Original Article

Gut microbiome-based dietary intervention in Parkinson disease subject: A case report

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Abstract

A 54-year-old woman was seeking medical treatment for Parkinson disease (PD) in the neurology outpatient department in JSS Hospital, Mysore, India. She was challenged in terms of reduced mobility and had sought several treatment options to control her PD symptoms without successful outcome. After examination and confirmation of diagnosis, the decision was taken to design a precision nutritional intervention using a gut microbiome-based diet combined with medical treatment. After 2 months of a superfood dietary intervention, the patient showed signs of clinical improvement as evidenced by improved mobility and a change in the Hoehn and Yahr clinical severity scale from stages 3 to 2. In conclusion, it is possible to modulate the gut microbiome to reverse the established gut dysbiosis associated with the neurodegenerative process in PD, which can lead to clinical benefit by reducing functional disability.

Keywords: Gut microbiome, Parkinson disease, Gut dysbiosis, Nutrition, Precision diet

Introduction

Parkinson disease (PD) is a progressive neurodegenerative disease that worsens over time and affects the central, peripheral, and enteric nervous systems.[1] As per the epidemiological reports released in 2019 from World Health Organization (WHO), the prevalence of PD has doubled in the last 25 years, owing to the global estimate of 8.5 million PD cases and 329,000 deaths, accounting to 81% increase in PD prevalence since 2000.[2] Also, the data from Global Burden of Diseases 2019 suggest that there is 204.06% change in incidence and 216.46% change in prevalence of PD in south Asian region from 1990 to 2019.[3]

Abnormal misfolding of the protein alpha-synuclein (αS) and its accumulation in dopaminergic neurons of substantia nigra brain region is a pathological hallmark of PD.[4] Despite the significant advancements in PD research, the precise mechanisms involved in the pathogenesis and progression of the disease remains largely unknown. αS deposits can be seen in the gut 20 years before the manifestation of PD motor symptoms. Aggregation of αS in the colon of PD patients increases intestinal permeability by translocating to the brain via vagus nerve.[5,6] Mounting evidence from preclinical and clinical studies have contributed to a better understanding of the complex interlink between microbiota, gut, and brain (microbiota–gut–brain axis) in PD, potentially paving the way for the development of new biomarkers and treatments. Alterations in the gut microbiota composition may be related to the cause or effect of motor or nonmotor

Access this article online

Quick Response Code:

Website: www.ijnpnd.com

DOI: 10.4103/ijnpnd.ijnpnd_8_23

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Received: 14 February 2023 **Revised:** 11 March 2023
Accepted: 20 March 2023 **Published:** 27 July 2023

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How to cite this article: Sulthana A, Paneyala S, HSS, Narayan MK, Hediyal TA, Sharma S, Senthilkumar A, Dave P, Mahalakshmi AM, Chidambaram SB, Monaghan TM, Sulakhe D. Gut microbiome-based dietary intervention in Parkinson disease subject: A case report. Int J Nutr Pharmacol Neurol Dis 2023;13:158-65.

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symptoms, but the specific pathogenic mechanisms remain unclear.[5,7]

Such studies have drawn attention to diet modification as well as the use of probiotics, prebiotics, and fecal microbiota transplantation as potential therapeutic approaches that may lead to new treatment paradigm for PD.

Here, we profiled the gut microbiome of a 54-year-old female PD patient prior to designing a microbiome-specific dietary intervention to help reverse the microbial dysbiosis associated with PD. Our aim was to restore intestinal eubiosis and by doing so, elicit a reduction in functional disability assessed using the Hoehn and Yahr Scale of disease severity.

Methodology

The gut microbiome–based dietary interventional study on PD was divided into two phases over a period of 4 months.

Phase 1 (Preintervention)

The study was approved by the Institutional Ethics Committee, and informed consent was obtained from the subject, which covered the data analysis and publications related to the study. A 54-year-old female patient with PD agreed to participate in this study following informed consent. Following the receipt of the informed consent in phase I, the patient was assessed for the severity of PD and cognitive ability through Hoehn and Yahr scale[8] and mini-mental state examination (MMSE)[9] scales, respectively to obtain the baseline clinical data of the subject along with other demographics details. Clinical assessments revealed a clinical severity of stage 3 on the Hoehn and Yahr scale and a cognitive assessment of 17 on the MMSE. Her pharmacotherapy included levodopa–carbidopa combined at 375 mg/day, rasagiline 1 mg/day, and trihexyphenidyl 4 mg/day. A stool sample was collected using Navipoint Health Gut Microbiome Testing Kit, India, and processed to extract deoxy ribonucleic acid (DNA), followed by polymerase chain reaction (PCR) amplification of V3 and V4 regions of 16S rRNA. PCR products were used for library preparation (NEBNext Ultra DNA Library Prep Kit), and sequenced on Illumina MiSeq NGS platform. High-quality 16S metagenomic sequence data were run through Divisive Amplicon Denoising Algorithm (DADA2) algorithm of QIIME2 pipeline, followed by annotation through Bayesian-based Lowest Common Ancestor method (BLCA) algorithm. The relative abundance of bacteria was mapped with Navipoint Health's proprietary microbial panel of PD to determine the outbound microbial markers in the patient's sample. The specific nutritional recommendations to reverse the unhealthy ranges of the outbound microbial markers were generated as per Navipoint Health's proprietary Microbiome-Food database.

Microbiome-specific Dietary Intervention

The patient received nutritional counseling to adhere to a microbiome-specific diet (Table 1) for a period of 2 months. Counseling was performed by an in-house certified nutritionist throughout the dietary intervention phase and clinicians recorded information on clinical symptoms.

Phase 2 (Postintervention)

Following the successful completion of the microbiome-based dietary intervention, a second stool sample was collected from the patient and 16S metagenomics sequencing was performed by the standard protocols as mentioned above. The relative abundance of microbial markers in the preintervention phase of the study and the *Firmicutes* to *Bacteroidetes* ratio (F/B) were compared with the postintervention data sets.

Results and Discussion

At baseline, the patient's gut microbiome showed a high relative abundance of taxa including *Lactobacillus* (genus level) (32.98%), *Firmicutes* (phylum level) (89.07%), *Prevotella* (genus level) (27.79%), and *Actinobacteria* (phylum level) (10.10%) [Figure 1], which was higher than the proprietary healthy cohort ranges set by the Navipoint Health, India. A number of studies indicate that a reduction in anti-inflammatory short-chain fatty acids

Table 1: Microbiome-Specific Superfoods.

Category	Foods	Portion	How to	When to
Super fruits	Gooseberry	1 in no per day	Eaten raw, can add salt	Mid-morning/evening snack
	Orange	1 on no per day	As it is	Mid-morning/evening snack
	Papaya	150 g/day	As it is	Mid-morning/evening snack
Super veggies	Capsicum	150 g/ day	Eaten raw, can add salt	Salad—lunch/dinner
	Spinach	200 g/ day	Cook, can add salt	Salad, sambar—lunch/dinner
Whole grains	Wheat	150 g (40 g/chapatti)	Cook, can add salt	Roti/chapatti—lunch/dinner
	Rice	125 g cooked wt (75 g raw wt)	Cook, can add salt	Rice ghanji—lunch/dinner
	Split mung dal	100 g soaked (50 g raw)	Cook, can add salt	Moong dhal ghanji/khichdi with rice—lunch/dinner
Spices	Ginger	5 g (minced)/1 tsp	Added as flavor	Add to ghanji
	Turmeric	5 g (to be taken along with pepper)	Added as flavor	Add to milk
Non-veg	Eggs	100 g (two eggs)	Boiled, can add salt	Can be consumed during breakfast and lunch
	Chicken	150 g (175 g raw wt)	Cook, can add salt	Can be consumed during breakfast and lunch

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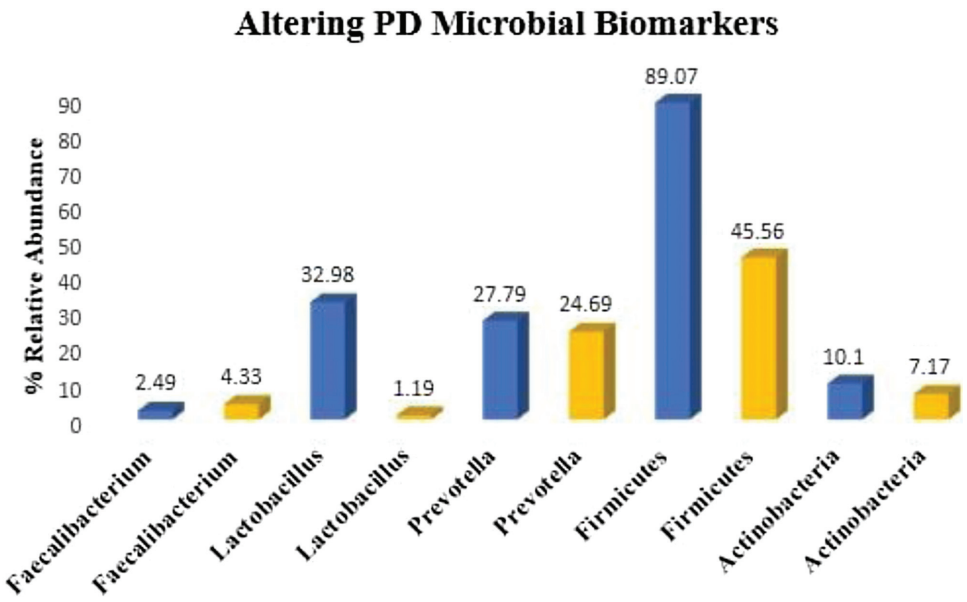

Figure 1: Parkinson disease (PD) microbial markers status in phase 1 (blue; preintervention) and phase 2 (yellow; postintervention).

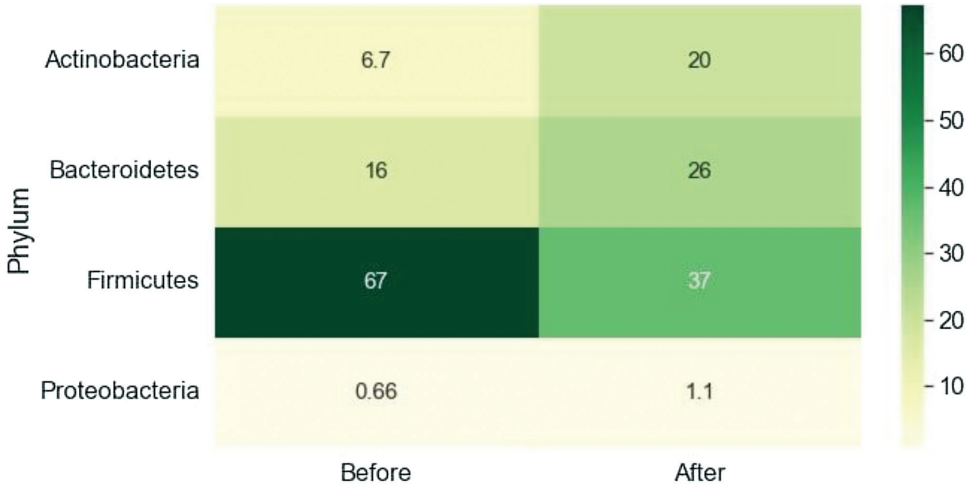

Figure 2: Phylum-level heatmap. *Firmicutes* phylum levels (67%) was very high before the intervention. After intervention we could observe an increase in *Actinobacteria* (6.7%–20%), *Bacteroidetes* (16%–26%), and *Proteobacteria* (0.66%–1.1%).

Table 2: Gut Microbiome Before and After Dietary Intervention

	Before	After
F/B ratio	2.07	1.06

(SCFAs) is linked to PD pathogenesis.[10–13] Hence, the SCFA producer *Faecalibacterium* (genus level) (2.49% at preintervention phase) was also targeted when designing the precision dietary intervention.

Recent studies show a strong association between *Lactobacillus* (*Firmicutes* phylum)-enriched gut microbiome and PD[14–17] and an increase in the relative abundance of *Lactobacillus* genus in the microbiota of PD patients can increase the secretion of αS via interactions with gut neurons.[16] Physical inactivity is reported to be high in *Firmicutes*-enriched enterotype of PD patients, whereas *Prevotella* is involved in the biosynthesis and augmenting circulating levels of branched-chain amino acid (BCAA) in body.[18] BCAAs are involved in the pathogenesis of neurodegenerative diseases such as Alzheimer disease, PD, and amyotrophic lateral sclerosis, by altering the central levels of neurotransmitters and through induction of excitotoxicity, hyperexcitability, inflammation, and oxidative stress.[19,20]

Actinobacteria phyla show significant correlations with clinical indicators of inflammation including monocyte percentage and neutrophil percentage in PD patients.[21] *Actinobacteria* and *Firmicutes* possess enzymes

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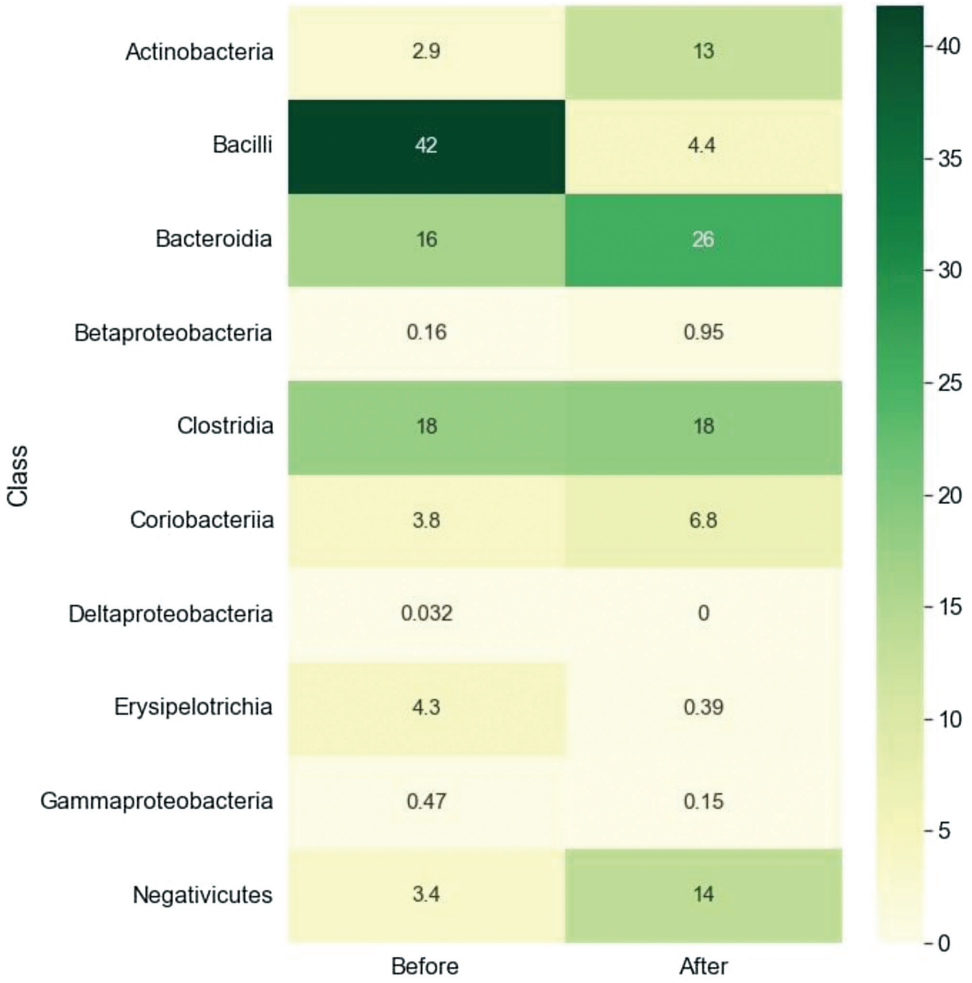

Figure 3: Class-level heatmap. Class *Bacilli* was very high (42%) which was reduced considerably (4.4%) after intervention. After intervention, we could observe an increase in *Bacteroidia* (16%–26%), *Actinobacteria* (2.9%–13%), and *Negativicutes* (3.4%–14%).

(trimethylamine [TMA] lyases) that convert dietary precursors (choline, betaine, and L-carnitine) to a proinflammatory bacterial metabolite TMA, which in turn convert to TMA N-oxide (TMAO) by hepatic flavin-containing monooxygenases (FMOs). High levels of TMA lead to inflammation[22,23] and an increase in plasma TMAO levels has been reported in PD patients.[24]

In the post-dietary intervention period, the patient's Hoehn and Yahr staging improved from stage 3 to stage 2 and the cognitive assessment (MMSE) score increased from 17 to 19. Comparisons in the relative taxa abundance data revealed a notable reduction in *Lactobacillus* genus level from 32.98 to 1.19%, which correlated with improved mobility.

Increased deposition and aggregation of αS in the substantia nigra are shown to decrease locomotor function.[25,26] Natural bioactives such as phenolic acids, flavonoids, tannic acids, and alkaloids are reported to decrease αS aggregation in turn to improve locomotor function.[27–32] Intriguingly, precision foods or personalized foods help to reduce αS accumulation, pathobionts, and can help attenuate gut inflammation, which leads to a reduction in PD symptoms.[33–35] In the present study, the recommended superfoods as outlined in Table 1, which were administered as the precision dietary intervention in this study, are known to contain the aforementioned bioactives which may have contributed to improved clinical outcome. However, further studies are required to understand which foods can lead to a reduction in *Lactobacillus* taxa and how different *Lactobacillus* strains contribute to aggregation of αS in colon.

The table represents the wholesome of the superfood precision diet suggested to the patient after the fecal microbiome analysis, the patient was adhering to the diet for a period of 2 months and the same was monitored by an in-house certified nutritionist.

Other bacterial phyla which sharply decreased in abundance following the superfood intervention included *Firmicutes* from 89.07 to 45.56%, *Prevotella* from 27.79 to 24.69%, and *Actinobacteria* from 10.10 to 7.17%. In contrast, there was also an increase in phyla abundance of *Faecalibacterium* from 2.49 to 4.33%. In addition to the targeted microbial markers, the dietary intervention reduced the F/B ratio [Table 2]. However, although there are no studies

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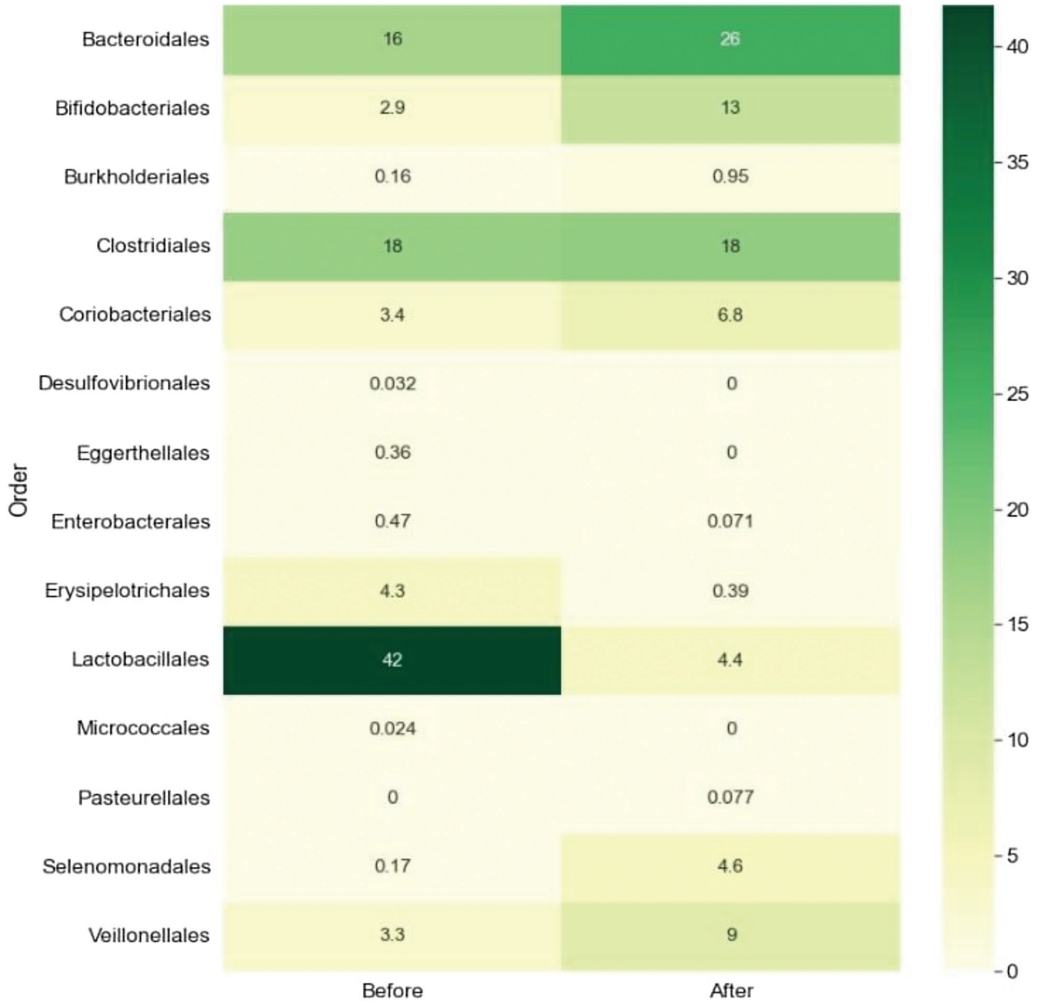

Figure 4: Order-level heatmap. *Lactobacillales* order which was high (42%) was reduced considerably (4.4%) after intervention. After intervention, we could observe an increase in the order *Bacteroidales* (16%–26%), *Bifidobacteriales* (2.9%–13%), *Coriobacteriales* (3.4%–6.8%), *Selenomonadales* (0.17%–4.6%), and *Veillonellales* (3.3%–9%).

explaining the predominant role of F/B ratio in neurodegenerative disorders, unlike its association with obesity,[36–38] it is widely accepted to have an important influence in maintaining normal intestinal homeostasis. The heatmap data of pre- and postintervention are presented in Figures 2–6.

Conclusion

In the absence of truly effective anti-PD drugs, gut microbiome–based dietary interventions may represent a promising adjunctive approach to standard pharmacotherapy to improve motor and cognitive functions in PD. Further studies should include prospective longitudinal randomized controlled clinical trials. These should be complemented with detailed mechanistic studies correlating microbial, metabolic, and immune responses with clinical outcomes and *in vivo* animal validatory studies. Herein, we conclude that a gut microbiome–based dietary intervention can potentially help improve motor and cognitive function in PD.

Acknowledgment

The authors thank their respective institutions for providing the required infrastructure to conduct this research work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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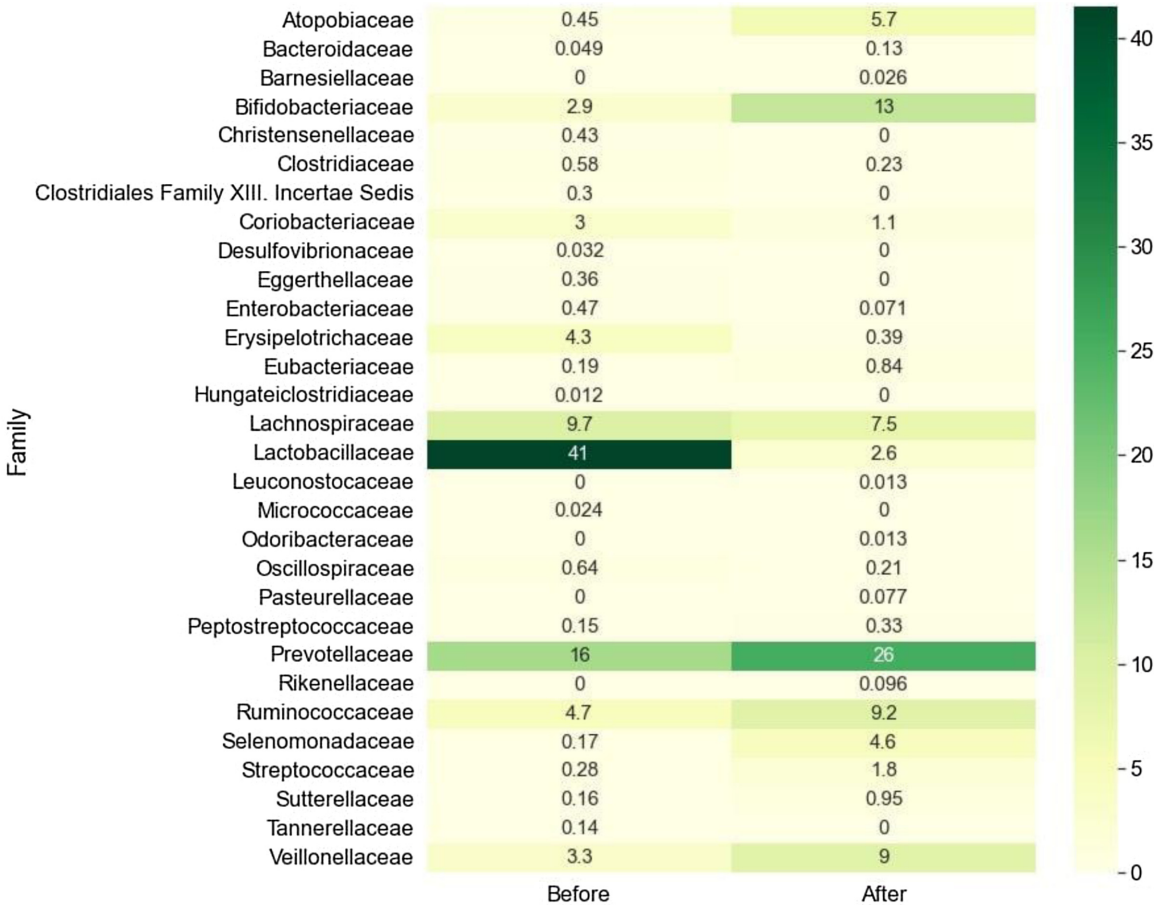

Figure 5: Family-level heatmap. *Lactobacillaceae* family (41%–2.6%) was high and after the intervention it was reduced and similarly *Lachnospiraceae* (9.7%–7.5%) was also reduced after intervention. After intervention, we could observe an increase in the family *Atopobiaceae* (0.45%–5.7%), *Bifidobacteriaceae* (2.9%–13%), *Prevotellaceae* (16%–26%), *Ruminococcaceae* (4.7%–9.2%), *Selenomonadaceae* (0.17%–4.6%), and *Veillonellaceae* (3.3%–9%).

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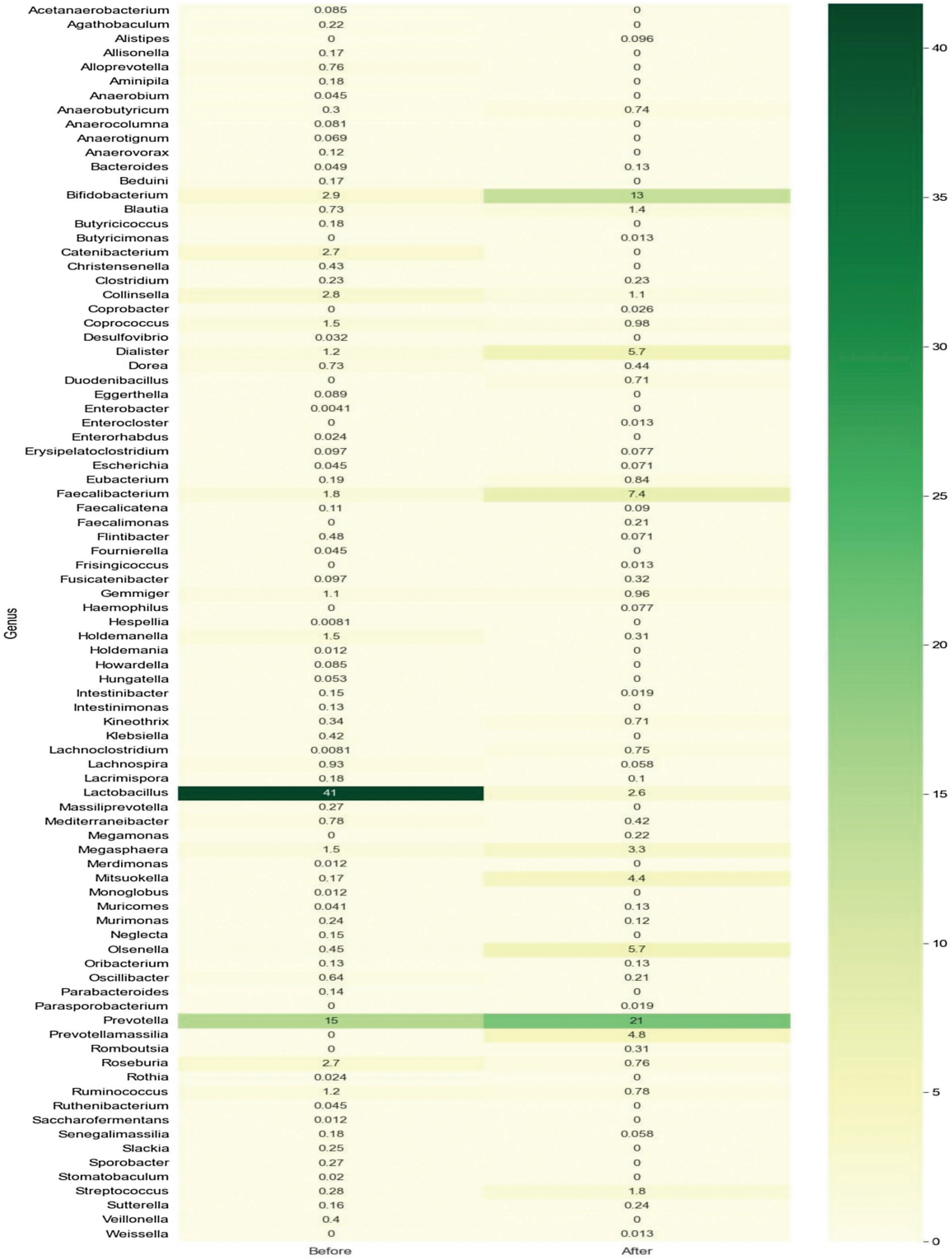

Figure 6: *Lactobacillus* genus (41%) was high and after the intervention was reduced (2.6%). *Roseburia* (2.7%–0.76%), *Catenibacterium* (2.7%–0%), *Collinsella* (2.8%–1.1%), and *Holdemanella* (1.5%–0.31%) were high before the intervention and was reduced after. *Prevotella* (15%–21%), *Bifidobacterium* (2.9%–13%), *Dialister* (1.2%–5.7%), *Faecalibacterium* (1.8%–7.4%), *Megasphaera* (1.5%–3.3%), *Mitsuokella* (0.17%–4.4%), and *Olsenella* (0.45%–5.7%).

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