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Effects of Cinnamaldehyde on the Gut Microbiota Composition in Patients with Type 1 Diabetes Mellitus

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Abstract: Objective To investigate the effects of cinnamaldehyde on the gut microbiota composition in patients with type 1 diabetes mellitus (T1DM). **[Methods]** A total of 20 T1DM patients meeting inclusion/exclusion criteria were enrolled in a randomized, double-blind, parallel-group controlled clinical trial. Patients were randomly assigned to two groups: the cinnamaldehyde group received 120 mg/day of cinnamaldehyde after breakfast alongside their existing medication regimen, while the control group continued standard treatment without cinnamaldehyde supplementation. The intervention lasted 42 days. Clinical data including fasting blood glucose levels were monitored, and fecal samples were collected via mid-stream swab sampling at both baseline and post-intervention stages for metagenomic sequencing analysis of gut microbiota. **[Results]** In the cinnamaldehyde group, reductions in HbA1c and blood glucose coincided with decreases in triglycerides, HDL-C, ALT, AST, and serum creatinine levels. Conversely, these parameters increased in the control group, with statistically significant elevations observed in total cholesterol and ALT ($P < 0.05$). These findings suggest that cinnamaldehyde adjunct therapy effectively enhances glycemic control while mitigating drug-related adverse effects. **[Conclusion]** Cinnamaldehyde administration promoted enrichment of probiotic bacteria including *Akkermansia*, *Bifidobacterium adolescentis*, and *Faecalibacterium prausnitzii*. It modulated the abundance of functional microbial taxa critical for metabolic disorders, thereby improving host glucose and lipid metabolism. Daily cinnamaldehyde supplementation combined with insulin therapy significantly improved glycemic control, reduced medication side effects, enhanced gut microbiome diversity, and optimized the intestinal microecological environment in T1DM patients.

Keywords: Cinnamaldehyde; Gut Microbiota; Type 1 Diabetes Mellitus.

1. Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease triggered by the destruction of pancreatic islet β-cells due to genetic and environmental factors (Sami et al., 2025) [1].Family linkage analysis and genome-wide association studies have identified more than 50 susceptibility genes for T1DM. Among them, the HLA - DR and - DQ genes account for approximately 40% to 50% of the disease risk. Genetic susceptibility cannot explain the rapid increase in the incidence of T1DM worldwide. The pathogenesis of T1DM is an organ - specific immune disease characterized by T - lymphocyte - mediated damage to pancreatic islet β - cells, which is initiated by environmental factors on the basis of genetic susceptibility(Mittal et al., 2024) [2]. The intestine is the largest immune organ in the human body. The exchange of substances between gut microbiota and the host on the intestinal mucosal surface promotes the establishment and development of the immune system. An increasing number of studies on human and animal models have explored the role of the gut microbiome in the pathogenesis of T1D from different perspectives, strongly suggesting that the gut microbiome may be a key hub for environmental factors. The disturbance of the intestinal immune response and the destruction of the intestinal mucosal barrier may be one of the main factors triggering T1DM(Nikola & Iva, 2024)[3].A Finnish study detected the gut microbiota of 8 children who had not yet developed autoimmune diabetes and found significant differences in the microbiota structure between children with T1DM and their peers of the same age. Children with T1DM had low gut microbiota diversity and poor stability(Liu et al., 2021)[4].Murri's study further found significant differences in the abundances of Bifidobacterium, Lactobacillus, Fusobacterium, and the ratio of Firmicutes to Bacteroidetes between the T1DM group and the normal control group (Zhou et al., 2020)[5]. Among them, the abundances of Bifidobacterium and Lactobacillus were negatively correlated with blood glucose levels, while the abundance of Fusobacterium was positively correlated with blood glucose levels(Zhou et al., 2020)[6].A population study in Mexico found that the genus Bacteroidetes was enriched in the intestines of newly diagnosed children with T1DM. Compared with the normal group, the abundances of Prevotella, Megamonas, and Acidaminococcus decreased significantly. After 2 years of insulin treatment, the gut microbiota abundance of children with T1DM was between that of newly diagnosed diabetic children and the control group. These studies all indicate that significant changes have occurred in the gut microbiota of people with T1DM, manifested as a decrease in the proportion of probiotics and microbiota diversity. In people with the same HLA genotype, the differences in disease occurrence are related to changes in the structure and function of the gut microbiota. Drug treatment not only improves the disease phenotype but also promotes the normalization of the gut microbiota structure. Therefore, the gut microbiota is an important target for the treatment and improvement of autoimmune diabetes. Since 2003, multiple research teams including Khan have reported that Chinese herbal medicine Cinnamon and its main active ingredient cinnamaldehyde can improve blood glucose and lipid metabolism in diabetic patients. To observe the effect of cinnamaldehyde on the gut microbiota of Chinese patients with T1DM, this small - scale, randomized, double - blind clinical trial targeting the gut microbiota with cinnamaldehyde intervention in patients with T1DM was carried out (Khan et al., 2003)[7].

2. Materials and Methods

2.1. Research Subjects

(1) Diagnostic Criteria for T1DM

1) The diagnostic criteria for all patients conformed to the 2020 American Diabetes Association (ADA) guidelines.

2) The course of the disease was more than 6 months; glycated hemoglobin (HbA1c) > 7.0% and fasting blood glucose (FBG) > 8.0 mmol/L.

3) Patients understood the whole process of the experiment, voluntarily participated, and signed the informed consent form.

4) There was no history of severe diseases in major organs such as the gastrointestinal tract, heart, liver, and kidneys. Liver function was normal, and serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were < 1.2 times the upper limit of the normal value.

5) Renal function was normal, serum creatinine < 140 μmol/L; patients were not complicated with severe acute or chronic diabetic complications and did not use insulin to control blood glucose.

(2) Inclusion Criteria for Patients

1) Glycated hemoglobin (HbA1c) > 7.0% and fasting blood glucose (FBG) > 8.0 mmol/L.

2) The age ranged from 15 to 45 years.

3) All subjects were Han Chinese individuals who had lived in Shenzhen for more than five years.

(3) Exclusion Criteria for Patients

1) Patients with type 2 diabetes complicated with severe diabetic complications.

2) Patients who had suffered from severe diarrhea or constipation in the past three months.

3) Patients with heart disease, renal insufficiency, uremia, and other autoimmune diseases.

2.2. Experimental

Grouping From September 2018 to December 2018, 20 patients with T1DM were enrolled in Shenzhen Sun Yat - sen Cardiovascular Hospital. Referring to the inclusion and exclusion criteria and following the standards of a randomized parallel - controlled clinical trial, patients were divided into two groups using a randomized double - blind method. There was no statistically significant difference in the basic data of the patients, as shown in Table 1. Cinnamaldehyde Group: On the basis of the original drug dosage remaining unchanged, 120 mg of cinnamaldehyde (Shanghai Yitian Biotechnology Co., Ltd., batch number: 20181005, Chinese health food approval number: G20110080) was added after breakfast every day. Control Group: Patients with T1DM took their normal medications without taking cinnamaldehyde.

2.3. Observation Methods and Indicators

The implementation period of the intervention experiment was 42 days. Clinical data of patients were collected. Patients were followed up once a week during the study period to monitor changes in fasting blood glucose, observe the drug effects and adverse reactions, etc. FBG and HbA1c were measured before medication and at the end of the 6th week after medication. Fecal samples were collected at the initial and end stages of the intervention experiment. Samples from the middle part of the feces were taken with a swab, placed in a sample storage tube, and then stored in a - 80°C freezer for the gut microbiota metagenomic sequencing test.

2.4. Statistical Methods

Data of clinical indicators such as body weight and blood glucose were statistically processed using SPSS 24 and Prism 6 software. The test results were presented as mean ± standard deviation (mean ± SD). One - way analysis of variance and t - test were used to conduct tests on the cinnamaldehyde group and the control group.

3. Main Results and Discussion

3.1. General Information

Table 1. Comparison of patients' basic data

Clinical factors	Cinnamaldehyde Group (n=10)	**Control Group** (n=10)	x2	P
Sex				
Male	6	8		
Female	9	7		
Age	33.6±2.3	31.8±4.6	2.946	0.067
Smoking history	2(43.5)	3(17.1)	16.281	0.054
History of alcohol consumption	3(12.8)	5(12.8)	0.036	0.849
Hypertension	7(74.4)	7(75.6)	2.113	0.146
TC(x±s, μmol/L)	5.7±0.7	5.4±0.8	0.629	0.431
LDL-C(x±s, μmol/L)	3.7±0.8	3.3±0.7	0.715	0.395
HDL-C(x±s, μmol/L)	1.1±0.6	1.1±0.4	1.316	0.294
HbAlc(x±s, %)	6.9±1.2	7.0±1.3	4.044	0.078
UA(x±s, μmol/L)	305.8±68.9	325±76.5	2.462	0.032
Cr(x±s, μmol/L)	70.4±14.7	77.0±17.5	1.430	0.670
hs-CRP(x±s, mg/L)	14.5±6.5	13.7±5.4	2.701	0.099
Body weight(Kg)	68.3	70.1		0.120

3.2. Integrity Check of 16S rRNA Sequences of the Gut Microbiota Structure in the Population Intervened by Cinnamaldehyde

The off - machine data of 16S rRNA high - throughput sequencing were processed using the QIIME standard analysis pipeline. Usearch was used for clustering at a similarity level of 0.97. Chimeric sequences were filtered from the clustered sequences to obtain the OTUs (Operational Taxonomic Units) for species classification. These OTUs were further compared with the SILVA 128 database for phylogenetic level annotation. The results of the data integrity check are shown in Table 3.2. A total of 20 intestinal samples were collected in this batch, yielding 908,213 reads and 5,408 OTUs. Among them, the number of non - singleton OTUs was 3,833, and the average number of sequences per sample was 41,955 reads.

Table 2. Quality control test results of 16S rRNA sequences

File format:	biom
OTU annotation:	QIIME
OTU number:	5408
OTUs with ≥ 2 counts:	3833
Number of experimental factors:	2
Total read counts:	908213
Average counts per sample:	41955
Maximum counts per sample:	102039
Minimum counts per sample:	11026
Phylogenetic tree uploaded:	No
Number of samples in metadata:	20
Number of samples in OTU table:	20
Sample names match (metadata vs. OTU table):	Yes
Number of sample names matched (metadata vs. OTU table):	20
Number of samples that will be processed:	20

3.3. Analysis of Gut Microbiota Alpha Diversity

Due to the large differences in the number of reads corresponding to different samples, we randomly rarefied the data of each sample and evaluated whether the sequencing depth of the samples met the analysis requirements. Under the condition of a sequencing depth of 15,000 reads, the richness index curves of species diversity all entered the plateau phase. This study evaluated the α-diversity of the two batches of samples based on the Chao1 index. The Shannon index of the cinnamaldehyde group was higher than that of the control group, indicating that the intake of cinnamaldehyde promoted the improvement of the gut microbiota diversity in patients with type 1 diabetes mellitus (T1DM), which was beneficial to the improvement of the microbiota microenvironment. As shown in Figure 2, during the cinnamaldehyde administration period, the median of the Chao1 index in the control group was slightly higher than that in the cinnamaldehyde group. The results of one-way analysis of variance showed no significant difference between the two groups, indicating that the administration of cinnamaldehyde had little effect on the gut microbiota richness between the two populations. Therefore, the effect of cinnamaldehyde supplementation on the α-diversity of the human gut microbiota was more reflected in the improvement of the homogenization degree of the gut microbiota within individuals during the administration period, and the differences between different groups were not significant.

3.4. Cluster Analysis of Core Microorganisms

This study used the method of core microbial detection to identify the core taxonomic units or features with invariant composition in the entire microbial community. When conducting core microbiome analysis, two parameters need to be considered. The first is sample prevalence, which is defined as the minimum fraction of samples that must adhere to a taxon or feature. The other parameter is the relative abundance of taxonomic units or features in order to consider them as part of the core members. The results of this analysis are presented in the form of a heatmap of core taxa or features, where the Y - axis represents the prevalence of core features within the detection threshold range on the X - axis. Figure 4 shows the results of the core microbiome presented in the form of a heatmap, and Table 3 summarizes the changing characteristics of the main dominant strains in Figure 4. Notably, in the cinnamaldehyde group, the relative abundances of Clostridium perfringens, Dialister invisus, Gemella sanguinis, and Bifidobacterium longum increased. The above - mentioned strains are mainly related to intestinal permeability, indicating that the intake of cinnamaldehyde can regulate the microenvironment of the intestinal endothelium, affect the transmission of metabolic small - molecule compounds and signaling molecules through changes in osmotic pressure, and further influence blood glucose regulation through receptor binding. The relative abundances of multiple probiotics increased in the cinnamon group, including Akkermansia, Bifidobacterium adolescentis, and Faecalibacterium prausnitzii. There were no significant differences in the relative abundances of the above three functional strains in the control group. This result is consistent with the changing characteristics of osmotic - pressure - related functional strains. The changes in the abundances of these functional strains together indicate that the intake of cinnamaldehyde can improve the intestinal microenvironment and promote the enrichment of more probiotics. In addition, the abundances of common Bacteroides such as Bacteroides adolescentis, Roseburia faecis, and Bacteroides genus showed a decreasing trend in the cinnamon group, and the ratio of Bacteroidetes/Firmicutes also decreased. Overall, these all reflect the transformation of the intestinal flora structure from the characteristics typical of type I diabetes to those of a healthy intestinal type. The intestinal characteristics of the control group generally showed a decrease in the number of bacteria producing short - chain fatty acids (SCFAs) and bacteria producing lactic acid. Further exploration of the distribution patterns of the intestinal flora structure of 20 samples at different taxonomic levels was carried out. We compared the distribution characteristics of the dominant flora at the species level. Bacteroidia belonging to Bacteroidetes showed a gradually decreasing trend in abundance ($p > 0.05$), while Deltaproteobacteria belonging to Proteobacteria showed a gradually increasing trend ($p > 0.05$). To evaluate the interaction relationships between the intestinal flora, we used the SparCC algorithm to conduct an interaction analysis of the abundance distribution of the flora structure of the two groups of samples at the class level. The relevant parameters are as follows: Analysis options: all groups; Permutation: 100; p - value threshold: 0.5; correlation threshold: 0.2. The correlations between the flora structures were obtained through calculation. As shown in Figure 6, we found that 16 genera had obvious interactions, including Bacteroidia, betaproteobactia, gammaproteobactia, etc. Among them, alphaproteobacteria and Synergistia were the most enriched core genera in the control group, while Fusobacteria was the most enriched core genus in the cinnamaldehyde group.

3.5. Effects of Cinnamon Intervention on the Succession of Gut Microbiota Structure

This study was designed to discover and interpret biomarkers in high - throughput sequencing data using linear discriminant analysis. By performing the non - parametric factorial Kruskal - Wallis (KW) rank - sum test, features with significant differences relative to experimental factors or categories of interest were identified. Then, linear discriminant analysis (LDA) was conducted to calculate the effective size of each differentially abundant feature. The results included all features, the logarithm of the maximum mean across all groups or categories. If the feature difference was significant, the group with the highest mean and the logarithmic LDA score (size) were reported. Features were considered important based on their adjusted p - values. The default value for the adjusted p - value cutoff was 0.05. Through the LDA analysis results, it was found that the abundances of multiple gut bacteria changed significantly during the cinnamaldehyde intervention. Among them, Bifidobacterium animalis, which ranked first in the LDA score, increased significantly two weeks after the intervention. The second - ranked Scopri, a bacterium associated with coprostanol, showed a significant decreasing trend in abundance over the sampling time. The third - ranked bacterium was Faecalibacterium prausnitzii, an anti - inflammatory bacterium that can improve colitis by producing butyrate. In addition, the abundance of Klebsiella decreased after the cinnamaldehyde intervention.

Table 3. Functionally significant strains with significant differences between the cinnamon group and the control group screened by LDA analysis.

	P values	FDR	Cinnamaldehyde Group	Control Group
s__animalis	1.25E-05	0.001122	1971.6	763.75
s__distasonis	3.92E-05	0.001766	2523.7	873.7
s__aureus	0.000297	0.008901	0	47.734
s__fragilis	0.004971	0.11185	24290	42006
s__adolescentis	0.01015	0.1827	2326.5	9881
s__parahaemolyticus	0.038108	0.57162	1183	0
s__longum	0.11618	0.87077	5086.8	4821.1
s__multacida	0.11975	0.87077	2523.7	47.734
s__flavefaciens	0.12308	0.87077	0	477.34
s__cateniformis	0.12519	0.87077	0	0
s__celatum	0.12816	0.87077	0	0
s__methylpentosum	0.12816	0.87077	0	0
s__pylori	0.12816	0.87077	0	0
s__butyricum	0.14779	0.87077	39.432	0
s__neonatale	0.15425	0.87077	0	95.468
s__caccae	0.15537	0.87077	13565	32841
s__perfringens	0.16448	0.87077	0	1050.1
s__turicensis	0.17689	0.88443	0	0
s__	0.18998	0.89991	4478000	5295400

The relative abundances of Streptococcus, Bacteroides fragilis, and Enterobacteriaceae all showed a gradually increasing trend. Notably, as an important functional strain involved in the regulation of metabolic diseases, Parabacteroides distasonis has been reported in previous studies to promote the host's blood glucose and lipid metabolism. In this study, the relative abundance of this bacterium increased in the cinnamaldehyde group, indicating that the cinnamaldehyde intervention promoted the enrichment of some functional microbiota in the gut.

4. Discuss

1. The influence of cinnamon intervention on blood glucose regulation in patients with type I diabetes mellitus

The results of this study showed that after treatment, HbA1c in the cinnamaldehyde group decreased by 0.67%, while there was no change in HbA1c in the control group. The average reduction of fasting blood glucose in the cinnamaldehyde group was 1.01 mmol/L, which was 4.8 times that of the control group. After administration in the cinnamon group, when HbA1c and blood glucose decreased, triglycerides, HDL - C, ALT, AST, and serum creatinine all decreased, while they increased in the control group. Among them, total cholesterol and ALT in the control group increased significantly ($P < 0.05$), suggesting that the combined use of cinnamaldehyde can effectively control blood glucose and also reduce the adverse reactions of drugs. Ping et al.'s research suggested that cinnamon oil can reduce fasting blood glucose in KK - Ay mice and also reduce serum triglycerides. The results of this study also showed that triglycerides decreased significantly after treatment in the cinnamon group, indicating that cinnamaldehyde helps to improve lipid metabolism disorders in patients with type 1 diabetes.

2.Improvement effect of cinnamon intervention on the gut microbiota environment in patients with type I diabetes

In 2011, Knip and colleagues conducted a longitudinal case - control study to explore the relationship between the gut microbiome and type 1 diabetes mellitus (T1DM) (Giongo et al., 2011)[8].16S pyrosequencing data indicated that children with islet autoantibodies had a higher ratio of Bacteroides/Bacteroides in gut bacteria and lower Shannon diversity. Further research showed a significant accumulation of Bacteroides in high - risk children. The expression of T1DM is associated with autoantibody positivity, and there is a decrease in the number of Lactobacillus in T1DM patients among bacteria that produce large amounts of short - chain fatty acids (SCFA) (Verduci et al., 2020)[9].The results of a cross - sectional case - control study on the differences in the gut microbiome between the cinnamon - treated group and T1DM control subjects showed that compared with the cinnamon - treated group, more Bacteroides and a lower abundance of two dominant Bifidobacteria species were found in T1DM patients. Mejía - León and Barca studied the gut microbiomes of newly diagnosed T1DM patients, long - term T1DM patients, and healthy controls. They found that newly diagnosed T1DM patients had a higher content of Bacteroides, while the healthy control group had more Prevotella. Recent research results suggest that the decline in insulin action ability and thus insulin resistance is closely related to the increased blood levels of branched - chain amino acids (BCAA). The two main bacteria driving the biosynthesis of BCAA by gut bacteria are Prevotella copri and Bacteroides vulgatus (Gojda & Cahova, 2021)[10].To test whether gut bacteria truly cause insulin resistance at the mechanistic level, researchers fed mice with Prevotella copri for 3 weeks. Compared with mice not fed with Prevotella copri, mice fed with Prevotella copri had increased blood levels of BCAA and developed insulin resistance and glucose intolerance. In this study, differential analysis of gut microbiota between the treatment group and the control group was carried out, combined with clinical indicators for statistical screening. The functional strains most significantly correlated with the main clinical indicators were identified and mainly distributed in the phylum Bacteroidetes, which were regarded as potential intervention targets. Since gut microbiota exerts biological effects through the cooperation of functional groups, constructing a co - abundance group (CAG) network based on Co - abundance group and combining Spearman correlation analysis to explore the relationship between the changes in co - varying groups of gut microbiota abundance and host phenotypes is more in line with ecological concepts. This study found that the abundance of CAG2, mainly composed of operational taxonomic units (OTUs) of the genera Bifidobacterium and Lactobacillus, increased significantly after the intervention in the treatment group and was negatively correlated with a series of glycolipid metabolism and inflammation indicators.

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