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KAHRAMANMARAŞ SÜTÇÜ İMAM ÜNİVERSİTESİ
BİLİMSEL ARAŞTIRMA PROJELERİ KOORDİNASYON BİRİMİ
PROJE YAYIN DİLEKÇESİ

Proje Adı		
Diyabetik sıçanlarda sinnamaldehitin Nesfatin-1 düzeyine etkisi		
Proje No	Başlama Tarihi	Bitiş Tarihi
2021/6-10 YLS	10-11-2021	17-07-2022
Yayın Türü	Yayın / Makele Başlığı	
Makale	Effect of cinnamaldehyde on nesfatin-1 levels in diabetic rats	
Dergi ISSN	DOI	Cilt / Sayfa / Yıl
1596-5996	10.4314/tjpr.v23i2.9	23 (2) / 299-305 / 2024
Yayınlandığı Dergi Kısa Ad	Yayınlandığı Dergi	
Trop J Pharm Res	TROPICAL JOURNAL OF PHARMACEUTICAL RESEARCH	

İLGİLİ MAKAMA

Yukarıda bilgileri verilen ilgili otomasyona girilmiş yayın bilgileri içerisinde ; "Söz konusu çalışma/yayın/sunum/poster/bildiri/ **KAHRAMANMARAŞ SÜTÇÜ İMAM ÜNİVERSİTESİ Bilimsel Araştırma Projeleri birimi** tarafından 2021/6-10 YLS proje numaralı "Diyabetik sıçanlarda sinnamaldehitin Nesfatin-1 düzeyine etkisi" konusu ile ilgili olup, ilgili birimce desteklenmiştir." ("This work is supported by the **Scientific Research Project Fund of KAHRAMANMARAŞ SÜTÇÜ İMAM ÜNİVERSİTESİ** under the project number 2021/6-10 YLS") ifadesi yer almaktadır.

PROJE YÜRÜTÜCÜSÜNÜN

Ünvanı, Adı-Soyadı : Doç.Dr. Behiye Nurten AKKEÇECİ

Tarih : 24-06-2024

Bu belge, güvenli elektronik imza ile imzalanmıştır.

Belge Doğrulama Kodu :6b854fd188

Belge Takip Adresi : <https://bapotomasyon.ksu.edu.tr/belgedogrula>

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Original Research Article

Effect of cinnamaldehyde on nesfatin-1 levels in diabetic rats

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Sent for review: 18 September 2023

Revised accepted: 2 February 2024

Abstract

Purpose: To evaluate the effect of cinnamaldehyde (CA) on fasting blood glucose (FBG), body weight, lipid profile, and nesfatin-1 levels in healthy and diabetic (DM) rats.

Methods: Ten groups with eight rats per group were used. Healthy and diabetic sham groups were administered 1 mL of saline for 28 days by intragastric gavage. Healthy and diabetic control groups were administered 1 mL 0.5 % dimethyl sulfoxide (DMSO) for 28 days by intragastric gavage. Other diabetic and healthy groups (HG) received 10, 20, and 40 mg/kg CA for 28 days by intragastric gavage, once daily. Diabetes was induced with streptozotocin (50 mg/kg intraperitoneally). Rats were defined as diabetic when FBG was > 250 mg/dL. Enzyme-linked immunosorbent assay (ELISA) was used to assess serum nesfatin-1 concentrations. Fasting blood glucose (FBG) values were evaluated with a glucometer.

Results: Day 28 weights of all DM and HG + 40 mg/kg CA groups were lower than day 1 weights ($p < 0.05$). Triglyceride values of DM + 40 mg/kg CA group were lower than DM sham and control group ($p \leq 0.001$). Low-density lipoprotein (LDL) and cholesterol levels of the CA-administered healthy groups were higher than healthy control groups ($p \leq 0.001$). Nesfatin-1 levels of all DM groups were lower than all healthy groups, and nesfatin-1 levels of all CA-administered healthy and DM groups were lower than healthy and DM sham and control groups, but these were not significant ($p > 0.001$).

Conclusion: Although not significant, the decrease in nesfatin-1 level is evidence that CA has an anti-obesity effect in both healthy and diabetic rats. In contrast to its antihyperlipidemic effect in diabetic conditions, CA has hyperlipidemic effect in healthy conditions.

Keywords: Anti-obesity, Cinnamaldehyde, Cinnamon, Diabetes, Lipid profile, Nesfatin-1

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Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, Web of Science, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Diabetes mellitus (DM) is characterized by chronic hyperglycemia in which either impaired insulin action or/and impaired insulin secretion occurs [1]. There is increasing interest in the development and use of antidiabetic plants for

DM treatment. Natural compounds of many plants and phytonutrients have antidiabetic effects [2]. Consumption of phytonutrients is considered a safe approach to diabetes management. Cinnamon (*Cinnamomum verum*) is a plant native to India and Sri Lanka, belonging to the Lauraceae family [2]. Cinnamaldehyde

(CA) is isolated from the bark of cinnamon trees and is one of the phytonutrients clinically evaluated for its antidiabetic effects [3]. Some studies have reported that CA has anti-obesity [4], antihyperlipidemic [5], antihyperglycemic [4], and antidiabetic [5] effects. However, the mechanisms underlying these effects of CA are yet to be fully explained [6].

Nucleobindin-2 (NUCB2) is the source of nesfatin-1, which has an anorexigenic effect [7]. Nesfatin-1 is a polypeptide with 82 amino acids and is a precursor of NUCB2 [7]. Studies have shown that nesfatin-1 has anti-obesity [8], antihyperglycemic [9], and antihyperlipidemic [10] effects. Nesfatin-1 is thought to affect glucose regulation by increasing insulin secretion in β cells under hyperglycemic conditions [11]. Numerous investigations have been performed to determine the level of nesfatin-1 in people with diabetes, but the results are controversial [11–13]. While some studies have demonstrated that the nesfatin-1 level is decreased in DM, [11,12] others have indicated that the nesfatin-1 level is increased [13]. Furthermore, a recent meta-analysis stated that the nesfatin-1 level is decreased in people undergoing antidiabetic therapy, and a low level of nesfatin-1 might be a target for antidiabetic therapy [11]. There are currently no studies that have investigated the effect of CA on the nesfatin-1 level.

This study examined the effect of CA (the primary active component of cinnamon) on lipid profile, body weight, fasting blood glucose (FBG), and nesfatin-1 levels in diabetic (DM) and healthy rats.

EXPERIMENTAL

Animal handling

Eighty male Wistar-albino rats weighing between 390 and 500 g were used. The animals were housed in cages in quiet, stress-free, well-ventilated rooms with standardized temperature and humidity (20 – 24 °C, 62 ± 7 % humidity) and under a 12-hour dark–light cycle. The rats had free access to water and food, and were fed 4 % fiber (w/w), 55 % nitrogen-free extract, 5 % fat, and 21 % protein feed with adequate vitamin and mineral content. Bodyweight on days 1 and 28 were recorded and any other changes observed were noted. Cinnamaldehyde/drug administration to the animals was performed at the same time each day according to circadian rhythm. The Kahramanmaraş Sütçü İmam University (KSU) Experimental Animals Ethics Committee approved this work (approval no. 2021/05-01).

Animal groups

The study consisted of ten groups with eight animals per group: 1: healthy sham, 2: healthy control (HC), 3: HG + 10 mg/kg CA, 4: HG + 20 mg/kg CA, 5: HG + 40 mg/kg CA, 6: DM sham, 7: DM control, 8: DM + 10 mg/kg CA, 9: DM + 20 mg/kg CA, and 10: DM + 40 mg/kg CA.

The weights of animals were recorded and injections were prepared according to their weights. For each rat in DM groups, 50 mg/kg of streptozotocin (STZ) diluted in citrate buffer (pH 4.5, 0.1 M) was injected intraperitoneally (IP) [14]. STZ was purchased from Sigma Aldrich (Sigma-S0130) and stored at -20 °C according to the cold chain conditions. Rat FBG levels were measured immediately before and 72 h after STZ administration, and rats were defined as diabetic when FBG was > 250 mg/dL.

Drug administration

Healthy sham and DM sham groups received 1 mL of saline as a single dose daily for 28 days by intragastric gavage method to establish how the injection and the stress factor might affect the experiment. There were two separate control groups each with eight rats, as healthy control and DM control, and 1 mL 0.5 % DMSO was given as a single dose daily for 28 days by intragastric gavage method to understand how the solvent might affect the experiment.

Other healthy and diabetic rats were separated into three groups and each group received a single daily dose of CA at varying doses (10, 20, or 40 mg/kg) dissolved in 1 mL 0.5 % dimethyl sulfoxide (DMSO) by intragastric gavage for 28 days [4]. Dimethyl sulfoxide and trans-CA (Sigma-C80687) were purchased from Sigma Aldrich. The experimental protocol was performed in Kahramanmaraş Sütçü İmam University, Experimental Medicine Research and Application Unit.

On day 29, 2 % 15 mg/kg xylazine (Alfazine; Alfasan IBV, Woerden, The Netherlands) and 10 % 75 mg/kg ketamine (Alfamine; Alfasan IBV, Woerden, The Netherlands) were administered intraperitoneally (IP) to the rats before they were sacrificed. Serum was collected after centrifuging intracardiac blood samples at 4000 rpm for 8 minutes in biochemistry (gel) tubes. Serum samples were transferred to Eppendorf tubes and stored at -80 °C until the time of the total cholesterol, low-density lipoprotein (LDL), serum triglyceride (TG), high-density lipoprotein (HDL), and nesfatin-1 tests.

Evaluation of parameters/indices

Enzyme-linked immunosorbent assay

Enzyme-linked immunosorbent assay (ELISA; BT LAB. Bioassay Technology Laboratory, China. Catalog No: E0878Ra) was used to assess serum nesfatin-1 concentrations. The measurement range of the ELISA test was 30 – 9000 ng/L, and its sensitivity was < 16.23 ng/L.

Fasting blood glucose and lipid levels

Fasting blood glucose (FBG) values on days 1 and 28 were evaluated with a glucometer (VivaChek Eco, VivaChek Laboratories, China). In addition, total cholesterol, TG, LDL, and HDL (Architect ci8200, Abbott) levels were evaluated.

Statistical analysis

Version 16.0 of SPSS software was used to analyze the data (SPSS Inc., Chicago, IL, USA). The homogeneity of the variances and data conformity to the normal distribution were evaluated with the Levene and Shapiro–Wilk tests, respectively. The Kruskal–Wallis H Test was used to compare independent groups of data where variances were not homogeneous and/or did not follow the normal distribution. The Wilcoxon Paired-Sample Test was used to compare repeated measurements. The findings were judged as significant if $p < 0.05$. To compare the two independent groups, the Bonferonni Corrected Mann–Whitney U test was used, and the findings were judged as significant if $p \leq 0.001$ in pairwise comparisons.

RESULTS

On days 1 and 28, FBG values were significantly different across the groups ($p^b < 0.001$; Table 1). When the FBG values on days 1 and 28 were

analyzed, it was observed DM sham and DM control groups had increased FBG values ($p = 0.011$ and $p = 0.018$, respectively; Table 1), while there was no significant difference in the other groups ($p^a > 0.05$).

While there was no significant difference between the groups in terms of day 1 weights ($p = 0.961$; Table 2); there was a significant difference in weight on day 28 ($p < 0.001$; Table 2). When the day 1 and day 28 weights of the groups were compared, the weight of the HG + 40 mg/kg CA, DM sham, DM control, DM + 10 mg/kg CA, DM + 20 mg/kg CA and DM + 40 mg/kg CA groups were significantly reduced ($p < 0.05$; Table 2).

When the blood lipid profiles of the groups were compared; TG, cholesterol, HDL, and LDL values were significantly different between the groups ($p < 0.001$; Table 3). Furthermore, there was a significant difference between the groups for serum nesfatin-1 values ($p = 0.019$; Table 3).

DISCUSSION

This is the first study to evaluate the effect of CA, the primary active component of cinnamon, on nesfatin-1 levels in DM and healthy rats. As a consequence of present research, in which it was assessed the effect of CA, which is known to have anti-diabetic effects, on FBG, weight, lipid profile, and nesfatin-1 levels in healthy and DM rats; it was discovered that CA has an anti-obesity effect in both healthy and DM rats. In addition, CA had an antihyperlipidemic effect in DM rats and interestingly, a hyperlipidemic effect in healthy rats. Furthermore, it was observed that the level of nesfatin-1 was lower in rats with DM than in healthy rats, and in all CA-administered DM and healthy rats compared with non-CA-administered DM and healthy rats.

Table 1: FBG values of the groups on days 1 and 28

Group	Day 1 FBG (mg/dL)	Day 28 FBG (mg/dL)	P ^a -value
Healthy sham	102.50 ±2.44	101.38±2.07	0.416
Healthy control	102.88 ±3.52	101.75±4.30	0.726
HG+10 mg/kg CA	101.50 ±5.48	102.88±5.14	0.336
HG+20 mg/kg CA	102.13 ±7.38	100.25±4.68	0.235
HG+40 mg/kg CA	104.75±4.23	102.88±6.33	0.348
DM sham	414.38±39.95	465.50±20.01	0.011 ^a
DM control	426.38±42.19	450.13±37.39	0.018 ^a
DM+10 mg/kg CA	427.63±49.39	426.13±46.98	0.161
DM+20 mg/kg CA	423.50±81.61	400.75±59.82	0.183
DM+40 mg/kg CA	436.50±28.36	423.13±42.96	0.123
p ^b -value	<0.001 ^b	<0.001 ^b	

P^a: Wilcoxon Test. p^b: Kruskal–Wallis Test. a: the difference within the groups is statistically significant. b: the difference between the groups is statistically significant. FBG: fasting blood glucose. CA: cinnamaldehyde. DM: diabetes mellitus. HC: healthy control. HG: healthy group

Table 2: Weight (g) measurement values of the groups on days 1 and 28

Group	Day 1 weight (g)	Day 28 weight (g)	p ^a -value
Healthy sham	456.50±12.50	450.25±17.35	0.058
Healthy control	450.63±29.88	445.13±28.91	0.137
HG+10 mg/kg CA	440.38±35.65	428.13±20.24	0.182
HG+20 mg/kg CA	445.63±28.09	445.00±24.23	0.933
HG+40 mg/kg CA	450.25±27.05	433.63±35.72	0.012 ^a
DM sham	451.75±16.92	399.00±29.96	0.011 ^a
DM control	441.88±38.92	379.75±40.83	0.012 ^a
DM+10 mg/kg CA	442.50±21.88	399.88±41.09	0.012 ^a
DM+20 mg/kg CA	437.00±32.30	359.88±59.60	0.012 ^a
DM+40 mg/kg CA	446.25±31.21	362.38±52.12	0.012 ^a
p ^b -value	0.961	<0.001 ^b	

P^a: Wilcoxon Test. p^b: Kruskal–Wallis Test. a: The difference within the groups is statistically significant. b: The difference between the groups is statistically significant. CA: cinnamaldehyde. DM: diabetes mellitus. HC: healthy control. HG: healthy group.

Table 3: Serum TG, total cholesterol, LDL, HDL, and nesfatin-1 values

Group	TG (mg/dL)	TC (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	Nesfatin-1 (ng/mL)
Healthy sham	60.00±5.55	26.13±4.32	7.71±1.00	9.85±3.01	1.31±0.16
Healthy control	65.50±7.46	28.13±4.29	8.11±1.56	10.24±1.92	1.38±0.18
HG+10 mg/kg CA	80.50±10.17	46.88±7.74	13.63±3.08	18.49±2.01	1.15±0.22
HG+20 mg/kg CA	70.00±17.44	43.88±8.49	11.23±2.65	16.26±3.00	1.15±0.28
HG+40 mg/kg CA	71.50±21.49	46.50±4.75	12.49±1.63	19.14±4.18	1.02±0.26
DM sham	538.50±96.71	79.38±5.66	19.52±8.68	20.76±7.44	1.17±0.15
DM control	517.63±83.87	77.25±5.37	18.38±9.06	18.99±5.05	1.18±0.07
DM+10 mg/kg CA	404.75±50.67	86.25±10.70	20.39±8.36	34.39±16.69	1.06±0.25
DM+20 mg/kg CA	373.50±47.94	88.63±8.73	19.49±6.25	37.56±16.37	1.06±0.08
DM+40 mg/kg CA	303.38±90.82	81.50±11.76	17.93±4.04	35.74±15.48	1.03±0.28
p ^a -value	<0.001 ^a	<0.001 ^a	<0.001 ^a	<0.001 ^a	0.019 ^a

P^a: Kruskal–Wallis Test. a: The difference between the groups is statistically significant. CA: cinnamaldehyde. DM: diabetes mellitus. HC: healthy control. HDL: high-density lipoprotein. HG: healthy group. LDL: low-density lipoprotein. TC: total cholesterol. TG: triglyceride

Diabetes mellitus (DM), a global public health problem is characterized by chronic hyperglycemia [1]. CA, which is isolated from the bark of cinnamon trees, is one of the phytonutrients clinically evaluated for its anti-diabetic effect [3]. In 2007, Subash *et al* [15] showed that CA has a hypoglycemic effect in DM rats. Abdelmageed *et al* [16], determined that after 30 days of 10 mg/kg CA administration, the FBG and insulin levels of diabetic rats decreased compared with the diabetic control group. Jawale *et al* [17] administered 10, 20, and 40 mg/kg CA to rats with diabetes for 3 weeks and found that 20 and 40 mg/kg CA decreased blood glucose levels. Li *et al* [18] showed that the FBG values of DM rats receiving 20 mg/kg CA for 28 days remained higher than the non-diabetic rats, however, at the end of 28 days the FBG values of DM rats decreased significantly compared with non-diabetic rats. In another study, Subash *et al* [19] gave three different doses of CA to DM rats for 45 days and reported that 20 mg/kg CA reduced the FBG level. Furthermore, they administered 20 mg/kg CA to healthy rats for 45 days and did not observe any change in FBG values. As a result, they concluded that CA has antidiabetic properties by protecting pancreatic β

cells under hyperglycemic conditions [19]. In present study, CA was given at 10, 20, and 40 mg/kg doses to healthy and DM rats for 28 days; although these results were not statistically significant, it was observed that DM rats treated with 20 and 40 mg/kg CA had lower FBG values at day 28 compared with day 1 and that the day 28 FBG values of the CA administered DM groups were lower than DM sham and control groups. Moreover, similar to Subash *et al* [19], no change was determined in FBG values of healthy rats treated with CA.

The hypolipidemic effect of CA in diabetic rats has been previously demonstrated [15]. Furthermore, the effect of improving the lipid profile of DM rats treated with CA has been shown in other studies [14,16,18]. After receiving 10 mg/kg CA for 30 days, DM rats' lipid profiles improved (HDL values increased while total cholesterol, TG, VLDL, and LDL values decreased) [16]. Li *et al* [18] found that HDL cholesterol increased as a result of 20 mg/kg CA treatment for 28 days, although levels of free fatty acids, TG, total cholesterol, and LDL did not significantly differ. In another study in which rats with diabetes received 20 mg/kg CA for 28 days,

it was shown that the HDL, total cholesterol, and TG levels improved [14]. The results of this study suggest that CA administration has an antihyperlipidemic effect by reducing TG levels in DM rats. Interestingly, in contrast to its antihyperlipidemic effect in DM rats, CA administration worsened the lipid profile in healthy rats. The findings of present study are consistent with the published literature, which reported that cinnamon causes hyperlipidemia by increasing cholesterol and LDL levels in healthy rats [20]. This study supports the findings of Huang *et al* [20] that daily cinnamon supplementation might impair lipid homeostasis in healthy rats, and the current study's findings indicate that healthy individuals should pay attention to daily cinnamon use due to its hyperlipidemic effects in healthy conditions.

Previous research has reported that CA has an anti-obesity effect [14,17,18]. Jawale *et al* [17] did not find any significant change in the body weight of DM rats as a result of the administration of different doses of CA for 3 weeks. Li *et al* [18] showed that the body weight of db/db mice given 20 mg/kg CA for 28 days decreased, reportedly due to the antidiabetic effect of CA. In another study, it was found that diabetic rats who received 20 mg/kg CA experienced a considerable reduction in body weight [14]. Consistent with the literature, it was found that 10, 20, and 40 mg/kg CA administration in diabetic rats and also 40 mg/kg CA administration in healthy rats had an anti-obesity effect.

The NUCB2-derived anorexigenic peptide nesfatin-1 is implicated in the control of food intake and hyperglycemia [21]. Nesfatin-1 is associated with the regulation of glucose homeostasis, regulation of food intake, regulation of appetite, weight loss, and malnutrition [21]. Change in body weight is also thought to affect the level of nesfatin-1 [21]. However, there is no consensus from studies comparing the nesfatin-1 concentrations of obese individuals with control values. Some studies report that obese individuals have low nesfatin-1 concentrations [22], while other studies suggest that obese individuals have high nesfatin-1 concentrations [23,24]. Yin *et al* [23] reported a positive correlation between nesfatin-1 levels, body weight, and body mass index (BMI), and that serum nesfatin-1 levels increased in obese children. Moreover, Özkan *et al* [24] observed that serum nesfatin-1 levels were higher in overweight individuals and lower in individuals with low body weight, and that serum nesfatin-1 levels decreased gradually in overweight individuals with low body weight. Although the

current study results were not significant due to a large number of comparison groups, it was observed that serum nesfatin-1 levels were insignificantly low in groups with low body weight as a result of CA-administration.

In addition to obesity, recent research suggests that nesfatin-1 plays a role in the pathogenesis of diabetes mellitus [12,13]. However, there is no consensus from studies comparing nesfatin-1 concentrations of diabetic individuals with control values. Some studies reported that diabetic individuals have high nesfatin-1 concentrations [13], while other studies have reported that diabetic individuals have low nesfatin-1 concentrations [12]. Consistent with previous studies, although the results of the present study were not significant due to a large number of comparison groups, it was observed that serum nesfatin-1 levels were lower in diabetic groups than in healthy groups. A recent meta-analysis reported that serum nesfatin-1 levels decreased in diabetic patients receiving antidiabetic therapy due to the effects of antidiabetic drugs in lowering blood sugar levels, increasing insulin sensitivity, and restricting calorie intake [11]. Consistent with this meta-analysis, it was observed that serum nesfatin-1 levels were lower in CA-administered DM and healthy groups than in DM and healthy control groups that did not receive CA, but these differences were not statistically significant. The results of this study suggest that the low serum nesfatin-1 level in CA-administered groups is a potential indicator of the antidiabetic treatment efficacy of CA.

Limitations of the study

The most important limitation of this study was that blood parameters such as insulin and hemoglobin A1c were not evaluated and histopathological examinations were not performed.

CONCLUSION

The decrease in nesfatin-1 levels, although not significant, is evidence that CA has an anti-obesity effect in both healthy and diabetic conditions. In contrast to its antihyperlipidemic effect in diabetic conditions, cinnamaldehyde has hyperlipidemic effect in healthy conditions.

DECLARATIONS

Acknowledgements

This study was supported by Kahramanmaraş Sütçü İmam University Scientific Research Projects (BAP, no. 2021/6-10 YLS).

Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was performed by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. Nazlıcan İgci: conceptualization, methodology, investigation, and writing of the original draft. Nurten Akkececi: conceptualization, methodology, investigation, writing of the original draft, reviewing, and editing. Mehmet Boşnak: methodology, supervision, writing, reviewing, and editing. Atila Yoldaş: methodology, supervision, writing, reviewing, and editing. Nadire Eser: methodology, supervision, writing, reviewing, and editing.

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