Title: The synergy between cannabidiol and probiotics curtails the glycemic indicators, enhances insulin production, and alleviates the symptoms of type 2 diabetes.

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Running Title: CBD and probiotics in the treatment of Diabetes

Abstract

Introduction: Diabetes continues to challenge healthcare system as one of the most growing epidemics with staggering economic burden. It is estimated that 783 million by 2045 will live with diabetes worldwide, 90% of those cases are type 2 diabetes (T2D). T2D is a multifaceted disease, its treatment requires a holistic approach with wide range and impactful efficacy. High cost, time, side-effects, and lack of target comprehensiveness are examples of major shortcomings of existing modalities for T2D, make it difficult to contain incidence and to improve symptoms. There is a dire need to explore and invent new therapeutic modalities for T2D.
Cannabidiol (CBD), a derivative from cannabis plant, is shown to have beneficial effects in several diseases. Despite few hypothetical suggestions and case reports, there has been no methodic studies on the potential effects of CBD in the treatment of T2D.

Methods: We used a mouse model of T2D to test whether a CBD-based beverage combined with probiotics could affect the glycemic indices and alleviate the symptoms.

Results: Our findings demonstrated that combination of CBD and probiotics not only reduced the HbA1c significantly and lowered the blood glucose, but also altered the microbiome profile, promoted beneficial bacteria. CBD-based beverage could reduce peripheral inflammatory cytokines and enhanced insulin production in pancreatic islets.

Conclusions: Our results suggest that consuming CBD-based beverage containing probiotics could be used as a natural, affordable, and safe alternative therapeutic modality to treat T2D, reducing the side-effects and complications associated with pharmacologic interventions for T2D.

Introduction

Type 2 diabetes (T2D), known as the "silent epidemic" is emerging as one of the most pressing health-related challenges of our time (1). Globally, there are over half a billion individuals living with diabetes, of those, 96% are T2D (2-5). While almost 12% of whole population in the USA are living with T2D, there are additional 96 million individuals with pre-diabetes status (1-5). Given the estimate of 1.3 billion diabetics by 2050 (6), there is a dire need for new therapeutic strategies to prevent and treat diabetes. Despite significant advances in the treatment of diabetes through medications, however, there are growing high demands by public and industry for novel diabetic modalities based on natural approaches rather than chemical compounds and medications. This is mainly because of potential side effects as well as many unknown about current medications and high impact of dietary habits on the progression of T2D.

Cannabidiol (CBD) is one of the major phytocannabinoids produced by cannabis plants. CBD is a non-psychoactive cannabinoid which makes it generally safe compound compared to tetrahydrocannabinol (THC), the other well-known cannabinoid with psychoactive effects. Recent work by our laboratory and others suggest beneficial effects of CBD alone or in combination with other cannabinoids and compounds in the treatment of a wide spectrum of pathologic conditions and diseases (7-8). Several studies have shown the effects of CBD in the treatment of diabetes and hypothetical mechanisms have been suggested to explain the potential alleviating effects of CBD in diabetes based on CBD's counter inflammatory and antioxidant features (9-11). However, there is a substantial knowledge gap in understanding any potential CBD's mechanism of action in general, and specifically regarding diabetes, warrants further research and scientific investigations.

Gut microbiome and its impact on metabolic diseases such as diabetes has been extensively investigated (12-13). Increasing evidence suggests that microbial profile of digestive system plays a crucial role in regulation of inflammatory responses and re-establishing homeostasis (14-15). Interventional strategies such as microbiome graft and dietary probiotics have shown beneficial effects in diabetes which may suggest the potential therapeutic connection between microbiome alteration and improving the symptoms of diabetes, particularly T2D based on its reliance on the dietary habits and quality.

In this study, we investigated if a new commercially available beverage containing a combination of CBD and probiotics could alleviate the symptoms of T2D. To test, a T2D mouse model, db/db mice were used and treated with beverage consists of CBD and probiotics. In addition to fasting blood glucose (FBG) and hemoglobin A1c (HbA1c) level, behavioral testing, as well as flow cytometric, histologic and immunohistologic analysis were performed. Our findings demonstrated that a combination of CBD and probiotics could improve the symptoms of T2D significantly, suggesting a novel therapeutic application for CBD in th treatment of T2D.

Materials and methods

- **Animals**: Fourteen-week-old male db/db mice were obtained from the Jackson Laboratories (Boston, MA, USA) and housed in the laboratory animal facilities at Augusta University. The db/db mice are well-established/accepted mouse models to study diabetes type II and obesity. Homozygous db/db mice for the diabetes

spontaneous mutation ($Lepr^{db}$) are characterized by major symptoms of morbid obesity, chronic hyperglycemia, pancreatic beta cell atrophy and come to be hypoinsulinemic. The use of animals for these studies were in accordance with ethical standards and was approved by the Institutional Animal Care and Use Committee.

- **Experimental design and treatment**: Mice were divided into two experimental groups of treated and non-treated. Treated group, received the beverage "CANABIX" provided by Hydro One beverages, LLC (Greenwood SC, USA). CANABIX drink is the commercially available formulation of combined CBD isolate (30mg) and probiotics (*Bacillus coagulans* MTCC 5856, LactoSpore®, Sabinsa USA). For treated group (n=8), the daily drinking water was replaced by beverage CANABIX for the period of 9 weeks (~45-50 ml/week). The non-treated group (n=8) received no treatment, only given regular drinking water.

- **Measurement of FBG and HbA1c**: To test FBG levels, all db/db mice were fasted for 15 hours once a week followed by blood collection through tail into a heparinized tube. Blood glucose meters (ACCU-CHEK; Roche, Indianapolis, IN, USA) was used to measure FBG. To test the average blood glucose level, HbA1c levels was measured weekly for a period of 9 weeks by A1CNOW® test systems (IN, USA) using mice tail blood.

- **Fecal Microbiome assessment**: Fresh fecal samples (2-3 pellets/mouse) were collected, immediately frozen, and stored in a –80 ◦C freezer until analysis. DNA Extraction, Library Preparation, Sequencing DNA extraction and library preparation were performed by Novogene Lab (Durham, NC, USA). Briefly, 16S rDNA amplicon was sequenced on Illumina paired-end platform to generate 250 bp paired-end raw reads (Raw PE), and then merged and pretreated to obtain Clean Tags. The chimeric sequences in Clean Tags were detected and removed to obtain the Effective Tags which can be used for subsequent analysis. After quality-filtering the sequencing files, high resolution assignment of operational taxonomic units (OTUs) was done using a sub-operational taxonomic unit (sOTU) approach, Deblur, to identify microbial sequences. Mothur was then used for taxonomy calling with the silva128 database, assigning microbial sequences at the genus level. The TRE file was constructed using FastTree.

- **Analytic Flow Cytometry**: For flow cytometry analysis, whole blood was collected using heparinized capillary tubes from hearts. Cells were first incubated with antibodies against cell surface markers CD 45, CD3, CD4, CD11b, CD68, and then fixed and permeabilized using fixed/permeabilized concentrate (eBioScience) before incubation with antibodies for intracellular labeling of TNFα and IL-17 (BD BioSciences, Bedford, MA, USA). After one wash, cells were run through a a NovoCyte Quanteun and analyzed by FlowJo analytical software. As a gating strategy, for each sample, isotype-matched controls were analyzed to set the appropriate gates. For each marker, samples were analyzed in duplicate measurements. To minimize false-positive events, the number of double-positive

events detected with the isotype controls was subtracted from the number of double-positive cells stained with corresponding antibodies (not isotype control), respectively. Cells expressing a specific marker were reported as a percentage of the number of gated events. The FlowJo plugin for the algorithm "uniform manifold approximation and projection" (UMAP) was used to perform dimension reduction of down-sampled and concatenated data sets.

- **Immunohistochemistry analysis**: Freshly harvested pancreas tissues from db/db mice were collected and processed for Immunohistochemistry staining and imaging. Briefly, pancreas tissues were fixed with 10% neutral buffered formalin (Sigma USA), processed, and then embedded with conventional dehydrated paraffin. All subsequent procedures were performed at room temperature as described previously (7). Briefly, all slides were rehydrated and endogenous peroxidase activity was blocked using hydrogen peroxide diluted 1:10 with distilled water for 10min. Sections were treated with proteinase K for 10min and washed twice in phosphate buffered saline (PBS). Next, slides were incubated with antibody against Insulin (R&D USA), for 2 h at room temperature. Biotinylated immunoglobulins (Biogenex USA) were added to all slides for 20min. After two washes with PBS, all slides were incubated with peroxidase-conjugated streptavidin (Biogenex) for 20 min followed by two washes in PBS. All slides were then treated with chromogen (Dako USA) until clearly detectable color appeared. Excess chromagen was decanted and all slides were washed by distilled water. All preparations were counterstained with hematoxylin for 3 min and mounted in an aqueous mounting (Lerner Laboratories) before the analysis using bright field Zeiss (AXIO Imager M2) light microscope and further analysis for area intensity using ImageJ software (version 1.53e).

- **Statistics**: For statistical analysis, Brown-Forsythe and Welch analysis of variance (ANOVA) was used to establish significance ($P<0.05$) among groups. For tissue quantification statistical analysis, we compared the area of expression in both treated with beverage and non-treated groups by using two-way ANOVA followed by post- hoc Sidak test for multiple comparison ($P<0.05$).

Results

- **Combination of CBD and probiotic showed antidiabetic activities, reduced HbA1c and plasma glucose.** Drinking of CANABIX beverage for nine weeks resulted in significant reduction of HbA1c (from 7 to 4, $P<0.05$) compared to drinking regular daily water (Figure 1A). In addition, drinking CANABIX lowered plasma glucose (from 306 to 235, $P>0.05$) compared to using regular water (Figure 1B), suggesting hypoglycemic activities of combined CBD and probiotic formulation in the treatment of T2D.

- **Combination of CBD and probiotic altered microbiome profile in mice with T2D.** Drinking CANABIX beverage for the period of nine weeks resulted in significant alteration of several bacterial phyla within gut microbiome. While changes were observed for most frequently phyla, however, Dubosiella and

Lactobacillus showed the most significant increase compared to the control diabetic mice drinking regular water (Fig 2A-B). in result of drinking combined CBD and probiotic beverage of CANABIX compared to group drinking regular water. This was an important findings because Dubosiella is shown to have anti-aging functions by reducing oxidative stress, improving vascular endothelial function, and redistributing gut microbiota (16). In addition, Lactobacilli are known to have inhibitory effects on harmful bacteria by producing lactic acid, significantly reduce HbA1c, fasting insulin levels, and HOMA-IR levels in T2D (17).

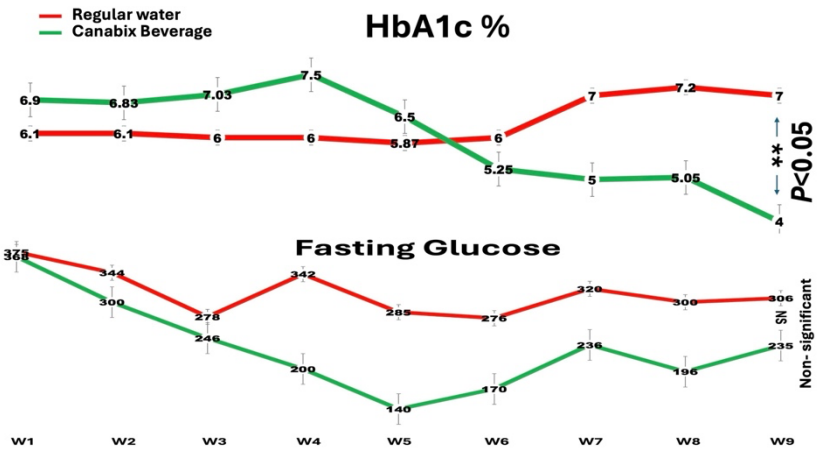

Figure 1. Combined CBD and probiotics formulation lowered glycemic control measures in a mouse model of T2D. Graphical representation of the pattern of hemoglobin A1c (HbA1c) (upper panel) trends in db/db mice with T2D drinking regular water (red line) or CANABIX beverage (green line). At 6 weeks after consuming CBD and probiotics beverage (CANABIX), HbA1c was reduced and at after 9 weeks it was significantly lowered compared to the mice drinking regular water only (4 versus 7, *P*<0.005). The lower panel demonstrates the trends of fasting blood glucose. Mice with T2D showed reduction of fasting blood glucose after drinking CANABIX starting at week 3 (green line) compared to their counterparts drinking regular water only (red line).

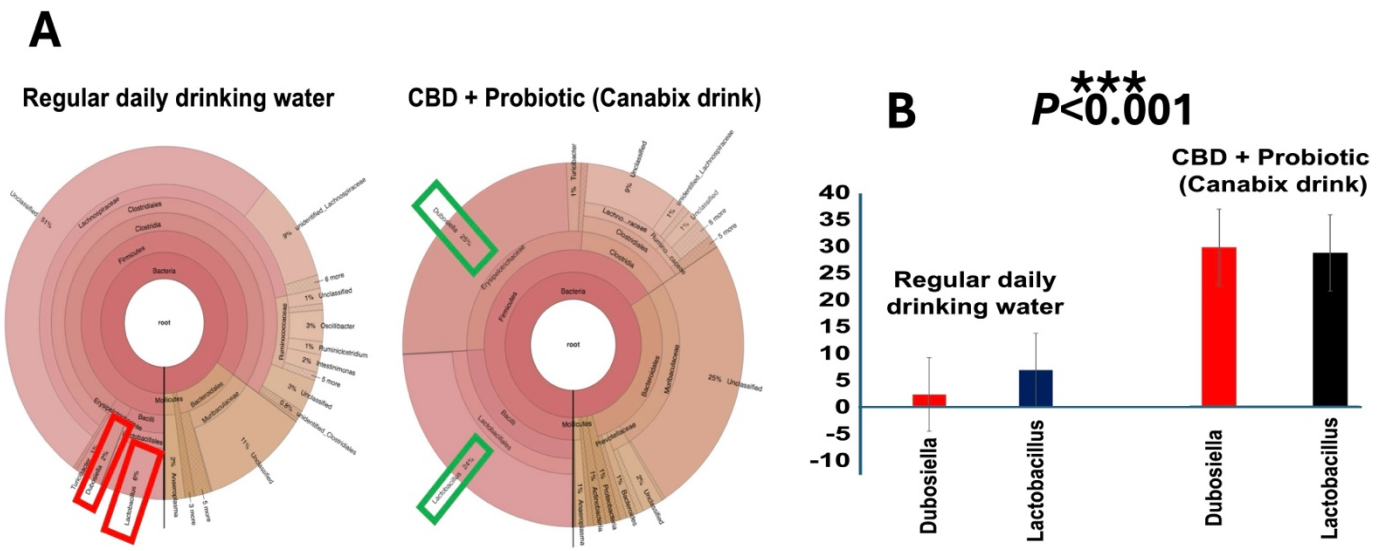

Figure 2. Combined CBD and probiotics formulation altered microbiome sketch in mice with T2D. Drinking CANABIX beverage for the period of nine weeks resulted in significant changes of several bacterial profile within gut microbiome. The most changes were observed in Dubosiella and Lactobacillus (A) showed the most significant (*P*<0.001). Both bacteria, Dubosiella and Lactobacilli, have protective and positive effects, helping alleviation of diabetic symptoms.

- **Combination of CBD and probiotic regulated proinflammatory responses, improving insulin resistance in mice with T2D.** Drinking CANABIX beverage for the period of nine weeks resulted in significant reduction of proinflammatory cytokines, TNFα and IL-17 (fig 3), to help re-establishing homeostasis and improving symptoms of T2D, particularly the insulin resistance which is directly related to those inflammatory cytokines (18-20). Figure 3A demonstrates the analysis of flow cytometry data using the FlowJo software plugin for the algorithm UMAP. The UMAP subtraction analysis revealed numerous spatial clusters with significant distribution differences between diabetic mice (db/db) drinking CBD/probiotic (CANABIX) and mice drinking regular daily water. Bargraphs chart in figure 3B demonstrates the quantified measures for cytokines, TNFα and IL-17, significantly reduced in mice drinking CANABIX versus regular drinking water.

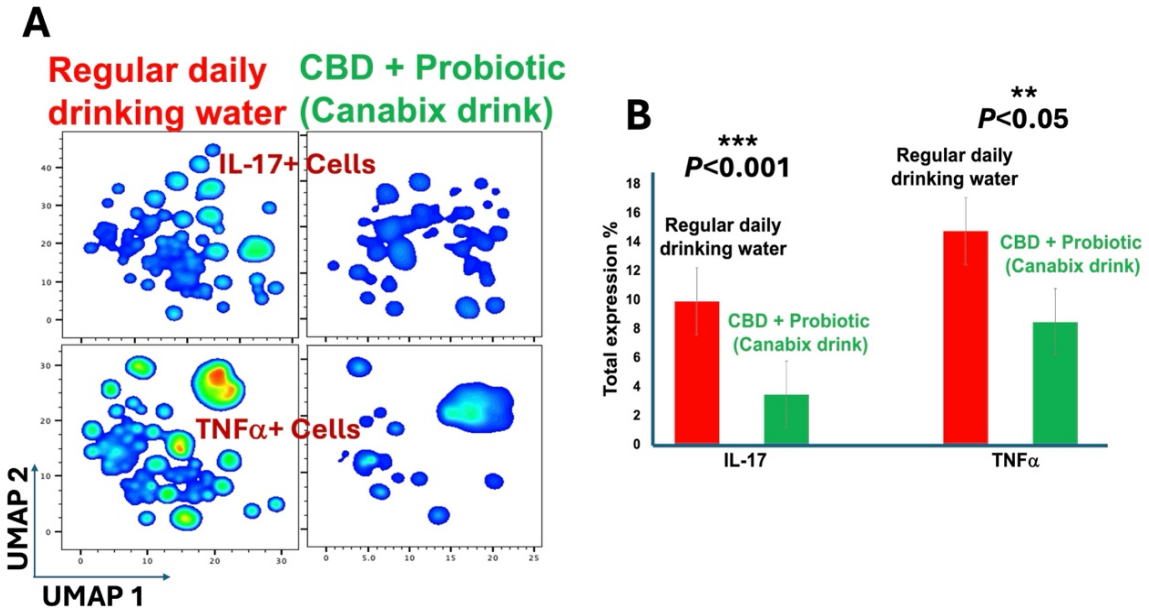

Figure 3. Combined CBD and probiotics formulation reduced inflammatory cytokines and changed the map of proinflammatory signals in mice with T2D.
A) Flow cytometry and UMAP analysis showed that consumption of CANABIX beverage with CBD and probiotics resulted in significant reduction of proinflammatory cytokines, TNFa and IL-17, and altered the distribution pattern of both TNFa and IL-17. B) The bargraphs in the chart show the quantification of cytokine expression in the peripheral blood in mice drinking regular water versus CANABIX beverage.

- **Combination of CBD and probiotic enhanced insulin production in pancreatic islets of mice with T2D.** Drinking CANABIX beverage for the period of nine weeks resulted in significant increase of insulin production in the pancreatic islets (Fig 4). Insulin production was minimized in pancreatic islets of db/db mice.

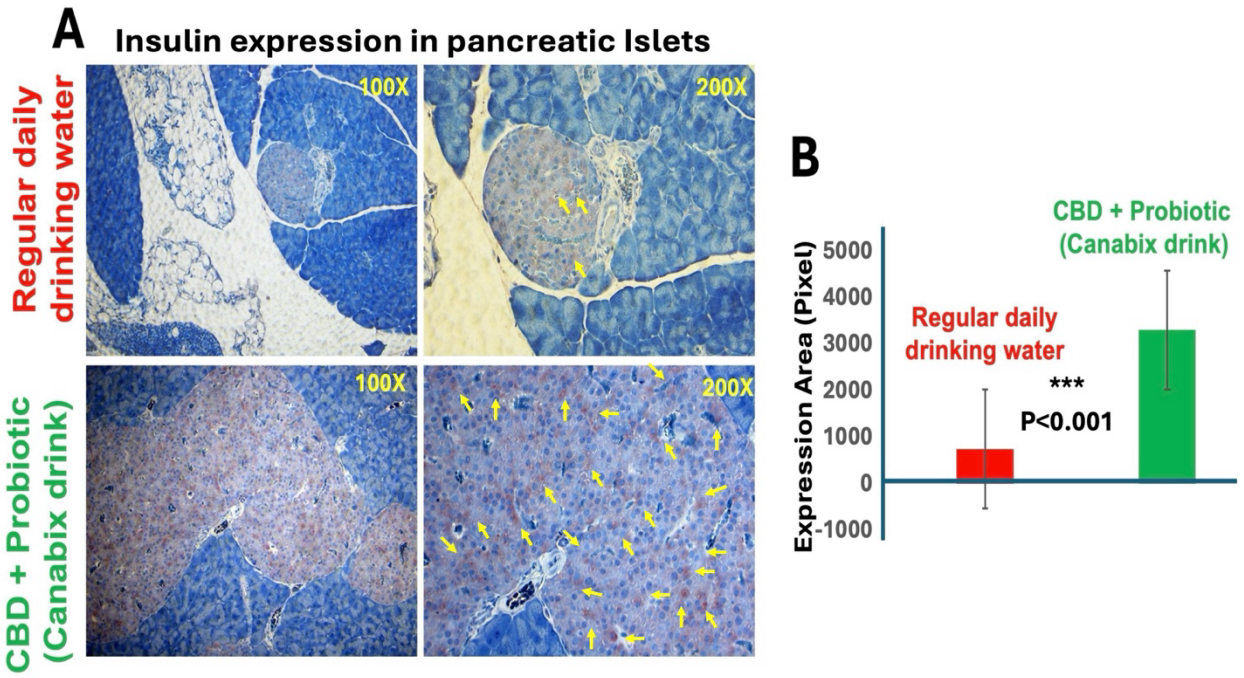

Figure 4. Combined CBD and probiotics formulation enhanced insulin production in pancreatic islets. Drinking CBD-based CANABIX beverage augmented insulin production in pancreatic islets of mice with T2D significantly higher than diabetic mice drinking regular water (resulted in significant changes of several bacterial profile within gut microbiome. The most changes were observed in Dubosiella and Lactobacillus (A) showed the most significant (*P*<0.001). Both bacteria, Dubosiella and Lactobacilli, have protective and positive effects, helping alleviation of diabetic symptoms.

Discussion

The novel findings here in this current study are the first to demonstrate a significant beneficial impact of a CBD-based beverage, CANABIX, on diabetic indices in a pre-clinical model of T2D. A significant reduction of HbA1c and lower fasting blood glucose (non-significantly) in a period of 9 weeks through a non-invasive and a CBD-based supplementary beverage could be a potential game changer in diabetic care.

Diabetes continues to threaten global health and remains as a major economic burden worldwide (1). Regarded to as one of the most challenging "post-modern world epidemics", T2D diabetes (90% of all total diabetes cases) not only incapacitates functional and working individuals worldwide, but also affects people's life quality and is resulted in a wide range of complex pathologic conditions with higher mortality (1). During last two decades, world has witnessed major advancements in the treatment of T2D including, not limited to, introduction of insulin analogs, development of new ways of insulin delivery systems, pharmacologic innovations (e.g., GLP-1 agonists etc.), genetic approaches and even psychologic and behavioral therapies (21-22). Despite all achievements, diabetes is expected to rise to a towering level of 643 million by 2030 and the total number of 783 million by 2045 worldwide (1,6), 90% of those will be T2D. Such exponential growth is simply because T2D is a disease with multifaceted nature and several factors including diet, dehydration, medications, stress, sicknesses, pain, physical activities, general lifestyle and importantly, the socioeconomic status will influence the

T2D management and clinical outcomes (23-24). Given the high cost and time of developing a drug, side-effects, issues with availability and monitoring, it is thus a dire need to explore and invent alternative strategies to prevent and treat T2D in an affordable, safe, and more effective ways.

The beneficial effects of CBD in reducing the HbA1c and controlling blood glucose were in form of a dietary supplement (CANABIX beverage) providing hydration, highly important in alleviating T2D symptoms. Further, the CANABIX beverage contains beneficial bacteria as a probiotic supplement. Mounting evidence accentuates the significant role of probiotics in glycemic control, helping prediabetes and improvement of digestion. Based on our novel findings, the combination of CBD and probiotics as tested here in this study, suggest a highly effective beneficial synergy between CBD and microbiome in reducing the major adversarial symptoms of T2D in a safe, non-invasive, highly feasible and very affordable fashion. Additionally, individuals with T2D are at higher risk of anxiety (25). CBD is known not only as a potent regulator of inflammation, but also as an effective anxiolytic agent, which could help people with T2D to maintain and continue their daily life with higher quality.

Further, our findings showed that consumption the CANABIX beverage containing CBD and probiotics in its formulation induced a significant reduction in the expression and distribution patterns of IL-17 and TNFα. Both IL-17 and TNFα are prominent inflammatory cytokines and well known for their contribution and roles in the development of insulin resistance (18-20). Therefore, the downregulation of both IL-17 and TNFα by CANABIX beverage could suggest a very effective and reliable strategy to improve and control the glucose level in diabetes, requires more investigations and clinical trials. More importantly, CANABIX beverage increased insulin production in pancreatic islets of db/db mice. This is highly significant observation since it can effectively control the blood glucose and improve the clinical outcomes significantly. This augmentation of insulin production by a CBD-beverage is highly significant due to lack and inadequacy of treatments to boost insulin production naturally in diabetic patients.

In conclusion, our findings here in this study shows that a combination of CBD and probiotics in form of a natural beverage could be highly effective in controlling the glycemic index and blood glucose in T2D. The beneficial effects observed in this study introduce the combination of CBD and probiotics as an alternative novel modality in the treatment of T2D with the holistic impact on total health, minimal side effects, affordable and highly non-invasive compared to all current costly and invasive existing pharmacologic treatments for T2D and their potential side-effects. There are limitations in current study such as power analysis and experimental groups. However, these novel findings and the dire need for more effective treatments of T2D provide sufficient rationale and justifications for a full human clinical trial and warrant further research on combination of CBD and probiotics, particularly in the form of beverage as presented and tested in this study.

Abbreviations:

CBD: Cannabidiol; FBG: Fasting Blood Glucose; GLP-1: Glucagon-like peptide 1; IL-17: Interleukin-17; HbA1c: Hemoglobin-A1c; THC: Tetrahydrocannabinol; TNFα: Tumor necrosis factor alpha; T2D: Type 2 Diabetes; UMAP: Uniform Manifold Approximation and Projection.

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Declaration of Competing Interest: 1- Lei P Wang, Babak Baban, and Jack Yu are members of Medicinal Cannabis of Georgia with no financial interest. 2- Babak Baban is affiliated with Hydro One beverages. 3- All other authors declare no conflict of interest. 4- Hydro One beverages is the provider of CANABIX beverage.

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Data availability statement: All data supporting the findings of this study are available within the paper and also are available upon request from the corresponding author.

Ethical publication statement: We (authors) confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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