200 Person Double-Blinded Placebo-Controlled Study of Equilibrium Brand Probiotic

Abstract

This study describes the results from a randomized, double-blinded placebo controlled trial of the effectiveness and side effect profile of General Biotics' Equilibrium probiotic in 200 healthy adult US residents of age 18 and older. Reported side effects for Equilibrium were indistinguishable from the placebo group, while stool composition was statistically distinct from the placebo (p 0.02) and moved significantly closer to the ideal Bristol Stool Scale value (within 0.5 standard deviations). The study was internally funded.

Introduction

Microbes

Although microbes have been with us since the dawn of time, and methods for preserving food and treating wounds predate recorded history, humanity's intellectual relationship with the microbial world begins with Anton van Leeuwenhoek's 1660 discovery that microbes, transferred via unwashed hands, were a leading cause of mortality in hospitals. Understandably, the relation between microbes and morbidity and mortality received the majority of scientific study in the centuries that followed. Some beneficial applications of microbes were discovered, but primarily through indirect applications, for example harvesting microbially produced poisons (antibiotics) for use in killing other microbes. Sterilization, as much as it was possible, was viewed as a medical necessity.

The only industries which viewed microbes as potentially beneficial were the cheese and yogurt industries, whose methods, coincidentally, predate van Leeuwenhoek's work. This attracted Eli Metchnikoff's interest, whose work resulted in the creation of lactobacillus containing probiotics as well as other microbial discoveries, for which he received a Nobel prize in 1908. Even more recently, as microbial growth abilities have improved and sequencing methods have decreased in cost, the scientific community has come to understand that the microbes which cause disease in humans, $\approx 100,000$ strains, make up less than a millionth of the total microbial strains (estimated at more than 100,000,000,000,000,000). Most microbes act in ways unrelated to human interests, and microbes vastly outnumber plants at the bottom of every food chain.

Human Microbiome

Microbes inhabit skin, digestive systems, reproductive systems, etc. Almost every bodily system is a result of symbiosis with these microbes. The ecosystem that is the human body, and the community of microbes that live in it, is called the Human Microbiome. It's an area of research that's advancing at a tremendous pace, with study after study showing new links between behavior, health, and microbes. It is within this extremely modern understanding of the role of microbes that General Biotics' Equilibrium makes sense: it takes the position that microbes common in rural diets should be judged "innocent until proven guilty" -that even if the precise nature of their mechanism of action is unknown, the safe bet is to include them in your diet. It is a collection of 115 digestive strains, and is the most microbially diverse probiotic in the world.

The make-up of this microbiome, both across persons and throughout the body, is determined by many factors. New microbes come from the sources one might expect: every lungful of air, each bite of food, every surface contact. These introduced microbes can have significant geographic variation. A fundamental organizing fact determining colonization outcomes is that microbes have generation times between 20 minutes and several days. In this way fast growers can colonize swiftly, but are sometimes out-competed by slower growers after establishment. This can lead to an ecological process called "succession" when bacteria colonize humans. Another issue affecting microbial makeup is that microbes can require other microbes in their ecosystem, leading to complex dynamics. As a person shifts geographic regions, the mismatch between the host's microbiome and the surrounding environment's can potentially lead to large scale conflict that can cause traveler's diarrhea and other unfortunate outcomes. Individual behavior also have a tremendous effect

on the microbiome. Showering, antibiotic treatments, and chlorinated water put strong, and sometimes unfortunate, selection pressure on the microbiome. Dietary choices, skin care products, and myriad other factors all drastically shift the nutrients and local environment of the microbes. One of the most dramatic examples of behavioral selection comes from the work of Prof. Knight et al. at Univ. of Colorado, where microbes that live on human hands were studied. The study showed that the similarities between the ecosystems of right and left hands were only 18%, and the preliminary data suggests that this is due to handedness (Fierer et al., 2008). Across the body microbiome densities and makeups shift, if the armpit is a swamp, then the back might be a desert, and just as in the larger environments, the species and population densities between the two are not interchangeable. In humans, age also becomes a factor, gradually shifting the nutrients and support the body provides to its microbiome. Massive microbial drop-off is common as people near retirement age.

Gut Microbiome

Microbes are a fundamental part of digestion. In fact, the digestive system contains the largest population of microbes in the human body. Like the immune system, it evolved to interact with organisms that evolve on shorter timespans than humans. By partnering with bacteria the stomach can rapidly adapt to new foods and changing diets. Microbes are required to fully digest most foods. A healthy gut microbiome also serves as the first line of defense for the immune system. When properly functioning, it competitively excludes pathogens like Clostridium difficile.

This microbiome also provides feedback to its host. The gastrointestinal tract contains the enteric nervous system, capable of releasing serotonin, dopamine and other psychologically active signaling chemicals. Microbially mediated release of these neurotransmitters is one of the causal mechanisms that serves as a link between the gut microbiome and the host's happiness and stress levels. The gut's ecosystem is so complex that many scientists have come to think of it as an organ.

In a natural environment (our ancestral one) there is a constant influx of microbes already beginning to digest consumed food. In the modern world, these microbes have been sterilized away. Fruits, vegetables, meats, nuts, grains – almost all food – is microbially unrecognizable from our ancestors'. The digestive tract did not evolve in this environment. Healthy digestion is powered by a complex ecosystem of over 50 trillion microbial cells from 1,500 different strains. On average, modern humans have less than half as many digestive strains as their ancestors. Traditional probiotics don't provide the missing strains. Most probiotics are simply large doses of the yeasts used to make bread, and the bacteria used to make yogurt. These aren't the strains missing from our diets. Until recently there was little that could be done. Sterilization is a necessity until better farming techniques can be found; it's the best known method to protect against food-borne illness. And, until quite recently, scientific opinion basically agreed with this assessment without reservation, as there was very little understanding that microbes could be anything other than pathogens. Now, however, the consensus is that the behavior of the human body depends on microbes.

Having a properly functioning gut microbiome is similar to getting enough sleep – many systems rely on it in complex, still unexplained ways, and it's known to be necessary by observing the effects of its loss (or dysfunction), but the details of why are still hard to tease out with current scientific tools. Below is a list of a few of the ongoing areas of study and the known results.

Allergies and the Immune System An estimated 50 million Americans suffer from allergies, which occur when the immune system becomes hypersensitive and reacts against otherwise harmless substances. Heredity and other factors have long been known, but current research suggests that childhood allergy development is related to the child's microbiota. Sjogren (2009) found that children colonized during their first 2 months with Lactobacilli Group I are less likely to develop allergies. Johansson et al. (2011), in their follow up study, found that inheritable factors for allergies can have an effect on the gut microbiome, but it is not the only factor on the risk of allergy. Early Lactobacilli (L. casei, L. paracasei, L. rhamnosus) colonization also seems to decrease the risk for allergy at five years of age despite allergic heredity. Stefka et al. (2014) have results that suggest that antibiotic-related microbiome depletion contributed to the 18% increase in food allergies among children in the United States between 1997 and 2007.

Rheumatoid Arthritis RA is a chronic, disabling, currently incurable and poorly understood autoimmune disease. There is new evidence that suggests that the microbiome plays an important part in this, with both a certain fungus and a certain bacterium identified as triggers for this disease in mouse models. The current view suggests that the presence of a particular microbiome can trigger the disease in genetically predisposed individuals (Scher and Steven 2011).

Alzheimer's This area is under active investigation, so the connections aren't completely clear. But the early evidence suggests that the microbiome might be one of the factors involved in Alzheimer's. Furthermore, some reviews suggest the possibility of a microbiome-based therapy (Forsythe et al. 2012 and Collins et al. 2013, Bhattacharjee et al. 2013, Hill et al. 2014)

Depression Another important link exists between microbes and clinical depressive episodes. Microbes seem to influence the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Messaoudi et al (2011) did experiments on human volunteers that suggest that a probiotic can reduce depression and psychological distress, among other effects.

Memory In 2014, Melanie Gareau conducted a review of studies on mouse and human cognitive function. One of those studies showed that mice without microbes had impaired memory. They ran an experiment in which they had: mice without microbes not subjected to stress, mice without microbes subjected to stress, mice infected with a pathogenic microbe not subjected to stress, mice infected with a pathogenic microbe subjected to stress, mice without microbes had impaired memory formation, regardless of stress. Mice infected with a pathogen not subjected to stress did not show behavioral anomalies. But, mice infected with a pathogenic microbe subjected to stress had memory dysfunctions 10 and 30 days after infection. Daily probiotic treatment of these mice restored their brain function. Another remarkable result is the fact that the mice treated with probiotic not only had their memory function restored, but also had a decreased swelling of cells, compared to mice infected and stressed but not treated with probiotics. (Gareau et al. 2014)

Clostridium difficile (C. difficile) infections Many healthy individuals have C. difficile in their stomachs. When the digestive ecosystem is healthy, C. difficile has a lot of competition. When the digestive ecosystem is destabilized (for example, through antibiotic treatment), C. difficile can grow to take over your stomach leading to copious diarrhea and, in 10% of cases, death. This happens because C. difficile is resistant to modern antibiotics. The two best antibiotics for the treatment of C. difficile are vancomycin and fidaxomicin. Treatment has a success rate of around 75%; fidaxomicin is designed specifically for C. difficile, but it is quite expensive and not typically the first line treatment. It is also not fully clear that it is the best option (Bartsch et al. 2013).

Intriguingly, there is also a microbial treatment: recolonizing weakened gut flora with the gut flora of a healthy donor. It's called FMT (fecal microbiota transplant). The treatment is economical and effective $^{79-90\%}$ of the time (Rubin et al. 2013, Bakken et al. 2013, Rohlke & Stollman 2012).

Crohn's Disease One of the two leading causes of inflammatory bowel disease, which causes severe diarrhea, fatigue, and weight loss. The current view is that it seems likely that the microbiome might be a marker for Crohn's disease (Erickson et al. 2012), and, furthermore, it is also suspected to be a causal factor in at least some of the cases. The effect of the microbiota on Crohn's is potentially mediated by the immune system. However, research on the relationship between Crohn's and the microbiome is still preliminary, but suggests that Crohn's disease associated microbiomes are less diverse.

Ulcerative Colitis Children with severe ulcerative colitis, the other leading cause of inflammatory bowel disease, have less diverse gut microbiomes than their healthy counterparts (Michail et al. 2012).

Colon Cancer Current understanding suggests that the gut microbiome might be a marker of the presence of colon cancer (Zackular et al. 2013, Baxter et al. 2014). In particular, Fusobacterium has been implicated as being present in colon carcinomas, while at the same time Bacteriodetes and Firmicutes are depleted

(Kostic et al. 2012). Whether the microbiome is a causal agent or one of the factors in colon cancer is something on which there is no clear consensus yet. A review paper by Tjalsma et al (2012) proposes a model for the effect of the microbiome in the development of colorectal cancer.

Kwashiorkor Kwashiorkor is a form of acute malnutrition, and it seems to be caused by environmental factors and a lack of protein in the diet. Recently, the team of Prof. Gordon at WUSTL established that the microbiome is one of the causal factors in this disease. It is not the only factor, but it is one of them rather than just a marker of the disease (Smith et al. 2013). A combination of Malawian diet and kwashiorkor microbiome was shown to lead to significant weight loss in recipient mice.

Obesity and metabolic syndrome Obesity/metabolic syndrome is a cluster of multiple conditions coming together to increase the risk of associated complications (such as diabetes, heart disease and stroke), and it's a complicated condition. One of the first results in this field was the association of a lean microbiome with lean mice and an obese microbiome with obese mice. At first, it seemed like they were clearly different. and transplanting them would make the obese mice become lean (Turnbaugh, 2006) and, if translatable to humans, solve the problem. They also found a relative abundance of Firmicutes and a relative scarcity of Bacteriodetes in obese mice when compared to lean mice (Ley et a., 2005, Ley et al. 2006), and suggested that manipulating the microbial community would allow regulation of the energy balance in obese humans. Later, Schwiertz et al. (2010) found that there were plenty of Bacteriodetes in overweight people. One thing that they agreed with in Gordon's previous work was the role of short chain fatty acids in the microbiota of obese people (they tend to have more of the short chain fatty acid metabolism). A follow up study by Jumpertz et al. (2011), looked at the diet of both obese and lean people. This study employed two groups, one made of lean people eating 2,400 calories per day and another of obese people eating 3,500 calories per day. When people ate a weight-maintining diet (2,400 calories per day), no differences in the bacterial abundance could be found between the lean and obese group. For the group on the 2,400 calories diet, their Firmicutes became more abundant to increase the energy intake. The group of obese people did not exhibit any clear-cut pattern. This could have been due to the small group size, underlying genetic factors, or something else. Another interesting study is the one by Vijay-Kumar et al. (2010). They used a special type of mouse that lacks the ability to recognize TLR-5, and this seems to result in something that resembles human metabolic syndrome (Vijay-Kumar et al. 2010). "These metabolic changes correlated with changes in the composition of the gut microbiota, and transfer of the gut microbiota from TLR5-deficient mice to wild-type germ-free mice conferred many features of metabolic syndrome to the recipients. Food restriction prevented obesity, but not insulin resistance, in the TLR5-deficient mice. These results support the emerging view that the gut microbiota contributes to metabolic disease and suggest that malfunction of the innate immune system may promote the development of metabolic syndrome." (Vijay-Kumar et al. 2010)

Parkinson's Disease This disease is one of the world's most common debilitating brain disorders. It is degenerative and largely affects the motor system. Researchers have found a functional link between gut microbiomes and the onset of the disease. Upon transplant of Parkinson's microbiome and healthy microbiomes to germ-free mice, those that received the Parkinson's microbiome began to show symptoms of the disease. The Parkinson's microbiome also has several features differentiating it from the healthy microbiomes (Sampson et al. 2016).

Scope of Study

This study was performed by General Biotics, GB, to determine the effects of the Equilibrium probiotic relative to a placebo in a 200 person group. It was a randomized, controlled study using volunteers from across the USA. The primary performance parameter under study was the effect of the probiotic on the Bristol stool number that participants reported both while on the study, and for 3 days afterwards. In addition to this, GB, wished to determine the extent of side effects caused by the probiotic relative to the placebo. This was monitored by asking participants questions about their appetite, energy level, alertness, and happiness, as well as any straightforward symptoms of digestive distress. The methods, results, and conclusions of the study are detailed below.

Methods

- 1. Enrollment survey: Potential participants were required to fill out an informational survey contained in Appendix A. In exchange for participation, they were promised 1 free bottle of Equilibrium after the end of the study. Potential participants were screened for immune deficiencies, and, if found to exist, were removed from the pool. Potentials were also removed due to incomplete or invalid information. The first 200, who were not invalidated, were selected to participate.
- 2. Seven pills containing either a probiotic or a placebo were sent to study participants along with an email congratulating them on their selection for the study. Both email and package contained instructions on how to take the pills. Specifically, participants were asked to fill out an online survey for 4 days prior to taking the pills, 7 days on the pills, and 3 days after the pills were finished.
- 3. Daily survey: Participants were required to fill out a survey covering their physical (focusing on the gut) and mental health each day (Appendix B). They were also told to record whether or not they were compliant with protocol, in taking the study pill.

Results and Analysis

- 1. After the daily surveys were completed, they were reviewed and any that had unintelligible data were discarded. After that, the individual responses were separated into probiotic and placebo categories, and the daily averages were taken. The daily averages for Equilibrium and the placebo were averaged across all days taking a pill, resulting in average values of 4.2 for Equilibrium and 3.3 for the placebo. Assuming the placebo to be the null hypothesis, a p-value of 0.02 was found for Equilibrium. A smoothed daily timeline of Equilibrium and the placebo is shown in figure 1. The timeline clearly shows the convergence of both plots after the daily regimen has reached an end. Finally, we present a Bristol Stool Scale in figure 2where the average data mentioned above is presented in the context of the stool index, so that end users can better understand where they lie on the scale, and what ideal stool should look like. The placebo was found to be 1.5 standard deviations from the Bristol Stool Scale ideal, while Equilibrium probiotic was 0.5 standard deviations away.
- 2. The daily averages for Equilibrium and the placebo across four distinct dimensions of physical and mental health and well-being: stress, happiness, alertness, and food cravings, were averaged across all days taking a pill. These were measured on a scale of 1 to 7, with 1 meaning not very stressed, happy, etc. and 7 meaning extremely stressed, happy, etc. Assuming the placebo to be the null hypothesis, p-values of 0.3, 0.2, 0.4, and 0.3 were found for Equilibrium across the previously stated dimensions. Thus, there is no significant difference in side effects between placebo and probiotic groups.
- 3. The number of daily reports of symptoms of digestive upset between Equilibrium, 72, and the placebo, 79, were within 10% of each other, further strengthening the case that there is no significant difference in side effects between the two groups.

Conclusions

Gut microbiome health is an important component of a person's overall health. This study demonstrated that the Equilibrium probiotic had effects that were distinct from a placebo and moved the average stool consistency closer to the ideal on the Bristol Stool Scale using a randomly-selected set of volunteers from the USA. In addition, these results showed that there was no statistically-relevant difference between side effects reported by placebo users versus probiotic users.



Figure 1: Bristol Stool Scale Timeline for Equilibrium and Placebo

200 Person Placebo-Controlled Product Study Results on Bristol Stool Scale



Figure 2: Pictorial Bristol Stool Scale with Average Values for Equilibrium and Placebo

Appendix A: Enrollment Survey for Probiotic Study

Step 1 of 3: Digestive Health

The first step is for you to answer a few questions about your digestive health (and your age/gender), so we can do better science with your data.

We promise to take the utmost care to protect your privacy.

- 1. Age?
- 2. Sex:
 - (a) Male
 - (b) Female
- 3. Do you have any digestive difficulties? Please check all that apply. (Note that our probiotics are not intended to treat any diseases.)
 - (a) Diverticulitis
 - (b) IBS
 - (c) Celiac
 - (d) Heartburn
 - (e) Ulcerative colitis
 - (f) Frequent diarrhea
 - (g) Frequent stomach/digestive pain
 - (h) Spicy food intolerance
 - (i) Skipping meal causes headache
 - (j) Frequent constipation
 - (k) Other digestive discomfort
 - (l) None
 - (m) Other:
- 4. Do you have any mood or psychiatric symptoms or diagnoses? Studies suggest a link between gut microbes, mood, and well-being.
 - (a) depression
 - (b) anxiety
 - (c) none
 - (d) other
- 5. Are you a vegetarian (including vegan)?

Step 2 of 3: Immune Health

Although probiotics are safe for general consumption, issues can arise for those with compromised immune systems.

We promise to take the utmost care to protect your privacy.

1. Please check if you:

- (a) have HIV/AIDS, or another disease that affects the immune system
- (b) are being treated with drugs that affect the immune system, such as steroids
- (c) are being treated for cancer with radiation or drugs
- (d) have one or more of the above issues

- (e) have a compromised immune system for some other reason
- (f) have none of these issues

Step 3 of 3: Contact Information

If you are selected to participate in this study, we'll need this information to send you either the probiotic or the placebo.

- 1. Your first name:
- 2. Your last name:
- 3. Your email address:
- 4. Your physical street address: This is required so that we can send you either the probiotics or the placebo if you're selected for the study.
- 5. City:
- 6. State:
- 7. Zip Code:

Thanks! For science! We'll be in contact if you've been selected.

Appendix B: 1-minute daily survey: For science!

- 1. Did you take a study-related capsule today?
 - (a) No -- they haven't arrived yet
 - (b) Yes
- 2. What time did you take the capsule?
 - (a) 12 am 4 am
 - (b) 4 am 8 am
 - (c) 8 am 12 pm
 - (d) 12 pm 4 pm
 - (e) 4 pm 8 pm
 - (f) 8 pm 11:59 pm
- 3. How happy were you today? 1 (Not very) to 7 (Extremely)
- 4. How energetic/alert were you today? 1 (Not very) to 7 (Extremely)
- 5. How stressed were you today? 1 (Not very) to 7 (Extremely)
- 6. Did you have food cravings today? 1 (Not very) to 7 (Extremely)
- 7. Check any digestive symptoms you experienced today:
 - (a) Post-meal digestive discomfort
 - (b) Bloating
 - (c) Abdominal pain
 - (d) Excessive flatulence
 - (e) Acid reflux (heartburn)
 - (f) Nausea
 - (g) Other digestion-related pain or discomfort
 - (h) None
- 8. Did you have a bowel movement today?
 - (a) Yes
 - (b) No
- 9. If yes: What was your Bristol stool number?
 - (a) Type 1
 - (b) Type 2
 - (c) Type 3 Normal/Hard
 - (d) Type 4 Normal
 - (e) Type 5 Normal/Watery
 - (f) Type 6
 - (g) Type 7
- 10. Optional: Is there anything else we should know? (Feel free to skip this one; we want to keep this fast.)

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