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ORIGINALES

Effects of Cinnamomum zeylanicum on glycemic levels in patients with type 2 diabetes: Randomized clinical trial

Efectos de Cinnamomum zeylanicum en niveles glucémicos en pacientes con diabetes tipo 2: ensayo clínico aleatorizado

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ABSTRACT:

Objective: To evaluate the effect of *Cinnamomum zeylanicum* (cinnamon) supplement use on the glycemic levels of Mexican adults with type 2 diabetes.

Methods: A single-blind randomized clinical trial was conducted with 30 patients over 18 years of age with type 2 diabetes. They were randomized into intervention and control groups where they took 2-gram capsules of *Cinnamomum zeylanicum* or wheat flour (placebo) daily for 12 weeks; then the anthropometric and biochemical variables HbA1c, FPG, triglycerides, total cholesterol, HDL and LDL were measured. IBM SPSS version 23 software was used and the Student's t-test and Mann-Whitney U test for independent samples (according to the behavior of the variable) were applied for differences between groups, p-values <0.05 were considered statistically significant.

Results: No significant changes in HbA1c were seen between the two groups (p>0.05). However, post-treatment, the HbA1c value in the intervention group decreased significantly when compared to their baseline (-0.41%, *p*=0.01), while no differences were found in the control group (+0.03%, *p*=0.64). There were no significant differences in the anthropometric or biochemical variables.

Conclusions: The consumption of 2 g of Cinnamomum zeylanicum in Mexican people with type 2 diabetes did not produce significant changes between the groups. New studies evaluating cinnamon supplementation on a larger sample size are suggested. ClinicalTrials.gov; NCT04023539.

Keywords: Type 2 Diabetes. *Cinnamomum Zeylanicum*. Cinnamon. Glycemic Control. Alternative Therapies. Randomized Clinical Trial.

RESUMEN:
Objetivo: Evaluar el efecto del consumo de suplemento de *Cinnamomum zeylanicum* (canela) en los niveles glucémicos de adultos mexicanos con diabetes tipo 2.
Métodos: Se realizó un ensayo clínico aleatorizado simple ciego con 30 pacientes >18 años con diabetes tipo 2, se aleatorizaron en los grupos: intervención y control; donde consumieron cápsulas con 2 gramos de *C. zeylanicum* o harina de trigo (placebo) diario por 12 semanas y se midieron variables antropométricas y bioquímicas (HbA1c, GPa, triglicéridos, colesterol total, HDL y LDL). Se utilizó el software IBM SPSS versión 23 y se aplicó la prueba T-Student y U-Mann Withney para muestras independientes (según el comportamiento de la variable) para las diferencias entre grupos, valores $p<0.05$ fueron considerados estadísticamente significativos.
Resultados: No se observaron cambios significativos en HbA1c entre grupos ($p>0.05$). Sin embargo, post-tratamiento el grupo intervención disminuyó significativamente HbA1c al compararlo con su línea base (-0.41%, $p=0.01$) mientras que no se encontraron diferencias en el grupo control (+0.03%, $p=0.64$). No hubo diferencias significativas en variables antropométricas ni bioquímicas.
Conclusiones: El consumo de 2 g de *C. zeylanicum* en mexicanos con diabetes tipo 2 no produjo cambios significativos entre grupos. Se sugieren nuevos estudios donde se evalúe el suplemento de canela con una muestra mayor. ClinicalTrials.gov; NCT04023539.

Palabras clave: Diabetes Tipo 2; Cinnamomum Zeylanicum; Canela; Control Glucémico; Terapias Alternativas; Ensayo Clínico Aleatorizado.

INTRODUCTION

Diabetes mellitus is a chronic disease that appears when the pancreas does not produce enough insulin or the body does not use efficiently the insulin it produces. The 2020 National Health and Nutrition Survey (*Encuesta Nacional de Salud y Nutrición 2020*) reports that the prevalence of diabetes is 15.7% among diagnosed and undiagnosed patients, of that percentage 30% of Mexican adults are unaware of their condition. In 2019, 1.5 million deaths due to diabetes were reported, of which 48% were people under 70 years of age[1].

The treatment of type 2 diabetes is based on pharmacological and non-pharmacological therapy. The aim of pharmacological therapy is to reduce glycogenolysis, neoglucogenesis, insulin resistance, and improve peripheral insulin sensitivity; non-pharmacological therapy is to improve lifestyles through dietary changes and increased physical activity, and in some cases the use of alternative therapies[2].

It is estimated that more than 100 million people in Europe use some form of alternative therapy, especially medicinal herbs, including *Cinnamomum zeylanicu*m (*CZ*). In vitro and in vivo studies have shown that cinnamon has biologically active substances with insulin mimetic properties[3,4]. Cinnamaldehyde is a predominant phytochemical compound in cinnamon that has shown antioxidant, anti-inflammatory, hypoglycemic, and antihyperlipidemic properties[5].

Among the 250 species of the genus *Cinnamomum*, the *CZ*, also called "true cinnamon" has been used as a spice and as a flavoring agent, in addition, in ancient times it was used for medicinal purposes to treat colds and flu, as well as diseases associated with the digestive system. Currently, thanks to the benefits shown in the in-vitro studies, it has been given more uses in the treatment of metabolic diseases[6].

No research in Mexico on the use of this alternative therapy was found. In vitro, in vivo and human studies on the potential effects of *Cinnamomum* have been conducted in

several other countries. Although some of these studies have suggested possible benefits, such as reduced blood glucose levels, improved insulin sensitivity and other positive effects, it is important to note that the current evidence is limited and sometimes contradictory.

In the United Kingdom a study found statistically significant changes in Glycated Hemoglobin (HbA1c)[7]; similarly, in Iran a study reported improvement in HbA1C, fasting insulin and insulin resistance in a sample of 140 participants[8]; in Brazil a study with a sample of 160 participants reported a statistically significant decrease of 0. 02% in HbA1C and 0.55 mmol/L fasting plasma glucose (FPG)[9]; similarly, a study conducted in Korea and the United States with 54 participants reported a statistically significant difference of 5 mg/dL in FPG ($p<0.05$)[10].

In Mexico, a clinical trial was implemented to evaluate another species of cinnamon (*Cinnamomum cassia*), with the primary objective of evaluating arterial stiffness and endothelial dysfunction in type 2 diabetes; HbA1c was also analyzed as a secondary outcome, and a significant difference between groups was found in this parameter (p=0.036); however, there were no significant differences in the FPG parameter[11]. Other authors did not obtain statistically significant results regarding the change in glucose levels in the participants of their controlled trials[12,13].

With regard to the Mexican population, no published scientific studies were found that address the use of *CZ* as an alternative therapy (alone or in combination) for the control of glycemic levels in patients with diabetes. Therefore, in this randomized clinical trial we propose the following hypothesis: the consumption of a 2 g daily supplement of *Cinnamomum zeylanicum* for 12 weeks will improve glycemic control in Mexican adults with type 2 diabetes, since it has substances with insulin mimetic properties. This study was conducted to evaluate the effect of *Cinnamomum zeylanicum* consumption on glycemic levels in Mexican adults with type 2 diabetes.

METHODS

The study design is a randomized, single-blind, two-arm clinical trial, with a randomized allocation of fifty percent per arm. The project was registered in ClinicalTrials.gov (NCT04023539) and approved by the Ethics and Research Committee of the Department of Nursing at the Universidad de Sonora (CEI-ENFERMERÍA-EPM-002/2019).

Participants were recruited from two primary healthcare clinics in the city of Hermosillo, Sonora, Mexico. The target population were patients with a diagnosis of type 2 diabetes, attending the selected primary healthcare centers: CAAPS (Advanced Primary Healthcare Center) and the ISSSTE Family Medical Clinic. Recruitment was conducted from September 13 to November 16, 2019. Follow-up was conducted from December 2019 to March 2020.

To calculate the sample, data from a previous study with a population of similar characteristics were used[7] and the following formula was implemented: calculation of the sample size for the study using the Student's t-test and considering the alpha and beta errors, from the book Epidemiology, Biostatistics, and Preventive Medicine[14],

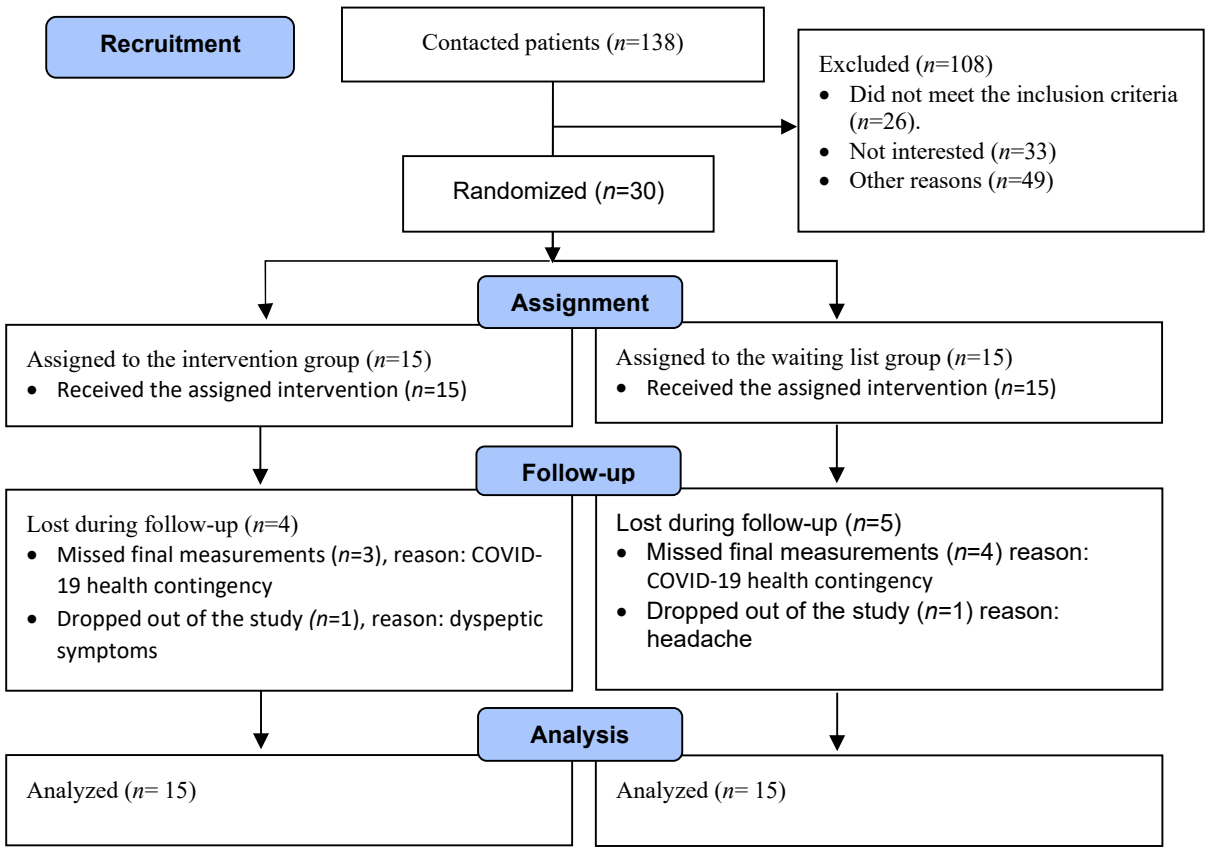
considering a confidence level of 95%, a type I error of 0.05 and a type II error of 0.20, with a desired power of 80%.

A total of 138 volunteers were contacted, of whom 30 met the inclusion criteria and signed the informed consent form. The participating patients were randomized by an investigator, who was not involved in recruitment; they were stratified by sex and HbA1c, assigned 1:1, with a blinding of participants to the belonging group and a parallel design, for the different groups: intervention group (n=15) or control group (n=15), as shown in Figure 1. The sequence of random numbers was generated with the software Available at https://www.randomizer.org/.

The inclusion criteria were: patients with a diagnosis of type 2 diabetes, older than 18 years, treated with oral hypoglycemic agents, HbA1c 6.5%-10% and attending the selected first level healthcare centers. We excluded from the study patients with insulin treatment, allergy to cinnamon or wheat flour, gastrointestinal, cardiac or renal disease, use of any extra supplement with effect on glucose levels, use of addictive substances such as drugs (with non-therapeutic effect) and pregnant or lactating women.

Patients underwent a 12-week treatment with oral supplementation of 2 grams daily of *CZ* or placebo (wheat flour) in capsule form. 2 grams of *Cinnamomum zeylanicum* was chosen based on the suggested glucose-lowering effect previously reported in a study with a population with similar characteristics [7].

Figure 1. Flow diagram of the participants in each phase of the study according to the CONSORT 2010 guide. Hermosillo, Son., Mexico 2020.



The whole process of storage and hygiene of the product was carried out in accordance with the WHO Codex Alimentarius[15]. Placebo capsules were administered to group 2 in the same pattern as the cinnamon, to verify that the decrease in HbA1c was not due to the psychological effect of ingesting the capsules.

At the beginning of the study, a questionnaire was applied to determine the sociodemographic and lifestyle characteristics, where questions were answered about the time of the diagnosis, treatment and other medical conditions (sociodemographic data questionnaire). Anthropometric measurements (weight, height, waist circumference and BMI) and blood pressure were taken; also, blood samples were processed at the Clinical Analysis and Research Laboratory of the Universidad de Sonora (LACIUS) to measure primary (HbA1c) and secondary (FPG, triglycerides, total cholesterol, HDL and LDL) biochemical variables. All measurements were performed according to the guidelines of the WHO STEPwise Manual[16].

IBM SPSS 23 statistical software was used for data analysis. The primary analysis was performed by intention-to-treat, involving all randomized participants. For missing data, the baseline level was used in the final measurement. According to the Shapiro-Wilk test, the distribution of the data of the main variable was non-normal (p<0.001). The Student's t-test for independent samples and the Mann-Whitney U test for nonparametric independent samples were used to look for differences between groups. The paired t-student test was applied for intra-group differences, with the exception of HbA1c where the Wilcoxon test was applied. Values p<0.05 were considered statistically significant for all tests.

The study was conducted in accordance with the guidelines of the Declaration of Helsinki and Good Clinical Practice. The protocol was approved by the Ethics and Research Committee of the Nursing Department of the Universidad de Sonora (CEI-ENFERMERÍA-EPM-002/2019). The study complies with the regulations established in the General Health Law Regulations on Health Research (SS, 1986; DOF, 2014)[17]. Personal data identifiers were replaced by codes to maintain the confidentiality of the data. Participation in this study was voluntary, all participants signed an informed consent form, no financial or any other type of remuneration was offered to participants.

All materials, equipment and expenses for this project were paid for by the Department of Chemical-Biological Sciences, the Department of Nursing of the Universidad de Sonora and with the support given to the author during the author's master's degree studies by the Consejo Nacional de Humanidades, Ciencia y Tecnología (CONAHCYT by its acronym in Spanish), under grant No. 719080.

RESULTS

The baseline data of the participants (n=30) are shown in Table I. The sample was stratified by sex; age and HbA1c were similar between groups. There were no significant differences in any variable at the baseline.

No participants reported changes in their medications for diabetes, hypertension, or dyslipidemia during the course of the study. Two side effects were reported during

follow-up, with one participant in the intervention group reporting dyspeptic symptoms and one participant in the placebo group reporting headaches.

Figure 1 shows the flow diagram of the participants according to the CONSORT 2010 Guidelines.

Table I. Sociodemographic, biochemical and anthropometric baseline characteristics of the participants of the study. Hermosillo, Sonora, Mexico, 2020.

Baseline Characteristics	Intervention (*n=15*) *n* (%) or Mean ± SD*	Placebo (*n=15*) *n* (%) o Mean ± SD*	*p* Value
Sex	-	-	0.70†
Female	10 (66.7)	9 (60)	-
Male	5 (33.3)	6 (40)	-
Age (years)	63.67±9.9	62.87±10.5	0.83†
Age (%)	-	-	0.81†
40-50	1 (3.3)	2 (6.7)	-
50-60	5 (16.7)	5 (16.7)	-
60-70	4 (13.3)	5 (16.7)	-
70-80	5 (16.7)	3 (10)	-
Level of education (%)	-	-	0.63†
Elementary	1 (3.3)	3 (10)	-
Middle School	4 (13.3)	2 (6.7)	-
High School	4 (13.3)	3 (10)	-
Technical or Bachelor's Degree	4 (13.3)	6 (20)	-
Postgraduate degree	2 (6.7)	1 (3.3)	-
Alcohol use (%)	-	-	1.00†
Yes	4 (13.3)	4 (13.3)	-
No	11 (36.7)	11 (36.7)	-
Tobacco use (%)	-	-	0.92†
Never	9 (30)	8 (26.7)	-
Former smoker	5 (16.7)	6 (20)	-
Smoker	1 (3.3)	1 (3.3)	-
Level of physical activity (%)	-	-	0.73†
Almost none	4 (13.3)	6 (20)	-
Light	7 (26.3)	6 (20)	-
Moderate	4 (13.3)	3 (10)	-
Vigorous	0 (0)	0 (0)	-
Time from diagnosis (years)	10.33±7.63	10.00±9.49	0.73‡
HbA1c§ (%)	7.53±1.09	7.44±0.93	0.95‖
FPG¶ (mg/dl)	181.93±59.17	159.46±43.07	0.25‡
Triglycerides (mg/dL)	155.13±78.03	145.86±81.21	0.75‡
Total cholesterol (mg/dL)	204.20±42.75	199.00±44.82	0.75‡
HDL (mg/dL)**	47.13±12.12	45.72±9.55	0.73‡
LDL†† (mg/dL)	131.35±41.76	123.10±36.67	0.58‡
Weight (Kg)	76.92±18.78	83.42±17.7	0.33‡
BMI‡‡ (kg/mts²)	30.11±6.07	31.35±5.10	0.55‡
WC§§ (cm)	101.62±16.31	106.07±13.37	0.44‡
SBP‖‖ (mmHg)	128.33±16.22	131.47±16.66	0.61‡
DBP¶¶ (mmHg)	79.00±12.56	80.33±9.89	0.77‡

*SD= Standard Deviation †Chi-square test ‡Student's t-test §HbA1c= Glycated Hemoglobin ‖ Mann-Whitney U test ¶FPG= Fasting Plasma Glucose **HDL= High-Density Lipoprotein ††LDL= Low-Density Lipoprotein ‡‡BMI= Body Mass Index §§WC= Waist Circumference ‖‖SBP= Systolic Blood Pressure ¶¶DBP= Diastolic Blood Pressure

Glycemic Results

Table II shows that the mean change of the main variable HbA1c when compared between groups did not reach statistical significance (p=0.23), however, we can observe in Table III and Figure 2 that when performing the intra-group analysis, the HbA1c of the intervention group decreased significantly after the 12 weeks of treatment with *Cinnamomum zeylanicum* compared to its baseline (HbA1c from 7. 53% to 7.12%, p<0.05), with a difference of -0.41%; while in the control group no significant difference was found (HbA1c from 7.44% to 7.46%, p=0.64), with an increase of +0.03%. The difference in the change between the groups' means was 0.43. Similarly, no changes in FPG were also found between groups.

Table II. Effect of *Cinnamomum zeylanicum* on post-intervention biochemical and anthropometric variables of the participants of the study. Hermosillo, Sonora, Mexico, 2020.

Variable	Intervention Group (*n=15*)	Placebo Group (*n=15*)	*p* Value
HbA1c[*] (%)	7.12±1.18	7.46±1.13	0.13[†]
Change (Δ)	-0.41±0.79	0.03±0.81	0.23[†]
FPG[‡] (mg/dL)	172.46±67.78	167.40±41.68	0.80[§]
Change (Δ)	-9.46±68.44	7.93±53.38	0.44[§]
Triglycerides (mg/dL)	131.66±70.24	161.00±75.14	0.28[§]
Change (Δ)	-23.46±79.57	15.13±57.38	0.39[§]
Total cholesterol (mg/dL)	200.40±52.62	198.93±37.35	0.93[§]
Change (Δ)	-3.80±38.87	-0.06±23.70	0.75[§]
HDL[‖] (mg/dL)	50.23±12.70	46.85±10.16	0.43[§]
Change (Δ)	3.09±5.95	1.13±4.13	0.30[§]
LDL[¶] (mg/dL)	125.55±43.46	116.49±35.11	0.54[§]
Change (Δ)	-5.74±30.77	-6.61±15.42	0.92[§]
Weight (kg)	76.78±18.23	83.70±17.77	0.30[§]
Change (Δ)	-0.13±1.30	0.28±1.48	0.42[§]
BMI[**] (kg/mts²)	30.06±5.83	31.45±5.01	0.49[§]
Change (Δ)	-0.05±0.51	0.09±0.57	0.47[§]
WC[††] (cm)	101.38±15.40	106.00±13.19	0.41[§]
Change (Δ)	-0.20±1.74	-0.13±3.04	0.94[§]
SBP[‡‡] (mmHg)	132.20±17.53	132.73±15.63	0.93[§]
Change (Δ)	3.86±13.13	1.27±6.28	0.49[§]
DBP (mmHg)	81.67±12.91	81.33±9.63	0.94[§]

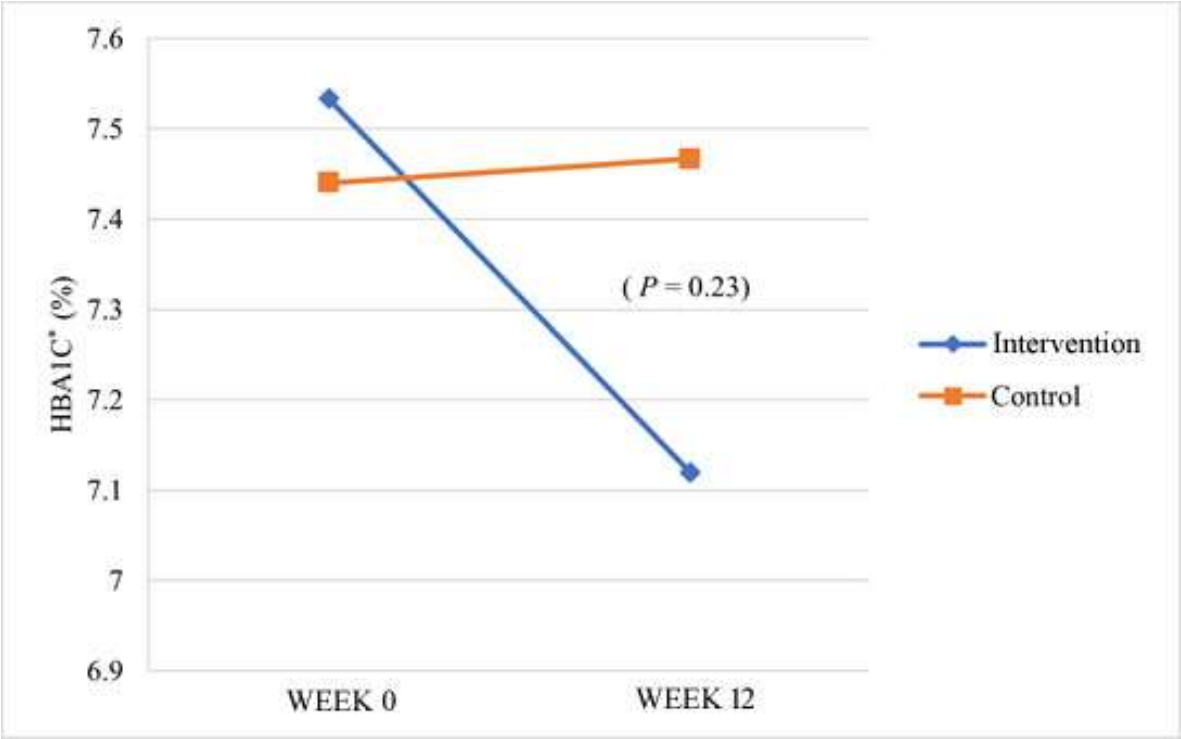
[*]HbA1c= Glycated Hemoglobin [†]Mann-Whitney U test [‡] FPG= Fasting Plasma Glucose [§]Student's t-test [‖]HDL= High-Density Lipoprotein [¶]LDL= Low-Density Lipoprotein [**] BMI= Body Mass Index [††] WC= Waist Circumference [‡‡] SBP= Systolic Blood Pressure [§§] DBP= Diastolic Blood Pressure

Table III. Intra-group effects of *Cinnamomum zeylanicum* on glycated hemoglobin (HbA1c) of the participants of the study with type 2 diabetes. Hermosillo, Sonora, Mexico 2020.

Group	Dosage of *CZ*/Placebo (2g/day)	HbA1c[*] ± SD[†] Baseline	HbA1c[*] ± SD[†] Final	Difference	*p* Value
1	*C. zeylanicum* (*n*=15)	7.53±1.09	7.12±1.18	-0.41	0.01[‡]
2	Placebo (*n*=15)	7.44±0.93	7.46±1.13	+0.03	0.64[‡]

[*]HbA1c= Glycated Hemoglobin [†]SD= Standard Deviation [‡]Wilcoxon test

Figure 2. Change in HbA1c (%) at weeks 0 and 12 of the treatment with *Cinnamomum zeylanicum* in the intervention and control groups.



*HbA1c= Glycated Hemoglobin

Results of Secondary Variables

Table II shows the results of anthropometric variables (weight, waist circumference, and BMI), biochemical analyses (fasting glucose, triglycerides, total cholesterol, HDL, and LDL), and blood pressure (systolic and diastolic). No significant changes were observed between groups in any of the secondary variables of this study.

DISCUSSION

This is the first study in Mexico to examine the effects of *Cinnamomum zeylanicum* on glucose levels, blood lipids and blood pressure in people with type 2 diabetes. This study found no statistically significant differences in HbA1c and FPG levels, blood pressure, biochemical and anthropometric measurements when comparing the groups.

Although no significant changes were found in the main study variable, HbA1c, when comparing between groups (p=0.22), a statistically significant decrease was noted in the group that received 2g of *Cinnamomum zeylanicum* (-0.42, p<0.05) compared to its initial value. In contrast, in the control group, an increase in HbA1c levels (+0.03%, p=0.64) was observed after ingesting the daily dose of 2g of placebo for 12 weeks.

To contextualize these results, the use of *Cinnamomum zeylanicum* showed a non-significant decrease of -0.41% (p=0.22) in HbA1c levels, which is slightly higher than levels reported in another similar randomized controlled trial, where the results reported were statistically significant (-0.36% HbA1c, p<0.005)[7].

Different mechanisms have been suggested for the hypoglycemic effects of Cinnamomum zeylanicum, so the literature suggests some glucose homeostasis mechanisms by metabolic pathways such as increasing glucose uptake in muscle and adipose tissue by production and translocation of glucose transporter 4, promoting glycogen synthesis in the liver, inhibiting glycogen synthase kinase 3β, and reducing gene expression of regulators of gluconeogenesis (phosphoenolpyruvate carboxykinase and glucose-6-phosphatase)[8,18,19].

The results of in vivo studies also suggest that Cinnamomum zeylanicum has the ability to regulate blood pressure levels through peripheral vasodilation[7,20]. However, no significant differences in systolic and diastolic blood pressure values were found. This could be attributed to the fact that the participants of our study had normal systolic and diastolic blood pressure values from baseline, and no values demonstrating an improvement were reported. Studies evaluating participants with hypertension, looking for a decrease in blood pressure and proving or ruling out an antihypertensive effect of Cinnamomum zeylanicum, are probably needed.

An in vivo study with rats reported that cinnamon polyphenol reduces hyperlipidemia by activating transcription factors and the antioxidant defense signaling pathway in the liver [21]. A meta-analysis of 13 randomized controlled trials concluded that cinnamon supplementation significantly reduced blood triglycerides and total cholesterol without any significant reduction in HDL and LDL[22]. A systematic review that analyzed data from in vitro and in vivo studies found that cinnamaldehyde can decrease total cholesterol, triglyceride levels and increase HDL[18]. Despite this, our study found that the lipid profile of the participants showed normal levels at baseline, therefore, the effect of *Cinnamomum zeylanicum* on lipid profiles could be minimal.

It has been demonstrated that in the months from November to January people tend to increase their caloric intake and may increase both anthropometric (weight, waist circumference and BMI) and biochemical variables[23]. However, no statistically significant results were found in the anthropometric variables (weight, waist circumference and BMI) between the groups, which coincides with the findings reported by Jamali N. et al. in a systematic review and meta-analysis where cinnamon supplementation had no significant effects on weight (p=0.211), BMI (p=0.120) and weight, waist circumference (p=0.103)[24].

We suggest conducting studies with different doses of *Cinnamomum zeylanicum* in a Mexican population to find out if with a higher intake or a longer treatment time, a reduction in biochemical or anthropometric variables can be observed. Khan et al. studied the effect of cinnamon doses on blood glucose and lipid profile in individuals with type 2 diabetes, they reported that the intake of 1, 3 or 6 g of cinnamon per day reduced fasting serum glucose (18 - 29%), triglycerides (23 - 30%), LDL (7 - 27%) and total cholesterol (12 - 26%)[25].

One of the limitations of the study is that it was not possible to obtain the final measurements of 9 participants, mainly due to the COVID-19 health contingency during 2020. This affected the sample size of our study and could be the cause of the absence of effect on the main study variable. The short-term effects of the administration of 2 g daily of *Cinnamomum zeylanicum* for 12 weeks, in conjunction with treatment for type 2 diabetes, seem to be beneficial in patients with poor glycemic

control; studies similar to this one contribute to scientific research on new methods and/or treatments to help control this chronic degenerative disease.

CONCLUSIONS

The 2 g dose of *Cinnamomum zeylanicum* used in this study was safe and well tolerated during the 12 weeks of treatment. When comparing the change in HbA1c between groups after the treatment with *Cinnamomum zeylanicum,* we found no statistically significant change, which may have been caused by the limited sample size of this study. However, supplementation with *CZ* seems to show a positive trend, so larger and more rigorous studies involving different types of patient groups, specific doses and long-term follow-up are required; this would allow health professionals and people with diabetes to make informed decisions about the use of *Cinnamomum zeylanicum* as a supplement or as an alternative to conventional treatments.

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