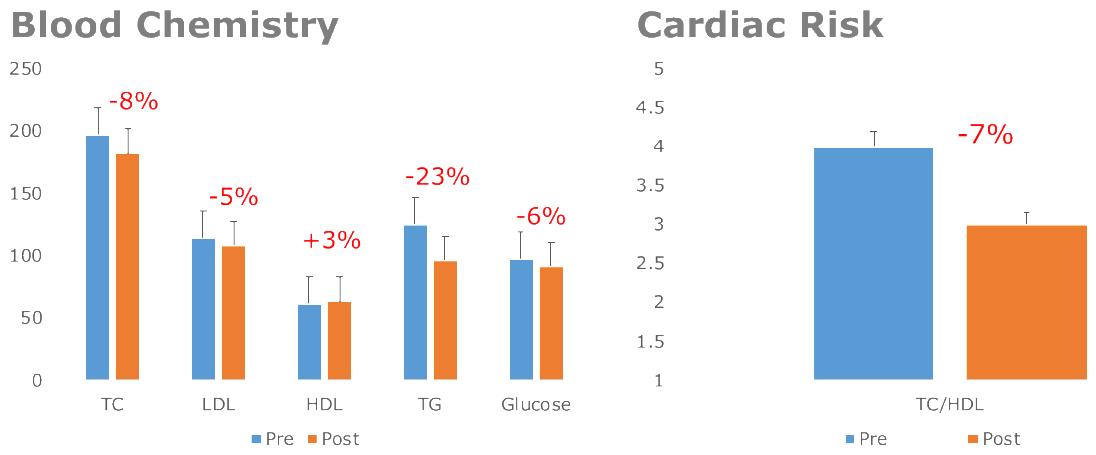

Figure 3B. Cardiovascular Parameters

Psychological Mood State

Psychological indices were significantly improved (all $p<0.05$) post-supplementation for both positive (+17% Global Mood; +23% Vigor) and negative mood states (-38% Depression; -41% Tension; -42% Fatigue; -31% Confusion; -39% Anger; **Figure 4**).

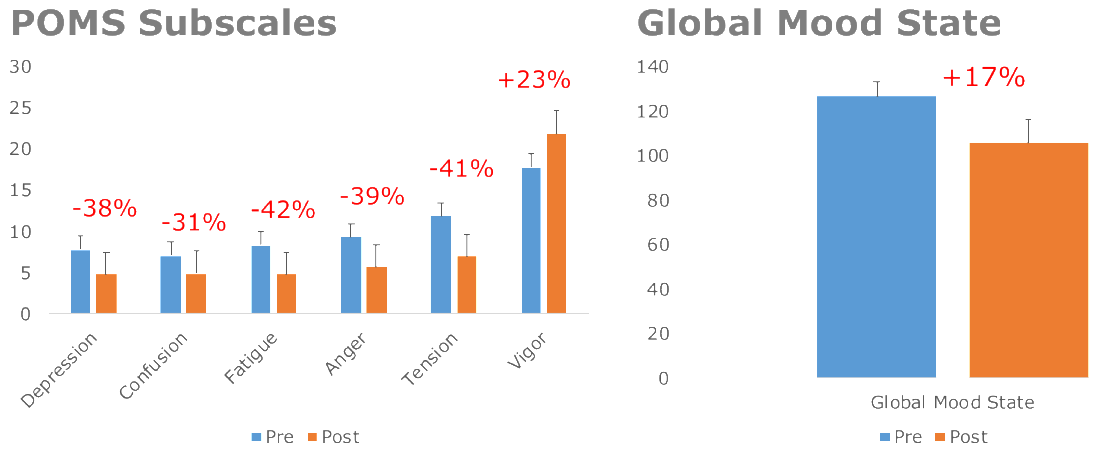

Figure 4. Psychological Mood States

DISCUSSION

The novelty of the current study is its combination of a number of previously-researched natural ingredients to positively and holistically influence the entire gut-brain axis (gut/microbiome; brain/mood; axis/metabolites) in a population of healthy-stressed subjects. Our subjects represent perhaps the largest subset of the American population who routinely complain of symptoms related to high stress, day-time fatigue, night-time restlessness, low mood, suppressed libido, brain fog, lack of enjoyment (anhedonia/burnout), and general malaise. Such individuals are poor candidates for prescription medications intended for severe disease states such as major depressive disorder

and generalized anxiety disorders (and their wide range of attendant side effects). As such, there is a pressing need for natural functional food approaches to improve psychological mood state – and the emerging understanding of the gut-brain axis in modulating mental wellness represents a promising non-drug approach to help people feel better.

Obesity increases the risk of multiple co-morbidities, including cardiovascular disease, diabetes, hypertension, depression/anxiety, and several cancers, and carries an associated reduction in predicted lifespan. While full obesity reversal is often impractical, even modest, sustained weight loss of ~5% reduces morbidity and mortality risk.

Potential benefits of gut-brain axis modulation for enhancing weight loss and/or improving mood are often confounded by the multi-factorial nature of each condition, as well as by the disparate nature of different probiotic strains (e.g., single or multi-strain formulation); structure of prebiotic fibers (e.g., preferential usage by certain bacterial species); supplementation dose; and duration of intervention, among others. Nevertheless, a number of recent meta-analyses have reported on dozens of clinical trials across thousands of individuals showing an overall positive benefit of microbiome modulation for weight loss [76-79] and mood improvement [80, 81].

The anti-obesity and anti-depressive activity of gut-brain-axis interventions may be associated with their ability to alter both the structure and function of the microbiome (and associated metabolites including neurotransmitters, hormones, cytokines, short-chain fatty acids, etc.); remodeling of energy metabolism; modulation of gene expression related to appetite and thermogenesis; glucose homeostasis; lipid metabolism; and attenuation of HPA axis activity, among others [76]. The brain sends a variety of signals to the gut via efferent vagal and neuroendocrine pathways, including serotonin, dopamine, and GABA that can modify the intestinal environment, including mucus secretion, immune responses, gut motility, and intestinal barrier function – each of which can influence microbial composition and function [79]. Similarly, the gut sends a variety of signals to the brain via afferent vagal pathways and a wide variety of blood-borne substances (e.g., ~70-95% of the body's serotonin and dopamine are gut-derived) including numerous bioactive molecules involved in appetite and energy balance (e.g., peptide YY, glucagon-like peptide-1, cholecystokinin, and ghrelin) [79].

The two largest phyla making up the gut microbiome in humans are Firmicutes and Bacteroidetes, representing ~90% of all gut microbiota. The relationship between these two large groups, expressed as the Firmicutes/Bacteroidetes (F/B) ratio, has been associated with a number of pathological conditions, including obesity, type 2 diabetes, systemic inflammation, and depression (specifically a greater abundance of Firmicutes and/or a drop in Bacteroidetes, thus an increase in the F/B ratio). A number of studies have shown that obese populations tend to have a significantly higher level of *Firmicutes* and a significantly lower level of *Bacteroidetes* compared to normal-weight and lean adults [2, 3, 82-84]. Recent interventional trials have shown that the administration of Lactobacillus and Bifidobacterium species can reestablish the F/B ratio and inflammatory tone, thus potentially affecting both mood disorders and obesity through the common gut-brain axis pathways [85, 86].

Highly processed Western-style diets, typically high in fat and sugar and low in fiber and micronutrients, have long been associated with inflammatory diseases, including obesity, diabetes, and depression. Public health recommendations to increase fiber intake, reduce processed food consumption, and increase whole food intake have a positive impact on gut health by stimulating

the growth and activity of beneficial gut bacteria [87]. In traditional hunter-gatherer societies, high fiber intakes of 50-150 g/day yield a much more diverse gut microbiota with higher colonization by beneficial bacterial species (e.g., Lactobacillus, Bifidobacterium, and Prevotella) and corresponding metabolite richness with higher SCFA production that are associated with lower levels of systemic inflammation [87].

A recent 6-month trial has shown that treatment with a probiotic supplement (10B CFU B. lactis B420), alone or in combination with a prebiotic fiber (12g Litesse Ultra polydextrose), controlled body fat mass, trunk fat mass, and waist circumference, and reduced energy intake in overweight adults [88, 89]. The B420 strain increases the relative abundance of *Akkermansia muciniphila* in the gut microbiota, a bacterium linked with improved metabolic health and anti-inflammatory properties. The relative change in body fat mass over six months was -3.0% with the probiotic alone, and -4.5% with the synbiotic combination of probiotic + prebiotic, which compares favorably with pharmaceutical interventions, in which 3-5% body weight changes are typically observed for 6-month treatment (e.g., orlistat/Alli/Xenical, liraglutide/Victoza, lorcaserin/Belviq). Reduced energy intake has been observed with supplementation of B420 alone (-300kcal/day) or in combination with polydextrose (-210 kcal/day), possibly related to the observed increase in microbiome-derived short-chain fatty acids [90]. Unfortunately, the 6-month intervention timeframe, while delivering promising benefits for subjects who successfully complete the full-duration of intervention, is often plagued by poor subject compliance (e.g., ~40% drop out rate), possibly due to the close association between obesity and depression.

One shorter study showed that 4-months of supplementation with Lactobacillus gasseri BNR17 significantly reduced visceral adipose tissue and waist circumference in obese adults [90], while another 4-month supplementation with Lactobacillus rhamnosus CGMCC1.3724, combined with probiotics (inulin and oligofructose), reduced both body weight and hunger scores in obese women [12].

The present study, investigating a very short 1.5-months (6-weeks) of supplementation with targeted probiotic strains, matched prebiotic fibers, and a blend of research-validated phytonutrients targeting gut-brain-axis modulation, showed meaningful improvements in both microbiome structure (bacterial abundance) and function (metabolic activity), as well as positive changes in parameters associated with both physical health (body fat percentage, blood lipids/glucose, and cortisol exposure) and mental health (reduced negative mood states and enhanced positive mood states).

CONCLUSIONS

The World Health Organization has identified both metabolic issues (e.g., diabetes/obesity) and psychological issues (e.g., depression/anxiety/stress) as urgent public health epidemics threatening global well-being and increasing global health burden. These results demonstrate the close relationship between microbiome balance and both physical and mental health. Importantly, these results also describe the effectiveness of multi-factorial targeted supplementation to positively influence the gut-brain axis for simultaneously improving mental wellness and physical health – owing in large part to the close bi-directional connections across the gut-brain axis and the long-observed associations between obesity and depression.

List of abbreviations: gamma-Aminobutyric acid (GABA), Polymerase chain reaction (PCR), Profile of Mood States survey (POMS), Short-chain fatty acids (SCFAs), galactooligosaccharide (GOS), isomaltooligosaccharide (IMO).

Competing interests: S.M.T. is an employee of Amare Global, the producer of the Project b3 dietary supplements.

Authors' contributions: S.M.T. designed the research protocol. J.A.T. coordinated the IRB submission, subject recruitment, and study monitoring. B.J.S. and M.J.O. performed and oversaw the microbiome assessments. All authors were involved in the preparation and presentation of these data.

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