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Research Article

Impact of a Cinnamon Extract Vs. Placebo on Metabolic Control in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Cinnamon preparations have been shown to reduce blood glucose and improve HbA1c in patients with Type 2 Diabetes mellitus. However, some meta-analyses have resulted in inconclusive data due to the heterogeneity of materials and patients in various published trials. In order to evaluate the effects of a cinnamon extract preparation on metabolic control, we performed a double-blind randomized placebo-controlled prospective study with a cinnamon extract from Cinnamomum aromaticum (C. cassia).

Subjects/Methods: We included 109 patients with type 2 diabetes and suboptimal glycemic control (HbA1 ≥ 7.0). Patients were randomized to receive one capsule daily containing 314 mg of cinnamon extract or placebo for four months on top of their regular treatment. Observation parameters were changes in HbA1c, HOMA-IR, hsCRP, adiponectin and lipids.

Results: HbA1c improved from 7.92 ± 0.98% to 7.39 ± 0.98% in the cinnamon group (-7%, $p < 0.005$) and from 7.73 ± 0.80% to 7.44 ± 0.94% in the placebo group (-3.8%; $p < 0.05$). Significant differences in favour of the cinnamon intervention were seen for almost all indicators of insulin resistance, inflammation and lipid distribution. Both treatments were well tolerated.

Conclusion: We found a consistent improvement in markers of glycaemic control, chronic systemic inflammation and insulin resistance during supplementation with cinnamon extract in comparison to further deteriorations with placebo. These results support the use of cinnamon extracts as dietary supplement for patients with type 2 diabetes and metabolic syndrome.

Keywords: *Cinnamomum; Cinnamon; Type 2 Diabetes and Metabolic Syndrome*

Introduction

The effects of cinnamon (*Cinnamomum sp.*) on glycaemic parameters in subjects with diabetes mellitus type 2 are still under debate. *In vitro* and *in vivo* studies have rather confirmed potential antidiabetic effects of cinnamon, but clinical results have been partly inconclusive. Potential underlying mechanisms for insulin sensitizing effects of cinnamon have been reported from cell culture experiments. They have been linked to the detection of oligomeric proanthocyanidines. The observed *in vitro* effects resulted in a facilitation of glucose transport through the cellular membrane by glucose transporters and a reduction of extra-cellular glucose concentrations [1,2]. It has been demonstrated that fractions of cinnamon increase the autophosphorylation of the insulin receptor [3], which may result in an increased NO production and NO activity [4,5]. With endogenous or exogeneous insulin present in the body, these effects may lead to improvements in microcirculation and endothelial function [6].

Cinnamon or some of its components may induce changes to the insulin-signalling cascade leading to an upregulated glucose uptake *in vitro* and *in vivo* by exerting insulin mimicking effects with increased glucose uptake, glucose concentrations, increased glycogen synthesis, and inhibition of the intestinal Na^+K^+-ATPase activity [2,3,7-9], which has led to reduction of plasma glucose in a diabetic mouse model (db/db mice) after 6 weeks of administration [10].

The potential effects have been studied in humans in clinical trials. Recent metanalyses confirmed a significant reduction of blood glucose and an improvement of insulin resistance (HOMA-IR), but conflicting results with respect to HbA_{1c} as a long-term indicator of blood glucose control were observed [11-14]. Meta-analyses are, however, hampered by the heterogeneity of the studies with respect to important study parameters. The Cochrane analysis of Leach and Kumar (2012) included 10 randomized clinical trials [15]. One of these studies was performed in patients with insulin-dependent type 1 diabetes [16], four had a too short study duration to properly assess changes in HbA_{1c} [17-20] and three studies were studying participants with normal HbA_{1c} values [21] or very close to therapeutic target values [20,22], as defined by the American Diabetes Association [23].

Interestingly however, two studies in type 2 diabetes with baseline HbA_{1c} values in the pathological range showed significant improvements with cinnamon treatment [24,25], whereas one study showed a significant HbA1c improvement in the cinnamon group versus baseline, but did not reach significance in the intergroup comparison [26], which could be explained by a high variability in starting HbA1c values and a low number of participants (n = 20 in total).

The meta-analysis of Costello., *et al*. (2016) identified only four studies where the HbA_{1c} at study start was higher than 7.0%. From these studies, it was concluded that 'cinnamon supplements added to standard hypoglycemic medications and other lifestyle therapies had modest effects on fasting blood glucose and HbA_{1c}' [23].

In summary, cinnamon appears to be a valuable addition to the recommended dietary and lifestyle management of type 2 diabetes, and appropriate nutritional support with cinnamon seems to correspond to the medically determined nutrient requirements of the affected patients.

To elucidate the above mentioned limitations we performed a prospective, placebo-controlled, double-blind, parallel study with a four month observation period to assess the effects of an aqueous cinnamon extract on glycaemic control and the underlying pathophysiological components of type 2 diabetes (HbA1c and biomarkers of insulin resistance, ß-cell failure and chronic systemic inflammation).

Subjects and Methods

Ethical considerations

The study was designed as a randomised, placebo-controlled, multi-centre double-blind, parallel group trial performed at seven centres for diabetes management in Austria.

The study was planned and conducted in accordance with the ethical principles of the Declaration of Helsinki and following Good Clinical Practice (GCP) guidelines. It was approved by the respective independent ethical review boards of the individual centres in Feldkirch, Graz, Linz, Salzburg and Vienna. All patients signed written consent after thorough information about the trial.

Inclusion criteria

Subjects with type 2 diabetes mellitus in the age of 18 - 75 years, treated with diet only or with oral antidiabetics (metformin and/or sulfonylurea or acarbose), could be included when their HbA_{1c} value was ≥ 7.0%. Treatment with thiazolidinediones or with insulin was defined as an exclusion criterium (as the use of such medication would cover the effect of cinnamon), as was the intake of dietary supplements, a known allergy against cinnamon, pregnancy and lactation, and other diseases than diabetes interfering with glucose metabolism (e.g. acute or chronic gastrointestinal diseases, hyperthyreosis, or progressive fatal diseases).

Study parameters

The primary study parameter was the change of HbA1c from baseline to endpoint. A reduction from baseline values by ≥ 0.3% was considered a response to treatment. Secondary parameters were insulin sensitivity (HOMA-IR, adiponectin, fasting glucose and fasting insulin), β-cell function (fasting proinsulin), oxidative stress (oxidated LDL, oxLDL) and chronic systemic inflammation and cardiovascular risk (hsCRP). Fasting blood samples were taken at baseline, at an interim visit after 10 weeks and at endpoint after four months. Safety parameters measured at study start and study termination were TSH, β-HCG, hemoglobin, hematocrit, red and white blood cell count, AST and ALT and creatinine. Further examination parameters included blood pressure, pulse, body weight, height, hip and waist circumference, and an assessment of dietary changes, exercise and other life-style modifications.

The laboratory determinations were performed in a central laboratory. Triglycerides, total cholesterol, LDL-cholesterol, HDL-cholesterol and hsCRP were measured by standard enzymatic reference methods (Falcor, Menarini, Neuss, Germany). Immunoassays were employed to assess adiponectin (RIA, Linco, St. Charles, MO), intact proinsulin and insulin (both ELISA, Linco, St. Charles, MO), and oxLDL (ELISA, Immundiagnostik AG, Bensheim, Germany). HbA_{1c} was determined by an HPLC method (Adams, Menarini, Neuss, Germany) and glucose was measured by a glucose oxidase method (Super GL, RLT, Möhnesee, Germany). Insulin resistance was determined by means of the HOMA-IR score [27]. Patients were considered to be insulin resistant if they either had elevated intact proinsulin values [28] or showed a $HOMA_{IR}$ score > 2 [29].

Treatment compliance was tested by capsule count of the returned study preparations at the interim visit after 10 weeks and the final visit after 16 weeks.

Study preparations

The study preparation consisted of capsules of a commercial product (Alsitan GmbH, Greifenberg, Germany) with 314 mg of cinnamon dry extract from *Cinnamomum aromaticum* (syn. *Cinnamomum cassia*) or *Cinnamomum burmani*, standardized to catechins, i.e. a minimum of 18 mg catechins per capsule. The extraction solvent was ethanol 13% m/m. The capsules further contained 60 µg chromium as chromium (III) chloride and 18 mg of vitamin B3 (niacin). Contaminants by heavy metals, pesticides and microbiological load were

excluded as set forth by European Pharmacopoea specifications. Coumarins were restricted to ≤ 0.5%. The essential oil constituents cinnamic aldehyde, saffrol and styrol were below ≤ 0.1%.

Placebo consisted of microcrystalline cellulose in undistinguishable capsules. The study drugs were to be taken once daily in the morning.

Randomization

Participants were allocated to treatment groups by a pre-prepared randomisation list in blocks of four. Blistering, packaging and labelling of the boxes with a participant number was made by the study sponsor.

Statistics

Sample size calculation was based on the expectation of a change of the primary parameter HbA_{1c} by 0.0 ± 1.4% with placebo treatment, and by 1.0 ± 1.4% with cinnamon. Assuming an alpha error of 0.05 and a power of 90%, the calculation indicated a sample size of 84 patients. Taking a drop-out rate of 16% into consideration, the required sample size was calculated to be at least n = 100 participants.

Pre/post paired values were analysed using student's t-test, with a significance level of 5% to reject the null-hypothesis. Analysis of HbA_{1c} had confirmatory status. Qualitative variables (e.g. gender) were described in absolute and relative frequencies and evaluated using standard exploratory and descriptive analyses. Missing values of the full analysis set population (Intention-to-treat population (ITT, all subjects who received at least one application of the study preparation) were treated by the last known value carried forward (LOCF) method. Missing values were not replaced in the per protocol (PP) population of all subjects with full pre/post values. The statistical software used was SPSS v16.0 (IBM). A p-value < 0.05 was considered statistically significant.

Results

After screening, 109 patients were included into the study (Intention to treat population ITT; 53 participants allocated to cinnamon and 56 to placebo, 47 females (43.1%) and 62 males (56.9%). All except for 3 participants of Asian origin were Caucasians. Based on the compliance assessment of the investigators (patients with less than 50% treatment adherence were excluded from the analysis), the per-protocol population (PP) was comprised of 104 patients (cinnamon: n = 49; placebo: n = 55). Patient allocation and reasons for drop-outs are given in figure 1. Main reasons for non-adherence were patient desire and difficulties to match the study visit schedule requirements. In particular, no patient withdrew from the study because of adverse events. The patient characteristics of the per-protocol analysis population is provided in table 1. With the exception of the baseline values for systolic blood pressure, there was no significant difference between the treatment groups for any of the observation parameters at baseline.

Parameter	Placebo	Cinnamon	Total	p-value Between groups
N	55	49	104	
age [years]	57.9 ± 9.0	60.2 ± 9.8	59.0 ± 9.4	0.218
body height [cm]	171 ± 9	172 ± 10	171 ± 10	0.686
body weight [kg]	93 ± 16	92 ± 22	92 ± 19	0.668
Waist-to-Hip ratio	0.97 ± 0.07	0.97 ± 0.08	0.97 ± 0.07	0.701
BMI [kg/m^2]	32.0 ± 5.2	30.9 ± 5.9	31.5 ± 5.4	0.33
Diastolic Blood Pressure [mmHg]	84 ± 10	81 ± 10	82 ± 10	0.158
Systolic Blood Pressure [mmHg]	142 ± 19	134 ± 17	138 ± 19	0.032
Radial pulse [bpm]	73 ± 11	74 ± 8	73 ± 10	0.917

Table 1: *Patient characteristics of the per protocol population.*

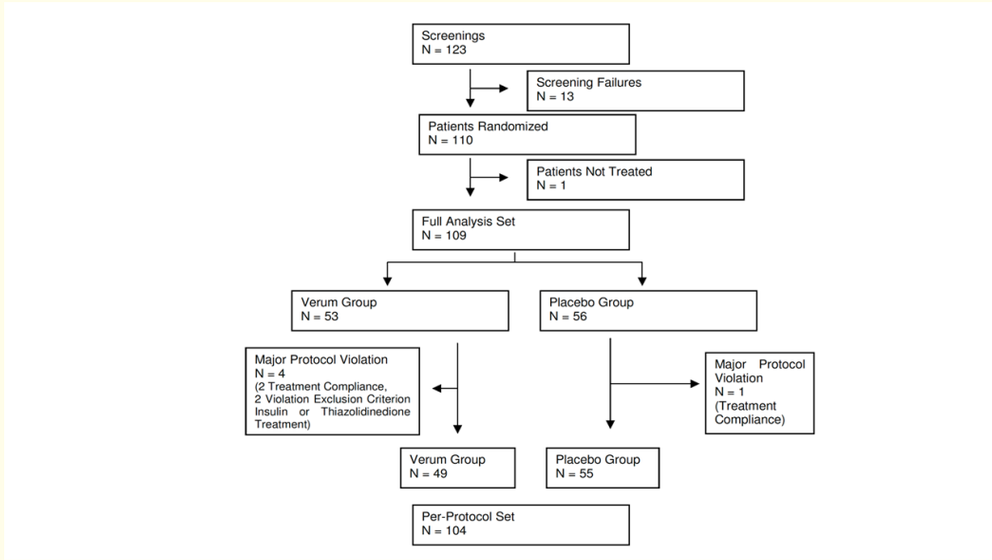

Figure 1: *Flow chart of participant allocation.*

The mean treatment duration was 135 ± 14 days in the cinnamon group, and 130 ± 26 days in the placebo group. During the four months of observation, there were no changes in the nutritional behaviour or in the performance of exercise.

HbA_{1c}

Inclusion criteria had defined an HbA_{1c} value of at least 7.0%. However, upon analysis of the values it was shown that 4/49 participants of the PP cinnamon group and 6/55 participants of the PP placebo group had lower starting HbA_{1c} values. Per investigator decision, they were not excluded from the analysis. The HbA1c range in the ITT population (n = 109) was 6.5 - 11.9% in the cinnamon group (n = 53) and 6.6 - 10.5% in the placebo group (n = 56).

After four months of supplementation, we observed a significant HbA_{1c} reduction in the cinnamon group ($p < 0.005$), and in the placebo group ($p < 0.05$). The between-group analysis did not reach statistical significance ($p = 0.186$, see table 2 and figure 2). The percent changes of the observation parameters from baseline to endpoint for both treatment groups are presented in figure 3.

	Placebo		**Cinnamon**	
	Week 0	**Week 16**	**Week 0**	**Week 16**
HbA_{1c} [%]	7.73 ± 0.80	7.48 ± 0.94	7.92 ± 0.98	7.39 ± 0.98
	p = 0.042		p = 0.002	
	p = 0.649			
HOMA-IR Score	5.28 ± 2.81	5.88 ± 3.27	4.99 ± 3.71	4.52 ± 2.00
	p = 0.081		p = 0.222	
	p = 0.014			
Insulin [pmol/L]	107.39 ± 59.00	115.45 ± 65.05	94.45 ± 61.58	88.89 ± 40.23
	p = 0.125		p = 0.249	
	p = 0.015			
Glucose [mmol/L]	8.09 ± 1.98	8.38 ± 1.89	8.52 ± 2.30	8.30 ± 1.83
	p = 0.259		p = 0.354	
	p = 0.835			
Proinsulin [pmol/L]	21.48 ± 20.55	22.95 ± 21.89	20.02 ± 17.21	18.12 ± 12.71
	p = 0.148		p = 0.174	
	p = 0.047			
Adiponectin [mg/L]	8.61 ± 4.27	8.91 ± 3.96	9.33 ± 4.56	10.15 ± 5.25
	p = 0.342		p = 0.021	

	p = 0.176			
hs-CRP [mg/L]	3.04 ± 2.44	2.78 ± 2.15	2.99 ± 2.43	2.88 ± 2.22
	p = 0.208		p = 0.792	
	p = 0.835			
Cholesterol [mmol/L]	5.21 ± 1.04	5.44 ± 1.02	5.16 ± 0.88	5.17 ± 0.86
	p = 0.018		p = 0.931	
	p = 0.141			
HDL [mmol/L]	1.18 ± 0.27	1.18 ± 0.26	1.19 ± 0.32	1.24 ± 0.32
	p = 0.822		p = 0.002	
	p = 0.320			
LDL [mmol/L]	3.26 ± 0.80	3.38 ± 0.79	3.22 ± 0.67	3.20 ± 0.66
	p = 0.069		p = 0.852	
	p = 0.212			
Triglycerides [mmol/L]	2.15 ± 1.15	2.47 ± 1.29	2.27 ± 1.04	2.16 ± 0.89
	p = 0.022		p = 0.286	
	p = 0.156			
oxLDL [mmol/L]	214.6 ± 352.3	208.2 ± 274.2	245.2 ± 298.5	299.2 ± 443.38
	p = 0.769		p = 0.218	
	p = 0.206			
BMI [kg/m^2]	32.1 ± 5.1	31.9 ± 5.3	30.9 ± 5.8	30.1 ± 5.1
	p = 0.136		p = 0.184	
	p = 0.393			

Table 2: *Observation parameters at baseline and endpoint (PP population, n = 104).*

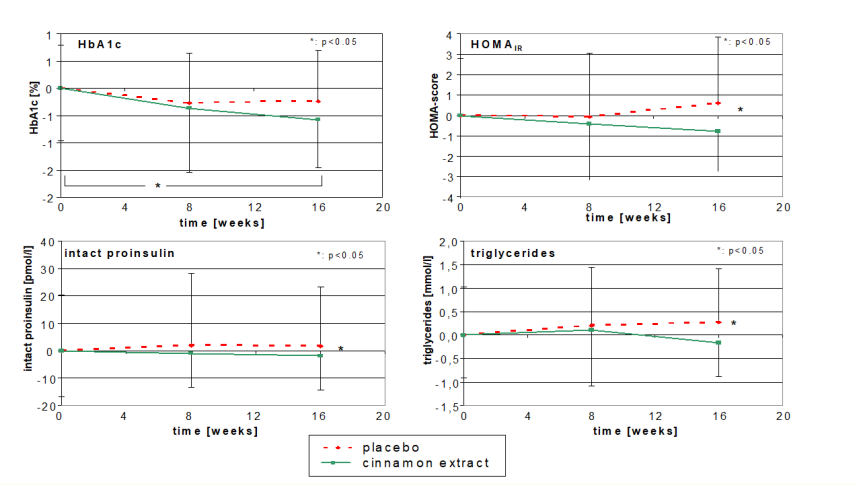

Figure 2: *HbA1c, HOMAIR, intact proinsulin and triglyceride concentrations during the observation period.*

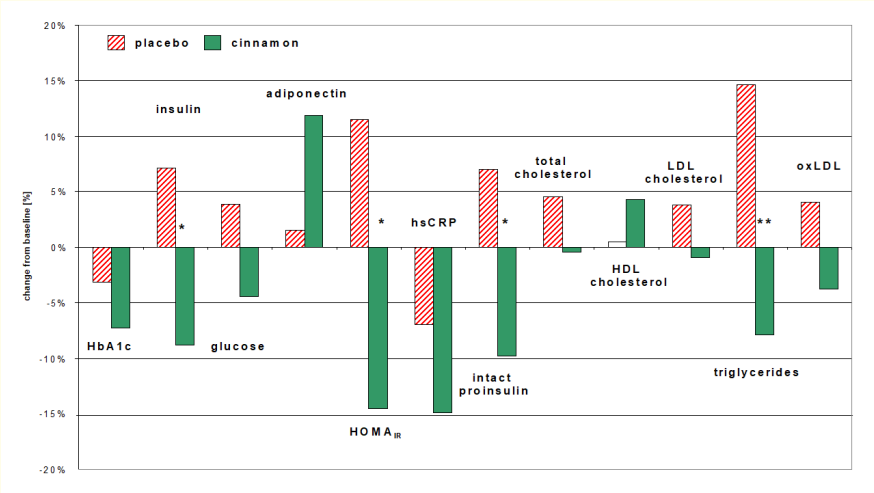

Figure 3: *Percent changes of the observation parameters from baseline to endpoint in both intervention groups (p for differences between the groups: *: p < 0.05 and **: p < 0.005).*

Because some patients were included with an HbA_{1c} below 7.0%, a subgroup analysis was performed with patients with HbA_{1c} > 7.0% only. This analysis resulted in a significant reduction of HbA_{1c} for subjects treated with cinnamon ($p < 0.05$), while the outcome was no longer significant in the placebo group ($p = 0.064$, between group analysis: $p < 0.05$).

Insulin resistance

insulin, intact proinsulin and the HOMA-IR score increased in the placebo group, while values decreased in the cinnamon extract treated group. The differences between the groups was statistically significant (See table 2 and figure 2).

A tendency towards improvements with cinnamon and impairment with placebo was also found for fasting glucose, but the changes within and between groups did not reach statistical significance (Table 1).

Lipids and cardiovascular parameters

Adiponectin values increased in both groups, with changes relative to baseline reaching statistical significance only in the cinnamon group. Again, the between-group changes did not reach statistical significance.

There were modest changes in the blood lipids (cholesterol and HDL and triglycerides) where the results favoured cinnamon with statistically significant results in the within-group comparisons. Other parameters such as hs-CRP, LDL, oxLDL and BMI indicated small changes in favour of cinnamon without reaching statistical significance (See table 2 and figure 3).

Safety

The occurrence of adverse events (AE) was equally distributed between groups. A total of 58 adverse events were reported by 47/109 patients. The same number of AEs occurred in both treatment arms (29 per group). There were 10 serious adverse events in 10 participants (5 participants per group). None of the adverse events was causally related to the study interventions. Overall, both treatments were well tolerated. In particular, no termination of study participation was reported because of an adverse reaction to the study preparation.

All laboratory parameters remained within the normal range. ALT decreased significantly during the study in the placebo group, but values remained within physiological values (data not shown).

Discussion

In this study, we observed a positive effect of a cinnamon extract on biomarkers for glycaemic and metabolic control and cardiovascular risk in subjects with type 2 diabetes mellitus. The improvements included positive changes in markers for insulin resistance and ß-cell dysfunction and an improved blood lipid profile. The observed pattern in these biomarker changes (increase in adiponectin, decrease in HOMA-IR, intact proinsulin, insulin, triglycerides and hsCRP) were similar in kind to the effects observed with thiazolidinediones [30,31], but much less pronounced.

The study results confirm earlier clinical observations that cinnamon does not have a pronounced effect on glycemic control when supplemented to subjects with almost normal HbA_{1c} values. The subgroup analysis performed in this study showed that the inclusion parameter of a HbA_{1c} with a minimum of 7% was selected too carefully to demonstrate the full potential of cinnamon. In addition, the statistical hypothesis had assumed no improvement of HbA_{1c} in the placebo group, whereas in fact there was a slight reduction, which can be related to a study effect. The observed changes of the markers in the placebo group may reflect the effect of a closer medical care during the study, with a better adherence to dietary recommendations. The supposed mechanisms of the anti-glycemic cinnamon activity are primarily related to improvement of insulin resistance through the polyphenolic constituents. Experience collected from the previous clinical trials allows to speculate that the observation of a distinct anti-glycemic effect of cinnamon depends on the starting values of HbA_{1c}, as cinnamon supplementation does obviously not actively lower blood glucose and HbA1c below normoglycemic values. In none of the studies published to date, hypoglycemia triggered by cinnamon was observed, and studies in healthy volunteers as well as in prediabetic patients with optimal values showed a normalizing impact on fasting and postprandial glucose, but no occurrence of values below the normal range [21,32,33]. The seemingly inconclusive study results about cinnamon impact on glycaemic control may therefore be induced by the selection of patient cohorts too well managed to allow significant and clinically important improvement.

In any case, the conclusions that can be extracted from the literature regarding positive cinnamon effects on glycemic control and type 2 diabetes become more and more evident. A most recent meta-analysis performed with 16 randomized controlled prospective studies indicated again that cinnamon significantly reduced fasting blood glucose and $HOMA_{IR}$ in patients with type 2 diabetes and prediabetes as compared to placebo [12], which is in line with our results. In addition, ethanolic preparations of cinnamon have recently shown dose-dependent antidiabetic effects and positive impact on diabetes-induced damage in several organs in a rat model for type 2 diabetes [34].

The effects of cinnamon on measures of glucose homeostasis in subjects with prediabetes was investigated in a double-blind, placebo-controlled, randomized clinical study with 54 subjects. From a similar baseline, fasting plasma glucose rose after 12 weeks with placebo but remained stable with cinnamon, leading to a mean between-group difference of 5 mg/dL ($p < 0.05$). When compared to the respective baseline, cinnamon, but not placebo, resulted in a significant decrease of the area under the glucose curve ($P < .001$) and of the 2-hour plasma glucose value ($p < 0.05$) measured during an oral glucose challenge test. The authors conclude that in individuals with prediabetes, 12 weeks of cinnamon supplementation improved fasting plasma glucose and glucose tolerance, with a favourable safety profile [35].

Next to the objective design (prospective, double-blind), a major strength of our study was its systematic approach to measure biomarkers of the underlying deteriorations of type 2 diabetes mellitus over an intervention period of four months in addition to parameters of glycemic control. These results indicate for the first time an improvement of insulin resistance and chronic systemic inflammation by cinnamon supplementation and gave a better picture for understanding the emerging improvement of glycemic control and blood lipids during cinnamon supplementation in comparison to the published literature.

Limitation of the Study

As a limitation, the concomitant use of oral antidiabetic drugs may be a confounder. However, the two groups were not different in this respect and the study design allows to conclude that this study shows consistent and partly significant improvements of biomarkers of glycemic control and diabetes deteriorations by employing cinnamon extract supplementation.

Conclusion

In conclusion, an overall improvement in multiple metabolic and non-metabolic biomarkers in comparison to placebo was observed when cinnamon extract was administered in addition to standard of care in this study, which together with most recent meta-analyses may support the recommendation for regular dietary supplementation with cinnamon extracts in patients with type 2 diabetes.

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Conflict of Interest

The study was sponsored by Alsitan GmbH (Greifenberg, Germany). The sponsor provided honoraria to the authors for the statistical planning and evaluation, case data compilation and reporting. The sponsor was not involved in the planning, execution, evaluation and publication of the clinical trial. These tasks were carried out under the responsibility of the principal investigator.

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