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# Efficacy of a Diabetes Specific Nutrition Supplement on CGM Outcomes in Adults with Type 2 Diabetes: Post Hoc Analysis of an RCT

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## Abstract

Efficacy of a Diabetes Specific Nutrition Supplement (DSNS) in improving glycemic and gut health markers through an RCT have been reported. A continuous glucose monitoring (CGM) device reports changes in interstitial blood glucose every 15 minutes. This post-hoc analysis elucidated the role of DSNS on the first few days of DSNS consumption. As an exploratory objective, impact of DSNS on fecal metagenomics post 12 weeks supplementation has also been reported. N = 210 adults were randomized to receive either DSNS with standard care (DSNS + SC; n = 105) or standard care alone (SC alone; n = 105). CGM data was obtained from n = 137 participants (DSNS + SC = 68; SC alone = 69) across days. Exploratory outcomes of fecal metagenomic (DSNS + SC = 2) and Short Chain Fatty Acids (SCFAs) (DSNS + SC = 5; SC alone = 5) analysis was carried out in a subsample at baseline and endline. For the DSNS + SC group, incremental area under Curve (iAUC) for first 24 hours (acute blood glucose response) post DSNS consumption reported to be significantly lower [−106 ± 36 mg*15 min/dL; p = 0.01] as compared to iAUC from "no DSNS consumption day", while SC alone showed no significant differences between the days. When compared between groups, DSNS + SC had a significantly lower iAUC [−106 mg/min·dl; p = 0.04] versus SC alone. Postprandial (PP) iAUC for day 1 after DSNS consumption as part of breakfast (first serve) was compared to PP iAUC on "no DSNS consumption day".

*These authors contributed equally to this work.

Within the DSNS + SC, PP iAUC was significantly lower [−99 ± 38 mg*15 min/dL; p = 0.005] vs no consumption. When PP iAUC was compared between groups, DSNS + SC had a significantly lower iAUC [−131 mg/min·dl; p = 0.02] versus SC alone. After 1 day of DSNS consumption, DSNS + SC showed significantly lower fasting interstitial glucose (FG) [168 ± 10 mg/dl; p = 0.01] versus SC alone [200 ± 11 mg/dl]. Preliminary metagenomic analysis of DSNS + SC indicated improved microbial diversity from baseline to endline. Fecal SCFAs showed no differences (p > 0.05). Basis CGM outcomes (iAUC, PP, FG), benefits on the glycemic response started showing positive effects from the first day and serve of the DSNS. Long term consumption of DSNS is suggested for further improvement of glycemic markers. The preliminary exploratory analysis on gut microbiome indicated encouraging trends towards improved gut health; however, larger studies are necessary to further substantiate this.

## Keywords

Diabetes Specific Nutrition Supplements, Continuous Glucose Monitoring, Incremental Area under Curve, Metagenomics, Short Chain Fatty Acids

## 1. Introduction

The escalating incidence of diabetes in India poses not only a significant public health issue, but also a socioeconomic burden. ICMR-INDIAB study recently indicated the prevalence of Non-Communicable Diseases (NCDs) specifically diabetes and prediabetes to be 11.4% and 15.3% (101 million and 136 million people, respectively), much higher than earlier studies [1].

In India, with diabetes reaching epidemic proportions, our understanding of the disease has significantly advanced. Over the past decades, pharmacological treatment, diagnostic, and therapeutic options for patients of diabetes have seen significant advancements. While pharmacological treatments are necessary, diet and lifestyle modifications are fundamental for effective blood sugar control. Diabetes-Specific Nutrition Supplements (DSNS) are employed as part of the therapeutic options to modify diet and help manage the progression and severity of the disease. These specialized supplements are designed to help manage dysglycemia and other cardiometabolic risk factors. The supplements are typically low glycemic index (GI) and include fiber, healthy fats, proteins, vitamins, and minerals in palatable, calorie-controlled portions that can be used as meal or snack replacements, depending on the clinical situation and at the discretion of healthcare professionals [2]. Horlicks Diabetes Plus is one such, low GI, well researched DSNS which has reported benefits for prediabetics and diabetics [3]-[5]. The macronutrient and fiber composition of the DSNS per serving is provided in Supplementary **Table S1**.

In patients with diabetes, excessive glucose fluctuation or glycemic variability (GV) is considered more dangerous than persistent abnormal blood glucose. GV

is related to micro and macrovascular complications, hypoglycemia, and a higher risk of death [6] [7]. Traditional blood glucose monitoring (self-monitoring blood glucose-SMBG) only provides monitoring the blood glucose level at that moment but does not obtain enough blood glucose data to reflect the daily blood glucose control, daily GV and the occurrence of nocturnal and asymptomatic hypoglycemia [8], hence, it provides only a limited understanding of the disease. Continuous Glucose Monitoring (CGM)—a more recent diagnostic approach, can detect changes in blood glucose in real time, provide more detailed data on GV, helping healthcare providers manage the disease better. The convenience and continuous monitoring can improve patient compliance with treatment. The CGM systems provide insights into how lifestyle modifications (diet and physical activity), and medications affect glucose levels by monitoring glucose levels continuously throughout the day, leading to better management of blood sugar levels. Recent trials support the effectiveness of CGM-facilitated nutrition strategies in T2DM. The IGNITE trial demonstrated that, within a medically supervised ketogenic diet program, CGM-supported approaches produced similar, clinically significant improvements in glycemic metrics, weight, and medication reduction over six months [9]. Similarly, in another randomized study using CGM—with or without an accompanying food-logging app and guided education—yielded notable reductions in hyperglycemia, increases in time-in-range, and improvements in Hb1AC and body weight among T2D patients even without concurrent medication changes [10]. Further recent intervention trials in similar populations with diabetes and prediabetes also showed improvement in CGM driven parameters. Thus, proving the strengths of CGM in randomized controlled trials [11] [12].

The gut microbiome is an ecosystem of microorganisms living in the human intestines, which plays a crucial role in digestion, immune function, and overall health. The salubrious ecology is beneficial as long as the human host maintains a conducive environment to contain this cohort of "guest workers" [13]. Any change in the environment can lead to a disadvantageous ecology that can affect homeostasis in the host. Hence dietary strategies that modulate the gut microbial ecosystem are becoming increasingly sought-after for improving human health. A key strategy involves the use of dietary fibers (DFs), which are widely recognized for their prebiotic effects, thereby modulating gut microbiota composition and its metabolic activities including the production of short-chain fatty acids (SCFAs) [14]. SCFAs are products of fermentation of DFs that assist in glucose and lipid metabolism by activating SCFA receptors on liver, adipose tissue, brain and pancreas. Gut microbiota-related SCFAs also affect the intestinal barrier integrity positively [15].

The study objectives, design and methods have been described in detail in our previous publication [5]. In the study, the intervention group received DSNS along with standard care (DSNS + SC; n = 105) and control group (n = 105) received standard care alone [5]. The current publication is presenting the post-hoc analysis of the CGM data on n = 137 participants (DSNS + SC = 68, SC alone = 69). Exploratory analysis of fecal SCFA was carried out in a sub-sample [~5% of participants (n = 10: DSNS + SC = 5 and SC alone = 5)] at baseline and at the end

of the study. Impact of the DSNS on gut microbiome was also assessed in 1% of DSNS + SC participants [n = 2 compared at baseline and endline].

## 2. Methods

A single-center, randomized, open-label clinical trial was conducted in adults with Type 2 Diabetes Mellitus (T2DM). The study aimed to evaluate the differences in glycemic markers, anthropometric and lipid parameters, and gut health between two groups after 12 weeks of oral ingestion of DSNS.

The study was conducted at the Madras Diabetic Research Foundation (MDRF) in Chennai, India, from January to December 2023. It adhered to the protocol, Good Clinical Practice (GCP) guidelines [16], local regulations governing clinical conduct, and the ethical principles originating from the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee of MDRF (ECR/194/Inst/TN/2013/RR-19) under protocol code NUN-HFD-003/22, with approval granted on November 24, 2022. Additionally, the protocol was registered with the Clinical Trials Registry-India (CTRI) under registration number CTRI/2023/01/049210 (CTRI https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=NzgwNzc=&Enc=&userName=) [5].

### 2.1. CGM

The Ambulatory Glucose Profile (AGP) was monitored using a CGM device (Freestyle Libre Pro). The CGM device recorded the glucose levels continuously over a 24-hour period for 14 days. The device was fitted on all participants during the first and last two weeks of the 12-week study. The participants reported to the site on Day 1 for CGM device application. The participants received care instructions for CGM and were advised to wear the device for 14 days while continuing their usual routines. Similarly, the CGM was fitted on Day 70. For detailed methodology and CGM outcomes from baseline to endline (12-week intervention) and CONSORT flow diagram refer [5].

In the DSNS + SC group, to achieve a "true blank" at the baseline, the first 7 days of CGM monitoring was conducted without DSNS supplementation. DSNS consumption was initiated in the intervention arm (DSNS + SC) from Day 8.

Thus, for this post hoc analysis:

1) The "no consumption day" was the Day 2 of CGM application.

2) Day 8 of the study was the first day of DSNS consumption.

3) Day 9 of the study was one day after DSNS consumption. The impact on fasting interstitial glucose was studied.

The device typically needs to be synced and stabilized overnight. On Day 1 of study, CGM was applied and the first day of study is Day 2.

### 2.2. Microbiome Methodology

Impact of the DSNS on gut microbiome was assessed in a small subsample of 1%

(n = 2) of DSNS + SC participants [n = 2] and compared at baseline and endline. The analytical method for assessing the gut microbiome was adapted from Kallapura *et al.* [17].

### 2.3. Fecal SCFAs

Exploratory analysis of fecal SCFA was carried out ~5% of participants (*i.e.* n = 10: DSNS + SC = 5 and SC alone = 5) at baseline and at the end of the study. Participants were provided with stool collection kits and instructed on collection and storage of samples. Samples were aliquoted, transported in a frozen state and stored at freezing temperatures. Fecal SCFAs were analyzed using Gas Chromatography and Mass Spectrometry (GC-MS); AGILENT GCMS/MS 700D autoanalyzer.

### 2.4. Statistical Analysis

Statistical analyses were conducted using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). Results are expressed as least square means with standard error (LSM ± SE). A Generalized Linear Model (GLM) was used to evaluate between-group changes over time and Paired t-tests were used to assess within-group difference. A significance level of $p < 0.05$ was used to determine statistical significance.

The iAUC was calculated using the linear trapezoidal method. To establish daily baseline glucose levels for each participant, fasting interstitial glucose values between 6:00 and 8:00 am were averaged. Baseline was the average of two readings taken at 15- and 30-minutes prior. The iAUC was then calculated from the remaining 22 hours of AGP data. Daily positive AUC values were derived from all 15-minute glucose readings and standardized by the number of available measurements [18]. The CGM-derived endpoints were directly used and no formal adjustments for comparisons were required. Data were expressed as mean ± standard error, with statistical significance set at $p < 0.05$.

The iAUC glucose values (mg*15 min/dL) were evaluated for:

- The 24-hour period (following two servings of the product)
- The postprandial period (after the first serving of the product)

After 24 hours of DSNS consumption (Day 9), the fasting interstitial glucose levels (6:00-8:00 am) were compared between the DSNS + SC and SC alone using 2-hour readings, collected using the same method applied at baseline.

## 3. Results

Detailed baseline characteristics have been reported in the main publication [9]. Table 1 indicates that there were no significant differences in the CGM variables before intervention between the two groups. For this post-hoc analysis, CGM data was available for n = 68 in the DSNS + SC group and n = 69 in the SC alone group. A total of 210 participants were randomized in the trial and n = 137 had analyzable CGM data at the end of the study. The reasons for data loss were sensor malfunctions/technical device failures/insufficient data (defined <7 days of usable data) and unwillingness for CGM assessment.

**Table 1.** Day 2 (baseline) comparison of the study participants.

| Variables | [$]Intervention (n = 68) | Control (n = 69) | p-value |
|---|---|---|---|
| 24 hrs iAUC (mg*15 mins/dL) | 845 (43) | 777 (48) | 0.28 |
| 2 hrs PP iAUC (mg*15 mins/dL) | 308 (31) | 290 (33) | 0.70 |

Data presented as least square Mean (standard error). [$]Intervention 30 g was consumed before breakfast and before bedtime. p-value is tested using independent t-test.

### 3.1. Acute Glycemic Response

When comparing the first 24 hours following DSNS consumption (2 servings) on Day 8 with the no-consumption on Day 2, the DSNS + SC group exhibited a significantly lower iAUC of −106 mg*15 min/dL (p = 0.01), indicating a notable glycemic lowering effect of DSNS. In contrast, the SC-alone group showed no significant change (p = 0.99) between the days (**Figure 1**). Furthermore, the between-group comparison (for first day of consumption vs control) revealed a significant difference in iAUC, with the DSNS + SC group showing a greater reduction of −106 mg*15 min/dL (−209.6, −2.4; p = 0.04) compared to the SC-alone group (**Figure 1**).

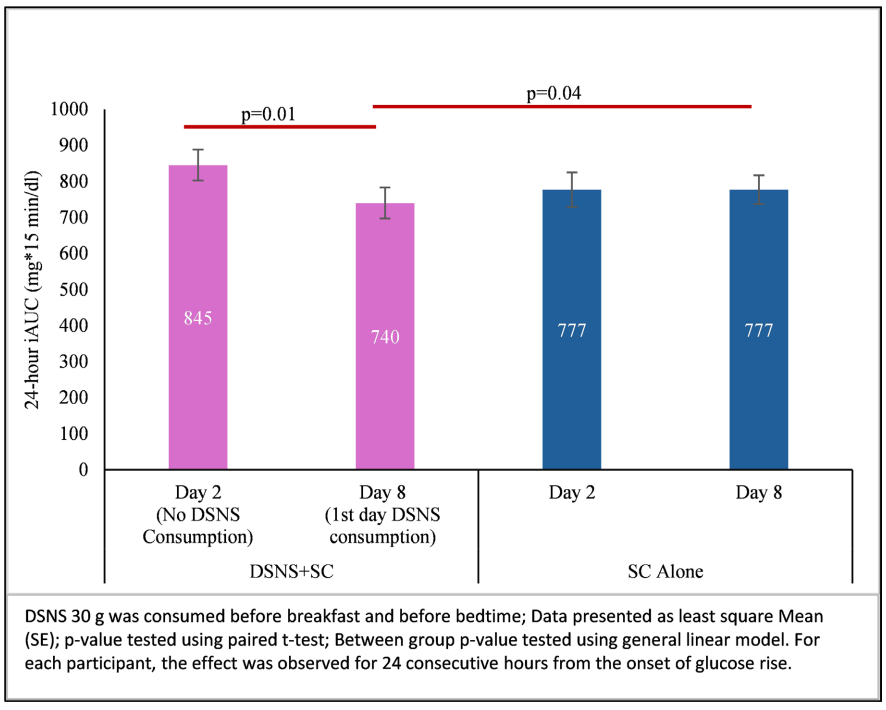


**Figure 1.** Comparison of iAUC 24 hours for 1[st] Day DSNS consumption versus no DSNS consumption using CGM data.

An analysis of postprandial (PP) iAUC changes between Day 2 (no consumption) and Day 8 (first consumption) within the DSNS + SC group revealed a significant reduction [99 (38) mg*15 min/dL; p = 0.005]. Additionally, a substantial between-group difference was observed between the DSNS + SC and SC-alone groups, with a mean difference of −131 (95% CI: −242 to −21) mg*15 min/dL (p

= 0.02) (Figure 2).

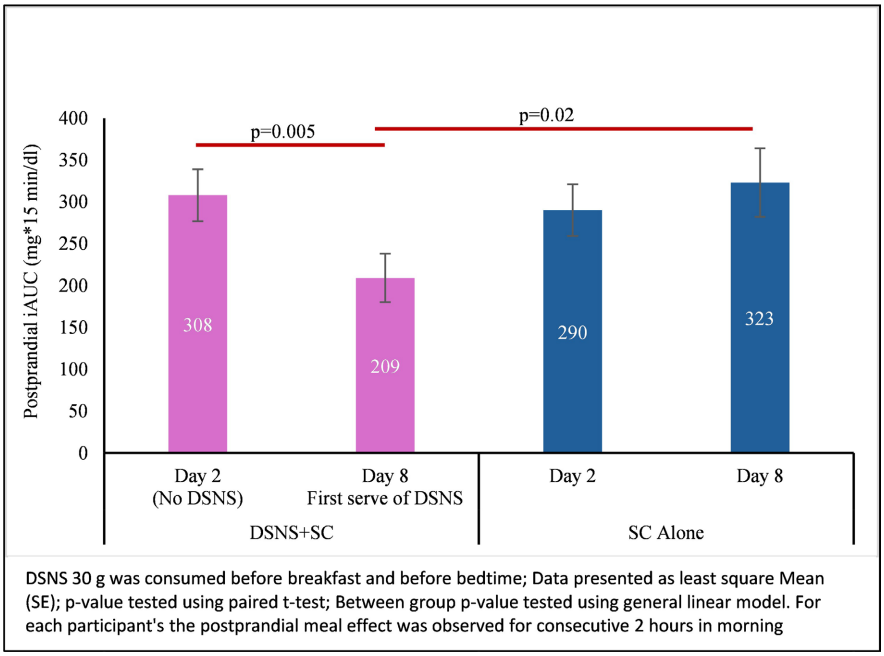


Figure 2. Comparison of 2 hour post prandial iAUC for 1st Day DSNS consumption versus no DSNS consumption using CGM data.

After day 1 of DSNS consumption (*i.e.* Day 8) the fasting interstitial glucose was measured on the next morning (Day 9) indicating impact of first day of DSNS consumption. The post one day of DSNS consumption (2 serves), revealed a significant reduction (p = 0.01), indicating a positive effect of DSNS after the first and single day of consumption (Figure 3).

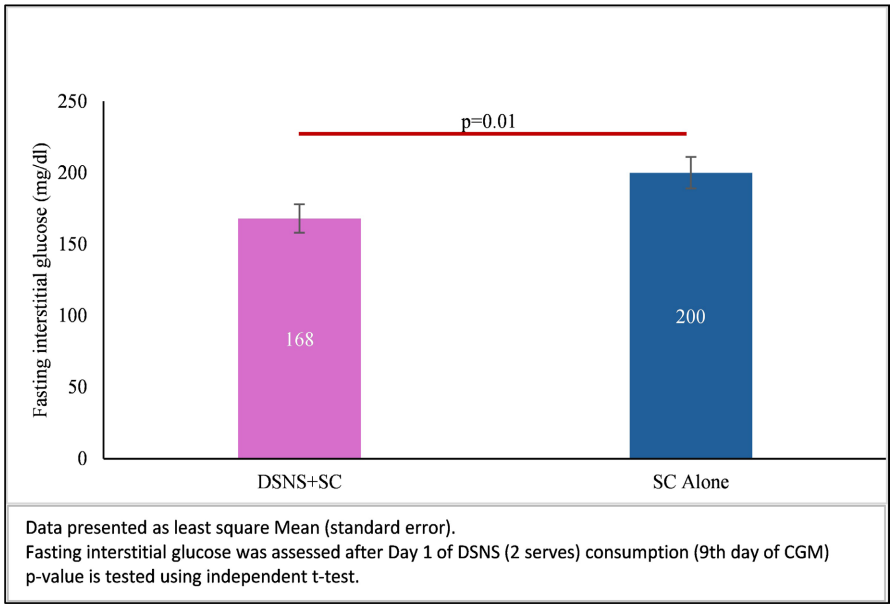


Figure 3. Fasting interstitial glucose after 1st day of DSNS consumption (9th day) consumption using CGM data.

### 3.2. Gut Microbiome

Basis the exploratory analysis, both Firmicutes to Bacteroidetes ratio and Actinobacteria to Proteobacteria ratio increased at the end of the 12-weeks study, indicating trends for impact of the intervention (refer supplementary material **Table S1** and **Table S2** and **Figure S1**).

#### Fecal SFCAs

A total of eight short chain fatty acids (SCFAs) were assessed in the plasma and fecal samples in both control and intervention group at baseline and endline. Plasma SCFAs had significantly improved in the DSNS + SC versus SC alone group [9]. In the fecal samples, no significant change ($p > 0.05$) was observed in SCFA's in DSNS + SC group and SC alone groups.

## 4. Discussion

This study investigated two key parameters of CGM: 1) the 24-hour iAUC following consumption of two servings of the product and 2) the postprandial glycemic response within two hours after the first serving of DSNS on Day 1 of consumption. The CGM data extraction enabled the 24-hour real time (every 15 minutes) glucose monitoring and indicated the ability of DSNS to better manage blood glucose response from the first day of consumption. The CGM findings also indicated that ingestion of one serve of 30 g of DSNS resulted in significantly lower iAUC or postprandial blood glucose as compared to when DSNS was not consumed. Therefore, the study suggests that the DSNS with standard care combination might be more effective in managing blood sugar levels over time as compared to standard care alone.

The reasons for the lowered postprandial glucose response seem to be mediated via different mechanisms. The DSNS is high in protein providing 22% energy from protein. A review by Comerford *et al.* reported that in subjects T2DM protein intake is as effective as carbohydrate intake at stimulating insulin secretion while in healthy subjects' protein intake has effectively only one-third insulin secretion that of T2DM subjects [19]. Besides this, non-insulin-dependent glucose regulation by specific amino acids (Leucine) is also being seen as an important mechanism for glucose control in insulin-resistant individuals such as those with T2DM [20]. Westerterp-Plantenga suggested that a high-protein diet in the presence of carbohydrate stimulates GLP-1 release which triggers insulin release [21] to better manage the glucose. While studies also suggest that consumption of dairy protein (specifically) at meals leads to more potent and quicker-acting glucoregulatory effects with insulin levels staying elevated for longer in dairy protein group as compared to cod and soy proteins [22]. In this study, DSNS was consumed twice in the day with the first serve of the day being as a part of the breakfast.

Additionally, the DSNS is a high fiber blend with 22 g fiber/100g powder and 6.6 g fiber/serving thereby providing 12% energy from fiber. It contains a dual fiber blend of prebiotic fibers (Nutriose and Fibersol). It is well established that

soluble fiber intake is closely related to the concept of GI by hindering or delaying the absorption of dietary carbohydrates due to the viscous, gel-forming properties of these fibers, thereby reducing postprandial glucose excursions [23]. Soluble dietary fiber is known to significantly increase the viscosity of the chyme in a dose-dependent manner. The study has previously confirmed a significant increase in the intake of dietary fiber by ~11 g and a decrease in carbohydrate intake by ~48 g [5] which is possibly addressing the postprandial reduction in the mean interstitial glucose from the very first serve in the diabetic population. These findings are consistent with observations in a prediabetic population [4] that received the same DSNS. The more viscous chyme, due to soluble dietary fiber, slows digestion and absorption, allowing nutrients to reach the distal ileum. This stimulates mucosal L-cells to release GLP-1, and is linked to reduced appetite, growth of pancreatic beta cells, improved insulin production and sensitivity, and decreased glucagon secretion [24]. The effect of fiber and protein also explains the reduction in fasting blood glucose. The results suggest that the nighttime consumption of the beverage is somehow able to decrease fasting glucose.

Studies have indicated that DSNS with high monounsaturated fatty acids (MUFAs) showed a better glycemic and insulinemic response in patients with T2DM (with malnutrition) within 2 - 3 hours of ingestion [25] [26] Qian *et al.* advocate better glycemic control and improved insulin sensitivity among patients consuming a high-MUFA diet, particularly when MUFA was used to replace carbohydrates [27]. A previous study on the DSNS has already indicated that this product has a low GI of 34 [3]. Also, Kaur *et al.* corroborate that low GI foods are associated with a lower postprandial blood glucose level, lower insulin demand, reduction in blood lipid level, increasing fermentation in the colon and improving satiety [28]. Khanna *et al.* previously reported that fat (≥10% - 27% energy) also contributes to GI [3]. This aligns with the current CGM findings, which also demonstrate lower postprandial glucose (PPG) levels.

It appears, therefore, that while the fermentation of the DSNS ingredients (protein and fiber) in the small intestine to short-chain fatty acids (SCFAs), high MUFA and changes in the gut microbiome are consequences of long term DSNS consumption that bring down the glycemic markers further, the quantity and combination of protein and fiber is just about right to work together, effectively lowering postprandial glucose levels and knocking down glycemic markers even in the short term.

An examination of gut microbiome and diversity analysis from the intervention group (DSNS + SC) indicated that there was a beneficial microbial shift towards greater enrichment of flora at the end of study. Previous research studies [29]-[37] suggest a link between gut microbiota and improved glycemic and anthropometric outcomes and other factors like gut permeability and inflammation. The significant increase in dietary fiber (DF) from the DSNS in this study appears to function as a prebiotic, positively modulating the gut microbiome, possibly influencing the previously discussed factors. However, the complex nature of interactions between the gut microbiome and glycemic factors warrant additional re-

search on a larger sample size to further elucidate the effects of the fiber in the DSNS on the gut microbiome in T2DM patients.

Our previous publication had highlighted that the sum of all plasma SCFAs increased significantly ($p < 0.0001$) in the DSNS + SC group as well as between the intervention (DSNS + SC) and control (SC alone) groups ($p = 0.03$) [5]. However, fecal SCFAs in the stool samples at the end of the 12-week period were not significantly different from that baseline. Nogal *et al.* reported a very low concordance between fecal and circulating (plasma) levels of short-chain fatty acids (SCFAs), which may be attributed to the fact that most absorbed SCFAs are utilized as an energy source by enterocytes and are not transported systemically [38]. Another study found that T2DM patients had lower fecal butyrate and propionate concentrations, as well as acetate concentrations, than healthy subjects [39]. Yet another study showed that fecal acetate was likely to be positively associated with serum acetate [40]. Hence it is clear that the existing evidence on the relation between serum and fecal SCFAs is still very uncertain. While the former holds true, De la Cuesta-Zuluaga *et al.* documented that fecal SCFA concentrations were inversely associated with microbiota diversity. Further the study added that higher fecal SCFA concentrations were associated with a measure of gut permeability, markers of metabolic dysregulation, obesity and hypertension [37]. The results from the study of fecal SCFAs ($p > 0.05$) suggest no worsening in gut permeability, obesity, or other related factors. Therefore, the findings on SCFAs (plasma and fecal) derived from the fermentation of fiber in the DSNS suggest that the DSNS can positively influence glucose homeostasis in the body.

This is the post-hoc analysis from the first clinical trials to report efficacy of a DSNS on multiple parameters like the improvement in glycemic markers (including CGM), anthropometric outcomes, lipid parameters as well as gut health markers (improvement in plasma SCFA) in adults with T2DM. Despite valuable outcomes, we do acknowledge the limitation that the sample size for microbiome studies needs to be larger as smaller subsamples may potentially limit the interpretation and generalizability of the findings. Future research should address this limitation to provide a more comprehensive understanding of the relationship between gut microbiome diversity and health outcomes in patients with diabetes.

## 5. Conclusion

It can be concluded that the DSNS owing to its features of being low GI, high fiber, high protein and rich in MUFA poses beneficial effects towards improving glycemic and gut health markers in adults with T2DM post 12 weeks supplementation. Based on the post-hoc analysis, these benefits on the glycemic response have been reported to start showing beneficial effects from the first day and serve of the DSNS, as measured by iAUC, post prandial and fasting blood glucose through CGM parameters. Long term consumption of the DSNS is preferred as it is likely to further improve glycemic markers. An improved microbial diversity ratio (both F/B and A/P) in the subsample may suggest that DSNS consumption has the po-

tential to further support an improvement in gut microbiome, however, this result should be interpreted as a preliminary finding and studies with larger sample size on more diverse populations will be needed to further understand the relationship between microbial diversity and health outcomes in patients of diabetes.

## Salient Features of the Present Study

- CGM findings indicate that ingestion of 30 g of DSNS on Day 1 of consumption resulted in significantly lower iAUC and postprandial glucose as compared to when DSNS was not consumed, thereby indicating that the DSNS starts to manage blood glucose response from the first day and serve of consumption.
- It can be concluded that the DSNS owing to its features of being low GI, high fiber, high protein and rich in MUFA poses the beneficial effects towards improving glycemic markers in adults with T2DM.

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## Authors Contributions

D.K., H.S.G., S.V., G.R. were primarily involved in the design and conceptualization of the study. G.R., and S.V., were involved in data collection, study conduct, protocol execution, quality checks and data verification. R.G.J., A.N., and G.K., were involved in microbiome and fecal sample collection, analysis and results interpretation. A.K. was responsible for the statistical analysis of results. S.V., A.K., G.R., R.G.J., and V.M. interpreted the study results and participated in data curation. S.J., D.K., S.V., R.M.A., and V.M. were overall responsible for the conduct of the study ethically and scientifically. H.S.G. drafted and led the manuscript for its intellectual content, literature searches and graph generation. H.S.G. and D.K. jointly led the manuscript creation and carried out interpretations regarding intellectual content. The final version of the manuscript was carefully reviewed and approved by all authors. All authors have read and agreed to the published version of the manuscript.

## Institutional Review Board Statement

Study was performed in accordance with the protocol, Good Clinical Practice

(GCP) guidelines, local regulations governing clinical conduct, and the ethical principles that have their origin in the Declaration of Helsinki. The study protocol was approved by the Institutional Ethics Committee of MDRF (Chennai, India), (ECR/194/Inst/TN/2013/RR-19) and protocol code NUN-HFD-003/22 [approval date, 24th November 2022]. The study objectives were explained to all participants, who voluntarily gave written informed consent prior to enrolment. The study was registered with the Clinical Trials Registry-India (CTRI https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=NzgwNzc=&Enc=&userName=) CTRI/2023/01/049210.

## Informed Consent Statement

The informed consent form was reviewed and approved by the Institutional Ethics Committee of MDRF (Chennai, India). All participants voluntarily gave written informed consent prior to enrolment.

## Data Availability Statement

Ethical restrictions imposed by the IEC prevent public sharing of the data for this study. The data used in this publication is owned by HUL (Foods). Data access requests will be evaluated by HUL (Foods) in consideration of IEC requirements. Interested researchers will need to sign a research collaboration agreement with HUL (Foods). Requests can be sent to D.K.

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## Conflicts of Interest

D.K., H.S.G., J.B., S.J. declare potential conflicts of interest as employees of Hindustan Unilever Limited (HUL), the study sponsor. All other authors declared no potential conflict of interest.

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## Supplementary Material

### Methodology

### Diversity analysis

Diversity measures based on certain diversity indices were performed to determine and identify the diversity within and across the samples. Largely, the microbial diversity was reported as **phylum ratio**, **alpha diversity** (within sample diversity-various taxa, phylum and genus identified) and **beta diversity**—between sample diversity. The diversity measures or indices were: Observed diversity, Chao's diversity index, Abundance based Coverage Estimator (ACE) and Shannon diversity index.

### Results

### Phylum Ratio [F/B and A/P] and Alpha Diversity

Alpha Diversity analysis demonstrated significant increases in diversity metrics (Shannon and Chao1 indices) in the "End" class compared to the "Base" class (p-value < 0.05 for both). This suggests that the supplementation led to an increase in both the richness (number of different species) and evenness (relative abundance of different species) of the gut microbial community indicating a positive impact of the DSNS (Figure S1(a), Figure S1(b)).

Table S1. Phylum ratio.

| Phylum | Baseline | Endline |
|---|---|---|
| Bacteroidetes | 75.784% | 67.089% |
| Firmicutes | 18.822% | 26.261% |
| Proteobacteria | 4.506% | 1.285% |
| Actinobacteria | 0.856% | 4.616% |

Table S2. F/B ratio & A/P ratio.

| | Baseline | Endline |
|---|---|---|
| F/B ratio | 0.25 | 0.39 |
| A/P ratio | 0.19 | 3.59 |

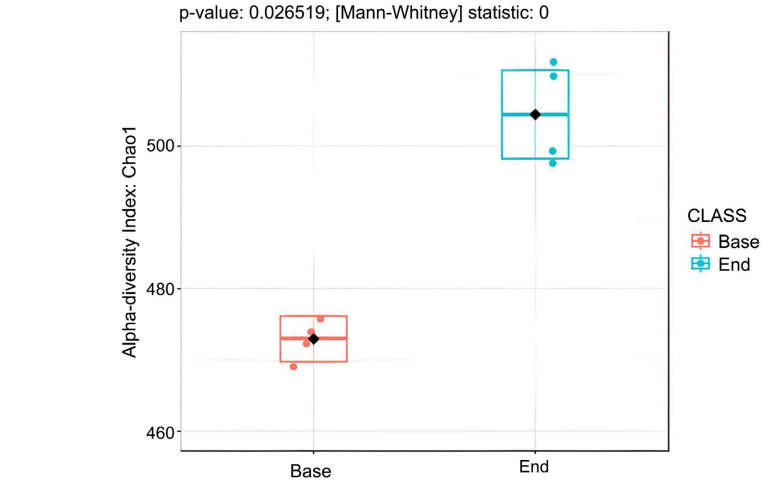
### Beta Diversity [NMDS]

Beta Diversity Analysis, a Non-metric Multidimensional Scaling (NMDS), based on Bray-Curtis dissimilarity, indicates a distinct separation between the "Base" and "End" microbial communities. The PERMANOVA analysis (F-value = 3.97, R-squared = 0.39, p-value = 0.038) confirms that the microbial community structure significantly differs between the two classes. This suggests that the supplementation induced a shift in the overall composition of the gut microbiome indicating a positive impact of the DSNS (Figure S1(c)). A higher number of samples within each cohort would further validate this positive shift in diversity.

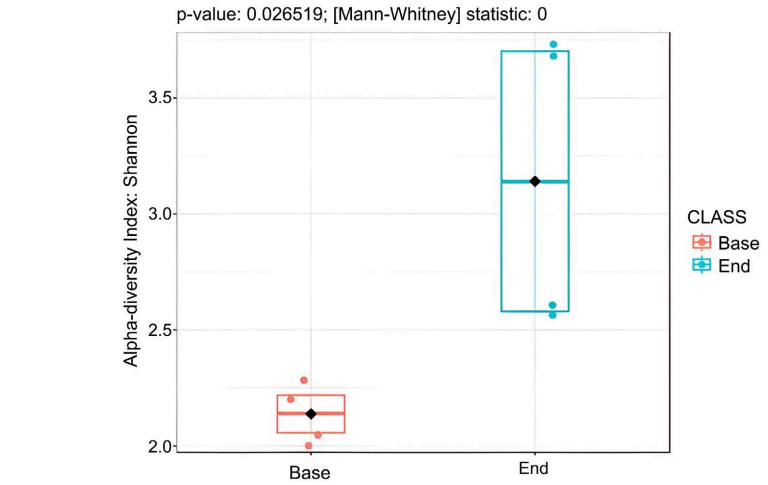
Differential Abundance Analysis estimated several phylum, genera and species to be significantly different in its abundance across the comparing groups. Gam-

maproteobacteria, which largely includes pathogenic species, showed a marked decrease in the abundance in the "End" class compared to the "Base" class. This aligns with the reduction observed for specific species like *Escherichia coli* and *Shigella sonnei* which belong to this class. Genus *Shigella* and specie *Shigella flexneri*, both were estimated to be decreased in their abundance the "End" group. Notably, several other species, including *Holdemanella biformis*, *Streptococcus lutetiensis*, and *Eubacterium sp TM05_53*, showed statistically significant reductions (low p-values and FDR values) in abundance after supplementation (**Figures S1(d)-(h)**).

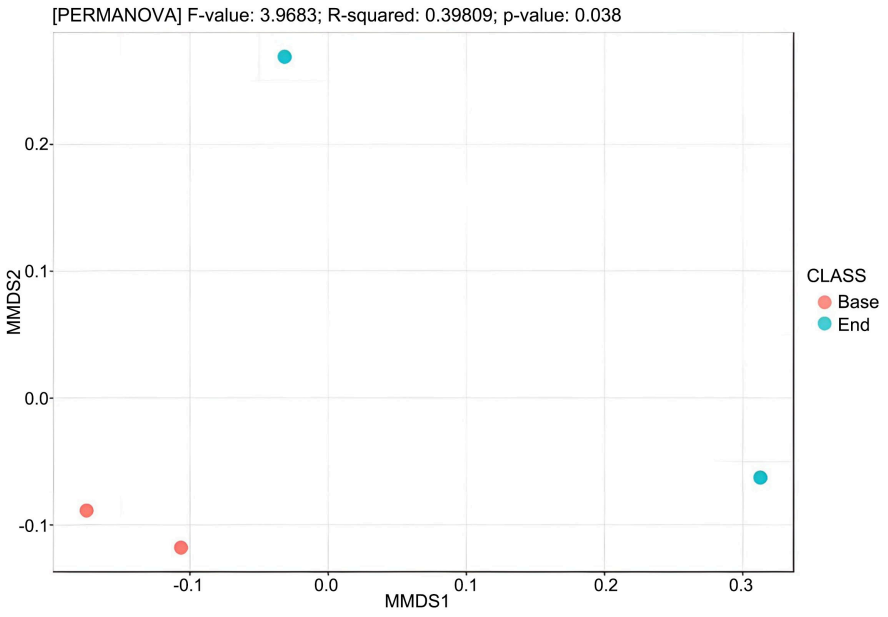
Overall, this preliminary exploration collectively suggests that the specific supplementation had a notable impact on the gut microbiome. This impact is characterized by an increase in overall microbial diversity (alpha diversity) and a significant restructuring of the microbial community composition (beta diversity). Furthermore, the analysis points to a consistent decrease in the abundance of several specific taxa, including members of Gammaproteobacteria like *Shigella* and *Escherichia*, and other species like *Holdemanella* and *Streptococcus*. These findings indicate a shift in the gut microbial ecosystem in response to the supplementation, with potential implications for host health that warrant further investigation.


p-value: 0.026519; [Mann-Whitney] statistic: 0
Alpha-diversity Index: Chao1
500
480
460
Base
End
CLASS
Base
End

(a)


p-value: 0.026519; [Mann-Whitney] statistic: 0
Alpha-diversity Index: Shannon
3.5
3.0
2.5
2.0
Base
End
CLASS
Base
End

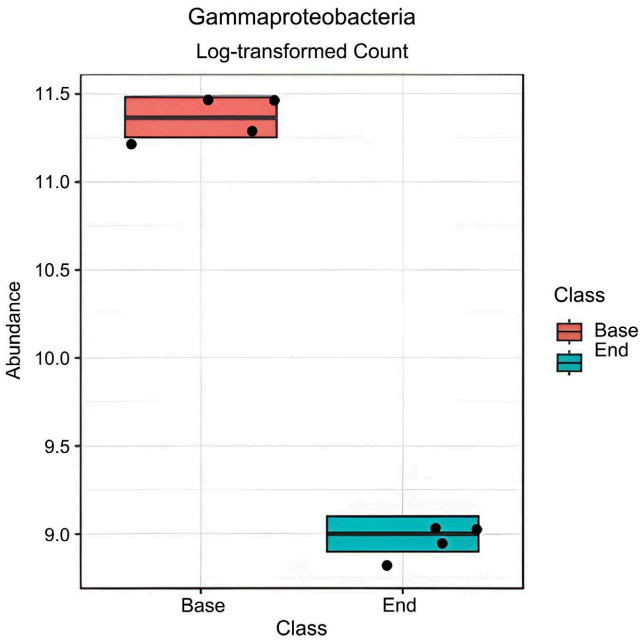
(b)


[PERMANOVA] F-value: 3.9683; R-squared: 0.39809; p-value: 0.038
MMDS2
0.2
0.1
0.0
-0.1
-0.1
0.0
0.1
0.2
0.3
MMDS1
CLASS
Base
End

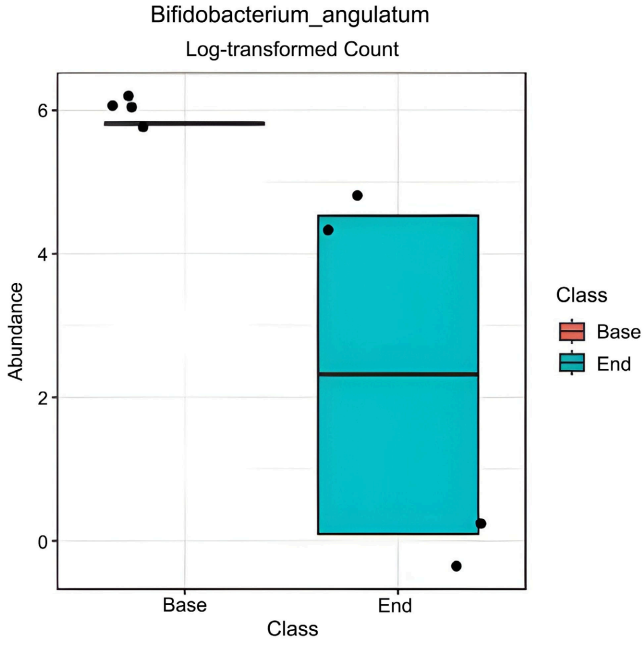
(c)

| Species | log2FC edgeR | Pvalue tt | FDR tt |
|---|---|---|---|
| *Holdemanella biformis* | -5.9851 | 1.7066E-10 | 8.738E-08 |
| *Shigella sonnei* | -5.1532 | 0.000244 | 0.00693 |
| *Escherichia coli* | -4.8225 | 0.000194 | 0.00583 |
| *Streptococcus lutetiensis* | -4.7436 | 0.000019 | 0.00095 |
| *Eubacterium sp TM05_53* | -4.4924 | 2.7117E-08 | 0.000004628 |
| *Escherichia sp MOD1_EC7003* | -4.4309 | 0.000064 | 0.00235 |
| *Holdemanella sp DFI_5_55* | -4.1905 | 6.3748E-08 | 8.1597E-06 |
| *Streptococcus equinus* | -3.8119 | 6.5944E-09 | 1.6882E-06 |
| *Holdemanella sp L34* | -3.6816 | 0.000036 | 0.00140 |
| *Coprobacillus sp K06* | -3.122 | 0.000003 | 0.00021 |

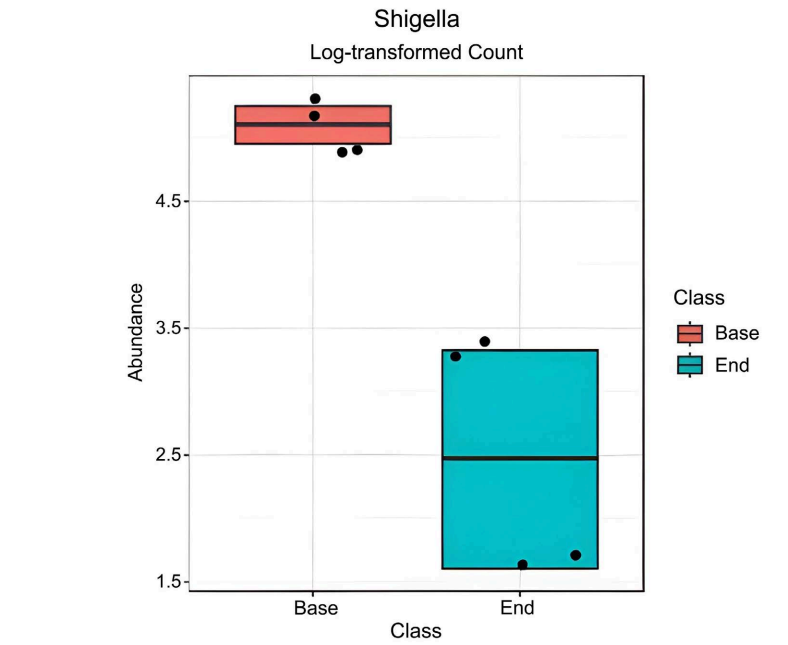
(d)



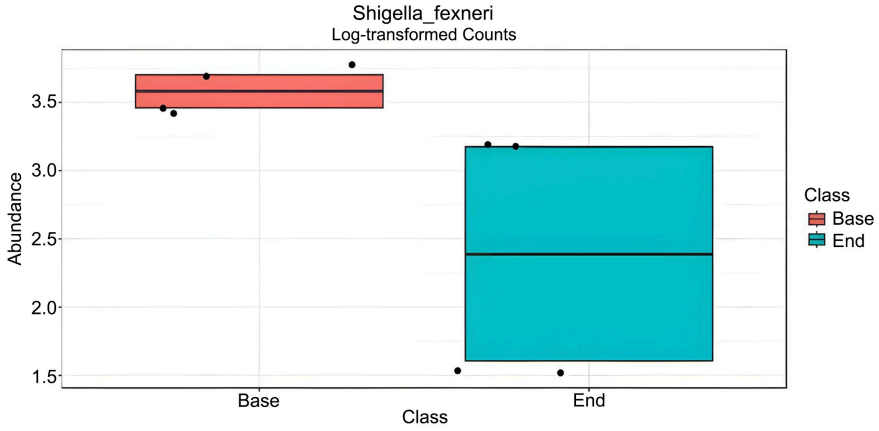

(e)




(f)




(g)




(h)

**Figure S1.** Alpha and beta diversity of intervention group.