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Probiotic and resveratrol normalize GLP-1 levels and oxidative stress in the intestine of diabetic rats

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ABSTRACT

Background: Recently, the use of incretins has been considered as a therapeutic target for diabetes. One of the important incretins in the improvement of diabetes is glucagon-like peptide (GLP-1), which is secreted by the gut and reduces the apoptosis of pancreatic β-cells and improves insulin sensitivity. In this experiment we determined the effects of resveratrol and probiotics on insulin resistance, oxidative stress, and GLP-1 in type 2 diabetes (T2D) rats.

Methods: In this study, 40 male Wistar male rats were divided into 5 groups: 1. Control group, 2. T2D, 3. T2D treated with probiotics, 4. T2D treated with resveratrol, 5. T2D group treated with probiotics and resveratrol. After four weeks, the intestine were removed for histopathological analysis, biochemical tests, and oxidative stress markers.

Results: Probiotics and resveratrol significantly decreased ($p < 0.001$) glucose and insulin resistance, and increased ($p < 0.001$) GLP1 and total antioxidant capacity compared to the diabetic group. Treatment with probiotics and resveratrol also returned intestinal histological changes in diabetic rats to normal.

Conclusion: Resveratrol and probiotics appear to be effective in controlling T2D by increasing GLP-1 levels and reducing oxidative stress.

1. Introduction

Diabetes is known as one of the most common endocrine disorders, and its mortality rates are increasing globally. Type 2 diabetes (T2D) is recognized by various pathological abnormalities such as elevated liver glucose production, insulin resistance, and reduced insulin function [1,2]. Diabetes also can increase the risk of various diseases [3–5].

At present, the first and effective treatment for diabetes is the insulin and blood glucose-lowering drugs. However, these agents have several side effects that can lead to drug withdrawals [6]. In this respect, the effort to find an approach with fewer side effects and more efficiency has increased. Glucagon-like peptide (GLP-1) is one of the most important hormones in the treatment of T2D. GLP-1 is secreted by enteroendocrine L cells in the gut in response to digestion and regulates glucose levels in the postprandial state [7]. In T2D patients, GLP-1 secretion is reduced compared to healthy individuals, consequently is an appropriate target for the development of new antidiabetic drugs [8].

GLP-1 increases the pancreatic β-cell mass and also inhibits β-cell apoptosis, subsequently increase insulin secretion. It also increases the differentiation of immature islet progenitor cells and converts them to beta cells [9]. GLP-1 also reduces gastric emptying, reduces appetite, and ultimately leads to weight loss. It also has beneficial effects on different organs, reduces oxidative stress and inflammation as well as has beneficial effects on learning and memory. The clinical worth of GLP-1 is limited by its short half-life and its harmful effects on the gastrointestinal tract at a specific dose. Therefore, an effective approach to increase the therapeutic benefits of GLP-1-based therapy is pharmacological improvement [10,11]. Biochemical modification of these optimized molecules allows for less administration, which places a lower drug burden on the patient [12]. Therefore, the use of GLP-1 agonists is used in the treatment of diabetes and obesity.

High glucose levels in T2D patients enhanced oxidative stress in

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the cells. Oxidative stress due to depletion of antioxidant system can increase the development of T2D complications and considered an important factor for insulin resistance. Oxidative stress has a vital role in the pathogenesis of gastrointestinal complications of T2D. Therefore, the antioxidants may be useful in the prevention and treatment of diabetic complications [13,14]. The use of antioxidants such as probiotics and resveratrol can be helpful in the management and treatment of diabetes [15]. Probiotics are living non-pathogenic microorganisms that part of normal intestinal flora, and when consumed in adequate amounts, have many beneficial effects for the body [16,17].

The administration of probiotics can increase insulin sensitivity by elevating beneficial bacteria and reducing harmful bacteria in the intestine. Probiotics can also reduce inflammatory markers and oxidative stress, which can delay the progression and development of T2D [18]. Previous studies have shown the beneficial effects of *Bifidobacteria,* and *Lactobacillus* strains on hyperglycemia, oxidative stress, and inflammation. These bacteria can reduce endotoxemia, stimulate short-chain fatty acid secretion (SCFAs, mainly butyrate, acetate, and propionate). The activity of *Bifidobacteria* and *Lactobacillus* in the gut has an important effect on the gastrointestinal hormone secretion, maintains gastrointestinal homeostasis, controls the differentiation and proliferation of epithelial cells, and participates in the synthesis of certain vitamins.

Resveratrol also can increase the GLP-1 secretion and improves glucose tolerance. Findings from previous experiments have suggested that resveratrol is useful in the treatment of diabetic patients by activating protein kinase B (Akt) signalling, which eventually increases insulin secretion [9]. It has been established that resveratrol has anti-cancer, antioxidant, anti-inflammatory and anti-inflammatory effects, and can increase the longevity of mammals [19].

As mentioned above, the GLP-1 agonist normalizes hyperglycemia, delays gastric emptying, motivates insulin release, decreases glucagon release, decreases food intake, and motivates β-cell functions. GLP-1 has numerous potential benefits for treatments of T2D. Therefore, the aim of this experiment was to determine the effect of resveratrol and probiotics on GLP-1 secretion, antioxidant enzymes, and insulin resistance in rats with T2D.

2. Materials and methods

In this study, 40 healthy male Wistar rats with an average weight of 250−300g, with for ten weeks age purchased from the Hamadan Medical University (Hamadan, Iran). Animals were divided into 5 groups (n = 8), including: group 1: control, group 2: diabetic (induced by 65 mg/kg STZ and 110 mg/kg Nicotinamide, single-dose injection), group 3: diabetic rats received probiotic (dissolve in water at the dose of 10×10^9 bacteria/kg body weight/day), group 4: diabetes rats received resveratrol (by oral gavage of 10 mg/kg resveratrol), and group 5: diabetic rats received resveratrol + probiotic for 4 weeks.

Rats were kept in separate cages, and they had free access to diet and drinking water. The rats were kept in the animal house with humidity of 60 ± 5% and standard light/dark cycle (12/12 h) with a temperature of 22 ± 2 °C. At the end of the experiment, blood was collected from the hearts rat and serum was separated for estimation of the various chemical tests [20]. The experiment was carried out according to the Animal Ethical Committee of Hamadan Medical University (ethic code: IR.UMSHA.REC.1397.551).

2.1. Induction of type 2 diabetes

To induce T2D, Streptozotocin and nicotinamide (Sigma Aldrich, USA) prepared with 0.01 M sodium citrate buffer (pH = 4.5), and keep on ice until IP injection. Streptozotocin (65 mg/kg) and nicotinamide (after 15 min, 110 mg/kg) were injected to animals. Seven days after drug injection (Streptozotocin and nicotinamide), the blood samples were prepared from the tail of rats, and glucose concentration was measured with a glucometer. Serum glucose concentration more than 250 mg/ml is considered diabetes [21].

2.2. Drug administration

Probiotics (Genuine Health Company, Canada) containing various bacteria, including *Lactobacillus plantarum, Lactobacillus bulgaricu, Lactobacillus casei, Bifidobacterium infantis, Lactobacillus acidophilus, Bifidobacterium longum, Bifidobacterium breve,* dissolved in drinking water at a dose of 50×10^9 for 4 weeks according to the previous published paper [22]. Resveratrol at the dose of 10 mg/kg (Natural Fact Company, USA) is administrated by oral gavage daily [23].

2.3. Measurement of GLP-1 in intestinal tissue

GLP-1 levels were determined by using enzyme-linked immunosorbent assay (ELISA) according to the manufacture instrument (Eastabiopharm, China). Briefly, the homogenate of the intestine was added to wells coated with GLP-1 monoclonal antibodies. Then the anti-GLP-1, and enzyme-conjugated streptavidin were added. The wells were incubated for 1 h and then the unbound enzymes were removed by washing. Then the substrate, and then stop solution was added. After 10 min, the standards and samples were read at 450 nm. The data expressed as nmol/mg protein. The protein level in the intestine was measured by the Bradford method.

2.4. β-cell function (HOMA-β)

The homeostasis model assessment of β-cell function (HOMA-β) was evaluated based on the following equation [24]. The glucose (Pars Azmoon, Iran) and insulin (Eastabiopharm, China) levels were measured using available kits.

$$HOMA-\beta = \frac{20 \times \text{fasting insulin}(\frac{\text{mU}}{\text{L}})}{[\text{fasting glucose}(\frac{\text{mmol}}{\text{L}}) - 3.5]}$$

2.5. Antioxidant activity

Total oxidative status (TOS) and total antioxidant capacity (TAC) were determined in the intestinal tissue. TAC was measured by the ferric reducing antioxidant potential (FRAP) method. In this reaction, antioxidant compounds reduce the ferric ion. The yield was measured by the spectrophotometer at a wavelength of 593 nm. TOS used to evaluation the overall oxidation state. TOS was determined according to the ferrous oxidation xylenol orange (FOX) assay. In this method, the oxidant compounds of the sample oxidized ferrous ion to ferric. This ferric ion reacted with xylene orange, and the absorption of the product was measured at 560 nm.

2.6. Histological changes

At the end of the experiments, the intestine in each group was immediately removed for histological examination. The tissues were fixed in 10% formalin for 48 h. In the next step, paraffin sections were prepared, and sections were prepared with a thickness of 5 μm by rotating microtome. The sections were then stained with Eosin and Hematoxylin. Histopathological slides were examined by light microscopy (Nikon E50i). Intestinal pathological changes were

observed and reported based on structural and cellular changes.

2.7. Data analysis

Results are expressed as a means ± SD. The findings were analyzed by SPSS 16 software using the Tukey test to compare the differences among the various groups. Differences at the level of $P < 0.05$ were considered significant.

3. Results

3.1. Effect of resveratrol and probiotics on insulin resistance index

Fig. 1 shows that probiotics lead to a significant decrease in insulin resistance index compared to the diabetic group ($p < 0.001$, 50% decrease compared to the diabetic group). However, this index reached near control rats. Administration of resveratrol caused a significant reduction of insulin resistance index ($P < 0.001$, 51% decrease compared to the diabetic group). Treatment of the diabetic group by probiotics reduce insulin resistance index compared to the diabetic group ($p < 0.001$, 60% decrease compared to the diabetic animals).

3.2. Effect of resveratrol and probiotics on the level of intestinal GLP-1

As shown in Fig. 2, administration of probiotics resulted in a substantial increase in the intestinal GLP-1 levels ($p < 0.001$, 69% increase compared to the diabetic group) compared with diabetic animals. Resveratrol also non-significantly increased the GLP1 in intestinal tissue. Our results also showed that co-administration of probiotics and resveratrol led to a significant increase in GLP-1 compared to the diabetic group. The increase in the combination group was similar to control animals ($p < 0.01$, 88% increase compared to the diabetic group).

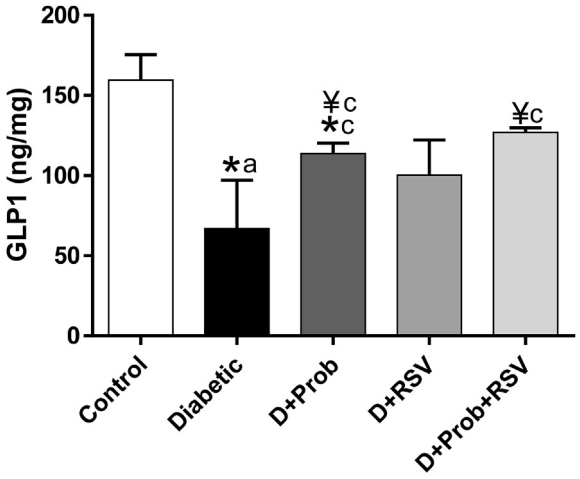

Fig. 2. GLP-1 levels in the intestine of study groups. Co-administration of probiotics and resveratrol led to a significant increase in GLP-1levels compared to the diabetic group. Data are shown in Mean ± SD. This increase was near healthy rats. D + Prob: Diabetic group received probiotic, D + RSV: Diabetic group received resveratrol, D + Prob + RSV: Diabetic group received probiotic and resveratrol. GLP-1: Glucagon-like peptide-1. Prob: Probiotic, RSV: Resveratrol. *: compared with control groups, ¥: compared with diabetic animals, #a: compared with alone treatment resveratrol. #b: compared with alone treatment probiotic. *a: $p < 0.001$ compared to the control. *c: $p < 0.05$ compared with the control. ¥c: $p < 0.05$ compared with the diabetic.

3.3. Effect of resveratrol and probiotics on total antioxidant capacity (TAC)

The results of TAC levels in intestinal tissue are shown in Fig. 3. Our results revealed that TAC significantly increased in the probiotic group ($p < 0.01$, 41% increase compared to the diabetic group) compared to the diabetic group. The change in the resveratrol group was not significant. Interestingly, treatment with resveratrol and probiotic combination significantly increased TAC compared to

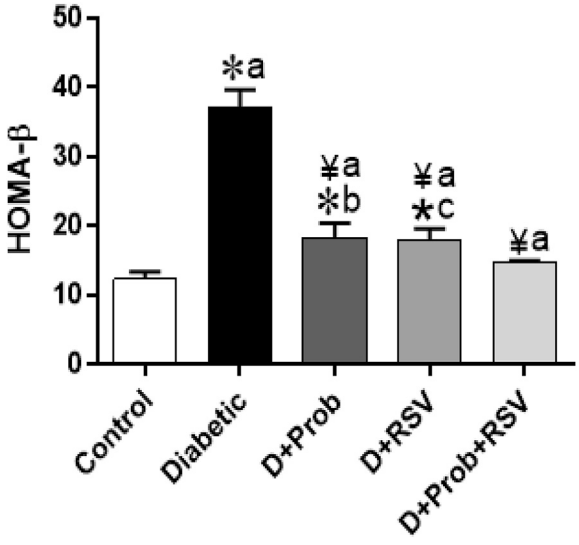

Fig. 1. HOMA-B index in the study groups. Combination therapy normalized HOMA-B as compared with diabetic groups. Data are shown in Mean ± SD. D + Prob: Diabetic group received probiotic, D + RSV: Diabetic group received resveratrol, D + Prob + RSV: Diabetic group received probiotic and resveratrol. HOMA-B: Homeostasis model assessment B cell function. Prob: Probiotic, RSV: Resveratrol. *: compared with control groups, ¥: compared with diabetic animals, #a: compared with alone treatment resveratrol. #b: compared with alone treatment probiotic. *a: $p < 0.001$ compared to the control. ¥a: $p < 0.001$ compared with the diabetic.*b: $p < 0.01$ compared with the control*c: $p < 0.05$ compared with the control.

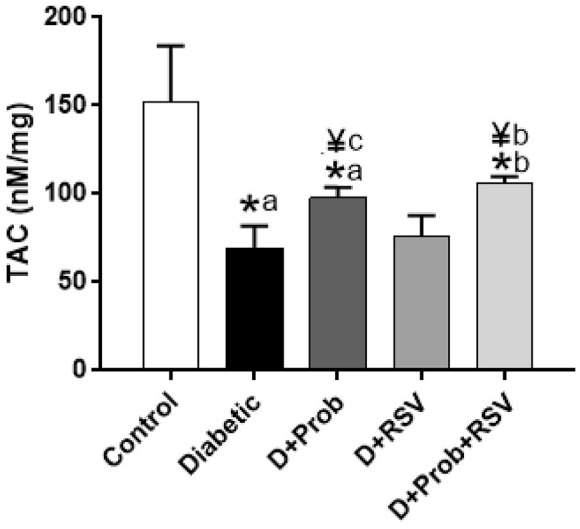

Fig. 3. TAC in the intestine of the study groups. Combination therapy led to a significant increase of TAC compared to the diabetic group. Data are shown in Mean ± SD. This increase was near healthy rats. D + Prob: Diabetic group received probiotic, D + RSV: Diabetic group received resveratrol, D + Prob + RSV: Diabetic group received probiotic and resveratrol. TAC: Total antioxidant capacity. Prob: Probiotic, RSV: Resveratrol. *: compared with control groups, ¥: compared with diabetic rats, #a: compared with alone treatment resveratrol. #b: compared with alone treatment probiotic. *a: $p < 0.001$ compared to the control. *b: $p < 0.01$ compared to the control. ¥b: $p < 0.01$ compared with the diabetic.¥c: $p < 0.05$ compared with the diabetic.

diabetic rats ($p = 0.046$, 53% increase compared to the diabetic rats).

3.4. Effect of resveratrol and probiotics on total oxidative status (TOS)

As shown in Fig. 4, the TOS markedly increased in the intestine of diabetic rats compared to the control rats ($p = 0.033$). In the probiotics group, the TOS level reduced compared to the diabetic group (36% decrease compared to the diabetic group) but this decrease was not statistically significant ($p = 0.348$). Like the probiotic group, the resveratrol group had lower TOS than diabetic rats (51% decrease compared to the diabetic group), but this decrease was not significant ($p = 0.072$). However, our results showed that treatment with combination of probiotics and resveratrol led to a significant reduction in TOS levels compared with the diabetic animals ($p = 0.014$, 65% decrease compared to the diabetic rats). The decrease in the combination group was similar to control rats, and the difference between these groups were not statistically significant ($p = 1.00$).

3.5. Intestinal histological results

Fig. 5 shows the histological changes of the intestine in different treated animals. Microscopic examination of different intestinal tissue showed a change in the length of the villi and reduced thickness of the mucosal layer, changes in the arrangement of epithelial cells, and the presence of mucosal lesions. Lymph cell infiltration and vascular fragility were seen in diabetic rats compared to controls. Treatment with resveratrol and probiotic restore intestinal alteration compared with diabetic rats. However, combination groups show better intestinal structure compared with other groups.

4. Discussion

The results of our study show the potential antioxidant properties of resveratrol and probiotics, particularly when administered simultaneously. The antioxidant and anti-diabetic effects of these drugs were also observed when administered alone, but the synergistic effects were observed in combination therapy. Our results showed that probiotics and resveratrol could normalize hyperglycemia and possibly prevent diabetes complications in diabetic rats. In agreement with these results, Yousaf et al. Showed that the use of probiotics effectively reduced blood glucose levels in diabetic rats[25,26].

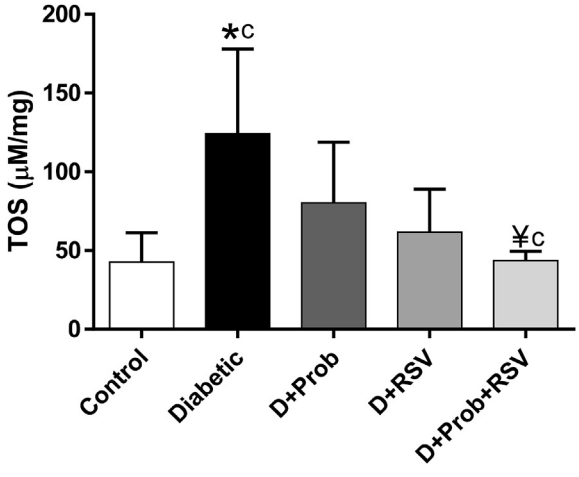

Fig. 4. TOS levels in the intestine of the study groups. Combination therapy led to a significant reduction of TOS compared to the diabetic group. This increase was near healthy rats. Control: Control group, Diabetic: Diabetic group, D + Prob: Diabetic group received probiotic, D + RSV: Diabetic group received resveratrol, D + Prob + RSV: Diabetic group received probiotic and resveratrol. TOS: Total oxidant status. Data are shown in Mean ± SD. Prob: Probiotic, RSV: Resveratrol. *: compared with control groups, ¥: compared with diabetic rats, #a: compared with alone treatment resveratrol. #b: compared with alone treatment probiotic. *c: $p < 0.05$ compared to the control. ¥c: $p < 0.05$ compared with the diabetic.

Pancreatic β-cell dysfunction and insulin resistance are vital mechanisms in the development of diabetes. HOMA-IR is commonly used as a procedure for estimating insulin resistance. This index is related to fasting blood glucose and insulin levels. The findings of our experiment showed that insulin resistance was markedly raised in T2D animals compared to the control rats. Treatment of animals with probiotics and resveratrol significantly reduced insulin resistance index as compared to the untreated diabetic group. However, this reduction was more significant when animals treated with the combination of probiotics and resveratrol. Of note, treatment of diabetic rats with probiotics improved insulin resistance better than resveratrol. The therapeutic effects of resveratrol may depend on the metabolic conditions, the length of treatment, and drug dose. Previous experiments have shown that probiotics inhibit pro-inflammatory cytokines which can affect insulin resistance. Rajkumar H et al., showed that administration of probiotics significantly reduces the high-sensitivity C-reactive protein (hs-CRP), as a sign of inflammation, in healthy people [27].

Previous evidence established the potential useful effects of gut microbiota to normalize metabolic disturbances and inflammation in diabetic animals. It seems that probiotics in the intestine by producing short-chain fatty acids (SCFA) induce the production of incretin such as GLP-1, which due to the insulinotropic properties of these hormones, can normalize insulin resistance in diabetic rats [28,29]. Lactate and acetate produced by *Bifidobacterium* and *Lactobacillus* can be converted to butyrate by another type of gut microbiota. Butyrate has significant roles in gastrointestinal inflammation and suppress the nuclear factor kappa B (NF-κB) signalling, favouring an antidiabetic condition. Acetate induces GLP-1 release by intestinal L cells, consequently normalizes glucose homeostasis, regulates appetite and decreases inflammation. Using SCFA-producing bacteria and their metabolites may have favourable effects in improvements of insulin resistance. Hence probiotics can improve microbiota-related mechanisms that lead to insulin resistance [30]. SCFA has been reported to activate the expression of G protein-coupled receptors (GPCRs) by intestinal L-cells. Binding of SCFA with GPCRs (e,g., GPR43 receptor) is likely to stimulate intestinal L cells to secrete GLP-1, and other gastrointestinal peptide hormones to exert anti-diabetic function. Some studies have reported that these SCFA-producing bacteria (like our experiment) can enhance GLP-1 secretion by regulating GPR43/41 activity [31]. Soleimani et al., showed that administration of various strains of *Lactobacillus* in diabetic patients reduces HbA1c and insulin resistance [32].

This experiment revealed that GLP-1 level was markedly decreased in the intestinal tissue of diabetic animals compared to the healthy rats. In a study of an animal model, Yadav et al., reported that the use of probiotics significantly increased intestinal GLP-1 levels by producing butyrate in the intestines of diabetic rats [29]. The use of resveratrol in the diabetic rats non-significantly increases the intestinal GLP-1 levels. Dao et al., showed that deletion of the GLP-1 gene in diabetic mice eliminates the anti-diabetic effect of resveratrol, indicating a direct link between antidiabetic properties of resveratrol and GLP-1 [33]. The effects of resveratrol on GLP-1 levels were not significant, but combination therapy led to a synergistic increase of this hormone. Only trivial amounts of resveratrol were absorbed from the intestine. However, probiotics

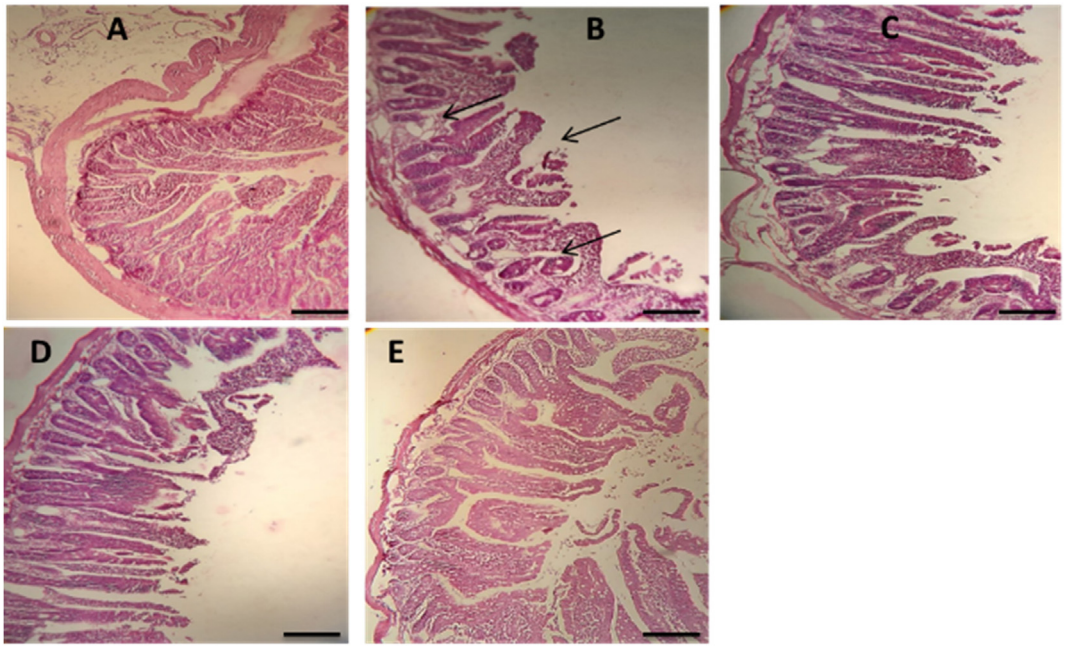

Fig. 5. Histological alteration in the intestine of different study groups. In diabetic rats, histological changes, include reduction in villi length, reduction in mucosal layer thickness, changes in epithelial cell arrangement, presence of mucosal lesions (lymph cell infiltration and vascular fragility) were observed in diabetic rats. Treatment with probiotics and resveratrol greatly improved intestinal morphological changes (magnification: *100). A: Control, B: Diabetic, C: Probiotic, D: Resveratrol and E: Combined group (Resveratrol + Probiotic, scale bar: 50 μm).

probably, by increasing resveratrol absorption, caused synergistic effects. Increasing GLP1 levels in diabetic animals strengthen the hypothesis of antidiabetic properties of these combinations. GLP-1 has glucose-dependent insulinotropic effects, reduces glucagon secretion, indicating the vital role in the treatment of T2D [34].

Free radicals participate in the pathogenesis of many disorders, such as diabetes mellitus, rheumatoid arthritis, cardiovascular disease, cancers, and amyloid disease [35]. Due to the vital role of free radicals in diabetes, one of the approaches in the treatment of this disease is the reduction of free radicals. The oxidative stress caused by high blood glucose levels in diabetes can disturb insulin signalling, leading to insulin resistance. Many experiments have established that oxidative stress participate in the development of insulin resistance, and pancreas β-cell injury. It has also been documented that free radicals are the main participant in the pathophysiology of diabetic complications. Evaluation of TOS and reduction of TOS are accepted as practical tests to assess oxidative stress. Our findings showed that TOS significantly decreased and TAC significantly increased in the intestinal tissue of diabetic animals. In agreement with our study, a decrease in TAC in diabetic patients has been established in a previous report [36]. Treatment with resveratrol and probiotics decreased TOS in the intestinal tissue compared to the untreated diabetic group. The amount of TAC was increased by resveratrol and probiotic in the intestine. The antioxidant properties of probiotics and resveratrol were seen in the diabetic group in the present study. However, better results can be seen by increasing the number of treatment days. The resveratrol plus probiotic in diabetic rats improved the antioxidant status and showed a synergistic effect. Recent studies have shown that probiotics in the gut have a significant effect on the absorption of some nutrients such as polyphenols in foods and supplements and increase the body's access to these nutrients. Probiotics in the intestine can increase the absorption of resveratrol and increase the antioxidant properties of this substance after absorption (28) and its bioavailability. Increased absorption of resveratrol in the presence of probiotics, is one of the most likely mechanisms for the synergistic properties of this combination [37].

It has been reported that diabetes lead to intestinal morphologic alterations includes increasing length, weight, crypt depth and villus height. The results of our experiment showed that combination therapy alleviates morphologic alterations induced by diabetes in the intestine. The histological findings confirm the antioxidant effects of these compounds. In the treated groups, histological changes such as necrosis and hemorrhage, crypt depth, villus height and structural changes, especially the combination group, were restored compared to the diabetic group. Various studies have reported that the use of resveratrol in diabetic patients can normalize oxidative stress and morphological changes in diabetic patients [38].

Our study also had some limitations. Firstly, due to rapid degradation of GLP-1 by DPP-4 in the blood circulation, this incretin has a very short half-life (less than 2 min) [10]. Hence, it was very low and non-significant among various groups in our measurements. Secondly, it essential to determine the SCFA in the blood of animals. Additional experiments are needed to determine the synergistic effect of probiotics and resveratrol in diabetic patients.

In conclusion, the incretin hormone GLP-1 decreased in T2D rats. Drugs that motivate GLP-1 secretion may have a role in the management of diabetes. Our findings revealed the synergetic effects of probiotics and resveratrol in reducing insulin resistance in diabetic rats. Our results showed that this combination increases GLP-1 levels in intestinal tissue, which may alleviate hyperglycemia. Therefore, due to the very effective role of probiotics and resveratrol in diabetes, it can be proposed as a treatment for diabetics.

Availability of data and material

Data are available upon reasonable request.

Author contributions

Atefeh Pegah: Conceptualization, Data curation, Writing - original draft, Methodology. Ebrahim Abbasi-Oshaghi: Project administration, Supervision, Data curation, Writing - review & editing. Iraj Khodadadi: Writing - review & editing. Fatemeh Mirzaei: Methodology, Writing & editing. Heidar Tayebinai: Writing - review & editing.

CRediT authorship contribution statement

Atefeh Pegah: Conceptualization, Data curation, Writing – original draft, Methodology. **Ebrahim Abbasi-Oshaghi:** Project administration, Supervision, Data curation, Writing – review & editing. **Iraj Khodadadi:** Writing – review & editing. **Fatemeh Mirzaei:** Methodology, Writing – review & editing. **Heidar Tayebinai:** Writing – review & editing.

Declaration of competing interest

The authors report no conflict of interest.

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