Journal of Diabetes & Metabolic Disorders (2020) 19:53–60
https://doi.org/10.1007/s40200-019-00474-3

RESEARCH ARTICLE

Effects of probiotic, cinnamon, and synbiotic supplementation on glycemic control and antioxidant status in people with type 2 diabetes; a randomized, double-blind, placebo-controlled study

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Received: 10 August 2019 / Accepted: 29 November 2019 / Published online: 23 December 2019

Abstract

Purpose The aim of this study was to investigate the effect of probiotic bacteria of *Lactobacillus acidophilus*, cinnamon powder and their combinations on the glycemic and antioxidant indices in patients with type 2 diabetes.

Methods A total of 136 patients randomized with type 2 diabetes entered the study and were randomly divided into four groups who were matched for age and gender. Thereafter, alongside their routine pharmacotherapy, each group followed one of the following diets: Group A: *Lactobacillus acidophilus* 10^8 cfu and 0.5 g of powdered cinnamon (synbiotic). Group B: *Lactobacillus acidophilus* (probiotic), Group C: powdered cinnamon. Group D: rice flour powder as placebo. At the beginning and end of the intervention, fasting blood sugar (FBS), HbA1c, advance glycation end products (AGE), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and antioxidant enzymes of superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) were measured.

Results Following 3 months of treatment, the mean FBS level was decreased significantly in probiotic, cinnamon, and synbiotic supplementation groups compared with control ($P < 0.01$). FBS levels in probiotic, cinnamon, and synbiotic groups were significantly decreased compared with the control group ($P = 0.001$, $P = 0.063$ and $P = 0.001$, respectively). The mean HbA1C in probiotic, cinnamon, and synbiotic groups were also decreased ($P = 0.001$, $P = 0.001$ and $P = 0.04$, respectively). The mean AGE in synbiotic group was significantly decreased ($P = 0.037$). Probiotic, cinnamon and synbiotic all could improve antioxidant enzyme activity modestly. However, the most significant effect was seen in probiotic group.

Conclusions According to the current results, the use of probiotic supplements (individually or in combination with cinnamon) leads to a reduction in blood glucose and an increase in antioxidant enzymes in people with type 2 diabetes.

Keywords Diabetes mellitus · Probiotic · Cinnamon · Synbiotic · Antioxidant enzymes

Background

Diabetes mellitus is one of the most common chronic endocrine disorders worldwide. It has been estimated that a total of 425 million people suffered from diabetes globally which is predicted to rise by 50% over the next 30 years [1]. Approximately one in every ten Iranian adults suffers from diabetes [2]. Because of its high prevalence, most countries spend 5% to 20% of their health budget on the control and treatment of diabetes [3]. Various studies have shown that a change in lifestyle can improve blood glucose in type 2 diabetes. However, lifestyle changes should be integrated with pharmacological agents for most patients. Because of the progressive deterioration of pancreatic beta cells, patients may need multiple drugs as well as insulin therapy [4]. Recent studies on nutritional supplements

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have suggested that some compounds, such as dietary fiber, vitamins, flavonoids, sterols, and antioxidants, may be involved in controlling blood glucose and preventing complications of diabetes and can be applied together with pharmacotherapy [5]. Probiotics are non-pathogenic microorganisms that favorably influence the health of the host by changing the balance of gut microbiota. When consumed in a sufficient amount and in a viable state, they can be considered as functional foods. However, their effects on diabetes have been controversial [6]. Lactic acid-producing bacteria, especially Lactobacillus and Bifidobacterium, are normally part of the digestive ecosystem and are known as probiotics. Oral administration of these probiotics may improve metabolic disorders such as diabetes by modifying the normal flora of the intestine [7, 8].

Prebiotics refer to special vegetative fibers that are fermented by the bacteria in the intestine and contribute to the growth, proliferation, and function of the digestive microbial community [9]. The combination of probiotic bacteria and a prebiotic compounds form synbiotics. Cinnamon is one of the most famous and widely-used spices that have prebiotic properties and therapeutic applications. Some studies have shown that cinnamon can improve the blood glucose and lipid profiles in people with diabetes [10, 11]. The advantages of cinnamon may be due to its prebiotic properties, phytochemicals, antioxidants, and essential oils [10, 11]. In keeping with the high beneficial effects of cinnamon, scarce data are available about its effects on glycemia and oxidative stress in diabetic patients. Additionally, rare surveys have been conducted to apprise the effects of probiotic bacteria and symbiotic products on diabetic patients. Thus, the present study was carried out to investigate the effects of *Lactobacillus acidophilus* probiotic bacteria, cinnamon powder, and their combinations on the glycemic and antioxidant indices in patients with type 2 diabetes.

Methods

Preparation of the supplements and placebo capsules

The symbiotic, probiotic, cinnamon and placebo capsules were prepared by Institute of Medicinal plants, Karaj, Iran. *Lactobacillus acidophilus* PTCC 1643 was obtained and used as probiotic treatment (Zist-yar Sina Co, Iran). Cinnamon (*Cinnamomum zeylanicum*) from the *Lauracea* family and the Laurales order was purchased, and the plant species was approved by an expert in medicinal plants. Rice flour was used as placebo in this study. Following treatments were prepared for groups: Synbiotic; *Lactobacillus acidophilus* 10^8 cfu mixed with 0.5 g of powdered cinnamon in hard gelatin capsules, Probiotic; *Lactobacillus acidophilus* 10^8 cfu in hard gelatin capsules, Cinnamon; 0.5 g of powdered cinnamon in hard gelatin capsules and placebo; 0.5 g of rice flour powder in hard gelatin capsules.

Participants

The inclusion criteria consisted of type 2 diabetes, no insulin use, 40 to 60 years of age, fasting blood glucose levels of 125–250 mg/dl, and HbA1c of 7–8%. The exclusion criteria included pregnancy, lactation, consumption of specific medicines (effective on blood glucose such as corticosteroids, diuretics, and antibiotics), use of vitamin supplements and medicinal plants, changes in anti-diabetic medications during the previous 4 months, history of lactose intolerance or allergies, chronic and uncontrolled hepatic, renal, psychological, or cardiac disease, cigarette or alcohol addiction. Additionally, people with a specific diet or heavy exercise were not included in the study. Patients were asked to bring their medications at each visit to determine how many medications they had used according to assigned plan. Additionally, during the visits, telephone calls were made to ask about the use of the drug. Additionally, patients were asked not to change their diet and exercise during the study.

Protocol

A total of 136 volunteers who met the inclusion criteria entered the study and were randomly divided into four groups of synbiotic, probiotic, cinnamon, and control. Groups were matched based on age and gender. This sample size was calculated to be sufficient to estimate a 20 mg/dl difference in fasting glucose between the groups, considering type I error = 0.05 and 80% power. The CONSORT diagram of patient recruitment is depicted in Fig. 1. Block randomization with computer-generated random-numbers table and sequentially numbered containers each representing a block consisting of 4 patients were used for treatment allocation.

The following supplement regimens were added to the patients' routine pharmacotherapy:

> Group A received a capsule of *Lactobacillus acidophilus* 10^8 cfu and 0.5 g of powdered cinnamon per day;
> Group B received a capsule of *Lactobacillus acidophilus* 10^8 cfu per day;
> Group C received a capsule containing 0.5 g of powdered cinnamon per day; Group D received a capsule containing 0.5 g of rice flour powder per day.

Initially, patients were provided with complete information regarding the implementation of the project and the potential side effects of the supplements. All participants signed written consent forms and were told they could leave the study at any time, after informing their physician of their decision to do so. Patients were instructed to take their treatment every morning with food for 3 months. The incidence of any side effects caused by the use of the supplements was to be reported by the patients. At the

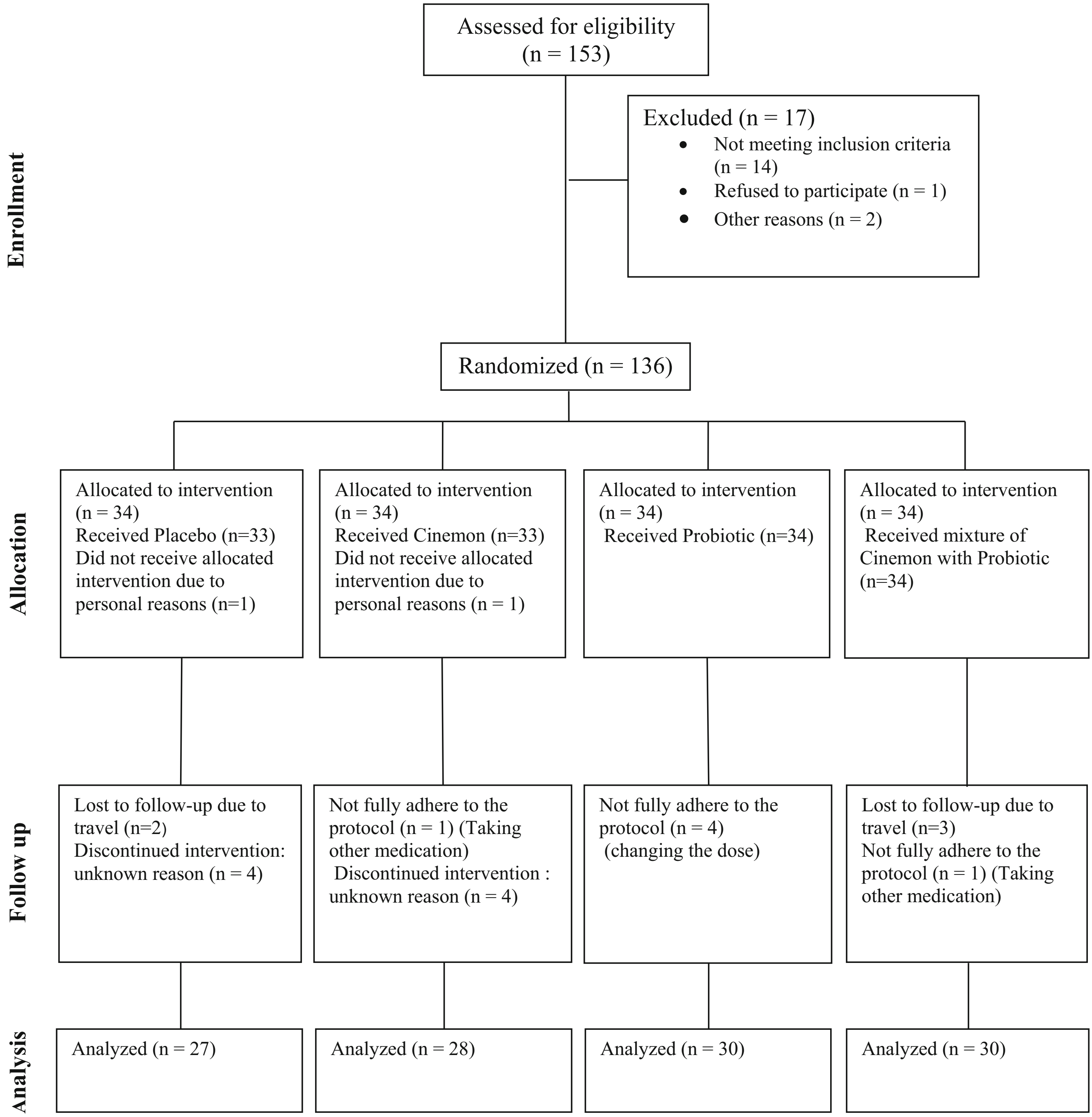

Fig. 1 CONSORT flow diagram for participants

beginning and end of the interventional period, 12-h–fasting venous blood samples were collected and HbA1c was determined. The sera were kept at −70 °C until used in biochemical tests. A human ELISA kit (Diaclone, France) was used to measure the antioxidant enzymes of superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). Standard kits (Pars Azmoon Co, Iran) were obtained for the FBS, AST, and ALT tests, and the Nycocard instrument kit was used to determine HbA1c. The study was registered in the Iranian Registry of Clinical Trials (IRCT20170305032883N2), and the protocol was approved by the ethics committee (IR.ABZUMS.REC.1394.92) of the Alborz University of Medical Sciences, Alborz province, Iran.

Assessment of adverse effects

All the patients were asked to report any adverse effects by phone to physician.

Statistical analysis

The sample size was calculated with 80% power using a two-sided test at the 5% significance level and based on the effect size of 0.5 (0.5% decrease in HbA1c). Randomization was done based on sex with stratified permuted blocked randomization method using "sealed envelope" online software with a block size of 4 (AABB, ABAB, ABBA, BAAB, BABA, BBAA). Researchers, subjects and data analysts were blinded to the treatment. The Statistical Package for the Social Sciences version 24.0 (SPSS Inc., Chicago, IL, USA) was used for statistical evaluation of data. Quantitative data are expressed as mean ± standard deviation. Within-group differences are compared using the paired *t*-test. Between- group differences are analyzed using one-way ANOVA following Tukey's post hoc test. *P* value less than 0.05 is considered statistically significant.

Results

Demographic characters of studied patients

A total of 136 patients in 4 different groups were entered to the study. Two patients were initially refused from treatment due to their personal reasons. Additionally, five patients due to travel, 8 patients due to anonymity, 4 patients due to changes in treatment protocol, and 2 patients due to delivery of other medications were excluded from the study. Finally, 115 patients were completed the study in the probiotic ($n = 30$), symbiotic (n = 30), cinnamon ($n = 28$), and placebo ($n = 27$) groups (Fig. 1). Table 1 reveals demographic characteristics of diabetic patients before intervention. Age of studied patients had the ranges of 58.2 ± 11.8 to 59.7 ± 12.2 years. Majority of studied patients in all examined groups were female. Weight of studied patients had the ranges of 79.3 ± 13.3 to 83.5 ± 13.6 Kg.

Table 1 Demographic characteristic of diabetic patients before intervention

Characters	Groups			
	Control $N = 27$	Probiotic $N = 30$	Cinnamon $N = 28$	Synbiotic $N = 30$
Age (year)	58.2 ± 11.8	59.7 ± 12.2	58.8 ± 12.8	58.4 ± 11.4
Sex (male/female)	12/15	10/20	14/16	13/15
Weight (Kg)	83.5 ± 13.6	79.3 ± 13.3	81.6 ± 12.6	79.5 ± 11.8

Data are presented as the mean ± SD. * $P < 0.05$ is considered as significant

Effects of probiotic, cinnamon and synbiotic on FBS, HbA1c and AGE

Table 2 signifies the effects of probiotic, cinnamon and synbiotic on FBS, HbA1c and AGE factors in diabetic patients. At the beginning of this study, no significant difference was observed between groups regarding mean age, body mass index and gender. Following 3 months of treatment, the mean fasting blood suger (FBS) level in probiotic, cinnamon, and synbiotic groups were significantly lower compared with the control group ($P = 0.001$, $P = 0.063$ and $P = 0.001$ respectively). Furthermore, HbA1c levels declined moderately corresponding to blood glucose. The mean HbA1C percent in probiotic, cinnamon, and synbiotic groups were lower compared with the control group ($P = 0.001$, $P = 0.001$ and $P = 0.04$, respectively). Advanced glycation end products (AGE) in synbiotic group was significantly lower compared with the control group during this study ($P = 0.037$). Otherwise the lowest amounts of FBS, HbA1c and AGE factors were found in the symbiotic (147.70 ± 3.71 mg/dL), probiotic (7.42 ± 1.23%) and symbiotic (62.78 ± 9.14%) groups.

Effects of probiotic, cinnamon and synbiotic on biochemical factors

Table 3 signifies the effect of probiotic, cinnamon and synbiotic on biochemical factors in diabetic patients. The highest amounts of CAT, GPx, SOD, and OxLDL were found in probiotic (2.44 ± 0.50 U/mL) and cinnamon (2.44 ± 0.26 U/mL), probiotic (92.15 ± 8.41 U/ mL), probiotic (4.58 ± 0.42 U/mL) and control (17.07 ± 1.01 mU/L) groups. However, the highest amounts of CAT, GPx, SOD, and OxLDL were found in control (1.95 ± 0.34 U/ mL), cinnamon (84.61 ± 13.43 U/ mL), control (3.99 ± 0.27 U/ mL) and synbiotic (15.88 ± 1.98 mU/L) groups. Probiotic, cinnamon, and synbiotic supplementation improved antioxidant enzyme activity modestly; however, the most significant effect was seen in the probiotic group.

Generally, probiotic and cinnamon could increase CAT level ($P < 0.001$ and $P = 0.04$ respectively). Probiotic was the only treatment that changed GPx and SOD ($P = 0.01$ and $P < 0.001$ respectively). OxLDL was affected mostly by synbiotic ($P = 0.03$). No side effects were reported.

Discussion

The results of this study showed that probiotics, cinnamon, and synbiotics (a combination of probiotic and cinnamon) all can reduce the levels of fasting blood glucose and HbA1c in diabetic patients, and none of the treatments had a significant superiority over the others. In the case of antioxidant enzymes activity, however, probiotic intake had the highest impact compared with the other groups. Previous studies have reported controversial results on the effects of cinnamon and probiotics for the treatment of

Table 2 The effects of probiotic, cinnamon and synbiotic on FBS, HbA1c and AGE in diabetic patients

Biochemical factors	Groups				
	Control $N = 27$	Probiotic $N = 30$	Cinnamon $N = 28$	Synbiotic $N = 30$	*P* value
FBS (mg/dL)	177.3 ± 23.02	150.43 ± 43.36***	152.50 ± 48.1*	147.70 ± 3.71***	0.001
HbA1c (%)	8.48 ± 0.59	7.42 ± 1.23***	7.68 ± 0.83***	7.66 ± 1.11*	0.001
AGE (%)	68.12 ± 5.60	67.06 ± 8.6	67.12 ± 6.9	62.78 ± 9.14*	0.03

Data are presented as the mean ± SD. *FBS* Fasting blood sugar, *HbA1c* Hemoglobin A1c, *AGE* Advanced glycation end-products. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$ compared with the control group

type 2 diabetes. Some experimental studies have shown the effect of probiotics on HbA1c. It has been shown that *Lactobacillus acidophilus* significantly reduced glycosylated hemoglobin in streptozotocin-induced diabetic mice after 14 days [12]. Yadav found that supplementation with probiotics in diabetic rats for 6 weeks significantly reduced fasting glucose and HbA1c [13]. On the other hand, the findings of Al-Salam et al. showed that probiotics were not effective on blood glucose in healthy rats [14]. The results of some clinical studies have been consistent with the present study reporting probiotics to be beneficial in reducing HbA1c. Ejtahed et al. found a significant reduction in glycemic indices and insulin resistance in people with diabetes following the consumption of probiotic yogurt compared with plain yogurt [15]. The precise mechanism of probiotics in reducing blood glucose is not clear, but several possible mechanisms have been proposed in this regard. The accumulation of lactic acid in the intestinal epithelium may reduce glucose uptake by the intestine [16]. In addition, probiotics can prevent and delay pancreatic degradation by inhibiting the production of pro-inflammatory cytokines [17, 18]. The positive effect of cinnamon on glycemic indices was observed in the current study. Cinnamon contains amidone, mucilage, tannin, calcium oxalate, sugar, cinnamomin, resin, and essential oils. The main component of cinnamon essential oil is cinnamaldehyde, which can determine the commercial value of cinnamon products [19]. The anti-microbial, anti-oxidant, anti-inflammatory, and anti-spasmodic properties which have been reported for cinnamon seem to be related to cinnamaldehyde. This plant has an anti-*Helicobacter pylori* effect and also inhibits the growth of *Escherichia coli*, *Listeria monocytogenes*, *Salmonella typhimurium*, *Staphylococcus aureus*, and Clostridium species [20, 21]. It has been shown that cinnamon extract inhibits tumor necrosis factor, cyclooxygenase 2, and nitric oxide synthase enzymes [22]. The terpene compounds of cinnamon have inhibitory effects on the metabolism of arachidonic acid. Polyphenols in the cinnamon prevent the formation of advanced glycated end products [23]. It has been reported that cinnamon strengthens insulin function in patients with diabetes and improves blood glucose, triglycerides, and cholesterol [24, 25]. In patients with type 2 diabetes, phosphorylation of the insulin receptor decreases. Moreover, cinnamon compounds stimulate insulin-receptor autophosphorylation and inhibit phosphotyrosine phosphatase, which is an enzyme responsible for de-phosphorylation of insulin-receptor and increases sensitivity to insulin. Studies suggest that cinnamon increases glucose uptake by activating the insulin receptor and also increases glycogen synthesis [24]. Khadem Haghighian et al. studied the effect of cinnamon on blood glucose levels in diabetic patients and reported that the average levels of fasting blood glucose, HbA1c, and insulin resistance decreased significantly in the intervention group compared with the control group, which is consistent with the results of the present study [26, 27].

Another study, however, showed that the use of 1 g/d cinnamon for 8 weeks had no effect on the level of blood glucose in patients with diabetes [28].

The results of the present study showed that the level of antioxidant enzymes increased moderately in all cinnamon, synbiotic, and probiotic groups with the most significant

Table 3 The effect of probiotic, cinnamon and synbiotic on biochemical factors in diabetic patients

Biochemical factors	Groups				
	Control $N = 27$	Probiotic $N = 30$	Cinnamon $N = 28$	Synbiotic $N = 30$	*P* value
CAT (U/mL)	1.95 ± 0.34	2.44 ± 0.50 *	2.44 ± 0.26 *	2.20 ± 0.31	< 0.001
GPx (U/mL)	84.89 ± 6.52	92.15 ± 8.41*	84.61 ± 13.43	89.71 ± 9.04	0.01
SOD (U/mL)	3.99 ± 0.27	4.58 ± 0.42 *	4.16 ± 0.60	4.13 ± 0.64	< 0.001
OxLDL (mU/L)	17.07 ± 1.01	16.85 ± 1.53	16.32 ± 1.21	15.88 ± 1.98 *	0.03

Data are presented as the mean ± SD. *CAT* Catalase, *GPx* Glutathione peroxidase, *SOD* Superoxide Dismutase, *OxLDL* Oxidized low-density lipoprotein. Statistical differences were determined using ANOVA followed by a Tukey post-hoc test; *, $P < 0.05$ compared with the control group change seen in the probiotic group. Various animal studies have shown that probiotics inhibit oxidative stress by reducing inflammatory damage and increasing levels of antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase [29].

The hepatic enzymes (AST, ALT) were investigated in the present study to monitor drug side effects and hepatic toxicity. Hepatic enzyme levels decreased significantly in all three groups. It can be concluded that drugs did not induce hepatic toxicity in the study's patients. The results of other clinical surveys indicated that probiotics prescribed for diabetic patients reduced hepatic enzyme levels [30–32].

Although some recent studies have shown that consuming synbiotic foods may have a beneficial effect on biochemical factors, inflammatory factors, and oxidative stress biomarkers, such effects have been found mostly in animal models or non-diabetic patients [33–35]. In the present study, however, synbiotic supplementation was not superior to probiotics or cinnamon alone in improving glycemic and antioxidant indices. Put together, the study strengths were classification of patients into 4 different groups, presence of single drug, combination and control groups and finally adequate time of the study. However, lack of insulin measurement and lack of patient height for measurement of BMI index were the weakness points of the present study.

Diverse surveys revealed boost incidence of some kinds of foodborne pathogens in different kinds of food samples [36–53]. Besides the clinical portion of using of natural medicinal plants, they also can control the growth and proliferation of diverse kinds of foodborne pathogens in different types of food. Thus, they also can use as a natural preservatives in food industry.

Conclusion

According to the current results, the use of probiotic supplements (individually or in combination with cinnamon) leads to a reduction in blood glucose and an increase in antioxidant enzymes in people with type 2 diabetes. The results of this study showed that probiotics, cinnamon, and synbiotics (a combination of probiotic and cinnamon) all can reduce the levels of fasting blood glucose and HbA1c in diabetic patients, and none of the treatments had a significant superiority over the others. The level of antioxidant enzymes increased moderately in all cinnamon, synbiotic, and probiotic groups with the most significant change seen in the probiotic group. According to all achieved results, probiotic had better results in improving blood glucose profile and antioxidant enzymes in type 2 diabetic patients.

Acknowledgements The authors would like to thank the vice-chancellor for research of Alborz University of Medical Sciences for financial support of the project. We also thank to Medicinal Plants Research Center.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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