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The effect of electron beam on oxidative stress and inflammatory factors in diabetes mellitus: An in vitro and in vivo study

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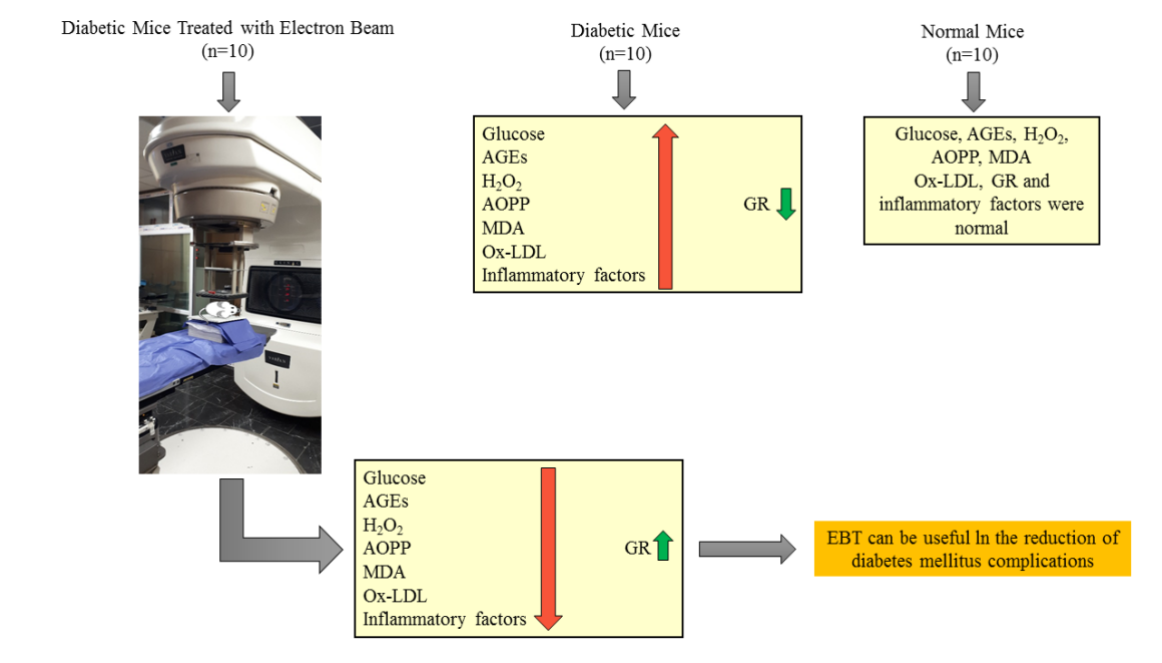
ABSTRACT

Background: The main purpose of this study was to investigate whether or not electron beam therapy (EBT) was an effective method in terms of moderating oxidative stress by reducing free radicals in BALB/c mice with type 1 diabetes mellitus.

Methods: The study was performed on thirty BALB/c mice in three groups including normal control, diabetic control, and EBT treated. Before studying the effect of electron beam on the studied groups, optimal level of constant source-to-surface distance, as well as the effects of EBT on glutathione reductase (GR) structure and function were determined. After studying the structure and the function of GR protein with three methods including fluorometry, circular dichroism (CD), and activity assay methods, SSD 100 was selected for EBT. Glucose, advanced glycation end-products, GR, oxidative stress factors such as hydrogen peroxide, malondialdehyde,

advanced oxidation protein products, oxidized low-density lipoprotein, and inflammatory factors were measured in the serum of all groups.

Results: The results of in vitro study showed that electron beam therapy could increase glutathione reductase activity, which was not significant. Also, the results were compared between and within groups using one-way analysis of variance. Significant differences were observed for all variables measured between the normal control group and the other groups ($P < 0.05$). There was also no significant difference in blood glucose levels between the electron beam therapy treated group and the diabetic one ($P > 0.05$).



Conclusion: The results suggested that electron beam therapy could be effective in reducing free radicals and oxidative stress. Electron beam therapy, as a complementary method, might aid in moderating the complications of diabetes mellitus.

Keywords: Diabetes mellitus, Electron beam, Inflammatory factors, Oxidative stress

INTRODUCTION

Diabetes mellitus (DM) (type 1 and type 2) is considered as one of the most prevalent chronic metabolic diseases [1]. Among the important risk factors for developing DM and its complications is insufficient physical activity [2-3]. It has been estimated that around 592 million people throughout the world will develop DM by the year 2035 [4]. In type 2 DM, also known as insulin-resistant DM, insulin is produced, but it loses its efficacy and results in insulin resistance [5]. Increased fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), and 2-h

plasma glucose levels are similarly known as diagnostic biomarkers of DM [6]. The production of oxidants, such as free radicals, in DM can also help with diagnosing pathogenesis and determining methods to treat it. Oxidative stress seems to be a major risk factor in the onset and progression of DM and its consequences [7]. Reactive oxygen species (ROS) also create oxidative stress. Moreover, hydrogen peroxide (H_2O_2) is one of the most common ROS types which plays a role in hydroxyl radical (•OH) production, and •OH has a position in the production of lipid peroxides [8]. Additionally, oxidative stress induces signaling pathways, contributing to immune and inflammatory responses [9]. Hyperglycemia with oxidative stress also plays an important role in the formation of advanced glycation end-products (AGEs) in patients with DM [10]. Accordingly, oxidative stress can be induced by AGEs [11], whose value in pathogenesis of DM and its consequences have not been fully understood [12]. Furthermore, evidence suggests that food-derived AGEs can contribute to development of DM and its complications [13-14].

Insulin-resistance and type 2 DM are identified by dyslipidemia and abnormal lipoproteins, such as oxidized low-density lipoprotein (Ox-LDL), which is a risk factor for DM consequences [15- 16]. Ox-LDL and denatured LDL have also been isolated by AGEs with scavenger receptors, (SRs) which can form foam cells contributing to atherosclerosis [17]. Malondialdehyde (MDA) and advanced oxidation protein products (AOPP) are components of oxidative stress and are found more in individuals with diabetes compared to individuals without diabetes. MDA is a peroxidized degradation product of polyunsaturated fatty acids (PUFAs), and increased serum MDA along with higher levels of conjugated dienes have been observed in patients with DM [18]. In some studies, a positive correlation has been also reported between serum AOPP levels and HbA1c concentration in patients with type 2 DM [19]. One of the causes of inflammation in the human body is inflammatory factors such as tumor necrosis factor alpha (TNFα), interleukin 1 alpha (IL-1α), and interleukin 6 (IL-6), which are associated with insulin resistance and type 2 DM [20]. The mentioned inflammatory factors can increase in untreated type 1 and type 2 DM. Furthermore, it has been reported that acetoacetate as a ketone body increases secretion of TNFα and IL-6 in hyper-ketonemic patients with DM [21].

It has also been found that oxidative stress affects microvascular and macrovascular diseases (as the complications of oxidative stress in type 2 DM) in the human body. Microvascular diseases contribute to the development of diabetic neuropathy and nephropathy. Reducing HbA1c is also of importance in reducing microvascular events and consequences of neuropathy in patients with DM [22-23]. Antioxidants and some antioxidant enzymes such as glutathione reductase (GR) are able to break down free radicals and compounds created from free radicals. Using functional foods as a source of antioxidants can play an important role in preventing DM, as discussed in our previous study [24]. In untreated patients with DM, hyperglycemia leads to inhibition of antioxidant activity such as GR [25].

In most patients with type 1 DM, insulin is recommended for DM control. According to the American Diabetes Association (ADA), lifestyle changes can have effects on preventing and managing type 2 DM. Moreover, use of anti-hyperglycemic drugs can help in controlling type 2 DM and prevent its progression. In this regard, metformin is one of the most commonly used and recommended drugs for the management of type 2 DM [26]. Free radicals also have one or more unpaired electrons [27]. Therefore, elimination of

free radicals and oxidative stress can be important in preventing DM consequences. The mechanism of action of electron therapy is related to its antioxidative effect. Electron therapy destroys free radicals [27]. Studies have reported the importance of EBT in the treatment and control of skin diseases and some cancers [28], as well as skin-related diseases caused by type 2 DM [29-30].There is no study on the application of EBT on free radicals and reduction of oxidative factors in diabetic samples, and this study could be a new study on the application of EBT.

The main purpose of this study was to evaluate the effect of EBT on oxidative stress and inflammatory factors, and to assess glucose and glutathione peroxidase levels in streptozotocin (STZ)-induced BALB/c mice with diabetes.

MATERIALS AND METHODS

***Materials*:** For the in vitro study, GR (G9297), glucose (G7021) and phosphate buffered saline (PBS) (P5368) were purchased from Sigma-Aldrich Co (USA). Activity assay kit of GR (ab83461) was also bought from Abcam Co (USA). Also, a 0.22 µm filter was obtained from Millipore Corp., Billerica, MA (USA). For the in vivo study, STZ (S0130) and nicotinamide (NA) (N0636) were purchased from Sigma-Aldrich Co (USA). Moreover, quantity assay kits of IL1β (MBS175967), AGEs (MBS704846), AOPP (MBS263319), MDA (MBS264973) and ox-LDL (MBS2512757) were acquired from MyBioSource Co (USA). Quantity assay kits of IL1α (BMS611), IL6 (LMC0061) and TNFα (BMC607-3) were bought from Termo Fisher Chem Co (USA). Also, quantity assay kits of H_2O_2 (E-BC-K102) and glucose (81692) were acquired from Elabscience and Crystal Chem companies (USA), respectively. It should be noted that EBT was performed by VARIAN model CLINAC 2100 C/D (USA).

Methods

***GR Glycation*:** The method of glutathione reductase glycation was performed according to our previous study [31]. In this study, glucose solution was prepared via combining pure glucose with PBS. A solution of pure substance of GR, with a concentration of 10 mg/ml, was also made through combining this protein with PBS at pH 7.4. Also, GR solution was prepared from pure GR solution. Then, a sample of the solution was mixed with glucose solution, with a concentration of 50 Mm/lit, and named glycated GR solution. A part of this solution was directly separated and labeled with the same name, but the rest of the recently prepared solution was exposed to a physical factor (i.e. EBT) and named affected glycated GR. Therefore, there were three solutions; pure GR, glycated GR, and affected glycated GR. Following filtration of all samples under sterilized status, they were maintained in an incubator at 37°C for 16 weeks. At the end of the 16th week, an aliquot of each of the three previously mentioned solutions was prepared and then saved at -80°C until it could be analyzed by fluorometry, circular dichroism (CD), and activity assay methods.

***Optimal Constant Source-to-Surface Distance (SSD) Set up*:** Before examining the effects of EBT on oxidative and inflammatory stress factors in the study group and determining the optimal level of SSD, as well as the effects of EBT on GR structure and function, different SSDs and their impacts on pure protein, glycated protein, and glycated protein exposed to EBT were evaluated. After studying the structure and the function of GR protein in three mentioned statuses via fluorometry, CD, and activity assay methods, SSD 100 was selected for EBT. In fluorometry, the samples at a concentration of 0.5 mg/ml were measured by Shimadzu

Spectrofluorometer RF-5000 (Kyoto, Japan). Excitation and emission wavelengths of 350 and 440 nm were also considered, respectively. The results were presented as percentages. In CD method, spectra assessment was done by JASCO-810 spectropolarimeter (Jasco, Tokyo, Japan). The structure of each of the previously mentioned samples containing a concentration of 0.1 mg/ml was also measured. The spectra were modulated and achieved as units of mean residue molar ellipticity [θ] (mdeg cm^2 $dmol^{-1}$), based on the average weight of the amino acids (112.4). Moreover, the equation [θ] λ= (θ×112.4)/cl showed the molar ellipticity and calculations were performed at 25°C. Furthermore, the function of GR was measured by a related activity assay kit (enzyme-linked immunosorbent assay method (ELISA)), enzymatic colorimetric method, and Tecan's Sunrise absorbance microplate reader (Switzerland). The measurement of enzyme activity was performed as mU/ml.

***Animals*:** A total number of 40 male BALB/c-type mice aged 6 weeks with an average body weight of 30 g (bought from Pasteur Institute, Tehran, Iran) were housed in a temperature-controlled vivarium (at a temperature of 23±3°C and a relative humidity of 50±10%) with a 12:12 h light-dark cycle and free access to rat chow and water ad libitum. The mice were given a normal diet. The experimental protocol was approved by the Animal Ethical Committee in accordance with the guidelines for the care and use of laboratory animals prepared by Tehran University of Medical Sciences. After one week of acclimation under these conditions, 30 mice showing favorable growth were selected and used for further studies. They were randomly allocated to three groups (n=10): (1) normal control group (normal ones without any interference), (2) diabetic control group (with diabetes ones involved by STZ but not affected by EBT), (3) EBT treated group (with diabetes ones affected by EBT). DM was then induced in mice (groups 2 and 3) via intraperitoneal injection (i.p) of a single dose of STZ (50 mg/kg) 15 min after an i.p administration of nicotinamide (120 mg/kg). One week after such injections, serum glucose ≥ 200 mg/dl was considered as DM. Hence, mice were divested of food for 10-12 h. Blood samples (20 µl) were also collected from mouse tail veins under ether anesthesia. Group 3 was then exposed to EBT after induction of DM owing to STZ. The experiments were carried out in compliance with the relevant national laws relating to the conduct of animal experimentation.

***EBT*:** In the present study, EBT was performed using a linear accelerator. Before exposure to electron beams, mice were divested of food for 10–12 h and then were anesthetized with xylazine and ketamine. The dose for per treat in all mice was 100 cGY of energy. Treatment was also performed in two fractions (one fraction twice in two weeks). The used amount of energy was 9 MeV (micro electron volt). The depth of treatment was 1.5 cm. After the EBT was completed, mice in all three groups were sacrificed following anesthesia. Then, blood samples were taken from their hearts. To separate the serum from the clot, the clot was centrifuged for 5 min at 5000 g. The isolated sera were then stored at -70˚C for further study. Serum glucose in all groups was subsequently measured according to the glucose kit instructions.

***Statistical analysis*:** Statistical analyses were performed using SPSS for Microsoft Windows (version 16.0; IBM, USA). The results were thus shown as means ± standard deviation (SD). The mean scores of the variables between and within groups were also

compared using one-way analysis of variance (ANOVA). After that, Tukey's honestly significant difference (HSD) post-hoc test for multiple comparisons was employed. To analyze the in vitro results, Mann-Whitney U test, as a nonparametric test, was utilized. A p-value ≤ 0.05 characterized the presence of a statistically significant difference.

RESULTS

***In Vitro Study*:** As mentioned before, the activity of GR protein in a glycated state was investigated to determine optimal levels of SSDs and the impact of different SSDs on the results of EBT. After establishing the optimal SSD (i.e. SSD = 100) activity and concentration, the structure of GR in glycated and electron-affected states was investigated by three methods. In addition to measuring the activity and structure of GR under the influence of EBT, the activity of this protein in pure and glycated states was also studied. GR structure, concentration, and activity assays were performed in three different modes–by CD, fluorometry and ELISA (according to the manufacturer's instructions) (Table 1). Evaluation was done in triplicate and results indicated a significant difference in concentration and structure of glycated GR and glycated GR exposed to EBT (p-value < 0.05). Comparison of GR activity between the two groups showed no significant difference (p-value > 0.05).

Table 1. Activity, concentration, and structure of GR in three forms, pure, glycated and glycated treated with electron radiation.

	Method type		
Samples	**Fluorometry (%)**	**Circular dichroism (θ/nm)**	**ELISA*(mU/ml)**
Pure GR	23.75±0.7	195248±3.64	32.5±1.28
Glycated GR	100±1.63	331267±4.19	21.7±1.06
Glycated GR exposed to electron radiation	91.36±1.32	326475±4.93	23.6±1.08
P-value**	< 0.001	< 0.001	< 0.001

GR, glutathione reductase. Data are expressed as mean ± SD. SSD for the sample treated with electron was 100

*The enzyme-linked immunosorbent assay

**Significant difference between pure GR and glycated GR exposed to electron radiation

***In Vivo Study*:** After the diabetic group was exposed to electron beams (Figure 1), the mice of all groups were sacrificed and the mentioned above biochemical parameters were examined. There was a significant difference between blood glucose levels in the diabetic control group and the EBT treated group (p-value = 0.001). However, there was no significant difference in blood glucose levels between diabetic control group and EBT treated group (p-value = 0.84). In addition to glucose, serum GR, AGEs, and oxidative factors were measured in all groups, and a significant difference was observed between the normal control group and the other groups. Comparison of these factors between the EBT treated group and diabetic control group was also significant (p-value = 0.001). These results are presented in Table 2.

Figure 1. Scheme of the radiotherapy system and the diabetic group were treated with electron beams (EBT group)

Table 2. Comparison between serum glucose concentration and other measured variables in different studied groups

Groups Parameters	Normal control (n=10)	Diabetic control (n=10)	EBT treated (n=10)
Glucose (mg/dl)	163.70 ± 2.90*	399.60 ± 22.72	395.60 ± 15.70
GR (mU/ml)	33.17 ± 1.26*	21.24 ± 1.54	24.04 ± 0.95†
AGEs (µg/ml)	5.37 ± 0.17*	9.20 ± 0.25	8.65 ± 0.26†
H_2O_2 (mmol/l)	31.88 ± 2.76*	131.94 ± 2.42	127.69 ± 1.45†
AOPP (mg/ml)	17.64 ± 0.80*	42.82 ± 1.73	38.25 ± 2.38†
MDA (nmol/ml)	5.10 ± 0.32*	9.09 ± 0.18	8.69 ± 0.42†
Ox-LDL (ng/ml)	8.04 ± 0.36*	18.46 ± 0.26	18.01 ± 0.37†

GR, glutathione reductase; AGEs, advanced glycation end-products; AOPP, advanced oxidation protein products; MDA, malondialdehyde; Ox-LDL, Oxidized low-density lipoprotein. Results are expressed as the mean ± SD.

* Significances of data comparing in the normal control group with the other of groups (P value < 0.001).

† Significances of data comparing EBT treated vs. diabetic control group (P value < 0.05).

In this study, inflammatory factors, which may be elevated in the blood as a result of untreated DM, were also evaluated. Comparison of inflammatory factors such as IL-1α, IL-1β, IL-6, and TNFβ showed a significant difference (p-value = 0.001) between the normal control group with other groups and the diabetic control group with the EBT treated group (Figure 2).

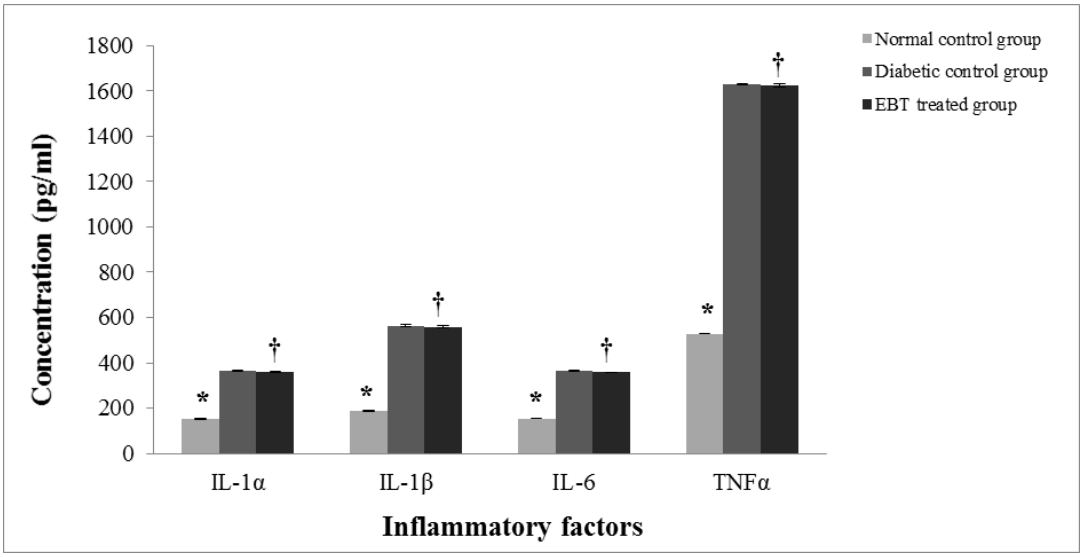


Figure 2. Concentration of IL-1α, IL-1β, IL-6 and TNFα in the normal control group, diabetic control group and EBT treated group.

* Significances of data comparing normal control group vs. other groups

† Significances of data comparing EBT treated group vs. diabetic control group

DISCUSSION

The main purpose of this study was to investigate the effects of EBT on serum glucose and some oxidative stress and inflammatory factors in mice with type 1 DM. Consequences of untreated DM are one of the most important issues in human communities. Accordingly, oxidative stress and free radicals, as well as some inflammatory factors caused by DM, are involved in the formation of DM consequences [32], and it is clear that untreated DM increases the variables of oxidative stress and inflammatory factors. These variables have already been investigated in numerous studies and it has been suggested that some elements play an important role in reducing them [33-40]. The pro-inflammatory mechanisms can also be of importance in the development of diabetic nephropathy; e.g. in the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB)-TNFα pathway, TNFα is stimulated by increased oxidative stress as well as glycated and oxidized products. This inflammatory factor in untreated DM similarly plays a leading role in the development of diabetic nephropathy [41].

Radiation therapy and laser therapy are now being utilized to treat patients with cancer. However, no study so far has investigated the effects of EBT on free radicals and inflammatory factors in patients with diabetes, although there have been investigations into laser therapy in patients with DM as well as animal models [42-45]. Radiation therapy may be harmful and can also lead to DM. In this respect, one study found that pancreas exposure to

radiation might increase the risk of DM in children with cancer [46]. In a study by Enosawa et al., serum glucose and malondialdehyde levels were reduced in electron-treated diabetic rats in the twelfth week [47]. The results of serum levels of glucose and malondialdehyde in our study were consistent with the results of the study of Enosawa et al. A study by Skrepnik et al. also showed that long-term EBT was useful for the treatment of skin lesions (i.e. scleroderma diabeticorum) caused by poorly controlled DM [30].

In the present study, the penetration depth of the electron beam was 1.5 cm, which might affect the skin and subcutaneous blood flow. Electron beams do not penetrate deep into the body and do not affect the tissues and organs of the body. It is possible that free radicals with the electrons given will complete their capacity and lose their oxidizing power. Probably for this reason, in the present study, the amount of H_2O_2 had been decreased in the mice in the EBT treated group compared to the untreated group. This might also be the reason for the decrease in Ox-LDL, AOPP, and MDA in EBT treated mice. The AGEs can be correspondingly involved in the development of diabetes. The production of AGEs occurs in hyperglycemic and oxidative stress conditions. It has been previously demonstrated in our study that the laser in vitro affects glycated catalase [31]. Electron irradiation may also directly or indirectly reduce glycated compounds such as AGEs at the serum level. In this regard, EBT can be a new method to reduction of glycated compounds. Free radicals can thus destruct antioxidant enzymes. By reducing free radicals, the activity of antioxidant enzymes such as catalase and GR can subsequently increase. In this study, minerals and vitamins were not measured, but in our previous studies [24, 48], minerals were studied and the effect of using functional foods on the increase of these elements and oxidative biomarkers [49] in diabetic samples was discussed. The growth in GR activity in the serum of mice treated with EBT confirms the results of this in vitro study, in which it was found that the activity of glycated GR treated with EBT had increased more than glycated GR. However, this increasing trend was not significant. In the present study, the small sample size was the most important limitation and larger sample size is required to verify these results.

CONCLUSION

In conclusion, EBT can be used as a complementary treatment to avoid the complications of conventional DM medications such as insulin and metformin. It can be stated that EBT may be involved in reducing some free radicals and oxidative stress caused by DM. Further studies, however, need to be carried out both in vitro and in vivo.

List of abbreviations: EBT: electron beam therapy, DM: diabetes mellitus, WHO: World Health Organization, FPG: fasting plasma glucose, HbA1c: glycated hemoglobin, ROS: Reactive oxygen species, H_2O_2: hydrogen peroxide, AGEs: advanced glycation end-products, Ox-LDL: oxidized low-density lipoprotein, MDA: Malondialdehyde, AOPP: advanced oxidation protein products, TNFα: tumor necrosis factor alpha, IL-1α: interleukin 1 alpha, IL-6: interleukin 6, GR: glutathione reductase, PBS: phosphate buffered saline, CD: circular dichroism, SSD: Source-to-Surface Distance, ELISA: enzyme-linked immunosorbent assay.

Author's contributions: The authors' confirmed contributions to the paper are as follows: DM

participated in the study design and the article editing. MSA performed experiments and treatment of samples with cold plasma by atmospheric pressure plasma jet device; MRA participated in the writing and analysis of the results; ASM assisted in experiments; MN and HM contributed to the original idea of the paper, doing the experimental work and data collection. All authors read and approved the final version before its submission.

Conflict of interest: The authors declare that there is no conflict of interest.

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